PHARMACEUTICAL DOSAGE FORMS: TABLETS

Third Edition

Volume 2: Rational Design and Formulation

Edited by

Larry L. Augsburger

Stephen W. Hoag

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To my loving wife Jeannie,
the light and laughter in my life.

—Larry L. Augsburger

To my dear wife Cathy and my children Elena
and Nina and those who helped me
so much with my education:
My parents Jo Hoag and my late father
Jim Hoag, Don Hoag, and Edward G. Rippie.

—Stephen W. Hoag

Foreword

We are delighted to have the privilege of continuing the tradition begun by Herb Lieberman and Leon Lachman, and later joined by Joseph Schwartz, of providing the only comprehensive treatment of the design, formulation, manufacture and evaluation of the tablet dosage form in *Pharmaceutical Dosage Forms: Tablets*. Today the tablet continues to be the dosage form of choice. Solid dosage forms constitute about two-thirds of all dosage forms, and about half of these are tablets.

Philosophically, we regard the tablet as a drug delivery system. Like any delivery system, the tablet is more than just a practical way to administer drugs to patients. Rather, we view the tablet as a system that is designed to meet specific criteria. The most important design criterion of the tablet is how effectively it gets the drug "delivered" to the site of action in an active form in sufficient quantity and at the correct rate to meet the therapeutic objectives (i.e., immediate release or some form of extended or otherwise modified release). However, the tablet must also meet a number of other design criteria essential to getting the drug to society and the patient. These include physical and chemical stability (to assure potency, safety, and consistent drug delivery performance over the use-life of the product), the ability to be *economically* mass produced in a manner that assures the proper amount of drug in each dosage unit and batch produced (to reduce costs and provide reliable dosing), and, to the extent possible, patient acceptability (i.e., reasonable size and shape, taste, color, etc. to encourage patient compliance with the prescribed dosing regimen). Thus, the ultimate goal of drug product development is to design a system that maximizes the therapeutic potential of the drug substance and facilitates its access to patients. The fact that the tablet can be uniquely designed to meet these criteria accounts for its prevalence as the most popular oral solid dosage form.

Although the majority of tablets are made by compression, intended to be swallowed whole and designed for immediate release, there are many other tablet forms. These include, for example, chewable, orally disintegrating, sublingual, effervescent, and buccal tablets, as well as lozenges or troches. Effervescent tablets are intended to be taken after first dropping them in water. Some modified release tablets may be designed to delay release until the tablet has passed the pyloric sphincter (i.e., enteric). Others may be designed to provide consistent extended or sustained release over an extended period of time, or for pulsed release, colonic delivery, or to provide a unique release profile for a specific drug and its therapeutic objective.

Since the last edition of *Pharmaceutical Dosage Forms: Tablets* in 1990, there have been numerous developments and enhancements in tablet formulation science and technology, as well as product regulation. Science and technology developments include new or updated equipment for manufacture, new excipients, greater understanding of excipient functionality, nanotechnology, innovations in the design of modified release

tablets, the use of artificial intelligence in formulation and process development, new initiatives in real time and on-line process control, and increased use of modeling to understand and optimize formulation and process parameters. New regulatory initiatives include the Food and Drug Administration's SUPAC (scale up and post approval changes) guidances, its risk-based Pharmaceutical cGMPs for the 21st Century plan, and its PAT (process analytical technology) guidance. Also significant is the development, through the International Conference on Harmonization of proposals, for an international plan for a harmonized quality control system.

Significantly, the development of new regulatory policy and new science and technology are not mutually exclusive. Rather, they are inextricably linked. The new regulatory initiatives serve as a stimulus to academia and industry to put formulation design, development, and manufacture on a more scientific basis which, in turn, makes possible science-based policies that can provide substantial regulatory relief and greater flexibility for manufacturers to update and streamline processes for higher efficiency and productivity. The first SUPAC guidance was issued in 1995 for immediate release oral solid dosage forms (SUPAC-IR). That guidance was followed in 1997 with SUPAC-MR which covered scale-up and post approval changes for solid oral modified release dosage forms. These guidances brought much needed consistency to how the Food and Drug Administration deals with post approval changes and provided substantial regulatory relief from unnecessary testing and filing requirements. Major underpinnings of these two regulatory policies were research programs conducted at the University of Maryland under a collaborative agreement with the Food and Drug Administration which identified and linked critical formulation and process variables to bioavailability outcomes in human subjects. The Food and Drug Administration's Pharmaceutical cGMPs for the 21st Century plan seeks to merge science-based management with an integrated quality systems approach and to "create a robust link between process parameters, specifications and clinical performance"[1] The new PAT guidance proposes the use of modern process analyzers or process analytical chemistry tools to achieve real-time control and quality assurance during manufacturing.[2] The Food and Drug Administration's draft guidance on Q8 Pharmaceutical Development[3] addresses the suggested contents of the pharmaceutical development section of a regulatory submission in the ICH M4 Common Technical Document format.

A common thread running through these newer regulatory initiatives is the building in of product quality and the development of meaningful product specifications based on a high level of understanding of how formulation and process factors impact product performance.

Still other developments since 1990 are the advent of the internet as a research and resource tool and a decline in academic study and teaching in solid dosage forms. Together, these developments have led to a situation where there is a vast amount of formulation information widely scattered throughout the literature which is unknown and difficult for researchers new to the tableting field to organize and use. Therefore, another objective to this book to integrate a critical, comprehensive summary of this formulation information with the latest developments in this field.

Thus, the overarching goal of the third edition of *Pharmaceutical Dosage Forms: Tablets* is to provide an in-depth treatment of the science and technology of tableting that

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[1] J. Woodcock, "Quality by Design: A Way Forward," September 17, 2003.

[2] http://www.fda.gov/cder/guidance/6419fnl.doc

[3] http://www.fda.gov/cder/guidance/6672dft.doc

acknowledges its traditional, historical database but focuses on modern scientific, technological, and regulatory developments. The common theme of this new edition is DESIGN. That is, tablets are delivery systems that are engineered to meet specific design criteria and that product quality must be built in and is also by design.

No effort of this magnitude and scope could have been accomplished without the commitment of a large number of distinguished experts. We are extremely grateful for their hard work, dedication and patience in helping us complete this new edition.

Larry L. Augsburger
Stephen W. Hoag

Preface

The ultimate goal of drug product development is to design a system that maximizes the therapeutic potential of the drug substance and facilitates its access to patients. Volume 2 addresses this goal with a series of chapters that are replete with practical illustrations and formulation examples.

A tablet may be viewed as a delivery system that must be designed to meet four specific criteria: first the drug must be "delivered" to the site of action in an active form in sufficient quantity and at the correct rate to meet the therapeutic objectives, second, the product must be physically and chemically stable to assure potency, safety, and consistent drug delivery performance over the use-life of the product, third, the tablet must be capable of being *economically* mass-produced in a manner that assures reliable dosing, and fourth, to the extent possible, the product must be patient acceptable. Accomplishing these tasks can be a substantial challenge. Formulation scientists are often confronted with a broad array of formulation and process variables that can interact in complex ways. The chapters on preformulation testing, drug product stability, and unit processes presented in Volume 1 provide an essential background for the rational development of dosage forms.

Volume 2 begins with a discussion of mass transport from solid dosage forms and discusses many of the implications of formulation and process variables on bioavailability. Since one of the major challenges in modern oral solid dosage form development is poor drug solubility, Chapter 2 discusses at length strategies for addressing this problem in tablet formulations.

The days of the "trial-and-error" approach to formulation development are over, as pharmaceutical scientists adopt systematic approaches for the design, formulation and optimization of dosage forms. Such systematic approaches are discussed in Chapters 3 and 4, which address experimental design and the use of artificial intelligence. An understanding of biopharmaceutic principles, coupled with such powerful software-driven optimization and decision-making tools, can give pharmaceutical scientists the ability to make logical and deliberate formulation design decisions.

In the ensuing chapters, where the formulation of tablets is addressed, attention is focused in large part on excipients which are generally included in tablet formulations to cause the desired drug delivery performance, provide product stability, facilitate manufacturability, and contribute to aesthetics. Chapters 5–8 provide a comprehensive discussion of excipient functionality, selection, and proper use in conventional immediate release tablet formulations. That discussion is extended in Chapters 9–13 to include such specialized formulations as orally disintegrating tablets, lozenges, vitamin and mineral tablets, veterinary tablets, botanical tablets, and others.

The next part of the book examines the design of oral modified release formulations. The major focus in the design and optimization of modified release formulations

is the development of systems that exhibit well-defined controlled release delivery. Chapters 14–16 address the formulation of matrix and osmotic systems. Chapter 17 addresses the technology of tableting of multiparticulate modified release systems. Each release mechanism provides a different set of variables to consider: "critical" variables that affect drug release, and "non-critical" variables that have little or no effect on drug release rate, but are important to the delivery system in other respects.

Larry L. Augsburger
Stephen W. Hoag

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1
Mass Transfer from Solid Oral Dosage Forms

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INTRODUCTION

This chapter will show how dosage forms release their content and how you can influence where and how quickly the drug is released.

For a patient, the use of a tablet or capsule is a simple act of mass transfer: unpacking and following the instructions, which usually implies swallowing the tablet or capsule. However, there is a lot of technology behind this as you will see in our first example.

Example 1: Using Nexium® 20

Figure 1 shows a photograph of some tablets and also a magnification of their cross section. The tablets have the trade name Nexium® 20; they are produced by AstraZeneca (London, U.K). The instructions tell that they contain a "proton pump inhibitor": a drug that reduces the secretion of protons (acid) by the parietal cells in the wall of the stomach. The tablet is said to contain coated granules containing the drug esomeprazol. The coating is to protect the granules against acid in the stomach.

The tablet is to be swallowed with water—and not to be chewed. If you have problems in swallowing the tablet, then you can first let it disintegrate into granules in a glass of water before swallowing. The usual dosage is one tablet per day, which is to be taken in at the same time every day. A tablet is said to contain 20 mg of the drug. However, each tablet has a mass of 410 mg. What does the rest of the tablet consist of? The instructions contain a list of ingredients which we have grouped according to their purpose in Table 1.

When you are reading the following paragraphs, keep the following questions in mind:

1. Where is the drug released in the body?
2. What are the reasons for the instructions?

FIGURE 1 Nexium 20 tablets.

3. What is the purpose of the different groups of ingredients?
4. Could you make a sketch of the construction of the tablets?

We discuss these points at the end of this section.

Drug in the Body

Most drugs are administered in the form of tablets or capsules that are taken orally (“swallowed”) (1). The amount of drug is in the range of micrograms to several hundred milligrams. The aim is to get the drug in the right place in the body, with a concentration that is neither too high nor low, so within a “therapeutic window”. Sometimes a more or less constant drug level is required; in other cases a short burst of drug is better. What happens largely depends on what the body does with the drug (a subject known as “pharmacokinetics”).

Orally taken drugs can enter the body in several places:

- via the membranes of the mouth (“buccal” or “sublingual” administration);
- via the membranes of the stomach;
- via the membranes of the intestines.

TABLE 1 Ingredients in Nexium Tablets

Ingredients (grouped)
Esomeprazol
Sucrose/starch granules
Microcrystalline cellulose
Hydroxypropylcellulose, hypromellose,
Methacrylic acid/ethylacrylate copolymer, polysorbate 80
Synthetic paraffin, triethyl citrate, macrogol 6000
Polysorbate 80
Iron oxide (E172), titanium dioxide (E171)
Crospovidone
Glycerol monostearate, magnesium stearate, sodium stearyl fumarate
Talc

For many drugs the first part of the small intestines, the "duodenum", is the site of absorption. The time a drug stays in the throat is too small to allow for much uptake. The wall of the stomach is not very permeable, so this route is not used by many drugs. In the large intestine (the "colon") much of the water content of food has already been absorbed in the body, and the remaining luminal content is too viscous to allow much transport into the body.

Where, when, and how quickly the drug is absorbed not only depends on the drug properties, but also on how the user applies it. Whether the tablet is kept in the mouth or swallowed immediately. It depends on what the stomach does with the drug: a meal can retard a tablet for several hours, but not small particles or dissolved drug. Where the drug is absorbed of course also depends strongly on the physico–chemical properties of the drug and the composition and structure of the tablet or capsule (the "dosage form").

Once the drug has been absorbed in the body, it is transported further by blood. The circulation time of blood is a matter of minutes, so the drug is rapidly distributed. How the concentration at a certain site develops, depends on a number of things:

- how quickly the drug is released by the tablet or capsule;
- how quickly it passes the membrane of the intestines;
- whether the drug is excluded from certain parts of the body (or the opposite: that it is preferentially accumulated in certain parts);
- how quickly the drug is metabolized in the body;
- how quickly the drug is excreted from the body.

Many drugs are excluded (more or less) from certain parts of the body by internal barriers. A well-known one is the barrier that protects the brain. Drugs can also be adsorbed[a], for example, on white blood cells (lymphocytes). This can affect the profile of the drug concentration. The body is continually metabolizing substances that are entering it (usually enzymatically). This happens in the intestines and liver, but some drugs can also be degraded by the highly acidic liquid in the stomach. Drugs are also excreted, mainly via the liver and kidney. All these processes depend on the patient and on the patient's condition, so they are highly variable.

This chapter deals with mechanisms that determine the rate of release of the drug from a tablet or capsule, and how the release rate can be predicted and controlled. However, one should realize that all the phenomena described above play a role in determining how the concentration of a drug in the body changes in time. We will investigate their interplay and how they affect drug concentrations in the body in the "Systems and Balances" section.

Dosage Forms

Common types of tablet are:

- plain tablets
- coated tablets

---

[a] You may not have noticed, but we need two related and similar words. They are confusing. The two words are:

1. absorption: transfer of a substance to a liquid, or to some system;
2. adsorption: transfer of a substance to a surface or interface.

Unfortunately, the term absorption is also used for the uptake of drug from the site of administration into the blood circulation.

- matrix tablets (non-swelling)
- matrix tablets (swelling)
- effervescent tablets.

Figure 2 gives a schematic cross section of the different types and an indication of how they work.

Plain Tablets

Plain tablets consist of the drug substance (the active material) and a number of auxiliary materials or “excipients”. There are many kinds of excipients:

- fillers (lactose monohydrate, mannitol, microcrystalline cellulose, di-basic calcium phosphate[b]);
- binders (methyl cellulose, hydroxypropyl methyl cellulose, polyvinyl pyrollidone, pregelatinized starch);
- lubricants (magnesium stearate, sodium stearyl fumarate, glyceryl tri-behenate, stearic acid);
- disintegrants (sodium starch glycolate, croscarmellose sodium, crospovidone);
- glidants or powder flow improvers (colloidal silicon dioxide, talc);
- colorants (ferric oxide red, ferric oxide yellow);
- flavoring agents (mint, lemon, cherry).

Finally a whole series of stabilizers:

- anti-oxidants (ascorbic acid, potassium metabisulfite, α-tocopherol);
- complexing agents (disodium edetate);
- buffers (citric acid/sodium citrate, phosphate);

We will encounter a few more excipients in other tablets.

Tablets must have a volume of a few hundred microliters: smaller ones cannot be handled easily and larger ones cannot be swallowed. If the volume of drug to be applied is less than this amount, then this will be compensated by a filler—an inert solid added to increase the volume. Drug particles are then dispersed between filler particles. Most drugs

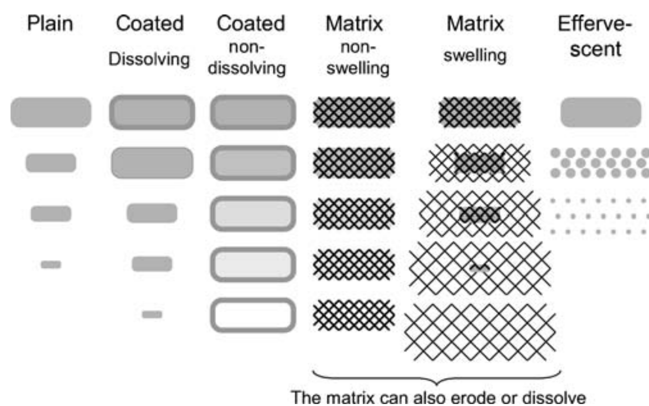

FIGURE 2 The different kinds of tablets.

[b]We have only given a few common examples or each kind of excipient.

cannot be tableted in their pure form: they yield tablets that are too weak, or that wear too easily. This can be overcome by using a binder: a material that bridges the contacts between the drug particles. Fillers are often also good binders: these are the filler–binders.

The solid particles in tablets are often quite abrasive. Also they may stick to metal surfaces, and this can give great problems in tableting machines. The solution is to add a lubricant. Unfortunately most lubricants also reduce the internal binding in the tablet, and the wettability of the pores in the tablet.

If no measures are taken tablets often dissolve very slowly. The rate of dissolution can be greatly increased by including a disintegrant: strongly swelling polymer particles that push the drug and filler particles apart when they are contacted with water. This effect is similar to that of the effervescent tablets that we discuss further on. Disintegrants can also improve transport of water into the tablet.

Coated Tablets

There are several reasons for coating a tablet:

- to apply a color (for identification);
- to mask the taste or smell of the drug;
- to avoid dusting of the tablet;
- to retard release till the drug is in the intestines (to protect it from the gastric environment);
- to control the release rate of the drug.

For the first three applications, the coating only has to work until the tablet is swallowed. This can be achieved with a number of materials. Typical examples are cellulose–esters (such as hydroxypropyl methylcellulose or methylcellulose) and polyvinylpyrrolidone. Next to the polymers, formulations used for the coating of tablets contain materials such as plasticizers (to enhance film formation), anti tacking agents (e.g., talc), and colorants (e.g., iron oxides).

Some drugs are degraded by the acid conditions in the stomach, so they have to be protected by a coating till they are in the intestines. It is more difficult to achieve this. The time a tablet stays in the stomach can vary between minutes and hours and cannot be accurately predicted. So time-activated systems are of little use. The most successful systems use a coating with a polymer with weak acid groups fixed to the polymer backbone. Under acid conditions these groups are not ionized, and the polymer is dense and impermeable. However, when the tablet enters the duodenum, the pH increases, and the weak acids dissociate. The polymer swells and becomes much more permeable (Fig. 3). This then allows a (slow) release of the tablet contents. Examples of such

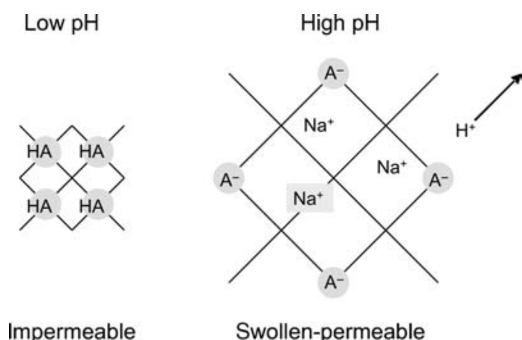

FIGURE 3 Swelling of a polymer with weak acid groups.

polymers are poly(methacrylic acid, ethyl acrylate) 1:1, poly(methacrylic acid, methyl methacrylate) 1:2, hydroxypropyl, methylcellulose, phthalate, and cellulose acetate phthalate.

Some drugs have to be released slowly after administration, either to reduce the frequency of dosing, or because high plasma concentrations give problems. One way to do this is by using a coating that it is permeable for the drug, but does not dissolve. This kind of design allows some special release characteristics, as we discuss in the section “Motion in Mixtures”

Polymers used for slow release coatings are ethylcellulose, poly(ethyl acrylate), and poly(methyl methacrylate). The release is often further slowed down by the application of lipophilic plasticizers like dibutyl sebacate or acetyl tributyl citrate.

Matrix Tablets (Non-Swelling)

In these tablets the drug is embedded in a poorly soluble matrix (such as ethylcellulose or a poly(methacrylate). This can be either a polymer or a structure of filler–binder particles. It is essential that the structure is permeable, so that water can enter. The drug is released by “leaching”: it has to diffuse through the pores in the tablet that have been emptied by dissolution.

There are two important limiting cases:

1. the matrix dissolves much more slowly than the drug (or not at all);
2. the matrix dissolves or erodes a little more slowly than the drug.

In the first case the release begins with a high rate and then decreases continuously as the diffusion distance increases. In the second case there is an initial release burst, but then the rate becomes more or less constant. (It still decreases slowly because the surface of the particle decreases.)

Matrix Tablets (Swelling)

The matrix in these tablets is a polymer. The drug is immobilized in the dry polymer. When the polymer gets in contact with water, it swells, and the drug can move through the swollen material.

The penetration of water often proceeds with a sharp front. The motion of the front can be governed by two different mechanisms:

1. by the transport of water through the swollen polymer, or
2. by the rate at which the polymer can swell.

In the first case we start with a fast release, but the rate goes down as the water has to travel further into the tablet (this is the most common situation). In the second case, the rate is more or less constant until the front approaches the center of the tablet.

Examples of the polymers that are used in these matrix tablets are: methylcellulose, hydroxypropyl, methylcellulose, polyvinylpyrrolidone, or sodium alginate. Next to the polymers, materials that affect the release rate through changing the solubility of the drug (e.g., buffers) or through changing the viscosity of the swollen polymer (e.g., mannitol) can be used.

Effervescent Tablets

We have already encountered the use of swelling polymer particles to disintegrate a tablet. There is another way of doing this: by including chemicals that form a gas when

contacted with water. A common combination is soda with a weak acid such as citric acid (HA). These react to give carbon dioxide:

$$Na_2CO_3 + 2HA \longrightarrow 2NaA + CO_2 \uparrow$$

If the tablet is not well designed it may happen that the gas blocks the pores. This retards the entry of water and can suppress disintegration.

Example 1: Discussion

As you will understand, manufacturers will not tell you all their secrets. So also we had to guess a few things on Nexium tablets.

The tablet is built up in several steps (Fig. 4). The core is formed by granules of sucrose and starch, on which the drug esomeprazol is layered using a binder. These granules are surrounded by a coating that is impermeable in acid conditions, so that the drug is not released in the stomach. The granules are held together in a tablet by a filler–binder. This part probably also contains the disintegrant, which accelerates the disintegration of the tablet once the coating has dissolved. Finally the tablet is covered by a water-soluble coating, colored pink with iron oxide and titanium dioxide.

The reasoning behind the instructions will be clear. There should be no chewing as this would damage the internal acid resistant coating. However, patients with swallowing problems can first dissolve the external coating and binder, before swallowing the much smaller granules.

Table 2 shows what we think is the purpose of the different ingredients.

MATERIAL PROPERTIES

Before we look at how drugs are released, we first consider the materials involved and their properties. There are three main groups:

1. the solvent—usually an aqueous body fluid,
2. "solids" such as the tablet or the membranes of the body;
3. solutes—materials dissolved in the solid or solvent.

In addition, we spend a few words on the interfaces between liquids and solids. We finish this section looking at how components distribute over the different materials at equilibrium.

Liquids

The bulk of the liquid in our body is aqueous. Even so, we look briefly at few other solvents to introduce the concept of polarity. Figure 5 shows four solvents and their energy of vaporization per volume.

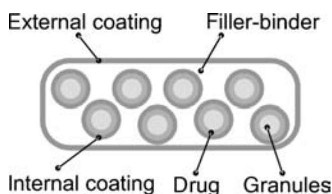

FIGURE 4 The construction of Nexium tablets.

TABLE 2 Purpose of the Ingredients

Ingredients (grouped)	Purpose
Esomeprazol	The drug
Sucrose/starch granules	Core for the granules
Microcrystalline cellulose	Filler–binder
Hydroxypropylcellulose, hypromellose,	Binders
Methacrylic acid/ethylacrylate copolymer,	Acid resistant coating
Synthetic paraffin, triethyl citrate, macrogol 6000	Plasticizers
Polysorbate 80	Surfactant
Iron oxide (E172), titanium dioxide (E171)	Colorants
Crospovidone	Disintegrant
Glycerol monostearate, magnesium stearate, sodium stearyl fumarate	Lubricants
Talc	Anti-tacking agent

Heptane is an apolar molecule: it has no electrical poles. Water, on the other side, is a very polar molecule: the two protons are positive and the oxygen atom is negative. Ethanol is less polar than water, but still quite polar. The aromatics (such as toluene) are less polar again, but not completely apolar. This is because double bond electrons can be slightly polarized by other charged molecules.

Polar molecules bind more strongly than similar apolar molecules. This is because the charges cause hydrogen bonding between the molecules. This is clear from the energies of vaporization per volume. That of heptane is low; that of water high.

Liquids with similar polarities mix with each other. Water and ethanol are miscible; so are ethanol and toluene. However, water and toluene hardly mix: they form two separate liquid phases. Water and heptane dissolve even less in each other: there are no hydrogen bonds between the two, so water tends to cluster.

Many of the materials used for constructing tablets decompose before they vaporize, so their polarity cannot be determined directly. This is done by comparing their solubilities in different solvents. You can often get a rough idea just by looking at the number of –OH, =O and $–NH_2$ groups in a molecule. If these dominate, the molecule is polar. On the other hand, if –CH, $–CH_2$ and $–CH_3$ groups dominate, the molecule will be apolar.

Solids

Most of the solids involved in drug release are permeable: they allow solutes and solvents to pass. There are two main groups of solids:

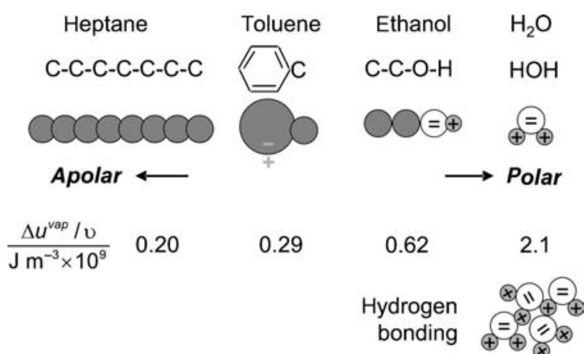

FIGURE 5 Polarity of four solvents.

1. polymers, both as coatings and as matrix,
2. porous media, the most common matrix.

The porous media are seldom homogeneous—they usually consist of different parts ("phases") which form a structure. These are the drug and the excipients that we have mentioned earlier.

Polymers

Polymers form a large and versatile group of materials (2). Here we can only indicate a few or their properties that are important for drug release.

Polymers are extremely long molecules (Fig. 6). They consist of chain units with dimensions similar to those of other molecules: they may contain thousands of such units. They are usually strongly coiled and entangled. The chain unit can be small, such as in the polyethylene used for packaging films. These small units give flexible polymers. If the units are bulkier, such as in cellulose or starch, the polymers can be much stiffer. As with solvents, chain units can be more or less polar. Ethylene is very apolar, and so is its polymer. Polyethylene is hydrophobic: it hardly interacts with water. Polymers like cellulose and starch, which contain large numbers of hydroxyl groups, are much more polar. The polarity can also be increased by coupling polar groups of atoms to the polymer. Polymers can be formed from different chain units (copolymers). Here the polarity can change along the length. An extreme case is formed by the proteins: natural polymers, in which each chain unit can be any one out of a collection of about twenty amino acids, with quite different polarities.

A cross-linked polymer forms a three-dimensional network (Fig. 7). Cross-linked polymers can swell in a solvent, but they are not soluble. Entanglements and crystallites (to be discussed below) give effects that are similar to those of cross links.

All polymers are at least partly amorphous, which means that they contain regions where the molecules show little ordering. However, many polymers also show contain "crystalline" parts where the polymer chains are more or less aligned. (Fig. 8). The crystalline areas are denser than amorphous parts: they are usually impermeable for all but the smallest solutes. So transport of a solute through a polymer occurs through amorphous regions.

Figure 9 shows the modulus of elasticity of a polymer as a function of temperature. There are two fairly sharp changes indicating phase transitions. At low temperatures the polymer is rigid and brittle: it forms a glass. At the glass transition temperature T_G the

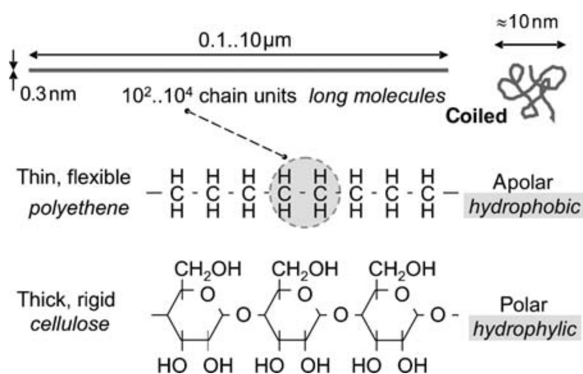

FIGURE 6 Dimensions of polymers.

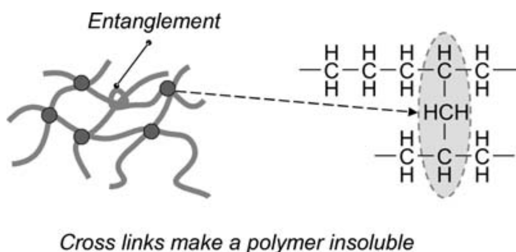

FIGURE 7 Cross linking.

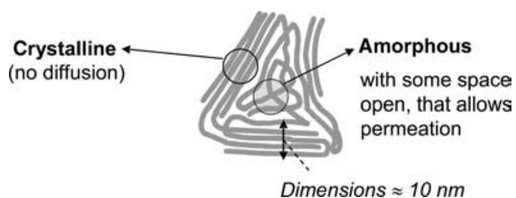

FIGURE 8 Crystalline and amorphous polymer.

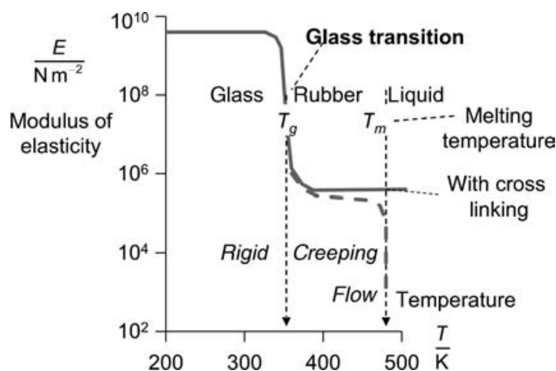

FIGURE 9 The glass transition of a polymer.

modulus drops dramatically, in the figure by a factor of ten thousand.[c] Above the T_G the polymer becomes soft and elastic: it forms a rubber. At higher temperatures the polymer may melt, to form a viscous liquid. This does not occur when a polymer is cross-linked. The polymers we know as glasses, such as polystyrene and window glass, have a glass transition temperature above ambient temperature. Polymers are almost impermeable below their T_G: above the transition temperature the permeability can increase enormously. We will see several applications of this in controlling the release of drugs from a tablet.

Solvents can greatly change the properties of a polymer. Even a small amount of water can reduce the glass transition temperature noteably; this is called plasticizing. Polar polymers can swell enormously in water (depending on their degree of cross-linking).

If polymers are not cross-linked they may dissolve. The dissolved polymer forms little coils in the solution: the coils tend to expand when the polarities of polymer and solvent are similar. If the concentrations are low enough, the coils do not overlap, but at higher concentration they get entangled. This greatly increases the viscosity of the solution.

[c] The glass transition temperature of a polymer depends a little on the rate of heating or cooling: it is less well-defined than phase transitions of simple substances such as water.

Porous Media

As noted, most tablets consist of a drug and a number of excipients. These are mostly solid particles, and when mixed and tableted they form a porous medium (3). How a tablet releases its drug content depends on the structure of this medium.

Each of the myriads of particles in a tablet has its own dimensions. In between the particles are voids or pores with irregular shapes. It is out of the question to consider each particle and pore separately, so we must use some kind of average description (Fig. 10). The most useful ones are:

- the diameter of the "equivalent" sphere;
- the void fraction (volume fraction of pores).

A sphere has a surface, a volume, and a surface-to-volume ratio given by:

$$A = \pi d^2, \; V = \frac{\pi}{6} d^3, \; \frac{A}{V} = \frac{6}{d} \tag{1}$$

The surface to volume ratio is inversely proportional to the diameter of the sphere. We use a measured surface area and the solid volume of the particle assembly to define the equivalent diameter[d]:

$$d_{\text{eq}} = 6 \frac{V_{\text{particles}}}{A_{\text{particles}}} \tag{2}$$

The drug and some excipients such as disintegrants are usually fine powders, with a diameter of perhaps 10 μm. Filler–binders, which form the bulk of most tablets, are much coarser at around 200 μm. As a result the effective diameter is often around 100 μm or 0.1 mm.

The void fraction ε is easier to understand. We will regard it as a given, and not consider its variation in position. In tablets, it usually has a fairly low value (typically 0.05–0.2).

A part of the void is connected as pores; the other part is not. If the void fraction falls below the "percolation threshold" ε_c, there will be no connected pores and the medium becomes impermeable. We can take this into account in transport relations by using an effective void fraction:

$$\varepsilon_{\text{eff}} = \varepsilon - \varepsilon_c$$

The percolation threshold varies, but is often in the range of 0.03–0.05. Pores are often assumed to be cylindrical (because that allows one to make simple estimates).

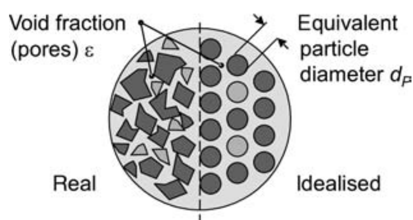

FIGURE 10 "Average" particle size and void fraction.

[d] There are many other ways of defining an equivalent diameter, as discussed in texts on particle technology.

Consider a unit volume of porous medium. The surface area and volume of the pores, and their area-to-volume ratio are:

$$A_0 = \varepsilon L_{\text{tot}} \pi d_0, V_0 = \varepsilon L_{tot} \frac{\pi}{4} d_0^2, \frac{A_0}{V_0} = \frac{4}{d_0} \tag{4}$$

Also here we can define an equivalent pore diameter:

$$d_0 = 4 \frac{V_0}{A_0} \tag{5}$$

There is a relation between this pore diameter and the equivalent diameter of the spheres. To obtain this we only need to realize that the area of the pores is the same as that of the particles, and that the ratio of the volumes is:

$$\frac{V_0}{V_p} = \frac{\varepsilon}{1 - \varepsilon} \tag{6}$$

This yields:

$$d_0 = 4 \frac{\varepsilon}{1 - \varepsilon} \frac{V_p}{A_p} = \frac{4}{6} \frac{\varepsilon}{1 - \varepsilon} d_P \tag{7}$$

The pore size is typically one order of magnitude smaller than the particle size. Transport in a porous medium will be in one of the three directions. So, on average, only one-third of the pores will contribute to water penetration and drug release.

Interfaces

The interfaces between phases—especially those between liquid and solid—are important for the wetting of tablets (4).

Interface Energy

Every interface has an energy, which is usually denoted by the symbol[e] σ. A few values for solid–vapor (SV) and liquid–vapor (LV) interfaces are given in Table 3. Values for liquid can be easily measured as surface tensions, but those of solids can only be found by

TABLE 3 Interface Energies of a Few Systems

Substance	σ_{SV} or σ_{LV} (mJ m^{-2})
Heptane	18
Toluene	28
Ethanol	34
Water	72
Lubricants	~20
Poorly wetting solids	~40
Good wetting solids	~100

[e]The symbol γ is also used, but we need that for other purposes.

indirect means. Also the values on a solid depend on how the interface is formed and they can vary across the surface. As a result they are only poorly known.

The energies of solid–liquid (SL) interfaces are in between those of the corresponding SV and LV values.

Wetting

A bed of solid particles will only wet when wetting decreases the interfacial energy. For this to occur, the SV energy has to be larger than the SL value. For good wetting solids the difference might be $+10\,\mathrm{mJ\,m^{-2}}$, for poorly wetting solids just above zero, and for lubricants (which do not wet at all) perhaps $-10\,\mathrm{mJ\,m^{-2}}$. For good disintegration and dissolution, tablets have to be wettable. So it is important to ensure that lubricants used in the tableting process do not cover all interfaces of the tablet.

A property that is closely related to the interfacial energies and fairly easily measured is the contact angle θ. When a small drop is placed on a flat solid surface, the interface energies show as surface tensions. These must balance at the contact line of the three phases (Fig. 11) giving:

$$\cos = \frac{\sigma_{\mathrm{SV}} - \sigma_{\mathrm{SL}}}{\sigma_{\mathrm{LV}}} \tag{8}$$

A bed of particles will wet when the contact angle is smaller than $\pi/2$. One can decrease the interfacial energies of a polar solvent such as water by adding a surfactant or wetting agent. Such molecules consist of polar "head" and an apolar "tail." The tails do not feel at home in the polar solvent and they accumulate on interfaces—and so lower the interface energy.

Solutes

To construct a framework for the behavior of solutes, we must review some basics from thermodynamics. Whether a solute dissolves in a solvent (and how it distributes between different phases) depends on its potential. The solute tends to move in the direction where its potential is lowest. Motion stops when the potential has become the same everywhere: the system is then at equilibrium. At this point the Gibbs energy of the system is minimal.

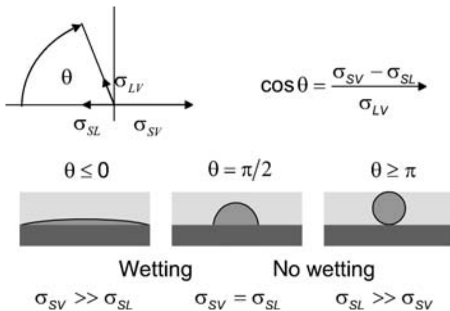

FIGURE 11 Contact angle and wetting.

[e] The symbol γ is also used, but we need that for other purposes.

Solute Potential

The potential of a solute depends on a number of factors. The three that can be important for us are:

1. the effect of the composition of the mixture (summarized in the "activity" of the solute);
2. the effect of an electrical field (only for charged particles such as ions);
3. the effect of pressure (for coated systems).

Also interfaces and gravity can give contributions, but we consider these separately.

The following formula gives the change of the potential:

$$d\mu_i = \boldsymbol{RT}\underbrace{\frac{d\alpha_i}{\alpha_i}}_{(1)} + \underbrace{\boldsymbol{F}z_i d\phi}_{(2)} + \underbrace{\upsilon_i dp}_{(3)} \tag{9}$$

All terms are in J mol^{-1} of the component i. Here $\boldsymbol{R}$ is the gas constant, T the absolute temperature, α_i stands for the activity of species i (on which more in a moment), $\boldsymbol{F}$ is the Faraday constant, z_i the charge number of the species (zero, except for ions), and υ_i the partial molar volume of i.

A few words on units. When dealing with chemical species in reactions and also with ions, molar units are by far the simplest. However, practical subjects such as pharmacy prefer mass units for obvious reasons. And to make things worse: many mass transfer problems are most easily understood in volume terms. We will need all three types of units[f], with their associated concentrations:

1. molar units with molar concentrations c (e.g., in mol m^{-3});
2. mass units with mass concentrations C (e.g., in kg m^{-3});
3. volume units with volume concentrations $\boldsymbol{C}$ (e.g., in m^3 m^{-3}).

The volume concentrations are also known as volume fractions. For the moment we continue in molar terms.

Effect of Composition

In many problems we only need to take the composition (activity) term (1) into account. The activity is defined as:

$$\alpha_i = \gamma_i c_i \tag{10}$$

Here γ_i is the activity coefficient of i (which depends on the composition of the mixture, so also on the components other than i). The activity coefficient can be a complicated function of composition. However, there is one important simple case that we will use in most of our examples: that of a solute, dilute in a solvent. In that case the activity coefficient of the solvent is equal to one, and that of the solute has a constant value, the "activity at infinite dilution":

$$\text{Dilute solutions}: \gamma_W = 1;\ \gamma_i = \gamma_i^\infty = \text{constant} \tag{11}$$

---

[f] A mole is a small unit with a volume of tens or hundreds of cubic centimeters. Its concentration gets a small letter c. The unit of mass, the kilogram, is intermediate with a volume of around 1 L. Its concentration gets the intermediate symbol C. The unit of volume, a cubic meter, is usually the largest, so the concentration gets the most dominant symbol $\boldsymbol{C}$.

Then

$$d\mu_i = \boldsymbol{RT}\frac{d\alpha_i}{\alpha_i} = \boldsymbol{RT}\frac{dc_i}{c_i} \text{ or } \mu_i = \text{constant} + \boldsymbol{RT}\,\text{In}\left(\frac{c_i}{c_0}\right) \tag{12}$$

This potential (usually known as the chemical potential) is a logarithmic function of concentration. Just as with elevation ("with respect to sea level") we can arbitrarily choose the condition at which the potential is zero. It is often handy to choose this such that the constant is zero for some limiting situation in the problem one is dealing with.

The constant c_0 has the dimension of a concentration. For the solvent (water in our case) the meaning is simple: in the pure solvent, the concentration will be equal to the pure solvent concentration. If we want the constant to have a zero value, we must choose:

$$\mu_w = \boldsymbol{RT}\,\text{In}\left(\frac{c_w}{c_{w0}}\right) \tag{13}$$

The solutes are discussed in the next paragraph.

Solubility and Partitioning

Consider poorly soluble, non-ionizing particles (a solute) and water (a solvent). Take a beaker of water and add sufficient solute; this will dissolve partly. However, dissolution stops when the concentration of solute in the water reaches the saturation value c_s. The chemical potentials of solute have then become equal in the solid (′) and in the liquid (″):

$$\mu_i' = \mu_i'' \tag{14}$$

In this problem, we are dealing with a dilute solution, so term (1) in Equation (9) is important. However, the activity coefficient is constant. There are no ions, so term (2) plays no role. Unless the beaker has huge dimensions, the pressure will be the same everywhere and also term (3) is unimportant. If we choose the chemical potential of the solid particles to be zero, we get:

$$0 = \boldsymbol{RT}\,\text{In}\left(\frac{c_i}{c_0}\right) \text{ so } c_0 = c_{\text{sat}} \tag{15}$$

We see that the constant c_0 is now equal to the saturation concentration or solubility. This solubility is an important property of a drug: it can have a large effect on how a drug is released and how it is distributed over the body. There is an enormous variation in solubilities (Table 4).

A few rules of thumb on solubilities:

- Solubility usually (but not always) increases with increasing temperature.
- Solubility tends to be high when the polarities of the solute and the solvent are similar: "like seeks like". So you may expect the polar molecule sugar to be soluble in water, but not in heptane. Non-polar fatty acids are soluble in heptane, but not in water.
- Small molecules tend to more soluble than large ones. Polymers only dissolve if they are not cross-linked and have a polarity very close to that of the solvent. The shorter molecules have a higher solubility than the larger ones.
- Salts, bases, and acids that ionize in water, have higher solubilities than one would expect otherwise. However, also here there are large differences. You may have noticed that the drugs with solubility above $300\,\text{g L}^{-1}$ are all salts.
- Crystalline substances have low solubilities when the molecules fit well in the crystal.

TABLE 4 Solubilities of Drugs in Water at 25°C

Drug	M (gm mol^{-1})	c_{sat} (μmol L^{-1})	C_{sat} (mg L^{-1})
Progesterone	314	24.8	
Estradiol	272	11.0	
Testosterone	288		46.3
Testosterone undecanoate	457		3
Budesonide	431	50	
Cyclosporin A	1203	10–50	7–40
Paracetamol	151		14,000
Diazepam	285		50
Delta-9-tetrahydrocannabinol	314		2.8
Itraconazole	706		0.001 (pH7) 0.6 (pH1)
Nifedipine	346		9.3
Amitriptyline	277		9700
Dexamethasone	392		89
More than 300 g L^{-1}			
Betahistine dihydrochloride			
Tobramycin sulphate			
Colistin sulphate			

There are methods for predicting solubilities. Unfortunately, the outcomes are often more an order-of-magnitude than a precise number.

Now consider a drug that can dissolve in two different phases. The first phase ($'$) might be a swollen polymer, the second ($''$) the pure solvent. At equilibrium the chemical potentials of the solute will be equal in the two phases:

$$\mu_i' = \mu_i'' \quad \text{or} \quad \frac{\boldsymbol{RT}}{M_i}\ln\left(\frac{c_i'}{c_{\text{sat}}'}\right) = \frac{\boldsymbol{RT}}{M_i}\ln\left(\frac{c_i''}{c_{\text{sat}}''}\right) \quad \text{so} \quad \frac{c_i'}{c_i''} = \frac{c_{\text{sat}}'}{c_{\text{sat}}''} = K_i \tag{16}$$

The ratio of the two concentrations is equal to the ratio of the two solubilities. Remember that this only applies to dilute mixtures. The ratio is known as the partition coefficient.

Weak Electrolytes

Many drugs are weak electrolytes and poorly soluble. We consider one of such, which is a base BOH. Here dissolution is a two-step process: the solid base dissolves, and the dissolved species dissociates (partly):

$BOH(s)\ BOH(l)\ B^{+} + OH^{-}$

This example is most easily treated in molar units, so we use molar concentrations. Also this problem can be handled using potentials, but the derivation is a bit lengthy, so we only consider the resulting equilibrium equations. The first step is an ordinary dissolution, and the undissociated base might have solubility:

$$c_{\text{BOH}} = 10^{-3}\,\text{mol}\,\text{L}^{-1}$$

The dissociation is governed by the equilibrium relation:

$$\frac{c_B c_{OH}}{c_{BOH}} = K_2 \tag{17}$$

As the base is weak, the dissociation constant will have a small value, say:

$$K_2 = 10^{-6} \mathrm{mol\,L^{-1}}$$

If there are no other ions present, the concentrations of B^+ and OH^- must be equal to give electroneutrality. The concentration of dissociated base is then:

$$c_B = c_{OH} = \sqrt{K_2 c_{BOH}} \tag{18}$$

The total base concentration under these conditions becomes:

$$c_{Btot} = c_{BOH} + \sqrt{K_2 c_{BOH}} \tag{19}$$

We can increase the solubility by adding a strong acid and so reducing the OH^- concentration:

$$\mathrm{HA} \longrightarrow \mathrm{H^+} + \mathrm{A^-} \quad \text{and} \quad \mathrm{OH^-} + \mathrm{H^+} \longrightarrow \mathrm{H_2O}$$

For the last reaction the equilibrium relation is:

$$c_H c_{OH} = K_3 \quad \text{with} \quad K_3 \approx 10^{-14} \mathrm{mol^2\,L^{-2}} \tag{20}$$

The equilibrium constant is very small. One can numerically find the concentrations of all ions in the solution using the two equilibrium relations above, a mass balance for B and the requirement of electroneutrality. However, one can also understand most of the effect of the acid added from the observation that the concentrations of H^+ and OH^- ions must be very low. To maintain electroneutrality, every A^- ion added must then be accompanied by a B^+ ion. The total concentration of acid is approximately:

$$c_{Btot} = c_{BOH} + c_A \tag{21}$$

So an acid can greatly enhance the solubility of a weak base. (The same applies to a strong base and a weak acid.) The concentration of the base is often plotted against the pH of the solution (which can be easily measured). One can also calculate this value. For our approximate solution:

$$c_{OH} = \frac{K_2 c_{BOH}}{c_A} \qquad p_H = \log(c_{OH}) \tag{22}$$

Note the two very different situations for the base that we have looked at:

- with no acid the base is hardly dissociated;
- with an excess of acid, the base is completely ionic.

The equilibria of weak bases are often described using a "pK_B". This is the value of the pH at which one half of the base is ionized. The relation between the equilibrium constant and the pK_B is:

$$pK_B = 14 + \log\left(\frac{K}{\mathrm{mol^2 L^{-2}}}\right) \tag{23}$$

Values of the pK_B and solubility for several drugs are given in Table 5.

TABLE 5 Equilibrium Data for Weak Electrolyte Drugs

Drug	pK_B	c_{sat} (mg L^{-1})*
Thioridazine	9.5	0.034
Impipramine	9.4	18
Amitriptyline	9.4	9700
Promazine	9.4	14.2
Acetaminophen	9.4	14,000
Chlorpromazine	9.3	2.5
Methadone	8.9	48.5
Apomorphine	8.9	17,000
Methylphenidate	8.8	1200
Haloperidol	8.7	14
Pimozide	8.6	10
Mephenytoin	8.5	1300
Phenytoin	8.3	32
Protriptyline	8.2	1.04
Morphine	8.2	149
Lidocaine	8.0	4100
procaine	8.0	9400
Perphenazine	7.9	28.3
Clozapine	7.5	12
Cimetidine	6.8	5000
Intraconazole	3.7	0.001
Flucitosine	3.3	10,500
Benzocaine	2.5	1300
Levodopa	2.3	5000

*Presumably in pure water; this is not always clearly reported.

Examples 2

Equivalent Dimensions

Consider a flat cylindrical tablet, with a diameter $d_T = 10$ mm and height $h_T = 6$ mm (Fig. 12). This has the volume, area, and area-per-volume:

$$V_T = \frac{\pi}{4} d_T^2 h_T \quad A_T = 2\frac{\pi}{4} d_T^2 + \pi d_T h_T \quad a_T = \frac{A_T}{V_T} = 733\,\mathrm{m^2\ m^{-3}}$$

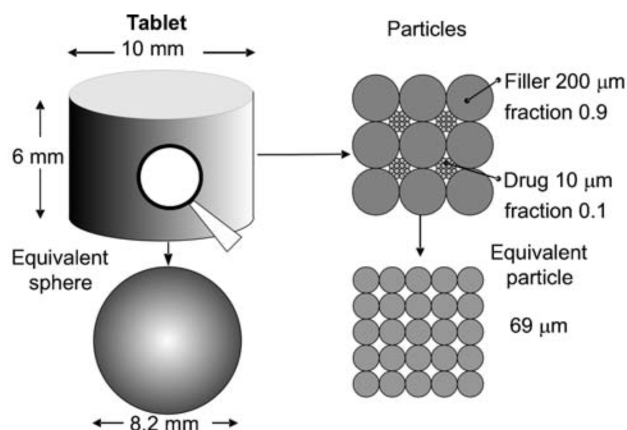

FIGURE 12 Equivalent dimensions of a tablet.

The sphere with the same area-per-volume has a diameter:

$$d_{eq} = \frac{6}{a_T} = 8.2\,\mathrm{mm}$$

Note that this "equivalent sphere" has neither the volume nor the area of the tablet.

The tablet consists of a filler (F), the drug (D) and voids (V). The volume concentrations (fractions) of the three are:

$$\boldsymbol{C}_F = 0.81; \boldsymbol{C}_D = 0.09; \boldsymbol{C}_V = \varepsilon = 0.10$$

The fractions based on the solid phases alone are:

$$\alpha_F = \frac{\boldsymbol{C}_F}{\boldsymbol{C}_F + \boldsymbol{C}_D} = 0.90;\ \alpha_D = \frac{\boldsymbol{C}_D}{\boldsymbol{C}_F + \boldsymbol{C}_D} = 0.10$$

The two components consist of spherical particles with diameters:

$$d_F = 200\,\mu\mathrm{m}; d_D = 10\,\mu\mathrm{m}$$

The area-per-volume of solid is:

$$a = 6\left(\frac{\alpha_F}{d_F} + \frac{\alpha_D}{d_D}\right) = 8.7 \times 10^4\ \mathrm{m}^2\ \mathrm{m}^{-3}$$

The spherical particles having the same area-per-volume have the diameter:

$$d_P = \frac{6}{a} = 69\,\mu\mathrm{m}$$

For such particles the equivalent pore diameter is:

$$d_O = \frac{4}{6}\frac{\varepsilon}{1-\varepsilon}d_P = 5.1\,\mu\mathrm{m}$$

The percolation threshold is $\varepsilon_c = 0.04$; this gives an effective porosity for transport $\varepsilon_{eff} = \varepsilon - \varepsilon_c = 0.06$.

Solubility of Salts

Let us now consider the poorly soluble solid $CaSO_4$. This forms Ca^{2+} and SO_4^{2-} ions with charge numbers +2 and –2. (Also other ions are formed, but we neglect them to keep things simple.) Because there are charged species in the system, we must also use the electrical term (2) in Equation (9).

We give Ca^{2+} the subscript "1" and SO_4^{2-} the subscript "2". We choose the potential in the solid phase to be zero. Equilibrium is reached when both ions have equal potentials in the two phases:

$$\mu_1' = \mu_1'' \quad 0 = \frac{\boldsymbol{R}T}{M_1}\ln\left(\frac{c_1''}{c_{10}''}\right) + \frac{\boldsymbol{F}(+2)}{M_1}\phi'' \tag{24}$$

$$\mu_2' = \mu_2'' \quad 0 = \frac{\boldsymbol{R}T}{M_2}\ln\left(\frac{c_2''}{c_{20}''}\right) + \frac{\boldsymbol{F}(-2)}{M_2}\phi'' \tag{25}$$

The constants c_{10}'' and c_{20}'' are not the same: calcium is more soluble than sulphate. However, the two concentrations in the liquid are found to be practically the same: $c_1'' = c_2''$ (the solution is "electroneutral"). We can now solve the two equations to obtain:

$$\phi'' = \frac{1}{4}\frac{\boldsymbol{RT}}{\boldsymbol{F}}\ln\left(\frac{c''_{10}}{c''_{20}}\right) \quad (26)$$

This small electrical potential difference (of the order of +10 mV) decreases the solubility of calcium and increases that of sulphate until they are equal. So, effectively, the system behaves as if it consists of two components: water and $CaSO_4$.

This simple behavior disappears if one adds a second soluble salt with a common ion (such as $CaCl_2$). Then $c''_1 > c''_2$. This will reduce the solubility of the sulphate, as you can easily understand from the equilibrium relations.

Pressure in a Granule

As a third example, we consider a thin-walled granule. It contains a dilute solution of a non-ionizing drug, but is surrounded by water. The granule is permeable for water, but not for the drug. As a result, water will diffuse into the granule (Fig. 13). The pressure will increase, until the diffusion ceases (or the granule bursts). At which pressure does diffusion cease?

Here, we take the pressure and the other terms of the chemical potential relation to be zero in the surrounding water. The concentration of water there is equal to the density. Here we can neglect term (2) in Equation (9) but not terms (1) and (3). The equilibrium relation for water becomes:

$$\mu'_W = \mu''_W \quad \text{or} \quad 0 = \frac{\boldsymbol{RT}}{M_W}\ln\left(\frac{c_W}{c_{W0}}\right) + \upsilon_W p \quad \text{and} \quad p = -\frac{\boldsymbol{RT}}{\upsilon_W}\ln\left(\frac{c_W}{c_{W0}}\right) \quad (27)$$

Because the specific volume of water is small, this pressure can easily reach values of 10–100 MPa, giving even higher stresses in the granule wall. Similar pressures are built up in the swelling polymers used as disintegrants.

Capillary Rise

As a last example, we consider the wetting of a porous solid (Fig. 14), where interface energies and gravity play a role. The question is how high the liquid will rise, or put otherwise, what the pressure will be just under the liquid interface. This is most easily analyzed by minimizing the Gibbs energy of the system.

The solid consists of spheres with a diameter d_P, which are polar and easily wetted. The surface energy of the spheres in air is σ_{GS}; that in water σ_{LS}. The difference $\Delta\sigma$ is negative, so the energy of the system goes down when water enters. The interfacial area of the spheres per volume of water is:

$$a = 6\frac{1-\varepsilon}{\varepsilon}\frac{1}{d_P} \quad (28)$$

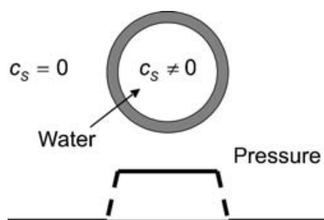

FIGURE 13 A granule, permeable for water.

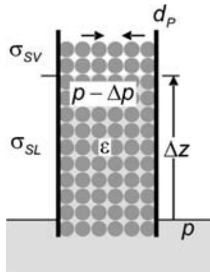

FIGURE 14 Wetting of a porous medium.

We consider a cross section with the unit area. When the liquid rises, the Gibbs energy decreases because the interfacial energy of the system goes down:

$$E_a(z) = az\Delta\sigma \tag{29}$$

However, the gravitational energy goes up. This increase is proportional to the amount raised and the increase in the average height:

$$E_g(z) = (\varepsilon\rho_W z)\left(g\frac{z}{2}\right) \tag{30}$$

The Gibbs energy of the system is the sum of these two (plus a constant if you wish). It has a minimum value when:

$$z_{\max} = a\frac{-\Delta\sigma}{\varepsilon\rho_W g} = 6\frac{1-\varepsilon}{\varepsilon}\frac{-\Delta\sigma}{\rho_W g d_P} \tag{31}$$

With $d_P = 10^{-4}$ m; $\varepsilon = 0.1$; $\Delta\sigma = -0.01$ J m^{-2} and $\rho_W = 1000$ kg m^{-3} the maximum rise is 0.55 m. This implies that the pressure difference across the LV interface is:

$$\Delta p = \rho_W g z_{\max} \tag{32}$$

or 5.4 kPa.

SYSTEMS AND BALANCES

There are many situations where one would like to understand the behavior of a tablet in the body quantitatively, so as to be able to predict what will happen when the design of the tablet, or the conditions after administration, change. This requires the setting up of a mathematical model of the drug release.

The steps in setting up such a model are:

1. Define the system that you are considering.
2. Set up mass balances for the drug.
3. Solve the resulting differential equation.
4. Play with the results to learn what the different variables mean.

System Boundaries

The starting point in analyzing drug release is the choice of a system. The system could be your body, a single organ such as the stomach, a dissolution vessel, a tablet, or a cell. The system has to have a well-defined boundary.

A system can have several kinds of boundaries:

1. closed boundaries, which are impermeable for the drug;
2. permeable boundaries, which allow slow drug permeation;
3. open boundaries, through which (drug containing) liquid flows.

Transport of the drug through permeable boundaries is mainly by diffusion; transport through open boundaries almost solely by convection along with the liquid.

Choosing systems and defining their boundaries is not always as simple as it might seem. A little further on we will be setting up a model for the behavior of a drug in the body. The system is chosen as "the volume of liquid in the body that is accessible to the drug". A drug that strongly binds to blood cells may only move around in the blood circulation. Other molecules may enter the fluid between cells, and some molecules may even be able to enter the cells. So the distribution volume of the system depends on the drug considered.

Mass Balances

The idea behind the mass balance of the drug is simple: the mass of drug in the system changes by adding ("in") or removing ("out"). In the form of an equation:

$$\frac{dm}{dt} = \dot{m}_{\text{in}} - \dot{m}_{\text{out}} \tag{33}$$

The symbols with a dot denote flows: here they could be in mg hour^{-1}. We can replace the mass in the left hand term with the product of system volume and the average concentration in the system:

$$\frac{d(VC)}{dt} = \dot{m}_{\text{in}} - \dot{m}_{\text{out}} \tag{34}$$

Here we use mass concentrations. If the volume of the system is constant, we can bring it outside the differential quotient:

$$V\frac{dC}{dt} = \dot{m}_{\text{in}} - \dot{m}_{\text{out}} \tag{35}$$

There can be several contributions to the mass flows:

1. due to diffusion through permeable boundaries;
2. due to convection through open boundaries;
3. due to metabolic formation or decomposition of the drug.

Example 3: Drug in the Body

To illustrate the use of mass balances we develop a model to predict the concentration of a drug in the body.

The system is the volume of liquid in the body that is accessible to the drug (Fig. 15). This has the value V_0. The drug has an initial mass m_0. It will be rapidly distributed over the volume V_0, and gradually excreted via the kidneys and the liver. Because distribution is rapid, the drug concentration is the same throughout the body. The maximum concentration that can be obtained is:

$$C_{\max} = \frac{m_0}{V_0} \tag{36}$$

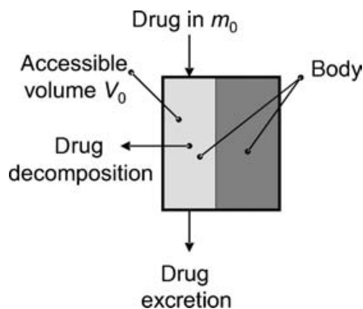

FIGURE 15 Schematic picture of the body.

In reality the concentration will always be lower because drug is excreted and metabolized while it is distributed. However, this maximum concentration is a useful reference point.

No Drug Removal

We begin with the situation that there is no removal of the drug, so that the mass flow "out" is zero. The mass balance of the liquid volume then reads:

$$V_0 \frac{dC}{dt} = \dot{m}_{\text{in}} \tag{37}$$

Often the drug will not be immediately released, but slowly. This is because the drug absorption is limited either by the membrane of the intestines (as we discuss in section "Motion in Mixtures") or by a slow release coating. Release usually begins fast, but then slows down. One can approximate this with an exponential function:

$$m_{\text{in}} = \frac{m_0}{\tau_1} \exp\left(-\frac{t}{\tau_1}\right) \tag{38}$$

Here τ_1 is the "time constant" for release. A small value (say 0.01 hour) indicates a rapid release, a large value (say 10 hours) a slow release. The constants before the exponential are such that the amount released after a long time is equal to m_0. We now have the differential equation:

$$V_0 \frac{dC}{dt} = \frac{m_0}{\tau_1} \exp\left(-\frac{t}{\tau_1}\right) \tag{39}$$

Using Equation (36) to eliminate the liquid volume and then separating the variables C and t gives:

$$\frac{dC}{C_{\text{max}}} = \exp\left(-\frac{t}{\tau_1}\right) d\left(\frac{t}{\tau_1}\right) \tag{40}$$

This has the solution

$$\frac{C}{C_{\text{max}}} = \text{constant} - \exp\left(-\frac{t}{\tau_1}\right) \tag{41}$$

At $t = 0$ the concentration will be zero, so the constant must be equal to one. The result is:

$$\frac{C}{C_{\text{max}}} = 1 - \exp\left(-\frac{t}{\tau_1}\right) \tag{42}$$

This function is plotted in Figure 16 for a number of values of the time constant. All times are in hours. We see the concentration rising towards the maximum value, but more slowly when the time constant is larger.

Burst Release of the Drug

We now assume that the drug is released as a burst (so all in a single moment at $t = 0$). The drug metabolizes in the liver, and is removed via the kidneys. The rates of both processes are proportional to the concentration of the drug in the body liquid:

$$m_{\text{out}} = \frac{m_0}{\tau_2} \frac{C}{C_{\max}} \tag{43}$$

Here τ_2 is the time constant for drug removal; the faster the removal, the smaller the constant. You can check to see that the units of the equation are correct. Except when the drug is brought into the body there is no flow "in":

$$V_0 \frac{dC}{dt} = -\dot{m}_{\text{out}} = -\frac{m_0}{\tau_2 C_{\max}} C \tag{44}$$

Separating variables and using Equation (36) to eliminate V_0 yields:

$$\frac{dC}{C} = -d\left(\frac{t}{\tau_2}\right) \tag{45}$$

The solution is:

$$\ln\left(\frac{C}{\text{constant}}\right) = -\frac{t}{\tau_2} \tag{46}$$

When $t = 0$, the concentration is C_m, and we see that the constant must have a value C_m. The result is:

$$\ln\left(\frac{C}{C_{\max}}\right) = -\frac{t}{\tau_2} \text{ or } \frac{C}{C_{\max}} = \exp\left(-\frac{t}{\tau_2}\right) \tag{47}$$

We see that the concentration decreases exponentially in time. The function is plotted in Figure 17 for a few values of τ_2. All times are in hours.

Slow Release and Removal

If we allow for both a slow release and removal of the drug, the differential equation becomes:

$$V_0 \frac{dC}{dt} = \frac{m_0}{\tau_1} \exp\left(-\frac{t}{\tau_1}\right) - \frac{m_0}{\tau_2} \frac{C}{C_{\max}} \tag{48}$$

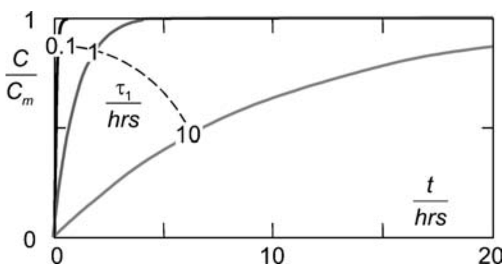

FIGURE 16 Concentration in the body with slow release and no removal.

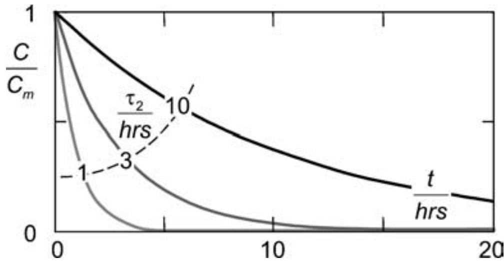

FIGURE 17 Concentration in the body with a burst release and slow removal.

Using Equation (36) and rearranging yields:

$$\frac{dC}{dt} = \frac{C_{\max}}{\tau_1}\exp\left(-\frac{t}{\tau_1}\right) - \frac{C}{\tau_2} \tag{49}$$

This is a linear equation in C. Solving it is not difficult, but a bit lengthy. We only show the result:

$$\frac{C}{C_{\max}} = \frac{\tau_2}{\tau_1 - \tau_2}\left(\exp\left(-\frac{t}{\tau_1}\right) - \exp\left(-\frac{t}{\tau_2}\right)\right) \tag{50}$$

This is the Bateman equation. Note that it is not defined when the two time constants are equal. The function is plotted in Figure 18 for $\tau_2 = 3\text{h}$ and several values of τ_1. The concentration first rises rapidly as the drug enters the body, and then goes down as it is removed by liver and kidneys. We can greatly influence how the concentration of the drug in the body changes by changing the time constant for release τ_1. A short release time gives a burst, a long release time a fairly constant concentration.

Tablets sometimes stay in the stomach for a few hours before releasing their drug content in the intestines. The whole graph will then be displaced to the right by an amount equal to the lag time.

Discussion

The Bateman model is useful for understanding the effect of the body on drugs, but it has its limitations. You will have realized that it contains a number of assumptions:

1. an exponential release of the drug;
2. immediate dispersion of the drug over a well-defined volume of fluid;
3. steady removal (by excretion or metabolism) of the drug, with a rate proportional to its concentration.

These assumptions are only roughly fulfilled, so you cannot expect the result to be accurate.

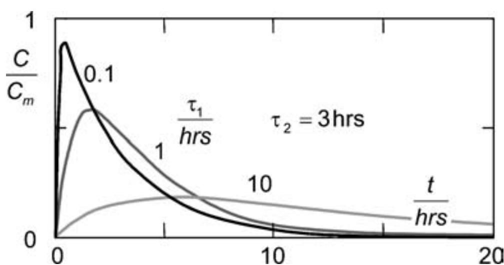

FIGURE 18 Concentration in the body with slow release and slow removal.

MOTION IN MIXTURES

A permeable boundary is a mixture. This may be a solute in a liquid, or a liquid with solutes in a solid matrix. In these mixtures, the components will be moving with different velocities[g]. The velocity differences are governed by two kinds of forces:

- the driving forces on the different components;
- the frictional forces with the surroundings.

In this section you will learn how to estimate these velocities and the resulting fluxes and flow rates (5).

Forces and Friction

Driving Forces

Important driving forces in pharmaceutical technology are:

1. "composition" forces;
2. electrical forces;
3. pressure forces.

The forces are gradients of the terms in the potential that we saw earlier. For a gradient only in the z-direction:

$$F_i = -\frac{d\mu_i}{dz} = -\left[\underbrace{\frac{\boldsymbol{RT}}{\alpha_i}\frac{d\alpha_i}{dz}}_{(1)} + \underbrace{\boldsymbol{F}z_i\frac{d\phi}{dz}}_{(2)} + \underbrace{\upsilon_i\frac{dp}{dz}}_{(3)}\right] \tag{51}$$

With the molar units used here, the force is in N mol^{-1}.The minus sign shows that the forces are down the gradient. The most important driving forces for us are those due to composition (concentration) gradients: these are the main cause of what is commonly known as diffusion. We discuss these in more detail further on. Electrical forces nearly always occur when there are charged species such as ions. Pressure forces can be important in coated systems.

Friction

When components move with different velocities they exert friction on each other. The hydrogen ions in an HCl solution exert a friction force on the surrounding water—and the water exerts an equal but opposite force on the ions. In a similar manner there can be friction between any component and a solid matrix: you can regard the matrix as just another component (or as part of the solvent).

The friction force is usually proportional to the velocity difference, to the fraction x_j of the other component, and to a friction coefficient $\zeta_{i,j}$ which is different for each pair of components and which does in general depend on the composition of the mixture.

It is the balance of all the driving forces and friction forces that determines the relative velocities of the components in the mixture. We can summarize this force balance for any component i with the equation:

$$[\text{Driving force on } i] = [\text{Sum of friction forces}]$$

---

[g] Here we are considering the average local velocity of the molecules of a given species, not the thermal velocities of the individual molecules. Those are orders of magnitude higher, but they are largely random and only give a small net transport.

The forces and velocities in the friction terms are vectors, but here we will only consider the case when all forces are in one direction (the z-direction). Then

$$F_i = \sum_j \zeta_{i,j} x_j (u_j - u_i) \tag{52}$$

This is the Maxwell–Stefan (MS) equation: a general equation for motion of a species in an isothermal mixture. There is one such equation for each component (which may also be a polymer or porous matrix).

Bootstraps

The MS equations only determine the differences in velocity, not the absolute value. In a mixture with two components, there is only one difference in velocities. This means that the two MS equations are dependent, and that one can be omitted. For n components one finds that there are at most $(n - 1)$ independent equations.

To obtain the absolute velocities one needs one or more extra equations, which are determined by the nature of the problem. Common ones are:

1. The solvent is stagnant (it is in most of our problems).
2. The solution is electroneutral (as in solutions of salts).
3. There is no net volume flow (as in sedimentation).

These equations are often called 'bootstrap relations'.

Diffusion–Fick's Law

The most important driving force for mass transfer processes is usually the gradient of the activity of a component. Here we will only consider dilute solutions, where the potential can be written in the form[h]:

$$\mu_i = \boldsymbol{RT} \ln\left(\frac{c_i}{c_0}\right) \tag{53}$$

The driving force is the gradient of this potential, with a minus sign to show that transport is down the gradient:

$$F_i = -\frac{d\mu_i}{dz} = -\frac{\boldsymbol{RT}}{c_i}\frac{dc_i}{dz} \tag{54}$$

This is a real force (in N mol^{-1}), and its numerical value can be huge. Forces on a molecular scale tend to be far larger than those in the macro world that we experience. The force is proportional to the concentration gradient.

We now assume that component i is moving through a stagnant solvent. As the solution is dilute, the fraction of solvent is almost one, and friction will be solely with the solvent. The MS equation then simplifies to:

$$-\frac{\boldsymbol{RT}}{c_i}\frac{dc_i}{dz} = \zeta_{i,W}(u_i - u_s) = \zeta_{i,W} u_i \tag{55}$$

[h] In textbooks of thermodynamics you will find a slightly different form. The differences are all accounted for by the constant c_0.

Here we have made use of the fact that the solvent is stagnant. We now rearrange the equation:

$$u_i c_i = -\frac{\boldsymbol{R}T}{\zeta_{i,W}} \frac{dc_i}{dz} \tag{56}$$

We can also write this as:

$$n_i = -D_i \frac{dc_i}{dz} \tag{57}$$

Here n_i is the molar flux of component i (in mol m^{-2} s^{-1}) and D_i is the diffusivity of the component in the solvent. This is Fick's (first) law: it tells us that the flux is proportional to the concentration gradient. One can derive similar equations using mass and volume concentrations:

$$\text{the mass flux in kg m}^{-2}\text{s}^{-1}: \qquad N_i = -D_i \frac{dC_i}{dz} \tag{58}$$

$$\text{the volume flux in m}^{-3}\text{m}^{-2}\text{s}^{-1}: \quad \boldsymbol{N}_i = -D_i \frac{d\boldsymbol{C}_i}{dz} \tag{59}$$

In dilute mixtures, the diffusivities have the same value in all three systems. Fick's law is often used as the basis of mass transfer theory, but you should realize its limitations. We have derived it for a system which

- is dilute (and as a result an ideal mixture);
- is driven by concentration gradients;
- in which the solvent is stagnant.

Fick's law can be applied in a few other special cases, but it is not valid in general. Even so, we will be using it in the coming examples as the results are quite illustrative. We will be using two variants as well. Fick's "second law" reads:

$$\frac{\partial C_i}{\partial t} = \frac{\partial}{\partial z}\left[D_i \frac{\partial C_i}{\partial z}\right] \tag{60}$$

This is a partial differential equation that describes the development of concentration profiles in transient situations. It is not really a separate law, as it can be derived from the "first" law. For diffusion around a sphere, we will need Fick's law in spherical co-ordinates:

$$\frac{\partial C_i}{\partial t} = \frac{1}{r^2}\frac{\partial}{\partial r}\left[D_i r^2 \frac{\partial C_i}{\partial r}\right] \tag{61}$$

In dilute solutions in a liquid, the diffusivity does not depend on concentration and typically has a value around 10^{-9} m^2 s^{-1}. Some values are given in Table 6. We can apply the same equations for diffusion of a dilute solute in a porous or polymer matrix. However, the diffusivities there can be orders of magnitude lower and strongly dependent on concentration, as we will discuss in the section "Effect of a Matrix".

Other Forces

When dealing with ions, we must include the electrical force in our diffusion equation, and with pressure diffusion we need the pressure term. The extension of the equations for dilute mixtures is simple; for the molar notation:

TABLE 6 Diffusivities in Water at 25°C

Species	D_i (m² s⁻¹)
Hydrogen ion H^+	10×10^{-9}
Hydroxyl ion OH^-	5×10^{-9}
Ethanol	1.7×10^{-9}
Small ions (Na^+, Cl^-, SO_4^{2-})	$1\text{–}2 \times 10^{-9}$
Large ions (Ca^{2+})	$0.5\text{–}1 \times 10^{-9}$
Drugs (200–600 g mol^{-1})	$0.5\text{–}1 \times 10^{-9}$
Proteins (buffered)	$0.1\text{–}0.2 \times 10^{-9}$

$$F_i = -\frac{d\mu_i}{dz} = -\frac{\boldsymbol{RT}}{c_i}\frac{dc_i}{dz} - \boldsymbol{F}z_i\frac{d\phi}{dz} - \upsilon_i\frac{dp}{dz} \tag{62}$$

Inserting this in the MS equation and rearranging yields the diffusion equation for ions in a dilute solution:

$$n_i = -D_i\left[\frac{dc_i}{dz} + \boldsymbol{F}z_ic_i\frac{d\phi}{dz} + \upsilon_ic_i\frac{dp}{dz}\right] \tag{63}$$

The corresponding equations in mass and volume units have the same form:

$$N_i = -D_i\left[\frac{dC_i}{dz} + \boldsymbol{F}z_iC_i\frac{d\phi}{dz} + \upsilon_iC_i\frac{dp}{dz}\right] \tag{64}$$

$$\boldsymbol{N}_i = -D_i\left[\frac{d\boldsymbol{C}_i}{dz} + \boldsymbol{F}z_i\boldsymbol{C}_i\frac{d\phi}{dz} + \upsilon_i\boldsymbol{C}_i\frac{dp}{dz}\right] \tag{65}$$

Remember that these equations only apply to dilute, stagnant solutions. In concentrated solutions with all components moving, the relations between the different unit systems are far more complicated.

Solving the above equations is often quite a task. However, for engineering estimates there is a procedure that gives good results for a limited amount of work. The starting point is to consider the mass transfer resistance as a thin flat film with a thickness Δz. The flux is then estimated using a difference equation, for example:

$$n_i = -D_i\left[\frac{\Delta c_i}{\Delta z} + \boldsymbol{F}z_i\bar{c}_i\frac{\Delta\phi}{\Delta z} + \upsilon_i\bar{c}_i\frac{\Delta p}{\Delta z}\right] \tag{66}$$

The differences and average concentrations are defined using values at the position α at the left side and β at the right side of the film. For example:

$$\Delta c_i = c_{i\beta} - c_{i\alpha} \quad \text{and} \quad \bar{c}_i = \frac{c_{i\beta} + c_{i\alpha}}{2} \tag{67}$$

We will discuss several uses of this technique in the examples. In the difference equations the quotient $k_i = D_i/\Delta z$ plays an important role. It is known as the mass transfer coefficient. It has the dimension of a velocity and is usually of the order of magnitude of the velocities of the species in the film.

Examples 4

Absorption in the Intestine

We consider the smaller intestine as a long cylindrical tube, with a thin membrane as the wall. A drug is initially distributed throughout a short cylindrical compartment that

gradually moves along the tube. Drug diffuses through the membrane into the body. The question is how quickly the drug will be absorbed (Fig. 19).

The intestine has a diameter d_I, a length L_I, and a membrane thickness Δz_I. The initial mass m_0 of drug is dispersed in the compartment with length L_C ("our system"). We will handle this problem in mass concentrations. The drug has a concentration C in the compartment; elsewhere the concentration drops to practically zero. We assume that the concentrations at membrane interfaces are related via a partition coefficient:

$$\frac{C'}{C} = K \tag{68}$$

The only flow out of the compartment is by diffusion through the membrane. A mass balance of the drug in the compartment reads:

$$\frac{dm}{dt} = -\dot{m}_{\text{out}} \quad \text{or} \quad V_c\frac{dC}{dt} = -NA_c \tag{69}$$

where V_C is the volume of the compartment, and A_C is the outer cylindrical area. N is the diffusion flux through the membrane. It is given by Fick's law:

$$N = -D\frac{dC}{dz} \tag{70}$$

The flux only changes slowly: at any given moment we can regard it as constant. Then the above equation shows that the concentration must vary linearly across the membrane:

$$N = -D\frac{(C'_\beta - C'_\alpha)}{\Delta z_I} = \frac{D}{\Delta z_I}C'_\alpha = kKC \tag{71}$$

where $k = D/\Delta z_I$ is the mass transfer coefficient. The mass balance now reads:

$$V_c\frac{dC}{dt} = -(A_c kK)C \quad \text{or} \quad \frac{dC}{C} = -\frac{dt}{\tau} \tag{72}$$

With the time constant

$$\tau = \frac{V_c}{A_c kK} = \frac{1}{4}\frac{d_I \Delta z_I}{DK} \tag{73}$$

This has the solution

$$\frac{C}{C_0} = \exp\left(-\frac{t}{\tau}\right) \quad \text{or} \quad \frac{m}{m_0} = \exp\left(-\frac{t}{\tau}\right) \tag{74}$$

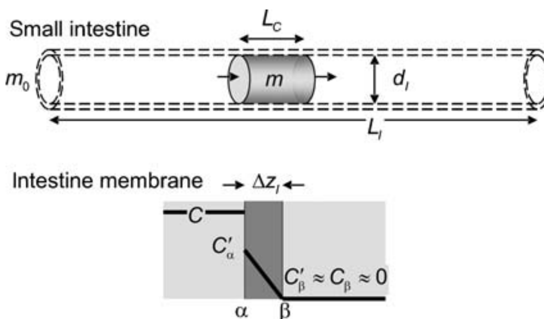

FIGURE 19 A model of the smaller intestine.

This is the expression that we have used to describe the release in the body in section "Systems and Balances".

We now look at the behavior of our solution. The only parameter in the time constant that we can hope to influence is the partition coefficient. Even so we can make a thought experiment in which the diameter and the membrane thickness of the intestines are varied. We see that a larger intestine diameter and a larger wall thickness both increase the release time; a larger diffusivity and a larger partition coefficient both decrease the release time. This looks all right. Plausible values of the parameters are:

$d_I = 0.03\,\mathrm{m}$
$\Delta z_I = 0.1\,\mathrm{mm}$
$K = 0.5$
$D = 0.5 \times 10^{-9}\,\mathrm{m^2 s^{-1}}$

These lead to a time constant of the order of an hour. The time of passage through the smaller intestines is about four hours, so with these values nearly all of the drug will be absorbed. If we want to retard adsorption, we would have to make the drug less soluble in the membrane, or to use a slow release tablet with a longer release time.

You may have noticed that the length of the compartment plays no role in the answer. A longer compartment gives a larger mass transfer area, but also a lower concentration in the compartment and these two effects compensate. This is an indication that the model is not sensitive to assumptions on how the drug is dispersed.

A final remark: it will be clear that this model is only a rough description of a complex piece of "biomachinery". Even so, it captures many of the mass transfer characteristics of the intestines.

Dissolution of a Sphere

In this example, we consider the rates of dissolution of homogeneous spherical particles (so those consisting of a single component). There are two different regimes in the dissolution of a spherical particle in a flow (Fig. 20). The first is for large particles (with a radius larger than about 0.1 mm) and the second for smaller particles.

Large particles are buffered by eddies in the liquid flow around them. Mass transfer from these particles depends on the flow conditions. Flow conditions in the body are poorly known and not well-defined, but fortunately the dependence on flow is not strong. For rough estimates (and we cannot give more) it turns out that the mass transfer coefficient of these particles can be taken as constant, with a value:

$k \approx 10\,\mu\mathrm{m\,s^{-1}}$

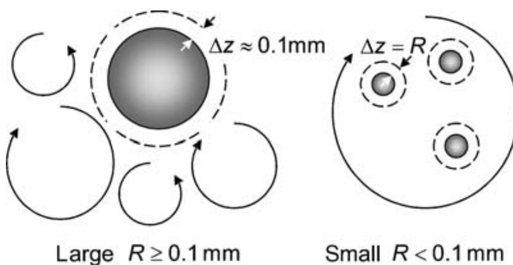

FIGURE 20 The two mass transfer regimes for particles in a flow.

With a typical value of the diffusivity of $D = 10^{-9}\ \mathrm{m^2s^{-1}}$ this implies a film thickness of about:

$$\Delta z = \frac{D}{k} \approx 10^{-4}\,\mathrm{m}$$

Small particles are carried along by the flow: they "see" their surroundings as stagnant. For such particles we will derive a formula for the mass transfer coefficient:

$$k = \frac{D}{R} \tag{75}$$

where R is the radius of the particle.

We now use these coefficients to calculate the rate of dissolution and the time required for dissolution. We begin with the large particles. A mass balance for the large sphere reads:

$$\frac{dm}{dt} = -\dot{m}_{\text{out}} \quad \text{or} \quad \frac{d}{dt}[\rho_S V_P] = kA_P(C_{\text{sat}} - 0) \tag{76}$$

where V_P is the volume of the particle and A_P the surface area (both of which depend on time). The mass transfer relation is the same as we have encountered in the previous examples. Using the relations for a sphere $V_P = (4/3)\ \pi R^3$ and $A_P = 2\pi R^2$, then working out the differential quotient and simplifying leads to:

$$\frac{dR}{dt} = -\frac{k}{2}\frac{C_{\text{sat}}}{\rho_s} \tag{77}$$

This has the solution

$$R = R_0 - \frac{k}{2}\frac{C_{\text{sat}}}{\rho_s}t \tag{78}$$

The radius decreases linearly with the time. The rate is proportional to the mass transfer coefficient and—importantly—on the solubility C_{sat} of the material of the sphere. The sphere will dissolve in a time:

$$t = 2\frac{R_0\rho_s}{kC_{\text{sat}}} \tag{79}$$

For large particles with a low solubility this can run into many hours, or even days (Fig. 21). It will be clear why this regime is avoided in pharmaceutical applications by

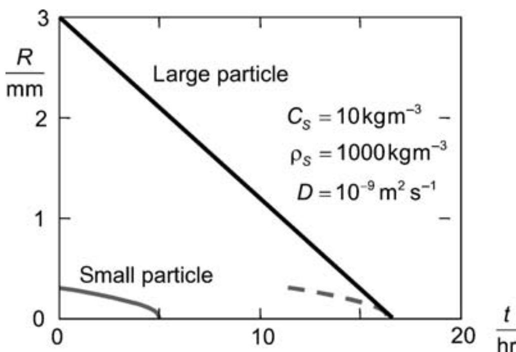

FIGURE 21 Radius versus time for a large and a small particle.

constructing tablets made up of small units. Note that although the radius of the particle decreases linearly, the release rate is not linear. Initially the particle has a large surface area and the release rate is high; the rate goes down as the particle size decreases.

Now the small particles. The reasoning is the same, but as the mass transfer coefficient now depends on the radius of the particle, the resulting equation is different:

$$\frac{dR}{dt} = -\frac{DC_{\text{sat}}}{2\rho_s}\frac{1}{R} \quad \text{or} \quad RdR = -\frac{DC_{\text{sat}}}{2\rho_s}dt \tag{80}$$

This has the solution:

$$R^2 = R_0^2 - \frac{DC_{\text{sat}}}{2\rho_s}t \quad \text{or} \quad R = \sqrt{R_0^2 - \frac{DC_{\text{sat}}}{2\rho_s}t} \tag{81}$$

where the radius decreases more and more rapidly as the particle gets smaller. The time required for complete dissolution becomes:

$$t = 2\frac{R_0^2\rho_s}{DC_{\text{sat}}} \tag{82}$$

This decreases rapidly with decreasing particle size (Fig. 21).

Of course the large particle eventually becomes a small particle which dissolves more rapidly. However, the effect is only important when the starting particle is just slightly larger than the small particle limit.

We finish this example with a derivation of the mass transfer coefficient for the small particles. These "see" the surroundings as stagnant. Diffusion in a dilute stagnant medium is governed by Fick's second law. In spherical coordinates this reads:

$$\frac{\partial c}{\partial t} = \frac{1}{r^2}\frac{\partial}{\partial r}\left[Dr^2\frac{\partial C}{\partial r}\right] \tag{83}$$

The general solution of the partial differential equation is difficult, but there is a special case that is both simple and useful. The case is that of a non-dissolving sphere (!) which is exuding a drug on its surface. Surprisingly, this system has a steady solution (which does not depend on time). The partial differential equation then becomes an ordinary differential equation:

$$0 = \frac{1}{r^2}\frac{d}{dr}\left[Dr^2\frac{dC}{dr}\right] \tag{84}$$

This can be integrated directly in two steps:

$$Dr^2\frac{dC}{dr} = B_1 \quad \text{or} \quad dC = \frac{B_1}{D}\frac{1}{r^2}dr \quad \text{giving} \quad C = B_2 - \frac{B_1}{D}\frac{1}{r}$$

The integration constants B_1 and B_2 are determined by the boundary conditions:

$$\text{at} \quad r = \infty \quad C = 0 \quad \text{so} \quad B_2 = 0 \tag{85}$$

$$\text{at} \quad r = R \quad C = C_{\text{sat}} \quad \text{so} \quad B_1 = -C_{\text{sat}}DR \tag{86}$$

where C_{sat} is the saturation concentration at the surface of the sphere. The final result is:

$$C = C_{\text{sat}}\frac{R}{r} \tag{87}$$

The concentration is inversely proportional to the distance from the center of the sphere. The flux at this surface is:

$$N = -D\frac{dC}{dr} = C_{\text{sat}}\frac{D}{R} = kC_{\text{sat}} \tag{88}$$

We see that the system has a mass transfer coefficient

$$k = \frac{D}{R} \tag{89}$$

This increases when the particle is smaller. The whole derivation above is for a non-dissolving sphere. However, you will understand that it should be a good approximation for a slowly dissolving sphere (so one with a low solubility). For materials with a high solubility the problems encountered when solving the mass transfer equations are more difficult. However, it is easily understood that dissolution rates there are higher than calculated with the "dilute" formulae.

A final remark on the example: real particles are seldom spheres. Even so, the behavior of spheres helps us understand the dissolution behavior of other particles.

Intrinsic Dissolution Rate

A test that is often done in the lab is the determination of the "intrinsic dissolution rate". This is the rate at which a drug or excipient dissolves in a fluid under well-defined stirring conditions. In this example, we analyze the dissolution of a weak basic drug under two conditions: with no acid (where the drug is hardly ionized) and with an excess of acid (where the drug is fully ionized and there are also other ions around). This problem is simplest in molar terms.

The equipment is a rotating disk. This gives a flow pattern that can be analyzed more or less exactly, and that has the surprising property that it gives a constant dissolution rate over the whole surface of the disk. The drug is pressed into a hollow in the disk, such that the surface is flat, and the rate of dissolution is measured by following the concentration in the surrounding fluid.

"Exact" calculations by Levich give the flux for dissolution of a single component as:

$$n = 0.62D^{2/3}\nu^{-1/6}\omega^{1/2}c_{\text{sat}} = kc_{\text{sat}} \quad k = 0.62D^{2/3}\nu^{-1/6}\omega^{1/2} \tag{90}$$

Variables you will not have seen earlier are the kinematic viscosity ν of the liquid, and the angular speed ω of the disk. As in the previous example, we can describe the problem using a mass transfer coefficient k. With $D = 10^{-9}\,\text{m}^2\text{s}^{-1}$, $\nu = 10^{-6}\,\text{m}^2\text{s}^{-1}$, $\omega = 10\,\text{s}^{-1}$ and $c_{\text{sat}} = 0.1$ mol L^{-1} we find $k = 1.96 \times 10^{-5}$ ms^{-1} and $n = 1.96 \times 10^{-5}$ mol m^{-2} s^{-1} (Fig. 22).

In engineering calculations it is common to view a mass transfer process as if it occurs by diffusion through a stagnant "film": here between the solid disk and the bulk fluid. This is a gross scheme of what happens in reality, but experience shows that it leads to useful results. The film thickness in our example is:

$$\Delta z = D/k = 5.1 \times 10^{-5}\,\text{m}$$

or 51 μm. We will also use this value in the next part of the problem.

In this second part, a strong acid is added to the bulk of the fluid. It has a molar concentration ten times higher than that of the saturated base alone. As a result the base will ionize. There will be three ions in solution: B^+, A^- and H^+ with charge

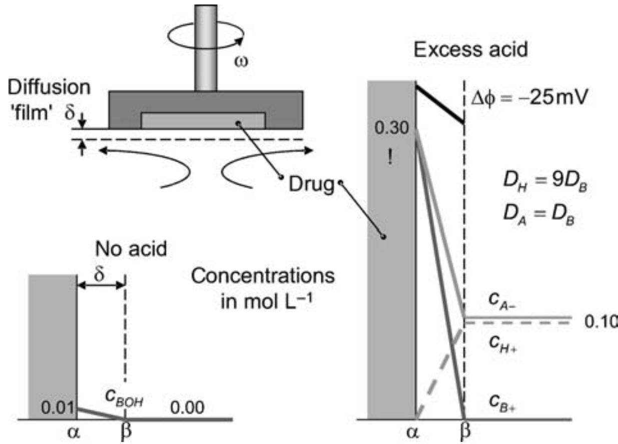

FIGURE 22 The rotating disk with two concentration profiles.

numbers 1, –1 and 1. Of these three, H^+ is far more mobile that the other two. In the calculation below we have given it a diffusivity which is nine times larger than that of the other two ions (this value gives nice round figures).

Before looking at the details of the calculations we first discuss the outcome. This may be surprising for those not used to mass transfer in electrolytes. The bulk fluid contains the H^+ and A^- ions of the acid with the concentrations that we have specified. At the solid interface the H^+ reacts immediately with the solid base BOH and the concentration of H^+ is zero. The concentrations of B^+ and A^- at the interface are as yet unknown: they will turn out to be much higher than one might expect offhand.

What happens appears to be like this. The H^+ ion, being very mobile, diffuses towards the solid, and causes a minute charge imbalance and an electrical field. This field forces the A^- ion in the direction of the solid, so that the concentration of A^- increases towards the solid. At the solid the concentrations of B^+ and A^- must be equal because of electroneutrality, so also B^+ has a high concentration there (in this example thirty times higher than the saturation concentration of the base alone). There is no flux of A^-: the electrical and concentration forces cancel for this component. However, for B^+ the two gradients both work in the same direction and this gives a high flux. The flux of H^+ has to be equal-but-opposite to maintain electroneutrality.

To estimate the profiles in the figure we have used a difference form of the MS equations for the three ions:

$$n_B = -D_B\left(\frac{\Delta c_B}{\Delta z} + \boldsymbol{F} z_B c_B \frac{\Delta\phi}{\Delta z}\right) \tag{91}$$

$$n_A = -D_A\left(\frac{\Delta c_A}{\Delta z} + \boldsymbol{F} z_A c_A \frac{\Delta\phi}{\Delta z}\right) \tag{92}$$

$$n_H = -D_H\left(\frac{\Delta c_H}{\Delta z} + \boldsymbol{F} z_H c_H \frac{\Delta\phi}{\Delta z}\right) \tag{93}$$

The differences are just those between the sides of the film, for example,

$$\Delta c_B = c_{B\beta} - c_{B\alpha} \tag{94}$$

where the subscript α denotes the solid side of the film, β the bulk liquid side. The concentrations are averages between those on the two sides, for example:

$$c_B = \frac{c_{B\beta} + c_{B\alpha}}{2} \tag{95}$$

You will find that there are six unknowns in the three equations: the three fluxes, the electrical potential difference and the two concentrations at the solid. So we need three more equations ("bootstraps") for which we have used:

$$n_A = 0 \quad \text{there should be no transport of A}^- \tag{96}$$

$$n_H = -n_B \quad \text{the fluxes of H}^+ \text{ and B}^+ \text{ must cancel} \tag{97}$$

$$c_{A\alpha} = c_{B\alpha} \quad \text{the two ions have the same concentration at the solid} \tag{98}$$

These six equations were solved numerically, giving the profiles shown. The electrical potential difference is a mere 25 mV, but even so the flux of the base is 450 times the flux without acid. You cannot expect these estimates to be accurate, but they will be fairly close.

The acceleration of mass transfer by the H^+ ion disappears if an excess of an inert electrolyte (such as NaCl) is added. We will not work this out (it requires even more equations) but note that in many ways the system then behaves in a simpler fashion. There is always an excess of other ions in body fluids, but you may have to add them in the lab.

Insoluble Coatings

This example considers two kinds of granule or tablet with a coating that remains intact during drug release (Fig. 23). The first type, known as an osmotic pump, has a small hole (usually made by a laser). The second has a closed coating. Water diffuses through the coating into the granule and the drug diffuses out. The driving forces for water transport are the difference in water concentration and the difference in pressure. Because water nearly always has a higher rate of diffusion, there can be a strong rise of pressure in the granule.

Both of these systems have a characteristic that is often desirable: as long as the solution inside the granule remains saturated, the release rate of the drug is constant.

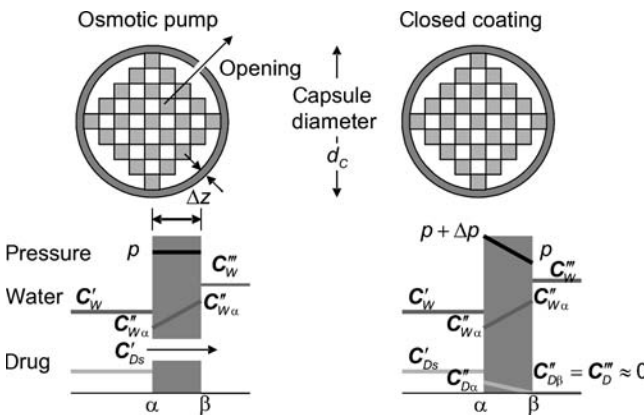

FIGURE 23 Two kinds of slow-release granules.

As we shall see, granules have to be quite small, and we shall take them to be spherical. The drug inside the granule is assumed to be easily accessible, so the concentration in the water diffusing into the granule is equal to the saturation value. For simplicity we assume that there are only concentration gradients in the wall of the granule. Also, we will be looking at the volume flows, as these are the most easily envisaged in these problems.

Even in simple devices like these, there are many parameters that can be varied in the design:

- the diameter of the granule;
- the thickness of the wall;
- the partition coefficients of water and drug;
- the diffusivities of water and drug;
- the solubility of the drug.

We will set up models to see how these influence the release time of the drug. However, before doing so, we first discuss the results.

The osmotic pump is the simplest. It gives a constant release, and it empties in a time:

$$t = \frac{1}{6}\frac{\boldsymbol{C}'_{D0} d_T \Delta z}{D_W K_W}\frac{1}{\boldsymbol{C}'^{2}_{D\mathrm{sat}}} \tag{99}$$

where $\boldsymbol{C}''_{D0}$ is the initial fraction of drug (including solids). The release time of the drug increases with this fraction, with the diameter of the granule and with a larger coating thickness. It decreases with an increasing diffusivity and solubility of water in the coating. The only influence of the drug is via its solubility in water: the release time is inversely proportional to the square of this value. Parameters of the granule might be:

$$d_T = 2\ \mathrm{mm};\ \Delta z = 0.03\,\mathrm{mm};\ D_W = 0.1\times 10^{-9}\mathrm{m^2s^{-1}};\ K_W = 0.2;\ \boldsymbol{C}'_{D0} = 0.5;\ \boldsymbol{C}'_{D\mathrm{sat}} = 0.1$$

These yield a release time of about 7 hours. We see that the granule has to be small and permeable, and that the drug has to be quite soluble to get reasonable release times.

Also the pressure granule gives a constant release, with a release time:

$$t = \frac{1}{6}\frac{\boldsymbol{C}'_{D0} d_T \Delta z}{D_W \boldsymbol{C}'_{D\mathrm{sat}}}\frac{D_W B_W - D_D B_D}{D_D(K_D B_W + B_D K_W)} \tag{100}$$

The first part of the equation is similar to that of the osmotic pump. However, the release time is now a simple inverse function of the saturation concentration, and the formulae also contains diffusion and pressure constants of the drug. To use this equation we need a few more parameters than in the case of the osmotic pump:

$$\upsilon_W = 2\times 10^{-5}\ \mathrm{m^3\ mol^{-1}};\ D_D = 0.01\times 10^{-9}\ \mathrm{m^2s^{-1}};\ K_D = 0.1;\ \upsilon_D = 10\times 10^{-5}\ \mathrm{m^3\ mol^{-1}}$$

Together with the values used earlier, we find a pressure difference of 14 MPa (140 bar) and a release time of about 11 hours. Release times of closed granules are even longer than those of the corresponding osmotic pumps.

The derivations of the release time formulae are not difficult. First consider the osmotic pump. If the hole is not too small, the pressure difference will be negligible and the volume flux of water into the tablet becomes:

$$\boldsymbol{N}_W = -D_W\frac{\Delta \boldsymbol{C}_W}{\Delta z} \tag{101}$$

The volume fraction of water inside the tablet is:

$$\boldsymbol{C}'_W = 1 - \boldsymbol{C}'_{D\text{sat}} \tag{102}$$

The volume fractions in the coating will be:

$$\boldsymbol{C}''_{W\alpha} = K_W\,(1 - \boldsymbol{C}'_{D\text{sat}})\text{ and }\boldsymbol{C}''_{W\beta} = K_W\,(1)\text{ so }\Delta\boldsymbol{C}''_W = K_W\boldsymbol{C}'_{D\text{sat}} \tag{103}$$

The volume flow of water into the tablet is:

$$\boldsymbol{M}_W = \boldsymbol{N}_W\,(\pi d_T{}^2) = D_W\,\frac{K_W\boldsymbol{C}'_{Ds}}{\Delta z}\,(\pi d_T{}^2) \tag{104}$$

This flows out through the hole and carries a volume of drug with it:

$$\boldsymbol{M}_W\boldsymbol{C}'_{D\text{sat}} \tag{105}$$

The initial volume of the drug in the granule (both solid and dissolved) is

$$\boldsymbol{C}'_{D0}\left(\frac{\pi}{6}d_T{}^3\right) \tag{106}$$

The release time is the ratio of the initial drug volume to the volume flow rate out.

Now consider the granule with the closed coating. Here water diffuses into the granule according to the pressure diffusion equation:

$$\boldsymbol{N}_W = -D_W\left(\frac{\triangle\boldsymbol{C}''_W}{\triangle z} + B_W\,\frac{\triangle p}{\triangle z}\right), \quad B_W = \frac{\upsilon_W\boldsymbol{C}''_W}{RT} \tag{107}$$

Note that the volume fractions are those inside the membrane and that $\boldsymbol{C}''_W$ is the average value. The pressure gradient works against the transport of water. The transport equation for the drug is similar:

$$\boldsymbol{N}_D = -D_D\left(\frac{\Delta\boldsymbol{C}''_D}{\Delta_z} + B_D\frac{\Delta p}{\Delta z}\right), \quad B_D = \frac{\upsilon_D\boldsymbol{C}''_D}{RT} \tag{108}$$

However, the drug will have a lower diffusivity and a higher molar volume (but lower volume fraction) than water. So the coefficients in the equations can be quite different. For the drug the concentration and pressure gradients work in the same direction.

The volume fraction difference of the drug in the membrane is:

$$\Delta\boldsymbol{C}''_D = 0 - K_D\boldsymbol{C}'_{Ds} = -K_D\boldsymbol{C}'_{Ds} \tag{109}$$

That of the water is:

$$\Delta\boldsymbol{C}''_W = K_W 1 - K_W(1 - \boldsymbol{C}'_{D\text{sat}}) = K_W\boldsymbol{C}'_{D\text{sat}} \tag{110}$$

If the coating is rigid (so that it does not expand) the two volume fluxes will immediately become equal-but-opposite:

$$\boldsymbol{N}_W = -\boldsymbol{N}_D\text{ or }D_W(K_W\boldsymbol{C}'_{D\text{sat}} + B_W\Delta p) = D_D(-K_D\boldsymbol{C}'_{D\text{sat}} + B_D\Delta p) \tag{111}$$

From this equation we can solve:

$$\Delta p = -\boldsymbol{C}'_{D\text{sat}}\,\frac{D_WK_W + D_DK_D}{D_WB_W - D_DB_D} \tag{112}$$

This is then used in the equations above to calculate the fluxes and flows and the release time.

EFFECT OF A MATRIX

The matrix—either a porous structure or a polymer—can greatly influence the rate of dissolution of the embedded drug. There are two main types of matrix (Fig. 24):

- poorly soluble porous matrices, where the drug diffuses out through the pores;
- non-porous polymer matrices, which release the drug after dissolution or erosion of the matrix.

Porous Matrices

Here the drug is leached out of the matrix through the pores formed by earlier dissolution. Before this happens, the matrix first has to be wetted by flow of liquid into the pores.

Flow of Liquid

Flow of a liquid through a fine porous medium can be slow. A semi-empirical formula that gives the velocity in the pores is the Carman–Kozeny equation:

$$u = -\frac{1}{180}\frac{\varepsilon_{\text{eff}}^2}{(1-\varepsilon_{\text{eff}})^2}\frac{d_P^2}{\eta}\frac{dp}{dz} \tag{113}$$

The original equation is based on data from structures that are more open than tablets. These do not take the occurrence of a percolation threshold into account as we do by using the effective porosity.

Diffusion in Pores

Diffusion only occurs through the pores. If these occupy a volume fraction ε, then the cross section available for diffusion turns out to be equal to the same void fraction (at least for media with random pores). The particles also lengthen the diffusion path (a phenomenon known as tortuosity). As a result the effective diffusivity will be lower. The effect is roughly described by the following empirical formula:

$$\frac{D}{D_0} = \varepsilon_{\text{eff}}^{1.5} \tag{114}$$

where D_0 is the diffusivity of the drug, free in solution.

In tablets, the diffusivity is typically ten to a hundred times lower than in free solution (Fig. 25).

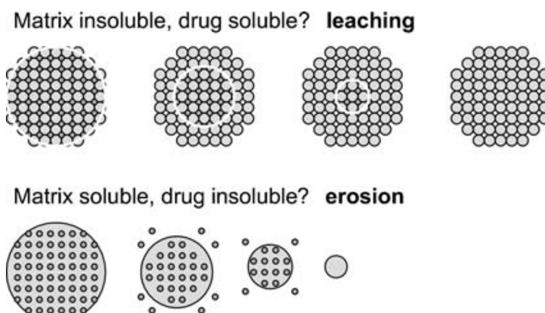

FIGURE 24 Porous and polymer matrices.

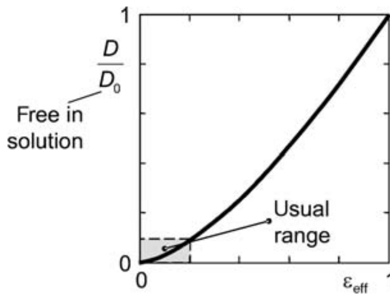

FIGURE 25 Diffusivities in porous media.

Polymer Matrices

In these, one uses a matrix of a swellable polymer which is compressed with a high pressure. As a result, the matrix has a pore fraction of less than 0.05 and transport occurs solely after dissolution of water in the polymer, followed by diffusion of the drug.

Diffusion in Polymers

Diffusivities in polymers vary enormously. Below and just above the glass transition temperature, polymers are almost impermeable except for very small molecules. Figure 26 shows the diffusivity of traces of benzene[i]. These are in a series of polymers with differing glass transition temperatures; what is plotted along the horizontal axis is the difference between the actual temperature of the measurement and the glass transition temperature.

Please note that the vertical scale is logarithmic, and that it varies over ten orders of magnitude. At the top of the range, the diffusivities are those in low-viscous liquids; at the bottom diffusion is only perceptible over extremely long times. The diffusivity also

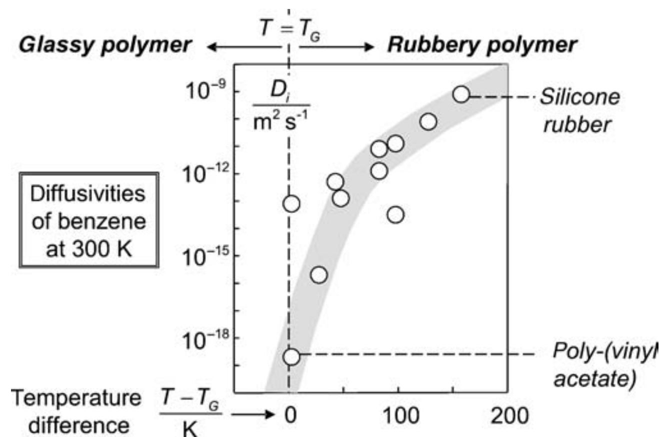

FIGURE 26 Diffusivities of traces of benzene in polymers at 25˚C.

[i] We use benzene as an example because there are many measurements on its diffusivity. Of course benzene is not a substance to use in pharmaceuticals.

depends strongly on the size of the molecule: the larger, the lower the diffusivity (Fig. 27). This effect is strongest in the almost glassy polymer.

As we have seen, solvents (including water) plasticize and lower the glass transition temperature of polymers. Even a minor amount of swelling can then greatly change the diffusivity (Fig. 28).

These effects are roughly described by the "free volume theory" which leads to:

$$\frac{D_i}{D_0} = \exp\left(-\frac{\upsilon_i}{\upsilon_F}\right) \quad \upsilon_F = C_P \upsilon_{F\Pi} + C_i \upsilon_{Fi} \tag{115}$$

where D_0 is a constant of the order of 10^{-8} m^2 s^{-1}, υ_i is the molar volume of the solute i and υ_F is the free volume per mol of i. The free volume is built up from contributions from the polymer (small, often less than ten percent of the molar volume of the chain unit) and from the solute (typically a few tenths of the molar volume of the solute). The formula describes the enormous effect of plasticizing, of the diameter of the solute (Fig. 29), and indirectly also that of the temperature. However, it is not predictive because the constants have to be fitted to diffusion measurements to get acceptable results.

Examples 5

Wetting of a Porous Tablet

A tablet has a void fraction $\varepsilon = 0.1$ and consists of spherical particles with a diameter $d_P = 69\,\mu$m. The percolation threshold is $\varepsilon_c = 0.04$, giving an effective porosity for transport $\varepsilon_{\text{eff}} = 0.06$. The tablet is a flat cylinder, with a height of 6 mm, so the maximum penetration depth is $L_P = 3$ mm. We wish to calculate how long it will take for water to penetrate into the tablet.

The interfacial area of the particles per volume of tablet is:

$$a = 6\frac{1-\varepsilon}{d_P} \tag{116}$$

The difference in interfacial energy between areas in contact with vapor (air) or liquid (water) is:

$$\Delta\sigma = \sigma_{SL} - \sigma_{SV} = -0.01\text{Jm}^{-2}$$

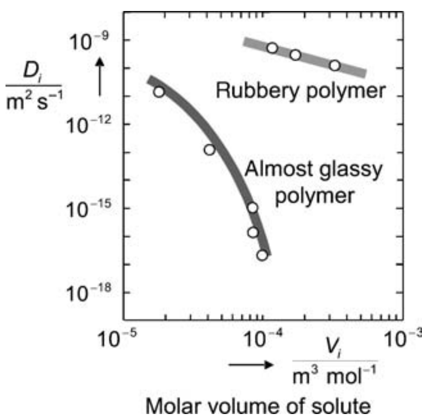

FIGURE 27 Effect of the solute volume on diffusivity in polymers.

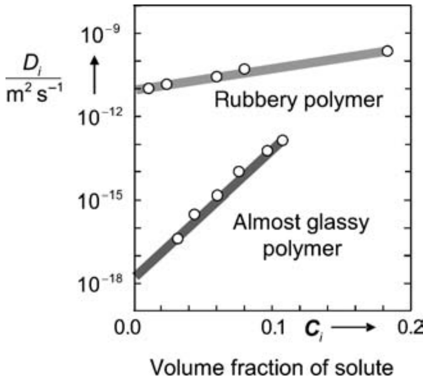

FIGURE 28 Effect of plasticizing on diffusivity in polymers.

In the section "Material Properties" we have calculated that the pressure difference across the air–water interface in the porous structure is:

$$\Delta p = 6\frac{1-\varepsilon}{\varepsilon}\frac{-\Delta\sigma}{d_P} \tag{117}$$

This is the driving force for wetting of the tablet. The velocity of the air–water front can be calculated using the Carman–Kozeny equation:

$$u = \frac{1}{180}\frac{\varepsilon_{\text{eff}}{}^2}{(1-\varepsilon_{\text{eff}})^2}\frac{d_P{}^2}{\eta}\frac{\Delta p}{z} \tag{118}$$

where z is the penetration depth, which follows from

$$dz = udt = \frac{1}{180}\frac{\varepsilon_{\text{eff}}{}^2}{(1-\varepsilon_{\text{eff}})^2}\frac{d_P{}^2}{\eta}\frac{\Delta p}{z}dt \tag{119}$$

or

$$z\ dz = \frac{1}{180}\frac{\varepsilon_{\text{eff}}{}^2}{(1-\varepsilon_{\text{eff}})^2}\frac{d_P{}^2}{\eta}\Delta p\, dt$$

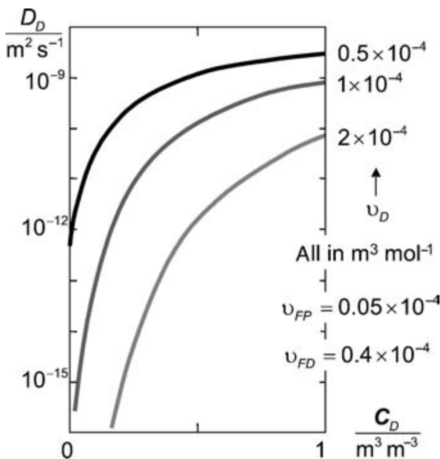

FIGURE 29 Diffusivities from the free volume theory.

which yields

$$t = 90 \frac{(1-\varepsilon_{\text{eff}})^2}{\varepsilon_{\text{eff}}^{\,2}} \frac{\eta z^2}{\Delta p d_P^{\,2}} \tag{120}$$

The time required increases with increasing viscosity, with the square of the penetration depth, and it is inversely proportional to the square of the diameter of the particles. It also increases strongly with decreasing void fraction. For the parameters given above, we find a value of a bit more than five seconds. Small, good wetting, porous media suck in water very rapidly. This can change dramatically when the medium becomes wholly or partly non-wetting due to a lipophilic lubricant. Wetting can also be retarded by swelling species that block pores.

Leaching of a Porous Sphere

Consider a spherical tablet consisting of spherical, non-dissolving filler particles (Fig. 30). Embedded between these are small dissolving drug particles. Drug first dissolves from the outer layers of the tablet. When these pores have opened, more can dissolve and diffuse outwards. As a result there are two regions in the tablet: a depleted outer zone and a saturated inner zone or core.

The question is how quickly the drug is released. The derivations below are a bit long, so we first discuss the results.

The total release time of the drug will be found to be:

$$t_D = \frac{1}{6} \frac{R^2 \boldsymbol{C}_{\text{tot}}}{D \boldsymbol{C}_{\text{sat}}} \tag{121}$$

where $\boldsymbol{C}_{\text{tot}}$ is the total initial volume concentration of drug in the tablet; the other variables will be clear. With the parameters:

$R = 3\text{mm};\ \boldsymbol{C}_{\text{tot}} = 0.1;\ \boldsymbol{C}_{\text{sat}} = 0.01;\ D = 10^{-10}\text{m}^2\text{s}^{-1}$

we find a release time of 1.5×10^5 s, or about one and a half days.

There is no closed solution for the release profile, but we can find a parametric solution to the problem. The parameter is the ratio of the radius of the core R^* to the radius of the sphere R:

$$\Theta = R^*/R \tag{122}$$

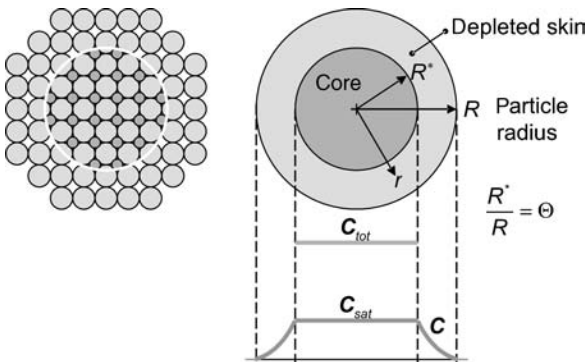

FIGURE 30 Leaching of a porous sphere.

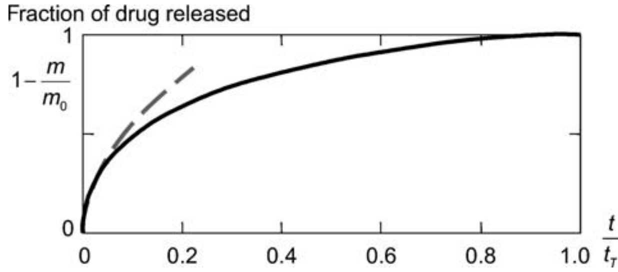

FIGURE 31 Release profile of a leaching sphere.

The fraction of the drug released for a given is:

$$F = 1 = -\frac{m}{m_0} = 1 - \Theta^3 \tag{123}$$

The ratio of the time to the total release time is also a function of ρ:

$$T = \frac{t}{t_D} = 1 - 3\Theta^2 + 2\Theta^3 \tag{124}$$

The result is shown in Figure 31. We see that the release is very fast initially—after only one tenth of the total release time; about one half of the drug has been released.

There is a simple formula for the initial part of the release curve:

$$1 - \frac{m}{m_0} = \sqrt{3\frac{t}{t_D}} \tag{125}$$

This "square root of time" behavior is characteristic of leaching processes. In pharmaceutical circles these were first studied by Higuchi.

Now the derivations. We assume that the volume concentration $\boldsymbol{C}_{\text{tot}}$ of drug in the core (which will mostly be as solid particles) is much higher than the saturation concentration in the liquid $\boldsymbol{C}_{\text{sat}}$. We also assume that the drug concentration at the surface of the tablet is negligible, and that the diffusivity of the drug in the pores is constant. Diffusion is governed by the Fick equation. In spherical coordinates:

$$\frac{\partial \boldsymbol{C}_i}{\partial t} = \frac{D}{r^2}\frac{\partial}{\partial r}\left(r^2 \frac{\partial \boldsymbol{C}_i}{\partial r}\right) \tag{126}$$

When the liquid concentrations are much lower than the concentration in the core, the time dependent term is not important[j] and the equation reduces to:

$$0 = \frac{D}{r^2}\frac{d}{dr}\left(r^2 \frac{d\boldsymbol{C}_i}{dr}\right) \tag{127}$$

Integrating this twice yields:

$$Dr^2\frac{d\boldsymbol{C}_i}{dr} = B_1, \quad \frac{d\boldsymbol{C}_i}{dr} = \frac{B_1}{D}\frac{1}{r^2}, \quad \boldsymbol{C}_i = B_2 - \frac{B_1}{D}\frac{1}{r} \tag{128}$$

The boundary conditions are:

$$\boldsymbol{C}_i(R) = 0; \; \boldsymbol{C}_i(R^*) = \boldsymbol{C}_{\text{sat}} \tag{129}$$

[j] You can check this after finishing the solution.

These give the constants:

$$B_1 = \boldsymbol{C}_{\text{sat}} D \frac{RR^*}{R^* - R} = \boldsymbol{C}_{\text{sat}} DR \frac{\Theta}{\Theta - 1}, \; B_2 = \boldsymbol{C}_{\text{sat}} \frac{R^*}{R^* - R} = \boldsymbol{C}_{\text{sat}} \frac{\Theta}{\Theta - 1} \tag{130}$$

So the concentration profile becomes:

$$\frac{\boldsymbol{C}_i(r)}{\boldsymbol{C}_{\text{sat}}} = \frac{\Theta}{\Theta - 1}\left(1 - \frac{R}{r}\right) \tag{131}$$

Figure 32 shows this profile for a number of values of $\Theta = R^*/R$.
The drug leaves the surface of the tablet with a flux:

$$\boldsymbol{N}_i = -D_i \frac{d\boldsymbol{C}_i}{dr} \text{ at } r = R \tag{132}$$

or

$$\boldsymbol{N}_i = -D_i \boldsymbol{C}_{\text{sat}} \frac{\Theta}{\Theta - 1} \frac{R}{R^2} = -D_i \frac{\boldsymbol{C}_{\text{sat}}}{R} \frac{\Theta}{\Theta - 1} \tag{133}$$

The release of drug is related to the change of the radius of the core:

$$\boldsymbol{N}_i \pi R^2 dt = -\boldsymbol{C}_{\text{tot}} \pi (R^*)^2 dR^* \; \boldsymbol{N}_i dt = -\boldsymbol{C}_t R \Theta^2 d\rho \; \frac{D\boldsymbol{C}_{\text{sat}}}{R^2 \boldsymbol{C}_{\text{tot}}} = (\Theta - 1)\Theta d\Theta$$

Integrating this yields:

$$\frac{DC_{\text{sat}}}{R^2 C_t} t = \text{constant} + \left(\frac{1}{3}\Theta^3 - \frac{1}{2}\Theta^2\right) \text{ with } \Theta(0) = 1 \tag{134}$$

So:

$$\frac{DC_{\text{sat}}}{R^2 C_t} t = \frac{1}{6} - \frac{1}{2}\Theta^2 + \frac{1}{3}\Theta^3 \tag{135}$$

When the release is complete $\Theta = 0$, so the total release time is:

$$t_D = \frac{1}{6} \frac{R^2 \boldsymbol{C}_{\text{tot}}}{D\boldsymbol{C}_{\text{sat}}} \tag{136}$$

Using this we can also write the result as:

$$\frac{t}{t_D} = 1 - 3\Theta^2 + 2\Theta^3 \tag{137}$$

This is where we started. The solution for the initial drug release is obtained by expanding the expressions for the time ratio and the fraction released into a series around $\Theta = 1$ and using only the lowest terms of the expansion.

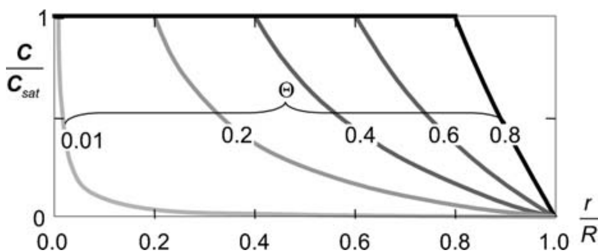

FIGURE 32 Concentrations in a leaching sphere.

The Eroding Sphere

There are several mechanisms which cause a matrix to erode or dissolve with a constant rate. All of these give the same release pattern of the drug.

We have already seen how a large solid sphere dissolves. Here the dissolution velocity is:

$$u = k\frac{C_{\text{sat}}}{\rho_P} \tag{138}$$

If the dissolution of the polymer matrix Π is limiting we get:

$$u = k\frac{C_{\Pi\text{sat}}}{C_{\Pi}} \tag{139}$$

where $C_{\Pi\,\text{sat}}$ is the saturation concentration of the polymer in the liquid, and C_{Π} the concentration of the solid polymer.

A fairly common situation with a swelling polymer matrix is shown in Figure 33. Here the core is dry and glassy, and the drug is immobilized. Water penetrates into the polymer, causing it to swell. As a result the drug is released and it diffuses outward through the gel layer. The gel layer is usually very weak, and it erodes when the polymer concentration will get below a certain value (depending on its mechanical properties). Since both water penetration and dilution of the polymer are time dependent, erosion starts when the thickness of the gelled layer exceeds a certain value Δz. Drug release is usually determined by the rate at which water diffuses into the polymer. This rate is a property of the polymer/solvent system.

In all cases the radius of the tablet decreases linearly in time:

$$R = R_0 - ut \text{ or } \frac{R}{R_0} = 1 - \frac{t}{t_T} \tag{140}$$

where t_T is the dissolution time of the tablet:

$$t_T = \frac{R_0}{u} \tag{141}$$

The proportion of the mass of tablet left becomes:

$$\frac{m}{m_0} = \frac{R^3}{{R_0}^3} = \left(1 - \frac{t}{t_T}\right)^3 \tag{142}$$

and the fraction released is:

$$1 - \frac{m}{m_0} = 1 - \left(1 - \frac{t}{t_T}\right)^3 \tag{143}$$

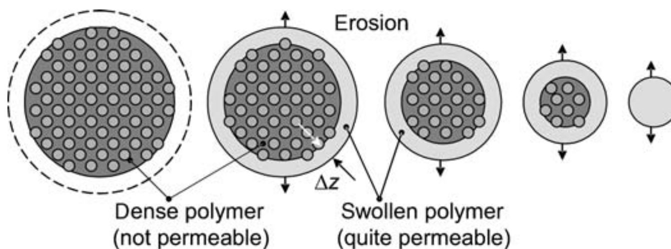

FIGURE 33 Erosion of a polymer matrix.

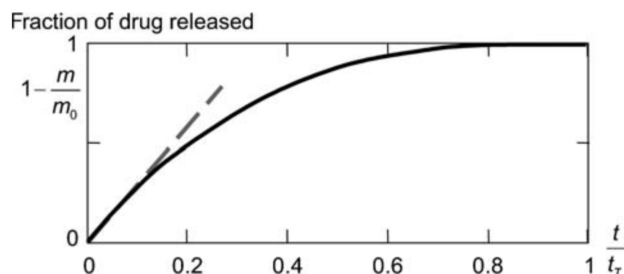

FIGURE 34 Release from an eroding matrix.

The release is linear initially, with about one half of the content released in a quarter of the dissolution time (Fig. 34).

Discussion

The liberal use of mathematics in the above models might give one the impression that "mass transfer from oral dosage forms" is an exact science. However, that is too optimistic. The models we have looked at are only gross model representations of reality. We have already discussed that our theories only apply to dilute solutions and that tablets are seldom spherical. There are two other assumptions in our models which are perhaps more seriously in error.

We have tacitly assumed that our tablets are homogeneous (having the same composition and structure everywhere) and that they are isotropic (with no preferred direction in the structure). Neither of these assumptions is valid. Tablets are formed with great forces and speeds, and the upper and lower faces of the tablet are denser than the middle part. As a result tablets often dissolve or leach more rapidly from the sides. There are also huge stresses in a tablet, and these can show up in cracking during the dissolution process. Our models do not take this into account.

SUMMARY

We have seen that the release of drugs from tablets and the subsequent absorption into the systemic circulation is largely governed by two sets of mechanisms:

- how the tablet releases the drug (the drug dissolution kinetics) and
- how the body deals with the drug (pharmacokinetics)

Solid particles with a low solubility dissolve slowly, especially when they are large. Most drugs are not very soluble, so they have to be applied as fine particles. However, these are not easily administered, so the particles are embedded in a tablet that releases the drug with a predetermined profile. This can be by disintegration of the tablet (which gives a burst release) or by using a slow release mechanism.

Disintegration can be immediate (in the mouth) or retarded by a coating that remains intact until the tablet reaches the point where the drug is to be released (e.g., the duodenum).

We have seen several kinds of slow release tablets:

1. those with a non-dissolving coating;
2. those with a porous matrix that is leached;
3. those with a swelling and eroding polymer matrix.

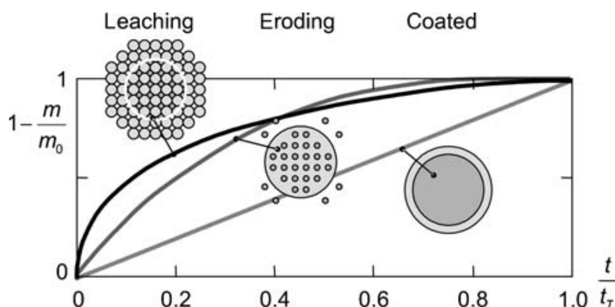

FIGURE 35 Release patterns from a leaching, eroding, and coated tablet.

In all three, one can define a time t_D at which all drug has been released. This time depends strongly on the physico–chemical parameters of the tablet: the solubilities of the ingredients, and the size and thicknesses of the parts. The release patterns of the three different types are shown in Figure 35.

Tablets or granules with a non-dissolving coating can give a linear release in time (which is often thought to be the best release characteristic). Those with a swelling and eroding matrix usually show a small burst followed by a linear release, but this tails off. Porous tablets that are leached give a large burst, with a release going up roughly with the square root of time.

Slow release tablets have to retard by times between one hour and half a day. Shorter times have little effect, as the retardation by the body then dominates; after half a day the tablet will be in the colon and there will be little further absorption of the drug.

Models of drug release and absorption are useful to understand the effects of the design parameters of tablets on drug absorption. However, they are models, not the real thing.

LIST OF SYMBOLS

Symbols used in one location only are not included.

Regular Symbols

A	area	m^2
A	area per volume	$m^2\ m^{-3}$
B	constant	[–]
C	molar concentration	mol m^{-3}
C	mass concentration	kg m^{-3}
C	volume concentration (fraction)	$m^3\ m^{-3}$
D	diameter	m
D	diffusivity	$m^2\ s^{-1}$
F	Faraday constant	C mol^{-1}
F	driving force	N mol^{-1}
K	equilibrium, partition coefficient	variable
K	mass transfer coefficient	m s^{-1}
L	length	
M	molar mass	kg mol^{-1}
M	mass	kg
m	mass flow rate	kg s^{-1}

N	mass flux	kg m^{-2} s^{-1}
N	molar flux	mol m^{-2} s^{-1}
$\boldsymbol{N}$	volume flux	m^3 m^{-2} s^{-1}
P	pressure	Pa
$\boldsymbol{R}$	gas constant	J mol^{-1} K^{-1}
R	radius	m
R	radial distance	m
R^*	core radius	m
T	absolute temperature	K
T	time	s
U	velocity	m s^{-1}
V	volume	m^3
$\boldsymbol{Z}$	charge number	[–]
Z	distance	m

Greek Symbols

Θ	ratio R^*/R	[–]
Δ	difference ("end"–"start")	
α	activity	mol m^{-3}
ε	void fraction	[–]
ϕ	electrical potential	V
γ	activity coefficient	[–]
η	viscosity	Pa s
μ	(chemical) potential	J mol^{-1}
θ	contact angle	rad
ρ	density	kg m^{-3}
σ	interface energy	J m^{-2}
τ	time constant	s
υ	molar volume	m^3 mol^{-1}

Subscripts

0	initial or reference condition
C	compartment
C	percolation threshold
D	drug (solute)
F	free
G	glass transition
I	species i
I	intestine
L	liquid
max	maximum
O	pore
P	particle
S	solid
sat	saturation
T	tablet
Tot	total
V	vapor
W	water (solvent)
Π	polymer
α	starting position
β	end position

Other

$\prime, \prime\prime, \prime\prime\prime$	different phases

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2

Approaches for Improving Bioavailability of Poorly Soluble Drugs

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INTRODUCTION

Poorly water-soluble drug candidates often emerge from contemporary discovery programs and present formulation scientists with considerable technical challenges. With the advent of combinatorial chemistry and high throughput screening, the number of poorly water-soluble compounds has dramatically increased. The absorption and bioavailability of such compounds when presented in the crystalline state to the gastrointestinal tract is poor and variable. Bioavailability is clinically important because pharmacologic and toxic effects are proportional to both dose and bioavailability. When bioavailability is very low (e.g., $<20\%$), inter- and intra-subject variability in bioavailability are magnified and incomplete oral bioavailability can become a great concern. The consequence of low and variable bioavailability is substantially difficulty in predicting and controlling the pharmacologic and toxic effects of a given dose. This is especially true when drugs have steep dose-effect curves or narrow safety margins. The poor solubility or pH-dependent solubility also generally causes significant food effects, which also limits the flexibility that a patient may like to have while taking a medicine. Cost may be another driving force for some compounds. If bioavailability averages 20%, for example, then 80% of a dose is wasted. Maximizing bioavailability contributes to increasing cost-effectiveness (1).

The relative importance of poor solubility and permeability towards poor oral absorption depends on the research approach used for lead generation. As Lipinski (2) pointed out, a "rational drug design" approach leads to time-dependent higher molecular weight, higher H-bonding properties, unchanged lipophilicity, and therefore, poorer permeability. A high throughput screening (HTS)-based approach leads to high molecular weight, unchanged H-bonding properties, higher lipophilicity, and, hence, poorer aqueous solubility. Despite great efforts in rational drug design, pharmaceutical scientists are often confronted with resolving bioavailability of poorly soluble compounds.

Considering the principle of drug absorption by a passive transport mechanism

$$J_w = P_w \times C_w,$$

where J_w is the absorption rate, P_w the Intestinal wall permeability, and C_w is the drug concentration at intestinal wall. Therefore, maximum absorption rate is $J_w(\max) = P_w \times \text{solubility}$.

Permeability being constant, the solubility as well as the rate of solubility (dissolution rate) is the rate-limiting step for the absorption. The dissolution rate limited absorption corresponds with the increase in dose. The concept of dose number was introduced to further understand the dose limitation in the rate and extent of absorption.

The dose number (Do) is defined as:

$$\text{Do} = \text{Dose}/(250 \times \text{solubility})$$

(*Note*: 250 mL is considered as volume in the stomach)

Therefore, a high dose number which is generally associated with a high dose for a poorly soluble drug results in poor, incomplete, and variable absorption. Generally, a dose number <10 is desired for higher absorption and bioavailability (3,4).

Before discussing the approaches in overcoming bioavailability of poorly soluble drugs, understanding of Biopharmaceutics Classification Systems (BCS) as well as in vitro–in vivo correlation for predicting or understanding the use of drug in the gut is important and will be discussed briefly.

The collaboration of Food and Drug Administration (FDA), academia, and industry has produced the BCS classification of drugs which is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability. When combined with the in vitro dissolution characteristics of the drug product, the BCS takes into account three major factors: solubility, intestinal permeability, and dissolution rate, all of which govern the rate and extent of oral drug absorption from immediate release (IR) solid oral-dosage forms (5).

The solubility classification of a drug in the BCS is based on the highest dose strength in an IR product. A drug substance is considered highly soluble when the highest strength is soluble in 250 mL or less of aqueous media over the pH range of 1.0–7.5; or else, the drug substance is considered poorly soluble. The estimation of the volume of 250 mL is derived from typical bioequivalence study protocols that prescribe the administration of a drug product to fasting human volunteers with a glass (about 8 ounces) of water.

The permeability classification is based directly on the extent of intestinal absorption of a drug substance in humans or indirectly on the measurement of the rate of mass transfer across human intestinal membrane. Animal or in vitro models capable of predicting the extent of intestinal absorption in humans may be used as alternatives, e.g., in situ rat perfusion models and in vitro epithelial cell culture models. A drug substance is considered highly permeable when the extent of intestinal absorption is determined to be 90% or higher. Otherwise, the drug substance is considered to be poorly permeable.

An IR drug product is characterized as a rapid dissolution product when not < 85% of the labeled amount of the drug substance dissolves within 30 minutes using USP Apparatus I at 100 rpm or USP Apparatus II at 50 rpm in a volume of 900 mL or less of each of the following media: (*i*) acidic media, such as 0.1 N HCI or USP-simulated gastric fluid without enzymes; (*ii*) a pH 4.5 buffer; and (*iii*) a pH 6.8 buffer or USP-simulated intestinal fluid without enzymes. Otherwise, the drug product is considered to be a slow dissolution product.

For immediate release dosage forms, the release rate relative to the transit rate and the permeability profile (including possible exotransport by P-glycoproteins) of the small intestine to the drug are crucial to both the rate and the extent of absorption. The BCS (3,4) classifies drugs into four categories (Table 1) depending on their solubility. Class I drugs are those which should have more than 90% absorption rate. Class II drugs are those with solubilities too low to be consistent with the complete absorption, even though

TABLE 1 Biopharmaceutics Classification System

Class	Solubility	Permeability
I	High	High
II	Low	High
III	High	Low
IV	Low	Low

they are highly membrane permeable. Class III is the mirror image of Class II. These drugs have good solubility but were not capable of penetrating the gut wall quickly enough for the absorption to be complete. Class IV compounds have neither sufficient solubility nor permeability for absorption to be complete. Although they certainly do not possess optimal properties, some drugs in this category may still be absorbed well enough to permit oral administration.

Since the introduction of the BCS, its validity and applicability has been the subject of extensive research and discussion (6,7). These efforts have resulted in an improved SUPAC-IR guidance (8), a dissolution guidance (9), and a FDA guidance on waiver or in vitro bioequivalence studies for BCS Class I drugs in IR solid oral-dosage forms (10).

The current BCS guidance issued by the FDA allows for biowaivers based on conservative criteria. Possible new criteria and class boundaries were proposed for additional biowaivers based on the underlying physiology of the gastrointestinal tract. The proposed changes of solubility and permeability in new class boundaries were as follows:

1. Narrowing of the required solubility pH range from 1.0–7.5 to 1.0–6.8.
2. Reduction of the high permeability requirement from 90% to 85%.

Typically dissolution rate limited drugs are BCS II and IV compounds. To predict the in vivo performance of a drug after administration, it is essential that the limiting factor to absorption can be modeled in vitro. In case of BCS class II drugs, dissolution is rate limiting to absorption, so the use of biorelevant dissolution tests can be used to predict differences in bioavailability among different formulations and dosing conditions. To achieve a priori correlation, the composition, volume, and hydrodynamics of the contents in the gastrointestinal lumen following administration of the dosage form must be accurately simulated. Dissolution media have been chosen/developed to model composition of the gastric and intestinal contents before and after the food. These are Simulated Gastric Fluid (SGF), milk, Fasted Simulated Intestinal Fluid (FaSSIF) and Fed Simulated Intestinal Fluid (FeSSIF), which models fasted and fed-state conditions in the stomach and small intestine, respectively (Table 2). Using these media, excellent correlations have been obtained with the following poorly soluble drugs: danazol, ketoconazole, atovaquone, and troglitazone. In all cases, effects of fed versus fasted state can be predicted from dissolution data, and where several formulations were available for testing, dissolution tests could also be used to determine the best in vivo performance (11).

Opportunities and Challenges

There is general consensus in the pharmaceutical industry that poorly water-soluble drug candidates are becoming more prevalent (2). If a drug candidate has reasonable membrane permeability, then often the rate-limiting process of absorption is the drug

TABLE 2 Composition of FaSSIF Medium (Simulating Fasting State) and FeSSIF Medium (Simulating Fed State) in Small Intestine

Ingredients	FaSSIF	FeSSIF
KH_2PO4	3.9 g	–
NaOH	Qs. pH 6.5	Qs. pH 5
Na taurocholate	3 mM	15 mM
Lecithin	0.75 mM	3.75 mM
KCI	7.7 g	15.2 g
Acetic acid	–	8.65 g
Distilled water	Qs. 1 L	Qs. 1 L

Abbreviations: FaSSIF, fasted simulated intestinal fluid; FeSSIF, fed simulated intestinal fluid.

dissolution step. Formulation plays a major role in determining the rate and extent of absorption of such drugs from the gastrointestinal tract. When water solubility is 1 μg/mL, which is often the case for contemporary drug candidates, the bioavailability from conventional tablet formulations may be unacceptable. However, there is a number of formulation strategies that could be used to improve the bioavailability of class II and class IV drugs, either by increasing the dissolution rate or by presenting the drug in solution and maintaining the drug in solution in the intestinal lumen.

The choice of formulation is often critical for establishing a successful product for oral administration of a class II drug. If bioavailability of the drug is recognized to be formulation dependent at an early stage, it is desirable to have a strategy for maximizing absorption as soon as possible. If poor formulations were used in early animal efficacy studies, the prediction of likely human dose can be overestimated, possibly compromising future development of the candidate drug. Use of a poor formulation in early toxicity studies can lead to an underestimation of the toxicity due to limited exposure resulting from low bioavailability.

Various successful approaches to formulate poorly water-soluble crystalline drugs into oral dosage forms include particle size reduction, formation of salts, complexes or cocrystals, amorphous formulations, lipid-based formulations, and prodrug approaches. The dissolution rate of a crystalline drug from a solid dosage form can be increased by reducing the particle size and increasing the surface area for dissolution. The bioavailability of a weak acid or weak base can be improved by the selection of an appropriate salt which is readily more soluble in the physiological fluids. Cocrystal approach uses solvates, hydrates' or eutectics to improve the solubility especially for non-ionizable drugs. Careful selection of ligand/guest molecules can increase solubility and/or permeability. Amorphous formulations include "solid dispersion and solid solutions" which can be formed using a variety of technologies including solvent-controlled precipitation, spray drying, hot melt extrusion, and fluid bed technology etc. Amorphous formulations may include polymers providing surface activity during dispersion and stabilization. Inclusion of polymers may be useful to improve the wettability of the drug, maintain the drug in a supersatuaration solution form in the physiological fluids and impart shelf-life stability of amorphous drugs. The long-term stability of the amorphous formulation is a critical issue in the design of such formulations. If the drug is not genuinely in solution, which is normally the case, then it must be immobilized in a metastable amorphous state long enough to give satisfactory shelf-life. The recent adoption of melt-extrusion technology is an interesting development which makes continuous production possible

without the need of organic solvents (7,11). Isotropic lipid solutions include simple solutions, self-emulsifying drug delivery systems (SEDDS), and self-microemulsifying drug delivery system (SMEDDS). Lipid formulations have shown to significantly improve oral absorption of some highly lipophilic drugs. Prodrugs are also a common approach for improving the bioavailability of poorly soluble drugs.

The above-mentioned approaches will be discussed in detail in the following sections.

PHYSICAL MODIFICATIONS–PARTICLE SIZE REDUCTION

Theoretical Aspects

The bioavailability of poorly water-soluble drugs are always limited by their low solubility in gastrointestinal fluid and low dissolution rate as the drug needs to be dissolved prior to being absorbed. Particle size reduction is one of the effective approach widely used in the pharmaceutical industry to enhance the dissolution rate mainly by increasing the total surface area, therefore, facilitating drug absorption. During the dissolution process, a solid dosage form, i.e., a tablet or a capsule will undergo the process of wetting, disintegration, deagglomeration, dislodgement, and dissolution. The size of the contact surface is critical for all the reactions and mass transfer. When the primary particle size of the drug is restored, the relationship of the rate of dissolution of a solid particle to the properties of the solid and the dissolution medium can be described by the modified Noyes–Whitney equation (12,13)

$$\frac{\mathrm{d}W}{\mathrm{d}t} = \frac{DA(C_\mathrm{s} - C)}{L},$$

where $\mathrm{d}W/\mathrm{d}t$ is the rate of dissolution., A the surface area of the solid, C the concentration of the solid in the bulk dissolution medium, C_s the concentration of the solid in the diffusion layer surrounding the solid. D the diffusion coefficient, And L is the diffusion layer thickness. Particle size reduction can increase the dissolution rate of a drug based on several aspects as follows.

Increased Surface Area

Surface area is a very important factor in the dissolution process, particularly for solid dosage forms, such as tablets and capsules. Particle size reduction results in increased effective surface area, which leads to an enhanced dissolution rate. For example, if a 1-cm long cube is divided into 1000 small cubes with a length of 0.1 cm, the total surface area will be increased to 60 cm^2 from 6 cm^2. A 10-fold particle size decrease causes 10 times the total surface area increase, when the particle shape remains the same. Most of the time, the particle size is reduced by mechanical means, which results in a ruptured surface, which will further increase the effective surface area. Although in general, the total surface area is inversely proportional to the particle size, the exact surface area still needs to be determined. The most widely used experimental method is the BET surface area method (BET stands for Brunauer, Emmett, and Teller, the three scientists who optimized the theory for measuring surface area), which is based on adsorption of a monolayer of inert gases to the solid materials at reduced temperatures. And the sorption isotherms obtained are interpreted by using equations developed by Brunauer et al. (14). Other techniques include adsorption from solution, calorimetry, nuclear magnetic resonance, and permeametry (15).

Decreased Diffusion Layer

Further, when particle size is reduced to below 5 μm, the diffusion layer is decreased with increasing curvature of the particles as represented by the Prandtl equation (16).

$$h_H = k(L^{1/2}/V^{1/2}),$$

where L is the length of the surface in the direction of flow, k is a constant and V is the relative velocity of the flowing liquid against the flat surface. Bisrat and Nyström (17) described that a decrease in particle size leads to a decrease both in L and V. And the net effect is a thinner diffusion layer around the particle. This results in a faster transport of the dissolved molecule to the bulk solution and enhanced dissolution rate.

Increased Saturation Solubility

Muller et al. (18) described that when a particle size is reduced to < 1 μm, an increase of the saturation solubility occurs. This can be explained by the Kelvin and the Ostwald–Freundlich equation. The Kelvin equation relates the vapor pressure to a curved surface of a liquid droplet in gas. It can also be applied to the dissolution process when the vapor pressure is replaced by dissolution pressure (19).

$$\ln\frac{P_r}{P_\infty} = \frac{2\gamma M_r}{rRT\rho},$$

where P_r is the dissolution pressure of a particle with the radius r. P_∞ the dissolution pressure of an infinitely large particle, γ the surface tension, R the gas constant, T the absolute temperature, M_r the molecular weight, and ρ is the density of the particle. According to this equation, a decreased particle radius leads to an increased dissolution pressure.

The role of particle morphology and curvature is also clearly shown from the Ostwald–Freundlich equation, which directly predicts that the saturation solubility of the particles increases with decreasing particle size.

$$\frac{RT\rho}{M}\ln\frac{S_1}{S_2} = 2\sigma\left(\frac{1}{r_1} - \frac{1}{r_2}\right),$$

where R is the gas constant, T the absolute temperature, M the molecular weight of the solid in solution, σ the interfacial tension between the solid and liquid, ρ the density of the solid, and S_1 and S_2 are the solubilities of the particle with radius r_1 and r_2, respectively.

Less Sensitivity to Luminar Hydrodynamics

When particle size is reduced to a few microns, studies showed that poorly water-soluble drugs are less sensitive to lumiar hydrodynamics (21). It has been observed that a further reduction of the particle size to nanosize eliminates the positive food effects (22).

During the particle size reduction process, the morphology and shape of the particle can also be altered besides particle size. These factors will also affect the dissolution behavior of drug particles, but in an uncontrollable way. Careful investigation is needed particularly when imperfection, such as localized street, structure defects, and dislocations are present during the particle size reduction process. If amorphous phase is formed, the saturation solubility can also be increased, the readers can refer to a later part of this chapter on amorphous approach.

Particle Size Reduction Technologies

Mechanical Comminution

Traditionally, the particle size reduction is accomplished by mechanical means, such as cutting, shearing, compressing, impacting, and attrition. Various types of equipment are designed based on the above mechanisms, for example, fluid energy mill, ball mill, hammer mill, cutting mill, and compression mill (23).

To reduce the particle size to below 10 μm, fluid energy mill, media mill or high pressure homogenizers were commonly used for dry or wet milling. The two wet milling (media and homogenizing) processes were also known to be able to produce nanosized particles.

Fluid Energy Mill

Dry milling in a fluid energy mill is the most frequently utilized micronization technique in the pharmaceutical industry. In the fluid energy mill, the drug particles are suspended and conveyed by high-velocity air, and collide with each other or with the surface of the grinding chamber. Particle size reduction is caused by the high-speed impact and abrasion.

However, the agglomeration and the aggregation of the milled fine particles are often encountered which reduces the effective surface area. The surface of the milled drug particle and particle aggregates tend to adsorb air and become difficult to wet in aqueous medium. Many approaches have been attempted to stabilize the ultra fine particles. A successful prevention of agglomeration of micronized drug by utilizing a hydrophilic carrier was described by Shah et al. (24). Nevertheless, the fluid energy mills are still a well developed and a practical technology.

Media Mill

Media milling is a process of dispersing a drug substance in a liquid dispersion medium (usually aqueous system) and applying mechanical force in the presence of grinding media to reduce the particle size. This is a high-energy process and can be used with media of high, medium, and low density. The milling media can be steel, zirconium salts, glass, or polymeric beads. It has been widely used to produce micron-size suspensions of discovery compounds.

To further increase the dissolution rate to obtain a higher bioavailability for poorly soluble drugs, the nanosized particles are targeted and successfully obtained by using one type of media mill–pearl/ball mill. The technology was developed by the company of Nanosystems (currently owned by Elan) with a trade name of NanoCrystal®. The media-milling process is illustrated in Figure 1.

Drug, water, milling media, and stabilizer are filled and recirculated in the milling chamber that contains a rotating impeller. The rotating impeller agitates the media, and the impaction between the milling media and the drug provides the energy to break the drug into nanosized particles (25). The process can be in either batch or re-circulation mode, and can be performed under controlled temperature. Due to low-energy input, crystallinity of the drug is usually maintained during the process. To maintain the physical stability, the nanocrystal suspension can be spray dried or deposited onto substrates to prevent agglomeration. The Products on the market made utilizing this technology include Rapamune® (Wyeth), Emend® (Merck), TriCor® (Abbott), and Megace® ES (PAR). The key to this approach is that the dried powder must be able to

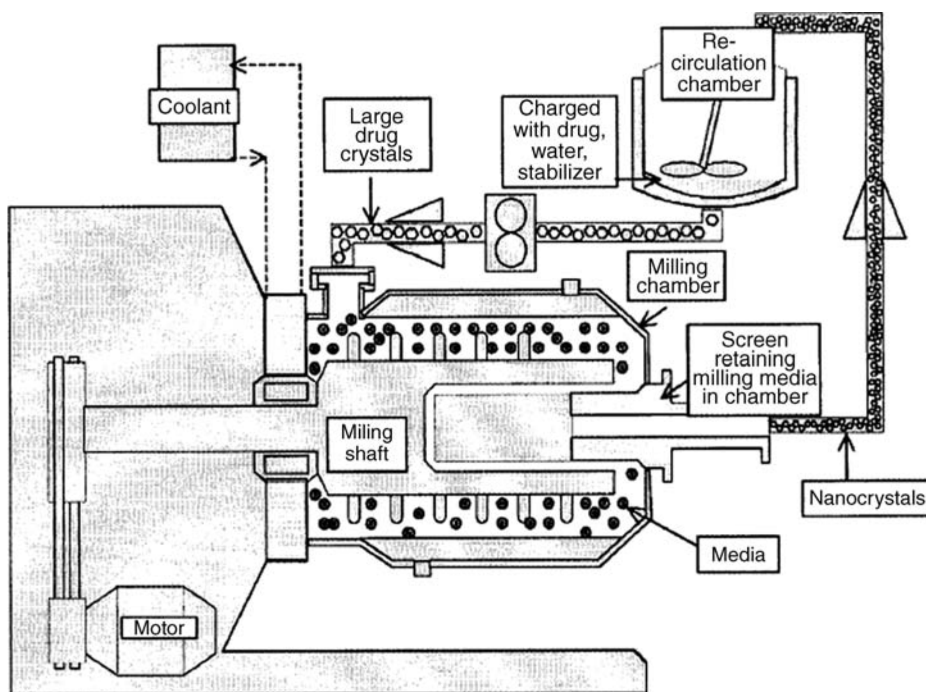

FIGURE 1 A schematic representation of media-milling process.

re-disperse into nanoparticulate dispersion when placed into water or physiological fluid. A significant increase in the oral bioavailability was reported by applying this technology (26). In addition, the elimination of the effect of food is another advantage of this method (27). Recently, this technique was successfully used for Fenofibrate tablets by Abbott to eliminate the effect of food, which helped to extend the life cycle of the product. A general problem with this process is the potential contamination caused by erosion of the milling media, such as white suspension may turn to grayish with stainless steel ball as media. Careful selection of the media can reduce or eliminate the contamination.

High-Pressure Homogenization

There are two types of high-pressure homogenizers, microfluidizers and piston-gap homogenizers. The microfluidizer is a jet-stream homogenizer. The drug suspension is accelerated and rapidly passes either a Z or Y-type chamber. The shear force and particle collision result from changing the stream direction or collision of two separated streams. The limitation of this technology is the high number of passes needed to obtain desirable particle size and the large fraction of micron-sized particles.

The piston-gap homogenizers can work with both aqueous media and non-aqueous media. The cavitation force is considered the main effect of producing nanoparticles in a piston-gap homogenizer. The drug suspension passes through a very narrow gap with extremely high velocity. According to the law by Bernoulli, in a closed system, the volume of the flow of the liquid is constant per cross-section (28). That means when the liquid passes through a narrow gap, the dynamic pressure is dramatically increased with a simultaneous drop in the static pressure. When the static pressure is below the vapor pressure of the liquid at room temperature, the liquid starts boiling; meanwhile the gas

bubbles are formed and implode after leaving the gap. The cavitation forces causes the particles breakage of praticles. The size of the nanoparticles depends on the power density of the homogenizer, the number of cycles and the operating temperature. This technology was first developed under the trademark of DissoCubes® (SkyePharma). The changes in crystallinity have been reported (29).

Particle Engineering

Micron- or nanometer-sized particles can also be produced by novel particle engineering processes via various mechanisms. Micron-sized drug particles can also be achieved by spray drying a drug solution. The particles formed are spherical and homogeneous, but in an amorphous phase in most cases (30), refer to Modifications of Crystals section of this chapter for more details. Due to low-water solubility, organic solvent is needed for poorly water-soluble drugs. Spray drying with organic solvents is not preferable due to the high cost of explosion-proof equipment and recovery of the organic solvent.

Supercritical fluid technologies: The use of supercritical fluid technologies (SCF) to produce micron-sized particles was reported by Loth and Hemgesberg two decades ago (31). Among all the gases, carbon dioxide is used the most frequently as the supercritical gas phase because of its chemical inertness and low supercritical temperature (31.1°C). Two techniques are described to produce nanosized particles based on different principles.

Rapid expansion of the SCF solutions: If a compound is soluble in supercritical carbon dioxide, fine particles can be precipitated by rapid expansion of the SCF solutions (RESS). This technology especially provides advantages for heat sensitive or waxy compounds. The particle size and the morphology were determined by the dimension of the expansion chamber and the expansion time (32,33). In milliseconds, micron- or nanosized particles with a narrow distribution range can be produced.

Precipitation with a compressed antisolvent: If a compound does not dissolve in supercritical carbon dioxide, it can be recrystallized by applying compressed supercritical carbon dioxide as an antisolvent. First, the drug needs to be dissolved in a solvent that is miscible with the supercritical carbon dioxide, and then the drug solution is sprayed into the compressed antisolvent to precipitate out. This technology is called Precipitation with a Compressed Antisolvent (PCA) (34).

In situ particle size control by precipitation: The first preparation of nanosized particles was by the precipitation method described by List and Sucker in the 1980s (35). Even though there are different techniques to perform the precipitation, the principle of this type of method is the same: dissolve the drug in one solvent and let the drug solution confront an antisolvent, in which the drug has no or much lower solubility. The precipitation can be generated by an acid–base reaction where there is no organic solvent present. The solubility difference is induced by a pH change. As the drug needs to be dissolved in aqueous solvent first, this technology cannot by utilized for poorly water-soluble drugs.

Precipitation in discrete emulsion droplets: The precipitation in discrete emulsion droplets is another way to produce drug nanoparticles. This method is used for β-carotene (36). The drug was dissolved in a lipophilic organic solvent or oil, and then emulsified in water with a stabilizer. After the oil-in-water emulsion with a droplet size in the nanosize range was formed, the solvent was evaporated by drying or distillation; nanoparticles were formed from the nanosized droplets.

In situ micronization: This technique has been reported recently. Micron-sized particles are produced by drug precipitation from a solvent change process in the

presence of hydrophilic polymers followed by spray-drying. The polymer stabilizer should possess affinity to the hydrophobic crystal surface as the polymer needs to be adsorbed onto the newly formed surface of the precipitated drug to prevent crystal growth. The in situ micronized products showed increased dissolution rate because of its reduced particle size and modified surface properties. The adsorbed polymer increased the wettability of the particle. In addition, naturally grown particles in this process showed uniform size and shape (37).

Evaporative precipitation into aqueous solution: Another novel nanoparticle production technology, evaporative precipitation into aqueous solution (EPAS) was developed and patented by the University of Texas at Austin and licensed to the Dow Chemical Company (38). During the process, the drug is dissolved in a low-boiling point liquid organic solvent, which is heated under the pressure to above its boiling point. Then the solution is sprayed into a heated aqueous phase. Particles nucleate and grow by rapid phase separation. The resulting aqueous suspension is either spray dried or freeze dried. Stabilizing agents are used to optimize particle formation and physical stability. Amorphous material is obtained by this process. An increased dissolution rate is attributed to increased surface area, increased saturation solubility, reduced crystallinity, and increased wettability by the coated stabilizers.

Spray-freezing into liquid: Spray-freezing into liquid (SFL) process is also patented by the University of Texas at Austin and commercialized by the Dow Chemical Company. It utilizes the atomization of feed drug solution, emulsion or suspension containing drug, and/or surfactants directly into a compressed liquid to form nanostructured particles (36). The frozen particles are then lyophilized to produce dry and free-flowing micronized powders. The intense atomization and ultra-rapid freezing rate led to amorphous nanostructured particles with high surface area and significantly enhanced dissolution rate.

The in situ particle size control technology is promising, but still not widely used because of some limitations: the use of solvents creates additional costs; a prerequisite for precipitation is that the drug is at least soluble in one solvent, and this solvent needs to be miscible with a non-solvent. For poorly water-soluble drugs, finding the right solvent is not always easy.

Stabilizers and Techniques of Stabilizing Fine Particles against Agglomeration and Aggregation

It is well known that ultra fine particles tend to agglomerate and aggregate. Their uncontrolled surface properties and possible electrostatic charge are liable to problems. Adsorption of air in the dry state or adsorption of other molecules and ions from solution is another issue that will have profound effect on dissolution behavior. Utilizing stabilizers to prevent these problems is a common approach. Stabilizers can be categorized into two types, steric stabilizers or surfactants. Steric stabilizers are mainly cellulose polymers; surfactants can either be ionic or non-ionic.

Stabilizers are more critical to nanoparticle production. Particle size reduction to the nanometer dimension generates high interfacial surface energy, and is inherently unstable. Stabilizers play a multifunctional role in nanoparticle dispersions. Not only do they facilitate particle preparation and stabilization during the process, they also determine stability in physiological fluid. Stabilizers usually are adsorbed onto the surface of nanoparticles to produce steric or electrostatic stabilization. The choice of stabilizers depends not only on the affinity of the stabilizer

to the particles generated, but also on the physical principles and the route of administration. In general, steric stabilizers are preferred, as they are less susceptible to electrolytes in vivo. In most cases, a combination of steric polymers and ionic surfactants are used. In industry, a proper stabilizer is usually chosen by a trial-and-error-based approach. Other techniques were also utilized to prevent fine particles from agglomerating or aggregating. Dispersing the particles in a hydrophilic carrier to form an ordered mixture was mentioned earlier in this chapter. Traditionally, vigorous convective and shear mixing can also deagglomerate; mixing coarse, equally sized particles of excipient with a cohesive fine powder can reduce the cohesiveness of the fine powder. Ultrasonic forces can be utilized to disperse agglomerates in a liquid.

Assessment of Technology and Future Trends

The particle size of a drug substance is important to the manufacturing process and the in vitro and in vivo performance of the drug product. The methods for reducing particle sizes can be described by two main mechanisms as illustrated in Figure 2.

By the conventional top-down method, the new particle shape, surface morphology produced by mechanical means are not well controlled and pose problems. By the non-conventional bottom-up method, stabilizers can be introduced during the particle-forming process, and the physical properties of the particles were modified in situ.

Nanotechnology is an exciting field of applied science and technology. It encompasses a broad range of disciplines, including colloidal science, chemistry, applied physics, biology, and other scientific fields. On a nanoscale, some existing science can be recasted into a new form. Promising nanomaterials, such as carbon nanotubes, exhibits extraordinary strength and unique novel properties. Materials made in the nanoscale can often have chemical or physical properties, such as magnetic properties, electrical or optical activity, heat flow, friction and mechanical performance, and chemical and biological activities, which were different from those of their larger counterparts (39). Although as a new entity in toxicological and environmental prospects, nanomaterial has great potential for the use in a vast array of products.

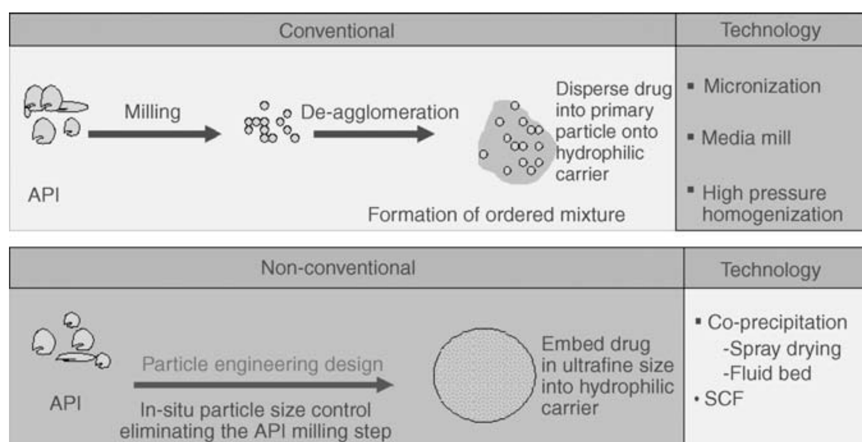

FIGURE 2 Main mechanisms of particle size reduction.

SALT FORMATION

Salt formation has been extensively used to improve the solubility of weak acids and bases. The improvement in the solubility of a compound is based on entropy changes associated with dissolution caused by configurational and thermal disorder. Selection of a suitable salt requires a thorough investigation of all the relevant solid-state properties for the various possible candidates. While salt formation is one of the most widely used approaches to improve the solubility of poorly soluble drugs, it presents significant challenges with regards to safety, stability, hygroscopicity, and polymorphism. In addition to derisking the safety aspects, several technical challenges pertaining to the physical, chemical and mechanical stability of the salt form need to be evaluated in order to manufacture stable and reproducible dosage forms. As changes in the solubility and dissolution rate can have significant effects on the pharmacokinetic (PK) profile of the therapeutically active compound, it is imperative that a suitable salt is selected early in development in order to minimize bridging preclinical and clinical studies that can significantly add to the cost and time of development. Recent advances in the analytical methodologies and laboratory automation allow the screening of several salt candidates in a very short time frame. In most cases, the screening is also extended to evaluate potential polymorphs to help select the best suitable candidate. Despite the technological advancements, it is extremely important to understand the basic mechanism of solubilization, and the impact of counter-ions and ionic strength on the solubility as well as stability of the salt form selected for the development to abate potential risks.

Theoretical Considerations

An important prerequisite for the salt formation approach is the presence of an ionizable group in the drug candidate. Most drug substances with ionizable groups are generally weak acids or weak bases with a p*K*a in the range of 4.5–9 (40). The solubility of ionizable compounds as a function of pH is determined by means of a pH-solubility profile that provides an estimate of the p*K*a. Mathematically this is expressed as follows and its pictorial view is shown in Figures 3 and 4.

For a monobasic compound at pH > p*K*a

$$S_T = [B]_s * \left(1 + \frac{[H_3O^+]}{Ka}\right)$$

and at pH < p*K*a

$$S_T = [BH^+]_s * \left(1 + \frac{Ka}{[H_3O^+]}\right),$$

where S_T is the total solubility and $[B]_s$ and $[BH^+]_s$ are the concentrations of free and protonated species of the base, respectively.

Similarly for a monoprotic acid at pH < p*K*a

$$S_T = [AH]_s * \left(\frac{1 + [H_3O^+]}{Ka}\right)$$

and at pH > p*K*a

$$S_T = [A^-]_s * \left(\frac{1 + [H_3O^+]}{Ka}\right)$$

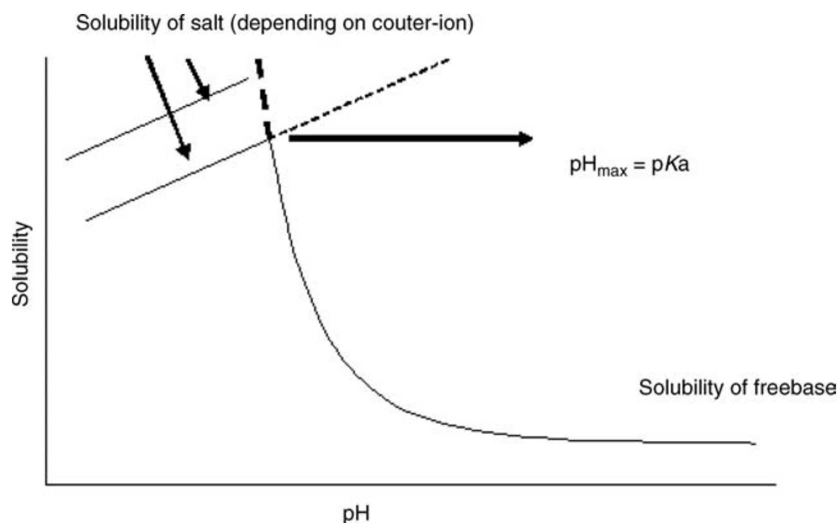

FIGURE 3 pH-solubility profile of salt of weak base.

where $[AH]_s$ and $[A^-]_s$ are the concentrations of free and ionized species of the acid, respectively.

In order to form a salt, there must be a difference of at least two pH units between the p*K*a of the drug and the conjugate acid/base.

The choice of particular counter-ions depends on the p*K*a, solubility product of the salt, required dose of the compound and the safety of the counter-ion. Computer simulations of the salt solubility can be generated using the entropic changes due to thermal and configurational disorder introduced by the salt formation. An extensive evaluation of the various cations and anions is discussed by Friedlieb Pfannkuch et al. (41). Some common ions are tabulated in Tables 3 and 4 (42).

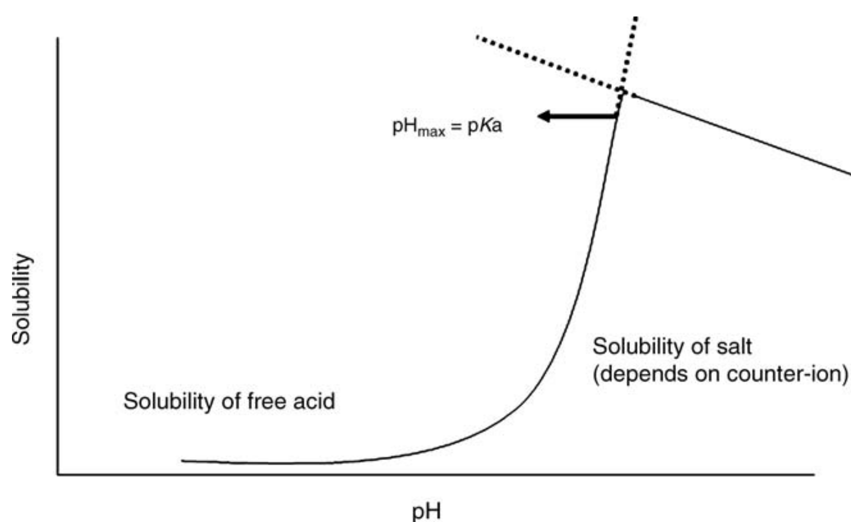

FIGURE 4 pH-solubility profile of salt of acid.

TABLE 3 Commonly Used Salt Formers (Counter Acids) for Monobasic Drugs

Counter-ion	p*K*a	Molecular weight
Acetic acid	4.76	60.05
Citric acid	3.13, 4.76, and 6.40	191.12
Fumaric acid	3.03 and 4.38	116.07
Hydrobromic acid	–9 to –6 (estimated)	80.91
Hydrochloric acid	–6 to –3 (estimated)	36.06
Lactic acid	3.86	90.08
Methane sulfonic acid	–1.2	96.10
Maleic acid	1.92 and 6.23	116.07
Nitric acid	–1.32	63.02
Pamoic acid	2.51 and 3.1	388.38
Phosphoric acid	1.96, 7.12, and 12.32	98.00
Sulfuric acid	–3 and 1.92	98.08
Tartaric acid	3.02 and 4.36	150.09

TABLE 4 Commonly Used Salt Formers for Weak Acidic Drugs

Counter-ion	p*K*a	Molecular weight
Ammonia	9.27	17.03
Arginine	13.2, 9.09, and 2.18	174.20
Benzathine	9.99 and 9.39	240.35
Calcium hydroxide	12.6 and 11.57	74.10
Choline	>11	121.18
Diethylamine	10.93	73.14
Lysine	1079, 9.18, and 2.16	146.19
Magnesium hydroxide	11.4	58.33
Potassium hydroxide	~14	56.11
Piperazine	5.68 and 9.82	86.14
Sodium hydroxide	~14	40.00
Tromethamine	8.02	121.14
Zinc hydroxide	~14 and 9.64	99.38

From a biopharmaceutical perspective, the important considerations in selecting the salt form for development includes: solubility and dissolution rate, physical and chemical stability, common-ion effect, physiological implications in terms of pH and common-ion, interactions with excipients, hygroscopicity and polymorphic conversions (hydrates and solvates) during processing and storage (43). The decision trees described in the later sections can be constructed to assist in the salt-screening process.

Solubility and Dissolution Rate of Salts

For most of the part the equilibrium solubility of poorly soluble compounds remains the same under the same conditions of pH, temperature, and ionic strength regardless of which salt form is used. However, the modulation of dissolution rate based on the microenvironment pH is the primary mechanism of action for the salt effect on the in vivo performance. For example, the pH of the sodium salt of a weak acid yields a

higher pH in the diffusion layer; similarly, the boundary layer pH of the hydrochloride salt of a weak base is always lower than the bulk. The salt effect on the dissolution rate and in vivo performance of the drug is generally associated with changes in the dissolution rate, counter-ion, and common-ion effect, crystal- form modification (solvate), micellar solubilization with long chain aliphatic acids (e.g., lauric acid), ion-pair, surface activity, and stability in physiological fluids. The counter-ion-dependent solubility is generally assessed by the differences in the solubility product of the salts. Other factors that can yield differences in solubility are crystal lattice and solvation energies. The potential disadvantages of salts include the common ion effect especially for hydrochloride salts, poor solid-state stability due to microenvironment, and precipitation of free acid/base on the surface.

Salt and Form Selection Strategies

The selection of an appropriate salt form is an integrative process requiring a balance of the various factors e.g., bioavailability with regards to the clinically relevant doses and the toxicology coverage, processing considerations, chemical/excipient stability, hygroscopicity, morphology, and compressibility. Various decision trees have been proposed to guide the salt and form selection process as shown in Figure 5 (40,44).

Due to the recent advances in the computational and analytical technologies, salt screening has become a highly efficient program where-in an extensive salt evaluation

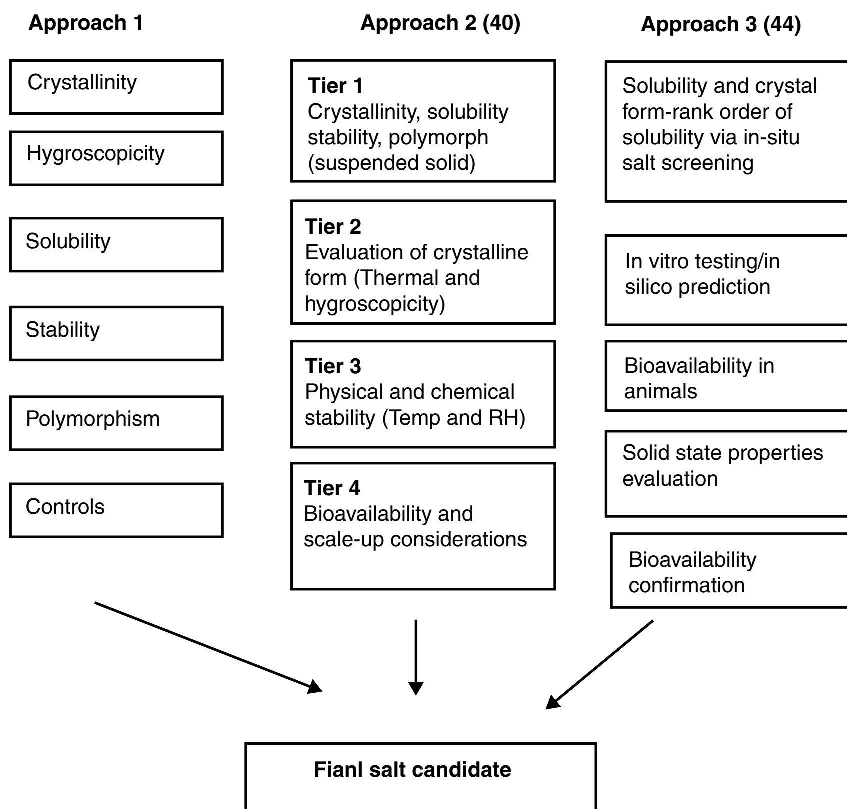

FIGURE 5 Salt selection decision tree.

can be performed with a minimal amount of drug in a very short time. The early screening as indicated in all of the above approaches is conducted in high throughput mode using several combinations of acids or bases. For example, the Biomek® 2000 automation workstation automates procedures used with stacker and plate-reader capabilities. The drug is dispersed into a 96-well plate and the acid is delivered by an automated method. The salts are first evaluated visually to observe the formation of oily versus solid material followed by investigation under a polarized light microscope to determine crystalllinity. After stepwise eliminations, the salts are scaled up to enable complete evaluation of the solid state properties (45). Several companies on a fee-for-service basis conduct complete salt and form screening such as SSCI, Inc. (Indiana, U.S.A.), Avantium Technologies (Netherlands), Solvias (Switzerland), Symyx Technologies Inc. (California, U.S.A.) and Accentus (U.K.).

CO-CRYSTAL FORMATION

Salt formation is primarily an ionic interaction between a weak acid or base and the selected acid/base counter-ion. In contrast, the co-crystals are complexes that are held together by hydrogen bonding or weak Van der Waals' forces between the guest and the host molecules. Commonly encountered cocrystals of pharmaceutical active compounds are hydrates and solvates. Co-crystallization of desired molecules other than the solvent can also be induced under suitable conditions (46), e.g., the formation of glutaric acid co-crystals or pyrene nanorods within a supramolecular framework. Academic research in the supramolecular chemistry and crystal engineering fields has created the foundation to successfully apply these techniques to systems containing biologically active molecules. The ability to modulate solid-state properties by directing the molecular assembly in the crystalline state without changing the covalent bonding is of significant value, particularly for non-ionizable compounds.

Co-crystals can be used to achieve certain goals such as improving stability, hygroscopicity, solubility, dissolution rate, and bioavailability. The analytical methodologies used to prepare and characterize co-crystals are a hybrid of salt and polymorph screening. One of the important considerations in evaluating co-crystals is the selection of the guest molecule. Several literature examples clearly demonstrate the advantage of co-crystals for poorly soluble, non-ionizable compounds (47,48). For example, co-crystals of fluoxetine hydrochloride were prepared with benzoic, succinic, and fumaric acids (47) by the interaction of the underutilized hydrogen bond acceptors capability of chloride ions with hydrogen bond donor guest molecules to get 1:1 co-crystals with benzoic, and 2:1 co-crystals with succinic and fumaric acids. The presence of a guest molecule along with fluoxetine hydrochloride in the same crystal structure resulted in a solid phase with altered physical properties when compared with the crystalline drug. Intrinsic dissolution rates and stability were used to compare and rank the practical utility of such an approach. Similarly, the co-crystals of olanzapine were prepared as hydrates to improve the pharmaceutical performance of the product.

In another example, co-crystals of carbamezipine (CBZ) were prepared with several guest molecules using two distinct strategies, i.e., the use of the exofunctional nature of the carboxamide dimer based upon the selection of complementary hydrogen-bond functionalities and the use of previously known synthons to perturb the carboxamide homosynthon by forming a heterosynthon between the carboxamide moiety of CBZ and the carboxylic acid moieties of the guest molecule to form co-crystals. The guest molecules used for this purpose are complementary to CBZ in terms of hydrogen bonding

and can therefore act as cocrystal formers, e.g., acetone, DMSO, benzoquinone, terephthalaldehyde, saccharin, nicotinamide, acetic acid, formic acid, butyric acid, trimesic acid, 5-nitroisophthalic acid, adamantane-1,3,5,7-tetracarboxylic acid, and formamide (48). Similarly the pyridine–carboxylic acid heterosynthons have also been attempted as potential co-crystal formers. There are numerous examples of heterosynthons that can be expected to be suitable in the context of API. Most importantly, the co-crystal approach means that the APIs are not covalently modified, thus enabling a diverse range of solid-state properties with different physical properties.

The use of co-crystals to improve the bioavailability of poorly soluble compounds has been shown by McNamara (49). The bioavailability of a poorly soluble, non-ionizable compound was significantly improved by making use of the hydrogen bonding between the compound and glutaric acid in 1:1 ratio. The formation of co-crystal was monitored using the Kofler technique. Glutaric acid and the compound were dissolved in a high boiling solvent on a microscope slide. The interface where the two compounds mix is where co-crystal formation occurs. Crystal growth is manipulated by adjusting the temperature. When the components mix, the concentrations vary across the slide and colligative properties cause a melting point depression effect.

Future trends: In summary, co-crystal approach uses previously well-known procedures such as solvates/hydrates and eutectics as a means to improve the solubility of poorly soluble compounds particularly non-ionizable compounds. Besides the solvates and hydrates that have been used in the pharmaceutical systems for long time, the co-crystal based on supramolecular structural assembly and heterosynthon is still in very early stage. The future work in this area aims at evaluating other supramolecular synthons, the use of GRAS material (Generally Regarded As Safe) or food additives as co-crystal formers, structure and functional property studies, and high-throughput crystallization experiments. Furthermore, its application in drug product needs careful evaluation of the scale-up of the co-crystals, its stability during drug product manufacturing and during storage.

COMPLEXATION USING CYCLODEXTRIN

Over the decades, the use of complexation in pharmaceutical industry has greatly shifted from covalent- and ionic-bonded complexes to hydrogen-bonded and non-bonded complexes such as inclusion complexes (clathration), partly due to the application of cyclodextrin to modify many facets of drug properties. The application of cyclodextrin complexation in pharmaceuticals has been extensively reviewed by Yalkowsky (50), Tong (51), and Uekama (52). The primary focus of the research has been on improving the complexation efficiency by improving the understanding of the specific structural and conformational requirements for the guest molecule to be solubilized in cyclodextrin cavity. Significant efforts are placed on the evaluation of new structural diversity in the cyclodextrin, process modification to assist in the formation of complexes and the use of polymeric modifiers to control the complexation as well as achieve target-specific drug delivery. There are at least 30 products covering wide range of applications from oral, parenteral, topical, ophthalmic to nasal sprays in the worldwide market using the cyclodextrin technology, e.g., Opalmon®, Brexin®, Nitropen®, Pansporin T®, Meiact®, Suramyl® for oral applications.

The growth of cyclodextrin application in pharmaceutical field is attributed to their biocompatibility, minimal oral absorption, biodegradation in the colon and the availability of large variety of functional derivatives to enable inclusion of wide range of host molecules.

Background

Cyclodextrins (CDs) are cyclic (α-1, 4)-linked oligosaccharides of α-D-glucopyranose, containing a relatively hydrophobic central cavity and a hydrophilic outer surface (Fig. 6) (53). Commercially they are produced by enzymatic conversions of starch. The naturally occurring CDs contain 6, 7, 8, and 9 glucose units and are designated as α, β, γ, and δ, respectively. Due to the lack of free rotation at the bonds connecting the glucopyranose units, the CDs exist in the shape of truncated cone in aqueous fluids. The primary hydroxyl groups are located on the narrow edge of the cone while the secondary hydroxyl group is located on the wider edge. The structural arrangement inside the cavity consists of a ring of hydrogen atoms, a ring of glucosidic oxygen atoms, and another ring of hydrogen atoms thus making the cavity relatively hydrophobic. The cavity volume increases with increase in the number of glucose units (α, 6-member ring, β, 7-member ring, and γ, 8-member ring).

The application of naturally occurring CDs is limited due to relatively low aqueous solubility (particularly β-CD) and low complexation efficiency (α-CD and γ-CD). The β-CD is the most commonly used naturally occurring CD. Several structurally modified CDs have been developed to overcome the limitations of natural CDs. A comprehensive review of the structural derivatives of CDs is presented by Uekama (52) and the derivatives are classified into three broad categories:

1. Hydrophilic derivatives such as methylated β-CD, hydroxylated β-CD, and branched β-CD (hydroxypropyl β-CD).
2. Hydrophobic derivatives such as alkylated and acylated β-CD.
3. Ionizable derivatives: Anionic β-CD (sulfobutylether 4 β-CD, sulfobutylether 7 β-CD).

Complex Formation

The formation of complex depends on the atomic (Van der Waals), thermodynamic (hydrogen bonding), and solvent (hydrophobic) forces in the hydrophobic environment of the CD cavity. The complex exists in equilibrium between the CD, the guest chemical

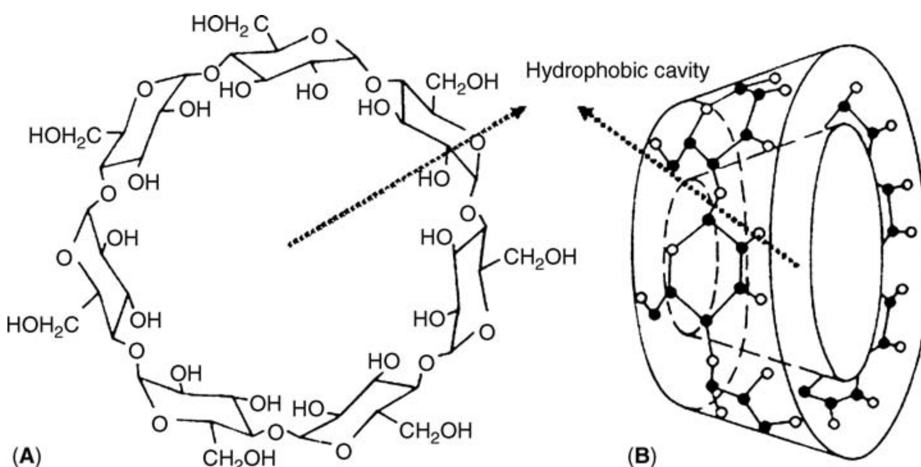

FIGURE 6 A generalized structure of cyclodextrin cavity. *Source*: From Ref. 53.

and water. The rate of formation of complex depends on the accessibility of the guest molecule to the CD cavity while the magnitude depends on the net thermodynamic driving force. The formation of complex is energetically favored due to the entropic factors related to the displacement of water from the hydrophobic CD cavity to the more hydrophilic pool and removal of the hydrophobic guest molecule from the aqueous environment and placement into the polar CD cavity. The accessibility is a statistical factor determined by the molecular geometry of the guest molecule and the particle size. For most drugs, equilibrium may be achieved in minutes whereas for some water-insoluble drugs the true equilibrium may not be achieved for hours or days due to the lack of hydration needed to get over the hydroxyl barrier of the outer ring. Once the molecule has entered the cavity, the "goodness of fit" is determined by the weak interactions between the molecule and the cavity. Release of drug (dissociation from the complex) is governed primarily by the concentration gradient.

Theoretical Considerations: Phase–Solubility Relationships

A mathematical treatment of the association and dissociation constants of CDs and chemical substances was first discussed by Higuchi and Connors (54). To assess the effect of complexation on the solubility of the compound, phase–solubility diagrams were constructed with the solubility of the ligand (S_T) as a function of total CD concentration (CD_T). According to the shape of the phase–solubility curve, the complexes were classified as Type A or B as shown in Figure 7 (51).

For a single 1:1 complex, the stability isotherm for the complex can be expressed as:

$$S_T = s_0 + \frac{K_{11}\, s_0\, CD_T}{1 + K_{11} s_0},$$

where S_T is the concentration of drug in solution, S_0 the concentration of free drug, CD_T the total concentration of cyclodextrin and K_{11} is the binding constant for 1:1 complex. The extent of solubilization and the dissociation of the complex depend on the magnitude of binding constant.

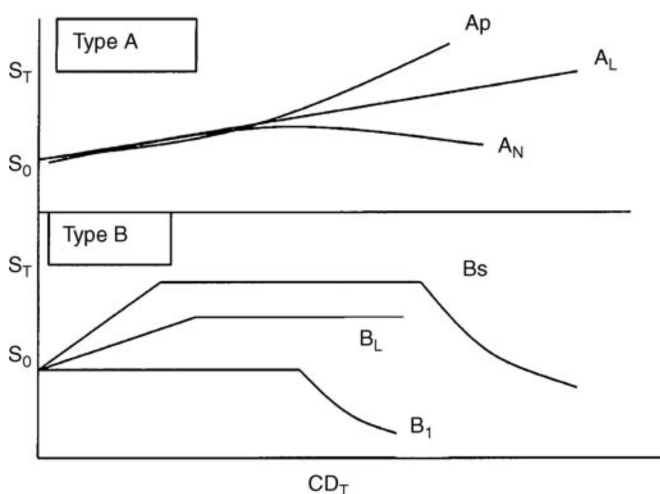

FIGURE 7 Phase-solubility diagrams of Type A and Type B systems. *Source*: From Ref. 54.

In Type A complexes, the solubility of the substrate increases with increased concentration of CD. The subtypes within each type of soluble complexes were summarized below:

A_L complex is first order in CD and $n = 1$.
A_N indicates non-ideal behavior that could be due to self-association of the ligand.
A_p suggests complex with $n > 1$ exists.

For Type A complexes, the binding constant can be easily estimated from the slope of the curve. Complexation efficiency is estimated by the product of equilibrium constant and the concentration of free drug in aqueous solution.

Type B complexes show a small increase in the solubility as a function of ligand concentration followed by a plateau region extending to where the entire drug is consumed. The different shapes can be observed due to either the lack of initial increase in apparent solubility (Type B_L) or decrease in the apparent solubility at high CD concentration depending on the limiting solubility of CD (B_L) or the complex (B_s).

Practical Considerations

The utility of complexation approach to improve the solubility depends on the binding constant (K_{11}). For most 1:1 complexes, the K_{11} is generally $< 20{,}000\,M^{-1}$ and the total CD concentration is usually < 0.2 M, therefore the maximum increase in solubility that can be expected is in the range of 1,000–2,000 times the intrinsic solubility. For example, for a drug with intrinsic solubility of 10 ng/mL and CD-binding constant of 20,000 will show solubility improvement in the range of ~0.2 mg/mL at the most. Several approaches such as the selection of appropriate CD, pH adjustment, use of co-solvents, temperature increase, and surfactant or polymeric modifiers such as PVP and HPMC have been used in the literature to improve the complexation efficiency (55).

Another important consideration for the utility of CD complexation in solid dosage form is drug loading. For example, a drug of 400 g/mol and a CD of 1400 g/mol and 1:1 complex with very high efficiency represents maximum drug loading of ~22%. Therefore, it requires about 1800 mg of complex to be included in the tablet for a 400-mg dose and this limits its application only to high potency drugs. With regards to the manufacture of drug CD complexes, several approaches have been employed in the literature ranging from co-grinding, kneading, granulation, melt extrusion, co-precipitation, spray drying, and lyophilization. The efficiency of complex can be affected by the method of manufacture if the time to reach equilibrium concentration is relatively long (longer than a few minutes) and hence the time to equilibration should be considered during the evaluation.

The dissociation of complex occurs via dilution and competitive displacement. It is generally shown to be fast. However, a careful evaluation is necessary especially when working with type A_p complexes as the dilution of the system may result in precipitation. In addition, the effect of other variables such as pH and ionic strengths should also be considered to assess the stability and dissociation of the complex.

MODIFICATION OF CRYSTAL

Conventional Approaches

Crystallization is the primary method of purification in the pharmaceutical industry. However, the drug substances frequently crystallize in more than one packing

arrangement. The resulting crystal forms are referred to as polymorphs. Polymorphs can differ in solubility, dissolution rate, stability, and mechanical properties.

A metastable crystal generally provides greater aqueous solubility, improving the bioavailability of poorly soluble compounds. Recent researches have been shown that certain species can stabilize metastable crystal forms (56). As the incorporation level of an additive increase, solid-state transformation rate of a metastable polymorph to a more stable crystal form decreases. A new solid form (Form IV) of celecoxib was prepared in the presence of polysorbate 80 and HPMC. The formation of the Form IV was dependent upon the concentration and the ratio of HPMC and polysorbate 80. A faster dissolution rate (> 2 times) of Form IV was observed compared with the thermodynamically stable form of celecoxib (Form III). There were no measurable changes in the solid state of Form IV either in dried solids or in the suspension for at least 6 months at 40˚C and 16 months at 25˚C (57). Control crystallization kinetics by tailoring additives has been the subject of extensive research. Anhydrous form generally exhibits greater aqueous solubility than the hydrate form, providing greater bioavailability. Due to the potential of the hydrate transformation, the aqueous wet granulation may not be amenable for processing of the metastable anhydrous polymorph; solvent granulation with ethanol or isopropyl alcohol could be an alternative to circumvent this technical challenge.

A full polymorph characterization is essential to ensure that desired polymorph is produced consistently and no polymorphic transformation occurs during manufacturing as well as during storage. In addition to achieving products with satisfactory and reproducible bioavailability, manufacturability and stability, the value of fully understanding the range of physical forms would help to maintain intellectual property protection.

A Eutectic mixture is another formulation concept first introduced by Chiou and Riegelman (58). However, the challenges associated with the high concentrations of eutectic-forming agent is typically required and their physical instability of the formulation are: (*i*) precipitation or crystallization from supersaturated solid solutions and (*ii*) potential particle growth of the dispersed phase upon the storage due to the reduced interfacial energy of the system.

Amorphous Formulation Approach

Amorphous formulation approach has recently gained a tremendous potential for improving solubility and bioavailability of poorly soluble compounds. It is well recognized that amorphous drugs exhibit greater molecular mobility compared with the equivalent crystalline material, thereby enhancing dissolution rate and bioavailability of poorly soluble crystalline compounds. For a robust dosage form, the “stable” crystalline form of the drug with adequate solubility is most desirable. Generally, it is preferred to convert crystalline to amorphous form only by choice with justifiable benefits.

Fundamental solid-state properties, method of preparation of amorphous pharmaceuticals, including characterization techniques for achieving maximum bioavailability and stability is presented below.

Fundamental Amorphous Solid-State Properties

Amorphous solids can be defined as non-crystalline material with short-range molecular order similar to that in a crystalline solid. Amorphous solids typically exhibit higher solubility and higher dissolution rate compared with the equivalent crystalline materials. However, there are still a number of difficulties associated with their physical stability

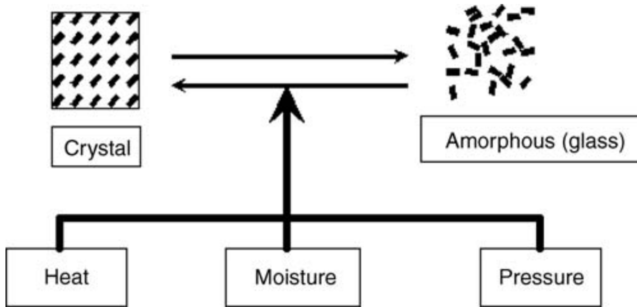

FIGURE 8 Critical processing parameters affecting physical stability of amorphous solids.

and processability. Due to the lack of three-dimensional crystalline lattice, amorphous solids have higher free volume and greater molecular mobility (59). Amorphous solids exhibit glass transition temperature (T_g) under Differential scanning calorimetry (DSC), but not endothermic peak-like crystalline materials. Amorphous solids are thermodynamically unstable and tend to revert to the crystalline form on storage (devitrification). Critical factors, which have a great influence on the physical stability of amorphous solids, are depicted in Figure 8.

1. *Temperature*: A schematic depiction of the enthalpy (H) or specific volume (V) of a solid substance as a function of its temperature is presented in Figure 9 (60). For a crystalline material at very low temperature, a small increase in enthalpy and volume with respect to temperature, indicative of a certain heat capacity (C_p) and thermal expansion (α) are usually seen. There is discontinuity in both H and V at the melting temperature (T_m) representing the first-order phase transition to the liquid state. Upon rapid cooling of the melt the values of H and V may follow the equilibrium line for the liquid beyond the melting temperature into a "supercooled liquid" region. On cooling further a change in slope is usually seen at a characteristic temperature known as the glass transition temperature (T_g).

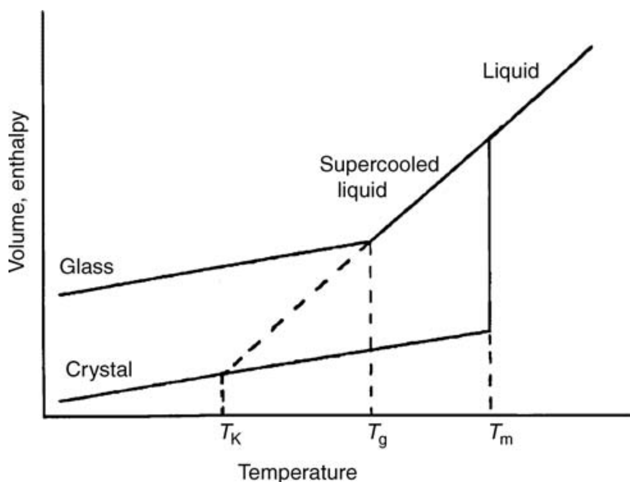

FIGURE 9 Schematic depiction of the variation of enthalpy (or volume) with temperature. *Source*: From Ref. 60.

Materials below T_g are rigid and brittle, and only rotational or vibrational short-range motions are possible. As the material approaches T_g, the molecules have sufficient mobility to reorganize and crystallize. Temperature enhances molecular mobility and crystallization rate of amorphous drug. T_g value is a useful parameter to predict the physical stability of amorphous solids. The higher the T_g value, the better the physical stability. As a rule of thumb, amorphous solids should be kept at least 50°C below its T_g. The T_g value depends on the heating and cooling rates. A fast cooling rate produces a higher value for T_g than does slower cooling rate. For a pure substance, T_g can be estimated based on the empirical relationship $T_g = 0.7\ T_m$ (ln K). The value of T_g/T_m is between 0.6 and 0.85 (61).

2. *Moisture*: It enhances molecular mobility of amorphous drug by decreasing T_g. Moisture is known to have a profound effect on the glass transition of amorphous solids, acting as a plasticizer by increasing the free volume of the material. Some amorphous solids can easily get plasticized by water, thereby turning to gel or rubbery state. The plasticizing effect is typically enhanced by shear and may lead to gelling of the amorphous solids. It would be quite difficult to remove the moisture or residue solvent, once plasticization has taken place.
3. *Pressure*: It can initiate nucleation of the drug, which could act as seeds and adversely impact long-term physical stability of the amorphous formulation.

Amorphous solids exhibit no birefringence with irregular particle shape under cross-polarized light, while crystalline compounds exhibit characteristic birefringence and crystal habit. Amorphous solids exhibit no sharp diffraction peaks under X-ray while crystalline compounds exhibit characteristic sharp diffraction peaks. The X-ray diffraction may not be sensitive to detect crystallinity below 5% level (62,63). The presence of crystalline material in an amorphous formulation could be detrimental for the physical stability of the formulation, because small amount of crystalline material could act as seeds for recrystallization of amorphous drug. Crystalline material tends to exhibit high levels of elasticity and brittleness when subjected to mechanical stress. In contrast, the amorphous material tends to exhibit varying degrees of viscoelasticity, depending on their temperature relative to T_g. Such viscoelastic behavior provides solids with the ability to flow under mechanical stress. This could explain how difficult it is to get particle size reduction with amorphous materials by a mechanical-grinding process.

Amorphous Preparation Methods

As depicted in Figure 9 (60) in the previous section, enthalpy (H) or specific volume (V) of a solid substance is a function of its temperature. Melt-quenched method is useful for the conversion of crystalline drug to amorphous form. The rapid cooling of a liquid below its melting point (T_m) may lead to an amorphous state with the structural characteristics of a liquid, but with a much higher viscosity. This amorphous state, so-called "rubbery state," is considered to be an equilibrium "supercooled" liquid. Below the glass transition temperature (T_g), the material is kinetically frozen into a thermodynamically unstable glassy state with respect to both the equilibrium liquid and the crystalline phase. Cooling rate can affect the rate of nucleation. Slow cooling allows the maintenance of a steady-state nucleation rate, whereas rapid cooling prevents a full development of viable nuclei. As a result, rapid cooling not only facilitates glass formation but also enhances glass stability against crystallization.

Grinding of crystals can remove all traces of crystallinity (64–66). Several passes of milling may eventually lead to an amorphous structure. Formation of the amorphous state is

feasible by ball milling with neusilin, whereas amorphization does not occur on milling the drug alone (64).

The use of media-milling technology to formulate poorly water-soluble drugs as nanocrystalline particles (<400 nm) is described earlier in the Physical Modification section of this chapter, whereas the particles exhibit a defined geometrical shape of crystalline form and are physically stabilized with a polymeric excipient to prevent particle agglomeration/aggregation. It is critical to ensure that grinding process do not adversely induce polymorphic transformations that lead to physical instability.

Physical stabilization of amorphous drugs: In many instances, amorphous drug itself could not sustain supersaturation when exposed to GI fluids or withstand conventional manufacturing processes of tablet or capsule-dosage forms.

The ultimate goals of amorphous pharmaceuticals development were:

To attain and sustain supersaturation solution of the drug in the GI fluids, which are linked to enhance oral bioavailability. Polymer imparts dissolution stability by enabling hydrophobic, hydrogen bond and electrostatic interactions with drugs (67) and microviscosity effect, inhibiting drug nucleation and crystallization.

To produce consistent and reliable products those are kinetically stable over their desired shelf-life. Polymer imparts shelf-life stability of amorphous solid-dosage forms, as it immobilizes and isolates amorphous drug in rigid glass, possessing adequate physical stability that can withstand the manufacturing processes and maintain drug product shelf-life (preferably >2 years).

The desirable attributes of polymers for amorphous stabilization were:

1. high T_g (i.e., >110°C);
2. high molecular weight (i.e., >80,000 Da);
3. ideally, solubility parameter close to that of the API;
4. maintains supersaturation solution of the drug via hydrogen bonding, electrostatic effect, microviscosity effect in the GI fluids, thereby maximizing drug exposure;
5. limited water uptake, preferentially adsorbing moisture (moisture scavenger);
6. crystallization inhibition;
7. prevents fusion/nucleation of amorphous API particles under compaction.

Before discussing the methods for preparing amorphous formulation, it is necessary to define the two types of amorphous systems first. While solid solution and solid dispersion have been used interchangeably, for the purpose of clarifications, both nomenclatures were defined as follows:

Solid solution: If amorphous drug is miscible with the polymer, the system is known as amorphous solid solution or molecular dispersion distinguished by one T_g value. Physical stability is expected to be concentration dependent. The major determining factors include solubility parameters, drug loading, and other properties of drug and polymer. Fedor group contribution method (68) is useful for solubility parameters calculation as first screening tool in selecting appropriate polymers. The differences in solubility parameters of <7.0 MPa$^{1/2}$, the materials are considered miscible, resulting in a one-phase system (69). For amorphous solid solutions, T_g of the drug/polymer can be predicted using the Gordon-Taylor (GT) equation shown below (60). This holds true only when the amorphous system is treated under heat without residual solvent.

$$T_{g\,mix} = \frac{w_1 T_{g1} + K w_2 T_{g2}}{w_1 + K w_2}$$

where T_g is the glass transition temperature, w_1 and w_2 the weight fractions of components, and K is calculated from the densities ρ and T_g of amorphous components.

One-phase system is preferred only when the system has high T_g improving physical stability of the formulation. However, the advantage of a solid solution may not be so significant, if the drug can only temporarily maintain a high supersaturation, leading to rapid precipitation when exposed to the GI fluids.

Solid dispersion: If amorphous drug is dispersed (immiscible) in the polymer matrix, the system is known as amorphous solid dispersion distinguished by two separate T_g values of the drug and the polymer. The physical stability relies on immobilization and isolation of the labile amorphous API in rigid glasses of inert polymer matrix. To maximize the stabilization effect, it is critical to ensure that an amorphous drug is embedded in the polymer matrix. Molecular weight of the polymer and drug loading play a major role in the immobilization and isolation of the amorphous molecules.

Commonly used methods for amorphous pharmaceuticals preparation are: (*i*) hot melt extrusion, (*ii*) solvent-controlled precipitation, and (*iii*) solvent evaporation method.

Hot melt extrusion: Hot melt extrusion (HME) equipment (Fig. 10) consists of an extruder, auxiliary equipment for the extruder, down-stream processing equipment, and other monitoring devices used for performance and product quality evaluation. The extruder is typically composed of a feeding hopper, barrels, single or twin screws, and the die and screw-driving unit. The auxiliary equipment for the extruder mainly consists of a heating/cooling device for the barrels, a conveyer belt to cool down the product and a solvent delivery pump. The monitoring devices on the equipment include temperature gauges, a screw-speed controller, an extrusion torque monitor and pressure gauges.

HME can be used to prepare amorphous pharmaceuticals in the form of solid dispersion or solid solution systems. HME offers many advantages over traditional processing techniques, such as: it is a solvent-free and well-controlled continuous process

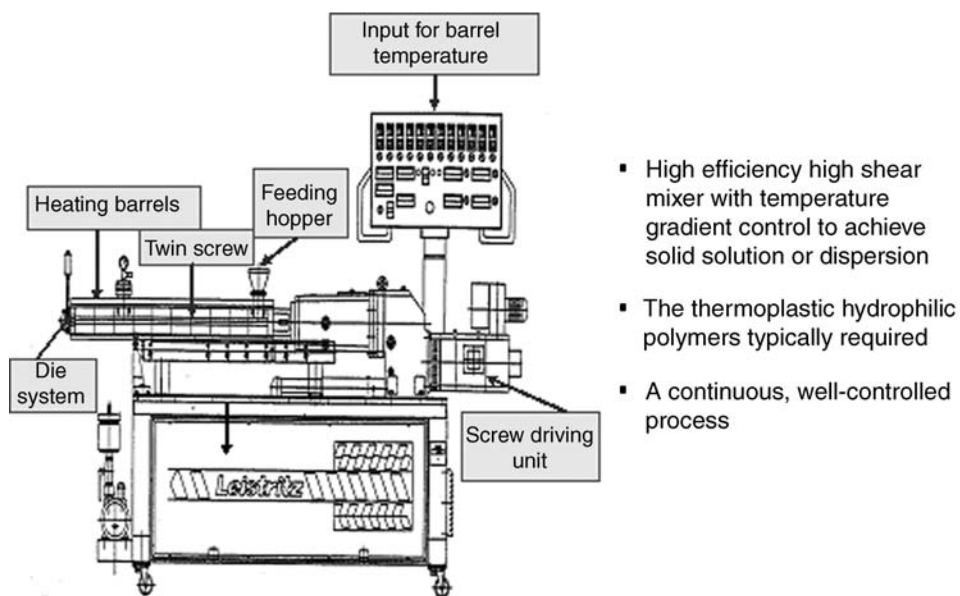

FIGURE 10 Hot melt extrusion design and potential applications.

which eliminates the densification process and eases up for scale-up. Typical co-extrudate (Fig. 11) is dense, minimizing moisture uptake and improving physical stability of amorphous solids. The melting point of the drug, T_g of the polymer, miscibility of the polymer and the drug predicted, as well as their thermostability must be considered through the HME formulation process. To assess their suitability for HME process as a means to manufacture solid dispersion/solution, physical, and viscoelastic properties of binary mixtures of the drug and the selected polymers must be well characterized (70). To ensure proper material flow in the extruder, the extrusion temperatures are generally set 10–20˚C above the T_g or T_m. The zero-rate viscosity (η_0) and activation energy (required to initiate the flow) were useful in evaluating the extrudability and predicting the miscibility for various drug/polymer blends. A linear correlation between η_0 and motor load was reported. Due to their relative insolubility in water, ionic polymers (i.e., Eudragit E100, HPMCAS) effectively immobilize amorphous drugs even exposed to high humidity, thereby providing excellent physical stability.

Solvent-controlled precipitation: Co-precipitation of the drug and the polymer can be achieved by solvent-controlled precipitation (SCP, the resultant product is also called Microprecipitated Bulk Powder or MBP). Ro 31-7453 represents a classical BCS II crystalline compound with low aqueous solubility (below 10 µg/mL and mp of 285˚C) and poor bioavailability (<5%) in animal models. Conversion of this poorly soluble crystalline drug into amorphous state (supported by the powder XRD patterns in Fig. 12) and stabilizing it in the ionic polymer can be achieved by a solvent-controlled method. The process flow diagram is presented in Figure 13. The resultant MBP was shown to increase C_{max} of Ro 31-7453 by 18-fold compared with conventional micronized drug suspension approach (Table 5). An instantaneous co-precipitation (drug and polymer) occurred at comparable rate. The intrinsic mean particle size of the amorphous drug in the MBP (after stripping the polymer in alkaline aqueous buffer) was <1 µm. The DSC profile showed a distinct separation of the T_g between the drug (110˚C) and the polymer (160˚C) indicating that MBP is solid dispersion (two phase). This process is applicable only for ionic polymers when aqueous system is used for precipitation. The co-precipitate is typically porous because of the penetration of the solvent front during mixing. Downstream densification process is generally required to improve flowability, particle size, and bulk density.

Solvent evaporation method: An important prerequisite for the manufacture of amorphous formulation using this process is that both drug and carrier must have adequate and comparable solubility in a low boiling point solvent practically <75˚C, such as acetone and ethanol. The solvent can be removed by evaporation, such as spray-drying or fluid-bed drying.

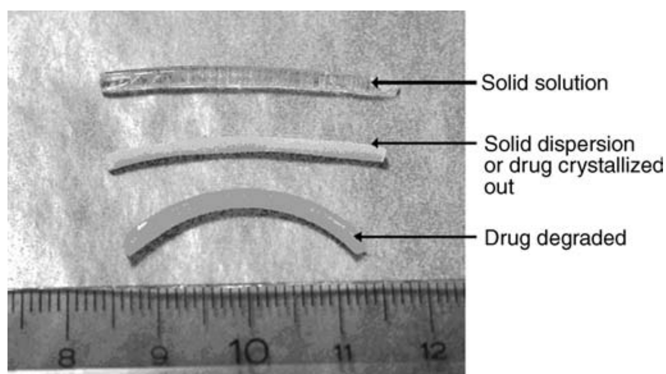

FIGURE 11 Typical extrudates produced by HME.

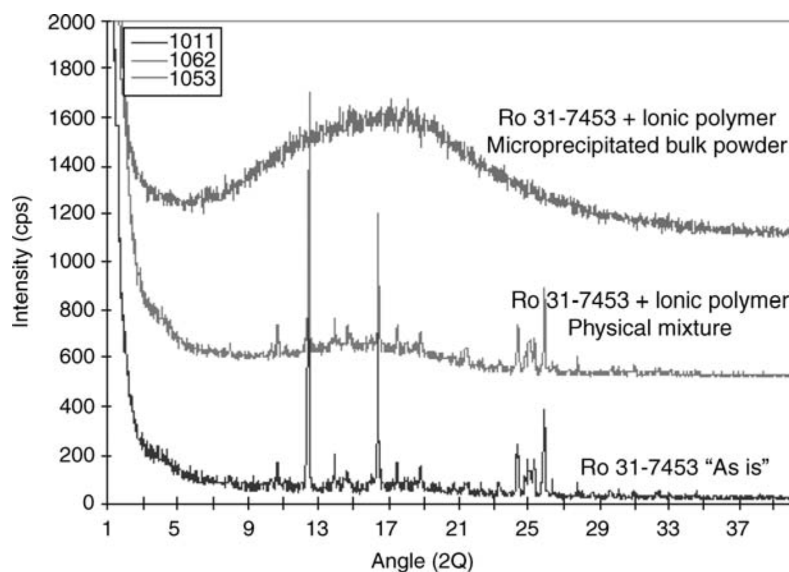

FIGURE 12 Powder X-ray diffraction pattern of the MBP (coprecipitate of amorphous Ro 31-7453 and Eudragit L100) compared with the initial crystalline form and the physical mixture.

Spray drying (SD): Schematic diagram of the spray-drying unit is depicted in Figure 14. This process has successfully produced amorphous API (i.e., amorphous nelfinavir mesylate) achieving consistent particle size via a nozzle size control. It is a flash evaporation using typical inlet air temperature (100–140˚C) and product temperature (< 30˚C), which is suitable for handling thermolabile substances. Subsequent amorphous nelfinavir mesylate was successfully granulated by aqueous wet granulation process using a highly porous excipient with rapid wicking capability, such as amorphous calcium silicate. This excipient minimizes the plasticizing effect of water and prevents fusion/nucleation of the amorphous drug particles under shear and compaction.

Spray-drying process has been commonly used to produce stabilized amorphous pharmaceuticals by polymer additive. Polymers play a critical role in maintaining

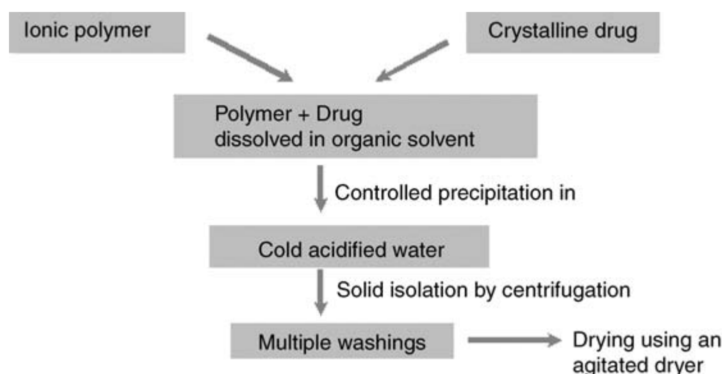

FIGURE 13 Flow diagram illustrating the manufacturing of the MBP by a solvent-controlled precipitation process.

TABLE 5 P*K* Parameters in Dogs ($N = 6$) After Oral Administration of Ro 31-7453 from Various Formulations (Dose: 10 mg/kg)

Formulation	C_{max}/Dose (ng/ml) (mg/kg)	AUC/Dose (ng.h/ml) (mg/kg)	% Absolute bioavailability
Micronized drug suspension	6 ± 1.7	30 ± 8.3	4
Nanosized drug suspension	14 ± 5.3	86 ± 13.7	11
MBP densified[a]	109 ± 44	653 ± 310	85
IV Formulation	N/A	766 ± 8.3	100

[a]By roller compaction process.

supersaturation solution of the drug in the GI fluids. The dissolution results (Fig. 15) clearly indicated that HPMC is the most appropriate polymer for SD-tacrolimus in maintaining a supersaturated drug solution compared with PVP and PEG 6000 (71). The bioavailability of SD-tacrolimus with HMPC was approximately 10-fold increase in comparison compared with the crystalline powder (Fig. 15).

Wurster fluid-bed coating: Some amorphous drugs may be easily plasticized by water, resulting in gelling and incomplete dissolution. Solid-dosage form development of such amorphous drugs is considered challenging. Fluid-bed coating process allows amorphous compounds with low T_g (i.e., 60˚C) having gelling tendency to be developed in solid-dosage forms with relatively rapid, reproducible and complete dissolution profiles, and maintained dissolution characteristics throughout the product shelf-lives. The fluid-bed coating equipment and manufacturing process flow diagram were presented in Figure 16. The process preferentially converted a crystalline drug (mp, 115˚C) to amorphous form (T_g, 60˚C) and micro-embedded them in ionic water-insoluble polymer matrices, which provided rapid, reproducible, and complete dissolution profiles. The ionic polymers, such as Eudragit® L100-55 and Eudragit® L100, were shown to

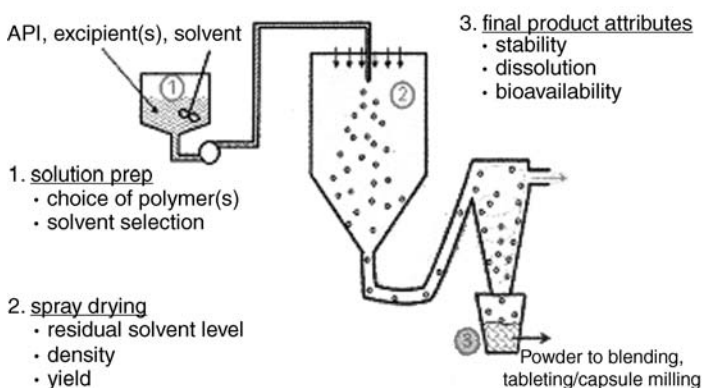

FIGURE 14 Schematic diagram of spray-drying unit. *Source*: Courtesy of ISP.

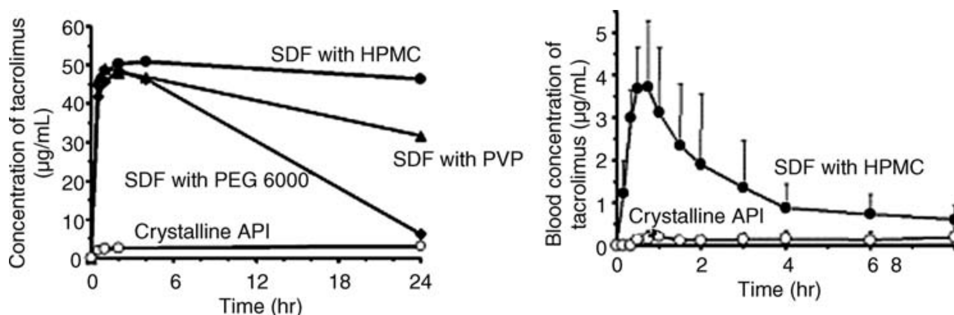

FIGURE 15 Impact of polymers in maintaining supersaturated solution of tacrolimus in the GI fluids (*left*) and improving oral bioavailability of tacrolimus in beagle dogs.

effectively protect the amorphous drug from gelling. Micro-embedding the compound in the ionic polymer matrix is essential to overcome the gelling of the drug when exposed to dissolution medium. It represents a highly reproducible particle engineering process in providing an intimate mixture of the drug and polymer in beadlets form with high density (> 0.7 g/cc) and excellent flowability. Itraconazole, a poorly absorbed antifungal drug, was successfully developed utilizing fluid-bed coating to produce amorphous formulation (Sporanox® by Janssen) stabilized by hydroxypropyl methycellulose polymer with enhanced oral bioavailability.

Criticality of Amorphous Processing Selection

The following case studies illustrate the importance of amorphous pharmaceuticals methods of preparation for achieving maximum bioavailability and physical stability.

Solvent-controlled precipitation versus spray-drying: Phase separation or segregation of the drug or the polymer could be a major concern for solvent evaporation method. Difference in the precipitation rate between Ro 31-7453 and Eudradit L100 by spray-drying (SD-MBP) with binary solvents resulted in drug segregation revealed by

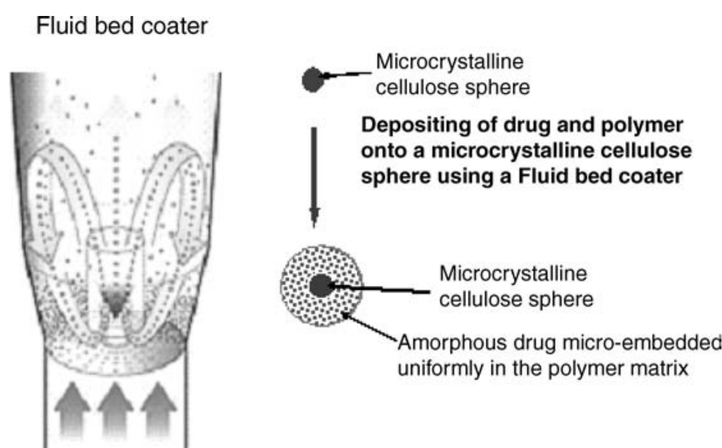

FIGURE 16 Schematic diagrams of fluid-bed coater (*left*) and manufacturing flow chart for micro-embedding amorphous drug with low T_g in the ionic polymer matrix (*right*).

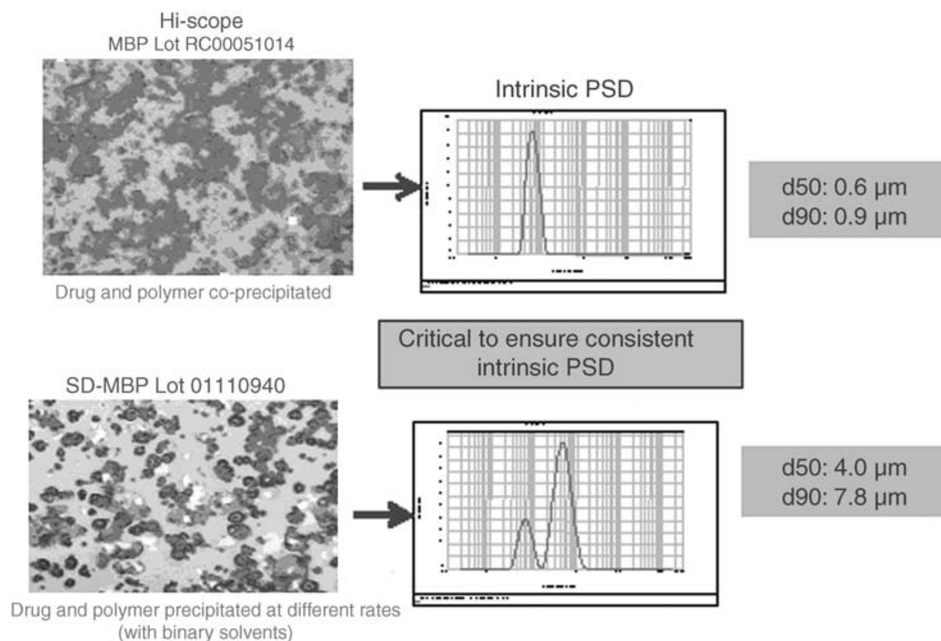

FIGURE 17 Particulate properties comparison MBP versus SD-MBP.

Hi-Scope microscopy (Fig. 17). Remarkable differences in drug and polymer solubilities in the binary solvents used in the spray-drying resulted in "co-drying" rather than "co-precipitation." The intrinsic mean particle size of the amorphous drug (d50 – 4 μm with bimodal distribution) in the SD-MBP was almost seven-fold larger than that in the MBP initially prepared by solvent-controlled precipitation. The wettability (determined by contact angle and intrinsic erosion measurements in the simulated intestinal fluid) of the SD-MBP was inferior to the MBP (Fig. 18). The bioavailability of the MBP was not affected by roller compaction; in contrast, the bioavailability of the SD-MBP was adversely affected by roller compaction (Table 6). This could be explained by the fact

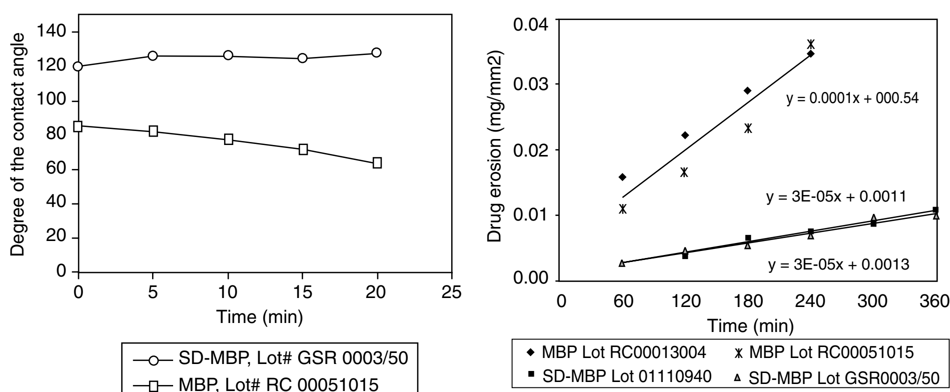

FIGURE 18 Wettability determined by contact angle (*left*) and intrinsic erosion (*right*) measurements of the SD-MBP versus MBP matrix in the simulated intestinal fluid.

TABLE 6 P*K* Parameters in Dogs (*N*= 12) After Administration of Ro 31-7453 90 mg Capsules Prepared by MBP vs. SD-MBP

Method of preparation	C_{max}/Dose (ng/ml)/(mg/kg)	AUC/Dose (ng. h/ml)/(mg/kg)	% Relative bioavailability
MBP as is	113 ± 39	630 ± 221	100
SD-MBP as is	96 ± 32	509 ± 214	81
MBP densified[a]	116 ± 45	678 ± 274	108
SD-MBP densified[a]	61 ± 24	329 ± 162	52

[a]By roller compaction process.
Abbreviation: MBP, microprecipitated bulk powder.

that segregation of the amorphous drug in the SD-MBP led to poor wettability, which is further diminished by roller compaction. Ro 31-7453 in the SD-MBP crystallized after 3-months storage at 40˚C/75% RH indicated by the powder XRD patterns. In contrast, the physical stability of the MBP was maintained throughout its stability shelf-life for at least 3 years.

These results clearly showed that micro-embedding amorphous drug in the polymer matrix are essential for achieving maximum bioavailability and physical stability of the amorphous compounds. Roller compaction may not be a process of choice for handling the segregated amorphous drug prepared by spray-drying. Down-stream amorphous processing choice must be selected based on the solid state and particulate properties of amorphous solids.

Solvent-controlled precipitation versus HME: An investigational drug represents a classical BCS II crystalline compound with low aqueous solubility (< 0.05 µg/mL, irrespective of pH and mp of 120˚C) and log *P* of 3.01. Bioavailability in rats at 50 mg/kg dose of amorphous granulates (40% drug micro-embedded in an ionic polymer matrix produced by SCP and HME were approximately 40-fold increase in Area under the curve (AUC) compared with nanosuspension (Table 7). Our preliminary data indicates that both processes converted the crystalline drug into amorphous solid dispersions with a glass transition temperature around 104–106˚C with similar spectroscopic and hygroscopic properties. The MBP was more porous and had a larger specific surface area (6.19 vs. 0.13 m^2/g indicated by the BET values) than the HME product. The HME product exhibited a slower dissolution profile, but 1.7-fold faster intrinsic dissolution rate than the MBP. This could explain why the exposure in rats at high dose (250 mg/kg) of the HME product was twice higher than that of the MBP. The HME product exhibited slightly lesser water uptake than the MBP. The two products had acceptable physical stability after storage in 40˚C/75% RH chamber for 3 months. However, the physical stability of the HME product as an aqueous suspension was superior to that of the MBP.

TABLE 7 P*K* Parameters in Rats After Administration of an Investigational BCS II Compound from Various Formulations

Parameters	50 mg/kg			250 mg/kg	
	Nanoparticle	MBP	HME	MBP	HME
C_{max} (ng/mL)	1,046	98,033	76,900	151,667	157,000
AUC (ng h/mL)	12,092	505,506	468,415	987,900	1795,540
T_{max} (h)	5.5	1.3	2	1.5	2.7

Physical Stability Prediction

For successful amorphous pharmaceuticals development, it is essential to attain and sustain supersaturation solution of the drug in the GI fluids, thereby maximizing drug exposure and to produce consistent and reliable products that are kinetically stable over their desired shelf-life.

Physical and chemical stability of amorphous solids is related to their molecular mobility, which is usually evaluated by means of the structural relaxation time (τ). Molecular relaxation takes place during storage may lead to physical instability of the amorphous pharmaceuticals. Understanding the dynamics of molecular motion at the storage conditions are essential. Molecular motions occurring below T_g is unquestionable and result in structural relaxation or "aging" of glassy material. The measurement of molecular mobility of amorphous solids can be achieved by various means including measurement of viscosity, dielectric relaxation (72,73), nuclear magnetic resonance (72,74), and enthalpy relaxation by DSC (75). If the relaxation kinetics can be utilized to predict the shelf-life of the amorphous pharmaceuticals, it would help formulation scientists to establish the optimal formulation, processing, and storage conditions where molecular mobility is minimized, so that the stability of the products can be attained.

Fundamental parameters of amorphous solids related to molecular mobility were cited in Table 8 (76,77).

TABLE 8 Fundamental Parameters of the Amorphous Solids Related to Molecular Mobility

Parameters	Relationship
Glass transition temperature (T_g)	The temperature above which the molecular mobility will significantly increase
Kauzmann temperature	The temperature, at which the extrapolated entropy of the amorphous solid would be equal to that of the crystalline solid, is the ideal storage temperature
Fragility	The slope of the scaled Arrhenius plot of viscosity versus temperature, which indicates how fast structural relaxation accelerates approaches and passes the T_g region (76) Fragility (m) can also be defined (77) as: $m = \triangle H/(2.303R\,T_g)$, where ΔH is the activation energy for molecular motions at T_g and R is the gas constant. A small value of m is representative of a non-fragile (strong) glass former.
Structural relaxation time (72)	For exponential relax, the relaxation time (τ) can be estimated by Vogel–Fulcher–Tamman (VFT) equation: $\tau(T) = \tau_0 \exp\left(\frac{A}{T - T_0}\right)$ T_0 is 0°K. For non-exponential decay, very often, the relaxation follows Kohlrausch–Williams–Watt (KWW) equation: $\phi(t) \propto \exp - \left(\frac{t}{\tau_{KWW}}\right)^{\beta_{KWW}}$ β quantifies the deviation from the exponential decay.

Points to Consider for Amorphous Formulation Development

Bioavailability of a poorly water-soluble crystalline compound was remarkably improved by amorphous formulation approach. Immobilization and isolation of the labile amorphous API in rigid glasses of inert polymer matrix has been shown to significantly improve the stability of the API. Polymers and processes play an important role in stabilization of the amorphous drug throughout its shelf-life and maintaining supersaturation of drug solution. Desirable attributes of polymers are high T_g, moisture scavenger capability, high molecular weight (MW), solubility parameters comparable with that of the API, and nucleation inhibitor. Selection of amorphous processing methods depend on the API and the polymer. Thorough understanding of polymers and processes are crucial for achieving a stable amorphous formulation with maximum bioavailability. Wettability and intrinsic particle size of the amorphous drug are of critical importance to ensure bioavailability of poorly soluble compounds. Micro-embedding amorphous drug in nano- or micron-size in polymer matrix tremendously improves wettability and physical stability of amorphous drugs. Drug and polymer must be co-precipitated simultaneously. Appropriate down-stream processing needs to be selected based on the physico-chemical and particulate properties of the drug and polymer. Various analytical methods are essential to ensure the product quality.

LIPID-BASED FORMULATION

Lipid-based formulations brought a tremendous change in formulating poorly soluble drugs for improving their bioavailability. In lipid-based systems, the poorly soluble drug is completely solubilized in lipid formulation. Therefore, the drug exists in lipid formulation at molecular level which gives great probability for improved absorption for poorly soluble drugs. Despite the fact that lipid formulation technology holds, the research and development activities in this area are limited and only a few products have reached market place based on lipid formulation.

Physiological factors which can influence the rate and extent of drug absorption from a lipid-based formulation include gastrointestinal lipid digestion (78–80) and the emulsion droplet size formed upon mixing with gastrointestinal fluids (81–83). From a formulation perspective, solubility of the drug substance in the lipid vehicle controls the drug loading of the formulation whereas the stability of the drug can be influenced by the lipidic excipient peroxide and acid values and the degree of lipid fatty acid saturation and hygroscopicity. Various categories of lipid formulations have been previously classified with respect to composition, content of hydrophilic co-solvents, dispersion droplet size, impact of aqueous dilution, and digestibility in vivo (84,85).

In this chapter, we will classify lipid formulations based on the miscibility of the system components. Lipid-based formulation as a single phase is classified as isotropic lipid solution. Whereas, a two-phase system in which the API is in a very fine solid state is classified as lipid suspension and lipid semi-solid dispersion. The two-phase systems may provide improved chemical stability of oxygen and moisture-sensitive compounds and sustained release; they may not provide the advantage in bioavailability as the API is in solid state. Therefore, in this chapter, we will only discuss the lipid isotropic solutions.

Isotropic Solutions

Isotropic solutions are single-phase systems and include lipid solutions, and SMEDDS. Isotropic solutions find application primarily for oral delivery of lipophilic drugs for

which a unit dose can be solubilized in an acceptable volume of the lipid vehicle. This type of lipid formulations offers special advantage in improving bioavailability of lipophilic drugs and stabilizing oxygen and moisture-sensitive drugs.

Lipid Solutions

In this type of lipid formulations, the drug is dissolved in a single lipid vehicle without the addition of surfactants. Emulsification process of the lipid solution will rely on external surfactants, such as bile salts, that are present in the intestinal fluids. Selection of the type of lipids deems critical to achieve maximum bioavailability. Pre-digested lipids of medium chain fatty acids, such as monoglycerides of caprylic/capric acids (Capmul® MCM), and propylene glycol monoester of medium chain fatty acids, are commonly used for improving bioavailability of poorly soluble compounds. These types of lipids can readily form emulsion when exposed to bile salts in the gut.

Self-Emulsifying Drug Delivery Systems

In the absence of water, the mixtures of oil(s) and non-ionic surfactant(s) form clear and transparent isotropic solutions that are known as SEDDS. One characteristic of SEDDS is their ability to form fine oil–water emulsions upon mild agitation when exposed to aqueous media. The digestive motility in stomach and intestine provides the agitation necessary for self-emulsification (86).

Efficiency of SEDDS can be defined as: (*i*) be able to form a fine emulsion having droplet size of $< 5\,\mu m$ upon dilution with aqueous media under mild agitation (82) and (*ii*) produce oil droplets of appropriate polarity which permits a faster drug release to the aqueous phase.

The effect of SEDDS on drug delivery and oral absorption are a subject of several excellent publications (82,84,87). The advantage of SEDDS was clearly shown by the example from Shah et al. (82) for a lipophilic drug that the SEDDS provided greater than three-fold increase in C_{max} and AUC compared with the other three dosage forms after oral administration in dogs.

Self-Microemulsifying Drug Delivery System

SMEDDS is an isotropic drug solution in oil, surfactant and co-surfactant mixture, which emulsifies spontaneously when mixed in the GI fluids or under gentle mixing. The resulting micro-emulsions are thermodynamically stable, isotropic clear dispersions of two immiscible liquids, such as oil and water, stabilized by an interfacial film of surfactant molecules (88). Mean droplet diameter of the resulting emulsion is typically $< 50\,nm$ and not so much dependent on the dilution factor, indicating a good SMEDDS. The SMEDDS offers some advantages of improving drug solubilization and protecting against enzymatic hydrolysis, as well as the potential for enhanced absorption by surfactant-induced membrane fluidity and permeability changes (89). Neoral®, a micro-emulsion preconcentrate of cyclosporine has shown to have higher bioavailability and reduced inter- and intra-patient variable pharmacokinetics parameters when compared with Sandimmune®, an oil-in-water emulsion (90).

Factors Impacting Bioavailability of Lipid-Based Formulations

Lipid Digestion

Lipid digestibility can be significant, as the gastric emptying rate affecting drug absorption, particularly if there is a large affinity of the drug to the lipid vehicle.

Accordingly, it can be expected that the absorption rate of the drug would be controlled by selecting the lipid vehicles. Gastrointestinal lipid digestion consists of three sequential steps: (*i*) the dispersion of fat globules into finely divided emulsion, (*ii*) the enzymatic hydrolysis of fatty acid esters at the emulsion–water interface, and (*iii*) the desorption and dispersion of insoluble lipid products into absorbable form. A diagram of lipid digestion process is given in Figure 19. In the presence of lipase, lipid emulsions break down in the stomach to monoglycerides and fatty acids. The presence of bile salts forms mixed micelles with fatty acids and monoglycerides. The mixed micelles facilitate aqueous transport of the drug to the intestinal wall in the GI tract. The drug in the concentrated form at cell wall is taken up by enterocytes for absorption. Lipids that are non-digestible should be completely avoided. The chain length of lipids has significant impact on lipolysis. The long chain lipids are lipolysed slowly, while for medium chain glycerides lipolysis occurs more readily (91). Surfactant can sometimes adversely affect the digestion process, as they are present at the inter-phase between water and lipid (79,91). The presence of surfactant at the inter-phase prevents lipase from diffusing through the inter-phase, thereby inhibiting digestion of the lipid and diminishing drug release. In addition, lipids that are not affected by negative effect of surfactant such as medium chain

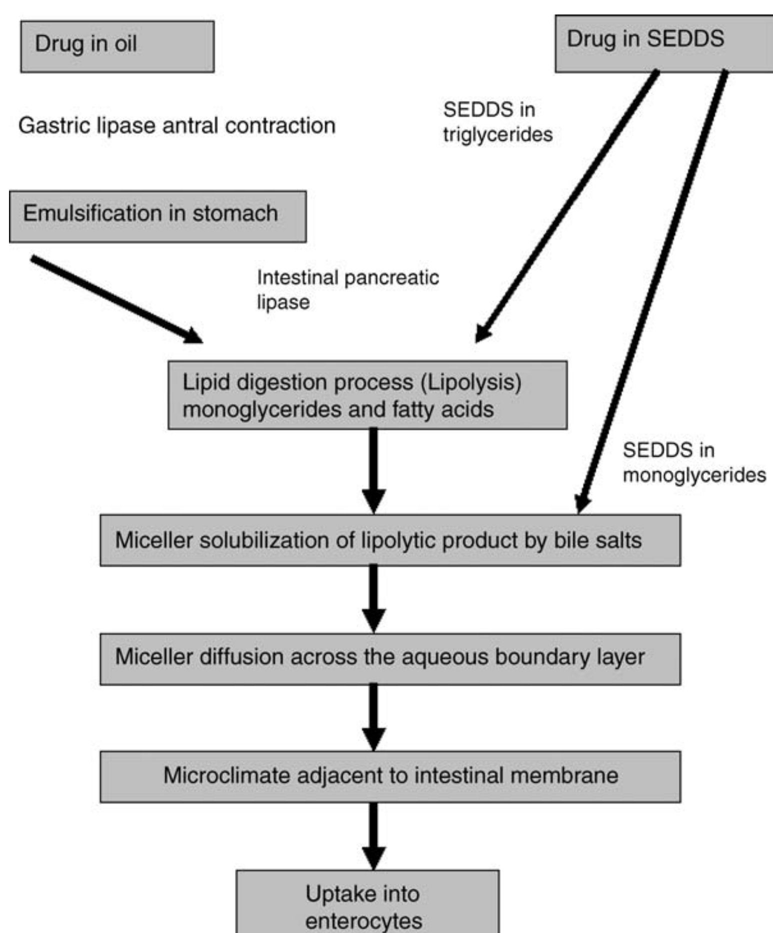

FIGURE 19 A schematic diagram for typical lipid digestion processes.

monoglycerides, fatty acids, and monoesters of fatty acids were preferred as vehicle for lipid delivery system.

Mean Emulsion Droplet Diameter

Mean emulsion droplet diameter (MEDD) is critical to assess the quality of self-emulsifying formulations. Such considerations are important for the enhanced surface area available to pancreatic lipase and/or the partition of lipophilic drugs into aqueous phases and ultimately for drug release. Droplet size of SEDDS upon dilution with aqueous media is primarily controlled by the type and concentration of emulsifier. The higher the concentration of the emulsifier, the smaller the emulsion droplet size and the faster the drug release (82,92,93).

Typically, SEDDS (125 μL) is diluted to 250 mL with water in a volumetric flask and gently mixed by inverting the flask. The droplet size distributions of the resultant emulsions are determined using Malvern Particle Size Analyzer. Two techniques are commonly used to measure MEDD of the self-emulsified systems. Low angle laser light diffraction is typically used for emulsions with droplet distributions above 1 μ and quasi-elastic light scattering is used for investigations of submicron dispersions and measurements can be made 24 hours after preparation. The particle size distribution of different samples of emulsions can have different patterns depending on the composition of the lipid formulation (87).

Mean emulsion droplet diameter seems to be a very critical factor in predicting in vivo performance of the undigested lipid-based formulations, such as long chain triglycerides as clearly seen in Cyclosporin case (Neoral® versus Sandimmune®), Kovarik et al. (90). On the other hand with predigested lipid such as medium chain monoglycerides or propylene glycol monoester of C8–C10 fatty acids MEDD may not be crucial.

Lipophilicity of Drugs

Very hydrophobic drugs (log *P* values >6) could be taken up into the lymphatic system by partitioning into chylomicrons in the mesentery (94), and this has been demonstrated to be crucial for the absorption of the anti-malarial compound halofantrine (95,96). The retinoids are highly lipophilic molecules and are known to be transported in the intestinal lymph after oral administration (97). Lipid solubility showed a general increase with increasing log *P* of the retinoid. The rank order of increasing lymphatic uptake appears to follow an inverse relationship with solubility of the retinoid in each of the three oils evaluated.

Type of Lipids

The nature or type of lipids is important as digestible lipids may influence absorption in a different manner from non-digestible lipids. Commonly used lipophilic vehicles are presented in Table 9.

Long chain unsaturated fatty acids disorganize the membrane structure more than medium chain saturated fatty acids (81,98). Among the lipids, unsaturated fatty acids in their monoglycerides enhanced the intestinal absorption of streptomycin more than saturated fatty acids. The lower the melting point of the fatty acid, the more the drug absorption was increased. Lipase enzymes are much more active on triglycerides with short chain than on those with long chain fatty acids (99–101).

The effect of fatty acid chain length and the saturation of fatty acid present in the glyceride on the drug release at 60% emulsifier and hydrophilic–lipophilic balance

TABLE 9 Commonly Used Lipophilic Vehicles

Classification	Lipophilic vehicles
Fatty acids	Oleic acid, Myristic acid, Caprylic acid, Capric acid
Ethanol ester	Ethyl Oleate
Triglycerides of long-chain fatty acids	Soybean Oil, Peanut Oil, Arachis Oil, Corn Oil
Triglycerides of medium-chain fatty acids	Miglyol 812, Captex 355, Labrafac

(HLB) of 10 is presented in Figure 20. Labrafac CM 10 provides a faster drug release than either Labrafil M 10 or Labrafil NA 10 due to the medium chain length (C_8–C_{10}) of the fatty acid present in its composition. Drug release was slightly faster with Labrafil M 10 than with Labrafil NA 10. That was explained by the degree of unsaturation present in the fatty acid chain length between Labrafil M 10 ($C_{18:2}$) and Labrafil NA 10 ($C_{18:1}$).

Drug Release

The natures of the drug and the lipid as well as aqueous solubility of the drug are crucial factors that control drug release and the absorption from lipid-based formulations (102). Other factors include whether the drug is formulated in oil, SEDDS or emulsified form, the absorption pathway of the drug, the droplet size of the emulsion present in the intestine, the role of surfactants, the metabolic pathway of the lipids and gastric motility changes by lipids. A schematic representation of the drug diffusion from oil droplets of emulsion, which is formed when SEDDS or SMEDDS exposed to the gastrointestinal fluid, is shown in Figure 21. The amount of drug diffused at time *t* (Q*t*) from oil droplet to

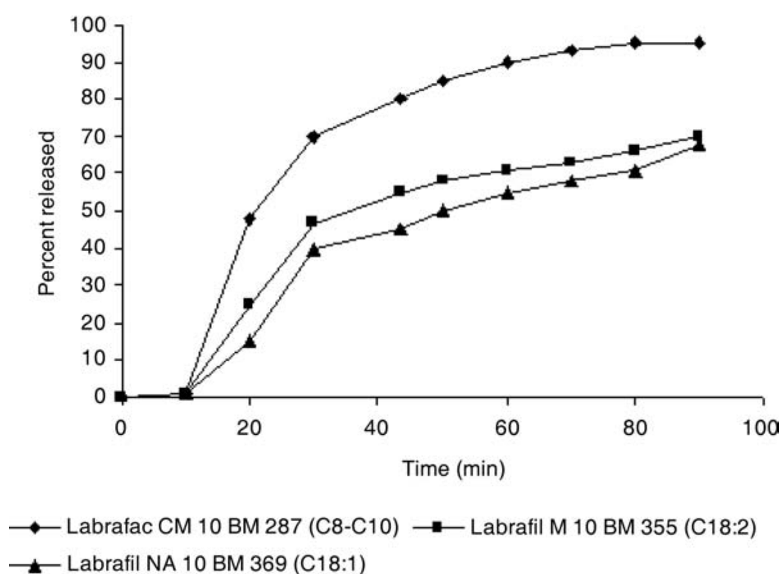

FIGURE 20 Effect of chain length and saturation of fatty acid present in the glyceride on drug release of a BCS II compound from peanut oil-based solutions containing 60% of emulsifier with HLB of 10 (Paddles, 50 rpm, 900 mL of 5% Cremophor EL aqueous solution).

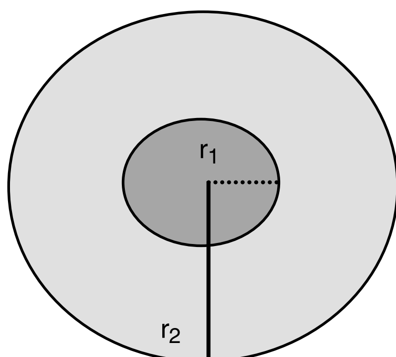

FIGURE 21 Drug diffusion from oil droplets. *Abbreviations*: Q_t, Amount of drug diffused at time t; r, Radius of the oil droplet; K, Partition coefficient (o/w); r_1, Radius of the smaller globule; r_2, Radius of the larger globule.

aqueous environment is primarily a function of the radius of the oil droplet (r), which is a reflection of the surface area, and the partition coefficient, polarity (K), which reflects the affinity of the drug for oil and/or water and concentration gradient formed.

For a solubilized drug in lipid vehicle, the more soluble the drug, the less efficient is the release from the vehicle. The release of a drug from a solution is an inverse function of its solubility in the solvent (103). Thus, a less efficient solvent will release the drug more readily, but the advantage is limited by the amount of drug which the solvent can dissolve.

Similarly, the aqueous solubility of the drug will be of importance as more freely soluble drugs will simply dissolve into the lumen of the intestine prior to absorption. Fraction absorbed (F_a) is proportional to aqueous solubility (S) and the volume of the gastrointestinal fluids (V), and is inversely proportional to the dose (D), assuming that membrane permeability is not a rate-determining step (104).

$$F_a \ \alpha \ SV/D.$$

If the oily solution which was administered and the gastrointestinal fluid are in equilibrium, the partition coefficient will become one of the critical factors for the evaluation of the efficiency of SEDDS. Orally administered lipid will almost certainly be subdivided in the gastrointestinal tract with a corresponding increase in interfacial area. This will be aided by emulsifiers present in the formulation and also by bile salts. The smaller the droplet sizes of the oil and the lower the partition coefficient (o/w), the more efficient will be the SEDDS.

$$\mathrm{MW} = \mathrm{Mo}/(K\phi)$$

where MW is the quantity of drug in the aqueous solution, Mo is the quantity of drug in the lipid phase, K is the partition coefficient (o/w), ϕ is the volume ratio of lipid to aqueous phase.

The lower the volume ratio, ϕ, the higher the quantity of drug released from lipid to aqueous phase due to the faster partitioning to aqueous phase. Therefore, volume ratio ϕ must be taken into account when selecting the type of lipid, partition coefficient, and molecular weight to achieve optimal release.

In order to ascertain that the drug is completely delivered from the formulation in a predetermined profile, it is necessary to develop a prognostic in vitro dissolution testing mimicking in vivo performance. Knowledge of the in vivo drug release mechanism of lipid delivery systems is necessary to provide valuable insight for in vitro dissolution method development.

Several challenges are associated with in vitro dissolution method development for lipid-based formulations. An in vitro lypolysis model to understand digestion process has been evaluated by several scientists. It is extensively described in publication by Zangenberg et al. (105). However, due to its complexity it is not routinely used. Lipid-based formulations are encapsulated in soft gelatin capsules or hard gelatin capsules and dispensed as unit dosage for ease of administration. Such dosage forms may not be soluble in commonly used aqueous media. Addition of surfactants or use of hydro-alcoholic media has been routinely conducted. Exposure of the gelatin shell to such media may induce physical and/or chemical changes arising through complex formation or cross-linking reactions.

Gelatin, a major component in the capsule shell, is a heterogeneous protein mixture of partially hydrolyzed animal collagen containing most of the essential amino acids, including the basic amino acids that are capable of potentially reacting with sodium lauryl sulfate (SLS). The isoelectric point of gelatin is around pH 5–8 and its overall net charge at $pH < 5$ is positive. SLS can interact (106,107) with gelatin through ionic charge–charge interactions and/or hydrophobic interactions. SLS has a very high HLB value of 40, acting as a solubilizer rather than an emulsifier and may not be an ideal surfactant to be used in a dissolution medium for a lipid formulation. Cetyl trimethyl ammonium bromide (CTAB), a cationic surfactant, may potentially interact with anionic excipients, such as fatty acids. The Presence of the counter-ion in a dissolution medium containing an ionic surfactant could have significant impact on drug release. To avoid the potentially unwanted interactions, a non-ionic surfactant appears to be the most appropriate choice.

The in vitro dissolution, partition coefficient (o/w), and mean particle size of oil droplet provided direct correlation to the rate and extent of absorption of nifedipine from triglycerides-based delivery system in beagle dogs shown in Table 10 (108).

In another study, in vitro dissolution does not correlate with the in vivo absorption in man under fed conditions of a HIV-PI drug formulated in isotropic solutions of monoglycerides with HLB values of four versus 14 values shown in Figure 22, respectively. The data clearly show that in vitro dissolution sometimes does not correlate in vivo drug absorption. Irrespective of release rate both formulations provided similar

TABLE 10 Summary of In Vitro and In Vivo Results for Nifidepine Lipid Solution

Formulation	Solubility (mg/g)	% Dissolution at 60 minute	Partition coefficient (o/w)	Mean particle size (nm)	AUC_{0-24} Mean ± SD (ng.h/mL)	C_{max} Mean ± SD (ng/mL)[a]
Miglyol 812	3.36 ± 0.03	50.19 ± 1.44	5.6 ± 0.45	Coarse	183 ± 115^{b}	56 ± 31^{c}
Miglyol 810/ Cremophor EL	4.86 ± 0.04	97.23 ± 2.52	1.1 ± 0.02	10.0 ± 1.0	231 ± 106^{b}	105 ± 36^{c}

[a]Fasted beagle dogs ($n = 6$) using a single dose (2.5 mg Nifidepine) crossover design.
[b]Not significant different (p value is 0.27, t-test for paired value for means).
[c]Significant different (p value is 0.036, t-test for paired value for means).

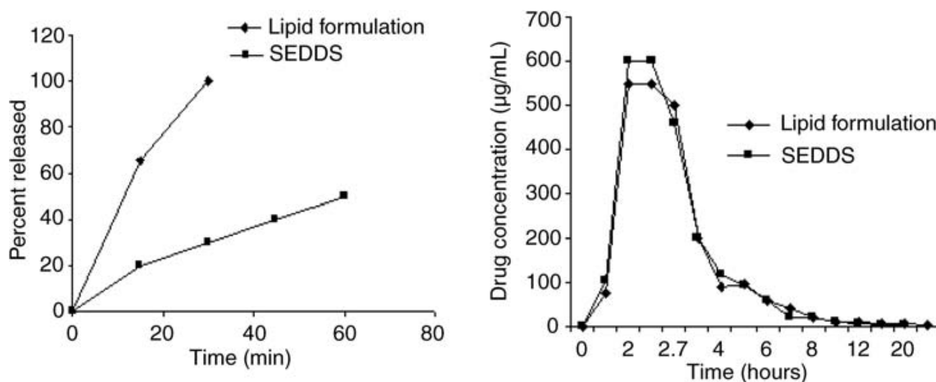

FIGURE 22 In vitro dissolution versus in vivo performance of two different lipid formulations of a HIV-protease inhibitor.

exposure indicating in vivo monoglycerides with HLB 4 or pegylated glyceride with HLB 14 may have been readily emulsified in the gastrointestinal tract by bile salts in man providing comparable exposure.

Therefore, in vivo performance of an isotropic lipid-based solution depends not only on in vitro dissolution but also the solubility of the drug in lipid, partition of the drug from lipid to water, droplet size of the final emulsion and lipid digestibility considerations. In many instances, lipid-based formulation is selected based on in vivo performance. The in vitro dissolution profile of the formulation should be established to reflect the in vivo absorption profile and used as a baseline for monitoring lot-to-lot reproducibility and ensuring product ensuring product quality.

Points to Consider in Developing Isotropic Lipid Solutions

Physico-chemical properties of the active as well as choice of lipids play a major role in designing isotropic solution whether it will be a simple lipid solution, SEDDS or SMEDDS. Some of the physico-chemical parameters which influence the design of isotropic solutions include: solubility which is impacted by solubility parameters, HLB, partition coefficient, dielectric constant, molecular weight, degree of saturation of lipid, and surface tension. Phase diagram will help to identify optimum region for isotropic solution and therefore, identify the ratio of drug, vehicle and emulsifier/surfactant to achieve optimal isotropic solution with maximum solubility.

Solubility of the Active Pharmaceutical Ingredients in the Lipid System

In order to develop a formulation in a reasonable sized capsule, the selection of the vehicle where the drug has maximum solubility is the most desirable. Solubility is one of the major factors which limit the use of lipid-based delivery system. Drug loading is critical, particularly when dealing with moderate potency (dose 100–200 mg) actives. For ease of administration of an acceptable capsule size, the fill weight should not exceed 1 g of the lipid formulation. Dose and solubility of the drug in lipid vehicles are the determining factors whether isotropic lipid formulation is practical or not.

Factors that can impact the solubility include solubility parameter (δ), HLB values, partition coefficient, MW, dielectric constant (ε) as well as its fatty acid chain length, saponification value, surface tension, and viscosity.

Solubility parameters (δ): Solubility parameters can be used as a predictive formulation tool. Substances that are more hydrophilic exhibit higher solubility parameters while substances that are more lipophilic have lower solubility parameters due to the lack of polar and intermolecular forces. Generally, substances of similar characteristics tend to be compatible within a formulation i.e., "Like dissolves like." The rule of thumb is that substances within 2–3 solubility parameter units can be considered molecularly similar, and therefore are soluble or miscible. As the difference between Hildebrand solubility parameters (HSP) increases, the solubility decreases. HSP is an effective way to measure the formulation characteristics of a particular compound. Much work has been done over the years on the relationship between the structure of molecules and chemical mixtures and their physical behavior. The solubility parameters presented here, as cited in the Croda Product Guide of 2000, are based on fundamental molecular properties: boiling point in Kelvin (BP), MW, and specific gravity (SG) parameters which determine the overall characteristics of a material. For specific gravity's calculation temperature (T) is in Kelvin:

$$\mathrm{HSP}\,(d) = \frac{[(23.7 \times \mathrm{BP} + 0.02 \times \mathrm{BP}^2 - 2950) - 1.98 \times T]^{1/2}}{(\mathrm{MW/SG})} \tag{1}$$

Hydrophilic–Lipophilic balance: HLB is an empirical formula that is used to select surfactants for microemulsions (88,109). Non-ionic and ionic surfactants are often considered for pharmaceutical applications as they are less toxic (89,110) and less affected by pH and ionic strength changes (111).

The HLB value of each lipid vehicle can be calculated using the following equation:

$\mathrm{HLB} = 20\ (1 - S/A)$,

where S is the saponification number of the ester and A is the acid number of the fatty acid (112). The higher the HLB value of the surfactant, the wider is the range of the micro-emulsion existence. In most cases, it is the right blend of a low and high HLB surfactant that leads to the formation of a thermodynamically stable micro-emulsion in the absence of high-energy mixing or a co-surfactant.

Emulsifiers with $\mathrm{HLB} > 10$, which are commonly used in isotropic lipid-based solutions, are provided in Table 11.

Co-emulsifiers with the HLB ranging from 4 to 6, which are commonly used in isotropic lipid-based solutions, are provided in Table 12.

The effect of HLB on the release rate of a lipophilic model drug at 60% emulsifier is shown in Figure 23 (82). Polglycolyzed glycerides (PGG) with an HLB of about 10 resulted in the fastest release rate. On the other hand, HLB of 14 did not achieve fastest release due to immiscibility of low HLB oil with Labrasol resulting in non-isotropic solution. The solution with two phases did not provide acceptable results. HLB of 10 in this study was optimum; however, such HLB range of 10 needs to meet qualifications, i.e., it should be obtained by appropriate combination of fatty acid and PEG.

Partition coefficient: Log P is used as an indicator of the lipophilicity of a molecule where log P is the logarithm to base 10 of the partition coefficient of a compound between two phases, usually 1-octanol and water. The solubility of a compound is an absolute measurement of the equilibrium of the solute between the solvent and its pure phase (113). In many instances, partition coefficients of the drugs and their melting points have been shown to be key factors on drug solubility in lipids. Solubility of an

TABLE 11 Emulsifiers Which are Commonly Used in Isotropic Lipid Based Solution

Classifications	Emulsifiers
Polyglycolyzed glycerides	PEG-8 glyceryl caprylate/caprate (Labrasol)
	PEG-32 glyceryl laurate (Gelucire 44/14)
	PEG-32 glyceryl palmito stearate (Gelucire 50/13)
Polyoxyethylene sorbitan fatty acid esters	Polyoxyethylene 20 sorbitan monolaurate (Tween 20)
	Polyoxyethylene 20 sorbitan monostearate (Tween 60)
	Polyoxyethylene 20 sorbitan monooleate (Tween 80)
Sorbitan fatty acid esters	Sorbitan monolaurate (Span 20)
	Sorbitan monostearate (Span 60)
	Sorbitan monooleate (Span 80)
Polyoxyethylene castor oil derivatives	Polyoxyl 35 castor oil (Cremophor EL)
	Polyoxyl 40 hydrogenated castor oil (Cremophor RH 40)
Polyethylene glycol based derivatives of Vitamin E	d-Alpha-Tocopheryl Polyethylene Glycol-1000 Succinate (TPGS)
Phospholipids, PEG based Phospholipids	Lecithin, Modified Lecithin

investigational anti-HIV agent in lipid has been shown to increase as ester bond of the lipid increases (114). Compounds with log $P > 4$ (i.e., being more lipophilic) are likely solubilized in oils. Compounds with intermediate log P (log $P < 4$) may require a blend of hydrophilic surfactants (HLB 4–12) or water-soluble co-solvents to form a self-emulsifying system with maximum solubility. It is also possible for a compound to have a large log P value but not necessarily high solubility in oil, whilst another compound may be very soluble in oil but has a relatively low log P value (115). Therefore, high solubility of a compound in octanol will not always relate to high solubility in long chain fatty acid triglycerides. These findings clearly indicate that partition coefficient appears to be only one of the predominating factors governing the drug solubility in lipid vehicles.

Phase diagram: The self-emulsifying behavior of a binary non-ionic surfactant–oil mixture has been shown to be dependent on both temperature and surfactant concentration. Pseudo-ternary phase diagrams are typically constructed identifying the efficient self-emulsification regions and to establish the optimum concentrations of oil, surfactant, and co-surfactant. In the absence of water, the oil–surfactant blends can be either clear isotropic solutions or oily dispersions depending on the nature of the oil and

TABLE 12 Co-Emulsifiers Which are Commonly Used in Isotropic Lipid Based Solution

Classifications	Co-emulsifiers
Polyglycolyzed glycerides	PEG-6 glyceryl monooleate (Labrafil M1944 CS)
Monoglycerides of long-chain fatty acids	Glycerol monooleate, Glycerol monostearate
Monoglycerides of medium-chain fatty acids	Glyceryl caprylate/caprate (Capmul MCM)
Mono and diglycerides of medium-chain fatty acids	Imwittor 972, Imwittor 988
Propylene glycol monoester of medium-chain fatty acids	Propylene glycol monocaprylate (Capmul PG-8; Capryol 90)
Propylene glycol diester of medium-chain fatty acids	Propylene glycol dicaprylate/dicaprate (CapTeX 200)
Poly-glycerol esters	Glyceryl tri-oleate, decaglycerol mono-oleate

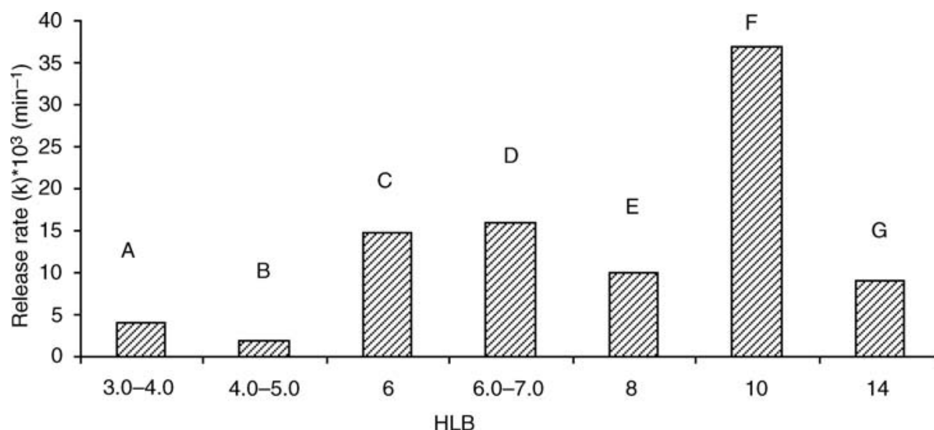

FIGURE 23 Effect of HLB on the release rate of A HIV-protease inhibitor (BCS II compound) from peanut oil-based solutions containing 60% of emulsifier (Paddles, 50 rpm, 900 mL of 5% Cremophor EL aqueous solution). *Abbreviations*: A, Labrafil M2125; B, Labrafac Hydro; C, Labrafac CM6 BM290; D, Labrafil WL2609; E, Labrafac CM8Bm 284; F, Labrafac CM 10 BM 287; G, Labrasol.

surfactant and the oil-to-surfactant ratio. Phase diagrams for a given drug should be individually constructed, because the impact of physico-chemical properties of the drugs (i.e., inherent polarity, surface active property) on efficiency of SEDDS is not predictive. Phase diagram for SEDDS containing drug, oil, and surfactant is constructed by varying the ratio of drug, oil, and surfactant. One can establish the different regions for good, intermediate, and poor self-emulsification.

Phase diagram for peanut oil, emulsifier (Labrafac CM-10), and model drug system is presented in Figure 24, differentiating among poor, good, and spontaneous self-emulsifying systems.

Phase studies are typically performed using a small quantity of the samples of oil–surfactant mixture diluted sequentially by the weighted addition of water. After equilibrium, the phase type is identified using a crossed polarized viewer and an optical microscope. Microscopic examination of the emulsion is very useful for the crude emulsion, because the creaming rate of droplets $> 100\ \mu m$ is so rapid that large droplets can be excluded from droplet size evaluation by laser light diffraction. Polarized light microscopy is an useful tool in examining the various phases of the phase diagram at ambient temperature and to verify the isotropic behavior of micro-emulsions.

Drug loading: It can affect long-term physical stability of the drug product. The saturation point in the lipid-based formulation should be carefully established. The plot obtained between specific viscosities against drug concentrations presented in Figure 25 shows an inflection point (where drastic change in the slope of the curve occurred) above which saturation of the drug may occur (116). Optimal drug loading in lipid solution must be established to avoid potential gelling or drug crystallization under shearing and during storage. Drastic change in the emulsifying property as indicated by the MEDD due to droplet coalescence and/or aggregation is indicative of the product instability.

Sorption/Desorption (Hygroscopicity) Isotherm

Hygroscopicity of the lipid may induce dehydration of the SGC or HGC shell, resulting in brittleness of the capsule shell. Impact of temperature and moisture on the drug solubility

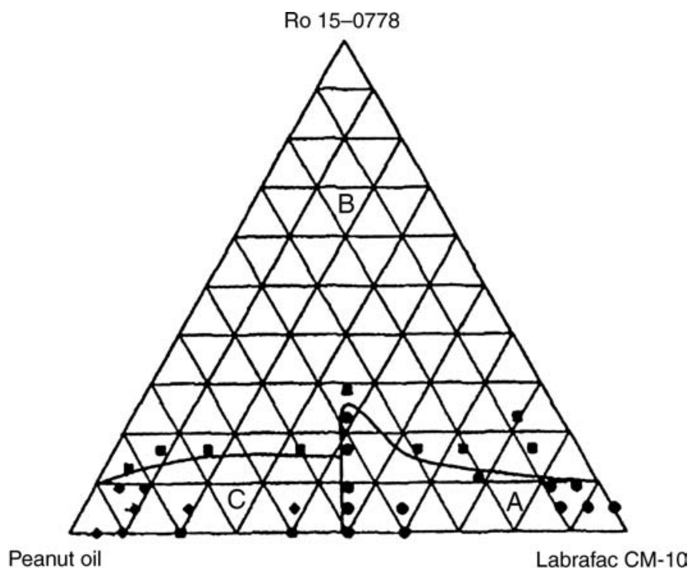

FIGURE 24 Phase diagram for peanut oil/emulsifier, Labrafac CM-10 BM 287/Ro 15-0778 system. Region A: good and efficient self-emulsifying systems; Region B: poor self-emulsifying systems; Region C: intermediate self-emulsifying systems.

characteristics must be investigated. Potential solute migration into the shell must be characterized during the formulation development, particularly when such a drug having good solubility in glycerin and sorbitol, which are commonly used as plasticizers in SGC. The characterization of lipid-based formulation has been extensively discussed by Craig (87) using low-frequency dielectric spectroscopy, surface tension, and particle size

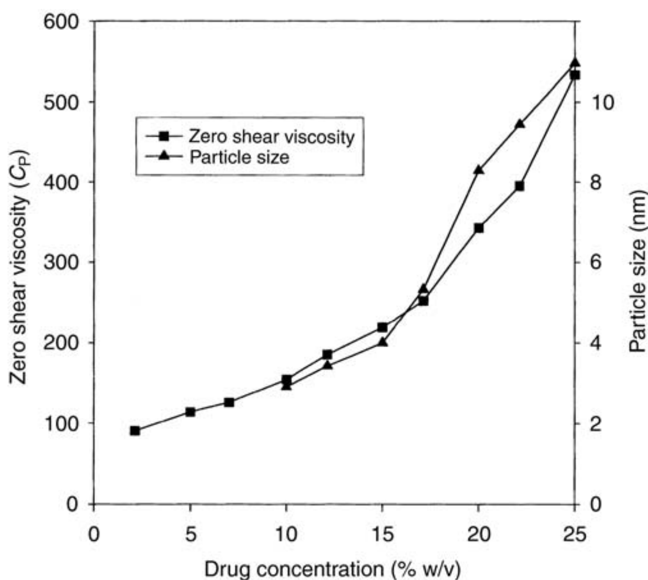

FIGURE 25 Effect of drug loading on zero shear viscosity and particle size of lipid solutions.

analysis. During soft gel encapsulation, water migration from a wet gelatin ribbon into the fill solution is unavoidable. The wet gelatin ribbon typically contains approximately 60–70% water. The rate and extent of water migration depend on the hygroscopicity of the fill solution. The migration of water may introduce precipitation of the fill solution. Water sorption and desorption profiles of the fill solution containing lipid formulation should be established.

Moisture sorption isotherms of various excipients that are typically used in lipid-based formulations are presented in Figure 26. It is critical to ensure that the formulation can withstand the water migration during soft gel encapsulation. In the meanwhile, the fill component(s) may migrate to the shell. The hygroscopicity of the fill solution could induce dehydration of the gelatin shell during long-term storage, resulting in brittleness of the capsules and potential leakage of the fill. These dynamic changes must be thoroughly investigated in the early stages of development.

Stability Considerations

Stability of the lipid-based formulation as a function of time and temperature is routinely evaluated to achieve its acceptable shelf-life. Lipid-based formulations are generally encapsulated in hard or soft gelatin capsules. Compatibility studies between the fill and the shell are very critical and must be well characterized. The excipient used in lipid-based delivery systems may be derived from natural products with varying degrees of purity, acid values, degree of saturation of fatty acids, or polymers with varying molecular weight, therefore batch-to-batch variability needs to be addressed. It is therefore essential to develop analytical methodology along with physical observations in order to avoid undesirable attributes of final product characteristics, such as polymorphism or phase changes.

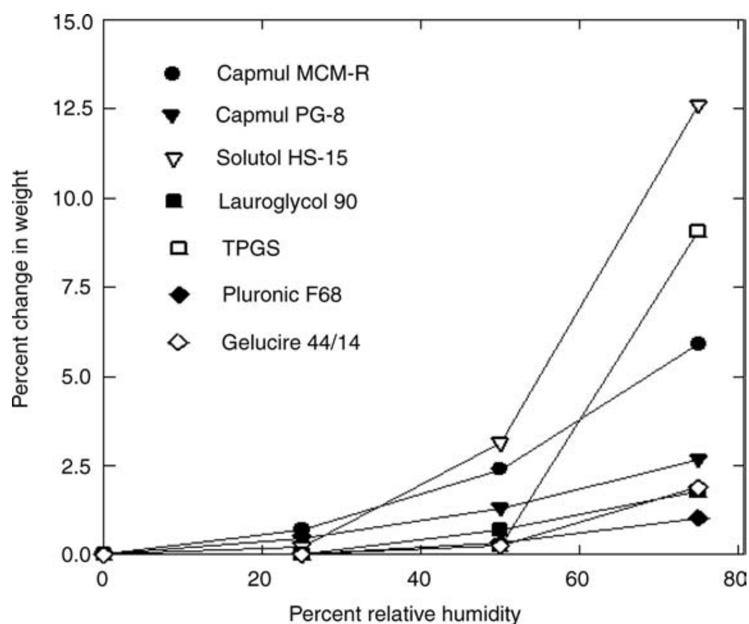

FIGURE 26 Moisture isotherms of typically used lipid excipients.

Chemical stability: Chemical stability of lipid-based formulation can be greatly affected by the type of lipid, degree of saturation of the fatty acids, peroxide content, free acids content, and saponification values. For oxidation-sensitive drugs, saturated lipids are preferred to unsaturated one. Butylated hydroxy anisole (BHA) alone and in combination of Butylated hydroxy toluene (BHT) were commonly used as anti-oxidants for lipid-based formulation.

Lipids with a high acid value can accelerate the acid catalyzed hydrolysis of the drug and must be carefully evaluated. It has been shown that glyceryl monostearate in cubic phase can improve the stability of cefazolin and cefuroxime to hydrolysis and oxidation, probably immobilizing the drug in cubic phase gel and preventing subsequent interaction between drug and water (117). Chemical stability of isotropic solutions follows solution-state kinetics.

Physical stability: Cross-linking reaction of low molecular weight such as aldehydes, impurities or degradation products of actives or excipients, with side chain amino groups of lysine and arginine residues of the gelatin can occur to an appreciable extent under stressed storage conditions. The cross-linked gelatin shell causes formation of a swollen, rubbery, and water-insoluble membrane (pellicle) during dissolution testing. The insoluble film acts as a barrier to drug release. Addition of antioxidants, such as BHT and BHA, in a lipid-based formulation is recommended to prevent the gelatin cross-linking, thereby minimizing potential decrease in the dissolution profiles of the SGC.

Manufacturability Considerations

Basic equipment: The manufacture of SEDDS and SMEDDS is rather simple, requires only the availability of the most basic mixing, jacketed vessel for appropriate temperature control. SEDDS and SMEDDS are thermodynamically favored; the order of addition of the components should not have any effect on the in vivo performance of the final product. The manufacture is to a lesser extent dependent on the careful control of manufacturing process when compared with emulsion. It is not a dusty process, therefore, it provides advantages on handling potent compounds which might be considered hazardous otherwise.

Encapsulation: The fill solution can be encapsulated either in soft gelatin capsules or hard gelatin capsules. SGCs are hermetically sealed during the manufacturing process, which prevents the leakage of the liquid fill. The semi-solid filled in HGC technology offers special interest from different perspective as it generally can be processed in-house. The LIQFIL™ machine (Shionogi Inc.) integrates automatic system, combining a high-speed filling machine for liquids with a banded-sealing machine, resulting in a hermetic seal on the filled capsules to prevent the leakage of the fill. The filling of liquids into HGC could be challenging because of the potential for leakage out of the capsule before the capsule can be properly sealed.

Hard gelatin encapsulation of liquid formulations necessitates the use of a secondary sealing process, which prevents the leakage of liquid fills. There are two sealing techniques: capsule banding and microspray gelatin fusion. Capsule banding can be used to seal liquid-filled hard gelatin capsules, but it is no longer the method of choice and is relatively expensive and difficult to scale-up. The recently developed microspray gelatin fusion (e.g., LEMS™ technology) eliminates the need for banding together with offering a practical approach for sealing hard gelatin capsules containing liquid or semi-solids. In this technology, the sealing fluid (typically a 50:50 solution of water and ethanol which results in a lower surface tension than water alone) is sprayed onto the joint between the cap and body, lowering the melting point of gelatin in the wetted area. Approximately

50 μL of fluid is sprayed during a 1-second cycle, followed by suction to remove excess fluid. Air, heated to 40–60°C, is gently blown across the capsule during a 1-minute cycle to complete the melting and fusion of the two gelatin layers. Gelatin setting is completed while the product returns to room temperature.

Shear effect: Prolonged shearing was shown to change the rheological behavior of an amorphous drug dissolved in mono and diglycerides from Newtonian to psuedo-plastic (116). The viscous modulus (G) determined from oscillatory measurements showed that there is a structure build up in the system, indicating interaction between the drug and the vehicle via hydrogen bonds confirmed by DSC and FT-IR. The shear effect was shown to be drug-concentration dependent. The drug solution at concentration(s) beyond the inflection (saturation) point is more prone to gel upon shear and/or precipitation upon storage as previously described in the physical stability section. No endotherm corresponding to the melting point of the drug is good indication of a complete solubilization of the drug.

PRODRUG FORMATION

The use of covalently bonded moiety to the therapeutic active compound that breaks down in vivo is a common approach to improve the bioavailability of therapeutic compounds. The choice of ligand depends on the properties of the compound to achieve the desired pharmacokinetic performance such as improvement in the solubility or permeability. In some instances both benefits could be achieved by judicial selection of the ligand. The science of developing reversible derivatives of the active compound to improve bioavailability, specificity, and efficacy has been used since 1970s in the drug design process. Examples of successfully developed prodrugs include capcitabine/5-fluorouracil (specificity and permeability), enalpril/enalprilat (improved permeability), valciciclovir/acyclovir (improved permeability and specificity), chloramphenicol succinate/chloramphenicol (improve solubility for parenteral use), and levodopa/dopamine (improved blood brain penetration) (118,119).

Theoretical Considerations

The primary considerations in designing a suitable prodrug are:

1. The aspect of the active compound that needs to be improved such as hydrophilicity or lipophilicity,
2. The availability of functional groups that are amenable to reversible derivatization (chemical or biochemical),
3. Physico-chemical and enzymatic stability of the prodrug, and the rate, extent, and the site of bioconversion to yield therapeutic active compound.

The most commonly used functional groups for prodrug formation are alcohols, acids, amines, and amides (120). In an example illustrating the application of prodrug to improve solubility and bioavailability, a series of diester prodrugs of ganciclovir (GCV) were synthesized with valine (Val) and glycine (Gly). Further evaluation of solubility, partition coefficient, and in situ stability helped distinguish these prodrugs to optimize different biopharmaceutical aspects. The Val–Val–GCV and Val–Gly–GCV diesters were found to exhibit greater aqueous stability compared with Val–GCV and Gly–Val–GCV while in situ hydrolysis showed Val–Gly–GCV and Gly–Val–GCV to be more stable. All the prodrugs possess much higher aqueous solubility than the parent drug

GCV thus resulting in improved bioavailability by improved solubility, enhanced permeability, and superior safety profile.

Nielsen et al. (121) used N-acyloxymethylation of the poorly soluble tertiary amine Lu 28-179 to make bioreversible quaternary ammonium derivatives possessing improved aqueous solubility in the range of 2–4 × 10^6. Significant enzyme-mediated cleavage of the prodrugs was found in human plasma, simulated intestinal fluid and duodenum juice from pigs and dogs assuring the availability of the active drug in plasma. The hydrolysis rates and the improved solubilities are summarized in Table 13 (121).

Although prodrugs can be made using several pro-moieties to achieve desired target profile, however, the most commonly used forms for improving the dissolution rate-limited bioavailability are formation of esters hemisuccinates, phosphates, dialkylaminoacetates, and amino acid esters. The more recently evaluated ligands such as pegylation and dendrimers provide specificity and longer half-lives. Polyamidoamine (PAMAM) dendrimers possess a well-defined structure that allows precise control of size, shape, and terminal group functionality. Dendrimers can function as drug carriers either by encapsulating drugs within the dendritic structure or by attaching drugs to their terminal functional groups *via* electrostatic or covalent bonds (prodrug). The covalent linkage of a drug to a dendrimer provides a stable system that is not dependent on dynamic or thermodynamic factors that apply in matrix systems, e.g., micelles. The release of drug from a prodrug occurs via chemical or enzymatic cleavage of a hydrolytically labile bond. The use of covalently linked PAMAM dendrimers was first shown by Emanuele to improve the oral bioavailability of propranolol by improving the solubility and bypassing the efflux transporter (122).

Najlah et al. (123) used PAMAM dendrimers to improve the solubility of naproxen, a poorly water-soluble drug. The drug was conjugated to dendrimers either directly by an amide bond or by ester bonds using either l-lactic acid or diethylene glycol as a linker. All the prodrugs showed improved solubility; however, the stability depends significantly on the type of conjugate allowing a control of drug release from rapid release to sustained release over the period of 24 hours. These examples indicated that the effect of promoiety on the improved solubility and permeability can be tailored by the selection of the pro-moiety.

TABLE 13 Second-order Rate Constants for Hydrogen Ion Catalysed (k_H) and Hydroxide Ion Catalysed (k_{OH}) Hydrolysis of Various *N*-Acyloxymethyl Lu 28-179 Prodrugs at 37°C ($\mu = 0.5$), and Aqueous Solubility at 37°C with RSD Given in Brackets

Compound	k_H (M/h)	k_{OH} (M/h)	Solubility (mM)
N-Acetyloxymethyl	0.42	3.1×10^5	31.8 (4)
N-Propanoyloxymethyl	0.39	2.3×10^5	1.4 (15)
N-Butanoyloxymethyl	0.25	1.4×10^5	1.9 (22)
N-Isobutanoyloxymethyl	0.22	1.7×10^5	14.8 (3)
N-Pivaloyloxymethyl	0.03	3.9×10^4	14.0 (4)
Lu 28-179 base			0.0000082[a]
Lu 28-179 (pH 5.5)			0.013[b]
Lu 28-179 (pH 5.0)			0.061[b]
Lu 28-179 (pH 4.5)			0.14[b]
Lu 28-179 (pH 3.75)			0.73[b]

[a]Estimated from the pH-solubility profile.
[b]Experiments done in duplicate in 50 mM acetate buffer with deviations from average values below 10%.

SUMMARY

In this chapter, we have discussed the approaches to overcome solubility and dissolution rate-limited absorption of poorly water-soluble drugs. The approaches discussed were particle size reduction, salt formation, co-crystal formation, prodrug, crystal modification, lipid delivery, and complexation. The selection of approaches mainly depends on the solubility in physiological pH and dose. As a rule of thumb as one utilizes the approaches starting from particle size reduction to ultimately achieve a true solution, bioavailability correspondly improved. If simple approach, such as particle size reduction, cannot provide desired results, non-conventional approach (lipid, complexation, and amorphous formulation) should be researched to improve oral absorption. In vitro dissolution model to mimic in vivo dissolution could be of significant value. Establishing in vivo in vitro correlation (IVIVC) during development will minimize the cost of performing human bioavailability for challenging poorly water-soluble drugs. Innovation in this area is far from over and in future to come we will come across novel approaches to overcome bioavailability issue of exciting drugs emerging from discovery.

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3

Aims and Objectives and of Experimental Design and Optimization in Formulation and Process Development

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The use of the "Statistical Design of Experiments" (DOE) has a long history with roots going back as far as the 1960s. While initially DOE was mainly used as a tool in academia (1,2), the pharmaceutical industry quickly realized the potential of DOE and numerical optimization based on mathematical models for a rapid, precise, and safe development of formulations and processes, as well as scale up, validation and troubleshooting (3,4).

The use of DOE is very efficient, as the outcome provides a fixed amount of information that has been gathered with considerably less effort than with the use of the traditional "one variable at the time" approach. In addition to the main effects deduced, the use of DOE also provides insight into variable interactions, which are important when attempting to optimize a formulation or process (5). One important feature of DOE is the random order, in which the experiments are carried out. This prevents making of premature decisions without considering the full evidence provided by all the data, and it also ensures a random distribution of the errors made during experimentation.

DOE evaluate the effects of simultaneous changes in conditions, but they do not necessarily reveal the underlying mechanisms that are responsible for the effect seen. Depending on their design they might simply provide "empirical feedback" required for the optimization of, for example, a process. These designs are highly economical and provide the required level of information with a minimum of experimental effort. One example is the optimization of a formulation using search methods based on "hill-climbing" (6). Here a minimum number of experiments are performed and the next required experiment is then predicted by the search algorithm. The process stops, when the optimum has been found. The so-called factorial, or fractional factorial designs, on the other hand, are planned completely in advance and are executed in full to allow the use of statistical methods such as Analysis of Variance or Perceptual Mapping in order to gain insights into the theoretical aspects of the problem, at the same time as providing sufficient data for formulation or process optimization. These designs are often less economical and might involve considerable experimental effort, depending on the number of variables studied and the rigor applied in terms of variable levels. Designs that only use "low" and "high" levels of each variable are not suitable to elucidate in depth

theoretical insight to the problem, whereas with an increasing number of levels per variable even complex non-linear relationships can be identified and modeled.

It is often assumed that experimental designs can be planned "at the desk" without any prior information about the problem. However, a design is only as good and predictive as the data space that is explored. If the data space does not envelope, for example, the optimum solution for a problem, then the data gathered are of no value, because extrapolations beyond the data space are normally not permissible. Thus, to be able to derive at an optimal experimental design will in many cases require obtaining preliminary results, on the basis of which the data space needed can be ascertained and the design built. DOE thus begins with an identification and assessment of the objectives of the experiment. The formulation or process factors to be included in the design depend on the objectives to be met. In this sense, the thinking process involved has two outcomes, which both benefit the investigation: (*i*) the investigator must clearly define the aims and objectives of the study; (*ii*) the investigator must identify the process variables/ factors that have an impact on achieving the objectives. It must be borne in mind that not all variables can be controlled; yet random influence factors such as environmental variables can affect the outcome of an experimental design considerably (4). Hence, the experimenter has to chose an appropriate design, which either assumes that random influence factors are well enough controlled or monitored and thus do not need to be incorporated into the design (this is the most often made assumption), or which is able to consider both systematically varied and random variables. Depending on the number of variables to be considered and the number of variable levels that need to be studied, full or fractional factorial designs can be selected to minimize the number of experiments to be performed, while maximizing the amount of information that can be obtained from the experiments performed.

The use of DOE is not the same as "optimization." The term optimization is often loosely used to highlight the desire to find a formulation or process that is robust and performing to a high quality standard. "Optimization," however, is a mathematical method that searches for an "optimum," i.e., the most advantageous solution to a problem (6). Mathematical optimization techniques should be employed to identify an optimal formulation and/or the optimal settings for the process variables to achieve the desirable properties of the product. While there are various optimization methods available, they all require that the variable(s) to be optimized are related quantitatively to their predictor variables (e.g., process or formulation variables), and that the function describing such relationship is consistent over the whole multidimensional space described by the predictor variables (7). Mathematical optimization techniques can be divided according to the nature of the mathematical function(s) used into linear and non-linear approaches, whereby the majority of model functions derived from DOE are linear or quadratic in nature. The aim of using such methods is to find a suitable compromise between otherwise contradicting quality criteria in a formulation and to adjust the process and/or formulation variables on the basis of the numerical model so that the "best" compromise solution is found, preferably resulting in a robust process and formulation.

BASIC STATISTICAL CONSIDERATIONS

Introduction

Statistical methods are used to quantify information contained in data material. They are not a replacement for incomplete or poorly performed experimentation. In order to use statistical methods correctly, the researcher must choose the method to be used prior to

setting up the statistical design. The experimental design must consider the requirements placed on the data material and the specific aspects of the statistical method.

Statistical Data

Data are the key to a statistical assessment. Data need to be obtained correctly and as completely as possible, but there will always be some uncertainty with respect to their accuracy, i.e., experimental methods have their limitations. Data describe an appearance, a property, the state of an object, the relationship between objects, etc., for example, the color of somebody's hair might be "brown" (appearance); the melting point of a crystal could be 76°C (physical property); an animal could be sleeping or awake (the state of the "object" animal); the concentration of a drug in the dissolution medium at time t could be 20% of its saturation solubility (relationship between drug dissolution and time). Data must be obtained on a number of objects to allow their use in a statistical assessment. The number of data obtained must contain sufficient information for statistics to be applied. The number of data required varies with the statistical approach, and the necessary requirements will be discussed below.

Ratio data are obtained if the variable is described by numerical values and the scale has an absolute zero. Ratio data are quantitative data and they are continuous. This means that they are numbers and that any number between zero and infinity is possible. For ease of use ratio data are rounded to a defined number of decimal places. This might make them appear "discrete" (i.e., discontinuous), but even if two numbers as written down are 2.3 and 2.4, a value of 2.34 is possible, it is just rounded off to 2.3.

It is also possible to quantify the difference between two interval scale values but there is no natural zero. For example, temperature scales are interval data with 25°C being warmer than 20°C, and the 5°C difference has some physical meaning. However, the definition of 0°C is arbitrary, so that it does not make sense to say that 40°C is twice as hot as 20°C. However, the Kelvin temperature scale has a true physically defined zero and thus on the Kelvin scale (at 0 K all molecular movement has stopped), which is a ratio scale, direct comparisons are possible. The same applies to dates. Again, interval data are quantitative data, and they are also continuous. As with ratio data, for ease of use interval data are rounded to a defined number of decimal places. This might make them appear discontinuous ("discrete"), but any value in between is possible.

Ordinal data indicate an order or ranking, but the difference between the values is not important or defined. It is also permissible to examine whether an ordinal scale datum is less than or greater than another value. Hence, one can 'rank' ordinal data, but one cannot 'quantify' the differences between two ordinal values. For example, "taste" is an ordinal datum with "lightly salted" being "left" of "strongly salted," but it is not possible to quantify the difference. Another example are preference scores, for example, ratings of pleasant smell where 10 = good and 1 = poor, but the difference between a rating with a 10 ranking and an 8 ranking cannot be quantified. Ordinal data are discrete, not continuous data.

The values of nominal data cannot be ranked in a meaningful order such as from "smallest" to "largest." Nominal data are classification data, with labels chosen arbitrarily. Examples are variables such as place of birth, hair color, hobbies, pets, make of cars. Nominal data are discrete data. They can be counted, but not measured. Nominal data typically have no decimal places (0, 1, 2, 3, etc.) and they are the least useful in statistical data treatment. Where possible, alternatives should be sought. The majority of nominal data is "multiple nominal" i.e., data have values between 0 and k, whereby $k \geq 1$. Single nominal data have only values of 0 or 1, i.e., these are Bernoulli data.

The nomenclature for test statistics and use of data is complicated. Categorial data summarize single and multiple nominal as well as ordinal data. The data are "categorized." In non-parametric tests normally discrete data are used, but these must be on an ordinal scale. However, under certain circumstances also parametric data have to be treated as non-parametric. Parametric data are continuous data, thus ratio and interval data.

Presentation of Data

Graphical presentations of data are used to present derived values and in rare cases also raw data in a visual manner. They are meant as visual aids and are thus a visual translation of information that is otherwise available in tabulated form. The choice of the graphical presentation tool must help the investigator to understand the underlying information more easily. A graph always consists of a picture and a text item. The text item (legend) must explain the picture item so that the wider context related to the data can be clearly understood. The picture item must be clearly labeled, i.e., axis labels, units of measurement, essential information must be given. Typical graphical presentations include histograms, bar and pie charts, line and scatter plots.

Measures of Central Tendency and Variability of Data

Frequency distributions provide only a visual impression of the data and they are cumbersome to compare. Number characteristics have the advantage of more direct comparability and the number characteristics are "shorter" and more definitive in their message. Frequency distributions are typically characterized by two numbers, i.e., a "Measure of central tendency" plus a measure of the width of the distribution ("variability"). Typical combinations are median and interquartile range, median and spread and arithmetic mean and standard deviation. However, there are other parameters for the description of the central tendency and variability also, and their use depends on what information is sought from the data.

The "mode" is a measure of central tendency. The mode of a distribution function is the class with the largest frequency. In most cases the mode is only of use if the distribution is mono-modal. However, some distribution functions, although bi or multimodal, are still well characterized using the mode with the largest frequency only, because the size of the second or any further mode is clearly inferior to the first.

The "median" is a measure of central tendency. The median is the value below and above which 50% of the cases of a set of data or frequency distribution lie. The median is best obtained from cumulative frequency distributions, because the under- and oversize distribution will cross at the 50% value. The median can also be found by simply ranking all data and then finding the value that is directly in the middle. The advantage of the median value is that it is little influenced by extreme values.

The interquartile range is a measure of variability and characterizes the spread or width of the distribution. It is obtained as difference between the 3rd and 1st quartile. The first quartile is the value corresponding to 25% of the cumulative frequency. The 3rd quartile is the value on the abscissa corresponding to 75% of the cumulative frequency distribution. The determination of the interquartile range excludes the extremes of the distribution function. It is important to note that the median is not necessarily in the centre of the interquartile range. The median might well be closer to the lower or upper quartile.

The average deviation from the median value Ξ_M is a measure of variability describing the deviation of the individual values from the median value:

$$\Xi_M = \frac{\sum_{i=1}^{n} |x_i - M|}{n}$$

where x_i denotes the individual observations, n is the number of observations, and M is the median value. For this approach to work individual values are required, not classified data. The deviation from the median value is strongly influenced by extreme values of the distribution.

The arithmetic mean value of a set of data is the most commonly used parameter to describe the central tendency. It is the average value. The symbol is typically a letter with a bar on top; more generally it is $\bar{x}$. While it can be calculated from ratio and interval data, it should not be used for ordinal data, because for ordinal data the difference between individual values is not defined or of no importance. The calculation is simply forming the sum of all data and dividing it by the number of data:

$$\bar{x} = \frac{\sum_{i=1}^{n} x_i}{n}$$

The number of decimal points of the individual observations depends on the accuracy with which the measurements were undertaken. If the measurement of a length in centimeters using a standard ruler is considered, an accuracy of up to 1 mm is feasible (e.g., 2.3 cm). The arithmetic mean value can thus have one more decimal place (e.g., 2.14 cm). The arithmetic mean value does not weigh any data, i.e., it is strongly influenced by extreme values.

The geometric mean value $\bar{x}_g$ is used when a few of the individual data deviate grossly from the majority of data (extreme values). This measure of central tendency provides a "typical" rather than average value for the data. It is calculated as the root-n of the product of all individual data.

$$\bar{x}_g = \sqrt[n]{\prod_{i=1}^{n} x_i}$$

The harmonic mean $\bar{x}_h$ is used in, for example, pharmacology/toxicology and microbiology, i.e., in studies testing toxicity. Survival experiments consist of times for death to occur next to some data for survivors. The time it takes to die for a survivor is "infinity," and thus both arithmetic and geometric mean would be infinity, despite of a number of death values. The harmonic mean accounts for the occurrence of infinitive large values, because it uses reciprocal values. The reciprocal of infinity is zero. Thus, the survivor data are excluded from the calculations.

When a number of arithmetic mean values are to be combined, this can be done either from the raw data of all groups, or by using the arithmetic mean values for each group of data. The first method would be used, if the raw data are easily accessible. The second method would be used, if only mean values are reported.

$$\bar{\bar{x}} = \frac{\sum_{j=1}^{k} \sum_{i=1}^{n_j} x_i}{\sum_{j=1}^{k} n_j} = \frac{\sum_{j=1}^{k} n_j \bar{x}_j}{\sum_{j=1}^{k} n_j}$$

where $\bar{\bar{x}}$ is the overall arithmetic mean value, n_j is the number of observations in the various samples j, and k is the number of samples.

Arithmetic mean values are typically reported with an associated value for the variability of the data. The use of the standard deviation s is more common, but as can be seen later the knowledge of the variance s^2 can be advantageous. The variance is simply the square value of the standard deviation.

$$s = \sqrt{\frac{1}{n-1}\sum_{i=1}^{n}(x_i - \overline{x})^2} = \sqrt{\frac{1}{n-1}\left[\sum_{i=1}^{n}x_i^2 - \frac{\left(\sum_{i=1}^{n}x_i\right)^2}{n}\right]}$$

Standard deviations are not additive, but variances are. Again, when combining the results of a number of samples, where available, the raw data could be used to find the overall standard deviation. However, in cases, where the raw data are not available, the additivity of the variances can be used:

$$\overline{s} = \sqrt{\frac{\sum_{j=1}^{k} n_j s_j^2}{\sum_{j=1}^{k} n_j}}$$

In the above equation $\overline{s}$ is the overall standard deviation value, n_j is the number of observations in the various samples j, and k is the number of samples.

Data Samples and Populations

Often, the required judgments and decisions are based on a small number of data (“sample”), which has been retrieved at random from the theoretically available number of measuring values (“population”). The number of data in the population can either by infinite, i.e., the number of theoretically available measuring values is unknown (e.g., the number of bacteria cells in a dead animal cadaver), or the population consists of a finite number of objects (e.g., a batch of tablets of 1,000,000). In the latter case, the number of objects in the population is rather large. Also in the case of a finite population, the use of a sample is sensible. For example, one could determine the disintegration time of all tablets of the batch, but in this case there would be no tablet left for sale. Hence, usually only 12 or 24 tablets, taken at random are tested. For the sample the key values are $\bar{x}$ and s. The equivalent values of the population are μ and σ. The latter can be estimated from $\bar{x}$ and s.

Sampling should be done at random, taking specimens from different containers, different positions inside a container, etc. Samples from live populations are more difficult to sample, because the living entities move around. If the size of the population is finite, one can use “tables of random digits” to select the sample specimens. If the population is infinite, then a sub-population must be established first. How many samples are required to be representative of the population is related to the scale of scrutiny and the calculation of the required number of samples using the concept of precision. For test statistics often a calculation of the required number of samples using the “power” approach is used.

Populations, which are essentially continuous, often follow a normal distribution. Examples are height, length, temperature. Even if the distribution of the original population is far from normal, the distribution of sample means tends to become normal under random sampling, as the size of samples increases. Normal distributions $N(\mu,\sigma)$ are fully described by their values of central tendency and variability, i.e., μ and σ. A random

variable X is normally distributed, if the probability for X to lie between x and dx, i.e., the probability density $(x)dx$ is defined as:

$$\varphi(x)dx = \frac{1}{\sigma\sqrt{2\pi}} e^{\frac{-(x-\mu)^2}{2\sigma^2}} dx$$

To be able to compare normally distributed populations normalization is undertaken so that the mean value becomes zero and the standard deviation becomes one:

$$u = \frac{x - \mu}{\sigma}$$

In this way, one and the same statistical table can be used to describe a normally distributed population. The value of u is called the standard normal variate, and the probability density $\varphi(u)du$ of the normalized normal distribution $N(0,1)$ is:

$$\varphi(u)du = \frac{1}{\sqrt{2\pi}} e^{\frac{-u^2}{2}} du$$

The graphical presentation of the normal distribution results in the well-known bell shape, and the integration to derive the cumulative probability density $\Phi(u)$ results in a sigmoidal curve. The latter is more frequently used, as it represents the area under the normal distribution curve.

$$\Phi(u) = \int_{t=-\infty}^{u} \varphi(t)dt$$

Many classical statistical tests are based on the assumption that the data follow a normal distribution. This assumption should be tested before applying these tests. In modeling applications, such as linear and non-linear regression, the error term is often assumed to follow a normal distribution with fixed location and scale. The normal distribution is used to find significance levels in many hypothesis tests and confidence intervals.

Skewness is a measure of symmetry, or more precisely, the lack of symmetry. A distribution, or data set, is symmetric if it looks the same to the left and right of the centre point. Kurtosis is a measure of whether the data are peaked or flat relative to a normal distribution. That is, data sets with high kurtosis tend to have a distinct peak near the mean, decline rather rapidly, and have pronounced tails. Data sets with low kurtosis tend to have a flat top near the mean rather than a sharp peak. A uniform distribution would be the extreme case.

Left shifted distributions can be transferred into a normal distribution using a logarithmic transformation of X. The result is a logarithmic normal distribution. A variable X is log-normally distributed if $Y = \ln(X)$ is normally distributed with "ln" denoting the natural logarithm. It is important to note that the logarithmic transformation does not make the original data normally distributed. It only produces a normal distribution of transformed data. A number of statistical tests and procedures become doubtful if undertaken on transformed data (e.g., linear regression) and an analysis of benefit versus loss is required.

Basic Principles of Test Statistics

The use of statistical methods and the interpretation of the results of the majority of statistical methods are based on the knowledge of the "degrees of freedom." The

following example aims to explain this term: A pharmaceutical company has to produce 25,000,000 tablets over a 5-day period. On the first and second day 4,000,000 tablets each are manufactured, on the third day 6,000,000 and on the fourth day 5,000,000 tablets. Hence, after the first four of the five possible production days the company has already produced 19,000,000 tablets. On the last day of production thus the remaining 6,000,000 tablets have to be manufactured. On the first 4 days of production the company was free to produce any number of tablets. However, on the last day the number of tablets remaining is fixed by the number of already produced tablets. From a statistical point of view this translates into a degree of freedom of $5 - 1 = 4$ for tablet production.

Statistical test procedures are often based on the arithmetic mean and standard deviation of two or more samples and aim to estimate the differences between the populations, from which the samples were drawn. Such tests work with two hypotheses: (*i*) the "null hypothesis" H_0, and (*ii*) the "alternative hypothesis" H_1. The null hypothesis is that all samples tested represent one and the same population. The alternative hypothesis assumes that at least one or all samples are from different populations. Due to the numerical construction of the test procedures employed only the alternative hypothesis can be proven to be correct under the assumption of a certain error. If the alternative hypothesis cannot be accepted as correct, this does not mean that the null hypothesis is correct instead. It only implies that there is not sufficient evidence to reject the null-hypothesis at this stage.

When using statistical test procedures, two different types of errors are distinguished: The α-error arises when accepting the alternative hypothesis as correct although it is, in fact, incorrect. The size of the α-error is controlled by the significance level *P*, i.e., "error probability." In (Fig. 1) the area under the normal distribution of a population that is equal to *P* is shown. In those cases, where the arithmetic mean value of the second population is situated between the arithmetic mean value of the first population and the area of the α-error, the alternative hypothesis cannot be proven as being correct and hence the null-hypothesis cannot be rejected. In those cases, where the arithmetic mean value of the second population is completely outside the area below the normal distribution of the first population, the alternative hypothesis will be accepted without restrictions. If the arithmetic mean value of the second population is, however, inside the area of the first population indicated as α-error, the null-hypothesis is rejected erroneously.

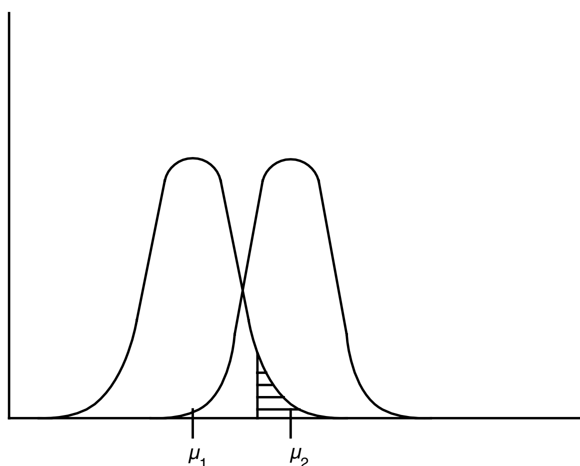

FIGURE 1 The α-error. The error probability *P* is highlighted with horizontal bars. The arithmetic mean of the second population μ_2 is inside the highlighted area.

The size of the α-error is usually set to $P = 0.05$ ($\alpha = 5\%$). The resulting area under the normal distribution can be positioned either completely on one side as shown in Figure 1, or can be equally positioned at either end of the normal distribution. The first case (so-called "one-sided" or "one-tailed" test procedure) is less commonly used than the "two-sided" ("two-tailed") test procedure. In a one-sided test the investigator pays attention only to deviations from the null-hypothesis in one direction. For example, the amount of degradation products of a drug in a dosage form can only be larger than zero, not below zero. In most cases, however, the direction of change of a measured variable is unknown. For example, a new drug substance could increase or reduce the number of white blood cells per milliliter blood from a given normal value (control). In such a case, a two-sided test procedure must be adopted.

When using modern computer programs the user is not required to predefine the value for *P*. The programs calculate the probability, with which the null-hypothesis can just be rejected. A comparison of the resulting error probability with a given maximum value for *P* (normally 0.05, or 0.01 for investigations bearing a larger risk) is then used to decide whether (*i*) the null-hypothesis can be rejected, and (*ii*) to estimate whether and to which extent the two distribution functions of the populations are different.

The β-error occurs if the null-hypothesis is not be rejected although being incorrect. The size of the β-error depends on the distance between the arithmetic mean values of the populations (Fig. 2). The β-error can theoretically be manipulated by alteration of the number of observations in the samples. A larger observation number can reduce the β-error. However, an estimate of the likely β-error has to be obtained before planning and designing the experiments. The estimate is usually obtained on the basis of the standard deviations of preliminary experimental data. If the variability of the data later observed in the experiment deviates from the estimates made prior to the experimental design, the concept breaks down. The control of the β-error is hence not used in modern statistical experimental design. The necessary sample size is commonly determined on the basis of the experimental effort, the costs and the importance of the results for future work and decisions.

Statistical test procedures have been developed for metric and categorical data. An entity, for which the measuring values can be compared with a test procedure, is termed "variable." A variable is hence a measured property, for example, the disintegration time of a tablet, the conductivity of an aqueous solution, or the content of glycosides in the leaves of a plant. Test procedures for metric values are termed "parametric" test

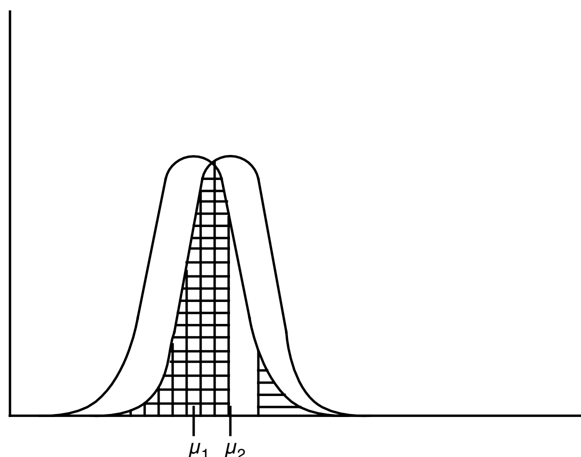

FIGURE 2 The β-error. The probability for the β-error to occur is equal to the crossed area. The α-error is again denoted by the horizontal bars.

procedures. Test procedures based on ordinal data are called "non-parametric." Nominal data have no intrinsic order and their sequence is arbitrary. They are hence not comparable and few statistical test procedures exist. In some cases, however, nominal data can be arranged along an ordinal scale due to a certain property. For example, the nominal variable "color" can be transferred onto an ordinal scale on the basis of the wavelength and light spectrum. In such cases non-parametric test procedures can be employed after scale transformation.

Univariate Analysis of Variance

Introduction

The Univariate Analysis of Variance (ANOVA) is used to test the differences between mean values in more than two samples. Results are used to make statements about the populations, and the method employs the calculation of mean values and variances. If only two samples are to be compared, ANOVA automatically converts into the appropriate *t*-test. It is often easier to treat all experiments the same, i.e., always to use ANOVA, as the final outcome is the same. This idea also removes the need to know about different distribution functions such as *F*-, *t*-, and χ^2-distribution, which eases understanding of the underlying statistical principles. This way of thinking also makes the use of statistical packages easier, both in terms of data input and data organization, interpretation and comparability of results. In this section, hence the inherent similarity between *t*-test and ANOVA is acknowledged fully, and thus all comparisons of mean values discussed are undertaken by means of ANOVA only.

General Principles of Analysis of Variance

The difference between the samples in view of the values of the measured variable can be the result of the following:

1. The determination of the numerical values of the variables is erroneous (is the case in most analytical or technical measuring procedures), or there is a natural source for variability (e.g., not all children at the age of 12 weigh 35 kg).
2. The differences are the result of random or systematic changes of one or more "influence factors," which formed the basis for the collection of the various samples.

Null-hypothesis of ANOVA:

The mean values of the measured variable are equal for all samples, and small deviations are the expression of experimental errors only.

Alternative hypothesis of ANOVA:

There is at least one difference between the mean values of the samples, which is the result of the changes in the influence factors.

ANOVA is based on three estimates of variance:

1. "Total variance," which is the estimate of the variance of the population on the basis of all available data without consideration of the split into different samples.
2. "Variance within the samples," which is an estimate of the variance of the population on the basis of deviations of all individual data of one sample from the related sample mean value.
3. "Variance between the samples," which is an estimate of the variance of the population on the basis of the sample mean values.

If all samples represent one and the same population, all three estimates of variance are equal. Otherwise the estimates of the variances represent the influence of factors, which have been considered when collecting the samples, on the measuring values. ANOVA hence compares the different variance estimates.

As in all statistical tests, ANOVA is based on a model distribution function, i.e., the F-distribution. The F-distribution is the distribution of choice, as it is the theoretical distribution of all possible variance ratios, whereby always the larger variance is divided by the smaller variance. Hence the F-distribution consists only of values ≥ 1. The decision about the acceptance of the alternative hypothesis is made by comparing the calculated F-value with a tabulated one. If the calculated F-value exceeds the tabulated value, the alternative hypothesis can be accepted as being correct.

Because of the nature of the influence factors two models have to be distinguished when using ANOVA:

1. Models with "fixed effects" (model I): The various levels of the influence factors are precisely defined in the experimental design, for example, different doses of drug or different amounts of excipients used (quantitative variation). Influence factors can also be varied qualitatively (e.g., exchange of drugs or excipients).
2. Models with "random effects" (model II): A typical example is the investigation of the content of glycosides in *digitalis lanata* leaves. The glycoside content in a leaf can be affected by the position of the leaf on the plant and by the plant as such. There are hence two random influence factors to be considered, i.e., the plant itself and the position of the leaf on the plant.

The numerical treatment of the two models is similar, but the interpretation of the effects depends on the model.

Single Analysis of Variance

Single ANOVA ("one-way classification") compares samples, which have been created by the variation of only one influence factor. To be able to use parametric ANOVA, the measuring values in each individual sample must be normally distributed, and also homogeneity of variance must exist. If these conditions are not fulfilled, or if the measuring values are on an ordinal scale, non-parametric ANOVA techniques have to be sought. Non-parametric simple ANOVA methods are, for example, H-test according to Kruskal and Wallis (independent samples), and Friedman test (dependent samples) (8). In dependent samples the objects of study are the same from sample to sample, whereas in independent samples no study object has been included in more than one sample.

When dealing with numeric data it is commonly assumed that the measuring values are normally distributed. However, if in doubt it is recommended to check for normal distribution. This should be done preferably using a statistical test procedure, but graphical methods can also be used. If, for example, plenty of data are available, the relative frequency distribution, which describes these data, can be obtained and drawn on probability paper. The measuring values are normally distributed if a straight line combines all points in the drawing. The statistical package "SPSS" (SPSS Inc., U.S.A.) offers the possibility of using graphical methods parallel to the numerical test procedures. As graphical methods SPSS offers several, of which the so-called Probit–Proportion (P–P Plot) appears to be the most suitable, because the method is closest to the use of probability paper. The ordinate shows the probabilities/relative frequencies as Probits, which reflect a standardized normal distribution.

When fitting data to a distribution function it has to be considered that the experimental data do not truly represent a continuous distribution function. In the cumulative frequency diagram a step curve results (the combining of the points by a line is often performed but statistically not acceptable). The cumulative frequencies can only be roughly estimated from the absolute frequencies (*k*) and the number of observations (*n*). An estimate using $(k-1)/n$ or k/n shifts the frequency value to the limits of the frequency classes and offers hence the worst estimate. A series of improvements has been reported, and SPSS permits the user to choose between the following possibilities:

1. Blom $([k-3]/8)/([n+1]/4)$
2. Tukey $([k-1]/3)/([n+1]/3)$
3. Rankit $([k-1]/2)/n$
4. van der Waerden $k/(n+1)$

All four methods estimate the frequencies in the interval $(k-1)/n$ to k/n. The method according to Blom is the default in SPSS and is regarded in the literature (8) as the most suitable one. SPSS also offers the so-called "detrended P-P-plot." Here, the distances of the frequencies from the normal distribution are shown. Normally distributed are data if in this plot the frequencies are on the null line.

The most often used statistical test procedure to compare data with any distribution function is the Kolmogorov–Smirnov test ($K-S$ test) (8). For each of the different distribution functions a fitting procedure must be developed. For the normal distribution such a fitting procedure was described by Lilliefors, who also tabulated the zero values for the test criterion D_n. Also here the normal distribution is estimated from the step distribution of the experimental data. The $K-S$ test determines the maximum vertical deviation of the step function from the normal distribution. The $K-S$ test is regarded as being robust and is the test of choice for a large observation number (8). If the number of observations is small, SPSS offers in addition a second test, i.e., the Shapiro–Wilk test. A definite statement about the data can be made if both tests reject the null hypothesis. If the tests come to different results and if the observation number is small, the Shapiro–Wilk test should be primarily considered. However, this test cannot be used as definite proof for the data to obey normal distribution because the test criterion of the Shapiro–Wilk test depends too much on the number of observations. The test only indicates whether one should doubt the presence of normal distribution in the data material. For large observation numbers the Shapiro–Wilk test becomes insensitive and the test is not helpful.

"Homogeneity of variance" means the variance of different samples is numerically similar. When comparing two samples, for example, using the *t*-test, the test for homogeneity of variance is a must and is performed using the *F*-test. Modern computer software such as SPSS performs such test automatically and corrects the *t*-values when appropriate (Welch approximation). ANOVA procedures appear to be more robust and the statistical software lets the user decide whether a test of homogeneity of variance is employed. Two methods are recommended in the literature for tests for more than two samples: (*i*) *F*-max test, and (*ii*) Levene test (8).

In the *F*-max test the basic idea of the test is that, if the two extreme variances of a series of samples are not different, then the variances of all samples must be similar. Practically the variances of the samples are ranked and an *F*-test is performed using the largest and smallest variance. The *F*-distribution has two degrees of freedom, which are calculated from the sample sizes involved: $f_1 = n_1 - 1$ and $f_2 = n_2 - 1$. (To calculate the variance of a sample, the deviation of the individual values from the arithmetic mean

values is calculated. The arithmetic mean value is a defined parameter and hence one degree of freedom is lost.) The tabulated value for the F-distribution at $P = 0.05$ is then compared with the tabulated value for the degrees of freedom and for homogeneity of variance to exist the calculated value must be smaller than the tabulated value.

The Levene test is based on the variability in measuring values of all samples and hence is more precise than the F-max test. However, it is not possible to identify those samples, which are different from the majority of samples tested. As measure for the variability of the individual values in the samples the mean absolute deviation of the single values from the arithmetic mean is used, not the variance. This makes the test less sensitive against wide, tailed distribution functions (distribution functions with positive kurtosis), as these would lead to a false rejection of the null hypothesis. The test is preferred over the classical Bartlett test for this reason.

After the basic requirements for sample comparisons by means of ANOVA have been confirmed, the null and the alternative hypothesis can be formed. Null-hypothesis: The samples are similar and measures of central tendency and variability differ only randomly. Alternative hypothesis: The results obtained for the different samples are statistically significantly different.

In ANOVA, the F-value is calculated as the ratio between the mean squares between and within the groups. The degrees of freedom of the F-distribution are determined as follows: $df_1 =$ number of samples − 1 (between the groups); $df_2 =$ total number of observations – number of samples (within the groups). The tabulated value of the F-distribution and the calculated F-value are then compared and a decision as to whether the null hypothesis can be rejected or not is made.

The single ANOVA does not tell whether the differences found between the samples are indeed between all samples or whether there is only one sample different from the other samples. To identify the individual samples the so-called "Post hoc tests" must be performed.

Multiple mean comparisons are used to identify differences between samples after the ANOVA has indicated that there is at least one significant difference between them. Multiple mean comparisons are paired comparisons of samples, which, following the null-hypothesis of the ANOVA, could be part of one and the same population. This is very important and means that the paired comparisons cannot be undertaken using the simple t-test. In order to keep the α-error on the 5% level ($P = 0.05$) corrections of the test procedure are required. There are several pair comparisons that could be used here, and SPSS offers numerous choices. The following summarizes some of these tests.

1. Least significant difference (LSD test): The test is not useful as, similarly to the t-test, there is no control over the α-error.
2. Bonferroni correction for LSD test: The Bonferroni correction is based on the calculation of the 95% confidence intervals. The test is thought to be robust and the α-error is kept in most cases on the threshold level of the error probability P. Small deviations are, however, likely.
3. Duncan's multiple range test: The test initially assumes that the result of the ANOVA is indicative of at least one significant difference between the samples included in the test. The test intends to optimize the ratio between α- and β-error in each paired comparison, so that the α-error is controlled but not kept on the threshold of the error probability P. For this reason the test should not be used.
4. Student–Newman–Keuls test: The method can only detect larger differences between the samples, compared to the LSD test. The α-error is not always

kept on the level of P, but the test is somewhat better than the LSD test. The mean values of the samples are ranked, and the maximum differences are tested first. The test is terminated when no further differences are detected, i.e., not all paired comparisons are performed.

5. Tukey's "honest" significant difference: The method works similarly to the Student–Newman–Keuls test, but all paired comparisons are performed. Hence, the deviations of the α-error from the set P value are more pronounced.
6. Scheffé test: This test controls the α-error precisely, i.e., the pre-set value of P is obeyed in all cases. Hence, this test is the most accurate, but also the test, which indicates significance between sample pairs less likely.

From the several possibilities of multiple comparisons in the SPSS package, preferably the Scheffé test or the Bonferroni method should be used. In both cases the difference between two mean values is calculated according to the following equation, whereby the value of T represents an estimate of the variance of the population based on all samples. The value of T is hence the same in both tests. The value of R is a weight, which is used to determine the difference between two mean values, and which depends on the test used:

$$\bar{x}_1 - \bar{x}_2 \geq T \cdot R\sqrt{\frac{1}{n_1} + \frac{1}{n_2}}$$

To summarize, single ANOVA can be used to compare two or more samples, which are the result of the variation of one influence factor only. ANOVA can consider only one variable at the time. If more than one variable was measured, ANOVA must be performed for each variable separately, or multivariate analysis of variance (MANOVA) could be employed.

Multiple Analysis of Variance

Multiple analysis of variance is employed if two or more independent influence factors have been used to split the data into samples. Depending on the number of influence factors included, one can distinguish between double ("two-way classification"), triple ("three-way classification") ANOVA, etc. The theoretical approach is here a model with a normally distributed population with independent, additive influences of several factors.

The methods require a complete design of samples, i.e., each level of each influence factor has to be combined with each level of the other influence factors. (SPSS also offers fractionated designs.) For a design with two influence factors, which have been tested on three/four levels, 12 samples would have to be studied:

	Influence factor 1	Level 1	Level 2	Level 3
Influence factor 2	Level 1	1	2	3
	Level 2	4	5	6
	Level 3	7	8	9
	Level 4	10	11	12

From the above example it is obvious that for more than two influence factors and/or several factor levels the number of samples required increases rapidly. It is hence often attempted to reduce the number of samples. For models with fixed effects one can use factorial designs (see below). Influence factors can affect the sample behavior fully

independent of each other, or the effect of one factor changes in response to the level of the other factor(s). The latter phenomenon is called "interaction." The following example aims to illustrate independent influence factors (a) and interactions between influence factors (b). In the example tablets with a fixed amount of drug and excipients were prepared. The concentration of the disintegrant (D) and the lubricant (L) as influence factors was varied. The following disintegration times (T) were observed:

D (mg)	5			10			20		
L (mg)	0.5	1.0	2.0	0.5	1.0	2.0	0.5	1.0	2.0
T (a) (min)	10	20	40	8	18	38	4	14	34
T (b) (min)	10	20	40	8	15	29	4	5	7

An independent effect (a) means that the change of the influence factor from one to the next level always results in the same increase or decrease of the value of the measured variable, no matter what level any other influence factor has. In the above example the disintegration time increases always by 10 minutes for any 0.5 mg of lubricant added. An addition of 5 mg disintegrant decreases the disintegration time always by 2 minutes. In the presence of an interaction between disintegrant and lubricant concentration (b), the effect will change. Here the addition of 0.5 mg lubricant results in an increase in disintegration time by 10 minutes, if 5 mg disintegrant are in the tablet, by 7 minutes, if 10 mg disintegrant are present, and by 1 minute, if 20 mg disintegrant are in the tablet. The addition of 5 mg disintegrant reduces the disintegration time by 2 minutes, if 0.5 mg lubricant is present, by 5 min, if 1mg lubricant is present, and by 11 min, if 2 mg lubricant have been used.

The MANOVA with fixed effects is a linear model. Deviations from linearity are not of such importance if the interest in the analysis is mainly to identify main effects and interactions. However, in such cases no precise statements about the error probability can be made. In models with random effects interactions are generally not calculated, and the deviations from linearity are hence of limited importance.

The conclusions to be drawn from a multiple ANOVA are not simply derived, and very often incorrect statements are found in research papers. If assuming the example of a three-way classification with three factors (1, 2, and 3) the following constellation of main effects and interactions could be found (+ is significant; – is not significant; three cases denoted with a, b and c are presented):

	(a)	(b)	(c)
Influence factor 1	+	+	+
Influence factor 2	+	–	+
Influence factor 3	+	+	+
Interaction (1st degree) 1×2	+	–	–
Interaction (1st degree) 1×3	+	–	–
Interaction (1st degree) 2×3	+	–	+
Interaction (2nd degree) $1 \times 2 \times 3$	–	+	+

In case (a) all 1st degree interactions are significant plus all main effects (influence factors). When interpreting this outcome, some numerical shortcomings of the calculation process of ANOVA have to be remembered. The results indicate that, because all 1st degree interactions are significant, there are no independent main effects. Hence, one should refrain from interpreting the main effects in this case! In case (b) none of the 1st degree interactions is significant. However, there exists a 2nd degree interaction. Main effects are significant for influence factors 1 and 3. Hence, the interpretation of influence factors 1 and 3 as a main

effect is justified, and so is the interpretation of the 2nd degree interaction. In case (c) all main effects plus the 1st degree interaction between influence factors 2 and 3 and the 2nd degree interaction are indicated to be significant. As influence factors 2 and 3 are part of the significant 1st degree interaction, only influence factor 1 presents a true main effect, which can be interpreted. Also, because the 2nd degree interaction is significant, the 1st degree interactions do not exist as such and should not be interpreted. Hence, in case (c) there is one main effect (influence factor 1) and one 2nd degree interaction to report.

Multiple Linear Regression Analysis

ANOVA of this kind is normally used to prepare the modeling of relationships between influence factors and the measured variable using linear regression models. A good regression model should only contain those influence factors, for which the significance has been proven by means of ANOVA. For the incorporation of interactions into the regression model different opinions exist. The majority of statisticians would restrict the regression model to incorporate only the valid main effects and only the valid interactions. Some books (and often pharmaceutical publications) would consider the hierarchy in the models and hence would also incorporate all other significant (and sometimes even insignificant) main factors, even if these were superseded by their relevant interaction terms. However, due to the correlation between the factors and the interaction often regression analysis procedures have difficulties in determining the model equation and exclude some factors. The excluded factor might, however, not be the true main factor isolated during the ANOVA procedure! Hence, it is advisable to check first that the regression model indeed is based on the correct factors. If the hierarchical model can be used it is best to calculate both the hierarchical and the simple model. One should then choose the model with the smaller deviations in the residual analysis. If both models are equivalent, the simpler model should be preferred.

The correlation between the variable and the influence factors is described with the correlation coefficient (R), the linear determinant (R^2), the adjusted linear determinant and the standard error. In multiple regression models the values for R and R^2 are of little meaning, because both values are strongly related to the number of influence factors and observations. A decrease of the observation number or an increase in the number of influence factors (main effects or interactions) considered in the regression model always results in an increase in the values for R and R^2. The absolute values can fool the user. The adjusted linear determinant is corrected for the number of influence factors and observations and hence is much more real. However, also the adjusted linear determinant is not a measure of the goodness of fit! It only describes the degree of correlation between the influence factors and the measured variable. Measures for the goodness of fit of the data to the regression model are, for example, the standard error and the "Root Mean Square" (RMS) deviation. The standard error defines by how much (in absolute units) a practical result of the measured variable will deviate up or down from the predicted value, which has been obtained on the basis of the regression model, in about 65% of all cases. The RMS (in %) defines, how much on average the experimental data deviate from the regression line. The F-test refers to the slope of the regression line, which should be significant. Note that even for an $R = 1.000$ and RMS $= 0$ % the slope of the regression line must not necessarily be significant, because all measuring values could be parallel to the abscissa, i.e., the influence factors would have no effect.

For each influence factor the regression coefficient (B); its standard error (SE_B), the normalized regression coefficient (β), and the significance (t and significance of t) should be observed. For the intercept with the ordinate (constant) standard error and significance

should also be tabulated. Here, the standard error defines by how much in 65 % of cases the value for *B* would be different if the experiment was repeated and a new regression equation calculated. The results for β are computed from normalized data material. (Normalized values are calculated so that their mean value is zero and their standard deviation is unity, i.e., $(x - \bar{x})/s$.) The value of β exceeds the importance of *B* as the latter depends on the units and scale of the influence factor in question. Whether and to which degree an influence factor contributed to the slope of the regression line can only be judged using β values. Every influence factor included in the regression model should contribute significantly to the slope of the regression line, i.e., the value for *t* should be large enough to indicate an error probability below $P = 0.05$.

As mentioned above it is possible to use the reduced or the hierarchical regression model. The model with the lower standard error and the smaller RMS value should be chosen. The adjusted linear determinant always shows that the reduced model can be regarded as part of the hierarchical model.

Non-Parametric Analysis of Variance

Non-parametric ANOVA is used if the measuring values of a variable are not on the numeric but the ordinal scale. The advantage of the non-parametric ANOVA is that the data must not follow a defined distribution function such as that of a normal distribution, and there are no measures of central tendency (e.g., arithmetic mean value) or variability (e.g., standard deviation) calculated. Hence, there is also no need for homogeneity of variance. Non-parametric ANOVA is therefore also used, when numeric data are not normally distributed and/or if there is gross inhomogeneity of variance between the samples.

The *H*-test after Kruskal and Wallis for independent samples is the equivalent of non-parametric ANOVA to the Mann & Whitney test for two independent samples. Again, it can be used for more than two samples, but also for the simple case of two samples only. The Mann & Whitney test will hence not be discussed for the reasons explained earlier.

First of all the data are sorted according to their increasing size and rank numbers are allocated regardless of the sample to which the values belong. If there are equal values in different samples, ranking is more complicated. The existence of equal rank numbers is termed “tie.” In these cases a correction will be carried out. The rank sums are then determined for each sample. The rank sums should be equal for each sample, if they were taken from one and the same population.

In the statistical test the criterion *H* is calculated from the rank sums and compared with the critical values of the χ^2-distribution for $k - 1$ degrees of freedom (k = number of samples). There are no paired comparisons for non-parametric ANOVA models.

The Friedman test for dependent samples is the non-parametric ANOVA equivalent of the Wilcoxon test for two dependent samples. The advantage of the Friedman test in comparison to the Wilcoxon test lies in the use of the χ^2-distribution, for which the null distribution is usually reported in statistics books. The Wilcoxon test, however, uses a special table, and in many areas of research it has hence become common practice to use the Friedman test also for the comparison of two samples only. This is reasonable as long as the data are on an ordinal scale. However, if two samples with numeric data material are to be compared because there is some violation of the requirements of normal distribution and/or homogeneity of variance, the Wilcoxon test is more accurate.

In the Friedman test again the measuring values are ranked neglecting the samples to which they belong, and the test criterion is calculated considering the division of the

data into samples. Also here the test value is compared to the χ^2-distribution using $k - 1$ degrees of freedom. Although the basic principle of ranking is identical to the Kruskal–Wallis test, it is important to note that the test criterion itself is calculated on a different numerical basis.

FACTORIAL DESIGN

Introduction

The outcome of a development exercise will depend on a number of variables. In factorial design the variables that have been selected for a study are called "factors." The problem is that typically not all variables influencing the outcome of an experiment are known. Some of them will probably never be discovered, while others might be detected during the progress of the experiment. Byrne and Taguchi (4) classified the factors that can be important for the outcome of an experiment into "controllable" and "noise" factors. Noise factors were described as "either difficult, impossible, or expensive to control." In most instances researchers restrict the variables studied to controllable factors, and thus factorial designs rarely involve "random factors." Thus, for the mathematical evaluation of the results that stem from factorial designs in most cases general ANOVA and multiple linear regression analysis are employed (see above). In rare cases, random factors or co-variates are considered.

There are different ways to set up the DOE for a factorial design (9). In the simplest case, two or more independent variables (factors, n) are tested at different levels, f. In a full factorial design, i.e., all factors are combined with each other on all levels, the number of experiments equals. f^n. As a result, in particular the number of factors but also the number of levels of each factor can increase the number of experiments to be performed to an excessive amount. For example, a 3^2 full factorial design involves nine experiments, a 4^2 full factorial design consists of 16 experiments, and a 5^2 full factorial design consists of 25 experiments. The addition of one factor (a 3^3, 4^3 or 5^3full factorial design, respectively) results in 27, 64 or 125 experiments, respectively. Hence, to minimize the number of experiments often only two factor levels are considered (10), and the number of factor levels rarely exceeds 3.

Factorial design combines a number of useful properties, and on first look it appears as though there are no major related disadvantages. Theoretically it will be possible to study an unlimited number of factors and their interactions on the same object and at the same time. Calculation procedures are comparatively simple and full software support for all types of full and fractionated ANOVA models and multiple linear regression analysis is available. However, the interpretation of the results requires skills and a full understanding of the underlying mathematical principles. This has already been highlighted when discussing the general principles of ANOVA (see above). Also, designs using two factor levels only imply a linear relationship between influence factors and response variables. Such designs can thus only be employed if the linearity has been proven beforehand by a number of preliminary experiments. In the literature, however, such proof is often missing invalidating the results reported. An increase to three factor levels may allow handling of quadratic relationships. However, to be able to fit the results to an exact nonlinear function, five or more factor levels are required. Nonlinear regression functions obtained from smaller designs are speculative at best. It is also important to remember that the regression equations obtained from factorial designed experiments are only applicable to the factor space they have been obtained from. Extrapolations beyond that space are invalid, which becomes particularly problematic if

such model equations are used in optimization or response surface methodology. To set up a useful factorial design requires thus a good knowledge of the behavior of the response variables with change in factor levels. Designs that could be expanded at any time and in any direction if necessary would be desirable, but have not yet been developed. Hence, the sequential development of an investigation (see below), if an optimum factor/level combination is desired, might be advantageous over a fixed form of factorial design.

Full Factorial Designs

Two level full factorial designs are the simplest designs. They go back to original work by Fisher (11), Yates (12,13), Hotelling (14) and Placket and Burman (15), to name some of the earliest studies only. In the case of a 2^2-design, the design matrix is similar to a square, while, for example, for a 2^3-design the design matrix is similar to a three-dimensional cube. Each factor is tested at a low (denoted with –1) and high level (denoted as + 1), and all possible factor combinations are explored. This is illustrated in Table 1 and Figure 3.

The outcome of experiments can be treated using ANOVA and multiple linear regression analysis, as described in the previous sections. Care has to be taken not to include insignificant factor combinations into the final mathematical model and hence ANOVA should be undertaken first, and the regression model should be constructed on the basis of the ANOVA outcome. To use multiple linear regression analysis alone will lead to models with redundant factors, even if a forward or backward elimination process for significant influence factors/interactions has been used. Saturated equations (i.e., equations which contain all main factors and interactions) are unable to estimate the experimental error due to uncontrolled factors and random variations in the response (16) and thus are of little help. If all interactions are insignificant then multiple linear regression analysis should not be used as it is then based on two points per factor only.

When conducting the experiments assigned to a factorial design, these should be undertaken in random order, i.e., each factorial combination should be assigned to a random number, which can be found using random digit tables available in the Appendices of most statistical text books. Ideally, all experiments belonging to the design should be replicated to ensure exact assessment of the experimental error (17). Very often, however, researchers replicate only one of the experiments, assuming that the

TABLE 1 Design Matrix for a 2^2 and a 2^3 Full Factorial Design
The 2^2 Design Space is Highlighted in Gray

Experiment	Factor			Property measured
	f_1	f_2	f_3	
1	−1	−1	−1	Zero level interaction
2	−1	+1	−1	Main factor effect (f_2)
3	+1	−1	−1	Main factor effect (f_1)
4	+1	+1	−1	Interaction between f_1 and f_2 (and f_3)
5	−1	−1	+1	Main factor effect (f_3)
6	−1	+1	+1	Interaction between f_1, f_2, and f_3
7	+1	−1	+1	Interaction between f_1, f_2, and f_3
8	+1	+1	+1	Interaction between f_1, f_2, and f_3

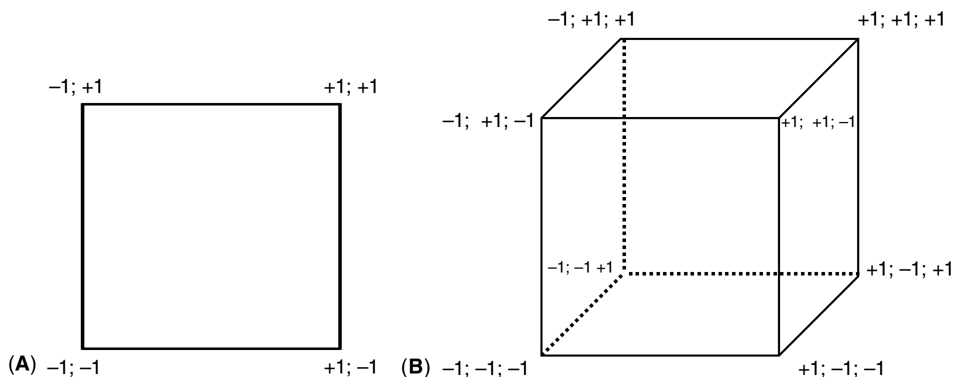

FIGURE 3 **(A)** Design matrix for a simple 2^2-design. There are four experiments to be carried out. Each factor has a low (-1) and a high ($+1$) level, and the levels are combined with each other. **(B)** Design matrix for a simple 2^3-design. There are eight experiments to be carried out. Each factor has a low (-1) and a high ($+1$) level, and the levels are combined with each other.

experimental error remains similar throughout the series of experiments. In many cases this might suffice, but there are cases, where the change in factor level could also result in a larger or smaller experimental error, in particular where living organisms are involved or material that has been obtained from natural sources. In those cases a full replication of all experiments is advisable.

Interactions are often difficult to be interpreted. Neither the ANOVA results nor the regression coefficients give a straightforward answer as to what happens if the levels of interacting factors change. A very useful technique is here the graphical presentation of the results (18). Figure 4 illustrates the three potential graphical findings. In these graphs the lines represent the effect at each factor level. If the lines are parallel (Fig. 4a), no interaction can be statistically observed. Both effects are statistically the same and are therefore additive. Lack of parallelism is an indication of factor interactions. If the two lines intersect (Fig. 4b) then there is a reversal in the rank order of the effects at the two factor levels. Such an interaction is classed as disordinal. If the two lines, however, do not cross (Fig. 4c), then the rank order of the effects is equal for both factor levels, even though the difference between the two effects is not the same for the two factor levels. Such an interaction is classed as ordinal.

Similarly to the 2^n full factorial design, the 3^n or higher level designs (k^n full factorial designs with $k =$ number of factor levels and $n =$ number of factors) indicate maxima and minima. In addition they also provide an estimate of nonlinear (mainly quadratic) effects (5). The ways of analyzing the results of higher level designs remain similar to the two level designs, i.e., multiple ANOVA followed by multiple linear regression analysis should be conducted (see above). The multiple linear regression equations should be kept as simple as possible, i.e., again only significant terms should be added, and in order to ensure that the test statistics remains meaningful, a large number of replicates is required. Under no circumstances should the regression equation be judged by its R^2 value. The limited number of experiments plus the introduction of nonlinear terms make R^2 insensitive and thus a full residual analysis should be undertaken to assess the goodness of fit of the regression equation in terms of the original data (16).

Central composite designs (CCD) are a special advanced form of full factorial designs and were first described by Box and Wilson (19). In contrast to ordinary full factorial designs, where the factorial space enclosed is a square or cube for two and

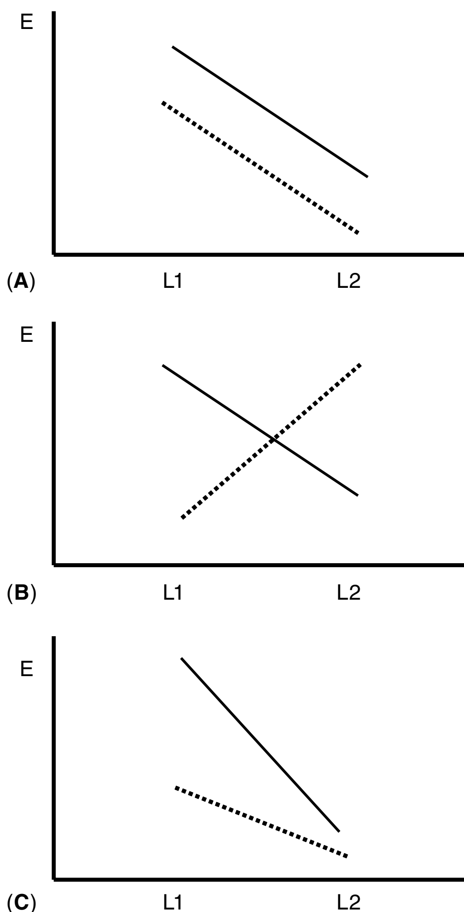

FIGURE 4 Two-factor interactions: graphical presentation as an aid to interpretation. (**A**) Parallel lines indicate that there is no interaction between the factors; (**B**) intersecting lines indicate disordinal interaction; (**C**) nonparallel, nonintersecting lines indicate ordinal interaction. E = effect; L = factor level for the second factor; full line and dashed line = levels for the first factor, respectively.

three factors, respectively, the factorial space of CCDs is circular or spherical for the two and three factors, respectively. These designs contain in addition to a 2^n full factorial design a centroid experiment and a set of experiments that can be classed as "axial" or "star" points. To achieve circular or spherical domains, the start points are situated in a defined distance from the centroid along the axes from the centre point. For two and three factors, respectively, the designs are illustrated in Fig. 5. Table 2 provides the design matrices for these two designs. The distances for the star points required to achieve a circular or spherical domain are 1.414 for two, 1.682 for three, and 2.000 for four factors.

Very often central composite designs are used in surface response methodology. However, there is some uncertainty about the response contours, as the variance of the response variable is at a minimum at the centroid point and increases in all directions when moving away from the centroid, similar to what is known about the confidence interval of a regression line. The centroid experiment is thus of great importance for the outcome and interpretation of the results. The centroid experiment is thus often the one experiment that is replicated several times. This provides information about the pure experimental error variance and the curvature of the response surface. In fact, the replicates of the centroid experiment can have major effects on the overall shape and orientation of the response surface derived (5).

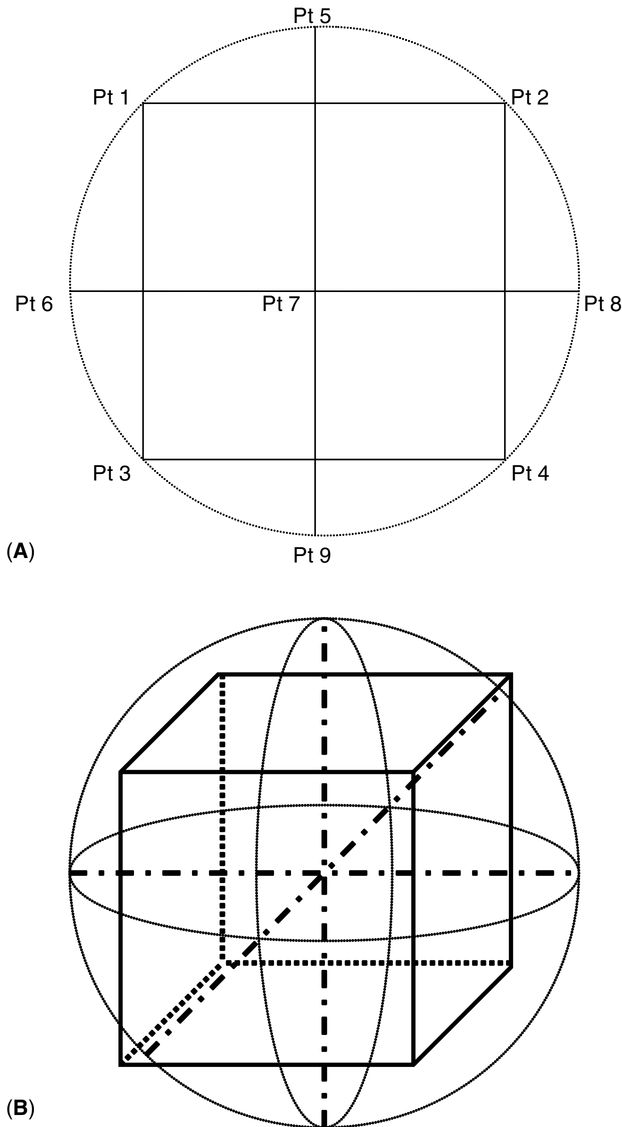

FIGURE 5 **(A)** Central Composite Design based on a 2^2-full factorial design. $\alpha = 1.414$; Points 1–4 refer to the underlying 2^2 factorial design. Points 5, 6, 8, and 9 are start points, and point 7 is the centre point of the design. The design forms a circular domain (as indicated by the thin dotted line). **(B)** Central Composite Design based on a 2^3-full factorial design. $\alpha = 1.682$; the design forms a spherical domain (indicated by the thin lines). The basic 2^3 full factorial design is represented by the cube, whereas the star lines are represented by the dash–dot lines. The experimental points ("star points") are situated at the ends of each of these dash–dot lines and the centre point is equal to the crossing of these lines in the centre of the cube.

A deviation from the CCD is the Centre of Gravity Design (20–22) which adds further points along the star axes to enhance the goodness of fit of the regression equations (Fig. 6a), and the Box–Behnken Design (23), where the start points are situated at the edges of the factorial space (Fig. 6b). In the latter case the experimental domain reverts back to square or cube shape.

TABLE 2 Design Matrices for a 2^2 and a 2^3 Full Factorial Design as Illustrated in Figure 5

Experiment	Factor f_1	f_2	f_3	Property measured
1	−1	−1	−1	Zero level interaction
2	−1	+1	−1	Main factor effect (f_2)
3	+1	−1	−1	Main factor effect (f_1)
4	+1	+1	−1	Interaction between f_1 and f_2 (and f_3)
5	−1	−1	+1	Main factor effect (f_3)
6	−1	+1	+1	Interaction between f_1, f_2, and f_3
7	+1	−1	+1	Interaction between f_1, f_2, and f_3
8	+1	+1	+1	Interaction between f_1, f_2, and f_3
9	α	0	0	Main factor effect (f_1)
10	$-\alpha$	0	0	Main factor effect (f_1)
11	0	α	0	Main factor effect (f_2)
12	0	$-\alpha$	0	Main factor effect (f_2)
13	0	0	α	Main factor effect (f_3)
14	0	0	$-\alpha$	Main factor effect (f_3)
15	0	0	0	Centre point

Fractional Factorial Designs

Fractional factorial designs attempt to be more economical by reducing the number of experiments further. This becomes in particular useful if the number of factors is larger than three (24).

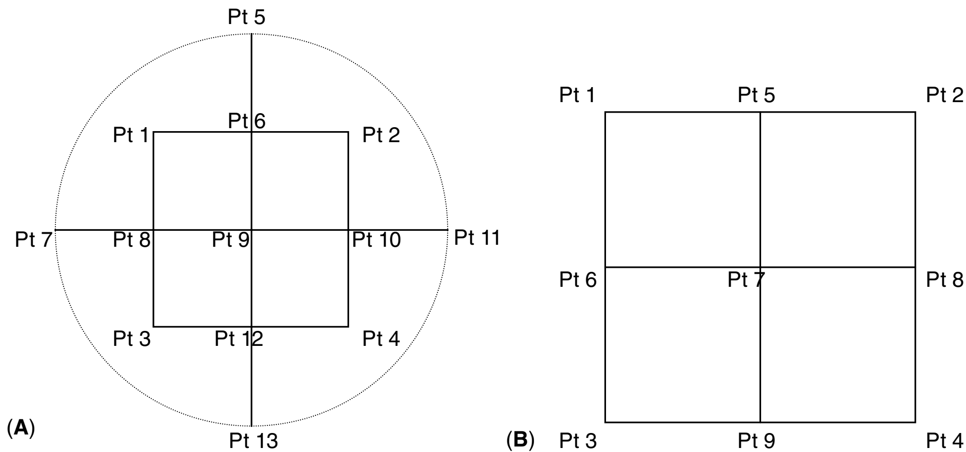

FIGURE 6 **(A)** Centre of gravity design based on a 2^2-full factorial design. Points 1–4 refer to the underlying 2^2 full factorial design. Pt 9 is the centre point. Points 5, 7, 11, and 13 are the star points, and points 6, 8, 10, and 12 are surface points. The distance between star and surface points equals the distance between the centre point and the surface points, i.e., all points are evenly spaced. Again the domain formed is circular (indicated by the thin dotted line). **(B)** Box–Behnken Design based on a 2^2-full factorial design. Points 1–4 refer to the underlying 2^2 full factorial design. Points 5–9 are the surface points, i.e., the "star points" are here situated at the edges of the original design space.

A first step to fractionation of full factorial designs is to divide the experiment into blocks. For example, a 2^3 full factorial experiment can be divided into two blocks of four experiments. This is illustrated in Table 3.

As a result of the two block structure another potential source of variation has been introduced, i.e., there could be a systematic difference between the results of the two blocks. The "between blocks difference" must become confounded within one of the $2^3 - 1$ effects of the design, because the total number of degrees of freedom cannot change. The subdivision into blocks will thus always result in loss of knowledge about the magnitude of one of the effects (for two blocks); typically the "+1+1+1 interaction" will be confounded. In general, when splitting a 2^n factorial design into 2^p blocks, p interactions will be confounded. To derive at fractional factorial designs, the full factorial design is divided into blocks with the intention to complete the experiments of only one block. One could choose the block to be researched at random, but typically the principle block, i.e., the one containing the experiment with all factors at the low level is selected. This would be block 1 in Table 3. The principle block is usually constructed so that it contains all combinations with zero, two, four, etc., level interactions, while the remaining block contains the main factor and three level interaction experiments. The calculation of the effects and interactions can now no longer be differentiated as these become aliased. If an independent assessment and estimation of main effects versus interactions is required, fractionated designs are not helpful.

There are a number of specialized designs available. The reader is referred here to more fundamental literature, for example, for mixture design see Refs. 17 and 25, and for D-optimal design see Chapter 8 in Ref. 10.

Fractional Factorial Designs in Sequence versus Taguchi Design

To divide a multi-factorial design into blocks and to carry out the blocks selectively in a defined order, one at a time, might bring considerable advantages. In this way it is possible to separate aliased effects from each other. Insignificant variables can be detected and removed and modified levels or new variables can be introduced. The

TABLE 3 Block Design for a 2^3 Factorial Design

	Factor			
Experiment	f_1	f_2	f_3	Property measured
Block one				
1	−1	−1	−1	Zero level interaction
2	+1	+1	−1	Two level interaction
3	+1	−1	+1	Two level interaction
4	−1	+1	+1	Two level interaction
Block two				
5	+1	−1	−1	Main factor
6	−1	+1	−1	Main factor
7	−1	−1	+1	Main factor
8	+1	+1	+1	Three level interaction

Note: In a fractionated design block one (the "principal block") would be studied first, and dependent on the outcome, block two would follow if necessary. The principal block is constructed so that it contains all combinations with zero, two, four, etc. level interactions, whereas the second block would contain the main factors and all three level interactions.

Japanese engineer Genichi Taguchi recommended beginning with a comprehensive experimental design, which should incorporate every factor that might be involved. However, if later the results indicate that one of the factors has an undesired adverse effect on the results if at a certain level, then all experiments undertaken at that level are of no use. At the worst, the full experimental plan has to be redesigned and repeated. Money and time might have been wasted. Hence large multi-factorial studies should be divided into blocks (5), whereby higher order interactions should be confounded. Within each block the experiments should be undertaken in a random order. The blocks should be performed one at the time. It is important to analyze the block results as soon as they are available. Corrections in the factorial design can be made between blocks. Once the main effects can be estimated with sufficient precision, the work should stop and no further blocks be studied. However, important aliases between the main factors and the two factor interactions should have been separated at this point. The advantages of such an approach are obvious, i.e., the first block might already reveal all information required. It might become obvious that one or few factors give a large effect, while others are negligible, and further work could thus focus on choice of more appropriate levels for the important factors. It could also become advantageous to redesign the experiment with fewer factors, maybe at new or similar levels, or factors could be replaced by others that might be important.

As mentioned before, Taguchi statistics is the opposite of fractionated factorial designs in sequence, i.e., here the most comprehensive design is worked out and performed. In a Taguchi design controllable factors and random or uncontrollable factors ("noise") are defined and combined in the experimental design. The design is "three dimensional" in that not only factors and their levels are combined, but the third dimension is formed by a similar design of the second set of factors and levels. Table 4 illustrates this. Interactions between uncontrollable factors are not normally investigated, but the design shown in Table 4 could be expanded by adding interaction terms between α and β. Data analysis now includes a "signal to noise" ratio, i.e., the mean response divided by a measure of variability. This ratio is calculated for each experiment under consideration of the replicates due to change in the α or β noise variable. This gives information as to the importance of the uncontrollable noise and might identify important environmental or other variables for which some form of control should be found. In conjunction with the signal to noise ratios suitable levels for an optimal process can be found. The calculation of the signal to noise ratio eliminates a need to define the interactions between controllable and uncontrollable factors, i.e., the computational effort is still mainly based on an ANOVA for the controllable factors (4). The Taguchi design is complex and time consuming and will certainly only be useful in special circumstances, for example, for scale up experiments and production.

RESPONSE SURFACE METHODOLOGY

Response surface methodology (RSM) makes use of multiple linear regression equations that are the result of experiments performed on the basis of factorial designed experiments. If only one or two factors have been used, it can provide graphical presentations of the change of a response variable with change in a single or the combination of the two factors. However, also for more than two factors methodology is available to represent the changes of the response variable in an understandable fashion. For more than two variables such a method is "numerical simulation." In many instances the final aim of using RSM is to find an optimum solution for a problem. The optimum must not

TABLE 4 The Taguchi Design

		Controllable factors			Uncontrollable factors	
Cycle	Experiment	*A*	*B*	*C*	α	β
1	1	−1	−1	−1	−1	−1
	2	+1	−1	−1	−1	−1
	3	−1	+1	−1	−1	−1
	4	−1	−1	+1	−1	−1
	5	+1	+1	−1	−1	−1
	6	+1	−1	+1	−1	−1
	7	−1	+1	+1	−1	−1
	8	+1	+1	+1	−1	−1
2	1	−1	−1	−1	+1	+1
	2	+1	−1	−1	+1	+1
	3	−1	+1	−1	+1	+1
	4	−1	−1	+1	+1	+1
	5	+1	+1	−1	+1	+1
	6	+1	−1	+1	+1	+1
	7	−1	+1	+1	+1	+1
	8	+1	+1	+1	+1	+1

Note: Factors *A*, *B*, and *C* are controllable factors, varied at two levels each, whereas factors α and β are uncontrollable factors, which have been simulated at two levels in this example. −1 refers to low level and +1 refers to high level. The design runs thus over two cycles and could be expanded to four cycles, if interactions between α and β were considered.

necessarily be "the best" solution, but could be one that is workable and robust and hence less affected by small changes in the value(s) of the influence factor(s). An example for the need to find the best factor combination could be to produce tablets which disintegrate instantaneously on contact with saliva, while an example for the need to find a robust factor combination could be the need to be able to accompany small changes in raw material properties due to batch to batch variability in a pharmaceutical formulation.

The graphical presentation of response surfaces is mainly in the form of contour plots (26–28). Contour plots show the scales of one influence factor on the abscissa and ordinate each. They show contour lines that represent a defined value of the response variable. The area between the contour lines represents "similar" response, whereby the degree of similarity depends of course on the density and definition of the contour lines. In Fig. 7 a contour plot illustrating the dependence of the breaking load of tablets on two different manufacturing parameters is illustrated. If the change of a response as a result of changes of more than two variables requires illustration, contour plots are no longer possible. However, Chernoff (29) presented a method that permits visualization of changes of a response variable due to changes of a number of influence factors using a cartoon face. Each part of the face responds to one or more of the in total 18 possible factors involved. While some readers might dismiss this technique as cartoon drawings with no scientific value, this technique has been successfully used to illustrate small changes in Swiss bank notes due to slight variations in their manufacturing process, allowing to distinguish false from real bank notes (30). Alternatively, simulation tables can be constructed, i.e., multiple linear regression equations are used to calculate tables of performance. By systematically changing all factors and their combinations the response of a system can be analyzed and again a "best performance" or a robust array of factor combinations can be found.

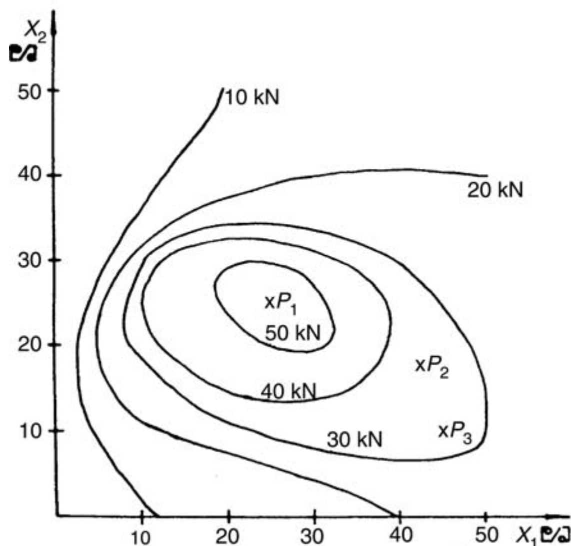

FIGURE 7 Contour plot illustrating the relationship between breaking load of tablets and two different formulation parameters, X_1 and X_2. The breaking load is given in kN, and the different contour lines illustrate the threshold values between which the formulation points P_1, P_2, and P_3 are situated, i.e., formulation P_1 has a breaking load in the range of 50 kN and above, whereas formulation points P_2 and P_3 have breaking loads between 30 and 40 kN.

The problem with RSM lies in the fact that the contour plots and simulation tables are only representative for the behavior of one individual response variable at the time. If, such as required in process or dosage form development, more than one response variable has to be monitored and the factors leading to the desired response have to be optimized, RSM is not really helpful. In many cases different responses change differently with change in factors, and could even be contradictory in their outcome. To find an "optimum solution," i.e., a scientific compromise between all response variables is difficult to ascertain in this way. Overlaying of contour plots is possible but leads to complex and in a way untidy graphs. Simulation tables are better in this respect, but to find an optimum solution for a problem with the aid of RSM alone is not advisable.

MATHEMATICAL OPTIMIZATION

Optimization is a mathematical method to search for and to find the "optimum," which is defined as the most advantageous state of the system in question (31). There is a wider range of optimization techniques available. A summary of common techniques is provided in Table 5. All methods require that a mathematical model function is available, which describes the structure of the system quantitatively. Multiple linear regression equations obtained from statistically designed experiments provide a solid basis for the quantitative description of the change of the response of a system as a function of a series of changes in controlling factors. Optimization also requires a mathematical description of the optimum, i.e., the best solution or best compromise solution, either one being the purpose of the investigation. This already points to the fact that different optimization techniques might well result in a different optimum setting for formulation and/or process variables, because the numerical definition of the optimum and strategy to find the optimum are different for different optimization techniques. All methods require that the response variable(s) to be optimized is/are related quantitatively to the predictor variables (factors), and that the function describing this relationship is consistent over the domain defined by the experimental design.

TABLE 5 Summary of Mathematical Optimization Techniques Available

Optimization class	Method	Sub-methods
Linear optimization	Simplex method	
	Revised simplex method	
	Iteration methods	
		Ellipsoid method
		Projection method
One-dimensional search	Fibonacci method	
	Golden steps method	
	Quadratic interpolation	
	Cubic interpolation	
Unconstrained nonlinear optimization	Direct search methods	Stochastic search
		Search along coordinates
		Polytop method
	Derivative methods	
		Steepest decent
		Conjugated gradient
		Newton–Method
		Variable metric method
Constrained nonlinear optimization	Direct search methods	Adaptive coincidental search
		Extended polytop method
	Quadratic optimization	
		Relaxation method
		Method of active constraints
	Derivative methods	
		Sequential quadratic approximation
		Extended Newton–Method generalized reduced gradient method
		Methods using penalty functions
Multicriteria Decision Making	Multi-criteria simplex method	
	STEM procedures	

One major problem in optimization is the need to compromise between response variables. For example, the optimum tablet formulation would have superior tablet strength, no friability, yet an extremely short disintegration time. Very often, however, an increase in tablet strength is combined with an increase in disintegration time beyond pharmacopoeial limits. Hence the optimum solution will have to be a compromise between these contradictory response variables. There are some methods such as Multicriteria Decision Making ("vector optimization") (32,33) or the modified Lagrange function (34), which can use more than one parameter to be optimized simultaneously.

However, the majority of optimization techniques can only handle one parameter at the time. Methods have been suggested to combine the set of response variables into one artificial optimization variable (35), but the ways of building such a variable are the key to success or failure.

In linear optimization the response variable(s) and a set of constraints defining the optimum space are linearly dependant on the influence factors chosen for the underlying

experimental design. The optimization procedure is geared to finding a solution that either minimizes or maximizes the response variable within the limits of the constraints. Some basic properties of linear optimization are:

1. The optimum solution to the problem is, due to the linearity of the mathematical equation describing the problem, only defined by a set of constraints.
2. The constraints limit the p-dimensional Euclidean space (R^p, infinite with p being the number of factors involved) considerably, and as a result a finite space G results. G contains a large number of solutions that are valid with respect to the constraints. One of these solutions provides an optimum value for the response variable.
3. Each constraint splits R^p into two semi-spaces, of which only one contains the valid solutions with respect to that constraint. The set of all upper and all lower constraints which form the boarder of the linear optimization problem ("LOP") are termed upper and lower vertex.
4. The finite space G is convex because of the linearity of the constraints. In a convex space two random points can be connected by a line, which is positioned fully inside the space. Any point that cannot be the midpoint of such a line will be termed "extreme" point.
5. In a multi-dimensional LOP the convex space G is a polyhedron, which is illustrated in Fig. 8. The number of corners of the polyhedron can be calculated from $\binom{m+p}{p}$ with m being the number of constraints and p the number of factors of the experimental design.
6. The optimal solution is always positioned at the edge of the polyhedron, i.e., either at a corner or somewhere along the edge. The edge forming the optimum solution is a special case, i.e., there are more than one solution to the problem. However, if the optimum solution coincides with a corner of the polyhedron then indeed this is a true optimum solution, as it is not possible to have more than one optimum corner.
7. The corners of G are called "base points" or "base solutions" and the base point providing the optimum solution is called "efficient point."

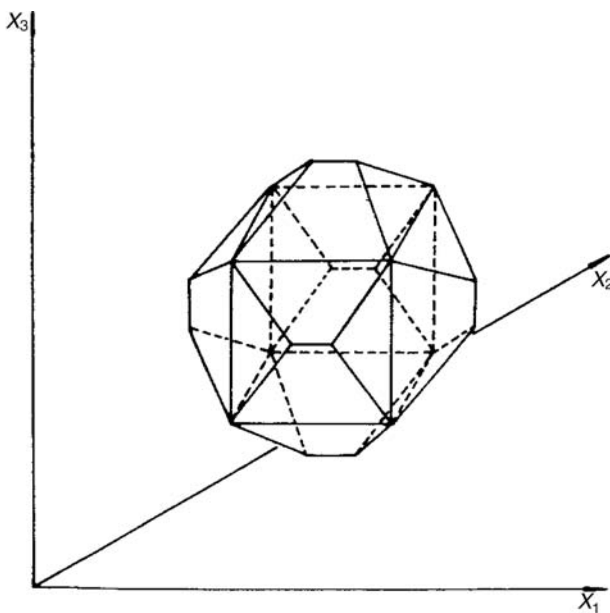

FIGURE 8 A three-dimensional linear optimisation problem results in a polyhedron with a defined number of corners. The optimal solution will normally lie at one corner of the polyhedron. *Source*: From Ref. 33.

In contrast to linear optimization techniques, nonlinear optimization methods are based on the fact that a nonlinear function has at least one local minimum or maximum, which can be determined universally by means of differential calculus. In practice, however, this becomes more difficult the more complex the nonlinear function is. Iterative methods are commonly employed to resolve nonlinear complex functions describing the relationship between experimental factors and response variables.

Multicriteria decision making permits the simultaneous optimization of a series of response variables without the need to form a single, combined variable. Software is rarely available, but commonly used numerical approaches are the multicriteria simplex method (36,37) and the STEM procedure (38).

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4

Knowledge-based Systems and Other AI Applications for Tableting

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INTRODUCTION AND THE SCOPE OF THE CHAPTER

The pharmaceutical industry is under continual pressure to speed up the drug development process, reduce costs, and improve process design. At the same time, FDA's new Process Analytical Technology initiatives encourage the building in of product quality and the development of meaningful product and process specifications that are ultimately linked to clinical performance. Together, these two issues present significant challenges to formulation and process scientists because of the complex, typically nonlinear, relationships that define the impact of multiple formulation and process variables (independent variables), and such outcome responses (dependent variables) as drug release, product stability, and others. The number of variables that must be addressed is substantial and include, for example, the level of drug substance, the types and levels of various excipients, potential drug-excipient interactions, and their potential positive or negative interactions with a host of process variables. Often, the relationships between these variables and responses are not understood well enough to allow precise quantitation. And, since an optimal formulation for one response is not necessarily an optimal formulation for another response, product development is further confounded by the need to optimize a number of responses simultaneously.

Clearly, formulation scientists work in a complex, multidimensional design space. In recent decades, scientists have turned more and more to such tools as multivariate analysis and response surface methodology, knowledge-based (KB) systems, and other artificial intelligence (AI) applications to identify critical formulation and process variables, to develop predictive models, and to facilitate problem solving and decision-making in product development. The goal of this chapter is to address AI applications and describe their role in supporting formulation and process development.

KB system (1–3), also known as an *expert system*, is an intelligent computer program that attempts to capture the expertise of experts who have knowledge and experience in a specific domain or area (e.g., granulation). A KB system is designed to simulate the expert's problem solving process or to achieve problem solving to the level similar to or better than domain experts. The use of KB systems in support of

formulation or process development is relatively new in pharmaceutical technology, with applications appearing around the mid-1980s. Among these pharmaceutical applications are formulating tablets and capsules, process troubleshooting, and the selection of equipment. Such systems have the potential to shorten development time and simplify formulations. Moreover, KB systems can provide the rationale for the decisions taken, serve as a teaching tool for novices, and accumulate and preserve the knowledge and experience of experts. However, KB systems suffer from the limitation that they literally are not creative. That is, they can deal only with situations that have been anticipated in the program.

A neural network (NN) (3–5) is a computer program that attempts to simulate certain functions of the biological brain, such as learning, abstracting from experience, or generalizing. Designed to discern relationships or patterns in response to exposure to facts (i.e., "learning"), the models developed through a NN may be viewed simply as multiple nonlinear regression models. NNs thus enable data developed in the laboratory to be transformed into pattern recognition models for a specific domain, such as tableting or granulation, which would make it possible for formulators to generalize for future cases within certain limits. One limitation of NNs is that the effectiveness of a model is limited by the training data itself. Another limitation is that in most cases, NNs lack explanation capabilities, making it difficult or impossible to obtain a justification for the results. Although they have been used in other applications for more than 50 years, NNs have only been applied to pharmaceutical development since the early 1990s. Over the past 15 years or so, NNs have demonstrated substantial applicability in a number of product development situations, such as predicting granulation and tablet characteristics and predicting drug release from immediate release formulations and controlled release formulations. The development of hybrid systems that integrate NNs and KB systems potentially can take advantage of the strengths of both NNs and KB systems while avoiding the weaknesses of either.

In the sections that follow, we will discuss the design of KB systems, NNs, and other AI systems, and demonstrate their practical application to product development. The focus will be on oral solid dosage forms in general and on tablets in particular.

KNOWLEDGE-BASED SYSTEMS

KB systems are intelligent systems that explicitly encode, store, and make use of domain knowledge in problem solving. KB system, when they first appeared in the early 1970s, were often called "expert systems" because either the domain knowledge they had was a direct encoding of the expertise of domain experts or their performances reached the level of human experts. For example, MYCIN, a medical diagnostic expert system developed at Stanford University in the 1970s, was able to make correct diagnoses for blood infections with the accuracy comparable to physicians experienced in infectious diseases (6). As depicted in Figure 1, a typical KB system has two major components, the KB where the encoded domain knowledge is stored and the *inference engine* which uses the knowledge in KB to draw new conclusions or to initiate new actions based on the case input and according to certain inference rules. Some KB systems also have a *learning* component, which learns new knowledge or revise existing KB based on case data, sometimes with the help of feedback on the inference results.

The defining feature of KB systems is how domain knowledge is represented in the KB. The issue of knowledge representation (KR) includes both the *syntax* of the language, in which the knowledge is encoded and the language's *semantics,* which connects

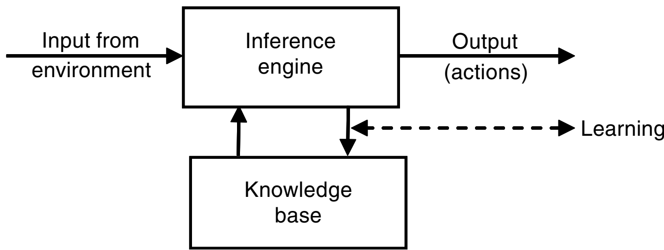

FIGURE 1 A typical KB system architecture. *Abbreviation*: KB, knowledge-base.

the encoded knowledge with the real world objects it is intended to represent. Moreover, KR is closely related to the inference engine of the system; each type of KR often requires its own set of inference rules and the reasoning procedure for using these rules.

Most modern KB systems are based on formal logics, more specifically on the type of logic known as *first order predicate logic* or first order logic (FOL), a formal system for deductive reasoning. Therefore, this section will start with a brief introduction to FOL before getting into specific KB systems. As representatives, we have chosen to cover only two types of KB systems, rule-based (RB) systems and decision trees, for their relative maturity and their popularity in practical applications.

First Order Logic

FOL formalizes deductive reasoning (1). It models classes of objects and their properties by a type of special functions known as *predicate*. Each predicate has a name and a list of arguments. For example, predicate Human(x) stands for the class of humans and Red(y) for things that have color red. For any particular object, a predicate can only have one of the two values, *True* (1) and *False* (0), depending on whether the object is an instance of that class. For example, Human(Confucius) = True and Human(Tweety) = False. More complex expressions or sentences can be formed by connecting predicates with logical operators such as *And* ($\wedge$), *Or* ($\vee$), *Not* ($\neg$), and *If-then* ($\rightarrow$)[a]. Special means are provided for stating whether a statement is true for all objects or only for some; they are *universal quantifier* ($\forall$) and *existential quantifier* ($\exists$). With some syntactic rules, one can write FOL sentences articulating the meaning of often ambiguous English sentences. For example, "All humans are mortal" can be written as

$$\forall_x \text{ Human } (x) \rightarrow \text{Mortal } (x).$$

"Not all roses are red" can be written as either

$$\neg\forall_x \text{ Rose } (x) \rightarrow \text{Red } (x), \text{or alternatively } \exists x \text{ Rose } (x) \wedge \neg\text{Red } (x).$$

FOL uses deductive rules to derive new sentences representing new conclusions. For example, if knowing "All humans are mortal" (the major premise) and "Confucius is a human" (the minor premise), then one can draw a new conclusion according to the

[a]These operators are also known in logic literature as conjunction, disjunction, negation, and implication, respectively. There are other logical operators, which are less popular and can be expressed by the operators listed here.

syllogism of deduction that "Confucius is mortal." This in the formal system of FOL can be done as follows:

1. $\forall_x$ Human(x) $\rightarrow$ Mortal(x)
2. Human(Confucius)
3. Human(Confucius) $\rightarrow$ Mortal(Confucius)
4. Mortal(Confucius)

where the new sentence at step 3 comes from step 1 by the rule of *universal instantiation*, the final conclusion at step 4 from steps 2 and 3 by the rule of *modus ponens*.

Techniques have been developed to support automatic deductive reasoning. The most noted technique is the *resolution* rule, a single rule that replaces all other deductive rules such as "universal instantiation" and "modus ponens" if the FOL sentences are transformed into the disjunctive normal form.[b]

FOL-based intelligent systems solve problems by deductive proofs. To use such a system, one first encodes the domain knowledge (e.g., "All humans are mortal") in FOL sentences and stores them in the knowledge base. Then the goal of the problem solving (e.g., to show "Confucius is mortal") is posted as a theorem or query (also in FOL sentences). The system's inference engine (a deductive reasoner) is then trying to automatically prove this theorem from the given case-specific input (e.g., "Confucius is a human") using the knowledge in the KB.

FOL is very powerful in terms of expressing precisely the domain knowledge. Furthermore, it has been established that if the theorem is indeed true, the system will prove it in a finite number of steps. However, this great expressiveness comes with a price. First of all, automatic deduction is very expensive because it is in essence a search process to find a particular sequence of deductions leading to the theorem among a huge number of possible deductive sequences without much of guidance. To make things even worse, the search process may proceed indefinitely if the theorem is in fact not true. This so-called semi-decidable problem happens rarely in practical applications, but it cannot be avoided completely, as shown by Gödel's incompleteness theorem.

The rigidity of the syntax and semantics of the language also causes problems. First, it is not always easy or even appropriate to encode knowledge in FOL sentences since not every piece of knowledge one knows is logical. For example, it is difficult to represent uncertain relations which are often measured by numerical values (e.g., 80% of flu patients have sore throat) and to represent actions (e.g., if the pressure in the container is higher than 100 then set off the alarm). Second, it is difficult to learn domain knowledge in the form of FOL sentences from case data except some simple relations. Finally, FOL is difficult to use for those who do not have training in logic or AI.

Rule-Based Systems

RB systems are probably the most widely used KB systems in real world applications, and most expert systems referred to in the literature are RB systems (2,3). As can be seen shortly, this type of system is very close to FOL systems. The great practicality of RB systems comes from relaxation of the rigidity of FOL and adaptation of some extra-logical heuristics.

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[b] Any FOL sentence can be transformed into a disjunctive normal form, which is a conjunction of disjunctions. A disjunction, called a clause, can be written either as a disjunction of literals, for example, $(\neg a \vee \neg b \vee c)$, or as an implication $(a \wedge b \rightarrow c)$.

In many application domains it is very natural for people to express their knowledge and experience in the form of "*if x then y*." This is what we take to express rules in RB systems. More precisely, a rule has the form of

$$C1, C2, \ldots Cn => A1, A2 \ldots Am.$$

where C1, C2, …, C*n* are the conditions, and A1, A2, …, A*m* are consequences which can be either new assertions or actions. This rule can be read as "If C1, C2, …, C*n* are ALL true for the current case then take the actions of A1, A2, …, A*m*." The following is an actual example rule written in C Language Integrated Production System (CLIPS), a popular language for defining rule-base systems:

```
(defrule determine-gas-level
(working-state engine does-not-start)
(rotation-state engine rotates)
(maintenance-state engine recent)
=> (assert (repair "Add gas."))).
```

Here the reserved word "defrule" indicates that this paragraph defines a rule named "determine-gas-level." This rule has three conditions, each of which can be understood as an "attribute/value" pair (e.g., the attribute "engine's working state" has the value "does not start"). Note that these conditions can also be viewed as predicates of FOL. The consequence part is a repair action of "Add gas."

The next example rule was taken from a hybrid intelligent system for the formulation of BCS Class II drugs in hard gelatin capsules (7):

```
bcs_Class(Id, 2) :- dose_value/Sol_value > 250,
                    Perm_value > 0.0004.
```

This rule, written in Prolog, says that a drug with the given "Id" belongs to BCS Class II if the ratio of its dose and solubility > 250 and its permeability > 0.0004.

The knowledge base of a rule-based system is called the Rule Base where the rules are stored. The case-specific input data is given as a list of assertions about the case which are also in the form of predicates or attribute/value pairs. These assertions are put in the working memory (WM) and are referred as WM elements. The inference starts with an attempt to match the WM with the condition part of any rules in the RM. If a match is found, that is the current WM can make all conditions in that rule true, then this rule is considered applicable to this case (or can be *fired*). Firing a rule may cause changes to WM (remove/add/change some elements there), and the match–fire process repeats with the new WM.

It is often the case that a WM may match more than one rule. Rule-based systems adopt some heuristics to select one of the matched rules to fire at the time. This makes the inference process a depth-first search. When the search reaches a dead end (where the WM cannot match any rule) or it goes too far along a path, the inference engine back tracks for other paths.

The reasoning process described here is called *forward chaining* because it follows the direction of the arrow (from conditions to consequences) when rules are used. It is also called data driven because the process starts with the input data in WM and can potentially derive all consequences implied by the input data. This kind of inference mode is suitable for applications such as monitoring a patient or a nuclear power plant and deciding appropriate actions to take based on the monitors' readings.

One problem for this forward chaining reasoning is its lack of attention. The search space (the set of all consequences derivable from the input data) is in general very large, and many consequences derived may be completely unrelated to the goal of the problem

solving. To ease this problem, a different procedure, called *backward chaining*, was developed. In contrast to forward chaining, backward chaining starts with the goal G one wants to establish, and it tries to match G with the consequence side of any rules in the rule-based. Suppose a match is found with the rule C1, C2, C3 => G. From this rule we know that to show G is true we only need to show that C1, C2, and C3 are true. In other words, the goal G is replaced by three subgoals C1, C2, and C3. We then repeat this process for each of these subgoals until a true fact (either in the rule based or in the case input) is reached in each thread. Since this kind of inference starts with the goal and proceeds with subgoals, it is also called *goal driven*. As an example, according to the rule given earlier, the query of whether a given drug belongs to BCS Class II in backward chaining reasoning will be reduced to two subqueries:

```
dose_value/Sol_value > 250:-
Perm_value > 0.0004:-
```

To achieve efficiency, rule-based systems circumvent some theoretical difficulties of FOL by heuristics. One such heuristic is that if we fail to establish A, then we treat A as false. With this so-called “negation as failure,” the semi-decidability problem of FOL is avoided. The drawback of adopting these heuristic provisions is that we cannot define a formal semantics for the system, the connection between the rules and the real world relies on the understanding between the system designer and the user. Consequently, the inference result is not guaranteed to be true as is with FOL.

Generality and expressiveness are also sacrificed for efficiency. For example, all variables in the rules are assumed universally quantified, there is no way to express existential qualification, and the predicates on either side of the arrow are restricted to be conjunctions (AND relations). Some subtle relations expressible in FOL may not be expressed in rules. For example, we may write a rule “if someone is the father of a human then he must also be a human” as

$$Father(x, y), Human(y) \Rightarrow Human(x).$$

However, it is difficult, if not impossible, to write a rule for “every human must have a human father” because existential quantification is needed here[c].

Similar to FOL, it is difficult to learn rules from data or to associate uncertainty with rules. Research has been conducted, sometimes extensively, on these issues in the past, and many approaches and methods have been proposed and experimented (1). However, none has received wide acceptance by AI practitioners.

Decision Trees

Figure 2 depicts a decision tree for a simple classification task: classify given objects into two groups, labeled + and –, respectively. The classification is according to three attributes of each object: the shape (square or round), the size (big or small), and the color (green, red, or blue). Instead of evaluating all attributes at the same time, the decision tree does the classification through a sequence of decisions, each of which is based on a single attribute. Each decision is represented by a nonleaf node in the tree, called *decision node*. Branches of a decision node correspond to possible values for that attribute. Leaf nodes of the tree are class nodes with the class labels.

[c] This can be easily written as a FOL sentence $\forall x$ Human(x) $\rightarrow \exists\, y$ Father (y, x) $\wedge$ Human (y).

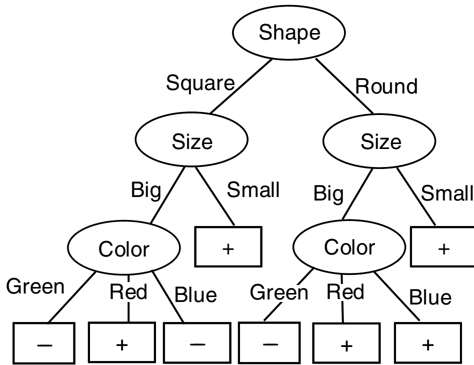


FIGURE 2 A decision tree for classification with 7 leaf nodes (square) and 5 non-leaf nodes (oval).

For example, to classify a big red square object, we start with the root (top), which makes decision according to the shape of the object. Since the object is square, we go down to the left branch and proceed to make the second decision based on the size. The process eventually leads to the second leaf node from the left at the bottom and we conclude that the given object belongs to class "+".

To construct a decision tree, one can start by selecting an attribute for the root, and its branches are determined by the attribute. The process is then repeated for each of the children of the root, and so on. One of the objectives for tree construction is to make the tree short (so that later on the decisions can be made fast). The attributes for decision nodes can be selected by experts based on their experiences and their understanding of the domain. They can also be learned from sample data. Here each sample is about one object, including its values for all of the attributes and the class label this object belongs to. For example, a sample for the tree of Figure 2 may look like

(big, blue, square, "-").

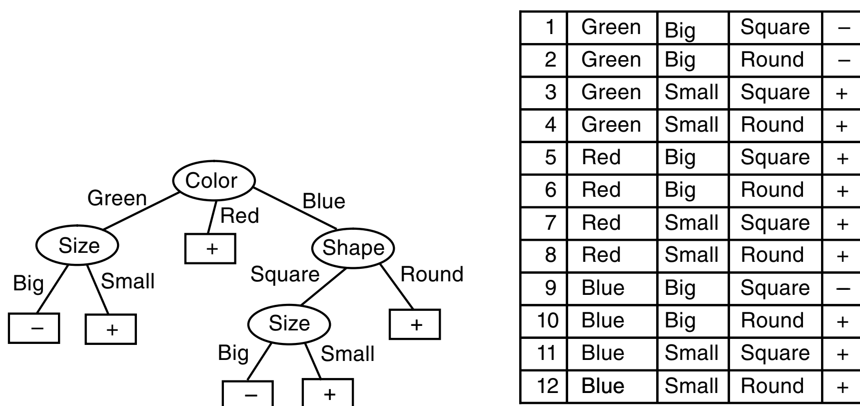
The label for each sample can be obtained from observation or assigned by humans. Using training samples with known class labels makes decision tree learning a supervised learning.

Among the many proposed methods for decision tree learning, the one that is most widely recognized is the ID3 algorithm by Quinlan (9). ID3 is based on the notion of information gain when selecting attributes: choose the one that has the largest expected information gain. For a group of training samples T, the information gain of partitioning T based on attribute X is measured by

$$\text{Gain}(X, T) = \text{Info}(T) - \text{Info}(X, T)$$

where Info(T) is measured by the entropy of the Ts probability distribution over the classes. To measure Info(X, T), we first partition T by X, then calculate the entropy for each subset T_i in the partition, and finally add these entropies together, each weighted by the size of T_i. Selecting the attribute that gives the maximum information gain guarantees to result in the smallest expected size of the tree. Figure 3 presents an example of decision tree learning. The table on the left of the figure contains 12 samples and their class labels. The tree on the right is learned using these 12 samples by ID3 algorithm. Comparing with the tree in Figure 2, which also correctly classifies all of the 12 samples, the tree in Figure 3 is much smaller (10 vs. 13 nodes) and shorter (average height of leaf nodes of 2.166 vs. 2.75).

Note that the decision at each node is simple and uses only the information local to that decision (e.g., the root of the tree in Figure 3 only cares about the color of the object without concerning with its shape and size), and that the decisions are irrevocable. These



1	Green	Big	Square	–
2	Green	Big	Round	–
3	Green	Small	Square	+
4	Green	Small	Round	+
5	Red	Big	Square	+
6	Red	Big	Round	+
7	Red	Small	Square	+
8	Red	Small	Round	+
9	Blue	Big	Square	–
10	Blue	Big	Round	+
11	Blue	Small	Square	+
12	Blue	Small	Round	+

FIGURE 3 Decision tree learning. A tree (on the left) was learned from 12 learning samples (*on the left*).

are the main reasons for its computational efficiency. Also note that this strategy of decomposing a large decision into a sequence of small decisions is taken by people everyday in dealing with complex problems. For this reason, people often use decision trees as a modeling tool to capture and mimic human experts' decision process. An example decision tree that models the formulation of BCS Class II drugs in hard gelatin capsules can be found in Ref. 7.

Languages and Tools

Many tool sets are available, both commercially and in public domain, to support the various KB systems, including those reviewed in this section. As mentioned earlier, each KR paradigm is associated with its own inference mechanism, so these tools usually include a language for encoding the domain knowledge in the given KR and an inference engine. The tool will construct the knowledge base from the encoded knowledge, and the inference engine will be evoked by either the case-specific input data (for forward chaining) or the goal to be achieved (for backward chaining) or both. Many tools come with graphic interface to help interacting with the user.

CLIPS and Jess

Early tools are so-called "expert system shells" such as EMYCIN (from Stanford University) and OPS5 (from Carnegie Melon University), which, as the term implies, came from real expert systems. For example, EMYCIN is the shell of the blood infectious disease expert system MYCIN. It retains everything of MYCIN except the content of the KB. To build a new expert system for some other application (say car diagnosis), one can simply fill the KB with domain knowledge encoded in MYCIN's language.

OPS5, a forward chaining rule-based system language, was further developed into CLIPS at NASA (10). CLIPS and its later version in Java named Java Expert System Shell (Jess) (11), developed at Sandia National Lab, are probably the most widely used tools for constructing and running forward chaining rule-based systems. Both CLIPS and Jess are in public domain and can be downloaded from a number of websites[d].

[d] For example, http://www.ghg.net/clips/CLIPS.html and http://herzberg.ca.sandia.gov/jess/

Prolog

Prolog, standing for "programming in logic," is a language that implements a subset of FOL. Sentences in Prolog are restricted to *Horn clauses*. A Horn clause is a disjunction of literals in which at most one literal is positive. Prolog is quite strong in its expressing power, it can be used to represent almost all we want to express in most applications. For example, a fact that John is a male can be written as

```
:-Male(John)
```

where ":-" is for logic operator "implication." We can also represent the rule that "if x is a parent of y and x is male then x is the father of y" as

```
Father(x, y):-Parent(x, y), Male(x);
```

and goals we want to prove as

```
Father(John, Bill):-
```

and so on. What are not allowed in Prolog are those disjunctive clauses with more than one positive (e.g., those on the left side of the implication) such as

```
Father(x, y) ∨ Mother(x, y):-Parent(x, y)
```

or

```
Father(John, x) ∨ Mother(Mary, y).
```

Prolog systems also adopt some extra-logical provisions for efficiency and convenience. For example, the search for the solution is done by depth-first search plus backtracking, and "negation as failure" is adopted for circumventing semi-decidability problem. Most Prolog systems conduct logical reasoning in the backward chaining fashion, making them popular tools for constructing backward chaining rule-based systems. Recently, forward chaining Prolog systems also have been developed (e.g., XSB) (12).

Logica's PFES

Product Formulation Expert System (PFES) was developed by Logica as a reusable software kernel to support a generic formulation task (13) in a number of industrial sectors, especially in pharmaceuticals. It was designed to speed up the selection of product ingredients, and the subsequent testing, analysis, and adjustment formulation procedures. Like CLIPS, PFES also uses exclusive forward chaining in the inference. An example of PFES application to tablet formulation can be found in Ref. 14.

Decision Trees

Because both the structure and the inference logic of decision tree are relatively simple, one can afford to implement a decision tree in a number of ways. It can be coded directly with any general purpose programming language such as C, C++, Java, or LISP (a primary AI programming language). It can also be implemented using expert system shells. For example, the Capsugel expert system, which is a decision tree in logic, was first implemented in C (15), and later reimplemented in SICStus Prolog (a Prolog system developed by Swedish Institute of Computer Science) for added flexibility to introduce additional rules (8).

If the purpose is to learn a decision tree from a collection of labeled samples, then the best available tool is probably a software package called C4.5 (9). The core of C4.5 is

the ID3 algorithm described earlier. It extends the basic ID3 learning with capabilities: (*i*) to handle missing values in training samples; (*ii*) to accommodate attributes with continuous value ranges; (*iii*) to prune the learned decision trees; and (*iv*) to avoid *overfitting*.[e] It is also able to derive implication-like rules from the learned tree.

NEURAL NETWORKS AND NEURAL COMPUTING

The logic-based approach of KB intelligent systems was inspired by *high* level human reasoning and cognition activities, and it attempts to model such activities in a formal way. In contrast, NNs take a different approach in solving complex problems typically requiring human intelligence. This approach attempts to model the low level activities of the nerve systems in human and animal brain. The origin of the present day NNs can be traced back to Pitts and McCulloch's 1943 model of biological neurons (16), which can be shown to be able to realize all Boolean functions. Hebbian's rule (17), a simple rule proposed in 1949 for modifying synaptic strengths in a nerve system, is also very influential in learning methods for various NN models.

Overview of Neural Networks

In essence, a NN as a computational model can be viewed as the following. The network has a large number of nodes connected by weighted links. To some extent, one can view a NN as a simplification of a biological nerve system where nodes correspond to neurons and weighted links to synaptic strengths between neurons. Each node has certain activation level and can send its activation as output to other nodes that are connected to it. It can also receive activations from other nodes and update its own activation according to certain rules or functions. This kind of interactive activities between nodes may be triggered by certain external input; the interaction continues until a stable state is reached over the network. At this time the pattern of activations over the network of nodes provides a solution to the problem.

Next we briefly describe the main components of NN (4).

Nodes

A node in a NN has one or more inputs from other nodes, and one output to other nodes, the values for its input and output can be binary (0 or 1), bipolar (-1 or 1), or continuous (either bounded or unbounded). The output represents the current activation level of the node and it is determined by the inputs and the activation function (also called node function) associated with that node. Typically, as illustrated in Figure 4, the activation function takes the weighted sum of the inputs from other nodes as its input and computes the node activation (output) by a simple mathematical function f.

Nodes with nonlinear node functions play crucial roles in neural computation. Commonly used nonlinear functions include step functions, sigmoid functions, and Gaussian functions. The input to the function is $x = w_1 x_1 + ... + w_n x_n$, the weighted sum of

[e] Overfitting refers to a common problem for machine learning that the learned model fits the training data very well but performs poorly with previously unseen data.

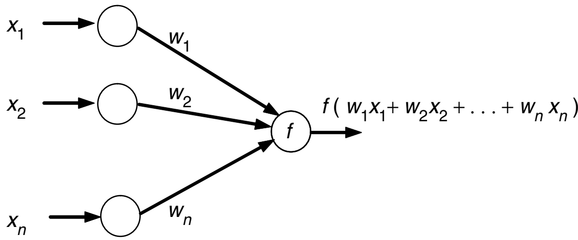


FIGURE 4 A single neuron and its activation function.

node inputs, where w_i is the weight associated with the input x_i, and the function value $y = f(x)$ is the node output.

Step function (also known as a *threshold function*) is a binary function with only two possible function values (or two states). Which of the two values will be the output depends on whether x is below or above the given threshold. For example, as depicted in Figure 5A

$$y = \begin{cases} -1 & \text{if } x < 0 \\ 1 & \text{if } x \geq 0 \end{cases}$$

is a step function with threshold = 0. A variation of the threshold function is the "Ramp function," as shown in Figure 5B, it provides a linear transition region between the two states.

Sigmoid function. One limitation of the step and ramp activation functions is that they are not everywhere differentiable, making mathematical analysis of NN models using such node functions very hard. Sigmoid (S-shape) functions overcome this difficulty by approximating the shape of the step/ramp functions with differentiable ones. There are a few candidates for sigmoid functions, the two most widely used ones are:

– Logistic function: for example, $y = \frac{1}{1+e^{-cx}}$ where c is a constant called slope.

– Hyperbolic tangent function: $y = \frac{e^{cx}-e^{-cx}}{e^{cx}+e^{-cx}}$.

As depicted in Figure 5C, a logistic function is rotationally symmetric about the point (0, 0.5), and it asymptotically approaches the two extreme values with x of great

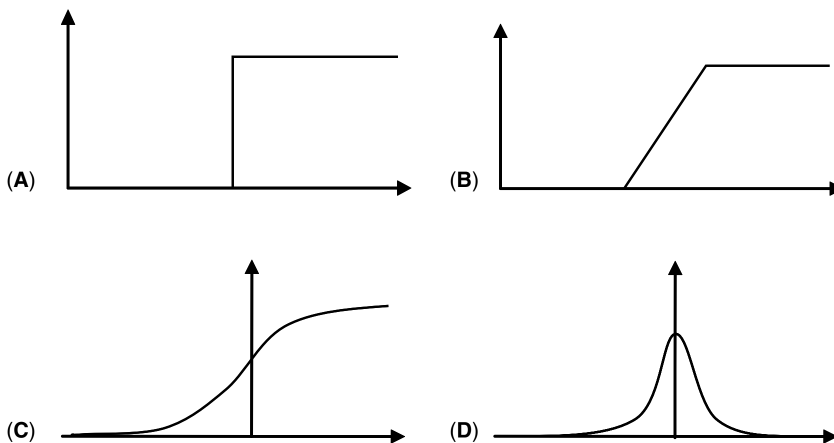


FIGURE 5 Common nonlinear node functions: (**A**) step or threshold function; (**B**) ramp function; (**C**) sigmoid function; and (**D**) Gaussian function.

magnitude (to 1 when $x \to \infty$ and 0 when $x \to -\infty$). Also note that change of x will cause large change in y when the magnitude of x is small (e.g., $|x| << 1$), and cause little change in y when $|x| >> 1$. In the latter case, we say that the function moves into a saturation region, where further increases of the magnitude of x would have not effect on the output of the function. The shape of the function curve is related to the slope c, smaller c yields flatter curve and larger c leads to steeper curve, and when c is really very large, the logistic function approaches the threshold function.

The hyperbolic tangent function has the same properties as the logistic function except that its two extreme values are -1 and 1.

Another nonlinear function with significant applications is the *Gaussian function*. Its curve has a bell shape, the output takes the maximum value at the center and approaches zero when the distance to the center goes to infinity (Fig. 5D).

Links and Link Strengths

As mentioned earlier, individual nodes in NN have very limited computing power because their node functions are very simple. Despite of this, NN have been shown to possess great computing power, capable of solving many difficult problems. This power comes from the richness of the connectivity of the networks. Put in another way, while the KB systems encodes its problem-solving knowledge in the logical sentences and rules in the knowledge base, the knowledge in NN is capture by the inter-node connections and the associated connection strengths.

Links have directions, the weights on the links from node A to B and from B to A may have different values and even different signs. The weights can be discrete (binary, bipolar or other integer values) or real values. There are three kinds of nodes, depending on whether the node's input and output links are within the network or not. They are the input nodes (those that receive external input from the environment); output nodes (those that present the output to the environment) and *hidden nodes* (those that do not have any interaction to the environment). Note that input and output nodes may overlap, but not with hidden nodes.

Inter-node connections define the architecture (or structure or topology) of a NN. Different NN models are developed for different types of applications, which differ with each other often on their architectures. Here are some widely used NN architectures.

Fully connected NN. Every node is connected by a link to every other node (including itself). One renowned example of this architecture is the Hopfield model, widely used as a basis for various NN models for associative memories and optimization. A fully connected network with randomly generated weights can be viewed as a model of total ignorance, and thus can be used as the starting network for learning.

Recurrent NN. A network not necessarily fully connected but containing at least one directed cycle. Therefore, a node can influence itself via the cycle, and the network forms a dynamic system. Mathematical analysis of recurrent networks is often complicated.

Acyclic NN. A network without a directed cycle. This type of network is easier to analysis than recurrent networks.

Layered NN. Nodes in a layered NN are grouped into layers, two nodes are connected only if they are either in the same layer or in adjacent layers.

Two-layer recurrent NN. There is no intra-layer connection, and nodes between the two layers are often fully connected. As a dynamic system, outputs of nodes in one layer become inputs to the nodes in the other layer, and the interaction takes iterations to reach equilibrium, a state in which no node will change its activation. Example, NN models with this kind of architecture include bidirectional associative memories in which

patterns in one layer can be recalled by patterns presented to the other layer, and self-organizing maps (SOM) that can be trained so that the topological relations existing in the input layer is preserved in the output layer.

Multilayer feedforward NN. A network that is both acyclic and layered (with at least two layers, not counting the input layer). In addition, there is no connection between nodes in the same layer. This architecture is the basis for the most widely used NN model in practical applications, the celebrated backpropagation (BP) model, which we will give a much more thorough coverage short.

Neural Network Learning

One of the noted strengths of NN is their ability to learn problem-solving knowledge from the sample data. What makes learning relatively straightforward is that learning in NN is basically a process of modifying the connection strengths by repeated presentations of training samples. Learning in most NN models is kind of a variation of the Hebbian learning rule, which says the strength between nodes A and B shall be increased if both A and B are excited (both are positive) when the given training sample is presented to the network.

One type of learning is called *supervised* when each training sample include both the input pattern describing a problem and the desired or target pattern representing the correct solution to the problem. In other words, the learning is seen as being supervised by a teacher, who for each input pattern provides the desired output pattern. During the training, the input pattern of a sample is presented to the input nodes, then the network's internal computation generates an output based on its current connection weights. This output is compared with the desired output, the difference then drives a modification to the current weights in the network.

In contrast, *unsupervised* learning learns associations and regularities from training samples without the benefit of answers or even any hints of correct answers from the teacher. The third type of learning, the *reinforcement* learning, is in between of these two. Similar to unsupervised learning, each training sample for reinforcement learning contains only the input pattern, not the desired output. When an input pattern is presented, the computed output is fed to a judge or arbitrator, which will provides a feedback of either this output is good (and the system is awarded, say, keeping the current weights unchanged) or bad (and the system is punished by requesting a change of the weights). The difficulty here is, when change is called for, one has to figure out which of the weights shall be changed and how much the change should be.

Backpropagation Networks

The name of the BP network comes from its error to backpropagation learning algorithm (4,18). Due to its popularity in real world applications, many people take BP networks as the synonym of NNs. BP networks also find a variety of applications in the area of drug formulation (3).

BP Network Architecture

As mentioned earlier, a BP network is a multilayer feedforward network. In addition, it must have at least one layer of nonlinear hidden nodes with sigmoid node functions.[f]

[f] Some people refer BP network as multi-layer perceptron for historical reasons because it is a generalization of a famed early NN model *Perceptron*. Strictly speaking, a multi-layer perceptrons use threshold node functions, not sigmoid ones.

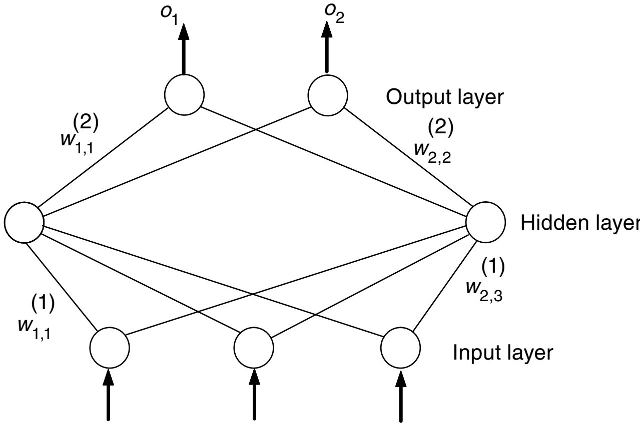


FIGURE 6 A two layer BP network. *Abbreviation*: BP, backpropagation.

Figure 6 depicts a two layer BP network. Note that the input layer is not counted here because nodes in input layer are not processing units, they are merely place holders for the external input without performing any computation. Most of the discussions in this subsection are based on two layer networks (with only one hidden layer), the key results can be easily generalized to networks with more than one hidden layer.

We adopt the following convention for notations. Values of all nodes on each of the layers form a vector, we denote the vectors on input, hidden, and output layers $x = (x_1, \ldots, x_i, \ldots, x_n)$, $x^{(1)} = (x_1^{(1)}, \ldots, x_j^{(1)}, \ldots, x_m^{(1)})$, and $o = (o_1, \ldots, o_k, \ldots, o_l)$, respectively. We denote the two weight matrices as $W^{(1)}$ (from input to hidden), and $W^{(2)}$ (from hidden to output). Each weight matrix is a set of weight vectors, one for each node, so for example, $W^{(1)} = (w_1^{(1)}, \ldots, w_j^{(1)}, \ldots, w_m^{(1)})$, and the weight vector $W_j^{(1)} = (w_{j,1}^{(1)}, \ldots, w_{j,i}^{(1)}, \ldots, w_{j,n}^{(1)})$ is a collection of weights from each of the input nodes to hidden node j.

The computation in a BP network is simple and straightforward. When an input pattern or vector $x = (x, \ldots, x_n)$ is presented to the input layer, it is passed through input nodes to the hidden layer. Each hidden node computes its output value by

$$x_j^{(1)} = S\left(\sum\nolimits_i w_{j,i}^{(1)} x_i\right) \tag{1}$$

where $S(.)$ denotes the sigmoid function. Taking $x_j^{(1)}$ from all hidden nodes as inputs, each output node computes its output in a similar fashion

$$o_k = S\left(\sum\nolimits_j w_{k,j}^{(2)} x_j^{(1)}\right) \tag{2}$$

General Function Approximator

It is clear that a BP network defines a multivariant function $o = f(x)$, for an given input vector x, the function value of f is computed according to Equations (1) and (2). Changes of weights in $W^{(1)}$ and $W^{(2)}$ will change function f. An interesting question is, what kinds of mathematical functions a BP network can compute, or put it in another way, for an arbitrary mathematical function F, does there exist a set of weights so that $f(x) = F(x)$ for all inputs x. It has been proven mathematically that feedforward networks with at least one hidden layer of nonlinear nodes are able to approximate any L_2 functions (all square-integral functions, including almost all commonly used mathematical functions) to any given degree of accuracy, provided there are sufficient many hidden nodes. In this sense, BP networks are called General function approximators.

This representational power of BP networks lies primarily on the nonlinearity of the hidden nodes. Nonlinear output nodes alone cannot play the trick, as has been shown that a perceptron (a single nonlinear output node with weighted links from inputs) cannot solve problems that are not linearly separable (e.g., weights can be found for a perceptron to solve logical functions AND and OR, but not Exclusive-Or). It can be shown easily that adding linear hidden nodes, no matter how many layers, to a perceptron does not increase its computing power.

Knowing the representation power of BP networks is only half of the story, a follow up question is, for a given (L_2) function F, how can we construct a feedforward network and find a set of weights so that the network approximates F well? Brutal force search for the weights is computationally intractable because the search space (of all possible weights) is a multi-dimensional continues one. BP algorithm is a learning algorithm that can quickly find a good set of weights from a set of training samples.

BP algorithm is an example of supervised learning. A training sample therefore consists of two parts: an input pattern $x_p = (x_{p,i}, \ldots, x_{p,n})$ and its desired output pattern $o_p = (o_{p,i}, \ldots, o_{p,l})$. From the function approximation point of view, we can think that the set of P samples are taken from a unknown function F, i.e., for each $x_p, o_p = F(x_p)$.

BP algorithm is also an example of error driven learning. For each x_p, we can compute the output pattern o_p based on the current weights. Then the learning is to be guided by the difference between the desired and the actual outputs: $\delta_p = d_p - o_p$ in vector notation and $\delta_{p,k} = d_{p,k} - o_{p,k}$ for individual output nodes. The general principle is that we want to modify the weights in such a way that the error $\delta_{p,k}$ gets reduced. To see this intuitively, consider $w_{k,j}^{(2)}$ in $W^{(2)}$ (from hidden node j to output node k) and $w_{j,i}^{(1)}$ in $W^{(1)}$ (from input node i to hidden node j) in Figure 7.

It is straightforward to see how $w_{k,j}^{(2)}$ should be changed with the error $\delta_{p,k} = d_{p,k} - o_{p,k}$. If both $\delta_{p,k}$ and $x_j^{(1)}$ are positive then we increase $w_{k,j}^{(2)}$ (which increases $o_{p,k}$ and in turn decreases $\delta_{p,k}$). The same goes when both $\delta_{p,k}$ and are $x_j^{(1)}$ negative. On the other hand, $w_{k,j}^{(2)}$ should be reduced when the signs of $x_j^{(1)}$ and are different. The update for $w_{k,j}^{(2)}$ outlined here is seen clearly an application of Hebbian rule.

It is not so easy for updating weight $w_{j,i}^{(1)}$ because we do not have the desired output value for hidden node j and thus cannot directly compute the error for node j. The novice idea behind BP learning is its way to compute the error for hidden nodes. Since $w_{j,i}^{(1)}$ influences $x_j^{(1)}$ [Equation (1)], and $x_j^{(1)}$ is taken as input by all output nodes (Fig. 7), $w_{j,i}^{(1)}$ affects errors $\delta_{p,k} = d_{p,k} - o_{p,k}$ for all output nodes and thus its update should be

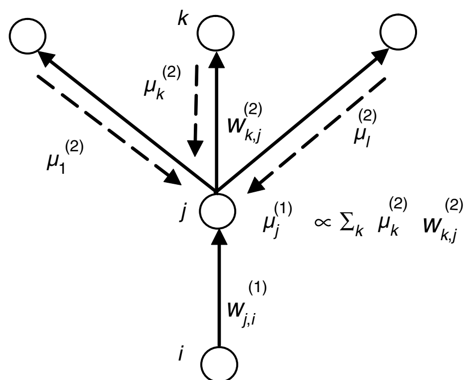


FIGURE 7 Output errors are weighted and propagated back to hidden nodes in BP learning. *Abbreviation*: BP, backpropagation.

determined by all of these errors. Specifically, BP algorithm calculates the error for hidden node j as a weighted sum of errors on all output nodes.

The actual weight update rules for BP learning are derived following the mathematical approach known as gradient descent. This approach determines the change to each weight in isolation (as if all other weights remain unchanged) and along the direction that maximizes the reduction to the total error, $E_p = \sum_k \delta_{p,k} = \sum_k (d_{p,k} - o_{p,k})$. Specifically, for each weight w (either in $w^{(1)}$ or $w^{(2)}$), the change, Δw is determined as

$$\Delta w = -\eta \frac{\partial E}{\partial w} = -\eta \frac{\partial}{\partial w} \sum\nolimits_k (d_{p,k} - o_{p,k}) \tag{3}$$

that is, the change to w is proportional and negative (thus the name of gradient *descent*) of the partial derivative of E. Here η in (3) is a constant known as the *learning rate*, which determines the size of changes at each step of learning. Partial derivatives for individual weights can be derived from (3) since E is a function of these weights [Equations (1) and (2)]. Specifically, let $net_l^{(,)}$ denote the total weighted input to node l, we have

$$\Delta w_{k,j}^{(2)} = \eta \cdot \mu_k^{(2)} \cdot x_j^{(1)} \tag{4}$$

for all weights in $W^{(2)}$, where

$$\mu_k^{(2)} = (d_{p,k} - o_{p,k}) S'(net_k^{(2)}) \tag{5}$$

is the error term on output node k and $S'(net_k^{(2)})$ is the derivative of its activation function. And for weights in $W^{(1)}$, we have

$$\Delta w_{j,i}^{(1)} = \eta \cdot \mu_j^{(1)} \cdot x_i \tag{6}$$

where

$$\mu_j^{(1)} = \left(\sum\nolimits_k \mu_k^{(2)} w_{k,j}^{(2)} \right) \cdot S'(net_j^{(1)}) \tag{7}$$

is the error term for hidden node j, which can be calculated by first *back propagating* the errors from the output nodes, weighted with the corresponding weights in $W^{(2)}$, and then multiplying with the derivative of the node's activation function.

The learning process repeats the following steps, starting from an initial set of weights for $W^{(1)}$ and $W^{(2)}$:

1. pick up a training sample (x_p, o_p);
2. calculate the output pattern o_p by Equations (1) and (2);
3. calculate errors $\delta_p = d_p - o_p$ at output nodes;
4. update weights in $W^{(1)}$ by Equations (4) and (5); and
5. update weights in $W^{(2)}$ by Equations (6) and (7).

This process continues until all weights stop to change (i.e., the process converges) or other termination criterion is satisfied.

The process outlined above is called a *sequential learning* because training samples are selected one at a time in a sequence and weights are changed per each selected sample. Learning can also be conducted in another mode, known as *batch learning*, which is the same as the sequential learning except that actual weight changes do not occur with each sample, instead, the calculated $\Delta\omega$ for each of the P samples are cumulated. When all P samples are processed, the cumulated Δw are averaged (over P) and used to make actual changes to the weights.

Properties of BP Learning

It has been proved mathematically that the BP learning always converges if the learning rate is sufficiently small. This is because the gradient descent guarantees that the total error $E = \sum_p E_p$ can only decrease at each step of learning. However, it is not guaranteed to converge to a set of weights that reduces the total error to zero. That is, it is only guaranteed that the learning converges to a *local minimum error state*, i.e., any small change of the learned weights will always cause E to increase. We can compare the gradient descent approach of BP learning with hill-climbing. If one, when climbing a hill, always moves along the steepest direction, he will certainly reaches the top of the hill, which is higher than its immediate vicinity but not necessarily higher than summits of other hills and mountains.

Several features of BP learning make it very attractive to practical applications. First, as discussed earlier, any L_2 function can be represented by a BP network, and in many cases such a network can be trained using BP learning with great accuracy. Second, it is fairly easy to apply BP learning to problems at hand. Unlike other formalism such as those logic-based approaches, BP learning does not require substantial prior knowledge or deep understanding of the domain itself, it only requires that a good set of training samples is available. This makes it a powerful modeling tool for ill-structured, ill-understood problems. Third, the implementation of the core BP algorithm is very simple. And finally, like many other NN models, BP learning naturally tolerates noise and missing values in training samples. In most of the cases, noise and missing values only degrade the learning quality, not lead to a completely wrong model nor disrupt the learning itself (graceful degrading).

On the other hand, BP learning can be frustrating, even when one has a good set of training samples. First, the learning often takes a long time to converge when there are many hidden nodes in the network and the sample set is large. Second, there is not much one can do if the learning converges with a large total error E except possibly to rerun the learning with a different set of parameters and initial weights and pray for a better result.

Quite a few proposals have been made to speedup the learning process. For example, one proposal suggests that the weight update rules not only include the terms caused by the error as given in Equations (4) and (6) but also the changes of previous steps (called momentum terms). This method avoids sudden change of directions of weight update, smoothens and often speeds up the learning process. Another widely used method is called Quickprob (19). Instead of slowly approaching the final weights through many iterations of (4) and (6), this method, whenever possible, calculates (by some simple procedure) the weights that are close to a local minimum error state. Other methods speedup the learning by manipulating the learning rates in different ways.

Another problem with BP learning is that what can be learned (i.e., the weights) are merely operational parameters, not general, abstract knowledge of the domain. As such, a trained BP network behaves like a black box, it produces an answer (in the form of the output pattern) for any given problem (as specified by the input pattern), but is not able to explain why the answer is correct or how good this answer is.

Finally, like many learning methods that build models from data, we are facing the problem of overfitting. That is, the trained network may fit the training samples perfectly (i.e., the total error E is very close to zero), but it does not produce correct or good outputs for previously unseen inputs. If overfitting happens we say the trained network generalizes poorly. Overfitting problem can be eased by moving the weight matrices

slightly away from the local error state. This can be done by adding noise into the sample set or stopping the learning earlier before the minimum error state is reached. The most widely used strategy in dealing with overfitting is known as *cross-validation*. Instead of using all samples for training, this strategy leaves a small portion (say 10%) of them as test data. The learning periodically pauses and checks the error over the test data, and it stops when error over test data starts to increase.

Parameter Selections and Other Practical Concerns

Learning algorithm is only part of the task of implementing BP learning, the other, more subtle part, is how to initialize the network and how to select learning parameters. Since the number of nodes in input and output layers are determined by the problem one intends to solve, so the initialization of the network topology involves only the determination of the number of hidden layers and their size. Theoretically, a single hidden layer is sufficient for any complex problems, however, there is no theoretical result on minimum necessary number of nodes in that hidden layer. The practical rule of thumb is to have twice as many hidden nodes as the input nodes for binary/bipolar data and many more for real value data. It has been reported in the literature that networks of multiple (2–4) hidden layers with fewer nodes may be trained faster for similar quality in some applications. After the hidden layers are decided, the weights for all links in the network are usually set to some small randomly generated initial values.

Besides the network topology, the quality of learning is also depending on the quality and quantity of training samples. The samples should be a good representation of the domain, they should be randomly sampled or guided by the domain knowledge if such knowledge is available. There is no theoretically ideal number for the samples, intuitively this number is dependent of the number of weights in the network and the accuracy desired for the results. Some has suggested the number of samples can be estimated as $|W|/e$ where $|W|$ is the total number of weights in the network and e is the acceptable error bound.

Another important parameter is the learning rate η. The gradient descent requires η be as small as possible, however, too small a rate makes the learning extremely slow. Common practice suggests to start with $\eta \leq 1$.

Finally, we need to select a criterion for terminating the learning. One obvious criterion is when $E \leq e$ if the acceptable error e is given. This criterion may not always be practical because of the "local minima" discussed earlier. Instead, people often stop the learning when the weight change becomes very small for every weight. Finally, one can set a maximum number of iterations for the learning and stop the process when this number is reached.

Other Neural Network Models

A large number of NN models have been developed in the past few decades, with different mechanisms and often for different types of applications. Here we list a few representative NN models for their popularity and potential for pharmaceutical applications.

Radial Basis Function Networks

Radial basis function (RBF) network is perhaps the most widely used NN model, after only the BP networks (20). A RBF network is very similar to the BP network, the main difference is that it uses RBF, not the sigmoid function, as the node function. A typical

RBF for this type of networks is the Gaussian function. As can be seen in Figure 5D, the output of a RBF node depends on the distance of the input vector to the vector stored in the node; and the output is maximal if the distance is zero. Similar to BP network, RBF network is also a universal function approximator, and can be trained by supervised learning. It has been found that RBF networks often performed better than BP networks in function approximation and classification.

Competitive Learning and Self-Organizing Map

Competitive learning is a kind of unsupervised learning often involves a single layer of output nodes. When a training sample is presented as the input vector to the network, all output nodes *compete* with each other, and the node whose weight vector is closest to the input vector wins. The winner then has its weight vector updated (moving further closer to the input vector) while all other output nodes will have their weights unchanged. Competitive learning learns regularity, clustering, similarity among the training data without the supervision of a teacher.

Self-organizing map (SOM) is a special competitive learning network with the aim of preserving the topological order (neighborhood relation) among the training samples (21). SOM differs from other competitive learning networks on how the weights shall be updated after the winner is determined for a given training sample. Not only the winner but also its neighboring output nodes will have their weight vectors changed toward the training sample. As the result, when two input vectors that are similar to each other are applied to the trained SOM, the corresponding output nodes will be close to each other, thus the topological order is said to be preserved. SOM model is motivated by sensory maps in biological nerve systems (e.g., retinotopic map) which preserve topological orders, but its applications go far beyond the simulation of biological maps.

Support Vector Machine

Single layer NNs have limited computing power. This is demonstrated by the problem of *linear separability*. Suppose we want to build a two class classifier for data points. For some datasets, a linear separator (a line for 2D data and a hyperplane for higher dimensional data) is sufficient to separate the data points in the two classes. For other datasets there is no linear separator, rather the separators must be nonlinear.[g]

Multilayer NNs such as BP networks overcome the linear separability problem by including a layer of hidden nodes of nonlinear functions. The price paid for the greatly increased computing power is the time it takes to train the network.

Support vector machine (SVM) (22) is a relatively new supervised learning method that overcomes this problem: it is able to learning nonlinear separators at a much faster speed. This nice property helps SVM to quickly gain popularity since mid-1990. A full coverage of SVM is beyond the scope of this chapter, readers interested in this method can start from the detailed tutorial by Burger (23). Roughly speaking, SVB is based on a simple

[g] A well-known linear non-separable problem is the logical operation of Exclusive Or", denoted $\oplus$. $A \oplus B$ = true if and only if either A and B are both true or both false. The four possible value assignments of A and B can be represented as four data point (1, 1) (0, 0), (1, 0), and (0, 1) in a 2-dimensional space. Then put the four points into two classes, those with truth value 1 ((1, 1) and (0, 0)), and those with truth value 0 ((1, 0) and (0, 1)). It is clear that there is no line on the 2D space that can separate these two classes.

property: if data points are not linearly separable in a given space, then they can become linearly separable if they are mapped into a space of sufficiently higher dimension.

Directly finding a linear separator in the high dimensional space (called the feature space F of the given data) is time consuming and is in danger of serious overfitting. SVB overcome these as follows. Since finding a separator can be cast as a quadratic programming problem that is based on the inner product of every pair of data points $x_i \cdot x_i$, then it becomes $F(x_i) \cdot F(x_i)$ for the feature space F. SVM does not directly work with $F(x_i) \cdot F(x_i)$ but utilizes some function called *kernel function* that computes $F(x_i) \cdot F(x_i)$ from $x_i \cdot x_i$. An example kernel function is $F(x_i) \cdot F(x_i) = (x_i \cdot x_i)^2$. Efficient learning methods based on kernel functions have been developed and implemented in various SVM packages.

Neural Network Development Tools

Many dozens of NN development tools have been developed in the past two decades or so. Many of them are in public domain (e.g., DPD++, JavaNNS, SNNS, etc.), others are commercial products (e.g., BrainMaker, NeuralMaker, NeuralShell, etc.). The set of NN models included in each tools package may be quite different, but almost all of them include BP networks. Most of tools in public domain were developed by academic research groups, and they often come with the source code. This allows the users to modify the NN models to their particular needs, and facilitates the integration of a NN as a component into a larger system. Commercial products, on the other hand, usually come with much better user interface and many auxiliary tools (e.g., statistical analysis procedures, procedures for pre and post processes). Some products offer application programming interface (API) via which the modules can be accessed and executed by the user's own program. This is very important for users who may need to modify the NN models in the package or integrate them with other programs.

Two NN toolkits are worth specially mentioning. The first is *MATLAB NN Toolbox*[h] from The MathWork, which extends MATLAB "for designing, implementing, visualizing, and simulating NNs." Since MATLAB itself is a numerical computing environment and a programming language, one can call NN models like any other MATLAB functions, and can easily build interface between NN models and other computing modules written in MATLAB. The second tool is *CAD/Chem* and its successor *INForm* by Intelligensys, which is specialized in formulation modeling and optimization for chemists and product designers and has found wide pharmaceutical applications.[i] Using BP neural networks, CAD/Chem helps the product design by automatically learning the underlying relationships between product ingredients, process parameters and resulting properties. It also provides modules for fuzzy logic and genetic algorithms (GA) (which will be introduced shortly in the following section) and statistical analysis tools that are needed for formulation optimization.

OTHER MODELS FOR INTELLIGENT SYSTEMS

Other models, based on different principles and theories, have been developed for building intelligent systems. In this section we briefly introduce a few of them, the

[h] http://www.mathworks.com/products/neuralnet/

[i] http://www.intelligensys.co.uk/models/inform.htm

Bayesian networks, fuzzy logic, and evolutionary computing. These models have quite different characteristics than the logic-based systems and neural computing, and they all have found a wide range of applications.

Bayesian Networks

Bayesian networks (BN), also called Bayesian belief networks, belief networks, or probabilistic causal networks, are a widely used mathematical model for KR and reasoning under uncertainty (24). In this graphical model, nodes represent random variables and the probabilistic interdependencies between random variables are represented by their interconnections. The joint probability distribution of these variables is decomposed into a set of conditional probability tables (CPT), one for each of these variables.

Formally, a BN of n variables $X = \{X_1, \ldots, X_n\}$ is a directed acyclic graph (DAG) of n nodes and a set of directed arcs, with CPT attached to each of the n nodes. Each variable is associated with a finite set of mutually exclusive states. The lower case x_i denotes an instantiation of X_i to a particular state, and $x = \{x_1, \ldots, x_n\}$ represents a joint assignment or an instantiation to all variables in X. An arc $<X_i, X_j>$, represents a direct causal or influential relation from X_i to X_j. This arc also indicates that X_i and X_j are probabilistically dependent of each other. The quantitative part of the interdependence is modeled by the CPT $P(X_i|\pi_i)$ of each variable X_i where π_i is the set of all parent nodes of X_i. If X_i is a root in the DAG which has no parent nodes, then $P(X_i|\pi_i)$ becomes $P(X_i)$, the prior probability of X_i. A conditional independence assumption is made for BN:

$$P(X_i|\pi_i, S) = P(X_i|\pi_i) \tag{8}$$

where S is any set of variables that are not descendants of X_i. Based on this independence assumption, the joint probability distribution of X can be computed from local CPT by the following chain rule: for any $X = x$,

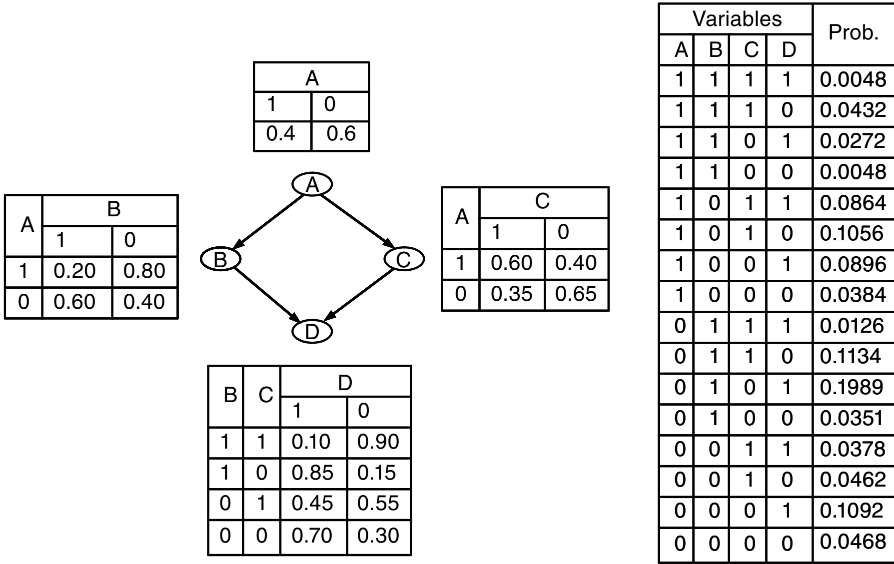
$$P(x) = \prod_{i=1}^{n} P(x_i|\pi_i) \tag{9}$$

With the joint probability distribution, BN supports, at least in theory, any probabilistic inference in the joint space. In other words, any probabilistic query concerning these variables can be computed from the joint distribution through Bayesian conditioning.

Figure 8 gives a simple example BN, including its DAG, CPTs and the joint distribution.

The conditional independence assumption can also be described by the notion of *d*-separation in terms of the network's topology. Figure 9 depicts examples of d-separation for the three types of connections in the network. In the situation of a serial connection, A and C can influence each other in either direction unless B is instantiated (A and C are said to be d-separated by B). In the diverging connection case, B and C are dependent of each other unless A is instantiated (B and C are said to be d-separated by A). In a converging connection, influence can only be transmitted between B and C if either A or one of its descendants is instantiated, *otherwise*, B and C are said to be d-separated by A.

If A and B are not d-separated, they are *d-connected*. In a BN, if A and B are d-separated, they are in independent of each other, and the changes in the belief of A have no impact on the belief of B.



A	
1	0
0.4	0.6

A	B = 1	B = 0
1	0.20	0.80
0	0.60	0.40

A	C = 1	C = 0
1	0.60	0.40
0	0.35	0.65

B	C	D = 1	D = 0
1	1	0.10	0.90
1	0	0.85	0.15
0	1	0.45	0.55
0	0	0.70	0.30

Variables				Prob.
A	B	C	D	
1	1	1	1	0.0048
1	1	1	0	0.0432
1	1	0	1	0.0272
1	1	0	0	0.0048
1	0	1	1	0.0864
1	0	1	0	0.1056
1	0	0	1	0.0896
1	0	0	0	0.0384
0	1	1	1	0.0126
0	1	1	0	0.1134
0	1	0	1	0.1989
0	1	0	0	0.0351
0	0	1	1	0.0378
0	0	1	0	0.0462
0	0	0	1	0.1092
0	0	0	0	0.0468

FIGURE 8 A simple BN of $X = \{A, B, C, D\}$, its CPTs, and the prior joint distribution. *Abbreviation*: CPT, conditional probability tables.

From the above three cases of connections, it can be shown that the probability distribution (or belief) of a variable X_i is only influenced by its parents, its children, and its children's parents, these variables form the Markov Blanket M_i of X_i. If all variables in M_i are instantiated, then X_i is d-separated from the rest of the network, i.e., $P(X_i|X\backslash X_i\}) = P(X_i|M_i))$.

A typical probabilistic reasoning with BN is known as *belief update*: what would be the probability (or belief) of a variable if some other variable(s) are known to be in (or be instantiated to) certain state(s). If we denote the instantiated variables as e (called evidence), then what we are looking for is the posterior distribution $P(X_i|e)$ for any uninstantiated variable X_i. Other, more complicated probabilistic queries can also be answered. One example is the maximum a posteriori problem $\max_y P(y/e)$, i.e., finding the most probable instantiation 4 of a set of variables $Y \subset X$, given e.

Solving these problems directly using the joint distribution $P(X)$ is practically infeasible because the size of the distribution grows exponentially with the size of the network (in the order of $2^{|x|}$). Various efforts have been made to explore the graph structure and d-separation in developing more efficient computation. The most noted is

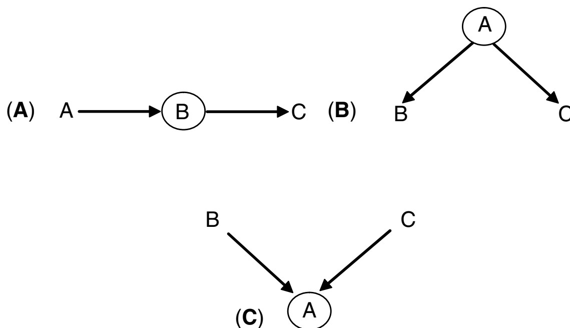


FIGURE 9 Examples of d-separation in BN: (**A**) serial connection; (**B**) diverging connection; and (**C**) converging connection.

the junction tree algorithm. This algorithm groups together those BN nodes that are tightly related into "cliques" and converts the BN into a *tree* of cliques called junction tree. CPTs are also converted into potentials for cliques. The junction tree significantly lowers the time complexity for probabilistic reasoning (from $2^{|X|}$ to $2^{|C_{max}|}$ where c_{max}, the largest clique in the junction tree, is usually a small subset of X).

Almost all BN packages (commercial or in public domain) implement the junction tree algorithm to support exact reasoning. However, even $2^{|C_{max}|}$ is a huge number when the network is really large and dense, making exact solution computationally intractable. For these large networks, people turn to methods for approximate solutions. The most widely used are various stochastic simulation techniques (25). These techniques aim to reduce the time complexity of exact solutions via a two-phase cycle: local numerical computation followed by logical sampling, which yields increasingly accurate results when the iteration continues. Different sampling methods have been investigated, including for example forward sampling, importance sampling, Gibbs sampling, etc. (1).

BN is powerful as a modeling tool for domains in which the relationship among their entities and components are not certain or cannot be described logically, and it provides efficient methods for probabilistic inference. However, construction of a BN is not an easy task. For small and simple problems, it might be possible to draw the network structure (i.e., the DAG) based on domain experts' knowledge and understanding of the causal relations between the entities of interest. However, it is difficult to obtain CPTs from the experts even for small BNs because people do not think things in terms of probability tables. Alternatively, we can construct the BN by learning both the DAG and the CPTs from the data (26).

It is easier to learn CPTs if the DAG is already known, it is much harder to learn DAG. Some methods separate these two tasks, learning DAG first and then CPTs (27); others learn both at the same time (28). For most of the existing BN learning methods, a training sample is required to be an full instantiation of $X = x$. Techniques have been developed to deal with missing values (some variables in some samples do not have a value) and missing variables (variables not in X, if present then a simpler probabilistic model can be built for the samples). Two criteria are followed by most learning methods. The first one is *fidelity*, the model (the learned BN) must be consistent (or with as little inconsistency as possible) to the training samples. This criterion is often judged by how close the probability distribution of the BN is to the distribution exhibited by the samples according to some distance measure (e.g., Kullback–Leibler distance or cross entropy). Since there are many BNs whose distributions are equally close to that of the samples, the quality of a learned BN is further judged by the second criterion, simplicity because a simpler BN runs faster in reasoning. The often used measure for simplicity is the maximum or average number of parents per node in the learned network. Many learning methods consider the fidelity the hard criterion and must be satisfied first, others try to strike a balance or compromise between the two (29).

Since there are too many possible BNs for a given set of variables (e.g., there are 25 different DAG of 3 binary variables, and the number jumps to 10^{18} with 10 variables), it is computationally intractable to guarantee finding the best BN according to any criteria. Therefore, the learning methods all follow some heuristic rules to focus the attention in search for a good but not necessarily the best BN. Even with these heuristics, BN learning, like BP learning in NN, usually takes a long time to complete.

Fuzzy Logic and Possibility Theory

Like probability theory, fuzzy logic is another formalism widely used to deal with uncertainty (30,31). However, as shall be seen shortly, the kinds of uncertainty these two formalisms attempt to model are conceptually quite different. Probability theory is based on the set theory; likewise, fuzzy set theory sets the mathematical foundation for fuzzy logic. In the ordinary set theory, a set A is associated with a Boolean membership function $f_A(.)$: for any object x, $f_A(x) = 1$ if $x \in A$, and 0 otherwise. If x is a random variable such as those representing outcomes of random experiments, then the chance that it is a member of A is the probability $P(x \in A)$. Please note that the uncertainty here is about the outcome *before* the experiment (we are not certain whether it will be head or tail before a coin is tossed). However, the outcome becomes certain after the experiment (the coin can only land on one face).

In contrast, we often face vague linguistic terms such as "tall person" and "fast car." If one tries to build a set that contains objects satisfying such a term, he will find it difficult to define a line to separate members and nonmembers. For example, it is easy to say a person with the height of 210 cm a member of "tall person" and of 140 cm not a member. However, it would be difficult to judge a person of 175 cm, because he is kind of tall but not really very tall. Fuzzy set theory is invented to characterize this kind of uncertainty, which is about facts (height = 175 cm), not chances of things in the future. By extending the membership function of the ordinary set theory, the fuzzy membership function becomes $F_A(x) = y$ where $0 \le y \le 1$ is the degree that x is thought to belong to set (or concept) A.

Figure 10 depicts three examples of fuzzy membership functions for the sets of young people, teenagers, and mid-aged people. The degree that a particular person is in such a set depends on that person's age and the set's membership function. For example, according to these functions, a 30-year-old person is definitely not a teenager, and is more of a mid-aged person than a young.

Similar to predicates in logic and prior distributions in probability theory, membership functions for sets of interest quantify one's understanding of the domain. Like other KRs, these functions can be obtained from the domain experts and can also be learned from data.

Fuzzy logic treats fuzzy membership functions as (fuzzy) predicates, and defines logical operators. For example, we have

$$\text{Negation}: \quad \neg F_A(x) = 1 - F_A(x);$$

$$\text{Conjunction}: \quad F_A(x) \wedge F_B(x) = \min\{F_A(x), F_B(x)\}; \text{ and}$$

$$\text{Disjunction}: \quad F_A \vee (x) F_B(x) = \max\{F_A(x), F_B(x)\}.$$

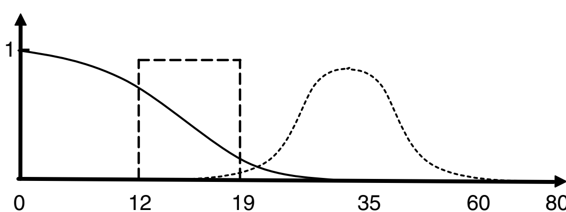


FIGURE 10 Three example fuzzy membership functions: YoungPerson (x) (*solid line*), Teen(x) (*dashed line*), and MidAgedPerson(x) (*dotted line*).

Fuzzy logic is a natural choice for constructing expert systems with rules of vague terms. For example, consider the statement concerning drug formulation that disintegrants can be added to increase the drug's solubility. This piece of knowledge can be easily encoded as a fuzzy rule:

IF not soluable THEN add more disintegrant.

Note here that both "soluble" and "add more" are linguistically vague and thus can be represented as fuzzy predicates (with their particular fuzzy membership functions).

Two interesting observations can be made in comparison with the rule based systems. First, recall that it is often the case that more than one logical rule can match their conditional parts with the current WM content. It is difficult to select one over others since logically they match the current WM equally well. However, the matches with fuzzy rules are fuzzy (a value between 0 and 1 not either 0 or 1) and often not equal, so we can rank the rules according to the numerical values of their matches and select the highest ranked one. In our drug formulation rule above, if the current formulation has very low solubility, then it matches the rule's conditional part ("not soluble") with a very high degree (close to 1), making it very likely to be selected and more disintegrant is added.

Second observation is also related to the numerical nature of the function values. In a rule-based system, if a rule is applied it will very unlikely to be applied again to the same data items because whatever actions this rule calls for has already been done. However, this is not the case for fuzzy rules. For example, application of the solubility rule once may only increase the solubility to a degree (say from 0.1 to 0.2), leaving the rule still applicable. What we see here is an iterative process in which the solubility of the drug increases at each iteration with more disintegrant added into the formulation. It is these features that make the fuzzy logic based expert system a popular choice for process control with wide variety of applications from home appliance control to subway locomotive auto piloting.

The relation between fuzzy logic and probability theory remains controversial. Some, including the inventor of fuzzy logic Lotfi Zadeh, consider they are two separate formalisms for different types of problems. Zadeh has created the *possibility theory* from fuzzy logic, which can be viewed as parallel to probability theory (32). Many others consider fuzzy logic as a new way to express probabilities, and some went even further as claiming that everything one can do with fuzzy logic can be done by probability theory. A minority felt another way around and consider fuzzy logic is more expressive and it includes probability theory as a sub-theory.

Evolutionary Computing

Evolutionary computing is a computational paradigm that seeks the globally optimal solutions for complex problems. Typically this kind of problem has many solutions, some of which are considered good or better than others according to certain criterion represented as an objective function. The goal here is to find the best from a huge solution space according to the objective function. Evolutionary computing is based on the technique called genetic algorithm (GA), which emulates the biological evolution process (33,34). As shown in Figure 11, GA starts with an initial population of individuals. Each individual represents a solution, the information it carries, including a description of the solution and features/attributes that contribute to the goodness of the solution, can be viewed as a sequence of chromosomes characterizing this solution. The goodness of an individual is computed by the *fitness function*, a name borrowed from the Darwinian evolutionary principle of "survival of the fittest." From the optimization point of view, the fitness function is a realization of the problem's objective function. Two computational procedures are executed in producing the next generation of population. The first is the one that selects

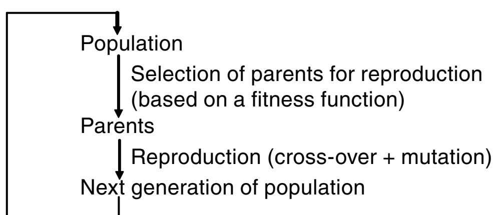


FIGURE 11 An overview of the GA. *Abbreviation*: GA, genetic algorithm.

parents for reproduction, this is a random process, but with higher probabilities for the individuals with better fitness function values. The selected parents are then paired and sent to the second procedure, reproduction, where cross over generates offspring, each of which taking half of its chromosomes from each of the two parents. The hope is that by combining the features of both parents, some of the children may be better solutions than their parents. The mutation during reproduction makes random changes to some chromosomes. This is necessary because, among other things, it allows introduction of new, previously unknown chromosomes. The reproduction continues with more and more individuals produced for the new generation until the population size limit is reached. The process then repeats with the new generation of population.

Evolutionary computing can be viewed as a stochastic search process because the randomness involved in the parent selection and mutation. It can be shown that if (*i*) the size of the population is allowed to be sufficiently large, (*ii*) the process is allowed to run for a sufficiently long time, and (*iii*) the true randomness is followed in the process, then the globally optimal solution is guaranteed to be generated.

Since usually we do not know what the *best* solution looks like or its fitness function value, there is no way one can tell the best solution is already generated and the process should terminate. Therefore, we use other criteria for termination. One such criterion is if the objective (fitness) function value of the best solution in the current population falls into the acceptable range (if such a range is provided); another is when the fitness of the best individual does not improve for a large number of generations. In either case, the global optimality is likely but not guaranteed.

SOME PRACTICAL APPLICATIONS IN PRODUCT AND PROCESS DEVELOPMENT

Application of Knowledge-Based Systems

The reader is referred to Lai's useful 1991 review (35) for an earlier discussion of the application of expert systems to pharmaceutical technology.

Immediate Release Oral Solid Dosage Forms

A few examples of the application of KB systems to immediate release tablet formulation have appeared in the open literature. Podczeck (36) described a system based in part on rules constructed from laboratory experiments designed to study the relationship between independent and dependent variables. These rules were combined with others in the expert system to determine the formulation composition.

The Cadila System (Cadila Labortories, India) for tablet formulation was developed by Ramani et al. (37). Written in Prolog, this interactive menu-driven program first requires the user to enter information on the drug properties. The system then consults its knowledge bases and selects compatible excipients with the required properties and gives

their recommended proportions. A best formulation may be selected from among several feasible alternative formulations that can be generated by the expert system. The system can be queried for explanations of the decisions taken in arriving at formulations.

Rowe (38,39) described a tablet formulation expert system that uses Logica's PFES shell. Similar to the Cadila System, the user inputs the basic information on a new drug substance, e.g., physicochemical and mechanical properties, dose, strategy based on number of fillers. The formulation may be optimized based on the results of testing the initial formulation. The optimization is interactive with the formulator who, based on experience and expertise, can override and modify the recommendations of the expert system within a relatively broad range. The selection of ingredients and their proportions for the initial formulation are based on algorithms and production rules determined from an extensive study of previously successful formulations and certain other rules.

Related Applications

Expert systems have also been developed for certain related applications. In one of the earliest examples, Lai (40) described a prototype expert system for selecting a mixer. The system was written in TURBO Prolog which used a backward chaining inference mechanism. Production rules were developed from a knowledge base obtained from published papers. In another example, Murray (41) described an expert system for troubleshooting and diagnostics of a Korsch rotary tablet press. A detailed decision tree structure was developed for each major subsystem of the tablet press, e.g., hydraulic force overload, automatic lubrication, main drive, force feeding, tablet weight verification and others. The user's answers to a series of questions enable the decision tree structure to ascertain the symptoms or circumstances related to a specific problem and determines in what direction the diagnostic process should be approached. The system then prompts the user through a series of diagnostic or remedial measures that previously have been shown to be effective. This knowledge base is intended to be updated periodically with information derived from recent problems that have been solved and documented. A KB system designed to diagnose and provide solutions to defects in film coated tablet has also been described (42,43).

Hard Shell Capsules

KB systems have also been developed to support formulation development for hard shell capsules. This topic is relevant to this discussion because modern capsule fillers for powder or granular formulations resemble tablet presses in that they employ both compression and ejection processes, i.e., capsule plugs are formed from the powder or granular formulation by a gentle compression or tamping process and the plugs are ejected into empty capsule shells. Moreover, the formulations for hard shell capsules typically employ the same excipients, such as fillers, lubricants, glidants and others as found in tablet formulations (44). Bateman (45) described an expert system developed using Logica's PFES shell. This is a customized system that incorporates the practices and policies of the Sanofi Research Center. Knowledge acquired through a coordinated series of meetings with formulators was incorporated by software engineers by encoding an appropriate set of rules that reproduce the formulation experts' decision-making. Another part of the system important to making formulation decisions is the excipients database. The formulation experts identified the most important properties to consider, e.g., particle size, bulk density, acid-base reactivity, amine reactivity, aqueous solubility, hygroscopicity and others. Because the information on these properties found in the

literature is based on different analytical methods and therefore couldn't be correlated, it was decided to make these measurements in-house. In a preliminary validation, three chemical entities were selected to challenge the system. The formulations generated by the KB system were judged by experienced formulators to be acceptable for manufacture and initial stability evaluation.

Unlike the Sanofi system, Capsugel's CAPEX expert system is a centralized system that incorporates worldwide industrial experience to support the formulation of powders for hard gelatin capsules (15,46). Development of the system was initiated at the University of London under the sponsorship of Capsugel, a division of Pfizer, Inc. The Capsugel expert system consists of three databases. One of these is "past knowledge," which was collected from the published literature and includes information on excipients used in many marketed formulations in Europe and the United States. The second database contains experiential and nonproprietary information acquired from industrial experts through classical knowledge engineering techniques. The third database consists of information generated through statistically designed laboratory studies aimed at filling knowledge gaps and providing quantitative information. These databases provided the knowledge base from which the facts and rules were derived to construct the decision trees and production rules that comprise the expert system. The system was programmed in Microsoft C and the core system was linked to a dBase driven database. The system has since been converted to a Microsoft Windows-based platform that significantly enhances its ease of use.

Under Capsugel's continuing sponsorship, the program created at the University of London was further developed and enhanced by the efforts of the University of Kyoto and the University of Maryland through additional laboratory research and a series of panel meetings in Europe, Japan, and the United States with industrial, regulatory, and academic experts.

Application of Neural Nets

Interest in the use of NNs in pharmaceutical technology and product development has been growing and has been the subject of several reviews (47–50). This interest in the nonlinear processing ability of NNs as a way to manage and solve pharmaceutical problems should not be surprising. The relationships that exist between formulation and process variables and desired outcomes are complex and typically nonlinear. The nonlinear processing ability and unique structure of NNs offer substantial promise in dealing with the problems we face in pharmaceutical product development and technology. The primary goals of applying NNs to pharmaceutical problems are optimization and prediction. The NN model that predominates in these areas is the feed forward/back propagation network, which often is simply referred to as the BP network (51).

Powder Properties and Unit Operations

Several applications have been reported that deal with powder properties and certain unit operations. For example, Kachrimanis et al. (52) evaluated the effects of bulk, tapped and particle density, particle size, and particle shape on the flow rate of three common excipients (Emcompress, Starch and Lactose) through circular orifices. Four sieve fractions were studied. The experimental data were modeled using a backpropagation NN. They found that the predictions of the NN were superior to those of a classic flow equation since the NN does not require a separate regression for each experiment and its predictive ability was higher. Behzadi et al. (53) reported on the validation of a modified

fluid bed granulator. Sucrose was granulated under different operating conditions and their effects on the size distribution, flow rate, repose angle, and tapped and bulk volumes of the granulation were measured. A generalized regression neural network (GRNN, a variation of RBF networks) was used to model the system. A good correlation was found between the predicted and experimental data.

Immediate Release Oral Solid Dosage Forms

A few reported studies employing NNs have addressed immediate release oral solid dosage forms. Using a BP algorithm to build the NN, Kesevan and Peck (54) attempted to predict tablet and granulation characteristics from material and process variables. The variables considered were granulation equipment, diluent, method of addition of binder, and binder concentration. Although the prediction of granulation properties (geometric mean particle size, flowability, bulk and tapped densities) were found satisfactory, predictions of the hardness and friability of the resultant tablets were less than satisfactory. However, the NN prediction in all cases was found better or comparable to conventional regression methods. The authors suggested that the NN prediction of hardness and friability may be improved by providing more data and additional independent variables.

Bourquin et al. (55) carried out a study aimed at investigating the influence of a number of formulation and compression parameters on tablet crushing strength, percent dissolved after 15 minutes, and time to 50% dissolution. The drug substance was granulated in two different formulations. The compression parameters studied were matrix filling speed, precompression force, compression force and rotational speed: each was considered at three levels in the study design. The dataset was mapped using three techniques: (*i*) a generalized feed forward NN employing a hyperbolic tangent function as an arbitrary nonlinear activation function for all processing elements, (*ii*) a hybrid network composed of a self-organizing feature map, and (*iii*) classic response surface methodology. NN models using an arbitrary function were found to have better fitting and generalization abilities than the response surface technique. The arbitrary hyperbolic tangent function was chosen to represent nonlinearity in the data.

Ebube et al. (56) found that a NN accurately predicted in vitro dissolution based on several experimental variables, provided the NN variables were optimized and training and validation sets were appropriately selected.

Working with a high-dose plant extract, Rocksloh et al. (57) optimized the crushing strength and disintegration time of the tablets after substantial experimentation. Best results were found with a plant extract that had been granulated by roller compaction prior to tableting. In an attempt to learn more about the different effects, feedforward NNs and a partial least squares multivariate method were used to analyze the data, with the result that NNs were found more successful in characterizing the effects that affect crushing strength and disintegration time. Shao et al. (58) found both NNs and neurofuzzy logic to successfully develop predictive models for the crushing strength and dissolution of an immediate release formulation, but the latter logic had the additional advantage of generating rule sets for the cause-effect relationships in the experimental dataset.

Peng et al. (59) used trained NN models to predict the dissolution profiles of immediate release beads loaded with 40% acetaminophen. The beads were prepared by extrusion and spheronization. The training set consisted of 18 batches that were prepared based on a full-factorial design. The variables were extruder type, screw speed, spheronization speed and spheronization time. The NN model trained with a GA exhibited better predictability than that trained with a neural algorithm.

Kuppuswamy et al. (60) used a BP network to model the relationship between the hardness and friability of direct compression tablets produced from nine mixtures of varying compactibility and tableting indices (Hiestand). The goal was to predict the hardness and friability of tablets from the index values. It was concluded that tableting indices did not have a general ability to predict compactibility since quantitative prediction was only possible when the model was trained with similar materials. Different materials having closely similar indices could have widely differing compactibility.

Modified Release Oral Solid Dosage Forms

A review of the literature suggests a strong interest on the part of researchers in applying NNs to the development of modified release oral solid dosage forms. One of the earliest reports in this application area is that of Hussain et al. (61) who used a BP network to discern the complex relationship between certain formulation variables and the in vitro release of chlorpheniramine maleate from a hydrophilic matrix capsule system. They found that NN analysis could predict the response values for a series of validation experiments more precisely than response surface methodology. In a later study, Hussain et al. (62) describe the use of a nonlinear feed forward network to recognize the relationships between the drug, formulation properties and the in vitro release of the drug from hydrophilic matrix tablets. Eleven drugs were studied in three different ratios with hydroxypropyl cellulose. The drugs were characterized by their intrinsic dissolution rate, salt type, pKa, and molecular weight. Three polymer molecular weight grades were characterized by their hydration times. The NN developed from this dataset was used to predict the in vitro release profile of the drugs, and the prediction error (RMS) was found acceptable for most, but not all, of the drugs and polymer ratios. The authors concluded that even though the formulation examples and test conditions are simplistic, the results of the study are useful in that they demonstrate the potential advantages and limitations of this approach.

Takahara et al. (63) reported the use of a multi-objective optimization technique based on a NN for a sustained release tablet. The quantities of microcrystalline cellulose, hydroxypropyl methylcellulose and the tablet compression pressure were considered the causal factors. The drug release order and release rate were the responses. The response surface of a NN was used to recognize the nonlinear relationship between the causal factors and the responses. Simultaneous optimization was carried out by minimizing the generalized distance between the predicted values of each response and the optimized one. Similarly, Takayama et al. (64) described the application of simultaneous optimization incorporating a NN to theophylline hydrophilic matrix controlled release tablets. The levels of a commercial 80:20 hydroxypropyl methylcellulose: lactose mixture and cornstarch, and the compression pressure were the causal factors. The release profiles were represented by the sums of the fast and slow release fractions. Release parameters were the initial weight, the rate constant in the fast release fraction, and that in the slow release fraction. A desired set of release parameters were obtained based on human pharmacokinetic data. NN response surfaces were used to recognize the nonlinear relationships between the causal factors and the responses. Simultaneous optimization was performed using a generalized distance function method which minimizes the distance between the predicted values of each response and the desirable one that was optimized individually. Fairly good agreement between the observed and predicted release parameters was found. The use of the generalized distance function combined with a GRNN to optimize aspirin extended release tablets has been reported (65). The tablets were formulated using Eudragit L 100 as the matrix substance.

Chen et al. (66) combined a NN with pharmacokinetic simulations to design a controlled release tablet formulation for a model sympathomimetic drug. Ten independent variables for 22 tablet formulations provided the model input. In vitro cumulative percent of drug released at 10 different sampling times was the output. The NN was developed and trained using CAD/Chem software, and the trained model was used to predict the best compositions based on two desired in vivo release profiles and two desired in vitro dissolution profiles. Three of four predicted formulations exhibited very good agreement between the NN-predicted and the observed in vitro dissolution profiles based on similarity metrics (f1, f2). Chen et al. (67) later used the above data as the basis to compare four commercially available NN software packages (NeuralShell2, BrainMaker, CAD/Chem, NeuralWorks) for their ability to predict in vitro drug release. The percent dissolved at 10 different sampling times was the output. The slopes of predicted versus observed percentage of drug dissolved ranged from 0.95 to 1.01 ($R^2 = 0.95$–0.99) for the four optimized models. The authors concluded that all four programs gave reasonably good predictions from this dataset, but one (NeuroShell2) was preferred based on similarity metrics, exhibiting lower f1 and higher f2 values compared to the others.

NNs also can be used to rank which of various formulation and process variables are most critical in influencing responses. For example, Leane et al. (68) described the successful use of input feature selection (IFS) to identify the most important factors affecting in vitro dissolution from enteric coated minitablets. Using Trajan software, IFS was implemented in two ways: stepwise algorithms that progressively add or remove variables and a GA. NNs were then trained using the BP algorithm to determine whether or not the IFS had correctly identified any unimportant inputs.

In other applications to modified release tablets, NNs have been applied to the optimization of osmotic pump tablets (69) and to model bimodal delivery (70). In the latter, the precision of the predictive ability of different training algorithms was compared.

Experience with a Hybrid "Expert Network" System

Under the sponsorship of Capsugel, a feasibility study was carried out at the University of Maryland to link an expert system for capsule formulation support with a NN (7,8). The goal was to create an intelligent system that can generate capsule formulations that would meet specific drug dissolution criteria for BCS Class II drugs, i.e., drugs that would be expected to exhibit dissolution rate-limited absorption. Piroxicam was selected as a model Class II drug with which to demonstrate feasibility. A modified expert system patterned after the Capsugel system was created for this project. The new system provided an opportunity to build certain additional features into the decision process and to use a more effective and more flexible programming language package. Unlike the original Capsugel system written in C, this expert system was constructed as a rule-based system, and encoded in Prolog. This structure provides certain advantages. In Prolog, knowledge is separated from the inference engine. Thus, the designer need only provide the knowledge base, since the inference mechanism is provided by the language package. Another advantage is that the rules are local and relatively independent of the inference engine. This feature makes maintenance and updating of the KB easy. A Prolog rule-based system is also more suited to managing complex formulation problems than a decision tree because it can represent more complicated decision logic and more abstract situations.

As depicted in Figure 12, the expert system is linked to a NN to form a hybrid system. The expert system is the "decision module" that generates a proposed formula based on data and requirements input by the user; the NN, trained by BP algorithm,

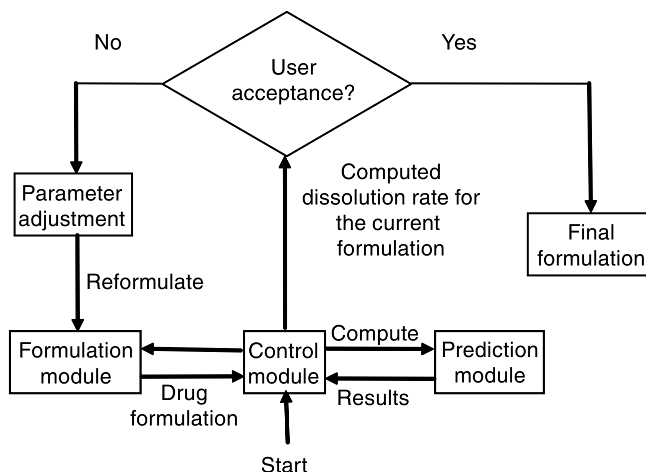


FIGURE 12 The hybrid system "Expert Network" for BCS Class II drug capsule formulation.

serves as the "prediction module" that predicts the dissolution performance of the proposed formulation. The "control module," driven by the difference that might exist between the desired dissolution rate and the predicted dissolution rate of the proposed formulation, controls the optimization process. The control module inputs the formulation from the decision module to the prediction module to compute the predicted dissolution rate and asks for the user's acceptance of the currently recommended formulation based on that predicted dissolution rate. If the user accepts the formulation, the control module will terminate the formulation process. If not acceptable, the control module will present a set of choices of parameter adjustments (e.g., excipients levels) to the user for improving the dissolution rate. This prototype was found to have good predictive power for the model compound, piroxicam. Later, a more generalized version of this system which included parameters to address wettability and the intrinsic dissolution characteristics of the drugs was found to show good predictability for several BCS II drugs representing a broad range in solubilities (71). The approach demonstrated here for capsule formulations should be readily adaptable to tablets.

THE FUTURE

Product development is a complex, multi-factorial problem requiring specialized knowledge and often years of experience. The need to speed up the development process and modernize manufacture and control will drive academic and industry researchers to develop a more fundamental understanding of product and process that will enable the identification and measurement of critical formulation and process attributes that relate to product quality and to model the relationships between product quality attributes and measurements of critical material and process attributes. The contributions that KB systems and other AI techniques can make to decision-making, product and process optimization and identifying critical variables, and codifying and preserving knowledge have already been demonstrated through numerous examples. But their full potential in pharmaceutical technology has not been realized. That will require more a fundamental understanding of our systems and a stronger commitment to build collaborative relationships with AI and information technology specialists who can help us exploit AI and translate the problems and goals of pharmaceutical technology into practical solutions.

Most AI methods with substantial applications in drug formulation (e.g., rule-based systems, decision trees, BP NN, GA) were “old” techniques developed in the 1970s and 1980s. Since then quite a number of techniques for intelligent systems have reached a level of maturity for real world applications. It would be interesting to see how these “new” techniques can be applied to help solve difficult problems in drug formulation. For example, SVM has been reported to outperform several other machine learning techniques, including BP networks, RBF networks, and decision trees, in both learning time and the validation accuracy in data analysis for drug discovery (72). Similar performance would be expected when SVB is applied to tableting and other formulation optimization tasks.

Similarly, the technique of BN, especially BN learning, is also very promising in drug formulation. BN can be seen to be advantageous over NNs in several aspects. First, BN models the interdependencies between variables, and not just a black box associating input patterns to their desired outputs as do BP networks, so every part of the BN can be evaluated and validated by human experts. Secondly, NN, when used as a predictor, generates the most likely/plausible output pattern for a given input pattern. In contrast, BN provides posterior distribution of output variables for the given input, as such not only one can find the most probable output pattern, but also knows its likelihood, and the likelihoods of other good patterns that ranked lower than the best one. Thirdly, the Bayesian analysis can be done using any combination of variables as the conditionals. This kind of flexibility goes far beyond what can be supported by any NN models, making BN a powerful modeling tool for what-if analysis.

Another new technique of interest is semantic web (SW) (73). Unlike most AI techniques reviewed in this chapter, SW is not a technique for data analysis or KR; rather it is a technique that helps a better sharing of data and knowledge. Pages in the current World Wide Web are intended for human consumption. Their contents are not understood by computer programs. To make web pages understandable by programs, the SW extends the current web by providing additional markups to articulate the semantics or meaning of the web contents. The semantic markups are according to shared ontologies written in a standard web ontology definition language based on a variation of FOL known as the description logic.

SW thus can be viewed as a web of data that is similar to a globally accessible database. How to build a shared ontology for drug formulation (as part of a much larger ontology for pharmaceuticals) and how to utilize the huge amount of data and knowledge that become available for machine processing is a research direction of great potential.

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5
Direct Compression and the Role of Filler-binders

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INTRODUCTION

Direct Compression (DC) is the tableting of a blend of ingredients, the compression mix, without a preliminary granulation or aggregation process. The compression mix contains the active pharmaceutical ingredient (API) blended with one or more excipients. The excipients may include binders, filler/diluents, disintegrants, and lubricants. Such DC compression mixes must flow uniformly into a die and form a robust tablet.

The terms compaction/compactability refer to the ability of a formulation to give a tablet of specified hardness and friability, and are therefore preferred to the terms compression/compressibility, which relate to the densification of powders under pressure, not necessarily giving a tablet. However the specific terms DC and "compression mix" are used in this chapter, given their widespread use.

Before the 1960s, most tablet production required granulation of the powdered constituents prior to tableting. The primary purpose of granulation is to produce a free-flowing compression mix with acceptable compactability. The availability of DC grade excipients, and faster tablet machines with assisted feed and precompression, enabled the rise of DC. The first significant discussion of the concept of DC was presented by Milosovitch in 1962 (45).

The distinction between DC and wet or dry granulation is not absolute, as the addition of extragranular ingredients ("post-granulation running powders") constitutes a DC step, where the granulate itself can be regarded as one of the DC ingredients. As granulation does not always deliver the necessary compactability the use of microcrystalline cellulose (MCC) post-granulation to increase tablet hardness has been common practice since the introduction of DC. Blending and compaction are two unit processes common to both wet/dry granulation and DC.

A further hybridization was proposed by Ullah (64) using a process called moisture-activated dry granulation. In this procedure, instead of drying the wet mass, MCC is added to absorb the small amount of moisture present. No traditional drying step is involved. Such granulations tend to be of low density with a relatively small particle size.

A DC binder is a material added to render the blend compactible as opposed to a filler, which is added to bulk up the formulation so that a conveniently sized tablet results. The distinction is not absolute as shown by the widespread use of the term filler-binder. A true DC binder is functional at low levels, whereas a low level addition of filler would not greatly influence the compactability of the compression mix.

DC is the simplest process but requires that the major components of the compression mix have adequate density, flow, and compaction properties. If the bulk density of the compression mix is low, such that the volume corresponding to the target dose exceeds the fill volume of the die, then DC is not feasible. Even with assisted feed good flow is required for high speed rotary tableting. Poor compactability may also be limiting. Most DC grade excipients offer superior flow and compactability.

Low API solubility may also be limiting as DC does not offer the "instantization" (also known as hydrophilization) of API particles afforded by wet granulation, where processing with dissolved polymer renders the API particles more hydrophilic and wettable.

All the preceding limitations are exacerbated at higher API loadings, but too low a drug loading may also prohibit DC, due to segregation or content uniformity problems. The design space for DC is illustrated in Figure 1, where the abscissa represents the impact of any one limiting property of the compression mix (density, flow, compactability, or solubility). It only takes one unfavorable attribute to render DC of a high drug infeasible.

You cannot directly compact a high loading of an API with unfavorable density, flow, compactability, or solubility attributes. A high loading of an unsuitable low potency API is usually limiting, due to the need to avoid an excessive tablet size if it is to be swallowed. Typically 1.2–1.5 g would be the limit for a pharmaceutical swallow tablet not containing significant quantities of (denser) inorganics. If the tablet can be chewed then it can be larger and the unfavorable API attributes are diluted out. It is assumed that the formulator will use DC grade excipients to avoid density, flow, and compactability problems unrelated to the API.

Whilst there is no absolute lower limit, typically an API loading below 1% would make DC difficult without a high level of mixing efficiency and resistance to segregation. Generally API size reduction, ordered mixing, high shear dispersion, and premixing will be required, as opposed to simple blending (25,32,68,77). Below a 0.1% loading API deposition from solvent onto a DC carrier will generally be required.

By eliminating several unit operations associated with granulation, DC processes substantially reduce the complexity, risk, and cost of processing in high value good manufacturing practice (GMP) containment facilities, as shown in Table 1. The more unit operations, the greater the scope for problems, and the heat and moisture challenge of wet granulation may not be acceptable for labile actives. However the simpler DC process results in direct expression of input material properties so the quality and consistency of DC materials is paramount.

Prior to the introduction of spray dried lactose (SDL) in 1962 and MCC in 1964 there were no useful DC excipients with the capacity to enable DC of high loadings of uncooperative APIs, hence the dominance of wet granulation at that time. Manufacture and

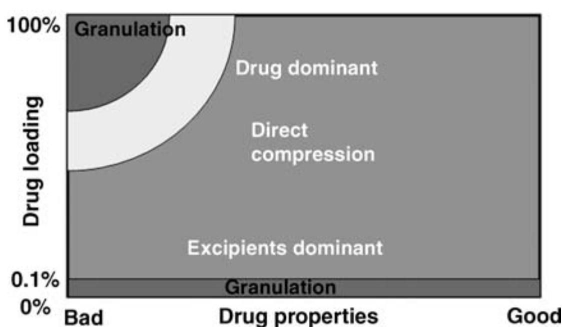

FIGURE 1 DC design space. *Abbreviation*: DC, Direct compression.

TABLE 1 Unit Operations in Wet/Dry Granulation vs. DC

Wet granulation	Dry granulation	DC
Blending	Blending	Blending
Granulation	Slugging or roller compaction	
Wet massing		
Drying		
Sizing	Sizing	
Blending (Extragranular & lubricant)	Blending (Extragranular & lubricant)	Blending (Lubricant)
Compaction	Compaction	Compaction

Abbreviation: DC, Direct compression.

trade were not as global as today and tariff barriers dictated use of locally sourced excipients of varying quality. The claim of wet granulation to "wipe the excipient history clean" may not be true in all cases but it was beneficial where consistent excipient supply could not be guaranteed. MCC is now manufactured and supplied globally and whilst it is not the only enabler (22), approximately half of worldwide tablet production is now by DC (17).

THE DC PROCESS

The simplicity of DC makes it the first choice in the laboratory so long as the properties and loading of the API are acceptable. Simply blend API with filler-binder and disintegrant, add lubricant, and compact into tablets. The higher the drug loading and the less compactible the API the more you would use a true DC binder such as MCC, rather than fillers such as lactose or dibasic calcium phosphate (DCP), used to bulk up lower API loadings so that a convenient tablet size results.

The DC process assumes that all materials can be purchased or manufactured to specifications that allow for simple blending before tableting. Unlike wet granulation, where the original properties of the raw materials are significantly modified, there is direct expression of raw material properties during tableting of DC formulations. Flow or compaction inadequacies may prove limiting in DC especially on scale-up. As it not always possible to tailor the API properties for DC it is essential to add only DC-grade excipients. Micronization of the API to enhance dissolution and bioavailability is an example where API properties are deliberately modified in a direction unhelpful to DC, especially in terms of flow (lack thereof). DC raw materials and the process by which these materials are blended must be carefully specified.

Some reduction in DC feasibility is to be expected on scale-up either due to speed-sensitive compactability, or flow limitations. Wet granulation will address compactability and flow but represents a major formulation change from DC, so early assessment of speed (strain rate) sensitivity of DC formulae is essential. Dry granulation, such as roller compaction (RC), will increase density and flow, but not compaction. It is however less of a formulation change so the practice of designing RC-capable DC formulations to handle increasing production requirements (as the product evolves commercially) will become more common, given the increased attention paid to design space under recent quality-by-design (QbD) initiatives. DC is ideal for most production purposes but at very high speed and volumes (including continuous production) may need to be augmented by roller compaction.

Speed (or strain rate) sensitivity per se need not be limiting, so long as the high speed compaction properties of the DC formulation are sufficient to yield a tablet of adequate robustness and release characteristics. There is no point simply substituting speed sensitive materials such as MCC with less speed sensitive materials such as lactose or DCP at the expense of compactability, as shown in Figure 2.

Figure 2 also illustrates why the level of DC binders such as MCC should not minimized based on low speed data. If relying on MCC as a DC binder, include enough to compensate for speed sensitivity.

Greater attention must be paid to API content uniformity in a DC formulation compared to a granulated compression mix with a similar API loading. Unlike granulation simple DC blending does always lock API and excipients together in a fixed ratio. If there is no interaction between API and excipients in a DC blend, there is a risk of segregation during handling and tableting. In such cases differences in particle size or density between API and excipient particles may need to be minimized. However this may conflict with DC imperatives, such as flow, especially with micronized drug. Killing flow is an effective way of dealing with segregation but hardly conducive to DC.

Segregation of API particles implies that they are non-cohesive particles. The concept of ordered mixing describes mixing of small cohesive particles to give a considerable degree of resistance to segregation. A basic principle of ordered mixing is that fine particles will adhere, especially to larger particles. The adhesive forces involved may be electrostatic or surface tensional. Early assessment of the physical stability of DC mixes in terms of segregation potential is essential, but if the mix is physically stable there is no need to match API and excipient particle size profiles or densities. On the contrary, the DC combination of large particle excipient and micronized drug gives the best of both worlds in terms of flow and dissolution. To ensure consistency the loading of fine particles adhering to unit surface area of the larger particles should be constant, and controlled through appropriate API and excipient specifications. Ordered mixing enables direct compaction of API at loadings as low as 0.1%.

QbD is facilitated by DC as there are fewer variables in mapping the design space. This is of value given the large number of prototype formulations in development, most of which will never be commercialized. DC avoids the additional heat and moisture challenge of wet granulation, which may lead to stability problems, often not always

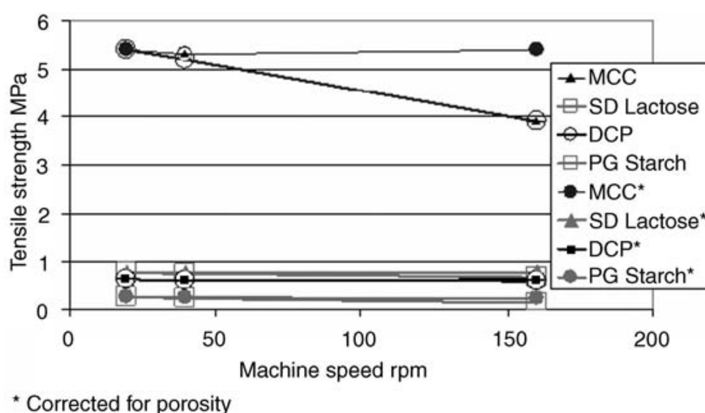

FIGURE 2 Speed (strain rate) sensitivity of common DC filler-binders. *Abbreviation*: DC, Direct compression. *Source*: Armstrong NA. Pharm Technol 1990; 14(9):106.

immediately apparent. The effect of tablet aging on dissolution rates must also be considered. Changes in dissolution profiles are less likely to occur in tablets made by DC than in those made from granulations.

In Production each additional unit operation introduced by wet or dry granulation introduces problems of validation, yield, cleaning, and documentation, in addition to the time and manpower in high cost GMP containment facilities. The major advantages and disadvantages of wet/dry granulation versus DC are compared in Table 2.

TABLE 2 Comparison of DC and Wet or Dry Granulation

	Granulation (wet/dry)	DC
Compactability	Harder tablets for poorly compactible substances (wet)	Potential problem for high loading of poorly compactible APIs
Flow	Excellent in most cases Improved by process (wet/dry)	Many formulations may require glidant. Cannot be used for high-load micronized APIs
Particle size	Larger with greater range (wet/dry)	Lower with narrower range
Content uniformity	Fixed by process (wet/dry)	Risk of segregation in absence of ordered mixing. May occur in transport, hopper, and feed frame
Mixing	High shear (overgranulation) may hinder drug release (wet)	High shear may reduce particle size (and flow).
Lubrication	Less sensitive to lubricant (wet)	Minimize shear and blending time with lubricant
Disintegration	Higher intragranular levels required due to adverse effect of wet granulation on disintegrants (Croscarmellose least affected) Granule disintegration not measured in tablet disintegration testing	Lower levels required No reduction in disintegrant functionality due to wetting and drying
Dissolution	Drug wetted and rendered more hydrophilic during wet granulation (instantization or hydrophilization) Slower dissolution from granules on storage, especially if intragranular disintegrant not used. (wet/dry)	Drug not wetted or instantized May need surface active agent Trade-off between flow and dissolution for high loadings of micronized drug
Cost	Higher equipment, labor, time, process validation, and energy costs (wet > dry)	DC excipient grades higher cost/kg (not necessarily higher cost in use)
Sensitivity to raw material variability	Some masking of raw material variability (wet > dry)	Direct expression of raw material variability Raw material QC paramount
Stability	Heat and moisture challenge to labile APIs (wet) Decreasing dissolution	No Heat & moisture challenge to labile APIs Less fall-off in dissolution
Tableting speed	Higher	Reduced speed if flow poor
Dust	Less dusty	More dusty
Color	Deep or pastel (dyes or lakes) (wet)	Pastel only (lakes only)

Abbreviations: DC, Direct compression; API, Active pharmaceutical ingredient.

DC FORMULATION

The simplicity of DC is illustrated by the general formula in Table 3.

Example DC tablet formulae, manufacturing methods, and tablet properties are shown in Appendix 1.

The choice of excipients is extremely critical in formulating DC tablets. This is most true of the filler-binder, which often serves as the tablet matrix or vehicle. DC filler-binders must possess both compactability and good flow and these functionalities should be specified in addition to the more traditional physical and chemical properties.

For high loadings of poorly compactible API the compactability and dilution capacity or potential of the DC binder (usually MCC) is paramount. The dilution capacity is the maximum proportion of API that can be compacted into an acceptable compact utilizing that filler. As the dilution capacity of a filler-binder depends on the properties of the API it is customary to compare filler-binder performance using a standard difficult-to-compact material, such as ascorbic acid. Fillers–binders range from highly compactible binders (MCC), with high dilution capacity, to fillers (low dilution capacity) such as Spray-dried lactose (SDL).

The introduction of superdisintegrants such as Croscarmellose (AcDiSol®), Crospovidone (Polyplasdone® XL), and sodium starch glycolate (Explotab®, Primogel®) facilitated the rise of DC. Their low use levels allow faster disintegration of tablets, minimizing the softening, and flow problems encountered when high levels of starch are used. DC formulations generally require less disintegrant than wet granulation formulations. 0.5–4% of superdisintegrant is recommended. Although MCC is self-disintegrating the disintegration time may be dependent on the compaction force. The addition of disintegrant removes this process sensitivity. High loadings of DCP cannot be used without a disintegrant for immediate release. Soluble filler is not always required for faster release (31).

Higher levels of disintegrant ($>2\%$) are required for soluble fillers otherwise release will be determined by slow erosion and dissolution, rather than disintegration.

Achieving the original API particle size distribution on disintegration of a DC tablet depends on the presence of sufficient disintegrating agent and its uniform distribution throughout the tablet matrix. High-drug concentrations can lead to cohesive particle bonding during compaction with no interjecting layer of binder or disintegrating agent. The fibrous nature and potency at low levels (0.5%) of Croscarmellose are ideal for this purpose.

Starches such as Starch 1500® are promoted as disintegrants and although much less potent than the superdisintegrants their use as a filler-disintegrant may be feasible, but generally at a level 5–10 times higher.

TABLE 3 General DC Tablet Formula

API	0.1–99%
Filler-binder (dependent on API loading and compactability)	1–99%
Disintegrant	0.5–2%
Lubricant	0.5–2%

Abbreviations: DC, Direct compression; API, Active pharmaceutical ingredient.

Lubrication of DC powder blends can be a problem if a film of lubricant builds up on the surfaces of plastically deforming materials such as MCC. Because such materials deform without creating fresh surfaces the lubricant, especially magnesium stearate, may interfere with bonding, reducing tablet hardness. It may be necessary to avoid the alkaline stearate lubricants in some DC formulations.

To minimize adverse softening or hydrophobic effects of alkaline stearate the lubricant should be added last and blended for the minimum time, as little as 2–5 minutes. It is not advisable to include lubricant in the blending of the API with the other DC excipients. Lubricant should never be incorporated into the main blend using high-shear mixing, but high-shear is ideal for making a lubricant premix, which can then be subsequently blended into the main mix at low shear, avoiding the problems associated with trying to directly blend in such hydrophobic cohesive materials.

Another approach is to use alternative lubricants such as stearic acid, hydrogenated vegetable oil (Sterotex®, Lubritab®), sodium stearyl fumarate (PRUV®) or glyceryl behenate (Compritol®). Higher concentrations may be necessary than would be required with magnesium stearate. Particle size and surface area of the lubricant should be carefully controlled.

One minor disadvantage of DC (and dry granulation) is the inability to produce colored tablets of the same color intensity as wet granulation (not a problem if the tablets are to be coated). It is possible through the use of high shear lake premixes to obtain a wide variety of pastel shade tablets. Pure dyestuffs should not be used for coloring DC tablets as they are relatively ineffective compared to lakes and will contaminate equipment (and the hands of the patient).

In order to reduce the likelihood of raw material failure, it is advisable to set quality specifications on particle size, bulk density flow, and compactability. The latter can be easily done by compaction under controlled conditions and determining the breaking strengths of the resulting compacts.

Compactability

Formulation should optimize tablet hardness without applying excessive compaction force, whilst simultaneously assuring rapid tablet disintegration and drug dissolution. Where the drug loading is low this is not usually a problem, and the focus will be on content uniformity. At high API loadings the API properties dominate and the issue is one of making the best of the limited amount of excipients that can be added to form an acceptable physically stable compact. The only true DC binder is MCC. It can add significant hardness to compacts at levels as low as 3–5%. It should always be considered first if the major problem in the formulation is tablet hardness or friability. There is no upper limit to the amount of MCC that can be used except where low levels of insoluble API might be encased in MCC aggregates on tablet disintegration. A superdisintegrant, a disintegrant filler (starch) or soluble filler (lactose) may be added in such cases. No other DC excipient compares to MCC as a DC binder in low concentration. The compactability of fillers ensures tablet formation at high use levels but they would have little practical effect at levels as low as 3–5%.

A comparison of the relative compactibilities of various DC fillers using magnesium stearate and stearic acid as lubricants is presented in Figures 3 and 4. As can be seen, MCC is by far the most compactible of the substances tested. Magnesium stearate causes a softening of compacts to the point that Starch 1500 cannot be tableted. However, the relative compactability of the fillers remains constant.

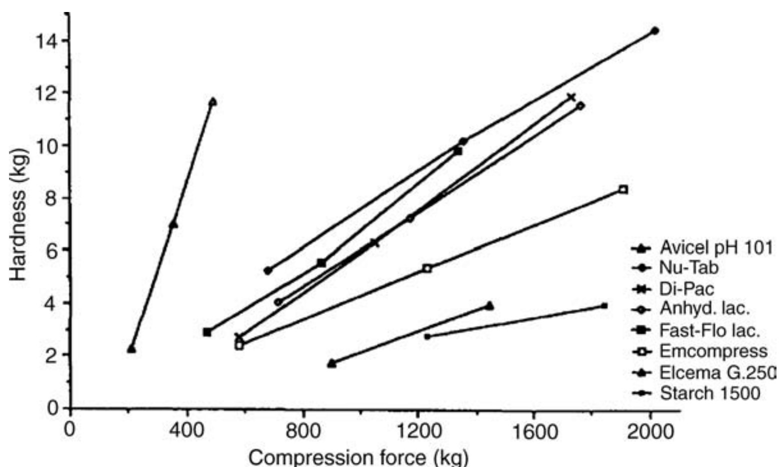

FIGURE 3 Excipient compressibility with 2% stearic acid as lubricant.

It might be expected that compactability properties would be additive (i.e., that a mixture of MCC and spray-dried lactose would have a compactability profile of some proportionate value between those of the individual ingredients). For instance, Lerk et al. (37) showed an additive effect between most lactose fillers when they were combined with other lactoses or MCC. However, an antagonistic behavior was demonstrated by blends of fast-dissolving vehicles such as dextrose or sucrose with cellulose or starch products. For instance, almost all combinations of MCC and compressible dextrose gave poorer compactability profiles and longer disintegration times than either ingredient alone. Bavitz and Schwartz (4) showed essentially additive effects in hardness when blending fillers, but their work did not include either sucrose or dextrose.

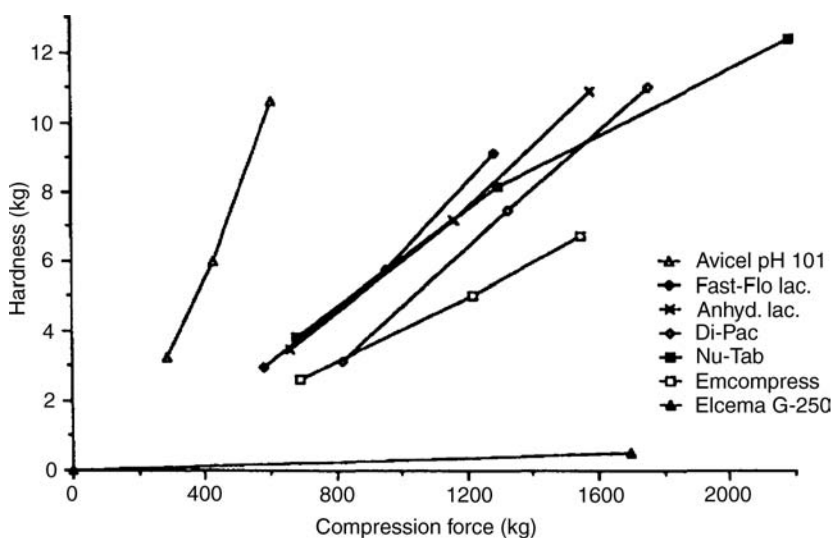

FIGURE 4 Excipient compressibility with 0.75% magnesium stearate as lubricant.

DC blends with marginal compactability may benefit from precompression or use of large compression rolls. There is no a priori reason why DC formulations should be less compactible than wet granulation formulation, especially if the DC formulation contains a significant quantity of MCC. Obviously, this depends to a great extent on the materials used. Katdare and Bavitz (33) demonstrated superiority of a DC norfloxacin tablet in terms of compactability, disintegration, and dissolution compared to a corresponding wet granulation tablet.

Flow

No flow, no tablets! Rotary tableting machines require the compression mix to flow from the hopper, with or without engineering assistance, into the die. Poor flow, if not prohibitive, will cause higher tablet weight variability, the problem getting worse as the speed of tableting increases. As one of the reasons for granulation is to improve flow, DC formulations are generally not as free flowing. DC grade excipients are essential as flow is intrinsic to the combination of materials unlike granulation, where it is a function of the particle engineering. A comparison of the bulk densities and particle size of some of the most common DC fillers can be found in Table 4.

TABLE 4 Physical Specifications of Direct-Compression Fillers

Filler	Moisture (%)	Bulk density (loose) ($g\ ml^{-1}$)	Particle size[b]
Spray-dried lactose Foremost	5.0[a]	0.68	100% through 30 (595 μm) 30–60% on 140 (105 μm) 15–50% through 200 (74 μm)
Fast-Flo® lactose	5.0[a]	0.70	0.5–1.5% on 60 (250 μm) 25–65% on 140 (105 μm) 15–45% through 200 (74 μm)
Anhydrous lactose	0.25–0.5	–	16% on 60 (250 μm) 65% between 60–200 (74–250 μm) 20% through 200 (74 μm)
Emdex®	7.8–9.2	0.64	1% on 20 (841 μm) 20% max. through 100 (149 μm)
Di-Pac®	0.4–0.75	0.58	3% max. on 40 (400 μm) 75% min. on 100 (149 μm) 5% max. through 100 (149 μm)
Nu-Tab®	<1	0.70	50% min. on 60 (250 μm) 10% max. through 120 (125 μm)
Microcrystalline cellulose			
Avicel® PH 101	<5	0.32	1% max. on 60 (250 μm) 7% through 200 (74 μm)
Avicel® PH 102	<5	0.34	8% max. on 60 (250 μm) 45% on 200 (74 μm)
Starch 1500®	12	0.62	0% on 8 (2380 μm) 0.5% max. on 40 (400 μm) 90% through 100 (149 μm)
Emcompress®	0.5	0.91	5% max. on 40 (400 μm) 15% max. through 200 (74 μm)

[a]Contains 4.5% water of hydration.
[b]Mesh size of screen.

Flow specifications are required for all major components (including API). Flow problems associated with minor components can be diluted out with DC grade excipients. However with high loadings of poor flowing API a glidant may be required, such as fine silica (Aerosil®, CaboSil®, Syloid®) at levels of 0.1–0.2%. At higher levels of glidant flow can decrease and tablet weight variation increase (2). However higher concentrations of silica may also be beneficial in terms of reducing segregation, punch filming, and picking problems. Segregation and flow are inversely related. No flow, no segregation.

Most DC grade filler-binders are designed for flow, which is generally particle size dependent. On a gravimetric basis MCC and Starch 1500 have lower mass flow rates compared to DCP but when allowance is made for their lower density it can be seen that their volumetric flow is comparable to that of DCP (75). The filling of a die is volumetrically controlled.

The trend towards higher tablet machine output has necessitated the development of more sophisticated feeders because in older designs the dwell time of the die cavity in contact with the feeder was not adequate to allow uniform filling. Usually rotary feeder paddles are used, which move the powder in the feed frame, ensuring a higher bulk density above the open die, which in effect force-feeds the material into the die. The interaction of material and engineering effects may confound the flow properties of the compression mix. Li et al. (41) got the poorer flowing 50 µm Avicel® PH101 to outperform the better flowing 90-µm Avicel PH102 in terms of die fill/tablet weight, simply by reducing the number of dies from 16 to 4, resulting in congestion in the feed frame. However, mechanically mixing material on the feed frame may increase the adverse effect of lubricants since the effect is to essentially extend the blending time of the lubricated mix.

Content Uniformity

Flow is required for segregation to occur. It is not always possible to avoid the large differences in particle size and density which can theoretically lead to segregation of non-interacting materials. However most materials interact, and together with the appropriate morphology it is possible to achieve physically stable ordered mixes, notwithstanding size or density differences. The irregular morphology of MCC makes it difficult for higher density particles to sift down through the spaces between the blend of materials. Major problems with segregation can occur with large spheroidal fillers, such as compressible dextrose (Emdex®). The irregular morphology of MCC also facilitates the interaction with micronized API. Preblending of micronized API with large-particle filler was recommended by Ho et al. (27), who achieved physically stable mixes of micronized sulfaphenazole with coarse DC tablet fillers. They hypothesized that blending of API and filler particles first rather than simply blending all materials at once, maximized surface attraction of drug particles to filler. Staniforth (60,61) and Verraes and Kinget (69) have emphasized the importance of ordered mixing to DC.

Lubrication

Lubrication has always been one of the most misunderstood aspects of formulation. Most formulators, aware of the adverse effects of magnesium stearate, seek to minimize the level used during development, thereby predisposing their formulations to sticking and picking problems during prolonged running on subsequent scale-up. The issue is most significant for DC filler-binders with plastic or low-fracture propensities.

The effect of lubricant mix time on the properties of DC tablets was studied by Shah and Mlodozeniec (54), who found that ejection force, hardness, disintegration, and

dissolution of lactose and MCC tablets were all adversely affected, depending on mix time. The type of blender may also be significant, especially when scaling up from laboratory to production equipment, when the decrease in crushing strength of tablets was much faster for the large industrial mixers than for the laboratory blenders (6).

DC BINDERS AND FILLERS

DC excipients, particularly filler-binders, are specialty excipients. In most cases they are common materials that have been physically modified during manufacturing to impart to them greater flow and compactability. The physical properties of these specialty products are extremely important if they are to perform optimally.

Many factors influence the choice of the optimum DC filler to be used in a tablet formulation. These factors vary from primary properties of powders (particle size, shape, bulk density, solubility) to characteristics needed for making compacts (flowability and compactability) to factors affecting stability (moisture), to cost, availability, and governmental acceptability. It is extremely important that raw material specifications be set up that reflect many of these properties if batch-to-batch manufacturing uniformity is to be assured. This is particularly true in the case of the filler-binders because they often make up the majority of the tablet weight and volume. However, this fact is still not fully appreciated by pharmaceutical formulators and production personnel. A list of factors involved in the choice of a filler-binder can be found in Table 5.

Nearly all of the classic tablet fillers have been modified in one way or another to provide flow and compactability. Scanning electron microscopy usually shows that the products do not consist of individual crystals. For many common DC fillers, such as lactose or mannitol, pure crystals are generally inferior in terms of compactability and flow. Most DC filler materials are aggregates (usually spray dried) with varying proportions of amorphous materials and or other components.

Hess (26) used scanning electron micrography to show the effect of compaction force and disintegrating agents on excipient and tablet morphology. Shangraw et al. (55–57) made extensive use of scanning electron micrographs (SEM) for the characterization of DC excipients related to their properties. SEMs are provided in most monographs of the *Handbook of Pharmaceutical Excipients* (1).

As seen in Figures 5 and 6, the spray drying of lactose results in agglomerates of small α-monohydrate crystals held together by amorphous glass. These agglomerates have superior flow and compactability compared to the constituent crystals.

The co-crystallization of sucrose with modified dextrins similarly renders the poorly compactible sucrose crystals highly deformable and free flowing (Figs. 7 and 8).

Fibrous cellulose could not be used as a tableting agent until mechanically aggregated, which improved flow but not compactability (Fig. 9). However, spray drying of the acid hydrolyzate gave free-flowing powder with unprecedented compactability, MCC, that revolutionized DC tableting (Fig. 10). MCC not only forms extremely hard compacts, but improves the compactability of other materials at levels as low as 5–10%.

SEMs of unmilled DCP show the aggregates of crystallites that shatter upon compaction to give tablet strength (Fig. 11). The agglomeration of starch with partially hydrolyzed starch to form a free-flowing compressible granulation can be seen in Figure 12.

MCC is the only high efficiency DC binder but DC fillers can be categorized by solubility and disintegration. Soluble binders, such as sugars or polyhydric alcohols, are

TABLE 5 Factors Influencing Choice of DC Filler-Binders

Factor	Considerations
Compactability	Alone Dilution factor or capacity Effect of lubricants, glidants, disintegrants Effect of reworking
Flowability	Alone In the finished formulation Need for glidant
Particle size and distribution	Effect on flowability Effect on compactability Effect on blending and ordered mixing Dust problems
Moisture content and type	Water of hydration (lactose, dextrose, DCP) Bound and free moisture Availability for chemical degradation Effect on compactability Hygroscopicity
Bulk density	Effect on flow and compactability Effect on handling and blending
Compatibility with active ingredient	Moisture pH Reducing sugar Effect on assay
Solubility (in GI tract)	Rate of dissolution Effect of pH
Stability of finished tablets	Color Volume Hardness
Physiological acceptability	Toxicity Osmotic effect Taste and mouth-feel (if appropriate)
Cost and availability	Cost in use Commercial availability Security of supply
Regulatory acceptability	Precedence of use Pharmacopoeial status (NF, Ph Eur, JPE) GRAS status

Abbreviations: DC, Direct compression; DCP, Dibasic calcium phosphate.

non-disintegrating but insoluble binders may be either disintegrating (MCC, starch) or non-disintegrating (DCP).

The perception that soluble filler is always required for rapid release from tablets was disproved by Hwang et al. who demonstrated faster release from disintegrating insoluble MCC tablets relative to a corresponding lactose formula (31). A disintegrating burst will generally outperform slow erosion/dissolution.

MCC

MCC is produced via hydrolysis of cellulose, the most abundant natural polymer on earth with an annual biomass production of 50 billion tons (9).

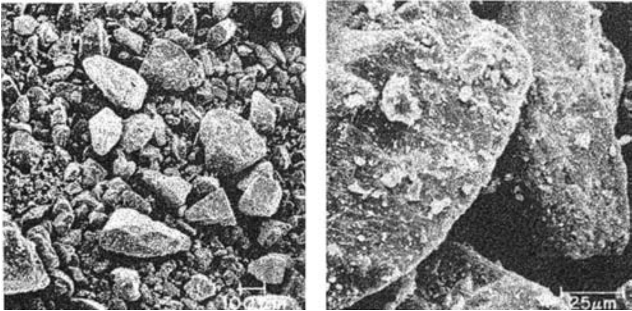

FIGURE 5 Crystalline lactose, N.F. (non-sprayed–dried).

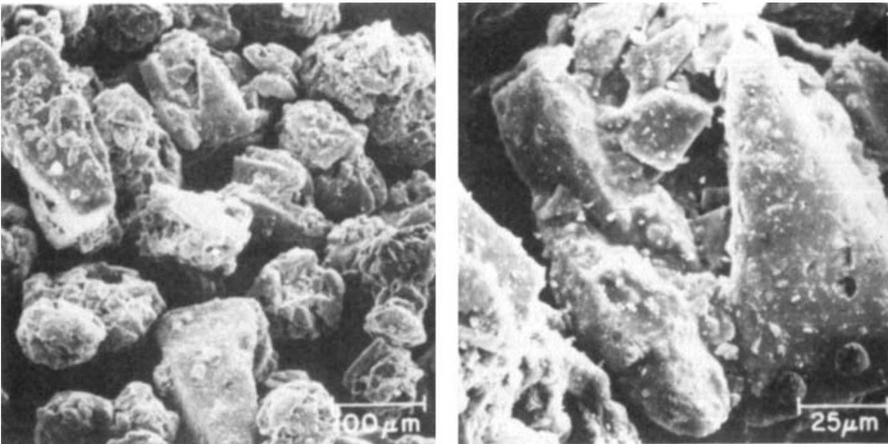

FIGURE 6 Lactose, N.F. Spray-dried (Fast-Flo).

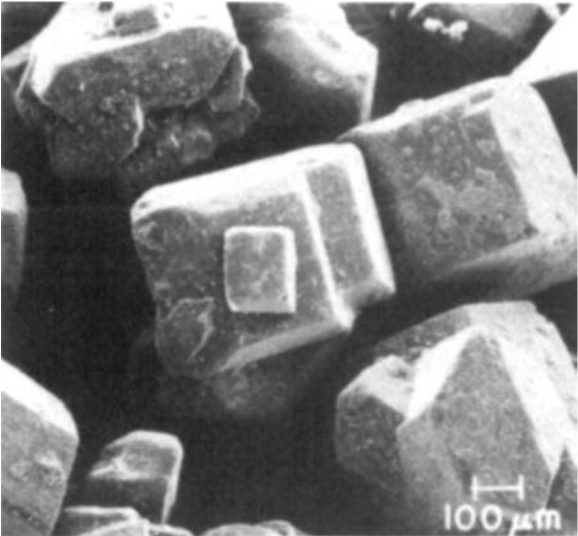

FIGURE 7 Sucrose, N.F. (crystalline).

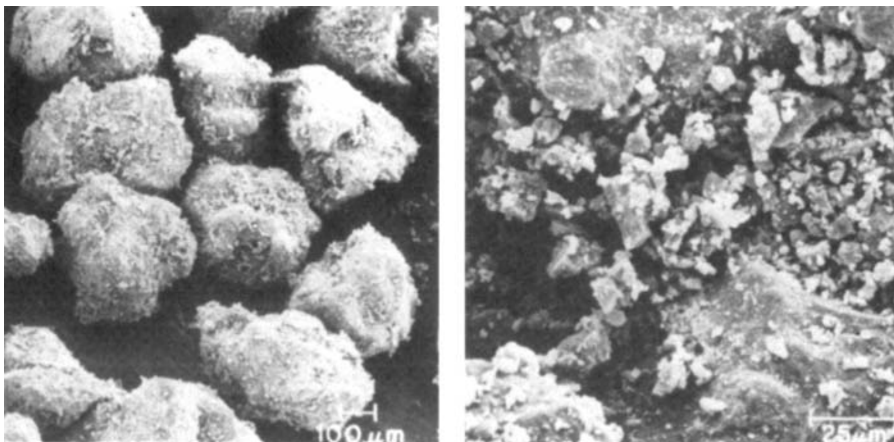

FIGURE 8 Compressible sugar, N.F. (Di-Pac).

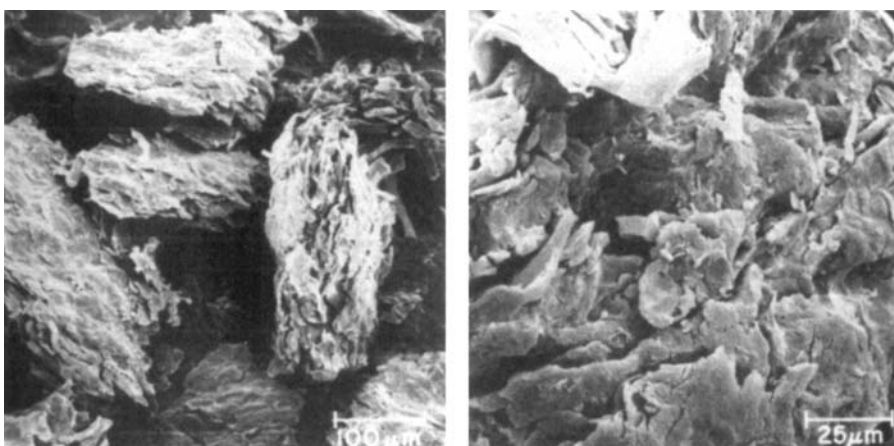

FIGURE 9 Powdered cellulose, N.F. (Elcema 250).

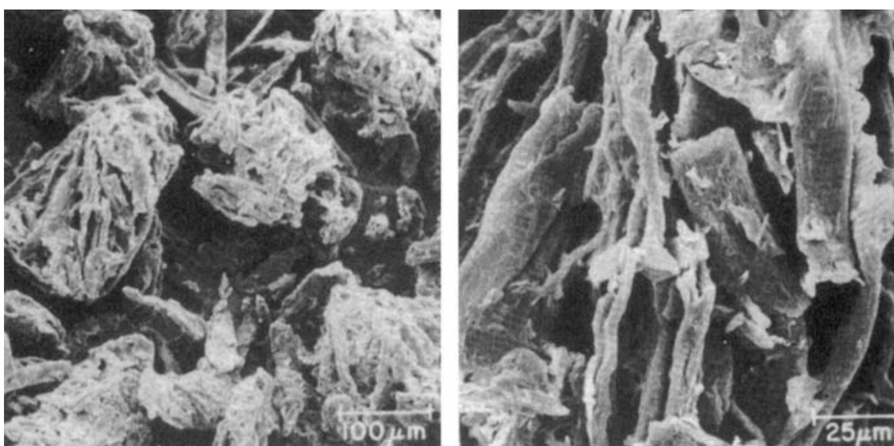

FIGURE 10 Microstalline cellulose, N.F. (Avicel pH102).

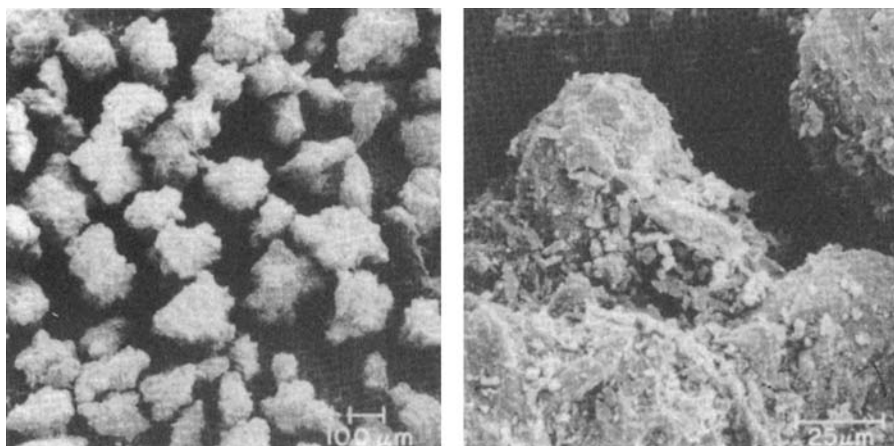

FIGURE 11 Dibasic calcium phosphate, USP Unmilled (Di-Tab, Emcompress).

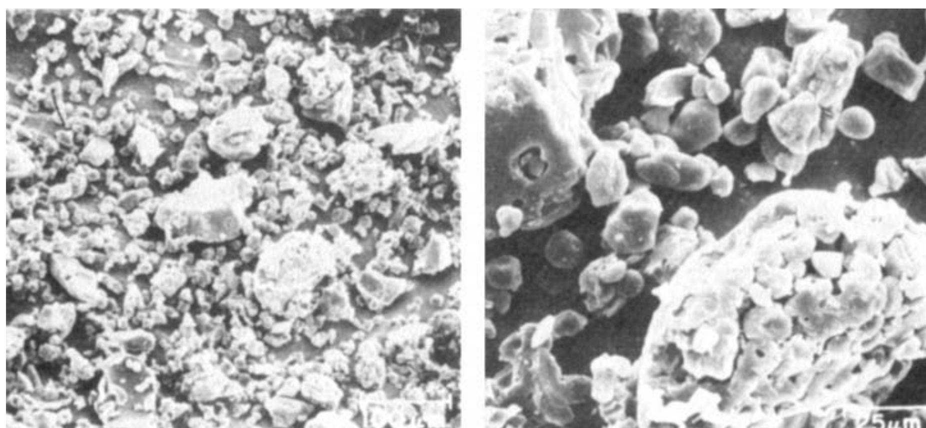

FIGURE 12 Pregelatinized starch N.F. Compressible (Starch 1500).

Cellulose consists of linear chains of β(l-4)-Iinked -D glucopyranosyl units (35). The degree of polymerization (DP) for cellulose isolated from wood, which is the source for pharmaceutical MCC, varies and can be as high as 9000 (28). In native cellulose the macromolecular chains are packed in layer held together mainly by strong hydrogen bonds (42). Natural cellulose has a fibrous structure and is typically semi-crystalline (43). The repeating dimer (cellobiose) unit is shown in Figure 13.

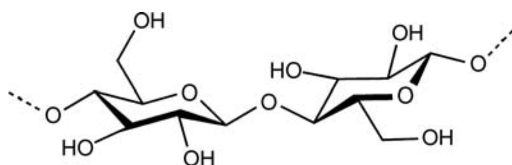

FIGURE 13 Cellobiose repeat dimer unit of cellulose.

Cellulose chains have regions which are relatively more crystalline or amorphous. The latter are more susceptible to hydrolysis so partial depolymerization (3) by hydrolysis results in shorter more crystalline fragments (MCC), the most important tablet excipient developed in modern times (18), with close to optimal DC tablet binder properties.

MCC is derived from purified high alpha wood pulps by acid hydrolysis under elevated temperature and pressure. This partial depolymerization removes the more amorphous portions of the cellulose, yielding particles consisting of bundles of needlelike microcrystals with a lower DP or number of glucose units. The rate of hydrolysis slows once a certain level-off DP (LODP) is reached. The LODP is a characteristic of a particular pulp. DP is used as an identity test, as Pharmacopoeial MCC is defined by a DP below 350 glucose units, compared to original native cellulose DPs in the order of 5–9000 units. DP has been proposed as a functionality related characteristic but DP values per se do not correlate with functionality. Powdered cellulose has a higher DP than MCC but is not as compactible, and there is little correlation of low DP (<350) with MCC compactability.

Dybowski (16) showed "that it is not the DP but the origin of the raw material and its production method that influence the characteristics of MCC…." "For the MCC manufacturer the DP is only a criterion used to help guide the hydrolysis process of MCC…. For the user DP remains mainly an identification test."

Schlieout et al. (53) claimed a correlation between DP and compactability based on two out of only three data points. There was no difference between MCC with DPs of 244 and 299 but both were more compactible than MCC with a DP of 190. This reflects the lack of distinction between LODP and non-level-off degrees of polymerization. The LODP is characteristic of a particular raw material, typically in the range 200–300 (14), and reflects the optimum operating range for hydrolysis of cellulose to form MCC. Above the LODP the MCC will retain more of the fibrous cellulose characteristics and may be more compactible but of lower bulk density and poorer flow. Below LODP the MCC will be less fibrous, denser, and less compactible. Therefore functionality is more related to the difference between a particular DP value and the LODP. However, variations in functionality due to excursions from LODP are indirectly controlled by bulk density specifications.

Schlieout et al. (53) also found that "crystallinity does not have a primary influence on the mechanical properties of the produced tablets." The wide range of reported values of degree of crystallinity for Avicel® PH (62.7–80.1%, 14) suggest little or no predictive value in using degree of crystallinity as a functionality related characteristic.

MCC has a very high intraparticle porosity with approximately 90–95% of the surface area being internal comparing geometric and adsorption surface areas (14).

MCC for DC tableting comes in a number of grades, the most widely used of which is PH 102, which is a partial spray-dried agglomerate with approximately twice the particle size of unagglomerated spray-dried MCC (PH101), resulting in better flow but with no significant decrease in surface area or compactability.

MCC is the most compactible of all the DC fillers and has the highest dilution potential. This can be explained by the nature of the microcrystalline particles themselves, which are held together by hydrogen bonds in the same way that a paper sheet or an ice cube is bonded (49). Hydrogen bonds between hydrogen groups on adjacent cellulose molecules account almost exclusively for the strength and cohesiveness of compacts. When compacted, the MCC particles are deformed plastically due to the presence of slip planes and dislocations on a microscale, and the deformation of the spray-dried agglomerates on a macroscale. A strong compact is formed due to the

extremely large area of clean surfaces brought in contact during the plastic deformation and the strength of the hydrogen bonds formed.

Other factors are important in the ability of a comparatively small amount of MCC to bind other materials during compaction, the low bulk density of the MCC, and the broad range of particle sizes. An excipient with a low bulk density will exhibit a high dilution potential on a weight basis, and the broad particle size range provides optimum packing density and coverage of other excipient materials. MCC has an extremely low coefficient of friction (both static and dynamic) and therefore has no lubricant requirements itself. However, when more than 20% of drugs or other excipients are added, lubrication is necessary. Because it is so compactible, MCC generally withstands lubricant addition without significant softening effects. However, when high concentrations (>0.75%) of the alkaline stearate lubricants are used, and blending time is long, the hardness of tablets compared to unlubricated MCC.

Comparisons with other DC fillers based on a weight per unit time flow through an orifice are misleading due to its inherently low-bulk density (75). A comparison of the relative volumetric and gravimetric flow rates of typical DC fillers can be seen in Table 6.

Tablets made from higher concentrations of MCC soften on exposure to high humidities due to moisture pickup and loosening of interparticulate hydrogen- bonds. This softening is often reversible when tablets are removed from the humid environment. Cycling of temperature and moisture over a period of time can cause both increases or decreases of equilibrium hardness, depending on the total formulation.

MCC is manufactured by spray drying the aqueous slurry resulting from the hydrolysis of cellulose. Most commercial grades are formed by manipulation of the spray drying process to control the degree of agglomeration (particle size) and moisture content. Higher density grades are also available by using different cellulose pulps, and particle sizes below 50 μm can be produced by milling the spray-dried MCC (Avicel PH105). The range of grades available is illustrated in Table 7. Most suppliers of MCC have adopted the nomenclature of Avicel PH, with the exception of Emcocel which is specified by μm particle size.

The spray dried crystallites of Avicel PH101 are shown in Figure 14, where there is little aggregation, and the nominal particle size is 50 μm.

As shown in Figures 15 and 16 there is an increase in agglomeration resulting in an increase in the nominal particle size to 100 μm (Avicel PH102) and 200 μm (Avicel PH200). The increasing particle size gives better flow whilst still maintaining the high

TABLE 6 Volumetric and Gravimetric Comparative Flow Rates of Selected DC Fillers

Filler-binder	Grade	Poured bulk density (g cm^{-3})	Gravimetric flow rate (kg min^{-3})	Volumetric flow rate (L min^{-3})
MCC	Avicel® PH102	0.314	1.300	4.140
Powdered cellulose	Elcema® G250	0.531	1.499	2.823
Pregelatinized starch	Starch 1500®	0.589	1.200	2.037
Hydrous lactose	Fast-Flo®	0.650	2.200	3.385
Compressible sugar	Di-Pac®	0.694	3.747	5.399
DCP	Di-Tab®	0.933	4.300	4.609

Abbreviations: MCC, Microcrystalline cellulose; DCP, Dibasic calcium phosphate.
Source: From Ref. 75.

TABLE 7 MCC Grades

Avicel PH	101	102	103	113	112	200	301	302	105
Particle size (μm)	50	90	50	50	90	180	50	90	20
Tap density (g/cc)	0.45	0.45	0.45	0.44	0.48	0.42	0.59	0.60	0.46
Moisture (%)	NMT 5.0	NMT 5.0	NMT 3.0	NMT 2.0	NMT 1.5	NMT 5.0	NMT 5.0	NMT 5.0	NMT 5.0

Abbreviation: MCC, Microcrystalline cellulose; NMT, Not more than.

surface area of the original 50 μm material. This porous morphology is ideal for ordered mixing of micronized drug with free-flowing large particle size MCC.

MCC milled to a nominal 20 μm (Avicel PH105) is shown in Figure 17. The reduction in particle size reduces the flowability but when added at low levels this grade provides additional compactability due to the higher surface area.

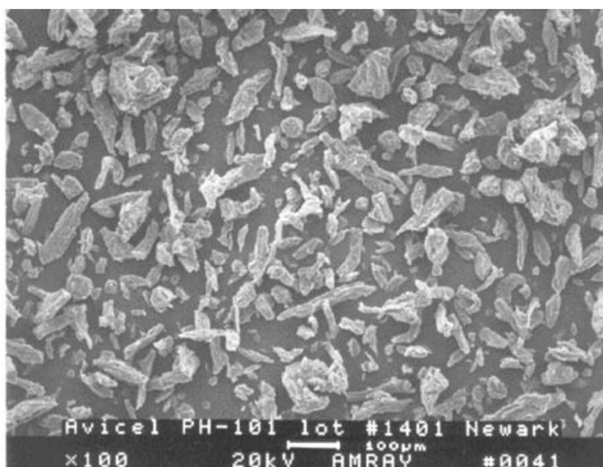

FIGURE 14 Scanning electron micrograph of 50 μm Avicel PH101.

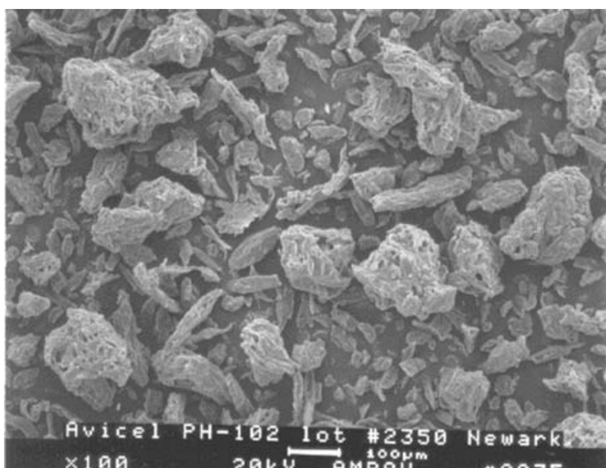

FIGURE 15 Scanning electron micrograph of 100 μm Avicel PH102.

FIGURE 16 Scanning electron micrograph of 200 µm Avicel PH200.

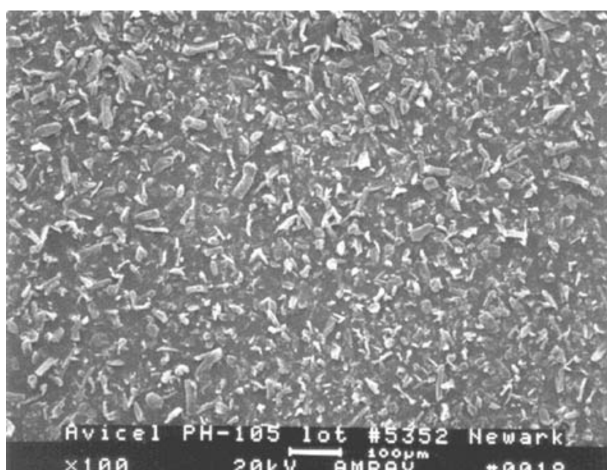

FIGURE 17 Scanning electron micrograph of 20 µm Avicel PH105.

There are a number of cellulose and MCC products, representing a continuum from cellulose floc to MCC. Personen and Paronen (48) compared the crystallinity, particle size, densities, flow, and binding properties of Emcocel and Avicel PH 101.

The most complete comparative evaluation of MCC products was conducted by Doelker et al. (13). They studied the tableting characteristics of NF grade MCC from seven manufacturers. The powders were examined for moisture content, particle size, densities, flow, and compactability. Significant differences in packing, compactability, and lubricant sensitivity were observed between products from various manufacturers. In contrast, lot-to-lot variability was much less. The functionality of MCC depended as much on physical form as it did on degree of crystallinity. Substitution of one product for another must be validated.

Another form of cellulose advocated for DC is microfine cellulose (Elcema). This material is a mechanically produced cellulose powder which also comes in a granular grade (G-250), the only form that possesses sufficient flow to be used in DC. Microfine cellulose is a compressible, self-disintegrating, antiadherent form of cellulose that can be made into hard compacts. However, unlike MCC, it has a low dilution potential, losing its

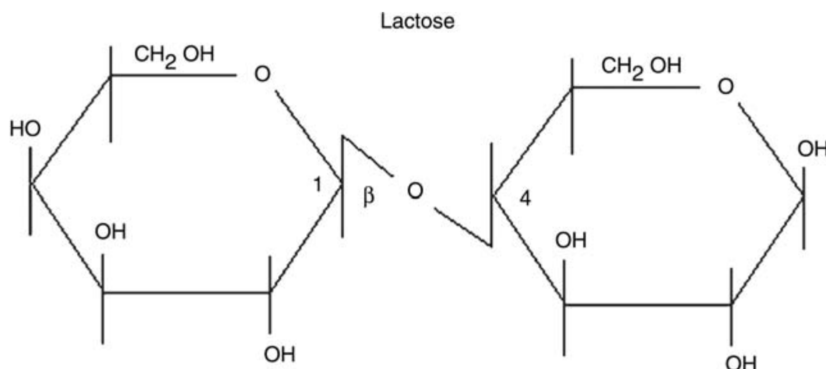

FIGURE 18 Disaccharide structure of lactose.

compactability rapidly at higher drug loadings. It is not a particularly effective dry binder due to the large particle size of the G-250 granules and the resistance to fracture under compression. Microfine cellulose forms few fresh or clean surfaces during compression because of the lack of slip planes and dislocations in the cellulose granules. Thus little interparticulate binding occurs, and surfaces contaminated by lubricant during mixing show little inclination to form firm compacts.

Lactose

Lactose, a disaccharide of galactose and glucose (Fig. 18), is a by-product of the dairy industry, isolated from cow's milk. Lactose has two anomers (stereo-isomers), α and β, differing only in the configuration of the hydroxyl group at the anomeric hemiacetal carbon. α has an axial hydroxyl whereas the β hydroxyl is equatorial. The β-isomer is obtained by crystallization above 93.5˚C as a non-hygroscopic anhydrous form (8). The α-isomer, obtained by crystallization at lower temperatures, forms a monohydrate, which can be dehydrated to yield a stable (non-hygroscopic) anhydrous form above 130˚C, or an unstable (hygroscopic) form at lower temperatures. Amorphous lactose is hygroscopic and will recrystallize in the presence of moisture (46).

In practice crystalline lactoses are not isomerically pure. The commercially available roller dried β-anhydrous lactose may have β-contents as low as 80% as exemplified in Table 8, adapted from Vromans (71,72) who quantified α/β ratios by gas chromatography of lactose trimethylsilyl derivatives.

Coarse (> 150 μm) crystalline α-lactose monohydrate has good flow properties but lacks compactability. The finer the particle size the better the compactability (11) but flow decreases. Tabletose® (Meggle) consists of free-flowing aggregates of α-lactose monohydrate without binder or amorphous lactose (65). Anhydrous α-lactose is approximately three times more compactible but has a similar particle size dependency

TABLE 8 α-lactose Content of Various Lactose Grades

	% α-lactose
α-lactose monohydrate	95
α-lactose anhydrous	80
Roller-dried β-lactose (anhydrous)	17
Crystalline β-lactose (anhydrous)	3

(71). Crystalline β (anhydrous) lactose has a similar compactability to α-lactose monohydrate but the roller dried β-lactose of commerce is similar to anhydrous α-lactose, due to the lower β content and more irregular morphology (73).

Anhydrous lactose can be reworked with less loss of compactabiity than occurs with other forms of lactose. At high relative humidities anhydrous lactose will pick up moisture, forming the hydrate. This may cause an increase in tablet size at high lactose loadings. At 45˚C/70%RH tablets of anhydrous lactose will increase in size by as much as 15%. The free surface moisture of anhydrous lactose is similar to that of the hydrate (0.5%). The intrinsic dissolution rate of anhydrous (β) lactose is faster than that of α-lactose monohydrate. Amorphous lactose is also more compactible but is only encountered as a component of spray-dried lactose.

Spray-dried lactose (SDL) is the earliest and still one of the most widely used DC fillers. Spray drying produces an agglomerated product that has better flow and is more compactible than regular lactose (45). Partial crystallization is allowed to occur and the resulting slurry is then spray-dried. The final product contains a mixture of α-monohydrate crystals and amorphous material. The finer the α-monohydrate crystals the better the compactability. The effect of the amorphous content depends on the moisture content. At 2% amorphous water content compactability decreased from a maximum (at 30% amorphous) at higher amorphous contents, but at 6% water, compactability was proportional to amorphous content (74). Fast-Flo® lactose has a higher amorphous content than regular SDL (30).

Although the compactability of SDL is slightly better than crystalline lactose, it is still borderline and SDL has relatively poor dilution potential. SDL is an effective DC filler at high loadings (> 80%), but it is not effective in diluting high-dose poorly compactible APIs. SDL has excellent flow, among the best for all DC fillers, due to the large particle size and sphericity of the spray-dried aggregates. It contains approximately 5% moisture, but most of this is water of crystallization, with less than 0.5% free surface moisture. It is relatively nonhygroscopic. Spray-dried lactose is available from a number of commercial sources in a number of forms (47). Because the processing conditions used by different manufacturers may vary, all spray-dried lactoses do not necessarily have the same properties.

Although it exhibits brittle fracture, lactose is lubricant sensitive due to its low fragmentation propensity, its more plastic amorphous content, small crystal size, and higher bulk densities. A low fragmentation propensity means that fragmentation occurs too late in the compaction process (after particle rearrangement) to allow mixing of fragments with fresh surfaces to ameliorate the adverse effects of lubricant films (66). There is an inverse correlation between lubricant sensitivity and bulk density for α (anhydrous or monohydrate) and β (anhydrous) (74). The critical particle size for lactose above which brittle fracture occurs is 45 μm, and below this size the behavior will be plastic (50).

Lactose is a reducing sugar due to the ability of the glucose unit to tautomerize between a ring hemiacetal and an open chain aldehyde, the reactive moiety, as shown in Figure 19. The aldehyde group can react with the amine groups common to many drug

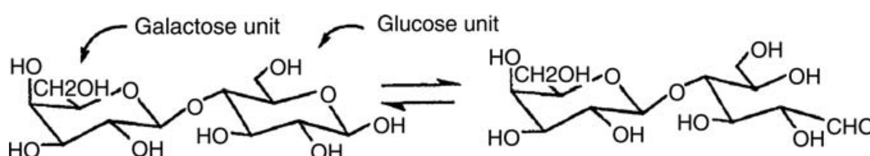

FIGURE 19 Lactose tautomerism between ring and open (reducing) chain.

substances, causing degradation of the API and yellowing or browning of the tablet on storage. This is the Maillard reaction and is a common contraindication to formulating amine-containing drugs with lactose.

INORGANIC CALCIUM SALTS

The most widely used inorganic DC filler is unmilled dicalcium phosphate (DCP, calcium monohydrogen phosphate), which consists of free-flowing aggregates of small micro-crystals that shatter upon compaction. This material is available in a tableting grade under the names Emcompress® or DiTab. DCP is relatively inexpensive and possesses a high degree of physical and chemical stability. It is nonhygroscopic at a relative humidity of up to 80%. DCP in its directly compactible form exists as a dihydrate. Although this hydrate is stable at room and body temperature, it will begin to lose small amounts of moisture when exposed to temperatures of 40–60˚C (63). This loss is more likely to occur in a humid environment than a dry environment. This anomaly is thought to occur because at low humidities and high temperatures the outer surfaces of the particles lose water of hydration and become case-hardened, preventing further loss. In a humid environment the loss continues to occur. When combined with hygroscopic filler like MCC, the loss of moisture may be sufficient to cause a softening of the tablet matrix due to weakening of the interparticulate bonds and to accelerate decomposition of moisture-sensitive drugs like vitamin A.

The flow of DCP is good, and glidants are generally not necessary. While it is not as compactible as MCC and some sugars (Fast-Flo lactose, Emdex), it is more compactible than spray-dried lactose and compressible starch. It deforms by brittle fracture when compressed, forming clean bonding surfaces and is therefore relatively lubricant insensitive. Because DCP is insoluble and forms non-disintegrating tablets it is not recommended for use at high levels with poorly soluble APIs. It does dissolve in acid but it is practically insoluble in neutral or alkaline media.

DCP dihydrate is slightly alkaline with a pH of 7.0–7.3. Tricalcium phosphate (TriTab) is less compactible and less soluble than DCP but contains a higher ratio of calcium ions (29). Calcium sulfate, dihydrate NF is also available in DC forms (Delaflo, Compactrol).

Cel-O-Cal is a co-spray dried 30:70 MCC:anhydrous calcium sulfate, which is more compactible than the corresponding physical blend.

Calcium carbonate has been used as a tablet filler, as opposed to therapeutic use as an antacid. For nutritional supplements it is a dual filler and calcium source. It is available in a number of directly compressible forms, and sources include precipitation, ground Oyster shells, and mined limestone. These differ in terms of whiteness, particle size, and impurities. Calcium carbonate has been coprocessed with various binders to make it directly compressible. Calcium carbonate is soluble in acid.

Starch

Native starch does not possess the two properties necessary for making good compacts, compactability, and flow. There have been many attempts to modify starch to improve its binding and flow properties. The only modification of starch that has received widespread acceptance in DC is Starch 1500. Starch 1500 is more fluid than regular starch and meets the specifications for pregelatinized starch, N.F. Starch 1500 consists of intact starch grains and ruptured starch grains that have been partially hydrolyzed and subsequently

agglomerated (59). It has an extremely high moisture content (12–13%), but there is little indication that this moisture is readily available to accelerate the decomposition of moisture-sensitive drugs (44).

Although neat Starch 1500 can be easily compacted, it does not form hard compacts. Its dilution potential is minimal, and it is not generally used as a DC binder, but as a DC filler disintegrant. The major advantage of Starch 1500 is that it retains the disintegrant properties of starch without decreasing the flow and compactability of the formulation, unlike native starch. Because Starch 1500, like all starches, deforms elastically it imparts little strength to compacts. As few clean surfaces are formed during compaction, it is lubricant sensitive, particularly with the alkaline stearate lubricants. Lubricants such as stearic acid or hydrogenated vegetable oils are preferred in such formulations.

Sugars and Sugar Alcohols

Sucrose: Sucrose has been extensively used in tablets as a filler, usually in the form of confectioners sugar. Pure DC grade sucrose crystals are not available, but various modified sucroses are used for DC, such as Di-Pac®, which is co-crystallized sucrose with 3% modified dextrins (21). Each Di-Pac granule consists of hundreds of small sucrose crystals "glued" together by the dextrin. Di-Pac has good flow properties and needs a glidant only above 50% relative humidity. It has excellent color stability on aging, probably the best of all the sugars. Moisture content can affect compactability, which increases rapidly at 0.3–0.4%, plateaus at 0.4–0.5%, and rises again rapidly up to 0.8% when the product begins to cake and lose flow (62). The moisture-compactability profile of Di-Pac is related to formation of mono- and multi-molecular layers of moisture on both the internal and external surfaces of the sucrose granules—a process that increases hydrogen bonding on compaction. The dilution potential of Di-Pac and most other sucroses is moderate, ranging from 20% to 35%. While a moisture concentration of 0.4% is probably optimal for most pharmaceuticals, material of high moisture content is extremely advantageous when making troches or candy tablets. Interestingly, as moisture levels increase, lubricant requirements decrease.

Tablets containing high concentrations of Di-Pac tend to harden slightly within hours of compaction, or when aged at high humidities and then dried. This is typical of most DC sucroses or dextroses.

Modified DC sucrose products are used primarily for chewable tablets. The process for making co-crystallized DC sucrose products and their properties are described by Rizzuto et al. (50).

NuTab is a DC sucrose with 4% invert sugar and 0.1–0.2% each of cornstarch and magnesium stearate (20). The latter two ingredients are process aids for the granulation rather than tableting disintegrant or lubricant. NuTab has a relatively large particle size distribution which makes for good flow but could cause blending problems if cofillers and drugs are not carefully controlled relative to particle size and amounts. In formulations NuTab has poor color stability relative to other DC sucrose and lactose grades.

Dextrose: Emdex spray-crystallized dextrose contains 3–5% maltose, and a small amount of glucose oligomers (5). It is available as both an anhydrous and a hydrous product (9% moisture). The anhydrous form is slightly more compactible than the monohydrate; but both are highly compactible, being second only to MCC when not diluted with drugs or other excipients. The most widely used product is the monhydrate

and the water of hydration does not appear to affect drug stability. At approximately 75% relative humidity Emdex becomes quite hygroscopic, particularly, if sheared on the table machine die table. Above 80% relative humidity the product may liquefy. Tablets produced from Emdex show hardening in the first few hours but little change thereafter on long-term ambient storage.

Emdex possesses the largest particle size of all the common DC excipients. Content uniformity problems can be reduced with blends of other smaller particle size excipients, but the morphology of Emdex lends itself to ordered mixing, where micronized drug can physically lodge in the pores and on the surface of the larger excipient particles.

Sorbitol

Sorbitol has several polymorphs as well as an amorphous form, which can affect compactability and stability. In the presence of moisture the less stable α and β polymorphs may convert to the more stable dendritic γ form, which may cause powder caking. Sorbitol 834 and NeoSorb 60 are mainly γ, but not all γ-sorbitols are crystallized in the same way and thus may have different compactibilities and lubricant requirements. Substitution of DC sorbitols should be validated. The effect of sorbitol crystalline structure on tableting properties was described by DuRoss (15). Ascorbic acid and γ-sorbitol tablets were evaluated by Guyot-Hermann and Leblanc (23).

Sorbitol is widely used in "sugar-free" mints and in chewable tablets. It forms a relatively hard compact, has a cool taste and good mouth-feel. However, it is hygroscopic and will clump in the feed frame and stick to the surfaces of the die table when tableted at humidities greater than 50%. Lubricant requirements increase when the moisture content of the sorbitol drops below 0.5% or exceeds 2%.

Mannitol

Mannitol does not make as hard a tablet as sorbitol but is non-hygroscopic. Mannitol is widely used in the DC of reagent tablets where rapid and complete solubility is required and can be lubricated for this purpose with micronized polyethylene glycol 6000. It is widely used as a filler in chewable tablets as it has a pleasant cooling mouth feel. The compactability of mannitol polymorphs was investigated by Debord et al. (12). Burger et al. (7) favored δ-mannitol due to lower elastic recovery and die wall friction, but surface area can also affect compactability and Yoshinari et al. (78) demonstrated superior compactability of a high surface area β-mannitol formed by conversion from δ-mannitol during wet granulation. The in situ polymorphic conversion had the benefit of maintaining the original coarse free-flowing particle size distribution with increased surface area due to needle-like microstructure of β on the particle surface, as opposed to the classic method of size reduction to increase surface area. A high surface area β-mannitol is commercially available as Parteck®. Most DC grades are β-mannitol (Pearlitol® DC, Mannogem®) or α (Pearlitol® SD).

Maltodextrin: A free-flowing agglomerated maltodextrin is available for DC under the name Maltrin®. The product is highly compactible, completely soluble, and has very low hygroscopicity.

Co-Processed Excipients

Most co-processing of DC excipients is directed at optimizing the balance of brittleness, ductility, and fragmentation propensity to maximize compactability and flow, whilst reducing lubricant sensitivity. Unfortunately nothing has superseded MCC and

MCC-containing co-processed DC excipients are generally inferior to MCC, but offering some superiority over the other starting material.

Plastic or ductile behavior, as found in MCC, is ideal for bonding. However, on deformation no fresh surfaces are formed, in contrast to brittle materials, and as a result plastic materials tend to be lubricant sensitive. In theory a balance of brittle and plastic should be complementary but in practice the inferior bonding of available brittle materials reduces the compactability of mixtures. DCP is brittle, relatively insensitive to lubricant, but much less compactible than MCC.

Nominally brittle materials may exhibit plastic behavior below a critical minimum particle size. Lactose behaves plastically below 46 μm and also has a low fragmentation propensity. The larger particles may not be brittle enough to fracture and will remain intact during particle rearrangement during compression. Fracture after rearrangement means that the fragments will remain together so the creation of fresh surfaces without distribution does not compensate for lubricant poisoning. Aggregates of plastic particles with a high fragmentation propensity may offer protection against lubricant coating of the aggregate, by forming fresh surfaces during rearrangement, in addition to improving flow.

Co-processing of MCC with colloidal silicon dioxide (Silicified MCC, Prosolv®) reduced the lubricant sensitivity and tendency to cap at high speeds but showed no extra contribution on tablet strength of lubricated tablets above that of physical mixtures (67).

A glossary of DC excipients, trade names, and suppliers can be found in Appendix 2 at the end of this chapter.

COPROCESSED ACTIVE INGREDIENTS

There is nothing less compactible or less rapidly soluble than a perfectly pure crystalline material, yet the emphasis in drug development is on producing the purest possible drug crystals. The formulator is then expected to take those crystals and improve compactability and dissolution by means of added excipients. Doping with known impurities or adding excipients to form directly compactible aggregates of microfine crystals is more logical. Some common drugs are available commercially as DC granulates.

Ascorbic acid has long been available in a number DC grades such as Roche ascorbic acid C-90 in which micronized ascorbic acid particles are granulated with starch paste. C-95 ascorbic acid utilizes methylcellulose as binder. Takeda Chemical Industries markets both a C-97 DC ascorbic acid and SA-99, a DC sodium ascorbate.

Acetaminophen generally occurs as large monoclinic crystals, a crystal form which is not easily deformed and resists compaction. A DC form of acetaminophen is available commercially from Mallinckrodt containing 90% acetaminophen and 10% of partially pregelatinized starch under the name COMPAP® (52). The spherical nature of the particles indicates that the material is prepared by spray drying; each particle is almost a perfect minigranule. Deformation can occur along any plane and multiple clean surfaces are formed during the compaction process. moreover, each granule consists of hundreds of small crystals with wetted surfaces which optimize dissolution. Tablets with rapid dissolution can be easily formed by the addition of small concentrations of AcDiSol® (2%) and lubricant (0.5% magnesium stearate). A self-lubricating version of this material is also available (COMPAP-L) as well as a combination of acetaminophen and codeine (Codacet-60).

Another DC acetaminophen is marketed by Monsanto under the name DC-90 (70). This product is prepared by fluidized bed granulation instead of spray drying. It has a compactability profile similar to that of COMPAP but is only available in the self-lubricating form. Both products exhibit rapid dissolution profiles when formulated with

effective disintegrant systems. The compactability of both materials can be enhanced by the addition of 10–20% MCC.

Mallinckrodt introduced a DC ibuprofen product under the name DCI. However, this product contains only 63% active ingredient and appears to be a classic granulation.

FUTURE OF DC TABLETING

Shangraw's prediction of a slow but increasing adoption of DC tableting by the pharmaceutical industry has been borne out so that approximately half of worldwide tablet production is now by DC (17).

DC (coprocessed) grades of some APIs are now available. The numerous coprocessed DC excipients that have been marketed have yet to supersede their component materials. Shangraw's observation still holds true that significant new filler-binders are unlikely because the basic building materials that are both chemically and physiologically acceptable have already been modified. The search still continues for DC binders that can mimic or exceed the properties of MCC and for an alternative to magnesium stearate.

Tablet development still requires a degree of skill and art, primarily due to the conflicting technological requirements and the uncertainty of the physics within the material under compaction, which thwarts simple correlation of input raw material properties with finished tablet properties, even for the simplest DC processes. Compaction simulators, process analytical technologies (PAT) and advanced computational techniques are being increasingly used to minimize this tableting black box® (24) but general or fundamental predictability remains elusive (36). Compaction simulators are becoming more common, not just within the major pharmaceutical companies but also among tableting excipient suppliers, in order to maintain consistency, assist tablet development and to troubleshoot problems.

Modern rotary machines are capable of production rates in excess of a million tablets per hour, which can be boosted, using multiple tools per die, to tens of million tablets per hour. Such outputs are rare due to the traditional small-volume batch-centered approach of the pharmaceutical industry, where regulatory and validation constraints discourage improvements and process evolution. The FDA 21st century cGMP initiative should facilitate continuous improvements and ultimately continuous production. This will favor the rise of dual DC/RC tableting where development and early commercial DC formulations can evolve with market demand into high volume roller compaction processes to support the demands of the high volume high speed tableting required for continuous production. material properties are currently more limiting than the equipment as illustrated by the novel centrifugally fed tablet machine (IMA), which, contrary to expectation, did not improve powder flow to the dies (10).

Enhancements to tableting technology include ultrasound during tableting to improve compactability (38–40) and the introduction of external lubrication systems on high speed rotary tablet machines.

PAT is a general term covering the application to drug manufacturing of process analytical chemistry tools, feedback process controls, information management and/or product/process optimization. Implementation could be by online measurement of quality and performance, together with multivariate statistical and pattern recognition methods. PAT attempts to drive intrinsic quality, non-parametric release, which is a challenge for tableting given the dependence on destructive test methods (disintegration, dissolution, and hardness) which do not lend themselves to online testing. Alternative non-destructive tablet hardness methods by NIR have been developed (34).

Alternative technologies exist which do not yet match current tableting technologies in terms of production output rates but which could be more attractive in the future if tablet development becomes rate-limiting, if drugs become too potent for content uniformity, or if the rise in peptides or biologics is not accompanied by commensurate developments in oral delivery. The newer technologies afford greater scope for validation and control and are relatively free from scale-up problems in that the few units produced for early clinical trials are identical to production units, scale-up in output being a matter of equipment multiplication.

Potential alternatives include the Sarnoff Delsys AccuDep® electrostatic deposition of API onto film, the Phoqus LeQtradose® electrostatic dry powder coating, Aprecia Three Dimensional Printing™ (76) and NRobe® from FMC. However, given the efficiency of production and consumer preference, high production rates and continuous production will continue to favor existing tableting technologies for the foreseeable future.

APPENDIX 1

The following tables are the examples of DC tablet formulae, which are adapted from FMC Problem Solver Vol. II.

Therapeutic Category: Cold/Sinus/Asthma

Active Ingredient/Dose: Chlorpheniramine maleate/4 mg & Pseudoephedrine HCI/60 mg

Formulation

Ingredient	Grade	Source	mg/tablet	Percent
Chlorpheniramine maleate	Powder	Gyma	4.0	1.82
Pseudoephedrine HCI	Powder	Ganes	60.0	27.27
Avicel PH	PH101	FMC	37.3	16.95
Lactose	Anhydrous	Kraftco	113.0	51.36
Ac-Di-Sol®	SD-711	FMC	2.2	1.00
Cab-O-SiI®	M-5	Cabot	1.1	0.50
Stearic acid	Triple pressed	Baker	1.3	0.59
Magnesium stearate	Fine powder	Witco	1.1	0.50
			220.0	100.00

Procedure

1. Screen Pseudoephedrine, Stearic acid, and Magnesium stearate through a 425 μm sieve.
2. Blend Chlorpheniramine, Pseudoephedrine, and Avicel PH in a V blender for 3 minutes.
3. Add Lactose, Ac-Di-Sol and Cab-O-SiI to blend from step 2 and blend for 17 minutes.
4. Add Stearic acid to blend from step 3 and blend for 3 minutes.
5. Add Magnesium stearate to blend from step 4 and blend for 5 minutes.
6. Tablet on Manesty Express 20 to a hardness of 5.3 kg using 5/16" standard concave punches.

Tablet Characteristics (Batch Size 30 kg)

Hardness	5.3 kg
Disintegration time	40 sec
Friability	0.41%
Thickness	4.7 mm
Average weight	221 mg
Standard deviation	50 mg
Coefficient of variation	21%

Therapeutic Category: Cold/Sinus/Asthma

Active Ingredient/Dose: Chlorpheniramine maleate/4 mg & Pseudoephedrine HCl/60 mg

Physical Stability: No color or odor change observed

	Room temperature			35°C			45°C		
Week	Hardness (kg)	Friability (%)	DT (sec)	Hardness (kg)	Friability (%)	DT (sec)	Hardness (kg)	Friability (%)	DT (sec)
Initial	5.3	0.41	49						
1				3.8	0.11	44	3.7	0.11	43
2	3.8	0.23	50	3.4	0.12	92	3.0	0.41	76
3							2.4	0.52	47
4	3.1	0.22	44	2.8	0.34	90	3.3	0.35	105
6				2.8	*0.12*	92			
8	3.3	0.36	42	3.6	0.69	87			
10				3.4	2.68	93			
12	3.4	0.39	44						
16	3.5	0.37	43						
20	3.4	0.38	44						
24	3.4	0.45	41						

Therapeutic Category: Cold/Sinus/Asthma

Active Ingredient/Dose: Theophylline/130 mg & Ephedrine sulfate/24 mg

Formulation

Ingredient	Grade	Source	mg/tablet	Percent
Theophylline	Anhydrous	Ganes	130.0	40.63
Ephedrine sulfate	Powder	Knoll	24.0	7.50
Avicel	PH-101	FMC	52.0	16.25
Lactose	Anhydrous	Kraftco	105.2	–32.87
Ac-Di-Sol	SD-711	FMC	3.2	1.00
Cab-O-Sil	M-5	Cabot	1.6	0.50
Stearic acid	Triple pressed	JT.Baker	2.4	0.75
Magnesium stearate	Fine powder	Witco	1.6	0.50
			320.0	100.00

Procedure

1. Screen Theophylline, Ephedrine, Stearic acid, and Magnesium stearate through a 425 μm sieve.
2. Blend Ephedrine, Avicel PH, and Ac-Di-Sol in a V blender for 3 minutes.
3. Add Theophylline to blend from step 2 and blend for 3 minutes.
4. Add Lactose and Cab-O-Sil to blend from step 3 and blend for 15 minutes.
5. Add Stearic acid to blend from step 4 and blend for 3 minutes.
6. Add Magnesium stearate to blend from step 5 and blend for 5 minutes.
7. Tablet on Manesty Express 20 using 3/8" flat bevel punches to a hardness of 7.0 kg using precompression equal to 25% final compression force.

Tablet Characteristics (Batch Size 40 kg)

Hardness	69 kg
Disintegration time	142 sec
Friability	0.17%
Thickness	38 mm
Average weight	319 mg
Standard deviation	23 mg
Coefficient of variation	0.71%

Therapeutic Category: Cold/Sinus/Asthma

Active Ingredient/Dose: Theophylline/130 mg & Ephedrine sulfate/24 mg

Physical Stability: No color or odor change observed

	Room temperature			35°C			45°C		
Week	Hardness (kg)	Friability (%)	DT (sec)	Hardness (kg)	Friability (%)	DT (sec)	Hardness (kg)	Friability (%)	DT (sec)
Initial	6.9	0.17	142						
1				5.6	0.66	200	6.4	0.62	191
2	5.4	0.32	183	6.8	0.97	162	5.6	0.65	149
3							6.1	0.32	134
4	6.1	0.31	114	5.7	0.33	170	5.2	0.33	241
6				5.9	0.19	188			
8	6.6	0.22	112	5.9	0.18	120			
10				5.8	0.17	140			
12	6.5	0.26	124	5.9	0.19	157			
16	6.3	0.24	138						
20	6.2	0.26	149						
24	6.1	0.32	10						

Therapeutic Category: Sleep/Calming

Active Ingredient/Dose: Diphenhydramine HCl/25 mg

Formulation

Ingredient	Grade	Source	mg/tablet	Percent
Diphenhydramine HCl	Powder	Ganes	25.00	10.00
Avicel PH	PH-1O1	FMC	50.00	20.00
Lactose	Anhydrous	Kraftco	170.50	68.20
Ac-Di-Sol	SD-711	FMC	2.50	1.00
Cab-O-Sil	M-5	Cabot	0.75	0.30
Stearic acid	Triple pressed	Baker	0.50	0.20
Magnesium stearate	Fine powder	Witco	0.75	0.30
			250.0	100.00

Procedure

1. Screen Diphenhydramine, Stearic acid, and Magnesium stearate through a 425 μm sieve.
2. Blend Diphenhydramine, Avicel PH, Ac-Di-Sol, and Cab-O-Sil in a V blender for 3 minutes.
3. Add Lactose to blend from step 2 and blend for 17 minutes.
4. Add Stearic acid to blend from step 3 and blend for 3 minutes.
5. Add Magnesium stearate to blend from step 4 and blend for 5 minutes.
6. Tablet on Manesty Express 20 using 3/8" flat bevel punches to a hardness of 50 kg using precompression equal to 12% final compression force.

Tablet Characteristics (Batch Size 36 kg)

Hardness	5.1 kg
Disintegration time	43 sec
Friability	0.20%
Thickness	3.0 mm
Average weight	251 mg
Standard deviation	17 mg
Coefficient of variation	0.7%

Therapeutic Category: Sleep/Calming

Active Ingredient/Dose: Diphenhydramine HCl/25 mg

Physical Stability: No color or odor change observed

	Room temperature			35˚C			45˚C		
Week	Hardness (kg)	Friability (%)	DT (sec)	Hardness (kg)	Friability (%)	DT (sec)	Hardness (kg)	Friability (%)	DT (sec)
Initial	5.1	0.20	43						
1				4.6	0.36	27	4.9	0.24	25
2	5.1	0.21	45				4.8	0.25	31
3							4.4	0.20	56
4	5.5	0.20	51	4.9	0.40	51	4.6	0.19	53
6				3.9	0.28	54			
8	4.9	0.24	50	4.8	0.24	39			
10									
12	5.3	0.26	25						
16	4.3	0.28	56						
20	4.5	0.44	25						
24	4.4	0.46	29						

Therapeutic Category: Sleep/Calming

Active Ingredient/Dose: Pyrilamine maleate 25 mg

Formulation

Ingredient	Grade	Source	mg/tablet	Percent
Pyrilamine maleate	Powder	Hexagon	25.00	12.50
Avicel PH	PH-101	FMC	34.00	17.00
Lactose	Anhydrous	Kraftco	136.80	68.40
Ac-Di-Sol	SD-711	FMC	2.00	1.00
Cab-O-Sil	M-5	Cabot	0.70	0.35
Stearic acid	Triple pressed	Baker	0.50	0.25
Magnesium stearate	Fine powder	Witco	1.00	0.50
			200.0	100.00

Procedure

1. Screen Pyrilamine, Stearic acid, and Magnesium stearate through a 425 μm sieve.
2. Blend Pyrilamine and Lactose in a V blender for 3 minutes.
3. Add Avicel PH, Ac-Di-Sol, and Cab-O-Sil to blend from step 2 and blend for 17 minutes.
4. Add Stearic acid to blend from step 3 and blend for 3 minutes.
5. Add Magnesium stearate to blend from step 4 and blend for 5 minutes.
6. Tablet on Manesty Express 20 using 5/16" standard concave punches to a hardness of 5.5 kg.

Tablet Characteristics (Batch Size 24 kg)

Hardness	5.5 kg
Disintegration time	95 sec
Friability	0.40%
Thickness	4.1 mm
Average weight	200 mg
Standard deviation	1 5 mg
Coefficient of variation	0.75%

Therapeutic Category: Sleep/Calming

Active Ingredient/Dose: Pyrilamine maleate 25 mg

Physical Stability: No color or odor change observed

	Room temperature			35˚C			45˚C		
Week	Hardness (kg)	Friability (%)	DT (sec)	Hardness (kg)	Friability (%)	DT (sec)	Hardness (kg)	Friability (%)	DT (sec)
Initial	5.5	0.40	95						
1				5.8	0.25	147	5.9	0.23	176
2	6.2	0.05	127	6.1	0.19	135	5.8	0.22	168
3							5.2	0.05	208
4	6.3	0.13	129	6.2	0.18	138	5.6	0.11	198
6				4.6	0.05	131			
8	6.1	0.21	158	5.6	0.21	147			
10									
12	5.4	0.23	113						
16	5.6	0.24	146						
20	4.6	0.25	149						
24	4.7	0.25	139						

Therapeutic Category: Antifatigue

Active Ingredient/Dose: Caffeine/150 mg

Formulation

Ingredient	Grade	Source	mg/tablet	Percent
Caffeine	Powder	Knoll	150.00	48.39
Avicel PH	PH-102	FMC	55.80	18.00
Lactose	Anhydrous	Kraftco	46.75	15.08
DiPac®	Granular	Amstar	50.00	16.13
Ac-Di-Sol	SD-711	FMC	3.10	1.00
Cab-O-Sil	M-5	Cabot	1.55	0.50
Stearic acid	Triple pressed	Baker	0.78	0.25
Magnesium stearate	Fine powder	Witco	0.78	0.25
Peppermint flavor	Powder.	Kohnstamm	1.24	0.40
			310.0	100.00

Procedure

1. Screen Caffeine, Stearic acid, and Magnesium stearate through a 425 μm sieve.
2. Blend Caffeine, Avicel, Lactose, DiPac, Ac-Di-Sol, Cab-O-Sil, and flavor in V blender for 20 minutes.
3. Add Stearic acid to blend from step 2 and blend for 5 minutes.
4. Add Magnesium stearate to blend from step 3 and blend for 5 minutes.
5. Tablet on Manesty Express 20 using 3/8” standard concave punches to a hardness of 7.0 kg using precompression equal to 33% of final compression force.

Tablet Characteristics (Batch Size 40 kg)

Hardness	6.5 kg
Disintegration time	97 sec
Friability	0.21%
Thickness	38 mm
Average weight	311 mg
Standard deviation	6 mg
Coefficient of variation	1 9%

Therapeutic Category: Antifatigue

Active Ingredient/Dose: Caffeine/150 mg

Physical Stability: No color or odor change observed

	Room temperature			35°C			45°C		
Week	Hardness (kg)	Friability (%)	DT (sec)	Hardness (kg)	Friability (%)	DT (sec)	Hardness (kg)	Friability (%)	DT (sec)
Initial	6.5	0.49	97						
1				5.5	0.16	110	7.8	0.24	95
2	6.3	0.16	87	6.0	0.12	125	8.7	0.16	85
3							6.9	0.17	95
4	7.5	0.13	99	5.9	0.09	126	5.2	0.21	99
6				5.5	0.25	103			
8	6.3	0.11	58	6.1	0.31	112			
10				6.4	0.16	74			
12	6.2	0.14	69						
16	6.1	0.13	72						
20	6.2	0.14	71						
24	6.0	0.21	71						

Therapeutic Category: Laxative

Active Ingredient/Dose: Yellow phenolphthalein/90 mg

Formulation

Ingredient	Grade	Source	mg/tablet	Percent
Yellow phenolphthalein	Fine powder	Hill	90.0	25.0
Avicel PH	PH-102	FMC	64.8	18.00
DCP	Unmilled	Stautfer	187.2	52.0
Ac-Di-Sol	SD-711	FMC	3.6	1.00
Cab-O-Sil	M-5	Cabot	3.6	1.00
Stearic acid	Triple pressed	Baker	7.2	2.00
Magnesium stearate	Fine powder	Witco	3.6	1.00
			360.0	100.00

Procedure

1. Screen Stearic acid and Magnesium stearate through a 425 μm sieve.
2. Blend phenolphthalein and Cab-O-Sil in a V blender for 3 minutes.
3. Add Avicel PH and Ac-Di-Sol to blend from step 2 and blend for 5 minutes.
4. Add DCP to blend from step 3 and blend for 12 minutes.
5. Add Stearic acid to blend from step 4 and blend for 3 minutes.
6. Add Magnesium stearate to blend from step 5 and blend for 5 minutes.
7. Tablet on Manesty Express 20 using 3/8" standard concave punches to a hardness of 10 kg.

Tablet Characteristics (Batch Size 46 kg)

Hardness	10 kg
Disintegration time	20 sec
Friability	0.1%
Thickness	3.45 mm
Average weight	360 mg
Standard deviation	3 mg
Coefficient of variation	1%

Therapeutic Category: Laxative

Active Ingredient/Dose: Yellow phenolphthalein/90 mg

Physical Stability No color or odor change observed

Week	Room temperature			35°C			45°C		
	Hardness (kg)	Friability (%)	DT (sec)	Hardness (kg)	Friability (%)	DT (sec)	Hardness (kg)	Friability (%)	DT (sec)
Initial	10.0	0.10	20						
1				10.9	0.11	22	11.5	0.14	25
2	10.6	0.11	21	9.4	0.29	24	9.4	0.43	25
3							10.4	0.09	35
4	8.9	0.28	21	10.2	0.11	27	11.1	0.18	19
6				9.0	0.28	25			
8	9.6	0.26	22	9.3	0.27	26			
10				7.8	0.36	25			
12	9.2	0.28	21	8.3	0.35	25			
16	9.3	0.31	23						
20	9.1	0.30	22						
24	9.2	0.32	21						

Therapeutic Category: Antidepressant

Active Ingredient/Dose: Amitriptyline HCl/10 mg

Formulation

Ingredient	Grade	Source	mg/tablet	Percent
Amitriptyline HCl	USP	Canes	10.00	9.09
Fast-Flo lactose	316	Foremost- McKesson	80.47	73.16
Avicel	PH-102	FMC	16.50	15.00
Ac-Di-Sol	SD711	FMC	2.20	2.00
Cab-O-Sil	M-5	Cabot	0.28	0.25
Magnesium stearate	NF	Whittaker, Clark, and Daniels	0.55	0.50
			110.0	100.00

Procedure

1. Screen Cab-O-Sil through a 850 μm sieve.
2. Screen Magnesium stearate through a 425 μm sieve.
3. Blend Amitriptyline, lactose, Avicel, Ac-Di-Sol, Cab-O-Sil in a twin shell blender for 5 minutes with intensifier bar and an additional 5 minutes without.
4. Add Magnesium stearate to blend from step 3 and blend for 5 minutes.
5. Tablet on Manesty Express 20 using 1/4" standard concave punches to a hardness of 7.0 kg.

Tablet Characteristics (Batch Size 27 kg)

Hardness	7.0 kg
Disintegration time	3.86 min
Friability	0%
Thickness	3.48 mm
Average weight	109.9 mg
Standard deviation	1.42 mg
Coefficient of variation	1.29%

Therapeutic Category: Antidepressant

Active Ingredient/Dose: Amitriptyline HCl/10 mg

Time (months)	Hardness (kg)	Thickness (mm)	Friability (%)	Disintegration time (min)
Initial	7.0	3.48	0.00	3.9
3 m RT	7.3	3.51	0.00	3.7
6 m RT	7.0	3.52	0.00	3.5
9 m RT	6.9	3.49	0.00	3.6
12 m RT	6.1	3.51	0.27	3.0
1 m 37˚C	6.9	3.48	0.00	3.3
2 m 37˚C	7.9	3.52	0.00	3.6
3 m 37˚C	7.7	3.52	0.05	3.3
1 m 45˚C	6.8	3.48	0.00	3.8

Therapeutic Category: Antidepressant

Active Ingredient/Dose: Amitriptyline HCl/25 mg

Formulation

Ingredient	Grade	Source	mg/tablet	Percent
Amitriptyline HCl	USP	Canes	25.00	22.73
Fast-Flo lactose	316	Foremost- McKesson	65.47	59.52
Avicel	PH-102	FMC	16.50	15.00
Ac-Di-Sol	SD711	FMC	2.20	2.00
Cab-O-Sil	M-5	Cabot	0.28	0.25
Magnesium stearate	NF	Whittaker, Clark, and Daniels	0.55	0.50
			110.0	100.00

Procedure

1. Screen Amitriptyline, lactose. and Magnesium stearate through a 425 μm sieve.
2. Blend Amitriptyline, lactose, Avicel, Ac-Di-Sol, and Cab-O-Sil in a twin shell blender for 5 minutes with intensifier bar and an additional 5 minutes without.
3. Add Magnesium stearate to blend from step 3 and blend for 5 minutes.
4. Tablet on Manesty Express 20 using 1/4" standard concave punches to a hardness of 7.0 kg.

Tablet Characteristics (Batch Size 27 kg)

Hardness	6.4 kg
Disintegration time	4.1 min
Friability	0%
Thickness	3.50 mm
Average weight	110.0 mg
Standard deviation	1.54 mg
Coefficient of variation	1.40%

Therapeutic Category: Antidepressant

Active Ingredient/Dose: Amitriptyline HCl/25 mg

Time (Months)	Hardness (kg)	Thickness (mm)	Friability (%)	Disintegration time (min)
Initial	6.4	3.50	0.0	4.10
3 m RT	7.3	3.50	0.0	5.27
6 m RT	7.9	3.48	0.0	5.08
9 m RT	7.4	3.48	0.0	4.92
12 m RT	7.6	3.48	0.05	5.03
1 m 37˚C	7.4	3.49	0.0	4.95
2 m 37˚C	7.9	3.45	0.0	5.45
3 m 37˚C	7.3	3.48	0.0	5.23
1 m 45˚C	7.2	3.9	0.0	5.03

Therapeutic Category: Diuretic, Antihypertensive

Active Ingredient/Dose: Furosemide/40 mg

Formulation

Ingredient	Grade	Source	mg/tablet	Percent
Furosemide	USP	ACIC	40.00	25.00
Avicel PH	PH-102	FMC	19.20	12.00
Ac-Di-Sol	SD 711	FMC	2.40	1.50
Fast-Flo lactose	316	Foremost- Mckesson	95.20	59.50
Cab-O-Sil	M-5	Cabot	0.80	0.50
Stearic acid	USP 3X	Baker	1.60	1.00
Magnesium stearate	NF	Whittaker Clark, and Daniels	0.80	0.50
			160.0	100.00

Procedure

1. Screen Cab-O-Sil through a 850 μm sieve.
2. Screen Stearic acid, and Magnesium stearate through a 425 μm sieve.
3. Blend Furosemide, lactose, and Avicel in a twin shell blender for 1 minute without intensifier bar, 0.5 minutes with and a further 15 minutes without.
4. Add Ac-Di-Sol and Cab-O-Sil to blend from step 3 and blend for 3 minutes.
5. Add Stearic acid to blend from step 4 and blend for 3 minutes.
6. Add Magnesium stearate to blend from step 5 and blend for 5 minutes.
7. Discharge via oscllating granulator with 425 μm screen.
8. Return to blender and mix for 5 minutes.
9. Tablet on Manesty Express 20 using 5/16" flat faced, beveled edge punches to a hardness of 6.0 kg.

Therapeutic Category: Diuretic, Antihypertensive

Active Ingredient/Dose: Furosemide/40 mg

Tablet Characteristics (Batch Size 27 kg)

Hardness	5.8 kg
Disintegration time	1.5 min
Friability	0.3%
Thickness	2.66 mm
Average weight	160.1 mg
Standard deviation	2.80 mg
Coefficient of variation	1.74%

Time (Months)	Hardness (kg)	Thickness (mm)	Friability (%)	Disintegration time (min)
Initial	5.8	2.66	0.30	1.4
3 m RT	6.4	2.65	0.16	2.0
6 m RT	4.8	2.64	0.25	1.8
9 m RT	5.4	2.66	0.23	1.6
12 m RT	5.8	2.64	0.25	1.2
1 m 37˚C	6.3	2.65	0.16	1.5
2 m 37˚C	6.1	2.65	0.19	1.5
3 m 37˚C	6.0	2.64	0.16	1.5
1 m 45˚C	6.3	2.64	0.09	1.8

Therapeutic Category: Minor Tranquilizer

Active Ingredient/Dose: Diazepam/5 mg

Formulation

Ingredient	Grade	Source	mg/tablet	Percent
Diazepam	USP	ACIC	5.00	2.94
Avicel MCC	PH-102	FMC	25.50	15.00
Fast-Flo lactose	316	Foremost- Mckesson	135.25	79.56
Ac-Di-Sol	NF	FMC	3.40	2.00
Magnesium stearate	NF	Whittaker, Clark, and Daniels	0.85	0.50
			170.0	100.00

Procedure

1. Screen all ingredients through a 425 µm sieve.
2. Premix diazepam with a roughly equal volume of Avicel.
3. Blend the diazepam premix, lactose, Avicel, and Ac-Di-Sol in a twin shell blender for 15 minutes.
4. Add Magnesium stearate to blend from step 3 and blend for 5 minutes.
5. Tablet on Manesty Express 20 using 5/16" flat faced, beveled edge lower bisect punches to a hardness of 7.0 kg.

Tablet Characteristics (Batch Size 33 kg)

Hardness	6.8 kg
Disintegration time	0.4 min
Friability	0%
Thickness	2.6 mm
Average weight	171 mg
Standard deviation	1.8 mg
Coefficient of variation	1.03%

Therapeutic Category: Minor Tranquilizer

Active Ingredient/Dose: Diazepam/5 mg

Time (Months)	Hardness (kg)	Thickness (mm)	Friability (% loss)	Disintegration time (min)
Initial	6.8	2.61	0.00	0.42
3 m RT	5.5	–	0.12	0.44
6 m RT	6.3	2.63	0.03	0.45
1 m 37°C	6.7	–	0.00	0.45
2 m 37°C	6.7		0.00	0.43
3 m 37°C	7.1	2.64	0.09	0.47
1 m 45°C	6.5	–	0.00	0.45

Therapeutic Category: Analgesic

Active Ingredient/Dose: Propoxyphene napsylate/100 mg, APAP/650 mg tablets

Formulation

Ingredient	Grade	Source	mg/tablet	Percent
90% Pregranulated APAP	—	Mallinckrodt/Monsanto	722.19	83.01
Propoxyphene napsylate	—	Ganes	100.00	11.49
Avicel PH	PH-102	FMC	34.77	4.00
Ac-Di-Sol	SD177	FMC	8.70	1.00
Cab-O-Sil	M-5	Cabot	1.30	0.15
Magnesium stearate	NF	Whittaker, Clark, and Daniels	3.04	0.35
			870.0	100.00

Procedure

1. Screen Propoxyphene and Magnesium stearate through a 425 μm sieve.
2. Screen Cab-O-Sil through a 850 μm sieve.
3. Blend APAP, Propoxyphene, Avicel, Ac-Di-Sol, and Cab-O-Sil in a twin shell blender for 15 minutes.
4. Add Magnesium stearate to blend from step 3 and blend for 5 minutes.
5. Compress on Manesty Express 20 to a hardness of 16 kg, with precompression equal to 33% final force, using capsule shaped (0.350" × 0.750" × 0.064" deep) punches.

Tablet Characteristics (Batch Size 172 kg)

Hardness	17.0 kg
Disintegration time	3.2 min
Friability	0.2%
Thickness	6.54 mm
Average weight	870 mg
Standard deviation	6.7 mg
Coefficient of variation	0.77%

Therapeutic Category: Analgesic

Active Ingredient/Dose: Propoxyphene napsylate/100 mg, APAP/650 mg tablets

Time (months)	Hardness (kg)	Thickness (mm)	Friability (%)	Disintegration Time (min)
Initial	17.0	6.54	0.21	3.2
3-m RT	17.0	6.52	0.21	3.3
6-m RT	>20.0	6.57	0.23	3.2
9-m RT	>20.0	6.56	0.27	3.2
12-m RT	>20.0	6.52	0.31	4.7
1-m 37°C	17.0	6.54	0.21	3.3
2-m 37°C	17.0	6.55	0.17	3.3
3-m 37°C	17.0	6.52	0.31	3.2
1-m 45°C	17.0	6.55	0.23	3.4

APPENDIX 2: DIRECTORY OF TRADE NAMES OF COMMON DC EXCIPIENTS

Trade name	Chemical name/description	Manufacturer
AcDiSol	Croscarmellose EP NF JPE	FMC Corporation, Philadelphia, PA 19103
Aerosil	Silicon Dioxide EP NF JPE	Degussa GmbH, D-60287 Frankfurt am Main, Germany
Arbocel	Powdered Cellulose EP NF JP	JRS PHARMA Gmbh, 73494 Rosenberg, Germany
A-Tab	DCP anhydrous NF	Innophos, Inc., Cranbury, NJ 08691
Avicel PH	Microcrystalline cellulose, EP NF JP	FMC Corporation, Philadelphia, PA 19103
Cab-O-Sil	Silicon Dioxide EP NF JPE	Cabot Corp, Tuscola, IL 61953
Solka Floc	Powdered Cellulose EP NF JPE	Int Fibre Corp, N Tonawanda, NY 14120
Compactrol	Calcium sulfate dihydrate NF	JRS PHARMA Gmbh, 73494 Rosenberg, Germany
Compritol 888 ATO	Glyceryl behenate EP NF JPE	Gattefossé, 92632 Gennevilliers, France
Di-Pac	Compressible sugar, N.F.	Domino Specialty Ingredients, Baltimore, MD 21230
Di-Tab	Calcium Hydrogen Phosphate Dihydrate, EP. Dibasic Calcium Phosphate, USP, Dihydrate	Innophos, Inc., Cranbury, NJ 08691
Elcema G-250	Powdered cellulose EP NF JPE.	Degussa GmbH, D-60287 Frankfurt am Main, Germany
Emcompress	Calcium Hydrogen Phosphate Dihydrate, EP. Dibasic Calcium Phosphate, USP, Dihydrate	JRS PHARMA Gmbh, 73494 Rosenberg, Germany
Emdex	Dextrates, N.F.	JRS PHARMA Gmbh, 73494 Rosenberg, Germany
Erncocel	Microcrystalline cellulose, EP NF JP	JRS PHARMA Gmbh, 73494 Rosenberg, Germany
Explotab	Sodium Starch Glycolate EP NF Sodium Carboxymethyl Starch, JPE	JRS PHARMA Gmbh, 73494 Rosenberg, Germany
Fast-Flo Lactose	Lactose NF, Spray Dried	Sheffield™ Pharma Ingredients, Norwich, NY 13815
Glycolys	Sodium Starch Glycolate EP NF Sodium Carboxymethyl Starch, JPE	Roquette Freres, 62080 Lestrem, France
Kollidon CL	Crsopovidone EP NF JPE	BASF, 67056 Ludwigshafen, Germany
Lubritab	Hydrogenated Vegetable Oil, NF, BP Hydrogenated Oil, JP	JRS PHARMA Gmbh, 73494 Rosenberg, Germany
Maltrin	Maltodextrin	Grain Processing Corporation, Muscatine, Iowa 52761
Neosorb 60	Sorbitol	Roquette Freres, 62080 Lestrem, France
Nu-Tab	Compressible sugar, N.F.	Chr. Hansen, Inc., Mahwah, NJ 07430
Parteck	β Mannitol	Merck KGaA, Darmstadt, Germany

Pearlitol DC	β Mannitol	Roquette Freres, 62080 Lestrem, France
Pearlitol SD	α Mannitol	Roquette Freres, 62080 Lestrem, France
Pharmatose	Milled αLactose Monohydrate EP NF JP	DMV Int., Veghel, Holland
Pharmatose, DCL11	SD Lactose EP NF JP	DMV Int., Veghel, Holland
Pharmatose, DCL14	SD Lactose EP NF JP	DMV Int., Veghel, Holland
Pharmatose, DCL15	Granulated Lactose EP NF JP	DMV Int., Veghel, Holland
Pharmatose, DCL21	Anhydrous β Lactose EP NF JP	DMV Int., Veghel, Holland
Pharmatose, DCL22	Anhydrous β Lactose EP NF JP	DMV Int., Veghel, Holland
Polyplasdone XL	Crospovidone EP NF JPE	International Specialty Products, Wayne, NJ 07470
Precirol ATO 5	Glyceryl palmitostearate EP NF	Gattefossé, 92632 Gennevilliers, France
Primellose	Croscarmellose EP NF JPE	DMV Int., Veghel, Holland
Primojel	Sodium starch Glycolate EP NF JPE (carboxymethyl starch)	DMV Int., Veghel, Holland
ProSolv SMCC	Silicified Microcrystalline Cellulose	JRS PHARMA Gmbh, 73494 Rosenberg, Germany
Pruv	Sodium Stearyl Fumarate, Ph.Eur., NF, JPE	JRS PHARMA Gmbh, 73494 Rosenberg, Germany
Starch 1500	Pregelatinized Starch	Colorcon, Inc., West Point, PA 19486
Sterotex	Hydrogenated Vegetable oil,	Abitec Corp, Columbus, OH 43216
Syloid	Silicon Dioxide EP NF JPE	Grace Davidson, Baltimore, MD 21226
Tablettose	agglomerated α lactose-monohydrate EP NF JP	Meggle, 83512 Wasserburg, Germany
Vivapur	Microcrystalline cellulose, EP NF JP	JRS PHARMA Gmbh, 73494 Rosenberg, Germany
Vivasol	Croscarmellose EP NF JPE	JRS PHARMA Gmbh, 73494 Rosenberg, Germany
Vivastar	Sodium Starch Glycolate EP NF Sodium Carboxymethyl Starch, JPE	JRS PHARMA Gmbh, 73494 Rosenberg, Germany

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6
Disintegrants in Tableting

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INTRODUCTION

Since man first began to treat illnesses using oral administration of herbs and other available materials, there have been a problems of how to take the medicines because many drugs, whether natural or synthetic, are bitter. Many of the early developments in formulations were designed with taste masking and convenience in mind. We formulate to convert bulk drugs into medicines that the patient can use. In the case of oral administration, both tablets and capsules are convenient for patients as they allow self-medication and can be easily designed to mask any unpleasant taste. Besides tablets and capsules, there are also powders, usually taken dispersed in water. But tablets and capsules are comparatively recent developments. In the past drugs were formulated as powders, cachets (made of rice starch), and pillules (pills). Tablets and capsules are used today because, in many respects, they are easier and quicker to manufacture, and lend themselves to more automated methods. Tablets in particular can be manufactured at very high speed on today's modern equipment.

Tablets are the most common type of pharmaceutical dosage form, both by volume produced and by the number of products and formulations marketed. As will be described elsewhere in this volume and its companion volumes, the tablet is one of the most convenient and versatile dosage forms. Tablets can be designed for use as immediate release products or by suitable modification of the composition and manufacturing process, can also be designed as modified release products, with many different potential release patterns.

During the development of tablet products, much effort is expended on ensuring that the tablet has the appropriate characteristics that will allow the patient to receive their medication in the correct amount, and at the correct rate each time they swallow the tablet. This requires that we understand both within and between batch consistency, and the stability of the product over its shelf-life, irrespective of whether it is an immediate release product or a modified release product. It follows that the tablets must remain intact in the dry state, and thus be of sufficient strength to allow them to be further processed, packed, and transported to the patient, and then handled by the patient (or care-giver).

However, once taken by the patient, the tablet should then release the drug in the required amount and at the required rate. The biopharmaceutical properties of the active pharmaceutical ingredient (API), and the required release profile will influence the rate of release and subsequent absorption of the drug. However, for immediate release tablets, tablet disintegrants play an important role in ensuring that the tablet matrix breaks up on

contact with the fluid in the stomach to allow the release of the active drug which then becomes available, in whole or in part, for absorption from the gastrointestinal tract (GIT). Although most drugs are absorbed from the GIT after passing through the stomach, it is nevertheless important with immediate release products that the tablet disintegrates properly in the stomach to release the drug and allow it to be absorbed quickly after passing through the pyloric sphincter and on into the duodenum and beyond. Some drugs, e.g., metoprolol, are only absorbed from a restricted region in the GIT. Under such circumstances there may not be sufficient time for the tablet to disintegrate after passing through the stomach, and release the drug into the lumen of the GIT to be available for absorption before the drug has passed below the absorption zone (absorption window) of the GIT.

A tablet disintegrant may be defined as:

> Any solid, pharmaceutically acceptable material included in the formulation that acts to cause the tablet matrix to break up when the tablet comes into contact with aqueous media.

Tablet disintegrants are usually divided into "superdisintegrants" and what can be called the "traditional" disintegrants. The term "superdisintegrant" was coined in the very early days after sodium starch glycolate (the first of the superdisintegrants), croscarmellose sodium, and crospovidone became available. It relates to the comparative effectiveness of the superdisintegrants compared to traditional disintegrants, i.e., how much less superdisintegrant is needed in a tablet formulation compared to a more traditional disintegrant. Traditional disintegrants include such materials as native starch of different origins, alginic acid, and ion exchange resins. There are other materials that can act as disintegrants that do not conform to this general classification.

A GENERAL STRUCTURE AND FORM FOR TABLET DISINTEGRANTS

The traditional disintegrants and superdisintegrants are typically hydrophilic materials comprising a hydrophilic colloid matrix that is insoluble at the pH of the stomach. In addition, to being hydrophilic, several of the disintegrants have a high affinity for water, and some, e.g., sodium starch glycolate, are hygroscopic. They can be "simple" cross-linked polymers such as crospovidone and the ion-exchange resins, or they can be more complex particles, such as native starch and sodium starch glycolate where there is an amylose core surrounded by an amylopectin coat. Since they are hydrophilic colloids and thus polymeric, it would be highly undesirable to have a highly soluble material since it would be more likely to extend disintegration and retard dissolution (1). The gelatinization of starch on heating is an example, where the release of the soluble amylose, the viscous component of starch mucilage, creates an effective wet granulation binder that has been used for many years.

There are exceptions to this general description of traditional and superdisintegrants. There is a soluble disintegrant system in fairly common use, namely the effervescent couple, i.e., a combination of a soluble organic acid (e.g., citric acid) and inorganic bicarbonate that works by chemical reaction to generate carbon dioxide in contact with water. The effervescent system is very susceptible to relative humidity and requires low humidity for manufacturing and primary packaging. It is not suitable for general application in conventional (i.e., non-effervescent) immediate release tablets.

Inorganic carbonates, e.g., calcium and magnesium carbonates, are sometimes included in immediate release tablet formulations. They may be included for a number of

reasons; to stabilize the API, to improve compactibility after granulation, etc. However, carbonates will react with the acid in the stomach with the evolution of carbon dioxide, and thus can be expected to aid in the disruption of the tablet matrix, i.e., tablet disintegration. In this respect they can be considered to be tablet disintegrants, but this action maybe secondary to the main purpose they are included in the formulation, e.g., to aid manufacture or processing.

Some inorganic clays, complex aluminum silicates, have also been used as disintegrants. These materials swell on contact with water, but are not polymers.

POSSIBLE MECHANISMS OF TABLET DISINTEGRATION

There has been a lot of research conducted over many years in trying to determine the mechanism of action of disintegrants, and there have been several excellent reviews (2–4). In some of the very early work, the research appeared to be directed towards finding a universal mechanism for the action of tablet disintegrants. However, it is now clear that different disintegrants act through different mechanisms, and that a particular disintegrant may work through more than one mechanism with a different balance of mechanisms for the different disintegrants and for different applications. In the following subsections we shall examine the various possible mechanisms for tablet disintegration, and how these different mechanisms apply for different disintegrants.

Logic suggests that interaction with water or aqueous media is a prerequisite for disintegrant activity (4). As stated above, we require the tablet to remain intact until after administration to the patient, and the big change after administration is that the tablet comes into contact with aqueous secretions in the upper GIT (mouth, esophagus and stomach). Typically, but not always, disintegration occurs in the stomach; exceptions include buccal and sublingual tablets, enteric coated tablets, colonic drug delivery systems, and controlled/prolonged release drug delivery systems. Many drugs are not absorbed to any appreciable extent until the drug has passed out of the stomach and into the small intestine. Nevertheless, for all conventional immediate release tablets, it is desirable that the tablets disintegrate in the stomach so that the drug is available for absorption as soon as possible after passing out of the stomach into the duodenum.

Hydrophilic Colloid Disintegrants

All traditional and superdisintegrants function best when incorporated into insoluble systems (e.g., dibasic calcium phosphate and microcrystalline cellulose). By contrast, one common drawback is that they function less well when the tablet matrix contains significant proportions of soluble components (e.g., lactose and mannitol) (5–7). This may be a consequence of the fact that, regardless of predominant disintegration mechanism, the disintegrants work by pushing the tablet matrix apart. With soluble or partially soluble matrix components, the matrix is dissolving and thus the disintegrant is deprived of some of what it might push against, thus reducing the disintegrant effect. It has also been suggested that the soluble components will also compete for the available water and thereby reduce the disintegrant efficiency (5).

Kanig and Rudnic (3), in reviewing tablet disintegration, suggested five different main mechanisms by which disintegrants could function:

1. swelling,
2. wicking (also known as the "capillary" effect),

3. recovery of energy of elastic deformation from compaction of the tablet,
4. repulsion,
5. heat of wetting.

There are also other potential mechanisms that have been proposed in the literature (2,4), and these will also be discussed.

Swelling

This is a consequence of the affinity of the disintegrants for water. They are mostly insoluble hydrophilic colloids. As a consequence they will absorb water from the surrounding medium. As the amount of water absorbed increases, the disintegrant particles will tend to swell. However, the amount of swelling will depend on the material, the structure of the particles and the degree of cross-linking or other phenomena that might constrain the expansion of the particle; e.g., a particle of a polymer with a high degree of cross-linking would not be expected to swell to the same extent as a particle with a much lower degree of cross-linking.

Wicking

"Wicking" may be defined as the phenomenon of drawing water into the tablet due to the presence of hydrophilic groups that are able to interact favorably with the water molecules penetrating the tablet matrix. Wicking is also referred to as "capillarity" or "capillary action." Components other than disintegrants may also be hydrophilic and add to the hydrophilic network within the tablet matrix (8), thereby contributing to the drawing of water into the matrix, and assisting in the disintegration of the tablet. It could be argued, therefore, that wicking is not a disintegrant action per se; but it is a very necessary adjunct property, since without water being taken into the tablet matrix, and being available to interact with and activate the disintegrant, the tablet would not disintegrate. However, as we shall discuss below, there is evidence that the presence of water disrupts particle–particle bonds thereby contributing directly to the dissagregation of the tablet matrix. If the penetration of water is somehow retarded, e.g., by over-lubrication with magnesium stearate, disintegration is typically slowed (9) and this may in turn reduce the rate of dissolution of the active (10).

Recovery of Energy of Elastic Deformation

During formation of a tablet, the materials are subjected to a high compressive force but constrained by the punch and die set. The pressures are typically in the mega Pascal (MPa) range. The physics of the compaction process are discussed elsewhere in this volume and its companion volumes. Suffice it to state that, under the conditions encountered during the formation of tablets, the powders deform and bond together to form the tablet. Pharmaceutical powders may deform in three ways, elastic deformation, plastic deformation, and brittle fracture. In the case of elastically deforming particles, because they become interlocked with other particles, they may not have the opportunity to regain their original shape on release of the compaction pressure. However, as water penetrates the tablet matrix, the particles are able to regain at least partially their original shape and thus disrupt the tablet matrix. Hess (11) showed that croscarmellose sodium in the surface of tablets did regain most of its original shape on exposure to moisture.

There are several possible reasons for the effect of water. Possibly it lubricates the particles and allows them to slip by each other. Possibly the water allows the polymer chains within the particles to readjust to a more energetically favorable orientation.

Possibly the bonds between adjacent particles are disrupted by the presence of water and thus no longer hold the deformed particle in its strained state. Most likely it is a combination of several effects.

Repulsion

This phenomenon has been reported for starch (12). In essence, in water, some materials disperse in such a way that the individual particles repel each other. It was proposed that this repulsion could be a mechanism by which starch acts as a disintegrant. However, the authors also suggested that the repulsion phenomenon could be linked to the breaking of the bonds (adhesion forces and/or hydrogen bonds) that hold the tablet together, when the tablet comes into contact with water.

When we consider how starch suspends in water, there is further doubt on the likelihood of repulsion as a general disintegration mechanism. In the preparation of starch mucilage the starch is first suspended in an approximately equal volume of water before the addition of the boiling water to form the mucilage. If left to stand the starch grains will settle out of suspension to form a deflocculated layer that is difficult to resuspend. If repulsion were an important mechanism, it seems logical to suggest that starch that has settled out of suspension should be much easier to resuspend.

On the balance of evidence, the energy generated through repulsion is likely to be very small, if it exists, and thus the effect on disintegration would also be small compared to other possible modes disintegrant action. Overall, it seems that repulsion is not likely to be a primary mechanism of disintegrant action, but if it occurs it might serve as a supporting mechanism.

Heat of Interaction with Water

Almost all materials, on interaction with water, will either generate heat (exothermic interaction) or absorb heat (endothermic interaction). Matsumara (13) has suggested that the heat generated from the interaction of the tablet disintegrant with water expands the air trapped in the tablet thus causing disruption of the tablet matrix. However, other workers have suggested that the amount of heat likely to be generated is small and unlikely to cause sufficient expansion of the trapped air to disintegrate the tablet (14). Indeed some disintegrant materials have a negative heat of interaction with water, and yet still function well as disintegrants (15). On balance, this potential mechanism for disintegrant activity is unlikely to be of importance for any disintegrant.

Hydrophilic Network

Many materials used in the manufacture of immediate release solid dosage forms are hydrophilic (water loving). These materials form a hydrophilic network (8) throughout the tablet that draws water into the tablet thus aiding disintegration. There are compressed tablet formulations in the literature (16,17) that do not contain a recognized disintegrant, and yet release the active drug sufficiently rapidly to qualify as immediate release products. Since the majority of the components are hydrophilic (typically with the exception of the lubricant), sufficient water is drawn into the tablet to induce disintegration through the disruption of bonding forces.

Interruption of Bonding Forces

When formulations are compressed to form tablets, the particles bond through particle-particle forces. The exact nature of these particle-particle bonds is not fully understood,

but may comprise different types of interaction, including van de Waals forces, hydrogen bonds, adhesive and cohesive forces, and mechanical interlocking (18). When an immediate release tablet comes into contact with water, the surfaces of the individual particles become hydrated thus interrupting the bonding forces in the tablet, ultimately leading to disintegration.

Inorganic Carbonates

Inorganic carbonates such as calcium carbonate and magnesium carbonate will react with aqueous mineral acids with the evolution of carbon dioxide. In this respect, although they may be included in the formulation for other reasons, they can aid tablet disintegration in immediate release tablets that disintegrate in the stomach. However, a tablet composed entirely of say calcium carbonate might be slow to dissolve as the rate of penetration of acid into the matrix would be impeded by the reaction and the reaction products. In reality, we do not generally make immediate release tablets entirely of calcium carbonate, and the inclusion of hydrophilic materials in the tablet would be expected to aid penetration of the stomach acid into the tablet and speed up disintegration.

INFLUENCE OF PHARMACEUTICAL PROCESSING ON DISINTEGRANTS

Pharmaceutical products are produced as a result of a complex set of interactions between the API, excipients and the manufacturing process. Hydrophilic colloid tablet disintegrants, because of the way they interact with water, their hygroscopicity and structure, can be adversely affected by the manufacturing unit processes. The type and magnitude of the effect will be influenced by the nature of the disintegrant and the type of manufacturing unit processes being used.

By contrast, the disintegrant effects of inorganic carbonates, being affected by acid rather than just water, will not be affected by the type of processing used to anything like the same extent as the hydrophilic colloid materials. More likely, the properties of the carbonate, e.g., compatibility and flowability, will influence the choice of granulation process.

Wet Granulation

Wet granulation is still probably the most common means of processing powders for compaction into tablets. Today, most wet granulations are water based. In former times solvent-based granulation was more common, but environmental and health and safety considerations have led to a substantial decrease in solvent-based processing.

Wet granulation is covered in detail elsewhere in this series. In summary, wet granulation uses a solution of the granulating agent to stick the particles of the formulation components together such that, after drying and subsequent final blend preparation, the resulting granulate has the necessary properties that allow the tablet to be formed, and the tablet produced has sufficient mechanical strength to retain its integrity through any subsequent further processing, packaging, and eventual administration to the patient. Wet granulation processing is well established and typically requires the addition of the granulating solution (typically water-based) with subsequent drying, i.e., the addition of water and application of heat. Both can be detrimental to tablet disintegrants; some disintegrants more than others. Water and heat can also be detrimental to the API and can promote degradation. However, there are ways in which the deleterious effects of

both heat and moisture can be reduced, and these will be discussed in the sections dealing with individual disintegrants (see below).

In the days when solvent-based granulations were more common, the granulating solvent typically had little or no effect on the starch-based or starch-derived excipients. By contrast, when water is the granulating solvent, care must be exercised when processing swollen (hydrated) grains of starch or its derivatives (see individual disintegrant reviews).

The disintegrant is also typically added to the formulation at both the wet massing step and the post-granulation blending stage just prior to compaction into tablets. This split between intra- and extragranular addition has been recommended by several authors. Using crospovidone, Eyjolfsson (19) found that the inclusion of both intra- and extragranular disintegrant was superior to the use of intragranular disintegrant alone. Khattab et al. (20) showed that an even split between intra- and extragranular disintegrant did not give the optimum disintegration for croscarmellose sodium. However, Gordon and Chowhan (21), also using croscarmellose sodium, found that extragranular incorporation gave faster disintegration times than either intragranular or a mix of intra- and extragranular disintegrant. Shotton and Leonard (22), using maize (corn) starch, showed that it is a balance; intragranular disintegrant produced a finer suspension of suspended particles but a slower disintegration time, whereas extragranular disintegrant gave a coarser suspension but a faster disintegration time. The advantages of the split incorporation of the starch were confirmed by Rubinstein and Bodey (23). Gordon et al. (24) using croscarmellose sodium also found that splitting the disintegrant between the granulation and the final blend was better than either incorporating the disintegrant entirely in the granulation, or entirely in the final blend. In addition, they also demonstrated that dissolution of a poorly soluble API was further improved if the quantity of disintegrant added to the final blend was greater than the quantity incorporated at the wet granulation stage.

It is important to remember that we want both the tablet and the granules to disintegrate to give the best opportunity for the release of the API. The combination of intra- and extragranular disintegrant is used to encourage just that, and thereby the dissolution of the active drug. This becomes increasingly important with the inclusion of poorly soluble and/or hydrophobic APIs in the formulation.

In processing terms, the same considerations apply to the incorporation of extragranular disintegrant as to apply to disintegrants used in direct compression formulations (see below).

Hot-Melt Granulation

In hot-melt granulation, the powders are granulated by using low melting materials, e.g., hydrogenated vegetable oils or polyethylene glycols (macrogols) that are solid at room temperature but are molten at around, e.g., 50°C. After thorough mixing at the higher temperature, the mass is cooled and the granulate formed. This is further blended and compressed into tablets. While this method avoids the use of water, heat is still required and the granulating materials may contain impurities that can exacerbate degradation of the active component. Simple pre-formulation experiments may be able to identify potential incompatibilities.

Because the heat applied to the formulation components may be greater than in conventional wet granulation, there is a risk that certain disintegrants may be adversely affected by hot-melt processing, especially if higher temperatures are used. In particular care needs to be taken when using starch-based disintegrants.

Dry Granulation

There are two methods available for dry granulation: roller compaction and slugging. The two techniques are similar but they can give different results. Both techniques use pressure to bond the components of the formulation together. The resulting large crude agglomerates (ribbon from roller compaction and slugs from slugging) are then broken down to form the granulate which is then further blended and compressed into tablets. Such processing avoids the introduction of water into the formulation, and avoids extended heating.

However, there is an implicit requirement that the formulation and the individual components must be able to withstand being compressed twice and still function as intended. Different disintegrants will show different responses to double compression. For example, a study comparing different types of starch in a slugged formulation showed that rice starch performed worst of all the starches for disintegration efficiency, but showed only marginally slower dissolution (25). By contrast, Gould and Tan (26–28) showed that rework of wet granulated formulations containing sodium starch glycolate, croscarmellose sodium or crospovidone required the extragranular addition of disintegrant prior to the second compression to maintain disintegrant efficiency. Presumably, in part, to overcome the effects of the extra hydrophobic lubricant required for the recompression.

Again, we require that both the tablet and the granules disintegrate and the use of a combination of both intra- and extragranular disintegrant should be considered. There is less potential for interaction with the other components in a dry granulation because of the lack of water, heat, etc.

Direct Compression

As the name implies, such formulations are simply blended and then compressed into tablets. A very simple process train, but one that imposes extra constraints on the formulation components compared to granulation processes. Overall, the formulation blend must flow and have sufficient compactibility to form adequately robust tablets at the required production speeds. However, there are further constraints in that the formulation must also exhibit resistance to segregation as reflected in content uniformity, and show satisfactory stability. In general terms, any material that is included in immediate release tablet formulation at a level greater than about 20% w/w can have a significant effect on the compactibility of the formulation.

The tablet disintegrant is just one component of the formulation, and typically a minor component. However, use in direct compression formulations does bring certain constraints, particularly in that the disintegrant should not adversely affect flowability or compactibility at the level of inclusion in the formulation, and that the disintegrant should form a stable blend (i.e., be resistant to segregation during the normal processing that such a blend would be expected to undergo).

Milling

The effects of milling will depend on the nature of the disintegrant and the energy of the milling. Where the disintegrant particles are more or less homogeneous, higher energy milling should simply result in particle size reduction, and the increased number of particles for a given mass of disintegrant may result in a better dispersion of the disintegrant though the tablet blend. Thibert and Hancock (29) showed that both ball milling

and end-runner milling (motorized mortar and pestle) were able to reduce the particle size of disintegrants, albeit to different extents, and that this did affect disintegration time in model direct compression systems. The effects depended on the nature of the tablet matrix and the type of disintegrant, and also on the compaction force. For both croscarmellose sodium and crospovidone, the effects of milling were less pronounced in an insoluble direct compression tablet matrix compared to a soluble matrix formulation.

If, however, the disintegrant particles are not homogeneous, i.e., there is a structure to the particle involving the orientation of particular types of molecules within the disintegrant particle, e.g., starch grains which comprise an outer amylopectin layer encapsulating the inner component—amylose, then milling may have a deleterious effect depending on the energy of milling used. The same authors (29) showed that milling sodium starch glycolate reduced the particle size and did increase disintegration time. However, the effects were compaction force and matrix dependent, with more pronounced effects being observed in an insoluble direct compression tablet matrix than in a soluble matrix.

In the context of unit processing to produce tablets, ball milling, and end-runner milling may be considered to be higher energy milling systems. In the normal handling of dry powder blends for the manufacture of tablets, lower energy mills, such as low energy comminuting mills, and oscillating granulators are typically used. Such processing is typically included in the process train to aid in the dispersion of agglomerates of formulation components, and would not be expected to reduce the particle size of the disintegrant to any great extent. Gould and Tan (26) have reported that milling of a model wet granulation containing superdisintegrants had no effect on disintegration efficiency of sodium starch glycolate, croscarmellose sodium, or crospovidone.

The effects of the particle size of disintegrants obtained without milling have also been investigated using size fractions obtained by air classification (30). These authors investigated the disintegration efficiency of native starch (rice and potato starch) and sodium starch glycolate. For both types of disintegrant, in the absence of magnesium stearate, increasing particle size reduced disintegration time. The effect was much more pronounced for the native starch, but sodium starch glycolate was a much more effective disintegrant in the model insoluble direct compression formulation.

The reasons for the poorer performance of the smaller particle size fractions of disintegrant must be related to the mode of action of the disintegrants and their structure. Presumably the larger particles exert their effect throughout a larger domain within the tablet (e.g., greater swelling), thereby causing more extensive disruption of the tablet matrix.

Compaction

Rapid penetration of water into the tablet matrix encourages rapid tablet disintegration. At very low pressure, disintegration time may be increased due to the high porosity of the tablets. As the pressure increases, the disintegration time decreases up to a threshold pressure, above which the disintegration time increases. Above the threshold pressure the porosity is getting lower, but more importantly the penetration of water into the tablets is retarded by the very narrow diameters of the capillaries in the tablet matrix (31).

Under normal compaction forces, compaction does not appear to have a deleterious effect on disintegrant activity. In fact, as discussed above under granulation, many immediate release formulations are being manufactured using dry granulation methods and then recompressed into tablets without observing any problems associated with the loss of disintegrant activity. Thus overall, we can conclude that under the compaction

conditions typically observed during manufacture of pharmaceutical tablets, or during dry granulation followed by further compression into tablets, there are no significant detrimental effects on the disintegrant.

Film Coating

Film coating is typically water-based today. However, historically much of the original film coating was solvent-based. In solvent-based film coating the potential for premature activation of the disintegrant is considerably reduced.

This is not the case for aqueous film coating, where over-wetting of the surface of the tablet could result in the activation of the disintegrant embedded in the surface of the tablet, in turn giving rise to surface irregularities. However, aqueous film coating has been used successfully over many years with tablet core formulations containing superdisintegrants. Provide the coating process is well designed and controlled, and the cores in the coating pan are not over-wetted, then there is no reason to assume that cores containing even the superdisintegrants at normal use levels will present major difficulties during aqueous film coating.

INTERACTIONS WITH OTHER FORMULATION COMPONENTS

In simple terms, when we consider excipient interactions, we generally think of drug–excipient interactions. These are important, but we must also consider the possibility of excipient–excipient interactions. These can be either chemical or physical, sometimes both may occur. They can also be either beneficial or deleterious. Chemical interactions will depend on the chemical nature of both the excipients and are generally predictable, although the moisture content of the formulation will have a significant influence on the rate of reaction. Physical interactions, on the other hand, are less easy to predict since they do not solely rely on the chemical composition of the materials, but also on the form and physical make-up of the excipients in question. Disintegrants are like any other excipient in a medicinal product. They will have the potential to interact with the other components, be they API or excipient, depending on their chemistry and form and physical make-up.

Interactions Between Disintegrants and Filler/Binders

The term filler/binder generally refers to the use of the material in direct compression formulations. These same materials, when used in granulated systems are usually referred as fillers or bulking agents. In this type of application they are used to increase the weight (size) of the tablet. The major filler/binders include microcrystalline cellulose, lactose, mannitol and inorganic carbonates, and phosphates. In general, the interactions between disintegrants and filler/binders are uncommon unless there is an obvious chemical incompatibility (e.g., an interaction between an acid and metallic salts). Any incompatibilities that do exist may be increased in aqueous granulations due to the use of water and heat for extended periods, and in hot-melt granulations due to the use of heat for an extended period. Provided that the moisture content of the filler/binder is sufficiently low to prevent premature activation of the disintegrant, most combinations of filler/binder and disintegrant can be used to manufacture tablets with sufficient stability and robustness for use as a commercial product. Stable product formulations are known using combinations

of many filler/binders and any of the three superdisintegrants and other disintegrants (16,17).

Interactions Between Disintegrants and Wet Granulation Binders

Wet granulation binders are simply adhesives and are used to stick the components of the formulations together. In wet granulation, the binder solution is dispersed over the surface of the other components during the wet massing stage. If there are also soluble components in the mix these will be at least partially solubilized too, and will also be spread through the mix. This is a form of very intimate mixing which increases the propensity for any chemical or physical interactions to occur. Since typically water and heat are both used in wet (aqueous) granulation, the propensity for chemical or physical interactions to occur is further increased. With solvent based granulations, water is not used and the amount of heat required to dry the granulate is also typically reduced. These combined may reduce the propensity of materials to interact.

There are many successful formulations prepared using wet granulation and most if not all disintegrants (16,17). In the absence of any obvious chemical interaction, the key issue is what happens to the disintegrant during wet granulation and the consequences for the eventual performance of the disintegrant if it is included in the granulated part of the formulation. This has been discussed earlier (see the section "Wet Granulation"), and will also be considered later in the "Review of Disintegrants" section).

Interactions Between Disintegrants and Hot-Melt Binders

Hot-melt binders, while not aqueous solutions, are molten during processing, and the binder is spread throughout the powder mix and thus comes into intimate contact with the other components of the granulation, thus the propensity for interaction with the other components is increased. The propensity to interact with the other components of the granulation is also increased because heat is applied to melt the binder. Hot-melt binders may be hydrophilic, e.g., higher melting polyethylene glycols, or hydrophobic, e.g., hydrogenated vegetable oil.

In general terms, the hydrogenated vegetable oils, since they are hydrogenated, may be considered to be chemically inert, and chemical interaction with the other components of the formulation, including the disintegrants, is unlikely. However, there may be traces of other components in the hydrogenated oil that do have the potential to interact. These are typically controlled below critical levels in the excipient monograph. During mixing of the molten binder into the powder mass, a thin layer of binder is deposited on the surface of the other formulation components. For hydrophobic binders, this layer could serve to increase disintegration time and reduce dissolution rate. Obviously the effect will be dependent on the nature of the hot-melt binder and the other components of the tablet. The amount of heat will be important for starch-based disintegrants because of the potential for gelatinization. If the minimum gelatinization temperature is not attained during processing, the chances of gelatinization occurring are negligible.

Hydrophilic hot-melt binders, by contrast, do not present such a risk for increased disintegration times and delayed dissolution, although there may be a slight increase and corresponding reduction in dissolution. This will be material and formulation dependent. Again the amount of heat will be important for starch-based disintegrants. Some potential hydrophilic hot-melt binders may contain other minor components that could interact chemically with the other components of the formulation, including the disintegrant. For example, the polyethylene glycols can contain traces of peroxide. The type and rate of

interaction will be governed by the nature of the interacting component, the level of peroxide, the amount of water, and the temperature. However, there do not appear to be any reported chemical incompatibilities between hydrophilic hot-melt binders and the commonly used disintegrants.

Interaction Between Disintegrants and Lubricants

Most lubricants commonly used in tablet formulations are hydrophobic, e.g., magnesium stearate, calcium stearate, hydrogenated vegetable oils, etc. There are some exceptions e.g., sodium stearyl fumarate. They also work by coating the other components of the formulation to reduce friction during compaction of materials to form tablets (32). Because of their hydrophobic nature, such lubricants have the potential to retard the penetration of water into the tablet and thus extend disintegrations times and decrease dissolution (33).

There have been several studies that have investigated the effect of lubricants, particularly magnesium stearate, on disintegration time, and dissolution rate (34). In general terms it appears the effects of magnesium stearate are more pronounced with less effective disintegrants (35).

Interaction of Disintegrants and Active Pharmaceutical Ingredients

Disintegrants have the potential to interact chemically with the API. In this respect they are just like any other excipient in the formulation. The hydrophilic colloid disintegrants contain either functional groups or ionic components (e.g., sodium starch glycolate, croscarmellose sodium) that can interact with certain types of API, or they may contain synthetic by-products that can interact with some APIs (e.g., crospovidone). These disintegrants are also hygroscopic and can bring water into the formulation. They can also act as moisture scavengers in a formulation if the packaging is suitably moisture tight, thereby reducing the likelihood of interaction.

The inorganic carbonates also have the potential to interact. For example, the magnesium and calcium ions are capable of promoting certain types of chemical degradation and interaction, such as ester hydrolysis, and the Maillard reaction between primary and secondary amines, and reducing sugars.

USE AND INCORPORATION OF DISINTEGRANTS IN TABLET FORMULATIONS

Disintegrants play a vital role in immediate release tablet formulations by causing disruption of the tablet matrix on contact with aqueous media, e.g., stomach contents, and thereby facilitating dissolution. The type of processing and the type of disintegrant must be carefully considered when developing robust formulations and processes so as to avoid potential interactions leading to reduction of the disintegrant effect in the final product, reduced dissolution, and possible reduced efficacy.

Direct Compression

Direct compression (or direct compaction) is, in theory, one of the simplest tablet formulation processes; the components are mixed together and formed into compacts (tablets). The disintegrant is thus subjected only to compaction of short duration and is

unlikely to be affected to any great extent. The effects of compaction on disintegrant function are discussed elsewhere.

One note of caution: The level and method incorporation of lubricants into tablet blends, whether direct compression or granulations, can have a significant influence on disintegration and dissolution. This is covered elsewhere in these volumes, however, the reader is advised to consider carefully the lubrication of tablet blends in relation to both in vitro and in vivo performance of the final tablet.

Granulated Systems

Most tablet formulations are processed by some form of granulation. Granulation (dry, wet, or hot-melt) is, in many respects, the most forgiving of the formulation processes, with wet granulation still being the most popular method. To achieve good dissolution with granulated systems it is important that the tablet matrix disintegrates rapidly on getting to the stomach, and that the drug is then released from the resulting granules. The nature of the API will obviously have a significant influence on the final formulation, and it is usually worthwhile including disintegrant in both the granulation and also the final blend stage just prior to compaction. If the disintegrant has been incorporated correctly, this division of the disintegrant will promote disintegration of the tablet and the granules. This is particularly important in the case of less soluble drugs where it is important to maximize the surface area of the drug suspension in the GIT to encourage absorption of the drug. However, the proportions of the disintegrant in the granulation phase and in the dry addition phase do not need to be equal and there is some evidence that e.g., a 25:75 split between the intra- and extragranular proportions of the disintegrant may be more appropriate than, e.g., a 50:50 split in some applications (20).

Dry Granulation

In dry granulation (whether roller compaction or slugging) compressive force is used to consolidate the material and bind the particles together. The ribbon or slugs are then milled using a suitable low-energy milling system, blended with the extragranular components, and finally compacted a second time to form the tablets. This double compression may reduce the effectiveness of some disintegrants. Some disintegrants are more susceptible than others to this double compression (25).

One point to remember, particularly with slugging, is that the granulation part of the mix will contain lubricant, and this lubricant can have a deleterious effect on disintegration of the tablet and subsequent dissolution of the API (see the "Direct Compression" section). When formulating dry granulated products, it will probably be beneficial to include both intra- and extragranular disintegrant able to withstand the double compression to counter the hydrophobicity of the lubricant (26,27).

Wet Granulation

Wet granulation can be either aqueous or non-aqueous. Non-aqueous granulation is less common today because of potential health, safety, and environmental concerns depending on the solvent used. Nevertheless it is still used, and the problems sometimes encountered using aqueous granulation with certain disintegrants mostly disappear. Quite simply, in the absence of water, disintegrants do not show the kinds of properties that can cause problems in aqueous granulation. For the most part, the disintegrant can be regarded as just one more component of the formulation during solvent-based granulation.

Aqueous granulation is very commonly used in tablet manufacture. The important point to understand is that water activates the tablet disintegrant. In the finished tablet, if it is exposed to moisture in the pack, for example, this can cause premature break up of the tablets. The water can be in the form of moisture vapor or liquid; if there is sufficient present, the tablet disintegration process may be initiated leading to rough tablets, crumbly tablets, and even broken tablets. During aqueous granulation water is added to the powder mix and the hydrocolloid disintegrant, being hydrophilic and probably hygroscopic, will absorb water from the granulating solution.

With the absorption of water there will be changes in the disintegrant. The nature and the extent of the changes will depend on which disintegrant is used in the formulation, and whether or not the disintegrant particles have a homogeneous (monolithic) structure (e.g., crospovidone) or a heterogeneous structure (e.g., sodium starch glycolate). The hydrated disintegrant particles will behave in a different way during the wet massing process than the unhydrated particles would. It is necessary to understand these differences and how they can affect both the granulation and drying processes. This will be discussed in greater detail during the review of the individual disintegrants (see "Review of tablet disintegrants" section). In general, disintegrants having a heterogeneous particle structure will require more careful selection of the grade to be used in the wet massing step of an aqueous granulation process. Such concerns are not relevant to the use of disintegrants in solvent-based granulation processes.

Hot-Melt Granulation

In hot-melt granulation molten materials that are solid at room temperature are used to bind the particles together. This requires both heat and a hot massing time. The temperature required will obviously be higher than the upper limit of the binder's melting range. The time the powder blend is subjected to heat may be extended with a protracted warming phase for the powders followed by the hot massing and then cooling. The temperatures that the powders are subjected to are higher than those typically encountered by the product in fluid bed drying of conventional aqueous granulations. Such temperatures and duration of heating may not be appropriate for all disintegrants. In particular, the gelatinization temperatures of some starches may be very close to the temperatures required for the hot-melt granulation for some hot-melt binders. These issues must be considered when selecting both a disintegrant and the hot-melt binder for a hot-melt formulation.

REVIEW OF TABLET DISINTEGRANTS

As formulation scientists, we are required to bring an understanding of the advantages and limitations of the excipients and unit processes we work with. Excipients are no exception, and they all have advantages and disadvantages. For these and other reasons there is no one universal excipient or disintegrant, and no one universal formulation. This section consists of short technical monographs assessing the advantages and disadvantages, use levels and other information about the different tablet disintegrants available and also those that have been reported in the literature over the years. The disintegrants have been divided into three broad groups:

- traditional disintegrants,
- super disintegrants,
- other materials.

Of necessity, the reviews of the individual materials will only highlight key points. If more information is required, The *Handbook of Pharmaceutical Excipients* (36), amongst others, is a useful source.

There is typically a range of use levels quoted for disintegrants for tablet formulations. There may be reasons to exceed the recommended range in applications where the disintegrant fulfils another role in the formulation. For example, starch can be used as a filler as well as a disintegrant; superdisintegrants can be used as carrier particles for micronized and amorphous APIs. In such cases the level of incorporation in the formulation can exceed the recommended use levels by a significant margin. However, when used as a disintegrant, particularly for the superdisintegrants, there is an upper limit to the useful range beyond which increasing the level of incorporation does not improve disintegration or dissolution. The reasons for this are not fully understood, but are presumable linked to the water uptake and the competition for the water between the hygroscopic disintegrant and the other components of the formulation.

Many disintegrants are of natural origin and the microbial burden must always be considered in such materials, as with any excipient or API. There are few problems with the synthetic and semisynthetic disintegrants when manufactured to the appropriate standards of cGMP since the amount of processing and the conditions used during manufacture tend to eliminate bacteria, yeasts, and molds. For materials that are simply harvested and processed, e.g., starch and alginic acid, the risk of microbial contamination is higher. Part of the technical due diligence during the evaluation of new sources of a disintegrant, or the continuing evaluation of existing sources, must include an evaluation of the microbial attributes and associated risks.

Traditional Disintegrants

The term "traditional" disintegrant refers to materials that were being used as tablet disintegrants before the introduction of the superdisintegrants (sodium starch glycolate was the first—introduced in the late 1960s). They are generally less effective on a weight for weight basis than the superdisintegrants. Native starches, alginic acid, and ion-exchange resins are the main ones still in use today.

Starch

Starch is a generic term for carbohydrate particles found in many plants. Starch grains swell in contact with water, and this appears to be an important property that relates to their use as tablet disintegrants. Starch was probably the first disintegrant used in tablets. The structure of starch grains is heterogeneous. By this we mean that there is a difference in the composition of the starch grain according to the position within the grain. Starch grains are composed of two main components: amylose (soluble) and amylopectin (insoluble). However, the composition of starch grains differs according to the botanical source material in terms of grain size, relative proportions of amylopectin and amylose, and the nature of the minor components present. The starch grain in simple terms can be considered to be comprised of an outer amylopectin layer encapsulating the inner amylose phase (37).

Chemically, amylose is a straight chain polymer of α-glucose (dextrose) units with α $(1 \rightarrow 4)$ linkages. Amylopectin is a branched chain polymer consisting of α-glucose units with α-$(1 \rightarrow 4)$ links, but in addition there are side-chain couplings through α-$(1 \rightarrow 6)$ bonds. Native starch grains are highly structured as evidenced by the characteristic birefringence seen under the microscope using crossed polarizers.

Besides its use as a tablet disintegrant, starch can be used in other ways in the tablet; notably as a filler, and as a wet granulation binder after the formation of starch mucilage (starch paste).

Starches can be used as is (native starches) or they can be modified. Modifications can be both physical and chemical. The modifications have been introduced to improve or modify the properties of the native starch. Many of these modifications have been made for use in other industries, e.g., the food industry. We shall restrict our discussions to those materials used as pharmaceutical tablet disintegrants. For further information on starches and modified starches beyond their use as tablet disintegrants, (see 38).

Native starches: The most common native starches used in the manufacture of tablets are corn (maize) starch and potato starch (farina). However, starches from other botanical sources have also been investigated. A list of some of the types of starch investigated and reported in the literature is given in Table 1.

In addition, the FDA's Inactive Ingredient Database (39) also lists tapioca starch as being used in oral tablets.

Generally, native starches are not directly compressible, thus the amount of a starch that can easily be incorporated at the final blend stage just prior to compaction is limited. In practice, the amount of dry starch added to the final blend for use as a disintegrant is typically around 10–15%w/w. The effectiveness of native starches as tablet disintegrants

TABLE 1 Types of Starch Investigated for Use as Tablet Disintegrants

Starch	Botanical source	Comments	Literature references
Corn (maize)	*Zea mays*	The traditional starch used in the formulation of tablets. Widely used.	22,25,40–42,44,45,48
Potato	*Solanum tuberosum*	Has also been used for many years in tablet manufacture. Less widely used than corn starch.	25,43,44,48
Wheat	*Triticum aestivum*	Appears to be less effective than most other starches.	25,44,45
Rice	*Oryza sativa*	There are mixed reports. Appears comparable to corn starch in some applications. The grains are small.	25,44–46,48
Tapioca	*Manihot esculenta*	Appears to be comparable to rice starch is many respects.	48
Arrowroot	*Maranta arundinacea*	Appears to be comparable to potato starch.	44,48
Sorghum	*Sorghum bicolor*	Appears to be comparable to corn or rice starch depending on the application.	48
Enset	*Ensete ventricosum*	From Ethiopia, appears comparable to potato starch.	47
Sweet potato	*Ipomoea batatas*	May be comparable to rice starch.	48
Waxy corn starch	*Zea mays*	Less effective than ordinary corn starch	44
Dioscorea	*Dioscorea abyssinica*	From Ethiopia. Appears comparable to corn starch.	49

varies with the botanical source. The size of the starch grains appears to be an important factor for the effectiveness of the starch as a disintegrant (30).

Native starches contain significant amounts of free moisture; up to 20% by loss on drying, but more typically 15%, depending on the source of starch. This moisture can be important in the context of the degradation of the API since moisture content affects water activity which is implicated in the degradation of APIs. Regardless of whether or not water is directly involved in the degradation reaction, water is often the medium that brings the two reactants together. The water activity (relative humidity) immediately adjacent to the starch particles can be quite high (>20%) and thus sufficient to initiate degradation reactions.

Of the starches listed in Table 1, those most commonly used in tablet formulations in Europe and the United States are corn (maize) and potato, and these have acceptable characteristics for use as tablet disintegrants. However, different starches are grown locally as staple foods around the world, e.g., rice is the staple crop in much of Asia. There are several reports in the literature concerning investigations of locally sourced starches for use in the formulation and manufacture of tablets, some more successful than others (Table 1).

There are various theories as to how starches function as a disintegrant. The consensus from the literature suggests a combination of mechanisms including swelling (42), disruption of particle–particle bonds through the formation of a hydrophilic network drawing water into the tablet matrix (12), but not recovery of the elastic deformation from the compaction process (50).

Modified starches: Native starches, although used for many years, do not have ideal properties as tablet disintegrants. They are not particularly effective and thus quite high levels are required for them to function properly (10–15%), neither do they possess adequate compaction properties for use in direct compression formulations. There have been numerous attempts to modify starch to improve different properties, mostly for use in commercial food products. The types of modifications used can be classified as either physical (no new chemical bonds formed) or chemical (new chemical bonds formed). Some types of modified starches may require both chemical and physical modification. The United States Pharmacopeia (USP) is now developing monographs for modified and pre-gelled starches. Not all the modified starches may be suitable for use as a tablet disintegrant, and this discussion, as previously stated, will be restricted to those modified starches that are intended for use as tablet disintegrants.

Pregelatinized (pregelled) starch. When starch is heated eventually the pressure inside the starch grain will increase to such an extent that the grain ruptures. When the starch grain is ruptured the inner amylose component of the starch is no longer totally encapsulated by the outer amylopectin layer, and this has significant implications for the physical properties of the starch. We make use of this property in the preparation of starch mucilage. Heating starch grains in water ruptures the grains and allows the amylose to migrate into the water to form a colloidal gel which gives the starch mucilage its characteristic viscosity and acts as the wet granulation binder. The rupture of the starch grains is referred to a gelatinization, and the temperature at which it occurs is known as the gelatinization temperature. This temperature varies according to the botanical source of the starch. It is not a sharp change with temperature but typically occurs over a range of 10–15°C.

If starch grains are heated in air to a suitable temperature, the grains will still rupture but, in the absence of a suitable medium to dissolve the amylose, the amylose will remain mostly inside the amylopectin sacs. Such starches are referred to as pregelatinized

or pregelled starches. Examined under the microscope the ruptured starch grains will have a characteristic slit in the amylopectin coat. Depending on the temperature used and the time of exposure of the starch grain to the heat, it is possible to obtain starches that are pregelatinized to different extents. The extent of pregelatinization has a major influence on their physical properties and thus their suitability for use in different applications.

One property that is changed and has implications for use in tablet formulations is the solubility of the pregelatinized starch. Fully pregelatinized starches are cold water soluble and have little or no disintegrant activity. Indeed they may retard disintegration and dissolution, particularly after aqueous granulation. The compactibility of fully pregelatinized starch is also poor. Fully pregelatinized starch is used as a wet granulation binder.

By contrast, partially pregelatinized starches have good compaction properties and retain adequate disintegrant activity. They may be used in direct compression formulations as both a filler/binder and as a disintegrant. However, like the parent native starch, the partially pregelatinized starches (and fully pregelatinized starches) contain high levels of free moisture which may be detrimental to certain less stable APIs. The typical grades of partially pregelatinized starch used in the pharmaceutical industry are about 20% pregelatinized (e.g., Starch 1500®, Colorcon Ltd., Dartford Kent, U.K.). There is a low-moisture grade of Starch 1500 available, Starch 1500 LM, with a moisture content of not more than 7% which helps address the issue of the high moisture activity of pregelatinized starch. However, the reduction in moisture content does change the compactibility.

Partially pre-gelatinized starch may be used as a direct compression binder/filler and as a disintegrant. Use levels as a direct compression disintegrant are typically around 15% by weight. It can be used at higher levels as a direct compression binder/filler. It can also be used in wet granulation but tends to act as a binder during the wet massing step because of the release of amylose by the ruptured starch grains.

Most pregelatinized starch used in the U.S. pharmaceutical industry is manufactured using corn starch. However, the FDA's Inactive Ingredient Database (39) also lists pregelatinized tapioca starch as being used in tablet products.

Chemically modified starches. The number of chemically modified starches used in pharmaceutical formulation is small. Three chemically modified starches that are used in pharmaceutical formulations are hydroxyethyl starch, hydroxypropyl starch, and sodium starch glycolate. In addition, the National Formulary 19 (USP 25-NF 19) has a monograph for Modified Starch which states that starch "may be modified by chemical means." The permitted modifications are acid-modified, bleached, oxidized, esterified, etherified or modified enzymatically. The stated intent of these modifications is to change the functionality of the starch.

Sodium starch glycolate is one of the superdisintegrants and is discussed below (see section Superdisintegrants).

Hydroxyethyl starch is used as an intravenous plasma volume expander.

Hydroxpropyl starch is used in antiseptics and cosmetics. It has also been evaluated as a binder and disintegrant for tablets. However, it is not approved for use in either Europe or the United States, although there is a monograph in Japanese Pharmaceutical Excipients (51).

Alginic Acid

Alginic acid is a linear glycuronan polymer consisting of a mixture of β-(1→4)-D-mannosyluronic acid and α-(1→4)-L-gulosyluronic acid residues, of general formula $(C_6H_8O)_n$. The molecular weight is typically 20000–240000 (36). It is extracted from

various species of marine algae; brown seaweeds of the Phaeophyceae. These seaweed species are found world wide.

Alginic acid is not soluble but it does swell in contact with water, and this is probably where its use as a tablet disintegrant comes from. Typically it is used up to about 5% w/w of the formulation.

Alginic acid will form salts with cations. Sodium alginates are water soluble and are used to increase viscosity of liquid formulations. Alginic acid will only function as a disintegrant in an insoluble form. Salts of alginic acid with divalent cations, e.g., calcium, are also insoluble, and calcium alginate has been used as a tablet disintegrant. The presence of the divalent cations creates a cross-linked gel structure that has been used in the preparation of controlled release solid dose forms. At higher pH, in the presence of monovalent ions, a viscous gel will form that will probably retard both disintegration of the tablet and dissolution of the API.

Polacrillin Potassium

Polacrillin potassium is the potassium salt of an ion-exchange resin. The polymer backbone of the ion-exchange resin is a copolymer of methacrylic acid and divinyl benzene. As the salt of an ion-exchange resin, this material is very hydrophilic. Importantly, on contact with water the polymer swells, and this may be an important contribution to its disintegrant behavior. Contributions to the disintegration effect would also be expected from wicking and recovery of elastic deformation. Typical use levels are in the range 2–10% (36).

Being a potassium salt, polacrillin potassium has the potential to interact with APIs. Both chemical and physical interactions are possible. Potassium salts, in general, can promote certain degradation reaction, e.g., ester hydrolysis. Such effects can be reduced if the water activity in the tablet matrix is kept below about 0.2. Since this material is an ion-exchange resin, there is also the potential for ion exchange with other cations, e.g., organic cations, in the presence of water. It may be difficult to reverse such interactions, and dissolution and efficacy may be reduced. This effect can be of use in controlled release drug delivery systems and taste masking, but those considerations are outside the scope of this discussion.

Besides polacrillin potassium, there are other ion-exchange resins using different combinations of monomers that could also be used as disintegrants, e.g., styrene and divinyl benzene copolymers, and phenolic polyamide condensates. However, regulatory approval for use in human pharmaceuticals administered via the oral route will be required before they can be used.

Superdisintegrants

The term "superdisintegrant" was introduced, probably in the late 1970s or early 1980s, to describe the then new generation of disintegrants that were much more effective and used at lower concentrations than the traditional disintegrants. The first superdisintegrant to be introduced was sodium starch glycolate in the late 1960s, followed by croscarmellose sodium and crospovidone in the early 1970s. At about the time these materials were developed there was a significant increase in our understanding of what was required for APIs to be absorbed from the GIT, and the concepts of dissolution of the drug in the stomach and subsequent absorption, together with the developing field of pharmacokinetics, were being developed. That is not to say that the developments in our understanding inspired the development of the new disintegrants. The development

was probably inspired by a need to have a disintegrant that was effective at lower concentrations and could be used more easily in direct compression formulations. The Company that introduced sodium starch glycolate was also promoting direct compression at that time.

On a regulatory note, while the three superdisintegrants are all approved for use in pharmaceutical products for oral administration, none of them are approved for use in food products.

Sodium Starch Glycolate

Sodium starch glycolate is the sodium salt of cross-linked carboxymethylated starch. When viewed under the microscope it has the characteristic appearance of starch grains, but with small particles of sodium glycolate and sodium chloride adhering to the surface of the starch grains. There are many different sources and several different grades of sodium starch glycolate available using different sources of starch, and different types and levels of cross-linking. These differences have a significant influence on the choice of the appropriate grade for a particular application and process.

Sodium starch glycolate is manufactured from the native starch by first cross-linking the starch using either an aqueous solution of sodium trimetaphosphate as the cross-linking agent, or by dehydration. In both cases, the cross-links form between adjacent chains on the surface of the starch grain. The cross-linked starch is isolated and dried, and then reacted with sodium monochloroacetate to form the carboxymethylated cross-linked starch. This reaction is carried out in an organic solvent, typically denatured ethanol, but methanol is also used. However, with the introduction of ICH[a] Q3C, ethanol (Class III solvent) might be preferred over methanol (Class II solvent) (52) unless there are other overriding considerations. After neutralization, the sodium starch glycolate is washed to remove reaction by-products (sodium glycolate and sodium chloride) and dried. Since it is manufactured in a hydrophilic organic solvent, and because of the structure of the starch grains the residual solvent levels are typically around 4–5% w/w by loss on drying.

From the above discussion it becomes obvious that it is possible to vary the degree of cross-linking, the degree of substitution and the extent of neutralization of sodium starch glycolate. Grades using one or more of these variations are, or have been, commercial grades in the global market. The changes that these variations bring to the final material can be substantial, and can mean success or failure of a formulation development project: not all sources and grades will be interchangeable for some applications, and some grades will be more suited to certain processes. The effects of degree of cross-linking and degree of substitution were investigated by Rudnic et al. (53) They found that the degree of substitution had less of an effect than the degree of cross-linking, and that the two modifications were opposite in effect. Thus, there was an optimum combination of the degree of substitution and degree of cross-linking, and the commercially available product was reported to be at that optimum. These results were also confirmed by Bolhuis et al. (54) who also reported that disintegration efficiency could be further improved by reducing the level of sodium chloride contained in the disintegrant. This was confirmed by Miseta et al. (55). Presumably, the sodium chloride competes for the water penetrating the tablet matrix, thus reducing the rate of swelling of the sodium starch glycolate. In a further study Bolhuis et al. investigated the effects of starch source on the properties of

[a] International Conference on the Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use.

sodium starch glycolate (56). They investigated the performance properties of sodium starch glycolate manufactured from potato, maize, waxy maize, wheat, rice sago, and tapioca starches. In summary, potato starch appeared to be the best starch source, and rice starch the least favorable. Gebre-Mariam and Schmidt investigated the performance of sodium starch glycolate prepared from Dioscorea starch. There were some differences in behavior between the two materials. Overall the Dioscorea sodium starch glycolate appeared comparable to sodium starch glycolate prepared from potato starch (57). The differences were believed to be related to both differences in the cross-linking method used in the manufacture of the two sodium starch glycolates, and to the differences between the two starches. Most of the sodium starch glycolate available in the U.S. and European markets is manufactured using potato starch.

Sodium starch glycolate is believed to act principally through swelling. The rate of swelling on contact with water appears to be directly correlated with the rate of water uptake (58). There may be other, lesser contributions to the disintegrant activity from wicking and recovery of elastic deformation.

An important consideration when using sodium starch glycolate is the grade to select for inclusion in the wet mixing step during aqueous granulation. Sodium starch glycolate will absorb water during the wet massing operation. As a consequence the sodium starch glycolate particles will swell, and in their swollen state are more fragile with respect to mechanical damage such as might be experienced during wet massing using a high speed mixer granulator. Should the integrity of the sodium starch glycolate particles be compromised during wet massing then we would lose disintegrant activity and gain wet binder activity, and both would serve to increase tablet disintegration time and decrease dissolution of the API. The effects of wet granulation on the disintegration efficiency of sodium starch glycolates having different degrees of substitution and cross-linking has been investigated (59). In summary, a higher degree of cross-linking reduces the amount of swelling, and ensures that the starch grains are less susceptible to mechanical damage during the wet massing operation. Presumably, the increased cross-linking increases the strength of the hydrated grains in two ways: by reducing the amount of swelling the amylopectin coat is less distended, and the extra cross-linking would also be expected to strengthen the coat.

Sodium starch glycolate is a sodium salt, and has all the potential incompatibilities associated with sodium salts; e.g., ester hydrolysis and other base catalyzed reaction. The fact that sodium starch glycolate is insoluble does not preclude such interactions, particularly if moisture is present. Sodium starch glycolate also contains levels of sodium chloride and sodium glycolate which are soluble and could also take part in such interactions. The water activity of the overall finished product will govern the rate of reaction, with low-water activity reducing the rate. This may be more of a problem in direct compression and dry granulation, since in direct compression the water activity is likely to be inhomogeneous through the tablet matrix, and local high water activity micro-environments may exist. In wet granulation, the granulation and drying processes tend to equalize water activity through the tablet matrix. The primary packaging will also play an important role since the product is required to remain stable (within specifications) throughout its shelf-life. It is not always possible to avoid materials that interact in some way. If the potential for such interactions exists, a high moisture barrier container-closure system will be required.

The typical use levels of sodium starch glycolate in direct compression formulations are in the range 2–4% depending on the hydrophobicity of the other components. In granulated systems the typical use levels are in the range 4–6%, with the sodium starch glycolate split between the intra- and extragranular phases.

Croscarmellose Sodium

Croscarmellose sodium is a cross-linked form of carmellose sodium (formerly known as sodium carboxymethyl cellulose). It is manufactured from high quality wood pulp or cotton linters. The cellulose is steeped in caustic soda to form alkali cellulose which is then reacted with sodium monochloroacetate to form sodium carboxymethyl cellulose (carmellose sodium). The excess sodium monochloroacetate is converted to glycolic acid which converts some of the carboxymethyl groups to the acid form, and catalyzes the formation of cross-links. Finally the croscarmellose sodium is washed with aqueous ethanol to remove the reaction by-products, sodium chloride and sodium glycolate (36).

When viewed under the microscope, croscarmellose sodium particles are fibers, i.e., long, narrow particles, but curved and twisted rather than straight. This morphology derives from its origin as cellulose from wood pulp or cotton linters. Croscarmellose sodium is insoluble in water, but swells to 4–8 times its original volume on contact with water (36).

Croscarmellose sodium appears to act partly through swelling (60). However, it seems to be effective at lower levels of incorporation than sodium starch glycolate, but does not swell as much (58). On the balance of evidence, it seems likely that croscarmellose sodium may also work through the recovery of energy of elastic deformation and wicking, and also because the particles are fibers. The long fibers will function over a longer distance in the tablet matrix and thereby cause disruption over a longer distance than the irregular crospovidone particle and the rounded sodium starch glycolate particles, and thus cause more extensive disruption of the tablet matrix. This would in turn be expected to allow efficient disintegration at a lower level of incorporation.

There are several different sources and different physical and chemical grades of croscarmellose sodium. Comparative evaluations have been reported in the literature and will be summarized here. Provided the correct grade is selected from the different manufacturers, the differences between materials produced by the different manufacturers are not considered significant, and all materials are highly efficient tablet disintegrants (61). However, there are several different physical grades available from at least one manufacturer, some of which are less appropriate for use as tablet disintegrants. The critical physical parameters for croscarmellose sodium for use as a tablet disintegrant appear to be degree of substitution and the amount of water soluble component (60).

Croscarmellose sodium may be used as a tablet disintegrant in direct compression, dry granulated and wet granulated products. The recommended level of incorporation for direct compression formulations is 1–2% by weight (36). The solubility of the other components of the formulation will influence the final level, with more disintegrant being required for formulations having a greater proportion of soluble components. For granulated systems, the recommended level of incorporation is higher, typically 3–4% by weight, again depending on the proportion of soluble components in the formulation (36). There appears to be consensus in the literature, particularly in more recent studies, that the disintegrant should be split between the granulated part and the final dry blend (24,62,63). The exact proportions of the split will depend on the overall formulation.

Croscarmellose sodium is a sodium salt and the same considerations for potential incompatibilities with other components of the formulation exist as have been described under sodium starch glycolate above. The levels of sodium glycolate and sodium chloride are lower than for sodium starch glycolate, but still sufficient to cause problems if the water activity in the formulation is sufficiently high.

Crospovidone

Crospovidone is cross-linked polyvinylpyrrolidone, or cross-linked povidone. Non-cross-linked povidone is a synthetic, water soluble polymer originally developed as a plasma expander in Germany in the 1930's. Povidone is manufactured from acetylene, formaldehyde and ammonia via butyrolactone, and vinyl pyrrolidone. Cross-linking is then carried out using a catalyst by a "pop corn" polymerization process (36). Crospovidone can contain traces of formaldehyde and peroxides which may have implications for compatibility with other components in the formulation.

Several different grades of crospovidone are available for pharmaceutical use. They are differentiated by particle size. The smaller sized grades are milled or micronized, and are used as auxiliary suspending agents in liquid suspension products. For use as a tablet disintegrant, the largest particle size grade is preferred (64). There can be differences in particle sizes of the larger particle size materials offered by the different suppliers, thus the grades from different suppliers may not be functionally equivalent. Under the microscope, crospovidone particles of the larger median particle size grades appear irregular with a macroporous structure. Not surprisingly, the individual particles from the milled and micronized materials show less porosity.

Crospovidone is used as a tablet disintegrant in direct compression, dry granulated and wet granulated formulations. The mode of incorporation into wet granulated formulations has been investigated. In general, intragranular incorporation of crospovidone appears straightforward and the crospovidone does not appear to be adversely affected by the wet massing process. Best results for both disintegration and dissolution were obtained when the crospovidone was incorporated into the formulation both intra- and extra-granularly, but not necessarily equally between the two phases (19). The levels of incorporation of crospovidone reported in the literature have varied, however, when used as a tablet disintegrant for immediate release products levels of 2–5% have been used in both direct compression and granulated systems. Incorporation of higher levels of crospovidone may eventually cause problems of friability, hardness, and weight variation (64).

Compared to the both sodium starch glycolate and croscarmellose sodium, crospovidone appears not to swell as much on contact with water (58); nevertheless it is an effective disintegrant. It is believed that recovery of energy of elastic deformation plays a major role in the disintegrant activity of crospovidone, along with capillary action and disruption of particle-particle bonds on penetration of water into the tablet matrix. There is probably a minor contribution from swelling, and this would be likely to be most significant at lower tablet porosities provided the penetration of water into the tablets is not decreased due to the very small size of the pores at lower porosities (higher compaction force) (6).

Other Materials

The traditional and superdisintegrants have been used for many years. However, it has long been recognized that there are limitations in the use of these materials, particularly in terms of chemical and physical incompatibilities, and the level required in a particular formulation for them to be effective. For example, both sodium starch glycolate and croscarmellose sodium are sodium salts; they potentially have all the incompatibilities associated with sodium slats and may not be appropriate for use with certain APIs. Crospovidone also has limitations and incompatibilities. The following sections will discuss some other materials that have been assessed and/or appear to possess tablet disintegrant activity that may be appropriate in certain circumstances. Some of these

materials are new, some have been available for many years but are no longer used for one reason or another.

Microcrystalline Cellulose

Microcrystalline cellulose is prepared by the acid hydrolysis of high purity wood pulp, so-called "dissolving grade" pulps. Cellulose is a β-(1→4) linked polymer of glucose. This is a simplistic view of native cellulose since we also know that there are other components in native cellulose, e.g., xylan (from xylose) and mannan (from mannose). Native cellulose is considered to be composed of alternating microcrystalline and amorphous regions. The microcrystalline regions appear to be denser; more tightly packed, whereas the amorphous regions are less dense; less tightly packed. The acid hydrolysis preferentially attacks the less dense amorphous regions leaving the microcrystalline regions largely intact.

Microcrystalline cellulose has several uses in tablet formulation. It is typically regarded as a direct compression binder/filler. It is also used in wet granulation to reduce the sensitivity of the wet mass to over granulation, and similarly in extrusion and spheronization. While not soluble in water, it is hydrophilic and swells somewhat in contact with water. Tablets of microcrystalline cellulose prepared by direct compression, and with no other excipients present, are self-disintegrating when put into aqueous media, e.g., dilute acid or water.

There are formulations where the disintegration effect is provided by microcrystalline cellulose (16,17). However, generally, the disintegration efficiency of microcrystalline cellulose is comparatively low and the amount of material included in the formulation will have a significant effect on its effectiveness. Levels in excess of 20% w/w may be required to ensure adequate disintegration of a non-hydrophobic API. If the API is hydrophobic, it will probably be necessary to include a recognized disintegrant in the formulation. Microcrystalline cellulose probably derives its disintegrant activity through a combination of wicking and disruption of particle-particle bonds due to the presence of water. Contributions from swelling and recovery of elastic deformation could also be anticipated.

Low Substituted Hydroxypropyl Cellulose

Hydroxypropyl cellulose is water-soluble cellulose ether. The low substituted form is not water soluble, but is still hydrophilic and swells in water. Under the microscope the grades used in direct compression and wet granulation are fibrous. It has been evaluated as a tablet disintegrant and has disintegrant activity, but it is not as effective as sodium starch glycolate, croscarmellose sodium or crospovidone (66,67). Typical use levels as a disintegrant are in the range 2–10%, but it can also be use as an aid to direct compression at higher levels.

Soy Polysaccharide

Soy polysaccharide is an extract of soy bean (*Glycine max*). During the processing of soy beans, the triglycerides and protein are separated and extracted for various uses. What is left is mostly soy polysaccharide, but also containing some residual triglycerides and protein. Soy polysaccharide is a food extract. It has been used in pharmaceutical tablet products available in the United States. However, today it is mostly used in herbal, "nutraceutical" and food supplement products in the United States, where its non-chemical/non-synthetic character are an advantage. It is also used in similar products in Europe.

Soy polysaccharide is comprised of mainly cell wall carbohydrates, but may contain up to 16% protein material, and up to 2% soy lipids. Chemically, the carbohydrate component appears to be non-reactive, however, the protein and fat components have the potential to interact with other components of the formulation. Typical use levels as a tablet disintegrant are in the 5–10% range by weight.

Polysaccharide materials from other crop plants have also been proposed for use as tablet disintegrants. Schmidt and Zessin (68) investigated the cell wall components from *Chenopodium album* (lambsquarters) and *Beta vulgaris* (common beet) and found that both materials had disintegrant properties, but that they were inferior to crospovidone, which correlated with a slower rate of swelling for the two experimental materials.

Xylan

Xylan is a polysaccharide; primarily comprising β-(1→4) linked chains of xylose which may be branched. It is part of the hemicellulose content of plant cell walls. Xylan is a by-product of the manufacture of xylitol, a polyhydric alcohol that is used in formulation and manufacture of low carbohydrate candy products. Juslin et al. evaluated Xylan as a potential filler and disintegrant, and compared it to a partially pregelatinized starch; Starch 1500 (69). In summary, xylan has potential as a filler. It also has some disintegrant activity, but in that respect it would appear to be comparable to microcrystalline cellulose, i.e., it has some inherent disintegrant properties, but is not regarded as a very effective disintegrant in tablet formulations.

The regulatory status of xylan is not known. It is not included in the FDA's Inactive Ingredient Database (39).

Xanthan SM

Xanthan SM is an insoluble material derived from xanthan by a specific heat treatment. The content of water soluble substances is low, and comparable to that of croscarmellose (ca. 1.5%). As a disintegrant, Xanthan SM gave comparable results to both sodium starch glycolate and croscarmellose sodium when used at a comparable level of incorporation. The dissolution data also suggested there was little or no difference in disintegration efficiency of Xanthan SM compared to croscarmellose sodium or sodium starch glycolate when incorporated into the tablet formulation at the same level (70,71).

The regulatory status of Xanthan SM for use in pharmaceuticals was unclear at the time of writing. It is not included in the FDA's Inactive Ingredient Database (39) whereas xanthan gum is. However, it appears to be approved for use in food processing in Europe.

Inorganic Materials

Most tablet disintegrants are hydrophilic colloid materials based on organic polymers of natural, synthetic or semi-synthetic origin. However, several inorganic materials have been investigated for potential use as tablet disintegrants, and some of these will be discussed here.

The effervescent couple: Effervescent products are either soluble, or form finely divided suspensions after coming into contact with water. As noted previously, the effervescent couple reacts to generate carbon dioxide which disrupts the tablet matrix thus aiding dissolution or dispersion of the API and other components. Effervescent products are usually added to a glass of water and taken after the main effervescence has subsided, and the tablet components are dissolved or dispersed. Obviously, taste will be an important consideration in the formulation of effervescent products, and will govern the choice of components used in the formulation. The effervescent couple typically

consists of a soluble organic acid and a soluble bicarbonate salt. The organic acid is most often citric acid. Other acids, e.g., tartaric acid, may also be used; however, citric acid is generally preferred. The soluble bicarbonate salt is usually anhydrous sodium bicarbonate. Soluble carbonate salts could also be used, but the bicarbonates are preferred because they are more efficient carbon dioxide generators. One composite material that has been introduced is sodium glycine carbonate. It may be regarded as a mixture of sodium carbonate and glycine.

Regardless of which effervescent couple is used, all effervescent products have two significant requirements: their manufacture and packaging must take place under carefully controlled humidity condition; i.e., less than 20% relative humidity to prevent premature activation of the couple, and their primary packaging must be moisture tight to prevent premature activation of the couple during transport and storage. There are other important issues that must also be taken into account when manufacturing effervescent products, including granulation method, flavor, lubrication, punch construction, etc. However, these are outside the scope of this chapter. Due to its stringent manufacturing and packaging requirements, the effervescent couple is not appropriate for use in conventional immediate release tablets.

Complex aluminum silicates: The complex aluminum silicates are clays, typically of the montmorillonite type. In general, these materials are able to absorb large quantities of water with swelling, and this is presumably an important factor in their disintegrant activity. However, some materials are more frequently used as suspending agents, e.g., bentonite. The chemical structure of some of the materials is well understood. In other cases, the elemental composition may be known but the exact molecular structure is not. They may also contain magnesium and other metal ions in their composition. These materials are highly absorptive, and this can cause problems with API molecules that are absorbed by these materials, leading to dissolution and bioavailability problems.

Magnesium aluminum silicate. Magnesium aluminum silicate is a polymeric complex of magnesium, aluminum, silicon, oxygen and water, plus traces of other metals. It has been used as a tablet disintegrant at a level of incorporation of 2–10% (36). Magnesium aluminum silicate may also be used in a variety of other applications, including the formulation of suspensions as a viscosity modifier. The key to its use may be in the time available for hydration and the sequence of events during the hydration. When used as a tablet disintegrant the time is short and the magnesium aluminum silicate may only have time to swell. When used as a suspending agent/viscosity modifier, the time available for hydration is much longer.

Smecta. Smecta is a non-fibrous attapulgite mostly comprised of smectite, from the montmorillonite group of clays. It has a high capacity to absorb water, in common with other clays, and for this reason it has been evaluated as a tablet disintegrant (72). When used in both direct compression and wet granulated formulations based on both soluble and insoluble fillers, Smecta gave very similar results for disintegration time in all four cases. It was marginally better than Starch 1500 and Veegum, but markedly inferior to croscarmellose sodium and crospovidone when used at the same level of incorporation (5% w/w). Interestingly, comparative dissolution using hydrochlorthiazide as a model drug showed that the Smecta formulation gave better dissolution than a comparable croscarmellose sodium formulation.

Attapulgite is used in products for the adjunct treatment of diarrhea, and it is listed in the FDA's Inactive Ingredient Database for use in oral powders (39).

Colloidal silica: Colloidal silica is often used in tablet formulations, and it has been used as a comparator in disintegrant studies. However, while it may contribute to the

establishment of a hydrophilic network within the tablet matrix, it does not appear to have a major disintegrant effect (45).

Inorganic carbonates: Inorganic carbonates react with mineral acid, e.g., hydrochloric acid present in the human stomach, with the evolution of carbon dioxide (CO_2). This interaction, and the gas generated, disrupts the tablet matrix and water is drawn into the tablet, at the same time the tablet is disintegrating, and thus dissolution of the API becomes more certain. Magnesium carbonate is used in pharmaceutical tablet formulations (16). Its primary use appears to be as a filler in wet-granulated products, however, it will have a secondary function as a tablet disintegrant when it reacts with the hydrochloric acid in the patient's stomach.

Soluble Polymers

In general, soluble polymers have more disadvantages than advantages when used as tablet disintegrants. The main problem is that soluble polymers tend to produce viscous solutions, and if the viscosity develops during disintegration, both disintegration and dissolution can be retarded. This is the basis for many oral modified-release drug delivery systems, albeit typically using high viscosity grades of polymers. Nevertheless, there are reports in the literature of their use as tablet disintegrants, and therefore they are discussed here.

Carmellose sodium: Carmellose sodium is included for completeness. Its manufacture is described under croscarmellose sodium. It has been assessed as a tablet disintegrant in the literature (73). Today, carmellose sodium would not be considered for use as a tablet disintegrant. It is a water soluble polymer, and as such would be expected to potentially impede disintegration and dissolution due to the formation of a viscous gel layer on contact with water. In the reports cited, carmellose sodium did not perform well as a tablet disintegrant. It is not recommended as a tablet disintegrant.

METHODS FOR THE EVALUATION OF TABLET DISINTEGRANTS

The ultimate test of whether or not a particular material or batch of material is suitable for a particular formulation or batch is the success of the manufacturing process and/or the attainment of the appropriate pharmacokinetic profile in the patient. There is increasing interest in tests that are predictive of material performance in the manufacture or use of the finished medicinal product, and that do not require the manufacture and testing of small scale batches of the finished product, i.e., tests that predict the "functionality" of the excipient (in this discussion, the disintegrant). In addition, the product manufacturing processes must be validated, and this requires that we understand our materials, the processing and how they interact, and what is necessary to ensure the manufacturing processes continue to produce product that meets specification throughout its shelf-life. It is beyond the scope of this review to go into the details of the critical parameters for powder blending, granulation, and compaction that will be required for the processing and manufacture to be successful, and the reader is referred to the chapters elsewhere in this book for the appropriate advice.

In evaluating materials for potential use as tablet disintegrants, the tests can be divided into those dealing with the physical characterization of the materials (presumed to be powders), and those that are likely to be relevant to the disintegrant activity (functionality) of the material, i.e., tests that measure a parameter during or after hydration. These latter tests are referred to as "performance tests" in the USP, and as "functionality-related characteristics" in the European Pharmacopoeia. The tests used to assess a

particular material will depend on the predominant mechanism(s) of disintegrant function for that material. The following is a list of the most likely tests that could be used. It is not a definitive list, other tests may be appropriate from time to time, but it is a place to start.

Particle shape: The form of the particles may be important. Long fibrous particles may be more effective in some circumstances than rounded or irregular particles because fibers may exert their effect over a longer distance through the tablet matrix.

Particle size: For disintegrants where swelling is a predominant mechanism of function, particle size will be important since larger particles swell more than small particles (30).

Swelling: There are several different aspects to swelling that need to be considered; the rate of swelling, extent of swelling and swelling force. From first principles, it would be anticipated that a material that swelled quickly would generate more "force" for disruption of the matrix than a slow-swelling material. Similarly, a material that showed extensive swelling would generate more force than one that swelled only to a limited extent. In actual use it will be a combination of both rate and extent that generate the swelling force. Several groups have investigated swelling phenomena and designed equipment to measure rate of swelling and swelling force (58,74,75). The extent of swelling can be assessed in two ways; at the level of individual particles (referred to as intrinsic swelling), and swelling of the bulk powder (bulk swelling). Intrinsic swelling may be determined using a microscope. Bulk swelling may be determined by measuring the change in volume with time of a powder bed in contact with water.

Sedimentation volume: A known weight of disintegrant is mixed with water in a measuring cylinder and allowed to stand for a specified period. The volume of the hydrated layer of disintegrant is measured. This parameter may be linked to the extent of hydration.

Water penetration into a powder bed: This parameter may be determined using the equipment for determination of bulk swelling. The rate of water penetration is linked to the hydrophilicity of the powder. In addition, using the same equipment it should be possible to determine the hydration capacity of the material. This type of measurement has also been used to determine the rate of hydration.

Beyond these few performance tests, most investigations reported in the literature also evaluated the disintegration efficiency of the materials using model formulations, and covering both insoluble and soluble matrices. In addition, model formulations containing model drugs, e.g., hydrochlorthiazide, have been evaluated for both disintegration and dissolution performance.

METHODS FOR THE EVALUATION OF TABLET DISINTEGRATION

The disintegration and dissolution of tablets is covered in greater detail in Volume 3. However, it is appropriate to discuss briefly here why we test tablet disintegration and when, and the methods used.

Tablet disintegration can be regarded as a surrogate for release of the API from the tablet (dissolution). Tablet dissolution, in turn may be regarded as a surrogate for drug absorption, assuming that the dissolution conditions in vitro bear some relation to the dissolution conditions in vivo, and the absorption of the drug is not dissolution rate controlled. There have been many papers in the literature over the years which suggest this is true for some drugs and formulations, but not all. The determination of tablet dissolution is a more complex and time consuming procedure than the determination of

tablet disintegration, and there are circumstances, such as during tablet production, when the shorter procedure has advantages. Today, tablet disintegration is more often used as an in-process control test than as a final product release test. For final quality assurance release of immediate release tablet products, dissolution is almost always included in the finished product specification; disintegration may not be.

Tablet disintegration tests have been included in the pharmacopeias for many years. Initially, each pharmacopeia had their own test and apparatus, but through the work of the Pharmacopeia Discussion Group[b] the disintegration test and apparatus are now harmonized between the three pharmacopeias, although the USP text does contain some "national" text.

The apparatus is described in the USP as follows (76):

> The apparatus consists of a basket-rack assembly, a 1000-mL low form beaker, 138–160 mm in height and having an inside diameter of 97–115 mm for the immersion fluid, a thermostatic arrangement for heating the fluid between 35° and 39°, and a device for raising and lowering the basket in the immersion fluid at a constant frequency rate between 29 and 32 cycles per minute through a distance of not less than 53 mm and not more than 57 mm.

The basket rack assembly has six tubes of specified dimensions, each having a mesh at the bottom of a specified weave. Disks of a specific design, dimensions, and construction are also sometimes used. Operation is simple. A tablet is placed in each of the six tubes. The basket rack assembly is then immersed in the immersion fluid, typically water, at the specified rate, and the time is recorded at which the final piece of the tablets falls through the mesh at the bottom of the tubes. To comply with specification all tablets must have fully disintegrated within a set time.

When used in a product development setting, there may be no preset specification. In such cases, it may be more appropriate for the individual disintegration times to be recorded for each tablet, or as a range from first to last. Even though disintegration does not equate with drug release, disintegration assessment is a useful aid in the optimization of tablet formulations during development and scale-up.

There are reports in the literature of the use of measurement of the force generated during tablet disintegration to characterize disintegration of formulations. Gould and Tan (27) found a correlation between the time to generate 50% of the maximal force and the disintegration time for wet granulated formulations that had been recompressed. Massimo et al. (77) used a similar approach and were able to determine the "disintegration propensity" of two tablet formulations containing poorly soluble APIs. These workers also reported that there was a relationship between disintegrating force and dissolution rate of the tablets.

CONCLUSION

For immediate release oral tablets, disintegration is a prerequisite for release of the API. There are several tablet disintegrants available for use. They work through a variety of

[b] The Pharmacopeial Discussion Group comprises representatives from the European, Japanese, and USP. It is a formal collaboration that meets twice yearly, usually at the same time as the ICH meetings, to collaborate on the harmonization of pharmacopeia general chapters and monographs for excipients. They have established a formal 7-step process for harmonization. Where full harmonization is not possible, 'harmonization by attribute' is used. In addition, each of the three pharmacopeias may introduce 'national' text which is not part of the harmonized monograph and is clearly annotated as such.

different mechanisms. Some may be more appropriate for a particular application than others. The ultimate choice of disintegrant for the intended application will depend on a number of factors including the dose of the API, its compatibility with the other components of the formulation, cost and company or personal preferences.

The formulation scientist requires a good understanding of the API, the excipients and the unit processes, including their advantages and limitations, and how they interact. A good understanding of tablet disintegrants is an important part of that understanding. The above discussion on tablet disintegrants cannot describe all aspects of their use and application. Rather, it should be considered as an introduction, upon which formulation scientists will build their own body of knowledge, understanding, and experience.

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7
Lubricants, Glidants, and Antiadherents

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INTRODUCTION

For a particulate solid to be compacted to form tablets of acceptable quality, it needs to have three essential properties.

1. It must have good flow properties so that the dies of the press are filled in a reproducible manner.
2. The particles must stick together when subjected to a compacting force, and must retain a coherent structure when that force is removed.
3. Once formed, the tablet must be easily ejected from the die without damage to the tablet or the press.

Very few solids possess all three of these essentials, and hence some modification is always necessary, perhaps by a physical process such as granulation, and almost invariably by the addition of other ingredients known as excipients. Of these excipients, that usually described as a lubricant is one of the most important, and it is the subject of this chapter.

In fact, the term "lubricant" is used to describe three different functions.

1. The lubricant can promote particulate flow, so that a reproducible die fill is obtained and hence there is a uniformity of tablet weight. The term "glidant" is used to describe this function.
2. The lubricant can prevent the punch faces from sticking to the faces of the tablet as the latter is ejected from the die. This is better described as an "anti-adherent" action.
3. The lubricant can prevent adhesion between the sides of the tablet and the die wall as the tablet is pushed out of the die by the ascending lower punch. Lubrication is essentially overcoming friction, and hence this function can be directly described as lubrication.

It is important to distinguish between these three functions. Their causes are different, as are their methods of evaluation, and few substances can successfully act as glidant, anti-adherent and lubricant, though some might act as two of these.

LUBRICANTS

The function of the lubricant is to overcome friction, and in particular die wall friction that occurs between the die wall and the side of the tablet. As a particulate mass is compressed in the die, particle rearrangement occurs, particles moving to fill pores and give a less porous aggregate. Contact between the particles and the wall of the die is increased. Only a small force is required for this stage of consolidation. As the compaction force increases, consolidation progresses by means of fragmentation or particle deformation, or most likely a mixture of both these mechanisms with one predominating. If the particles deform under pressure, then their vertical dimension will decrease, with a corresponding increase on their horizontal dimension, the magnitude of which is governed by the Poisson ratio of the solid. This further increases the force on the die wall.

Friction and Lubrication

Friction is a force that resists the sliding of one solid surface over another, and is caused by forces of attraction between the contact regions of the surfaces which are always microscopically irregular. The shearing of these points of contact and the "ploughing" of irregularities on the harder surface through the softer gives rise to the frictional force.

Perhaps contra-intuitively, friction is independent of the surface areas in contact. An often-quoted example is that of a brick, which would exert the same frictional force on a given surface, irrespective of which of its faces was in contact with that surface. As friction is independent of surface area, its units are those of force (N) rather than pressure (N m^{-2} or Pa). The frictional force is however dependent on the force that presses the surfaces together. Thus a pile of three bricks would exert three times the frictional force of one brick (Fig. 1). The coefficient of friction is the ratio of friction to load, and because both friction and load are measured in terms of force, the coefficient of friction is a dimensionless constant.

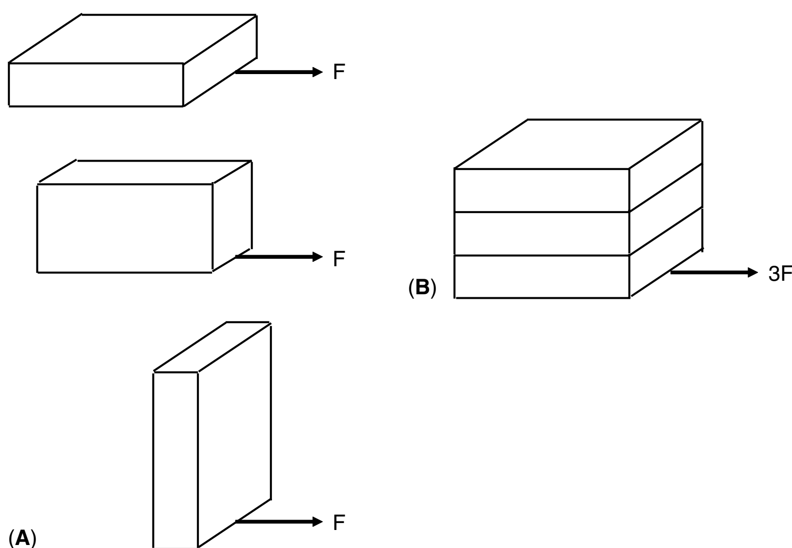

FIGURE 1 Frictional force: (**A**) independent of area of contact, (**B**) dependent on load.

With respect to the tablet, the die-wall friction is independent of tablet thickness, provided the force at the die wall is constant. An increased compaction force will in turn lead to increased transmission of force to the die wall, and so the frictional force will increase.

The word "lubricant" is derived from the Latin verb "lubricare" meaning "to make slippery." The purpose of a lubricant is to reduce friction, and this is achieved by interposing a film of lubricant to separate the two sliding surfaces. One general property of lubricants is that they have structures that are easily deformed. In everyday life, machinery is normally lubricated by liquids of hydrocarbon origin, but these are generally unsuitable for use in tablet formulations. In the latter, the lubricant is almost invariably an organic or inorganic solid that by virtue of its structure, can be readily deformed.

Friction and lubrication have been comprehensively discussed by Bowden and Tabor (1).

Lubrication in the Tableting Process

The act of consolidating particles in a die will inevitably lead to a force being exerted at the die wall. This will generate a frictional force that must be overcome before the tablet can be ejected from the die. Hence a lubricant is almost invariably a component of a tablet formulation.

An ideal tablet lubricant would exhibit the following properties:

1. It must have regulatory approval for use in medicines.
2. It should significantly reduce friction.
3. It should be effective at low concentrations so as not to unduly increase the bulk of the tablet.
4. It should have no adverse effects on the formulation or the properties of the tablet.
5. It should be chemically inert.
6. It should be cosmetically inert–in practice, this means it should be white, tasteless, and odourless.
7. It should be unaffected by changes in processing variables.
8. It should show batch-to-batch consistency.
9. It should be cheap and readily available.

An ideal lubricant has yet to be discovered–indeed many that have been used are seriously deficient in more than one of the above criteria.

Inadequate lubrication in a tablet formulation results in difficulty in ejecting the tablet from the die. This is often associated with a scraping noise as the tablet moves in relation to the die wall, and the sides of the tablet may show striations. In extreme cases, the tablet expands radially as it leaves the die and this causes disruption of inter-particulate bonds and an overall weakening of the structure of the tablet.

Evaluation of Lubricant Activity

Because of the importance of the lubricant in tablet formulations, it is not surprising that considerable effort has been made to devise methods whereby lubricant activity can be assessed and different lubricants can be compared.

Since frictional force is governed by the force applied by the tablet press, the development of methods to assess lubricant activity has depended largely on the introduction of the instrumented tablet press. In these devices, the applied force is measured

by transducers such as strain gauges, and if these are fitted to the upper and lower punches, the change in upper and lower punch force can be measured against time (2). Such changes on an eccentric tablet press are shown in (Fig. 2).

One of the earliest studies on lubrication using an instrumented tablet press was carried out by Nelson et al. (3) in 1954. They noted that the force detected at the lower punch (*L*) was always smaller than that applied by the upper punch (*U*). They observed that as lubrication was increased, the ratio between the lower and the upper punch forces also increased, and so they made the suggestion that lubricant activity could be expressed by means of the *R* value, which is a dimensionless number equal to L/U. The nearer *R* was to unity, the better the lubrication. Though initially a popular method of assessing lubricity, *R* was found to be highly dependent on the applied force. Müller et al. (4) have shown that for reproducible results, the tablet thickness and compaction force must be kept constant, and that the *R* value is not sensitive enough to distinguish between well-lubricated granulations.

Further work by Higuchi et al. (5) found that the difference between *U* and *L*, as well as their ratio, was also dependent on the degree of lubrication.

More dependable methods of assessing lubrication are those related to the force needed to remove the tablet from the die. Two of these have proved particularly valuable. The first is the force detected on the lower punch immediately before ejection commences, shown as RES in Figure 2 (6). The second is the force required to eject the tablet from the die, shown as EJF in Figure 2 (7).

Hölzer and Sjögren (8) have compared these methods and found that provided a correction was made for differences in contact area between the tablet and the die wall, a linear relationship was obtained between compression force and the three parameters (*U*-*L*), RES, and EJF. They concluded that the ejection force, corrected for area of contact, was the best predictor of adhesion problems.

A further possible application of instrumented tablet presses to study lubrication problems came with the introduction of methods to measure the force transferred via the side of the tablet directly to the die wall (9). These workers devised "friction coefficients"

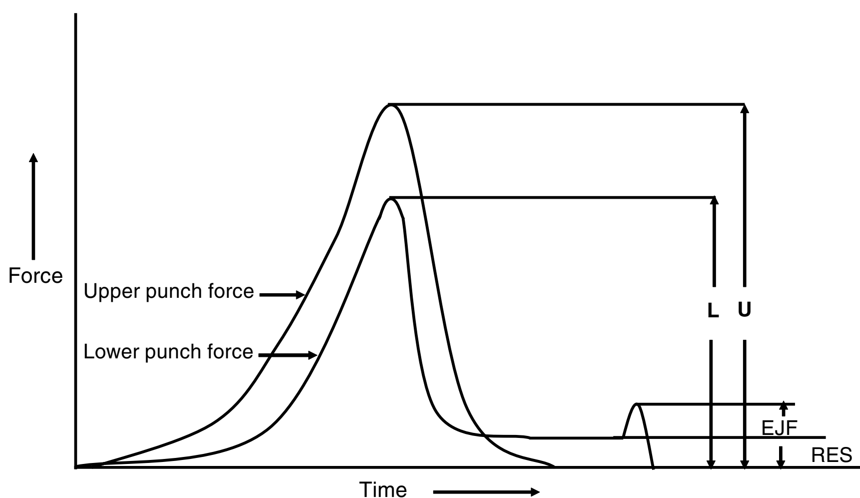

FIGURE 2 Changes in upper and lower punch force as a function of time, as measured on an instrumented eccentric tablet press.

which were equal to the ratio of the axial and the radial forces at maximum axial force and during ejection. They found that lubricants such as magnesium stearate have friction coefficients of about 0.1, well lubricated tablet formulations about 0.2–0.4, non-lubricated materials 0.7–2 and if adhesion to the die wall occurred, coefficients in excess of 2 were obtained. Though this technique actually measures the force applied by the tablet to the die wall, and therefore the force that has to be overcome to move the tablet, the difficulties of obtaining meaningful measures of the radial force should not be underestimated (2).

Using an eccentric press fitted with force transducers on upper and lower punches, Delacourte et al. (10) attempted to measure the value of the upper punch force that caused the press to jam. They gradually increased the upper punch force until tablet production for three minutes was not possible without ejection problems such as a grinding noise, scratches on the tablet edge or disturbance of the lower punch force signal. They used a standard mixture of lactose and dicalcium phosphate dihydrate mixed with a range of lubricants.

Baichwal and Augsburger (11) pointed out that all methods of evaluating lubricants using a tablet press involved a mixture of components, just one of which was the lubricant. They suggested that a more meaningful evaluation of lubricant activity would be obtained if friction between a pure lubricant and a metal wall material could be measured under controlled conditions. They modified an annular shear cell of the type used to measure failure properties in powders, using a smoothly polished surface on the underside of the lid. The shear cell was filled with lubricant, and shear stress determined at increasing and then decreasing normal load.

Tablet Lubricants

A list of some lubricant that has been used in pharmaceutical tablets is given in Table 1. These include metallic salts of fatty acids, fatty acids and alcohols, esters of fatty acids, and oils. Those marked with an asterisk are the subject of monographs in the 5th ed. of the *Handbook of Pharmaceutical Excipients* (12).

Magnesium stearate is by far the most commonly used tablet lubricant and is an ingredient of the majority of tablet formulations. It is an extremely effective lubricant at concentrations as low as 0.25–0.5%, and because of its popularity, it has been the subject of considerable research. It is thus the yardstick by which other lubricants are judged. However magnesium stearate is by no means an ideal lubricant and it serves as a good example of the uses and disadvantages of the metallic fatty acid salts as lubricants, and of other lubricants which are derived from fatty acids.

Magnesium Stearate

Table 2 gives a list of current standards for magnesium stearate in the Japanese Pharmacopoeia 2001 (31), the European Pharmacopoeia 2005 (32) and the United States Pharmacopoeia National Formulary 24 (33).

Magnesium stearate is defined in the USPNF 24 as "a compound of magnesium with a mixture of solid organic acids and consists chiefly of variable proportions of magnesium stearate and magnesium palmitate. The fatty acids are derived from edible sources. It contains not less than 4.0% and not more than 5.0% Mg, calculated on a dried basis." The relative content of stearic and palmitic acids are derived by a chromatographic test. The stearate peak is not less than 40% and the sum of the stearate and

TABLE 1 Tablet Lubricants (Proprietary Names are Given in Brackets)

Lubricant	Concentration in tablet (% w/w)	Comments	References
Metallic salts of fatty acids			
Aluminium stearate			
Calcium stearate[a]	0.5–1	Water insoluble	13
Magnesium lauryl sulfate[a]	1–3	Soluble in warm water	14
Magnesium stearate[a]	0.25–5	Water insoluble, excellent lubricant, reduces tablet strength, prolongs disintegration and dissolution times	15
Sodium lauryl sulfate[a]	1–2	Water soluble, moderate lubricant, but good wetting properties, often employed in conjunction with stearates (Empicol®, Stearowet C®)	14
Sodium stearyl fumarate[a]	0.5–2	Sparingly soluble in cold water, soluble in hot water (Pruv®)	16
Zinc stearate[a]	0.5–1.5	Water insoluble	17
Esters of fatty acids			
Glyceryl behenate[a]	0.5–3	Water insoluble (Compritol 888®)	18
Glyceryl behenate plus polyethylene glycol behenate[a]	0.5–3	Water insoluble (Compritol HD5®)	19
Glyceryl palmitostearate[a]	1–3	Water insoluble (Precirol ATO5®)	20
Glyceryl monostearate		(Tegin®)	21
Glyceryl trimyristate		(Dynasan 114®)	22
Glyceryl tristearate		(Dynasan 118®)	
Fatty acids and alcohols			
Palmitic acid			23
Palmitoyl alcohol			23
Stearic acid[a]	1–3	Water insoluble	24
Stearyl alcohol			23
Oils			
Castor oil hydrogenated[a]	0.1–2	Water insoluble (Cutina®)	25
Mineral oil			
Vegetable oil hydrogenated[a]	1–6	Water insoluble, may be used in conjunction with talc (Lubritab®, Sterotex®)	26
Miscellaneous			
Fumaric acid[a]	5	Water soluble	27
Polyethylene glycol 4000 or 6000[a]	2–5	Soluble in water, moderately effective, also known as macrogols (Carbowax®)	22
Polytetrafluoroethylene		(Fluon®, Teflon®)	28
Sodium benzoate[a]	5	Water soluble	29
Starch[a]	3–10		
Talc[a]	1–10	Insoluble in water but not hydrophobic. A moderate lubricant	30

[a]*Source*: From Ref. 12.

palmitate peaks are not less than 90% of the total area of all the fatty acid ester peaks in the chromatogram. A very similar definition appears in the 2005 edition of the *European Pharmacopoeia*, with an identical standard for the relative content of stearate and palmitate.

TABLE 2 Pharmacopoeial Specifications for Magnesium Stearate

Test	JP 2001	PhEur 2005	USPNF 24
Identification	+	+	+
Characters	–	+	–
Microbial limits	+	+	+
Aerobic microbes	≤ 1000/g	≤ 10^3/g	≤ 1000/g
Fungi and yeasts	≤ 500/g	–	≤ 500/g
Acidity or alkalinity	+	+	+
Acid value of the fatty acid	–	195–210	–
Freezing point	–	≥ 53°C	–
Nickel	–	≤ 5 ppm	–
Cadmium	–	≤ 3 ppm	–
Specific surface area	–	–	+
Loss on drying	≤ 6.0%	≤ 6.0%	≤ 6.0%
Chloride	≤ 0.1%	≤ 0.1%	≤ 0.1%
Sulphate	≤ 1.0%	≤ 0.5%	≤ 1.0%
Lead	–	≤ 10 ppm	≤ 0.001%
Heavy metals	≤ 20 ppm	–	–
Relative stearic/palmitic content	+	+	+
Organic volatile impurities	–	–	+
Residual solvents	–	–	+
Assay (dried, as Mg)	4.0–5.0%	4.0–5.0%	4.0–5.0%

Magnesium stearate is thus not a pure compound but consists of a mixture of the magnesium salts of a range of fatty acids, both saturated and unsaturated. Indeed though the name of the substance is "magnesium stearate," magnesium salts other than the stearate, i.e., $(C_{17}H_{35}COO)_2Mg$, could comprise up to 60% of its weight. It is thus not surprising that such a mixture can show variability in its chemical, physical, and lubricant properties, and since magnesium stearate is made from naturally occurring fatty acids, such variation is only to be expected.

Pharmacopoeial monographs usually provide only chemical standards, but several studies have shown that in the case of magnesium stearate, characterization of physical properties is equally important. For example in an early study, Butcher and Jones (34) demonstrated variation in particle density, packing characteristics and lubricant properties for five batches of magnesium stearate, all of which met pharmacopoeial specifications.

Perhaps the most comprehensive study of this type was carried out by Dansereau and Peck (15). They obtained a series of 20 samples of magnesium stearate, all of which were used by a multinational pharmaceutical company in its world-wide operations, and which were obtained from 16 different sources. These samples were characterised by their physical and chemical properties (Table 3), and significant differences were found in respect of chemical purity, particle size, and surface area. Dansereau and Peck found that the properties of lots of magnesium stearate obtained from the same company were very similar, but samples obtained from different suppliers were significantly different.

They then lubricated a standard microcrystalline cellulose formulation with 16 of these lubricants, and measured powder and tablet properties (Table 3). They found that magnesium stearate with the smallest particle size (and hence the highest specific surface area) had the most detrimental effect on tablet properties. They concluded that though

TABLE 3 The Variation of Physicochemical Properties Among 20 Samples of Magnesium Stearate

Property	Range
USP assay (as MgO) (%)	7.6–8.6
Stearric acid content (%)	43.6–77.9
Free fatty acids (%)	0.5–3.3
Ash (%)	6.5–8.7
Loss on drying (%)	0.1–0.8
Melting point (°C)	117–149
True density (g cm^{-3})	0.89–1.16
Bulk density (g cm^{-3})	0.26–0.57
Porosity (%)	51–75
Particle size (μm)	2.4–10.2
Surface area (m^2 g^{-1})	6.0–14.8

Source: From Ref. 15.

magnesium stearate appears to be the most effective tablet lubricant, it led to decreased compressibility, decreased wettability and prolonged disintegration and dissolution times. The most important factors relating to performance were size and surface area.

Irrespective of the inherent variability of magnesium stearate, its inclusion in a tablet formulation can give rise to two major problems, which though apparently different, are essentially caused by the same property of the lubricant. The first of these is that magnesium stearate can confer a water repellant layer to the external surface and the internal pore structure of the tablet. This occurs because the magnesium stearate molecules, as with other lubricant molecules of similar structure, are believed to position themselves with the metallic component in contact with the substrate and hence with their hydrocarbon chains perpendicular to the substrate surface. Hence access of an aqueous liquid to the latter is hindered if not totally prevented (35). This results in an increase in tablet disintegration time and a slowed release of active ingredient (36,37).

The second major problem caused by magnesium stearate is that it often reduces the physical strength of the tablet. This is attributed to the magnesium stearate forming a thin layer around each of the other particles in the tablet formulation. As a result, the distance between particles is increased and instead of substrate-substrate interactions, there are lubricant–lubricant interactions. These are mediated between the hydrocarbon chains of neighboring lubricant particles and will be weak. Hence the strength of the overall structure of the tablet is decreased.

Thus the reduction of the ingress of water and the weakening of tablet strength are both due to the progressive formation of films of ever-increasing completeness around every other particle as the components of the formulation are mixed together. Before mixing, the lubricant in a tablet formulation will usually be in the form of aggregates of smaller particles. Therefore as mixing proceeds, attrition of these aggregates occurs, with the formation of a more complete film of lubricant around every other particle. Bolhuis et al. (38) have shown that using six direct compression tablet diluents, each lubricated with 0.5% magnesium stearate, tablet crushing strength decreases as mixing time is lengthened, though the size of the decrease was dependent on the nature of the substrate.

Thus the extent of film formation depends on factors that will contribute to the attrition of the original lubricant particles. For example, lubricant type, concentration and surface area can all govern film formation. Lerk et al. (39) found in a study of tablets made from pregelatinized starch that tablets containing lubricant with a large particle size

were stronger than those with smaller particles of lubricant. For a given mixing time and fixed mixing conditions, film formation was slower with a smaller concentration of lubricant, but provided a sufficiently high concentration to give a monomolecular film was present, lubricant concentration had a minor effect (40).

The surface area of the lubricant can have a more important effect. Frattini and Simeoni studied three batches of magnesium stearate of differing surface areas. They found that if each lubricant was present in equal area rather than equal concentration, their effects on tablet crushing strength were almost identical. This led to their suggestion that rather than adding a lubricant to a formulation in terms of its mass, it should be added on a surface area basis (41). This in turn has led to the introduction of a standard for specific surface area being introduced into some pharmacopoeial monographs for magnesium stearate. The *European Pharmacopoeia* of 2005 reads:

> The following test is not a mandatory requirement but in view of its known importance for achieving consistency in manufacture, quality and performance of medicinal products, it is recommended that suppliers should verify this characteristic and provide information on the result and the analytical method applied to users. The method indicated below has been found suitable, but other methods may be used.
>
> The following characteristic is relevant for magnesium stearate used as a lubricant in solid dosage forms (compressed and powder). Specific surface area: determine the specific surface area in the P/P_0 range of 0.05–0.15.

The method described in the *European Pharmacopoeia* involves gas adsorption and the application of the Brunauer, Emmett, and Teller isotherm. Whilst agreeing that a standard for surface area is important for magnesium stearate, Andrès et al. (42) have pointed out difficulties in measuring this by gas adsorption. They found that determination by nitrogen or krypton adsorption after a standard degassing technique gave questionable data, the obtained values being dependent on the original water content of the magnesium stearate. Furthermore, adding magnesium stearate on the basis of surface area does not take into account the new surface area that will be generated as the original magnesium stearate particles are abraded.

In addition to mixing time, other mixing conditions such as mixer design, speed and batch size can influence film formation. The critical factor is the rate of energy input during mixing. Bolhuis et al. (43) mixed a lactose: microcrystalline cellulose formulation with 0.5% magnesium stearate in seven different mixers, operating at differing mixing speeds. They found that the decrease in tablet crushing strength occurred much more rapidly in production-scale mixers than in laboratory-scale mixers, and for a given mixer, tablet strength decreased more as the mixing speed was increased.

Other components in the formulation can also play a role in lubricant film formation. The most important factor here is the behavior of particles under a compressive load. De Boer et al. (44) found that the bonding properties of brittle materials such as dicalcium phosphate dihydrate showed little change when lubricated. They suggested that clean, lubricant-free surfaces are created by fragmentation of the particles during consolidation, and hence interparticulate bonds could form. Conversely tablets made from excipients such as starch that undergo deformation are greatly affected by the addition of magnesium stearate, since no new surface is generated during consolidation.

Though the deleterious effects of magnesium stearate on tablet properties are important, they can to some extent be avoided. Several workers, e.g., Hölzer and Sjögren (9) and Johansson (45) have shown that the lubricating effect of magnesium stearate becomes apparent after very short mixing times, whereas film formation takes a longer period of mixing. This means that film formation is not a prerequisite for good

lubrication. Hence a short mixing time is indicated, either for the whole formulation, or by interrupting the mixing process at a late stage to add the lubricant.

The sensitivity of tablet properties to lubrication has been comprehensively reviewed by Bolhuis and Hölzer (46).

Despite its shortcomings, magnesium stearate is probably the best all-round lubricant available, as shown by the research designed to circumvent its deficiencies rather than abandoning its use for another, better lubricant. In a study of sodium chloride tablets lubricated with 13 different lubricants, Hölzer and Sjögren (25) showed that magnesium stearate brought about the greatest reduction in the friction coefficient at ejection, even when present in a concentration of only 1%.

The amount of research carried out on magnesium stearate is indicative of its importance as an excipient, and far exceeds that done on any other lubricant. However it is reasonable to predict the behavior of other lubricants by extrapolation from results obtained with magnesium stearate. For example, it is likely that other metallic salts of fatty acids such as calcium stearate and zinc stearate will exhibit similar variations in chemical and physical properties since they are prepared from the same source of "stearic acid" as magnesium stearate. They will also show the same tendency to orientate at solid surfaces so that their fatty acids chains form a hydrophobic layer around the other components of the formulation. Hence a weakening of tablet structure and reduced release of the active ingredient can be anticipated.

Fatty acid esters such as glyceryl palmitostearate will also be made from raw materials of variable composition (12), and though esters may not be orientated quite so specifically as fatty acid salts, they have a water-repellent nature and delayed release of active ingredient must be expected.

As stated earlier, magnesium stearate is usually used as the standard by which other lubricants are judged. Its variable properties that in turn influence its lubricity make such a role questionable. For example, specific surface area has a major influence on the lubricant efficacy of magnesium stearate, so depending on the specific surface area of the magnesium stearate "standard," another lubricant may appear either superior or inferior to magnesium stearate. Thus comparisons between magnesium stearate and other lubricants must include chemical and physical characterization of both the magnesium stearate and the other excipients.

Talc

It is one of the few inorganic substances that can be used as tablet lubricants. It was once widely used, though less so at the present time. It is a naturally occurring magnesium silicate, and its physical properties, including its lubricant action, depend on its source and method of preparation. It is practically insoluble in water.

Ribet et al. (47) examined several different grades of talc, and found that mean particle diameter and specific surface area were factors that played an important role in the efficacy of talc as a tablet lubricant. Dawoodbhai et al. (48) showed that, based on ejection forces, tablets lubricated with talc were less well lubricated than those containing magnesium stearate. Talc is a laminar solid, the layers of which slip and roll over one another. Hence the lubricant action of talc is unlikely to increase with an increase in compaction force because the rolling action becomes more restricted. Higher concentrations of talc are required because talc forms a layer one particle thick around the other particles in the formulation, whereas magnesium stearate forms layers one molecule thick.

Matsuda et al. (49) showed that better lubricant efficiency was obtained when magnesium stearate and talc were mixed with the other components of the formulation just prior to compaction. Though both magnesium stearate and talc are insoluble in water, magnesium stearate caused more interference with bonding between particles. Therefore talc leads to a smaller reduction in tablet physical strength than does magnesium stearate, and does not decrease the dissolution rate of the active ingredient.

Water Soluble and Water Miscible Lubricants

Very few of the lubricants listed in Table 1 are soluble in water. Most are derived from fatty acids and alcohols that are hydrophobic and so the penetration of aqueous fluids into the interior of the tablet will be reduced. Those not of hydrocarbon origin, such as talc, will not impede water penetration, but are insoluble in water. For tablets that are intended to be swallowed or chewed, these problems can be circumvented. For example, use of a disintegrating agent or a wetting agent can, at least to some extent, counteract the effect of a water repellant lubricant, and a mixture of sodium lauryl sulphate and magnesium stearate has been mareketed as Stearowet C® (Mallinckrodt specialty chemicals co., st. Louis, Missouri, U.S.A.).

If however the tablet is designed to be dissolved in water before use, then the lack of a water-soluble lubricant poses a considerable formulation problem. High molecular weight solid polyethylene glycols, e.g., PEG 4000 and PEG 6000 are soluble in water and have been used as lubricants in tablet formulations, though they are not so effective as lubricants as is magnesium stearate (22). Sodium and magnesium lauryl sulfates are also water soluble, but a relatively high concentration is needed for effective lubrication. Roscheisen and Schmidt (27) have used fumaric acid as a lubricant in effervescent tablets, where there is a need for complete solubility. However there is no doubt that a water soluble lubricant that meets most of the criteria listed earlier remains to be discovered.

ANTIADHERENTS

The antiadherent function in a tablet formulation as opposed to the lubricant function is often overlooked partly, one suspects, because substances that are good lubricants often have an antiadherent function as well. However lubrication and antiadherence are quite distinct. Lubrication is overcoming friction that arises when two solid surfaces that are in contact with each other move so that one attempts to slide past the other. In the case of a tablet, the two surfaces are the die wall and the side of the tablet, and thus friction occurs during ejection of the tablet from the die. Antiadherence is the sticking together of two surfaces, and becomes apparent when it is necessary to separate those surfaces. In tableting, this occurs immediately after compression when the upper punch begins its upward movement, and also when the tablet, after ejection from the die is complete, is removed from the face of the lower punch. It is thus not a frictional effect, and methods that are used to measure problems in the tableting process due to friction are not necessarily suitable for assessment of antiadherence.

Assessment of Antiadherent Activity

Adherence is caused by the compressed tablet or components of the formulation sticking to the faces of either or both punches. If the attraction between the tablet and the punch face is greater than the interparticulate attractions on which the integrity of the tablet

depends, then when an attempt is made to separate the tablet from the punch faces, parts of the tablet will become detached from the rest of the tablet structure. With mild adherence, this will result in the tablet having a mottled surface like orange peel, an effect sometimes called picking. In extreme cases, the whole structure of the tablet is torn apart.

Adherence usually begins at some imperfection of the punch face which then acts as a focal point for progressive build-up of powder. There is no doubt that perfectly smooth punch faces are an effective prevention of adherence problems. However this is not always practicable. Punch faces can become worn or damaged during use, though punch maintainance programs should reduce this. However a more common irregularity on punch faces is the presence of engraved or embossed characters that add identification to the tablet surface.

A further common cause of adherence is moisture on the punch face. This can originate from the formulation or can be atmospheric moisture condensing on the punch face. In the author's experience, this can occur in environments that have no humidity control, especially at start-up on cold mornings. Moisture on the punch face may dissolve small amounts of soluble components, and this may give a sticky and perhaps hygroscopic film. Thus materials such as sugars can be a particular problem.

On a rotary tablet press, the tablet is detached from the face of the lower punch when it comes into contact with the sweep-off blade that forms the leading edge of the feed frame. Mitrevej and Augsburger (50) fitted a strain-gauged cantilever arm to the feed frame ahead of the sweep-off blade so that the force necessary to detach the tablet from the upper punch face could be measured. They considered that the adhesion force was the total force measured by the arm after correction for the momentum of the tablet, which in turn is a function of its mass. They found that for all formulations examined, an increase in compression force caused increased adhesion as the punch face is brought a more intimate contact with the tablet. Adhesion was reduced by an increase in magnesium stearate concentration but not in the same proportion as the change in true lubricant activity, demonstrating that antiadherent and lubricant properties are different. Adhesion was shown to be a function of the area of the punch face. In a subsequent study, Mitrevej and Augsburger (51) showed that for any given compression force, adhesion of microcrystalline cellulose tablets lubricated with magnesium stearate decreased with increases in blending time and intensity of blending.

An instrumented beam was also used by Wang et al. (52), who were able to relate adhesion forces to the intermolecular attraction between ingredients of the tablet formulation and the metal surface of the punch face.

A different approach was adopted by Waimer et al. (53). They pointed out that adhesion measurements based on the force at the sweep-off blade may be suspect. At high press speeds, the momentum of the tablet is high, and a correction applied for this may well be considerably greater than the force of adhesion. Furthermore the adhesive bond between the tablet and the punch face may already have been disrupted during ejection. Waimer et al. fitted strain gauges to the upper punch of a rotary tablet press. This punch rises immediately after compression is complete, and if adhesion occurs, the punch is stretched until the adhesion force is eventually overcome. Such forces are very low (only a few newtons), so an extremely sensitive measuring system is needed. Waimer et al. found that adhesion force built up to a plateau during a production run. Addition of magnesium stearate always led to a reduction in adhesion force, though the relationship between adhesion force and compression pressure differed depending on the behavior of the major component of the formulation under a compressive load.

In a subsequent publication (54), the same workers screwed small cones into the face of the upper punch to study the effect on adhesion of embossing or engraving the

punch face. They found that in general forces were increased when the punch face was modified. The cones modified the stress distribution pattern within the tablet due to shear forces on the punch face.

As stated earlier, most of the lubricants listed in Table 1 have antiadherent properties, and so one component of the formulation carries out two functions. Two exceptions are starch and microcrystalline cellulose. They have no lubricant activity, but because of their ability to absorb water, they can act as antiadherents if sticking of the tablet to the punch faces is caused by moisture.

GLIDANTS

A universal requirement for tablets is that they meet specifications for uniformity of weight. Though this does not necessarily mean that the content of active ingredient is uniform, the reverse is true. Tablets of non-uniform weight are very unlikely to exhibit an acceptable uniformity of content. Yet achieving uniformity of weight can be a challenge. It must be recalled that the die of a tablet press is filled volumetrically, and the weight of a tablet is governed by the volume of a formulation that flows into the die within a fraction of a second.

Many tablet formulations are cohesive, and their constituents can stick together for a variety of reasons. A fundamental cause of cohesion is the presence of attractive forces between adjacent particles. Such forces are proportional to the mass of the individual particle, and though this is low, in an aggregate of millions of particles, the total force can be significant. These forces are inversely proportional to the square of the distance separating the particles and in practice are effective only when the particles are touching each other. It follows that the more points of contact there are in a given powder mass, the greater the cohesion will be. This in turn is a function of particle size, since smaller particles have a higher number of points of contact. Particle shape is also important. Spherical particles move more easily than irregular particles that can exhibit surface interlocking.

These cohesive forces may prevent uniform flow of the formulation, and it is the function of the glidant to improve flow so that specifications on uniformity of tablet weight can be met.

Assessment of Glidant Action

Several methods have been suggested for measuring the flow properties of a formulation and therefore the ability of a glidant to improve such properties.

One of the earliest methods used to assess glidant activity was that of measuring the angle of repose of the solid particles (55). The solid is poured on to a flat surface under standardised conditions to give a cone of radius r and height h. The angle of repose is $\tan^{-1}(h/r)$. Though the method is apparently simple, cohesive solids often do not form a regular cone, and so calculation of the angle of repose is inaccurate. Considerable variation in replicate determinations has been reported (56).

The rate of flow of a powder through an orifice of specified dimensions has also been used to assess glidant activity, an approach pioneered by Gold et al. (57,58). They compared data from their flow meter with angle of repose measurements, and found that the latter was not a reliable method for evaluating flow. Flow meters employing the same principles as Gold et al. are commercially available. Augsburger and Shangraw (59) took the view that the most logical method of assessing powder flow in a tablet press was to

TABLE 4 Tablet Glidants (Proprietary Names are Given in Brackets)

Glidant	Concentration in tablet (%)	Comments	References
Calcium silicate	0.5–2		
Cellulose, powdered[a]	1–2	(Elcema®, Solka Floc®)	61
Colloidal silicon dioxide[a]	0.05–0.5	Excellent glidant (Aerosil®, Cab-o-Sil®)	39,62
Magnesium oxide[a]	1–3		
Magnesium silicate[a]	0.5–2		
Starch[a]	2–10		63
Talc[a]	1–10	Insoluble in water but not hydrophobic	30

[a]*Source*: From Ref. 12.

make tablets and determine their uniformity of weight. This is usually expressed as the ratio between the standard deviation of the tablet weight and the mean weight. This is the coefficient of variation, also known as the relative standard deviation. The drawback to this method is that large quantities of material are needed, since the hopper of the press must be sufficiently full for reproducible flow to be obtained.

Tablet Glidants

Often tablet formulations show sufficiently good flow properties that they do not need the addition of a glidant. Many formulations are prepared by the wet granulation method, the principal purpose of which is to increase particle size. This in turn cuts down the number of points of interparticulate contact and hence reduces cohesion. An increasing proportion of tablets are now prepared by direct compression, and an important property of direct compression diluents is that they can be compressed into tablets of acceptable weight uniformity. A large number of direct compression diluents are now available (60).

A number of glidants are listed in Table 4.

Colloidal silicon dioxide is very widely used as a glidant in tablet manufacture. It has a very small particle size (about 15 nm) with a correspondingly high surface area of several hundred $m^2 g^{-1}$. Concentrations as low as 0.05% have been shown to be effective, though this will depend on the underlying cohesiveness of the other solids in the formulation (64). Colloidal silica is believed to act by filling the surface pores of the other solids so that the latter are prevented from interlocking and thus can move more freely relative to each other. York (56) has shown that there is an optimum concentration of colloidal silica, above which little increase in flow occurs. He showed that this optimum was approximately that which would give a layer of silica one particle thick around each particle of the other components.

Colloidal silica also absorbs relatively large amounts of water, and so will improve flow if cohesion is due to dampness.

Probably the second most important glidant is talc. Talc is a naturally occurring hydrated magnesium silicate, and several grades are available, the properties of which are dependent on their source and method of preparation (24). Dawoodbhai et al. (30) have shown that though the flow rate of formulations depends on the grade of talc used, all grades showed an optimum flow rate at a concentration of about 0.1%.

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Surfactants and Colors in Tablets

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INTRODUCTION

Pharmaceutical tablets may be defined as solid dosage forms containing drug substances with or without adjuvants and prepared either by molding or compression. The features of compressed tablets which propel their popularity with both producers and users include ease and economy of production, precision of dosage, physical and chemical stability of drug, durability, portability, compactness, elegance, and convenience of dispensing and administration. Pharmaceutical tablets vary greatly in size, shape, and color. Size is generally related to the amount of drug required for the desired dosage. The shape is usually discoid with flat or biconvex surfaces although a wide variety of other shapes can be found. Tablets may also be scored to facilitate tablet division or embossed for identification. Tablets may be sugar-, film-, or enteric-coated. Coating tablets helps in taste-masking and gives protection against air, light, and moisture. Film coating offers better moisture protection than sugar coats and is popular in the development of controlled drug delivery systems. Enteric coatings resist dissolution in gastric fluid and prevent deactivation of acid-sensitive drugs in the acidic environment but allow dissolution in the alkaline intestinal fluid. Sometimes, enteric coating is applied for the purpose of prolonged release.

Tableting Excipients

Drug substances themselves rarely possess the suitable properties of flow, lubrication, compression, and release necessary for successful tableting. They are usually formulated with various excipients to produce pre-mix suitable for granulation or tableting. In most formulations, binders, lubricants, and disintegrants are added. Binders are cohesive agents which in solution often act as to lubricate the granulation process and produce strong compressible granules on drying. Binders may be added dry, but they would be more effective when added as a solution. Surfactants are sometimes added to aid wetting, especially for poorly wetted powders. Disintegrants are important to ensure tablet break-up upon ingestion. For low dose drugs, fillers are commonly required to increase bulk.

The more specialized tableting excipients are sorbents, moisture scavengers, and colorants. Sorbents are necessary for incorporating small quantities of liquid drug or flavor into tablet dosage forms. The addition of moisture scavengers to hygroscopic or moisture

sensitive drugs reduces the detrimental effect of moisture on the drugs, both during processing and after compression. Colorants are coloring agents used for providing color to tablets. Colorful tablets not only serve to provide an aesthetic dosage form but also a means of quick identification. The color can assist the manufacturer in controlling the production process especially during mixing.

Tablet Disintegration and Dissolution

Tablet disintegration testing provides a means of comparing different formulations. The disintegration test can provide at least an assurance of the ability of the tablet to disintegrate upon ingestion. Disintegration time is defined as the time taken for the complete passage of broken up tablet material through the retaining screen during a disintegration test. The mechanism of action of tablet disintegrants depends on the disintegrant type used, other tablet components, influence of compaction pressure, and the disintegration method employed. The diverse disintegrant types and their mechanisms of action had been reviewed by Lowenthal (1,2). The main mechanisms of action of tablet disintegrants discussed are gas evolution, heat of immersion and wetting, hydration and swelling, and disruption of physicochemical bonds. Tablet disintegration in product quality assessments determines batch-to-batch variations. With the rather extensive variety of tablet disintegrants, various mechanisms of disintegration action have been proposed for a particular disintegrant by different investigators to explain their experimental observations, with particular attention to the influence of surface active agents on the disintegration of tablets. More emphasis should also be given to the effect of surfactant on the property of the disintegrants as disintegration is the prerequisite to drugs being available for dissolution. Various researchers have reported that surfactants decrease (3–5) or increase disintegration time.

Dissolution may be considered as the “inverse process of crystallization” (6). At the solid–liquid interface level, the process of dissolution involves the mass transfer of molecules from the solid surface into the immediate liquid film then escaping into the liquid bulk. It was Nernst (7) who first proposed the existence of a diffusion layer or liquid film around a dissolving crystalline solid. This model, popularly referred to as “film theory”, assumes the presence of a liquid skin or diffusion layer of negligible velocity surrounding the dissolving solid. Solute concentration just adjacent to the solid surface is at saturated solution concentration, falling linearly to the solute concentration of the liquid bulk at the fringe of the diffusion layer. Beyond the diffusion layer, rapid mixing is present and no concentration gradient exists. Within the diffusion layer, solute movement is determined almost entirely by Brownian motion diffusion and the concentration gradient. Further modifications to the film theory suggest a film of changeable thickness or “effective film thickness” (8). Using the film theory model, the primary process of dissolution involves: (*i*) the disengagement of molecules from the crystal surface, and (*ii*) the transfer or diffusion of the solvated molecules into the bulk solution. Control of the dissolution rate is therefore exerted at the interface by the rate of solvation or referred as interfacial resistance and within the liquid film through diffusional resistance (6,9).

Generally, the dissolution of poorly water-soluble compound is interfacially controlled whereas that of highly soluble compounds is diffusion controlled. Factors affecting the rate of dissolution can broadly be categorized into: (*i*) physical factors influencing the dissolution process like the type of apparatus and agitation, (*ii*) physiochemical characteristics of the dissolving compound, and (*iii*) the effect of additives on and the method of manufacture of the solid dosage forms (6).

SURFACTANTS

Functions of Surfactants

Lubricants

Lubricant action can be divided into three types: anti-friction, anti-adherent, and glidant. As an anti-friction agent, lubricants reduce friction, and aid the ejection of tablet from the die cavity after compression and as an anti-adherent, lubricants help prevent picking and sticking of the tablet. The process of picking occurs when a piece of tablet surface breaks off and adheres to the upper punch after compression. Where sticking of tablet to the lower punch occurs, part of the tablet may be sheared off by the rake. Glidants are used to ensure the uniform flow of particulate mixtures to be tableted and prevent segregation of the drug and tableting excipients added. The ability of glidants to improve powder fluidity has been attributed to the ability of the fine glidant powder to coat the rough granule surfaces, reducing interparticulate friction (10). Rough granule surfaces predispose to mechanical interlocking and deviation from sphericity increases rolling friction. The rolling of some lubricants themselves under stress may produce a ball-bearing effect and reduce friction (11). An ideal lubricant should therefore aid free and uniform flow without segregation of materials from hopper to die cavity for compression and lubricate tablet ejection with no picking or sticking to punches.

Several theories for the mechanisms of action of lubricants in tableting had been proposed (12). The most popular is the shear strength theory which suggests that lubricants reduce interfacial shear between the tablet and die wall. Another proposed that lubricants behave as a conductor to reduce static charges thereby generating flow. Commonly employed tablet lubricants are stearic acid, alkaline stearates, talc, hydrogenated vegetables oils, microcrystalline cellulose, corn starch, silicon dioxide, and polyethylene glycols. Magnesium stearate and talc are the older and better established lubricants whereas microcrystalline cellulose and corn starch are better known for their disintegrant properties. Many commonly used lubricants such as magnesium stearate and talc are insoluble and hydrophobic and may cause "waterproofing" of particles and granules and that of the resultant tablets. Consequently, the quantity of lubricant used should not be excessive (13). Prolonged mixing of tableting ingredients with lubricants can affect tablet hardness, disintegration, and dissolution (14,15). Tablet hardness falls on prolonged mixing. The deleterious effect of magnesium stearate on tablet disintegration and dissolution was found to be more pronounced with a moderate swelling disintegrant such as corn starch than one that is strongly swelling, such as sodium starch glycolate (16). Prolonged mixing of magnesium stearate with dried microcrystalline cellulose also decreased tablet hardness but the disintegration times were improved (17). It was suggested that for very hydrophilic microcrystalline cellulose, bonding strength, and tablet porosity are the more dominant factors affecting disintegration.

Attempts were made to overcome the deleterious effect of the hydrophobic magnesium stearate by the use of surface active agents. Several surfactants possess significant lubricative properties (18) and many have used surfactants as lubricants or lubricant adjuncts. Sodium lauryl sulfate is sometimes used to overcome the waterproofing problem due to hydrophobic tablet lubricant. Surfactant-coated magnesium stearate and calcium stearate were found to enhance the disintegration and dissolution of capsules and tablets (19). The evaluation of several surface active agents for their lubricating properties had been done (20). It was found that several metallic salts of fatty acids with hydrocarbon chain lengths between 12 and 18 carbons are good lubricants. The polyvalent metal salts are better lubricants while the metal salts themselves are more effective lubricants than their corresponding free fatty acids.

In the search for an effective but hydrophilic lubricant, the surfactant magnesium lauryl sulfate has attracted much attention (20–23). The water-soluble magnesium lauryl sulfate was found not to possess the waterproofing effect of magnesium stearate (20,21) and to reduce compressibility of fillers to a smaller extent (22). However, it was found that for direct compression, magnesium lauryl sulfate produced tablets with longer disintegration time than those tablets formulated with magnesium stearate except at low compaction pressure (23). The longer disintegration time was attributed to the particle size of the magnesium lauryl sulfate.

Improve Drug Dissolution and Bioavailability

By far, most surfactants added to tablet formulations were aimed at improving drug bioavailability although improved disintegration and dissolution are usually the primary objectives.

Mechanism of action: In dissolution studies, tablet dissolution depended largely on the disintegration mode of the tablets. Where tablets disintegrate rapidly and into fine particles, a marked increase in surface area for dissolution was generated. Disintegration of tablets containing surfactant generally produced finer dispersions of disintegrated particles. These fine particles were light, tending to be circulated in the dissolution medium, thereby producing a large surface area available for drug dissolution. Hence improved dissolution rate was obtained. In the case of tablets with long disintegration times, dissolution was disintegration limited. The dissolution $T_{50\%}$ correlated with the disintegration time.

In dissolution studies, the importance of surfactants in dissolution media had been discussed by various researchers (24–26). Clearly in dissolution testing, drug solubility characteristics in the dissolution media is of importance, especially for low solubility drugs. With immediate release carbamazepine tablets, it was demonstrated that the dissolution rate of carbamazepine was directly proportional to the aqueous concentration of sodium lauryl sulfate in the dissolution media (27). Similarly, it was shown that the effect of polysorbates on drug release from film-coated atenolol tablets was a function of the concentration of polysorbate in the dissolution media used (28).

Differences in drug release in acidic and neutral media was found to be significant for acetaminophen tablets containing sucrose and croscarmellose sodium or sodium starch glycolate (29). The difference was attributed to the hydrophobicity in different pHs and incorporation of sodium lauryl sulfate helped decrease the difference.

The dissolution rate of benzoic acid tablets in distilled water and 0.2% sodium lauryl sulfate solution was investigated by Wurster and Seitz (30). Surface area of the tablets was varied by drilling holes. With increased surface, benzoic acid dissolution in sodium lauryl sulfate solution was found to increase but not in water. For air evacuated tablets, the dissolution in water was analogous to that in sodium lauryl sulfate solution. It was thus concluded that for dissolution in distilled water, the pores in the tablets were occluded by air. The surfactant solution by decreasing surface tension was believed to improve dissolution through greater solvent penetration into the pores, enlarging the area for dissolution. The dissolution of benzoic acid in high concentration of surfactants had been done (31). It was reported that benzoic powder dissolution in solutions of tyloxapol, polysorbate 80, sodium lauryl sulfate and poloxalkol increased slightly at pre-critical micellar concentrations (cmc), probably due to improved wetting and the most effective was polysorbate 80. At post-cmc, the dissolution rate increased to a maximum then decreasing for tyloxapol, polysorbate 80, and sodium lauryl sulfate. The dissolution rate for poloxalkol however was retarded at post-cmc. Employing nonionic surfactants,

2-ethylhexyl sodium sulfosuccinate, and polyethylene glycol monostearate, Aoki et al. (32) studied the disintegration effects of the surfactants on granules made from drugs of differing solubilities. The surfactants added in the disintegration medium generally did not affect the granule disintegration for water-soluble drugs but improved disintegration or permeation was enhanced by the surfactants. It was concluded that where granule disintegration was improved, wetting of the granule allowed faster water penetration and disintegrant action was responsible.

Bano et al. (33) investigated the influence of surfactants on the tablet disintegration times. The surfactants, polysorbates 20, 21, 40, 60, 65, 80, 85, and benzalkonium chloride were found to promote tablet disintegration. The nonionic polysorbates at concentrations of 0.5–1% of tablet weight appeared suitable. However, tablet hardness decreased. Increased compaction pressure was recommended to overcome the decreased tablet consistency. Ritschel and Rahman (34) tested a range of surfactants for their ability to hydrophilize drug powders and reduce dust problem during tableting. It was reported that polyethylene glycol 500 tridecyl ether mixed with urea (Renex 35) was most suitable for the purpose.

Finholt and Solvang (35) reported increased dissolution of phenacetin powder (0.21–0.30 mm) in 0.1 N hydrochloric acid containing various concentrations of polysorbate 80 (0–0.2%). The increase in dissolution was shown to have a linear relationship with the surface tension of the dissolution medium. It was concluded that wetting by decreased interfacial tension rather than solubilization was the more likely mechanism by which the surfactant improved dissolution. In an earlier study (36), it was reported that polysorbate 80 added to the dissolution medium of 0.1 N hydrochloric acid improved phenacetin dissolution, the dissolution rate increasing with decreasing particle size of the powder. Sodium lauryl sulfate was also found to accelerate the dissolution of phenobarbital granules granulated with gelatin but had little effect on the dissolution rate of phenobarbital tablets (37). Using a biosurfactant, lysolecithin at 0.05% in 0.1 N hydrochloric acid, Lin et al. (38) also showed improved dissolution rate of drug particles of glutethimide, griseofulvin, and a new diuretic. The enhanced dissolution was attributed mainly to micellar solubilization of the drugs. Lecithin however was reported to retard dissolution of cholesterol, the retarding effect attributed to a large interfacial barrier caused by lecithin (39).

Improved wetting by surfactant facilitating aqueous penetration into tablet mass resulting in reduced disintegration time was reported by Chodkowska-Granicka and Krowczynski (40,41) using both hydrophobic, salol and nitroquanil [1-(p-nitrophenyl)-3-amidinourea-HC1], and hydrophilic, ammonium chloride, and dipyrone, drugs. The surfactants used, sodium lauryl sulfate, polysorbate 80 and 20 increased water absorption by counteracting the hydrophobicity of the lubricant, talc or magnesium stearate, used. Incorporation of surfactants into ammonium chloride and nitroquanil tablets also improved dissolution (42). The effect of nonionic surfactants, polysorbate 20, 40, 60, and 80 on the weight variation, hardness, and disintegration of phenacetin and salicylamide tablets were examined by Pandula and Keseru (43). It was found the amount of surfactant required for optimal wetting effect produced tablets which were too soft. It was necessary to reduce the surfactant content to obtain tablets of suitable quality.

Further investigation by Burzunov and Shevchenko (44) using strongly hydrophobic drugs, calcium iodobehenate and ethocarlide, showed that 0.2% polysorbate 80 with a strongly swelling agent, ultraamylopectin (2% w/w) improved tablet disintegration significantly. These tablets contained 25% corn starch employed as a capillary-forming agent. Studies (45) on the hydrophilization of drug powders using polysorbate 80 and polyoxyl 40 stearate were also carried out to determine the minimum amount of

surfactant required to completely hydrophilize the drug powder. The minimum amount of surfactant required for each drug was dependent on the hydrophile lipophile balance (HLB) of the surfactant and the particle size and hydrophobicity of the drug.

Studying the dissolution rate of aspirin in various dosage forms (plain, buffered, and timed-release tablets and capsules) using the rotating-flask method, Weintraub and Gibaldi (46) reported that the dissolution rate of plain and buffered aspirin tablets was decreased in 0.01% polyoxyethylene (POE) [23] lauryl ether (Brij 35 SP) solution. In their earlier findings (47) however, pre-micellar concentrations (0.005, 0.01, and 0.03%) of POE [23] lauryl ether improved aspirin tablet (buffered, commercial) dissolution using the beaker method. The difference in findings was attributed to the different methods of quantifying dissolution. It was postulated that in the beaker method, disintegrated particles form a compact mound impervious to the dissolution medium at the bottom of the beaker reducing the effective area for dissolution. Surfactant added in the dissolution medium increased dissolution by reducing contact angle and enabling the solvent to penetrate the pores of the mound and to enhance dissolution. Since the rotating-flask did not allow the mound formation, the positive influence of surfactant was not seen. Decreased dissolution was attributed to the de-wetting phenomenon described by Zografi (48). The earlier publication (47) also reported improved dissolution of salicylic acid powder in POE (23) lauryl ether and lysolecithin, a biosurfactant, solutions at pre-micellar concentrations. Sodium glycolate, another biosurfactant, improved the dissolution of salicylamide powder in pH 6.0 buffer. Good correlation between surface tensions and dissolution rates for aspirin tablets was reported.

Sucrose monoesters of stearic acid and palmitic acid used as tablet additives were reported (49) to increase mechanical strength of tablets and enhance tablet dissolution. The effectiveness of sucrose monostearate and monopalmitate as a hydrophilic lubricant was earlier reported by Maly (50,51). Using POE glycol 400, POE glycol monostearate (Myrj 53), and sucrose monostearate, Maly (51) reported that sucrose monostearate had the best lubricating properties. The tablets of sucrose monostearate possessed high radial strength and was fast dissolving. POE glycol 400 and POE glycol monostearate were less effective. The dissolution of chlorpromazine HC1 (commercial, coated) tablets was found to increase with 2% polysorbate 80 solution. In comparing the dissolution rate with the effect of the released drug on goldfish death time, Florence (52) found that the biological activity of chlorpromazine in 2% polysorbate 80 was similar to that of water containing one-third the amount of chlorpromazine. It was demonstrated that the drug absorptive activity by the goldfish (measured by death time) in polysorbate 80 peaked around the cmc decreasing thereafter.

From studies of drug release from capsules, Rowley and Newton (53) demonstrated the limitations of relating drug dissolution from capsule to improved liquid penetration of the capsule content. Drug with 0.5% and 1% sodium lauryl sulfate showed improved water penetration but release from capsule was retarded.

Huttenrauch et al. (54) studied the disintegration effect of surfactant solutions on compressed tablets of lactose, potato starch, and gelatin [40:10:1]. The surfactant used polysorbate 80 in concentrations ranging from 0% to 0.025% as disintegration media had no effect on the disintegration time although the surfactant incorporated into the tablet was described as a good disintegrator. It was thus concluded that determinants of disintegration were hydration of the bonding agent and dissolution of binding bridges rather than surface tension of the disintegration medium. However, in a later paper, Huttenrauch et al. (55) theorized that the low surface tension of gastric juice (35–40 dynes cm^{-1}) can not only improve disintegration but also dissolution. These deductions were based on the findings of enhanced disintegration and dissolution from compressed tablets by adding

surfactant into the tablet. It was noted that even in pre-micellar concentrations, improved tablet dissolution was elicited. The surfactant effect on disintegration of tablets compressed to a specified hardness however was not marked.

The tablets containing 10% starch, gelatin, and talc with surfactant concentrations ranging from 0.0001% to 3% did not improve disintegration. It was concluded that surface tension lowering and micellar solubilization of the added surfactant was inadequate to improve the disintegration of phenacetin tablets. Samaligy and Szantmiklosi (56) studied the effect of several surfactants on the in vitro release from tablets of fendiline (Sensit) and magnesium trisilicate. The effectiveness of the surfactants on drug release in decreasing order was sodium lauryl sulfate > polysorbate 80 > polysorbate 20 > sorbitan monolaurate (Span 20) > sorbitan monopalmitate (Span 40). In vivo studies in rats were found to correlate well with in vitro results. The surfactant was found to affect diffusion rather than dissolution of drug. Drawing from the results of several investigations, Huttenrauch and Jacob (57) proposed the mechanism through which surfactants decrease tablet strength as being related to the degree of crystal fracture or deterioration of crystallinity during compression. Tablets of lactose with varying amounts of polysorbate 80 were prepared and the crystallinity of the tablets was determined densimetrically. Close relationship between the fall in tablet strength with increasing surfactant content and the decrease in deterioration of crystallinity was obtained. It was proposed that surfactant diminished the effect of tableting energy on crystal fracture or particle 'activation' consequently resulting in a weaker compact. An earlier report by Chalabala and Maly (58) proposed that lubricant can prevent destruction of large crystals or granules during compaction and hence improve tablet disintegration.

Nagata et al. (59) studied the influence of polysorbate 80 solutions on the dissolution of phytonadione (various brands, commercial) tablets. It was found that dissolution generally increased with increasing polysorbate 80 concentrations in the dissolution medium. The release of tablets prepared using surfactant treated sulfonamide drugs was investigated by Jayaswal and Bedi (60). The sulfonamide tablets containing starch were compressed to specified hardness. For sulfanilamide tablets, the surfactants, sodium lauryl sulfate, polysorbate 20 and 80 all improved dissolution, the order of decreasing efficiency, polysorbate 80 > polysorbate 20 > sodium lauryl sulfate > no surfactant. For sulfaguanidine, the order was, polysorbate 80 > polysorbate 20 > no surfactant > sodium lauryl sulfate, and that for sulfadimidine tablets, polysorbate 20 > sodium lauryl sulfate > polysorbate 80 > no surfactant. It was noted that for poorly water-soluble sulfadimidine, surfactant with higher HLB values appeared more effective. In vivo studies in dogs however revealed no significant effect of polysorbate 80 on in vivo sulfanilamide release when compared with the release of sulfanilamide tablets without surfactant.

For a poorly water-soluble drug, a sodium lauryl sulfate-enriched matrix could be used to enhance drug release by gradual surface erosion (61). The rate and extent of drug release was highly dependent on the mean particle size of the bulk drug, independent of the compression force above that required for an accepted tablet.

Larazepam tablets formulated with surfactants, sodium lauryl sulfate, polysorbate 80, sodium taurocholate or sodium tauroglycolate showed higher in vitro permeation rates through rabbit jejunum sacs (62). Effect of surfactants was attributed to increased drug solubility as well as possible direct action of surfactant on the jejunal membrane. Enhanced dissolution rate as well as in vivo bioavailability in rabbits was found for phenylbutazone tablet formulations contain 0.5% Brij 96 (63). The maximum blood concentration exhibited a 2-fold increase and the area under the curve, a 3-fold increase.

Effects of Surfactants on Certain Tablet Formulations

Starch

The mechanism of action of starch as a tablet disintegrant has variously been discussed in the literature. There is little consensus as to the main mechanism by which starch acts to disintegrate tablets. The more commonly cited mechanisms include swelling of starch grains, formation of hydrophilic network within tablets, and effects on tablet porosity (1,2). It is likely that an interrelationship exists between the various mechanisms proposed. The success of starch as a widely used and popular tablet disintegrant perhaps testifies to the multifarious qualities of starch, being capable of fulfilling roles under different physicochemical environments. Studies of the corn starch components, amylose, and amylopectin, showed that the soluble amylopectin fraction was responsible for binding whereas the insoluble amylose was the disintegrant (22). The swelling of starch is often cited as the mechanism by which starch acts as a tablet disintegrant (1,2). There are however many who dispute the ability of the moderate swelling power of starch to disintegrate the tablet. Studies of starch swelling at 37˚C in water have reported volume increases between 70% and 80%, assuming spherical shape (64,65). Where swelling of starch grains is responsible for disintegrating a tablet, tablet porosity can have a significant role in determining the effectiveness of the disintegrant. Tablets with high porosity have lots of space and hence starch swelling becomes ineffective in building sufficient swelling pressure to promote disintegration. On the other extreme, severely compacted tablets of low porosity reduce liquid penetration thereby prolonging disintegration (66,67). An optimum porosity therefore exists where the tablet is most sensitive to the effect of starch swelling. The formation of a network of hydrophilic conduits by starch allowing better and faster liquid penetration and hence more rapid tablet disintegration had been proposed by various investigators (68–70). Curlin (68) reported that aspirin tablets containing starch had prolonged disintegration time in hot water. Since the swelling of starch is greater in hot water, it was concluded that an improved capillary action causing more rapid liquid penetration rather than swelling was responsible for starch disintegrant action. Ringard and Guyot-Hermann (70) also demonstrated the close association between improved water penetration by starch and the disintegration time. They proposed the existence of a continuous and adsorbent hydrophilic network of starch in aspirin tablets.

Cooper and Brecht (3) investigated the possible application of surfactant in tablet formulations with the aim of improving disintegration. The evaluations of 21 surfactants in calcium lactate tablets were presented. The excipient mix of 10% starch with 0.2% surfactant was found most effective and was used in the formulations. Application of surfactant was by spraying in an alcoholic solution using an atomizer onto the granulation and dried. The surfactants, dioctyl sodium sulfosuccinate (Aerosol OT), and di(1-methylamyl) sodium sulfosuccinate (Aerosol MA) were found to produce tablets with the lowest disintegration times. It was proposed that starch and surfactant acted synergistically in disintegrating tablets. The surfactant acted by reducing interfacial tension thereby promoting more rapid softening of the tablet, faster liquid availability to the starch and hence faster disintegrant action. Although a relationship between disintegration time and surface tension was discussed, no significant correlation could be found.

Using two drugs of different solubilities, Ward and Trachtenberg (71) evaluated 10 disintegrants and reported that starch containing 20% sodium lauryl sulfate was the most efficient. Formulations of amphenidone and sulfadiazine were prepared by first granulating the drugs with 10% starch paste, then drying. Five percent of the disintegrant to be studied was then added as external disintegrant and tableted to a controlled hardness. The

disintegration action of starch-sodium lauryl sulfate in improving disintegration time was attributed to wicking, swelling and the influence of surfactant, probably referring to the wetting effect of surfactant. The use of maize starch-sodium lauryl sulfate combination as disintegrant was also reported (72). Levy and Gumtow (73) using salicylic acid tablets containing 20% starch concluded that the hydrophobic magnesium stearate (3%) used as lubricant-retarded salicylic acid dissolution by decreasing the effective drug dissolution medium interfacial area. Substitution of magnesium stearate with 3% sodium lauryl sulfate was found to enhance dissolution as the hydrophilic surfactant allowed better wetting and increased aqueous penetration into the tablet and component granules resulting in a larger interfacial area available for dissolution. Using non-disintegrating disks (without starch), it was noted that 3% sodium lauryl sulfate did not improve the dissolution of salicylic acid thus indicating that alteration of the micro-environmental pH and solubilization was ineffective in improving drug dissolution.

The investigators, Duchene et al. (74,75) studied the effect of a wide range of nonionic surfactants, macrogol ethers (Brijs), macrogol stearates (Myrjs), polysorbates (Tweens), and sorbitan esters of fatty acids (Spans) on granule and tablet properties. The drug used, sulfanilamide was formulated with potato starch and 4% surfactant. Most surfactants were found to improve the flow and dissolution of granules. The dissolution effect was generally related to the HLB of the surfactants. For tablets compressed to a specified hardness, the surfactants prolonged disintegration. Spans and Tweens increased disintegration time more than Myrjs and decreased friability. With Myrjs, friability was shown to be a function of the number of ethylene oxide groups of the surfactant, increased ethylene oxide groups increased tablet friability. It was later reported by Duchene et al. (76) that for sulfanilamide tablets containing Myrjs and Brijs, the tablet hardness was reduced with increasing ethylene oxide groups in the surfactant molecule. For Tweens and Spans however, the reverse was noted.

Tablet formulations containing starch showed prolonged disintegration in the presence of polysorbate 80 (77). Particle size determinations of starch grains in water and surfactant solutions showed depressed starch grain swelling with increasing surfactant concentrations. This reduced swelling was probably responsible for the prolonged disintegration. Aqueous penetration into tablets containing starch was reduced in the formulations containing surfactant (78). It was likely that liquid uptake was dependant on the disruption of the tablet matrix since the volume of uptake was much larger than the pore space in the non-wetted tablet. As surfactant prolonged disintegration, there was reduce liquid uptake. Ibuprofen tablets containing starch had much improved release rate when sodium lauryl sufate was incorporated (79).

Microcrystalline Cellulose

Microcrystalline cellulose is insoluble in water and alcohol. Despite its water insolubility, microcrystalline cellulose promotes rapid aqueous penetration into the tablet matrix through capillary action and causes disintegration by breaking hydrogen bonds between the bundles of cellulose microcrystals (80–82). Using deuterium exchange, Huttenrauch (83) confirmed the existence of hydrogen bonds responsible for the mechanical strength and disintegration of microcrystalline cellulose tablets. Nogami et al. (84) investigated the properties of potato starch and microcrystalline cellulose and their influence on aspirin tablet formulation. Water penetration was more rapid in microcrystalline cellulose than starch. Considering the contact angle of 68.5° for microcrystalline cellulose and 84.5° for starch, the more rapid water penetration of microcrystalline cellulose was not unexpected. Although microcrystalline cellulose enabled more rapid aqueous penetration

than starch, disintegration times of aspirin tablets containing microcrystalline cellulose was not necessarily shorter than those tablets containing starch. Neither the mean capillary diameter nor the tablet hardness could be correlated with the disintegration time. It was suggested that starch and microcrystalline cellulose may act synergistically if both are added as disintegrant since microcrystalline cellulose enhances aqueous penetration enabling more rapid swelling of starch. Lerk et al. (82) also demonstrated rapid water penetration into directly compressed tablets containing microcrystalline cellulose. Blending microcrystalline cellulose with insoluble dibasic calcium phosphate improved tablet disintegration, but with highly soluble excipients such as dextrose, disintegration was prolonged. Water penetration was also influenced by highly soluble excipients. It was shown that highly soluble excipients upon dissolution first promote penetration by pore enlargement, but the dissolving substance would sharply increase the viscosity of the penetrating liquid thereby retarding the penetration rate.

Polysorbate 80 improved the disintegration and aqueous uptake of tablet formulations containing microcrystalline cellulose (78). The surfactant acts by improving the wettability of the tablet interior facilitating liquid access into the tablet thereby promoting disintegration. The faster disintegration could also in return increase liquid uptake by generating cracks in the tablets. However, for formulations containing microcrystalline cellulose, the surfactant added retarded the dissolution rate from granules but promoted the dissolution rate of tablets (85). It was found that the surfactant did not assist in the break up of granules but decreased the disintegration time of tablets. Tablets containing microcrystalline cellulose and croscaramellose or sodium starch glycolate showed increased disintegration times with increasing concentrations of sodium lauryl sulfate (5).

Alginate

The strongly swelling sodium calcium alginate appeared to "waterproof" the tablet interior (86). Disintegration of tablets containing sodium calcium alginate was mainly by slow surface erosion. When added, the surfactant was found to improve both the disintegration and aqueous uptake of the tablets. The improved disintegration could be brought about by the reduced cohesiveness of the tablet matrix allowing faster and less hindered dissociation of particles from the tablet surface. Although surfactants have the ability to reduce hydrophobicity, surfactant effects on the physicochemical properties of the tablet, and its excipients may accentuate or negate their advantage.

Polymeric Matrices

The role of a non-ionic ampholytic surfactant on the swelling properties of polymeric matrices was studied and it was found that the surfactant enhanced the swelling capacity of hydroxypropyl methylcellulose (87). The effect on poly(oxyethylene) was unclear while for sodium alginate, the dominant factor was its water solubility. With thermosensitive polymers, poly(N-isopropylacrylamide), and a co-polymer with N-vinyl-acetamide, the lag time of release was influenced by the surfactant species and amount (88).

Tablet Coatings

Surfactants may be added to tablet coating formulations for certain specific purposes. In general, it is not desirable to add surface active agents into coating solutions or dispersions due to their foam inducing properties. Polysorbate 20 was used as a drug release regulator in ethyl cellulose films of sodium salicylate tablets (89,90). As the amount of surfactant increased, sodium salicylate release increased and lag time shortened.

Meltable Matrices

Wax coatings are commonly used for taste masking purposes. While the lipoidal coating may be effective in masking taste, the adverse consequence of poor bioavailability needed to be overcome. Inclusion of sucrose fatty acid ester enhanced the dissolution of the hydrogenated oil coating (91). Tablets from hot-melt extrudates containing the nonionic surfactant, a polyoxyethylene–polyoxypropylene copolymer, and methacrylate copolymners enhanced indomethacin release with increasing surfactant content (92).

Effects of Surfactants on the Physical Properties of Tablets

Studies on the effect of surfactant on the properties of granules and tablets were carried out to determine the role of surfactant in altering the granule and tablet properties. In the investigation of surfactant effects on tablet disintegration and dissolution, the surfactant is usually either added to the test medium or incorporated into the powder or granules before compression. The addition of polysorbate 80 to sulfanilamide granule formulations containing starch improved the flow property of granules (93). However, high surfactant content imparted a degree of tackiness to the granules. The effects of the surfactants on tablet properties differed from that of granules since tablets were formed from granules which had undergone severe compaction forces. The main similarity was the decreased hardness of both granules and tablets when surfactant was incorporated. In the friability measurements, granules with low surfactant concentrations showed high friability rate, decreasing at higher surfactant content. These findings indicated that granule friability, unless correlated with granule hardness should not be assumed (94).

It was found that the influence of surfactant on the disintegration and dissolution rate of granules and tablets were dependant on the choice of disintegrant used. Polysorbate 80 was found to increase the bulk density of granules. This property strongly influenced the dissolution of sulfanilamide granules containing starch (77,93). As starch swelled, the more densely packed granules were more responsive to the swelling action of starch. In the dissolution measurements, these granules were fragmented into fine particles enabling more rapid drug dissolution. The presence of surfactant "sandwiching" between constituent particles in the dosage form enabled it to be more responsive to the swelling effects of starch (95).

It was reported by Agrawal et al. (96) that water or surfactant treated potato starch as disintegrant generally produced softer tablets with shorter disintegration times but increased friability compared to untreated starch. Treatment of starch was by stirring in water or surfactant solutions for 2 hours then collected and dried. In dissolution of sulfanilamide tablets, polysorbate 80, and water treated starches produced tablets with better dissolution than those using untreated starch. Sodium lauryl sulfate and polysorbate 20 treated starches did not improve dissolution. In fluidized bed granulation, the addition of sodium lauryl sulfate was reported to improve the granulation process (97). The salicylic acid–lactose tablets made showed improved dissolution. The effect of polysorbates 20, 40, 60, and 80 on the disintegration of phenacetin tablets compressed to specified hardness has been investigated by Wan (98).

Surfactants have been known to form soft compacts (57,75,96–98). Tablet hardness tends to decrease with the inclusion of surfactants. However, it was reported that decreased tablet hardness caused by the addition of a surfactant did not always correlate with reduced disintegration time (99).

COLORING

Uses of Colors in Tablet Dosage Forms

One of the main reasons for coloring tablet dosage forms is to facilitate product identification and differentiation at the various stages of the drug product's life cycle (100–102). The use of different colors for different products allows for rapid identification of products and enhances product control during manufacture. Color is also used by manufacturers in combination with shape, size, and logo to prevent counterfeiting of products. As healthcare professionals and patients usually use color as a means for distinguishing different medications, tablets containing different strengths of the same drug are often made available in different colors to prevent mix-up and errors during dispensing and use by patients. In addition, tablets are colored for aesthetic and marketing reasons (100). Unattractive color and/or non-uniformity in color of drugs or raw materials in tablet formulations can be masked by the addition of colorants. The application of an elegant color coat enhances the appearance of a tablet dosage form. Furthermore, opaque color coats containing certain insoluble colors, such as titanium dioxide and iron oxides, can offer some protection to light-sensitive drugs in tablet formulations (102).

Types of Pharmaceutical Colorants/Coloring Agents

Colorants or coloring agents used to impart color to pharmaceutical products may be of natural or synthetic origin. Examples of natural colorants include mineral colors, such as titanium dioxide and iron oxides, and plant colors, such as chlorophyll and beta-carotene (103). Mineral and plant colors are often termed as pigments. A number of plant colors have also been synthesized and are obtainable commercially as synthetically-derived nature-identicals. Dyes are water-soluble synthetic substances that can impart color. Water-insoluble lakes are formed by the adsorption of a water-soluble dye onto a hydrous oxide, often aluminum hydroxide. On the whole, synthetic colorants are used more widely in coloring pharmaceutical products. Their advantages over natural colorants include: their more intense coloring ability, use of smaller amounts of synthetic colorants and better color uniformity.

Regulatory Aspects/Issues

Many countries exercise regulatory control over colorants for use in pharmaceutical products. Due to safety concerns, the number of permitted colorants is limited. However, different countries have their own listing of permitted colorants for coloring pharmaceutical products and have set down specific purity criteria for the colorants. There may also be quantitative restrictions and additional label declarations imposed on certain colorants. The regulatory/use status of a particular colorant is subject to change and not universal across the different regions in the world. Consequently, it is important during the product development stage to refer to the latest legislations of the country or countries in which the product will be marketed to select a colorant that is deemed acceptable for pharmaceutical use in those regions.

United States

In the United States, all color additives to be used in pharmaceutical products must be approved by the Food and Drug Administration (FDA). The FDA directs the listing of color additives permitted for use in food, drugs, and cosmetics. The regulations for color

additives are provided for in Title 21 of the Code of Federal Regulations, Parts 70–82 (104). The color additives are categorized as "exempt from certification" or "certifiable." Color additives that are exempt from certification include pigments obtained from natural sources, e.g., of animal, plant or mineral origin, and synthetic equivalent of naturally-derived substances. Certifiable color additives are synthetically-derived, and each batch has to undergo color additive certification by the FDA.

Following the Federal Food, Drug and Cosmetic Act of 1938, three categories of certifiable synthetic dyes were created: FD&C colors are color additives that are certifiable for use in food, drugs, and cosmetics; D&C colors are color additives deemed safe for use in drugs and cosmetics when ingested or when in contact with mucous membranes, and external D&C colors are color additives not certifiable for use in products for ingestion but deemed safe for use in products to be applied externally. In general, FD&C and D&C color additives are used for coloring oral dosage forms while external D&C can only be used for products to be applied externally (Tables 1 and 2).

European Union

The legislation that governs coloring materials for incorporation into pharmaceutical products in the European Union is Council Directive 78/25/EEC of 12 Dec 1977 (105). Reference is made in this directive to Annex I, Sections I and II, to Council Directive of 23 October 1962 (concerning coloring matters approved for use in foodstuff intended for human consumption) and its subsequent amendments, for colorants permitted for use in foodstuff to be used in medicinal products. However, pertaining to medicinal/pharmaceutical products, no differentiation is made between coloring materials for mass and surface coloring, and coloring materials for surface coloring. To date, the 1962 legislation concerning coloring matters has been revoked and replaced by Council Directives 94/26/EC of 30 June 1994 (106) and 95/45/EC of 26 July 1995 (107), which lists the permitted colorants and their specific purity criteria, respectively. The former Scientific Committee on Medicinal Products and Medical Devices has also deliberated on the suitability and safety of E173 Aluminum, E123 Amaranth, E161 Canthaxanthin, E127 Erythrosine, and E174 Silver as colorants in pharmaceutical products. Their opinions given were that Aluminum, Amaranth, Canthaxanthin, and Erythrosine may be considered acceptable for use as colorants in pharmaceutical products, while the use of Silver should be prohibited (108–112). Examples of colorants permitted for pharmaceutical use in the European Union are given in Table 3.

Incorporation of Color into Tablet Dosage Forms

Colors can be incorporated into tablet dosage forms during the granulation phase prior to tableting, or in a separate coating process after tableting. With water-soluble dyes, the conventional approach for incorporating color during wet granulation is to first dissolve the water-soluble dye in the binder liquid before effecting granulation. This step aids in ensuring that the dye is uniformly distributed into the powder mass. Alternatively, water-soluble dyes in aqueous or alcoholic solutions can be adsorbed onto carriers, such as starches and calcium sulfate, to prepare dried powders that can be subsequently dry-mixed with other formulation components before proceeding to granulation (113,114). When insoluble pigments and lakes are used, they are first dry-blended with other ingredients prior to direct compression or wet granulation. As for color coating of tablets, this can be carried out by sugar coating and film coating using water-soluble dyes, lakes or insoluble pigments.

TABLE 1 Color Additives Subject to Certification, Permitted for Use in the United States for Coloring Oral Solid Dosage Forms (as of April 2006)

FD&C or D&C name	Common name	Color index (CI)	Uses and restrictions
FD&C Blue 1	Brilliant blue FCF	42090	Color drugs
FD&C Blue 2	Indigotine; Indigocarmine	73015	Color ingested drugs
FD&C Green 3	Fast green FCF	42053	Color drugs generally
FD&C Red 3	Erythrosine	45430	Color ingested drugs
FD&C Red 40	Allura red AC	16035	Color drugs
FD&C Yellow 5	Tartrazine	19140	Color drugs generally & label declaration
FD&C Yellow 6	Sunset yellow FCF	15985	Color drugs generally
D&C Red 6	Lithol rubin B	15850	Color drugs; Combined total of D&C Red 6 & D&C Red 7: Not more than 5 mg/daily drug dose
D&C Red 7	Lithol rubin B Ca	15850:1	Color drugs; Combined total of D&C Red 6 & D&C Red 7: Not more than 5 mg/daily drug dose
D&C Red 21	Tetrabromofluorescein	45380:2	Color drugs generally
D&C Red 22	Eosine (Eosin Y)	45380	Color drugs generally
D&C Red 27	Tetrachlorotetrabromofluorescein	45410:1	Color drugs generally
D&C Red 28	Phloxine B	45410	Color drugs generally
D&C Red 30	Helindone pink CN	73360	Color drugs generally
D&C Red 33	Acid fuchsin D	17200	Color ingested drugs; ADI: 0–0.75 mg
D&C Red 36	Flaming red	12085	Color ingested drugs; ADI: 0–1.0 mg
D&C Yellow 10	Quinoline yellow WS	47005	Color drugs generally

Abbreviations: ADI, acceptable daily intake (per kg body weight); FD&C, Food, Drug and Cosmetic dyes; D&C, Drug and Cosmetic dyes.

TABLE 2 Color Additives Exempt from Certification, Permitted for Use in the United States for Coloring Oral Solid Dosage Forms (as of April 2006)

Color name	Color index (CI)	Uses and restrictions
Alumina; Dried aluminum hydroxide	77002	Color drugs generally
Annatto extract	75120	Color drugs generally
Beta carotene	40800	Color drugs generally
Calcium carbonate	77220	Color drugs generally
Canthaxanthin	40850	Color ingested drugs generally
Caramel	–	Color ingested drugs generally
Cochineal extract; Carmine	75470	Color ingested drugs generally
Iron oxides, synthetic		Color ingested drugs; ADI: Not more than 5 mg elemental iron
Iron oxide—black	77499	
Iron oxide—red	77491	
Iron oxide—yellow	77492	
Mica based pearlescent pigments	–	Color ingested drugs; Up to 3%, by weight of final drug product; Maximum amount of iron oxide: Not more than 55% by weight in finished pigment
Talc	77019	Color drugs generally
Titanium dioxide	77891	Color ingested drugs generally

Note: In FDA's listings as for "coloring drugs generally" but not common elsewhere are italicized.
Abbreviations: ADI, acceptable daily intake (per kg body weight).

Mottling, seen as an uneven distribution of color on tablets, is a common problem usually associated with the use of water-soluble dyes in wet granulation and color coating. Being water-soluble, the dye tends to migrate from the interior to the drying surface with the gradual removal of moisture during the drying step. The influences of various manufacturing and formulation variables in wet granulation that may give rise to tablet mottling have been evaluated by Armstrong and March (115–117) using a photographic method for quantifying mottling on colored tablet surfaces. As a result of intragranular dye migration, the granules prepared by wet granulation tend to be colored unevenly, with color-rich surfaces but color-deficient cores. To minimize intragranular dye migration, granules should ideally be made as small as possible but without compromising their bulk flow characteristics. Upon tableting, breakup of the granule structure exposes the non-uniform color distribution within the granules, leading to the appearance of mottling on the resultant tablet surfaces. Thus, Armstrong and March (116,117) also recommended that granules should not be comminuted after drying as the process of comminution causes granules to break up, revealing their color-deficient cores.

When water-soluble dyes are used as colorants in wet granulation, it is important to optimize drying conditions to minimize the extent of color migration during drying. Continuous stirring/agitation of the granules is necessary to facilitate uniform drying. From their comparison of tray drying and fluid bed drying, Armstrong and March (116) observed that tray-dried granules gave rise to greater tablet mottling than fluid bed-dried granules. Besides intragranular dye migration, intergranular dye migration can take place

TABLE 3 Colorings Permitted for Pharmaceutical Products in the European Union

E number	Common name	Color index (CI)	FD&C name
E100	Curcumin; Tumeric	75300	
E101	Riboflavin	–	
E102	Tartrazine	19140	FD&C Yellow 5
E104	Quinoline yellow	47005	
E110	Sunset yellow FCF	15985	FD&C Yellow 6
E120	Carmines; Cochineal; Carminic acid	75470	
E122	Carmoisine; Azorubine	14720	
E123	Amaranth	16185	FD&C Red 2
E124	Ponceau 4R; Cochineal red A	16255	
E127	Erythrosine	45430	FD&C Red 3
E129	Allura red AC	16035	FD&C Red 40
E131	Patent blue V	42051	
E132	Indigotine; Indigo carmine	73015	FD&C Blue 2
E133	Brilliant blue FCF	42090	FD&C Blue 1
E140	Chlorophylls and chlorphyllins		
	a. Chlorophylls	75810	
	b. Chlorophyllins	75815	
E141	Copper complexes of chlorophylls and chlorophyllins	75815	
E142	Green S; Brilliant green BS	44090	
E150	Caramel	–	
E151	Brilliant black BN; Black PN	28440	
E153	Vegetable carbon; Carbo medicinalis vegetalis	77266	
E160	Carotenoids		
	a. Alpha-, beta-, gamma-carotenes	75130, 40800	
	c. Capsanthin, Capsorubin, Paprika	–	
	oleoresins	75125	
	d. Lycopene	40820	
	e. Beta-apo-8’ carotenal	40825	
	f. Ethyl ester of beta-apo-8’ carotenoic acid		
E161	Xanthophylls		
	b. Lutein	–	
	g. Canthaxanthin	40850	
E162	Beetroot red; Betanin	–	
E163	Anthocyanins	–	
E170	Calcium carbonate	77220	
E171	Titanium dioxide	77891	
E172	Iron oxides and hydroxides		
	Iron oxide black	77499	
	Iron oxide red	77491	
	Iron oxide yellow	77492	
E173	Aluminum	77000	

in the static granule bed during tray drying, thereby aggravating the problem of dye migration. Fluid bed drying is therefore preferred over tray drying as intergranular dye migration does not take place during fluid bed drying due to the dynamic nature of the fluid bed.

Various alternative formulation approaches have been suggested for alleviating tablet mottling. Additives that may function as inhibitors of dye migration have been incorporated into tablet formulations. These additives include tragacanth, acacia, attapulgite, and talc which have been used with FD&C Blue No. 1 in lactose formulations (114,117,118). The use of adsorbents, such as starches, with affinity for water-soluble, anionic dyes has been proposed by Zografi and Mattocks (119) for reducing tablet mottling by preventing dye migration. In their study on the influences of binding agents, diluents and dye-adsorbents on tablet mottling, Armstrong and March (117) verified that tablet mottling was indeed reduced when starches were incorporated in the tablet formulations. However, they attributed this observation to the effect of starches in decreasing the degree of granule fragmentation during tableting rather than to their role as adsorbents for preventing dye migration. Tablet mottling was found to be less obvious when acacia was used as a binding agent; this was not because acacia prevented dye migration but because it was able to lower the overall color saturation of the tablet surfaces. Lakes may be used in place of their water-soluble dye counterparts in granulation as they are insoluble and would not migrate during drying. Nevertheless, it should be noted that the dye may elute from the lake at pH extremes or when anions are present. Consequently, it is essential to screen and choose compatible excipients for developing the tablet formulations. The careful selection of colorant concentration, choice of color and "colored" additives aids in reducing the prominence of mottling on tablet surfaces. The degree of mottling increases with an increase in colorant concentration. Mottling is also more prominent when strong colors are used. In the choice of colors, pastel shades have been reported to give rise to the least mottling (100,112). The degree of mottling can be reduced by employing additives that are colored corresponding to the color of the granules to be used for tableting (114).

With regard to color coating, sugar coating with water-soluble dyes can give rise to a more elegant sugar coat with a "cleaner and brighter final color" (120). However, as in wet granulation, color migration may occur with the use of water-soluble dyes, giving rise to an uneven distribution of color in the sugar coat. Unevenness in the color distribution becomes more prominent when darker colors are chosen for coating. Lakes and pigments can be employed to circumvent the problem of dye migration during sugar coating. As they are insoluble in water, they do not migrate but remain where they are deposited on the coat surface. The advantages of sugar coating with lakes and pigments include reduced processing time and costs. A disadvantage is that it can be more difficult to completely wet and uniformly disperse a water-insoluble colorant into a syrup solution. During aqueous film coating, color migration may occur when water-soluble dyes are used. As such, lakes and pigments are usually used instead. However, care has to be taken to disperse the insoluble colorants uniformly into the coating formulation to ensure that an even deposition of the color is applied during the film coating process. Mixtures of water-soluble dyes and lakes have also been employed in the form of coating suspensions to reduce cost and give coats with brighter color shades (121). As water-soluble dyes are less expensive than lakes, efforts have been directed to develop aqueous color coating suspensions using water-soluble dyes in which metal salt immobilizing agents have been added to prevent migration of the water-soluble dyes during coating.

Color Selection for Tablet Dosage Forms

Unlike the active drug, the colorant in a dosage form does not function to exert a pharmacological action. Its role is to impart color to the product. However, the choice of color and the resultant color of the dosage form hold considerable import in influencing

consumer perception. In relation to quality, consumers may associate unevenness in color within a tablet, between tablets within a batch or between tablets from different batches with poor product quality. On a more practical note, the selection of the right color or color combination for the dosage form can contribute to improving patient compliance, especially among the young and elderly. For example, aside from choosing attractive colors to match the flavors of chewable tablets to make the products more appealing (101), color-flavor matching can lead to increased compliance among children. In their study on patients' preference of shape, size, and color of tablets and capsules, Overgaard et al. (122) observed that while the majority of the patients liked white tablets best, those who were on more than 10 tablets per day had a preference for tablets with bright colors, possibly because these patients used color for product identification and differentiation. In particular, elderly patients with impaired vision and who are on several types of medications a day may encounter difficulty in differentiating between their different drug products. Color perception studies carried out by Hersberger and Hatebur (123) using capsules with different colors (monochromatic) and color combinations (bichromatic) on elderly subjects with impaired vision and on polymedication showed that elderly subjects had difficulty in differentiating between brown, orange, purple, and pink colors under low light intensity conditions. The subjects also found it harder to differentiate color combinations of brown/purple, green/brown, dark blue/purple, white/pink, yellow/pink, and dark blue/brown as compared to white/red, yellow/red, and white/light blue color combinations. The psychological influences of capsule colors on the therapeutic effects of drug products have been investigated by Lüscher and Bas (124) and Bauer et al. (125). They reported that while everyone perceives the same color in the same way, preference and dislike of certain colors may vary between individuals. As colors can rouse certain sensations and reflect feelings, it was put forward that psychosomatic causal factors can be interpreted from a patient's choice of colors. Studies employing the Lüscher color test have identified colors and color combinations for various therapeutic indications (Table 4). According to Lüscher, the ideal color for a capsule can be found by first selecting the basic color based on the patient's preference and subsequently the particular color shade by considering the intended therapeutic effect of the drug product. In addition to indication, the color of a drug product may influence patients' perception of its potency. In their study on the relationship between capsule color and perceived potency,

TABLE 4 Selection of Colors for Pharmaceutical Drug Products Based on Pharmacological Action

Pharmacological action	Colors
Anti-diarrhoeals	Brown, turquoise
Anti-obesity agents	Yellow, dark blue
Anti-tussives	Maroon, light blue
Appetite stimulants	Green, orange
Digestives and enzymes	Olive, orange
Hypnotics	Mauve, violet
Laxatives	Olive green, light brown
Muscle relaxants	Maroon, dark blue
Sedatives	Dark blue, brown
Stimulants	Orange, yellow
Vitamins	Green, red

Source: From Ref. 124.

Sallis and Buckalew (126) found that red and black were perceived to have the strongest potency among the capsule colors evaluated while the other colors, orange, yellow, green, blue, and white, were perceived to be weaker. Consequently, during the product development stage, the formulator may consider choosing appropriate colors and shades to complement and support the intended therapeutic indication and the pharmacological action of the drug (127) as well as take into account the role of color in influencing patients' perception of the potency of the drug product, particularly in the development of placebo dosage forms for clinical trials (126).

CONCLUSION

Surfactants can be used to increase the wetting ability of tablets containing hydrophobic drugs. This will likely lead to faster dissolution and consequently, improved bioavailability of the active component. While surfactants have the ability to reduce surface tension of poorly wetted drugs and help in drug solubilization, their often adverse influence on the mechanical properties of the tablet dosage forms need to be considered. Surfactants generally improve granule flow and reduce interparticulate friction during compaction but their presence can also reduce the mechanical strength of tablets. As the gastrointestinal tract has its share of surface active constituents, the need to incorporate surfactant which can compromise tablet integrity can sometimes be questionable. Nevertheless, where clear advantages can be demonstrated, like improvement of the wettability of highly hydrophobic drugs, surfactant may be incorporated.

Essentially, color additives do not have a functional role in the tablet formula other than to impart color to the finished product. Unlike other excipients in a tablet formulation, they do not affect the intended performance and quality of the product per se. However, color plays a significant part in improving patient compliance and may also influence consumer perception of a product's quality, potency, and indication. In practice, tablet dosage forms are often made available in different colors for purposes of aiding product identification and differentiation, and to make a more appealing and elegant product. For the above reasons, it is important that the formulator takes into consideration regulatory issues associated with the selection of color additives, and the technical and formulation aspects relating to their successful incorporation into tablet dosage forms.

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9

Orally Disintegrating Tablets and Related Tablet Formulations

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INTRODUCTION

Orally disintegrating tablets (ODTs) are solid single-unit dosage forms that are designed to be placed in the mouth, allowed to disperse or dissolve in the saliva, and then swallowed without the aid of additional water. Despite a surge of orally disintegrating tablets in the market in the recent years, they potentially can be confused with other solid oral dosage forms that are consumed without additional water intake, including lozenges, buccal tablets, and chewable tablets. Lozenges and buccal tablets are intended to dissolve slowly in the mouth, whereas, orally disintegrating tablets must disperse or dissolve in the mouth quickly, within seconds. Chewable tablets are also different from orally disintegrating tablets because they require manual chewing action by the patients before they can be swallowed. The disintegration times are longer for the chewable tablets compared to the orally disintegrating tablets. For a tablet to be classified as an orally disintegrating tablet the disintegration time should be sufficiently rapid for the patient to not feel the need or compulsion to chew. Orodispersible tablets (1), rapidly disintegrating tablets (2), and fast-dissolving tablets (3) have been used as synonyms for orally disintegrating tablets. Examples of orally disintegrating tablets include over-the-counter drugs such as Claritin® RediTabs® (loratadine rapidly-disintegrating tablets) and Alavert™ (loratadine orally disintegrating tablets), and prescription drugs such as Maxalt-MLT™ (rizatriptan benzoate) and ZOFRAN® (ondansetron) Orally Disintegrating Tablets.

One of the greatest benefits of orally disintegrating tablets over conventional tablets is enhanced patient compliance and acceptance related to both feasibility and convenience of dosage administration (4). As many as 50% of the population have difficulty swallowing intact tablets and hard gelatin capsules (5). These include pediatric and

[1] The opinions expressed in this chapter do not necessarily reflect the views or policies of the U.S. Food and Drug Administration.

geriatric populations who have difficulty swallowing large tablets. Patients who are bedridden, mentally retarded, uncooperative, nauseous, and those suffering from nervous or anatomical disorders of the larynx or esophagus, or on reduced liquid intake diets also cannot swallow conventional tablets. In such patients practitioners would expect much better compliance and therapeutic outcomes by administering orally disintegrating tablets instead of conventional tablets (6). Patient compliance can be enhanced by designing orally disintegrating tablets that have pleasant taste and texture because many people simply do not enjoy swallowing solid tablets. People who take medicines on an as-needed basis and active people who do not have convenient access to water could easily take them as well.

Orally disintegrating tablet drug delivery does, however, have certain limitations. Because orally disintegrating tablets require the users to produce their own saliva, those with very dry mouth may not benefit. Production of saliva depends not only on the drug product formulation but the ability and condition of the user. Also, the administration of orally disintegrating tablets to increase compliance in uncooperative patients, such as those being treated for mental illness, does not guarantee compliance. Patients have found various ways of hiding the medication such as sticking the Zydis tablet behind the teeth to avoid swallowing the medication (7). Nonetheless, orally disintegrating tablets offer practitioners an added tool in enhancing compliance in some patient populations (3).

The candidate drug categories for orally disintegrating tablets are diverse, such as cardiovascular drugs used for chronic conditions with large geriatric population as users, and drugs taken on as-needed bases, including analgesics, drugs to treat erectile dysfunction, and antihistamines. Patient interest and demand provide a substantial opportunity for the pharmaceutical industry to expand product lines and develop new marketing initiatives. However, in expanding product lines, manufacturers should consider the potential differences in bioavailability between the orally disintegrating tablets and traditional tablets. With traditional, or conventional, tablets, the contact times between the drug substance and oromucosal tissues are minimal, and most of the absorption takes place in the stomach and/or the intestines. However, drug released from orally disintegrating tablets also has the opportunity to be absorbed by local oromucosal tissues and pregastric regions, especially if the residence time in the mouth is prolonged. Oromucosal and pregastric absorption can potentially produce a rapid response, and partial avoidance of first-pass effects and gastrointestinal irritation (5). Therefore, formulation as a "bioequivalent" line extension of a conventional oral dosage form may be difficult for some drugs because of varying degrees of pregastric absorption which can have an impact on C_{max} (maximum plasma concentration), T_{max} (the time to reach C_{max}), and AUC (area under the curve of plasma concentration plotted over time). As an example, a different pharmacokinetic profile for an orally disintegrating tablet compared to a conventional oral dosage form was found with hydrochlorothiazide. Based on the biopharmaceutical classification system (BCS) hydrochlorothiazide is classified to be highly soluble and poorly permeable (BCS Class III) (8). Corveleyn and Remon compared pharmacokinetic parameter values (AUC, C_{max}, T_{max}, and half life) obtained from subjects who took the conventional hydrochlorothiazide tablet, freeze-dried orally disintegrating formulation A, or freeze-dried orally disintegrating formulation B (9). Formulation A contained maltodextrin, polyethylene glycol 6000, xanthan gum, and hydrochlorothiazide to make an aqueous suspension. Formulation B contained miglyol, maltodextrin, methocel LV, and hydrochlorothiazide to make an emulsion. The suspension or emulsion was poured into PVC blisters and the samples were freeze-dried. The dissolution rate for formulation A was faster than the other dosage forms both in water and in 0.1 N hydrochloric acid. At the end of 30 minutes complete dissolution occurred for formulation A, but only about 80%

TABLE 1 Conventional Hydrochlorothiazide Tablets versus Orally Disintegrating Tablets–Average Pharmacokinetic Parameters Determined from 6 Healthy Volunteers

Formulation	AUC_{0-24h} (ng/hr/mL)	C_{max} (ng/mL)	T_{max} (min)	$T_{½}$ (h)
Formulation A[a]	1843.4 ± 476.2[d]	244.2 ± 44.3	142.5 ± 47.4	5.4 ± 1.8
Formulation B[b]	1072.8 ± 368.6	201.8 ± 38.5	135.0 ± 35.8	5.2 ± 2.2
Esidrex® 25[c]	1009.5 ± 399.8	200.1 ± 34.9	183.7 ± 40.7	5.8 ± 2.3

[a]Formulation A: Orally disintegrating tablets containing maltodextrin, polyethylene glycol 6000, xanthan gum, and hydrochlorothiazide.
[b]Formulation B: Orally disintegrating tablets containing miglyol, maltodextrin, methocel LV, and hydrochlorothiazide.
[c]Esidrex® 25 (Ciba, Basel, Switzerland): Conventional reference formulation.
[d]$p < 0.05$; AUC was significantly higher for Formulation A compared to the other two formulations.
Source: From Ref. 9 with permission from Elsevier.

dissolution occurred for the other formulations. As shown in Table 1, the AUC_{0-24h} value for formulation A was significantly higher than either the reference formulation or Formulation B. The C_{max} was also higher for formulation A, but not significantly. Differences in T_{max} and $T_{1/2}$ (half life, or the time for the plasma concentration to decrease by one half) were also not significant. Based on these observations it is apparent that the formulation of orally disintegrating tablets can significantly change the bioavailability of some drugs.

FORMULATION CONSIDERATIONS OF ORALLY DISINTEGRATING TABLETS

Aside from the bioavailability issues that may affect how the manufacturer expands the product line, additional challenges of developing oral disintegrating tablets include achieving palatability and assuring practical hardness and friability without increasing the disintegration time. Achieving palatability may require taste masking of the active ingredients which may be bitter in taste. Taste masking can be achieved by coating the active ingredient particles with a polymer by spray drying, spray congealing, or coacervation (5). For example, Khan et al. (10) were able to formulate rapidly-disintegrating tablets for bitter tasting ondansetron hydrochloride by using aminoalkyl methacrylate copolymer (Eudragit® EPO, Roehm GMBH, Darmstadt, Germany). For taste masking purposes they formed a drug–polymer complex by precipitation. Saturated solutions of ondansetron hydrochloride and Eudragit EPO in ethanol were prepared. The solution was injected into 0.1 N sodium chloride under stirring. The resulting foamy matrix on top was separated and dried under vacuum. The dried matrix was then pulverized and stored for use. In vitro drug release was evaluated by dissolving the drug-polymer complex (equivalent to 10 mg of ondansetron hydrochloride) in 10 mL of simulated salivary fluid (SSF, pH 6.2), and shaken for 60 seconds. Several different drug polymer ratios were tested and when the polymer concentration was greater than or equal to 20% the dissolution of the drug in SSF was not detectable. Several different formulations were made and bitterness was not detected by the test subjects even in unflavored tablets.

Taste masking is also achieved by the addition of sweeteners and flavoring agents. Kayumba et al. (11), were able to develop quinine sulfate pellets for taste masking purposes in pediatric dosing. In this study the quinine sulfate pellets were produced by mixing the active ingredient with microcrystalline cellulose. The blend was wetted with water then subjected to extrusion–spheronization. Eudragit EPO, which is a cationic

copolymer consisting of butylmethacrylate-(2-dimethylaminoethyl) methacrylate-methyl methacrylate (1:2:1), was chosen because it dissolves readily in low pH in the presence of gastric fluid (pH 1.0–1.5) but can prevent the release of drug in saliva where the pH is higher (pH 6.8–7.4).

An example of successful taste masking is Mirtazapine SolTab® which uses OraSolv® (CIMA Labs, Minneapolis, Minnesota, U.S.A.) technology (12). In REMERON SolTab® the active ingredient, mirtazapine, is coated. The coated pellets are held together by water-soluble ingredients. When the patient takes REMERON SolTab® the water soluble ingredients and flavors disperse and dissolve in the mouth while the coated pellets remain intact until the pellets reach the stomach where they dissolve. Despite the available technologies taste masking may not be successful if the loading of the bitter drug is high or if the residence time of the tablet in the mouth is prolonged. A formulation scientist must also make careful selection of excipients and their particle sizes to avoid grittiness.

TECHNOLOGIES FOR MANUFACTURING ORALLY DISINTEGRATING TABLETS

Technologies for manufacturing orally disintegrating tablets include the freeze-drying method, cotton candy technology, and compressed tablets. Some examples of orally disintegrating tablet technology and products are listed in Table 2. The Zydis® (R.P. Scherer, Troy, Michigan, U.S.A.) technology is used to make freeze-dried wafers which dissolve nearly instantly in the mouth and leave no gritty residue. Compressed tablets usually dissolve slower than the freeze-dried wafers and may leave a gritty mouth feel if insoluble excipients are used. However, the compressed tablets technology is less expensive and may be more suitable for loading large amounts of active ingredients.

TABLE 2 Examples of Orally Disintegrating Tablets Technology Platforms

Platform	Patent holder	Principle	Example product (manufacturer)
Zydis®	Cardinal health	Liquid dispersion of active ingredients and excipients are lyophilized in preformed blister packs	Caritin Reditabs® (Schering Plough) MAXALT-MLT™ (Merck)
Flash Dose®	Fuisz technology	Directly compressed tablet; combines active ingredient with an amorphous floss of saccharides or polysaccharides, and other excipients	Ultram® ODT (Biovail)
DuraSolv®	CIMA Labs	Directly compressed tablet; contains soluble fillers	NuLev®(Schwarz Pharma)
OraSolv®	CIMA Labs	Directly compressed tablet; contains effervescing excipients	REMERON SolTab® (Organon USA Inc.)
WOWTAB®	Yamanuchi	Compressed tablets; uses fluid bed granulator to coprocess sugar-based materials (mannitol, lactose, maltose et al.) to optimize compactibility with solubility	Benadryl Fastmelt (Pfizer)

Freeze-Drying Technology

The first entrance of freeze-drying or lyophilization technology into the field was the Zydis delivery system developed by R.P. Scherer. It is a mixture of gelatin, sugar(s), active ingredient, and other components poured into the depression of a blister pack. Water is sublimed away during lyophilization leaving a highly porous, relatively soft solid. The resulting wafers dissolve or disperse on the tongue rapidly in about three to five seconds. Some of the limitations of the freeze-dried wafers are drug solubility and a drug loading limitation of about 60 mg for water-soluble drugs (5). The wafers are also moisture sensitive and very fragile, requiring special packaging. Maxalt-MLT™ (rizatriptan benzoate orally disintegrating tablets) manufactured by Merck & Co., Inc. is an example of lyophilized tablets. The tablets are individually packaged in unit blister packs with peel off backing which are placed inside aluminum pouches for added protection. The pouches are placed inside a carrying case. Patients are instructed not to remove the blister pack from the pouch until ready to consume the tablets.

Cotton Candy Technology

Another technology for manufacturing orally disintegrating tablets is the cotton candy process, also known as the candy-floss process, which involves centrifugation to produce a floss-like crystalline structure. In this technology, the matrix is formed from saccharides or polysaccharides processed into an amorphous floss through a shearfoam process. The matrix is cured and milled to make a flowable, compactible, and highly soluble filler. Because of the formation of porous three-dimensional structures with the active ingredients encased in the pores, the resulting surface area is high. Therefore, dispersion and dissolution occur quickly when the product is placed in the mouth. This technology is patented as FlashDose® by Fuisz Technology (Chantilly, Virginia, U.S.A.) (13,14). FlashDose is characterized as having a bulk density of ranging from about 150 mg/mL to about 1300 mg/mL and porosity ranging from about 10% to about 90% of the dosage form volume. Therefore, there is much opportunity to manipulate the density in such a manner to not only make orally disintegrating tablets, but also chewable tablets.

Tablet Compression Technology

The tablet compression method generally relies on conventional manufacturing technology. Orally disintegrating tablets can be formed by either direct compression, wet granulation or by a wet compression method. Formulations can be optimized using traditional polynomial regression or an artificial neural network. Artificial neural networks (ANN) are commonly used for pattern recognition, such as in voice recognition, financial predictions, weather forecasting, insurance statistics, transportation, and even in pharmaceutical development in recent years (15–17). ANNs can be especially useful in dealing with complex relationships between input and output data, as in the case with formulation development involving multiple variables. The reader is referred to Chapters 3 and 4 in this volume for more details.

In the wet compression method, water is added to a powder blend and the mixture is kneaded until a homogenous wet powder mass is formed. The mass is then extruded through a sieve. Wet granules are then compressed into tablets. Using this method, Sunada and Bi (2) were able to develop rapidly disintegrating lactose tablets with disintegration times of less than 15 seconds. The rapidly disintegrating tablets were composed of α-lactose monohydrate of various particle sizes as follows: Lactose 450 M

with average particle size of 13.2 μm, Lactose 200 M with average particle size of 23.9 μm, and Lactose 80 M with average particle size of 61.4 μm. Moisture content of the tablets was also varied from 4.70% to 18.80%. Using an ANN model it was determined that increases in moisture content increased the tensile strength of the tablets. The authors postulated that when lactose particles were wetted, the particles became coated with a layer of lactose solution. Then, during the drying process, the lactose solution forms solid bridges between particles by recrystallization. Thus, increased tensile strength resulted from increases in the extent of such bonding. Similarly, smaller particle sizes of lactose yielded tablets with greater tensile strengths, most likely from increased numbers of bonds formed. Compression of larger particle was thought to produce a greater number of cracks and pores. Disintegration times followed the patterns for tensile strength. Increased tensile strength was accompanied by an increase in disintegration time.

The wet compression method may not be suitable for active materials that are physically or chemically unstable in the presence of water. The direct or dry compression method is generally preferred because it is simpler, easier to automate, and avoids direct contact of water with the active material. As with wet compression, it is often capable of producing orally disintegrating tablets with sufficient physical robustness to allow physical handling and packaging. As demonstrated in Figure 1, an increase in compression pressure led to an increase in tensile strength of mannitol tablets and mannitol/freeze-dried sucrose tablets (18). However, a decrease in tensile strength led to higher porosity and faster oral disintegration times. In order to achieve fast disintegration, highly porous tablets are desired for fast wicking of water into the tablet structure. However, the lower compression force that produces porous tablets can compromise the tablet strength, leading to excessive friability. Because of these conflicting parameters it is important for the formulator to find a proper balance between compression force, tablet porosity, and physical robustness.

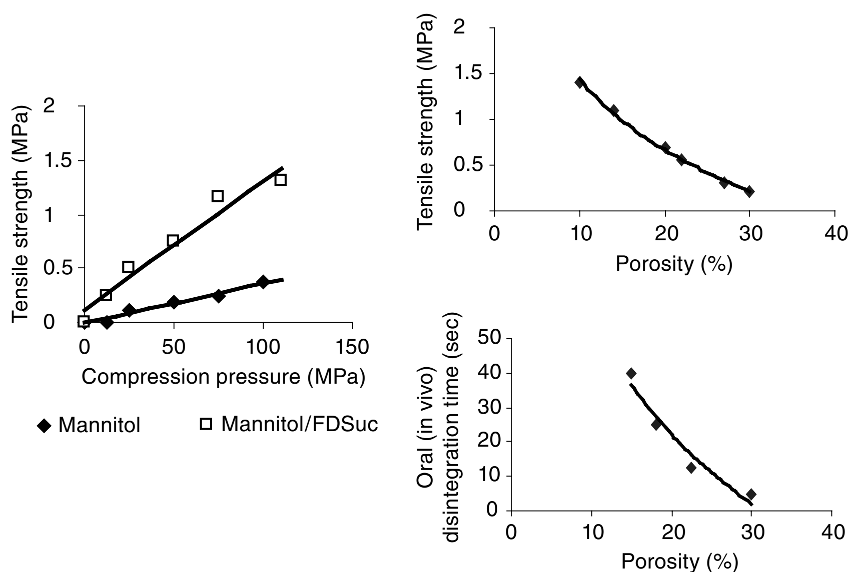

FIGURE 1 Relationship between compression pressure, porosity, and disintegration time for an experimental orally disintegrating tablet. *Abbreviation*: FDSuc, Freeze-dried sucrose. *Source*: Redrawn from Ref. 18.

For example, a study was conducted to evaluate the effects of tablet composition and compression pressure on disintegration time and friability using an ANN model (19). In a formulation containing various amounts of calcium silicate and compactible sugar (DiPac®), the relative amounts of the two excipients were varied. Calcium silicate was chosen as a model insoluble filler because of its desiccant-like property and compactible sugar was chosen as a model soluble filler because of its sweet taste which would be useful in orally disintegrating tablets. In general, low compression force and high amounts of disintegrants yielded faster disintegration. As shown in the contour graph in Figure 2, when a low compression pressure of 20 MPa and a high disintegrant level of 15% were kept constant, 50–60% calcium silicate and 60–100% compactible sugar were necessary to achieve fast disintegration and lower friability. The USP <1216> friability test allows for 1.0% loss of weight for conventional tablets (20), but many orally disintegrating tablets may not be able to meet the requirement. Special packaging, such as blister packs, may be used to help compensate for the limitations of their higher friability. In any case, orally disintegrating tablets should be at least sufficiently robust so that patients would have intact tablets that are elegant in appearance before they place them in their mouths.

In an example of the use of statistical experimental design, Schiermeier and Schmidt (21) described an optimized ibuprofen (enteric coated particles) direct compression formulation derived from a central composite design. The optimized variables were mannitol (34%), crospovidone (13%), and compression force (7 kN). The coated ibuprofen particles made up 50% of the total mass. The predicted 38.5 N tablet crushing strength and 16.9 seconds wetting time agreed well with the experimental results of 40.3 N and 17 seconds, respectively. Wetting time, defined as the time for complete wetting when the tablet is immersed in 10 mL water at room temperature, was used in lieu of disintegration time measurement as it was considered to mimic the action of saliva on the tablet (21).

Though direct compression offers many advantages in the manufacture of orally disintegrating tablets, wet granulation may offer additional opportunities. For example, Adelbury et al. (22) described the granulation of acetaminophen (37.4%) with D-mannitol using a hydrophilic waxy binder (PEG-6-stearate). One formulation included 2% AcDiSol (croscarmellose sodium) intragranularly. Two methods of granulation were tried: wet granulation with an emulsion of the binder, and melt granulation). Final formulations consisted of the granules dry blended with crocarmellose sodium, aspartame and magnesium stearate. Both methods were found able to produce tablets with hardness of 47.9 ± 2.5 N and disintegration times of 40 ± 2 seconds, but the melt granulation gave better hardness results, while wet granulation gave better disintegration results. It was concluded that the waxy binder enhanced compactibility without

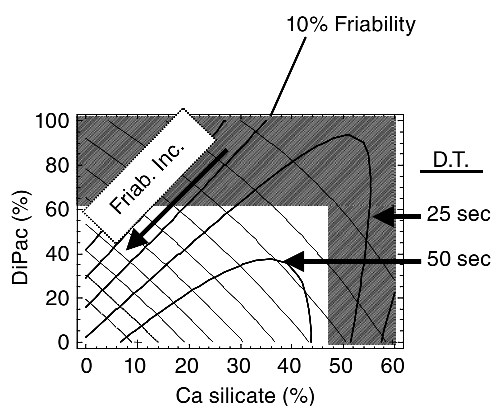

FIGURE 2 An experimental direct compression formulation containing various ratios of DiPac (*compactible sugar*) and calcium silicate. 15% super disintegrant and 20 MPa of compression force was used. D.T: Disintegration time (*seconds*) Friab. Inc.: Increasing friability. *Source*: Redrawn from Ref. 19.

exceeding the disintegration time limits of <3 minutes established by the EP (1) for orodisperse tablets.

CHOICE OF EXCIPIENTS

The excipients listed for a number of orally disintegrating products are provided in Table 3. Orally disintegrating tablets typically are composed of sweet fillers and flavoring agents. Freeze-dried tablets also generally contain gelatin that provides a melting sensation in the mouth. Compressed tablets typically are formulated with highly water-soluble fillers and relatively high levels of disintegrants. Insoluble fillers such as microcrystalline cellulose are sometimes used in these formulations but the formulator must make sure that their particle sizes are small and that their levels in the formulation are not excessive to avoid grittiness or any other unpleasant mouth-feel. Like conventional tablets, compressed orally disintegrating tablets need glidants (e.g., colloidal silicon dioxide) to help the particles flow and lubricants (e.g., magnesium stearate) to prevent sticking of the materials to the punches and facilitate ejection from dies.

TABLE 3 Inactive Ingredients Listed for Orally Disintegrating Tablets

Drug product	Technology platform	Listed inactive ingredients
MAXALT-MLT™ (rizatriptan benzoate orally disintegrating tablets)	Zydis®	Gelatin, mannitol, glycine, aspartame, and peppermint flavor
Caritin® RediTabs® (loratadine rapidly-disintegrating tablets)	Zydis®	Citric acid, gelatin, mannitol, mint flavor
Carinex® RediTabs® (desloratadine orally disintegrating tablets)	Zydis®	Microcrystalline cellulose, pregelatinized starch, sodium starch glycolate, magnesium stearate, butylated methacrylate copolymer, crospovidone, aspartame, citric acid, sodium biocarbonate colloidal silicon dioxide, ferric oxide red and tutti frutti flavoring
Ultram® ODT (Tramadol hydrochloride orally disintegrating tablets)	Flash Dose®	Aspartame, copovidone, crospovidone, ethylcellulose, magnesium stearate, mannitol, mint flavor, and silicon dioxide
Alavert™ (loratadine orally disintegrating tablets)	DuraSolv®	Artificial and natural flavor, aspartame, citric acid, colloidal silicon dioxide, corn syrup solids, crospovidone, magnesium stearate, mannitol, microcrystalline cellulose, modified food starch, and sodium bicarbonate
REMERONSolTab® (mirtazapine orally disintegrating tablets)	OraSolv®	Aspartame, citric acid, crospovidone, hypromellose, magnesium stearate, mannitol, microcrystalline cellulose, natural and artificial orage flavor, polymethacrylate, povidone, sodium bicarbonate, starch, and sucrose
Children's Benadryl® Allergy & Cold Fastmelt (diphenhydraine citrate and pseudoephedrine HCl)	Wowtab®	Aspartame, citric acid, D&C red no. 7 calcium lake, ethylcellulose, flavor, lactitol, magnesium stearate, mannitol, polyethylene, soy protein isolate, and stearic acid

DISINTEGRATING AGENTS

Disintegrants are very important components of compressed orally disintegrating tablets because they often are primarily responsible for the fast disintegration in the mouth (23). Orally disintegrating tablets can contain either a super disintegrant or an effervescent system as a disintegrating agent. Sometimes a combination of different disintegrating agents is used for better disintegration. An effervescent system (e.g., sodium bicarbonate and citric acid combination) generally provides a highly effective disintegrating system. The release of carbon dioxide when the effervescent agents come in contact with water helps to collapse the tablet matrix. To minimize any possible unpleasantness owing to a fizzing sensation in the mouth, formulators may choose to minimize the levels of effervescent ingredients used in the formulation.

In conventional tablets, super disintegrants, such as croscarmellose sodium, sodium starch glycolate, and crospovidone are generally effective at lower concentrations than the traditional disintegrant, starch, and may be used at 2–5%. Although higher levels of super disintegrants do not necessarily produce faster disintegration in conventional tablets, as much as 15% of super disintegrants may be beneficial in orally disintegrating tablets. Super disintegrants are strongly hygroscopic materials that aid in wicking water from the saliva into the internal structure of the tablets. An advantage of using super disintegrants over the effervescent system is that they are less vulnerable than effervescent systems to the detrimental effect of moisture. Nevertheless, the hygroscopicity of super disintegrants is such that both their functionality and tablet stability can be compromised by excessive exposure to high humidity. Of the three widely used super disintegrants, croscarmellose sodium seems to be less effected by high moisture level in regards to functionality, but all disintegrants and disintegrant systems are vulnerable to the detrimental effects of humidity (19). High levels of disintegrants, high levels of soluble fillers, heat generated from the tablet presses, and atmospheric moisture can easily induce or promote stickiness at the punches which may pose a challenge to the formulation scientist.

In an attempt to find a distintegrant having high compactibility and disintegration ability suitable for an orally disintegrating direct compression tablet formulation, Bi et al. (24) studied the ratios of microcrystalline cellulose (MCC) and low-substituted Hydroxypropylcellulose (L-HPC). Ethenzamide and ascorbic acid were selected as models for poorly and easily water soluble drugs, respectively. In general, they found shortest disintegration times when the MCC/L-HPC ratio was in the range of 8:2 to 9:1.

Ozeki et al. (25) compared several disintegrants in a 200-mg rapidly disintegrating oral formulation. The drug load was aspirin granulated with 5% acid-treated yeast cell wall (AYC granules). Prior data had suggested that AYC functions as both a binder and as a disintegrant. The mixture of granules and 10% disintegrant were compressed at 100 MPa in a universal testing machine with external lubrication. Compared with croscarmellose, L-HPC, and calcium carboxymethyl cellulose, carboxymethyl cellulose produced tablets exhibiting the fastest water uptake rate and lowest in vivo disintegration time (mean = 20.1 second) while generating what was judged an acceptable hardness of at least 3 kgf.

SWEETENERS

Sugars, sugar alcohols, and other artificial sweeteners are preferred fillers in orally disintegrating tablets. Sugars and sugar-based excipients provide good mouth feel because

they are water soluble. Together with other flavoring agents and artificial sweeteners such as aspartame, they help to mask the taste of active ingredients, many of which are bitter even in small doses. Some examples of sugars and sugar-based excipients used in orally disintegrating tablets are amorphous sucrose, dextrose, maltitol, mannitol, and xylitol. Sugar alcohols such as maltitol, mannitol, and xylitol have the added advantage of containing fewer calories compared to sucrose and do not promote tooth decay. Mannitol and xylitol have negative heats of solution, thereby imparting a cooling sensation in the mouth.

Sugimoto et al. (26) studied orally disintegrating tablets containing amorphous sucrose prepared by the crystalline transition method (CTM) and found that a level of 10–20% amorphous sucrose in the tablet was suitable. The method requires storage of the tablet under certain conditions of relative humidity and temperature, during which there is a conversion of amorphous to crystalline sucrose, accompanied by an increase in tablet hardness and an alteration in porosity and disintegration time. In the 10–20% amorphous sucrose range, tablets of "a little less" than the desired 1 MPa tensile strength or greater were produced yielding in vivo disintegration times in the approximate rage of 10–50 seconds.

Common artificial sweeteners in orally disintegrating tablets are acesulfame potassium, aspartame, and saccharin sodium. Acesulfame potassium and aspartame are about 200 times sweeter than sucrose and saccharin sodium is about 300 times sweeter than sucrose (27). Although they impart similar sweet taste in the mouth their physical characteristics, including particle size, flow, and mechanical properties vary widely (28). Because these artificial sweeteners have sweetening intensities much higher than that of sucrose, they can be used in smaller quantities. However, sucrose generally has superior flow properties and exhibits lower brittleness. When used in moderate quantities, sucrose may help reduce the likelihood of capping or lamination of tablets containing brittle drug substances. Acesulfame potassium particles are generally smaller than sucrose particle but have similar flow characteristics and their compacts have mechanical properties (brittle fracture index and bonding indices) similar to sucrose compacts. Therefore, with its sweetening intensity of 200 relative to sucrose, acesulfame potassium can be used in place of sucrose in order to achieve smaller tablet sizes. Aspartame has similar sweetening intensity as acesulfame but its particles have needlelike shape leading to poor flowability. Aspartame compacts also exhibit high brittleness, but if used in small amounts aspartame may contribute to good tablet strength because of its high bonding index. Saccharin, with its irregular particle shape and high brittle fracture index of the compact, also exhibits poor flowability and a propensity to capping and lamination when present in high quantities. However, it may be useful in small quantities where it does not impact the overall flowability, uniformity, and strength of the tablets.

Sucralose is a relatively new sweetener approved by the FDA in 1998. It has a similar chemical structure as sucrose with three hydroxyl groups substituted by chlorines. Its sweetness intensity is 300–1000 times that of sucrose. One of the advantages of sucralose is that it is stable in high heat. Therefore, it may used in products requiring sterilization, pasteurization, and baking (27).

MEASUREMENT OF TASTE

The success of orally disintegrating tablets relies heavily on the taste and texture of the product, as well as the disintegration time (29). The texture or mouth-feel of a

product can easily be predicted by the formulation based on the amount of soluble excipients and the amount and particle sizes of the insoluble excipients. However, predicting the taste masking of bitter drugs is more challenging. Taste recognition occurs at three levels: the receptor level, the circuit level, and the perceptual level (30). At the receptor level are the taste buds that detect different tastes such as bitter, sour, salt, sweet, umani, and trigeminal. Umani refers to the glutamate taste, such as monosodium glutamate. Trigeminal refers to the burning sensation produced by spices and peppers. At the circuit level is the neural transmission of the sensation to the brain. At the perceptual level is the thalamus of the brain where the sensation is recognized as a certain taste. While a human taste trial for orally disintegrating tablets is necessary to confirm acceptability before marketing the drug product, manufacturers may conduct an in vitro test as a routine screening tool for ease and cost-savings. In a study conducted by Murray et al. (30), an electronic device called e-tongue (Alpha M.O.S., Toulouse, France) was utilized to measure the reduction of bitterness of active ingredients by changing the sodium chloride concentration in the formulation. The e-tongue is composed of probes mimicking the taste buds, transducer for neural transmission, and computer for the human brain. Measurements are performed potentiometrically with readings taken against a $Ag/AgCl_2$ reference electrode. Then the signals are quantified and digitized, and the data are analyzed by software. The reduction of bitterness of the active ingredients, quinine hydrochloride and magnesium sulfate, with increase in salt content, was measured against a known bitter agent, urea. With a salt concentration of 0.50 M, reductions of bitterness for urea, quinine hydrochloride, and magnesium sulfate were 76.83%, 54.37%, and 24.34%. The results were comparable to the trained taste panel results, but the variances in e-tongue testing were much lower than the variance observed in human testing. Although the in vitro test cannot replace human taste testing, such technology may provide a useful screening tool where routine testing in humans is expensive or unsafe.

MEASUREMENT OF DISINTEGRATION TIME

Current compendial disintegration test methods are limited in their ability to assess orally disintegration tablets because of the rapid disintegration of ODTs and the strong agitation and large volume of medium employed in the compendial test method. Several novel approaches have been developed that may be more suitable for research and development (R&D) and quality control (QC). For example, Morita et al. (31) described a method involving a disintegrating bath and a CCD camera. The camera was interfaced to a PC running motion capture and image analysis software. With the ability to detect morphological changes during disintegration, the authors suggest that their method would have utility both in formulation development and quality control. El-Arini et al. (32) described the use of a texture analyzer (TA) in which the flat-ended cylindrical probe penetrates into the disintegrating tablet while it is immersed in water. The results are plots of distance moved by the probe under a small set force as a function of time. From these disintegration profiles, the start and stop times of disintegration may be determined.

A simpler method based on the use of a linear variable displacement transformer (LVDT) that also provides a digital output of disintegration time and tablet thickness has been reported (33). By examining the change in the tablet thickness over time it was possible to determine subtle differences in disintegration efficiency between several model tablets. As shown in Figure 3 the tablet containing Primojel® (Fonterra™ Ltd., Auckland, New Zealand) with a higher moisture content of 21.5% exhibited similar

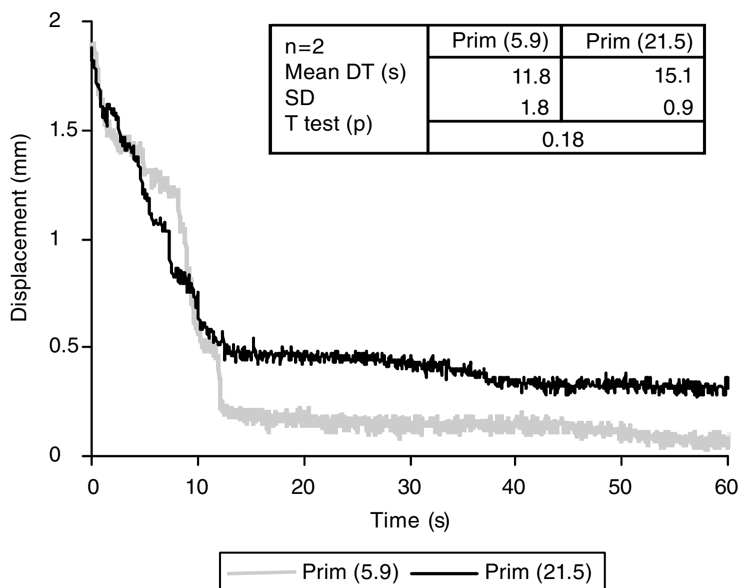

FIGURE 3 Disintegration profile of an experimental tablet containing a super disintegrant, Primogel, with 5.9% or 21.5% moisture content. *Source*: From Ref. 33.

disintegration rate as the tablet containing Primojel with lower moisture content of 5.9%. However, Primojel with lower moisture content appeared to yield a more complete dispersion of residual particles.

More recently, Abdelbary et al. (34) describe another device that measures the penetration distance (versus time) of a probe travel (under a fixed load of 50 g) into a tablet that is submerged in disintegration medium. They described their approach as more closely mimicking the situation in a subject's mouth than some earlier methods by (*i*) putting the test tablet on a moveable platform, thereby eliminating the use of adhesive attachment tape required by some earlier methods and exposing both sides of the tablet, and (*ii*) allowing detached particles to be gradually eliminated. A diagrammatic representation of the output for Spasfon® (Himont Pharmaceuticals, Ltd., Lahore, Pakistan) and Flash Tab® (Ethypharm, Houdan, France) is provided in Figure 4. The beginning of the plateau area represents the disintegration time. The effects of medium and temperature on the disintegration times of orally disintegrating tablets, Spasfon®, Flash Tab®, and Wowtab® were evaluated. Compared to distilled water, artificial saliva generally provided faster

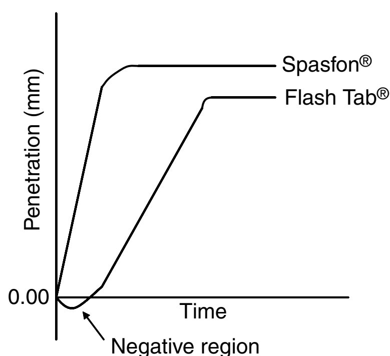

FIGURE 4 Diagrammic representation of disintegration as measured by probe penetration. *Abbreviations*: Spasfon®, lyophilized oil in water emulsion; Flash Tab®, formulation including disintegrating agents. *Source*: Redrawn from Ref. 34.

disintegration. The temperature of the media (room temperature versus 37°C) did not appear to effect the disintegration time in any predictable manner. However, when the acetaminophen orally disintegrating tablets were evaluated, the disintegration rates were faster when the temperature of the medium was 37°C compared to when room temperature medium was used. In the same study, the in vitro disintegration times were compared to the in vivo disintegration times. For the in vivo study, 14 healthy volunteers were used. They were instructed to initially rinse their mouths with distilled water. The timer was started when the tablet was placed on the tongue and stopped after the last noticeable particle was disintegrated. Volunteers were allowed to move the tablet against the upper palate with the tongue, but biting, side-to-side movement, or swallowing of saliva was not permitted. Measurements were taken in three replicates. A good correlation of the in-vitro disintegration times and the in vivo disintegration times was found.

While disintegration testers with specialized probes can be very helpful during research and development, it may sometimes be desirable to use more widely available and standardized equipment for routine in vitro testing. In such cases, formulators may be able to use the compendial disintegration apparatus as described in USP <701> with slight modification in determining disintegration times. The current USP <701> provides disintegration requirements for uncoated tablets, plain-coated tablets, enteric coated tablets, buccal tablets, sublingual tablets, hard gelatin capsules, and soft gelatin capsules (35). However, the USP does not specify requirements for the orally disintegrating tablets because the USP <701> is designed to be a limits test where the disintegration times are assumed to be potentially long. For orally disintegrating tablets, the disintegration times of tablets can be individually quantified. However, the USP disintegration test is an in vitro test using about 900 mL of medium and vigorously oscillating basket, providing conditions very unlike in vivo environment. Therefore, the USP test may be more suitable for quality control purposes rather than for research and development.

Currently, there is no clear consensus in regards to how fast the orally disintegrating tablets should disintegrate in a person's mouth or in vitro. However, the preference is, the faster the better. As described by Yoo et al. (13) in their U.S. Patent for FlashDose®, "it is to provide a rapidly dispersing dosage form that can disperse in less than about five minutes, preferably less than about ninety seconds, more preferably in less than about thirty seconds and most preferably in less than about ten or fifteen seconds." The European Pharmacopeia calls orally disintegrating tablets the orodisperse tablets, which is defined as "uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed." The European Pharmacopeia allows a disintegration time of 3 minutes for the orodisperse tablets (1). However, other regulatory bodies may require shorter disintegration times. For example, the USP monograph for Ondansetron Orally Disintegrating Tablets the in vitro disintegration time requirement is "not more than 10 seconds (36)." While some manufacturers of orally disintegrating tablets may be inclined to use the upper limit of 3 minutes as a guidance for ease of manufacturing, in general, any orally disintegrating tablet that does not exhibit sufficiently fast in-vivo disintegration and pleasing mouth-feel would not fare well in the competitive market.

Fang et al. (37) evaluated several over-the-counter medications labeled to be fast disintegrating or dissolving, as listed in Table 4. They compared the mean in vivo disintegration times of these products to an in vitro disintegration test. The desktop disintegration test as proposed by the authors is a fast and simple test using a 1 mL plastic syringe to deliver water to the tablets. The orally disintegrating tablet is placed on a flat surface and 1 mL of water is slowly delivered to the tablet using a plastic syringe within about 5–10 seconds. At the end of 30 seconds in contact with water, the tablet is checked

TABLE 4 Over-The-Counter Drug Products Labeled to be Fast Disintegrating or Dissolving

Product Name	Labeling	Direction for consumer
Claritin RediTabs	Orally disintegrating tablets	Place 1 tablet on tongue; tablet disintegrates, with or without water
Alavert	Orally disintegrating tablets	Tablet melts in mouth. Can be taken with or without water
Children's Benadryl Fastmelt®	Dissolving tablets	<There is no special direction on labeling for taking this medicine other than the suggested dose>
Triaminic Softchews	Softchew Tablets	Let Softchew dissolve in mouth or chew Softchew tablet before swallowing, whichever is preferred

Source: From Ref. 37.

by manual palpation for completeness of disintegration. Completion of tablet disintegration is indicated by collapsing of the tablet matrix with no palpable core. As presented in Table 5 both Claritin RediTabs and Alavert passed the 30 second desktop disintegration and exhibited relatively fast in-vivo disintegration times of less than one minute. Children's Benadryl Fastmelt and Triaminic Softchews did not pass the desktop disintegration and the mean in-vivo disintegration times were also prolonged. Upon examination of the labeling the ones that passed the desktop disintegration test were labeled "orally disintegrating tablets," whereas, ones that did not pass the test were labeled "dissolving tablets" and "Softchew Tablets." Interestingly, the Triaminic Softchews which were comparatively large tablets, failed to disintegrate within 30 seconds using the desktop testing method, even when the volume of water was doubled from 1 mL to 2 mL. The tablets were probably labeled as Softchew because of their large size which would encourage the chewing action by patients. As shown in Table 4, patients are instructed to either dissolve or chew the Softchew tablets, whichever is preferred. Because the volume of saliva that a patient can produce is highly variable between patients and is partially dependent on the taste, texture, and size of the tablets, it makes good sense to keep the size of the orally disintegrating tablets small.

The over-the-counter drug market is highly competitive and products without high consumer satisfaction would not survive. Products specifically labeled orally disintegrating tablets appear to require very fast disintegration times in the presence of minimal amount of water for them to gain market success. Therefore, to ensure

TABLE 5 In Vitro Desktop Disintegration Versus In Vivo Disintegration Times of Over-the-Counter Drug Products

Product name	Desktop disintegration in 30 seconds	Mean in-vivo disintegration time
Claritin RediTabs (loratadine 10 mg)	Pass	20 seconds
Alavert (loratadine 10 mg)	Pass	59 seconds
Children's Benadryl Fastmelt (Diphenhydramine Citrate 19 mg)	Fail	2 minutes 29 seconds
Triaminic Softchews (Acetaminophen 160 mg, Dextromethorphan HBr 5 mg)	Fail	1 minute 52 seconds

Source: From Ref. 37.

good-marketability of the products, manufacturers should conduct taste testing and patient acceptability testing of the orally disintegrating tablets.

OTHER TABLET FORMULATIONS

Other non-conventional solid dosage forms that are placed in the mouth include buccal tablets that are placed in the buccal pouch of the mouth, sublingual tablets that are placed beneath the tongue, lozenges that are slowly dissolved or disintegrated in the mouth. For USP description of these dosages forms are shown in Table 6 (1,38) Additional information may be found in Chapter 12 in volume 2 of this series. Chewable tablets and effervescent tablets are also non-conventional solid dosage forms that share many characteristics with the orally disintegrating tablets and are further described below.

Chewable Tablets

The USP defines chewable tablets as, "… [tablets] that may be chewed, producing a pleasant tasting residue in the oral cavity that is easily swallowed and does not leave a bitter or unpleasant aftertaste." As mentioned in the introduction, chewable tablets differ from orally disintegrating tablets because they are intended to be chewed in the mouth prior to swallowing, rather than dissolve or disperse quickly in the saliva. However, they share many characteristics with orally disintegrating tablets. They are manufactured in

TABLE 6 Compendial Descriptions of Orally Disintegrating Tablets and Related Tablet Formulations

Tablet type	Compendial source USP or EP	Description
Orodispersible tablets	EP	Uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed; disintegrates within 3 minutes
Oral lyophilisates	EP	Solid preparations intended either to be placed in the mouth or to be dipersed (or dissolved) in water before administration; obtained by freeze drying; disintegrates within 3 minutes in 200 mL water
Buccal tablets	USP	Intended to be inserted in the buccal pouch; active ingredient is absorbed directly through the oral mucosa
Sublingual tablets	USP	Intended to be inserted beneath the tongue, where the active ingredient is absorbed directly through the oral mucosa
Soluble, effervescent tablets	USP	Intended to be dissolved or dispersed in water before administration; prepared by compression and contain, in addition to active ingredients, mixtures of acids and sodium bicarbonate, which release carbon dioxide when dissolved in water
Chewable tablets	USP	Formulated and manufactured so that they may be chewed, producing a pleasant tasting residue in the oral cavity that is easily swallowed and does not leave a bitter or unpleasant aftertaste

Source: From Ref. 1 and 38.

similar ways as orally disintegrating tablets, mainly by direct compression of powders and pellets using various types of sugar and fillers. They are generally formulated as immediate release dosage forms and are intended for convenience, compliance, and patient acceptance. They can be taken without additional water, but need to be easily crushed in the mouth. Whereas, orally disintegrating tablets generally need to be small in size, chewable tablets may be larger and may be more accommodating for loading high amounts of active ingredients. Therefore, chewable dosage forms have become popular for delivering bulky ingredients like vitamins, minerals, antacids, and dietary supplements. Bitter tasting and bulky active ingredients like acetaminophen can also be formulated in chewable tablets. Like orally disintegrating tablets, taste-masking and ensuring good texture can be a challenge. Bitter tasting active ingredients are coated or pelletized with waxy polymers. Hot melt pelletization can be applied to bitter active ingredients to coat the active particles with melting binder such as polyethylene glycol. Different grades of polyethylene (e.g., PEG 2000, 3000, 6000, 8000, 10000, and 20000, from lowest to highest viscosity) yield pellets of different physical properties, such as granule size, intragranular porosity, and uniformity (39). Another method of taste masking bitter ingredients is to add taste masking agents to powder. Suzuki et al. (40) describes the use of hard fats and sweetening agents to formulate chewable acetaminophen tablets with suppressed bitterness, good taste and mouth feel. They found that Witocan®, hard fats used to make chocolates, made a satisfactory matrix for acetaminophen chewable tablets. Lecithin (Bencoat BMI-40) and saccharin were also added to the formulation.

Effervescent Tablets

According to the European Pharmacopeia, effervescent tablets are defined as "uncoated tablets generally containing acid substances and carbonates or hydrogen carbonates, which react rapidly in the presence of water to release carbon dioxide." A commonly used acid in effervescent tablets is citric acid because of its citrus taste. Other less commonly used alternatives are malic, tartaric, adipic, and fumaric acids. Sodium bicarbonate is the most commonly used base, but potassium bicarbonate, sodium carbonate, and potassium carbonate are also used. As discussed earlier, some orally disintegrating tablets may have effervescent characteristics to aid in disintegration. However, unlike the orally disintegrating tablets, those labeled as effervescent tablets are generally intended to be placed in the water for dispersion prior to oral administration. Therefore, effervescent tablets can be much larger than orally disintegrating tablets or chewable tablets. They need special packaging like the orally disintegrating tablets in order to protect the tablets from humidity and handling. The manufacture of effervescent tablets is similar to that of conventional tablets, but special care must be exercised to protect the formulation from humidity. The formulations are also similar to compressed orally disintegrating tablets. A notable difference is that unlike other types of tablets effervescent tablets require the use of water-soluble lubricants in the formulation or prelubricated punches. Hydrophobic lubricants such as magnesium stearate are replaced with water-soluble lubricants like polyethylene glycol with molecular weight of 6000 or greater and sodium benzoate (27,41).

SUMMARY

Orally disintegrating tablets afford many opportunities yet challenges to the pharmaceutical industries. They provide therapeutic benefits to patients who cannot take or do

not prefer conventional tablets. Existing technologies such as the compressed tablet method, freeze-dried method, and cotton-candy process provide various options for manufacturing orally disintegrating tablets. However, the real challenges in manufacturing the orally disintegrating tablets are feasibility and marketability. Freeze-dried method and wet compression are not desirable for water-labile active ingredients. Highly bitter active ingredients would pose a greater challenge, and many require pre-coating of the active ingredients. Active ingredients that need higher drug loading may be easier to make into compressed tablets than lyophilized tablets, but formulators need to be careful not to make the tablets too big. Otherwise they would be more appropriately called chewable tablets. Also, bioavailability studies may need to be conducted to determine if the pharmacokinetic parameters of individual drugs are different for the orally disintegrating tablets compared to the conventional tablets. Tools such as artificial neural network can help the formulator develop orally disintegrating tablets with desirable strength and release characteristics. The development of orally disintegrating tablets as a delivery system has presented challenges that spawned interesting new technologies. Ongoing research and development can be expected to improve on orally disintegrating tablets technology and broaden its applicability to drug therapy.

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10

Formulation Challenges: Multiple Vitamin and Mineral Dosage Forms

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INTRODUCTION

In the early 1960s vitamin and mineral formulations were products of major pharmaceutical companies. Products like Theragran, Unicaps, and various products intended for use by children and pregnant women were actually thought of as quasi-drug products and were routinely prescribed by physicians. Decavitamin tablets and capsules were the subject of a United States Pharmacopoeia (USP) monograph where test methods and acceptance standards were set. In the late 1960s or early 1970s these products in multiple ingredient form were no longer subjects of USP monographs. Very soon thereafter the market was flooded with every possible combination of vitamin and mineral products, including some containing herbals.

Regulatory agencies and consumer advocate groups began to sample and test these products, only to discover and disclose that many of them did not meet label declarations. Many of the small garage type operations had no knowledge of the complexity of creating a stable formula that contained multiple ingredients. Some of the larger and more technologically sophisticated firms may have had the expertise to formulate a tablet or capsule, but still lacked the ability to create a stable formulation, containing multiple components having unique characteristics.

Since most of the chapters in this text are dedicated to the basics of formulation technology and the necessary mechanical properties of the dosage form components, this chapter will address, what is believed to present the most significant challenge to formulation of stable vitamin or vitamin/mineral combination products. The formulation of pharmaceutical quality vitamin products having adequate physical and chemical stability as well as suitable taste, odor, color, and freedom from bacterial contamination can entail numerous problems arising from different physical forms, stability, and solubility characteristics of the individual vitamins.

For liquid preparations, the inclusion of the optimal pH is a crucial factor. Interactions between some of the vitamins and between vitamins and other product constituents must also be considered.

Successful development of vitamin products requires knowledge of the fundamental aspects of the physical and chemical properties of the various forms of the

vitamins available, the use of adequate techniques of manufacture and the addition of suitable manufacturing overages based upon critical stability studies.

ELEMENTS THAT AFFECT VITAMIN STABILITY

1. The stability characteristics of the individual vitamins.
2. Factors that enhance vitamin stability.
3. Formulation of vitamin products.
4. Industry experience with predicting vitamin stability, both from long term and accelerated aging studies.
5. Stability indicating assays is also a critical element, but will not be addressed in this chapter.

In the development of a multiple vitamin preparation one needs to be concerned with the stability characteristics of the individual vitamins, the interaction of the vitamins among themselves and the effects upon formulations of those factors. The factors that affect vitamin stability are: Solubility, pH, moisture, light, heat, and formulation additives (diluents and excipients).

SOLUBILITY CHARACTERISTICS

Vitamins may be divided into two well-known groups, namely fat soluble and water soluble vitamins. The fat soluble group includes:

1. Vitamin A
2. Vitamin D
3. Vitamin E
4. Vitamin K

Combinations of one or more of these fat soluble vitamins in the same formula with water soluble vitamins requires the use of efficient emulsifying agents such as polysorbates to produce homogeneous and stable liquids. In tablet formulations, moisture is a major issue when combining fat soluble and water soluble vitamins.

The water soluble group includes:

1. Vitamin B1–Thiamin
2. Vitamin B2–Riboflavin; Riboflavin 5 Phosphate Sodium
3. Vitamin B6–Pyridoxine
4. Vitamin B12–Cyanocobalamin
5. Vitamin C–Ascorbic acid; Sodium Ascorbate
6. Pantothenic acid; Calcium Pantothenate
7. Niacin; Niacinamide
8. Folic acid
9. Biotin

The water soluble vitamins respond to a wide range of solubility parameters. Each one of these differences has a significant impact on tablet or capsule formulations, where water or moisture is a critical factor.

Solubility Profiles at 25˚C

Vitamin	mg/mL
Thiamin Hydrochloride	1000
Thiamin Mononitrate	27
Niacinamide	1000
Panthenol	Freely Soluble
Calcium Pantothenate	356
Ascorbic acid	333
Sodium Ascorbate	620
Pyridoxine Hydrochloride	220
Cyanocobalamin	12.5
Biotin	0.00
Riboflavin	0.066 to 0.33
Riboflavin five phosphate sodium	43 to 112

Some other important stability characteristics of the individual vitamins under various conditions of stress are affected by:

1. air
2. heat
3. light
4. pH
5. oxidizing or reducing agents.

These conditions require special consideration when formulating vitamin products. Some of the vitamins are classified as stable or relatively stable and present no real problems regarding stability in multiple vitamin products. These include:

1. Vitamin E
2. Riboflavin
3. Niacinamide
4. Pyridoxine
5. Biotin

The vitamins that usually present problems of stability are:

1. Vitamin A
2. Vitamin D
3. Thiamin
4. Pantothenate
5. Vitamin B12
6. Folic acid
7. Vitamin C

THE STABILITY CHARACTERISTICS OF THE INDIVIDUAL VITAMINS

Vitamin A

1. Sensitive to air oxidation especially in the alcohol form.
2. Oxidation is catalyzed by trace metals notably iron and copper.
3. Vitamin A is inactivated by ultraviolet light.
4. It isomerizes at acid pH.
5. It is stable in alkali with stability increasing with increasing pH.

Vitamin D

Vitamin D is similar to Vitamin A in stability characteristics, but more stable.

Vitamin E

1. Free tocopherol is sensitive to air oxidation, especially in alkali.
2. It is oxidation catalyzed by trace minerals, notably copper and iron.
3. The acetate ester is very stable.

Vitamin K

1. Vitamin K is stable to air and acid.
2. It is unstable in strong alkali.
3. It is decomposed by sunlight.

Riboflavin (Vitamin B2)

1. Vitamin B2 is sensitive to light, especially in alkaline solution.
2. It is stable in acid solution and relatively unaffected by pH changes in the acid range.
3. It is sensitive to reducing agents.
4. It is decomposed by reducing sugars.

Thiamin (Vitamin B1)

1. Thiamin is increasingly unstable as pH rises.
2. It is sensitive to oxidizing and reducing agents.
3. The HCl form is more hygroscopic than the mononitrate form.

Niacin or Niacinamide

1. Niacin and niacinamide are relatively stable compounds, and has demonstrated no stability problems.
2. It is not affected by changes in pH in the acid pH range.

Pantothenic Acid

1. Pantothenic acid is hygroscopic, especially dl-calcium panthothenate.
2. It is unstable in acid pH.
3. It is decomposed by hydrolysis.
4. Stability is maximized at pH 6–7.

Panthenol

1. Panthenol is more stable that panthothenic acid compounds.
2. It is stable within pH ranges 5–7.

Folic Acid (Pteroylglutamic Acid)

1. Folic acid is unstable in acid pH at ranges lower than 5.
2. It is decomposed by sunlight.

3. It is unstable in solution (Better stability in suspension).
4. Vitamin B1, B12, oxidizing and reducing agents causes decomposition when in
5. liquid products.
6. Folic acid works best when formulated as a solid dosage product.

Cyanocobalamin (Vitamin B12)

1. Vitamin B12 is slightly unstable in acid or alkaline solution.
2. Its optimal pH is 4 to 5.
3. It is decomposed by reducing agents.
4. Ascorbic acid and Thiamin accelerates decomposition.
5. Vitamin B12 is sensitive to light in very dilute solutions.

Ascorbic Acid (Vitamin C)

1. Ascorbic acid is stable to air when dry.
2. It is readily oxidized in a solution.
3. Copper and Iron act as catalyst to promote decomposition.
4. It is most unstable at pH 4 when in the presence of metallic ions.
5. In open systems, Vitamin C stability increases as pH varies from 4.2.

Biotin

1. Biotin is stable to air in neutral pH.
2. It is slightly unstable in alkaline conditions.
3. Multiple vitamin solutions should be made to pH 5–7 for best stability.

Pyridoxine Hydrochloride (Vitamin B6)

1. Vitamin B6 is a relatively stable compound.
2. It is relatively unaffected in the normal acid pH range.
3. It is light sensitive when in solution.

Stability Problems Relative to pH

As already noted, stability relative to pH is most critical in liquid preparations. High pH gives good stability for all vitamins except B1 and results in odor development. A pH around 4 creates excess pressure which effects vitamin stability. A pH of 3.5 offers the best compromise and provides the best test to use.

An example of a pH relationship is demonstrated between thiamin and calcium pantothenate in acid solution. The pH affects the relation rate of destruction of calcium pantothenate and thiamin (B1 HCL) in 0.1% solutions. Both were subjected to 15 minutes in an autoclave at 15 pounds of pressure. In contrast to thiamin, calcium pantothenate shows good stability at ph 6–7, but its stability decreases or increases when moved from this range (Fig. 1).

In tablet or capsule formulations pH becomes a factor if too much moisture is present, allowing for the solubilization of some of the more labile and moisture sensitive vitamins. High moisture content will cause degradation of Vitamin B1, thiamin, and Vitamin C in the presence of metallic ions.

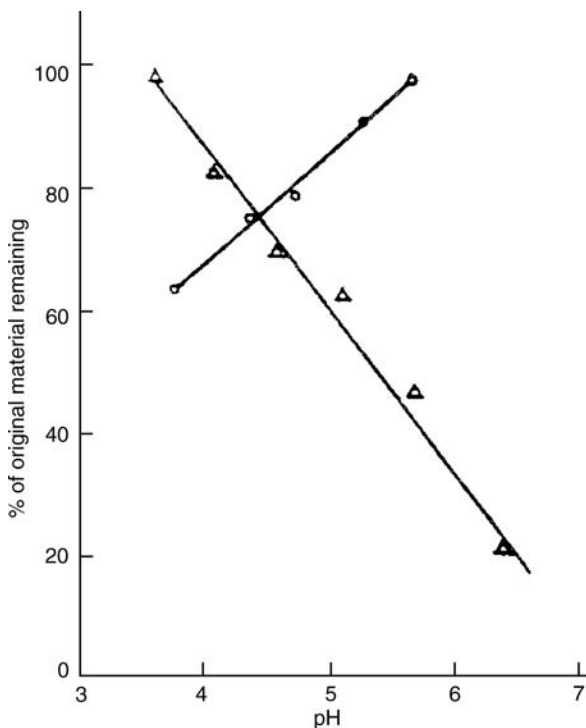

FIGURE 1 Relative rates of destruction of calcium panothenate and thiamin hydrochloride in acid solution: (○) 0.1% solution of calcium panothenate; (△) 0.1% solution of thiamin hydrochloride. All solutions were run in an autoclave at 15lb. Pressure for fifteen minutes. *Source*: From Ref. 9.

Comparative Stability Data for Panthenol and Pantothenate in Relation to pH

Another example of a pH stability indicating relationship is shown in Figure 2, which describes the comparative stability data for panthenol and pantothenates in relationship to pH. There is a rapid decrease in stability for both the panthenol and the salt forms (pantothenates) in acid pH. Maximum stability is achieves around pH 6–7.

Ascorbic acid degradation is also pH dependent. In aqueous solutions assays for both reduced ascorbic acid and dehydroascorbic acid showed maximum loss of Vitamin C at pH 4.2. Excessive pressure development in multivitamin liquids can be a serious problem when the pH is close to 4.2.

EFFECTS OF MOISTURE AND HUMIDITY ON VITAMIN PREPARATIONS

The pH effects and the interaction of vitamins can occur only in the presence of water. In liquid preparations the decomposition of vitamins is kept at a minimum level by selecting the optimum pH and replacing the water to the maximum degree with glycols and sugars wherever possible. In solid dosage forms, further stabilization is possible by use of special forms of vitamins and by keeping the moisture content at the lowest practical level.

An impression of the effect of moisture in solid vitamin mixtures is shown in Figures 3 and 4. In Figure 3, the effects of free water on the stability of Vitamin C is noted in mixtures with or without Silica Gel stored for 3 weeks at 45˚C. The loss is directly related to the free water.

In Figure 4, the water content is varied at two levels of silica gel. Utilizing equal amounts of ascorbic acid 300 mg in each test, and varying the amount of silica gel In one

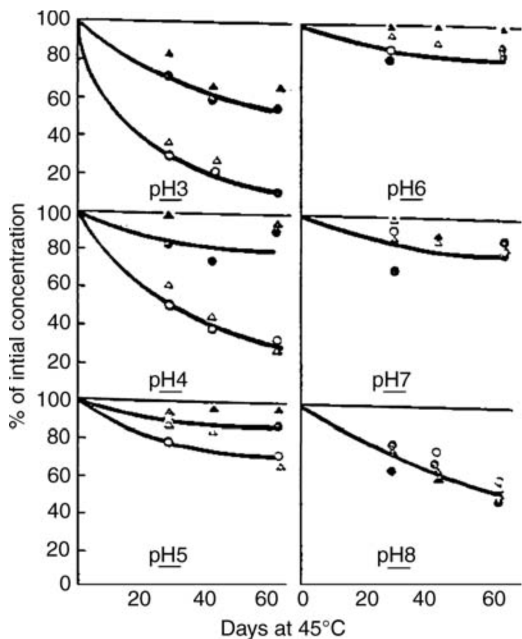

FIGURE 2 Comparative stability of panthenol and sodium pantothenate: (●) Panthenol, curative bioassay in rats; (○) Panthenol, excretion bioassay in rats; (▲) Sodium pantothenate, curative bioassay in rats; (△) Sodium pantothenate, microbioassay. *Source*: From Ref. 2.

test, 80 g of silica gel was used and in other test 640 mg of silica gel used. The higher level exerts a protective effect indicating some binding of water by the silica gel takes place. This work showed that silica gel binds a certain fraction of the water present and that the loss of ascorbic acid is directly proportional to the amount of unbound or free water in the system. Sodium ascorbate is even more sensitive to water than ascorbic acid (1).

Figure 5 shows the effect of moisture in a calcium pantothenate and Vitamin C mixture. The percentage of retention after 1 month in 45˚C varies from 98% with no added water to about 34% retention with 3% added water.

In another study the moisture relative stability of calcium pantothenate in a multiple vitamin tablet mix and in a chewable multiple vitamin tablet mix was demonstrated. The study demonstrated how the percentage of moisture contributes to the vitamin

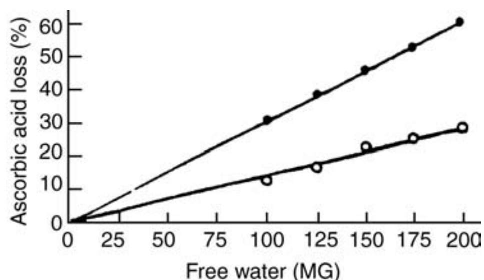

FIGURE 3 Effects of free water level on stability of ascorbic acid in mixtures with or without silica gel: storage in closed tubes for three weeks at 45˚C. Key: (○) 300 mg, ascorbic acid alone: (●) 300 mg, ascorbic acid + 80 or 640 mg silica gel. *Source*: From Ref. 1.

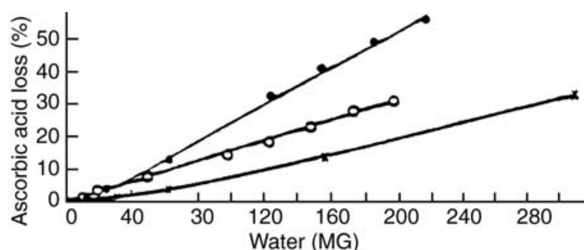

FIGURE 4 Effects of silica gel on stability of ascorbic acid with graded weights of water added. Mixtures stored in closed tubes for three weeks at 45°C. Key: (○) 300 mg ascorbic acid alone, (●) 300 mg ascorbic acid + 80 mg silica gel, (×) 300 mg ascorbic acid + 640 mg silica gel. *Source*: From Ref. 1.

degradation. Three percent moisture for 3 months held at 45° for 3 months resulted in 45% degradation in the chewable vitamin as compared to 35% for the for the multiple vitamin mix which absorbed less moisture.

Chewable products as a rule contain more water soluble ingredients and tend to absorb more moisture. The data also showed that the decomposition of the calcium pantothenate increases with time.

MUTUAL INTERACTIONS OF VITAMINS IN COMBINATION WITH EACH OTHER

Thiamin–Riboflavin

An incompatibility between thiamin and riboflavin in aqueous Vitamin B complex solutions have been reviewed. The oxidative action of riboflavin and thiamin leads to the formation and precipitation of thiochrome. Subsequently, chloroflavin thecreduction product of riboflavin may also precipitate. In the Vitamin B complex solutions containing ascorbic acid, thiochrome formation is not observed.

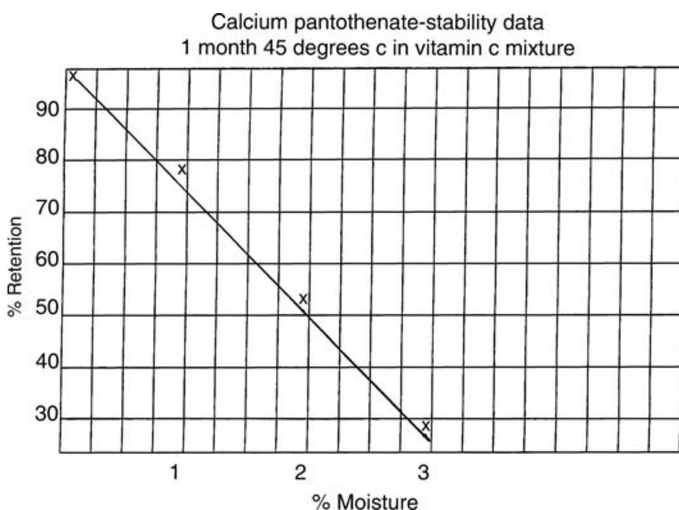

FIGURE 5 Slater et al, 1979 (3). Calcium pantothenate effect of moisture in a calcium pantothenate and Vitamin C mixture; 98% potency retention with no water added decreasing to approx. 30% with 3% water added.

Thiamin–Folic Acid

Thiamin causes considerable decomposition of Folic acid at pH 5.9 and 6.9 in aqueous buffered solutions. The breakdown of Folic acid is accelerated by the presence of decomposition products of thiamin. The key element was the hydrogen sulfide produced during the breakdown process.

Thiamin–Cyanocobalamin

The combination of thiamin and niacinamide in the presence of moisture causes decomposition of cyanocobalamin Low levels of thiamin from 1 to 10 mg per dose showed considerably less losses than when higher levels of thiamin are used. Accellerated conditions enhance the decomposition process.

Riboflavin–Niacinamide

The presence of niacinamide increases the solubility of riboflavin due to the formation of a soluble complex formation. This condition takes place when the concentration of niacinamide is greater than 1% of the total matrix.

Riboflavin–Folic Acid

The combination of light and water with riboflavin has a deleterious effect on the stability of folic acid. It increases rapidly at pH 6.5. Protection from air and light retards the process, but does not eliminate it.

Riboflavin–Ascorbic Acid

Riboflavin catalyzes the photochemical decomposition of ascorbic acid when exposed to light and air.

Ascorbic Acid and Cyanocobalamin

There is an incompatibility between ascorbic acid and cyanocobalamin with losses of Cyanocobalamin being least at pH 1 and increasing to a maximum at pH 7. Copper ions greatly enhance the destructive action of ascorbic acid on cyanocobalamin.

Ascorbic Acid–Vitamin D (ergocalciferol)

Ergocalciferol in powder preparations is readily isomerized by ascorbic acid, folic acid, thiamin hydrochloride, and pyridoxine hydrochloride but not by niacinamide or calcium pantothenate.

FACTORS THAT ENHANCE VITAMIN STABILITY

Reduction of Water Content

The most common protective measure for improving vitamin stability is the reduction of water content. This is true for liquid formulations as well as solid dosage forms. Water is generally substituted with glycerin and propylene glycol to enhance stability. Drying powders to reduce the water content in solid formulations goes a long way to promote

product stability. In those cases where granulation is necessary to render a tablet formula compressible, moisture content becomes a critical process control.

Antioxidants

The stability of vitamins sensitive to oxidation decomposition can be increased by addition of antioxidants. Vitamin A and Cholecalciferol are decomposed by exposure to air and are generally stabilized in concentrates are well as dietary supplement products by addition of small amounts of antioxidants. Some commonly used antioxidants that are being added to fat soluble vitamins are, tocopherol, butylated hygroxyanisole, butylated hydroxyl toluene, propylgallate, and ascorbyl palmitate.

Chelating Agents

Both acorbic acid and pyridoxine hydrochloride have been stabilized by adding chelating agents to formulations. This practice is not popular in the Dietary Supplement industry where consumers are concerned with the concept of natural.

Coating and Encapsulation

Improving stability of labile vitamins under stress conditions is an important function of coating agents. And they are also useful for converting liquid vitamins into free flowing dry powders, masking taste in chewable vitamins and improving handling and tableting characteristics. It is also used for stabilizing color of ascorbic acid tablet, which otherwise may develop a tan color on aging.

Adsorbate Preparations

Adsorption of fat soluble vitamin on suitable adsorbents has been utilized as a means of conversion of the vitamin to dry, free-flowing powders as well as to enhance their stability. Vitamin A has been successfully adsorbed onto calcium silicate. Neutral or weakly alkaline carriers such as magnesium oxide tend to stabilize Vitamin A and Cholecalciferol.

Ethanolamine and polyoxethllene compounds are very effective in preventing the isomerization or ergocalciferol caused by surface acidity of excipients, both Vitamins A and D adsorbant products are commercially available and are commonly used in multiple vitamin tablets.

Lyophilization

In the pharmaceutical industry, lyophilization has been used to achieve improved stability in liquid preparations. This process has been applied in the preparation or multidose vials of Vitamin B complex vitamins for parenteral use. Lyophilization has proven useful to stabililize cyanocobalamin in the presence of ascorbic acid in liquid preparations.

FORMULATION OF VITAMIN PRODUCTS

Liquid Formulations

Since liquid formulations no longer popular in today‘s market, only a few problems regarding liquid products will be addressed.

Liquid vitamin products have been prepared in the form of drops for infants, and multiple vitamin syrups for the elderly and those who have difficult in swallowing tablets. Vitamins are also formulated as injectables for pharmaceutical use and for the treatment of serious vitamin deficiencies.

The most common problems with liquid products are:

1. Gas formation and pressure,
2. Clarity and emulsion stability,
3. Vitamin stability, especially A, B1, C, and panthenol.

These problems can satisfactorily be resolved by:

1. Selection or proper pH. High pH affects B1 and creates excess gas. Adjusting pH to 3.5 or lower gives the best results.
2. Glycols and tweens when used to form emulsions and to solubilize certain vitamins must be adjusted to the proper levels. Glycols must be balanced to prevent oxidation of vitamin C and also to prevent emulsion separation.
3. Vitamin C is best formulated in liquids at levels no higher than 50 mg/0.6 ml.
4. Proper overages should be established based on critical stability studies.

Tablet and Capsule Formulations

The most common forms of solid dosage forms for vitamin products are tablets and capsules (both 2-piece and soft gelatin capsules). While the stability issues may be obvious from the foregoing examples of the stability problems with the individual vitamins and to a lesser degree in combination with each other, it will be addressed in this section as a part of the formulation challenges.

The second aspect of the formulation challenges for these products lies in the multiple active dietary ingredients products where homogeneity is a problem. First the ingredients need to be protected to minimize degradation and then be commingled to provide a blend that will result in a dosage form that meets label claims. Finally excipients must be selected for functionality and at the same time must be compatible with all of the product active components.

Protection to Enhance Stability

The fat soluble vitamins A, E, D, and K are normally incorporated into tablets and two-piece capsules in the form of dry stabilized coated products or as adsorbates described previously. These are commercially available from most vitamin ingredient manufacturers.

The B complex vitamins, thiamin, riboflavin, niacinamide, and pyridoxine are usually coated if used in chewable tablets due to taste, otherwise they are added as is. The products manufactured for chewable tablets usually contains 25–33% of the active coated with fatty acids or mono and diglycerides of fatty acids which is very effective in masking taste and enhancing product stability.

Ascorbic acid is currently availably at percentages from 90 to 100, with varying amounts of granulating excipients making up the difference. A small percentage of ethyl cellulose and lactose is available as a granulation for direct compression, but has the added benefit of retarding discoloration of Vitamin C. Most Vitamin C products available today can be used in directly compressible products.

Folic acid, cyanocobalamin and biotin are used in tablets and capsules in the form of triturates, adsorbates or spray-dried powders containing 0.1–1.0% of the vitamin to facilitate distribution of the microgram quantities that are normally used for these nutrients.

For those multiple vitamin products that also contain multiple minerals, additional problems are created due to reactions between some of the vitamins and minerals. Iron and copper are incompatible with a number of the vitamins. In response to this situation, there are coated mineral products available to be used in these formulations. Minerals are also available as triturates at the levels commonly added to these formulas.

Homogeneity in Blending

In the dietary supplement industry the most common products are multiple vitamin and multiple mineral formulas. It is not uncommon to have at least 10 vitamins and 6 minerals in the same formula to be dosed in one tablet or capsule. A formula could contain 6 mu;m of Vitamin B12 and 500 mg of Vitamin C. These actives can be combined with all of the B complex vitamins in various amounts. Minerals in the same varying ratios can also be incorporated into this blend.

There are two methods of blending used in the dietary supplement industry: wet granulation and dry blending. Dry blending is usually referred to as the "direct compression or direct encapsulation methods."

Before selecting the appropriate method of blending the physical properties of powders must be evaluated. The parameters checked are flowability, particle size, particle shape and bulk density. Free-flowing powders are easy to mix. Sticky or cohesive powders tend to form clumps and are more difficult to mix. Ingredients with high variation in particle size is also difficult to mix. Spherical powders are easier to mix than fibrous solids or ingredients with needle-like particles. Ingredients with particles of similar densities blend easily, while ingredients with an excess of small particles will tend to rise to the top of the blend or become unmixed. Vitamin blends with multiple components nutrients will have components with multiple parameter variations.

The task of blending is also dependent upon the type of blending equipment to be used. Tumbler blenders (V-type) or slant cones work differently from convection mixers (Ribbon mixers) and both require and experimental design in order to maximize the blending for efficiency and product quality.

Suggested Blending Procedure for Direct Compression or Encapsulation

1. Test all active ingredients for identity and potency limits.
2. Test all excipients for identity and physical properties. Such as flow characteristics, particle size distribution, bulk density.
3. Purchase ingredients that have consistent particle size distribution or that have a narrow range or variation.
4. When using a V-type blender, add the ingredients through the exit valve. If you must add them through the legs of the vessel, divide the ingredients into equal parts, and then add one portion to one side and the other portion to the other side.
5. Screen lumpy or cohesive ingredients as you add them to the blender. It will reduce agglomeration during mixing.

6. Always add a portion of the largest quantity ingredient (usually an excipient)to the blender first. It will coat the blender and prevent lesser ingredients from sticking to the walls.
7. Before adding small-quantity active ingredients to the blend, gravimetrically dilute each one in several steps until the quantity reaches an amount that will facilitate a homogeneous blend.
8. Blending duration, intervals and the level of fill in the vessel play a critical role in determining the adequacy of blending. Parameters should be established during the development stages.
9. Test the blend for adequacy of mixing by taking adequate samples for testing. At a minimum samples should be taken from the top middle and bottom of the blender. Test should be performed on several ingredients but should include the smallest quantity ingredient with results falling between 85% and 115 %.

EXAMPLES OF TYPICAL VITAMIN AND MINERAL TABLET FORMULATIONS UTILIZING STABILITY ENHANCING COMPONENTS (A2)

The two formulations are being reproduced with compliments of DSM Nutritional products, formerly Hoffman-LaRoche, Inc.

The first formula is an example of a multiple vitamin with minerals where the formulator has taken into consideration the stability characteristics of the individual vitamins and made the best choices of minerals and excipients to provide a formulation that will sustain a two year expiration date under proper storage conditions. Noteworthy is the use fat soluble vitamins in adsorbate forms and Vitamin C, as a 90% granulation.

The minerals of choice were selected to minimize as much as possible, the tablet size. In particular, dicalcium phosphate was selected because it can function as a source of calcium and phosphorus as well as act as filler. All other minerals were used to provide the highest concentrations of the elemental metal, selected again to minimize tablet size. Microcrystalline cellulose serves to absorb moisture and prolong the life of the moisture sensitive vitamins as well as function as a dry binder and disintegration time enhancer.

In the second formulation, a chewable multiple vitamins with minerals, the formulator utilizes the vitamins that have been well coated with fatty acids. These products were selected to mask taste and promote vitamin stability. Also all of the minerals are also coated to minimize reactions between the vitamins and minerals in a matrix that is prone to moisture absorption. The low potency vitamins are added as triturations in order

Multivitamin Mineral 2 Tablets Dry Vitamin E Acetate 950 NS (30 IU Vitamin E)

Ingredients	Claim	Overage	Mg/Tablet
1. Beta carotene as betatab 20%	2,000 IU	25	7.50
2. Dry vitamin A acetate 500	3,000 IU	35	8.10
3. Vitamin D as vitamin D_3 type 100 CWS/HP	400 IU	35	5.40
4. Vitamin E as dry vitamin E acetate 950 NS	30 IU	5	33.16
5. Vitamin C as ascorbic acid 90% granulation	60 mg	5	70.00

6. Vitamin B_1 as thiamine mononitrate USP	1.5 mg	10	1.65
7. Vitamin B_2 as riboflavin USP-FCC	1.7 mg	10	1.87
8. Vitamin B_6 as pyridoxine HCL	2.0 mg	10	2.67
9. Vitamin B_{12} as cyanocobalamtn 0.1% SD	6.0 mcg	30	7.80
10. Folic acid as folic acid USP	0.4 mg	25	0.50
11. Niacin as niacinamide Free Flow	20.0 mg	5	21.00
12. Biotin as bitrit-1	30.0 mcg	25	3.75
13. Vitamin K_1, as dry phytonadione 5% SD – K_1	25.0 mcg	50	0.75
14. Pantothenic acid as d-Calcium panthothenate	10.0 mg	35	14.67
15. Iron as ferrous fumarate (32.87% Fe)	18.0 mg	–	54.76
16. Copper as cupric oxide (79.88% Cu)	2.0 mg	–	2.51
17. Zinc as zinc sulfate (36.43% Zn)	15.0 mg	–	41.17
18. Manganese as manganese sulfate monohydrate (32.5% Mn)	2.5 mg	–	7.70
19. Iodine as potassium iodide stabilized (68% I_2)	0.15 mg	–	0.22
20. Potassium chloride (52.4% K and 47.6% Cl)	–	–	76.34
– Potassium	40 mg	–	–
– Chloride	36.3 mg	–	–
21. Magnesium as magnesium Oxide DC (60% Mg)	100.0 mg	–	166.67
22. Dicalcium phosphate anhydrous (29.46% Ca and 22.77% P)*	–	–	457.54
– Calcium	135.0 mg	–	–
– Phosphorous	104.0 mg	–	–
23. Crospovidone as polyplasdone XL	–	–	7.00
24. Vitacei (microcrystalline cellulose/calcium carbonate 30 mg)*	–	–	194.39
25. Avicel PH102 or Ex-Cell 102 (MCC)	–	–	80.00
26. Silicon as syloid 74 (46.75% Si)	2.0 mg	–	4.28
27. Stearic acid	–	–	4.00
28. Magnesium stearate	–	–	4.00
	Total/Weight (mg)		*1279 .40*

* Total Calcium from Dical Phos Anhydrous and Vitacei = 162 mg.

to facilitate adequate blending. Even though the best selections are being made to facilitate blending efficiency, the formulator still utilizes geometric dilution to ensure blending adequacy.

Manfacturing Procedure

1. Mix Items 1–5 with item 11 for 5 minutes. Set aside as Part A.
2. Blend items 6–10 with items 12–14. Screen through a #30 or 40 mesh sieve. Remix for 5 minutes and set aside as Part B.
3. Blend items 15–19 with item 26. Screen through #30 or 40 mesh sieve. Remix for 5 minutes and set aside as Part C.
4. Blend Parts A, B, and C with Items 20*, 21, 22, 23, 24, and 25 for 10 minutes. *Note*: Screen any lumpy materials through #20 mesh before adding to mix.
5. Add items 27 and 28 as a premix with a portion of the blend, screen through #30 mesh, combine and mix for 5 minutes.
6. Compress on a Manesty Rotary tablet press at appropriate pressure with 5/16 × ¾ capsule shaped punches at 40 RPM.

Tableting Results Cores

Compression force (lb)	4100	5000	6100	7100	8000	9100
Hardness Avg (sc)	22.2	26.6	30.8	35.1	38.3	40.6
Disintegration (min)	2	5	10	16	20	24

Product may be sugar coated or film coated for ease of swallowing. Follow optimum conditions for specified coating equipment.

Formula 2

Children's Chewable Multivitamin–Mineral Tablets (A2)

Ingredients	Label claim	% Mg/ Tablet	Average	Actual mg/Tab
Vitamin A as palma beads 500	2000 IU	4.0	25	5.0
Beta Carotene (0.3 mg) vitamin A activity as beta carotene 2.4s	500 IU	12.50	25	15.63
Vitamin D3 as vitamin D3 type 100 ws	200 IU	2.0	25	2.50
Vitamin E as dry vitamin E acetate 50%	15 IU	30.00	5	31.50
Vitamin C as c-90 as sodium ascorbate	60 mg	22.23	5	23.35
		45.00	5	47.25
Folic acid	200 mcg	0.2	40	0.28
Vitamin B1 as B1 rocoats 33.3%	0.75 mg	2.25	10	2.48
Vitamin B2 as B2 rocoats 33.3%	0.85 mg	2.25	10	2.81
Niacinamide as niacinamide rocoats 33.3%	10 mg	30.03	10	33.03
Vitamin B6 as B6 rocoats 33.3%	1 mg	3.64	10	4.0

Ingredients	Label claim	% Mg/ Tablet	Average	Actual mg/Tab
Vitamin B12 as B12 0.1% SD	3 μm	3.0	40	4.2
Biotin as bitrit-1	25 μm	2.5	40	3.5
Pantothenic acid as calcium pantothenate SD	5 mg	5.44	4.0	7.62
Vitamin K as K1 1%SD	5 μm	0.50	50	1.0
Calcium as calcium carbonate 90A[a]	100 mg	278.0	–	278
Magnesium as magnesium oxide DC[b]	50 mg	83.00	–	83.0
Iron as iron fumarate 60% coated	6 mg	30.30	–	30.30
Zinc as zinc oxide	5 mg	12.45	–	12.45
Copper as cupric oxide	0.5 mg	1.25	5	1.32
Manganese as manganese sulfate 50% coated	0.5 mg	2.75	–	2.75

[a]Desmo Chemical
[b]0 E. Mendell

Ingredients	Label Claim	mg/Tablet	Average	Actual mg/Tab
Rose Hips	0.5 mg	0.5	-	0.5
Rutin	0.5 mg	0.5	-	0.5
Bioflavonoids	0.5 mg	0.5	-	0.5
Iodine as potassium iodide	37.5 μm	0.055	5	0.058

Theoretical weight of actives		409.378 mgms
Inactives		
Starch 1500		125.00
Dipac compressible sugar		1241.472
Sugar 6 × powdered		50.0
Syloid 244		7.0
Microcel C		7.0
Citric acid		50.0
Carrageenan		70.0
Prosweet flavor enhancer Mm50		30.0
Natural strawberry flavor		100.0
Magnesium stearate		13.0
	Total/Weight	2287.00

MANUFACTURING PROCEDURE

Vitamin Premix

1. Mix folic acid, Vitamin B1, Vitamin B2, biotin, Vitamin B6, calcium pantothenate and Niacin amide in a suitable blender using geometric dilution when necessary.
2. Pass through a #30 mesh screen or equivalent milling procedure and remix for 5 minutes.
3. Mix sodium ascorbate, Vitamin E, ascorbic acid, c-90, beta carotene, Vitamin B12, Palma beads Type 500, Vitamin d3 and Vitamin K using geometric dilution when necessary and let mix for 10 minutes or until a uniform blend is obtained.
4. Charge steps 2 and 3 into a suitable blender and mix for 10 minutes or until a uniform blend is obtained.

Mineral Premix

1. Mix potassium Iodide, Rosehips, Rutin, Bioflanonoids, Cupric Oxide, and Manganese Sulfate, Zinc oxide and Ferrous fumarate, using geometric dilution when necessary.
2. Pass step 1 through a #30 mesh screen if necessary and remix for 5 minutes.
3. Add Calcium Carbonate and Magnesium Oxide to step 2 and mix for 5 minutes or until a uniform blend is obtained.

Final Blend

1. Add the vitamin premix to the mineral premix in a suitable blender and mix for 5 minutes or until a uniform blend is obtained.

2. Add Dipac, Starch 1500, Carrageenan, Ctrric acid and Prosweet to step 1 and mix for 5 minutes or until a uniform blend is obtained.
3. Mix and screen flavor, Magnesium Stearate, Syloid 244 and Microcel C through #30 mesh.
4. Add step 3 to step 2 and mix for 2–3 minutes.
5. Store the final blend in suitable drums lined with polyethylene bags.

Compression

1. Part of the final blend was compressed on a suitable tablet press equipped with 5/8 tooling and showed the following properties:

(a) Tablet Hardness, Strong Cobb Units (SCU)*	14
(b) Tablet Friability (%)	4

2. Part of the final blend was compressed with 3/4 tooling

(a) Tablet hardness	14
(b) Tablet Friability (%)	1.3

Dietary Supplement 2007 FDA Good Manufacturing Practices Requirements for Formulations

Effective August 25, 2007, all manufacturers of Dietary Supplements, which includes Vitamin and Mineral preparations will be required to comply with the new cGMPs for Dietary Supplements.

Title 21 CRF Part 211 require the following.

Master Manufacturing Record

1. You must prepare and follow a written master manufacturing record for each unique formulation of dietary supplement that you manufacture, and for each size, to ensure uniformity in the finished batch from batch to batch.
2. The master manufacturing record must:
   a. Identify specifications for the points, steps or stages in the manufacturing process where control is necessary to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record.
   b. Establish controls and procedures to ensure that each batch of dietary supplement that you manufacture meets the specifications identified in accordance with paragraph (b) (1) of this chapter. [Code of Federal Regulations, Title 21, Part III, Section E (b)(1)].

What must the master manufacturing record include?

The master manufacturing record must include:

1. The name of the dietary supplement to be manufactured and the strength, concentration, weight, or measure of each dietary ingredient for each batch size;

*Strong Cobb Unit (SCU): Comparative unit of measure utilized in pharmaceutical or nutritional supplement units. Hardness is also measured in KP units.

2. A complete list of components to be used.
3. An accurate statement of the weight or measure of each component to be used.
4. The identity and weight or measure of each dietary ingredient that will be declared on the Supplement label and the identity of each ingredient that will be declared on the ingredients list of the dietary supplement.
5. A statement of any intentional overage amount of a dietary ingredient.
6. A statement of theoretical yield of a manufactured dietary supplement expected at each point, step, or stage of manufacturing process where control is needed to ensure the quality of the dietary supplement, and the expected yield when you finish manufacturing the dietary supplement including the maximum and minimum percentages of the theoretical yield beyond which a deviation investigation of a batch is necessary and material review is conducted and disposition decision is made.
7. A description of packaging and a representative label, or a cross reference to the physical location of the actual representative label.
8. Written instructions, including the following:
   a. Specifications for each point, step or stage in the manufacturing process where control is necessary to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record.
   b. Procedures for sampling and a cross reference to procedures for tests or examinations.
   c. Specific actions necessary to perform and verify points, steps, or stages in the manufacturing process where control is necessary to ensure the quality of the dietary supplement and that the dietary supplement is packaged and labeled as specified in the master manufacturing record:
      i. Such specific actions must include verifying the weight or measure of any component and verifying the addition of any component.
      ii. For manual operations, such actions must include:
         A. one person weighing and another person verifying the weight or measure;
         B. one person adding the component and another person verifying the addition;
         C. special notations and precautions to be followed;
         D. corrective action pans for use when a specification is not met.

This newly released final rule has drastically changed the requirements for composition of a master manufacturing record. This is the only version of a current Good Manufacturing Practices Regulation that prescriptively spells such requirements as process controls and material review or corrective action plans as a part of a master record.

Additional Stable Formulation Information

Single or multiple vitamin tablets have been made by both wet granulation and dry granulation processes. Wet granulation is performed to a much lesser degree, since most ingredients and excipients can be purchased meeting the physical parameters necessary to formulate tablets and capsules. Dry granulation techniques are cost effective and renders more stable products because of the elimination of water. Alcoholic solutions have also been successfully employed to granulate vitamin formulations, However this method is also becoming obsolete due to environmental controls imposed on factories for solvent emissions.

Tablets can be uncoated or coated by film or sugar coating processes. Sugar coating of vitamin tablets is becoming obsolete, since vitamin users, except for children prefer not to have sugar added to the products. Chewable products are usually created for the children‘s market.

Sugar coated vitamins had a shorter shelf life that the current film coated tablets, due to the introduction of water and the faster drying times.

Sustained released vitamin products have been a matter of interest, however very little has been published on the technology and formulation of such products. The major problem in formulating a sustained release multivitamin product is achieving full bioavailability of the vitamin addition to sustained release for a significant number or hours. Riboflavin is particularly troublesome in this regard due to its very low solubility in water (2).

SHELF LIFE

The shelf life of a product is determined by the stability of its most unstable ingredient. In multiple vitamin products there are usually three to five limiting ingredients, making it impossible to generate data at elevated temperatures and predicting shelf life by the classical application of the Arrhenuis plot. Accelerated testing has most often resulted in erroneous predictions due to excessive variations in analysis (3).

Suggested Methods for Predicting Stability for Vitamin Products

While the final rule "Good Manufacturing Practices Regulation for Dietary Supplements" does not include a requirement for expiration dating, it has become the industry standard imposed by customers and consumers alike. It is for this reason that expiration dating is not likely to go away in spite of what may become the final rule. More than likely, it will probably become a requirement in the future (8).

The Nutrition Health and Labeling Act on the other hand states that dietary supplements must maintain 100% of its labeled ingredients throughout its shelf life. Based upon this requirement, predicting product stability becomes a requirement by default. To meet these needs stability studies and expiration dating must be the topic for methods of predicting shelf life.

Since single ingredient vitamin products can be tested by the classical stability predicting method, popularized by the pharmaceutical industry, these products present the fewest of concerns. Also single ingredient products have always been topics of the USP, there are volumes of real time stability data available to manufacturers, particularly from raw ingredient suppliers.

Secondly, multiple vitamin combination product manufacturers are usually fast followers in the marketplace, who do not enjoy the luxury of product patents and proprietary information. The return on investment does not permit them to invest time and money in waiting for long term studies to be completed before launching a new product. Thus, product labels must bear an expiration date based upon "best guess" and literature searches.

The following three suggested methods may provide some input to those manufacturers who may be interested in utilizing methodology that is currently being used for interim expiration dating. These methods are being utilized by some of the more responsible industry members who also do not have the resources to conduct real time studies before launching a new product.

Suggested Methods to Collect Supporting Data for Interim Expiration Dating

1. New Products: A minimum of one batch in the commercial package held for 3 months at 40˚C/75% relative humidity with a documented commitment to test the product at labeled storage conditions at, 6 months, 1 year and at the end of the declared shelf life and removed it from the market if it fails at any test interval. (Testing three batches under these conditions is preferred when the manufactured volumes and frequency of manufacture will permit.)
2. New Products with ingredients similar to existing products with real time data. One batch minimum tested under accelerated conditions run side by side with the existing product. Excipient base must also be the same and in similar ratios. Commitment to long term studies must be documented and completed as above
3. Existing products for which stability studies have not been conducted-Conduct stability test on at least three samples from retains, preferably un-opened identical containers that have reached the expiration date. Place one additional new lot or batch sample on stability annually to confirm test data.

Test results from all of the above shall be termed interim expiration dating until long-term data becomes available.

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11

Botanicals and Their Formulation into Oral Solid Dosage Forms

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INTRODUCTION AND SCOPE

The Dietary Supplement Health and Education Act of 1994 (DSHEA) amended the Federal Food, Drug, and Cosmetic Act to establish standards with respect to dietary supplements and for other purposes. The DSHEA formally defined supplements and assigned them a unique regulatory status between foods and drugs under the oversight of FDA's Center for Food Safety and Applied Nutrition. Before this time, dietary supplements were subject to the same regulatory requirements as were other foods (1). Under the DSHEA (2), the term *dietary supplement* means a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following "dietary ingredients":

- a vitamin,
- a mineral,
- an herb or other botanical,
- an amino acid,
- a dietary substance for use by man to supplement the diet by increasing the total dietary intake (e.g., enzymes or tissues from organs or glands), or
- a concentrate, metabolite, constituent, or extract.

The DSHEA also describes the forms, e.g., capsule, powder, softgel, gelcap, and tablet, in which these products can be ingested.

The DSHEA also distinguishes a "new dietary ingredient" as one that meets the above definition for a "dietary ingredient" and was not sold in the United States in a dietary supplement before October 15, 1994 (1). Products formulated with "new dietary ingredients" must meet substantially tougher regulatory scrutiny. In the case of a "new dietary ingredient," FDA requires premarket review for safety data and other information required by law. Aside from that exception, firms generally do not have to provide FDA

with the evidence they rely on to substantiate safety or effectiveness before or after marketing their products. Nor does the amount of "dietary" ingredient in supplements require FDA review or approval. However, firms are responsible for determining that the dietary supplements they manufacture or distribute are safe and that any claims or representations they make about them are substantiated by evidence adequate to demonstrate that they are not false or misleading. It is clear that FDA is granted substantial policing power under the DSHEA to stop distribution if government personnel believe they can show that the product is not safe; however, the burden of proof is on FDA.

Since no authoritative list of the dietary ingredients marketed prior to October 15, 1994, exists, manufacturers and distributors are themselves responsible for determining if a dietary ingredient is "new" (1). If not, they must document that the dietary supplements they sell, containing the dietary ingredient, were marketed before October 15, 1994.

The DSHEA gave FDA the authority to establish good manufacturing practices regulations that establish the minimum standards of practice for the preparation, packing, and holding of dietary supplements that ensure their safety. These regulations were to be modeled after the current good manufacturing practice regulations (cGMPs) in effect for the rest of the food industry (2). But until the final rule establishing regulations to require cGMPs for dietary supplements was announced by FDA on June 22, 2007 (3), more than 10 years after the DSHEA became law, there were no cGMPs specific to dietary supplements. Until then, dietary supplements were subject to the cGMPs in effect for other foods. The intent of the final rule is to prevent including wrong ingredients, too much or too little of a dietary ingredient, contamination by substances such as natural toxins, bacteria, pesticides, glass, lead and other heavy metals, and improper packaging and labeling (4,5). The final rule includes, among others, requirements for establishing quality control procedures, designing and constructing manufacturing plants, testing ingredients and the finished product, and requirements for recordkeeping and handling consumer product complaints. Manufacturers are required to evaluate the identity, purity, strength, and composition of their products. If a dietary supplement contains contaminants or does not contain the dietary ingredient it is represented to contain, the product would be considered by FDA to be adulterated or misbranded. There is no question that this is a major development in the regulation of dietary supplements and that the minimum standards established by the final rule will go a long way toward protecting the public from unsafe practices. But the final rule leaves unaddressed certain critical areas: i.e., there are no specific requirements for dissolution, disintegration, bioavailability, or expiration dating. At least in the case of botanical supplements, where research is lacking or incomplete, these omissions are understandable. Unlike pharmaceutical products, which consist of one or two well-characterized drug substances, botanicals are complex substances and the exact source of activity is generally unknown. This fact provides a substantial and as yet unresolved scientific challenge to developing test methods, understanding the impact of formulation and processing variables, establishing stability, and establishing appropriate quality and performance standards. FDA appears to recognize this, at least in part, in pointing out that: "The final rule includes flexible requirements that can evolve with improvements in scientific methods used for verifying identity, purity, strength, and composition of dietary supplements" (4). But the statement does not seem to go far enough.

The assurance of identity, purity, strength, and composition is not sufficient to assure the appropriate release and bioavailability of active constituents, bioequivalence between brands, or product stability. GI absorption depends on the release profile of active component(s) from the ingested form (tablet, capsule). Release of actives depends on the choice and levels of excipients, method of manufacture, and others. Stability

depends on such factors as ingredient compatibility, processing conditions, and proper packaging.

Of all the substances that qualify as dietary supplements under DSHEA, herbs, or botanicals are of particular interest because of their widespread usage and their scientific and technical challenges. An evaluation of the physical, chemical, and mechanical properties of a drug substance provides an essential foundation upon which to predict problems, which may occur in formulation and process development, and ultimately, in manufacture of oral solid dosage forms. In contrast to drugs which are usually well defined single chemical entities, botanicals are complex substances containing multiple chemical components, and often several classes of compounds in a single product. Many of these compounds are unstable to heat, light, oxygen, alkaline pH, and elevated humidity. In addition, crude botanical powders and powdered extracts may have poor flow, low bulk density, variable particle size distributions, and compression properties significantly different from typical pharmaceutical excipients. When activity cannot be reasonably assigned to specific components or component ratios, meaningful formulation development is extremely difficult, if not impossible.

This chapter will first provide an overview of the nature and production of the botanical extracts used to formulate supplement products. Then, two case studies will be presented to compare and contrast the technical issues in the development of oral solid dosage forms for two botanicals: feverfew(based on a consideration of a single active marker compound, parthenolide) and St. John's wort (based on a consideration of the phytochemical profile of multiple components of interest). The case studies will consider hygroscopicity, stability, solubility, excipient compatibility, flowability, compactibility, dissolution, and others.

BOTANICAL EXTRACTS

Manufacturing Process of Botanical Extracts and Preparations

Strictly speaking, the manufacture of botanical extract starts from the collection of fresh plant material. After cleaning and/or drying, the plant material can be extracted with various solvents, which may be water, organic solvent, or even oil. The extract solution may or may not experience further processing (e.g., evaporation, drying, and dilution) to form different kinds of botanical extracts, which can be finally made into a variety of dosage forms such as tablets, capsules, liquids, and ointments (Fig. 1).

The preparation of botanical crude material, including the collection of fresh plant, cleaning and drying, is typically performed by the producers of plants.

Fresh plants may be harvested from natural habitats in the wild (wild crafting) or from cultivation. Compared to cultivated plants, wild-crafted plants may have less pesticide residues. However, the use of wild-crafted plants are accompanied by a greater risk of misidentification and variation in therapeutic effect. This causes a substantial difficulty for producers to exercise control over the quality and quantity of plants. Currently, most of the plants used to produce botanical extracts are cultivated.

After the plants are harvested or gathered, they must be cleaned. Cleaning may involve screening, washing, peeling, or stripping leaves from stems. Any unnecessary parts are removed to avoid further excessive processing. Cleaned fresh plants may be used for extraction directly; however, they are generally dried first. Fresh plants must be dried or processed as soon as possible after harvest because they begin to deteriorate immediately. The purpose of drying is to reduce the water content so that the plant can be stored or transported to the producers of extract. Dried materials are also easier to mill in

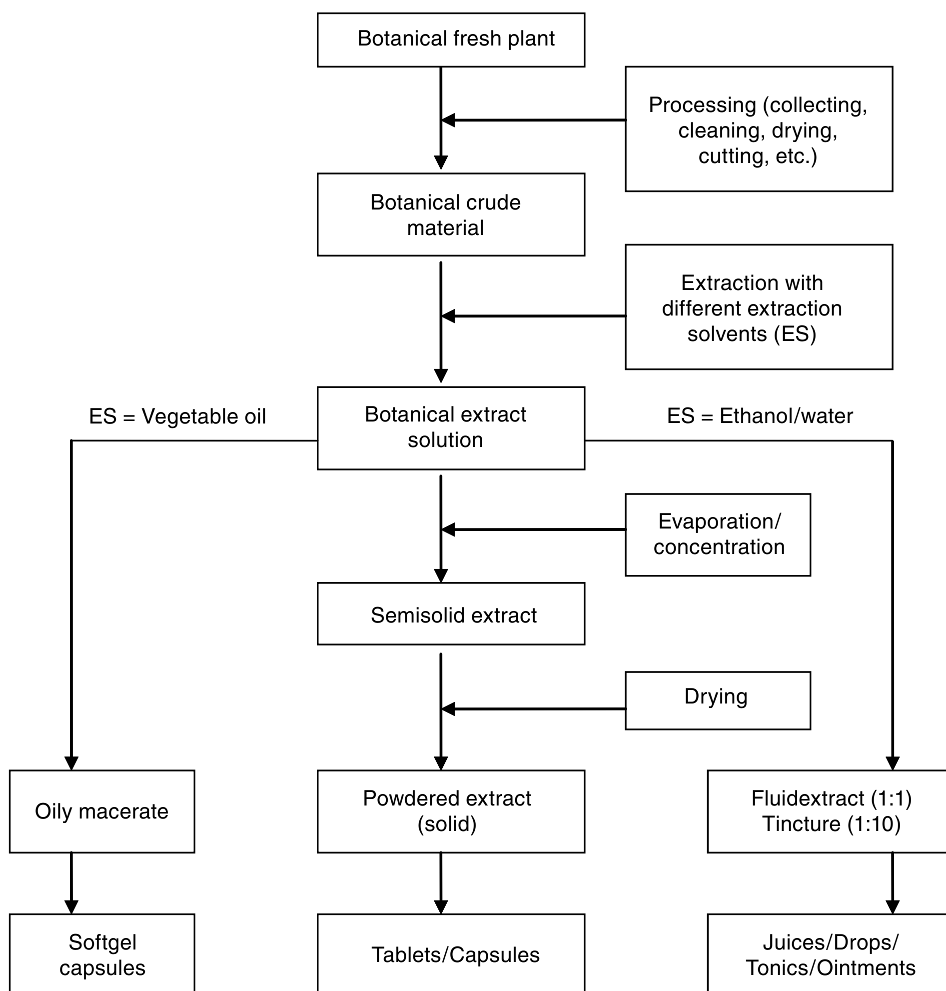

FIGURE 1 Overview of manufacturing process of botanical extracts and products.

preparation for extraction. Milling increases the surface area accessible to extraction solvents and ruptures cells to expose cellular contents.

Extraction is a process to transfer the desired constituents from botanical crude material to the extraction solvent. Several methods can be used to prepare extracts, including organic solvent extraction, supercritical gas extraction, and steam distillation. Organic solvent extraction is the most popular method currently used in the industry. The solvent is selected depending on several factors including the physicochemical characteristics of the constituents being extracted, cost, and environmental issues. Depending on the ratio of botanical crude material to the extraction solvent, the extraction procedure can be classified into maceration or percolation. During maceration, the crude material/extraction solvent ratio is fixed. The plant material is treated with a specified amount of solvent corresponding to its quantity. In percolation, the crude material is treated with a variable quantity of extraction solvent until the extractable matter is completely separated. Therefore, the crude material/extraction solvent ratio may vary from batch to batch within a certain range. Percolation is generally thought to be more efficient than maceration (6).

The botanical extract solution represents an important intermediate product in the total manufacturing process. If the extraction solvent is ethanol or water or a mixture of both, the resulting preparation is a fluidextract after filtration, which can be further diluted to produce a tincture. If the crude material is extracted with vegetable oils, oily macerates are obtained, which are usually filled into soft gelatin capsules (6).

If the desired preparation is a dry extract, evaporation is necessary to remove the majority of extraction solvent. The resultant semisolid extract is dried completely using a suitable dryer, e.g., spray dryer, belt dryer, or freeze dryer. The technique for drying depends on the stability of the active ingredients and the amount of moisture that must be removed. In most cases, suitable excipients such as maltodextrin, lactose, or silicon dioxide must be added to the semisolid extract before subsequent drying. In practice, most herbal preparations cannot be dried or ground without the addition of excipients, which may be attributed to their hygroscopicity and high content of fats and pectin. The powdered dry extract is obtained after grinding and sieving and is suitable for further formulation and processing into a solid dosage form (6).

Botanical Extracts: Chemical Complexity and Classification

Although popularly regarded as one single active substance, every botanical extract is actually a complex mixture of various substances. These substances, acting individually or in combination, produce the pharmacological or physiological effect of the botanical preparation. In theory, the individual constituents in botanicals can be classified into active compounds, coactive compounds, marker compounds, or other compounds according to its contribution to the activity of botanicals (7).

"Active compounds" and "coactive compounds" are both understood to exert a direct pharmacological or physiological activity. When tested at similar level in isolation and as part of the total botanical extract, active compounds can exhibit the same or a similar activity as the total botanical extract (e.g., sennosides in senna extract) (7). In contrast, coactive compounds do not exhibit the same level of activity as the total extract (e.g., procyanidines/flavonoids in pine bark extract) (7).

Strictly speaking, "marker compounds" should have no correlation with the physiological activity of the extract. Marker compounds only serve technical purposes in the manufacturing process, such as identify confirmation, stability evaluation, etc. However, in practice, it could be difficult to determine whether a given compound is an active/coactive compound or a marker. There is often conflicting data about the physiological activity of a compound. Even when the physiological activity is certain, the classification of this compound may depend on the intended use of the product in which it occurs (8).

"Other compounds" refers to those constituents in botanical extracts which do not serve any activity or analytical purposes. They can be either a normal part of a botanical extract (e.g., resins, carbohydrates, protein, and fatty oil) or substances, which may affect safety and must be limited within an acceptable range (e.g., heavy metals and pesticides).

Based on the above definitions of the chemical composition of botanical extracts, the *European Pharmacopoeia* classified botanical extracts into standardized extracts, quantified extracts and other extracts. Standardized extracts are herbal preparations where active compounds are known and adjusted to a specific content. Quantified extracts refers to those preparations containing a defined realistic range of coactive compounds. Other extracts are those products for which no active compound or coactive compound is known (9). However, the definition of a standardized extract is somewhat different in the United States, and will be discussed in greater detail later.

Other popular classifications of botanical extracts include those based on their physical state and whether excipients will be added into the final extract or not. Depending on the physical state, extracts can be identified as fluidextracts, oily macerates, semisolid extracts, powdered extracts, and tinctures (6). Fluidextracts, also known as liquid extracts, are usually so made that each milliliter of extract represents the activity of 1 g of crude material (1:1). A fluidextract can be further diluted to form a tincture (1:10 is traditional). Semisolid extracts, also known as soft extracts, fall between fluidextracts and powdered extracts (10). The primary focus of this chapter is the manufacture of botanical solid dosage forms; therefore, dry extracts will be discussed in greater detail.

Botanical extracts can be categorized into native extracts and nonnative extracts, depending on whether or not excipients have been included. Native extracts consist solely of the genuine botanical extractable matter and they do not contain additional inert excipients. Nonnative extracts contain the genuine herbal extractable matter, as well as excipients and/or extraction solvent (6,10); therefore, liquid and semisolid extracts are nonnative extracts. A powdered extract may be native or nonnative, depending on whether excipients are added or not.

Product Specification and Quality Standard for Botanical Extracts

In the final rules (3), FDA defined the quality of dietary supplement in terms of identity, purity, strength, composition, and limits on contaminants. However, different from other dietary ingredients, such as vitamins and minerals, the inherent chemical complexity of botanicals presents a substantial challenge to setting appropriate specifications for the extracts. A botanical extract can never be completely identical among different manufacturers, or even among different batches from the same manufacturer. Generally, the following tests should be considered to set a product specification for a botanical extract to ensure its quality.

Identification Test

Intentional or unwitting adulteration of one plant species with other plant species is a serious problem for botanical products, which can affect both efficacy and safety. Hence, identification testing is of utmost importance for the quality assurance of botanicals. Morphological, anatomical, and/or organoleptic characteristics are the bases for validating the identity of botanicals, either at the time of collection or later for unprocessed botanicals. If necessary (e.g., for powered botanicals), microscopic and/or chemical examination (TLC, GC, HPLC) can provide a wealth of information for positive identification. An important note is that the detection and identification of known active components or marker compounds only would not be considered a sufficient identification test. The presence of concomitant constituents also must be tested. In addition, adulterants and admixtures of other botanicals may be detected and excluded (6,10).

Composition and Strength

Given the chemical complexity of botanical extracts, it is virtually impossible to set a complete constitution profile for the quality assurance of a botanical. The testing of specific compounds is actually not required in the Final Rule unless linked to specifications set by the manufacturer (3). However, for botanical extracts with known active/coactive compounds, quantitative assay of these compounds can definitely help assure good product quality. In the case of botanical extracts where the active constituents are

unknown, the quantitative assay of marker compounds without activity can be used to control the whole manufacturing process; however, they can neither guarantee reproducible quality of extract nor consistent therapeutic activity.

Purity and Limits on Contaminants

The purity test is closely related to the safety of botanical extracts. A test requirement for foreign matter would ensure that the extent of contamination of extraneous matters such as filth and other botanicals is limited. Since sand and soil are predictable contaminants of botanicals, the ash test is also necessary. Heavy metal testing is most relevant for plant parts growing under the ground versus the aerial parts. To ensure that there is no contamination from the processing operations, such as grinding or milling, a limit test for heavy metal should be performed. While some botanicals are cultivated in the United States, most are available in large quantities only from foreign sources. Many foreign countries permit or tolerate the use of pesticides banned in the United States; therefore, a limit for pesticides is also a major issue to ensure botanical quality. Due to their natural origin, the microbial contamination of botanical crude material may be high. Although the manufacturing process (e.g., extraction with organic solvent, drying) provides a certain degree of decontamination, restrictive limits on microbial contamination are still necessary.

Additional Product Specifications

DER_{native}, the ratio of the mass of botanical crude material to the mass of resulting native botanical extract, is a parameter closely related to the quality of raw material and the extraction procedure, and thus is important for the evaluation of botanical extract quality and batch-to-batch consistency. This value may be used to calculate the daily dose of botanical extract, especially when the active constituents are unknown. However, DER_{native} is not a fixed value. A realistic range may be established based on the production of a sufficient number of batches. In addition, a change of DER_{native} does not necessarily mean an alteration in the qualitative and quantitative composition of extract, because the change may be due to processing after extraction (6).

In order to achieve product consistency, other quality-relevant parameters, such as residual moisture, particle size, bulk density, solubility, etc. should be limited to a certain range.

Quality Control of Botanical Extracts

Due to the chemical complexity of botanical products, it is almost impossible to get two batches of botanical extracts with the same physicochemical characteristics. Therefore, how to produce a consistent product is a very challenging topic for the botanical industry.

The quality of the final botanical extract is affected by many factors, which are summarized in Table 1. Some of these are controllable, but for certain others variability is unavoidable. All in all, control must to be implemented over both the raw material supply and the manufacturing process to produce a botanical extract with consistent quality.

Control on Botanical Raw Material Supply

Botanical crude materials are subject to considerable natural variation in quality relevant constituents. Several agronomic factors may affect the quality and quantity of botanical crude material (Table 1). In most cases, material should be sourced from the same species to minimize inherent botanical variety. In some extreme cases, the specific strain is

TABLE 1 Factors Influencing the Constituent Profiles of Botanical Extracts

Fresh plant	Herbal species and strain	
	Plant part	
	Growing conditions	Temperature
		Sun intensity and exposure
		Rainfall
		Soil type
		Pests (insects)
		Agricultural practices (planting, density irrigation, etc.)
Harvesting condition	Harvest time, period and stage	
Post harvest treatments	Washing, Peeling	
	Drying	Method, duration, temperature
	Storage	Light, oxygen, humidity, temperature
Milling	Type of millers	
	Milling conditions	Speed, screen size, time
Extraction	Solvent	Type
		Quantities
		Ratio between botanical material and solvent
	Procedure	Type, duration, temperature, pressure
Evaporation and drying		Method, duration, temperature

controlled to develop the unique chemical attribute of the botanical extracts. Because active/coactive compounds are usually localized in one part or another, consistent selection of the plant part or parts may be necessary. Growing condition has a significant impact one the chemical composition of the plant; therefore, guidelines on good agricultural and wild-crafting practices should be strictly followed. Harvesting and post-harvesting are also critical factors. Thus, the plant should be collected at the appropriate stage of growth and maturity and under proper conditions. After harvest, the plant should be properly cleaned to remove physical contaminants and any unnecessary parts.

Drying is always an important step to preserve the plant against deterioration. However, it should be performed carefully to preserve its color and chemical composition as much as possible. It is usually assumed that freeze drying can properly preserve the medicinal qualities of plants and is superior to other drying methods. However, some researchers have found that ambient air-drying and 45°C oven-drying can preserve more volatile compounds as well as the sensory characteristics of plants than freeze-drying (11,12). If possible, drying conditions should be optimized and monitored in terms of temperature, humidity, light intensity, air flow, time, and final moisture content. In addition, proper storage is also essential to maintain the botanical's integrity and quality. Protection against light, oxygen, moisture, and/or heat are usually required by botanicals (7).

However, even if sufficient attention has been paid to all these procedures and practices, a certain natural variation is generally unavoidable from batch to batch and harvest year to harvest year. This variation must be accepted.

Control on Manufacturing Process

Milling: Botanical crude material or powdered botanical extract may need to be milled to be reduced to the desired particle size. Particle size can affect extraction efficiency, blend uniformity, and product stability, and thus should be clearly specified. The milling method is selected based on the hardness of the material, the particle size desired, and the stability of the active/coactive compounds in the plant. Generally, the botanical should be milled gently because elevated temperature can significantly degrade the material (7).

Extraction: The type and concentration of extraction solvents can affect both extractability and the resulting extract composition. However, high extractability does not necessarily mean a high level of active components of interested. Liu et al. (13) used seven kinds of solvents (water, 50% ethanol in water, ethanol, 50% ethanol in acetone, acetone, chloroform, and hexane) to extract St. John's wort (SJW). The extractable material weight (EMW) and seven different components of interest were determined. Among all the solvents, 50% ethanol in water gave the highest EMW (59%), whereas chloroform and hexane only extracted 3% and 2%, respectively. However, 50% ethanol in water only exhibited the highest extraction efficiencies for quercitrin. Its extraction efficiencies for rutin and isoquercitrin were much lower than those found with ethanol, acetone and 50% ethanol in acetone. It is thus apparent that the qualitative and quantitative composition of an extract may vary greatly depending on the lipophilicity or hydrophilicity, polarity, and selectivity of the extraction solvent. However, it may still be possible to produce extracts with equivalent constituent profiles within specific ranges of extraction solvent composition, which must be determined experimentally and established specifically (13).

The final composition profile of botanical extracts also dependent on the extraction method. Exhaustive percolation generally has better extractability than simple maceration. For maceration, the ratio of botanical crude material to extraction solvent can significantly influence the quality of extract and its constituent profile, especially when the quantity of total extractable matter is increased with the amount of extraction solvent. However, with the aid of stirring or shear forces, and with a suitable herbal material/ solvent ratio, maceration may lead to an equivalent constituent profile obtained by percolation (6).

The extraction time and temperature also play decisive roles on the extract composition. Hinneburg et al. (14) demonstrated that when temperature increased from 25˚C to 60˚C to extract buckwheat, the rutin percentage in the final extract can be increased 4–8 times, depending on the length of extraction time. When the extraction time is extended from 2 to 24 hours, the rutin percentage decreased. However, the extraction of chlorogenic acid in buckwheat extract was not significantly affected by extraction time and temperature. It was concluded that the transfer of quality-relevant constituents from botanical crude material to extract (rate and quantity) is closely related to the physicochemical interaction between constituents and solvents. Different constituents may require different extraction conditions. Therefore, suitable extraction conditions should be experimentally determined and based on a consideration of the constituents of interest (14).

Evaporation and drying: The temperature for evaporation and drying, as well as the corresponding process time, is of special importance for the quality assurance of botanical extracts, especially if the extract contains volatile or thermolabile constituents that could be lost or destroyed. Some exposure to heat for various durations is often necessary for the removal of solvent residue and microbial contamination. In some cases, a compromise has to be made between these two requirements.

Standardization, an Important Practice for Quality Control

There is no globally accepted interpretation of standardization. Basically, standardization refers to all measures that manufactures may use to ensure their product consistency. A uniform manufacturing practice is a necessity. This comprises standards which are related to: (*i*) detailed specification of plant material; (*ii*) the selection of extraction method and solvent; (*iii*) the setting of other manufacturing condition such as drying temperature and time; (*iv*) in-process control; and (*v*) conformity to the final specification for the resulting botanical extract (6).

In some cases, standardization may involve identifying a specific chemical compound to ensure a consistent product. Ideally, the chemical compound chosen for standardization would be an active compound responsible for a botanical's physiological effect; therefore, each lot of the product would have a consistent health benefit. The European Pharmacopeia defined standardized extracts in this way. However, the components responsible for the effects of most botanicals have not been identified or clearly defined. In these cases coactive compounds or marker compounds may also be used for standardization, which produce "quantified" extracts and "other" extracts, respectively.

Dietary supplements are not required to be standardized in the United States. No legal or regulatory definition exists for standardization as it applies to botanical dietary supplements. So the presence of the word "standardized" on a supplement label may have various interpretations and may simply refer to uniform manufacturing practice, and/or the adjustment of specific compounds to a defined range.

Standardization based active/coactive compounds will no doubt help ensure that the botanical extracts will have the same physiological effect. However, the role of marker compounds in standardization is still under debate. A marker compound can provide an objective reflection of the history of the material. The disappearance or level change of an expected marker indicates that some aspect of the manufacturing process may have gone wrong. The marker may also serve as stability indicator if selected carefully. However, since marker compounds bear little or no correlation with physiological effect, the guarantee of their level in an extract does not necessarily assure product quality (7).

Standardization can be achieved by the addition of excipient or blending several batches of the same herb that contains different level of constituents of interest. Some manufacturers have also tried to achieve standardization by adding purified active constituents. Both approaches will produce a uniform amount of the standardized components in the final extract. This measure provides a degree of quality control, especially, when active compound is standardized. However, when the coactive compounds are standardized, the effect of the other nonstandardized components remains unclear. The addition of pure marker may alter the original balance of chemical components in the extract and result in an unpredicted effect. Thus, the positive effect of standardization is only achievable when it comprises a wide variety of raw material and process control, rather than an adjustment to a specified level of a specified compound.

CURRENT RESEARCH ON BOTANICAL FORMULATION AND PROCESSING

Although teas, decoctions, and tinctures are common preparations, tablets or capsules which can be made from powdered botanical raw material or extract are still the most popular forms for botanical products in the current market. Most formulators work with finely powdered extracts, which usually exhibit physicochemical characteristics, that can

present substantial a challenge to the manufacture of products with good quality. Among these challenges are poor flowability and/or compactibility, difficulty in evaluating the typical multiple-component profile, instability of active components, and unpredictable dissolution performance.

Manufacturing Challenge from Poor Flowability and Compactibility of Botanicals

Often, a major formulation challenge of powdered extracts is poor flowability. Having appropriate flowability is extremely important to the processing of powders, especially when feeding high-speed tablet presses or automatic encapsulation equipment. Poor or very poor flowability has been widely reported for dry botanical extracts (15–18), which if not properly addressed, can lead to inconsistent filling of the tablet die or capsule body, resulting in poor weight uniformity, and contributing to poor content uniformity. In general, poor flowability can be attributed to several factors, such as small particle size, irregular particle shape, and rough surfaces, cohesive forces between particles, etc.

The flowability of botanical extracts may vary greatly if produced by different manufacturing processes (e.g., extraction solvent, the addition of carrier, drying method and conditions, etc.). But flowability can vary even for an extract produced by the same process if the plant source varies. For example, Von Eggelkraut et al. compared the flowability of eight different batches of SJW dry extracts produced by the same process. The angle of repose of these extracts varied greatly even for those batches with similar particle size distribution, which indicated a relationship between flowability and the plant source itself (18).

Another extract property important for the formulation of solid dosage form is its compactibility. The mechanical strength of a compact is a function of bonding forces and the area over which they act. Therefore, the permanent deformation of the material under compression to a form an extensive interfacial contact area is important for bonding. Many researchers suggest that botanical extracts mainly deform plastically (15,17,19). However, plastically deforming materials may exhibit time-dependency and strain-rate sensitivity, which may lead to problems with capping or laminating during high-speed tableting (17).

Despite the plastic nature of botanical extracts, the formation of a cohesive compact is still likely to be a problem for botanical extracts. Two extreme cases can be exhibited by the same kind of botanical extract from different sources (20). One case is represented by poor compactibility, which cannot be improved by the increase of compression force. The other case is extreme compactibility, resulting in tablets that are unbreakable and deform upon application of breaking force, which may exhibit problems in fluid penetration and disintegration (20).

Compactibility may vary with the extraction conditions. For example, Endale et al. extracted the seed of *Glinus lotoides* with different extraction solvents (60%, 70%, and 80% methanol) and found the extract from 80% methanol exhibited much higher compactibility than the other two extracts. This higher binding property may be attributable to the extraction of such components as oils, fats, or other extraneous materials (21).

Often, botanical extracts do not exhibit the appropriate flowability and compactibility needed for direct compression. Furthermore, because the active components of the extracts are diluted by coextracted substances, high doses are usually required, which limits the formulator's ability to improve the manufacturability of the extract by addition of excipients. Several techniques have been reported that address these issues, including adding fumed silica to liquid or soft extracts to improve their manufacturability, dry or

wet granulation, and the selection and optimization of suitable excipients for the formulation (15,18,22–25).

A common practice in the botanical industry is to add suitable excipients, such as maltodextrin or silicon dioxide to the soft extract during drying, because many botanical extracts cannot be dried or ground alone due to their hygroscopicity or high content of fat and pectin. This practice can also be used to obtain a dry extract with satisfactory flowability and compactibility. Palma et al. (24) found that silicon dioxide has a high absorption capacity and is a good candidate to produce solid loaded silica products (LSP). They prepared three different LSPs with different loading ratios of extracts. They found that increasing the silica load ratio produced LSPs having higher density and better flowability. The resultant LSP also presented good compactibility (24).

Granulation, a widely practiced method to improve the flowability and compactibility of high dose drug substances, has been reported to improve the processing characteristics of some botanical extracts. For example, Diaz et al. found that the nonaqueous wet granulation *Plantago lanceolata* extract with Eudragit®E (Röhm & Haas GmbH, Darmstadt, Germany) resulted in superior flow properties compared to dry extract alone and good dissolution properties (22). Onunkwo et al. (23) prepared tablets of *Garcinia kola* with wet granulation, utilizing four binders (acacia, gelatin, maize starch, and sodium carboxymethyl cellulose) at various concentrations. They concluded that the resulting tablets had good disintegration time, dissolution, and hardness/friability profiles. The tablets formulated with starch exhibited the best disintegration properties but were consequently very friable. An increase in the binder concentration resulted in harder tablets but slower release of active component (23).

Due to stability considerations, dry granulation may be a more suitable technique than wet granulation. Soares et al. (15) studied the impact of dry granulation on the physical properties of *Maytenus ilicifolia* extract, using both slugging and roll compaction. They found that flowability and density were improved after granulation. No difference was found between the flowability of slugged or roll-compacted granules. Heckel analysis revealed that upon compression, granules exhibited an initial fragmentation followed by plastic deformation, while the extract itself consolidated mainly by plastic deformation. However, a higher compression force was needed to obtain the same crushing strength as obtained with tablets of the nongranulated powder mixture. This reduction in crushing strength was attributed to the material's decreased capacity for plastic deformation and increased resistance to further processing owing to the compaction and densification that occurred during dry granulation (15). Von Eggelkraut-Gottanka et al. (18) reported that the addition of lubricant was required for the roller compaction of dry herbal extracts to prevent sticking and that the amount of lubricant needed is significantly higher than that which would be used for roller compaction of chemically defined substances. They found that roller compaction not only improved the flowability of SJW extract but also made the flow more uniform among different extract batches. Although dry granulation reduced the crushing strength of the tablets somewhat, it did reduce dust and feeding problems during tableting and prevented tablet capping. In addition, they found that granulation decreased disintegration time and increase dissolution rate (18).

The selection of filler-binder plays an important role in the manufacturability of the final formulation. De Souza et al. (19) studied the impact of two different kinds of fillers, microcrystalline cellulose (MCC) and dibasic dicalcium phosphate on the compression behavior of *Phyllanthus niruri* extract. The addition of MCC did not modify the mean yield pressure of the extract while dibasic dicalcium phosphate increased the mean yield pressure significantly. In addition, the change from MCC to dibasic dicalcium phosphate decreased the tensile strength of tablets substantially. This fact may be explained by the

brittle property of dibasic dicalcium phosphate which seems to form weak bonds between the particles of the formulation (19). In their study of a high dose granulated (slugged and roller compacted) plant extract, Soares et al. found that the addition of MCC externally to the extract granules seemed to enhance the plastic deformation potential of all formulations, leading to tablets with crushing strength values higher than those obtained by granules without MCC that were compressed directly at the same compression force (15). Linden et al. suggested that response surface analysis can be applied to determine the best level of excipient used in a botanical formulation (26).

Regulational and Technical Challenge in Performance Testing of Botanical Products

Different countries have different regulatory guidelines for the performance testing of botanical products. Currently, USP requires the disintegration time of botanical products (immediate dosage form) to be <20 minutes. Although it is widely accepted that dissolution performance plays an important role in quality assurance, dissolution tests are currently available in the USP for four botanicals only: ginger, garlic delayed release, milk thistle, and ginkgo (10). FDA's final rule on cGMPs for dietary supplements also leaves unaddressed any specific requirements for dissolution or disintegration (3). In Europe, botanical products made from quantified extracts and other extracts need not undergo dissolution testing as long as they are formulated as immediate-release products. For botanical products made from standardized extracts, dissolution testing is required in Germany. However, the European Medicinal Evaluation Agency (EMEA) proposed that a disintegration test may substitute for a dissolution test if the active ingredient is known to be highly soluble in aqueous media at pH values typical of the gastro-intestinal tract (27).

This lack of dissolution standard may be partly due to the chemical complexity of botanicals. Even for the most popular botanicals, little is known about their pharmacological or toxicological profiles, which causes great difficulty in identifying the individual components of botanical products which can represent their pharmacological activity and thus be used for evaluation of release properties.

The relatively few published papers on the dissolution of botanical products often report notable differences among brands, with some brands exhibiting rather poor release properties when judged by typical pharmaceutical standards. For example, in two papers that compared the dissolution performance of commercial Saint John's wort and Ginkgo biloba products, respectively, different brands in each case exhibited different release profiles: some brands reached 90% dissolution in <30 minutes, while others did not dissolve at all in one hour (28,29). These release differences possibly could be accounted for by a number of factors related to formulation and manufacture. Such factors as the choice and amount of excipients, compression force, lubricant blending time, possible interactions between excipients and extracts, or even the failure to include appropriate excipients could all influence disintegration and dissolution. Different from chemically identified drugs, the physicochemical characteristics of the botanical extract itself may be also an important factor affecting the release of active components in botanical extract, although few papers have been published addressing this aspect. Von Eggelkraut et al. observed the disintegration performance of SJW tablets which have the same formulation except that different batches of extract powder were used. The disintegration time was dependent on the content of saccharose in the extracts (18).

Von Eggelkraut et al. also found that three potentially active components (hyperforin, hypericin, and rutin) were more rapidly released from tablets containing granulated extract than tablets containing the extract powder at the first 15 minutes, but not after

30 minutes. Tablets containing extract powder disintegrated much more slowly than tablets containing the granulated extract. This is indicative of a relationship between disintegration and dissolution. After contact with water, the highly hygroscopic extract forms a gel on the tablet surface, preventing water from further penetration into the tablet. On the other hand, tablets containing granulated extract disintegrate quickly into smaller particles, releasing the granulated extract for further solvent penetration (18).

The type and level of excipients not only affect the manufacturability of the final formulation, but also the disintegration and dissolution performance of the dosage form. De souza et al. suggested that the presence of a filler-binder has the strongest effect on the dissolution profile of tablets containing a high dose of the spray-dried extract of *M. ilicifolia*, followed by the type of disintegrant. When the filler-binder used was lactose, the extract showed first-order release kinetics, while when cellulose was used, a zero-order profile was observed, independent of the other excipients added to the formulations. Formulations containing cellulose presented a slower release than formulations containing lactose, which may be explained by the solubility of the filler-binder. While cellulose is insoluble in aqueous medium, lactose is soluble. However, the dissolution measured in this paper is not for a specified active component, but the whole absorbance under a specified wavelength (25). The level of lubricant and the method to add lubricant in the formulation may also affect the disintegration of the tablet and subsequently the dissolution profile. An increase of magnesium stearate in the external phase of a formulation of from 0.5% to 1%, and from 1% to 2% can result in a 10-minutes increase in disintegration time of tablets containing an herbal extract (30). In contrast, an increase in the amount of magnesium stearate incorporated into the granules of from 0.5% to 5% increased the disintegration time by only four minutes.

Stability Challenge During the Storage of Both Material and Products

Formulators should consider is the physical and chemical stability of botanicals during manufacturing processes and the proposed shelf life. A strongly hygroscopic nature is very common for botanical extracts (21,31), which may affect material processing and stability of finished products. With some very hygroscopic materials, the moisture content may increase at relative humidities as low as 40–50%. Such powders would require special low humidity areas for processing, in addition to special packaging and storage instructions. In such cases, traditional gelatin capsules should be used with caution, since hygroscopic fill material can remove physical bound moisture from shells on storage and then cause them to become brittle (32,33). Shells composed of hydroxypropyl methylcellulose may be more suitable in such cases.

Compared to chemically defined single drug substances, most botanicals are expected to have relatively shorter shelf lives because of their chemical complexity. Heigl et al. tested the stability of flavonoids in two different herbal materials, birch leaves and passion flower, and found that the flavonoid content of both decreased significantly in the first three months under stressed condition [40˚C and 75% relative humidity (RH)], but with different rates. This indicates the role of material itself on stability (34). Compared to crude material, dry extract may be more unstable due to greater total surface area, alteration of degradation pathway, the impact of solvent, etc. (35,36). Kopelman et al. tested the stability of the phytochemical profile in powdered SJW extract and pointed out the difficulty of storing botanical extracts. Storage of the extracts under humid conditions, even at moderate temperature (25˚C and 70% RH) and protected from light and oxygen, resulted in the rapid degradation of several phytochemicals. Even under 5˚C/0% RH, hyperforin showed significant decrease in

4 weeks (31). In the finished, formulated botanical product, the addition of excipient is also likely to slow down or accelerate the degradation of botanicals, depending on the type and level of excipients. For example, the overall greater percentage of phytochemicals in Saint John's wort extract can be preserved upon storage with MCC and pregelatinized starch versus lactose and dibasic calcium phosphate, which may be due primarily to pH differences and possibly hygroscopic tendencies (37).

FEVERFEW CASE STUDY

Tanacetum parthenium, commonly known as feverfew, has a long history of use in Europe to prevent migraine headaches and treat rheumatoid arthritis. In recent years its use has become more and more common in America and it is ranked among the top 20 selling herbs in North America (38). Like all botanicals, feverfew is chemically very complex and researchers still have almost no idea about its pharmacological profile. So far, only parthenolide has been thought to be the most active chemical component in feverfew and is widely used as marker for standardization and quality control (39). Here, feverfew is selected as an example of single-active component botanical to systemically evaluate the influence of formulation and processing variables on product quality.

Physical Properties Important for Manufacture and Formulated Product Quality

Jin et al. compared the physical and chemical properties of five Feverfew powdered extracts, which were obtained from four nutraceutical companies (A1, A2, B1, C1, and D1) (40). Based on the certification of analysis, these companies use different plant parts (flower, leaf, or the whole aerial part) to produce their extracts. Even for the same company, the plant parts used may vary with production batch. Different excipients such as maltodextrin and cellulose may or may not be added for standardization. Apparently, these variations in production may cause significant differences in physical and chemical properties among different manufactures or even different batches from the same manufacturer (40).

Several physical properties important for manufacture and formulated product quality were compared, including flowability, hygroscopicity, compressibility, and compactibility (40). All commercial Feverfew extracts tested exhibited poor to very poor flowability in terms of Carr's index. However, the flowability data from minimum orifice diameter test does not match well with Carr's index test. C1 showed the smallest minimum orifice diameter, but its Carr's index was almost the biggest among these five extract. The lack of agreement of these two flowability test results may be explained by the addition of excipients and the lack of sufficient sensitivity of Carr's indices to predict the changes caused by excipients in these complex compositions (41).

Flowability is known to be largely dependent on interparticulate interactions, which is closely related to particle size of powder bed. Jin et al. further investigated particle size of these five extracts (40). However, the particle size data did not support the flowability data. Considering that particle size is just one important factor affecting particle–particle interactions, the authors decided to measure the change of particle size with feeding pressure to better reflect particle-particle interaction. Because the botanical extract powder is sticky, a feeding pressure is needed to separate the aggregate into primary particles during particle size analysis. When the feeding pressure is large enough to achieve apparently complete separation, the measured particle size will be constant and

independent of feeding pressure within a certain range. Thus, feeding pressure can be an indirect indicator of the magnitude of particle–particle interactions. It was found that the order of feeding pressure needed to get complete particle separation correlated well with the minimum orifice diameter results.

The hygroscopic nature of feverfew extracts varied greatly with source (40). Among these five extracts, two extracts from the same manufacture (A1 and A2) were moderately hygroscopic, while the other three extracts (B1, C1, and D1) were very hygroscopic. More seriously, these three extracts began to deliquesce under relative humidity as low as 43%. The high hygroscopicity of B1 and C1 could be partly attributed the addition of hygroscopic excipients. However, the hygroscopicity differences between the two extracts without excipients indicated that the material source and extraction procedure may also cause a significant difference in hygroscopicity (40).

Heckel analysis indicated that the feverfew extracts may deform plastically (40). However, the order of mean yield pressures did not correlate well with compactibility. For example, B1 has a much higher mean yield pressure than A1 or A2, which means lower plasticity and then implied poorer compactibility. However, B1 exhibited the best radial tension strength/compression pressure profile. This may be explained in part by the smaller particle size of B1, which implies more initial surface area per unit weight. The surface characteristics of the material itself may be another key determinant for interparticulate bonding. Considering the chemical complexity of botanicals, the different modes of extraction and the different excipients that may be used to prepare the dry extracts, it is not that easy to predict the compactibility of botanical extracts.

In summary, these research results on the physical properties of feverfew powdered extracts indicated that the physical characteristics of the botanical extract can be significantly affected by multiple factors, such as the crude material, the method of extraction and any further processing, and the nature of any excipients added.

Parthenolide Stability in Feverfew

It has been widely reported that commercial feverfew products exhibit a broad range of parthenolide levels and many products can't meet their label claims or the minimum levels required by USP, 0.2% (40,42,43). At least in part, the poor quality of feverfew products may be attributable to the source and processing of feverfew raw material. Feverfew grown in the United Kingdom and Germany is well known to have high parthenolide content, while plants from the United States, Mexico, and Serbia appear to be nearly devoid of parthenolide (44). The leaves, flowers, and seeds contain higher parthenolide levels than the stalks and roots. Harvesting the plants in spring yields a much higher concentration of parthenolide than harvesting in the fall (45). Plant processing can also affect the parthenolide content in feverfew. Commercial producers normally dry Feverfew before delivering it to the formulation processors. According to Rushing et al. drying temperature significantly influenced the amount of parthenolide recovered from dried tissues. There was an almost linear decrease in the parthenolide content in leaf tissue from 0.429% at 40˚C to 0.304% at 90˚C (46).

However, the influence of source and processing cannot completely explain the low parthenolide content in feverfew, particularly, in the case of extracts which have ostensibly been standardized to a fixed level. It was reported that various commercial extracts revealed large differences between actual parthenolide content and their label claims. Even different batches from the same manufacture showed significantly different parthenolide content (40). Clearly, a standardization statement does not guarantee the

parthenolide content in the products. In this case, the instability of parthenolide may be a cause for poor parthenolide content.

The degradation of parthenolide in feverfew extract solution appears to fit a typical first-order reaction and the reaction rate was dramatically affected by the pH of Feverfew solution (47). Parthenolide is comparatively stable when the solution pH is in the range of 5–7, becoming unstable when the solution became more acidic and alkaline. Given the existence of an ester group in parthenolide, this V shape of pH-stability profile indicated that hydrolysis may be the predominant degradation pathway of parthenolide in feverfew solution (47).

Temperature and RH were both shown to be able to accelerate the degradation of parthenolide in feverfew extract powder (47). However, different from kinetics in solution, parthenolide degradation in feverfew extract powder does not fit any obvious reaction model. Multiple reaction pathways expected in complex botanicals may be the most important reason to cause this difference. In the solution state, the reactant molecules have more flexibility to interact with each other and the reaction will follow one or more pathways being favored energetically, which means hydrolysis in this case, especially when acid or base catalysts are present. However, in the feverfew extract powder, because of the low concentration of parthenolide and its movement restriction, the decomposition pathway of the parthenolide molecule may be more dependent on the chemistry of the surrounding molecules, making multiple pathways highly possible (47).

Suppliers of commercial feverfew extracts often claim at least a 2-year shelf life or retest period under room temperature storage. However, research by Jin et al. showed that if the feverfew extract powder was stored at room temperature, even with low humidity (31%), significant degradation of parthenolide would occur in 6 months (47). This observation raises concern if the manufacturers have enough long-term stability data to set a reasonable shelf life and storage conditions for their products. This research also indicated that if stored under 5°C/31%RH, feverfew extract powder can maintain a stable parthenolide content for at least six months, which suggests the possibility that adequate stability could be attained under suitable storage conditions. In addition, the multiple degradation pathway and unpredictability of degradation behavior of parthenolide in feverfew extract powder indicated that its shelf life should be proposed on the basis of a stability study carried out over the entire proposed shelf life. Because chemical complexity is very common in botanicals, this rule may be applicable for most of botanicals (47).

Pharmaceutical Quality and Dissolution Performance of Commercial Feverfew Products

In the United States, feverfew products are introduced into the market as dietary supplements. However, a monograph for feverfew finished products is not available in USP; thus, there is neither an official dissolution test nor a daily dose specification. However, the feverfew monograph in Canada suggests a daily dose of 50–250 mg feverfew dried leaf containing at least 0.2% parthenolide and not exceeding the equivalent of 4 mg parthenolide per day (48).

Feverfew products are present in the current market mainly as capsules. Five brands of feverfew capsules were selected and compared in terms of weight uniformity, compliance with the label strength and dissolution performance in one paper (49). It was found that the products from different manufacturers have different formulations. feverfew powdered crude parts, excipients or other botanical extracts may or may not be included. Some feverfew manufacturers suggest a daily dose in their product label claims, which exceeds the maximum daily dose recommended by the Canadian Feverfew

monograph. The actual parthenolide content of all five products investigated cannot meet their label claims. One product contained no parthenolide at all and thus had to be excluded from further dissolution study (47).

Based on the dissolution profiles of the other four products, dissolution seems not to be a big problem for these commercial products because all exhibited more than 85% dissolution in 1 hour (49). However, one interesting finding in their dissolution profiles is a marked release lag-time for some products. In the first 10 minutes, one product can release more than 80% parthenolide, but the parthenolid release of the two other products cannot be detected at all during that time (49). This dissolution lag may be partly explained by disintegration time differences. The order of disintegration did match the order of release rate. However, the biggest disintegration difference among these products is less than 4 minutes, which apparently cannot completely explain the 10 minutes release lag (49).

Further study was performed to check the formulation of these products (49). It was found that the two products with faster release contain only feverfew extract and/or feverfew powder, while the other two products with release lag included excipient and one even contained vitamins and another botanical extract. Thus, the interaction between parthenolide and other components in the formulation may contribute to a slow down in parthenolide release. In addition, different manufacturers may get their feverfew extract powder from difference sources. The nature of the extract itself could play a very important role affecting parthenolide release. Smith and Burford (50) proposed that parthenolide was present at different sites in the feverfew plant matrix. Some are “free” parthenolide on the surface which are readily dissolved, but in other sites, the parthenolide may be more tightly bound (50). Apparently this free/bound parthenolide ratio, in addition to extract chemical composition and particle size can greatly affect the release rate of parthenolide from extract powder and finished products.

A release lag has been observed to occur with other botanical products (29). Such a release lag may pose a challenge to some guidelines. EMEA proposed that if active components of standardized extracts are known to be highly soluble throughout the physiological pH range, a disintegration test may substitute for the dissolution test so long as they are formulated as immediate-release products. The previously cited research (49) showed that the 4-mg parthenolide in feverfew, the maximum daily dose defined by the Canadian Feverfew monograph, can be dissolved in <50 mL buffer medium, which indicates that parthenolid in feverfew can be categorized as highly soluble. Thus, as proposed by EMEA, the disintegration test may substitute for the dissolution test. However, the finding of a release lag indicates that this substitution needs to be considered case-by-case. The chemical complexity of botanicals may decrease the correlation between disintegration and dissolution. Formulation and manufacturing variables may also adversely affect release characteristics. However, if the relationship between disintegration and dissolution has already been established for a given product, the substitution may be feasible and dissolution testing may be used just as a periodic test (49).

SAINT JOHN’S WORT (SJW) CASE STUDY

Hypericum perforatum is one of the more popular dietary supplements. It is commonly known as Saint John’s wort (SJW), and is indicated in the treatment of mild to moderate depression. A typical dose is 300 mg standardized to 0.3% hypericins, taken three times daily.

Similar to most botanicals, SJW has a complex phytochemical profile with pharmacologic activity attributed to several phytochemicals. SJW’s phytochemical profile

consists of several groups of phytochemicals including the phenolic acids (chlorogenic acid) (1), flavonoids (rutin, hyperoside, isoquercitrin, quercitrin, quercetin) (2–6), napthodianthrones (hypericin, pseudohypericin) (7,8), and the phloroglucinols (hyperforin, adhyperforin) (9–10) (51). Some researchers have noted that the flavonoids (2–6) may have some antidepressant activity (52–54), and antioxidant activity (55). The antioxidant activity may increase overall extract efficacy by preventing oxidative degradation of other phytochemicals within the SJW matrix. Hypericin and pseudohypericin are napthodianthrones and are commonly used as marker compounds for SJW standardization. These compounds were once thought to impart SJW's antidepressant activity (56), but actually demonstrate anti-viral activity (57). The main contributors to SJW activity are the phloroglucinols. Hyperforin has demonstrated a possible dose related re-uptake inhibition of the neurotransmitters serotonin, norepinephrine, and dopamine (58–60). It is likely that the overall activity of SJW extract cannot be attributed solely to hyperforin content. There may be other constituents with antidepressant activity and/or hyperforin's activity is modulated by other phytochemicals (60).

A report of the physicochemical characterization of several commercial extract sources determined that overall, the commercial SJW extracts tested were moderate to free-flowing, yet very hygroscopic in nature (31). Low-force compression and compaction studies, similar to what would be encountered in the formation of plugs for automatic capsule fillers, revealed that extracts from various sources exhibited ordered differences in their compression and compaction properties with compression properties significantly different from the general use excipient, MCC (31). Within the complex phytochemical profile, the nine aforementioned phytochemicals of interest were analyzed in both neat and formulated SJW extract. Interestingly, there were significant differences in the contents of constituents related either directly or indirectly to the antidepressant activity of SJW; however, the content of the marker compound (hypericin) was similar (31), indicating that standardization to one or two marker compounds is not sufficient to guarantee the same product and potentially, the same potency. Raw material quality control, quality of the formulated product, clinical trial outcomes, and stability testing could be greatly impacted by standardization to a few marker compounds.

A stability study was performed on the extracts. A significant reduction in most compounds of interest was noted within two weeks when humidity was increased from 50% to 70%. As expected, under conditions of decreased temperature and humidity (5˚C/0% RH), the stability was much better; however, by 12 weeks, all nine phytochemicals of interest significantly degraded (31). A key challenge to the formulator could be ensuring product stability over a reasonable shelf life and under normal conditions.

The report concluded that storage of the neat extract should be a key concern of manufacturers. The neat extract should be placed in the lowest temperature storage facility available and care should be taken to avoid not only oxygen and light but humidity as well. In addition, all stages of extract processing from chemical extraction of the crude material to processing to prepare powdered commercial extract could potentially impact the physical and chemical characteristics of the final product (31).

The influence of extract processing is also a key concern. A study was performed determining the influence of compression force on the phytochemical profile of SJW was performed. Capsules and tablets of formulated SJW extract were prepared on a Zanasi LZ-64 (Zanasi, s.t.j. Modena, Italy) and Colton 321, respectively, examining both low- and high-compression forces. The phytochemical profiles of compressed and noncompressed material were compared (61). There was no statistically significant difference in the percentage of each phytochemical remaining for compressed versus noncompressed material at encapsulation forces of 60 and 120 N. The phytochemical

profiles were compared utilizing similarity metrics in a method described later in this chapter, and there was no difference in the profiles. A much greater effect is realized when the formulated SJW was compressed at the higher compressive forces necessary for tableting (3.81, 7.62, 11.4 kN). A small, but statistically insignificant ($p > 0.05$) decrease was noted for most phytochemicals with increased compression force; however, the isoquercitrin and hyperforin contents were significantly reduced with increased force ($p = 0.0365$ and 5.91E-6, respectively). The napthodianthrones, pseudohypericin, and hypericin, did not exhibit clear trends. Comparison of the overall phytochemical profiles via similarity metrics indicated that the profile as a whole was not adversely influenced by the higher compressive forces. Neat SJW extract exhibited a decrease in all phytochemicals of interest; however, only hyperforin, isoquercitrin, and quercetin had statistically significant reductions in their content with increased compression forces. The study concluded that low force compression forces, such as those experienced during encapsulation, do not adversely influence the phytochemical profile. The content of individual key components was reduced under the higher compressive forces of tableting on a single station press, indicating possible thermal or chemical degradation. The formulation did not appear to protect the phytochemical profile. It is important to note that the forces generated in this study are representative of small scale equipment. Compression forces on high speed tableting equipment are significantly greater than the single station press utilized in this study. More pronounced effects could be found on production equipment. Overall, compression forces clearly influenced individual phytochemicals (61).

Obviously, a key challenge in formulation development of SJW is imparted by its unique physicochemical properties, in particular, it's complex phytochemical profile. Since the activity of botanicals is often attributed to several compounds, stabilization of the phytochemical profile may be a key objective of the formulator. Therefore, during preformulation excipient compatibility studies, it is important to determine the influence of excipients on several phytochemicals of interest and not merely one or two marker compounds. Further compounding the challenge is the instability of many of these compounds in SJW to heat, light, oxygen, alkaline pH, and elevated humidity (31,35,57,62–64). The complex phytochemical profile of SJW presents a unique challenge to establishing product stability and excipient compatibility. Although not excipient compatibility studies per se, some researchers have evaluated the effect of different excipients on the individual phytochemical yields of botanicals other than SJW after spray drying with variable results (65–67).

The typical isothermal stress testing approach to drug–excipient compatibility evaluation usually involves challenging realistic ratios of a drug:excipient mixtures with moisture, since the majority of drug degradation reactions involve moisture. Blends may be binary, tertiary, or higher, and the moisture content is controlled by adding water or altering environmental humidity. Some researchers have proposed that under conditions of high humidity, the drug–excipient interaction is dependent upon the free moisture present and relative hygroscopicities (68). Presumably, the drug degradation could vary depending on the hygroscopicity of the excipients (68,69) The researchers propose that a constant amount of water be added to facilitate interactions between the excipient and drug, and to surround undissolved particles with an aqueous layer saturated with drug, excipient, and any impurities present, in addition to microenvironmental pH. Recommended percentages of additional water range from 5% to 20% (68–70). Control samples are typically blends of drug and excipient stored refrigerated without added water. The drug–excipient samples may be stored at 50˚C with 20% added water (aw) for 3 weeks and protected from light if necessary. The data are reported as percentage

drug remaining relative to the control samples. This approach must be modified for botanical extracts due to their complex phytochemical profiles and potential instability towards heat, light, moisture, pH, etc. A key challenge is that optimum sample storage conditions must be rigorous enough to promote an interaction, yet not destroy the samples. Further, to discern the effects due to storage versus the effects due to phytochemical–excipient interaction, a significantly more complex system of controls is necessary.

In one report, researchers utilized similarity metrics to adequately and concisely account for the influence of the nine aforementioned phytochemicals in SJW (37). Similarity metrics are most often used to aid determination of bioequivalence by comparison of pH profiles and dissolution profiles. The entire shapes of the two profiles are directly compared utilizing all data points at the same time points. The direct curve comparison results in a single evaluation (71,72).

Adapting that method is accomplished by substituting the %w/w of each of the nine phytochemicals of interest (e.g., SJW stored under one condition compared to SJW stored as controls) for the concentration or percent dissolved at each time point, as would be commonly performed with similarity metrics. The entire phytochemical profiles of extracts may be compared and their similarity or dissimilarity discernable by a single value (37). An example is the comparison of excipient:SJW blend to neat SJW that have been stored under the same conditions. The samples are assayed and the percentage remaining of each phytochemical in the blend is compared to the percentage remaining of the corresponding phytochemical in the SJW neat. In terms of the classic f_2 equation (see below), $n = 9$ for the nine phytochemicals of interests, with test (T) representing SJW: excipient blends, and reference (R) indicative of SJW neat. Contributions of each phytochemical of interest are represented and the similarity of the phytochemical profiles of the neat extract and the blend may be discerned (37).

Moore and Flanner introduced the f_2 test [Equation (1)], which is commonly used in the SUPAC IR guidance to assess the impact of various formulation and manufacturing changes on drug dissolution (72). In the context here of comparing phytochemical profiles, f_2 is

$$f_2 = 50\log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100\right\} \tag{1}$$

where f_2 is the similarity factor, R_t and T_t are the percentages of the phytochemical of interest remaining ($t =$ phytochemicals 1–9) for reference and test materials, respectively. When $f_2 = 50$–100, the two profiles are considered to be similar, as this range indicates an average point-to-point difference of 10% or less.

Polli and McLean introduced the use of ratio metrics (ρ) for comparison of two plasma profiles (71), where entire profiles are compared and all plasma profile data are utilized (71). In contrast to the f_2 equation, various equations may be utilized to weight the data towards points of greater importance. Again in the context of comparing phytochemical profiles in SJW, the equations are as follows:

$$\rho = \frac{\sum_{t=1}^{n}(R_t + T_t) \times \mathrm{RATIO}_t}{\sum_{t=1}^{n}(R_t + T_t)} \tag{2}$$

(similar when $\rho < 1.1$)

$$\rho^u = \frac{1}{n}\sum_{t=1}^{n} \text{RATIO}_t \tag{3}$$

(similar when $\rho^u < 1.1$)

$$\rho_h^u = \frac{1}{n}\sum_{t=1}^{n} \text{RATIO}_t + \%\ \text{Hyperforin}(4)$$

(similar when $\rho_h^u < 1.1$)

where ρ is the comparison metric, with all n pairs of points are included by using the ratios of percentage remaining of test (T) and reference (R) of phytochemical t, where the larger of T/R or R/T is employed (RATIO_t) (37). In Equation (2), ρ is weighted towards higher concentrations by the sum of the test and reference concentrations (37). Equation (3) (ρ^u) is the unweighted metric where all time points and pairs of data are given equal importance. Equation (4) ($\rho_{h\cdot}^u$) is weighted towards hyperforin with contributions of this compound counted twice since it is the phytochemical that has shown the most promising antidepressant activity (58). The criteria for similarity in these cases [Equations (2)–(4)] are also a mean point-to-point difference of 10% or less. This study was performed to explore excipient compatibility storage paradigms, determine the extent of interactions between phytochemicals of interest (1–9) in SJW with commonly used excipients from different functional categories and to explore the application of various similarity metrics to the control and excipient:SJW blend phytochemical profiles to aid formulation development (37).

Fillers included dibasic calcium phosphate, MCC, pregelatinized starch, and anhydrous lactose. Lubricants studied were magnesium stearate and hydrogenated vegetable oil. Disintegrants examined were croscarmellose sodium and crospovidone. The stabilizers were ascorbic acid:citric acid (10:1) and malic acid (37). These excipients represent various functional categories are widely used in commercial SJW products and have various physicochemical properties.

The protocols were loosely modeled on the aforementioned protocol that was proposed by Serajuddin et al. (68). Based on a 300 mg SJW extract product with 400 mg fill weight, binary blends in realistic ratios of excipient to drug were prepared. The blends contained SJW (75% for 300 mg) and lubricants (0.5% for 2 mg), disintegrants (6% for 24 mg), fillers (17.5% for 70 mg), and stabilizers (1% for 4 mg). Blend samples were contained in inert glass vials and protected from light. A range of 5–20% aw has been reported in excipient compatibility studies (70,73,74). Since many of the phytochemicals in SJW are moisture sensitive (63), 5% water was added to some of the samples to facilitate phytochemical–excipient interactions (37). Samples were briefly blended utilizing a vortex blender (37). Binary blends of SJW and excipient and SJW neat were stored at 5°C/0% aw as controls; 5°C/5% aw; 50°C/0% aw; and 50°C/5% aw. Samples were analyzed on day 0 and day 21; appearance was noted weekly. The percentage of each phytochemical remaining relative to control samples was reported with similarity metrics (f_2, ρ, ρ^u, ρ_h^u) applied to the data to compare the phytochemical profiles of SJW neat to SJW:excipient blends to differentiate true interactions due to excipients from degradation of phytochemicals within SJW extract itself (37).

Storage

Several storage conditions were examined to determine the true effects of heat and moisture on the excipient:SJW blends, as well as SJW neat. The process is complex due

to the number of phytochemicals of interest. When the influence of storage conditions of one phytochemical (e.g., hyperforin-9) and one excipient class (e.g., fillers) was examined, the percentage remaining of hyperforin in SJW neat was almost equivalent to blends stored at 5˚C/0%aw. When the moisture was increased to 5%aw, hyperforin was degraded in both SJW neat and filler:SJW blends. Increasing temperature from 5˚C to 50˚C had a greater negative impact. Aside from MCC:SJW blends, filler:SJW blends retained a greater percentage of hyperforin compared to SJW neat, indicating that the degradation is likely due to storage conditions versus the fillers. When both temperature and moisture are increased, the excipient and SJW interactions and subsequent influence on the percentage hyperforin remaining, irrespective of storage conditions may be discerned. For example, it was determined that pregelatinized starch decreases hyperforin by 16.1% compared to dibasic calcium phosphate which decreased hyperforin content by 49.1% relative to SJW alone. The researchers concluded that the conventional excipient compatibility method is appropriate when suitable controls are employed. By challenging the samples to both heat and moisture and comparing results to neat botanical extract stored under the same conditions, appropriate exicipient choices based truly on excipient compatibility may be made for heat and moisture sensitive botanicals.

Excipient Compatibility

Fillers

At 50˚C/5% aw, the phytochemical profile exhibited a larger negative impact upon storage with lactose and dibasic calcium phosphate compared to storage with MCC or pregelatinized starch. These differences were primarily attributed to hygroscopicity and pH differences of the fillers. The slightly acidic nature of MCC and pregelatinized (corn) starch (75) may have contributed to the greater survival of the phytohemical profile. In addition, it may be possible that the hygroscopicity of these fillers may have *enhanced* stability. Researchers have reported on the stabilizing effect of cellulose derivatives on pyridoxal hydrochloride (76), theorizing that the free hydroxyl groups in the amorphous regions of the cellulose strongly bind excess water, resulting in reduced water activity and hence, degradation. Dibasic calcium phosphate is nonhygroscopic, typically a desirable property for formulation with actives that are moisture sensitive; however, it is slightly alkaline (75). The alkaline nature may contribute to severe degradation of many of the phytochemicals (64).

Disintegrants

Croscarmellose sodium is slightly acidic (75); however, excluding the napthodianthrones (7,8), most phytochemicals were severely degraded when stored with this disintegrant. Except for the napthodianthrones, a much greater percentage of each phytochemical was retained when stored with crospovidone. It was noted that a possible protective effect was observed with a much higher percentage of each constituent than SJW neat. Crospovidone is only slightly acidic and is generally regarded as inert and insoluble (77). The stabilizing effect of crospovidone on the dissolution stability of hydrochlorothiazide has been reported previously by Desai et al. These researchers attributed the prevention of deleterious interactions from occurring to the moisture scavenging properties of crospovidone (77).

Lubricants

The slightly alkaline magnesium stearate may have exerted a protective effect on the phytochemicals compared to hydrogenated vegetable oil, which tends to be inert. This

positive effect has been noted with a drug substance as well (76). The laminar nature of magnesium stearate (78) also may have provided a greater barrier to moisture relative to the hydrogenated vegetable oil by more effectively coating the host particles (SJW extract) with a protective hydrophobic film.

Stabilizers

The acidifying and antioxidant properties of ascorbic acid:citric acid (10:1) and malic acid did not stabilize the phytochemicals. A similar response was reported for ascorbic acid:citric acid in combination with formulated SJW capsules by Bilia et al. (15). Challenging conditions, such as formulation with alkaline excipients or subopitimal storage (e.g., where oxidation is likely) may reveal the true value of the stabilizers. Further, greater concentrations may be necessary. More research in the use of chemical stabilizers for botanical formulation development is warranted.

Similarity Metrics

The application of similarity metrics to excipient:SJW binary blends and SJW neat stored at 50˚C/5% aw was a convenient method to summarize the complex data into a single evaluation. The metrics compared both phytochemical profiles which consisted of the mean percentage remaining for each phytochemical. The four metrics (f_2, ρ, ρ_u, ρ_h^u) indicated that SJW and hydrogenated vegetable oil, magnesium stearate, or croscarmellose sodium binary blends retained a similar percentage of components 1–9 (had similar phytochemical profiles) as SJW neat stored under the same conditions. In addition, the f_2 test also indicated that blends of MCC:SJW and pregelatinized starch:SJW had similar profiles to SJW neat.

Although the metrics allowed the direct comparison of the phytochemical curves, a notable disadvantage is the inability of the metrics to indicate the direction of the difference. That is, whether the percent remaining for the blends was greater than or less than that of SJW neat stored under similar conditions. An example is the f_2 value of 30.45 obtained when the phytochemical profiles of SJW neat and crospovidone:SJW blend are compared. An $f_2 < 50$ is indicative of a profile difference. The other metrics evaluated (ρ, ρ_u, ρ_h^u) also indicated that the profiles were different. As previously mentioned, this difference was actually due to the stabilizing effect of the crospovidone and the excipient should not be rejected. This example highlights the importance of understanding why the profiles are different and correctly interpreting the data.

Visual Analysis

The samples became resinous in appearance upon storage at 50˚C/5% aw. No color change was observed; however, most extracts are dark brown in color and color change could be difficult to discern. Overall, visual inspection did not provide significant insight into chemical degradation that may have occurred.

SUMMARY

Overall, the systemic research described in these two case studies demonstrates that good science and quality control methods commonly used to develop and produce quality pharmaceutical solid dosage forms can also be used to build quality into botanical dietary supplements formulated as solid dosage forms. The frequent reports of poor quality of

supplements that appear in professional and lay literature make clear that many (but not all) supplement manufacturers fail to employ such methods. Despite relatively lax regulatory policies and their apparently limited enforcement by FDA there can be no excuse for marketing products that, for example, contain highly variable amounts, let alone no detectable amount of key component(s) in dosage units. Manufactures should commit to the use of appropriate scientific methods and proper quality control procedures that ensure that their label claims for content and dose are accurate and realistic. Formulations should also be designed to provide rapid, consistent release characteristics. Stability should be assured through the proposed expiration date based on appropriate study, including the use of appropriate packaging materials and storage conditions specifications as justified by the data. This is what consumers have the right to expect and are entitled to when they purchase supplement products.

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12
Formulation of Specialty Tablets for Slow Oral Dissolution

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INTRODUCTION

Lozenges/Troches

Dosage forms that dissolve slowly in the mouth, or that can be easily chewed and swallowed, are gaining in popularity, especially among pediatric patients. Hard (compressed or molded) preparations of this dosage form are called lozenges, troches, or drops. Soft (molded) lozenges/troches are often called pastilles, and chewable, gelatin-based lozenges/troches are often called gummy, novelty-shaped products. The term lozenge will be used in this chapter to refer to all variations of the dosage form.

DEFINITIONS/TYPES

Lozenges are solid preparations that are intended to dissolve or disintegrate slowly in the mouth. They contain one or more medicaments, usually in a flavored, sweetened base. They can be prepared by molding (gelatin and/or fused sucrose or sorbitol base) or by compression of sugar-based tablets. Molded lozenges are sometimes referred to as pastilles while compressed lozenges are often referred to as troches. They are usually intended for treatment of local irritation or infections of the mouth or throat but may contain active ingredients intended for systemic absorption after swallowing (1). Molded lozenges have a softer texture because they contain a high percentage of sugar or a combination of a gelatin and sugar.

Hard lozenges have hard candy bases made of sugar and syrup and often incorporate an adhesive substance such as acacia. Commercial lozenges are made on a tableting machine using high-compression pressures. Ingredients should be heat stable if they are to be incorporated into compounded lozenges.

Recently, soft lozenges and chewable lozenges have been reintroduced into pharmacy and are enjoying increased popularity. Soft lozenges generally have a polyethylene glycol (PEG) base, whereas chewable lozenges have a glycerinated gelatin base. These dosage forms usually are chewed and are a means of delivering the product to the gastrointestinal tract for systemic absorption.

HISTORICAL USE

Lozenges have long been used to deliver topical anesthetics and antibacterials for the relief of minor sore throat pain and irritation. Today, they are used for analgesics, anesthetics, antimicrobials, antiseptics, antitussives, aromatics, astringents, corticosteroids, decongestants, demulcents, and other classes, and combinations of drugs.

In the 3rd edition of *The Pharmaceutical Recipe Book* (American Pharmaceutical Association, 1943), the following list of troche formulas was included (2); they were all sucrose-based with either tragacanth or acacia added; Ammonium Chloride Troches, Charcoal Troches, Cubeb Troches, Gambir Troches, Menthol Troches, Peppermint Troches, Phenolpthalein Troches, Potassium Chlorate Troches, Quinine Tannate Troches, Santonin Troches, Compound Santonin Troches, Sulfur and Potassium Bitartrate Troches, and Tannic Acid Troches.

Soft lozenges are similar to a historical form of medication that is now making a comeback—the "confection." Confections are defined as heavily saccharinated, soft masses containing medicinal agents. Their growing popularity is largely due to the use of polymers, such as the PEGs as the matrix for the dosage form (Figs. 1–3). Confections are easy to use, convenient to carry, easy to store (i.e., at room temperature), and generally pleasant tasting. PEG-based lozenges have a tendency to be hygroscopic and may soften if exposed to high temperatures. Consequently, storage in a cool, dry place is recommended for these lozenges.

Today, a popular lozenge for pediatric use is the chewable lozenge, or "gummy-type" candy product (Fig. 4). The gelatin base for these chewable lozenges is similar to

FIGURE 1 Different shapes of chewable lozenges of the PEG type. *Abbreviation*: PEG, polyethylene glycol.

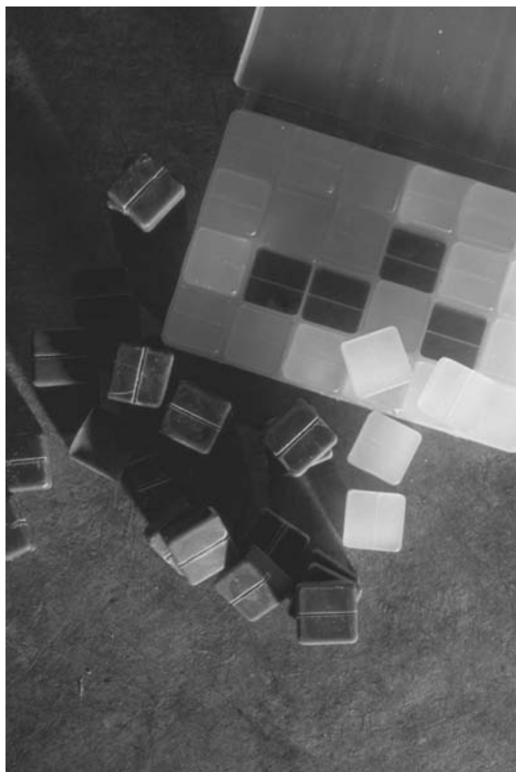

FIGURE 2 Different types of chewable lozenges that can be halved if necessary.

the historical glycerin suppositories, or glycerinated gelatin suppositories that consisted of 70% glycerin, 20% gelatin, and 10% purified water. Some of the earlier soft lozenges consisted of a gelatin or a glycerogelatin base. These lozenges were prepared by pouring the melt either into molds or out on a sheet of uniform thickness.

FIGURE 3 Chocolate-flavored soft chewable lozenges.

FIGURE 4 Gummy-type chewable lozenges. These can be made using different molds for different types of patients, both pediatric and geriatric.

The dosage forms were then punched out using various-shaped punches. The last step often included dusting of the product with cornstarch or powdered sugar to decrease tackiness.

APPLICATIONS

Lozenges are experiencing renewed popularity as a means of delivering different drug products, especially for patients who cannot swallow solid oral dosage forms. Lozenges are also used for medications designed for slow release. This dosage form maintains a constant level of the drug in the oral cavity or bathes the throat tissues in a solution of the drug. Medicated lozenges are usually intended for local treatment of infections of the mouth or throat; however, they may contain active medications that produce a systemic effect.

The lozenge dosage form has a number of advantages. It is easy to administer to both pediatric patients and patients of advanced age, it has a pleasant taste, and it extends the time that a quantity of drug remains in the oral cavity to elicit a therapeutic effect. Also, pharmacists can prepare lozenges extemporaneously with minimal equipment and time.

The lozenge can also be adapted to form a lollipop using a mold that allows the insertion of a stick. These lollipops can then be held in the mouth and removed as desired (Fig. 5).

In a Swedish study on how 3- to 5-years-old children handle a lozenge, it was observed that 62% of the children could keep parts of the lozenge in the mouth for at least 10 minutes. This provided support for further study on the use of the lozenge for topical oral delivery of fluoride for preventing caries (3).

FIGURE 5 Example lollipops of different formulations, including colors and flavors.

One disadvantage of the lozenge is that children can mistake it for candy. Parents should be cautioned not to refer to medications as candy and to keep the product out of the reach of children.

CONTEMPORARY STUDIES ON LOZENGES/TROCHES

There are many reported contemporary research studies on the troche or lozenge dosage form, especially in the area of their use as an anesthetic, anticariogenic, antimicrobial, and other effects for topical administration and for their ability to deliver hormones, cough suppressants, and other drugs systemically.

ANESTHETIC FOR SORE THROAT

Ambroxol

Sucking lozenges containing 20 or 30 mg ambroxol hydrochloride has a beneficial pain-relieving effect in patients with acute sore throat as it has local anesthetic properties (4,5).

ANTI-INFLAMMATORY FOR SORE THROAT

Flurbiprofen

Flurbiprofen lozenges have been found to be quite effective for treatment of sore throat at a dose between 5.0 and 12.5 mg (6–8).

ANTIMICROBIAL

Antimicrobial lozenges were removed from the pharmaceutical market by the Food and Drug Administration about 40–50 years ago but are now making their way back as subjects of additional research and approved drug applications, including various drugs and combinations as bacitracin, clotrimazole, and gentamicin (BCoG) (9), amphotericin B (10,11), clotrimazole (12–14), gramicidin/tyrothricin (15,16), nystatin (17), and others (18).

Mucositis occurs in the majority of radiotherapy-treated head and neck cancer patients, those receiving hematopoietic marrow transplantation and in about 40% of all patients receiving chemotherapy. BCoG lozenges (containing bacitracin, clotrimazole, and gentamicin) administered four times daily was found to be tolerable and microbiologically effective, achieving elimination of Candida in all patients and a reduction in gram-negative flora in most patients (9).

CARIES PREVENTION

Xylitol

Xylitol delivered by gum or lozenge appears to be effective clinically in reducing cariogenic bacteria and caries levels (19). The use of a xylitol lozenge after sucrose can be an advisable practice for fixed orthodontic patients to prevent future dental caries (20).

Fluoride

Many fluoride supplements sold in Norway are lozenge-type tablets, which allow for extended enamel exposure to fluoride (21,22).

COMMON COLD-ZINC

Zinc Lozenges

Zinc lozenges have been found in studies to support the value of zinc in reducing the duration and severity of symptoms of the common cold when administered within 24 hours of the onset of common cold symptoms (23). The use of zinc has been shown, in a number of studies, to reduce cold duration and antibiotic use. Its limitations include its bad taste and possible side effects (24–29).

COUGH SUPPRESSANTS

Noscapine

Lozenges and chewing gum were evaluated as delivery systems for noscapine with the aim of developing improved antitussive preparations. The formulations containing noscapine base were without any appreciable base and fulfilled the requirement of taste acceptability and adequate release properties (30).

DIURETICS

Hydrochlorothiazide bioavailability was studied from a molded isomalt-based tablet administered orally and as a lozenge. The relative bioavailability of the dosage form

administered as a lozenge was 106.2% and as a swallow tablet was 89.4%. Direct molding of isomalt tablets may be a suitable technique to administer a poorly soluble drug either as a conventional tablet or as a lozenge (31).

HORMONES

Testosterone

In a study of 10 bilaterally oophorectomized women on the pharmacokinetics of testosterone following administration using transdermal gel or buccal lozenges, it was found that buccal absorption following administration of the lozenge produced a rapid and brief elevation of testosterone levels, with levels reaching upper limits of the male range. In contrast, topical gel absorption resulted in a prolonged elevation of testosterone levels, which were in the hyperandrogenic female range but resembled steady state pharmacokinetics (32).

Estradiol, Progesterone, Testosterone, and Dehydroepiandrosterone

The pharmacokinetic profiles of estradiol, progesterone, testosterone, and dehydroepiandrosterone in postmenopausal women following single and multiple dosing using a troche and the transbuccal route of administration was studied. Their results showed the transbuccal route is a novel approach to providing therapy for the management of menopause-related symptoms of postmenopausal women without the poor and often erratic systemic availability associated with other routes of administration (33).

ORAL MALODOR

A study on the use of anti-malodor properties of oxidizing lozenges, as compared to breath mints and chewing gum, was undertaken. This study involved two brands of breath mints, chewing gum with no active ingredients, regular and full-strength oxidizing lozenges and a no-treatment control. Only the full-strength oxidizing lozenge significantly reduced the tongue dorsum malodor and yielded a significant increase in the modified oral rinse test, presumably due, at least in part, to residual oxidizing activity retained in the oral cavity (34).

PAIN MANAGEMENT

Fentanyl

Oral Transmucosal Fentanyl Citrate (OTFC; Actiq, Cephalon, UT) is well tolerated and mucosal absorption avoids first-pass metabolism, yielding a bioavailability greater than that of oral administration (35–38).

SMOKING LOZENGES

Nicotine

Medicinal nicotine should be preferentially encouraged for smokers or smokeless tobacco users wishing to switch to lower-risk products (39,40). The use of the 4 mg nicotine

lozenge appears promising for the clinical treatment of withdrawal symptoms and craving associated with tobacco abstinence in smokeless tobacco users (41,42).

Silver Acetate

Silver acetate has been studied for a number of years as an aid in smoking cessation programs (43,44).

XEROSTOMIA

Salivary Stimulation Lozenges for Xerostomia

Anhydrous crystalline maltose 200 mg lozenges administered three times daily improved salivary output and decreased complaints of dry mouth and eyes in patients at a total of 33 sites in the study. This safe and simple intervention may provide clinical benefit to individuals with distressing dry mouth symptoms (45).

Chewing gum and lozenges were ranked equal in a study on the effect of chewing gum and lozenges in relieving the signs and symptoms of xerostomia in a 2-week cross-over clinical trial in 18 rheumatic patients with dry mouth symptoms and low salivary flow rates (46).

In a comparison of five saliva stimulation formulas, V6 chewing gum and Salivin lozenges were ranked as the two best products by patients in a 106-patient study of patients with low salivary flow rate and a long history of dry mouth (47).

OTHERS

Human Interferon

Human interferon alpha oral lozenges were studied in patients with hepatitis C(HCV). Patients were instructed to take one lozenge daily, in the morning, on an empty stomach and retain it in the mouth until completely dissolved. The treatment was well tolerated and the patients reported and increase in drive and appetite as well as an improvement in their exercise tolerance (48).

Herbal Lozenge

A randomized double blind, placebo controlled trial of the electrical activity of the human brain was undertaken after exposure to a lozenge containing four different herbal preparations (lavender oil, extracts from hops, lemon balm, and oat). The results of the study suggest that one could expect from the ingestion of the lozenge to better cope with psychological and emotional stress (49).

Virucidal Lozenge

A potent virucidal mixture of amyl metacresol and dichlorobenzyl alcohol at low pH inactivates enveloped respiratory viruses influenza A, respiratory syncytial virus and severe acute respiratory syndrome coronavirus but not viruses with icosahedral symmetry, such as adenoviruses or rhinoviruses. The authors concluded that a throat lozenge containing amyl metacresol and dichlorobenzyl alcohol could have significant effects in reducing the infectivity of certain infectious viruses in the throat and

presumably in cough droplets, thus possibly reducing opportunities for person-to-person transmission (50).

Magnesium Chloride Lozenge

Magnesium chloride (100 mg) throat lozenges producing 100^{+} mM magnesium ion concentration in saliva were tested to determine if they had any beneficial effects in asthma rescue and prevention as compared to inhaled and injected magnesium. The results showed the throat lozenges containing magnesium chloride produced much more rapid and stronger benefits than from the inhalation and injection routes of administration. An additional benefit was relaxation (51).

The long-term effect of capsaicin and short-term effect of menthol lozenges on oral thermal sensory thresholds was studied. The use of 0.52% menthol containing lozenges significantly altered the thermal sensory thresholds in the oral cavity (52).

Radiation-induced xerostomia was effectively treated using pilocarpine 5 mg lozenges in patients with head and neck cancer. This was a double-blinded, placebo-controlled trial. Visual analog scales were used and saliva was sampled and tested initially and after 30, 60, 90, 120, 150, and 180 minutes (53).

Capsaicin Lozenges

Capsaicin troches were studied for swallowing dysfunction in the elderly. The troches were administered prior to every meal for 4 weeks. Measurements included assessment of individual latency time of the swallowing reflex and cough reflex sensitivity. They found that daily capsaicin lozenge supplementation resulted in a significant improvement in upper protective respiratory reflexes, particularly in the elderly with a high risk for aspiration (54).

COMPOSITION

Hard Lozenges

Hard candy lozenges are mixtures of sugar and other carbohydrates in an amorphous (noncrystalline) or glassy condition. These lozenges can be considered solid syrups of sugars and usually have a moisture content of 0.5%–1.5%. Hard lozenges should not disintegrate but instead provide a slow, uniform dissolution or erosion over 5–10 minutes. They should have a smooth surface texture and a pleasant flavor that masks the drug taste. Their primary disadvantage is the high temperature required for preparation. Hard candy lozenges generally weigh between 1.5 and 4.5 g.

Excipients such as sorbitol and sugar have demulcent effects, which relieve the discomfort of abraded tissue caused by coughs and sore throat. A portion of the active drug product may actually be absorbed through the buccal mucosa, thereby escaping the first-pass metabolism that occurs when a drug is swallowed and absorbed through the gastrointestinal tract.

Soft Lozenges

Soft lozenges have become popular because of the ease with which they can be extemporaneously prepared and their applicability to a wide variety of drugs. The bases

usually consist of a mixture of various PEGs, acacia, or similar materials. An alternative and older form of soft lozenges is the pastille, which is a soft lozenge, is usually transparent, and consists of a medication in a gelatin, a glycerogelatin, or an acacia: sucrose base. These lozenges may be colored and flavored, and they can be either slowly dissolved in the mouth or chewed, depending on the intended effect of the incorporated drug.

Chewable Lozenges (Gummy, Novelty-Shaped Products)

Chewable lozenges have been on the market for a number of years. They are highly flavored and frequently have a slightly acidic taste. Because their fruit flavor often masks the taste of the drug, they are an excellent way of administering drug products. These lozenges are relatively easy to prepare extemporaneously. The most difficult part involves preparing the gelatin base. Chewable lozenges are especially useful for pediatric patients and are an effective means of administering medications for gastrointestinal absorption and systemic use.

PREPARATION

Lozenges are prepared by molding a mixture of carbohydrates to form hard candies, by molding a matrix to form a soft lozenge, or by molding a gelatin base into a chewable mass. Each approach is described.

Hard lozenges are usually prepared by heating sugar and other components to a proper temperature and then pouring the mixture into a mold or by pulling the mass out into a ribbon while it cools and then cutting the ribbon to the desired length. A commercial method is to compress the materials into a very hard tablet. Both soft lozenges and chewable lozenges are usually prepared by pouring a melted mass into molds. Another method, which depends on the ingredients, involves pouring the mass out to form a sheet of uniform thickness and then punching out the lozenges by using a punch of the desired shape and size.

Molds used in the preparation of lozenges must be calibrated to determine the weight of the lozenge using the applicable base. The calibration can be done as follows:

1. Prepare the lozenge mold, and confirm that the cavities are clean and dry.
2. Obtain and melt sufficient lozenge base to fill 6–12 molds.
3. Pour the molds, cool, and trim if necessary.
4. Remove the blank lozenges and weigh.
5. Divide the total weight by the number of blank lozenges to obtain the average weight of each lozenge for this particular base. Use this weight as the calibrated value for that specific mold when using that specific lot of lozenge base.

The powders contained in the lozenges may also occupy a specific volume, and an adjustment may be required in the quantity of the base used. These “dosage replacement calculations” are analogous to those used with suppositories.

In general, the quantity of flavoring agent added to medicated lozenges is about 5–10 times that used in candy lozenges to compensate for the flavor of the medication. If the flavoring agent (an oil) is immiscible with the base, it can be dissolved in glycerin; the glycerin solution is then incorporated into the product.

The same technique can also be used to incorporate an oily drug into a lozenge. The solvent technique often uses a ratio of 1 part solvent to 3–5 parts drug.

PHYSICOCHEMICAL CONSIDERATIONS

A binder is used in most lozenges. Binders are substances added to tablet or lozenge formulations to add cohesiveness to powders, providing the necessary bonding that contributes to the maintenance of the integrity of the final dosage form. Binders are usually selected on the basis of previous experience of the formulator, particular product needs, literature or vendor information, and individual preferences. Binders can be added at any of several steps in the process, depending on the specific procedure being used and the speed at which the lozenge should disintegrate.

Dosage forms are removed from the mouth at various rates. Generally, the rate of removal, going from the most rapid to the slowest, is as follows: tablets/capsules, solutions, suspensions, chewable tablets, and lozenges. According to salivary kinetics, there is about 1.07 mL of saliva resident in the mouth before swallowing and about 0.71 mL after swallowing. The baseline flow rate for saliva of about 0.3 mL/min may be increased to about 10.6 mL/min when stimulated. The frequency of swallowing is about 0.6–2.3 times per minute. Based on these calculations, a lozenge can increase the residence time of a drug in the oral cavity.

If flavors and preservatives are included in the product formulation, their characteristics should be considered. For example, the odor of a 0.08% solution of methylparaben has been described as "floral," "gauze pad," or "face powder" sweet. A 0.015% solution of propylparaben has a tongue-numbing effect, producing a slight sting, and minimal aroma. A 0.125% butylparaben solution has the least aroma of all. Preservatives have a tendency to partition into flavors, because they are not always water soluble, and most flavors are oily in nature.

FORMULATION STUDIES

The effectiveness of cetylpyridinium chloride (CPC) lozenges was studied with various excipients. The authors found that the presence of magnesium stearate decreased the availability of CPC in solution due to adsorption of CPC on to the magnesium stearate. They authors concluded that magnesium stearate should comprise not more than 0.3% w/w of the lozenge weight (55).

Another study involved the pH at which cetylpyridinum chloride was most effective in a lozenge dosage form. The investigators concluded that cetylpyridinum chloride should be formulated at a pH greater than 5.5 (56).

A bioadhesive lozenge was studied consisting of an active layer and a bioadhesive layer. The purpose of the dosage form was to prolong the effective levels of cetylpyridinium chloride in the oral cavity. The drug loading, wax content of the active layer and the composition of the bioadhesive layer were important variables affecting the performance of this lozenges (57).

A study on the volatility of menthol and borneol was undertaken to determine the rates of vaporization of the two ingredients. They found that borneol was more volatile than menthol and this information may be utilized to improve the quality of lozenges containing menthol and/or borneol (58).

The type of medication prepared as a lozenge is limited only by flavor, dose restrictions, and/or chemical compatibility. Some materials are so unpalatable or irritating that they are unsuitable for this type of administration. The following are examples of different active ingredients used in lozenges:

1. *Benzocaine*. The usual dose of benzocaine is in the range of 5–10 mg per lozenge. It is extremely reactive with the aldehydic components of candy base and flavor components. As much as 90%–95% of available benzocaine may be lost when added to a candy base, but a PEG base is compatible.
2. *Hexylresorcinol*. The dose of hexylresorcinol is about 2.4 mg per lozenge. It is somewhat susceptible to reaction with aldehydic components. No flavoring or "mouthfeel" problems are associated with this material because of its low dose and lack of appreciable flavor.
3. *Dextromethorphan*. The dose of dextromethorphan hydrobromide is about 7.5 mg per lozenge. It is easy to incorporate into a candy base because of its melting point (122–124°C) and solubility (1.5 g in 1000 mL of purified water). It is compatible with most flavors, and it is stable over a wide pH range. Conversely, it does have a bitter taste, an anesthetic mouth feel, and an unpleasant aftertaste. Masking doses greater than about 2 mg per lozenge requires special considerations.

QUALITY CONTROL

The weight and uniformity of individual lozenges can be easily determined and documented, as well as the appearance, odor, hardness, weight, specific gravity, color, and surface texture. An active drug assay can be done by a contract laboratory as well as a melting and dissolution test.

STORAGE/LABELING

Lozenges (hard, soft, and chewable) should be stored either at room temperature or in a refrigerator, depending on the active drug incorporated and the type of vehicle used. These products should be kept in tight containers to prevent drying. This measure is especially needed for chewable lozenges, which can dry out and become difficult to chew. If a disposable mold with a cardboard sleeve is used, it is best to slip this unit into a properly labeled, sealable plastic bag.

STABILITY

Completed products are dry and, thus, generally provide a stable dosage form, as long as they are protected from moisture and heat. Hard candies are hygroscopic and are usually prone to absorption of atmospheric moisture. Considerations must, therefore, include the hygroscopic nature of the candy base, the storage conditions of the lozenges, the length of time they will be stored, and the potential for drug interactions.

Lozenges should be stored away from heat and out of the reach of children. They should be protected from extremes of humidity. Depending on the storage requirement of both the drug and the base, either room temperature or refrigerated temperature is usually indicated.

Because lozenges are solid dosage forms, preservatives are generally not needed. However, hard candy lozenges are hygroscopic; therefore, their water content may increase, and bacterial growth can occur if they are not packaged properly. Because any water present would dissolve some sucrose, the highly concentrated sucrose solution that results can be bacteriostatic in nature and will not support bacterial growth. The paraben preservatives were discussed earlier.

All hard candy lozenges eventually become grainy, but the speed at which this tendency occurs depends on the ingredients that are used. When the concentration of corn syrup solids is greater than 50%, the graining tendencies decrease, but moisture absorption tendencies can increase. Increased moisture absorption increases product stickiness and causes the medications to interact. Sucrose solids in concentrations greater than 70% tend to increase graining tendencies and the speed of crystallization. Formulations that contain between 55 and 65% sucrose or 35 and 45% corn syrup solids generally offer the best compromise in dealing with problems related to graining, moisture absorption, and preparation time.

Acidulents, such as citric, tartaric, fumaric, and malic acids, can be added to a candy base to strengthen the flavor characteristics of the finished product and to control pH to preserve the stability of the incorporated medication. Regular hard candy has a pH of about 5–6, but it may be as low as 2.5–3 when acidulents are added. Calcium carbonate, sodium bicarbonate, and magnesium trisilicate can be added to increase the lozenge pH to as high as 7.5–8.5.

PATIENT COUNSELING

The patient should be counseled about the purpose of a hard lozenge, which is to provide a slow, continual release of the drug over a prolonged period of time. Hard lozenges should not be chewed. Soft and chewable lozenges are to be taken only as directed and should not be considered candy. They should be kept out of the reach of children.

Because the hard lozenges are designed to provide a slow, uniform release of the medication directly onto the affected mucous membrane, the formulator is faced with the challenge of developing flavor blends that mask any unpleasant taste produced by the medication, while maintaining a smooth surface texture as the lozenge slowly dissolves. If the medication has no significant taste, flavoring will not be a problem. If the medication has a strong, disagreeable taste, however, that taste should be minimized to enhance patient compliance.

If the lozenges to be used are acidic, the patient should be cautioned regarding excessive use. A study was conducted to analyze the erosive effect of acidic lozenges and to compare them with that of orange juice. Two acidic, sugar-free lozenges and orange juice were tested. It was concluded that excessive consumption of acidic lozenges can have the potential to enhance existing dental erosion (59).

SAMPLE FORMULATIONS

Lozenge Vehicles

For the following vehicles, the gelatin is dissolved in a hot mixture of the glycerin/water/sorbitol solution in which the parabens have been previously dissolved. It is advisable to

use a tared vessel to determine water loss during heating, so that an appropriate amount can be replaced. The amount of flavor oil can be determined by trial-and-error taste tests. One can start at about 9% and make adjustments as needed.

Vehicle Ingredients	A	B	C	D	E	F	G
Sodium saccharin (g)	0.1	–	0.1	0.05	0.05	0.05	0.05
Gelatin (g)	20	20	20	30	30	30	20
Glycerin (mL)	70	20	40	30	30	30	40
Sorbitol 70% (mL) Solution	–	50	30	30	25	26	26
Polyethylene Glycol 6000	–	–	–	–	5 g	4 g	4 g
Methylparaben (g)	0.15	0.15	0.15	0.15	0.15	0.15	0.15
Propylparaben (g)	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Flavor oil (mL)	qs	qs	qs	qs	qs	qs	qs
Purified water (mL) qs USP	100	100	100	100	100	100	100

Ingredient-Specific Formulations

Sample formulations are presented to illustrate the differences in the types of lozenges and their applications. These formulas can be adjusted according to the quantity of active drug to be used.

Hard Lozenges

Rx Hard Sugar Lozenges

Powdered sugar	42 g
Light corn syrup	16 mL
Distilled water	24 mL
Active drug, example	1.0 g
Mint extract	1.2 mL
Food coloring, green	qs

1. Calculate the quantity of each ingredient required for the prescription.
2. Accurately weigh or measure each ingredient.
3. Combine the sugar, corn syrup, and water in a beaker and stir until well mixed.
4. Cover the mixture and heat on a hot plate at a high setting until the mixture boils; continue boiling for 2 minutes.
5. Uncover and remove from heat at 61°C. Do not stir the mixture until the temperature drops to 55°C.
6. Quickly add the active drug, mint extract, and food coloring and stir until well mixed.
7. Coat the mold to be used with a vegetable spray.
8. Pour the melt into the molds.
9. Cool, package, and label.

Rx Anti-Gag Lollipops (36 Lollipops)

Sodium chloride	46.56 g
Potassium chloride	3 g
Calcium lactate	6.12 g
Magnesium citrate	2.04 g
Sodium bicarbonate	22.44 g
Sodium phosphate monobasic	3.84 g
Silica gel	3.60 g
PEG 1450	qs

1. Calculate the quantity of each ingredient required for the prescription.
2. Calibrate the lollipop mold for the formula.
3. Accurately weigh each ingredient.
4. Triturate all the powders together to obtain a small, uniform particle size.
5. Melt the PEG 1450 at a temperature in the range of 50–55°C in a suitable beaker or other container.
6. Slowly add the powders with thorough mixing.
7. Cool to approximately 45°C.
8. Pour into a mold that has been previously sprayed with a vegetable-based oil, wiping off the excess.
9. Cool for approximately 90 minutes and remove from the molds.
10. Package and label.

Rx Pediatric Chocolate Troche Base

Chocolate (good quality)	60 g
Vegetable oil (bland)	40 g

1. Calculate the quantity of each ingredient required for the prescription.
2. Weigh or measure each of the ingredients.
3. Heat the vegetable oil by using low heat or a double boiler/water bath.
4. Add the chocolate and stir until melted. Cool.
5. Package and use for compounding.

Rx Sildenafil Citrate 25 mg Sublingual Troches (#24)

Sildenafil citrate	600 mg
Aspartame	500 mg
Silica gel	480 mg
Acacia	360 mg
Flavor	qs

PEG 1450 22 g (will vary depending on mold and size of tablet used as the source of the drug)

1. Calculate the quantity of each ingredient required for the prescription.
2. Accurately weigh each ingredient and obtain the required number of sildenafil citrate tablets (24 of the 25 mg, 12 of the 50 mg, 6 of the 100 mg tablets).
3. In a mortar, triturate the sildenafil citrate tablets to a very fine powder.

4. Add the aspartame, silica gel, and acacia and triturate further to a fine powder.
5. Melt the PEG 1450 to about 55–60°C.
6. Add the powders from step 4 and mix well.
7. Cool a few degrees, add the flavor(s), and pour into troche molds.
8. Allow to solidify.
9. Package and label.

Soft Lozenges

*Rx Steroid Linguets *** mg*

Fattibase/cocoa butter	76 g
Steroid powder	** g
Acacia	3 g
Cinnamon oil	5 gtts
Artificial sweetener	14 gtts

1. Calculate the quantity of each ingredient required for the prescription.
2. Accurately weigh or measure each ingredient.
3. Melt the Fattibase/cocoa butter at about 40°C/35°C.
4. Add the acacia powder followed by the steroid and mix well.
5. Add the artificial sweetener and the cinnamon oil and mix well.
6. Pour into 1 g molds and place in a refrigerator to cool and harden.
7. Package and label. Store in a refrigerator.

Rx Polyethelene Glycol Troches

PEG 1000	10 g
Active drug, example	1 g
Aspartame sweetener	20 packets
Mint extract	1 mL
Food color	2 drops

1. Calculate the quantity of each ingredient required for the prescription.
2. Accurately weigh or measure each ingredient.
3. Melt the PEG 1000 on a hot plate to about 70°C and gradually add the active drug powder and the aspartame sweetener by stirring
4. Add the coloring and flavoring and pour into troche molds.
5. Allow to cool at room temperature.
6. Package and label.

Rx Polyethelene Glycol Troches with Suspending Agent

PEG 1000	34.5 g
Active drug, example	4.8 g
Silica gel	0.37 g
Acacia	0.61 g
Flavor	5 drops

1. Calculate the quantity of each ingredient required for the prescription.
2. Accurately weigh or measure each ingredient.

3. Blend the powders together until uniformly mixed.
4. Heat the PEG 1000 until melted at approximately 70˚C.
5. Add the powder mix to the melted base and blend thoroughly.
6. Cool to less than 55˚C, add the flavor, and mix well.
7. Pour into troche or cough drop molds.
8. Cool, package, and label.

(*Note*: This formulation is based on a mold that weighs approximately 1.8 g. The formula can be adjusted to other mold weights.)

Rx Powdered Sugar Troches

Powdered sugar	10 g
Active drug, example	1 g
Acacia	0.7 g
Purified water	qs

1. Calculate the quantity of each ingredient required for the prescription.
2. Accurately weigh or measure each ingredient.
3. Mix the acacia and purified water together in a mortar to form a mucilage.
4. Sift the powdered sugar and active drug together and gradually add sufficient mucilage to make a mass of the proper consistency.
5. Roll the mass into the shape of a cylinder and cut into 10 even sections (approximately twice the length of the diameter).
6. Allow to air dry, package, and label.

Gelatin Base

Glycerin	155 mL
Gelatin	3.4 g
Purified water	21.6 mL
Methylparaben	0.44 g

1. Calculate the quantity of each ingredient required for the prescription.
2. Accurately weigh or measure each ingredient.
3. Heat a water bath to boiling.
4. In a beaker, add the purified water, glycerin, and methylparaben; stir and heat for 5 minutes.
5. Over a 3-minute period, add the gelatin very slowly while stirring until it is thoroughly dispersed and free of lumps.
6. Continue to heat for 45 minutes.
7. Remove from heat, cool, and refrigerate until used.

Rx Drug Product in Gelatin Base

Gelatin base	43 g
Bentonite	800 mg
Aspartame	900 mg
Acacia powder	720 mg
Citric acid monohydrate	1.08 g
Flavor	14–18 drops
Active ingredient	–

1. Calculate the quantity of each ingredient required for the prescription.
2. Accurately weigh or measure each ingredient.
3. Calibrate the particular mold to be used for this product.
4. Melt the gelatin base using a water bath.
5. Triturate the powders together and add to the gelatin base melt; thoroughly mix until evenly dispersed.
6. Add the desired flavor and mix.
7. Continuously mix and pour the melt into the pediatric chewable lozenge molds and allow to cool. If the mixture congeals while pouring, it may be necessary to reheat and then continue pouring.
8. Package and label.

Rx Morphine 10 mg Troches (#24)

Morphine sulfate	240 mg
Aspartame	250 mg
Flavor	qs
Polybase	24 g

1. Calculate the quantity of each ingredient required for the prescription.
2. Accurately weigh or measure each ingredient.
3. Melt the Polybase using gentle heat to about 60˚C.
4. Add the morphine sulfate and the aspartame powders and mix well.
5. Cool a few minutes and add flavor while the mixture is still fluid.
6. Mix thoroughly and pour into 1 g molds.
7. Cool, package, and label.

Rx Fentanyl 50 μg Chewable Gummy Gels (24 Chewable Gels)

Fentanyl citrate	1.884 mg
Chewable gummy gel base	23.35 g
Bentonite	0.5 g
Aspartame	0.5 g
Acacia powder	0.5 g
Citric acid monohydrate	0.65 g
Flavor concentrate	10–12 drops

1. Calculate the quantity of each ingredient required for the prescription.
2. Accurately weigh or measure the ingredients.
3. Blend the fentanyl citrate, bentonite, aspartame, acacia powder, and citric acid monohydrate together.
4. Heat the chewable gummy gel base on a water bath until fluid.
5. Incorporate the dry powder from step 3 into the base and stir until evenly dispersed.
6. Add the flavor concentrate and mix well.
7. Pour into suitable molds and allow to cool.
8. Package and label.

Since mold capacities vary, it may be necessary to calibrate the specific mold being used and to adjust the formula before actual preparation.

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Formulation and Design of Veterinary Tablets

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INTRODUCTION

Veterinary pharmaceuticals have an important role in the preservation and restoration of animal health. For companion animal species such as dogs and cats, medicinal products are needed to treat a range of disease conditions, many of which parallel those associated with human patients. For example, in dogs, drugs are used to treat infections diseases, parasitic infections, metabolic disorders, epilepsy, post-surgical pain, pain associated with osteoarthritis, heart disease, anxiety, obesity, and cancer. For poultry, livestock and aquatic species, therapeutic needs include the treatment of bacterial and parasitic infections, the management of metabolic disorders, productivity enhancers (e.g., enhancing growth, reproduction, feed efficiency and milk production), and control of pain and pyrexia.

The issues and concerns that challenge the development of veterinary tablet formulations are similar to those that are associated with human medicine. In this regard, any of the other chapters in this book are equally applicable to veterinary and human tablets formulation and manufacturing. However, because we must deal with multiple animal species and their specific dosing requirements, physiology and behavior, there are formulation issues that are unique to veterinary medicine. With this in mind, the objective of this chapter is to address these issues as they impact the development of veterinary tablet formulations.

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Economic Considerations

A fundamental challenge in the development of veterinary pharmaceuticals is the relatively narrow profit margin associated with these products. A comparison of the time and costs associated with drug development for humans versus veterinary species, as well as the differences in the public expenditure on these products, is provided in Table 1.

TABLE 1 Time and Cost Expenditures: Comparison of Human versus Veterinary Pharmaceutical Products

Activity	Veterinary	Human
Time from bench top to market	10 years	12–15 years
Estimated cost to develop a new drug product	$40 million	$800 million
Public spending on pharmaceutical products	$5 billion	$168 billion
Research and development investment for new pharmaceuticals[a]	$556 million	$39.4 billion

Note: Based upon 2004 estimates unless otherwise indicated.
[a]Based upon 2005 figures.
Source: From Refs. 1–6.

As seen by this comparison, the economic differential between human and veterinary medicine serves to intensify the challenge facing efforts to optimize methods for delivering those compounds that are essential components of the veterinary therapeutic arsenal.

Many veterinary drug products are formulated for parenteral injection to allow for ease of administration (e.g., under hospital conditions or for herd treatment), or to allow for a sustained delivery of drug for a duration of weeks to months. However, there are also a multitude of situations where drugs need to be formulated for oral delivery. For example, oral formulations enable pet owners to dose their dog or cat at home. In farming situations, oral drug delivery in food and/or water is needed to enable drugs to be administered to large groups of animals (such as chicken, fish, and swine) in an efficient and cost-effective manner. In ruminants, large oral boluses are used to deliver several grams of drug within a single dosage unit. Boluses can also be formulated as parenteral "tablets" to provide for a sustained release of medication.

Growth of the United States companion animal pet population (canine and feline), has led to an increasing demand for veterinary pharmaceutical and nutritional supplement-type products. In 2007, CVM estimates that the United States canine population exceeds 73,000,000 while the corresponding United States feline population exceeds 90,000,000. The increase in households with pets is particularly evident in the homes of older Americans, where in 2007, approximately 50% of all pets were owned by individuals older than 50 years of age.

Physiological Considerations

When matching an oral dosage form to a target animal species, the drug physicochemical characteristics, animal behavioral and husbandry practices need to be considered (7). The limitations associated with the gastro-intestinal (GI) physiology of the target animal species also need to be considered. Excellent discussions of these interspecies differences are provided by Steven and Hume (8), Cunningham (9), Kararli (10), Baggot and Brown (11), and Kider and Manner (12), Martinez et al. (7,13), and Sutton (14).

Interspecies' diversity in GI anatomy and physiology reflects the differences in their respective diets (8,9). For example, consistent with a diet that is low in fiber but

high in fat and protein, carnivores (e.g., dogs and cats) possess a relatively simple colon but a well developed small intestine (long villi) (13). Pigs, as omnivores, also possess a well-developed small intestine but have a more complex lower intestine to compensate for their diversified diet. The lower intestine of pigs also allows for dietary fiber fermentation. A comparison of the villus height (proximal small intestine) and ratio of body size to small intestine length is provided in Table 2. This comparison provides insight into the surface area available for drug and nutrient absorption.

The vast majority of approved orally administered drugs are absorbed via passive transcellular diffusion (18). The ability to diffuse through lipophilic cell membranes is highly correlated with the ability of a drug to partition between water and an organic solvent such as octanol. Alternatively, some compounds are passively absorbed by paracellular diffusion. This process involves both diffusion and a convective volume flow through water-filled intercellular channels. Whether a drug is absorbed via paracellular or transcellular mechanisms is determined by both physico-chemical and physiological factors. While the primary determinant is usually related to the drug's properties, host physiology (e.g., membrane diffusion surface, diffusion distance and the membrane permeability) also can play a key role (19). In humans, the small intestinal surface area for paracellular absorption is approximately 0.01% of the total membrane surface area. For this reason, unless the molecule is extremely small (e.g., <200 Da), paracellular transport will have a minor role in drug absorption in humans (18). However, the markedly larger pore diameters in the intestine of dogs and cats allow for paracellular diffusion to have a greater role in drug absorption in these species. In this regard, since the size and number of paracellular spaces influence the intestinal absorption of hydrophilic compounds, it is not surprising that the bioavailability of small hydrophilic compounds tend to be greater in species such as the dog where both pore diameter and surface area tend to exceed that in humans (20).

Understanding the physico-chemical properties of a compound and the effect of formulation on product dissolution rate is critical when developing formulations that are intended to be used in more than one animal species. For example, the relationship between drug p*K*a, hydrophilicity, and the pH of the GI tract will largely determine the formulation needed to maximize product absorption. Interspecies differences in GI transit time and the species-specific impact of food on gastric emptying will influence the window of time available within which in vivo dissolution needs to be completed. Furthermore, an understanding of the differences in the pylorus sieving properties will determine if the dosage form will be retained in the stomach or if it will pass into the small intestine. For example, a drug that erodes may be retained in the canine stomach for a much longer duration than a formulation that rapidly disintegrates. This difference can

TABLE 2 Comparison of Intestinal Characteristics Across Veterinary Species

Species	Villus height (μm)	Villlus diameter	Length ratio, body/small intestine
Human	500–1500	200	1:4
Horse	405		1:12
Bovine	363		1:20
Swine	470		1:6
Dog	800[a]	180[a]	1:6
Cat	1072[a]	200[a]	1:4

[a]Specifically refers to the villus height in the duodenum.
Note: This table does not consider differences in villus geometry as a function of intestinal segment.
Source: From Refs. 13, 15, 16, and 17.

be used to alter GI residence time. In addition, it is important to understand the idiosyncrasies of the animal species when selecting excipients. For example, if sustained oral drug delivery is desired in sheep, goats or cattle, then the use of cellulose-containing excipients should be avoided because cellulose-based materials are rapidly degraded by the rumenal bacteria.

The four major veterinary species for which there are approved tablet formulations include the horse, bovine, canine and feline. Therefore, this discussion will be limited to the unique GI characteristics associated with these four species.

Horses: Due both to the highly variable pH of the equine gastric contents (pH = 1.3 – 6.8, mean = 5.5) and its highly fibrous diet, drug absorption may be poor in much of the small intestine. This is particularly true for weak bases (where the higher pH will interfere with drug dissolution) and for drugs whose dissolution will be impaired by a decrease in diffusivity caused by the viscosity of the ingested fibrous materials. Consequently, a large fraction of drug absorption in horses often occurs in the large intestine. Two other unique features of the equine GI tract are the lack of a gall bladder and a relative inability to vomit (21).

Equines are hindgut fermentors, with a small intestine whose fluid capacity is substantially less than that of the large intestine. Fermentation processes that release vitamins and volatile fatty acids occur primarily in the large intestine where only the energy-rich volatile fatty acids are efficiently absorbed. Due to the poor absorption of the other nutrients released in the hindgut, equids need to consume food for about 18 hours per day to meet their nutrient requirements.

Ruminants: Cattle, sheep, and goats are examples of are foregut fermentors. Because fermentation of fiber takes place proximal to the small intestine, the efficiency of nutrient absorption is markedly improved over that of the horse. This difference enables the ruminant to reduce grazing time from the 18-hours per day associated with horses to only 6–8 hours per day (21,22). An excellent reference regarding the GI physiology of ruminants is available as a free publication from The Pennsylvania State College of Agriculture Sciences (22).

Ruminants contain four stomach compartments: The reticulum, the rumen, the omasum, and the abomasum. Digestion of feedstuffs by microorganisms takes place in the reticulum and in the rumen. Anatomically, the reticulum is the first of the four stomach compartments, serving as a sieve that prohibits the movement of foreign objects into the rest of the digestive tract. Feed that enters the reticulum is later regurgitated and re-masticated. The reticulum can contain up to 2.5 gallons of material.

The rumen is a fermentation vat that can hold between 100 and 225 L in cattle and 10 to 24 L in sheep and goats. It also contains approximately 150 billion microorganisms per teaspoon. The conditions of the rumen reflect the environment necessary to maintain its microflora, including a temperature that ranges from 100° to 108°F and a pH of 5.8 and 6.4. The high ruminal pH reflects the large volume of alkaline saliva (pH 8 to 8.4) that is secreted and swallowed. This saliva buffers the organic acids produced in the rumen. Although gastric juices are not secreted in the forestomach, the rumen has a large capacity for drug absorption, particularly for weak acids. Ruminal retention time can be 20 to 30 hours, depending upon the nature of the feed material (22).

The omasum is the site where excess water is absorbed from the food and the particle size of the digesta are reduced. The omasum can contain up to 4 gallons of digesta.

Lastly, the abomasum or "true stomach," contains the acids and enzymes needed to further digest the food. The walls of the abomasum secrete enzymes and function similarly to the stomach of monogastric species. The abomasum pH is approximately 2 to 4. It can hold up to 5 gallons of material and is responsible for some fat digestion (23,24).

Bacterial fermentation is a critical element in ruminant digestion (8,9,25). The advantages of microbial digestion include the liberation of energy from cellulose, as well as the bacterial production of B-complex vitamins and vitamin K. Rumenal bacteria are also capable of degrading drugs, thereby limiting the compounds appropriate for oral administration in these animals. Few drugs, with the exception of sulfa drugs, can resist chemical degradation in the harsh environment of the abomasum of a ruminating cow. As demonstrated by their relative bioavailability in ruminating (e.g., bovine) versus non-ruminating (e.g., swine) species, the five sulfa drugs that posses sufficient chemical stability for medicating ruminants are sulfathiazole [ruminants (26–29) and non-ruminants (30–32)], sulfadiazine [ruminants (33–35) and non-ruminants (36)], sulfadimethoxine [ruminants (37,38) and non-ruminants (39,40)], sulfamethazine [ruminants (41–46) and non-ruminants (47)], and sulfamerazine [ruminants (48–49)]. In contrast, drugs such as trimethoprim and chloramphenicol are degraded within the rumen and therefore should not be administered to ruminanting species (51). At the other extreme, 20–30% of the dietary protein bypasses rumenal digestion, which may increase the relative bioavailability of protein-related drugs.

The movement of molecules through the four chambered stomach of a ruminant is multiphasic. There is the initial slow movement through the rumen, which is best described as a sinusoidal function, a time delay within the omasum, followed by a rapid transit through the abomasum. The rate constants associated with these movements vary as a function of diet and particle size (52). The general timeframe for transit half-life is on the order of 30 hours for dry matter and approximately 5–7 hours for fluids (53–55). As discussed later in this chapter (section on boluses), this slow gastric transit is frequently the rate-limiting step in drug absorption, thereby allowing some products with dissimilar in vivo release profiles to nonetheless demonstrate equivalent oral bioavailability.

Poultry: The poultry digestive tract consists of a crop, which is a storage area; a proventriculus, which is a glandular stomach; and a ventriculus (more commonly known as the gizzard) where grit is stored to aid in the physical grinding of the food. The small intestine of birds consists of a duodenum and jejuno-ileal segment. The length of the small intestine is much longer in the herbivorous birds. The turkey also has two enlarged ceca that join the colon at the iliocecocolic junction. The ceca function in fermentation of dietary fiber and serve to recover water from fluid refluxed into the colon from the cloaca (13).

Carnivores: The vast majority of solid oral dosage forms used in veterinary medicine are formulated for administration to dogs and cats. As seen in Table 3,

TABLE 3 Overview of Oral Tablet Formulations Approved for Use in Companion Animal Species (Numbers Include Generics and Withdrawals)

	Number of approved applications	
Species associated with approvals	Tablet	Capsule
Total no. 2006	221	54
Dogs	141	51
Cats	60	23
Horses	17	1
Dogs and cats	49	22
Dogs and horses	9	
Cats and horses	1	
Dogs, cats, and horses	1	

carnivores generally, possess a relatively simple colon and a well-developed small intestine (long villi). Dogs tend to have a lower (fasting) basal acid secretion than do humans (56), leading to a higher pH. The gastric pH of fasted dogs also tends to be highly variable, ranging between 1 and to about 6 (56,57). Conversely, following a meal, gastric acid secretion rates in dogs exceed those of humans and slowly return to baseline. Thus, in contrast to the fasted state, under postprandial conditions, the pH of the canine stomach tends to be lower than that associated with the fed human stomach. The higher pH found in the canine small intestine of dogs (versus that in humans) may result in better absorption of drugs that are weak bases.

The time for gastric emptying in dogs depends upon multiple variables, including particle size and density (smaller particles empty faster than larger particles, emptying first increases and then decreases with particle density), meal viscosity (emptying rate varies inversely with meal viscosity), and particle shape (which becomes an important factor consider as particle size increases). Although the time for particle transit is increased as a function of meal viscosity (58,59), the importance of this observation may be minimal under normal clinical conditions. The viscosity of a typical canine meal is on the order of 1 cP, which is markedly less than the high fiber/high viscosity conditions generated under experimental conditions (59).

With regard to particle size, very small particles (e.g., 1 g/cm^3, 1.6 mm diameter) empty more rapidly from the canine stomach than do particles whose diameter exceed approximately 2.4 mm (60). Particles greater than 7 mm are often not emptied from the canine stomach until 6–8 hours after food intake (61). Despite human versus canine similarities in the rates of gastric emptying rates of liquid and small particles under fasted conditions, food causes a substantially greater delay in the emptying of large particles (tablets) and pellets in dogs as compared to humans (58). This difference is important to recognize when considering the possibility of developing non-disintegrating tablets for use in dogs. Similar considerations also apply to cats.

The canine GI tract is adapted for a carnivorous diet, consumed as large, poorly masticated food chunks. Therefore in dogs, the strength of the gastric contractions (e.g., fed and fasted beagles administered 20 mL water with the capsule) has been measured as 3.2 N (62). Conversely, in man, gastric crushing strength ranges between 1.5 N and 1.9 N under both fasted versus fed conditions, respectively (63). Thus, formulations that may not be crushed in humans may do so in dogs. This can be particularly important when attempting to develop gastro-retentive devices for use in dogs (57), or when trying to develop colon-targeted delivery systems.

The Veterinary Biopharmaceutics Classification System (vBCS) Initiative

The USP Veterinary Drugs Expert Committee formed an ad hoc committee to explore whether or not the conventional criteria for defining highly soluble and highly permeability compounds can be extrapolated to dogs and to generate recommendations on the relationship between the in vitro dissolution and in vivo oral absorption characteristics of veterinary pharmaceuticals.

The extrapolation of human-based BCS criteria to veterinary species is not straightforward. For example, especially for small hydrophilic compounds (paracellular absorption), there may be differences in the intestinal permeability seen in dogs, and cats versus people. This can lead to some compounds exhibiting poor oral bioavailability in man but good oral bioavailability in dogs (e.g., atenolol) (64). It is believed that this

difference in membrane leakiness is the reason why excipients such as poly-ethylene glycol (PEG) that act as osmotic stimulants and reduce drug oral bioavailability in human have a markedly reduced effect on oral drug bioavailability in dogs. In other words, while PEG is not absorbed in humans, it does get absorbed across the canine intestine (65). In this regard, molecules as large as 600 Da have been shown to pass across the canine intestinal mucosa (20). PEG 400 is 400 Da. To further complicate the matter, the magnitude of membrane "leakiness" appears to vary across canine breeds (20,66).

Another difference affecting BCS drug classification is that unlike human medications, veterinary medicines are generally dosed on an mg/kg basis. However, it is unlikely that the fluids to which the dosage form will be exposed (either as inherent gastric fluid volume or volume of fluid consumed) scales linearly to body weight. Considering the size differential across breeds, this may lead to a very wide range of dose/fluid volume ratios. Thus, the use of a set volume of fluid and dosage strength for defining drug solubility may not be appropriate in veterinary medicine.

The cat appears to have a tighter pyloric sieving action under postprandial conditions as compared to the dog (14). This is not surprising when considering the canine-feline difference in body size. In this regard, the sieving property of large dogs appears to differ (allow for larger particles to pass) as compared to that of smaller dogs (67). However, there does not appear to be any data that compares the sieving action of dogs and cats that are of a similar body size. What is known, however, is that relative to body size, the cat does has a smaller stomach as compared to that of the dog, thereby encouraging the feline to consume smaller but more frequent meals than their canine counterpart (68).

Lastly, the current criteria used for defining a rapidly dissolving product may not be appropriate in animal species where the GI transit rate can be markedly greater than that observed in humans. GI transit time ranges from cats tend to have a long fused spike burst (migrating spike complex) that is interspersed with short periods of irregular spiking. This results in a different pattern of gastric emptying in dogs and cats. The difference in motor complex in dogs and cats result in differing patterns of gastric emptying in the two species. In both species, liquids, digestible food and indigestible solids are emptied in separate phases (69).

Marketing Considerations

When assessing the marketability of veterinary oral pharmaceutical products, formulators need to consider the lifestyle of the pet owner or the husbandry practices of the food-producing animal.

The dosing of companion animal species can pose similar challenges as those encountered in the administration of medicines to pediatric patients: in both cases, the medicine must be administered by a human caretaker. Solid oral dosage forms, such as tablets and capsules, tend to be more readily accepted by dogs as compared to cats. Medications for dogs can be flavored, administered as chewable tablets, or disguised in a taste treat (e.g., imbedded in a chunk of cheese or frankfurter). However, cats tend to be more discriminating with regard to tastes and consistency, and they will often refuse to consume medications that are disguised in food. Many liquid medications or broken tablets are so unpalatable to cats that they will salivate and resist attempts to administer the drug. Thus, for feline medicine, liquid formulations may be easier to administer.

The types and numbers of products that have been approved as tablet formulations for use in dogs, cats, and horses are provided in Table 3.

Defining "Tablet"

Tablets are solid dosage forms containing medicinal substances with or without suitable diluents. Based upon its method of manufacture, the tablet may be classified as either compressed or molded. Within these two general classifications, there are numerous subclasses of tablet forms that can be developed. These include (70):

- *Molded tablets*: These tablets are prepared by forcing dampened powders under low pressure into die cavities. Solidification depends upon crystal bridges built up during the subsequent drying process, and not upon compaction force.
- *Tablet triturates*: These are generally small, usually cylindrical, molded or compressed tablets that were traditionally used to provide a convenient, measured quantity of a patented drug for compounding purposes. Such tablets are rarely used today.
- *Hypodermic tablets*: These are molded tablets that are made from completely and readily water-soluble ingredients. These were formerly intended for use in making preparations for parenteral administration. An example of this in veterinary medicine is the implantable pellet.
- *Buccal and sublingual tablets*: These tablet formulations are intended to be inserted into the buccal pouch or beneath the tongue.
- *Soluble effervescent tablets*: These tablets are prepared by compression and contain a mixture of acids and sodium bicarbonate to release carbon dioxide when dissolved in water.
- *Chewable tablets*: These tablets are formulated and manufactured so that they may be chewed without leaving an unpleasant aftertaste.
- *Plain coated tablets*: The coating applied to these tablets has a variety of potential functions. These include maintaining tablet integrity, promoting ease of swallowing, taste masking, waterproofing, etc.
- *Delayed release tablets*: These tablet formulations are intended to prevent drug dissolution in the stomach. In some cases, the tablet is formulated to release drugs at specific sites in the GI track.
- *Extended-release tablets*: These tablets are formulated to allow the active ingredient to be released over an extended period of time following ingestion. Expressions such as "prolonged-action," "repeat-action," and "sustained-release" have also been used to describe these dosage forms.

While not all of these dosage forms are currently the subject of approved veterinary drug applications, with the growing importance of the pet as a family member, it is likely that most of these types of tablets will eventually be a component of the veterinary pharmaceutical arsenal.

THE DEVELOPMENT OF VETERINARY TABLET FORMULATIONS

Choice of Excipients

As a class, tablets are one of the most challenging of all pharmaceutical products to design and manufacture. In the veterinary industry, tablet weights can be as small as a few mg and as large as 40 g (oral boluses). The choice of an excipient for a particular formulation is governed by various critical parameters that include:

- functional category
- quality and purity

- impurity levels
- compatibility with the active ingredient
- compatibility with the packaging material
- stability in the formulation.

Although excipients are important tools for designing the release characteristics of a finished product and for protecting the active pharmaceutical ingredient (API) from in vivo degradation, excipients themselves can sometimes be the cause of API degradation. In some cases, API instability is due to impurities in the excipient rather than to the excipient itself. These impurities are small molecules that can be generated during the synthesis of the excipients, by excipient degradation during its manufacture, or by contact between the excipient and the excipient's packaging materials.

Impurities

In most cases, the impurities (reactive species) consist of water, small electrophiles, such as aldehydes, carboxylic acid derivatives, peroxides, and metals. Water can hydrolyze some drugs. Aldehydes and carboxylic acids can form molecular adducts. Peroxides can oxidize some drug. Metals can catalyze oxidation, hydrolysis, and other degradation pathways. The formulation challenges posed by each of these impurities are discussed below.

Water

Water is omnipresent in drug products. It can come from the excipients, from the manufacturing process, e.g., wet granulation, or from the API itself. Chemical stability issues with water are generally associated with hydrolysis of susceptible side-chains (71). The pharmaceutical literature contains many examples of where the exposure of drug crystals to water during the granulation process, or the loss of water through a drying process, has adversely affected the dissolution and solubility of the drug by altering the drug's crystal form (72).

Water is present in many of the excipients used to compound the drug product. While the vendor's specifications will list the excipient's moisture content, what is not known is how readily each excipient will release this moisture (i.e., how tightly the water is bound). For example, an excipient may contain >10% moisture, but this moisture will not influence API stability if the water is tightly bound as a crystal hydrate. Alternatively, the excipient may contain less than 1% moisture, but if this water is readily released, it can interact with and alter the API. When sealed in a tight package and/or when exposed to elevated temperatures, the moisture can be released. When this occurs, the water can adversely impact the stability of the API or the performance of the dosage form. Therefore, formulators generally measure the intrinsic moisture of the formula and dry the wet granulation until the moisture content meets or drops slightly below this value.

Peroxides

These are reactive materials present in several excipients. Peroxides can be present either as a result of the excipient manufacturing process or due to the oxidative instability of the excipient itself. In both cases, the issue is most prevalent in polymeric excipients, where they act as initiators in polymerization processes. Excipients with this source of peroxides are difficult to identify because of the proprietary nature of the excipient manufacturing process.

Well recognized examples of polymeric excipients containing peroxide impurities include polyethylene glycols. Prior to recognition of the stability problems caused by this impurity, these compounds contained levels of peroxides that were responsible for the formation of pellicles via peroxide–gelatin capsule cross-polymerization reactions. This pellicle formation resulted in product dissolution failure during stability testing. For this reason, currently marketed pharmaceutical grade polyethylene glycol is low in peroxide content (73,74).

Two classes of excipients frequently associated with peroxide impurities are the polymeric esters and polyvinyl pyrrolidone (povidone)-based excipients. With regard to polymeric esters, in addition to levels of peroxides present as supplied by the vendor, these esters are subject to auto-oxidation, which leads to peroxide formation. Examples of these compounds include:

- polyethylene glycols,
- polyethylene oxides,
- polysorbates,
- polyoxyethylene alkyl esters,
- polyoxyethylene stearates,
- other ethylene oxide-based materials.

To minimize this degradation pathway, the excipient may be supplied with an antioxidant, typically BHT.

The polyvinyl pyrrolidone (povidone)-based excipients, such as povidone and crospovidone, commonly contain 100–200 ppm of peroxide impurities (75). The peroxides are formed by auto-oxidation of the povidone moiety, and additional amounts of this impurity can be generated during product granulation and tableting. The formation of peroxides during tablet compression can explain why an API may be stable during the granulation process but degrade during tablet compression. Although peroxide formation for the solid oral dosage form is generally slow when tested under standard aging conditions, the aging and storage of this excipient can lead to variable peroxide levels.

The peroxide impurities exist either as hydrogen peroxide (H_2O_2) or as organic peroxides (ROOH). Both species can oxidize susceptible drugs. These oxidation processes can be classified either as direct reaction (that is, once the peroxides are exhausted, the process is self limiting) or radical chain reaction (where the peroxides generate free radicals that can catalyze chain reactions with the drug). In both types of reactions, peroxides can induce significant drug degradation, especially in situations with high excipient-to-drug ratios.

The signature of the radical chain reaction is that, once the process is initiated, it is self perpetuating. Metals may initiate the radical chain reaction, and a common source of metal is magnesium from magnesium stearate. If this is the case, formulation stability may be enhanced either by switching from magnesium stearate to calcium stearate, or by eliminating the metal stearate altogether by using stearic acid.

Aldehydes

Aldehydes may interact directly with the API. Therefore, even trace amounts of these compounds can adversely affect the stability and efficacy of the drug product. The most commonly encountered aldehyde impurities include formaldehyde, acetaldehyde, furfural, and glyoxal.

Low molecular weight aldehydes can be generated during the oxidation of common excipients such as, unsaturated fats, polyethylene glycol and polysorbates. This oxidation

reaction generally occurs during heat stress or high humidity (76). Polyethylene glycol is often found in commercial tablet coating products. Unsaturated fats are generally used as tablet lubricants.

In some cases, aldehydes are produced by hydrolytic reactions. This is seen in the formation of furfural and its adducts in the acid-catalyzed degradation of hemicellulose and other sugar based excipients (77). For example, 5-hydroxymethylfurfual, the compound responsible for the characteristic odor present in spray-dried lactose, is generated by the thermal decomposition that occurs during the spray-drying process (78). In other cases, the source of the aldehyde is functional additives present in the excipients, either as aldehydes themselves or as materials that oxidize or hydrolyze to generate the aldehydes. Examples of this include preservatives, cross-linking agents, flavoring agents and dyes. Corn starch, a common tablet excipient, often contains hexamethylene-tetramine as a preservative, which hydrolyzes to give ammonia and formaldehyde. The formaldehyde reacts with the amino groups on lysine residues causing protein cross-linking, which in turn changes the dissolution characteristic of gelatin capsules (79,80). Formaldehyde has also been implicated in the degradation of loperamide to form 2- and 4-hydroxymethyl loratadine (81).

Glyoxal is an impurity that can be found as a cross-linking reagent in hydroxymethylcellulose or as an impurity in hydroxypropyl methylcellulose (82). Many commercial film coating agents contain hydroxypropyl methylcellulose. The presence of glyoxal in film coating formulas may explain the phenomenon of a drug being stable in the tablet cores while it degrades in the film coated tablet.

An example of a reaction between a low molecular weight aldehyde and an API is the reaction between formaldehyde and phenylephrine to form 1, 2, 3, 4-tetrahydro 4, 8 dihydro-2-methyl isoquinoline and the 4, 6 counterpart via the Pictet Spangler reaction (Fig. 1). In this example, formaldehyde reacts with a methyl group on the side chain of phenylephrine. Water is lost from this product and the side chain on the species resulting from this reaction closes to form a pyridine ring.

Maillard Reaction

A number of tablet excipients contain reducing sugars (glucose, maltose, and lactose). Reducing sugars will react with secondary amines (the Maillard reaction) to cause brown

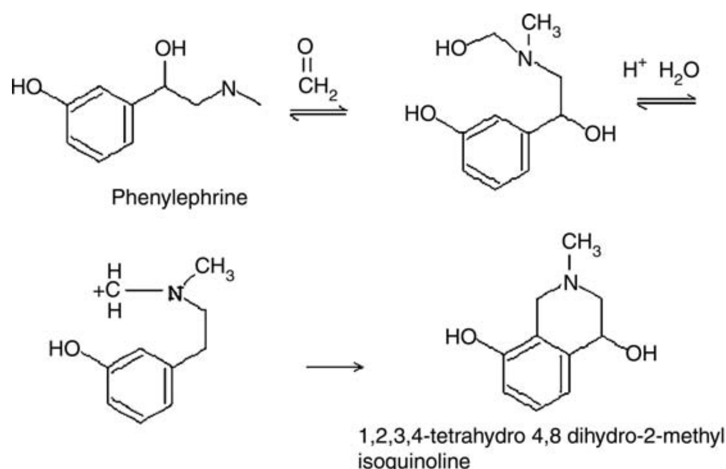

FIGURE 1 Pictet spangler reaction between phenylephrine and formaldehyde.

mottling in tablets. The Maillard reaction is a type of non-enzymatic browning involving involves the reaction between the carbonyl groups of simple sugars and the free amino groups of the amino acids.

The mechanism of the Maillard reaction is well described in the food science literature. Maillard reactions occur at lower temperatures and at higher dilutions than do caramelization processes. The Maillard reaction is a complex series of reactions leading to the formation of a several products. The initial reaction is the condensation of the carbonyl group of a reducing sugar with a free amino group of a protein or an amino acid a molecule of water, resulting in the formation of an N-substituted glycosylamine. The sources of sugar in these reactions include dextrose, fructose, high fructose corn syrup, sucrose, corn starches, and maltodextrins. Sources of the N-terminal amines include gelatin, whey proteins, aspartame, and emulsifiers such as lecithin. A generic representation of the Maillard reaction is provided in Figure 2.

The mechanism of the Maillard reaction is very complicated. However, it is generally divided into three stages (83–92):

1. The first stage involves sugar-amine condensation, forming the N-glycosylamine. The N-glycosylamine is unstable, and therefore undergoes the "Amadori rearrangement," resulting in the formation of the group of compounds known as "ketosamines." While no browning occurs at this stage, the Amadori rearrangement is considered to be the key step in the formation of major intermediates for the browning reaction. Ketoses such as fructose react with amines to form aminoaldoses. Aminoaldoses are relatively unstable, readily reacting to form the Amadori compound.
2. The second stage involves sugar dehydration and fragmentation, and amino acid degradation, thereby producing additional reactants.
3. Browning occurs in the third stage. The reactants formed in the second stage react further with amino acids, leading to the formation of heterocyclic nitrogen compounds.

Pentose sugars (ribose) react more readily than do hexoses (glucose and fructose). These in turn are more reactive than are disaccharides (lactose and galactose). Sucrose is not a Maillard reactive sugar. Of the amino acids, lysine results in the most intense color in the Maillard reaction. Therefore, foods containing proteins rich in lysine residues (milk proteins) are likely to brown readily. As can be seen in Figure 2, water is produced during

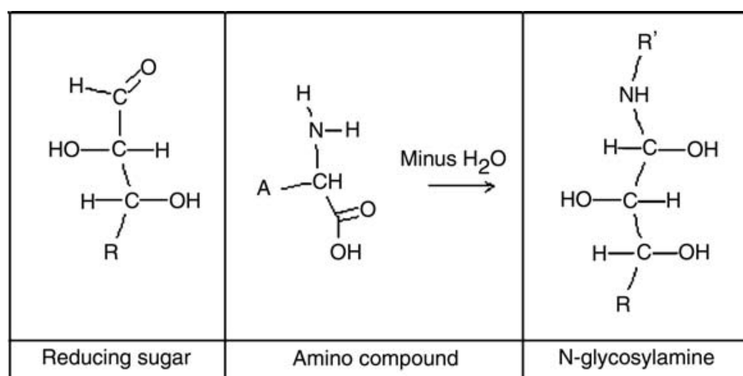

FIGURE 2 The Maillard reaction between a reducing sugar and an amino acid or protein.

the Maillard reaction. Water can also be produced at the other stages of Maillard reaction. Thus, consistent with the law of mass action, the reaction occurs less readily in systems with a high water activity value. In addition, the reactants are diluted at high water activity values. However, in contrast with expectation, the reaction is also limited in the presence of low water activity. The latter limitation is due to the constrained mobility of the reactants when insufficient amounts of water are present, despite their presence at increased concentration.

An example of this reaction is the interaction between aspartame and any reducing sugar (e.g., dextrose). Aspartame, having a free $–NH_2$ group, can react with a reducing sugar through the Maillard reaction to form diketopiperazine, which is a colored reactant. Diketopiperazine, unlike many other products of the Maillard reaction, has been well studied not only with respect to its structure but also in terms of its toxicology. The *Federal Register*, 48(132), July, 1983, pp. 31378–80, states that after evaluating the reproductive, mutagenic, and chronic bioassays in two rodent species, the agency derived a diketopiperazine no effect level of 3000 mg/kg body weight. The structure of aspartame and diketopiperazine are shown below (Fig. 3).

Metal Impurities

Metals are present in almost all excipients. Certain excipients inherently contain high level of metals, such as minerals (e.g., talc and kaolin) or inorganic compounds derived from minerals (e.g., phosphates, silicates, and titanium dioxide). The types and levels of metals present in excipients can vary significantly, depending upon the excipient type, its source, and the production process used to extract or produce the excipient.

Metals can be deleterious to drug products because of their ability to catalyze oxidative and hydrolytic reactions. The metals most commonly associated with oxidation are iron and copper. Both of these compounds act as catalysts by facilitating the reduction of molecular oxygen, thereby increasing its reactivity. A well-know example of such degradation is the hydrolysis of aspirin, catalyzed by iron, to form acetic acid and salicylic acid.

There are three distinct oxidative reactions that can occur with metals (93). These include:

- Direct metal catalysis where the metal acts as an electron exchanger to reduce oxygen.
- Simultaneous binding of the metal to oxygen and to the drug substance.
- Fenton-type reactions where transition metal ions reduce peroxide, thereby generating the highly reactive hydroxyl radical (Fig. 4).

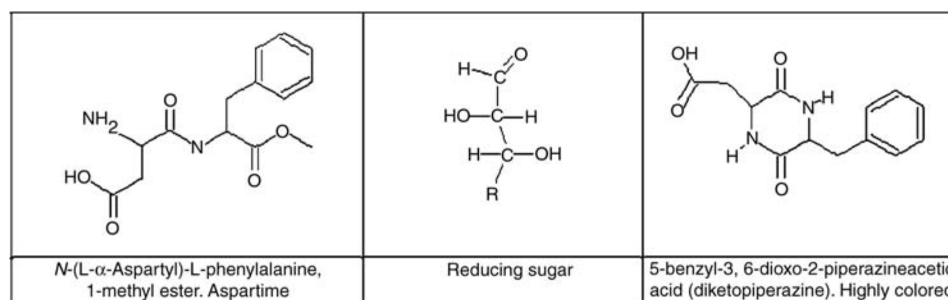

FIGURE 3 The reaction between aspartame and a reducing sugar.

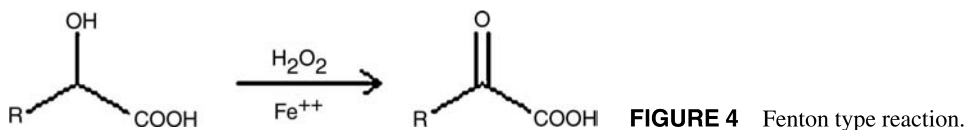

FIGURE 4 Fenton type reaction.

- Metals can also catalyze hydrolytic reactions. For example, Revelle et al. (94) identified 11 impurities in stressed chlorhexidine digluconate solutions.

Small Molecule Impurities

Small molecule carboxylic acids can be found in may polymeric excipients, sugars, and unsaturated fats. Generally, the most reactive carboxylic acids that are present as excipient impurities include formic acid, acetic acid, and glyoxalic acid. The sources of these small molecules are often unreacted monomeric carboxylic acids that have been carried over from previous reaction processes. Examples of popular excipients containing acetic acid include sodium carboxymethyl starch (sodium starch glycolate) and sodium carboxymethyl cellulose. In general, any substance capable of catalyzing the oxidation of an alcohol to an aldehyde will likewise catalyze the oxidation of a carboxylic acid. Figure 5 provides the basic scheme involving the oxidation of a carboxylic acid.

Small molecule carboxylic acids can interact with drug molecules by one of two mechanisms:

- Changes in the acid content of adsorbed moisture can shift the formulation into a less stable pH and initiate or accelerate the solid state degradation of the API.
- Carboxylic acids can react with drug molecules containing nucleophilic functional groups, such as primary or secondary amines, or it can interact with hydroxyls, resulting in the formation of amides and esters, respectively. A well studied example of these reactions is the solid state dehydration of tetracycline to form anhydrotetracycline

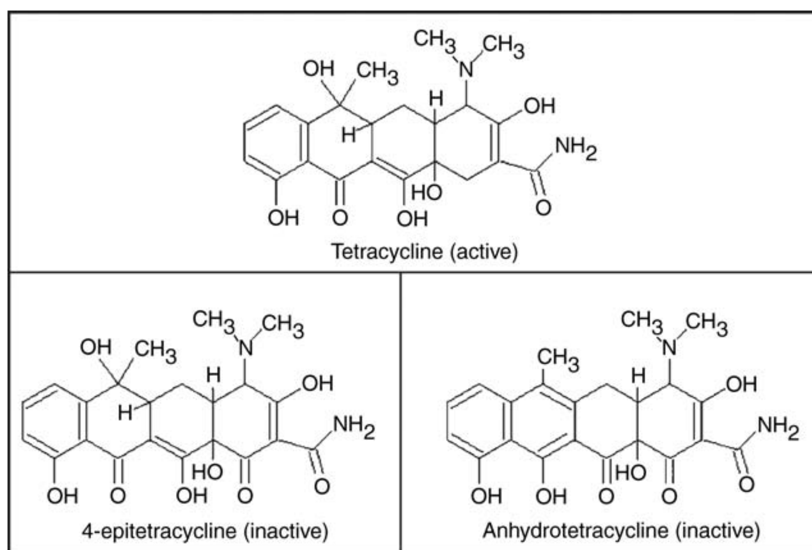

FIGURE 5 Solid state dehydration reaction involving tetracycline.

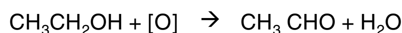

FIGURE 6 Oxidation reactions involving alcohol and carboxylic acids.

(Fig. 6) (95–98). Anhydrotetracycline is nephrotoxic, and the ingestion of an expired tetracycline drug product has been reported to produce Fanconi's syndrome (99).

The likelihood of tetracycline degradation is greatly increased by the presence of citric acid and exposure to adverse condition of heat and humidity. Even though citric acid is no longer used to formulate the tetracycline capsule, this reaction is of relevance to the modern practice of veterinary medicine as citric acid containing products are often used to keep animal watering lines free from bio-film growth.

Antioxidants

Antioxidants such as BHA and BHT, tocopherols, L-ascorbyl palmitate, ascorbic acid, propyl gallate, and sodium metabisulfite are added to some excipients to minimize oxidative degradation of the API over time. Propyl gallate has become widely used as an antioxidant to prevent the rancidity of oils and fats.

To be useful, the antioxidant must have a lower oxidation potential than the drug. The antioxidant participates in the oxidation reaction, in preference to the drug and thereby protecting the drug. However, there is an optimum concentration of the antioxidant. When used in excess of this optimal concentration, the antioxidant may result in the degradation rather than the protection of the API.

Important considerations associated with the use of these antioxidants include the following examples (100):

- BHA and BHT, which are often used to prevent the degradation of plastics and waxes in packaging materials, can be a concern when used in some pharmaceutical formulations because of its tendency to form strongly colored by-products.
- Alpha, beta, delta, and gamma tocopherol are valuable oil soluble antioxidants. Their antioxidant effectiveness can be increased by the addition of oil soluble synergists such as lecithin and ascorbyl palmitate.
- L-ascorbyl palmitate, another stabilizer for oils used in oral pharmaceutical preparations, has been used either alone or in combination with alpha tocopherol. When used in combination with alpha tocopherol, a marked synergism with L-ascorbyl parlmitate occurs, thereby allowing for a reduction in the necessary concentration of this antioxidant.
- Ascorbic acid is used widely in pharmaceutical systems. When mixed with compounds having a primary amine nucleus, there is a tendency for interaction to form a highly colored Schiff base.
- Sodium metabisulfite is used widely in oral, parenterals, and topical pharmaceutical systems. Primarily, metabisulfite is used in acidic preparations and sodium sulfite is preferred for alkaline preparations. Sodium bisulfite will add to double bonds, react with aldehydes and certain ketones and contribute in bisulfite cleavage reactions. Many of the reactions with bisulfite are irreversible, and the resulting sulfonic acids are frequently biologically inactive. Sometimes these interactions are reversible, as in the case of adrenocorticosteroids.

Examples of commonly used antioxidants and the amounts frequently found in pharmaceutical preparations are provided in Table 4.

TABLE 4 Antioxidants and Their Concentrations in Pharmaceutical Preparations

Common chemical name	Normal usage
Ascorbic acid	0.01–0.1%
L-ascorbyl palmitate	
Butylated hydroxyanisole	FDA regulations direct not more than 0.02% USDA regulates require not more than 0.01%
Butylated hydroxytoluene	0.0009–0.1%
n-propyl gallate	Up to 0.1%
Sodium metabisulfite	Less than 550 ppm
Tocopherol	0.001–0.05%

Manufacturing Considerations

Tablets are expected to deliver an accurate dose of drug with a high degree of precision. Generally, manufacturing problems center on compressibility, fluidity, dissolution, and content uniformity. While compressibility and fluidity can be adjusted through the modification of excipients, problems with tablet dissolution and content uniformity may necessitate modification of both the formulation and the manufacturing processes.

One process variable than can be used to adjust product performance is granulation. The primary purposes of granulation are to produce free flowing and compressible particles in which the active ingredient is homogeneously distributed. Granulations can be prepared by either a wet or a dry method. Wet granulation is the most commonly used method to manufacture veterinary tablets. In wet granulation, the binder (usually hydrophilic colloid) acts as glue to aggregate smaller particles into larger ones. This reduces the inter-particulate friction and improves the fluidity and compressibility of the powder. The binder, which is distributed over large surface areas, acts as glue to overcoming the lack of cohesiveness of the original drug substance and the fillers. Wet granulation also improves the blend uniformity for soluble low dosage drugs and is an effective technique to improve the dissolution rate of hydrophobic compounds.

Due to the similarity between the manufacturing processes of human and veterinary dosage forms, the reader is referred to the other chapters in this book for information regarding considerations associated with the various manufacturing processes.

VETERINARY DOSAGE FORM-SPECIFIC CONSIDERATIONS: THE CHEWABLE TABLET

Oral dosage forms for companion animal species may be developed as "swallow tablets" (i.e., tablets that need to be manually pilled), chewable tablets (which may be marketed as either compressed formulations that can be administered whole or crushed into food, as extruded tablets that tend have a gummy consistency, or as molded tablets), or as oral solutions, suspensions and, in horses, as oral pastes. "Pilling" a pet (placing the medication on the back of the tongue and forcing the animal to swallow) can be challenging, especially when trying to pill a large, aggressive, or resistant animal. To improve the likelihood of successful dosing, veterinarians often instruct dog owners to place the pill in a small piece of meat or cheese. While this practice certainly encourages the pet to swallow its medication, the administration of a tablet in food is not always an option. In some cases, medications have substantially lower oral bioavailability when administered in the presence of food. Alternatively, the pet may be anorexic and unwilling to eat. In the

case of cats, unless the tablet can be crushed into wet feed, encouraging consumption by the administration of a pill with food is frequently unsuccessful. For this reason, the inclusion of taste masking methods and the inclusion of flavorants is often necessary.

History of the Development of Chewable Tablets for Dogs and Cats

In 1960s, companion animal pharmaceutical products were similar in design and formulation to conventional human pharmaceutical products. In fact, it was the human pharmaceutical tablet that was often administered to the dog or cat. This practice continued until mid-1970, when the first "chewable" tablets were developed for dogs.

The first "chewable" tablets were manufactured using standard pharmaceutical processing equipment. Most of these chewable tablets were made via wet granulation technology, using water, corn syrup, and other liquid animal by-products as the granulating agents. These initial chewable tablet formulas had good palatability in dogs, with palatability scores of 70–85%. These new chewable tablets were a huge success in the marketplace. Previous to the advent of these chewable tablets, most non-chewable tablet pharmaceuticals for pets had to be hidden within pieces of cheese, peanut butter on bread, and other human food product.

The major weaknesses to the first generation of companion animal chewable tablet dosage forms were as follows:

- Canine free choice palatability of 70–85% was far from ideal, since up to 30% of all dogs failed to eat the product free choice.
- Feline free choice palatability was much lower, often less than 50%.
- The initial flavoring attempts produced less than optimal results. Milk and cheese flavors were tried in 1980s for both dogs and cats. Canine palatability never exceeded 80% free choice acceptance and feline palatability never exceeded 70%. Fruit flavors were common in companion animal chewable oral liquids, but fruits are not part of a companion animal's natural diet. Garlic, which has long been considered palatable to dogs, lead to a free choice acceptance of only about 30–60 %. When the garlic flavor was removed and a different flavor system used, a free choice level of 95% was achieved.
- There were several stability problems associated with veterinary chewable tablets:
  - The use of water and corn syrup as granulating agents resulted in a media that supported bacterial growth. There was also wide variation in the magnitude of the moisture content. This residual moisture affected API stability, tablet flow and compaction problems, and lead to changes in tablet friability, disintegration, and dissolution over the proposed product shelf-life.
  - The initial palatability enhancing agents often included animal by-products of questionable quality and reproducibility. Common palatability enhancing agents included bovine pancreas digest, bovine liver extracts, bovine meat by-products, fish meal, fish digest, and other ingredients that were not fit for human consumption. The high fat content of these flavors made them prone to rancidity. Even if stabilized with anti-oxidants, rancidity was an important stability issue (101). Furthermore, the animal and fish by-products often had very high microbiological counts (greater than 50,000 cfu/g) and were contaminated with *Escherichia coli*, salmonella, and other coliform bacteria.

These stability problems can lead to the voluntary recall of products due to instability of the actives or, more often, due to bacterial growth within the product itself.

This bacterial growth caused the chewable tablets to turn from brown to green and to emit offensive odors.

Driven by the growth of companion animal populations in Europe and Japan, the close of the 1980s saw an expanding market for companion animal products. With this international increase in the demand for pet products, there was a need to develop palatability agents that did not contain animal-derived flavorants. Therefore, United States manufacturers of companion animal pharmaceuticals in the early 1990s began to develop alternative chewable tablet formulations. This second generation chewable tablet had the following characteristics:

- The quality of palatability enhancing agents was greatly improved. The new palatability enhancing agents were stable, readily reproducible from a production viewpoint, and contained negligible to non-detectable levels of bacteria, mold, yeast, and fungi. These new palatability raw materials would easily meet human food-grade and/or pharmaceutical grade quality standards. These new palatability enhancing agents (flavors) were added to a variety of companion animal products for sale in a world-wide market.
- The development of stable flavors allowed for development of flavors that were also aromatic. Palatability, whether for humans or pets, is based on initial arousal of smell (aroma), followed by the successful consumption of the product (free choice palatability). Having flavors that exhibit an attractive aroma and taste leads to an increase in free choice acceptance.
- The development of stable flavors for companion animal chewable tablet products led to the development of stable products with expiration dates that can be equal to or greater than 36 months.

Current Challenges and Considerations

Chewable oral tablets are well known in the human pharmaceutical industry and are growing in popularity as a dosage form of choice for the companion animal industry. Generally, chewable tablets are made by direct compression. A softer tablet may be prepared by adding a disintegrant such as alginic acid, or by reducing the level of pressure used during the compression process. The latter will result in softer tablets, but these tablets may also be more fragile, more brittle and easily chipped. Moreover, compressed, chewable tablets generally have less than desirable mouth feel, such as chalkiness or a dry, powdery taste.

The palatability, or acceptability, of a chewable tablet is determined by its smell, taste and texture. The combination of smell and taste is termed 'flavor.' Sugar or sweetener will have a sweet taste but no smell aroma and no flavor. Alternatively, meat provides both taste and smell, the combination of the two being recognized as a meat flavor. While mouth-feel (touch that the tablet produces in the mouth upon chewing) does not affect the chemical simulation of olfactory nerves or taste buds, aftertaste can be problematic. An example of a compound that induces after-taste in humans is saccharin.

The smell and taste of the API(s) are the two most important variables in the development of a highly palatable chewable tablet. In some cases, if the active(s) exhibits an offensive smell or bitter taste, this problem can be overcome by formulating the product with greater than 20% weight/weight flavorant: drug, along with some natural or artificial sweeteners such as sucrose, fructose, or aspartame. If these formulation attempts are not successful, the API can be coated using either "hot melt" technology or "Wurster" coating technology.

Bad tasting or high dose drugs are difficult to formulate into chewable tablets, causing problems with taste, mouth feel, and after-taste. Depending upon the intensity of the flavor, odor, and physico-chemical properties of the drug, palatability may be improved through the use of flavorants and/or other taste-masking technologies. A flavorant provides both odor and flavor to a product. Both of these attributes are important for encouraging the pet to ingest the oral drug. These flavorants can either be natural or artificial. As defined in 21 CFR 101, 22(a)(3), the term "natural flavor" implies that the essential oil, oleoresin, essence or extractive, protein hydrolysate, distillate, or any product of roasting, heating or enzymolysis, which contains the flavoring constituents derived from a spice, fruit or fruit juice, vegetable or vegetable juice, edible yeast, herb, bark, bud, root, leaf or similar plant material, meat, seafood, poultry, eggs, dairy products, or fermentation products thereof, whose significant function in food is flavoring rather than nutritional. Thus, unlike the flavorants used in human medicine, many of the flavorants used for dogs and cats are lipophilic and can impose manufacturing and stability problems. This is particularly problematic when large amounts of the flavorants are needed to cover a very bitter API. Alternatively, artificial flavors may be used. However, even with the artificial flavorants, lipophilicity remains an issue of concern. Examples of commercially available flavors for dogs and cats are provided by Thombre (102).

For any oral medication, the selection of a flavorant will depend upon the flavor and odor preferences for the intended targeted animal species. Cats are attracted to meat, fish, liver and yeast flavors. Dogs are attracted to meat, liver, chicken, yeast and sugars (102). From an evolutionary perspective, it is has been suggested that the canine ancestors may have relied not only upon animal prey but also upon plant materials when prey was scarce (68). For this reason, dogs will often consume foods containing either animal-derived or vegetable-derived flavors. In contrast, cats remained dependent upon frequent meals of small prey. There was a minimal consumption of vegetables. Therefore, vegetable-derived flavors generally do not improve the palatability of feline medications. Furthermore, while both dogs and cats exhibit a carnivore pattern of taste preferences, cats further display a differential pattern of response to certain animal acids (e.g., stimulated by L-Lysine but inhibited by 2-tryptophan) (68).

Cats also have neither an attraction nor an aversion to sweet carbohydrates (103). Based upon studies of taste-induced electrophysiological nerve activity, this behavior is consistent with a lack of neuronal stimulation in response to these flavors (104). In contrast, dogs are attracted to sucrose, glucose, fructose, and lactose. However, they are not attracted to maltose (104). Again, this is consistent with the neurophysiological response to these substances. Interestingly, the intensity of the canine response to these flavors is influenced by the presence of monovalent cations (e.g., Na^{+}), divalent cations (e.g., Ca^{2+}), and to the amount of these ions relative to the amount of sugar that is present (105). Accordingly, formulation changes that may have no impact on the bioavailability of the tablet could influence palatability (even without any changes in the amount of sugar or the API).

An additional consideration is the safety of the excipient. The safety of a particular component of human food and drugs does not necessarily equate with its safety for consumption by a veterinary species. For example, xylitol, a population human sugar substitute found in a variety of sugar-free and dietetic cookies, mints, and chewing gum is proving to be highly toxic, or even fatal, when given to dogs (106). Currently, there is no evidence that xylitol is toxic to pets other than dogs.

In addition to flavorants, more rigorous taste masking measures may help to insure that animals will be willing to consume particularly bitter drug substances. In this regard, taste masking methods comparable to those used for human drug products may be applied

A recent review on taste masking lists such strategies as multiple emulsion systems (liquid dosage forms), coated particles, ion-exchange resins, cyclodextrins, and tablet coating (107). Common techniques for chewable tablets such as adsorption, ion exchange, coating by conventional granulation, use of amino acids and protein hydrolysis, spray congealing and spray coating, and microencapsulation are also described in detail in other chapters in this text. Of interest, however, is that some of these taste masking techniques may impart a different effect on the oral bioavailability of the API when used in formulations intended for dogs versus for cats (unpublished observation). This difference can be particularly evident from the perspective of the impact of food on drug product bioavailability. In this regard, cats tend to be more sensitive to the impact of food on certain oral formulations as compared to that seen with dogs, even if the API was without a significant food effect. Therefore, it is important to consider not only the unique taste and odor preferences of dogs versus cats, but also the unique characteristics of the canine versus feline GI tract that may impart different product absorption characteristics.

These new flavors are more "pharmaceutically friendly" and can be used in existing types of equipment and technologies. The resulting chewable tablets can either be made by direct compression, wet granulation (using either water or alcohol), or dry granulation (slugging or roller compaction). Of these, direct compression technology is both simple to produce and is generally cost effective.

The use of these flavors helped to expand the international market by eliminating concerns previously associated with the use of fish and animal-derived raw materials. Currently, chewable tablet products account for over $500,000,000 in the US sales alone. Examples of chewable tablets currently marketed in the United States are provided in Table 5.

Recent work on a soft chew dosage form (Huron et al., US Patent Application 2005/0226908; publication date October 13, 2005) describes a forming process for the manufacturing of various oral dosage forms for companion animals. The forming process described differs from an extrusion process since no steam is required. The excipients are selected so that the blend can be formed into shapes through a forming machine. In this process, the dry components, which include the flavor, starch, the API, and sugar, are dry blended. The uniformity of blending is controlled in process using near infra-red (NIR) technology to assure blend homogeneity. The liquid components are added together and are mixed prior to forming the final tablet shape. Figure 7 shows an example of a schematic for a forming machine with a round molding plate. Other shapes and sizes can be obtained by varying the dimensions of the molding plate.

In terms of the selection of tableting methodology, "direct compression" is easy to apply and necessitates minimal capital investment. As this new palatable chewable tablet is formulated, tablet weight and hardness become important variables. For example, when formulating feline chewable tablets, the generalized "ideal" hardness is in the range of 3–4 Kp. As hardness exceeds 6 Kp, the palatability tends to decrease, all other factors being held constant. The identical formulation at 6 Kp tablet hardness may have a 95% free choice acceptance in cats, but only 50% free choice when formulated with a 12 Kp tablet hardness (108). Considering the size of an adult feline mouth, tablet weight in excess of 500 mg may be difficult to consume.

Development of Off-Flavors and Odors

The development of off-odors has long been recognized as one of the primary causes of quality deterioration in chewable pet tablets. Off-odors include odors commonly

TABLE 5 Examples of Veterinary Chewable Tablets

NADA #	Drug	Indication	Species	Manufacturer
041-665	Propiopramazine HCl	Sedation	Dog	Fort Dodge Animal Health
108-863	Diethylcarbamazine Citrate	Antiparasitic	Dog	Wendt Laboratories
120-326	Diethylcarbamazine Citrate (wafer)	Antiparasitic	Dog	Schering-Plough Animal Health Corp
128-069	Diethylcarbamazine Citrate	Antiparasitic	Dog	Boerhinger-Ingelheim Vetmedica
135-544	Stanozolol	Anabolic steroid	Dog	Upjohn, Co.
136-483	Diethylcarbamazine Citrate, Oxibendazol	Antiparasitic	Dog	Pfizer Animal Heath
136-483	Diethylcarbamazine Citrate, Oxibendazol	Antiparasitic	Dog	Pfizer, Inc.
139-191	Pyrantel pamoate	Antiparasitic	Dog	Farnam Companies, Inc.
139-191	Pyrantel Pamoate	Antiparasitic	Dog	Farnam Companies, Inc.
140-886	Ivermectin	Antiparasitic	Dog	Merial Ltd.
140-958	Phenylbutazone	Anti-inflammatory/Analgesia	Horse	Luitpold Pharmaceuticals
140-971	Ivermectin, Pyrantel Pamoate, Praziquantel	Antiparasitic	Dog	Merial Ltd.
141-007	Praziquantel, Pyrantel Pamoate, Febantel	Antiparasitic	Dog	Bayer Healthcare LLC, Animal Health Division
141-035	Lufenuron	Antiparasitic	Dog	Novartis Animal Health US
141-062	Lufenuron	Antiparasitic	Cat	Novartis Animal Health US
141-078	Ivermectin	Antiparasitic	Cat	Merial Ltd.
141-084	Lufenuron; Milbemycin Oxime	Antiparasitic	Dog	Novartis Animal Health US
141-087	Moxidectin (gel)	Antiparasitic	Horse	Fort Dodge Animal Health
141-111	Carprofen	Anti-inflammatory/Analgesia	Dog	Pfizer, Inc.
141-203	Deracoxib	Anti-inflammatory/Analgesia	Dog	Novartis Animal Health US, Inc.
141-230	Firacoxib	Anti-inflammatory/Analgesia	Dog	Merial Ltd.

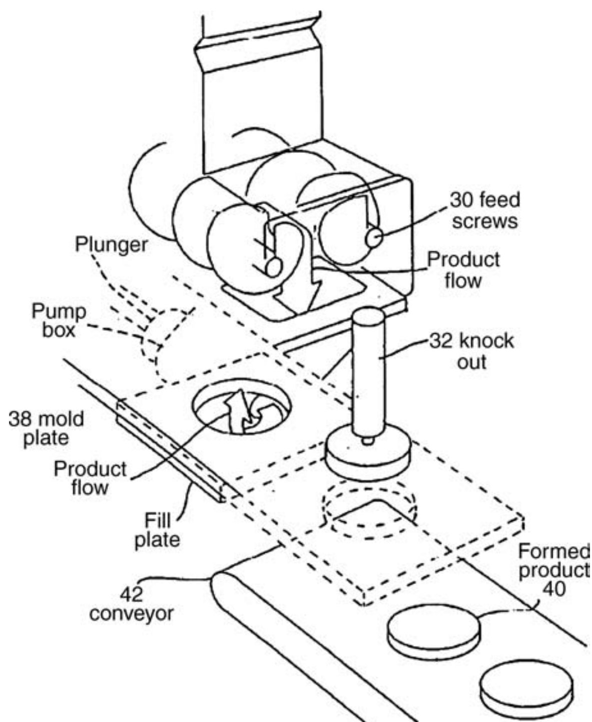

FIGURE 7 Schematic diagram of forming machine for chewable dosage forms.

described as "stale," "cardboard-like," "painty," or "rancid." Off-odors start with the oxidation of fatty acids (109,110). Polyunsaturated fatty acids are more likely to oxidize than saturated fatty acids. Polyunsaturated fatty acids are prone to lose additional hydrogen atoms at locations on the carbon atom that are adjacent to the points of unsaturation. Hydrogen subtraction from these points results in the formation of lipid free radicals, which are extremely reactive and tend to rapidly oxidize. The ethylene interrupter group between two double bonds (–CH=CH–CH–CH=CH–) is particularly prone to the loss of a hydrogen atom. The lipid radical form of ethylene group (R·) rapidly reacts with oxygen to form a proxy radical via a free radical chain reaction. The proxy radical (ROO·) can gain a hydrogen atom to form a lipid hydroperoxide (ROOH), which is relatively stable and exists in significant quantities in many natural fats. The lipid hydroperoxide has no off-flavor but rapidly degrades (particularly in the presence of heat and a metal catalyst) to form rancid flavors.

The hydroperoxide degradation begins with the loss of a hydroxy radical (·OH) to form a lipid alkoxy radical (RO·). The alkoxy radical rearranges and splits the molecule into two moieties, including an aldehyde that is volatile and emits a rancid odor. The aldehydes formed (pentanal, hexanal, and 2, 4-decadienal) are often so odor active that humans can detect concentrations as low as a few ppm (111). Meats containing polyunsaturated fats are more likely to oxidize and develop off-odors. Because of their relative polyunsaturated fatty acid content, the rate of off-odor development due to oxidation is fish > poultry > pork > beef > lamb (112).

A variety of manufacturing processes can trigger oxidation. In most cases, these processes either add the energy needed to initiate the oxidation reaction (heat and light), or they act as catalysts, reducing the amount of energy necessary for these reactions to occur (metals or high energy oxygen). The heat released during tablet processing can

cause the loss of water from excipients. High temperatures can cause the release of oxygen and the generation of free radicals (113). When these events occur, contact between the trace amounts of metals derived from processing equipment and polyunsaturated fatty acids can initiate the oxidation reactions. Any free iron that is present will be converted from its reduced state (Fe^{2+}) to its oxidized form (Fe^{3+}), leading to the generation of free radicals from meat fats. In addition, sodium from excipients, such as sodium starch glycolate, can accelerate oxidation of polyunsaturated fatty acid (113). Since oxidation is by nature a chain reaction, once polyunsaturated fatty acid oxidation begins to occur, it continues as polyunsaturated fatty acid free radicals catalyze additional free radical-generating reactions (114). The rate of fatty acid oxidation increases exponentially.

The most lipid pro-oxidative metals are transition metals, undergoing single electron transfer during a change in its oxidation states (115). Transition metals can react directly with lipids in oxidation reactions by decreasing the amount of energy necessary for the formation of the free radicals. They can also catalyze the decomposition of the lipid hydroperoxide, leading to the production of additional free radicals.

Light interacts with "photoactive" meat pigments, elevating the available oxygen to a high-energy state, thereby increasing its participation in oxidation reactions (115). Some kinds of light sources, such as fluorescent tubes, are particularly likely to precipitate oxidation reactions. This point has been long recognized by manufacturers of vitamin supplements, who have long used special lighting in their manufacturing facilities.

The generation of off-odors can be prevented in several ways (115):

- Antioxidants can be incorporated into the product. Antioxidants protect polyunsaturated fatty acids from oxidation to delay the onset of oxidation by extending the induction period. Primary antioxidants are "free radical terminators" that bind the oxidative radical. Their protective effect is concentration dependent, but it is also dependent on their fat-solubility and on the number of antioxidative sites on the antioxidant molecule.
- Oxidation, initiated or propagated by metal ions, can be effectively suppressed or delayed by chelating agents such as citric acid and EDTA. Ascorbic acid and erythorbic acid function as oxygen scavengers and serve to prevent lipid oxidation.
- Compounds found in herbs and spices can be used to contribute a variety of antioxidant substance to chewable pet tablets without adding to the flavor. Rosemary contains a number of phenolic compounds including carnosic acid (odorless), rosmanol (odorless), rosmariquinone, and rosemaridiphenol that are effective antioxidants at concentrations of 100 ppm.

The volatile components that produce off-flavors in liver, milk, and meat products have been isolated and identified (115–118). Acids, esters, aldehydes, ketones, and alcohols made up the major portion of the volatile components while pyrazines, hyphens and indoles were minor components. The characteristics of these odor causing molecules are provided in Table 6.

Soy based products are a common component of chewable companion animal products. As the fat in soy meal and flour is polyunsaturated, the fatty acids are prone to oxidation and have been well studied (119–126).

Similar to geriatric human patients, dogs and cats often exhibit changes in both gustatory and olfactory senses with age. It is unclear how this will impact the acceptability and ease of administration of a medication to the older animal.

TABLE 6 Odor Causing Molecules that may be Associated with Pharmaceutical Preparations

Component	Odor description	Component	Odor description
Aldehydes		*Ketones*	
Hexanal	Green, grassy	2-heptaone	Green
Heptanal	Unpleasant	3-octanone	Varnish, ketone
(E)-2-octenal	Nutty, tallow	2-octanone	Varnish, walnut
Methional	Mashed potato	Cyclohexanone	Almond
(E,E)-2,4-heptadienal	Fishy	1-octane-3-one	Metallic
Decanal	Orange peel	6-methyl-5-heptene-2-one	Green, estery
Benzaldehyde	Almond-like	2-nonanone	Ketone
(E)-2-nominal	Cucumber, cardboard-like	2-nonen-2-one	Orange-peel
(Z)-4-decenal	Cardboard-like	2-undecanone	Geranium, varnish
Phenylacetaldehyde	Hyacinth	*Furan*	
(E,E)2,4-decadienal	Deep-fried	2-pentylfuran	Green bean-like
5-methyl-2-phenyl-2-hexenal	Grapefruit-peel	*Thizoles*	
		2-ethylthiazole	
Alcohols		2-acetylthiazole	Liver-like
Hexanol	Metallic, grassy	*Phenol*	Nutty
1-octen-3-ol	Mushroom	Phenol	
6-methyl-5-hepten-2-ol	Musty, metallic	O-cresol	Phenolic
Heptanol	Unpleasant	*Pyrroles*	
Furfurylalcohol	Woody	2-pentylpyrrol	
Ester		*Acids*	Pungent
Methyl-6,9-octadecadienoate		Acetic acid	
		Butanoic acid	Vinegar
		Dodecanoic acid	Buttery
		Tetradeconoic acid	
		Pentadecanoic acid	
		Hexadecanoic acid	Waxy

SUSTAINED RELEASE TABLETS

In human medicine, sustained release tablet formulations provide an important tool for enhancing patient compliance. By modifying the rate of in vivo drug release, the dosing unit provides a prolonged in vivo exposure to the therapeutic moiety. Oftentimes, these long-acting, slowly releasing tablet formulaions allow the patient to have a dosing schedule of only once-daily drug, thereby increasing the likelihood of patient compliance.

Within veterinary medicine, there likewise is an ever-growing demand for long acting products. In some cases, (e.g., the antiparasitic medications), the target is to have a duration of action that extends over several months. In most cases, when a long systemic residence time is not associated with the properties of the drug itself, the available sustained-release technologies limit the dosing of these products to topical or parenteral administration. Nevertheless, the need for sustained release oral formulations continues to grow as the veterinary community finds the need to treat physiological conditions and diseases in animals that parallel conditions found in human patients.

Although the majority of the published studies on the absorption of long acting formulations in dogs were written from the perspective of the dog serving as a model for formulation feasibility in humans, these articles nevertheless provide insights into potential application of these technologies in canine medicine. One of the difficulties associated with the development of oral sustained release products for use in dogs and cats is that the very rapid GI transit time associated with these species provides a markedly shorter time over which the tablet can dissolve and drug can be absorbed. Generalizations of time differential for movement of particles across the various portions of the GI tract of humans, dogs and cats is provided in Table 7. Furthermore, gastric emptying times can be unpredicable. For example, the gastric emptying time of a poorly soluble drug formulated in an experimental polymeric matrix tablet in seven healthy, fasted beagle dogs ranged from 15 to 300 minutes. The small intestinal transit time ranged from 23 to 390 minutes. The estimated time to reach the colon ranged from 39 to 390 minutes (127). Clearly, with this type of variability, it is difficult to formulate an oral sustained release product that is intended to slowly release drug as it traverses the canine GI tract. In addition, considering the importance of colonic absorption when formulating sustained release oral formulations, it is important to consider the apparent variability in total GI residence time that appears to exist as a a function of canine breed and body size (128). Therefore, it may be difficult to achieve favorable pharmacokinetic profiles in dogs and cats when using controlled release formulations that are based upon delays in tablet disintegration and drug dissolution.

The impact of human-canine differeces in GI transit time was underscored by the failure of beagle dogs to adequately model the human bioavailability of acetominophen sustained release tablets (129), griseofulvin tablets (130), valproic acid (131), and ampicillin (132). Even in cases where an in vivo/in vitro correlation can be established in dogs, the oral sustained release product tended to have a lower bioavailability than the corresponding immediate release formulation (133). For this reason, the development of alternative gastro-retentitve systems may be particularly important in companion animal medicine.

Because of the relatively short GI transit time of dogs, a possible sustained release formulation strategy may be the prolongation of gastric residence. To accomplish this, several approaches have been examined, including the intragastric floatation devices (137), systems that lodge themselves in the stomach by altering their geometric configuration upon exposure to gastric fluids (57,138), and mucoadhesive devices (139). An

TABLE 7 Comparison of Time for the Movement of Small Particles Across the GI Tract of the Dog, Cat, and Man

	Human	Dog	Cat
Total small intestine transit time (MRT, min)[a]	180	60	144
Periodicity of housekeeper wave (fasted, min)	106	113	NA
Fasted gastric emptying T½ of non nutritive liquid (min)	8–15	8–15	
Return of housekeeper wave after a meal (min)	2.6–4.8	5.4–13.3	
Total fasted GI transit time (hr)[b]	20–30	6–8	8
Total fed GI transit time (hr)[b]	46	23 (miniature poodle), 59 Giant Schnauzer)	13

[a]Across species, small intestinal transit time shows only minimal changes with food.
[b]This assumes that particle readily passes through the pylorus.
Abbreviation: A, Cat has a different pattern of IMMC as compared to dog and man
Source: From Refs. 14, 56, 129, 134–136.

example of the benefit derived achieved by prolonging gastric residence time was seen when mucoadhesive granules were formulated with carbomer 934 plus ethylcellulose granules is provided in Figures 8–10. In this study, the migration of radio-labeled mucoadhesive versus nonbioadhesive granules were tracked as it moved from the stomach to the anus. The results demonstrate substantially prolonged GI retention (140).

The very strong crushing force of the canine stomach needs to be considered when formulating sustained release products. The crushing strength (hardness) of sustained release tablets often exceed 19 N prior to administration but can drop to as low as 0.5 N after 4 hours of exposure to aqueous fluids (141). Therefore, any formulation intended for prolonged gastric residence will need to withstand these forces. Failure to do so will result in formulation failure. For example, when superporous hydrogels composites were administered to fasted Beagle dogs, the capsules remained in the stomach for 2–3 hours before breaking into pieces and being emptied. However, when food was given, the capsule remained in the stomach for more than 24 hours, even though the fed condition was maintained for only the first few hours (142). Therefore, if the gastric crushing force of the dog is not considered, particularly when formulating hydrophilic matrix tablets, wax matrix tablet, enteric-coated tablet, and colon-targeted devices, these products may fail to perform due to their release at unintended sites in the canine GI tract.

TABLET IMPLANTS

Some medications (e.g., growth promotants for food-producing animals and anti-parasitic products) are intended for release over a duration of weeks to months. In these cases, oral formulations are not appropriate and the products need to be formulated for parenteral administration. One type of parenteral formulation intended for sustained release is the subcutaneous implant, of which a tablet implant represents one of several options.

Revalor-XS® (Intervet, Inc. Millsboro, Delaware, U.S.A.) is an example of a tablet implant. It is indicated for increased rate of weight gain and improved feed efficiency in steers (143) (Figs. 11 and 12). A single dosage unit consists of 10 pellets, each pellet containing 20-mg trenbolone acetate and 4-mg estradiol. It is injected subcutaneously behind the ear, releasing drug for up to 200 days.

These injectable tablets are designed for both an initial and a delayed release of the hormones. Despite the complexities of the release kinetics for this product, it is manufactured using the traditional granulation and tableting process (see US Patent

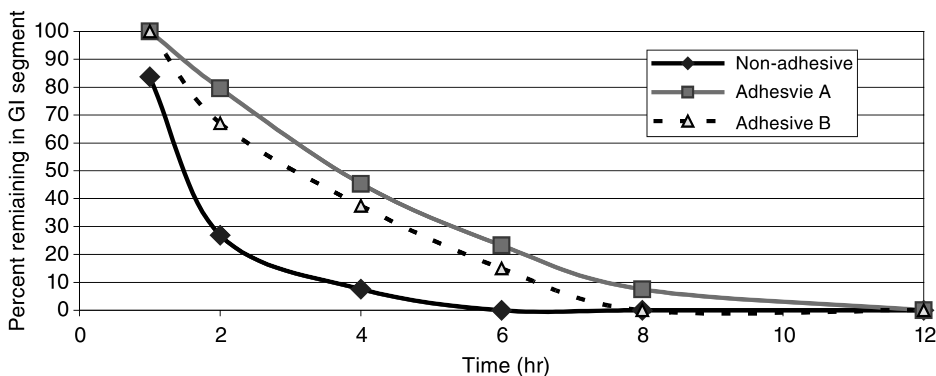

FIGURE 8 Residence of granules in the stomach of 3 fasted beagle dogs. *Source*: Based on data contained in Ref. 140.

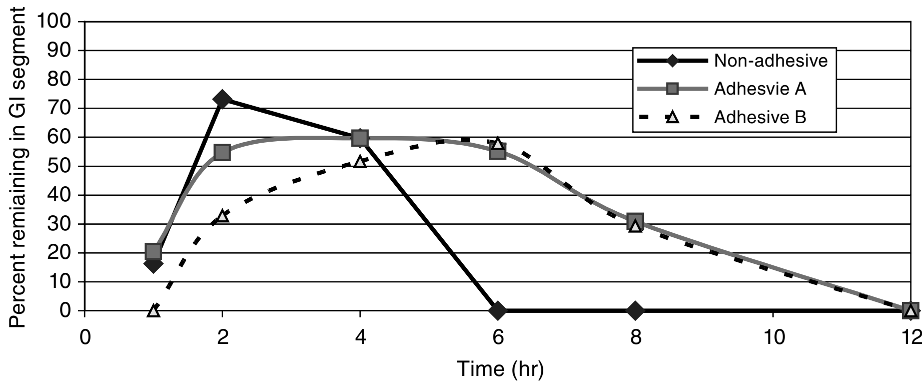

FIGURE 9 Residence of granules in the small intestine of 3 fasted beagle dogs. *Source*: Based on data contained in Ref. 140.

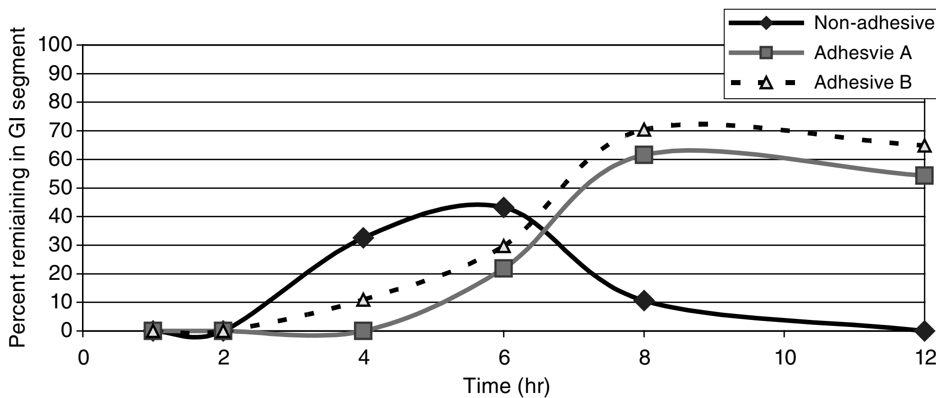

FIGURE 10 Residence of granules in the colon of 3 fasted beagle dogs. *Source*: Based on data contained in Ref. 140.

6,498,153 B1). Estradiol and trenbolone acetate are combined with the other excipients in a wet granulation step. The resulting granulate is dried and compressed on a tablet press to give small (~3 mm $\times$ 4 mm) cylindrical pellets. These uncoated pellets provide the drug release associated with early drug exposure. To achieve prolonged hormone delivery, some pellets are coated with a biodegradable polymer.

The rate of in vivo drug release is dependent upon the choice of biodegradable polymer. The biodegradable polymer coating is applied using a fluid bed or pan coater. Quality control of the coating thickness is a critical parameter during the manufacturing process. The coating thickness is monitored in process using an in-line NIR system, as shown in Figure 13.

ORAL BOLUS

Role of the Bolus in Therapy

Although parenteral administration is a frequently used method for administering drugs to large food-producing animals, these parenteral formulations risk damaging the tissue at

FIGURE 11 Implantation device for Revalor-XS® sustained release parenteral pellets. *Source*: Courtesy of Intervet. Inc.

FIGURE 12 Revalor-XS® pellets and packaging material. *Source*: Courtesy of Intervet, Inc.

the injection site, particularly when considering the volume of product needed when dosing an animal that weighs in excess of 500–1000 pounds. Sustained release parenteral products can also lead to high injection site residues, which will prolong the duration of time needed to allow for drug concentrations to deplete to a level determined to be safe for human consumption (i.e., the withdrawal time) (144). Alternatively, the topical route is also a convenient way to deliver insecticides and ectoparasiticides. However, there is minimal transdermal bioavailability of some compounds, thereby limiting its use to those moieties with either a direct topical effect or that are readily absorbed through the skin.

In lieu of topical or parenteral drug administration, the complex stomach of the ruminant can be used to allow for prolonged gastric retention of very large oral

FIGURE 13 Use of near IR for pellet quality control. *Source*: Courtesy of Intervet. Inc.

formulations. Consequently, recent decades have seen the veterinary bolus formulation evolve into a science that produces a sophisticated product capable of either immediate release or of an extended duration of release over many months. The release of the active ingredient generally relies on erosion, diffusion from a reservoir, dissolution of a dispersed matrix, or an osmotic "driver." Regurgitation during rumination is prevented by the formulating the bolus with a density of ~3 g/cm^3. Examples of FDA approved oral bolus formulations are provided in Table 8. As can be seen in this table, with the exception of one product, all bolus formulations have been approved for oral administration.

In addition to sustained-release boluses, there are intraruminal erodible systems that can be formulated as intraruminal pellets (also known as bullets) and as soluble glass boluses. Glass boluses are retained in the rumen for up to 9 months.

While large boluses have been available for horses (e.g., 1 gm phenylbutazone tablets), these are generally crushed, mixed into a thick paste (e.g., with molasses or corn syrup), and administered with a dosing syringe. In contrast, when administering the oral bolus to cattle, a "balling gun" or dosing device is needed. The balling gun is simple device that is inserted into the mouth of a restrained calf, delivering the bolus to the back of the tongue, whereupon it is swallowed. It basically consists of a tube with a capsule shaped holder that receives the bolus and a plunger that travels the length of the tube and ejects the bolus down the throat of the animal. Therefore, when designing the shape of the compression die, the bolus must be shaped to fit into a number of balling gun available on the market. Examples of the many balling guns available may be seen in Figures 14–16.

Utilizing melting and die molding technology, another novel oral controlled release drug delivery system consists of the API suspended in a slow dissolving hydrophilic wax. This core is surrounded by a cylindrical plastic housing containing a single orifice. As the matrix dissolves, a compressed spring that is located inside the housing presses the matrix against the orifice. By holding the exposed surface area constant, the delivery of the drug is kept constant over the course of the therapy.

Figure 17 provides an example of the manufacturing equipment upon which these cylindrical boluses are produced. Figure 18 provides an example of bolus device and associated components. The devise has foldable wings to prevent the regurgitation of the device. To prepare the device for administration, the wings are folded against the body of

TABLE 8 FDA-Approved Bolus Formulations for Use in Ruminanting Species and Horses

NADA #	Drug	Content	Route	Species
009-809	Chlorhexidine HCl	1 gm	Intrauterine	Cattle, Horse
010-987	Phenylbutazone	2–4 gm	Oral	Horse
011-532	Sulfabromomethazine sodium	2.5 gm	Oral	Cattle
011-590	Piperazine-carbon disulfide complex	20 gm	Oral	Horse
012-734	Chlorothiazide	2 gm	Oral	Cattle
012-956	Trichlorfon	7.3–18.2 gm	Oral	Horse
030-435	Dexamethasone	10 mg	Oral	Cattle, Horse
031-447	Griseofulvin	2.5 mg	Oral	Horse
031-448	Iodochlorhydroxyquin	10 gm	Oral	Horse
031-715	Sulfadimethoxine	2.5–15 gm	Oral	Cattle
033-127	Sulfachlorpyridazine	2 gm	Oral	Cattle
034-621	Furosemide	2 gm	Oral	Cattle
039-356	Levamisole hydrochloride	2.19 gm	Oral	Cattle
045-188	Furosemide	2 gm	Oral	Cattle
049-892	Sulfamethazine	27 gm	Oral (SR)	Cattle
055-018	Chlortetracycline hydrochloride	25 mg	Oral	Cattle
055-039	Chlortetracycline hydrochloride	25–500 mg	Oral	Cattle
055-056	Ampicillin trihydrate	400 mg	Oral	Cattle
055-074	Ampicillin trihydrate	400 mg	Oral	Cattle
055-087	Amoxicillin trihydrate	400 mg	Oral	Cattle
065-004	Tetracycline hydrochloride	500 mg	Oral	Cattle
065-270	Tetracycline hydrochloride	500 mg	Oral	Cattle
065-481	Chlortetracycline hydrochloride	250 mg	Oral	Cattle
091-826	Levamisole hydrochloride	2.19 gm	Oral	Cattle
092-483	Haloxon	10.1 gm	Oral	Cattle
093-107	Sulfadimethoxine	12.5 gm (SR)	Oral	Cattle
093-329	Sulfamethazine	22.5 gm (SR)	Oral	Cattle
093-903	Morantel tartrate	2.2 gm	Oral	Cattle
011-052	Levamisole hydrochloride	0.184 gm	Oral	Sheep
120-615	Sulfamethazine	32.1 gm (SR)	Oral	Cattle
122-271	Sulfamethazine	2.5–15 gm	Oral	Cattle
140-270	Sulfamethazine	30 gm (SR)	Oral	Cattle
140-909	Sulfamethazine	5 gm	Oral	Cattle
140-988	Ivermectin	1.72 gm (SR)	Oral	Cattle
141-002	Oxytetracycline hydrochloride	250 mg–1 gm	Oral	Cattle

the device and it is inserted into a balling gun. The balling gun constrains the wings while the bolus is being administered. The wings remain folded as the bolus moves down the esophagus. However, the wings swing open once it enters the rumen, thereby lodging it in the bovine stomach where it releases the necessary amounts of drug over time.

Formulating boluses is extremely difficult because design errors are magnified by its great size. Furthermore, because of the amount of drug in these tablets, efforts to use standardized in vitro dissolution test method are generally met with several challenges such as selection of appropriate dissolution apparatus and the design of the dissolution medium. A key to the latter is that the conditions must be selected so that sink conditions are present and the buffering capacity of the medium must be adequate to minimize changes in pH as very large quantities of drug are dissolved. Until recently, test conditions that met the latter attributes were not available. However, in a study by

FIGURE 14 Plastic balling gun.

FIGURE 15 Metal balling gun with spring clips.

FIGURE 16 Metal balling gun with plastic head.

Fahmy et al. (145), a potentially discriminating in vitro dissolution test for veterinary boluses containing up to 5 gm of sulfa drugs was identified, employing USP apparatus II with conventional volumes (900 mL of buffer). In this method, the stirring rates and the aqueous medium was specially designed to provide and maintain sink conditions. Based upon this work, it is now recognized that the design of an appropriate buffer system for oral boluses containing weakly acidic or weakly basic drugs can be defined through the use of standard theoretical relationships fitted to real solubility and buffer data.

In conjunction with the creation of an in vitro method that was repeatable and that used standardized equipment, the question was whether or not these in vitro methods could predict in vivo formulation effects (45). To explore this question, two sulfamethazine bolus formulations exhibiting markedly different in vitro dissolution characteristics were examined in cattle. The in vitro dissolution test was conducted in in 900 mL of 0.1% SLS in 0.1 N HCL, and employed the USP Apparatus 2 (paddle) at 75 rpm. Despite the observed differences in in vitro drug release (the slow dissolving bolus released 90% of its contents in 9 hours while the rapidly dissolving bolus released 90% of its contents in 5 hours), the Cmax and Tmax values for these formulations were comparable. In fact, the Cmax of these bolus formulations succeeded in meeting traditional in vivo bioequivalence criteria both to each other and to a sulfamethazine oral solution (Fig. 19). This observed difference in in vivo versus in vitro product performance is consistent with the known delay that occurs in bovine gastric emptying. Therefore, for immediate release bolus formulations, the rate limiting step will be bovine gastric transit time rather than product in vivo dissolution time.

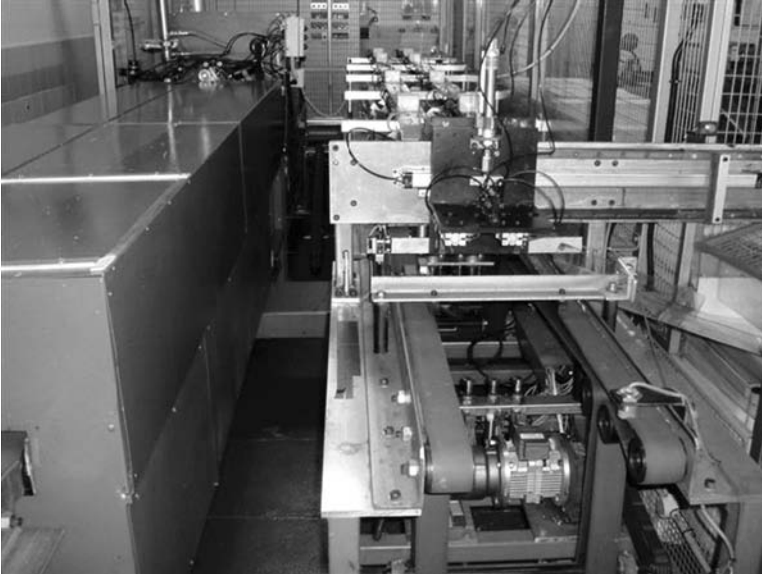

FIGURE 17 Process equipment use to prepare the solid core. *Source*: Photograph courtesy of Elanco Animal Health, a Division of Eli Lilly Company.

In contrast, the rate and extent of drug release appears to be the rate limiting factor when an oral bolus is developed for prolonged drug release. For example, Frazier and Nuessle (146) observed markedly different in vivo profiles for sulfamethazine sustained release oral boluses when these products exhibited differing in vitro release profiles (their

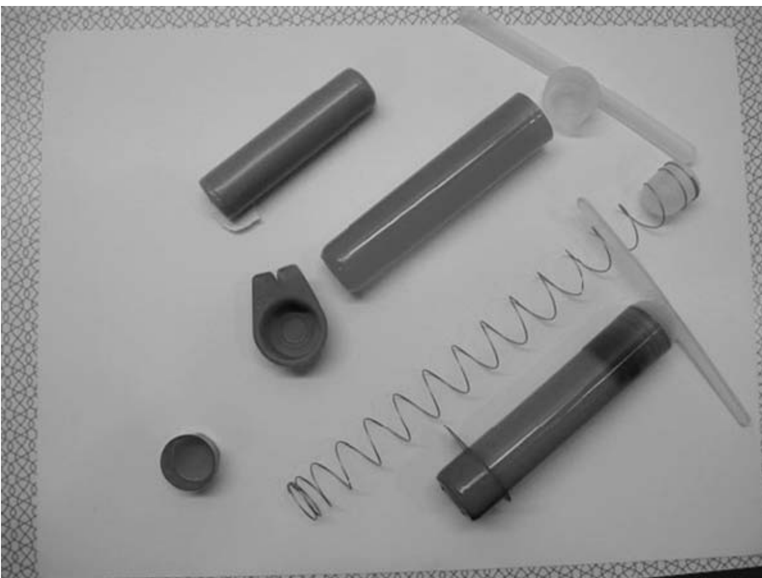

FIGURE 18 Examples of sustained release oral delivery systems for ruminants. The waxy core is assembled in the plastic housing with the compressed spring. *Source*: Photograph courtesy of Elanco Animal Health, a Division of Eli Lilly Company.

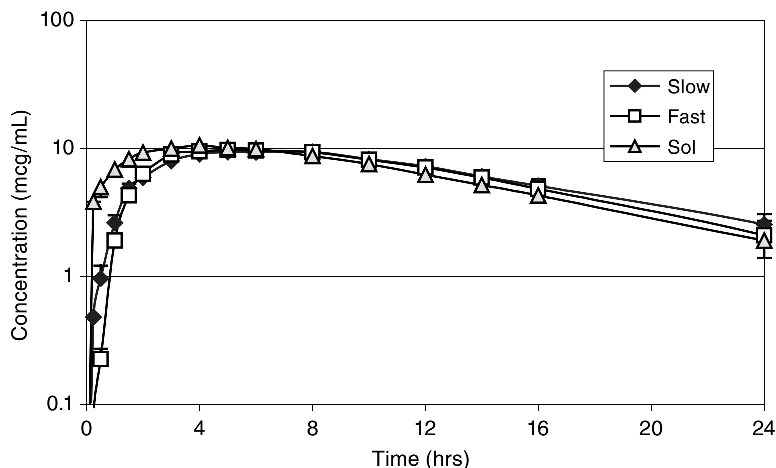

FIGURE 19 Effect of formulation on concentration/time profile of sulfamethazine (mean ± SEM): fast = rapidly dissolving formulation; slow = slowly dissolving formulation; sol = oral solution.

in vitro test did not utilize a USP apparatus). These bolus formulations contained iron, which increased the weight of the tablets and caused it to remain in the rumeno-reticular sac until disintegration was complete. Similarly, inequivalence of sulfamethazine in vivo oral bioavailability was observed across different formulations of sustained release bolus formulations in sheep (147).

Challenges in Product Design

Boluses, being a class of large tablets, are the most challenging of tablets to formulate, particularly when the drug exhibits poor solubility and poor wetting properties, such as that seen with the sulfa antibiotics. The corresponding difficulty in formulating boluses that result in good cohesive compacts and reliable drug bioavailability has been widely discussed in the literature. However, even for drugs with where solubility and permeability are not an issue and where the drug exhibits good compression characteristics, bolus product design and manufacture can be challenging. This is largely a consequence of the many competing objectives for developing this dosage form. For example, any action that is taken to improve hardness and friability may lead to slow and erratic in vivo dissolution and poor oral bioavailability.

Once a stable formulation has been developed, the robustness of the formulation processing parameters should be established. The robustness of a manufacturing procedure is a measure of its capacity to remain unaffected by the small but deliberate procedural parameter variations listed in the manufacturing directions. It provides an indication of the manufacturing procedure's suitability and reliability while being carried out during normal conditions. Although not traditionally considered a validation parameter, an evaluation of procedural robustness may require an up-front time investment, but it safeguards against the unforeseen problems that can occur during scale-up for marketing. For example, in a wet granulation process, typical variations are granulating solution volume, rate of addition of the granulating solution, wet mass mixing time with choppers off, wet massing time with choppers on, and mesh size for screening the wet granulation.

Robustness studies can also be used in a holistic approach to make sure the validity of the entire system (including the formula, manufacturing equipment, and manufacturing directions) is maintained throughout implementation and use. Holistic tests generally tend to be more effective because they evaluate the entire system rather than simply the system's individual modules.

Designing a Robustness Study

For years, formulators have conducted both optimization and robustness studies according to a "one factor at a time" approach. This approach, while certainly methodical in character, can be needlessly time consuming, and often, important interactions between variables remain undetected. Changing several variables simultaneously, rather than one at a time, allows the effects of these concurrent changes on the process to be studied simultaneously.

When evaluating the robustness of the system, an experimental design should be established based upon the concept of a design space for the manufacturing process. The objective of these studies are to define the limits of the critical manufacturing parameters (the design specifications), so that there is an assurance that if each of these parameters are within these limits, the boluses will perform in a safe and effective manner. The objective is not to define the limits for product failure. Rather, factors are chosen symmetrically around a nominal value, forming an interval that slightly exceeds the variations that can be expected during the manufacturing procedure.

The following example is provided to clarify the steps involved with an evaluation of system robustness for bolus formulations. In this illustration, it is assumed that the bolus is produced using a wet granulation method. The fourth sub-batch represents the on-target condition for all process variables.

Wet Granulation Step

The sample protocol begins with the production of a mother batch of API containing a powder blend that will be wet granulated. The wet granulation is processed using three different volumes of granulating solution, three wet-massing mixing times, and three mesh sized screens for sizing the wet granulation. When completed, a set of seven granulations will be produced, resulting in a spectrum of particle size distributions and granulation's hardness.

- The first sub-batch is under-wetted and mixed for less than the target wet-massing time. Nevertheless, the textured granulation is acceptable. This granulation is wet screened through a slightly finer mesh screen than the mesh of the target screen. When dried, this granulation will have a fine particle size distribution and be a soft granulation.
- The second sub-batch is under-wetted but mixed for the target wet-massing time. This granulation can be made from the first granulation by extending the wet massing time after a sample has been removed from the mixer. This granulation is wet screened using either a slightly finer screen or, if necessary, the target screen. When dried, this granulation should have a particle size distribution that lies between that of the first and the fourth sub-batch. However, the granulation will be harder than that of the first sub-batch.
- The third sub-batch is produced by using the target volume of granulating solution and by under wet-massing. This granulation is wet screened using the targeted

mesh size. When dried, this granulation should have a particle size distribution that lies between that of the first and the fourth sub-batch, but it should contain a harder granulation than that of the first sub-batch. By comparing the boluses produced by compression of the second through fourth sub-batches, the formulator can determine the impact of mixing time on the bolus characteristics.

- The fourth sub-batch is produced using both the target volume of granulating solution and the target mixing time. This granulation is wet screened with a screen of the target mesh size.
- The fifth sub-batch is produced by under wetting and over wet-massing. Mixing is stopped while the wet granulation still has an acceptable texture. This granulation can be made by extending the wet-massing time of the second sub-batch. The granulation is wet screened using slightly larger than target mesh size screen. When dried, this granulation will have a coarser particle size distribution. However, depending on the formulation, the granulation may be softer or harder than the on-target batch.
- The sixth sub-batch is produced by over wetting and under wet-massing, but the mixing is stopped while the wet granulation still has an acceptable texture. This granulation is wet screened using slightly larger than target mesh size screen. When dried, this granulation should have a coarser particle size distribution. However, depending on the formulation, the granulation may be softer or harder than the on-target batch. By comparing the resulting boluses compressed form this sub-batch with those from the fifth and fourth sub-batch the formulator can understand the affect of changes to the granulating solution volume.
- The seventh sub-batch is made by over-wetted and over-mixing. However, this sub-batch will still yield an acceptable texture. This granulation can be made by extending the wet mass mixing time of a sample from the sixth sub-batch. The granulation is wet screened with a coarser mesh size screen than targeted. When dried, this granulation will have a coarser particle size distribution and a harder granulation than does the on-target batch.
- After drying, and sizing, sieve analysis is performed on the seven sub-batches to obtain data on the particle size distribution of the granulations.

Lubrication Step

The seven sub-batches of dried granules are mixed with the "dry adds," which includes the disintegrant and any additional bulking excipient. The lubricant is blended into each separate sub-batch. If desired, the lubricant blending time may be varied producing further subdivisions with in the sub-batches.

Bolus Compression

The sub-batches of granules are compressed into boluses. Each sub-batch may be compress at the low, target, and high end of the desired compaction force range.

Data Gathering

The various batches of boluses are tested for their physical properties (disintegration, hardness, friability, and dissolution). From this data calculate the process capacity (Cp) and the process capability index (Cpk) for each sub-batch. Samples are placed on an accelerated stability program. A matrix approach can be used so that not all of the sub-batches need to be tested at all stability pull intervals. All of the resulting data must be statistically analyzed, providing the justification for product release and stability specifications. Ultimately, the limits defined by the robustness study are used to set the manufacturing parameters.

Challenges in Bolus Process Validation

In this section, emphasis will be placed on the validation of boluses from the early stages of product development through pilot scale-up and the manufacturing process. The concept of process validation and the regulatory aspects associated with current good manufacturing practice (cGMP) and their application will not be covered because this information is discussed elsewhere in this book.

All pharmaceutical scientists are familiar with the axiom that quality is not tested into a product but rather is built into a product. This is an important concept, since it serves to support the underlying definition of validation, which is a systematic approach aimed at identifying, measuring, evaluating, documenting, and re-evaluating a series of critical steps in the manufacturing process that require control to ensure a reproducible final product.

All aspects of process validation that pertain to tablets likewise apply to boluses. These include:

- blend uniformity,
- potency,
- validation of the granulation process (i.e., mixing times, rate of addition of granulating solution, describing equipment and/or instrument conditions required to promote optimal drying, optimum milling conditions of the dried particles, optimum moisture content range of the dried granules, optimum dried granulation particle size distribution, and optimum lubricant blending time).

Definition and Control of Process Variables

Process validation involves the challenging of a process during its early stages of development by making deliberate changes that identify the critical process variables. Once identified, these are the variables that must be controlled to ensure the consistent production of a product or an intermediate.

The activity begins with the collection of the kinds of information described above. Data are gathered during the stages of preformulation, formulation development, process development, and manufacturing scale-up. Once the critical variables are identified, a numerical range of each parameter is determined (e.g., assessing the range of tablet hardness that achieves desirable performance characteristics as characterized by friability, disintegration, and dissolution). A bolus needs to be harder and less friable than a small tablet because it must withstand the rigors of traveling in a saddle bag or in the veterinarian's pickup truck over rough terrain.

Statistical techniques determine the acceptable extremes of acceptable hardness (high and low) that would provide 95% assurance that the friability, disintegration and dissolution specifications will be met. These then form the upper and lower control/release limits for that product. Because many boluses are bi-layered and/or sustained release, they must be manufactured with special attention paid to consistency of the compression process to achieve batch to batch consistency. Therefore, it is necessary to determine how well the specification limit indicates that the process is under control.

Optimizing Compression Operation for Bolus Hardness

Because of manufacturing challenges associated with its size, the compression force applied to the bolus should be checked for its affect on bolus properties. The relationship between compression bolus properties is one of the critical manufacturing variables that

need to be considered. That is, the tablet press rotational speed affects the dwell time (the time the powder mass is under compression by the tablet punches), which can affect hardness, friability, dissolution, etc. In general, an increased in dwell time will result in a harder tablet. In some bolus formulations, this increase in hardness will likewise increase the time required for disintegration and dissolution.

A multivariate approach can be used to evaluate the relationship between press speed and tablet hardness on bolus weight, thickness, disintegration time and dissolution time. In so doing, specifications for the compression process can be established. An example of a protocol for this kind of assessment is provided in Figures 20 and 21 (148).

Bolus Hardness Testing

As with any tablet formulation, excessive hardness can retard product dissolution and excessive softness can lead to friability (149–151). Owing to its very large size, it is particularly important to control this variable during the manufacture of boluses. However, standardized methods for evaluating tablet hardness cannot be directly applied to boluses. Rather, these procedures need to be modified to accommodate the very large size of these tablets.

Historically, the term "hardness" has been used to describe the physical tablet strength. However, from strength of materials standpoint, this definition is not strictly correct. Normally, material hardness (for metals) is measured using an indentation test, such as the Vickers Hardness Test. This method is not suitable for testing tablets because tablets are relatively brittle. Rather, tablet "hardness" actually refers to the compressive strength of a dosage unit rather than its physical strength.

The first tablet hardness tester was introduced around the mid-1930s. This was a simple hand held mechanical device. The tablet rested between two concave platens and force was applied to the by turning a wing-nut screw until the tablet fractured. The hardness was read from a sliding scale graduated in half kilogram increments. This device was followed by the Strong–Cobb tester which was introduced around 1950. Again, the tablet rested vertically on a concave platen. The force was generated by a manually operated air pump and the tablet breaking force was measured on a dial graduated into 30 arbitrary units that were designated as "Strong–Cobb" units. The results generated by the Strong–Cobb tester were not consistent with those of the earlier test procedure.

Currently, tablet hardness is generally measured using an electro-mechanical device. Several different types are available from a variety of manufacturers. When using these devices, the tablets rest in a horizontal position between two flat platens. A motor drive system generates the force, electronics automate the test procedure, software calculates statistics, and measurements are printed or downloaded to a computer.

For standard sized tablets, the Brazilian test, named for its inventor Dr. Brazilian, is the method commonly used for testing hardness. Typically, the tablet is crushed between two jaws while the instrument measures the force needed to generate the fracture. Although the compressive force is applied equally to the disc, tablet tends to fracture along their diameter. In other words, the limits of tablet plasticity are best visualized along the outer limits of the disk.

Because boluses do not fit longitudinally between the jaws of most testers, the three-point bending method can be used to test the hardness of these large dosage forms. If the bolus is scored for administering divided dosages, three-point bending method

Step 1: Set the press at the lowest desired speed and adjust the fill cam to yield boluses with the target weight. Record the punch penetration, granulation feeder paddle speed, and the average pre-compression thickness so that the experiment can be repeated. Adjust the press main compression force to determine the minimum and maximum acceptable bolus hardness based on dissolution and friability results.

Step 2: With the press operating at the minimum desired speed, sample about 75 boluses from the press at the minimum and maximum hardness to provide sufficient samples for testing. Perform the following testing.

- Weigh 10 boluses for individual weights.
- Test 10 boluses for individual thickness.
- Test 10 boluses for individual hardness. Hardness testing should be performed on bolus taken immediately off the press as the hardness will change over time (hours or days) until it reaches a plateau.
- Measure disintegration time.
- Measure the dissolution of 12 boluses.

Step 3: Repeat the press setup, sampling, and testing for the highest desired press speed.

FIGURE 20 Sample protocol steps for setting specifications for the compression process.

simulates bolus fracture when snapped between the thumb and forefingers. Special jaws for three-point bending can be purchased from some instrument manufacturers or they can be fabricated in house to meet the design of the bolus.

The relationship between applied forces and yield loads is given by the following equation.

$$\sigma_t = \frac{\pi P}{2Dt},$$

where σ_t is the tensile strength, P the yield load in Newtons, D the disc diameter in mm, and t is the thickness of the disc in mm.

Most materials testing are performed using the International System of Units (SI). The Newton is the most widely used unit of force and is consistent with the SI system. However, the kilogram is also commonly used. Therefore, compression force may be expressed in a variety of ways, including:

- *Kilogram force*: The kilogram force is a derived unit of force. It is not an SI unit. It is the force exerted by one kilogram mass acted on by the force of gravity as sea level.
- *Newton* (N): The Newton is the SI unit of force and is the unit that should be used for tablet hardness testing 9.807 Newtons = 1 kilogram force.
- *Pound force* (lbf): The pound is the correct unit of force in the English system of measurement. The slug is the unit of mass in the English system and the common pound mass is a derived unit.
- *Kilopond* (kp): The kilopond is synonymous with the kilogram force. It is considered an obsolete unit.
- *Strong–Cobb* (SC): The Strong–Cobb unit is a legacy of the first tablet hardness testing machines. It is an arbitrary unit and varied from instrument to instrument. In

Step 1: Set the press at the lowest desired press speed and adjust the press to produce boluses having the target weight and hardness. Record the punch penetration, granulation feeder paddle speed, and average pre-compression thickness so that the experiment can be repeated. Do not re-adjust the settings while running these tests: the goal is to demonstrate that the granulation will process through the press without adjusting the press.

Step 2: Run the press at the target weight and target hardness for about 5 minutes to allow the granulation to come to steady state rate of flow through the hopper and the feeding apparatus. Over the next 45 minutes, sample about 50 boluses at 5 minute intervals. This will yield 10 sets of 50 boluses.

Step 3: Perform the following testing on each of the ten sets of boluses:

- Weigh 10 boluses for individual weights. In the case of a bi-layered bolus, the weight of the bottom layer and the overall weight should be recorded.
- Test 10 boluses for individual thickness.
- Test 10 boluses for individual hardness. Hardness testing should be performed on bolus taken immediately off the press as the hardness will change over time (hours or days) until it reaches a plateau.

Step 4: Set the press for the highest desired speed and repeat sampling and testing.
Step 5: Calculate the average (*avg*) and the standard deviation (σ) for the weight, hardness and thickness data.
Step 6: Using the average and standard deviation, calculate the process capacity (Cp) and process capacity index (Cpk) values for each sample group at each press speed. These parameter values are calculated as follows:

Cpk = Minimum{Cpu, Cpl} where:

$$Cpu = \frac{USL - avg}{3\sigma} \qquad Cpl = \frac{avg - LSL}{3\sigma}$$

Cpu = Process capability index upper limit
CPl = Process capability index lower limit
USL = Upper Specification Limit
LSL = Lower Specification Limit

$$Cp = \frac{USL - LSL}{6\sigma}$$

Step 7: Set the acceptance criteria for weight, thickness and hardness. For example:

- Weight: Cp > 1.33 and Cpk > 1.25
- Thickness: Cp > 1.33
- Hardness: Cp > 1.33 and Cpk > 1.25, where the specification range is adjusted by a multiplier of 1.82. This adjusted specification range contains 90 % of the distribution within the stated Cp and Cpk specification.

Step 8: If the press qualification fails either the Cp or Cpk for a given parameter, the process is considered to be unacceptable. Upper and/or lower specification may be re-evaluated if the new specifications are obtainable and are acceptable for all other critical parameters,(i.e., disintegration, dissolution, and friability). If changing the specification is not possible, then appropriate adjustments should be made to the machine and the test for that speed should be re-run.

FIGURE 21 Sample protocol for performing press qualification.

1960s a study was done comparing various Strong–Cobb hardness testers and an average conversion factor of 1.4 SC units/kg was reported.

The following table is presented to help convert between the various units measure employed to describe tablet hardness.

TABLE

Unit of force			Unit of force
1 kp	=	9.807	Newtons
1 kp	=	1.4	Strong Cobb Units (SCU)
1 kp	=	2.205	Pound force
1 SCU	=	7.005	Newtons
1 SCU	=	0.714	kilopond (kp)
1 N	=	0.102	kilopond (kp)
1 N	=	0.143	SCU
1 N	=	0.2248	Pound force
1 lbf	=	4.448	Newtons
1 lbf	=	0.4536	Kilopond (kp)

SETTING SPECIFICATIONS FOR VETERINARY TABLET DOSAGE FORMS

The quality of veterinary tablets depends upon their design, the use of in-process controls, GMP, the application of process validation, and the appropriateness of product specifications.

Specifications are set for those parameters that will influence the safety and efficacy of the finished dosage form. They include a list of tests, references to analytical procedures, and proposed acceptance criteria. The acceptance criteria are determined during product development, as well as from stability and scale-up/validation batches, with emphasis on the primary stability batches. Certain tests may be excluded or replaced, depending upon their relevance to product performance. For example, dissolution testing for immediate release tablets manufactured using highly soluble and highly permeable drug substances may be replaced by disintegration testing if these products have been demonstrated to have consistently rapid drug release characteristics.

The manufacturing testing requirements for veterinary tablets are comparable to those used for human tablets. These tests, as detailed in the VICH guidance GL39 (152), are applicable to both coated and uncoated formulations, and include (but are not limited to) the following:

- *Dissolution*: The specification for solid oral dosage forms normally includes a test to measure release of drug substance from the tablet. Single-point measurement is normally considered to be suitable for immediate-release dosage forms. However, the single time point specification should not be construed as being indicative of product relative bioavailability should there be changes to either the formulation or the manufacturing process. For modified-release or delayed-release dosage forms, multiple time-point sampling and/or two-stage testing may be appropriate. Ultimately, the dissolution method should reflect the magnitude of variability present between batches and should be sufficiently discriminative to detect alterations in product performance resulting from change in manufacturing method and/or formulation.
- *Disintegration*: A disintegration test may be preferable to a dissolution test when the drug is rapidly dissolved (i.e., dissolution >80). Disintegration testing is most appropriate when a relationship to dissolution has been established or when disintegration is shown to be more discriminating than dissolution.

- *Hardness/friability*: Generally, hardness and/or friability testing are performed during in-process control. These attributes can have a critical impact on quality (e.g., chewable tablets, or the ability to maintain tablet integrity during storage) and performance (e.g., bioavailability).
- *Uniformity of dosage units*: To be released for marketing, tablets need to demonstrate a uniformity of weights across dosage units, and each dosage unit is expected to contain a specified percentage of the targeted amount of the API. Content uniformity may be an in-process test (e.g., coated tablets) or it can be determined after manufacturing has been completed. The acceptance criteria should be included as one of the dosage form specifications.
- *Water content*: For hydrophobic compounds, the water content of the finished dosage form should be quantified. The acceptance criteria for water content may be justified by data that have been collected on the effects of hydration, or water absorption, on the integrity of the tablet.
- *Microbial limits*: In general microbial content should be tested in the finished dosage form unless the components have been tested prior to product manufacture. Acceptance criteria should be set for the total counts of aerobic microorganisms, the total count of yeasts and molds, and the absence of specific objectionable bacteria (e.g., *E. coli* and *Salmonella)*. The testing of additional organisms may be appropriate according to the U.S. Pharmacopeia (USP). The type of microbial test(s) and acceptance criteria should be based on the nature of the drug substance, the method of manufacture, and the intended use of the medicinal product. Under certain situations, there are no required microbial limits for solid oral dosage forms.
- *Stability*: The purpose of stability testing is to document product quality over time, regardless of the presence of environmental stressors such as heat, humidity, or light. Recommendations for the design of stability protocols for veterinary drug substances and medicinal products are summarized in the VICH guidance (153). Validated analytical procedures should be used to quantify the concentration of the API and should be capable of resolving the API and impurities.

When designing a stability study for veterinary tablets, the physicochemical properties of the API and the nature of the excipients need to be considered. Therefore, these tests pertain not only to the API but to the dosage form as well. Accordingly, the stability studies should include testing for all parameters that affect the product quality, safety, and/or efficacy. These include the physical, chemical, biological, and microbiological attributes, preservative content (e.g., antioxidant, antimicrobial preservative), and functionality tests (e.g., for a dose delivery system).

The expiration date is determined on the basis of stability information on the API (which was obtained during preformulation assessments), and from available clinical stability data. It should be noted, however, that the acceptable amount of impurity in the dosage form may be set to different specifications for batch release versus for stability criteria. In this case, it is not unusual for the batch release specification to be more conservative than those used when setting expiry.

In general, the stability program includes the first three production batches, two of which can be pilot scale batches. Where possible, batches of the finished drug product should be manufactured using different batches of the drug substance. The stability program usually includes 3% of the production batches (with minimum of one lot per year), with the stability batches containing the same formulation and packaged in the same container closure system as proposed for marketing.

Stability studies should be performed on each individual strength and container size of the medicinal product unless bracketing or matrixing is applied. Should a batch fall outside of the established stability specification, reasons for this finding should be investigated.

CONCLUDING COMMENTS

Although the chemistry and manufacturing issues associated with veterinary tablets are identical to those associated with human tablets, there are also several challenges unique to veterinary medicine that need to be considered. These include the bioavailability and administration issues resulting from interspecies differences in physiology, dosing needs, and husbandry practices, problems associated with flavoring agents that can affect product stability and bioavailability, and the unique manufacturing challenges associated with boluses. These veterinary-specific issues not withstanding, the basic science of product formulation and manufacturing is similar, regardless of the species for which the tablet is intended. For this reason, an individual expert in the production of human tablets could easily move into the production of veterinary tablets. With this in mind, the other chapters within this book that cover the processes associated with the development and manufacturing of tablets are equally pertinent to human and veterinary medicine. Therefore, readers should refer to these other chapters on general issues in tablet manufacture and performance characterization.

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14

Swellable and Rigid Matrices: Controlled Release Matrices with Cellulose Ethers

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INTRODUCTION

Controlled release of drugs is a dynamic activity of pharmaceutical companies, due to the indisputable advancement provided by delivery technology to pharmacotherapy. In addition, this activity give rise to new patented products for a market in which new substances are reducing and the approved ones more and more face dispensing problems. Today, no drug product enters the market without its own delivery program built in. In front of this requirement, pharmaceutical technology researchers proposed the so called drug delivery "technology platform," i.e., drug administration based on the use of devices capable to contain, meter and deliver the drug at appropriate rate and duration.

Typically, without considering drug conjugates, drug delivery devices are classified reservoirs or matrices. The choice between them depends on drug properties and delivery kinetics sought. In general, matrices are considered more reliable in term of delivery, less costly as manufacturing and easier to formulate. They are also less exposed to malfunctioning problems.

Matrices are monolithic systems constituted of active substance dispersed and entrapped in a continuum of excipient (adjuvant), i.e., the "matrix forming" substance. The matrix requisite is the non-immediate disintegration of the monolith in contact with dissolution media. The usual appearance of this device is the tablet form, commonly manufactured by compression, that introduced in water does not apparently disintegrate. The maintenance of the solid structure permits the establishment of the mechanism for drug release control.

Matrix keeps a substantial integrity or structure for the time needed to release the dispersed or dissolved drug. This does not mean that the matrix has not to dissolve but

simply that dissolution is slowed down by the typical release mechanism. This behavior differentiates the disintegrating tablets from the matrices, the first promptly providing drug for dissolution and absorption, the second controlling in time drug dissolution and absorption. Here, drug release is obtained by elution from the polymeric (in general) continuum that can actively or passively participate to the release.

Comparing reservoir and matrix devices, the first constitutive difference resides in the location of the drug deposit that in the reservoir systems is concentrated in the nucleus, whereas in the matrix it is dispersed in the entire monolith mass. The second difference is due to the control element of the release. In reservoir systems this element is clearly identified in the membrane composition and thickness. By definition the membrane is not modified by the solvent and this makes possible for reservoir systems to exhibit in steady state a zero-order release. In matrix the control element is build up during system release, since it consists on the external layer emptied by drug. The control element of release, in dependence on its behavior kinetics, gives drug releases from diffusion to zero order.

Three types of matrices, namely inert, erodible or swellable matrices, can be constructed and their release kinetics changes according to the category. Inert matrices leave residual skeletons, erodible matrices slowly disintegrate and the swellable ones jellify. As a general concept, also swellable matrix undergoes erosion during its release life, but the drug release can be concomitant or anticipate the matrix erosion or dissolution. This is strictly depended on the combination of hydrophilic polymers used for making the matrix. When the swellable polymer is enough soluble, the polymer dissolution process overlaps the swelling and the drug release kinetics results affected.

Swellable matrices will be the subject of this chapter with the main focus on the swelling phenomenon and on the related drug release kinetics, in dependence on the components and matrix geometry used. Swellable matrices are typical moving boundary release systems. This means that the diffusive barrier for drug release control is continuously changing dimension. This barrier is the layer thickness externally formed on the matrix that controls drug transport through it. In swellable matrices the barrier is called gel layer. Similar situation is faced with the other types of matrices differently from the reservoir systems in which the diffusive path (membrane thickness) remains constant during the release time. In inert matrices, starting from the external surface, this path increases continuously during drug elution and the depleted layer, made of matrix forming material not dissolved by dissolution medium, constitutes the control barrier. In erodible matrices, the path increases and decreases at the same time, so the possibility exists that the thickness remains constant with a resulting zero-order control on the drug transport.

In the pioneer publication of Higuchi (1) on drug delivery mechanism from an inert matrix, the release flux was studied from the analysis of the concentration/position relationship inside the matrix. This is illustrated by the schematic representation in Figure 1, where a matrix made by drug particles and inert polymer is supposed to dissolve on the two sides, disregarding the edge dissolution. Drug is extracted from the matrix layer by layer allowing the solvent to advance in the matrix structure. The knowledge of this schema is the base for understanding the release kinetics presented by all the types of matrices. As illustrated, in the depleted matrix volume, where only dissolved drug is present, the drug concentration profile is linearly decreasing from saturation concentration to the dissolution medium concentration. The linearity of this profile is based on the assumption of quasi-steady state conditions. An approximate solution of this diffusive problem is represented by Equation (1), frequently used by the researchers for describing the results of the release studies from inert matrices. The equation shows that drug release

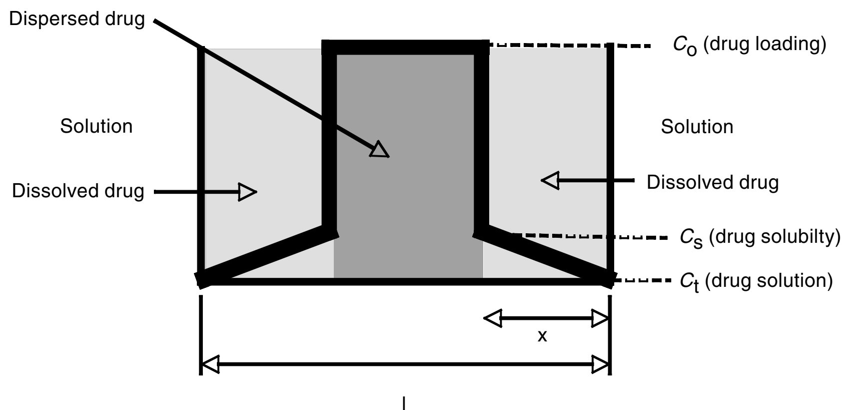


FIGURE 1 Schematic representation of the dependence of the drug concentration (*thick line*) from the position (l = matrix thickness; x = drug depleted layer thickness) in a inert matrix containing solid dispersed drug undergoing dissolution from the two sides.

in a moving boundary system, assuming quasi steady-state conditions, can be approximate as the dependence of the quantity of drug released from the square root of time (1).

$$Q = \sqrt{2DC_0C_st}, \tag{1}$$

where Q is the amount of drug released per unit area, D is the diffusion coefficient, C_0 is the drug loading, C_s is the drug solubility.

In this chapter, dedicated to swellable systems, the variations of this basic schema that produce differences in drug release kinetics will be illustrated.

RELEASE PARAMETERS IN SWELLABLE MATRICES

Depending on the drug to be delivered and the polymer selected to manufacture the system, matrix swelling in aqueous medium is the key phenomenon that determines the drug release rate from a system undergoing a continuous transformation process, eventually ending with the complete dissolution. Swelling represents a typical phase transition phenomenon of materials such as polymers, resulting from the interaction between the polymeric macromolecule and a solvent thermodynamically compatible with the polymer, i.e., able to form non-covalent interactions with the polymeric chains.

Why does a polymeric network swell? In the solid dry state, usually the long polymeric chains are quite disorganized and highly entangled rather than regularly ordered as in crystalline state. This condition is defined as "glassy state" since the chains' flexibility and mobility are very limited and the matrix's structure is rigid. The polymer maintains this state in dependence on the temperature; hence, a temperature increase can provide the system with enough energy to break the inter-chain bonds and enable the phase transition that makes the chains more flexible. This second physical state of the polymeric material is defined as "rubbery," an adjective that illustrates the higher mobility of polymeric chains. The temperature value at which the transition occurs is the typical glassy/rubbery transition temperature of the material (T_g) (e.g., 170–180°C in the case of hydroxypropylmethylcellulose, HPMC). The interaction between the polymer and a compatible solvent lowers the polymer T_g value and induces the phase transition

already at body temperature (37°C). Considering the situation at the molecular level, the glassy-to-rubbery phase transition is the first step toward polymer dissolution, endpoint where each polymeric chain is completely surrounded by solvent molecules.

Now, if one looks at the situation of a drug-loaded polymeric matrix, how the glassy-to-rubbery transition will affect drug release? When the matrix is in the dry state (glassy), it is unlikely that the drug can find its way out of the system moving across the entangled chains. However, if the drug/polymer matrix becomes rubbery in consequence of the polymer transition promoted by the aqueous medium, larger spaces filled of solvent in between the polymeric chains will become available for the drug molecules to move out. However, when swelling is followed by polymer dissolution, the phase transition contributes to system erosion and the swellable matrix will also behave as an erodible system. Macroscopically, when the polymer constituting the matrix undergoes the glassy-to-rubbery phase transition, the system swells and its volume increases. If the polymer also dissolves, erosion takes place and the system's volume tends to decrease.

The most convenient way to manufacture monolithic swellable matrices is tableting a powder mixture containing drug (filler) and swellable/soluble polymer (HPMC, HPC, HEC, MC, NaCMC) particles (Table 1). As for any tableting process, the compression force is a relevant parameter to consider for tablet porosity, hardness and release. Nevertheless, for swellable systems swelling levels off the differences in porosity due to different compression forces.

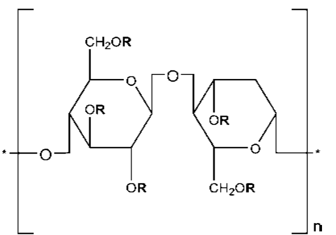
Drug diffusion, polymer relaxation and dissolution promoted by water contribute to release mechanisms. It is quite easy to recognize that the "game" is played by three elements, which are drug, polymer and water. In particular, water (the compatible solvent) initiates the release process and the interactions between water, polymer and drug are primary factors for controlling the drug release rate. Once the "players" identified, a series of variables has to be taken into account that can affect drug release, namely:

- drug to polymer ratio,
- drug solubility,
- polymer grade (molecular weight, viscosity),
- filler solubility,
- drug and polymer particle size,
- compaction pressure.

In addition, the matrix shape and size and the surface area to volume ratio have to be recognized as factors relevant to matrix hydration and drug release.

Looking in more detail at the *mechanism of drug release* from a swellable matrix, in consequence of the contact with water, a layer of gel of variable thickness is formed around the matrix, acting to prevent disintegration and slow down further water penetration. In particular, the gel formation is governed by a series of phenomena involving all the system's components, and gradually leads to a significant transformation of the system. In the first step water penetrates the matrix structure by diffusing across the polymeric network while the system is dry and the polymer still in the glassy state. As soon as a critical amount of water becomes available inside the matrix, *polymer swelling* and *drug dissolution* take place. The effect of the polymer swelling is the actual formation of the gel layer on the surface of the glassy matrix core. Actually, the gel is polymer in rubbery state and its consistency will vary depending on the type of polymer (hydrophilicity, molecular weight) and its concentration. Since swelling completely disrupts the matrix structure, a continuous change of the drug diffusive pathway arises. In fact, in order to be released, the drug molecules necessarily have to diffuse across the gel layer (*drug diffusion*), a quite different environment in terms of diffusion compared to an

TABLE 1 General Structure and Physicochemical Characteristics of Swellable Cellulose Ethers Used in Drug Delivery



Name	Acronym	Substituents (R)	Synonims and grades	MW (Da)	Viscosity (mPa s)	Solubility
Hydroxypropylmethylcellulose Hypromellose	HPMC	$–CH_3–CH_2CH_2CH_2OH$	Methocel K E F J	10000–1500000	3–100000 (1% w/v)	Cold water, methanol, ethanol CH_2Cl_2
Hydroxypropyl cellulose	HPC	$–CH_2CH_2CH_2OH$	Klucel EF LF JF MF HF GF	50000–1250000	HF 1% w/v 1500–3000 EF 10% w/v 200–600	Water, methanol, ethanol, propylen glycol, CH_2Cl_2
Hydroxyethyl cellulose	HEC	$–CH_2CH_2OH$	Natrosol HHR H4R HR MR LR	–	2% w/v 15–100000	Hot and cold water
Methylcellulose	MC	$–CH_3$	Methocel A	10000–220000	2% w/v 15–4000	Swells/disperses in water
Sodium carboxy methylcellulose	NaCMC	$–CH_2COONa$	Akucell Blanose	90000–700000	1% w/v 10–12000	Solubilized/ dispersed in water

Source: From Ref. 106.

aqueous pore. Moreover, the characteristics of the gel layer do not remain unmodified, but the layer's thickness increases or decreases with time, depending on whether swelling is accompanied or not by *polymer dissolution* and/or *matrix erosion* (detachment of small pieces of gel from the swollen matrix).

The presence of the *gel layer* is the key element of drug release, as it acts at the same time as a physical barrier for the drug leaving the system, but also for water moving inwards toward the matrix core. Thus, the possibility to control the rate of drug release very much depends on how the gel layer thickness evolves over time, which is something not immediately predictable. Since the polymer is not the only component in the matrix, the presence of other excipients must be taken into consideration by evaluating the swelling and dissolution behavior of the polymer-drug mixture with respect to drug solubility, drug loading, polymer characteristics. Finally, the hydrodynamic conditions of the medium must be expected to act as an additional source of variability of the gel layer's thickness by possibly affecting the erosion process.

Given the relationship between gel layer thickness and drug release, how can this thickness be measured and its changes followed while the matrix swells? Swellable matrices are classified as moving boundary drug delivery systems. In fact, the gel formed at the matrix surface is spatially delimited by sharp boundaries or fronts which are well-defined positions inside of the matrix where specific physical phenomena take place. On the inner side, the gel starts where the polymer undergoes the glassy-to-rubbery transition, which also corresponds to the furthest position reached by water inside the matrix. This position is called *swelling front* and separates the region of the still glassy polymer from the one where the polymer is in the rubbery state (gel). On the opposite side, the gel layer ends at the border between the swollen matrix and the surrounding dissolution medium. This second boundary is the *erosion or dissolution front* because here polymer erosion occurs. Furthermore, in some cases a third front between the other two (*diffusion front*) can be identified, whose presence is related to the amount and solubility of the drug in the matrix, i.e., the boundary between the solid and still undissolved drug and the dissolved drug within the gel layer.

Now, since these fronts exist in consequence of physical phenomena continuously ongoing within the matrix, they are not fixed, but do move and change position over time. Consequently, the modifications of the gel layer thickness are mainly dependent on the moving boundaries delimiting the different physical conditions inside matrix (dry core/swollen polymer, dissolved/undissolved drug, matrix/solvent). Basically, the rate and direction of fronts' movement depend on the relative importance of matrix swelling and polymer/drug dissolution. Hence, in order to understand how diffusion takes place in an environment whose boundaries are moving, one needs to know the rate and direction of the fronts. In particular, it has to be highlighted that the rate of water uptake affects the position of swelling front as well as the rate of drug dissolution is related to the position of diffusion front and the rate of matrix erosion to the position of erosion front.

A schematic representation of the situation within a swellable matrix in terms of drug concentration as a function of position (thickness) is given in Figure 2, where, on the *X*-axis, S, D, and E indicate the positions of swelling, diffusion, and erosion fronts, respectively. At "time zero," i.e., before getting in contact with water, the matrix thickness corresponds to point "a." When water initiates the polymer phase transition, the matrix external border displaces from "a" to E (erosion front) because of swelling. Conversely, at the opposite side (from the dissolution medium to the center of the matrix), the solvent front moves inwards, reaching the glassy polymer and interacting with it (swelling front). The distance between E and S positions is the gel layer. Assuming sink conditions and pseudo steady-state, drug concentration changes across the

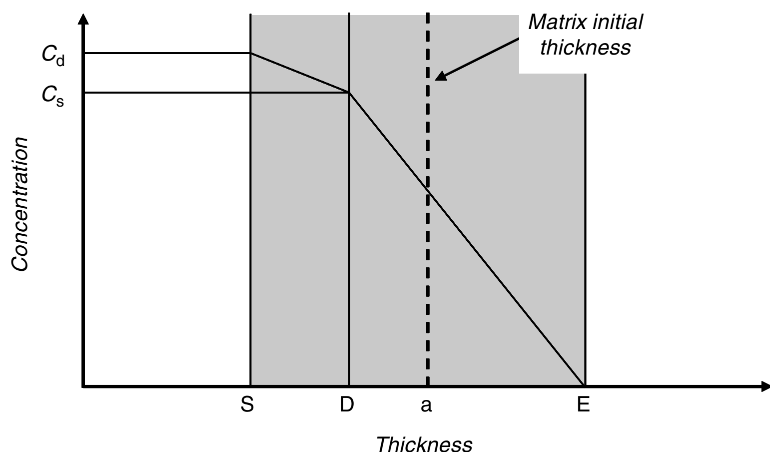


FIGURE 2 Schematic representation of drug concentration as function of position within a swellable matrix. S, D, and E indicate the positions of swelling, diffusion and erosion fronts.

matrix: at front E it is very low, whereas at front S it corresponds to the amount of drug loaded in the matrix (C_d), which is usually higher than the drug solubility (C_s). Moreover, when close to front S the drug is not completely dissolved, the diffusion front can be also present, separating undissolved drug from dissolved drug.

A simple device has been described to visually measure fronts' movement and release area development during matrix swelling and drug release (2). This device consists in two parallel transparent Plexiglass® discs. When a cylindrical matrix is clamped between the discs, only its lateral side is exposed to the solvent, thus hydration and swelling occur only radially. By means of this device, the swelling and release behavior of HPMC matrices containing buflomedil pyridoxalphosphate (BPRD) was investigated with respect to several variables, including polymer molecular weight, matrix porosity, pH and ionic strength of the dissolution medium (3). As BPRD was a colored drug and had been loaded at relatively high concentration (about 60% w/w), in certain cases it was possible to identify the diffusion front together with the other fronts. Changing the pH and ionic strength of the dissolution medium resulted in a change of BPRD solubility that affected the movement of the diffusion front and the thickness of the region where the drug is still undissolved within the gel layer. In fact, when drug solubility was higher (in acidic pH), the dissolved drug layer was thicker and the drug release rate higher. Consequently, the *dissolved drug layer thickness* appeared to be important in determining drug release as it is the region where the effective concentration profile relevant to drug flux is established.

Figure 3 shows a cylindrical swellable matrix in the experimental setting previously mentioned where the solvent penetrates only from the lateral side. It can be seen that the erosion front is not perfectly continuous but presents some "holes" due to pieces of gel that have come off. The matrix is loaded with the colored drug BPRD that gives a yellow color when in solution. The yellowish corona that surrounds the white matrix dry core in correspondence of the swelling front, allows visualizing the diffusion front, where drug all is present in solution. Moving outward from the diffusion front to the erosion front, an intense orange color gradient is evident due to the decreasing concentration of the drug dissolved in the gel. As said, the diffusion front is not always present, but depends on the drug's solubility and loading. In general, low solubility and high loadings lead to the formation of this front (4).

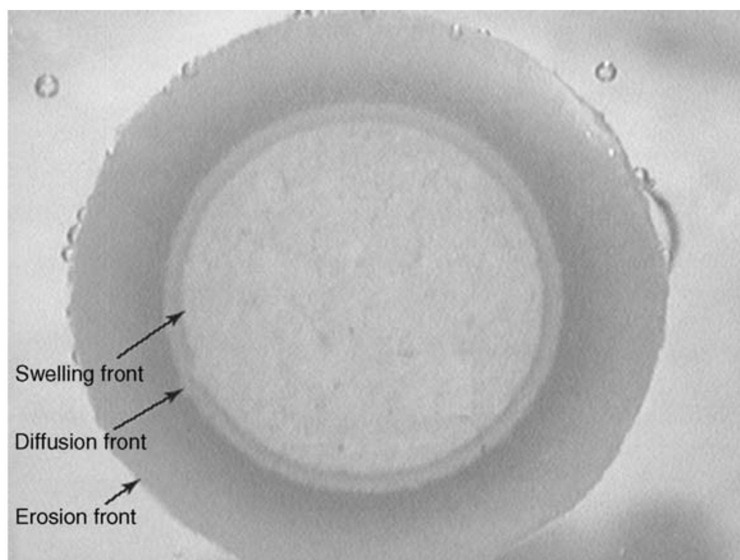


FIGURE 3 Picture of the upper base of a HPMC cylindrical matrix containing 60% of BPRD, placed in between two transparent discs after one hour of swelling-release. *Abbreviations*: HPMC, hydroxypropylmethylcellulose; BPRD, buflomedil pyridoxalphosphate.

The behavior of the gel layer thickness in swellable matrices loaded with increasing amounts of the same soluble drug BPRD was studied using a colorimetric technique to assess the effect of drug loading on the presence and movement of the diffusion front. The results showed that the gel layer thickness (distance between fronts E and S) was not significantly different in case of drug loadings ranging between 10% and 80% (w/w), whereas the thickness of the dissolved drug layer (distance between E and D, or S) was higher at lower loadings. Looking at the matrices through the Plexiglass® discs, the gradient of color across the gel layer was the proof of the existence of a concentration gradient of dissolved drug beginning at the diffusion front and ending at the erosion front. As dissolution went on, the color profile changed while the swelling and diffusion fronts moved inwards, thus showing an evolution of the drug concentration profile over time. By image analysis, the researchers measured the color level that was correlated with the drug concentration (5).

At the molecular level, the actual polymer chains situation inside the swollen matrix had been figured out by Ju et al. (6) as reproduced in Figure 4. Moving outward from the core

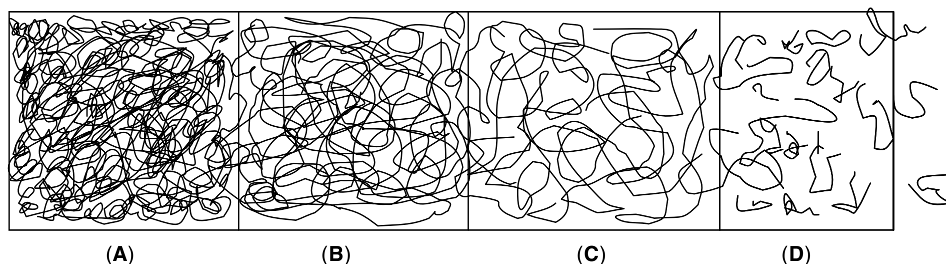


FIGURE 4 Sketch of chain entanglement in a swellable matrix.

following the increase of water concentration within the matrix, the polymer dry glassy core (not hydrated region) is followed by a partially swollen glassy layer, where the low water concentration maintains a certain level of glassy polymer. As water content becomes significant, the actual gel layer shows a reduced level of polymer chain entanglement. Finally, the amount of water is high enough to induce chain disentanglement toward dissolution.

Drug transport across this environment will obviously depend on how the fronts change position, especially the swelling (S) and erosion (E) fronts. A relationship exists between the rate of fronts' movement and the drug's release kinetics. Three different cases can be envisaged:

1. S moves faster than E (i.e., polymer swelling faster than erosion): in the early time of dissolution the two fronts move in opposite directions, increasing the matrix volume. In this case, the drug release kinetics will neither be linear (zero order) nor-fickian (just diffusive), but anomalous-fickian, i.e., intermediate between the two.
2. S and E move at the same rate in the same direction (front synchronization): the gel layer thickness remains constant, while the volume of the matrix decreases. The consequence of having a constant diffusion pathway is a zero-order drug release kinetics.
3. S moves more slowly than E when the solvent has reached the center of matrix and the entire polymer has swelled: gel layer decreases due to matrix dissolution. The kinetics of drug release in correspondence it is not linear and strongly depends on drug solubility.

In theory, all three situations could take place at different moments throughout the entire life of the swellable system, determining the variation of gel layer thickness during delivery time. In fact, if in early times the gel layer thickness mainly increases due to polymer swelling, when the movement of S and E becomes synchronized, the gel layer thickness remains constant till when, at the end of the swelling process, the gel completely dissolves.

Studies to demonstrate the movement of relevant fronts were conducted on swellable cylindrical matrices made of different polymers and drugs (7). For simplifying the analysis and measurements, the cylindrical swellable matrix was coated in a way to expose a constant release area obtaining a core-in-cup system. One base and the lateral side of the cylindrical matrix were coated with an insoluble film allowing only one base to remain exposed to the solvent. The effect on drug release of polymer type was studied using three polymers having different water solubility and swelling behavior, namely polyvinylalcohol, (PVA, Mowiol 40-88), hydroxypropylmethylcellulose (HPMC, Methocel K4M) and sodium carboxymethylcellulose (NaCMC). Identical matrices loaded with sodium diclofenac were prepared at same polymer concentration. It was found that the soluble PVA determined a constant release of drug since the beginning of the dissolution experiment, whereas for the other two polymers, less soluble and more swellable, a linear profile was reached only after an initial burst effect for HPMC and a time lag for NaCMC. This different release kinetics was explained measuring the fronts' movement during drug release: in the case of the PVA matrix, front synchronization responsible of constant gel thickness was attained almost immediately. Conversely, with HPMC and NaCMC constant release rate was delayed as the gel layer grew thicker before reaching the synchronization phase.

The same PVA polymer able to give immediate front synchronization was used to investigate the effect of drug solubility on release kinetics by loading the same amount of three model drugs having different and increasing aqueous solubility, namely diclofenac sodium, diprophylline, and cimetidine hydrochloride. In these core-in-cup systems, the in vitro release profiles of all three drugs were straight lines with identical slopes

indicating that the release kinetics was independent on drug solubility. It was discovered that with all the three drugs front synchronization was attained and the gel layer thickness was constant in time, although different in value for each drug. In particular, the value of constant gel layer thickness was found to be linearly related to drug solubility, being higher in the case of the most soluble cimetidine HCl, intermediate with diprophylline, and lower with diclofenac sodium. Hence, in these matrices, the polymer dominated the rate of drug release and the solubility of the drug became a less relevant variable (7).

In the above reported studies the matrix release area was constant as the matrices were partially coated. When the uncoated release area was changed, keeping the proportion between drug and polymer (PVA, sodium diclofenac), a neat linear relationship was found in vitro between release area and release rate, confirming that the surface area is an accessible tool to control the release rate. Administered in vivo, a poor in vitro-in vivo correlation was found for three systems having different release rate in dependence of the area exposed. However, when the matrices were made with high-viscosity HPMC instead of PVA, the sodium diclofenac bioavailability was complete. The result was attributed to the more significant polymer swelling relaxation that displaced the swollen mass outward of the core-in cup matrix.

Drug release in a system where all these events continuously alter the release environment, will be not only based on diffusion, but a concomitant contribution has to be taken into account (the "anomalous" part) due to polymer relaxation. Then, a fraction of drug can be transported by convective mechanisms in tight dependence on drug solubility. It has been demonstrated that in swellable matrices drug particles can be displaced by the swelling phenomenon. The contribution of polymer relaxation was typically seen when considering the release of drugs having different solubility from HPMC matrices (8). It was found that the rate and amount of drug released was not only dependent from drug dissolution and diffusion, but also from translocation of solid drug particles, whose presence was more evident with drugs having low solubility. These particles, physically translocated across the gel layer under the effect of swelling, altered the swelling behavior of polymer and reduced the chain degree of entanglement. This resulted in a modified resistance of the gel towards erosion and made the matrix more erodible.

In general, swelling is an isotropic phenomenon, as it takes place both radially and axially in the matrix. Since in swellable matrices the drug is released while the system swells, the presence of a coating that limits/delays in part the contact area with the dissolution medium and physically restricts swelling, modulates the drug release kinetics. The linear relationship between amount of drug released and surface area at the same time point indicated a direct dependence of release from the amount of releasing area developed. By normalizing the instantaneous release rates by the corresponding area values, the systems with different coating extension showed practically the same flux (drug release rate per unit area), despite the different kinetics.

MANUFACTURING TECHNIQUES

Cellulose derived polymers offer a wide range of materials with mechanical and physico-chemical properties able to satisfy different drug delivery kinetics from swellable matrices (9,10). In particular, with the aim of producing swellable matrices (11,12), several manufacturing processes have been proposed. HPMC is the first choice cellulose ether used for the manufacturing of swellable controlled release matrices, being water soluble, enzyme resistant, indifferent to gastrointestinal pH values and classified as safe by FDA and EMEA (13).

For the manufacturing of cellulose ethers matrices, the classical technique is powder compression. Direct compression is the first choice because of the minimum of manufacturing steps required: after mixing the powdered active ingredient and excipients, tableting is directly performed. The compaction properties of cellulose-derived polymers make this process easily feasible. In the specific case of HPMC matrices, polymer particle size, moisture content, viscosity grade, substitution type, along with polymer content are the key factors affecting the mechanical and drug release properties of the compact (14). HPMC content in the matrix formulation controls the drug release properties (15). Matrices with high polymer content develop a thick and strong gel that controls the release of the drug by diffusion and slow erosion (16,17). In particular, drug/polymer ratio is crucial for drug release rate (18); the partial substitution of the polymer with other excipients, either soluble or insoluble, generally leads to an increase in drug release rate because of disturbance in the gel layer formation (19) and, consequently, of faster water uptake (20).

The degree and ratio of methyl and hydroxypropyl substitution determines the physico-chemical characteristics of different HPMC types. The more hydrophobic methoxy groups decrease the capability of polymer chains to form hydrogen bonding, influencing the interaction with water (21). The HPMC type also affects the tensile strength of matrices, the hydration rate of the polymer and, in consequence, drug release rate (22); however, once a certain polymer content has been reached (30–40%), HPMC substitution degree has less significance and similar drug release profiles are obtained (23).

Several pharmaceutical grade HPMCs with various viscosities are currently commercially available. Higher viscosity grade HPMCs lead to a faster hydration and rapid formation of a dense and thick gel that slows down further water uptake and drug diffusion, affecting drug release (2,24). Also in this case, high polymer contents are reported to diminish the effect of HPMC viscosity on release profiles (23). Other studies evidenced that an increase in the viscosity grade negatively affect the compaction properties of the polymer, slightly decreasing the tensile strength of the compacts obtained with different samples of dried HPMC (25).

Hydroxypropylmethylcellulose is a hydrophilic polymer able to retain large amount of tightly bound water (26). Hydration water was found to have a significant effect on the mechanical properties of the polymer. An increased moisture content reduces the elastic recovery of compacts obtained using HPMC and acts as plasticizer decreasing the resistance of particles to deformation (27,28).

Particle size distribution of HPMC affects matrix behavior through modulation of hydration rate and drug release. Various authors reported that increasing the polymer particle size determines an increased porosity of the compact. The slower hydration of HPMC particles, as well as an irregular gel layer formation, determined faster release rate or even a failure in controlling the drug release because of matrix disintegration. This behavior, however, was overridden by polymer content higher than 20% (w/w) (29–31). On the other hand, smaller particle size polymers allowed the formation by compaction of a denser and harder matrix, due to more important inter-particle bonding (14,25).

Tablet manufacturing variables, such as compression force and compression rate, influence HPMC matrices characteristics (27). Increasing the compression force applied, a linear increase in matrix tensile strength corresponding to a decrease in porosity has been evidenced. Nevertheless, an increase in the compression force did not produce marked differences in drug release profiles (32). High compression speed was observed to have a negative effect on matrix hardness, especially those obtained with low viscosity HPMC, because of a reduction of particles' plastic deformation, a decrease in inter-particle bonds formation and a higher elastic recovery (14).

Even if direct compression is preferred, granulation is an option in those cases in which segregation of components, unfavorable drug technological properties (poor flow properties and compressibility), inconveniences in the tableting process (capping, lamination, picking, sticking, high friability) characterize the powder mixture. Different technological approaches have been proposed in order to obtain a size enlargement of the initial powder mixture and thus, a robust manufacturing process for the controlled release matrices. Dry granulation offers low production costs and does not use solvents. The pre-compression step is performed by slugging or by roller compaction (33). Cellulose ethers and in particular HPMC have been used as binders suitable to give to the powder mixture the necessary compactability (34). In the case of HPMC controlled-release matrices, studies on a model system containing theophylline have been performed to evaluate the impact of equipment, process and formulation variables on the matrix characteristics. It was evidenced that equipment and process variables, such as roll surface design, powder feeding rate, roll speed had little influence on the mechanical and drug release properties of the matrices. When compared to direct compression, matrices produced by dry granulation showed lower crushing strengths. On the other hand, differences observed between wet and dry granulation were related mostly to the characteristics of granules. The granules obtained by roller compaction were smoothed and denser. Regarding drug release, no significant difference was found between the manufacturing processes, being the polymer content the parameter dominating the release rate (35). Even if in recent years dry compaction has gained a growing interest, in some cases it shows disadvantages such as the production of non-compacted or non-granulated fraction of the initial powder mixture that can lead to segregation, poor drug content uniformity or low flowability. The use of micronized polymer has been reported not to have significant effect on this problem. On the contrary, an almost complete reduction of the fine particle fraction produced during granulation was observed after the moistening with water of the powder mixture immediately before pre-compression (36).

Wet granulation of controlled release formulations containing cellulose derivatives can be performed in various industrial apparatuses such as planetary, high-shear mixers or fluid bed processors. When planetary or high-shear mixers are used, the amount of water used for granulation, the fluid spray rate and mixing time have been shown to influence granulate size distribution, density and compressibility. The eventual addition of low viscosity HPMC to the granulation fluid could be beneficial in those cases in which problems of irregular wetting of the powder are evidenced (32,37,38). A recent study has shown that also in the case of wet granulation, HPMC physico-chemical properties play the major role in determining the result of the process in terms of granules properties. In particular, it was found that granules produced by wet granulation in a high shear mixer using low molecular weight HPMC were smaller, denser, with better flow properties than those obtained with high molecular weight polymers. However, more favorable compression properties were shown for the coarser high molecular weight HPMC granules, which produced matrices with higher tensile strengths. HPMC substitution degree did not appear to have a significant impact on wet granulation (39). When fluid bed processor was used for wet granulation, airflow and temperature should be taken in account as important process parameters. This process generally avoid the problems of over-massing of granulate sometimes observed for other mixers. Concerning drug release from HPMC matrices, a slower drug release and a decrease in the importance of the matrix polymer content were observed for fluid bed processing when compared to direct compression manufacturing (23).

However, wet granulation of powder mixtures containing HPMC using water alone or an aqueous solution of a binder may represent a challenging operation due to uneven

penetration of the granulating fluid in the powder bed and rapid formation of lumps, while dry spots remain deprived of binder. A hydro-alcoholic granulating fluid provides more rapid permeation of powder bed and reduces the polymer hydration, which may lead to excessively hard granules (40).

Beside the granulation process of the matrix, important factors affecting the drug release in controlled release formulation obtained by powder compression are shape and geometry of the compact. Since early studies on the drug release kinetics of polymer matrices, the shape and geometry of the tablets has been found to modulate the release rate (41–43). Reynolds and coworkers (44) thoughtfully demonstrated that in the case of HPMC based tablet matrices surface to volume ratio (*S*/*V*) is a key factor in controlling the drug release. In particular, it was found that irrespectively of different size, shape and drug dose, constant surface area/volume ratios led to similar drug release profiles. Tablets having the same surface area but different surface area/volume ratio values did not result in similar drug release. In fact, tablets with smaller *S*/*V* values showed slower release, because in diffusion-controlled systems this means longer diffusion pathways. This discovery has led to very interesting development in the field of matrix drug delivery, because by designing particular size and shape of matrices, optimal drug release profiles can be achieved without modifications of the formulation (45). Tablet shape modification and/or partial coating some of the matrix surfaces have been proposed to affect the *S*/*V* ratio of tablet matrices. For example, a donut-shaped matrix has been proposed to achieve zero-order kinetics with programmable release rate by adjusting parameters such as tablet and hole size, partial coating of the matrix and physico-chemical properties of the hydrophilic polymer used (46,47). Geomatrix™ (Skye Pharma, London, U.K.) system represents another successful application of this approach. This multi-layered system obtained by compression, consists in a drug core layer, whose release properties are modulated by impermeable, swelling or erodible drug-free barrier layers that cover one or both the bases of the cylindrical matrix core (48,49).

Other interesting and innovative development in this field has been multifunctional matrix drug delivery systems. These systems according to their geometry or assembly show properties suitable for different forms of controlled release. The system proposed by the group of Bodmeier, for example, is composed of HPMC matrices placed in an impermeable polymeric tube with at least one end opened. According on the configuration of the device (Fig. 5), extended release, floating or pulsatile drug delivery systems could be obtained (50). The Dome Matrix® technology described later, is a system based

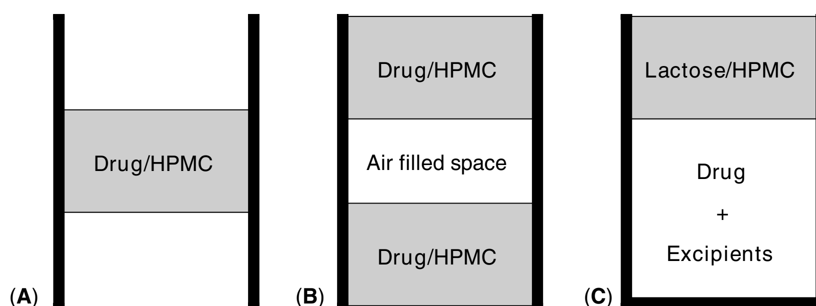


FIGURE 5 Schematic representation of prolonged release (**A**), floating (**B**), and pulsatile release (**C**) configurations in a multifunctional drug delivery system composed by HPMC matrices inserted in an impermeable polymer tube. *Abbreviations*: HPMC, hydroxypropylmethylcellulose. *Source*: From Ref. 50.

on HPMC compressed matrices of peculiar shape that could provide the same type of versatility (51,52).

An alternative manufacturing process suitable for the production of matrices is melt extrusion. The extrusion process consists in the conveying through an extruder (a screw rotating inside a stationary cylindrical barrel) of a molten polymeric viscous carrier material containing the drug dispersed or dissolved to a die was the material is formed in the desired shape. This process can be applied to produce uniform granules or pellets, but also for direct tablet manufacturing. Cellulose ethers such as EC, HPMC, HPC, are among the polymers that have been used for the production of controlled release formulations this type of processing (53–55). Typical process variables influencing the extrudate characteristics are screw speed, feed rate, and temperature profile (56). The main drawbacks related to melt extrusion process are related to high shear forces and temperature to which molten material is subjected. However, the technical solutions based on the geometry of screw and die, the precise temperature control of the system and the very short processing time reachable with current equipment make this process a promising alternative to classic manufacturing techniques (57).

Recently, ultrasound assisted compaction of powders has been proposed for the production of drug delivery matrices. This technique, already in use in metal, plastic and ceramics processing, is new in the pharmaceutical industry (58). The compaction process involves partial thermal fusion of particles and for this reason, the choice of the excipients is pivotal for the successful application of the technique. Until now, the most common polymers used for this technique have been methacrylates (59–61), however also the use of microcrystalline cellulose or cellulose derivatives has been reported to enable manufacturing of controlled release matrices (58,62,63).

MATERIALS AND FORMULATION

Swellable hydrophilic matrices are characterized by the formation of a gel layer on the matrix surface (16). Phenomena that govern gel layer formation and the consequent drug release are water penetration, polymer swelling, drug dissolution and diffusion and matrix erosion. The gel layer and its behavior govern the kinetics of drug delivery from swellable matrix systems. Numerous papers deal with the effect of formulation composition on the physical characteristics and drug release of controlled-release matrices. A recent review (13) has well overviewed many aspects of HPMC based matrices; the effect of several factors on matrix characteristics and drug release kinetics are highlighted, such as polymer level and drug solubility. The hydrophilic polymer fraction in the matrix is the most important parameter for determining drug release profile to such an extent that 30–40% of polymer in weight overrides other polymer properties as substitution degree, viscosity, and particle size. Drug solubility represents another key factor in determining the release kinetics. Highly soluble drugs act as pore formers leading to fast drug release. On the contrary, poorly soluble drugs will be released mainly by matrix erosion: drug particle translocation occurs during the swelling of the matrix and drug may experience an abrupt change in release rate at the end of the swelling process (13).

In the last two decades, the use of hydrophilic cellulose derivative polymers has attracted considerable attention for the development of controlled release pharmaceutical products. In this chapter, a limited number of papers containing innovative aspects of drug delivery from swellable matrices of HPMC have been selected and discussed.

Williams et al. (64) investigated the influence of excipient type and percentage on the release of alprazolam, a highly lipophilic drug, from matrix tablets containing HPMC,

TABLE 2 Composition of Aprazolam Matrix Tablet Formulations

Components	Formulation (% w/w)			
	A	B	C	D
Alprazolam	2.5	2.5	2.5	2.5
HPMC K4MP	40	40	40	40
MCC	20	20	20	20
Silicon dioxide	0.5	0.5	0.5	0.5
Magnesium stearate	0.5	0.5	0.5	0.5
Lactose monohydrate	36.5	27.4	9.1	_
Dicalcium phosphate dihydrate	_	9.1	27.4	36.5

Abbreviation: MCC, microcrystalline cellulose.
Source: From Ref. 64.

magnesium stearate, water soluble excipients (lactose monohydrate, sucrose, or dextrose) and water insoluble substances (dicalcium phosphate dihydrate, dicalcium phosphate anhydrous, or calcium sulfate dehydrate). Drug and HPMC concentrations were maintained constant in the formulations (Table 2). Varying the quantity and the type of excipients, it was observed that 36.5% (w/w) of dicalcium phosphate dihydrate slowed the release rate of the drug. Moreover, the release extent was decreased with respect to the formulations containing soluble excipients, in which a more permeable hydrated gel layer was present for drug release. In the case of lactose monohydrate, rapid drug dissolution was obtained within the formulation containing 36.5% (w/w) of the sugar. On the other hand, when both soluble and insoluble excipients were included in the formulation, an intermediate release profile was observed.

Samani et al. (65) investigated the effect of polymer blends on in vitro release profile of diclofenac sodium loaded matrices. It was observed that the drug release kinetics was related to the type of polymer used, its proportion in the formulation and viscosity grade. In particular, the use of HPMC (viscosity grade 60 mPa s) as matrix former, gave a fast drug release; on the contrary, the release time was extended up to 10 hours with HPMC (viscosity grade 500 mPa s) at high polymer/drug ratios (Table 3). The use of Carbopol 940 alone extended the release time appreciably, but also in this case a zero-order kinetic was not obtained. At the beginning, the release of diclofenac sodium was very slow (less than 25%), while it increased after 4 hours. When blends of HPMC and Carbopol 940 were used, the drug release kinetic approached to zero order. Better results were observed by using HPMC at low viscosity. However, the use of polymer blends reduced the total amounts of polymer in each formulation.

TABLE 3 The Ingredients of Various Formulations of Diclofenac Sodium Matrices

Components	Formulation (mg)				
	A	B	C	D	E
Diclofenac sodium	100	100	100	100	100
HPMC 60 mPa s	70	–	–	50	–
HPMC 500 mPa s	–	80	–	–	55
Carbopol 940	–	–	70	20	15
Lactose	50	50	50	50	50
Magnesium stearate	2.2	2.1	2.2	2.2	2.2

Abbreviation: HPMC, hydroxypropylmethylcellulose hypromellose.
Source: From Ref. 65.

Vueba et al. (66) studied the effect of cellulose ether polymers and type of diluent on the release mechanism of ketoprofen. Methylcellulose (MC), hydroxypropylcellulose (HPC) and HPMC were used as polymers, while lactose monohydrate and β-cyclodextrin were tested as diluents. Some formulations are reported in Table 4. In the case of matrix tablets containing MC25 or HPC the amount of water uptake was lower than for formulations containing HPMC K15M or HPMC K100M. In particular, the absence of hydroxypropyl groups in MC25 matrices reduced the hydrophilicity and the tablet disintegrated, leading to a fast release of drug in 1 hour. In turn, although a low level of hydration was observed for HPC-containing formulations, about 90% of ketoprofen release was reached after 6 hour exposure to phosphate buffer medium. Formulations containing HPMC K15M or HPMC K100M evidenced a high hydration degree already after the first hour of water exposure. After 20 hour, about 70–80% and 60–65% of drug were released from HPMC K15M and HPMC K100M matrices, respectively. Moreover, the release profiles of the formulations containing β-cyclodextrin were slightly slower than those containing lactose and this effect was probably due to an inclusion process of ketoprofen within the β-cyclodextrin cavity. Successively, the authors studied the role of cellulose ether polymers on ibuprofen release from matrix tablets (67).

The influence of cyclodextrins on drug release from HPMC matrix was investigated. Pina and Veiga (68) observed that β-cyclodextrin promotes an increase in the apparent solubility and dissolution rate of theophylline co-ground with the cyclodextrin. The enhancement in the dissolution profile was attributed both to the dispersion of the drug in the β-cyclodextrin after grinding and the almost amorphous state. Pose-Vilarnovo et al. (69) studied how the characteristics of the drug and the cyclodextrin could condition the relative contribution of the different mechanisms involved in the release from matrix tablets. The paper reported the effect of β-cyclodextrin and hydroxypropyl-β-cyclodextrin on diffusion and release behavior of diclofenac sodium and sulphamethizole from HPMC K4M matrix tablets with or without lactose. When cyclodextrin was present in the HPMC tablet formulation, it behaved as dissolution rate promoter. The incorporation of cyclodextrins and lactose in different proportions provided a way of modulating drug release profiles. In the case of diclofenac sodium, a hydrophilic drug, a higher cyclodextrin/lactose ratio significantly decreased the release rate. In contrast, the formulations containing sulphamethizole, a hydrophobic drug, showed an increase of the release rate, an effect that was more important using hydroxypropyl- β-cyclodextrin, which is more

TABLE 4 Composition of the Hydrophilic Formulations of Ketoprofen

	Formulation (mg)					
Components	A	B	C	D	E	F
Ketoprofen	200	200	200	200	200	200
MC25	70	–	–	–	–	–
HPC	–	70	–	–	–	–
HPMC K15M	–	–	70	70	–	–
HPMC K100M	–	–	–	–	70	70
Lactose	–	–	71	–	71	–
β-cyclodextrin	71	71	–	71	–	71
Talc	6	6	6	6	6	6
Magnesium stearate	3	3	3	3	3	3

Abbreviations: HPC, hydroxypropylcellulose; HPMC, hydroxypropylmethylcellulose hypromellose.
Source: From Ref. 66.

hydrophilic than β-cyclodextrin. Then, during the process cyclodextrins acted as solubilizing agents, promoting sulphamethizole release; at the same time, it could hinder the diffusion of the hydrophilic drug.

Nerurkar et al. (70) investigated the effects of carrageenans (ι-carraggeenan, Gelcarin GP-379; and λ-carrageenan, Viscarin GP-209)) and cellulose ethers (HPMC K4M, sodium carboxymethylcellulose–Na CMC, MC, and HPC) on the drug release of ibuprofen controlled-release matrices prepared by direct compression. The tablets were made using a combination of the two hydrophilic polymers; microcrystalline cellulose and magnesium stearate were used as filler and lubricant, respectively (Table 5). Increasing the concentration of a gelling polymer such as Gelcarin or HPMC led to slower drug release from the matrix. The viscosity increasing polymers such as MC, NaCMC, Viscarin, and HPC were essential for maintaining tablet integrity and their roles were complementary to the predominant gel forming polymers. The matrices that contained a blend of Viscarin and HPMC could sustain the release of ibuprofen up to 10 hours. This was possible due to slower erosion of HPMC while Viscarin helped to keep the hydrated gel layer intact. As expected, the formulation that contained the lowest concentration of each polymer (10% w/w) failed to control the drug release and disintegrated in 2 hours. Formulations that contained MC in combination with Gelcarin or HPMC, as well as HPC and HPMC in combination, were ineffective in controlling the release of ibuprofen at polymer concentration below or at 20% of tablet weight. Tablets containing 10% (w/w) of both Na CMC and HPMC disintegrated in about 4 hours. The premature disintegration of matrix with 10% (w/w) of HPMC or Gelcarin was due to very rapid hydration of the gelling polymer particles. Release rates slowed down when the concentration of Gelcarin or HPMC increased from 20% to 40% (w/w): as the proportion of these polymers increased in the matrix, there was an increase in the amount of water uptaken and greater swelling leading to a thicker gel layer. Addition of viscosity enhancers also contributed to interference with the water penetration rate, water absorption and polymer swelling. The difference in hydrophylicity explained the lower rates of water absorption in the HPC/HPMC and MC/HPMC matrices consequently leading to the initial rapid release. On the other hand, the presence of anionic polymer (Viscarin and NaCMC) had a beneficial effect on the viscosity and gave almost linear release of ibuprofen over a 10–12 hours period. The capacity of Viscarin and NaCMC to form hydrogen bonds with the hydroxyl groups of HPMC led to a synergistic effect on gel viscosity that explains the better control that

TABLE 5 Formulation of 500 mg Ibuprofen Swellable Matrices

	Formulation (mg)					
Components	A	B	C	D	E	F
Ibuprofen	100	100	100	100	100	100
MC	120	–	–	–	80	–
Gelcarin GP-379	120	–	–	–	–	–
MCC	160	160	160	320	240	240
NaCMC	–	120	–	–	–	–
HPMC	–	120	120	40	80	80
Vscarin GP_209	–	–	120	40	–	–
HPC	–	–	–	–	–	80

Abbreviations: MC, methylcellulose; HPC, hydroxypropylcellulose; MCC, microcrystalline cellulose; NaCMC, sodium carboxymethylcellulose; HPMC, hydroxypropylmethylcellulose.
Source: From Ref. 70.

these polymers had on the release of ibuprofen (65, 71). A similar explanation is also valid for MC/Gelcarin matrices that gave zero-order release profiles, since the higher is the viscosity of the gel layer, the greater is its resistance to erosion (72). The gel erosion plays an important role in the release of drugs with low water solubility such as ibuprofen. The formulation containing a blend of Viscarin and HPMC gave the slowest release throughout the 12 hours test period, followed by HPC/HPMC matrices. Tablets containing a blend of MC/Gelcarin gave the slowest release in the first 3 hours, followed by a quick release, probably due to rapid erosion of the gelled matrix. A similar trend was also observed for the NaCMC/HPMC tablets where the release quickened after 8 hours of linearity. Formulations that contained MC/HPMC showed a reverse trend with a rapid initial release followed by a slower release, which was due to slower erosion.

The modulation of drug release kinetics from linear to bi-modal for caffeine, a water soluble drug, from HPMC matrices containing polyvinylpirrolidone (PVP) was investigated by Hardy et al. (73). The formulations were prepared by using two fixed HPMC loadings (10% and 20% w/w), while the range of PVP content varied from 0% to 20% w/w (Tables 6 and Table 7). The in vitro dissolution profiles showed that the formulations containing either 10% or 20% (w/w) HPMC contents and no PVP exhibited a typical first-order release behavior. On the other hand, as the PVP amount in the formulation was increased, the release profile became increasingly linear (zero-order profile) between 2 and 20 hours in formulations A–E and F–I, then decreasing as the release profile became bi-modal at higher PVP loadings (formulations L and M). The mechanism behind the change in kinetics was investigated also by near-infrared spectroscopy (NIR) and rheology measurements. It was observed that in the initial stages of hydration, the release properties of caffeine were governed by the HPMC content in the matrix, regardless the amount of PVP, which was dispersed throughout the matrix. As caffeine diffused out of the tablet, the matrix became progressively rich in both PVP and HPMC.

TABLE 6 Composition of Formulation of Caffeine Extended Release Containing 10% of HPMC

	Formulation (%, w/w)				
Components	A	B	C	D	E
Caffeine	89	87	86.3	85.6	84
HPMC	10	10	10	10	10
PVP	0	2	2.7	3.4	5
Stearic acid	1	1	1	1	1

Abbreviations: HPMC, hydroxypropylmethylcellulose; PVP, polyvinylpirrolidone.

TABLE 7 Composition of Formulation of Caffeine Extended Release Containing 20% of HPMC

	Formulation (%, w/w)					
Components	F	G	H	I	L	M
Caffeine	79	74	69	66.5	64	59
HPMC	20	20	20	20	20	20
PVP	0	5	10	12.5	15	20
Stearic acid	1	1	1	1	1	1

Abbreviations: HPMC, hydroxypropylmethylcellulose; PVP, polyvinylpirrolidone.

The latter diffused from the matrix at faster rate compared to PVP, letting the matrix become progressively rich in PVP. At a critical PVP concentration, the polymer reduced the strength of the HPMC gel causing a break-up of the matrix. For matrices with high amounts of PVP this phenomenon occurred early leading to a bi-modal release profile resulting from the formation of smaller extended release sub-units. In contrast, for lower amounts of PVP, this occurred when swelling and erosion of the gel were synchronized, leading to a linearization of the drug release profile.

PVP/HPMC polymer blends were also used for the development of pulsatile chronotherapeutic release formulations consisting of coated matrices: the internal layer contained felodipine, while an external homogeneous coating layer was made of different PVP K30/HPMC K4M blends for the adjustment of the initial felodipine release (74).

In the aim of developing a monolithic HPMC (viscosity 4000 cPs) matrix tablet exhibiting a dual release of acetaminophen in comparison with commercial bi-layered tablets (Tylenol® ER McNEIL/Johnson & Johnson, New Brunswick, New Jersey, U.S.A.), the effect on the in vitro release profiles of the incorporation of pharmaceutical excipients such as surfactants, disintegrants and auxiliary additives, was examined (75). The most significant formulations are summarized in Table 8. In the presence of disintegrants, such as sodium starch glycolate (Primojel® Campina Nederland, Zoltbommel, The Netherlands), croscarmellose sodium (Ac-Di-Sol® FMC Corp., Philadelphia, Pennsylvania, U.S.A.) or starch 1500 (Prejel® Cooperatie Avebe U.A., Veendam, The Netherlands), a higher drug release from HPMC tablet was obtained as compared to corn starch, but no significant differences were observed between the release rate induced by Primojel, Ac-Di-Sol or Prejel. On the other hand, the release profile was found to be dependent on the surfactant type. Acetaminophen was rapidly released from HPMC tablet containing a small amount of anionic sodium lauryl sulfate (SLS, 1.3% w/w) and Prejel (4% w/w): more than 30% of drug was released within the first 15 min and 100% release was attained within 2 hours. By decreasing the surface tension of the dissolution medium (simulated intestinal fluid), SLS allowed higher and faster water penetration into HPMC matrix. However, as the amount of SLS was increased (1.3–6.5 % w/w) a stronger and more viscous gel network was formed, which hindered water penetration and reduced drug release. This phenomenon was also observed by Feely and Davis (76) and Nokhodchi et al. (77). However, in the presence of Prejel, the nonionic polaxamer 407 and poloxyl 23 lauryl ether (Brij 35) both induced sustained zero-order drug release for 8 hours.

TABLE 8 Formulation Prepared for Acetaminophen HPMC Matrices

	Formulation (mg)						
Components	A	B	C	D	E	F	G
Acetaminophen	650	650	650	650	650	650	650
HPMC	50	50	60	30	30	30	30
Primojel	30	–	–	–	–	–	–
Prejel	–	–	30	50	40	25	25
Corn starch	–	30	–	–	–	–	–
SLS	–	–	10	2.5	2.5	2.5	1
Avicel	–	–	–	20	25	25	25
NaH_2PO_4	–	–	–	–	–	5	2.5
Aerosil	6	6	6	6	6	6	6
Lubricant	4	4	4	4	4	4	4

Abbreviations: HPMC, hydroxypropylmethylcellulose; SLS, sodium lauryl sulfate.
Source: From Ref. 75.

Moreover, also the amount of HPMC was a key factor with respect to drug release control. In fact, in the presence of Prejel the release rate during the 8 hours was found to gradually decrease as the amount of the polymer increased (50–70 mg), due to a more viscous gel formed.

In order to obtain a formulation with a release profile equivalent to that of Tylenol ER tablets both in water and at pH 1.2 and pH 6.8, other excipients were progressively added. When microcrystalline cellulose (Avicel PH101) was added to the formulation in combination with SLS and Prejel, an increase in drug release rate was observed. At certain ratios of Avicel, SLS and Prejel (formulations D or E) dissolution profiles were essentially similar to that of Tylenol ER in gastric and intestinal fluids, but not in water medium. The addition of a small quantity of NaH_2PO_4 (<5 mg) allowed to obtain a formulation (formulation G) having release profiles approaching that of by-layered Tylenol ER also in water medium. Moreover, the in vivo bioavailability in healthy human volunteers was compared and no significant differences in pharmacokinetic parameters were observed between the two preparations.

MATHEMATICAL MODELING OF DRUG RELEASE

As discussed above, the underlying mechanisms controlling drug release from matrix tablets based on cellulose ethers are generally very complex. Often, various physico-chemical processes occur simultaneously and are of importance for the resulting drug release patterns (78–80). This may include: the penetration of water into the system upon contact with aqueous media, the dissolution of incorporated drug particles, the swelling of the polymer, the diffusion of dissolved drug molecules through a partially or fully swollen polymer network as well as polymer dissolution. Polymer swelling can be very pronounced in the case of cellulose ethers. Two of its major consequences for drug release are: (*i*) a significant increase in the length of the diffusion pathways (which can lead to *de*creasing drug release rates), and (*ii*) increasing macromolecular mobility (potentially resulting in *in*creased drug release rates). The relative importance of the various physico-chemical processes can strongly depend on the composition of the system (e.g., type and amount of drug, type and amount of polymer) as well as on the size, geometry and preparation method of the matrix tablets. Thus, for each specific device it must be verified that the mathematical model takes into account all relevant phenomena (e.g., saturation phenomena in the case of moderately/highly dosed poorly water-soluble drugs).

To minimize the computation time and number of required system-specific parameters for model simulations, negligible processes should not be considered in the respective theory. Ideally, mechanistic realistic mathematical theories should be applied. Great care must be taken when using empirical or semi-empirical mathematical models. In these cases, no reliable information can be obtained on the underlying mass transport phenomena and the predictive power of the theories is generally very low. In the following, only more complex, mechanistic mathematical theories allowing to quantify drug release from cellulose ether-based matrix tablets are described.

Each model considers a specific geometry. It has to be pointed out that the shape and dimensions of the matrix tablet can be of major importance for the resulting drug release kinetics (45). They affect for instance the length of the diffusion pathways for water and drug. Generally, controlled release tablets are cylindrical in shape. It is very important to take this fact into account. Figure 6A shows a schematic presentation of a cylindrical matrix tablet for mathematical analysis. The time-dependent radius and half-height of the cylinder are represented by R_t and Z_t; r, and z denote the radial and axial

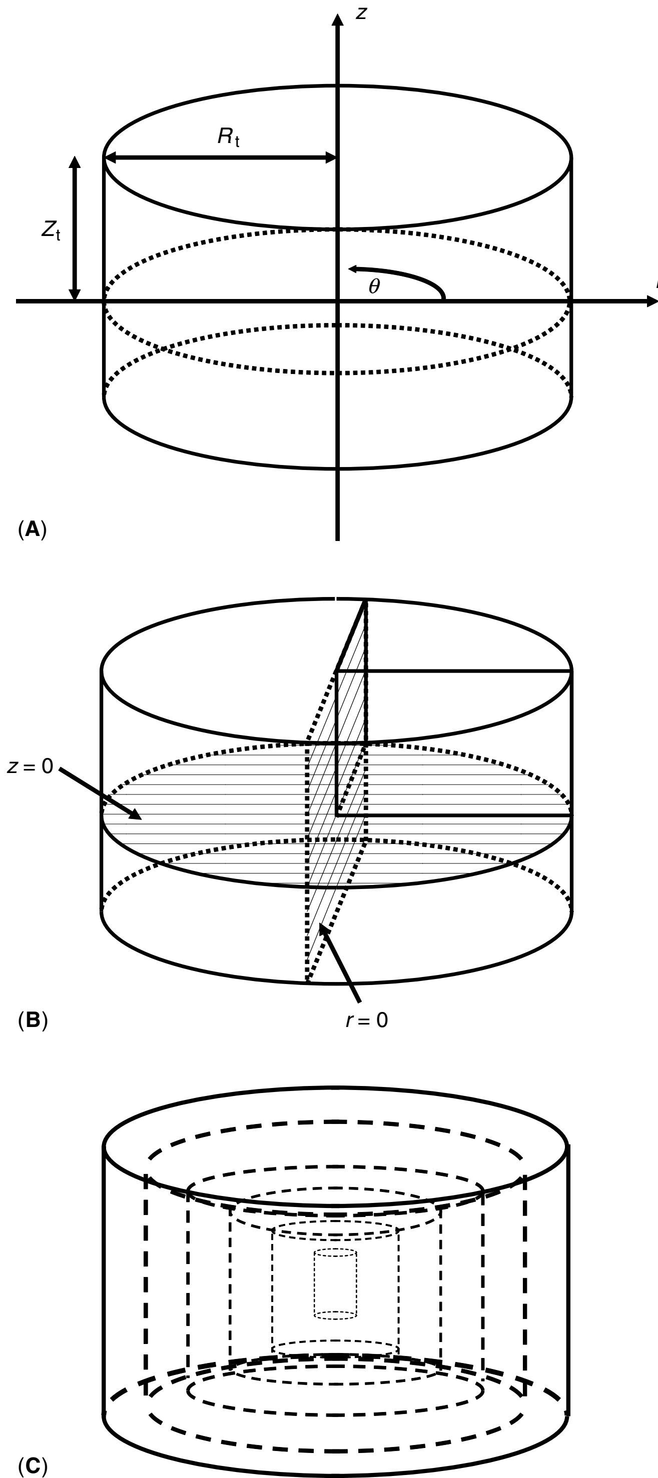


FIGURE 6 (**A**) Scheme of a cellulose ether-based matrix tablet for mathematical analysis, with (**B**) symmetry planes in axial and radial direction for the water and drug concentration profiles, (**C**) "sequential layer" structure for numerical analysis. *Source*: From Ref. 81.

coordinate, and θ the angle perpendicular to the r–z-plane. If all tablet components are initially homogeneously distributed within the system, various symmetries exist within the device. Figure 1B shows for instance the symmetry planes for $r = 0$ and for $z = 0$. In addition, there is generally no water, drug or polymer concentration gradient with respect to the angle θ. Thus, the mathematical analysis can be reduced to the two-dimensional rectangle illustrated in the upper right part of the cylinder in Figure 6B.

Importantly, the matrix tablet does not homogeneously and entirely swell upon water penetration into the system: at the beginning only the outer polymer layers swell, the inner ones remain unaffected. This fact needs to be taken into account in a mechanistic realistic mathematical approach (81). The tablet can for instance be considered to consist of a series of "sequential layers" as illustrated in Figure 6C. Upon contact with water, the latter first penetrates only into the most outward tablet layer and only this one should be considered to swell. Subsequently, – one by one – also the inner polymer layers become affected.

Drug dissolution can be considered for instance based on the Noyes–Whitney equation (82). The diffusion of water and drug (and – if present – also other diffusing species) can best be described using Fick's second law of diffusion considering the cylindrical geometry of the device (83):

$$\frac{\partial c_k}{\partial t} = \frac{1}{r}\left\{\frac{\partial}{\partial r}\left(rD_k\frac{\partial c_k}{\partial r}\right) + \frac{\partial}{\partial \theta}\left(\frac{D_k}{r}\frac{\partial c_k}{\partial \theta}\right) + \frac{\partial}{\partial z}\left(rD_k\frac{\partial c_k}{\partial z}\right)\right\}. \tag{2}$$

Here, c_k and D_k are the concentration and diffusion coefficient of the diffusing species (k indicates the type of diffusing species, e.g., $k = 1$: water; $k = 2$: drug); r and z denote the radial and axial coordinate, and θ the angle perpendicular to the r–z-plane; t represents time. As there is no concentration gradient of any component with respect to θ (Fig. 6A and B), Equation (2) can be transformed into:

$$\frac{\partial c_k}{\partial t} = \frac{\partial}{\partial r}\left(D_k\frac{\partial c_k}{\partial r}\right) + \frac{D_k}{r}\frac{\partial c_k}{\partial r} + \frac{\partial}{\partial z}\left(D_k\frac{\partial c_k}{\partial z}\right). \tag{3}$$

With increasing water content the mobility of the cellulose ether molecules significantly increases. Consequently, also the mobility of water, dissolved drug and potentially present excipient molecules increases. This fact can be taken into account based on a Fujita-type exponential dependence (84) as follows:

$$D_k = D_{\mathrm{kcrit}}\exp\left(-\beta_k\left(1 - \frac{c_1}{c_{1\mathrm{crit}}}\right)\right), \tag{4}$$

where the β_ks are dimensionless constants, characterizing these concentration-dependencies; $c_{1\mathrm{crit}}$ denotes the water concentration and D_{kcrit} the diffusion coefficients of the diffusing species at the interface "tablet matrix-release medium," where polymer disentanglement occurs (6,85–89).

Appropriate boundary conditions can be defined to take into account that the tablet dimensions generally *in*crease at early time points (due to polymer swelling) and *de*crease at later time points (due to polymer dissolution). Knowing the initial distributions of the tablet's components, the initial conditions can be defined. The resulting set of partial differential equations can then be solved numerically (note that no analytical solution is available if the diffusion coefficients are time- and position-dependent). Figure 7 presents a scheme of a cellulose ether-based matrix tablet for such a numerical analysis. The time-dependent radius, R_t, and half-height, Z_t, of the cylindrical tablet are divided into I and J space intervals, Δr and Δz, respectively, generating a grid of $(I + 1) \times (J + 1)$ grid points. The time is divided into g time intervals Δt. Using the above described sets of partial

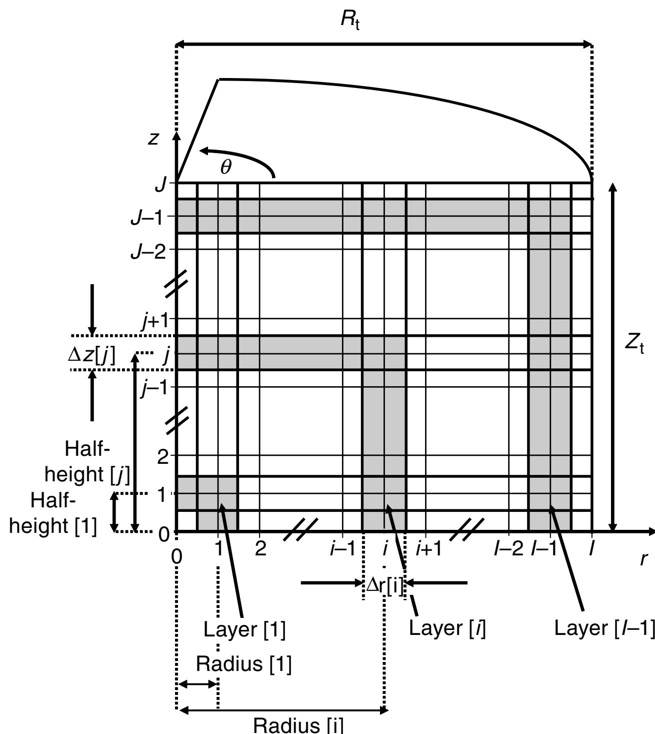


FIGURE 7 Scheme of a cellulose ether-based matrix tablet for numerical analysis. *Source*: From Ref. 81.

differential equations, the concentration profiles of the diffusing species for a new time step ($t = t_0 + \Delta t$) can be calculated, when the concentration profile is known at the previous time step ($t = t_0$) (Fig 8). The concentration at a certain inner grid point ($i \times \Delta r, j \times \Delta z$) for the new time step ($t = t_0 + \Delta t$) is calculated from the concentrations at the same grid point ($i \times \Delta r, j \times \Delta z$) and its four direct neighbors [(i–1) $\times \Delta r, j \times \Delta z$; $i \times \Delta r$, (j–1) $\times \Delta z$; $i \times \Delta r$, $(j + 1) \times \Delta z$; $(i + 1) \times \Delta r, j \times \Delta z$] at the previous time step ($t = t_0$). The concentrations at the outer grid points ($i = 0 \ v \ i = I \ v \ j = 0 \ v \ j = J$) for the new time step ($t = t_0 + \Delta t$) are calculated using the boundary conditions. At time $t = 0$ the concentration profiles of the tablet's components are given by the initial conditions. Hence, the concentration profiles at $t = 0 + \Delta t$, $t = 0 + 2\Delta t$, $t = 0 + 3\Delta t$,..., $t = 0 + g\Delta t$ can be calculated sequentially. This type of mathematical models can be implemented using programming languages such as C++, Fortran or Pascal.

Figure 9 shows an example for the practical application of such a mechanistic mathematical theory to sets of experimentally measured release kinetics of acetaminophen-loaded, HPMC-based matrix tablets. The initial drug content was varied from 1% to 70%, drug release was measured in 0.1 M HCl and phosphate buffer pH 7.4, respectively. The curves show the fitted theory, the symbols the experimental results. Clearly, good agreement was obtained in all cases.

This type of mathematical analysis offers two major benefits:

1. It allows to get deeper insight into the underlying drug release mechanisms in a specific type of cellulose ether-based matrix tablets (based on the system specific parameters that can be determined, e.g., the diffusion coefficient of the drug and its dependence on the water content of the tablet).

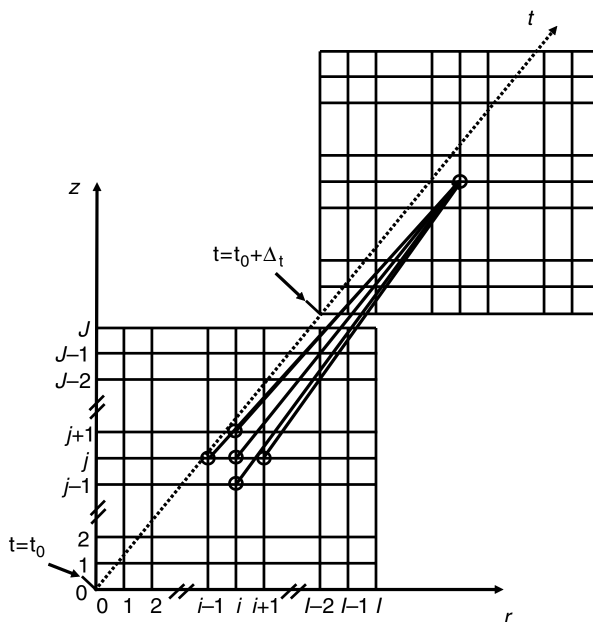


FIGURE 8 Principle of the numerical analysis: calculation of the concentration profile of a diffusing species at a new time step from the concentration profile at the previous time step. *Source*: From Ref. 107.

2. Mechanistic realistic mathematical models allow to quantitatively predict the effects of different formulation and processing parameters (e.g., amount of drug, initial radius, and height of the tablet) on the resulting drug release kinetics. This can help to facilitate the optimization of this type of controlled drug delivery systems: The number of required (often time- and cost-intensive) experiments can be reduced.

Figure 10 shows as an example the effects of the initial tablet size (at a constant "initial tablet height:initial tablet radius" ratio) on the resulting release kinetics of chlorpheniramine maleate from HPMC-based matrix tablets in 0.1 M HCl. Figure 10A illustrates the *relative* drug release rates, Figure 10B the *absolute* ones. In contrast to Figure 9, the curves now represent the theoretical model predictions and the symbols the independent experimental results. Clearly, good agreement was obtained in all cases.

HYBRID MATRICES

Hybrid matrices, including elements of matrix and reservoir delivery systems, have been realized with the aim of obtaining constant drug release rate with swellable systems. Many attempts to manipulate the relative influence of diffusion and relaxation mechanism have been made. Zero-order release from a matrix has been obtained by using either the appropriate matrix geometry (90), initially non-uniform drug distribution (91), ionic-exchange resins (76), hydrophobic porous materials (92), hydrophilic soluble polymers capable of modifying the effective diffusivity of the active principle (93), surface cross-linking of the matrix (94), etc. One successful approach for the attainment of zero-order release is linked to the capability to control the releasing area of the system. The approach introduced by Colombo et al. (95) consists in the application of a coating that

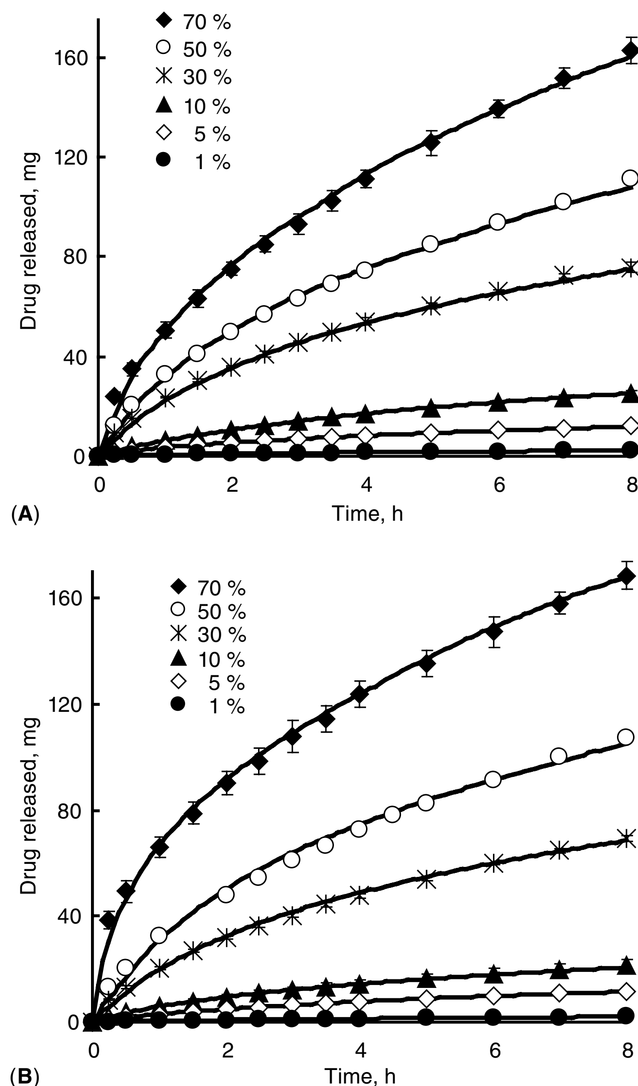


FIGURE 9 Example for a practical application of a mechanistic realistic mathematical theory to sets of experimentally measured drug release kinetics from HPMC-based matrix tablets: Effects of the initial acetaminophen loading (indicated in the diagrams) on drug release in: (**A**) 0.1 M HCl; and (**B**) phosphate buffer (pH 7.4) (symbols: experimental results, curves: fitted theory). *Abbreviation*: HPMC, hydroxypropylmethylcellulose. *Source*: From Ref. 108.

covers different surface portions of the hydrogel matrix. The manufacturing procedure, without modifying the diffusion characteristics of the drug, can give rise to a variety of systems in which the dimensionality of the swelling of the matrix is changed. Matrices containing a swellable polymer, a drug and eventually filler, were partially covered with either impermeable, semipermeable or erodible coatings.

A compressed core composed by diclofenac sodium and soluble polyvinyl alcohol was coated on the later a surface and on one base with an impermeable coating in order of maintaining a constant releasing area. Upon contact with water, this core-in-cup system undergoes swelling followed by erosion that keeps the releasing area constant, thus

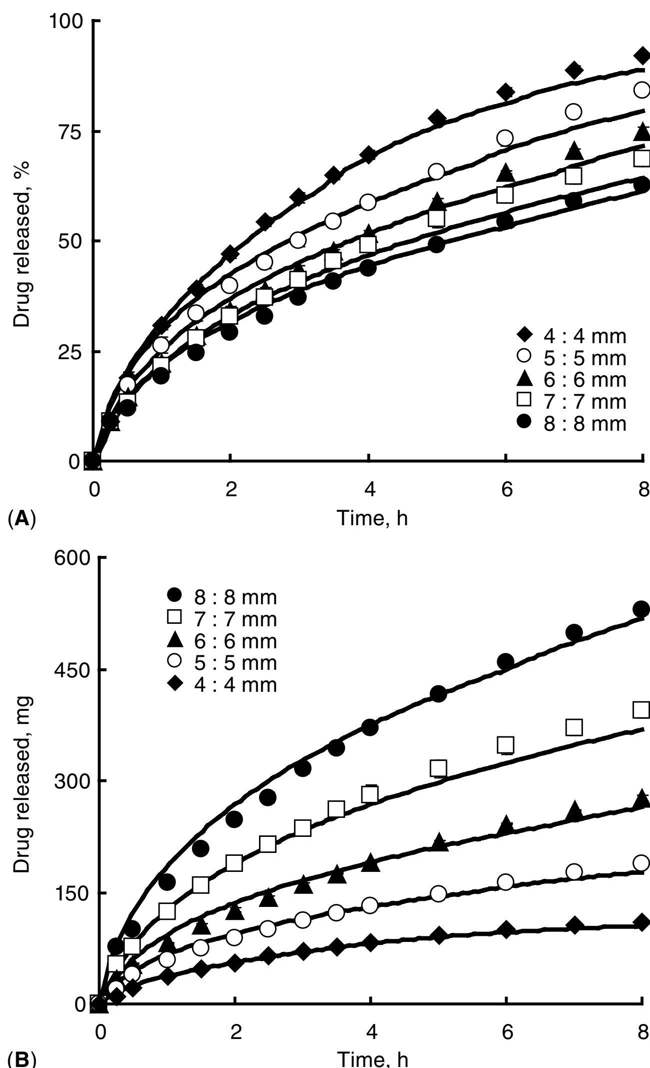


FIGURE 10 Example for the practical application of a mechanistic mathematical theory quantifying drug release from HPMC-based matrix tablets: Theoretically predicted and experimentally verified effects of the initial tablet size (the "initial tablet height:initial tablet radius" is indicated in the diagrams) on chlorpheniramine maleate release in 0.1 M HCl: (**A**) relative amount of drug released; and (**B**) absolute amount of drug released vs time (curves: predicted release patterns, symbols: independent experimental results). *Abbreviation*: HPMC, hydroxypropylmethylcellulose. *Source*: From Ref. 108.

producing a strict zero-order drug release. The film-coated portion of matrix was inert and impermeable to water penetration and to drug diffusion. The variation of the amount of swellable and soluble polymers in the core could modulate the release rate of the system. The release area of the system was employed as a control element to program the release rate of drug, because in vitro release rate and in vivo area under the curve resulted linearly correlated to the releasing area (7). The mechanisms governing drug release in such a type of system, by using swellable polymers (PVA, HPMC, and CMC) exhibiting different water-interaction was ascertained. Owing to the unidirectional swelling induced

by coating, it was possible to measure front movements (erosion and swelling fronts) over the course of the experiment. The results obtained showed that the synchronization of swelling and eroding front's movement determined the achievement of the linear-release kinetics of loaded drug. Moreover, the swelling and dissolution characteristics of the polymer employed governed front movement (7).

However, very often hydrogel matrices are not in conditions to attain synchronization of the fronts, particularly when poorly soluble polymer is used. In this situation, during drug release, matrix swelling predominates over erosion/dissolution (78).

An evolution of this coating approach was the application of impermeable coats to different portions of a compressed swellable matrix (Case 0), namely one base (Case 1), two bases (Case 2), lateral surface (Case 3), one base plus lateral surface (Case 4), as shown in Figure 11 (96,97).

The rationale was to affect the swelling of the matrix by changing the dimensionality of the plain matrix swelling, leaving the composition of formulation intact. It was shown that the swollen matrix, as a function of the extension or position of impermeable coat, had different shape. In particular, the matrix with two coated bases (Case 2) presented the largest increase in diameter, meaning that in this case the swelling was mainly radial. Considering the increase in thickness, the uncoated matrix (Case 0) exhibited the maximum increase, whereas the one with two coated bases (Case 2) had the lowest increase. Overall, the coating application on the bases changed the swelling of the plain matrix from axial to radial direction. Concerning drug release, it was shown that it decreased with the extension of coating, due to the reduction of the available releasing area of the system. Figure 12 compares the fractional release of diltiazem from the

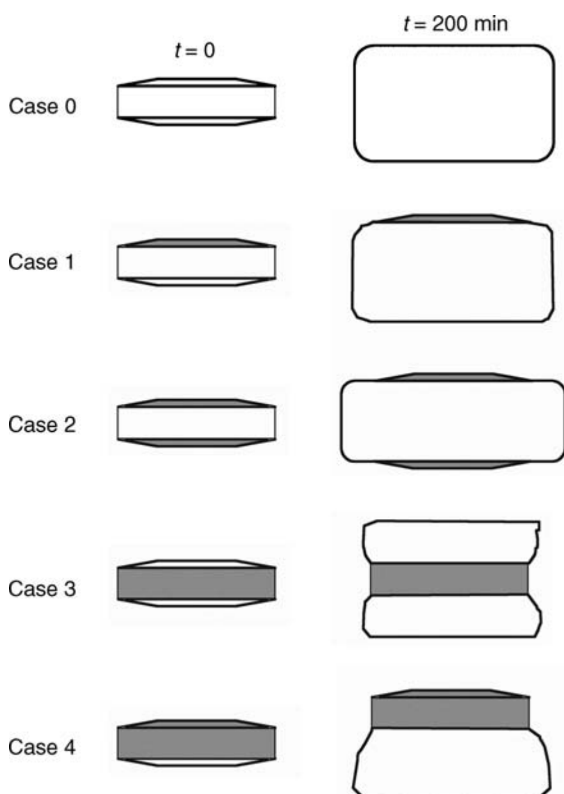


FIGURE 11 Sketch of swelling behavior of the compressed matrices coated with different impermeable coat extension (*grey sections*) showing the shape modification of the system due to the effect of the impermeable coat.

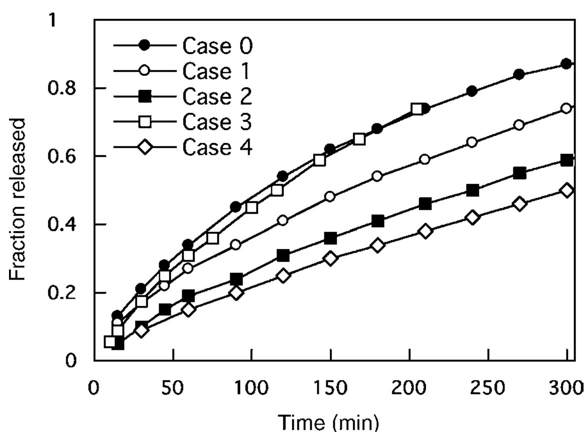


FIGURE 12 Fraction of diltiazem released from five systems prepared as a function of time. *Source*: From Ref. 78.

partially coated systems: the uncoated matrix shows the highest amount of drug release, followed by Case 3, Case 1, Case 2, and Case 4. More importantly, the release kinetics changed according to the position of the coating since the polymer relaxation was more important as the coating extension increased. However, taking into account the different area developed during matrix swelling in Cases 0–4, the release rate per exposed area remained unchanged.

The system with two bases coated was tested in vivo (78). Three identically coated matrices containing diltiazem were administered orally in a hard gelatin capsule (dose of diltiazem 180 mg). The bioavailability study was done in comparison with Tildiem tablets (dose of diltiazem 60 mg). The results showed a complete bioavailability and sustained plasma levels useful for a once-a-day administration schedule.

Hybrid matrices were also realized coating with permeable and semipermeable films (98). The rationale of using such films was to improve the drug-delivery performance of partially coated matrices by adding another control element to the swelling-dependent delivery mechanism. Both the semi-permeable and permeable core-in-cup systems gave rise to an increase of drug release rate as compared to the impermeable cup. All the systems coated with films of cellulose acetate and PEG as channeling agent presented drug release kinetics very close to linear. In this case three mechanisms govern drug release: (*i*) drug diffusion through the gel layer, which is present in uncoated portion of all systems; (*ii*) drug transport through the gel layer due to osmotic contribution, when the systems are coated with semi-permeable films; and (*iii*) drug diffusion through the pores of the film generated by the dissolution of the PEG incorporated in the film. The relative importance of each contribution depends on the characteristics of the film, regulated by the amount of PEG present. The systems with 1%, 13%, and 33% (w/w) PEG, which allowed for the preparation of semi-permeable cups, behaved in part as osmotic systems, whereas the system with a permeable cup (66% w/w of PEG) behaved as a hybrid reservoir system. The presence of an osmotic supported drug release from matrix in semi-permeable cup systems allows for an improvement in linearity, an increase of delivery rate and a lower dependence on hydrodynamic conditions, compared to the impermeable cup system.

However, all the systems described so far required the application by casting of the film on a portion of the matrix tablet and this process is difficult to obtain industrially. The possibility of applying a polymeric barrier layer on the core by compression was explored (48,49). When a barrier layer was made of an inert polymer such as

ethylcellulose, the barrier tends to detach from the central core within 1 or 2 hours after water immersion, due to the mechanical stress produced by the core swelling. Matrix coating layer made up of a hydrophilic swellable and/or erodible polymer was more successful (48,49). The easiest manufacturing was represented by either two layer (Case 1) or three-layers (Case 2), in which one or two polymer layers modulate drug release from the core containing the active ingredient. The time-dependent coating effect of polymer layers modulates water penetration and drug release in the core for a programmable period of time, until the coating was swollen and eroded. Using for barrier construction a swellable polymer, such as high viscosity HPMC, the polymer layer swells simultaneously with the core, so maintaining the whole extension of the base surface of the tablet covered until the end of the dissolution process. In case of coating with low viscosity HPMC the barrier was quickly dissolved and the release process depended only on the formulation characteristics of the active core. The swellable coating provided double effect because even when completely gelled still acted as a modulating barrier, preventing the core erosion. The swellable barrier was more suitable to control the release of soluble drugs, while the erodible barrier provided a control of the dissolution profile of poorly soluble drugs (49). Moreover, multi-layered systems in the end of the release life dissolve, leaving no residue in the body. These compressed barriers are feasible from an industrial standpoint and proved to be very versatile in the modulation of drug release profile (48).

These papers gave rise to the development of the successful marketed technology, Geomatrix Technology. Geomatrix technology consists of a hydrophilic matrix core containing the active ingredient and one or two impermeable or semi-permeable polymeric coatings (films or compressed barriers) applied on one or both bases of the core (Cases 1 and 2 in Figure 11). The hydrophilic core is made of hydrophilic swellable polymers, such as HPMC or polyethylene oxides (PEO) (99). In a comparative study, HPMC was found to be generally more efficient in controlling drug release rate in three-layer Geomatrix systems than PEO (99). The presence of the coatings modifies the hydration/swelling rate of the core and controls the surface area available for drug release. These partial coatings provide a modulation of the drug dissolution profile: they reduce the release rate from the device and shift the typical square root time-dependent release rate towards constant drug release (Fig. 12). Dilacor XR capsules, an extended-release formulation of diltiazem based on Geomatrix Technology, has been developed for the treatment of hypertension. Dilacor XR (Rhone-Poulenc Rorer Pharmaceuticals Inc., Collegeville, Pennsylvania, U.S.A.) uses the Geomatrix® controlled-release system to deliver diltiazem at quasi constant rate for 24 hours (100).

Multi-layer matrices, in which the drug was distributed in three layers, have been also proposed for oral delivery control. In these systems the control of the overall release kinetics was primarily determined by the composition of each layer and by the layer-to-layer interactions. On a three layers system, an effect on the release rate due to the relative position of the individual layers could be envisaged. An oral controlled release system for the delivery of levodopa methylester (LDME) and carbidopa in the upper part of the gastrointestinal (GI) tract was designed as three-layer tablet (101). Each individual layer of the tablet exhibited a different release mechanism, i.e., one layer was swellable (S), the second was erodible (E) and the third was disintegrating (D). The three layers were differently located in the matrix, giving rise to three monoliths differing for the relative layer position. It was found that in the monolith the three layers interacted, producing in vitro the release profiles depending on their relative position. The difference between the in vitro release kinetics of the three-layer monoliths in dependence of the layer position was confirmed in vivo.

FUTURE TRENDS

Despite there are several polymers useful for the preparation of swellable matrices, HPMC remains the more reliable one. The quality of this substance is well defined and monographs exist in the major pharmacopoeia. The future trends of the field reside on the search of polymers capable to respond to stimuli such as pH, in order to manufacture oral systems useful for drug delivery in particular section of the GI tract. This means that the future attention is addressed to charged polysaccharide polymers to mix with HPMC, capable to exhibit a swelling behavior and drug release as function of the external environment pH.

Examples of this concept have been studied by several authors (102,103). Bonferoni et al. (104) showed that λ-carrageenan, a sulfated polymer from algae, was able to control initial release of a basic drug also at low pH values. λ-carrageenan matrices were subject to erosion at a rate dependent on pH value and ionic strength of the medium. It was noticed that the sensitivity of erosion process to dissolution medium could be reduced by addition of a more slowly erodible polymer such as HPMC.

Jimenez-Kairuz et al. (105) studied the delivery properties of drug/polyelectrolyte matrices of alginic acid or carbomer with diclofenac. The alginate complex showed a remarkable zero order delivery in different kind of media and the erosion of hydrogel was the main delivery mechanism. The carbomer-drug complexs showed a delivery rate of drug determined by diffusion phenomena until salt addition did not modify the rate delivery. The different delivery mechanisms exhibited by alginic acid and carbomer based matrices were primarily ascribed to differences in the physical properties of their respective gel layers.

A second future trend will be the study of peculiar tablet geometries that could allow accurate drug delivery, more due to the volume or surface/volume ratio modifications than to formulation changes. A technology named Dome Matrix, in which individual drug modules have been constructed to be assembled in a system by stacking together two or more of these individual modules, has been recently described (51,52). Colombo and coll. introduced this new strategy for the development of an adaptable and flexible drug delivery platform. The technology, termed “release module assemblage,” is based on swellable matrices (modules) having peculiar shape. The delivery module was named Dome Matrix. The module is an individual unit having a proper delivery program. It is a swellable compressed matrix having shape of disc with one base convex and the other one concave, to facilitate the stacking operation by inserting the convex base of one module into the concave of the other.

Drug delivery systems (DDS) composed by different modules fitted together can be prepared in two base configurations, namely piled and void configuration. In the piled or stacked configuration, one module concave base is stuck within convex base of a second module. In the void configuration, two modules are stuck concave base against concave base; in this configuration there is a void chamber present in the assembled system. Also mixed configuration could be prepared since over the convex base of a void configuration system is possible to stuck other modules obtaining a void-piled configuration.

The assemblage of this module make possible to made DDS that perform different time and site controlled delivery in dependence in the way the modules have been assembled. Thus, the individual administered dose can be easily adjusted, or multikinetics can be achieved if the module composition is different.

A picture of this new system is presented here where four separated modules are assembled in one system in order to obtain a device capable to float and to exhibit controlled release kinetics of clindamycin and artesunate for the malaria treatment (Fig. 13).

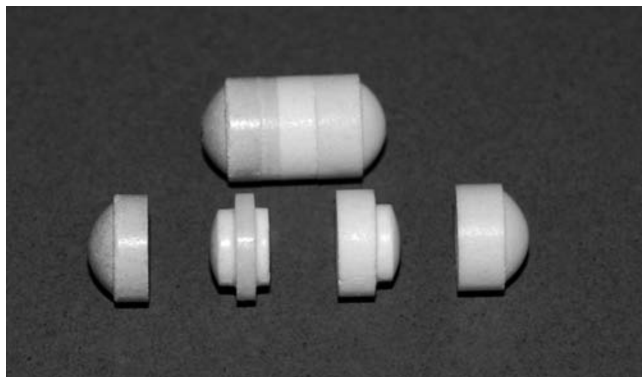


FIGURE 13 Dome matrix assembly for malaria therapy. The assembled DDS is composed of two prolonged release modules assembled in void configuration (modules in the middle); a clindamycin immediate release module (*right*) and an artesunate immediate release module (*left*) are stuck on the void configuration. After disintegration of the immediate release modules, the central part of the system floats. *Abbreviation*: DDS, drug delivery system.

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15

Carrageenans in Solid Dosage Form Design

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INTRODUCTION

Polymers are widely used to control drug release. Carrageenans are natural polysaccharides extracted from red seaweed and they show hydrocolloidal properties. These natural polysaccharides have only been used since 1945, because a substitute for agar was needed after the Second World War. For a long time similar to other natural gums it was difficult to standardize these products since the raw material showed different compositions in dependence on harvesting (1). Nowadays, these seaweeds can be cultivated and thus the raw material is much more homogeneous. Only during the last decade more intensive research on the use of carrageenans in pharmaceutical dosage form development has started.

Besides their use in pharmaceutical dosage form development carrageenans have been used extensively to induce oedemia in animals experimentally in order to study the potential of anti inflammatory agents (2). Furthermore, carrageenans possess antiviral activity which has stimulated further interest most recently (3).

OCURRENCE AND STRUCTURE

Carrageenans have been used for several 100 years in Europe and the Far East. They are natural polysaccharides and belong to a family of polydisperse long chain galactans which can be extracted from the algae of the class of Rhodophyceae. Thus they are similar to alginates (extracted from brown algae) and agar (extracted from red algae). The algae used for production of Carrageenan originate from Ireland, Bretagne, Denmark, the United States, and Philippines. Their name is linked to the Irish coastal village Carraghen where Irish moss (*Chondrus crispus*) was harvested and utilized in milk products (4). The most important members used for extraction were *C. crispus* and *Gigartina stellata*. During the last decade the harvesting of natural Irish moss populations has been reduced. Environmental issues are being discussed in several countries as an important factor. Nowadays, the natural resources are mostly harvested in temperate regions as, e.g., Canada, Chile, and France, and at present the largest consumption is based on cultivated tropical seaweeds such as *Kappapycus alvarezii* (5,6).

Types

The carrageenans have their own monograph in the USP (7). They were firstly isolated in 1953 (8) and their structure was analyzed in 1955 (9). They are of anionic nature. Carrageenans consist of alternating 1,3-linked β-galactose (G-units) and 1,4-linked α-galactose (D-units), which can be partly substituted by sulfate groups (S). In carrageenans with the ability to form a gel the major part of the 4-linked units consists of 3,6-anhydro galactose (DA). More recently a short hand nomenclature system based on letters has been introduced (10) in order to simplify the old system based on Greek letters (11,12). According to this system κ-carrageenan consists of 4-linked DA units and 3-linked G4S units, *ι*-carrageenan consists of 4-linked DA2S-G4S units and 3-linked G4S units, λ-carrageenan consists of 4-linked D2S, 6S-G2S units and 3-linked G2S units, and finally β-carrageenan consists of 4-linked DA units and 3-linked G units.

Historically the three major commercial carrageenans types were named κ, *ι*, and λ along with their corresponding structures. Originally the two former (gelling family) were isolated based on their insolubility in KCl (8), whereas the latter formed the soluble fraction (nongelling family). The three basic types κ-, *ι*-, and λ-carrageenan are presented in Figure 1. They can be differentiated due to their sulfate content. It increases in the following order: κ-carrageenan (25–30%), *ι*-carrageenan (28–35%), and λ-carrageenan (32–39%).

The Greek nomenclature normally will be used in the following since it is the standard nomenclature for all commercial products.

PRODUCTION

For production of carrageenan the algae are washed and dried. The carrageenan content can vary between 15% and 70% depending on the source of seaweed. The dried algae are treated with alkali and ground to a paste. Alkaline conditions allow the extraction of the macerated algae, retard acid-catalyzed depolymerization of the galactan units, and they catalyze the conversion of C-6 sulfated precursor residues to 3,6-anhydrogalactopyranosyl residues. The obtained raw extract is purified by sieving and filtration, and in the last step of extraction pigments are removed with activated carbon. To prevent gelling, all of these operations must be carried out at higher temperatures (13).

In the next step, the extract is concentrated and the carrageenans are precipitated in alcohol, preferentially isopropanol is used. The raw carrageenan is produced by drying, mostly spray or sometimes drum drying. The method of drying significantly influences material properties, a spray-dried product tends to be fluffier, a drum-dried product is more rigid. Alternatively, κ-carrageenan can be produced by extruding the extract into a KCl solution, pressing the precipitate, and removing water from solution by a freeze-thaw cycle.

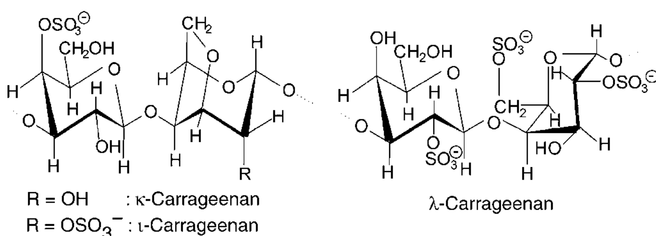

FIGURE 1 Chemical structure of the carrageenans.

The obtained product is milled and different commercially available types of carrageenan can be produced by mixing fractions with different substitution or different potassium content. The article size of the obtained products can vary and it is influenced by the method of precipitation, the method of drying and the final milling step.

The carrageenans can also be standardized for their gelation properties by the addition of salts and sugars. Furthermore, by selecting a milder alkaline extraction process than the conventional alkaline consitions, carrageenans with a small fraction of precursor units remain and hence altered function might be obtained (14).

The most innovative processing procedures include enzymic tools based on molecular biology as for, e.g., used by Goemar Laboratories (Roscoff, France). Stable enzyme preparations of glycosylhydrolases, which produce carrageenan oligosaccharides as well as sulfohydrolases, which produce 3,6-anhydrogalactose have been cloned (15).

In the late 1990s, a semirefined carrageenan called processed euchuma seaweed (PES) has been offered (16). Such carrageenan products can be obtained by treating the algae with hot potassium hydroxide solutions, washing them with water, and drying, bleaching, and grinding them to obtain a suitable particle size (17). PES contains more acid insoluble matters and fiber components such as cellulose due to the use of hot potassium hydroxide solutions (18).

PROPERTIES

The properties of these polymers are important to understand their function as controlled release matrices. The following properties have to be stated: Physicochemical properties are important in the solid state as well as in solution and can influence general formulation decisions. Powder technological properties are important during tablet production and formulation of other dosage forms: Gel formation properties are the most outstanding property of these products and thus these materials will be preferentially used in formulation and drug delivery processes, which are based on this property. Finally, the formation of polyelectrolyte complexes enables innovative applications in drug delivery and is the underlying base for this purpose.

Physicochemical Properties

All types of carrageenan show a broad distribution of molecular weight between 100,000 and 500,000 (13). At present the common method is HPLC based size exclusion chromatography (HPSEC) coupled to a multi-angle laser-light scattering (MALLS) detector. The absolute mass and the molecular mass distribution can be obtained (19). Another method is Field Flow Fractionation coupled to a MALLS (20). However the latter has not been used extensively for this purpose.

By far the most powerful technique for conformational analysis of carrageenan is NMR spectroscopy (21). ^{13}C-NMR spectroscopy has been preferentially used to identify the different units of the carrageenan molecular chain. For ^{1}H-NMR spectroscopy the sensitivity is better but a distinction between the different components is more difficult (13). Thus ^{1}H-NMR spectroscopy is presently not the method of choice.

IR-spectroscopy can be applied to study the position of the sulfate groups but it is limited with respect to quantitative analysis. IR-spectroscopy can be applied directly to the raw carrageenan (22) but also to dried and milled commercial products by the use of FTIR diffuse reflectance spectroscopy (23). Additionally using partial reductive

hydrolysis after methylation allows discriminating between the agaran and carrageenan backbone and its substitution (24).

X-Ray diffraction patterns of the carrageenans show that the carrageenans are mostly however not completely amorphous. The measured peaks at 28 and 36.2°C in the powder diffraction patterns of κ- and ι-carrageenan could be related to the presence of calcium and potassium salts (28).

The glass transition temperature T_g of the carrageenans has firstly been determined for lyophilized products (25). In dependence on humidity the resulting values were in between −10°C and −80°C. Own determinations by DSC, which were confirmed by modulated DSC, showed that the T_g is for all analyzed types of carrageenan by -2.0 ± 1.1° C (26). As a result the amorphous parts of all measured carrageenans are in the rubbery state.

Powder-Technological Properties

Information on the powder-technological properties of carrageenans is scarce. Own determinations show a variety of powder-technological properties as given in Table 1 (27,28). Further own determinations by laser diffraction with six carrageenans showed that the mean particle size and the cumulative particle size distribution can be compared to those of microcrystalline cellulose (MCC) (Avicel PH 101). However this is not withstanding that other particle sizes and distributions can be obtained by choosing appropriate milling conditions.

Based on tap and bulk density the Carr index was calculated which gives information on the flowability of the powders. The higher the Carr index the better is the compressibility of the powder and following flowability is worse. In the specific study for the flowability the order λ- > ι- > κ-carrageenan was determined. Furthermore the flow properties of the carrageenans are similar to those of the celluloses and thus acceptable.

The apparent particle densities of the carrageenans were determined to be higher than those of celluloses, lactoses, and starches. This behavior can be caused by included potassium and calcium ions. Furthermore, the apparent particle density of the carrageenans is similar for κ- and λ-carrageenan and significantly higher for the ι-carrageenan which contains 3,6-anhydrogalactose units.

The properties of the carrageenans are influenced by relative humidity since they are hydrophilic polymers. Figure 2 shows the sorption isotherms of some carrageenans compared to MCC (28). All the carrageenans exhibit a higher water sorption tendency than MCC. Water sorption is more than three-fold at 60%, RH 20% (w/w) water were sorbed. In conclusion, the relative humidity during analysis, production, and storage of the excipient and also of the formulated products should be controlled.

Of additional interest is the morphology of the carrageenans. A typical example of particle morphology is exhibited in Figure 3. Principally, all carrageenans consist of long threads and show some structuring on the surface (29). The results showed that particle structure is influenced by the potassium content. More examples of particle shape are given in the literature (28).

Gel Formation Properties

Until recently, the carrageenans were mainly used as jelling and thickening agents, however, some types are able to generate gels with different characteristics which can influence release behavior.

TABLE 1 Powder Technological Properties of Six Different Types of Carrageenans (Mean ± SD)

Material	Quality	Water content (% (m/m))	Medium particle size (μm)	Apparent particle density (g/cm³)	Bulk density (g/cm³)	Tap density (g/cm³)	Carr index (%)
ι-Carrageenan	Gelcarin GP-379 NF	13.64 ± 0.15	65	1.812 ± 0.007	0.710 ± 0.005	0.0980 ± 0.015	27.51 ± 1.36
κ-Carrageenan	Gelcarin GP-911 NF	12.50 ± 0.12	65	1.744 ± 0.011	0.444 ± 0.008	0.674 ± 0.038	33.93 ± 2.65
κ-Carrageenan	Gelcarin GP-812 NF	14.04 ± 0.10	55	1.754 ± 0.004	0.465 ± 0.000	0.738 ± 0.017	36.95 ± 1.48
mixture of κ- and λ-Carrageenan	Viscarin GP-328 NF	14.75 ± 0.08	65	1.730 ± 0.003	0.446 ± 0.015	0.643 ± 0.023	30.60 ± 0.60
λ-Carrageenan	Viscarin GP-109 NF	11.61 ± 0.01	65	1.754 ± 0.005	0.625 ± 0.001	0.840 ± 0.031	25.61 ± 2.71
λ-Carrageenan	Viscarin GP-209 NF	15.71 ± 0.05	75	1.744 ± 0.003	0.737 ± 0.013	0.907 ± 0.017	18.66 ± 2.05
MCC	Avicel PH 101	4.99 ± 0.09	50	1.580 ± 0.002	0.352 ± 0.003	0.507 ± 0.017	30.48 ± 1.87

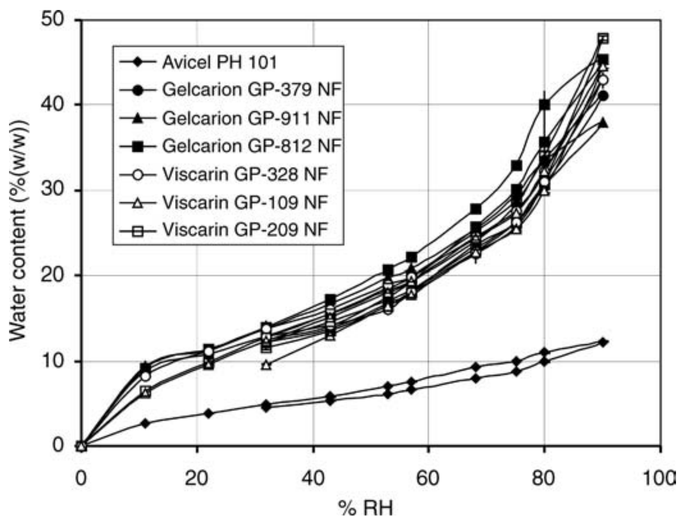

FIGURE 2 Sorption isotherms of six different carrageenans compared to MCC (mean ± SD). *Abbreviation*: MCC, microcrystalline cellulose.

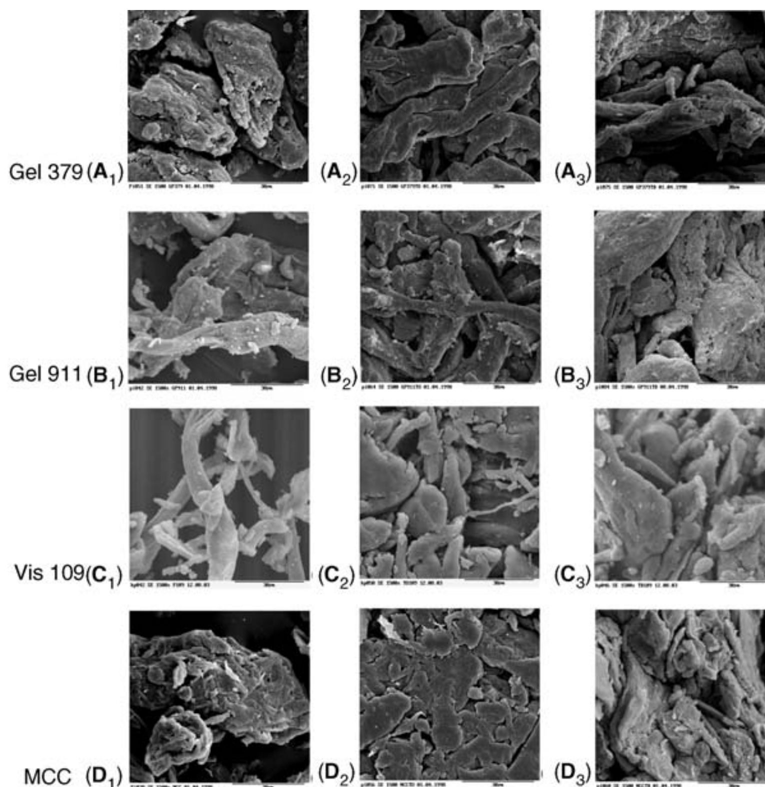

FIGURE 3 SEM of powders (1), upper tablet surface (2), and breaking surface (3) of the tablets of (**A**) Gelcarin GP-379 NF, (**B**) Gelcarin GP-911 NF, (**C**) Viscarin GP-109 NF, and (**D**) Avicel PH 101 (magnification: 1500×).

All forms of λ-carrageenan as well as the sodium salts of κ- and ι-carrageenan are soluble in cold water. The potassium and calcium salts of κ- and ι-carrageenans, however, dissolve only at 70°C and form gels or viscous systems upon cooling. This occurs in dependence on the ionic strength (13).

All carrageenans are able to form viscous solutions and this behavior is dependent on carrageenan concentration. The viscosity increases with increasing carrageenan concentration. The resulting solutions are highly viscous, since in a solution with low ionic strength, the carrageenan chains are extended due to the electrostatic repulsion of the negatively charged sulfate groups. However, viscosity decreases by addition of salts due to charge shielding and it decreases furthermore upon heating.

The viscosity of soluble carrageenan forms can be measured in 1 % solutions at room temperature. However, caused by the ocurring gelation at intermediate temperature, viscosity is normally measured in 1.5% solution at 75°C. Most experiments for material characterization are performed with rotational viscometers, since carrageenan solutions have pseudoplastic behavior.

Carrageenans are not stable under acidic conditions, because the 3,6-anhydro ring and the 1,3 linkages can be easily hydrolyzed. The substitution with sulfate groups at carbon 2 introduces some stability. Gelled carrageenans are more stable. Thus stability and gel formation properties of the carrageenans have to be regarded separately for the different types:

λ-carrageenan contains no 3,6 anhydrogalactose unit and is highly sulfated. It does not gel and is only used as a thickening agent.

κ-and ι-carrageenan are very similar except ι-carrageenan which is sulfated at carbon 2. Both polymers swell and form gels. κ-carrageenan forms strong rigid and brittle gels. κ-carrageenan forms a gel with potassium ions, but also shows gelation under salt-free conditions. However, gels prepared in the presence of cations were substantially stronger than those obtained under salt-free conditions (30).

The gelling and melting temperatures of κ-carrageenan are strongly dependent on the concentration of potassium ions. Also, addition of sugar increases the gel strength. Both additions also increase the setting temperature as well as the melting temperature of the gels. The hysteresis remains small. The gels are brittle and have a tendency to become opaque and show syneresis. This can be prevented by adding ι-carrageenan.

ι-carrageenan forms elastic gels, which show thixotropy, mainly in presence of calcium salts (31). Gels of ι-carrageenan alone are transparent, they show no syneresis and little hysteresis. Due to the presence of 3,6-anhydrogalactose groups the gels are rather weak.

Furthermore, the observation that gelation of a commercial ι-carrageenan showed a small specificity towards monovalent cations was interpreted as being due to the inclusion of a small proportion of κ-carrageenan (32).

Besides these general gelation properties, it is of special interest to know the gelation mechanism in detail. To obtain a gel the carrageenan molecules must undergo a transition from a random coil structure into helices that aggregate upon cooling. In general the ions induce a network formation (33), which is an intermolecular association that requires a minimum degree of polymerization. It is still under debate whether the fundamental ordered state is a single or a double-stranded helix. Originally, results obtained by high performance size exclusion chromatography coupled to a low angle light scattering detector (HPSEC-LALLS) indicated double helixes. Most recently, newer results by HPLC based size exclusion chromatography, coupled to a LALLS or MALLS detector favor especially for ι-carrageenan single helixes (13). Although the details of the gelation mechanisms proposed are different, the essential point is that the κ-carrageenan

gels consist of junction zones connected by some kind of long flexible chains. The present gelation mechanism can thus be described as in Figure 4.

The carrageenan gel formation is thermo reversible, and upon heating, the helices unfold, the molecules go into solution again as random coils and the gel melts. In the gel state the aggregation of helices may continue, the network contracts, and the gel becomes brittle and shows syneresis.

Apart from these detailed gel formation and stability studies, it is worthwhile to know that common microorganisms found outside the marine environment do in general not degrade the carrageenan.

Formation of Polyelectrolyte Complexes

When a carrageenan as a polyelectrolyte is combined with a uni- or multi-valent ion of the opposite charge, it may form a physical hydrogel which is based on ionic interaction. Such so-called ionotropic hydrogels can degrade and eventually disintegrate and dissolve since they are held together by molecular entanglements and/or secondary forces including ionic, H-bonding or hydrophobic forces (34). All of these interactions are reversible since they can be disrupted by changes in physical conditions such as ionic strength, pH, temperature, application of stress, or addition of specific solutes that compete with the polymeric ligand for the affinity site on the protein (35).

Of particular interest is the formation of polyelectrolyte complexes of κ-carrageenan with locust bean gum, chemically a galactomannan. By partially replacing the κ-carrageenan with locust bean gum, which does not gel on its own, a stronger gel with improved properties is obtained. The gel properties can be described as more elastic compared with the pure κ-carrageenan gel, and the gel tends less to syneresis and the ability to become opaque (13).

Similar observations were made with konjac glucomannans. The regions with no galactose or glucose side groups of the mannan chain are thought to bind to the double

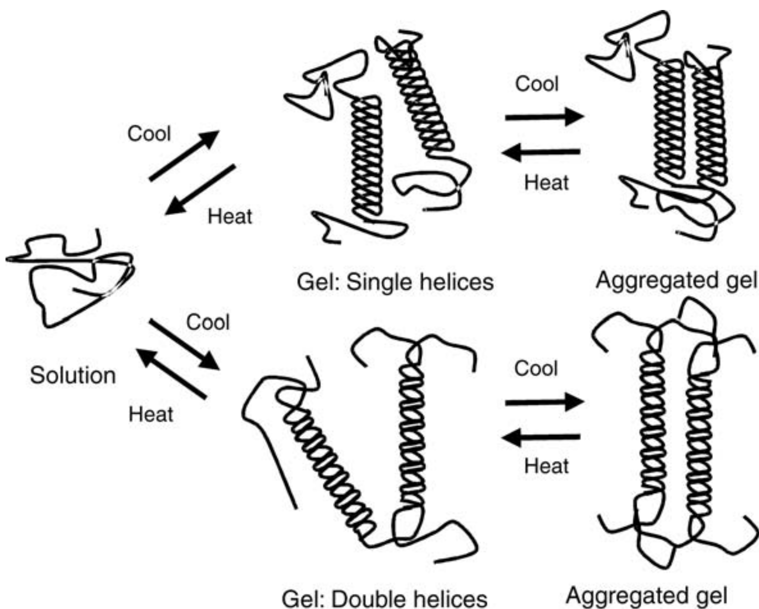

FIGURE 4 Gelation mechanism of carrageenans.

helices of the κ-carrageenan. Thus they are able to form strong polyelectrolyte complexes (36) which have a lower tendency to form tightly packed aggregates.

Carrageenans are also useful in altering the textural properties of a starch system, however, the ability for this purpose depends on the type of carrageenan Adding ι-carrageenan (0.5 %) to a starch system increases the viscosity as much as 10 times, whereas no effect is obtained by adding κ-carrageenan (37).

Furthermore polyanion–polycation polyelectrolyte complexes with chitosan can be formed and most recently there is a growing interest in such complexes (38). They have been used in the formulation of beads and microcapsules (39) and more recently for the development of tableting excipients (40–42).

Carrageenans possess a strong anionic character because of their sulfate groups and since the λ-carrageenan contains more sulfate groups than κ- and ι-carrageenan it is slightly more anionic. These charges and also associated ions, e.g., sodium versus potassium and calcium and the conformation of the sugars in the chain determine the properties of carrageenans. As a result reactivity with proteins can be observed both with carrageenans of the gelling and the nongelling family (13).

Some chain regularity is important in different types of interactions (1). Below the pH of the isoelectric point of the protein the positively charged protein and the negatively carrageenan form a complex which might result in a precipitate depending on the net charge ratio. Above the pH of the isoelectric point, the interactions are mediated by polyvalent cations such as calcium. Furthermore, an interaction with a positively charged part of a molecule with a net negative charge may occur.

In milk systems a highly specific interaction between κ-casein and the gel forming κ- and ι- carrageenans has been established. When the molecular mass of the carrageenans is sufficient, helical regions can form and aggregate and a gel network is obtained. λ-carrageenan is not able to do so.

It is of special interest to know the mechanism of the interaction with milk proteins in detail. At carrageenan concentrations as low as 0.02%, weak networks form which can fix casein particles. In chocolate milk, for instance, these networks hold the cocoa suspension and in creams, for instance, these networks hold the lipid globules. The reaction between milk proteins and carrageenan may synergistically increase the gel strength about 10 times, and carrageenans forms milk gels such as flans at a concentration of 0.2% (13). ι-carrageenan forms elastic, κ forms brittle, and λ-carrageenan forms weak milk gels.

There is most recently a growing interest in the use of carrageenans in pharmaceutical applications, partially because of the formation of polyelectrolyte complexes. Different solid dosage forms are formulated and the release of drugs is controlled by using these interesting polyelectrolyte complexes.

USE

General

During recent years carrageenan has been used increasingly in pharmaceutical formulation studies (35,39,42,43–47,48). The interest is growing since the major problem of the standardization of the raw material is no longer a problem and more and more standardized materials become available on the market. The highly sulfated λ-carrageenan does not gel, but both the other types, κ- and ι-carrageenan, are able to generate gels with different characteristics which can influence release behavior of mixtures as described above. Furthermore, polyanion–polycation complexes with drugs

can be used in drug delivery. Thus, there have been studies on the formation of tablets, on tablets with controlled drug delivery characteristics—both with and without complex formation—and on other solid dosage forms as beads and microcapsules. Furthermore, special compaction characteristics of the carrageenans give a potential for soft tableting of pressure-sensitive materials, e.g., polymorphic drugs, pellets with functional coatings, enzymes, or microcapsules with special release properties (49).

Tablets

Up to 10 years ago, the carrageenans were mainly used as jelling and thickening agents. Only a few studies examined their use as potential drug delivery excipients (43,50–52), but these studies dealt only with drug delivery from tablets fabricated on a hydraulic press or from tablets which contain the carrageenans in mixture with other excipients. Never tablets from the pure material were manufactured on a tableting machine as used in production and up to that time there was no study dealing with the compaction and consolidation behavior of the carrageenans. Because these tableting machines are normally used in production, it was of special interest for dosage form development to study the drug release from directly compressed matrices from such machines under production conditions.

Tablet Formation Properties

Carrageenans form tablets by plastic deformation. Simultaneously, the materials exhibit elastic relaxation of the tablets, particularly for ι- and κ-carrageenans. After tableting, relaxation continues to different extents for the various types of carrageenan. Overall, elastic recovery is higher compared with most of the usually used tableting materials. However, mechanically stable tablets are formed. The compaction energy is used for plastic deformation and a reorganization of the fiber structure. Part of the energy is released in the form of elastic recovery. Thus, less energy is transformed into pure plastic deformation. This makes these materials especially useful for soft tableting (53).

Tableting: The tableting behavior was characterized by 3-D modeling, Heckel analysis, determination of the parameters of the pressure–time function, and energy calculations from the force–displacement profile in comparison.

3-D modeling uniquely characterizes the three variables during the tableting process (normalized time, pressure, and density) simultaneously. For this purpose the data gained during a single compaction cycle, namely force, time and displacement are plotted in a 3-D data plot as pressure (y), normalized time (x), and porosity according to Heckel (z) (54). To this 3-D data plot a twisted plane can be fitted by the least-squares method according to Levenberg-Marquard. The plane is twisted at $t = t_{\max}$. The equation is as follows:

$$z = \ln\left(\frac{1}{1 - D_{\text{rel}}}\right) = ((t - t_{\max}) \cdot (d + \omega \cdot p_{\max} - p)) + (e \cdot p) + (f + d \cdot t_{\max}) \quad (1)$$

where D_{rel} is the relative density, t is the normalized time, and p is the pressure,

$$d = \frac{\delta \ln(1/(1 - D_{\text{rel}}))}{\delta t}, e = \frac{\delta \ln(1/(1 - D_{\text{rel}}))}{\delta p}, f = \ln\left(\frac{1}{1 - D_0}\right) 1$$

$t_{\max}$ is the normalized time at maximum pressure, $p_{\max}$ is the maximum pressure, and ω is the twisting angle at $t_{\max}$.

For fitting only those data exceeding a pressure of 50% of the maximum pressure are used since a compromise between a minimum error of residues and the inclusion of as much data as possible had to be chosen. Since the main deformation of the particles happens in this stage, this procedure was regarded to be legitimate.

From this fitting process different parameters can be calculated: d, the slope of porosity over time called "time plasticity," e, the slope of porosity over pressure called "pressure plasticity," and ω, the twisting angle which indicates "fast elastic" decompression.

The resulting parameters d, e, and ω are used to characterize the tableting process. Time plasticity, d, describes the plastic deformation with respect to time. Increasing time plasticity indicates faster deformation during tableting. A material which shows high d-values exhibits high time plasticity and thus fast deformation. Pressure plasticity, e, describes the relationship between density and pressure. Large pressure plasticities are observed with materials that require only a small amount of pressure for deformation. A material which shows high d-values thus exhibits high pressure plasticity and needs low pressures for deformation. The twisting angle, ω, is a measure for the elasticity of the material. Elasticity decreases with increasing ω. ω can be interpreted as the ratio between compression and decompression, and thus describes indirectly fast instantaneous elastic decompression during the decompression process. A material which shows low ω-values, thus exhibits high fast elastic decompression and elasticity. Pressure dependent and time dependent deformation can be clearly distinguished and separated from elasticity using this method.

For every tableting condition, which means a certain maximum pressure or minimum porosity under load for a given weight of the tablet, a specific compaction cycle results which can be characterized by fitting the twisted plane. Specific d-, e-, and ω-values can be calculated. By plotting the different characteristic parameters for each tableting excipient with increasing maximum relative density in a 3-D coordinate system a 3-D parameter plot can be obtained, which gives a simple yet characteristic description of the tableting properties. This 3-D parameter plot allows to distinguish between brittle fracture and plastic deformation (54). Materials which exhibit brittle fracture show steep plots with strongly decreasing ω-values, materials which exhibit mostly plastic deformation show more flat plots and higher d- and e-values compared to brittle materials: for example, dicalcium phosphate dihydrate exhibits low d- and e-values with strongly decreasing ω-values and MCC exhibits medium to high d- and e-values whereas the ω-values change only slightly with increasing densification.

For different types of carrageenan (κ, ι, and λ), which were compared with MCC, pressure plasticity (e) was lower and fast elastic decompression (indicated by ω) was higher compared with MCC (Fig. 5). The κ- and λ-carrageenans behaved similarly. The λ-carrageenan showed lower e- and ω-values compared with both κ- and the ι-carrageenan. In addition, for all the carrageenans, time plasticity (d) was lower compared with MCC. Thus, the carrageenans are less plastic than MCC and exhibit much more elasticity already during tableting. Brittle fracture can be excluded because the materials do not show the typical decrease in ω-values (55). The order of elasticity is $\iota > \kappa > \lambda$. Because of its anhydrogalactose groups, which are also substituted with sulfate, ι-carrageenan is the most elastic material and shows lower ω-values than both the other carrageenans.

For composite materials that consist of both κ- and λ-carrageenan it was shown that it is much more plastic in its behavior; d and e are higher compared with the pure types. Furthermore, fast elastic decompression is lower because ω is higher. A reason for this high plasticity might be that in this composite product the texture of the fibers is less homogeneous and thus, the fibers deform more plastic (53).

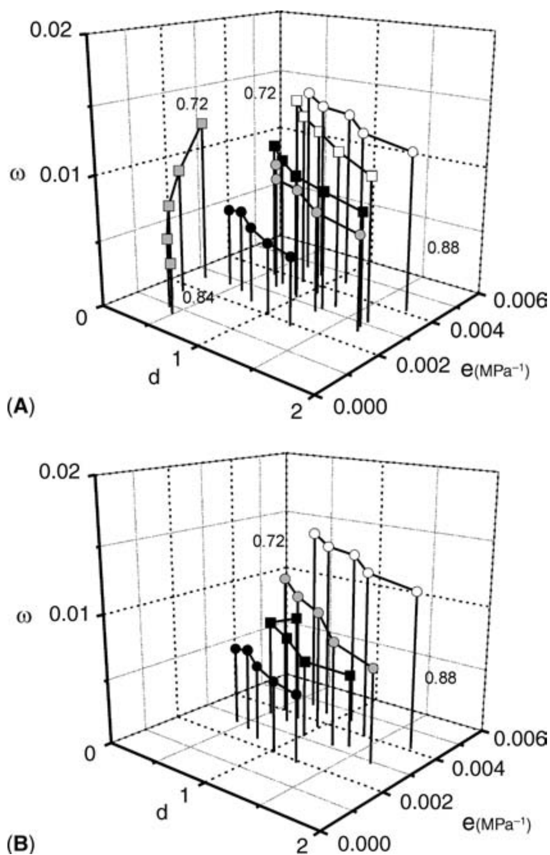

FIGURE 5 3-D-parameter plot of (**A**) ○ MCC (Avi 101), □ MCC (Avi 200), ■ DCPD, ● Gel 379, ■ Gel 911, and ● Gel 812; (**B**) ○ MCC (Avi 101), ● Gel 379, ■ Vis 209, and ● Vis 109.

Beside the tableting behavior has been analyzed by other methods (53). For most carrageenans the slope of the Heckel function is lower compared with MCC, indicating less deformation. However, the slope of the Heckel function includes plastic and elastic deformation. As known from 3-D modeling, the deformation of the carrageenans is mainly elastic deformation. Thus the order of elasticity is the same as by 3-D modeling. The results of the pressure–time analysis show that all carrageenans are much more elastic than MCC. Distinguishing the different carrageenans is not as easily possible using this method. However, ι-carrageenan exhibits the highest β-values and is thus the most elastic material. Finally, energy analysis from force–displacement profiles indicates that ι-carrageenan is the most elastic material. However, the differences between the carrageenans are slight using this method.

Furthermore, it could be shown that tableting properties are influenced by particle size and relative humidity. Tableting at different relative humidities showed that with increasing humidity and increasing water content, the 3-D model parameters time plasticity d, and pressure plasticity e increased, and fast elastic decompression, the inverse of ω decreased.

Final formation of the tablet: To describe the tablet formation process completely it is important to analyze the final formation of the tablets.

For all carrageenan tablets, elastic recovery was higher compared with those tablets produced from MCC. Relaxation, which already started during tableting, continued. Elastic recovery was different for the different types of carrageenan. Tablets made of κ-carrageenans showed higher elastic recovery than those made of the ι-type (56). The order was inversely for fast elastic decompression. Tablets made of the λ-carrageenan

and of the composite materials exhibit less elastic recovery. This behavior conforms to the behavior during tableting.

In summary, for a great deal the process of tablet formation continues after tableting. Thus, to fully illustrate tablet formation, elastic recovery after tableting was determined in dependence on time (53). The results for elastic recovery obtained by thermomechanical analysis at constant temperature show for all three types of carrageenan, in the beginning an increase in elastic recovery followed by a decrease in elastic recovery. To rule out the influence of the applied slight force during thermomechanical analysis, experiments were also performed with the automatic micrometer screw, a contactless measurement. Similar results as with thermomechanical analysis were obtained. Most probably parallel to the relaxation of the tablets after tableting a shrinking of the tablets occurred. This process is most pronounced for tablets made with κ- and ι-carrageenan. Tablets made of λ-carrageenan exhibit less shrinking. Thus, a shrinking (S) order can be established: S(κ-carrageenan) > S(ι-carrageenan) > S(λ-carrageenan). During all experiments tablet mass remained constant and thus, the tablets did not dry.

By density measurements with carrageenan tablets after tableting it could be shown that the apparent density of the tablets, as determined by helium pycnometry, increased with storage time. This density increase could be caused by reorganization in the fiber structure initiated by the force applied during tableting. Environmental scanning electron micrographs (ESEMs) produced by video analysis at constant humidity in the ESEM show that indeed a fiber shrinking occurred after tableting. Precisely the same breaking surface of a tablet: (*i*) 30 minutes and (*ii*) 12 hours after tableting was analyzed and the fiber shrinking could be observed. The fiber strength decreased and also the gaps between the fibers increased (53).

Thus following tableting, changes in the material took place, which are the reason for the increase in density. To analyze the fiber structure more precisely, the breaking surface was analyzed by transmission electron microscopy after freeze fracturing. The breaking surface was analyzed 2 and 24 hours after tableting. After 24 hours stripes were visible that could not be detected 2 hours after tableting. A mechanical activation occurred that caused changes in the fiber structure and lead to the tablets shrinking.

This mechanical activation can contribute to bonding and is responsible for the sufficient crushing strength of the tablets, which was about 100 N despite the fact that the tablet formation process contained high portions of elasticity.

Physical Tablet Properties

For the application of tablets and their therapeutic use it is of utmost importance that the tablets are mechanically stable. Thus as usual the crushing force of the tablets has to be analyzed and further the morphological characteristics are helpful to get an insight in the bonding and inner structure of the tablets.

Morphological studies on the upper and breaking surfaces after tableting and relaxation show a high porosity and a loose entanglement of the fibers, even the upper surface of the tablets is not plane (53). Mechanical interlocking is of importance for bonding. The fibers are less deformed than the MCC fibers, and this could enable their suitability for soft tableting.

A reason for this behavior might be the low glass transition temperature (T_g) of the carrageenans. The carrageenans are at room temperature in the rubbery state, MCC is in the glassy state. Thus, MCC reversibly transgresses the T_g during tableting whereas carrageenan does not (26).

Tablets produced of λ-carrageenan seemed to be more loose in structure than tablets made of the ι- and κ-carrageenans.

Despite the loose structure of the carrageenan tablets, mechanically stable tablets were obtained for all types of carrageenan, the crushing force values were as high as 100 N and at high densification even higher. However, the slope in the compactibility plot is much lower compared with MCC. Obviously, the high elasticity of the carrageenans reduces crushing force.

Summarizing, for all analyzed carrageenans, the crushing force was satisfying and thus, bonding inside the tablet was sufficient for mechanical stability.

Application in soft tableting: The described tableting and tablet properties (27,28,53) of the carrageenans reveal that the carrageenans are largely elastically deforming excipients, which deform with a great deal of elasticity, which is released during and after tableting. One reason for this behavior is their being in the rubbery state (26). The high elasticity is interesting with special respect to the theory of 'Soft Tableting" as developed by Picker (49). Because of their high elasticity carrageenans were thus able to protect enzymes as amylases from inactivation during tableting (57,58); they were furthermore able to avoid the transformation of amorphous indomethacin into the crystal γ-from (59) and to avoid the transformation of other metastable polymorphs (60,61) into their stable but not wished modifications for a great deal; and finally they also protected brittle functional coatings as Eudragit L 30 D from rupture (62,63) (Fig. 6). With regard to these properties carrageenans were used as formulation additives by other scientists (64). As an example for formulation, it might be useful to include carrageenan

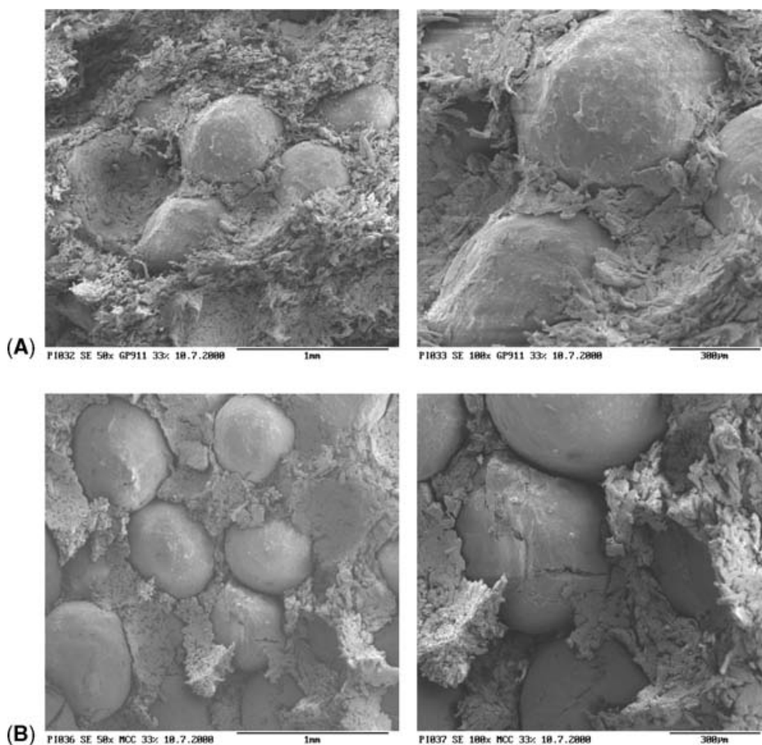

FIGURE 6 Scanning electron micrographs inside the tablets at the inner surface: Tablets made with (**A**) carrageenan (Gel 379) and (**B**) microcrystalline cellulose (Avi 101).

as an additional excipient in tablet formulations in order to avoid the above mentioned problems. The concentration can carry in dependence on the problem between 10% and 40%.

In conclusion, there is huge potential of the carrageenans in formulation development with special respect to softly embedding pressure sensitive materials. Furthermore, the number of such pressure sensitive materials is expected to increase in the near future, since proteins and metastable polymorphs have to be increasingly used in formulation development.

Controlled Release Properties

Controlled release properties of excipients are of utmost importance for patient compliance. The reduction of daily dose intake improves patient compliance significantly. Thus, different mechanisms to control drug release from tablet matrices were studied. The highly sulfated λ-carrageenan does not gel, but both the other types, κ- and ι-carrageenan are able to generate gels with different characteristics which can influence release behavior of mixtures. Furthermore, on the basis of the special polyelectrolyte complex formation properties of the carrageenans it was tried to control drug release from tablets.

Without complex formation: Since carrageenan was mainly investigated after the Second World War as a substitute for cellulose in food industry there was for a long time no interest in carrageenan in pharmaceutical dosage form design and thus studies on this subject were missing.

There exists one study which was performed as early as 1984 (50), however, the results were not promising since a non standardized material was used.

In the early 1990s when people were looking for alternative materials to control drug release in tablets the interest was increasing (43,51,52,65). The κ-, ι-, and λ-carrageenan were explored for drug release characteristics, κ-carrageenan first in Japan (52), λ-carrageenan in Italy (65) and ι-carrageenan in Belgium (51). The research group of Caramella in Italy explored in detail the controlled release properties of the highly sulfated λ-carrageenan (43). The results were partially promising partially not. λ-carrageenan was able to control drug release but it had no gelling properties.

Some studies revealed that carrageenans can be used as an additive which is able to control drug release in dependence on pH (65). Drugs with anionic, cationic and nonionic nature were investigated. Potential interest is given for cationic drugs since carrageenans are anionic polymers. Another research group found carrageenans not to be useful in controlled drug delivery and suggested other excipients (51). Further carrageenans were used in mixtures with hydroxypropyl methycellulose to modify the release. These studies were successful (52,65,66) and allow further options. The interest increased in the late 1990s. It was shown that ι-carrageenan showed controlled release for 8-hours tending to zero-order kinetics (45,67) (Fig. 7). These investigations were performed in parallel by other research groups and the results showed that also λ-carrageenan was able to control drug release with zero-order kinetics (44).

Considering these findings it is of special interest to understand the matrix formation process of carrageenans. Drug release from hydrocolloid matrices is dependent on their gel forming properties, their swelling behavior, and in combination on the sorption tendency of the polymers. This is similar to HPMC matrices; however, the formed gels are less viscous.

The viscosity of the gel layer formed by expansion of the tablets during swelling influences the mobility of the drug molecules in the tablet and thus drug release.

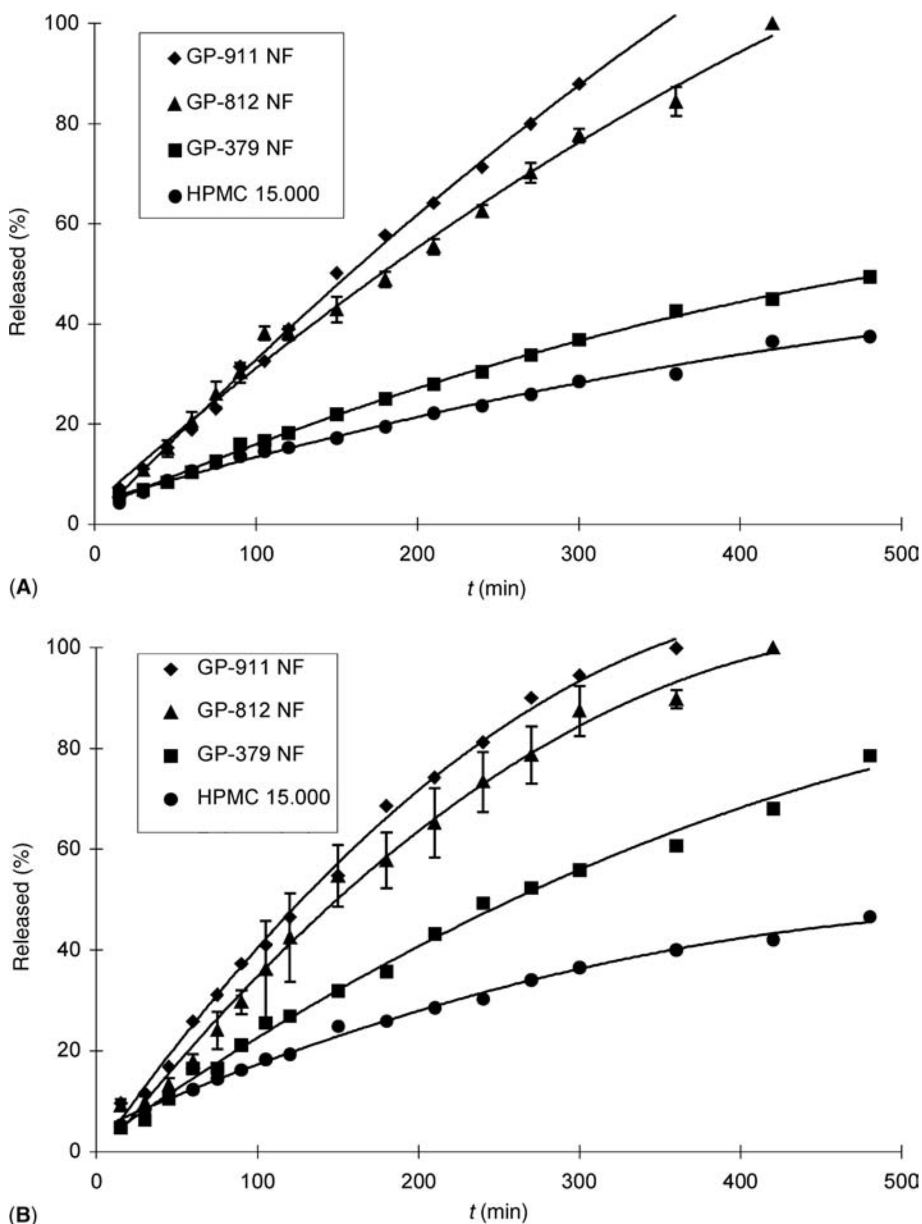

FIGURE 7 Drug release of the carrageenans and HPMC: (**A**) theophylline monohydrate, (**B**) sodium diclofenac (mean of $n = 3$, SD exemplary). *Abbreviation*: HPMC hydroxypropyl methylcellulose.

Therefore, first, the properties of the different types of carrageenans like sorption behavior, rheology, and swelling behavior were of interest. A theory was developed to connect sorption, rheology, and swelling behavior and finally the drug release of these viscoelastic substances (45). Additionally, the influence of potassium and calcium ions on swelling and release behavior was investigated. These ions are able to change the jelling properties of gels made with these substances. An influence on drug release could

be shown. Studies on mixtures of carrageenans with other excipients gave further insights into drug delivery (66,68,69). The materials used were cellulose ethers and MCC. For diclofenac sodium and theophylline monohydrate, two drugs with potential interest in formulation, the concentration of drug in delivery was investigated (70). The effect of formulation factors, moisture, and storage on the release was studied (71–73). Most recently a study performed on mixtures gave further insight into effect of formulation factors on dissolution rates and the swelling behavior of tablets with carrageenan using cryogenic scanning electron microscopy (74).

Since carrageenans are relatively new excipients, there do not exist a lot of formulation suggestions. However, a few factors should be kept in mind. In dependence on the drug in combination with the type of carrageenan, the percentage necessary to allow sufficient jelling has to be chosen for direct compression. It should be usually higher compared to polymers, e.g., hydroxypropyl methylcellulose.

Apart from these release studies it has been tried to produce granules of carrageenan and MCC, however, drug release was always higher than with other polymers and thus these studies were not deemed to be successful (75). Another attempt focused on the production of floating tablets (76). Finally, mucoadhesive tablets have been explored using carrageenan: these studies revealed that carrageenan can contribute to modify adhesion properties (77).

There is ongoing interest in the drug release with carrageenans and further studies are expected.

With complex formation: Since carrageenans are anionic polymers they are able to form complexes either with cationic drugs or with cationic polymers. Thus, complex formation is from the beginning a major issue in applying these polymers in drug release (46,78). It was explored that cationic drugs are of special interest in formulation and further that the pH is affecting drug release (79). Drug release is much slower at conditions with medium or higher pH as in the gastrointestinal tract than at a low pH as in the stomach.

In conclusion, it was worthwhile to produce drug polymer complexes to control drug release besides the possibility to control drug release by the gel formation behavior of the excipients. It is obvious that this method can only be applied to cationic drugs and further it depends to a great extent on the physicochemical properties of the drug (47,80–82). Special studies deal with the characterization of such complexes (83,84). Of special pharmacological interest is the complex of carrageenan with diltiazem which also showed good compression characteristics.

The interaction between λ-carrageenan and diltiazem-HCl was studied in detail. By dialysis equilibration relevance of the interaction in hydrophilic matrix systems was confirmed: a relationship was found between the binding capacity and the release profiles of matrix tablets containing a fixed amount of drug and different percentages of λ-carrageenan. The interaction was insensitive to the pH of the medium while it was reduced by increasing ionic strength (83).

More recently, polyelectrolyte complexes with polymers were explored for drug release in pharmaceutics. Of special interest were complexes formed with chitosan (38,42,85). Whereas polyelectrolyte complex formation in solution and in hydrogel application has been studied for some time the evaluation and preservation of these complexes in solid excipients has only been studied recently (41). Nevertheless, such excipients contain a potential for future developments.

Another approach is the possibility to produce complex formation instantaneously during drug release. This possibility exists for the formulation of drugs as well as for the use special excipients. A recent study evaluates the instantaneous formation of

polyanion–polycation complexes with carrageenan and chitosan (48). Until now there exist no published formulation suggestions for such products since presently only a few attempts have been published in literature to use such systems. However, there will be growing interest in such possibilities since this is an effective way of using complex formation.

Other Solid Dosage Forms

Beads: As for other charged polymers it is possible to crosslink the polymer chains of carrageenan and by this method it is possible to produce beads. The interest in such formulations with carrageenan started late compared to, e.g., alginates. Only a decade ago, preliminary studies on spherical agglomerates prepared with a cross-linking agent were successfully performed (86). It has been tried to tablet such spheres from and with carrageenan, however, drug release was always higher than with other polymers and thus these studies were not continued (87).

Using the ionotropic gelation method at the beginning of the new century the interest started again (88). The influence of formulation factors as drug content, polymer concentration, counterion type and concentration, outer phase volume on the particle size, encapsulation efficiency, and in vitro release characteristics of beads was investigated (89). In another study, carrageenan was applied in taste masking of a drug in solid-lipid beads (90).

In biotechnology it became of interest to immobilize enzymes in κ-carrageenan beads (91–93). The purpose of these studies was to improve stability of these enzymes. Only κ-carrageenan was used for this purpose. A final curing of the beads was necessary. The porcine pancrease lipase was immobilized and also the retention of hydrolytic activity of lipase and compressive strength of the beads were examined (91). The immobilized enzymes exhibited a little shift towards acidic pH for its optimal activity.

Later on, a novel continuous two-phase dispersion process was developed to produce κ-carrageenan gel microspheres, using static mixers (94). This process was applied for immobilization of α-chymotrypsin (92). The α-chymotrypsin encapsulation efficiency could be increased two times by preliminary enzyme crosslinking by glutaraldehyde. Also, urease was encapsulated within κ-carrageenan beads. Various parameters, such as amount of κ-carrageenan and enzyme activity were optimized for the immobilization of urease (93). Further studies allowed entrapment of papain and α-amylase in κ-carrageenan beads (35,95).

These applications in biotechnology are promising and will influence pharmaceutical applications in the next decades.

Microcapsules: At first, multilayered microcapsules, which contained pharmaceuticals, perfumes, or food were prepared using water-immiscible fluids as the inner layers, and polysaccharides, e.g., κ-carrageenan cross-linked with potassium surfactants, as the outer layer (96). The general procedure is similar to the production of beads, just the size of the products is much smaller.

Another approach was the preparation of microcapsules by complex formation with polyelectrolyte complexes. For example, κ-carrageenan/chitosan polyelectrolyte complex membrane capsules were prepared (97). The release from the capsules followed zero-order kinetics, and the release rates were independent of pH of the dissolution medium. Similarly, carrageenan-locust bean capsules were prepared by a modified multiphase emulsification technique (39). In this case ι-carrageenan was used, the microcapsules containing drug formed spontaneously.

Besides the delivery of drugs as used in pharmaceutics, microcapsules were used to encapsulate bacteria and enzymes. The encapsulated bacteria were, e.g., the mosquito pathogen Bacillus sphaericus 2362 (98), probiotic bacteria (99), and enzymes (100). The aim of such studies was to enhance the stability of the bacteria. Thus for Bacillus sphaericus 2362 increased sporal resistance was achieved as compared to the free bacterium. The encapsulation of probiotic bacteria is also a method to protect the bacteria in the gastro-intestinal system.

However, there is a need to design and develop equipment that will be able to generate precise and uniform micro or nano capsules in large quantities for industrial applications. There is a huge development potential in this respect.

Similar to the encapsulation of enzymes in beads these techniques will influence pharmaceutical formulation beside applications in food development.

FUTURE TRENDS

The present studies indicate that there is much potential in carrageenans for further formulations. Carrageenans will continue to be used in controlled drug release because of their gel forming and complex formation properties. There is ongoing interest regarding this issue and further studies are expected.

The preservation of the polyelectrolyte complexes in solid excipients has only been studied recently (41) and such excipients are of ongoing interest. A recent study evaluates the instantaneous formation of polyanion–polycation complexes with carrageenan and chitosan. (48). Such possibilities will most probably futher be explored in drug delivery since this concept is an effective way of using complex formation in solid dosage form development.

In biotechnology it became of interest to immobilize enzymes in carrageenan beads (91–93) or to microencapsulate enzymes with the purpose of improving the stability of these enzymes. Similarly, bacteria were encapsulated. The applications in biotechnology are promising and will influence developments in the food industry as well as pharmaceutical applications.

Apart from these controlled release properties the carrageenans possess special characteristic tableting properties which allow them to be used to tablet pressure sensitive materials.

Thus the studies performed until now indicate a further use of carrageenans in drug delivery and there will be even potential for dosage forms on a nano-scale level. However, there is an ongoing need to standardize the products and to set up Good Manufacturing Practices guidelines for the production excipients as for all other excipients in order to reduce lot to lot variability and manufacturer to manufacturer variability of the excipients with the final aim to achieve high standards in dosage from quality. It can only be hoped that the PAT initiative will even include this issue.

Summarizing, it can be stated that carrageenans are neglected natural polymers whose potential has only started to be explored during the last decade.

SUMMARY

Carrageenans are natural polysaccharides and belong to a family of polydisperse long chain galactans, which can be extracted from algae of the class of Rhodophyceae. They

consist of alternating 1,3-linked β-galactose (G-units) and 1,4-linked α-galactose (D-units), which can be partly substituted by sulfate groups (S). The three major commercial carrageenans types were named κ, ι, and λ, both the first belong to the gelling family the latter to the non-gelling family. All types of carrageenan show a broad distribution of molecular weight between 100,000 and 500,000. X-ray diffraction patterns of the carrageenans show that the carrageenans are mostly, however, not completely amorphous. The amorphous parts of all analyzed carrageenans are in the rubbery state. The powder technological properties are similar to celluloses. As all charged polymers the carrageenans have the ability to form polyelectrolyte complexes, which influences their use in drug delivery.

During the last decade the carrageenans have started to be used in pharmaceutical applications besides their long term use in food industry. Especially, two types, the κ- and ι-carrageenan are able to generate gels with different characteristics which can influence drug release. Due to their gel forming properties the formed tablets possess even mucoadhesion properties.

Furthermore, it was tried to control drug release from tablets since the carrageenans are anionic polymers, which are able to form complexes either with cationic drugs or with cationic polymers. Thus complex formation is from the beginning a major issue in application of these polymers in drug release. The λ-carrageenan which possesses the highest ratio of sulfate substitution was of special interest.

In addition as for other charged polymers it is possible to crosslink the polymer chains of carrageenan and by this method it is possible to produce beads. The interest in such formulations with carrageenan started late compared to, e.g., alginates, however, it is ongoing. Nowadays, the potential to from microcapsules which can contain pharmaceuticals, perfumes, or food have been prepared using water-immiscible fluids as the inner layers, and carrageenan cross-linked with potassium surfactants, as the outer layer. The general procedure is similar to the production of beads, just the size of the products is much smaller. Another approach was the preparation of microcapsules by complex formation with polyelectrolyte complexes. It can be expected that even nanocapsules can be produced by such formulation processes.

Furthermore, all formulation procedures applied to the carrageenans up to now only in food industry can be expected to be applied in pharmaceutics.

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16
Osmotic Systems

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THERAPEUTIC OBJECTIVES

Because drug delivery is programmed in osmotic systems, fluctuations of drug levels in the body are substantially reduced compared with conventional, immediate-release (IR), or sustained-release (SR) products. IR of drug may result in peak levels and higher-than-desirable doses shortly after administration and less-than-adequate doses as the tablet dissolves. In contrast, osmotic systems keep blood or tissue drug levels within a pre-determined range to enhance safety, efficacy, and reliability of treatment (Fig. 1).

Another benefit of programmed delivery by osmotic system technology is the reduction or elimination of side effects resulting from the rapid rise and high plasma drug concentrations seen with IR dosage forms. Metering the drug within a suitable concentration range may improve patient acceptability, particularly in chronic regimens (Fig. 2).

Additionally, unlike many traditional platforms, some osmotic systems can be designed to deliver two or more drugs at different rates; such combinations may optimize the efficacy of each drug and improve therapeutic value. Osmotic systems also allow controlled delivery of drug over time, and dosing is reduced as compared to that with conventional IR therapies taken several times a day. In most cases, once- or twice-daily administration is possible using osmotic technology, and this may improve patient compliance.

DESIGN

Though many variations have been proposed, osmotic systems can be classified in one of two categories, regardless of site of delivery (*i*) those with an osmotic driving member that swells and (*ii*) those without. Further, beyond this categorization, most osmotic systems feature a rate-controlling membrane and some means for drug release (e.g., a delivery orifice, or membrane pores).

The first modern-day application of osmotic pressure in an implantable device for fluidic delivery was described by Rose and Nelson (1). Subsequently, similar principles were invoked by Theeuwes (2) in the design of a series of platforms allowing zero-order release of drugs to the gastrointestinal tract (GIT). The first of these, the elementary

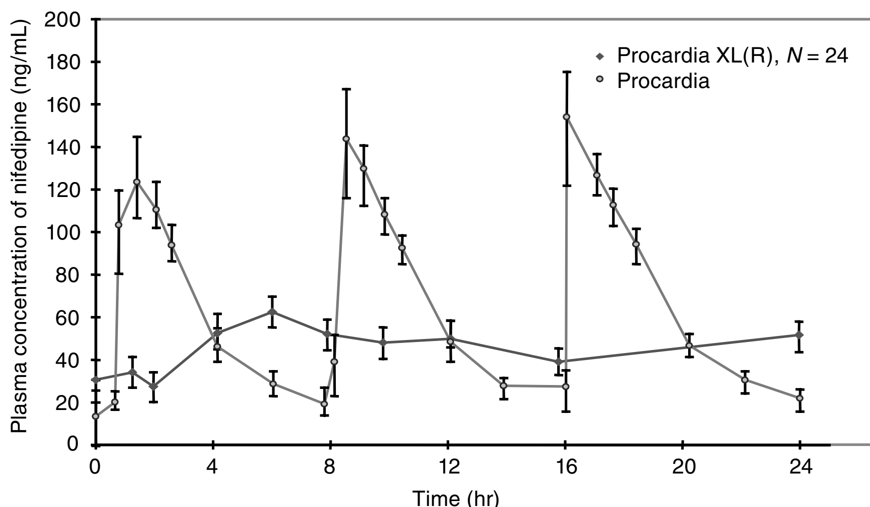

FIGURE 1 Steady state plasma profiles of nifedipine on day 5 for single dose Procardia XL® compared to immediate-release nifedipine capsules (t.i.d.).

osmotic pump (EOP), represents the simplest type of osmotic systems and comprises a solid compact surrounded by a rate-controlling membrane that has an exit portal, or orifice (Fig. 3). In practice, water from the GIT passes through the membrane and dissolves the hydrophilic components (e.g., drug and any adjunct osmotic agents), and these are subsequently expelled through the orifice.

As suggested in the general design equation below, the steady-state rate of delivery (Z_0) is governed by the permeability (K) and thickness (h) of the rate-controlling membrane, the aqueous solubility of the drug (S_D), the difference in osmotic pressure across the membrane ($\Delta\pi$), and the surface area available for water transport across the membrane (A):

$$Z_0 = KA\Delta\pi S_D/h \tag{1}$$

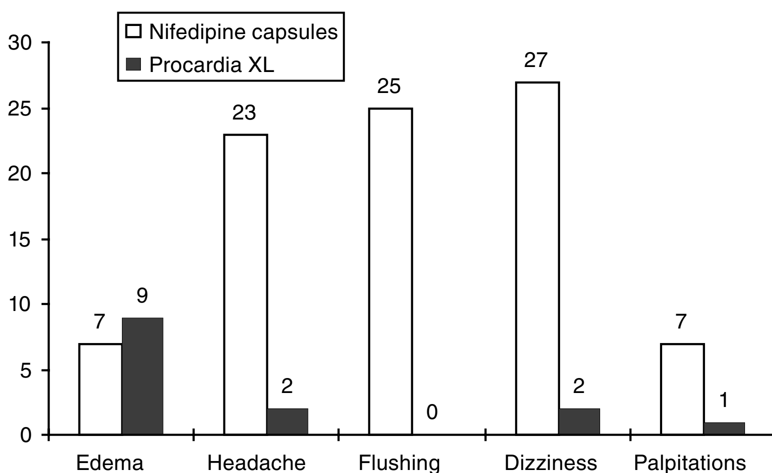

FIGURE 2 Relative frequency of side effects in anginal patients treated with immediate-release nifedipine capsules or Procardia XL.

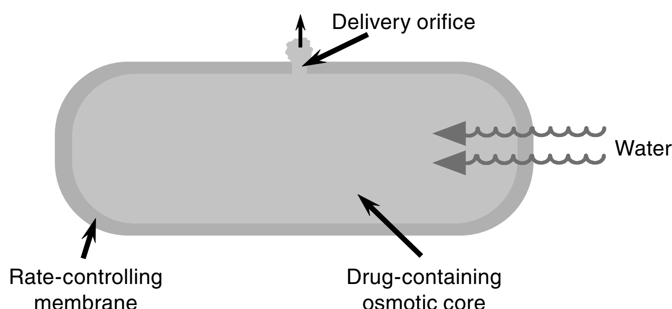

FIGURE 3 Schematic of EOP. *Abbreviation*: EOP, elementary osmotic pump. *Source*: From Ref. 2.

Zero-order delivery is maintained as long as a saturation concentration is sustained within the osmotic core. As additional water is imbibed into the tablet, the delivery rate (Z) follows $t_{1/2}$ kinetics, as described in Equation (2):

$$Z = Z_0/(1 + Z_0 t/S_D V)^2 \quad (2)$$

where t is the time of release and V is the core volume.

The EOP can be quite effective in delivering compounds of moderate solubility, ideally in the range of 50–400 mg/mL. For others that are less soluble, the achievable release rate as defined in Equation (1) is low, as the steady-state rate is proportional to the aqueous solubility of the drug. Alternatively, for entities with extremely high solubility, the fraction of drug delivered at zero-order (F_{Z0}) is low relative to that delivered under $t_{1/2}$ conditions per Equation (3), where the zero-order fraction approaches zero for an infinitely soluble compound:

$$F_{Z0} = 1 - S_D/\rho \quad (3)$$

where S_D is the drug solubility and ρ is the osmotic core density.

To resolve the shortcomings of the EOP, a second type of osmotic multi-compartment platforms, known as Push-Pull™ osmotic systems, were developed to include an expandable component that effectively displaces a hydrating drug formulation (3). In its simplest form, a single drug compartment is conjoined with a polymeric expansion compartment that forms a bi-layer tablet. The modified core is, in turn, enveloped by a rate-controlling membrane that contains a delivery orifice for the drug layer (Fig. 4). In practice, the osmotically active drug compartment and push compartment hydrate as water from the GIT passes through the rate-controlling membrane. While a hydrophilic drug solution or, alternatively, a lipophilic drug suspension is formed in the drug layer (4), water entering the push layer begins hydrating a water-swellable hydrophilic or lightly cross-linked polymer that sometimes contains osmotic agents. The push-compartment composition in turn expands, displacing the drug solution or suspension, through the delivery orifice. As both the push (expansion) layer and pull (drug) layer are osmotically active, the principle design equation governing drug release (Z_0) represents a sum of the two components:

$$Z_0 = K/h(A_D \Delta\pi_D + A_P \Delta\pi_P)C_D \quad (4)$$

where A_D, A_P are the surface areas available for water transport across the membrane into the drug layer and push layer, respectively; $\Delta\pi_D$, $\Delta\pi_P$ are the osmotic pressure

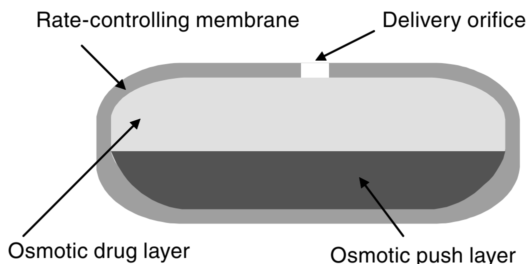

FIGURE 4 Schematic of bi-layer Push-Pull™ osmotic system. *Source*: From Ref. 4.

differentials across the membrane for the drug layer and push layer, respectively; and C_D is the drug concentration at the delivery orifice and is a function of formulation type and degree of hydration.

As the delivery rate is dependent on drug concentration and not necessarily drug solubility, further utility is gained with the Push-Pull system relative to the EOP. Moreover, a multitude of drug layer and push layer combinations are possible in addressing specific delivery requirements, two of which are displayed in Figure 5. A listing of various osmotic systems in use is shown in Table 1. Included are platforms for oral, subcutaneous, colonic, and ruminal delivery. Of particular note are those that have been used in commercial products:

1. *Osmodex™*: Allegra D® 24-Hour [Osmotica (Wilmington, NC, USA)/Sanofi Aventis (Paris, France)].
2. *SCOT™*: Altoprev™ [Andrx, Division of Watson (Corona, CA, USA)], Fortamet® (Andrx).
3. *EOP-PM*: Teczem® [Merck (Whitehouse Station, NJ, USA)], Tiamate® (Merck).
4. *Zer-Os™:* Tegretol® XR [Novartis (Basel, Switzerland)].
5. *MODAS®*: Brom-12 [Elan (Dublin, Ireland)].
6. *EOP*: Accutrim® [ALZA, Division of Johnson & Johnson (Mountain View, CA)/ Novartis], Osmosin® (ALZA), Efidac/24® (ALZA/Novartis), Sudafed® 24 hour (ALZA).
7. *EOP-NEC*: Volmax® [ALZA/Muro, Division of Glaxo Smith Kline (Brentford, UK)].
8. *Push-Pull*: Procardia XL® [ALZA/Pfizer (New York, NY)], Ditropan (Lyrinel) XL® (ALZA), Glucotrol XL® (ALZA/Pfizer), Cardura® XL (ALZA/Pfizer), Minpress XL® (Alpress™ LP) (ALZA/Pfizer), DynaCirc CR® (ALZA/Novartis).
9. *COER™*: Covera-HS® [ALZA/Searle, Division of Pfizer (New York, NY)].
10. *Push-Pull LCT*: Concerta® (ALZA), INVEGA™ [Janssen, Division of Johnson & Johnson (Titusville, NJ)].
11. *DUROS®*: Viadur® (ALZA/Bayer Healthcare, W. Haven, CT, USA).

Osmodex™

In its simplest form, the Osmodex osmotic system (5) comprises a drug-containing core and, optionally, other osmotic excipients with appropriate dissolution aids, binders, and lubricants, all surrounded by a semi-permeable membrane with at least one delivery orifice. The membrane-coated tablet is covered by a film or compressible layer that contains the active agent, or a second drug, and other film-forming materials and dissolution aids. The composition of the external coating may be adjusted to moderate the

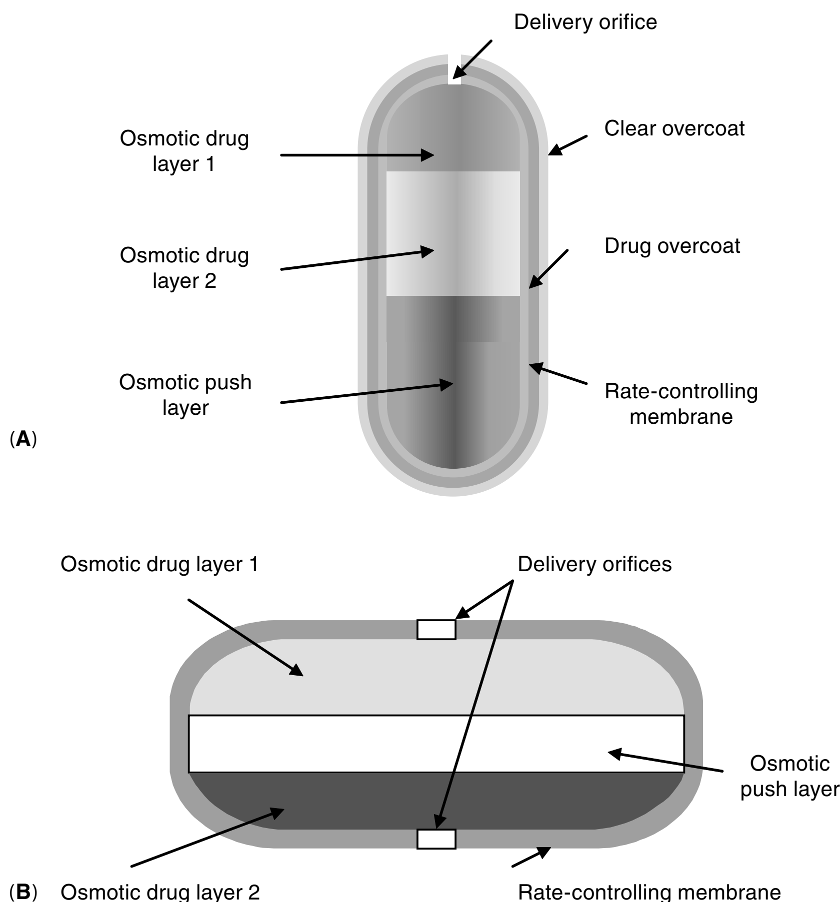

FIGURE 5 Schematics of two tri-layer osmotic systems. Schematic (**A**) represents a three-layer LCT Push-Pull system composed of two drug layers with differing drug concentrations, wherein $c_1 < c_2$ for generating ascending release profiles. Schematic (**B**) expresses a three-layer tablet with two drug layers externally positioned to an internal push layer. Drug concentration or type can be varied to achieve the appropriate delivery pattern. *Source*: From Refs. 12 and 14.

delivery of the active agent upon introduction to the GIT. With activation, the external layer hydrates and eventually dissolves, leaving the membrane-coated osmotic core, which functions similarly to an EOP.

SCOT™

In its basic form, SCOT™, or Single Composition Osmotic Tablet (6), is composed of an osmotic core containing drug, an osmotic agent, a water-swellable polymer, and, optionally, a water-soluble polymer encompassed by a membrane of water-insoluble polymer and augmented with optional plasticizers or pore formers. During operation, water from the GIT penetrates the membrane, dissolves the pore-forming component, and, at the same time, hydrates the osmotic core. The water-swellable polymer assists in enlarging the tablet. Because of hydrostatic pressure build up within the core, the membrane forms openings that allow the passage of hydrated core material to the GIT.

TABLE 1 Osmotic System Classification and Application

Platform	Type[a]	Application
Elementary osmotic pump (2) (equilibrium core)	1	Moderately water-soluble drugs; zero-order delivery
Push-Pull (4) (bi-layer tablet)	2	Low-to-highly water-soluble drugs; zero-order delivery
Osmodex (5)	1	Low-to-highly water-soluble drug or drugs
ALZET™ (15)	2	Liquid/slurry/suspension drug delivery in animal studies
OSMET™ (15)	2	Liquid/slurry/suspension drug delivery in human studies
EOP-porous membrane (7)	1	Moderately water-soluble drug delivery
COER (11)	2	Low-to-highly water-soluble drugs; delayed release delivery
Push-Pull LCT (12)	2	Low-to-highly water-soluble drugs; patterned delivery
L-OROS® (16) (liquid OROS®)	2	Liquid/suspension/emulsion drug delivery; zero-order release
MOVS (17)	1 or 2	Low-to-moderately water-soluble drugs; extended zero-order or step function delivery
OROS®-CT (18)	2	Low-to-highly water-soluble drugs; colonic delivery
SCOT (6)	1	Low-to-highly water-soluble drug delivery
Zer-Os (8)	1	Slightly water-soluble drugs; zero-order delivery
EnSoTrol® (19)	1	Low (requiring dissolution enhancement) to highly water-soluble drug delivery
Pull–Push–Pull (14) (tri-layer tablet)	2	Low-to-highly water-soluble two-drug or single drug patterned delivery
MODAS® (9)	1	Moderately water-soluble drug (with buffering option) delivery
EOP–non-equilibrium core (10)	1	Moderately water-soluble drugs; patterned delivery
Push-Stick™ (20)	2	Low water-soluble drugs; high drug loading, zero-order delivery
DUROS (13)	2	Liquid/suspension/emulsion subcutaneous delivery of potent drug for up to 1 year
VITS™ (21)	2	Liquid/suspension/emulsion subcutaneous drug delivery in bovines and porcines for up to 1 year
RUTS™ (22)	2	Drug delivery from a wax matrix to bovine rumen for up to 1 year

[a]Type 1: osmotic platform without expandable driving member; Type 2: osmotic platform with expandable driving member.
Abbreviations: CT, colonic therapy; EOP, elementary osmotic pump; LCT, longitudinally compressed tablet; MODAS, Multiporous Oral Drug Absorption System; MOVS, membrane osmotic valve system; RUTS, Ruminal Therapeutic System; SCOT, Single Composition Osmotic Tablet; VITS, Veterinary Implantable Therapeutic System.

EOP-PM

The EOP-Porous Membrane (PM) (7), is a direct variant of the EOP. More specifically, an osmotically active core of drug and optional osmotic excipients is surrounded by a rate-controlling membrane composed of a water-insoluble polymer and leachable, water-soluble components. In practice, water enters the membrane and dissolves the water-soluble components, leaving passageways for counterflow of the solubilized core materials; a discrete delivery orifice is not necessary.

Zer-Os™

The Zer-Os osmotic system (8) comprises a core of active agent (typically lipophilic) with osmotic agents, a gelling polymer and, optionally, a drug crystal habit modifier enveloped by a rigid rate-controlling membrane with a delivery orifice. Upon exposure to the GIT, water penetrates the membrane and begins hydrating the osmotic core, which becomes fluid. Owing to the gelling polymer, sufficient viscosity is maintained in the core to form a drug suspension that allows its delivery through the orifice.

MODAS®

Particularly useful for the delivery of water-soluble compounds, the Multiporous Oral Drug Absorption System (9) is similar to the EOP-PM, except that soluble components in the semi-permeable, rate-controlling membrane may be tailored so there is proper permeation of water into the core and drug diffuses through the membrane to the GIT. Core buffers may also be included to minimize the effect of pH on drug dissolution.

EOP-NEC

The EOP-Non-Equilibrium Core (NEC) (10), is a direct variant of the EOP. The designs of the two platforms are similar–drug plus osmotic excipients in a core surrounded by a rate-controlling membrane featuring a delivery orifice—but the difference between the equilibrium core and the NEC is the specific mass ratio of osmotic excipient to drug. In the former, this ratio expresses the mutual solubility of drug in an osmotic-excipient-saturated solution for an EOP; in the latter, osmotic excipients that affect drug solubility (e.g., common-ion effect for drug solubility suppression) are used. Because drug solubility is modulated by the osmotic excipient concentration in the core, increasing or reducing the mass ratio of osmotic excipient to drug allows extended zero-order or pulsed delivery.

COER™

As the name suggests, the Controlled-Onset Extended-Release (COER) platform (11), allows control over the onset of delivery, when such a release pattern is indicated (e.g., early morning delivery to coincide with natural circadian rhythms). An effective form for chronotherapy, the COER can be designed to offer a delay in onset of drug delivery of about 0.5–7.0 hours, depending on the composition and thickness of the polymeric film applied to the osmotic core. Typically, slowly hydrating hydrophilic polymers are employed as the basis for the formulation because they slow the penetration of water into the osmotic core and delay the release of drug through the orifice.

Push-Pull™ LCT

The Push-Pull LCT (12), an example of which is exhibited in Figure 5(A), differs from the previously described Push-Pull in its geometry. By decreasing the contact surface area between the drug layers and push layer, residual drug levels are reduced, typically to $<2\%$ of the total dose in the LCT. Also, the revised geometry in an LCT composed of up to five layers may comprise any combination of drug, push, and delay compartments to achieve the delivery pattern of choice (e.g., ascending, pulsed).

DUROS®

Designed as an implantable dosage form, the DUROS system is capable of delivering potent drugs for up to 1 year for systemic or tissue-specific therapy (13). The platform consists of a titanium tube with a delivery portal at one end and a rate-controlling membrane at the other. Internally, an expandable piston of high molecular weight hydrophilic polymers and adjunct osmotic agents is placed adjacent to the membrane. Finally, a drug reservoir situated next to the piston contains potent drug compounds in solution or suspension. Upon activation, water passes through the membrane and into the piston, which expands upon hydration and displaces a like volume of the drug compartment. As a result, drug is delivered at a controlled rate through the delivery portal and into the surrounding tissue.

FORMULATION

Many of the formulation attributes of IR dosage forms are applicable in the successful design of an osmotic system. For example, drug stability, particle size distribution, polymorphism, intrinsic dissolution, and excipient interactions, among others, remain concerns for the osmotic systems formulator. In addition, particular attention is paid to drug and osmotic excipient mutual solubility and the osmotic pressure of the key constituents for the EOP (equilibrium core). To maximize the amount of drug delivered at a zero-order rate, the mutual solubility should be minimized, but only to the extent that an appropriate release rate can be maintained. Equation (5) is often used to estimate the fraction of zero-order release (F_{Z0}) from an equilibrium core:

$$F_{Z0} = 1 - S_T/\rho \tag{5}$$

where S_T is the mutual solubility (drug + osmotic excipient) and ρ is the osmotic core density.

Another factor to consider is the solubility ratio of drug to prospective osmotic excipient (S_D/S_O). Too high or too low a ratio may impact tablet size, depending on the dose required.

In addition to selecting an appropriate drug-osmotic excipient combination that maximizes the fraction of drug delivered at zero-order and maintains a reasonable tablet size for the given dose, other ingredients such as binders, lubricants, buffers, disintegrants, or wicking agents may be necessary to reduce to tablet friability during subsequent processing (e.g., membrane coating) and optimize dissolution of the core as water is imbibed through the rate-controlling membrane.

Common osmotic excipients in the EOP include organic and inorganic salts and mono- or polysaccharides of compendial status. For some drug substances, incorporation of an osmotic agent with buffering capacity may be advantageous in fixing core pH, in maintaining a preferential pH for solution stability, or in improving the solubility characteristics of the drug (23).

Binders, such as hydroxypropyl methylcellulose (HPMC), polyvinyl pyrrolidone (PVP), or hyroxypropylcellulose, are routinely used in the formulation to strengthen the tablet, while lubricants, such as magnesium stearate, calcium stearate, or stearic acid, are included to facilitate the compression process.

To ensure that core dissolution is not a rate-limiting factor in the release of drug through the orifice, disintegrants, or wicking agents may be necessary to maintain a saturated solution within the EOP. Materials including cross-linked PVP,

croscarmellulose sodium, or microcrystalline cellulose are typically considered for these applications.

The rate-controlling membrane in an EOP modulates the rate of water entering the core and helps the osmotic system resist the hydrostatic pressures of gastrointestinal transit. Further, depending on its reflection coefficient, the membrane may also moderate changes in pH as the EOP or Push-Pull system traverses from the stomach (pH 1–2) to the small intestine (pH 5–7). As such, cellulosic polymers are included as the base material in many osmotic system membrane applications. More specifically, cellulose acetate and its derivatives offer a useful range of permeabilities, as well as sufficient film mechanical strength. In some cases, flux enhancers, such as HPMC, polyethylene glycol, or polyethylene–polypropylene oxide copolymers, are included in the membrane formulation for permeability adjustment of the base polymer. Further, in some osmotic system designs (7), hydrophilic pore-forming materials are added to create passageways in the membrane in situ, thus allowing solubilized core material to pass from the coated tablet.

For the Push-Pull osmotic pump (3), the inclusion of an expandable member requires proper selection of base material. Generally, hydrophilic polymers such as carboxymethylcellulose sodium, cross-linked polyacrylic acid, or polyethylene oxide are used along with adjunct osmotic excipients to produce appropriate water imbibition characteristics in both the drug (pull) layer and the push layer.

More specifically, high molecular weight hydrophilic or lightly cross-linked polymers comprising the push compartment are highly viscous and are capable of expanding 2–10 times their original volume upon hydration. Additionally, sufficient gel strength is maintained at the boundary layer to minimize mixing between the drug and push regions as each hydrates.

For inclusion of water-insoluble drugs in the Push-Pull osmotic system (4), a hydrophilic polymer must retain sufficient viscosity to form an in situ suspension of drug in the hydrating polymer and remain sufficiently fluid to be expelled through an orifice. Depending on the specific Push-Pull design, the low molecular weight grades of the polymer species utilized in the push compartment may be appropriate as suspending agents in the drug compartment.

MANUFACTURE

Many of the unit operations for manufacture of traditional dosage forms are applicable to osmotic systems with a solid drug formulation. As displayed in Figure 6, the process train for an EOP encompasses up to eight distinctive steps that commence with granulation (or dry blending, if applicable) and finish with drying to remove excess process solvent from the membrane coating procedure or, alternately, with overcoating and printing.

Several options are available for preparing the dry core ingredients for compression into an appropriately sized compact. If the formulation is directly compressible, a simple component blending in a diffusion mixer (24) may be possible. However, if granulation is necessary to impart better uniformity or tablet characteristics, one of several techniques may be employed, as summarized in Table 2.

Compression can be conducted by conventional means. Typically, any high-speed rotary tablet press from Fette (Schwarzenbek, Germany), Manesty (Knowsley, UK), and Courtoy (Halle, Belgium), or other manufacturers will suffice (24).

The rate-controlling membrane is generally applied by one of two means in the manufacturing process. The first involves a coating solution comprising the membrane

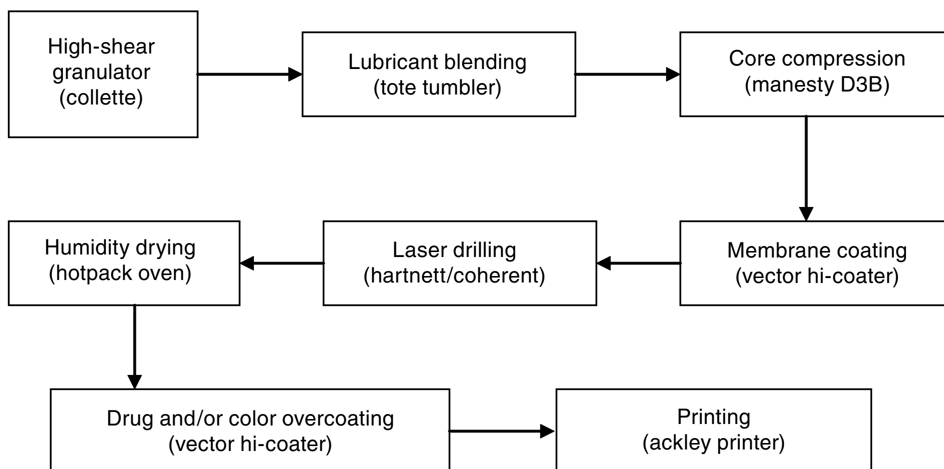

FIGURE 6 Example process flow diagram for manufacture of EOP. *Abbreviation*: EOP, elementary osmotic pump.

polymers dissolved in the appropriate solvent sprayed from a gun assembly onto a bed of tablets rotating in a partially or fully perforated pan coater. Examples of suppliers include Vector (Marion, IA, USA), Nicomac (Milano, Italy), and Glatt (Ramsey, NJ, USA), among others (24). The coating process continues until the appropriate weight gain per tablet is achieved or, alternately, the specified solution volume is applied. The second technique employs a fluid-bed procedure, in which coating solution is sprayed from the bottom of a column containing a fluidized bed of tablets. Equipment suitable for the fluid-bed process can be supplied by Fluid Air (Aurora, IL, USA), Aeromatic-Fielder, a Division of Niro Pharma Systems (Bubendorf, Switzerland), and BWI-Huttlin (Steinen, Switzerland), among others (24). The coating endpoint is again determined by the weight gain per tablet or the volume of solution applied.

Of all the unit operations involved in the synthesis of osmotic systems, the orifice-drilling step is unique in the industry. The first-generation equipment comprises a Hartnett carrier system coupled with a Coherent laser (Santa Clara, CA, USA) (25). Sensors are placed in advance of the laser firing point to detect the presence of a tablet in the individual carrier slot. Should a misfire occur, additional sensors downstream activate a reject mechanism that physically removes undrilled tablets from the batch. Throughputs of up to 200,000 tablets per hour are now possible in commercial laser units (26).

Next, a drying step may be instituted to reduce the levels of process solvent in the final product. Tablets can be placed into an environmentally controlled tray dryer

TABLE 2 Granulation Options for EOP Core Preparation

Technique	Example	Application
	Equipment	
Planetary mixing	Hobart	Aqueous or solvent wet granulation
High-shear mixing	Collette	Contained aqueous or solvent wet granulation
Roller compaction	Chilsonator	Dry granulation
Fluid bed	Vector FBG	One-step aqueous or solvent granulation

Abbreviation: EOP, elementary osmotic pump.

[e.g., Hotpack (Warminster, PA, USA)] for a specified period, depending on the characteristics of the core and membrane formulations.

In some instances, dried tablets may be returned to the coater for the application of an aqueous-based color overcoat, before being sent on to a printing step [e.g., Ackley Machine (Moorestown, NJ, USA)] for product identification.

The process applied to the manufacture of the Push-Pull osmotic system is, in many ways, similar to that of the EOP (Fig. 7). There are some notable exceptions though, particularly in the granulation and compression steps. In the former, as both the push and drug formulations can contain a hydrophilic polymer, the use of an aqueous-based, planetary granulation process is problematic, as the water applied can induce an irreversible plasticization of the polymer, leaving the resultant granulation difficult to process further.

In the compression step, because Push-Pull type formulations routinely comprise two or more distinct compartments, a tablet press capable of producing bi-layer, tri-layer, or core-within-a-core compacts is necessary. Equipment manufacturers such as Manesty and Korsch (Berlin, Germany) supply machines for these applications. In fact, Korsch systems can accommodate up to five layers in a single tablet (27).

The remaining unit operations, membrane coating, orifice drilling, drying, and, if necessary, color overcoating and printing, are similar in the manufacture of the EOP and Push-Pull osmotic systems. Slight variations are necessary in the drilling process, because the equipment must distinguish the drug compartment side of the tablet from the non-drug regions. Color sensors provide the necessary discrimination within the tablet, which normally contains light-colored drug-containing compartments and dark-colored non-drug compartments.

EXAMPLES OF ORAL OSMOTIC DELIVERY SYSTEMS

The desire to improve compliance and convenience is often cited as the rationale for combining a new delivery system and an existing drug, and a number of commercially successful products have been developed in response to this challenge. Oral osmotic systems have been widely used with therapeutics for cardiovascular, endocrine, urologic, and central nervous system (CNS) applications.

OROS Nifedipine (Procardia XL®)

The early success of OROS technology was realized with cardiovascular drugs such as nifedipine (Procardia XL®) and verapramil hydrochloride (Covera HS®). Both agents are calcium-channel blockers indicated for the treatment of hypertension. Procardia XL is commonly used for the treatment of angina pectoris as well. Calcium-channel blockers administered from IR dosage forms may be associated with vasodilatory side effects and reflex activation of the sympathetic nervous system (28). Kleinbloesem and van Brummelen (29) studied the effect of the rate of delivery on hemodynamic effects of nifedipine. Two regimens of IV infusion were administered to evaluate hemodynamic effects in six healthy volunteers. The first regimen resulted in steady-state blood plasma concentrations over 5–7 hours, and the second regimen achieved the same results within 3 minutes; the concentrations were similar. During the gradual-rise infusion, heart rate was unchanged, and diastolic blood pressure fell slowly by 10 mmHg. With a faster infusion rate, the heart rate increased immediately and remained elevated for the duration

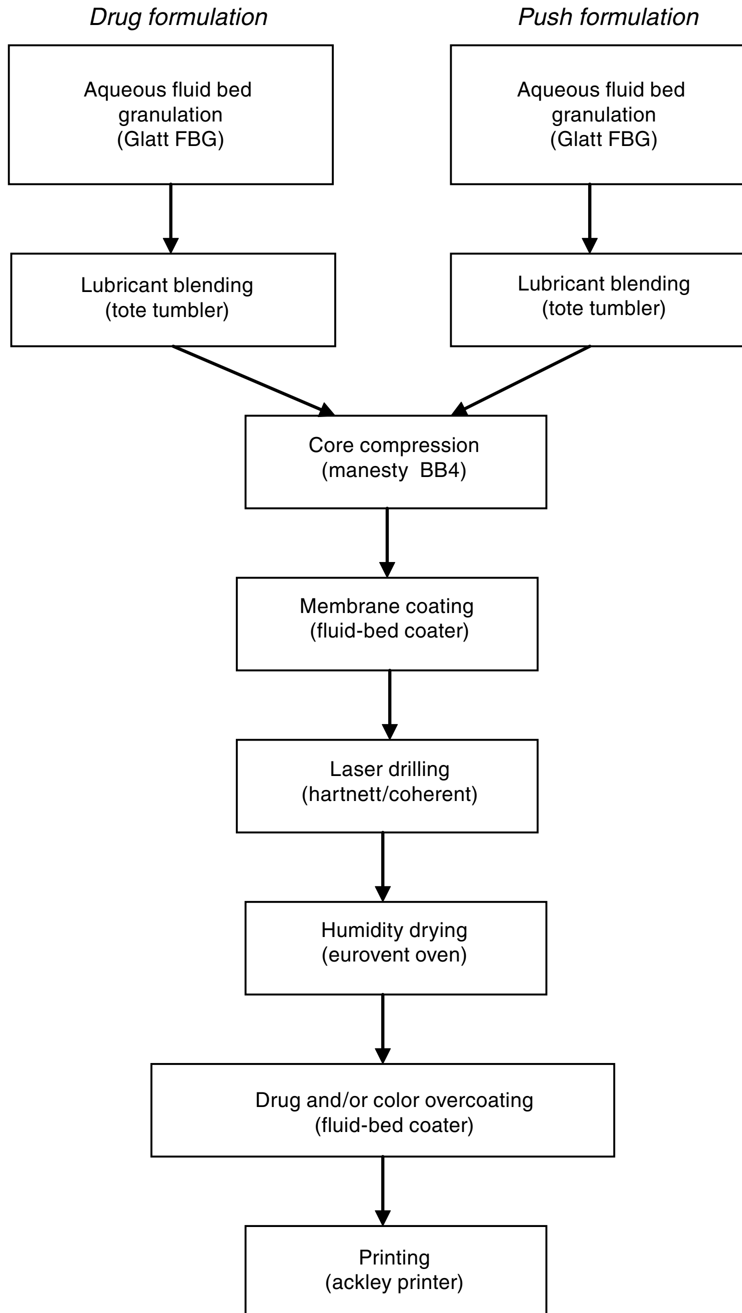

FIGURE 7 Sample process flow diagram for manufacture of Push-Pull system.

of the infusion. At the end of the gradual-rise regimen, a sudden increase in the infusion rate for 10 minutes produced tachycardia and an unexpected increase in blood pressure. The authors hypothesized these unexpected effects could be due to baroreceptor activation.

A slowly rising and consistent 24-hour drug release from OROS nifedipine has been shown to improve the safety profile and efficacy compared to an (IR) formulation (30). In a study that switched patients from an IR to OROS treatment, the latter resulted in reduction in angina and nitroglycerin usage. Furthermore, based on questionnaires that asked about frequency of symptoms, activity, work performance, and energy level, 87% of the patients reported stable or improved quality of life after switching to OROS nifedipine.

Another calcium-channel blocker, COER verapramil hydrochloride (Covera HS), uses a unique modification of the basic OROS technology to establish a drug-release profile that manages circadian changes in blood pressure.

Hypertensive patients have been shown to have higher blood pressure and heart rate readings in the morning hours than compared with when they are asleep, and cardiovascular events frequently occur within 4 hours after awakening. As such, drug release from Covera HS is delayed for 4–5 hours so that peak concentrations are achieved 8–12 hours after bedtime administration to reduce early morning blood pressure (31).

OROS® Oxybutynin (Ditropan XL®)

The anticholinergic, antispasmodic agent, oxybutynin hydrochloride, is indicated for the treatment of overactive bladder and urge-urinary incontinence. Oxybutynin binds to the muscarinic receptors on the detrusor muscle of the bladder, inhibiting involuntary bladder contractions. Unfortunately, IR formulations have been associated with systemic cholinergic side effects, such as dry mouth, which may limit compliance with dosing regimens.

OROS oxybutynin was designed to release drug in a constant zero-order manner over 24 hours. By design, no appreciable quantity of the drug is delivered in the first 2–3 hours after a patient ingests the system. In fact, most of the drug is released when the system reaches the colonic portion of the GIT some 3–5 hours following dosing.

OROS controlled-release delivery of oxybutynin improved bioavailability and reduced dry mouth compared with IR formulations. In one study, bioavailability with OROS was 153% (32) and peak and trough plasma concentrations were 66–81% lower with OROS system. These values may be the result of delivering drug primarily to the lower part of the GI tract, which reduces gut-wall first-pass metabolism and avoids cytochrome-P450-mediated metabolism in the upper part of the GI tract. Dry mouth severity and saliva output indicated dry mouth severity correlated with the concentration of the metabolite, desethyloxybutynin. Levels of metabolite and dry mouth severity were lower with the OROS formulation, and saliva output was higher. Another single-day, healthy-volunteer, placebo-controlled study compared both OROS oxybutynin and controlled-release tolterodine (Detrol® LA) with IR oxybutynin and showed saliva output was higher with the controlled-release formulations (33).

OROS® Methylphenidate (Concerta®)

Concerta® is indicated for treatment of attention deficit/hyperactivity disorder (ADHD) and contains methylphenidate, a CNS stimulant long used in IR and conventional SR formulations for ADHD. Concerta has an ascending-release profile that allows a fast onset of action followed by a sustained effect for an additional 12 hours and is designed for a single morning dose that allows controlled release of drug over school day and late afternoon. The system is tri-layer, membrane-coated tablet core surrounded with a drug overcoat layer. The overcoat contains approximately 20% of the dose, and the core and middle layers contain increasing concentrations of drug. The OROS design successfully

overcomes the deficiencies of the existing IR and SR methylphenidate products. IR formulations need to be taken several times a day for effective treatment and the SR product [Ritalin SR®, Novartis, E. Hanover, NJ, USA] lacks a fast onset of action and yields a flat plasma profile that may encourage the development of tolerance to the drug (34).

A study of the pharmacodynamic effects of methylphenidate delivered by Concerta showed drug plasma concentrations increased over the first 2 hours following release from the drug overcoat layer, and a further increase was achieved as drug from the first layer of the tablet core was released. Peak plasma concentrations were achieved 6–8 hours after administration following release from the second layer of the tablet core.

In clinical trials in children between 6 and 12 years of age, Concerta was significantly more effective than placebo. The efficacy of Concerta was similar to IR methylphenidate administered three times a day and demonstrated similar onset of action (35).

Methylphenidate is a controlled substance and is subjected to abuse. The Drug Abuse and Warning Network mentions OROS methylphenidate 50 times compared with 588 mentions of all other methylphenidate brands between years 2000 and 2002; of the 548 citations for abuse of oral methylphenidate, only 49 concerned the OROS formulation. There was no mention of any abuse of the OROS formulation via other routes, (sniffing or snorting and injecting). The OROS market share is estimated at 5–48% of the total, and abuse of OROS formulation has been significantly less than that of other methylphenidate products (36).

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Tableting of Multiparticulate Modified Release Systems

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INTRODUCTION

Interest in oral controlled release dosage forms has brought increasing attention to multiparticulate modified release systems usually consisting of barrier coated pellets. The advantages of such multiparticulate systems over single unit peroral sustained release systems are:

1. Greater statistical assurance of drug release and so more reproducible and constant drug concentration after oral administration. Therefore, inter- and intrapatient variability is reduced (1).
2. Single unit systems potentially could become lodged at some site in the gastrointestinal tract. Multiparticulate systems are more likely to be more uniformly distributed through the gastrointestinal tract. For this reason, the effect of food on drug absorption is less critical for a multiparticulate oral delivery system than for a single-unit dosage form.
3. Single unit systems may fail to release the maintenance dose from the slow release core. This point can be critical for low solubility drugs and/or if there is an absoption window where absorption must take place in a limited region of the gastrointestinal tract.
4. Failure of a single unit sustained release product may lead to "dose dumping." With the drug distributed through a multiparticulate system, there is little likelihood that the entire dose could be so "dumped."
5. There is a greater probability of achieving total drug release from a multiparticulate system than from a monolithic single-unit sustained release dosage form, so bioavailability can be better for multiparticulate than for monolithic dosage forms.
6. In multiparticulate systems, it is possible to combine incompatible drugs in the same formulation seperated by coated membranes.
7. Multiparticulate systems allow for the combination of particles with different drug release characteristics.

Usually, pelleted modified drug delivery systems are dispensed in hard gelatin capsules because they are not subjected to compression which could compromise the integrity of the coating or otherwise destroy the pellets. In recent years, however, there has been an increasing interest in incorporating coated pellets in compressed tablets. The advantages of tableting are:

1. Tableting is less costly. Tablets can be produced at higher rates and tableting avoids the added cost of the gelatin shell and the spot welding, sealing or other mechanism of positive closure required for capsules.
2. Tablets are more difficult to tamper with than capsules.
3. Tablets are less prone to difficulties in esophageal transport than capsules and may often be easier to swallow when high doses of active ingredients are used. In such cases, tablets can be more compact and their smaller volume may lead to a higher patient compliance than capsules.
4. Divisibility. Some multiple-unit disintegration tablet formulations can be divided into two or more parts if required.

The best conditions for tableting multiparticulate systems without destruction of the particles and/or their coating and the consequent modification of their drug release characteristics will be described in this chapter, including the selection of the more appropriate excipients and tableting conditions (effect of compression forces, etc.).

In a different application, the tableting of coated particles has been traditionally employed as an easy way to obtained matrix tablets. This is a simple method to obtain single-unit dosage forms and some tablet formulations of theophylline and acetyl salicylic acid have been marketed based on this principle. In this case, the fusion of the coated wall of pellets is desirable in that it leads to the formation of a monolithic matrix system. Any further discussion of this type of system is beyond the scope of this chapter. The reader interested in matrix tablet formulations is referred to Chapters 14 and 15 of this volume which deals with this topic.

MULTIPARTICULATE SYSTEMS: DEFINITIONS AND CHARACTERISTICS

Different terms for solid particle systems are employed in drug delivery. Among them are: pellets, beads, millispheres, microcapsules, microspheres, aggregated particles, and others. Definitions are not clear and some confusion and misunderstandings are usually related to the selection of the most appropriated term for each multiparticulate system. Obviously, marketing is a major factor contributing to confusion with the terminology because companies and scientists who wish to claim that they have a different type of drug carrier often will add a new term to the list of multiparticulate systems. To date, clear and uniform criteria have not been adopted by the pharmaceutical scientists for defining these systems. Although a complete definition and description of the different multiparticulate systems used in Pharmaceutical Technology is beyond the scope of this chapter, a brief summary of the most relevant multiparticulate systems is provided here. According to Ghebre-Sellassie and Knoch (1) pellets can be defined as “small, free flowing, spherical particles manufactured by the agglomeration of fine powders or granules of drug substances and excipients using appropriate processing equipment.” The size of these particles is usually between 0.5 and 1.5 mm. The excipients should provide a plastic behavior to the particle to facilitate their adoption of a spherical shape during processing. Sphericity and intragranular porosity are the two important quality attributes

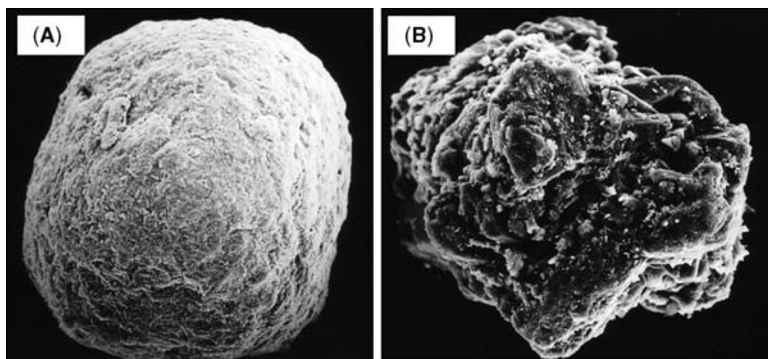

FIGURE 1 Scanning electron micrograph of a pellet particle (**A**) and a conventional granule (**B**).

of pellets. Figure 1 shows an example of a pellet (Fig. 1A) and a conventional granule (Fig. 1B). It is clear that the smoother, more regular surface of the pellets resulting from the spheronization process makes them more appropriate than conventional granules for coating. The terms "spherical granules" and "beads" have sometimes been applied interchangeably to pellet systems. Coated pellets have been traditionally considered as a type of microcapsules. Microencapsulation is defined by Bakan (2) as "a process in which very thin coatings of polymeric material(s) are deposited around particles of solids or droplets of liquids." The microcapsules thus formed range dimensionally from several nanometers to several thousand nanometers in diameter. Actually, if the size of the particle is < 1 μm, then the term nanoparticle is preferred. One of the microencapsulation methods is pan coating which is useful for coating solids and to obtain final particles of a size between micrometers and a few millimeters. Obviously, these microcapsules can also be defined as pellets.

The term microsphere is also related to pellets. Microspheres are defined by Burgess and Hickey (3) as "solid, approximately spherical particles ranging in size from 1 to 1000 μm. They are made of polymeric, waxy, or other protective materials, that are biodegradable synthetic polymers and modified natural products such as starches, gums, proteins, fats and waxes." The similarities between microspheres and microcapsules are clear and a graphical illustration of these particles is shown in Figure 2. The term "microcapsule" is usually preferred if the entrapped substance is completely surrounded by a distinct capsule wall and the terms "matrix microcapsule" or "microsphere" are used if the entrapped substance is dispersed throughout the microsphere matrix.

Both types of microparticles, microspheres and microcapsules, can be obtained by many different procedures and their final characteristics depend on their compositions

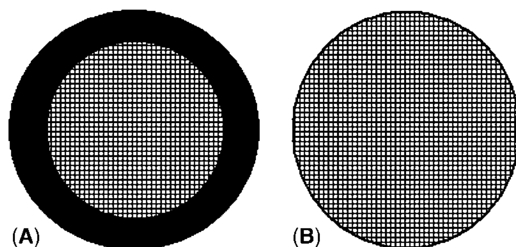

FIGURE 2 Schematic diagram illustrating a microcapsule (**A**) consisting in a microsphere with a clear difference between the core and the coating zones and a matrix microcapsule or microsphere (**B**).

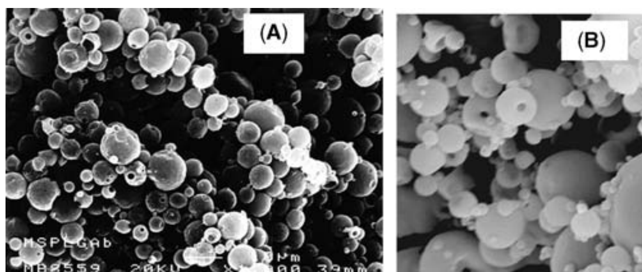

FIGURE 3 Scanning electron micrograph of different types of microspheres: (**A**) poly (D,L-lactide-coglycolide) microspheres obtained by a double emulsion method; (**B**) human albumin microspheres obtained by a spray-drying process.

and elaboration procedures. Depending on their size, toxicity characteristics, cost of raw materials, and drug release properties, certain types of microparticles may be more suitable for a specific drug administration route than for others. For instance, polylactic and polyglycolic acids provide an interesting slow drug release property, but they are too expensive for current application in oral drug delivery. Nevertheless, these excipients and derivatives are frequently used for parenteral controlled release formulations. Figure 3 shows microspheres obtained either by an emulsion (Fig. 3A) or by a spray drying (Fig. 3B) method. Usually, particles obtained by an emulsion method are more spherical than those obtained by alternative procedures (Figs. 4A, 4B). However, emulsion methods have the disadvantage of leaving remnant oil and solvents in the particles which decrease the flowability and increase cohesiveness of the system. Moreover, the risks of toxicity attributable to solvents which are sometimes used in the emulsion procedures have to be considered when designing a microencapsulation procedure and solvent-free microencapsulation procedures are preferred.

The flow properties, tableting and drug release characteristics of different examples of pellet systems will be discussed in detail below.

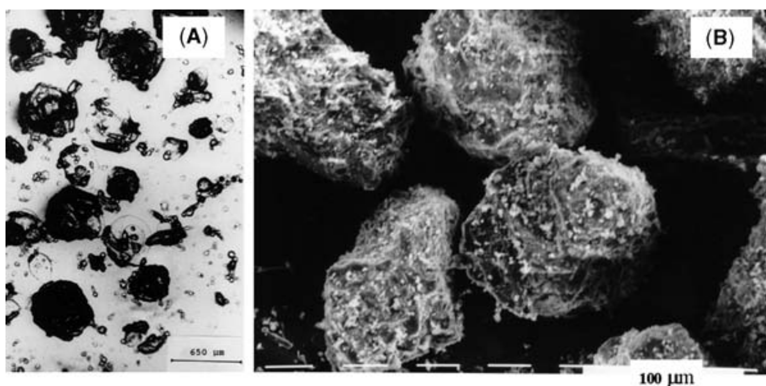

FIGURE 4 Micrograph of microaggregated egg albumin particles with acetaminophen obtained by an emulsion method (**A**) and scanning electron micrograph of egg albumin particles with acetaminophen obtained by direct coagulation (**B**).

FLOW CHARACTERISTICS OF MULTIPARTICULATE SYSTEMS

The flow characteristics of pellets are excellent due to their size and spherical shape. Nevertheless, two important limitations that can affect tableting need to be recognized. One of these is the development of an electrostatic charge on pellet surfaces which can interfere with their flow. This problem is usually solved by adding talc at 1% concentration, although this excipient can decrease the tensile strength of tablets made with microcrystalline cellulose. The second limitation is related to the mixing of pellets with other excipients. Pellets are usually of a size between 0.5 and 1.5 mm and conventional tablet excipients are of a smaller size. This difference in size between components is a serious problem in obtaining a suitably uniform mixture. A workable solution to this problem may be obtained by preparing inert pellets of excipients with a size and density similar to the drug pellets. The inert pellets can also be useful to avoid or minimize physical alteration of the drug pellets and/or their coating during compression. A related problem is the possible segregation of the pellet mixture depending on the differences in shape of the pellets. It is clear that spherical particles exhibit the greatest flowability and are, therefore, more easily mixed, but they are also segregated more easily than non-spherical particles (4). In general, segregation can be reduced by working with a relatively narrow size particle size distribution, that is, 0.7–1 mm pellets.

Since the surface area to volume ratio of pellets will be at a minimum as compared to the other shapes, spherical multi-unit formulations may require only a very small amount of lubricant. Therefore, the amount of, and mixing time with, the lubricant must be carefully considered. Usually, proportions of $<0.5\%$ of magnesium stearate are recommended and a mixing time of <30 Seconds is often sufficient for laboratory scale mixers.

Conventional microcapsules obtained by emulsion methods traditionally are smaller than pellets, but if remnant oil is present, poor flowability can be expected even in larger particles. Moreover, the remnant oil can be unpleasant in the mouth if microcapsules are going to be used in chewable tablet formulations. For this reason, oils should be avoided during the manufacturing of microcapsules. For instance, chewable tablets of acetaminophen have been obtained with egg albumin microaggregated particles as an alternative method to the conventional oil emulsion procedure (5). The microaggregated particles improved the poor flow properties of the acetaminophen raw material and were able to partially mask its bitter taste. Since for chewable tablets the size of the particles should be ideally <0.4 mm, microcapsules may be preferred to larger size conventional pellets in this case.

Spray-drying microencapsulation procedures are frequently used for oral administration for several reasons. The rounded or generally spherical shape of the particles promotes good flow characteristics. In addition, the spray-drying procedure is a very efficient way to remove organic solvents. Furthermore, spray-dried products are often porous solids with good tableting characteristics. Finally, this fast drying procedure allows for the microencapsulation of volatile fragrances which are then used as dry excipients in oral drug formulations. In fact, most of the flavor agents used as excipients in tablets are microencapsulated.

TABLETING AND DRUG RELEASE CHARACTERISTICS OF MULTIPARTICULATE FORMULATIONS

Several studies have been performed in recent years to determine the best conditions to tablet multiparticulate formulations. It is clear from this work that distinctions must be

made based on the nature of the pellets and the resulting tablets. Multiparticulate formulations may be classified based on whether the particles/pellets are uncoated or coated. Furthermore, the resulting tablets may be classified based on whether the tablets form a monolithic matrix system (see Chapters 14 and 15 of this volume) or whether the conditions of tableting have been carefully controlled to obtain a tablet that behaves in vitro as a multiparticulate drug delivery system. Examples are provided at the end of the chapter.

Tableting of Uncoated Particles

Microcrystalline cellulose is often considered a key excipient for pellet production. Although this excipient in its powder form is universally recognized as a very compressible (compactible) material, the pellets obtained with this excipient are not. Microcrystalline cellulose pellets are usually very hard and not easily deformable or broken. Thus, to obtain tablets with higher crushing strength, small quantities of lactose or dicalcium phosphate can be added (6). These excipients can also modulate the drug release properties of the resultant tablets.

It is well known that the size and shape of particles and their potential bonding sites affect the compaction characteristics of pharmaceutical materials. Maganti and Çelik (7) studied the compaction characteristics of different materials, mainly microcrystalline cellulose plus small quantities of dicalcium phosphate dihydrate or lactose. It was found that the powders examined compacted primarily by plastic deformation and produced strong compacts, whereas their pellets exhibited elastic deformation and brittle fragmentation which resulted in compacts of lower tensile strength. Similar results have been reported by others (8). The inclusion of external powders as additives to the pellets affected their compaction characteristics. The mechanical strength of their compacts increased with the presence of microcrystalline cellulose, and decreased with the inclusion of either pregelatinized starch, soy polysaccharide, or magnesium stearate as external additives (7). In relation to the addition of stearates to pellet formulations for tableting, Çelik and Maganti (9) pointed out that since the surface area of spherical pellets will be at a minimum as compared to the other shapes, pellet formulations will require only a very small amount of lubricant. Therefore, the amount of, and mixing time with, the lubricant must also be carefully considered.

In addition to the incorporation of other co-diluent excipients, the nature of the granulation fluid and drying conditions during pellet formation can also affect the compactibility of microcrystalline cellulose pellets. Compression of microcrystalline cellulose pellets (0.71–1 mm) produced using only water as the liquid phase produces weak tablets, whereas if ethanol is included in the liquid phase, stronger tablets are produced (10). In this paper, it was concluded that ethanol induces higher porosity in the resultant pellets which improved pellet compactibility. The degree of pellet deformation increased with increased original pellet porosity, whereas the mechanical strength of the pellets was not a primary factor in the compression behavior of the pellets. The compactability of the pellets was thus related directly to the original pellet porosity. The results of this work indicate that pellet porosity determines the degree of their deformation during compression which, in turn, affects the pore structure and the tensile strength of the compact formed. A high degree of pellet deformation gave a low intergranular separation distance in the compact and promoted the formation of intergranular bonds of a high bonding strength. The pellets compressed by plastic deformation rather than by fragmentation. In a later reported study (11), the compression behavior of granules was compared to that of pellets and it was concluded that the dominant mechanism during compression appeared to be plastic deformation in each case.

However, during the compression of high porosity granules, fragmentation or attrition seemed to occur along with deformation. Tablets formed from granules had a closer pore structure than those formed from pellets of equal intragranular porosity and the granules seemed to deform to a higher degree during compression.

The porosity of pellets can be easily affected by the drying technique. Bashaiwoldu et al. (12) studied microcrystalline cellulose pellets produced by a standard extrusion/spheronization process with a 40% ethanol/water mixture as the fluid component. The pellets were dried by four different techniques: freeze-drying, fluid bed drying, hot air oven drying, and desiccation with silica-gel. Pellets produced by freeze-drying were more porous, with most of the pores open to the atmosphere, and had a higher surface area than pellets dried by the other methods. The porous pellets needed a higher compressing pressure and work of compaction to produce tablets of the same mass and dimensions. The strength and volumetric elastic recovery of the compacts increased with increased pellet porosity. Scanning electron microscopy confirmed the permanent structural change of the pellets after compaction. In a study of the compression of coated pellets, Tunón et al. (13) found that high porosity core pellets are preferable to low porosity core pellets to avoid damage to the coating.

The effect of the pellet drying procedure has also been studied. Dyer et al. (14) reported that tray-dried ibuprofen and lactose pellets are stronger, less elastic, and more brittle than their fluid-bed dried counterparts. Thus, the fluid bed drying process was recommended for pellets that are intended to be compressed (14).

Berggren and Alderborn (15) found that the drying rate during static drying clearly affected the physical properties of pellets. An increased drying rate resulted in more porous microcrystalline cellulose pellets. Moreover, the drying rate also affected the deformability of the pellets and their ability to form tablets. An increased drying rate generally resulted in more deformable pellets during tableting.

The addition of other excipients to microcrystalline cellulose can modify the tableting characteristics of pellets. For instance, the addition of a hard, brittle material such as dicalcium phosphate dihydrate to microcrystalline cellulose is useful in attaining more rigid pellets. The more rigid nature of these pellets leads to a change in the mode of deformation during compaction, from bulk deformation toward surface deformation of the pellets (16). However, this deformation could be decreased by lubrication of the pellets with 0.5% w/w magnesium stearate (17). It can also be concluded from this work (17) that fragmentation of highly porous pellets during compaction was minimal and that the pellets remained as coherent units after compaction, without significant crack formation. If a soft waxy material, such as polyethylene glycol 6000, is used instead of the hard dicalcium phosphate excipient, then the opposite effect is obtained (18). The deformation propensity of the pellets was, in general terms, increased due to the presence of the soft material. However, the character of the deformation behavior changed toward an increased tendency for local deformation during compression. Thus, if a soft material is used in the composition of pellets, then the main deformation process will tend to occur at a lower tableting pressure. This increased deformation propensity and, especially, the changed mode of deformation associated with the soft pellets may contribute to the protection of the coating around drug pellets when two pellet types, drug pellets and "cushioning soft pellets," are mixed before tableting. The addition of polymeric controlled release agents during the formation of the pellets can be useful for the manufacture of matrix pellets. Young et al. (19) described the properties of tablets containing controlled-release pellets prepared by a hot-melt extrusion and spheronization process. A powder blend of theophylline, Eudragit Preparation 4135 F, and functional excipients was melt-extruded and then spheronized. The pellets were mixed with different excipients and then compressed

at different forces between 5 and 20 kN. The effective porosity and surface area of the melt-extruded pellets were not influenced by compression. Moreover, the percentage of theophylline released from rapidly disintegrating tablets was not affected by compression force or excipient selection. Furthermore, the pellet to filler excipient ratio and filler excipient selection did not influence the rate of drug release from compacts.

Matrix pellets can be compressed into tablets without facing the problem of film damage. For that reason, this approach can be an interesting alternative for certain formulations. Vergote et al. (20) described how matrix pellets containing nanocrystalline ketoprofen can be manufactured by the melt pelletization technique. This pellet formulation was mixed with cushioning placebo wax/starch pellets (at a proportion 50:50 w/w) and then compressed. The resultant tablets delayed the drug release in comparison with the uncompressed pellets. These formulations were then administered to dogs and their bioavailability characteristics were evaluated (21).

A granulation method with controlled release polymers can thus be an easy way to obtain matrix granules. These granules can be interesting for taste masking purposes. Taste-masked granules can be prepared using Eudragit E-100 by the extrusion method. Ishikawa et al. (22) reported how the taste of bitter drugs, such as pirenzepine HCl and oxybutinin HCl, can be masked due to a delay in their dissolution behavior. For instance, at pH 6.8, $<5\%$ is released after 480 minutes. However, the drugs dissolved rapidly at pH 1.2. Disintegrating tablets can be prepared using the prepared taste-masked granules and a mixture of excipients consisting of microcrystalline cellulose (Avicel PH 102) and low substituted hydroxypropylcellulose (L-HPC, LH-11) at a ratio (8:2). Thus, tablets of sufficient strength, rapid disintegration time (within 20 Seconds), and without bitter taste could be obtained.

Tableting of smaller size particles than conventional pellets can be interesting for some special tablets such as chewable tablets. To this end, microcapsules may be of interest to mask the bitter taste of some active ingredients. Usually, the presence of particles larger than 0.5 mm in the mouth is unpleasant and smaller particles are required. Microaggregated egg albumin particles (0.25–0.4 mm) containing acetaminophen were tableted to obtain chewable tablets of acetaminophen (5,23).

The mean yield pressure of microaggregated particles with acetaminophen was 30.5 MPa, which is lower than the mean yield pressure obtained with acetaminophen raw material (97.5 MPa). Acetaminophen behaved as a fragmenting material when tableting, whereas the coagulated egg albumin particles had a compression behavior similar to that of a plastically flowing material. Moreover, acetaminophen tablets formed from microaggregated egg albumin particles did not show the capping characteristic of conventional acetaminophen tablets. Tableting of the egg albumin particles containing approximately 50% of acetaminophen produces a monolithic matrix system which delays the release of acetaminophen. To mask the bitter taste of a drug, a delay of drug release of only 2 or 5 minutes is enough. A longer delay can compromise the fast oral absorption usually required for this type of analgesic formulations. To avoid the delay in drug release, either crospovidone or microcrystalline cellulose was mixed with the microaggregated acetaminophen particles at a 1:3 ratio (microaggregated:excipient proportion) and tableted at different compression forces. Figure 5 shows the drug release results. Avicel PH 101 and crospovidone seem to partially avoid the binding of microaggregated particles and the subsequent changes in drug release produced by the compression. Figure 5 shows that crospovidone provides more effective drug release protection than Avicel PH 101.

Many papers have been published on the manufacture of microspheres and microcapsules and their tableting characteristics, especially related to drug release. Compression of these delivery systems usually leads to tablet matrix systems. If fast disintegration tablets are required, then cushioning excipients are required at a proportion

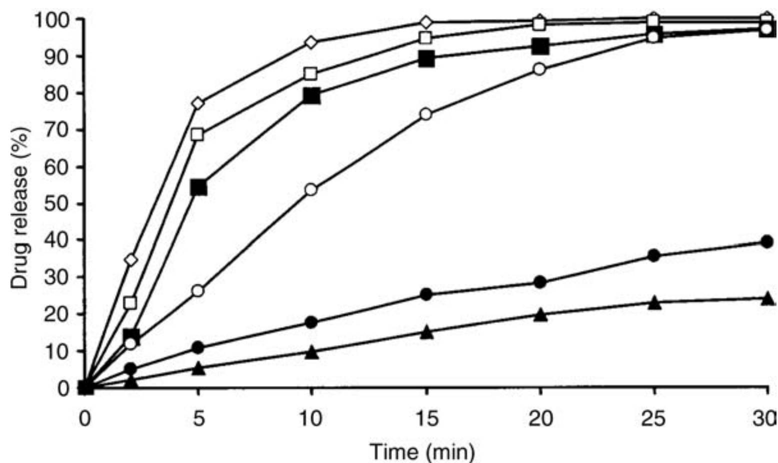

FIGURE 5 Drug release at different times of the following formulations. ◇ Microaggregated particles containing acetaminophen: tablets of microaggregated particles containing acetaminophen with crospovidone (ratio 3:1), tableted at □ 115 MPa and at ■ 197 MPa; tablets of microaggregated particles containing acetaminophen with Avicel PH 101 (ratio 3:1), tableted at ○ 129 MPa and at ● 185 MPa; and ▲ tablets of micro-aggregated particles containing acetaminophen tableted at 108 MPa. *Source*: From Ref. 23.

of at least 50% (w/w) (24). Vilivalam and Adeyeye (25) prepared diclofenac wax microspheres and their mixtures with microcrystalline cellulose and Explotab were compressed. Slightly faster release was noticed with tableted microspheres compared with that of uncompressed microspheres. The authors reported that the microspheres appeared deformed but remained intact irrespective of compression pressures. Increased microsphere size from 215 to 630 μm had very little effect on tablet dissolution.

Tableting of Coated Particles

It is important that the coated particles in the formulation are able to withstand the process of compaction without being damaged. Figure 6 shows a non-compressed pellet (Figs. 6A), tablets containing pellets (Figs. 6B, 6C), and a close view of a pellet within a compressed tablet. It is clear from this figure that although high proportions of microcrystalline cellulose (Avicel PH 101) have been used as protective agent in the tablet matrix, the surfaces of the pellets in the tablets have been damaged, exhibiting clearly evident fractures. Drug release data can be used as an indirect method to study the possible damage of the coating during compression, and differences in drug release between coated non-compressed pellets and fast disintegrating tablets obtained after tableting of the coated pellets can have important biopharmaceutical implications. Provided that matrix tablets are not formed, changes in drug release are attributable to damage of the coating membranes. Drug release can be easily studied and is reported in most of the published papers which deal with this subject. Figure 7 shows the ibuprofen drug release of pellets alone and two tablet formulations of the pellets obtained at two different pressures. It is clear that an alteration of the drug release has occurred after compression of the pellets. However, the controlled release characteristics are not completely destroyed and the release kinetics are still useful for control release therapy (more details of these formulations are provided in the example 2 of this chapter) (26).

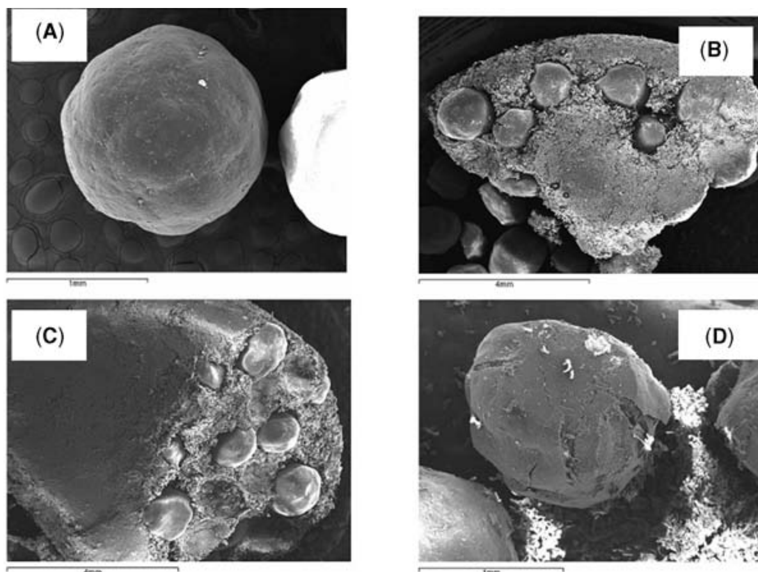

FIGURE 6 Scanning electron microscopy of a non-compressed pellet (**A**: 50 × magnifications), tablets containing pellets (**B** and **C**: 15 × magnifications) and a compressed pellet (**D**: 20 × magnifications).

Many variables are involved in the process of compression of coated pellets. Among the most critical factors to be considered to maintain the desired drug release properties of the particles are: the type and amount of coating agent, the size of the particles, the selection of external additives, such as cushioning excipients, the rate and magnitude of the applied compression pressure, and the residual porosity of the resulting tablets. The effect of some of these factors has been reviewed by Çelik and Maganti (9) and Bodmeier (27) and the following basic considerations are clear:

1. The addition of a coating material usually modifies the deformation characteristics of uncoated pellets by introducing plasto-elastic properties to their previously brittle

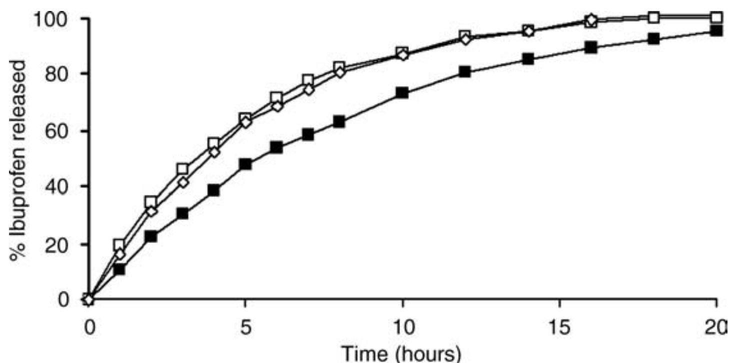

FIGURE 7 In vitro drug release from compacted and uncompacted pellets formulations containing 800 mg ibuprofen. Key: non-compacted ibuprofen pellets (■), ibuprofen 800 mg tablet compressed at 2.8 kN (□) and 4.7 kN (◇). *Source*: From Ref. 26.

and elastic nature. Thus, coated pellets require lower applied pressures to produce compacts of the same in-die porosities as the uncoated pellets.

2. The dissolution studies of most of the reported research indicate that if a matrix tablet is not obtained, the sustained release and enteric properties of the coated pellets diminish on application of compaction pressure, regardless of the amount of coating applied. This effect can be due to the formation of cracks within the coating and to the fragmentary/elastic nature of the core pellets. To minimize damage to the polymer coating, cushioning excipients can be used. Moreover, the proportion of plasticizer in the coating is critical to avoid damage to the coating during compression and high proportions of plastizicers are usually recommended [sometimes as much as 30% w/w of coating polymer (28)], although for some specific coating polymers it was possible to compress coated pellets without the further addition of plasticizer (29).
3. Compaction of coated pellets at high velocities resulted in a decrease in the tensile strength values and an increase in the volumetric strain recovery values. Thus, a careful scale up study is required for these formulations. Pellets with increasing amounts of Surelease coating exhibited relatively greater punch velocity dependence (30).

From the previous considerations it is clear that many variables are involved in the tableting of coated pellets. The effects of some these factors are still not clear and there are controversial results reported by various authors. It is common to find a particular excipient to be useful as a protective agent for the compression of one particular type of coated pellet, but not as useful for another type of coated particle. Tables 1 and 2 give a summary of the different formulation variables to consider during the development of a coated multiparticulate tablet system. The problem is complex because there are obvious interactions among these variables. Usually, reported studies explore the effect of several variables in the context of three basic formulation elements: pellet core, polymer coating, and tableting excipients. In the sections that follow, we discuss the impact of many of these variables on both the tabletability of the formulation and the drug release profile.

Pellet Core

The pellet should have some degree of elasticity which can accommodate changes in shape and deformation during tableting. Ideally, it should deform and recover after compression without damage to the coating. On the other hand, plasticity is also another important requirement for the pellet core and usually it is achieved using microcrystalline cellulose, although other co-excipients can be added to improve the compression characteristics of the pellets. Sugar pellets have been used as a core with good results wherein the drug is applied by layering, a coating applied and the finished pellets compressed (29). Most of the previous comments relating to the tableting of uncoated particles are also pertinent here.

Although the nature of the coating is often described as the most critical factor in many papers, Tunón et al. (13) recently reported that the initial pellet intragranular porosity can also play a significant role in both pellet compression and the preservation of dissolution performance after compression. These authors prepared three batches of salicylic acid and microcrystalline cellulose pellets in the proportions 1:9 (w/w) using different proportions of water:ethanol in the granulation liquid. Pellets of different intragranular porosity were produced. Each pellet batch was coated with ethyl cellulose to a weight gain of 10–15% under similar conditions. The coated pellets were then tableted at punch pressures of 10, 80, and 160 MPa. The integrity of the pellets after compression was studied by different methods, including drug release, and compared to

TABLE 1 Main Formulation Variables to Consider When Tabeting Coated Pellets

Pellet core
Composition
Microcrystalline cellulose either alone or with co-excipients
Sugar pellets
Intragranular porosity
Particle size
Polymer coating
Nature of polymer: usually acrylic better than cellulose derivative
Proportion of polymer: 10–30%
Plasticizer: usually triethyl citrate or propylene glycol
Proportion of plastizicer: 0–30%
Tableting conditions
Cushioning excipients: microcrystalline cellulose, polyethylene glycol; soft pellets with barium sulphate, glycerol monoestearate, wax pellets …
Superdisintegrant: crospovidone, sodium carboximethyl cellulose, …
Proportion of the protective excipients: Theoretically particle size of excipients: Smaller size may be more efficient at least 30%
Size of the excipients: The smaller size the more efficient than bigger size particles (possible segregation problem)
Multilayered bead formulation
Compression force
Scale up and production rate

uncompressed pellets. Surprisingly, these authors observed that the coating appeared to be less important to the successful tableting of these pellets than their initial porosity (13). The coating used in this study seemed to adapt to the densification and deformation of the pellets and remained tightly adhered to the pellet cores, even after tableting. But the effect of initial intragranular porosity on compression behavior and drug release from the coated pellets was substantial. The pellets having high original porosity were greatly densified and deformed in the tableting process, but drug release was unaffected. In contrast, there was only slight densification and deformation of low porosity pellets, but the drug release rate was markedly increased. Thus, pellet porosity is a potential factor to be exploited by formulators.

The size of coated pellets can affect both their compaction properties and drug release. At the same coating level, smaller chlorpheniramine pellets were more fragile than larger pellets. This was attributed to the reduced film thickness of the smaller pellets due to the larger surface area (31). On the other hand, Debunne et al. (32) studied the effect of size on the compression of coated piroxicam pellets and concluded that pellets with a smaller particle size, 0.31–0.5 mm versus 0.8–1.2 mm, form a larger number of bonds during compaction as a result of their greater surface area, resulting in an increase in tablet mechanical strength and a slower disintegration of the tablets. Ragnarson et al. (33) noted that increasing the particle size resulted in more damage to the coating. Also related to the size and density of pellets are the segregation concerns previously discussed.

Polymer Coating

With reservoir-type coated pellets, the polymeric coating must be able to withstand the compression force; it can deform but it should not rupture. Polymers used in the film-coating of solid dosage forms fall in two broad groups based on whether they are

TABLE 2 Best Conditions to Avoid the Drug Release Alteration by Compression of Multiparticulate System

Type of particulate system	Particle size (mm)	Compression pressure or force	Protective excipient (% in tablet)	Reference
Acetylsalicylic acid microcapsules	0.23–0.7	20 kN	20% of microcrystalline cellulose (Avicel PH 101) high proportion of plasticizer (30%) in the coating membrane	(28)
Theophylline coated pellets	0.41–0.6	2–100 MPa	55% of a mixture of microcrystalline cellulose (50%), polyethylene glycol 3350 (25%) and crospovidone (25%)	(35)
Ibuprofen coated pellets	1	2.8–4.74 kN	40% of a mixture of lactose and microcrystalline cellulose	(26)
Albumin acetaminophen microaggregated	0.25–0.4	115–197 MPa	25% of different excipients (Fig. 4B)	(23)
Theophylline coated pellets	1–1.4	6.6–39 kN	40% of soft pellets consisting of barium sulphate, microcrystalline cellulose and glyceryl monostearate (50:20:30 w/w/w)	(41)
Bisacodyl enteric coated pellets	1	20 kN	40% of a mixture of different excipients (most Avicel PH 101) High proportion of coating agent (25% final weight) and plasticizer (10% w/w of coating)	(37)
Diltiazem coated pellets	0.8–1.2	10 kN	50% of paraffin beads of approximately 1 mm diameter made by melt pelletization	(39)
Piroxicam enteric coated pellets	0.8–1.2 0.31–0.5	10–30 kN	50% of paraffin beads of approximately the same size made by melt pelletization and also 10% of Kollidon CL	(32,40)
Salicylic acid pellets	0.71–1	10–160 MPa	Intragranular porosity of coated pellets	(13)
Verapamil coated pellets	0.8–2	12 kN	60% of a mixture of Avicel PH 102, mannitol and Kollidon CL at the proportions of approximately 1.5:5:1	(49)

cellulosic or acrylic polymers. Ethyl cellulose is the major cellulosic polymer used for extended release, often in the form of an aqueous dispersion or latex (e.g., Surelease® Colorcon Inc., West Point, Pennsylvania, U.S.A., and Aquacoat® FMC Biopolymer, Drammen, Norway). Eudragit® (Roehm GMBH, Darmstadt, Germany) and Kollicoat® (BASF AG, Ludwigshafen, Germany) are the trade names for commonly used acrylic polymers and their aqueous dispersions.

Most studies on the compaction of pellets coated with ethyl cellulose revealed damage to the coating with a loss of the sustained release properties (27). For example, the compaction of diltiazem pellets coated with ethyl cellulose resulted in a faster drug release irrespective of the formulation used when compared to release from non-compressed pellets (34). On the other hand, Tunón et al. (13) reported good results with compression of ethyl cellulose coated pellets.

Compared to ethyl cellulose films, films prepared from acrylic polymers, for example, Eudragit RL/RS, NE 30 D, RL/RS 30D, L 30 D-55 and Kollicoat SR 30 D, and mixtures of MAE 30 DP and EMM 30 D, are more flexible and therefore more suitable for the compression of coated pellets. Dashevsky et al. (29) reported that some of these polymers are suitable for coating and compression even with low proportions of plasticizer. For Kollicoat SR, better results were obtained with triethyl citrate at 10% than with propylene glycol (29).

Although it is very difficult to avoid alterations of the coating membrane during compression, a partial recovery of the drug release characteristics may be possible after heating the tablets. Béchard and Leroux (31) reported this effect on tablets containing chlorpheniramine pellets (250–420 μm) coated with an aquous ethylcellulose pseudolatex dispersion plasticized with 24% dibutyl sebacate and tableted with microcrystalline cellulose (39.3%) that were stored in a convection oven at 75°C for 24 hours. It was observed that the disintegration time was less than 10 Seconds and dissolution was improved. After 30 minutes, only 55% of chlorpheniramine was released for the tablets dried at 75°C as opposed to 85% for the non-heated tablets. Probably, certain fissures in the coating membranes were sintered by exposing the compacted pellets to a temperature above the film glass transition temperature, which in this example is about 44°C. It has to be pointed out that this is only a partial recovery because the coated non-compressed pellets release 38.4% of clorpheniramine which is clearly less than the 55% and 85% obtained with the heated and non-heated tablets, respectively.

Tableting Conditions and the Role of Cushioning Excipients

The use of cushioning excipients is an important strategy that can be followed to avoid or minimize damage to the coating of tableted pellets. Often, tablet disintegration is also improved. These excipients can be used either as powder, granules, or pellets. In some applications, they can be incorporated as additional coatings to the beads so forming multilayered bead formulations.

Torrado and Augsburger (35) studied the relationship between their yield pressure and the protective effect of different excipients on the compression of coated theophylline pellets. Even at low-compressional forces there was always damage to the coatings. The best cushioning effect was obtained with the following composition of low yield pressure excipients: microcrystalline cellulose (50%), polyethylene glycol 3350 (25%), and crospovidone (25%).

In relation to the cushioning excipients, the crushing strength of the coated pellets is crucial. Soft pellets can be deformed more easily than hard pellets (36). It is important that the drug coated pellets have a sufficiently high crushing strength to avoid critical

damage to their coating membranes. However, the excipient particles to be mixed within the drug coated pellets should be of lower crushing strength so they will be deformed preferentially.

To avoid segregation the particle size of the cushioning excipients and the proportion of coated pellets are important considerations. Some researchers prefer filler-binders that are almost equal in size to the drug pellets (9), whereas others have reported no segregation effect when using the relatively small particle size microcrystalline cellulose (Avicel PH 101) powder (37). According to this latter report (37), segregation also depends on the proportion of pellets in the mixture. At 70% (w/w) of pellets, tablets could be obtained that comply with pharmacopeial weight and content uniformity requirements. For potent drugs, if lower proportions of drug pellets are used, segregation can be an important issue in formulation development. In that same study, small particle size microcrystalline cellulose (Avicel PH101) was reported to be a better protective agent for coated pellets than larger sized Avicel granules during compression, especially at high production rates (37). It appears that the relationship between the particle size of the cushioning excipient, segregation and the protective effect have to be carefully considered on a case-by-case basis.

The composition of the cushioning agent is also a topic of debate. Microcrystalline cellulose, even at low proportions (20% w/w), can improve the plastic characteristics of the mixture to compress (38). Figure 8 shows the force–time compression curves of acetylsalicylic acid pellets alone (Formulation A) and with a 20% (w/w) of microcrystalline cellulose (Formulation B). Elastic recovery changes from 6% (Formulation A) to 13.6% (Formulation B). Lubricant efficiency (R-value) also improves, from 0.65 (Formulation A) to 0.88 (Formulation B). It is clear that addition of microcrystalline cellulose improves the tableting properties of the coated pellets. Although microcrystalline cellulose is perhaps the more frequently used protective excipient, several others have also been successful in this application. For instance, Vergote et al. (39) proposed wax beads as the most suitable cushioning agent in the compression of coated diltiazem pellets. To this end, a mixture of drum-dried corn starch, Explotab® (JRS GMBH, Rosenberg, Germany) and parafinic wax at the following proportions: 33.3/16.7/50% w/w was prepared by melt pelletization. The size and proportion of the cushioning agent were critical. The larger the particle size of the cushioning agent, the higher the proportion required to obtain a protective effect. In the work of Vergote et al. (39), good results were achieved with protective beads of approximately 1 mm diameter (same as the diltiazem pellets) and with a 50% w/w proportion of this cushioning agent. Using a compression simulator, the effect of pre-compression force and compression time on the dissolution rate were found to be insignificant. The same cushioning agent has been used with piroxicam formulations at a 60% proportion with the drug coated pellets (40). These authors have also added Kollidon CL as disintegrant at a 10% w/w proportion in the tablets to obtain a disintegration time of less than 15 minutes. When the Kollidon CL powders were replaced by disintegrant pellets to avoid segregation problems, the resulting tablets showed longer disintegration times. Thus, a similar effect of excipient particle size on disintegration as that previously reported by Wagner et al. (37) with Avicel was found with Kollidon CL. It is clear that particle size is a critical parameter for excipient efficacy.

Soft pellets produced by mixing barium sulphate, microcrystalline cellulose (Avicel PH 101), and glyceryl monostearate (50:20:30% w/w/w) have also been reported to provide an effective cushioning effect. This excipient at 40% has been shown to be effective in the protection of theophylline coated pellets (41). In this work, an experimental design was used to explore the relationship between the properties of the pellets and those of the tablets. The breaking load and disintegration time of the tablets were

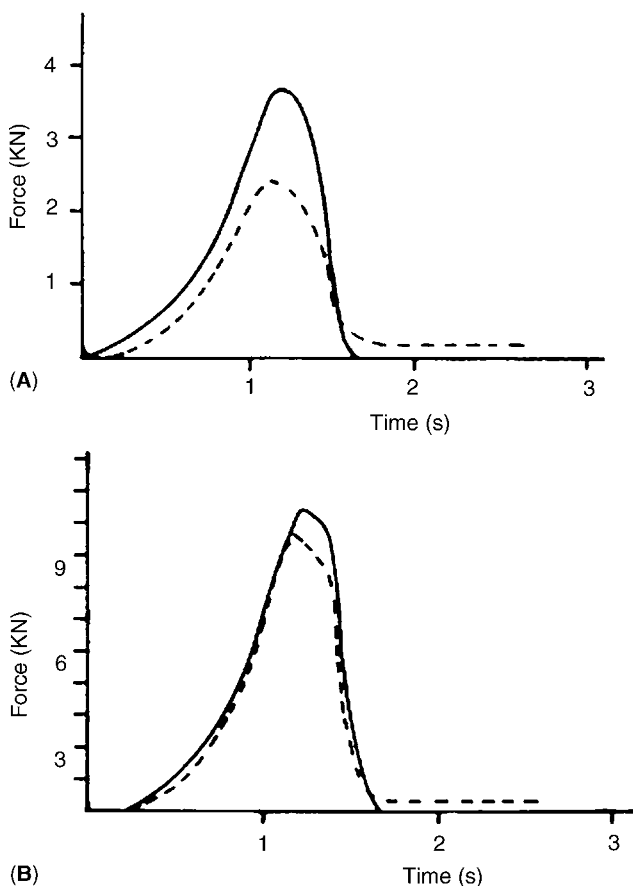

FIGURE 8 Force–time compression curves of acetylsalicylic acid pellets coated (**A**) with Eudragit RS (20% w/w) without microcrystalline cellulose (Formulation **A**) and (**B**) with microcrystalline cellulose at 20% (w/w) (Formulation **B**). The force exerted by the upper punch is drawn in continuous line and the force transmitted by the lower punch is drawn in discontinuous line. *Source*: From Ref. 38.

related to the tableting pressure and the proportion of disintegrant. The dissolution of the tablets was related to the tableting pressure, the type of disintegrant, the proportions of the drug and disintegrant, and especially the thickness of the film coating surrounding the pellets.

One interesting point related to cushioning pellets is their porosity. If porosity is increased, for example, by freeze-drying, the resultant beads may have better compression and compactability characteristics. Habib et al. (42) reported how beads containing microcrystalline cellulose and different superdisintegrants can be produced by extrusion–spheronization followed by freeze-drying. The presence of high levels of microcrystalline cellulose and different superdisintegrants, especially croscarmellose sodium, increased the granulation liquid requirements, thus producing freeze-dried pellets with higher porosities and compactability. These pellets have low mean yield pressures and compressed by both plastic deformation and brittle fracture.

Altaf et al. (43,44) prepared consisting of pellets several alternating layers of acetaminophen and polymer coats (Aquacoat) and an outer layer of mannitol as a

cushioning excipient. Spray layering of the cushioning excipients is an effective way to avoid the segregation issues associated with mixing of the coated pellets and powdered or spherical/non-spherical cushioning excipients. This is due to the fact that the multilayered pellets can be directly compressed without the addition of further excipients. Disintegration of several of the tablet formulations was achieved in less than 20 minutes and although alteration of the drug release of the pellets was reported, a certain therapeutic sustained release was observed. Polyethylene oxide coating was also applied in an outer layer coat. These latter coated pellets could be compressed at pressures of 125, 500, and 1000 pounds into caplets. The tablet disintegration characteristics varied and under certain experimental conditions, a matrix tablet was obtained. The effect of polyethylene glycol 8000 and microcrystalline cellulose as cushioning excipients was also reported. This procedure may be particularly useful for highly potent drugs, for which the uniform mixing of a small amount of drug with large amounts of powder is problematic.

EXAMPLES OF MULTIPARTICULATE MODIFIED RELEASE TABLETS

The compaction of pellets is a challenging area. Only a few multiple unit-containing tablet products are available (29), such as Beloc® ZOK (45), and Antra® MUPS (46) (Astra Zeneca, Södertälje, Sweden). Beloc ZOK releases metoprolol succinate with zero order kinetics. Antra MUPS is a multiple unit pellet system (MUPS) the proton pump inhibitor omeprazol. Many companies are involved in the development of novel drug delivery systems and several patents are related to tablets of multiparticulates. These different drug delivery systems (47) can be divided into either oral controlled release or fast dispersing dosage forms. Among the oral controlled release systems are: Ceform microsphere technology (Fuisz Technology Ltd., U.S.A.), Dimatrix Multipart or Multiparticle Drug Dispersing Shuttle (Biovail Corporation International), IPDAS or Intestinal Protective Drug Absorption System (Elan Corporation), Pharmazone or Microparticulate Drug Delivery Technology (Elan Corporation), PPDS or Pelletized Pulsatile Delivery System and Peltab System (Andrx Pharmaceuticals), SODAS or Spheroidal Oral Drug Absorption System (Elan Corporation), KV/24 (KV Pharmaceuticals), and Triglas technology (Ethical holdings Plc.). Among oral fast-dispersing dosage forms are Flashtab and Multiflash (Prographarm, France) and Orosolv (Cima Labs Inc., U.S.A.). A detailed description of these new systems is beyond the scope of this review, but several other examples of the tableting of multiparticulate modified release systems obtained from the scientific literature are described below.

EXAMPLE 1. TABLETS OF ENTERIC MICROENCAPSULATED ACETYLSALICYLIC ACID

Dechesne (28) described the development of a multiple-units enteric tablet of acetylsalicylic acid (ASA). ASA crystals (230–700 μm) were coated with acrylic latex (Eudragit L 30 D) in a fluidized bed. The coating conditions were:

- spraying solution feed: 12 g/min/kg;
- exhaust air and tablet bed temperature: 30–35°C;
- spraying air pressure: 30 N/cm^2;
- drying air temperature: 60°C;
- final drying time: 20 minutes.

An experimental design was used to study the effect of three variables on the formulation. The studied variables and levels were:

- proportion of coating polymer (15%, 22.5% and 30%);
- nature of plasticizer (triacetine or propyleneglycol);
- proportion of plasticizer (10% or 30% w/w compared to the polymer).

It was reported that the content of salicylic acid in the microencapsulated ASA was < 3%, even after 12 months.

An in vitro dissolution test was performed to study the ASA release of the coated microcapsules in gastric fluid and it was observed that at least 22.5% (preferably 30%) of polymer was required to obtain < 10% ASA released after 2 hours. In intestinal fluid, about 80% of ASA was dissolved within the first 20 minutes. Tablets containing 500 mg of ASA were obtained with a single punch tablet machine at 20 kN. The die and punches were 12 mm diameter and the resultant tablets had a minimal crushing strength of 5 kg (Erweka) and a maximal disintegration time of 2 minutes. To obtain this fast disintegration time, 20% of microcrystalline cellulose was required. The tableting characteristics of the different formulations were studied by a modification of the Heckel equation. It was clear that an increase in plasticity of the coated ASA particles was obtained when the plasticizer was used at the higher proportion (30%). Moreover, when the plasticizer was used at the 10% level, a decrease in the plasticity combined with fragmentation resulted in more ASA dissolved during the gastric dissolution test (> 27% within 2 hours). Decrease of fragmentation during compression (30% plasticizer) resulted in lower ASA release (< 9% after 2 hours) during the gastric dissolution test. Propylene glycol produced less permeable films than triacetine and for this reason it was the recommended plasticizer in this application.

EXAMPLE 2. TABLETS OF IBUPROFEN SUSTAINED RELEASE COATED PELLETS

Pellets of ibuprofen (48) with 20% w/w microcrystalline cellulose (Avicel PH101) were manufactured by extrusion and spheronization and then dried in a fluidized bed dryer at 60 °C for 60 minutes. This drying process was preferable to tray drying in a hot air oven because fluidized-bed dried pellets were mechanically weaker, more elastic and less brittle than their tray drying counterparts (14). Different aqueous dispersions were used to coat the pellets. The nature of the coating is critical in to avoid loss of coat integrity during tableting. In their experimental conditions, the best results were obtained with a polymethacrylate dispersion (Eudragit RS30D/RL 30D). The pellets were coated to achieve a 4.5% w/w weight increase. Coated pellets of 1 mm diameter size were tableted to obtain tablets with 800 mg of ibuprofen. The large drug dosage required use of a minimum quantity of diluent to fill the void volume within the tablet during compression. As a first approach, large particle size excipients were chosen to avoid segregation and to this end, placebo pellets of lactose and microcrystalline cellulose were prepared. The mechanical strength of the resultant placebo pellets was far in excess of that of the ibuprofen coated pellets such that if tableted together the ibuprofen coated pellets would be preferentially crushed to form the tablet structure. For this reason, instead of placebo pellets, commercially available large particle size lactose and microcrystalline cellulose powdered excipients were chosen. The optimized diluent blend was found to be lactose 19.5% (Meggle D10, mean particle size 500 μm), microcrystalline cellulose 20% (Avicel PH200) and magnesium stearate 0.5%. The minimum amount of the mixture of

excipients required to efficiently fill the void space between the pellets was found to be 40%. At this proportion, the mixture of excipients was able to facilitate bonding and cushioning of the pellets. The mixing of coated pellets with lactose and microcrystalline cellulose was performed in a Turbula mixer for 15 minutes. Magnesium stearate at a 0.5% level was then added to the bulk and blended for a further 10 minutes. Tablets were compressed in a single-punch tablet machine (Manesty F3) with concave punches of 25 mm $\times$ 9 mm at a compression force of 4.75 kN to produce tablets of a crushing strength of about 200 N and a friability of 1.74%. These tablets disintegrated within 90 Seconds releasing apparently intact coated pellets. The uniformity of content of ibuprofen in the compacted tablets was within 4.2% relative standard deviation (RSD), that is, within the target value of 5% RSD. The authors (26) pointed out that although under the pilot-scale conditions reported, segregation of the diluent blend from the active pellets does not appear to be a problem, that may not be the case on scaling up the process. The in vitro drug release from the polymer-coated compressed pellets compared with uncompressed pellets is shown in Figure 7. It is evident that slight damage is caused to the pellets as a consequence of compression. This is highlighted by an increase in the rate of drug release from compacted pellets compared with non-compacted pellets. However, the controlled release characteristics of the dosage form are not destroyed and the release kinetics are still useful for control release therapy. The damage to the pellets is mainly associated with those pellets present at the surface of the tablets during compression. This observation indicates that it is not compaction pressure which causes damage to the pellets but the actual act of compression. For this reason, no effect of compression forces between 2.8 and 4.75 kN is observed on drug release (Fig. 7). The damage of the pellets is probably associated with factors relating to excessive distortion of the pellets and their coating when in contact with the die wall and tablet punch.

EXAMPLE 3. TABLETS OF ENTERIC COATED BISACODYL PELLETS

Beckert et al. (36) and Wagner et al. (37) described different formulations of disintegrating multiple-unit tablets of bisacodyl. The best formulation used placebo pellets type 08430 (particle size: 90% within 850–1000 μm) as core. These placebo pellets were loaded with bisacodyl to obtain approximately 4% w/w of active ingredient. The bisacodyl pellets were prepared in a fluidized bed coater by top spraying. Batches of 4500 g of placebo pellets were coated with bisacodyl (244 g) suspension using Eudragit L 30 D-55 (270.9 g) as a binder, talc (40.5 g) as a glidant and triethyl citrate (8.1 g) as a plasticizer. The spraying conditions were: 40°C inlet air temperature, 32–34°C outlet air temperature, 2.5 bar atomizing air pressure, 60 minutes coating time, 5 minutes preheating. These pellets were dried for 10 minutes and then an enteric coating was applied. The enteric coating applied to the bisacodyl pellets (4873.5 g) was Eudragit FS 30 D which was sprayed at 25% w/w in the same conditions as described before and the coating time was 90–170 minutes after a preheating period of 15 minutes. The enteric coating also has triethyl citrate as plasticizer (10% w/w based on dry coating substance), glycerol monostearate (97.4 g) and polysorbate 80 (154 g of 33.3% w/w). More detailed conditions are described in Ref. (37). To avoid sticking the pellets were mixed with 0.5% Aerosil 200 for 20 Seconds immediately after coating. Although lower proportions of enteric coating (12.5% w/w) and plastizicers (5%) were tested, the best results were obtained with the higher proportions previously described. Tablets of 400 mg were obtained with an instrumented rotary tablet press at different speed levels (26, 50, 75 and 100 rpm) while compressing at 20 kN. The best tablet formulation was obtained with 60%

of pellets. Higher proportions of pellets (70%) induce more degradation of the coatings. The best cushioning effect was achieved with microcrystalline cellulose powder (Avicel PH 101) at 30.7%. Avicel granules at similar proportions were less effective as a protective agent, especially at high production rates. The other components of the tablets were: Kollidon CL (6%), talc (2.5%), Aerosil 200 (0.3%), and magnesium stearate (0.5%). At these conditions, tablets with a crushing strength of approximately 110 N were obtained and no significant effect of compression speed was observed. The disintegration time was about 10 minutes. Drug release in simulated gastric fluid was of less than 10%, within the requirements of USP 23. The authors (36,37) pointed out that bisacodyl is a water soluble drug with a higher solubility than acetylsalicylic acid making the development of an enteric multiple-unit is a more difficult task.

EXAMPLE 4. TABLETS OF ENTERIC COATED PIROXICAM PELLETS

Debunne et al. (32,40) described the conditions to obtain tablets of enteric coated piroxicam pellets. The aim of this formulation is to avoid local gastrointestinal irritation from piroxicam. Due to the fact that piroxicam is a poorly water soluble drug, different excipients and combinations were tried in an attempt to optimize its dissolution (microcrystalline cellulose, different sodium carboxymethyl celluloses, β-cyclodextrin, and hydroxypropyl-β-cyclodextrin). The best composition for the core pellets with a 2.5% w/w loading of piroxicam was a mixture of microcrystalline cellulose (Avicel PH 101) (24.4% w/w) and sodium carboxymethyl cellulose (Avicel CL 611) (73.1% w/w). These materials were dry mixing and then wetted with demineralized water and granulated. Next the wet mass was extruded and spheronized. The pellets were tray dried in a hot air oven at 40˚C and then the 800–1200 μm size selected. The pellets were coated with a flexible polymer film consisting of Eudragit L 30 D-55 and FS 30 D (ratio 6:4) using the bottom-spray technique with a Wurster setup. The spraying conditions were: 35–45˚C inlet air temperature, 26–28˚C outlet air temperature and 1.5 bar atomizing air pressure. Both aqueous Eudragit dispersions were mixed by means of a magnetic stirrer. The excipient dispersion was prepared separately: water, triethyl citrate (plasticizer at 20% of dried polymer), and polysorbate 80 (dispersing agent) were homogenized with a rotor-stator mixer for 10 minutes, after which glyceryl monostearate (anti-adhesive) was added. The excipient dispersion was added to the Eudragit mixture and stirred for 30 minutes. Upon completion of coating, the pellets were dried for 10 minutes at 26–28˚C and cured on trays for 48 hours at room temperature. At least 10% dry polymer substance was applied to obtain enteric protection.

To protect the enteric coating during compaction, soft placebo wax beads consisting of Paracera P/drum dried corn starch/Kollidon CL (50:33.3:16.7; w/w/w) and ranging from 800 to 1200 μm were prepared by melt pelletization (39). The ratio piroxicam pellets/cushioning beads was 60:40 w/w. Tableting was performed in a compaction simulator at different compression forces from 10 to 30 kN. Tablets were of 600 mg weight and had a diameter of 12 mm. At these conditions, disintegration after tableting was too slow and a disintegrant agent, Kollidon CL at 10% was required to obtain tablets with a hardness of approximately 30 N and a disintegration time of less than 15 minutes. To avoid segregation problems, the disintegrant Kollidon CL previously added in powder from was replaced by disintegrant pellets, but the resulting tablets showed longer disintegration times.

The in vitro dissolution profile of the tablets was similar to the pellets, so it was concluded that the film coat was not damaged during compression. Under acid conditions

less than 1% of piroxicam was released after 120 minutes. At a pH of 6.8 more than 75% was dissolved at 60 minutes. An in vivo evaluation study was done with dogs and different formulations were orally administered (32). Coating of the pellets and compression of the coated pellets delayed the onset of the piroxicam plasma concentration, but did not affect the extent to which piroxicam was absorbed.

EXAMPLE 5. TABLETS OF FLOATING PELLETS WITH VERAPAMIL HYDROCHLORIDE

Sawicki and Łunio (49) reported a tablet formulation of floating pellets containing verapamil hydrochloride in a dose of 40 mg. The tablet is designed to disintegrate in the stomach to release undeformed pellets that would float in this environment for 5–6 hours, thereby releasing the drug in a controlled way.

Core pellets of the following composition were prepared: verapamil hydrochloride (20% w/w), microcrystalline cellulose (Avicel PH 101) (10%), sodium hydrocarbonate (20%), powdered cellulose (Arbocel® P290) (33.4%), and lactose (12.3%). These products were dry mixed and then moistened with an aqueous solution of povidone K-30 (4.3% w/w final proportion in the dried mixture). The wet mass was passed through a 1.25-mm sieve and then spheronized to obtained pellets of 0.8–2 mm diameter. Once dried, the pellets were coated in a fluid bed (Uni-Glatt) at the following conditions: 40°C inlet air temperature, 30°C outlet air temperature, 3 ml/min peristaltic feeding rate and 2 bar atomizing air pressure. The best coating membranes were obtained with the following mixture (the final proportion as solid material in the coating membrane noted in parentheses): Kollicoat SR 30 D (60%), propylene glycol (10%), povidone K-30 (16%), and talc (14%). The film obtained around the pellets was of 50 μm. Different excipients and proportions were tested in an attempt to avoid damage of the coating membranes and to control the disintegration characteristics of the tablets. The best results were obtained with the following excipients and proportions: coated pellets (38.2%), Avicel PH 102 (13.5%), mannitol (37.8%), Kollidon CL (9.5%), and magnesium stearate (1%). Tablets of 550 mg weight containing 40 mg of verapamil hydrochloride were obtained with spherical punches of 12 mm at a compression force of 12 kN. The dissolution profile of verapamil release from these tablets was identical to that of the noncompressed pellets (approximately 50% released about 3 hours). Microscopic inspection confirmed that neither the core nor the film coat on the pellets was severely damaged as a result of compression. The tablets have low friability (0.1%), high hardness (0.116 kg/mm^2) and proper content uniformity of verapamil. The start of flotation time observed during the in vitro dissolution test was approximately 8 minutes.

MONOLITHIC MATRIX DRUG DELIVERY SYSTEMS

Pellets, microcapsules and microspheres may be compacted in a similar way to conventional granules. Tableting is especially easy if particles have an appropriate size (0.5–1 mm). If the microparticles to be compressed have in their composition drug release polymers, then these excipients can fuse during tableting, and if the tablets do not disintegrate, then monolithic matrix systems can be obtained. These systems can be useful either for oral or parenteral administration. Readers interested in this topic are referred to Chapters 14 and 15 of this volume which deals with this subject.

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Pharmaceutical Science

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The ultimate goal of drug product development is to design a system that maximizes the therapeutic potential of the drug substance and facilitates its access to patients. ***Pharmaceutical Dosage Forms: Tablets, Third Edition*** is a comprehensive treatment of the design, formulation, manufacture, and evaluation of the tablet dosage form. With over 700 illustrations, it guides pharmaceutical scientists and engineers through difficult and technical procedures in a simple easy-to-follow format.

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