AAPS Introductions in the Pharmaceutical Sciences

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Essential Pharmaceutics

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Contents

Chapter 1
Essential Pharmaceutics in the Flipped Classroom

Abstract This chapter provides a guide on how to implement a flipped-classroom model into a pharmaceutics course. Course design, daily class organization, strategies for student success, and how to implement prereading materials (specifically this text) are discussed in detail.

Keywords Case studies · Pharmaceutical education · Flipped classroom · Problem-based learning · Teaching methods · Active learning · Information literacy

Essential Pharmaceutics, as its name implies, provides PharmD students with the critical concepts and knowledge foundation as a part of their pharmaceutics training. These essential concepts are complemented by additional materials and applications in our "flipped" pharmaceutics course, the design, and implementation of which is explained herein.

This book was developed over several years as an accompaniment to the flipped classroom pharmaceutics course taught by Professors Hugh DC Smyth and Robert O. Williams III at The University of Texas College of Pharmacy (UTCoP). Following two years of planning and study, and with input from education and instructional experts, in the spring of 2014 the "Pharmaceutics" course within the UTCoP PharmD curriculum was restructured from a conventional lecture-based content delivery to a flipped instruction, team-based, classroom model.

What does a "flipped class" mean in terms of pharmaceutics? In short, it is the application of facts, foundational knowledge, information literacy skills, and team-based learning to solve real-world drug delivery and formulation science problems. Students leave our course with an understanding of pharmaceutics that goes beyond rote memorization of facts and in parallel develop the critical thinking and communication skills necessary to become leaders in clinical, industry, and academic settings.

This text, *Essential Pharmaceutics*, provides the cornerstone of our flipped classroom approach and the basis of students' pre-class readings that prepares them for in-class applications and in-depth utilization of these basic concepts and principles. This approach can be applied successfully in universities around the world. In our own experience, we have found that the incorporation of this text has been an

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invaluable asset in promoting student understanding of key concepts and ensuring the success of the flipped classroom model as applied to pharmaceutics.

1.1 Overview of "Flipped Pharmaceutics" Course Format and Structure

Team-based learning and communication skills are critical components to the flipped pharmaceutics course. Prior to the beginning of the semester, students are randomly assigned to five-member permanent teams, which they continue working with through the duration of the course. Our class is thus run in a format similar to a project team meeting or board meeting, in which students are expected to respectfully acknowledge the input of team members, challenge teammates in a professional manner, and engage in concise and compelling communication with the expectation that their position is backed with facts, not opinions.

Generally, the semester proceeds in the following manner: students are assigned factual-based content one week before attending class (referred to as the "Pre-class Reading Assignment"). The pre-reading assignment consists of reading chapters from this book and answering specific questions on key concepts (obtained from this book and other assigned relevant peer-reviewed original research and review papers from the literature). Thus, the purpose of this book is to provide the essential facts related to dosage form design and drug delivery that provide the necessary foundational knowledge for students to successfully engage in the in-class case study assignments.

Class time is focused on the strategic application of the pre-class reading assignments through practical, hands-on activities. All teams are required to complete two research-based drug product design assignments (referred to as "case studies"). Sixty minutes are allotted for each assignment with subsequent time for team discussion and case study completion. To successfully complete the assignment, groups are required to utilize a variety of online information resources in order to answer a series of analytical questions. During the 60-min case study, faculty, graduate student teaching assistants and PharmD student assistants continuously interact and engage the teams to facilitate learning (our student:instructor ratio is typically 15:1). At various points in each 60-min case study, the clock is stopped and the faculty delivers two or three mini-lectures consisting of 2–3 slides each on different aspects of the case study, thus linking the students' pre-reading class assignments (facts) to the case study (applying facts to concepts).

Our course is structured as 13 modules, each of which is focused on an aspect of pharmaceutics and dosage form design. The chapters of this book are based upon these modules and are intended to provide students with an understanding of the foundational concepts that they will need in order to successfully complete the real-world case studies assigned in the classroom.

1.2 Building the Required Foundation for Student Success in "Flipped Pharmaceutics"

Implementation of our model required input and coordination with faculty across the PharmD curriculum at the University of Texas. Incoming students to our flipped pharmaceutics course are in the second semester of their first year of the PharmD program. By this point in the curriculum, students have completed a number of foundational courses which are crucial in laying the groundwork for the topics covered in the flipped pharmaceutics course (Fig. 1.1). We mapped each of these prerequisite courses to confirm that students would have the necessary background before beginning our flipped class. We also note that the placement of our course in the curriculum is such that the students have not yet completed their second semesters of Physiology/Pathophysiology and Pharmaceutical Biochemistry, which take

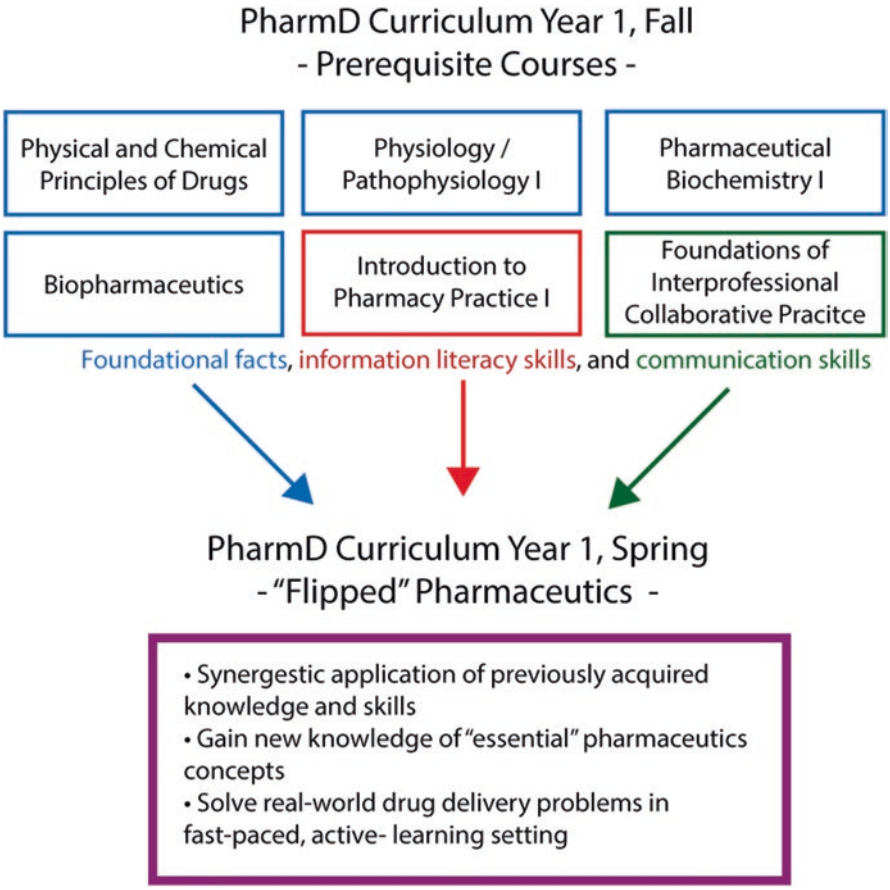

Fig. 1.1 The flipped pharmaceutics course is strategically placed in the PharmD curriculum to ensure students have the necessary foundational knowledge and skills to achieve success in class

place concurrently with this pharmaceutics course in the spring semester of year one of the PharmD program. We thus strategically structure our flipped course content such that the students are assured to have covered a specific topic before it is used in class (e.g., we ensure that anatomy of the eye is covered outside our course prior to the introduction of ophthalmic drug products).

As the flipped pharmaceutics course has evolved over the past six years, we have come to understand that student acquisition of the necessary information literacy skills prior to beginning our course is a key component to ensuring student success. In-class activities require extensive utilization of primary literature, patents, and databases. This information is analyzed by student teams, who are already armed with the knowledge obtained from concepts provided in this book. Extensive work conducted by PharmD/MSc student Natalia Malesa as part of her master's thesis revealed that integration of information literacy training in coursework prior to the start of flipped pharmaceutics increased student performance in the course. Students also reported increased confidence in their own information literacy abilities after prior introduction of these skills. In response to these findings, faculty have incorporated an introduction to these information literacy skills in the "Introduction to Pharmacy Practice" course that students complete in the first fall semester of their first year. Through this course, students gain experience using bibliographic databases for biomedical research, including Google Scholar, PubMed/MEDLINE, ScienceDirect, and Web of Science. With assistance from a pharmacy subject specialist librarian, students learn optimal search strategies for these databases, such as the utilization of Medical Subject Headings (MeSH). Students are also instructed in how to locate tertiary resources, and how to appropriately cite references. In our flipped pharmaceutics course, we continue to build these information literacy skills by introducing search strategies that are more specific to drug products, including the use of patents, the US Pharmacopeia/National Formulary Online, drug substance databases (e.g., TOXNET, Reaxys), medication package inserts, and FDA resources including the Orange Book and the Inactive Ingredients Database. With assistance from the University of Texas at Austin library system, we have designed a course web portal that contains links to each of these resources, in addition to guides on how to use each database, how to read US patents and how to appropriately cite references. Students utilize these resources in class and beyond, with many students reporting years later to us how helpful the web portal is throughout the PharmD curriculum. Overall, the information literacy skills that are developed in flipped pharmaceutics become invaluable to our students as they progress through the curriculum and begin work in clinical and industry settings.

1.3 Achieving Learning Objectives

In designing this "flipped class" course, the following learning objectives are communicated to students:

Learning outcome #1: Methodically identify, describe, analyze, and solve pharmaceutics-related problems.

Concept: Critical thinking and problem solving.

Performance criteria:

1. Recognize a problem.
2. Analyze a problem.
3. Find and evaluate potential solutions.
4. Choose optimal solution.
5. Evaluate outcome.

This is accomplished in the flipped classroom course by incorporating active learning to solve real-life case studies about drug products using knowledge gained through previously assigned reading materials and real-time literature searches during the case study.

Learning outcome #2: Function effectively in groups to accomplish objectives.

Concept: Interpersonal/collaboration skills.

Performance criteria:

1. Participate effectively and work cooperatively with others, including healthcare providers and patients.
2. Recognize, respect, and encourage diverse views.
3. Recognize and manage conflict.
4. Lead as the need arises to accomplish the group's objectives.
5. Evaluate and motivate others to improve performance as necessary.

This is accomplished in the flipped classroom course by establishing teams of students in which successful completion of the assignment required team members to effectively communicate, both written and verbally, in order to solve problems.

Learning outcome #3: Demonstrate the pharmaceutics body of knowledge as specified in pharmaceutics' outcomes below that encompasses the discipline of pharmaceutics.

Concept: Knowledge.

Performance criteria:

1. Demonstrate appropriate depth and breadth of knowledge in the pharmaceutical sciences.
2. Demonstrate mastery of integration of pharmaceutical sciences.
3. Demonstrate application of knowledge in the pharmaceutical sciences and in the resolution of pharmaceutics-related problems.
4. Contribute to the development of knowledge.

This is accomplished in the flipped classroom course by assigning the reading materials that will be mastered before class, testing each individual on the content of the reading materials, and applying the knowledge learned from the reading materials to solve the problems posed to the teams. Students were also tested on this knowledge in a midterm and final exam.

Learning outcome #4: Demonstrate responsibility for own learning and professional competence.

Concept: Self-directed learning.

Performance criteria:

1. Independently acquire new knowledge and skills.
2. Evaluate new information critically.
3. Incorporate new knowledge and recommendations into the practice of pharmacy and the management of medication use systems.
4. Develop and enhance skills to contribute to the development of new knowledge.

This is accomplished in the flipped classroom course by assigning students' activities which must be completed on their own (pre-class reading assignment).

Learning outcome #5: Demonstrate a rational and systematic process to comprehensively assess and evaluate pharmaceutics-related information.

Concept: Literature skills.

Performance criteria:

1. Develop and document a rational and systematic search strategy to retrieve information.
2. Comprehend benefits and limitations of different forms of literature.
3. Critically evaluate basic science and clinical information with respect to appropriateness and validity of the evidence and implications of the major findings for the practice of pharmacy.
4. Apply critically evaluated information to formulate and communicate an appropriate response.

This is accomplished in the flipped classroom course by assigning real-life problems that the students must strategically evaluate and solve using the pharmaceutics-related knowledge acquired through their independent reading or team research conducted during class. Students must master the "Pharmaceutics" portal and gain the skills to effectively use and cite the literature to support their answers.

1.4 Specific "Flipped Class" Structure: How to Implement

On the first class of Flipped Pharmaceutics, we introduce discipline-specific information resources during an interactive tutorial session. Students participate in an instructor-guided case study, in which they are provided hands-on training and opportunities to practice accessing and retrieving specialized scientific information from a variety of online resources such as e-books (e.g., Remington: The Science and Practice of Pharmacy, US Pharmacopeia/National Formulary Online), drug substance databases (e.g., TOXNET, Reaxys), package inserts (e.g., DailyMed), and patents (e.g., US Patent and Trademark Office, US Food and Drug Administration

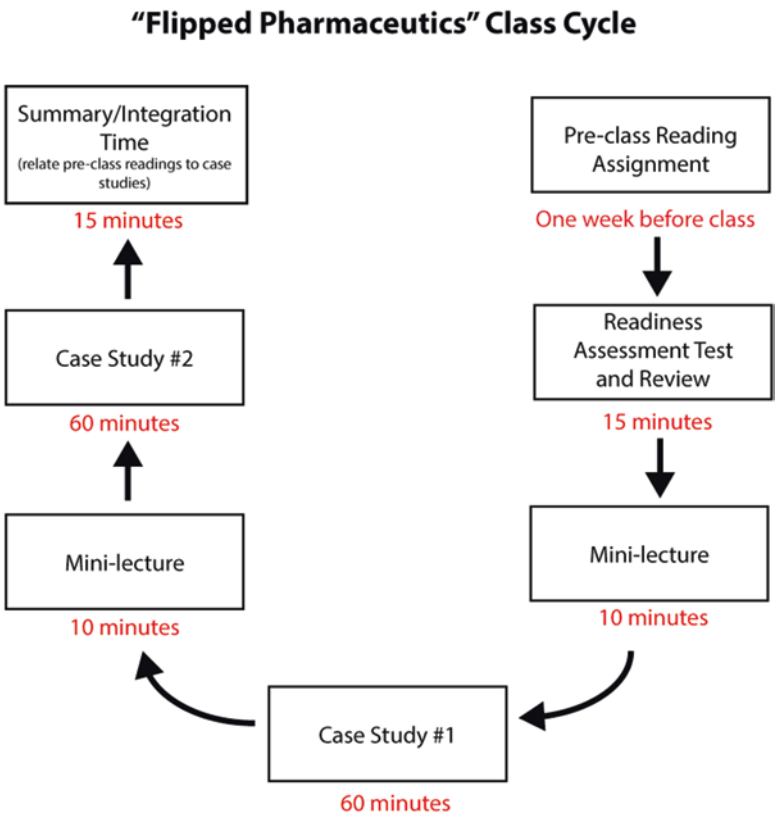

Fig. 1.2 Cycle of a typical flipped pharmaceutics class

Orange Book, Google Patents). At this point, students are introduced to the Pharmaceutics Web Portal, which consolidates these various drug product resources into a student-friendly course guide. Figure 1.2 provides a graphic overview how the typical Flipped Pharmaceutics class is conducted after this initial introductory session.

One week prior to the class meeting time, students are given a pre-reading assignment consisting of research articles and review papers relevant to the topic of the upcoming case study, as well as one of the chapters provided in the text (corresponding to the module that will be studied in the upcoming class period). A list of relevant papers are included at the end of each chapter of this book to provide examples of possible "pre-reading assignments" for instructors who wish to implement their own flipped classroom model. Additionally, a list of learning objectives are provided to guide at-home study, which are incorporated into each chapter of this text.

At the start of the class, students are given a quiz over the assigned reading assignment, referred to as a "Readiness Assessment Test." These quizzes, which make up a portion of the final course grade, not only ensure that students are motivated to complete the pre-reading assignments but also allow instructors to see which concepts require further review and explanation before starting the case studies. Following the quiz, a mini-lecture is typically given to students to provide context to the products featured in the case studies.

The teams then begin work on the product case study, which is provided in the form of a structured worksheet, typically with 12–13 questions covering various aspects of the drug product design and key pharmaceutical concepts. During the course of the case study, instructors meet individually with teams to provide guidance with areas of difficulty. Structured breaks are taken to review concepts with the entire class. During these breaks, teams are regularly called upon to provide answers to questions regarding their drug product design assignments. Finally, drug product design assignment questions are formatted to emphasize keywords that may be helpful for students when optimizing search strategies. As the semester progresses, this format is dropped to allow students to determine their own keywords.

1.5 Flipped Pharmaceutics: A Pathway to Success

The first PharmD cohort to participate in our flipped classroom model graduated in 2017. North American Pharmacist Licensure Examination (NAPLEX) first-time attempt past rate for UTCoP that year was 95.16%, compared to a national average of 87.95%. We have worked to improve our course each year it is taught, and this is reflected in the 2018 first attempt NAPLEX pass rate for UTCoP, which was 97.30%.

In addition to providing a solid foundation for prospective clinical pharmacists, we have also had great success in utilizing our course to teach first-year PhD students in the University of Texas at Austin's Molecular Pharmaceutics and Drug Delivery program. Our students have reported that the integration of information literacy skill building in the course has improved their confidence and performance in effectively and efficiently solving patient health-related and pharmaceutics-related problems.

Application of the flipped classroom model to the subject of pharmaceutics has been demonstrated to promote the development of the necessary skills to achieve student success in the classroom and beyond. We hope that through this foundational text and corresponding online materials, similar success can be obtained in pharmaceutical programs around the world.

Further Reading

Suggested readings for the student include the following texts:

1. Herreid CF, Schiller NA. Case studies and the flipped classroom. J Coll Sci Teach. 2013;42(5):62–6.
2. Schwartzstein RM, Roberts DH. Saying goodbye to lectures in medical school—paradigm shift or passing fad? N Engl J Med. 2017;377(7):605–7.

Chapter 2
Preformulation in Drug Product Design

Abstract This chapter provides an overview of the factors that are considered in dosage form design, including physicochemical properties of drugs, drug solubility and dissolution, drug bioavailability, membrane permeability, and solid-state characteristics. Commonly performed preformulation studies including dissolution testing, X-ray diffraction, thermogravimetric analysis, differential scanning calorimetry, particle size analysis and drug degradation testing are discussed.

Keywords Preformulation studies · Physicochemical properties · Dosage-form design · Bioavailability · Biopharmaceutics Classification System · Solid-state characterization · Drug stability

Learning Objectives

- Describe the factors that are considered in dosage form design.
- Describe the physical and chemical properties of drugs that are characterized during preformulation studies.
- Explain the importance of solubility to the therapeutic effect of a drug.
- Explain the relationship between drug ionization and drug bioavailability.
- Describe what factors affect the dissolution rate of a drug.
- Describe the importance of the partition coefficient for the distribution of a drug in the body.
- Describe the factors that affect the membrane permeability of a drug.
- Compare and contrast BCS Class 1, 2, 3, and 4.
- Compare and contrast crystalline and amorphous forms of solids.
- Explain the importance of determining if a drug displays polymorphism.
- Describe the different analytical methods used to identify amorphous and crystalline morphologies.
- Explain the importance of melting point in pharmaceutical product development.
- Explain the concept of particle size distribution.
- Explain the relationship between particle size and dissolution.
- Describe the different methods of particle size reduction.

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- Describe the common mechanisms of drug degradation and how they are prevented.
- Explain how hygroscopicity can affect a drug product.
- Describe the rationale for utilizing prodrugs.

Key Concepts

Students should know and be able to describe each of the following concepts as they review this chapter:

- Preformulation studies
- Amorphous
- Bioavailability
- Bulk density
- Chemical stability
- Crystalline
- Differential scanning calorimetry (DSC)
- Diffusion
- Dissociation constant
- Dissolution
- Donor and receptor compartments
- Dynamic vapor sorption (DVS)
- Epimerization
- Eutectic
- Excipients
- Extrinsic property
- Fick's first law
- Gibbs free energy
- Glass transition temperature
- High-performance liquid chromatography (HPLC)
- Hydrolysis
- Hygroscopicity
- Intrinsic property
- Ionization
- Lipophilic/hydrophilic
- Median diameter
- Melting point
- Membrane permeability
- Microbiological stability
- Noyes–Whitney equation
- Oxidation
- Partition coefficient
- Phase transitions
- Photolysis
- Physical stability
- Physicochemical properties
- pK_a

- Polymorph
- Preformulation studies
- Prodrug
- Relative humidity
- Saturated solution
- Solubility
- Solvate/pseudopolymorph
- Stereoisomer
- Supersaturated solution
- Tapped density
- Thermogravimetric analysis (TGA)
- Volume-weighted distribution
- X-ray diffraction (XRD)
- Zwitterion

2.1 Introduction: Importance of Preformulation Studies in Dosage Form Design

The study of pharmaceutics is centered on the development and manufacturing of dosage forms for the acceptable delivery of therapeutic agents. Dosage form design is based upon many factors including but not limited to:

(a) The therapeutic indication for the drug
(b) The age of the intended patient
(c) The bioavailability of the drug
(d) Stability and physicochemical properties of the drug
(e) Anticipated adverse drug effects

The decisions made about the design of a particular dosage form are guided by the information obtained about the drug through preformulation studies, which refer to characterization studies on and determination of the physical and chemical properties (i.e., physicochemical properties) of a drug (i.e., drug substance, active pharmaceutical ingredient). Preformulation studies are performed prior to designing a dosage form. The physicochemical properties of the drug substance include properties such as:

(a) Solubility
(b) Dissociation constant
(c) Partition coefficient
(d) Crystalline state
(e) Melting point
(f) Stability

To achieve the desired therapeutic effect, it may be necessary to overcome the limitations of a drug through various formulation and processing techniques and/or inclusion of specific functional excipients. **Excipients** are defined by the FDA as any ingredient other than the drug substance contained in the dosage form and are typically presumed to exert no therapeutic effect. Characterization of the drug in combination with excipients is often performed as a part of preformulation studies.

By determining the physicochemical characteristics of a drug, the pharmacist/formulation scientist can better understand the most suitable approaches to develop the drug into a pharmaceutical dosage form, including which excipients are needed, which excipients will be compatible with the drug, and which dosage form is best utilized. Physicochemical characterization of the drug may also allow for the approximation of drug absorption.

2.2 Preformulation Studies: Factors Affecting Drug Bioavailability

Bioavailability is defined by the FDA as the rate and extent to which the active drug ingredient is absorbed from a drug product and becomes available at the site of drug action. Several physicochemical characteristics of a drug can influence bioavailability, including solubility, the dissociation constant, dissolution, partition coefficient and membrane permeability.

2.2.1 Solubility

Solubility is defined as the concentration of solute (e.g., drug in this context) that will dissolve to form a saturated solution at a given temperature and pressure. A ***saturated* solution** is defined as a solution in which a thermodynamic equilibrium exists between the dissolved solute and the solid solute phase. Under certain conditions, it is also possible to form a ***supersaturated* solution**, in which the solution contains a greater amount of solute than it contains at its equilibrium solubility (also known as saturated solubility). Solubility is an **intrinsic property,** meaning that its value is inherent to the drug and is dependent on the chemical composition and crystalline structure of the drug. The solubility of a drug in a given solvent depends on the chemical and physical properties of both the drug and the solvent. In general, the rules of solubility follow "like dissolves like." For aqueous solvents, the polarity of a solute as well as its ability to form hydrogen bonds can be key factors affecting the drug's extent of solubility. Solubility can be enhanced in a number of ways, for example, by modifying the drug into a salt or ester form, complexing the drug with an excipient (e.g., a cyclodextrin), or utilizing a co-solvent (e.g., ethanol, propylene glycol) in the formulation.

Table 2.1 USP descriptive solubility terms

Descriptive term	Parts of solvent required for one part of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble	10,000 and over

Solubility is typically determined by adding an excess amount of solid drug to a liquid and shaking at a constant temperature until the suspension system reaches equilibrium and no more drug effectively dissolves. The solution is then analyzed to determine drug content in solution by separating the dissolved drug from the suspended drug. The United States Pharmacopeia (USP) defines the extent of solubility for drugs in terms of parts of solvent required to dissolve one part of solute, and the USP uses descriptive categories (Table 2.1) based upon parts of solvent required. These descriptors of drug solubility are often included in the prescribing information for pharmaceutical products.

The solubility of a drug is critically important for its therapeutic action. Generally for a drug to exert its pharmacological effect, it must be dissolved in its molecular form so that it can permeate a membrane, interact with a biological pathway, and/or bind to receptors. For example, to permeate the membrane of the gastrointestinal (GI) tract and reach systemic circulation, an orally delivered drug must first dissolve in the gastric or intestinal fluids. A drug that is insoluble in aqueous fluids may have erratic or incomplete absorption. Similarly, drug solubility affects decisions regarding dosage form design and administration route. For example, considering delivery via an intravenous injection, a physiologically safe liquid solvent must be utilized and the volume of the injection may be limited. Overall, determining drug solubility is an important component of preformulation studies, and the formulation and delivery of poorly water soluble drugs is a major challenge in the pharmaceutical industry.

2.2.2 Dissociation Constant (pK_a)

The acid **dissociation constant** (K_a) is defined as the equilibrium point at which half of an ionizable compound (e.g., drug in this context) is unionized and half is ionized. **Ionization** refers to the process of a molecule acquiring a negative or positive charge through gain or loss of electrons. The dissociation constant is commonly expressed as its negative base-10 logarithmic form, **pK_a,** which corresponds to the pH at which the two forms of the molecule, ionized and unionized, are present in equal amounts. The pK_a can be determined by performing a titration of the ionizable substance.

By knowing the pK_a, the extent of ionization of a weak acid (HA) can be determined at a given pH according to the Henderson–Hasselbalch equation:

$$pH = pK_a + \log \frac{[A^-]}{[HA]}$$

Similarly, the extent of ionization of a weak base (B), can be determined according to the following equation:

$$pH = pK_a + \log \frac{[B]}{[BH^+]}$$

The pK_a of a drug can give insight into its potential bioavailability under different conditions, since the ionization state affects both the drug's rate of dissolution and its membrane permeability. Ionized drugs tend to have greater aqueous solubility due to their increased polarity, thus allowing for more rapid dissolution. The unionized form of a drug, which is typically more lipophilic, will generally have greater cell membrane permeability which can enable faster absorption of the drug and onset of therapeutic effect.

Many drugs are weak acids or weak bases. Therefore, the pH of a drug-containing solution will influence the degree of ionization of the drug. For example, the addition of an acid (lowering the pH) to a system containing a weakly basic drug can result in increased concentration of the ionized species of drug, and thus an increase in aqueous solubility. Addition of a base (increasing the pH) to a system containing a weakly basic drug can result in an increased concentration of the unionized species of drug, and thus a decrease in aqueous solubility. The opposite is true for a weakly acidic drug, where increasing the pH results in an increased concentration of the ionized species and therefore an increased solubility.

Some drug molecules are classified as **zwitterions**, which are defined as drug molecules with at least two pK_a values, one of which is acidic (hydrogen donor group) and one of which is basic (hydrogen acceptor group). Depending on the pH of the environment, the molecule may be neutral, negatively, or positively charged, which is important to consider during formulation. An example of a drug that is a zwitterion is ampicillin. Additionally, due to the presence of both an amine ($–NH_2$) and a carboxylic acid ($–CO_2H$) functional group, amino acids are considered zwitterions. The point at which the overall charge of the amino acid is neutral is defined as the isoelectric point.

2.2.3 Dissolution

Dissolution is the time-dependent process of a drug dissolving into a solvent to form a solution. Dissolution is typically the first step in absorption of a drug and is a critical factor in the drug's bioavailability. For drugs that are poorly soluble in

aqueous fluids, dissolution can be the rate limiting step for absorption. While solubility is an intrinsic property of a substance, dissolution is an **extrinsic property**. This means that dissolution can be modified through changes to the drug's particle size distribution, surface characteristics, solid-state, or through inclusion of certain excipients, among other factors.

Dissolution is described mathematically by the **Noyes–Whitney equation**:

$$\frac{dm}{dt} = \frac{DS}{h}\left(C_s - C\right)$$

Where,

m = Mass of solute
t = Time
dm/dt = Mass rate of dissolution
D = Diffusion coefficient of the drug
S = Surface area of the drug
h = Thickness of the diffusion layer
C_s = Saturation solubility of the drug
C = Concentration of the drug in solution at a specific time

The USP describes specific apparatuses (Fig. 2.1) and conditions to be utilized for the testing of drug dissolution (Table 2.2). Dissolution requirements are specified based upon the drug monograph, and whether the drug is in immediate or modified release dosage form (Fig. 2.2).

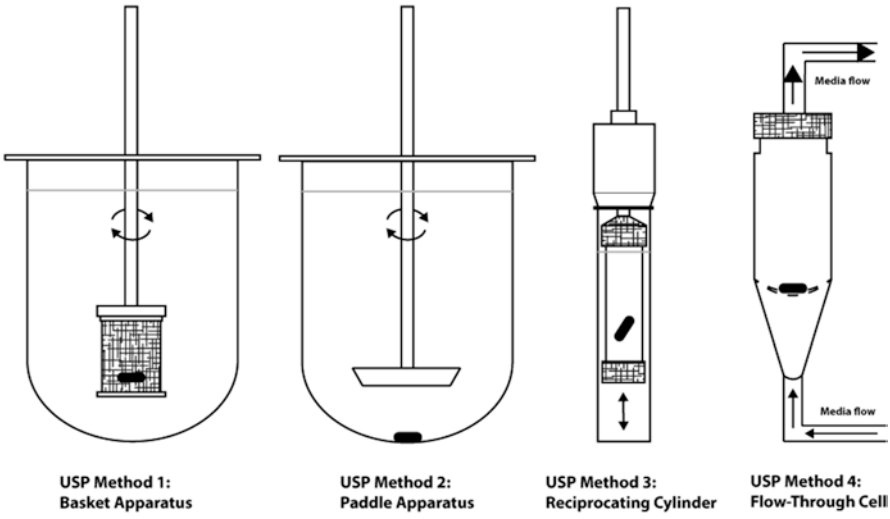

Fig. 2.1 USP Methods 1–4 for dissolution of solid oral dosage forms

Table 2.2 USP dissolution methods

USP method 1: basket apparatus	Unit dose is placed in a basket that rotates which is submerged in the dissolution medium
USP method 2: paddle apparatus	Unit dose is placed in the bottom of the vessel while the paddle rotates above it
USP method 3: reciprocating cylinder	Consists of a set of cylindrical, flat-bottomed glass outer vessels, a set of glass reciprocating inner cylinders, and stainless steel fittings and screens that are designed to fit the tops and bottoms of the reciprocating cylinders. Agitation is programed as dip per minute (dpm)
USP method 4: flow-through cell	Unit dose is placed in a flow-through cell through which the dissolution medium is pumped

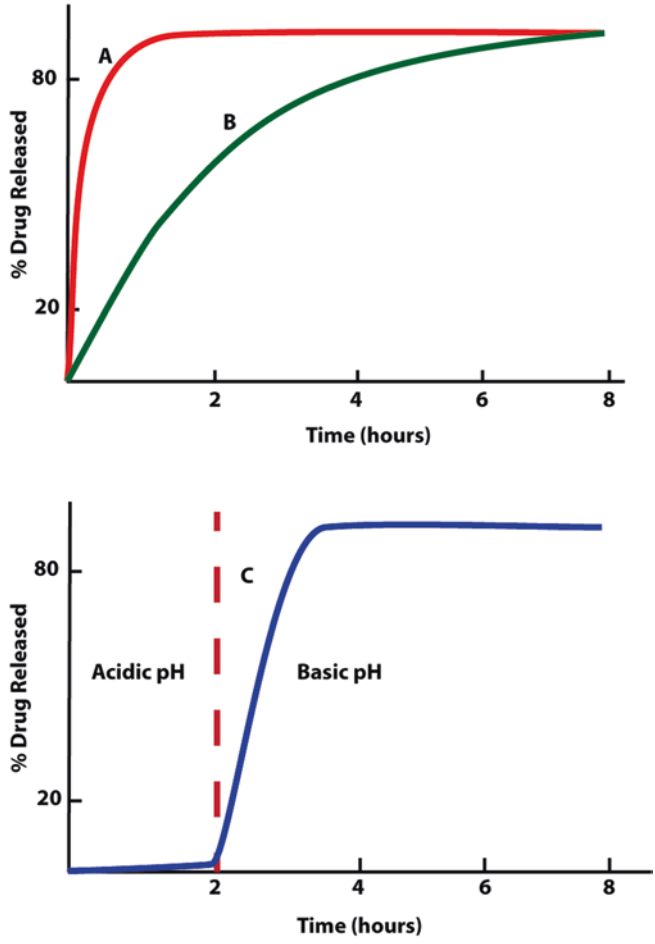

Fig. 2.2 Drug release profiles of hypothetical formulations: (**a**) immediate release, (**b**) extended release, and (**c**) delayed release dosage solid oral dosage forms

2.2.4 Partition Coefficient

The **partition coefficient** is defined as the ratio of concentration of a drug in two immiscible phases (e.g., water and octanol). In the pharmaceutical sciences, the ratio of the solubility of a drug in a nonpolar, lipophilic substance, such as octanol, to the solubility in water is often used. The logarithm of the octanol/water partition coefficient is taken and is reported as $\log P_{o/w}$.

The partition coefficient describes the degree of hydrophilicity and lipophilicity of the drug and provides useful information regarding distribution of the drug in the body and compatibility of the drug with the dosage form. A **lipophilic** drug will have a greater tendency to dissolve in fatty or nonpolar solvents (e.g., octanol) and will generally accumulate in tissues, fat, and intracellularly. A **hydrophilic** drug will have a greater tendency to dissolve in water and may remain in the plasma or blood. Typically a negative value for log*P* indicates that the drug has a higher affinity for the aqueous phase, while a positive log*P* value indicates that the drug has a higher affinity for the fatty or nonpolar phase.

The partition coefficient of a drug can also affect its release from the dosage form. For instance, if a drug with a high $\log P_{o/w}$ (e.g., >3–5) is placed in a fat-based suppository vehicle, it will tend to remain in the dosage form rather than diffuse out into surrounding aqueous fluids in the rectum.

2.2.5 Membrane Permeability

Membrane permeability refers to the ability of a molecule to passively diffuse across a biological membrane. **Diffusion** refers to a process of passive movement of molecules, generally from an area of higher concentration to lower concentration.

For a drug to exert systemic activity, it must be able to cross the biological membranes. The ability of a drug to cross the membrane is dependent upon its degree of ionization, partition coefficient, and molecular size. Lipophilic drugs can typically passively diffuse across cell membranes, but it is more difficult for drugs that are insoluble in lipids to diffuse across. As such, membrane permeability is often the rate-limiting step for the absorption of ionized water-soluble drugs.

Fick's first law explains diffusion in a steady-state system as well as the diffusion of a drug from a dosage form.

$$J = D\left[\left(C_1 - C_2\right)/h\right]$$

Where,

J = The diffusion flux (the amount of a substance that will diffuse through a unit area in a unit time).

C_1 and C_2 = The concentrations of the donor and recipient compartments. The **donor compartment** refers to the region of higher drug concentration, while the **recipient compartment** refers to the area of lower drug concentration.

h = The membrane thickness.

D = The diffusion coefficient. The diffusion coefficient may be influenced by increased concentrations of the drug, which drives the system to re-establish equilibrium by increasing diffusion to the compartment with a lower concentration of drug. The temperature and pressure of the system as well as the solvent can also influence the diffusion coefficient.

2.2.6 Biopharmaceutics Classification System (BCS)

The Biopharmaceutics Classification System (BCS) is used to characterize the absorption of a drug based on its solubility and permeability. There are four BCS classes, shown in Table 2.3:

Categorizing a drug into one of the BCS classes can help guide decisions on the drug administration route and dosage form design. The solubility and permeability of a drug are determined experimentally during the preformulation studies.

2.3 Preformulation Studies: Solid-State Characterization

Many dosage forms utilize the solid form of a drug, which necessitates thorough characterization of the solid state as part of the preformulation studies for the drug. Solid-state characteristics such as crystalline form, powder behavior, and particle size have an effect on the dissolution, solubility, and stability of a drug and can thus help guide formulation decisions.

Table 2.3 Biopharmaceutics classification system

BCS Class I High solubility High permeability	**BCS Class II** Low solubility High permeability
BCS Class III High solubility Low permeability	**BCS Class IV** Low solubility Low permeability

A drug substance is considered HIGHLY SOLUBLE when the highest dose strength is soluble in <250 mL of water over a pH range of 1–7.5

A drug substance is considered HIGHLY PERMEABLE when the extent of absorption in humans is determined to be >90% of an administered dose, based on mass balance or in comparison to an intravenous reference dose

A drug product is considered to be RAPIDLY DISSOLVING when >85% of the labeled amount of drug substance dissolves within 30 min using USP apparatus I or II in a volume of <900 mL buffer solutions

2.3.1 Organoleptic Properties

An important aspect of solid-state characterization includes organoleptic properties of the drug substance and proposed dosage form. **Organoleptic properties** consist of color, odor, and taste. "Color" suggested terminology includes off-white, cream, yellow, tan, or shiny, "odor" suggested terminology includes pungent, sulfurous, fruity, aromatic, or odorless, and "taste" suggested terminology includes acidic, bitter, bland, intense, sweet, or tasteless.

2.3.2 Amorphous and Crystalline Morphology

The solid form of a drug may be structured as crystalline or amorphous form. **Crystalline** describes structural order of molecules in a solid, while **amorphous** describes a solid that has no long-range structure or distinguishable crystalline lattice (e.g., disordered) (Fig. 2.3). Crystalline solids have a defined melting point while amorphous solids do not. Instead, amorphous solids undergo a transition from a hard, glassy state into a rubbery state. The temperature at which this transition happens is called the **glass transition temperature (T_g)**.

A **polymorph** refers to a solid that is capable of existing in more than one crystalline form. The FDA includes in its definition of a polymorph the crystalline and amorphous forms of the drug, as well as solvate and hydrate forms. One or more polymorphs of a drug will be typically more stable than the other polymorphic

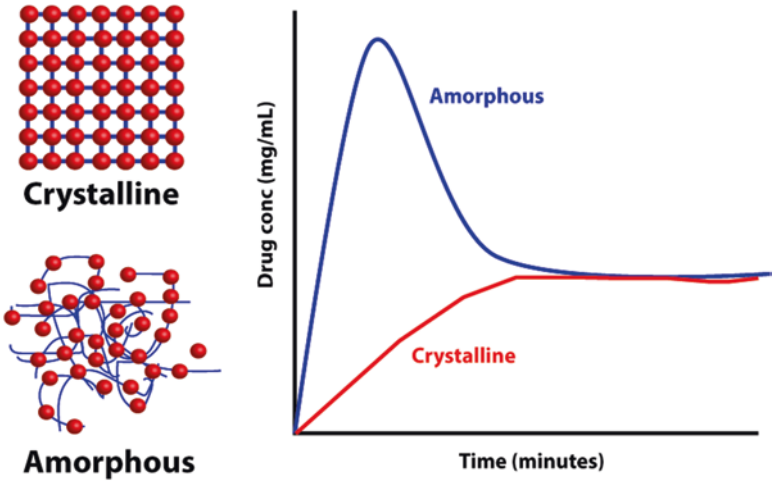

Fig. 2.3 The molecules that make up a crystal are arranged in a structured order. In contrast, the molecules of amorphous solids exist in a disordered state. As a result of this disorder, amorphous solids have higher thermodynamic energy and exhibit an increased dissolution extent and propensity toward a supersaturated solubility state compared to crystalline solids

forms. This is determined by the thermodynamic quantity of **Gibbs free energy**. A polymorph with lower Gibbs free energy will be more stable than a polymorph with a higher Gibbs free energy, which will have a thermodynamic tendency to transform over time to the polymorph with the lower Gibbs free energy. If only one thermodynamically stable polymorph is formed at normal pressure, the polymorph system is defined as being monotropic. A system that has several thermodynamically stable polymorphs is termed an enantiotropic system.

Polymorphs often have different physical properties such as solubility and melting point. Because these properties are so important in pharmaceutical dosage form design and development, it is essential to identify and define the potential polymorphs of a drug molecule.

Formation of polymorphs may occur as a result of many factors such as processing conditions, impurities in the drug substance, or level of supersaturation during crystallization. During storage, the transition of one polymorph to another may render the pharmaceutical product chemically or physically unstable. Because of this, it is often best to choose the polymorph that appears most thermodynamically stable, in order to avoid this transitioning.

Solvates, which are sometimes referred to as pseudopolymorphs, consist of solvent molecules complexed into the crystalline structure of the drug. Hydrates specifically refer to the case in which water is complexed within the crystalline structure. Solvates are sometimes formed during the processing of the drug formulation. The formation of a solvate may lead to changes in the physicochemical properties of the drug.

Because manufacturing processes can induce changes in crystalline morphology, it is important to determine the presence of amorphous regions or polymorph transitions. Typical analytical approaches used in the identification of amorphous and crystalline morphologies include:

(a) X-Ray diffraction (XRD)
(b) Thermogravimetric analysis (TGA)
(c) Differential scanning calorimetry (DSC)

2.3.2.1 X-Ray Diffraction (XRD)

XRD is an analytical method primarily used to determine crystallinity of a drug. A material is exposed to a source of X-rays, and the diffraction of the X-rays by the material can be detected. The manner in which a solid substance diffracts X-rays is dependent upon its crystalline structure. Each crystalline form of a compound has a unique diffraction pattern, making XRD a powerful tool for the analysis of crystalline morphology. Crystalline materials typically exhibit clearly defined diffraction patterns with recognizable peaks, while amorphous materials typically exhibit a more diffuse pattern that lacks clearly defined peaks, which is sometimes referred to as a “halo” (Fig. 2.4).

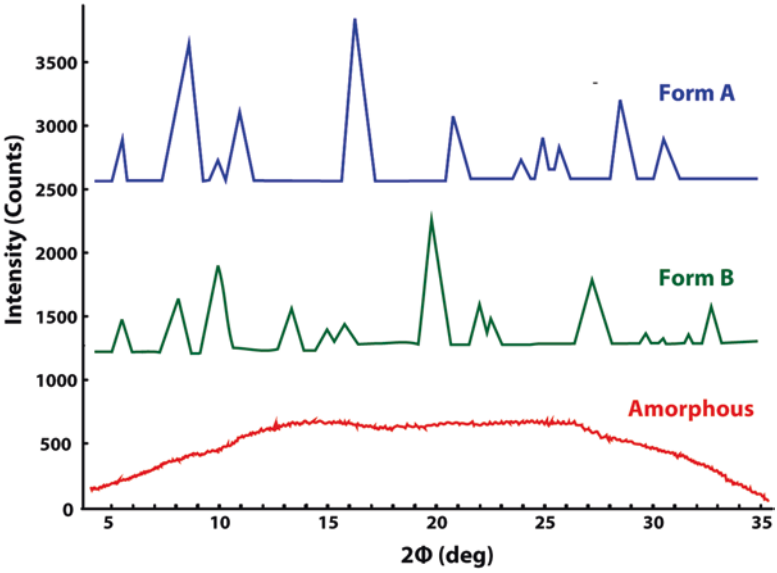

Fig. 2.4 XRD patterns of different polymorphs (forms **a** and **b**) of a hypothetical drug and its amorphous form. XRD provides insight into the crystallinity of a substance as each crystalline phase of a substance will produce a characteristic XRD pattern

2.3.2.2 Thermogravimetric Analysis (TGA)

TGA measures the amount and rate of weight change in a material, either as a function of increasing temperature or at a constant temperature as a function of time (isothermal), in a controlled atmosphere. TGA is used to assess for the presence of solvates or hydrates, provide information on dehydration and to monitor drug decomposition events, thereby gaining insight into a drug stability (Fig. 2.5).

2.3.2.3 Differential Scanning Calorimetry (DSC)

DSC is a type of thermal analysis technique that is used to measure the **phase transitions** (e.g., solid to liquid or liquid to gas) and other physicochemical characteristics that are associated with heat transfer within the drug substance or drug product. DSC can be used to evaluate the purity of a compound, crystalline state, presence of polymorphs, Tg, melting point, or the existence of amorphous morphology. In DSC, the sample is heated over a range of temperatures while measuring the heat flow into the sample and comparing this to a blank reference (Fig. 2.6).

The **melting point or melting temperature** is defined as the temperature at which a crystalline solid exists in equilibrium between the liquid and solid phases. Heat of fusion is the heat required to increase the distance of the intermolecular

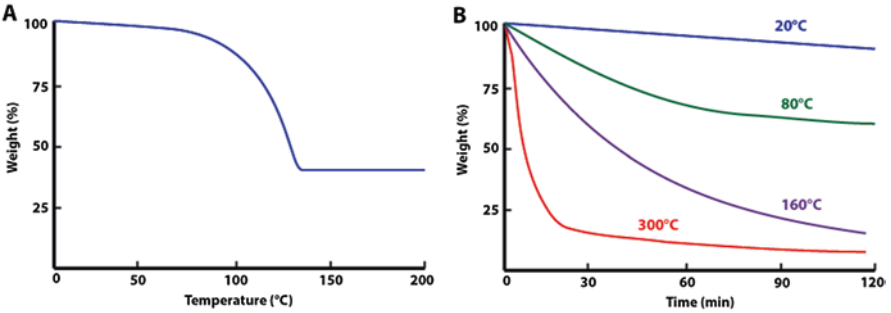

Fig. 2.5 (**a**) A thermogravimetric thermogram of a hypothetical hydrate. As the temperature is increased, the change in weight represents removal of the solvent from the crystalline lattice. TGA can provide insight into the stability of solvates/hydrates and can be used to find the ratio of solvate to host molecule. (**b**) Isothermal thermograms of a hypothetical crystal form at different temperatures. The decrease in weight in the higher temperature thermograms is indicative of decomposition of the drug. TGA can be used to determine the thermal stability of a crystal form

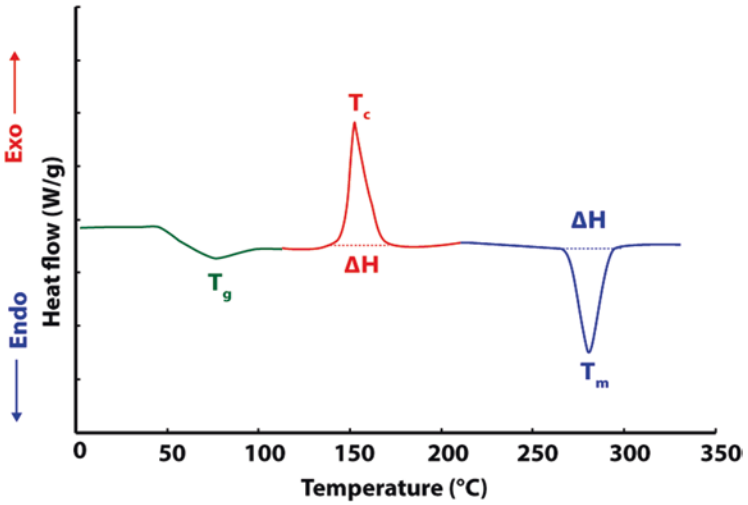

Fig. 2.6 DSC scan of a hypothetical compound. T_g glass transition temperature, T_c re-crystallization temperature, and T_m melting endotherm temperature

forces between molecules of the crystal to the extent that melting will occur. Melting point is extensively used for:

(a) Identifying polymorphs. Because polymorphs have different molecular arrangements, they will require varying amounts of heat for melting to occur and will thus have different melting points.

(b) Determining the purity of a drug substance.
(c) Assessing compatibility with other excipients. Mixing a drug with an excipient may cause changes in melting point to occur.
(d) Manufacturing decisions: for example, a compound with too low of a melting point may soften upon exposure to heat produced during processing.

In some cases, the mixing of two or more drugs together results in the mixture melting at a lower temperature than either drug alone would melt. This is referred to as a **eutectic mixture** and is a useful technique in the formulation of drugs.

2.3.3 Particle and Powder Characteristics

Particle and powder characteristics of a drug that are commonly analyzed as part of preformulation studies include:

(a) Particle shape
(b) Surface energy
(c) Surface area
(d) Bulk density
(e) Tapped density
(f) Hygroscopicity

All of these characteristics can affect:

1. Powder flow, which is often important during manufacturing of the drug product
2. Dissolution of a drug
3. Stability of the drug formulation over time

For example, the shape of a particle can affect how well it will flow through manufacturing machinery, with smooth, spherical particles often flowing easier than needle-shaped particles. The surface area of a particle will affect dissolution, with a larger surface area particle often exhibiting more rapid dissolution than a particle with a smaller surface area. The shape and surface characteristics of particles are typically identified using microscopy such as scanning electron microscopy (SEM) (Fig. 2.7).

Powder density also provides a measure of powder flow. This is assessed by comparing the bulk density of a powder sample to its tapped density. The **bulk density** of a powder is the ratio of the mass of an untapped powder sample and its volume. **Tapped density** of a powder is the ratio of the mass of a tapped powder sample and its volume. Typically, bulk and tapped density are expressed in g/mL.

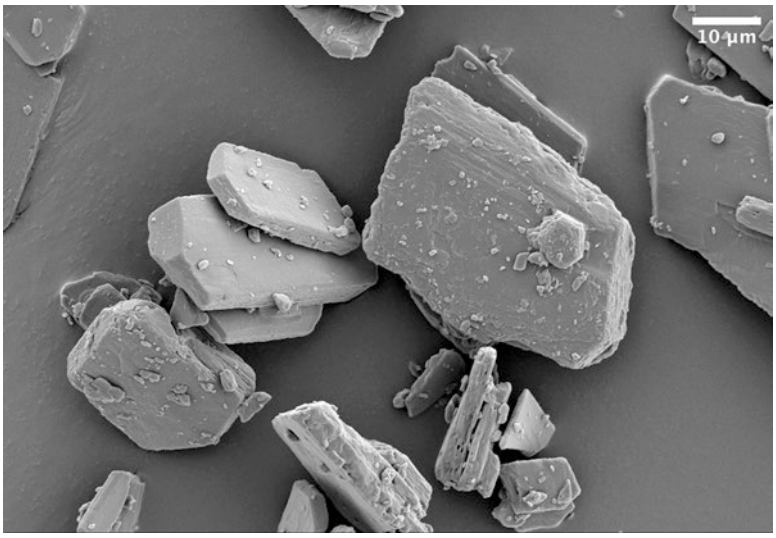

Fig. 2.7 An exemplary scanning electron micrograph. Scanning electron microscopy allows for analysis of particle surface characteristics

2.3.4 Particle Size and Distribution

The particle size is defined as the dimensions of a particle and is commonly reported as the particle size distribution (PSD), which describes the amount of each size of particle present in the population. Particle size measurements are conducted using techniques such as laser diffraction, microscopy, and sieving. Each technique will measure a different type of size depending on the principle of size classification. The PSD is commonly reported in terms of D_{10} (referring to the diameter at which 10% of the particles are smaller than this diameter), the D_{50}, or **median diameter** (referring to the diameter at which 50% of the particles are smaller than this diameter), and the D_{90} (referring to the diameter at which 90% of the particles are smaller than this diameter). When measured using laser diffraction, the PSD is typically reported as a **volume-weighted distribution**, where the particles with a larger volume are given a greater weight in the distribution.

Particle size can have important effects on:

(a) Drug stability
(b) Drug solubility
(c) The delivery routes of administration that may be considered

For instance, particle size can affect how well a drug or excipient may be suspended in a liquid formulation, and whether or not a drug is in the respirable size range for inhalation to the lungs. Particle size reduction is sometimes used to increase dissolution rates, enhance drug absorption, and aid in the formulation of pharmaceutically acceptable dosage forms. However, with decreasing size, particles

may become more cohesive due to higher surface areas, leading to difficulty with powder flow during the manufacturing process.

Micronization refers to the reduction of particle size into the micron range. Methods for reducing particle size include grinding with a mortar and pestle, milling, or high pressure homogenization. While the mortar and pestle is the method typically used in most pharmacies, milling and high pressure homogenization can be scaled up to the industrial setting.

2.4 Formulation Stability

Drug product stability is a major concern for the practicing pharmacist and formulation scientist, as it has a direct effect on patient safety and therapeutic efficacy. Instability or degradation of the drug product can lead to:

(a) Deviations from the labeled potency
(b) Reduction in therapeutic effect
(c) Creation of toxic byproducts

The stability of a drug may be defined in terms of physical stability, chemical stability, or microbiological stability. **Physical stability** refers to the many properties of the drug and formulation such as preservation of the drug product's physical appearance, particle size, disintegration rate, solubility, viscosity, and palatability (taste and odor); and crystalline form, meaning that the drug does not undergo transformation to another polymorph or solvate, or re-crystallizes from an amorphous state. **Microbiological stability** refers to the maintenance of sterility or resistance to microbial growth over time. Microbial stability must be considered for injectable and ophthalmic dosage forms to ensure patient safety. The FDA has specific guidelines relating to microbiological testing requirements. **Chemical stability** of the drug or drug product refers to the tendency of the drug to chemically degrade when exposed to catalysts such as water, light, oxygen, or varying pH.

The drug and byproducts of drug degradation (i.e., degradation products) are typically identified using **high-performance liquid chromatography (HPLC)** which is an analytical technique used to separate, identify, and quantify components in a mixture based upon their differing affinity for a solid adsorbent versus a solvent mobile phase. Typically the separated compounds are then identified and quantified by their UV absorbance at a specific wavelength. The output of HPLC analysis is often represented as a chromatogram (Fig. 2.8). The individual components in the mixture injected into the HPLC are identified on the chromatogram using the retention time of the peak, which represents the time at which the substance eluted from the solid adsorbent into the mobile phase. The area or the height of the peak is used to identify the amount of a component present in the mixture based upon Beer–Lambert's Law, which relates the concentration of a compound to the amount of UV absorption.

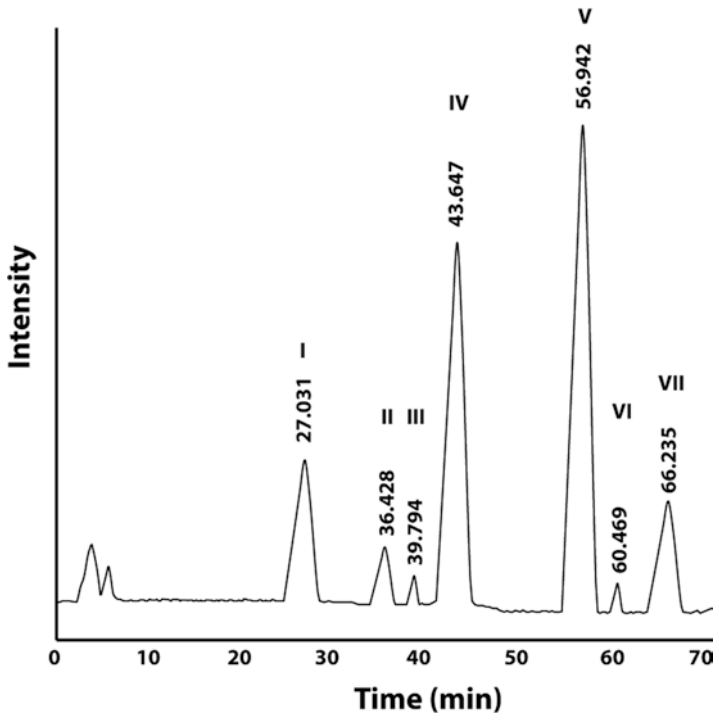

Fig. 2.8 HPLC chromatogram of a hypothetical formulation. Chromatograms can be used to determine the presence of degradation products by comparing with a reference standard and to identify the components of a mixture based upon their retention times

2.4.1 Degradation by Hydrolysis

Hydrolysis occurs when a drug molecule interacts with water and breaks down. Functional groups that are susceptible to hydrolysis (Fig. 2.9) include:

(a) Esters
(b) Substituted amides
(c) Lactones and lactams

A susceptible drug may be at risk for hydrolysis if an aqueous solvent is used, but exposure to water may also occur through adsorption of water from the atmosphere onto the solid drug surface. The use of waterproof coatings, desiccants, and/or tightly sealed containers can reduce the risk of hydrolysis, and in some cases an aqueous solvent can be substituted with a non-aqueous solvent such as glycerin, propylene glycol, or alcohol. Refrigeration of the drug product may also reduce hydrolysis.

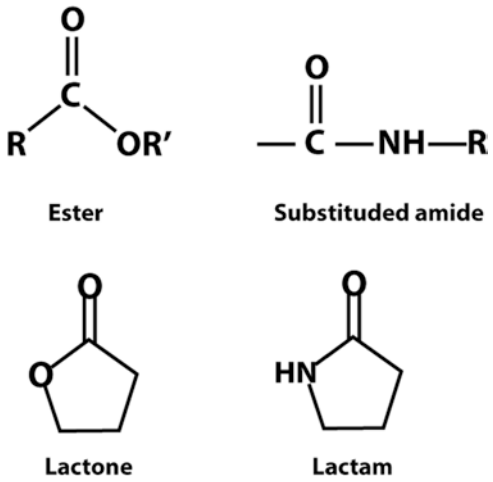

Fig. 2.9 Examples of functional groups susceptible to hydrolysis

2.4.2 Degradation by Oxidation

Oxidation is the process of electron loss. The process may occur through interaction of the drug with atmospheric oxygen and can lead to a loss of therapeutic efficacy. Groups susceptible to oxidation (Fig. 2.10) include:

(a) Aldehydes
(b) Alcohols
(c) Phenols
(d) Sugars
(e) Unsaturated fats

Oxidation can sometimes be prevented by including in the formulation antioxidants such as ascorbic acid.

2.4.3 pH-Dependent Degradation

Variations in the pH of a drug formulation may lead to loss of stability or precipitation of the drug, particularly in the case of ionized acidic or basic drugs in solution. Buffering agents such as acetates, citrates, or phosphates may be included in the formulation to reduce changes in pH.

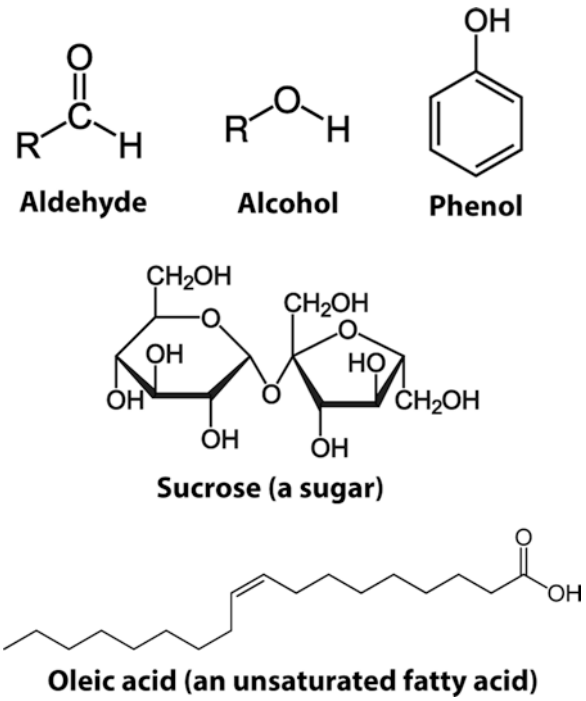

Fig. 2.10 Examples of molecules susceptible to oxidation

2.4.4 Degradation by Photolysis

Photolysis is a process of degradation catalyzed by absorption of light in the UV range. Drugs that are susceptible to photolysis should be packaged in suitable packaging such as amber bottles in order to reduce the exposure to light.

2.4.5 Hygroscopicity

Hygroscopicity refers to the tendency of a substance to take up water from the atmosphere at varying relative humidity. **Relative humidity (RH)** is a term used to describe the amount of water vapor in a mixture of water vapor and air. Water vapor may be adsorbed onto the surface of the drug particle, absorbed into the solid, or liquefy onto the surface of the drug and lead to dissolution of the drug.

The extent of hygroscopicity can be used to identify an acceptably stable crystalline or salt form of a drug. If a salt form is moderately or very hygroscopic (e.g., increases in mass by more than 15% when stored at 25 °C/80% relative humidity

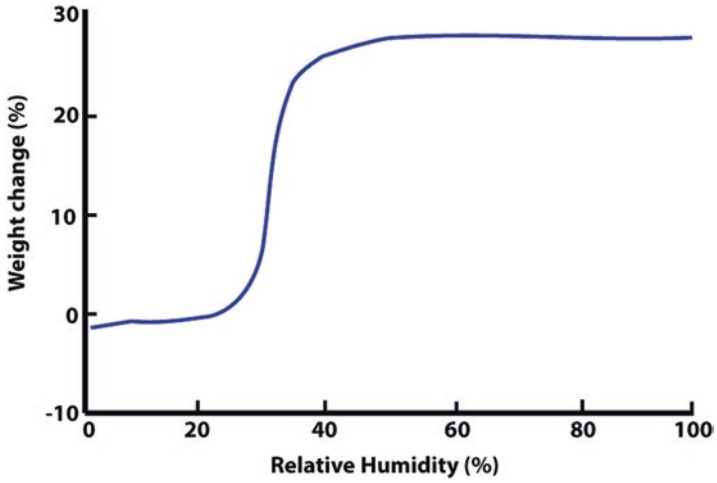

Fig. 2.11 DVS profiles for a hypothetical compound. The rapid weight change seen in the profile is indicative of formation of a hydrate

for 24 h), it may be less suitable as a candidate for development into a pharmaceutical product. Likewise, different polymorphic forms of a drug will often have different moisture sorption and desorption profiles. The tendency for water vapor sorption is used to guide excipient selection and determine the need for special packaging such as foil blisters and inclusion of desiccants to prevent uptake of moisture. Other factors affected by hygroscopicity include powder flow, compaction, lubricity, dissolution rate, and polymer film permeability. Additionally, if encapsulated (i.e., enclosed within a capsule), a hygroscopic drug may absorb water from a capsule shell, causing the capsule to become brittle and break.

The extent of hygroscopicity can be assessed using **dynamic vapor sorption (DVS)**. In DVS, the relative humidity is cycled between low and high levels. The changes in the weight of the substance are assessed as a function of the relative humidity. While gradual weight change that reverses with desorption (release) of water indicates a stable, highly crystalline product, sharp weight changes with changing humidity suggest formation of a hydrate (Fig. 2.11). For these substances, careful processing and storage are needed to ensure long-term stability.

2.4.6 Epimerization

Epimerization is the process by which an epimer (one of a pair of stereoisomers) is transformed into its counterpart. This process is considered degradation in cases in which the action of a drug on a receptor is stereoselective. Epimerization may occur spontaneously or through catalyzation by an enzyme.

2.5 Other Considerations in Preformulation Studies

Other important considerations in preformulation include determining the necessity of a prodrug and determining the stereoselectivity of the drug's effects.

2.5.1 Prodrugs

Prodrugs are chemically modified versions of pharmacologically active molecules that undergo transformation in the body to reveal the active form of the drug. Prodrugs are typically pharmacologically inactive until this transformation occurs. They may be used in order to overcome barriers such as poor aqueous solubility, rapid metabolism, chemical instability, poor blood–brain barrier penetration, and irritating effects on tissue.

2.5.2 Stereoisomers

Stereoisomers are molecules that have identical atomic composition and bonding but exhibit differing three-dimensional arrangement of their atoms. Enantiomers are subcategory of stereoisomers that are mirror images of each other, but nonsuperimposable (similar to your right and left hand). This property is referred to as chirality. Stereoisomers can differ in their distribution in the body as well as their pharmacological activity based upon differences in protein binding and receptor interaction. Based upon this, some drug products have been developed using only a single enantiomer in an effort to enhance efficacy or reduce adverse effects. An example of this is the proton pump inhibitor, esomeprazole, which is the S enantiomer of omeprazole.

Further Reading

Suggested readings for the student include the following texts:

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Chapter 3
Capsule and Tablet Dosage Forms

Abstract This chapter provides an overview of the design, manufacturing, and formulation of capsule and tablet-based drug products. Manufacturing methods for producing both capsules and tablets are extensively discussed, and figures are incorporated to aid student understanding. Frequently used excipient categories are provided along with general functions and examples. A review of USP-recommended analytical tests is also included. Lastly, this chapter introduces techniques for formulating poorly water soluble drugs in capsule and tablet dosage forms.

Keywords Capsule · Tablet · Amorphous solid dispersion · Film-coating · Tablet manufacturing · Pharmaceutical excipients · Poorly water soluble · Pharmaceutical analysis · Analytical methods

Learning Objectives

- Describe a capsule dosage form and list its advantages.
- Describe how moisture and humidity are important factors affecting the stability of hard gelatin capsules.
- Describe the solubility properties of gelatin as it relates to oral administration of a capsule dosage form.
- Describe the types of formulations utilized in hard gelatin capsules versus soft gelatin capsules.
- Describe the manufacturing process for capsules.
- Describe the different manufacturing processes for tablets.
- Explain the advantages of coating tablets.
- Describe the typical excipient categories utilized in tablet dosage forms and the function of each of these categories.
- Describe the different analytical tests used to insure tablet and capsule product integrity.
- Describe methods for overcoming poorly-water soluble drugs in tablet formulation.
- Explain the concept of spring and parachute in amorphous solid dispersions.

A. D. Brunaugh et al., *Essential Pharmaceutics*, AAPS Introductions in the Pharmaceutical Sciences, https://doi.org/10.1007/978-3-030-31745-4_3

- Understand how food may affect the absorption of drugs from the gastrointestinal tract.

Key Concepts
Students should know and be able to describe each of the following concepts as they review this chapter:

- Amorphous solid dispersion
- Anti-tacking agent
- BCS Class II
- Binder
- Capsule
- Colorant
- Content uniformity
- Cracking (tablet coating)
- Crystalline solid dispersion
- Diluent
- Disintegrant
- Disintegration
- Drug monograph
- Dry granulation
- Film coating
- Film coating polymer
- Food effect
- Friability
- Gelatin
- Glidant
- Granule
- Hopper
- Hot melt extrusion
- Immediate release
- Lubricant
- Modified release
- Opacifier
- Peeling (tablet coating)
- Plasticizer
- Polymer
- Roller compaction
- Sieve
- Slug
- Solid dispersions
- Spray drying
- Spring and parachute
- Surface active agent (surfactant)
- Tablet
- Mottling (tablet coating)

- Orange peel (tablet coating)
- Picking (tablet coating)
- Tablet ejection
- Tablet punch
- Tableting die
- United States Pharmacopeia (USP)
- Wet granulation

3.1 Introduction

Capsules and tablets are among the most widely used solid oral dosage forms. They provide a convenient and safe way for patients to self-administer therapeutic agents. Capsules and tablets can be manufactured to release drug immediately, or they may include excipients or technologies that modify the release profiles of the drug.

3.2 Capsules

A **capsule** dosage form is composed of an edible shell (typically gelatin or cellulose) that contains a blend of one or more drugs and excipients, which may be in solid or liquid form. Capsules may be classified as hard or soft shell (Fig. 3.1). Some advantages of capsules include:

(a) Easy to swallow
(b) Patient-friendly, elegant appearance
(c) Minimal stress on the materials during processing and manufacturing

3.2.1 Hard Shell Capsules

Hard shell capsules consist of two interconnecting rigid, thin shells that contain the drug and excipient composition. Ingredients used for capsule shells should be nontoxic and soluble in order to release drug formulation and should additionally demonstrate resistance to mechanical stress that may be encountered during manufacturing and shipping of the product. Capsules are commonly manufactured from **gelatin** (a protein-based material derived from animal collagen) or hydroxypropyl methylcellulose (HPMC; also known as hypromellose). Both of these materials are **polymers**, meaning that their molecular structure consists of multiple repeating subunits. Gelatin and HPMC are pharmaceutically acceptable materials for capsule shells, as they are edible and soluble at body temperature, but form a thin, strong film capable of withstanding manufacturing stresses at room temperature.

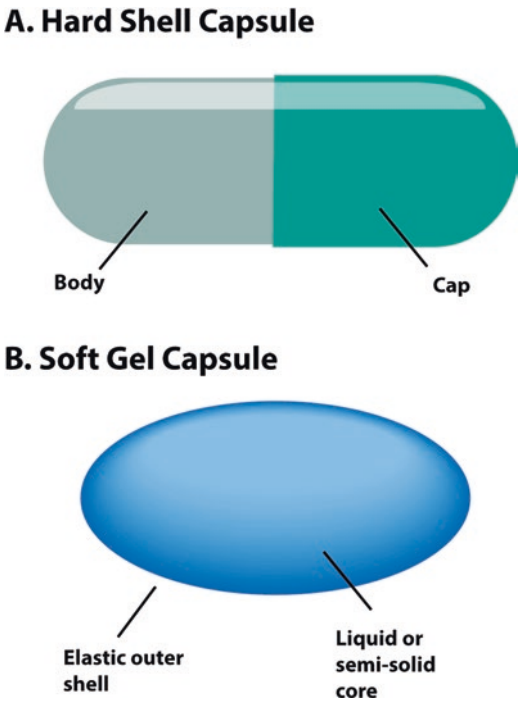

Fig. 3.1 Capsules may be manufactured as hard gel capsules (**a**) or soft gel capsules (**b**)

Hard capsules are manufactured as two separate pieces with the cap being slightly larger to allow for overlap of the pieces when placed together. During the manufacturing process, the shells are created by dipping and removing capsule-shaped pins into a reservoir of melted gelatin or HPMC. Once hardened, the gelatin and HPMC are trimmed and removed from the pins and filled with the formulation, and the capsule body is inserted into the cap. Different designs are available. For example, one type of capsule, the Coni-Snap®, is produced with a tapered rim in the capsule body to help alleviate problems with capsule alignment during high-speed manufacturing.

The flexibility of gelatin shells comes from the presence of water within the gelatin polymer, which acts as a plasticizer. A **plasticizer** is a substance that reduces brittleness and enhances the flexibility of the capsule shell material. Because water is critical to the performance of the gelatin capsule, special considerations must be taken into account when gelatin is utilized as the ingredient for capsule shells. These include:

(a) The occurrence of water loss from the shell over time, which can occur if the capsule is filled with a hygroscopic (water absorbing) material. Because water acts as a plasticizer, its removal can result in the capsule shell becoming more brittle and more easily prone to breakage.

(b) Degradation of the drug, particularly if the drug is moisture-sensitive. Hard gelatin capsule shells are generally avoided for encapsulation of moisture-sensitive compounds.
(c) High-humidity storage conditions, which affects the stability of gelatin capsules by inducing crosslinking of the gelatin molecules during storage and leads to a reduction of the solubility of the capsule shell in water- or aqueous-based liquid. This can affect the release of drug from the dosage form.
(d) Solubility of gelatin. Aqueous-based formulations cannot be incorporated into hard gelatin capsules; however, fixed or volatile oils, or dry powder formulations can be suitably incorporated.

3.2.2 Soft Gel Capsules

The primary difference between hard and soft gel capsules is the addition of a plasticizer, such as glycerin or a polyhydric alcohol (i.e., sorbitol), to the gelatin or cellulose polymer. This results in the creation of a shell with greater elasticity than a hard gelatin capsule. Soft shell capsules are used to encapsulate liquid or semi-solid formulations. They are advantageous in that they may facilitate an increase in the rate of absorption of poorly water soluble drugs if the drug is dissolved within a vehicle/solvent in which they are soluble. For example, a lipophilic drug may be dissolved in an oil, and then this liquid composition encapsulated in a soft gelatin capsule. Some patients may also find them easier to swallow, which can enhance compliance. However, aqueous-based formulations, water-soluble or volatile organic compounds like alcohols, ketones, acids, amines, and esters, should not be manufactured in soft gelatin capsules, as these liquids can migrate through the capsule wall over time.

Soft gelatin capsules are typically manufactured by first melting the gelatin and then incorporating plasticizers and colorants to form a hot gelatin mass. This gelatin mass is formed into two separate ribbons on a rotary die machine (Fig. 3.2), which seals the two ribbons together as they are being filled with the drug formulation.

3.3 Tablets

Tablets are solid dosage forms that contain a dose of one or more active pharmaceutical ingredients, which are formed through compression of powder (in the form of particles and/or granules). They have the advantages of being convenient to administer by patients and can provide greater chemical and physical stability compared to liquid dosage forms. There are many variations of tablets, which are outlined in Table 3.1.

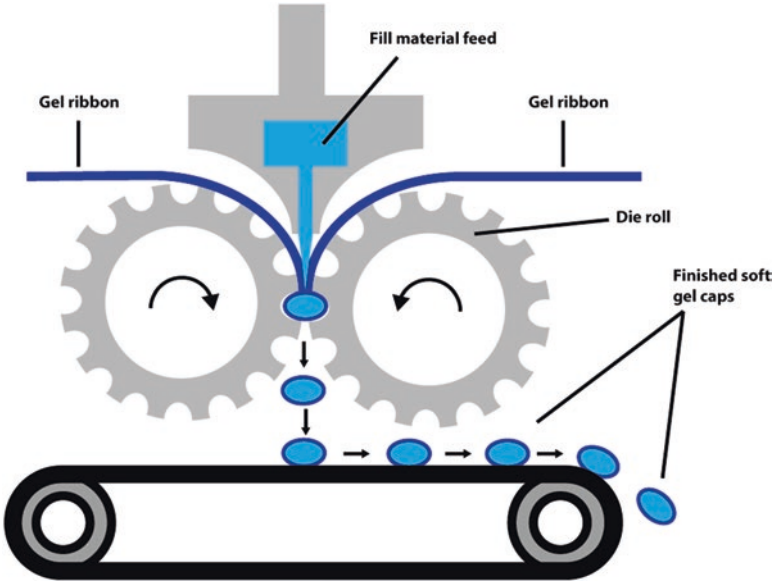

Fig. 3.2 An example of a rotary die machine for the production of soft gel capsules

3.3.1 Manufacturing Methods

Tablets are typically manufactured by a compression process (Fig. 3.3). Tablet compression consists generally of three phases:

1. Filling: The powder formulation (e.g., drug + excipients blended together to form a homogeneous mixture) is stored in a **hopper**, a container that holds the powder and dispenses it through the force of gravity. In the filling stage, the tablet powder is volumetrically filled from the hopper into a **die**, which helps form the size and shape of the tablet.
2. Compression: The die contains a lower **punch**, which compresses the powder held within the die when an upper punch descends into the die.
3. **Ejection:** The upper punch is then removed, allowing the compressed tablet to fall out of the die.

Suitable powder flow is needed from the hopper to the die to ensure reproducible dosing. To improve flow properties, the powder is often granulated prior to compression. A **granule** (Fig. 3.4) is defined as an agglomerate of powder particles that are bound together through compression or by the use of a **binder** (i.e., an excipient that promotes powder cohesiveness and facilitates formation of granules) such that the original particles can still be identified. Granulation can increase the homogeneity and bulk density of the mixture to allow for easier filling into the tablet dies. This is similar to the improved flow properties observed with granulated sugar, compared

Table 3.1 Types of tablets

Type of tablet	Description	Advantages	Other comments
Compressed tablet	Powder or granules of drug combined with excipients, blended, and compacted under pressure	Easier manufacturing	Performance of tablet dependent on specific properties of drug, excipients, dose, etc.
Sugar-coated tablet	Compressed tablet that is subsequently sugar-coated	Provides additional protection of the drug from the environment, masking taste and enhancing appearance	May add up to 50% more weight to tablet and adds additional processing step to manufacture
Film-coated tablet	Compressed tablet that is subsequently coated with a thin layer of polymer-based coating	More durable, less bulky, less time-consuming manufacturing process than sugar coatings	
Gelatin-coated tablet	Compressed tablet with a layer of gelatin-based coating. An example is a gel cap	Facilitates swallowing and provides tamper evident technology	
Enteric-coated tablet	Compressed tablet coated with an enteric coating (e.g., pH dependent; time based)	Allows for delayed release of the drug until the drug passes through the stomach, to prevent degradation of drug by stomach acid or to decrease gastric irritation caused by the drug	
Buccal tablet	Intended to be dissolved slowly in the buccal pouch for absorption through the oral mucosa	May enable faster onset of action. Useful for drugs that degrade in gastric environment or undergo extensive first-pass metabolism	
Sublingual tablet	Compressed tablet that is intended to be dissolved rapidly beneath the tongue for the absorption of drug through the oral mucosa	May enable faster onset of action. Useful for drugs that degrade in gastric environment or undergo extensive first-pass metabolism	
Chewable tablet	An immediate-release tablet that is intended to be chewed and then swallowed	Intended to be pleasant tasting and typically contains an excipient like mannitol that creates a creamy mouth feel	
Effervescent tablet	A compressed tablet that contains effervescent salts that release gas (e.g., carbon dioxide) when in contact with water	Typically increases break-up of tablets and enhances dissolution of drug	

(continued)

Table 3.1 (continued)

Type of tablet	Description	Advantages	Other comments
Immediate release tablet	Compressed tablets (including coated compressed tablets) intended to be swallowed that contain no rate-controlling features	Release drug promptly upon administration (e.g., 80% of drug dissolved in 30 min for BCS Class I and 80% of drug dissolved in 15 min for BCS Class III drugs). For drugs with low solubility (Class II and IV), dissolution is tested at 15 min and at a later time point (30, 45, or 60 min), with typically 85% of the drug to be dissolved at the later time point	
Rapid dissolving tablet (orally disintegrating tablet)	Compressed tablet that disintegrates rapidly in the mouth	Disintegrates rapidly in the mouth without the aid of chewing or drinking liquids, and having a fast disintegration time of typically 30 s or less Manufacturing methods include lyophilization or soft-direct compression, and these tablets typically contain highly water soluble excipients	
Extended-release tablet	Tablets formulated to release drug over an extended period of time following ingestion. Synonyms include controlled release and sustained release	Covered in Chap. 3	
Vaginal tablet	Uncoated tablet intended for insertion into the vagina, typically for local therapeutic effect		
Modified-release tablet	Tablets designed in such a way as to alter the release of drug from the tablet, such as by delaying drug release or extending drug release. The term modified release is used to describe both delayed release and extended release dosage forms, including tablets	Covered in Chap. 3	

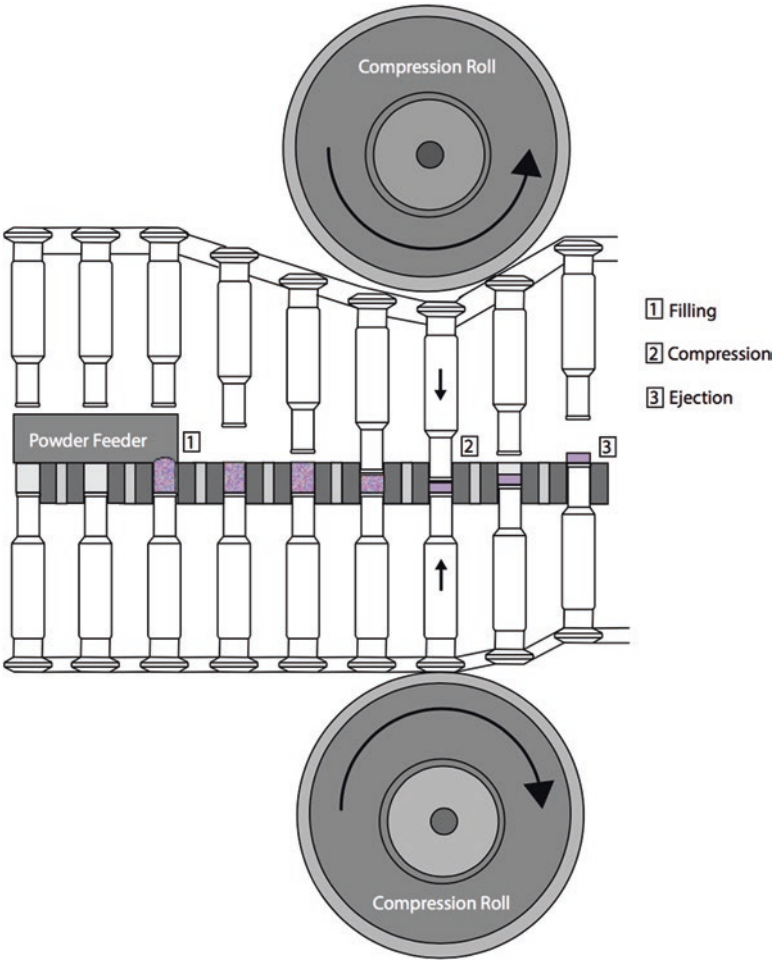

Fig. 3.3 A schematic of a tablet compression process using a tablet press

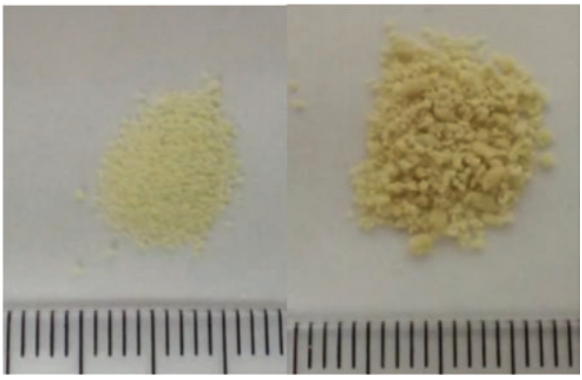

Fig. 3.4 Granulation of powder is performed to improve powder flow in tablet manufacturing. An exemplary powder is shown before (left) and after (right) granulation. Images provided courtesy of S.V. Jermain, University of Texas at Austin

to a fine powder (i.e., a powder having a small particle size distribution) like confectioners' sugar.

Granules are created through a process of wet or dry granulation. Rapid disintegration of granules in water or aqueous-based liquid increases the available surface area of the particles and facilitates dissolution of drug.

In **wet granulation**, the drug powder is first mixed with a diluent. The powder blend is wetted with a binder and water or non-aqueous solvent and thoroughly mixed, resulting in the formation of a wet mass. The solvent is removed by a drying process to form a dried solid mixture, which is then sieved to create uniformly sized granules. Additional excipients (Table 3.3) are then added to the mixture to facilitate the function of the tablet and/or manufacturing.

Dry granulation involves the application of a dry binder to the powder formulation without the use of a liquid. The blend is then compressed together in a tablet press to form a large tablet called a **slug**. A **sieve**, a mesh screen with small, uniform openings, is used to separate the slug into uniformly sized granules that are compressed again to form the final tablet. Alternatively, **roller compaction** may be used, in which the powder mixture is passed between two contra-rotating cylindrical rollers to form a compacted powder ribbon (Fig. 3.5). This ribbon is sieved, mixed with additional excipients (Table 3.3), and then compressed into tablets.

After compression, tablets may be coated. Tablet coatings serve a variety of functions, such as:

(a) Enhancing esthetic appearance
(b) Providing product identification
(c) Acting as a physical barrier between the drug and the environment
(d) Increasing strength
(e) Facilitating swallowing
(f) Taste-masking
(g) Modifying the release characteristics of the drug from the dosage form

The typical method of coating tablets is **film coating** (Fig. 3.6), in which a liquid composition containing polymer(s), plasticizer, pigment, and solvent is sprayed onto the tablet core while the solvent is concurrently dried during the application of the liquid to the tablet surface. Aqueous film coatings are often used instead of non-aqueous film coatings that employ organic solvents, due to environmental, toxicity, and cost concerns.

The choice of excipients for the film-coating process is dependent upon the intended purpose of coating and the desired release profile of the drug. Manufacturing concerns related to the viscosity of the coating formulation, and the mechanical strength, flexibility, and adhesion properties of the coating onto the tablet surface will also influence the selection of coating excipients.

Defects in the tablet coating (Table 3.2) may occur, including picking, mottling, orange peel effect, cracking, and peeling of the coating, and resolution of these

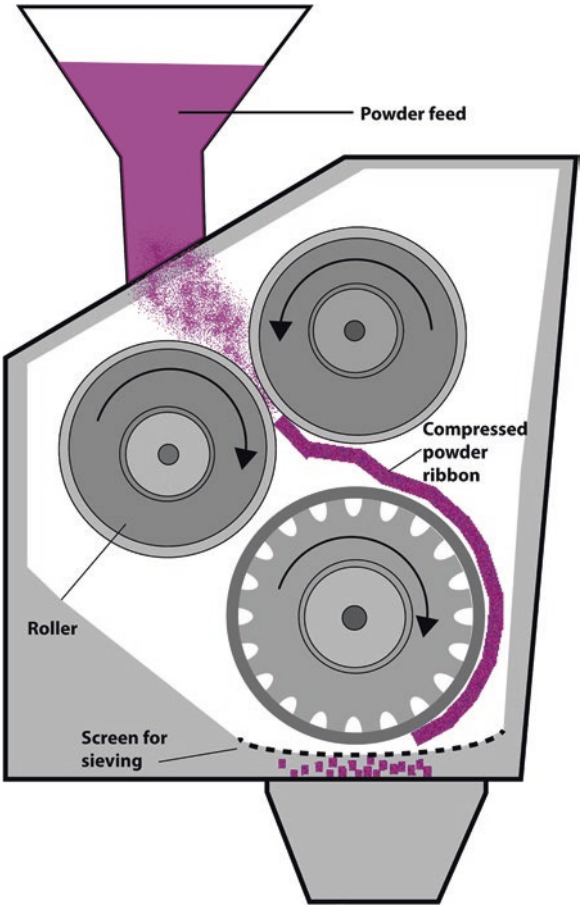

Fig. 3.5 Granulation of a powder can be achieved using roller compaction

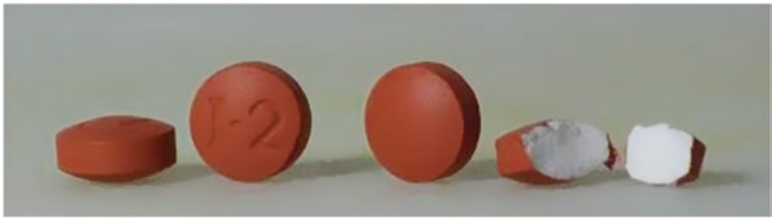

Fig. 3.6 Example of a cross section of a film-coated tablet

Table 3.2 Tablet coating defects

Picking: Occurs when tablets stick together and separate, resulting in areas of the coating being pulled away from the tablet core	 *Reprinted with permission from Porter S. Tablets & Capsules. 2008*
Mottling: Uneven distribution of color within the tablet coating. May result from poor colorant dispersion or migration of filming coating components in which the colorant is soluble	
Orange peel: Surface roughness on tablet resulting from poor spreading of film coating	 *Reprinted with permission from Porter S. Tablets & Capsules. 2008*
Cracking: Splitting of the tablet coating that may occur as a result of tablet core expansion, poor flexibility of the coating, or mechanical stress upon the coating	
Peeling: Separation of film coating from tablet core due to poor adhesion between coating and core, stresses on film coating, or poor flexibility of film coating	

issues requires alterations in the film-coating process or choice of excipients. The pharmacist must watch for any of these defects when dispensing film-coated tablets because these defects may affect the performance of the tablet.

3.4 Excipients Utilized in Capsules and Tablets

Various excipients are included in capsules and tablets for the purpose of improving manufacturing processes, appearance, and drug release. Some typical excipient categories utilized include diluents, disintegrants, lubricants, glidants, plasticizers, opacifiers, colorants, and surface active agents (also known as surfactants). The function and examples of these excipients are described in Table 3.3. Some excipients may serve more than one function.

Table 3.3 Capsule and tablet excipients

Excipient	General function	Examples
Anti-tacking agent	Prevents stickiness or tackiness of the polymeric film coating on tablets	Talc Glyceryl monostearate
Binder	Substances used to cause adhesion of powder particles in tablet granulations	Ethylcellulose Copovidone Hydroxyethyl cellulose Hydroxypropyl methylcellulose (hypromellose) Hydroxypropyl cellulose Methylcellulose Polycarbophil Polymethacrylates Povidone Starch
Colorant	Added for esthetic and identification purposes	FD&C Red No. 3 FD&C Red No. 20 FD&C Yellow No. 6 FD&C Blue No. 2 D&C Green No. 5 D&C Orange No. 5 D&C Red No. 8 Ferric oxide, red
Diluent	Acts as a bulking agent to achieve adequate capsule fill volume or tablet size; reduces drug particle cohesion	Dibasic calcium phosphate Cellulose, powdered Lactose monohydrate Mannitol Microcrystalline cellulose Starch Pregelatinized starch

(continued)

Table 3.3 (continued)

Excipient	General function	Examples
Disintegrant	Promotes rapid break-up of the capsule or tablet upon contact with the aqueous fluid (e.g., gastrointestinal fluid), which results in increased surface area of drug exposed to the fluid and faster dissolution	Starch Pregelatinized starch Crospovidone Sodium starch glycolate Low-substituted hydroxypropyl cellulose
Film coating polymer	Provides an immediate release coating for tablets or provides a modified release coating for tablets or pellets/beads, depending on the polymer chosen	**Immediate release polymers:** Eudragit® E 100 Eudragit® E 12.5 Hypromellose **Delayed release polymers:** Eudragit® L 30 D-55 Eudragit® L 100-55 Hypromellose acetate succinate Cellulose acetate phthalate Ethylcellulose **Extended release polymers:** Eudragit® RS Eudragit® RL Eudragit® FS 30 D
Glidant	Improves powder flow during processing when filling capsule shells or compressing tablets	Colloidal silica Silicon dioxide Magnesium silicate Talc
Lubricant	Prevents adherence of powder to tablet press or encapsulating equipment by reducing friction	Magnesium stearate Sodium stearyl fumarate Stearic acid
Opacifier	Improves the stability of light sensitive drugs	Titanium dioxide
Plasticizer	Enhances flexibility of film coating; added to hot melt extrusion formulations to lower the glass transition temperature of the polymer and facilitate processing	Diethyl phthalate Dibutyl phthalate Dimethyl phthalate Glycerin Polyethylene glycol Propylene glycol Triacetin Triethyl citrate
Surface active agent (i.e., surfactant)	Enhances wetting of drug by the aqueous fluid (e.g., GI fluid), thus improving dissolution of poorly water soluble drugs Solubilizes an otherwise water insoluble drug Their inclusion in a coating composition may also homogenize the coating liquid used on tablets and enhance spreadability	**Anionic:** Sodium dodecyl sulfate (i.e., sodium lauryl sulfate) **Cationic:** Cetrimide Benzalkonium chloride Cetylpyridinium chloride **Nonionic:** Poloxamer 407 Tween® 20, 40, 60, 80 Span® 40, 60, 80 Cremophor® RH Solutol® HS 15

3.5 Analytical Testing

Capsules and tablets manufactured for the pharmaceutical market must undergo rigorous analytical testing to ensure product integrity/proper performance. These tests include:

(a) Disintegration
(b) Dissolution
(c) Weight variation
(d) Content uniformity
(e) Hardness
(f) Friability

Guidelines for these analytical tests are published in the **United States Pharmacopeia and National Formulary (USP-NF, also referred to as USP)**, an annually published reference that also contains reference standards for dosage forms, drug products (**drug monographs**), and excipients.

3.5.1 Disintegration

Immediate release solid oral dosage forms that are not intended to be chewed are required to undergo disintegration tests by the USP-NF. The USP-NF specifies that a dosage unit must disintegrate within a prescribed time. **Disintegration** is defined as a state in which the dosage unit exists as a soft mass with no palpably firm core present and only fragments of the insoluble coating or capsule shell remaining. Disintegration does not imply complete dissolution of drug from the dosage unit.

The apparatus used to perform the disintegration assay is a basket-rack assembly (Fig. 3.7), in which tablets or capsules are placed in tubes with a mesh or disks on top, and then raised and lowered at a constant frequency while immersed in a specified media; disintegration time is recorded as the time at which no residue of the dosage form is remaining in the tube, other than small fragments of coating remaining. The duration of the test is specified in the drug monograph.

3.5.2 Dissolution

Dissolution testing to measure the rate of drug release from the dosage form is achieved using the USP apparatuses (Fig. 3.8) previously described in Chap. 2; and a method developed for the specific properties of the formulation (i.e., immediate drug release or modified drug release).

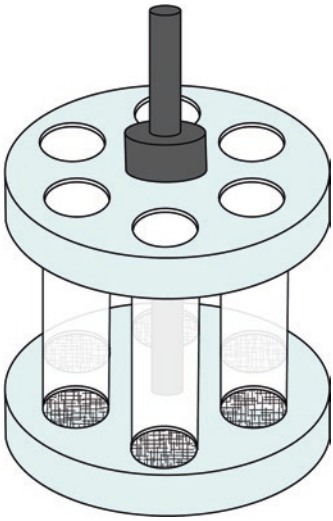

Fig. 3.7 USP disintegration apparatus

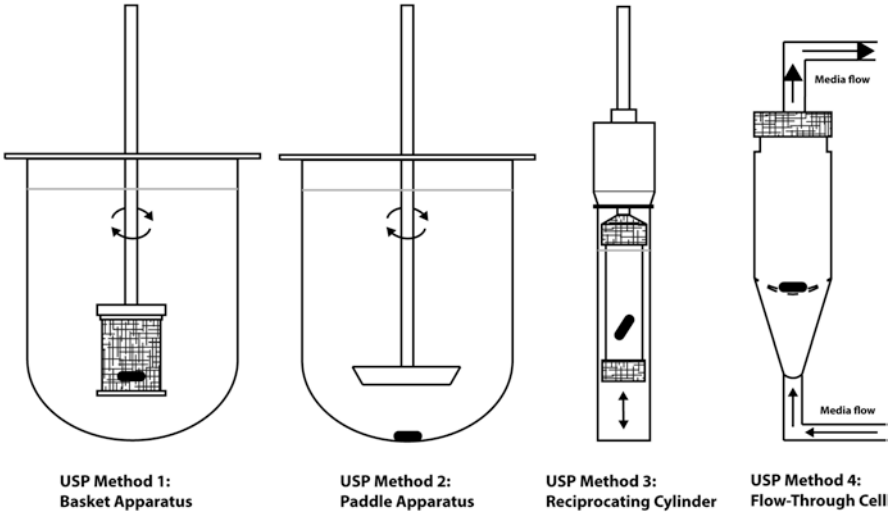

Fig. 3.8 USP dissolution apparatuses

3.5.3 Weight Variation and Dose Content Uniformity

The USP requires that tablets and capsules are assessed for weight variation or content uniformity, depending on the quantity of drug or the ratio of drug to excipients. The weight variation test for tablets, and hard and soft capsules requires 10 dosage

units to be weighed. For hard capsules, the powder is then emptied from the capsules and the empty capsules are individually weighed and the net powder weight is calculated. For soft capsules, the shell is pierced and the contents are removed by washing with solvent. The solvent is then evaporated, and the empty shells are weighed and the net content weight is calculated. To determine **content uniformity**, 10 units are selected and assayed with an appropriate analytical method, such as HPLC to determine the amount of active ingredients present. Generally, the amount of active ingredient or the weight of the dosage unit must be within 85%–115% of the label claim for 9 out of 10 of the capsules, with no individual capsule exceeding the range of 70%–125%.

3.5.4 Tablet Hardness

To quantify tablet strength, tablets are subjected to a force until breakage occurs. The force at which the tablet breaks is called the tablet hardness. The manner in which the tablet breaks should also be noted, as lamination and capping (Fig. 3.9) can be indicative of problems in the manufacturing process.

3.5.5 Friability

Friability refers to the propensity of a material to crumble or be reduced to a powder. To test the likelihood of a tablet breaking into smaller pieces during transportation or processing (e.g., tablet coating), tablets undergo friability testing. This test

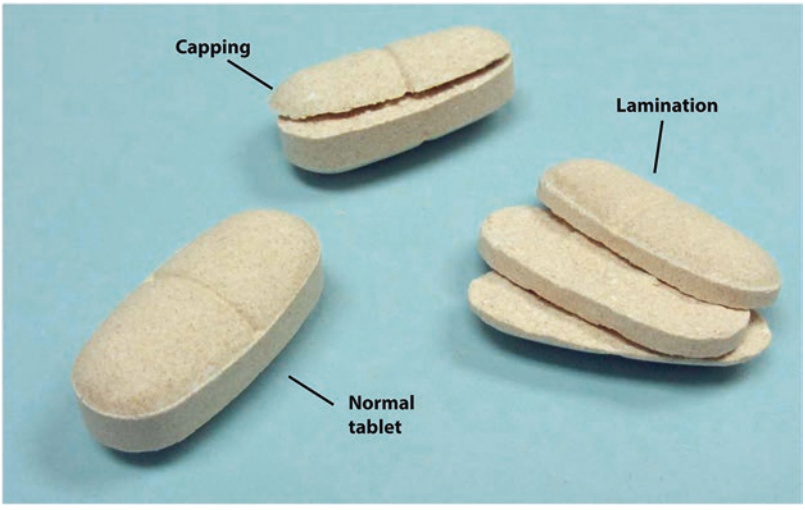

Fig. 3.9 Lamination and capping are examples of tablet failure

involves repeatedly dropping a sample of tablets over a fixed time, using a rotating wheel with a baffle, and afterwards checking whether any tablets are broken, and what percentage of the initial mass of the tablets has been chipped off.

3.6 Formulating Poorly Water Soluble Drugs

The formulation of poorly water soluble drugs represents one of the most significant challenges in the pharmaceutical industry, as drugs must dissolve before absorption and therapeutic effect can occur.

There are several pharmaceutical formulation approaches that may be taken to overcome poor aqueous solubility, such as:

(a) Using an alternative polymorph
(b) Formulating the drug in its amorphous form
(c) Reducing the particle size of the drug, such as by milling. Milling of a particle into the micron size range (e.g., less than 10 μm) is often referred to as micronization
(d) Formulating the drug in a solid dispersion

The formation of solid dispersions is a promising technique. In a **solid dispersion**, the drug is dispersed within a polymeric carrier matrix, either in the form of a molecular solution or dispersion of particles. Solid dispersions can increase the dissolution rate of the drug through reduction of particle size, and through a solubilization effect provided by the carrier material.

Based upon the molecular state (see Chap. 2, Sect. 2.3.2) of the drug dispersed in the carrier polymer phase, solid dispersions can be categorized as:

(a) Crystalline solid dispersions
(b) Amorphous solid dispersions
(c) Amorphous solid solutions

In **crystalline solid dispersions**, the crystalline form of the drug is dispersed in an amorphous carrier matrix. This type of formulation is characterized by the presence of a melting endotherm (T_m; see Chap. 2) in the DSC profile of the formulation that corresponds to the drug. Crystalline solid dispersions can be used to achieve a controlled release of a highly water soluble drug.

An **amorphous solid dispersion** is created by formulating a drug in an amorphous state and placing it in a single-phase system (a solid solution) or a two-phase system (a solid dispersion) with another solid substance, typically a polymer (Fig. 3.10).

Amorphous solid dispersions and solid solutions may be formed through a process of solubilization and solvent removal (i.e., spray drying) or melting and mixing with the carrier material (i.e., hot melt extrusion).

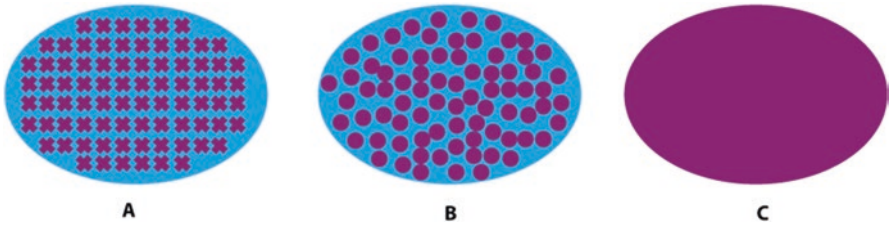

Fig. 3.10 Solid dispersions are classified as crystalline solid dispersions (**a**), amorphous solid dispersions (**b**), or amorphous solid solutions. In all cases, the drug is dispersed within an amorphous carrier polymer

Table 3.4 Exemplary polymers utilized as carriers for solid dispersions

Polyvinylpyrrolidone (Kollidon®, Plasdone®)
Polyvinylpyrrolidone-*co*-vinyl acetate (Copovidone; Kollidon® VA64)
Polyethylene glycols (Carbowax®)
Polyethylene oxide (PolyOx® WSR)
Poly(dimethylaminoethyl methacrylate-*co*-methacrylic esters) (Eudragit E®)
Polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer (Soluplus®)
Hydroxypropyl cellulose (HPC) (Klucel™)
Hydroxypropyl methylcellulose (HPMC) (Methocel® and Affinisol®)
Hydroxypropyl methylcellulose acetate succinate (HPMCAS, known also as Hypromellose Acetate Succinate) (Affinisol® and AquaSolve®)

Amorphous solid dispersions are frequently used to increase the bioavailability of poorly soluble drugs by improving the wetting and dissolution profiles of these compounds. The amorphous form of a drug will generally dissolve faster than the crystalline form because no energy is needed to break up the crystal lattice and because these systems have a higher thermodynamic activity than the crystalline form. However, the physical instability of the amorphous form can result in reversion back to the more stable crystalline form.

Polymers typically utilized as carriers in the creation of amorphous solid dispersions are listed in Table 3.4.

3.6.1 Spring and Parachute Concept

The **"spring and parachute"** (Fig. 3.11) concept is typically used to help describe the preferred dissolution of a poorly water soluble drug from a solid dispersion as follows:

(a) Generation of a supersaturated solution of drug within the intestinal lumen (spring)

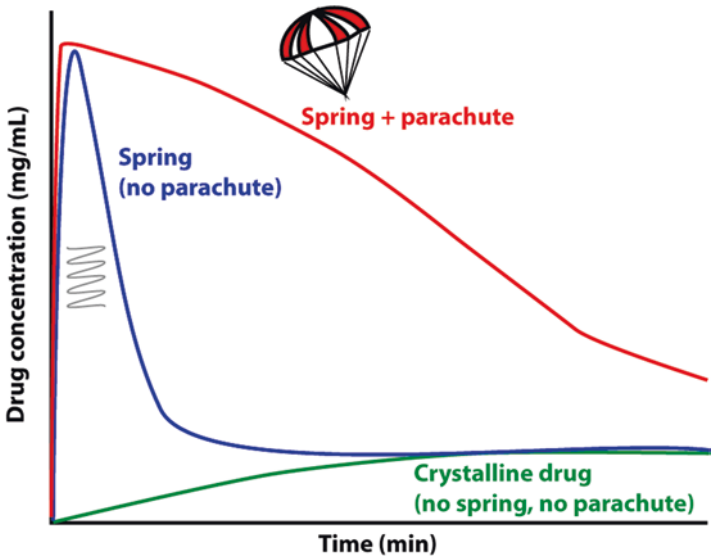

Fig. 3.11 Utilization of the high-energy amorphous form of a drug (the "spring") provides a higher drug concentration in solution than the crystalline form (supersaturation). A "parachute," in the form of an excipient that prevents crystal formation and growth, helps to sustain the supersaturated state

(b) Maintenance of a supersaturated solution of drug within the intestinal lumen (parachute)

This is a useful approach for increasing the gastrointestinal absorption of poorly water soluble drugs, particularly for **BCS Class 2** drugs (high permeability, low solubility; see Chap. 2). For these types of drugs, drug absorption is limited by the solubility of the drug in the intestinal lumen, and thus by its dissolution.

The supersaturated solution is obtained from a high energy form of the drug with a higher apparent solubility, such as the amorphous form. This is called "spring." However, supersaturated solutions are thermodynamically unstable, and the system will have a tendency to revert to equilibrium solubility through precipitation of the drug. In order to prevent precipitation of the drug prior to absorption, a "parachute," in the form of an excipient that inhibits precipitation by interfering with crystal formation and growth, is incorporated in the formulation. Excipients that may serve as a parachute include polymers, surfactants, and cyclodextrins. An example polymer is hypromellose.

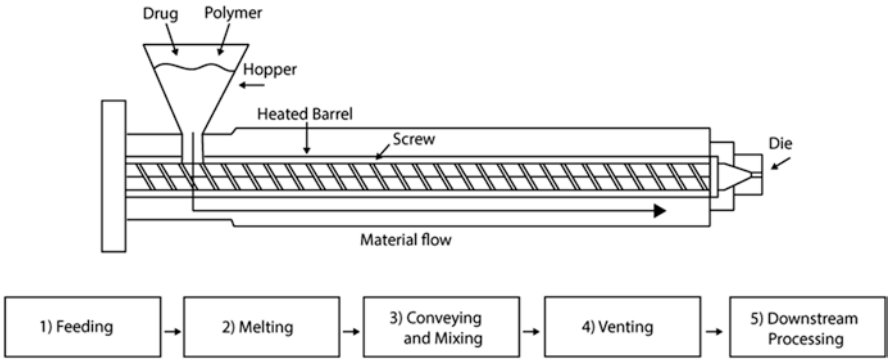

Fig. 3.12 A schematic of the hot melt extrusion process used for the manufacturing of amorphous solid dispersions

3.6.2 Hot Melt Extrusion

A process originally developed for the plastics industry, hot melt extrusion is now adapted for the manufacture of pharmaceutical amorphous solid dispersions. In **hot melt extrusion**, the drug is melted and mixed with a heated carrier, and then extruded into the desired shape of a solid dosage form or in the form of granules.

Hot melt extrusion can be subdivided into five steps (Fig. 3.12):

1. Feeding
2. Melting
3. Conveying and mixing
4. Venting
5. Downstream processing

The material is introduced to the feeder via a hopper. The materials are transported along the length of the barrel where it is melted, mixed, and compressed using the shear forces generated by the rotating screws as well as the heating elements present in the barrel. Generally, the temperature of the process is chosen to be above the glass transition temperature (T_g) of the polymer, in order to ensure that the carrier is softened and has a low viscosity. Plasticizers may be added, if needed, to the formulation to improve the flow of the melt. In general, it is important for the drug to be miscible in the carrier to ensure formation of a stable product.

3.6.3 Spray Drying

Spray drying is another technique utilized in the formulation of amorphous solid dispersions. In **spray drying** (Fig. 3.13), a solution containing the drug and the carrier material is transformed into a solid material by rapidly drying an atomized

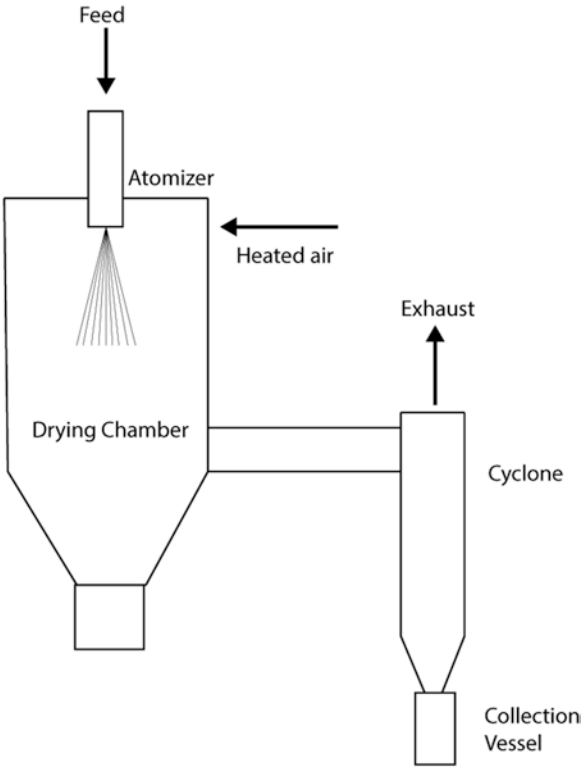

Fig. 3.13 A schematic of the spray drying process is shown. Spray formation occurs via atomization of the liquid feed, followed by exposure of droplets to heated air or gas in the drying chamber, which results in the formation of solid particles. Solid particles are separated from the wet drying gas in the cyclone, and the dried particles are collected in the collection vessel

spray. The rapid evaporation of the solvent during the process leads to trapping of the drug within the carrier matrix and the formation of a solid dispersion.

3.7 Physiology and Food Effects

Based on the prevalence of the delivery of drugs via the oral route, it is worthwhile to consider the effect of food on the absorption and bioavailability of a drug. Depending upon the physicochemical properties of the drug, ingestion of food may lead to changes in the absorption and bioavailability of a drug. This is called a **food effect**.

There are four general food effects possible:

(a) For some drugs, the presence of food leads to an increase in bioavailability that can potentially compromise safety.
(b) The food–drug interaction may decrease the bioavailability and thus lower the efficacy of the drug.
(c) Food–drug interactions may lead to a delay in absorption.
(d) Food–drug interactions may lead to an acceleration in absorption.

The ingestion of a meal leads to physiological changes which may contribute to changes in drug absorption and bioavailability. These include:

(a) Delayed gastric emptying (typically two hours in the unfed state and four hours in the fed state).
(b) Increased solubilizing capacity of the intestinal fluids.
(c) Increased stomach environment pH from pH 0.8 in the fasting state to pH 4.0–5.0 in the fed state. This change in pH is a potential concern with drugs that are ionizable, as it may lead to changes in solubility.

Further Reading

Suggested readings for the student include the following texts:

1. Huang S, Mao C, Williams RO III, Yang CY. Solubility advantage (and disadvantage) of pharmaceutical amorphous solid dispersions. J Pharm Sci. 2016;105(12):3549–61.
2. Jermain SV, Brough C, Williams RO III. Amorphous solid dispersions and nanocrystal technologies for poorly water-soluble drug delivery–an update. Int J Pharm. 2018;535(1–2):379–92.
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4. Ma X, Williams RO III. Characterization of amorphous solid dispersions: an update. J Drug Deliv Sci Technol. 2019;50:113–24.
5. Varum FJ, Hatton GB, Basit AW. Food, physiology and drug delivery. Int J Pharm. 2013;457(2):446–60.
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Chapter 4
Modified Release Solid Oral Dosage Forms

Abstract This chapter presents an extensive overview of the concepts of delayed-release, sustained-release, and pulsatile-release for drug delivery. Formulation approaches and delivery technologies are discussed in detail, along with the required performance testing for modified-release dosage forms. Abuse-deterrent technologies are also introduced.

Keywords Controlled release · Delayed release dosage form · Extended release dosage form · Modified release dosage form · Pulsatile release system · pH-dependent drug release · Enteric coating · Dissolution testing · Dose dumping · Abuse deterrent

Learning Objectives

- Describe the rationale for developing delayed release dosage forms.
- Describe the rationale for developing extended release dosage forms.
- Compare and contrast delayed release and extended release dosage forms.
- Explain the mechanism of hydrophilic matrix drug delivery systems.
- Explain the mechanism of insoluble (hydrophobic) matrix drug delivery systems.
- Explain the mechanism of membrane controlled drug delivery systems.
- Explain the mechanism of osmotic drug delivery systems.
- Describe the rationale for developing pulsatile release drug delivery systems.
- Compare zero-order drug release to first-order drug release.
- Describe typical excipients used in modified release drug delivery systems.
- Explain the dissolution requirements for modified release dosage forms.
- Describe what effect alcohol may have on modified release delivery systems.
- Describe the abuse-deterrent mechanisms recommended by the FDA for extended release opioid dosage forms.

Key Concepts

Students should know and be able to describe each of the following concepts as they review this chapter:

A. D. Brunaugh et al., *Essential Pharmaceutics*, AAPS Introductions in the Pharmaceutical Sciences, https://doi.org/10.1007/978-3-030-31745-4_4

- Abuse (FDA)
- Circadian rhythm
- Controlled release
- Delayed release dosage form
- Dose dumping
- Extended release dosage form
- First-order release
- Hydrophilic matrix system
- Insoluble (hydrophobic) matrix systems
- Membrane controlled systems
- Modified release
- Monolithic
- Multiparticulates
- Nonpareils
- Osmotic pump systems
- pH-dependent enteric coating
- Press coating
- Prolonged release
- Pulsatile release systems
- Push-pull system
- Sustained release
- Zero-order release

4.1 Introduction

The FDA describes **modified release** as a dosage form that includes delayed release products and extended (e.g., controlled, sustained) release products. A modified release dosage form is intentionally designed to alter the release of drug from the delivery system, resulting in changes in the onset and duration of therapeutic action. There are many reasons why it may be desirable to modify the release of a drug from a dosage form like a capsule or tablet. These include:

(a) Reducing the frequency of dosing regimens
(b) Reducing adverse effects associated with peak plasma concentration
(c) Minimizing therapeutic troughs

Modified release may be subdivided into:

1. Delayed release (DR)
2. Extended release (ER)

Delayed release dosage forms are described by the FDA as products that release the drug(s) at a time that is later than promptly upon administration (i.e., these drug products exhibit a lag time in quantifiable drug blood concentrations). In the case of delayed release solid oral dosage forms, coatings (e.g., pH-dependent enteric coat-

ings) are typically used to delay the release of drug until the dosage form has passed through the acidic medium of the stomach.

Extended release dosage forms are described by the FDA as dosage forms that allow a reduction in dosing frequency as compared to when the drug is present in an immediate release dosage form. In other words, an extended release dosage form is formulated in such a manner as to make the contained drug substance release over an extended period of time following ingestion.

It is important to utilize the correct nomenclature when describing drug release from a dosage form. The terms delayed release and extended release refer to different technologies, and the dosage forms are not bioequivalent.

4.2 Delayed Release Solid Oral Dosage Forms

Delayed release solid oral dosage forms can be used to:

(a) Protect drugs from the acidic environment of the stomach
(b) Reduce gastric irritation caused by the drug
(c) Target drug release to the small intestine or colon to enhance therapeutic efficacy or increase drug absorption

Mechanisms for delayed release may be based on the following:

(a) pH-dependent release
(b) pH-independent release
(c) Time-based release
(d) Enzyme-based release

Delayed release can be achieved through a **pH-dependent enteric coating**, which uses a film coating of polymer(s) that has pH-dependent aqueous solubility (Table 4.1). At an acidic pH, the coating is insoluble, thereby preventing the release of drug in the stomach. When the tablet passes into the small or large intestine, which is at a higher pH than the stomach, the pH-dependent coating dissolves and the drug is released from the dosage form. Polymers used in pH-dependent enteric coatings contain ionizable functional groups that are unionized at low acidic pH (rendering the film insoluble) and ionized at elevated pH (allowing for dissolution of the film). The specific pH value that a pH-dependent enteric coating becomes ionized and dissolves depends on the specific polymer making up the film coat. It should be noted that a pH-dependent enteric coating will dissolve in the gastrointestinal tract at the point at which it is exposed to the pH value in which it ionizes. This requires consideration of factors which may alter the pH of the gastrointestinal tract. For example, if a patient has taken a dose of an antacid or a proton pump inhibitor that raises the pH of the stomach just prior to administration of the delayed release product, the pH of the stomach contents may be raised to a pH value at which the pH-dependent enteric coating of the delayed release dosage form ionizes, resulting

Table 4.1 Excipients utilized in delayed release dosage forms

Polymer	Properties
Hydroxypropyl methylcellulose phthalate (HPMCP) (also referred to as hypromellose phthalate) (e.g., *Mantrocel®*)	Soluble ≥ pH 5.0
Hypromellose acetate succinate (e.g., *Aqoat®*)	Divided into subclasses based upon pH at which polymer dissolves • L (low): pH ≥ 5.5 • M (medium):pH ≥ 6.0 • H (high): pH ≥ 6.8
Polyvinyl acetate phthalate (PVAP) (e.g., *Opadry®*)	Soluble ≥ pH 5.5
Cellulose acetate phthalate (e.g., *Aquacoat CPD®*)	Soluble ≥ pH 6.0
Methacrylic acid and ethyl acrylate copolymer (e.g., *Eudragit® L 30 D-55 and L 100-55*)	Soluble ≥ pH 5.5
Methacrylic acid and methyl methacrylate copolymer (e.g., *Eudragit® L 100, Eudragit® L 12.5*)	Soluble ≥ pH 6
Methacrylic acid and methyl methacrylate copolymer (e.g., *Eudragit® S 100, Eudragit® S 12.5*)	Soluble ≥ pH 7
Methacrylic acid and methyl methacrylate copolymer (e.g., *Eudragit® FS 30 D*)	Soluble ≥ pH 7
Shellac (e.g., *Mantrolac®*)	Soluble ≥ pH 7

in dissolution of the dosage form in the stomach environment rather than the intended location.

Another mechanism of delayed release is incorporation of an erodible coating that provides a time lag until the drug is released. In this mechanism, the method of delayed release is therefore time dependent.

4.3 Extended Release Solid Oral Dosage Forms

Extended release dosage forms are those that prolong the release of drug over time in order to sustain therapeutic effect. The term extended release is sometimes used interchangeably with the terms **controlled release, prolonged release**, and **sustained release**.

Depending on the pharmacokinetic profile of a drug substance, a patient may need to take an immediate release medication administered multiple times per day to maintain therapeutic effect. Repeated dosing throughout the day leads to a series of peaks and troughs in the therapeutic blood level of the drug. This fluctuation can result in unwanted side effects when blood levels of the drug are high and breakthrough symptoms when drug levels low. Furthermore, multiple daily dosing requires compliance on the part of the patient and is considered an inconvenience and may lead to poor therapeutic outcomes.

Extended release dosage forms generally aim to eliminate these cyclical changes in the drug levels by slowly releasing the drug over time, in order to obtain a smooth

and sustained plasma concentration–time curve. Extended release dosage forms have the potential advantages of reduced fluctuation in blood levels, a reduction in the frequency of dosing, increased convenience of administration, and improved patient compliance.

The types of drugs that are suitable for extended release dosage forms generally include those that have one or more of the following characteristics:

(a) Require multiple daily administrations
(b) Have a relatively short pharmacokinetic half-life (e.g., ≤8 h)
(c) Are uniformly absorbed along the different regions of the GI tract
(d) Require relatively small doses for efficacy
(e) Possess a wide safety margin

Drugs that are generally **not** suitable for or do not require extended release are those that have one or more of the following characteristics:

(a) Have a long half-life
(b) Require a relatively large dose for efficacy, as the large dose may result in formulation difficulties
(c) Have a narrow therapeutic index where the risk of dose-dumping through technology failure or incorrect use by the patient poses serious risks

Drug solubility is also a concern. Low drug solubility can make developing an extended release dosage form a challenge, as the mechanism for release may involve the diffusion of the drug through a polymeric membrane. If the aqueous solubility is too high then it may be difficult to sustain the release of the drug by conventional means.

Different types of extended release delivery systems have been developed. These include:

1. Hydrophilic matrix systems
2. Insoluble matrix systems
3. Membrane controlled systems
4. Osmotic pump systems

These systems often follow Fick's laws of diffusion (see Chap. 2) for drug release. The dosage form can be designed to be a whole tablet or capsule **(monolithic)**, or individually coated pellets or beads (**multiparticulates**) that are then incorporated into a tablet or capsule. Multiparticulate dosage forms may be produced using a process of **spheronization**, in which a wet mass of material is extruded and formed into pellets or beads. Alternatively, inert sugar spheres (**nonpareils**) may be coated with drug and excipients, and this is typically layered on or included in a polymeric film coat.

The manufacturing techniques (e.g., hot melt extrusion, compression, film coating) that are reviewed in Chap. 3 are also utilized in the production of extended release dosage forms. Hot melt extrusion, in particular, is important for the production of matrix-based extended release systems.

4.3.1 Hydrophilic Matrix Drug Delivery Systems

A **hydrophilic matrix system** describes a tablet formulation that contains drug in a non-cross-linked polymer matrix (Fig. 4.1). The polymer swells upon contact with the aqueous gastrointestinal fluid (Fig. 4.2) and forms an entangled gel layer surrounding the core of the tablet, which is dry. This gel layer acts as a diffusion barrier, slowing the release of drug from the dosage form. The hydration and formation of the gel layer must occur rapidly to prevent premature and uncontrolled drug release. Over time, the polymers on the outer surface of the tablet relax and disentangle from each other and gradually erode from the surface. Eventually, the entire matrix undergoes hydration and may erode completely.

Drug release is controlled by diffusion of the drug through the gel layer and/or by erosion of the gel layer. In the case of water-soluble drugs, release occurs by diffusion through the gel layer. If the drug is water-insoluble, it is released after erosion of the polymer matrix containing the drug with minimal diffusion occurring. In general, the greater the amount of polymer in the dosage form, the slower the drug release rate.

Polymers used to create hydrophilic matrix systems (Table 4.2) are often the same as those used to prepare tablet film coatings. The polymers used to create hydrophilic matrix systems should exhibit the following characteristics:

(a) Undergo rapid hydration/swelling
(b) Feature pH independent solubility
(c) Non-toxic

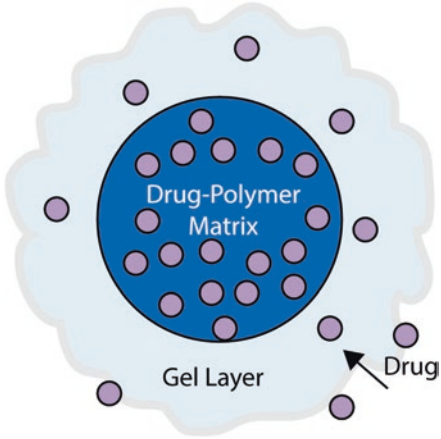

Fig. 4.1 A hydrophilic matrix tablet. Upon contact with the aqueous fluid, the hydrophilic polymer swells and creates a gel layer. Drug release is achieved by diffusion of the drug through the gel layer and gradual erosion of the gel layer

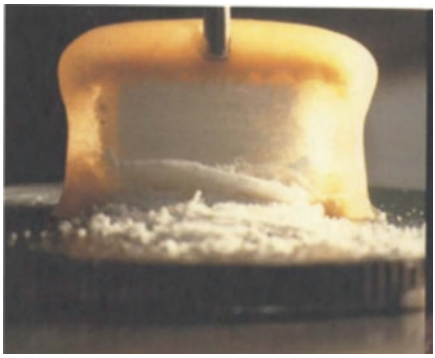

Fig. 4.2 Exemplary hydrophilic matrix tablet with gel layer formed upon contact with aqueous solution. (Adapted from Conte U, Maggi L, Colombo P, La Manna A. Journal of controlled release. 1993 Jul 1;26(1):39–47. Reproduced with permission of ELSEVIER BV in the format Book via Copyright Clearance Center)

Table 4.2 Examples of polymers used in hydrophilic matrix systems

Category	Examples	Notes
Cellulosic	Hydroxypropyl methylcellulose (HPMC/ hypromellose)	T_g = 157–180°C Available in different grades of varying viscosity
Non-cellulosic gums/ polysaccharides	Sodium alginate Xanthan gum Carrageenan Ceratonia (locust bean gum) Chitosan Guar gum	
Non-cellulosic others	Polyethylene oxide (PEO) (*Polyox*®)	T_m = 65°C Available in different grades of varying molecular weight (MW) and viscosity **Low MW**: N-10, N-80, N-750 **Medium MW:** N-1105, N-12K, N-60K **High MW:** 301, 303 Also utilized in crush and abuse resistant tablets

4.3.2 Insoluble Matrix Systems

Insoluble (hydrophobic) matrix systems differ from hydrophilic matrix systems in that the polymers do not swell or dissolve upon exposure to the GI fluid. Instead, the drug gradually diffuses from the insoluble matrix system as the GI fluids enter the system through pores in the matrix (Fig. 4.3). This matrix is typically composed of waxes, solid lipids, or inert polymers (Table 4.3). A water-soluble excipient is typically included in the formulation for the purpose of forming pores (i.e., a

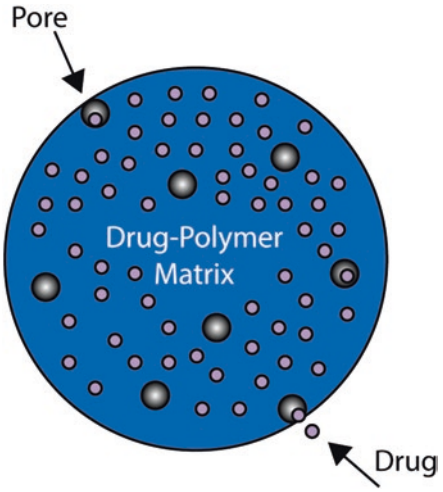

Fig. 4.3 A hydrophobic matrix tablet. Water-soluble pore-forming agents are included in the formulation to allow for the slow diffusion of drug from the tablet

Table 4.3 Excipients for insoluble matrix systems

Category	Examples
Lipids	Glyceryl behenate Carnauba wax Cetyl alcohol Hydrogenated vegetable oils Polyethylene glycol monostearate
Water-insoluble polymers	Polyvinyl acetate Polymethacrylate Ethyl cellulose
Hydrophilic (water-soluble) pore-forming agents	Sucrose Lactose Polyethylene glycols (PEGs) Starch Micronized cellulose Soluble cellulose ethers (HPMC, HPC) Poly(vinyl alcohol) Poly(vinylpyrrolidone) (also known as Povidone; PVP)
Solubilizing agents	PEGs Surfactants

porogen or pore-forming agent) in the insoluble matrix. The control and optimization of the pore size and number provide a means to control the rate that the aqueous medium enters the matrix to dissolve the drug and the dissolved drug to diffuse out of the insoluble matrix. Hydroxypropylcellulose (HPC) and hydroxypropyl methylcellulose (HPMC) are two examples of water-soluble polymers that may be used as porogens.

The extent of porosity of the matrix and the tortuosity of the channels formed will affect the release rate of the drug. Depending on the solubility of the drug, it may also be necessary to include a solubilizing agent in the formulation to enhance dissolution.

4.3.3 Membrane Controlled Release Systems

In **membrane controlled systems**, drug is placed in a reservoir that is surrounded by a rate-controlling polymer membrane (Fig. 4.4). Unlike matrix systems, the polymer coating does not swell or erode upon contact with water. Instead, the membrane is permeable to both drug and water. The core of the tablet hydrates and the drug dissolves and is then released from the membrane. The thickness of this membrane as well as the partition coefficient of the drug control diffusion of the drug from the delivery system, as described by Fick's laws of diffusion.

Other strategies used for the controlled release of drug from film-coated tablets include the use of pore formers (porogens) (Table 4.4), layering of coatings with different functionality, or the modification of polymers in the film coating to increase permeability (i.e., Eudragit® RL).

Membrane controlled release systems typically exhibit **first-order release,** meaning that the drug release rate is dependent upon the concentration of the drug. Drug release occurs as a result of the concentration gradient between the dosage unit and the surrounding medium. The concentration gradient is greatest in the initial phase of the drug release and decreases with time. In contrast, a **zero-order release** dosage form would exhibit drug release at a constant rate, independent of concentration.

Rate-controlling membranes are utilized in single-unit delivery systems, such as a tablet, or in multiple-unit systems, such as beads or pellets. For example, a drug

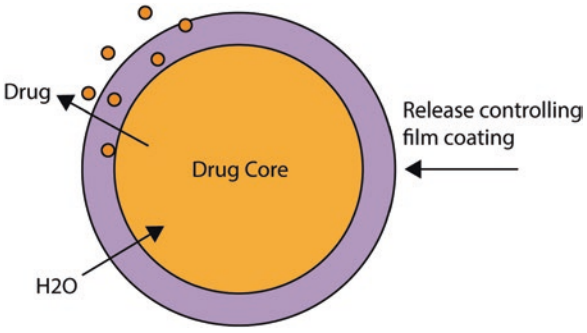

Fig. 4.4 A membrane controlled release tablet. The film coating is permeable to the drug, which allows for the slow release of drug from the reservoir core over time. Coating permeability may be enhanced through the addition of pore-forming agents or chemical modification of the film-coating polymers

Table 4.4 Excipients utilized in membrane controlled release systems

Category	Examples	Properties
Film coating	Ethyl cellulose ethers (*Ethocel™, Surelease®*)	Water insoluble
	Methacrylic acid and methyl methacrylate copolymer (*Eudragit® NE 30D, NM 30D, and NE 40D*)	Water insoluble, low permeability, highly flexible polymer
	Methacrylic acid and methyl methacrylate copolymer (*Eudragit® RL 100, RL PO, RL 30 D, RL 12, 5*)	Water insoluble, high permeability
	Methacrylic acid and methyl methacrylate copolymer (*Eudragit ® RS 100, RS PO, RS 30 D, and RS 12, 5*)	Water insoluble, low permeability
	Polyvinyl acetate (*Kollicoat®*)	Water insoluble
Plasticizer	Dibutyl phthalate Diethyl phthalate Triethyl citrate	Increases flexibility of film coating

can be coated onto the surface of inert sugar spheres (i.e., nonpareils), surrounded by a polymer film, and then filled into a capsule shell.

4.3.4 Osmotic Pump Systems

The **osmotic pump system** (Fig. 4.5) describes a tablet core that is film coated with a semipermeable membrane through which only water can diffuse. A laser is typically used to create a hole in the membrane. Diffusion of water into the dosage form and dissolution of the drug results in a buildup of osmotic pressure, and the drug solution is forced through a pre-drilled orifice. In the case of poorly water soluble drugs, a layer that swells upon contact with water may be included to push the drug out of the system (Fig. 4.6). This is known as a **push-pull system.**

Osmotic pump systems exhibit **zero-order release**, meaning that the release rate of the drug occurs at a constant rate independent of the concentration of the drug in the dosage form.

Osmotic pump systems utilize some of the same polymers as membrane systems (see Table 4.4). The formulation in the core must be sufficiently soluble to generate osmotic pressure.

4.4 Pulsatile Release Systems

Pulsatile release systems are another type of modified release system in which doses of a drug are released in one or more sequential pulses. In some cases, one dose is released immediately, while the release of the subsequent doses are delayed.

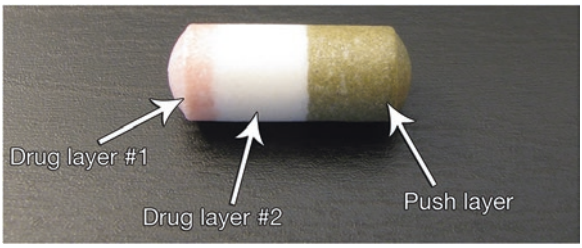

Fig. 4.5 An example of an osmotic pump delivery system, OROS™, used in Concerta® tablets. Attribution: Wikimedia user Garzforth, image licensed for reuse under https://creativecommons.org/licenses/by-sa/4.0/deed.en

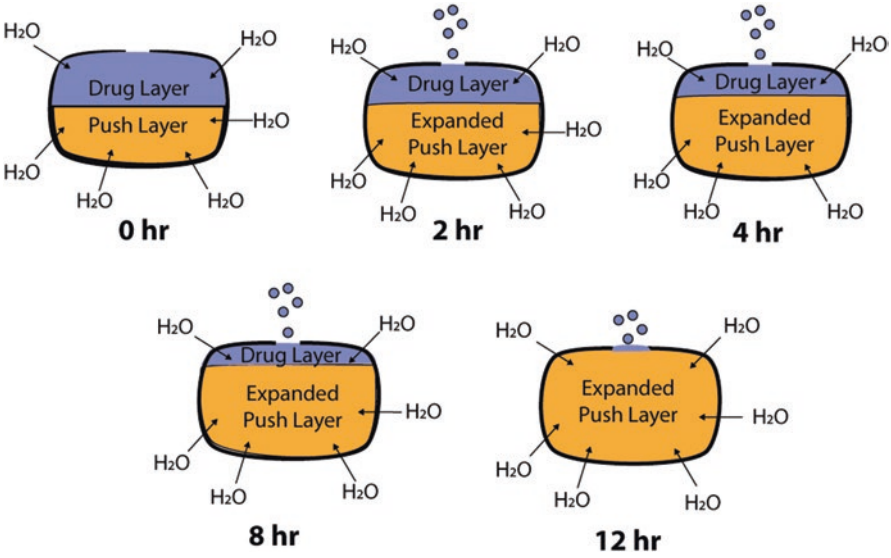

Fig. 4.6 A schematic of drug release from and exemplary push-pull osmotic pump system over time. Push-pull osmotic system. The aqueous GI fluid diffuses in through the semipermeable membrane, leading to expansion of the push layer. This swelling pushes the drug out through the predrilled orifice

These types of dosage forms are useful in the administration of medications intended to treat diseases in which the severity of symptoms follows **circadian rhythm** (i.e., follows an endogenous timing mechanism within the body). In these cases, the release of the dose can be timed to minimize the onset of symptoms.

Pulsatile drug release may be achieved by using the modified release systems as previously described, as well as by using a tablet manufacturing technique called press coating. In press coating, a dry outer shell is compressed around a tablet core using a modified tableting machine.

4.5 USP Dissolution Testing for Modified-Release Dosage Forms

As one would expect, dissolution requirements for modified release dosage forms differ from immediate release dosage forms. Release rate reproducibility between batches is extremely important to prevent therapeutic failure or adverse drug events. The specific drug release profile that the modified-release dosage form exhibits will depend upon the mechanism by which the release has been modified (Fig. 4.7).

For extended release dosage forms, samples are taken at different time points in the dissolution experiment (e.g., 1, 2, 4, 8, and 12 h) corresponding to early, middle, and late stages of the dissolution profile.

For delayed release dosage forms, drug release is tested at two different media pH, according to USP guidelines. In the acidic stage of the dissolution process, no more than 10% of the drug may be dissolved within 2 h, while in the basic stage no less than 80% is dissolved within 45 min. There are two methods for performing the delayed release dosage form test. In Method A, buffer liquid is added to the acid stage and pH is then adjusted to 6.8. In Method B, the vessel is first drained of the acidic fluid and then filled with buffer liquid.

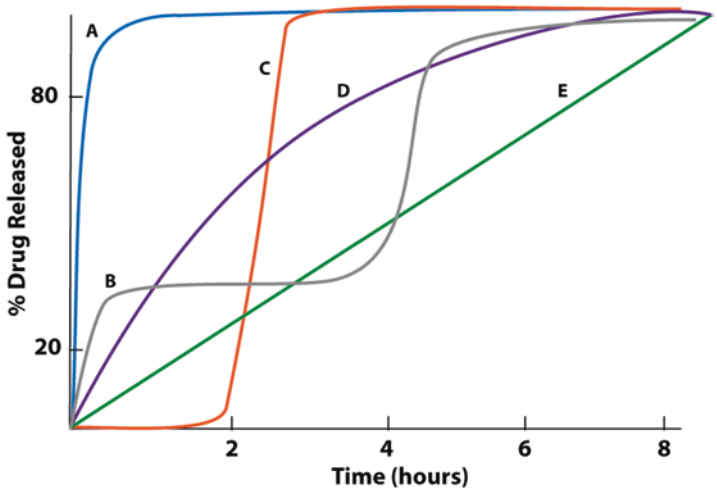

Fig. 4.7 Example drug release profiles of hypothetical formulations: (**a**) immediate release, (**b**) pulsatile release, (**c**) delayed release, and (**d**) extended release (first order), and (**e**) extended release (zero order) oral dosage forms

4.6 Dose Dumping and Alcohol Effects

Consumption of alcohol with a modified-release coated medication can sometimes destroy the modified drug release mechanism. This can result in **dose dumping**, which refers to the unintended release of a significant fraction of drug from a modified release formulation.

Some modified release coatings are formulated from excipients that are soluble in organic solvents such as alcohol but have limited or no solubility in aqueous environments. Additionally, a higher pH in the fed state is associated with alcohol consumption, which may result in early release of the drug from pH-dependent delayed release dosage forms.

4.7 Abuse-Deterrent Technologies for Extended Release Opioid Formulations

Opioids are typically used in the treatment of severe or chronic pain. Patients with chronic pain often require around-the-clock dosing to manage their symptoms. In these patients, ER opioid formulations can provide greater relief than IR formulations, as they may improve patient compliance, reduce the occurrence of breakthrough pain, and provide pain control throughout the night. However, the danger of ER opioid formulations is that they contain a much higher amount of active ingredient per dosage unit compared to IR formulations. This can make them targets for **abuse,** which is defined by the FDA as "the intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desirable psychological or physiological effect." ER formulations may be tampered with to release the drug in a more rapid manner. The delivery system may be chewed and swallowed, or crushed and administered via another route, such as through insufflation into the nasal cavity, smoking, or injection.

ER opioid formulations are now being developed with what the FDA refers to as "abuse-deterrent technologies." These technologies are intended to make manipulation of opioid products more difficult or make the manipulated product less rewarding. The FDA has released guideline information to aid the pharmaceutical industry in developing new abuse-deterrent opioid products. The FDA considers all opioids with abuse-deterrent properties against the standards set by currently available products; thus, the standards will evolve based on the products currently available on the market. The abuse-deterrent properties that the FDA outlines in its guidance document are physical or chemical barriers, agonist/antagonist combinations, aversion, delivery system, new molecular entities or prodrugs, combination, or novel approaches.

Further Reading

Suggested readings for the student include the following texts:

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Chapter 5
Solution-Based Dosage Forms and Sterile Products

Abstract This chapter expands upon the concept of drug solubility and dissolution as it relates to dosage form design. Excipients utilized in solution-based dosage forms and parenteral products are discussed in detail, including solvents, cosolvents, antioxidants, preservatives, complexing agents, and surfactants. Special considerations which must be made for parenteral dosage forms are introduced. Lastly, a review of lyophilization and sterilization techniques is provided.

Keywords Sterile product · Intravenous administration · Intramuscular administration · Parenteral drug delivery · Solubility · Lyophilization · Dissolution · Surfactant · Injectable · Sterilization

Learning Objectives

- Describe the relative terms of solubility as defined by the USP.
- Describe the factors that affect the solubility of a drug when preparing a solution.
- Compare and contrast the different solvents that may be utilized in pharmaceutical preparations.
- Compare the use and ranges of preservatives typically used in pharmaceutical solutions.
- Explain what cyclodextrins are and why they are used in pharmaceuticals.
- Compare and contrast intravenous, intramuscular, and subcutaneous routes of administration.
- Describe the methods used to sterilize pharmaceutical products.
- Explain what pyrogens are and how their level is controlled in pharmaceutical preparations.
- Describe the different excipients used in parenteral formulations.
- Describe the three stages of the lyophilization process.
- Describe the typical formulation components (i.e., functional classes of excipients and examples of each and their role) used in lyophilized products.
- Explain syringeability and injectability as related to injectable dosage forms.
- Summarize the typical containers and closures used for injections.

A. D. Brunaugh et al., *Essential Pharmaceutics*, AAPS Introductions in the Pharmaceutical Sciences, https://doi.org/10.1007/978-3-030-31745-4_5

- Explain the differences between a single-dose container and a multi-dose container for injections.
- Explain the advantages of the nasal route for drug delivery.
- Describe the different excipients used in nasal formulations.

Key Concepts

Students should know and be able to describe each of the following concepts as they review this chapter:

- Antioxidants
- Bulking agent
- Cake (lyophilization)
- Chelating agents
- Co-solvent
- Completely miscible
- Critical micelle concentration
- Cryoprotectant
- Cyclodextrins
- Depot injections
- Dissolution
- Injectability
- Injectable administration
- Intramuscular (IM) administration
- Intravenous (IV) administration
- Isotonic
- Large-volume parenterals
- Lyophilization
- Lyoprotectant
- Micelles
- Miscibility
- Negative heat of solution
- Noyes–Whitney equation
- Oxidation
- Parenteral drug delivery
- Partially miscible
- Phlebitis
- Positive heat of solution
- Preservatives
- Pyrogens
- Relative solubility
- Salting-in
- Salting-out
- Small-volume parenterals
- Solution-based dosage forms
- Solvent
- Subcutaneous (SC) administration

- Sublimation
- Surfactants
- Syringeability

5.1 Introduction

A **solution-based dosage form** is defined as a liquid preparation that consists of a solute, such as a drug or an excipient, dissolved in a solvent to form a homogeneous, single-phase, molecular solution. The solvent is typically aqueous based and may also include an organic co-solvent, depending on the physicochemical properties of the drug. Solution-based dosage forms are utilized in almost all administration routes of delivery, including

1. Oral
2. Parenteral (e.g., injectable)
3. Ophthalmic
4. Nasal
5. Pulmonary
6. Transdermal

5.2 Drug Solubility

The solubility of a drug indicates the maximum amount of the drug that can be dissolved in a solvent at a specific temperature and pressure. As described by the USP, equilibrium solubility is determined by forming a saturated solution of a drug at a constant temperature and pressure, followed by sampling an aliquot of the solution at a time point at which dissolution has plateaued (i.e., changed by less than 5% over 24 h or less than 0.2% per h), and then chemically analyzing it to determine the amount of the substance dissolved under those given conditions. Alternatively, a drug may be categorized in terms of **relative solubility**, in which solubility is defined as the parts of solvent required to dissolve one part of solute (e.g., the drug). Relative solubility is a descriptive term. The USP defines solubility qualitatively as described in Table 5.1.

5.2.1 Factors Influencing Solubility

Solubility is dependent upon the physicochemical properties of the drug, as well as the temperature, pressure, and pH of the solvent. The pK_a of the drug plays an important role in solubility, as it will determine the degree of ionization of the drug

Table 5.1 USP descriptive solubility terms

USP term	Parts of solvent required to dissolve one part of solute (e.g., drug)	Solubility (mg/mL)
Very soluble	Less than 1	>1000
Freely soluble	1–10	100–1000
Soluble	10–30	30–100
Sparingly soluble	30–100	10–30
Slightly soluble	100–1000	1–10
Very slightly soluble	1000–10,000	0.1–1
Practically insoluble	Greater than 10,000	<0.01

Table 5.2 General rules of aqueous solubility for organic molecules (e.g., drugs)

One polar functional group	Soluble up to chain length of five carbons
Branched chain	More soluble than unbranched chain
High molecular weight	Less soluble than low molecular weight
Increased similarity between solute and solvent	Increased solubility

at a particular solvent pH. The concepts of pK_a, ionization, and solubility are explained further in Chap. 2, Preformulation Studies.

For a solute to dissolve into solution, both solute–solute and solvent–solvent interactions must be broken, and new solute–solvent interactions must form. In general, solubility follows the rules of "like dissolves like." Polar substances dissolve in polar solvents through dipole–dipole interactions and hydrogen bonding, while nonpolar substances dissolve in nonpolar solvents through Van der Waals interactions. General rules for solubility of drugs are described in Table 5.2.

The temperature of the system can affect solubility. Most drugs have a **positive heat of solution**, meaning they absorb heat when they are dissolved, and thus have greater solubility at higher temperatures. In other cases, the drug may have **negative heat of solution** and the addition of heat decreases its solubility.

The solubility of drugs that are weak acids or weak bases is affected by the pH of the solvent, as the ionized form of the drug will be present based upon the pKa of the ionizable group. As discussed in Chap. 2, Preformulation Studies, the ionized species typically has a higher solubility than the unionized species in aqueous environments. Thus, adjustment of solvent pH can be an effective means of increasing solubility.

The presence of electrolytes can increase or decrease the solubility of nonelectrolytes. When the solubility decreases with the addition of an electrolyte, it is referred to as **salting-out**. This occurs as a result of interactions between the electrolyte and

water exceeding interactions with the non-electrolyte and water. If solubility increases with the addition of an electrolyte, it is defined as **salting-in**.

In the case of liquid–liquid solutions, the solubility of the individual components is defined in terms of their **miscibility**. In the context of liquid solvents, miscibility describes the ability of one liquid to mix (or dissolve) in another liquid. Miscibility is also used to describe the ability of a drug to mix (or dissolve) in a polymer to form a solid solution.

(a) **Completely miscible** refers to the ability of the solution components to homogeneously mix to form a molecular solution.
(b) **Partially miscible** refers to the state in which certain amounts of two solvents are mixed together and two liquid layers are formed, each of which contains some of the other liquid dissolved.

5.2.2 Factors Influencing Dissolution

Dissolution refers to the time-dependent process of a material (e.g., drug) dissolving in a solvent to form a solution. When preparing a solution, certain factors can affect the rate at which the drug dissolves in the solvent. The **Noyes–Whitney equation** describes the rate at which a solid (e.g., particles of drug) dissolves in a solvent.

$$\frac{dm}{dt} = \frac{DS}{h}\left(C_s - C\right)$$

Where,

M = Mass of solute
t = Time
dM/dt = Mass rate of dissolution
D = Diffusion coefficient of the drug
S = Surface area of the drug
h = Thickness of the diffusion layer or stagnant layer
C_s = Saturation solubility of the drug
C = Concentration of the drug in solution at a specific time

A drug particle in a solvent will be surrounded by a layer of stagnant solvent that moves along with the particle, represented by “h” in the Noyes–Whitney equation. The particle’s ability to dissolve in the solvent is dependent upon the rate at which the dissolved molecule of drug is able to move through this stagnant solvent layer and out into the bulk solution. The difference in drug concentration between the stagnant layer and the bulk solution (i.e., the concentration gradient) is what drives the drug molecule to diffuse to the bulk solution. The greater the difference in concentration, the faster the dissolution rate. Likewise, the greater the thickness of the

stagnant layer, the slower the dissolution rate will be. Agitation of the liquid system decreases the thickness of the stagnant layer and increases the chance that the drug molecule will come into contact with unsaturated solvent.

The dissolution rate is also influenced by the size of the particle. Smaller particles generally exhibit a faster dissolution rate. This is due to the increase in surface area, which results in increased exposure of the drug to unsaturated solvent.

5.3 Excipients for Pharmaceutical Preparations

5.3.1 Solvents

A **solvent** is liquid in which other substances are dissolved. The choice of solvent will be dependent upon the compatibility with the drug and excipients in the pharmaceutical formulation and the desired route of administration. Route of administration is critical to consider, as certain solvents are toxic if delivered by a particular route. Other factors such as the desired viscosity and palatability will also differ based upon the desired route of administration.

In cases where a drug has poor solubility in a desired solvent, a co-solvent may be used. A **co-solvent** is a solvent used in combination with another miscible solvent to solubilize a drug. Common pharmaceutical co-solvents include polyethylene glycol (PEG), ethanol, propylene glycol, and glycerin. Oil-based solvents may also be utilized for poorly water-soluble drugs.

Examples of different solvents utilized in pharmaceutical preparations are listed in Table 5.3.

5.3.2 Antioxidants

Oxidation is a degradation process that occurs through reaction of compounds with free radicals. The oxidative process can be catalyzed by the exposure of trace amounts of oxygen to UV radiation or trace metals, leading to the formation of oxygen-free radicals.

Antioxidants work by decreasing the rate of oxidation (retardants) or by prolonging the period before oxidation is initiated (inhibitors). Antioxidants are classified based on the mechanism of oxidation reduction, which includes

(a) Breaking the free radical chain reaction.
(b) Preferentially oxidizing and reacting with free radicals due to their low redox potential.
(c) Chelating trace metals which catalyze oxidation reactions.

Examples of antioxidants are provided in Table 5.4.

Table 5.3 Exemplary solvents for pharmaceutical preparations

Solvent	Relevant properties
Purified water, USP	Purified by distillation, ion exchange treatment, or reverse osmosis to remove impurities to meet purity standards specified in the USP
Water for injection, USP	Purified by distillation or reverse osmosis, and carries the additional requirement that it is pyrogen-free, meaning that it is free of fever-causing substances
Sterile water for injection, USP	Preservative-free
Bacteriostatic water for injection, USP	Contains preservatives (benzyl alcohol)
Sodium chloride injection, USP Dextrose injection, USP Ringer's injection, USP Lactated Ringer's, USP	Isotonic
Alcohol, USP	Miscible with water Antimicrobial properties
Dehydrated alcohol, USP	Must not contain less than 99.5% ethanol by volume
Diluted alcohol, NF	Comprised of equal parts of ethanol and purified water
Rubbing alcohol, USP	Comprised of 70% ethanol, with the remainder consisting of purified water, denaturants, perfumes, and stabilizers, and the bitter substances sucrose octaacetate and denatonium benzoate to discourage oral ingestion. The denaturant consists of acetone, methyl isobutyl ketone (MIBK), and ethanol, and it prevents the separation of the ethanol from the other components using ordinary distillation equipment
Isopropyl rubbing alcohol	70% isopropyl alcohol, with the remainder composed of water, stabilizers, and perfumes
Cottonseed oil Peanut oil Corn oil Soybean oil Sesame oil Castor oil Coconut oil	Must be of vegetable origin
Glycerin	Viscous liquid Miscible with water, propylene glycol, and alcohol Preservative properties
Propylene glycol	Similar viscosity and preservative effect as glycerin and may be substituted for glycerin in solvent applications Miscible with water, alcohol, and glycerin

Table 5.4 Examples of antioxidants

Mechanism	Examples
Compounds that break the free radical chain reaction	Butylated hydroxyanisole (BHA) Tocopherols Ascorbic acid esters
Compounds that are preferentially oxidized and react with free radicals, due to their low redox potential	Ascorbic acid Sodium ascorbate Sodium bisulfate Sodium metabisulfite Sodium formaldehyde sulfoxylate Thiourea
Chelating agent (i.e., chelation of trace metals)	EDTA Citric acid Fumaric acid Tartaric acid

5.3.3 Chelating Agents

Chelating agents are incorporated into solutions to complex trace metals, thereby improving the efficacy of preservatives and antioxidants. See Table 5.4 for examples of chelating agents used in pharmaceutical formulations.

5.3.4 Preservatives

Preservatives help prevent microbial growth in a solution. Examples of some commonly used preservatives in solution-based dosage forms are provided in Table 5.5.

5.3.5 Complexing Agents

A method of improving the solubility of a poorly water-soluble drug is through the use of a complexing agent, an example of which are cyclodextrins. **Cyclodextrins** are starch-derived cyclic oligosaccharides. The oligosaccharide components form a cone shape, with the hydroxyl groups facing the exterior of the cone and the hydrophobic groups facing the interior of the cone. The presence of the exterior hydroxyl groups allows the cyclodextrin to be soluble in water, while the hydrophobic interior creates a pocket where all or a portion of a drug molecule can fit. For an increase in solubility to occur, the drug must strongly interact with the hydrophobic portion of the cyclodextrin. In most cases, the drug forms a 1:1 complex with a cyclodextrin, and the concentration of the dissolved drug increases with increasing concentration of the cyclodextrin. Alternatively, one drug may form a complex with two cyclodex-

Table 5.5 Examples of preservatives for solution formulations

Category	Name	Percent required for effect (%)	Optimal pH	Soluble in water?	Other properties
Alcohols	Ethanol	>15		Yes	
	Benzyl alcohol	1–3	<5	Yes	Contraindicated in pediatric patients less than 2 years Antimicrobial activity is reduced by nonionic surfactants
Acids	Benzoic acid	0.1–0.5	<4.5	Low aqueous solubility, enhanced by the addition of citric acid or sodium acetate	
	Sorbic acid	0.05–2	Acidic	Low aqueous solubility	Prone to oxidation
Esters	Parabens (propylparaben and methylparaben)	0.01–0.18	4–8	Aqueous solubility decreases with increasing molecular weight	Antimicrobial activity increases as chain length of alkyl moiety increases Binds to nonionic surface active agents, which can decrease activity Used with propylene glycol or other antimicrobial agents to enhance efficacy
Quaternary ammonium compounds	Benzalkonium chloride	0.002–0.02	4–10	Yes	Incompatible with anionic compounds and can bind to nonionic surfactants Used in preparations for external use Used with 0.1% edetate disodium to enhance antimicrobial activity against pseudomonas
Others	Propylene glycol	15–30		Yes	
	Glycerin	>50		Yes	

trins. Commonly used water-soluble cyclodextrins are hydroxypropyl-beta-cyclodextrin and sulfobutylether-beta-cyclodextrin (i.e., Captisol®).

5.3.6 *Surfactants*

Surfactants, also called surface active agents, are molecules containing both a hydrophobic and hydrophilic component. They can be incorporated into solution formulations to increase the solubility of drugs and facilitate wetting of the drug in the liquids. Surfactants adsorb onto the surface or interface of a system and alter the surface or interfacial free energy, thus reducing the surface/interfacial tension (Fig. 5.1).

Above certain concentrations, surfactant molecules can self-assemble to form aggregates called **micelles** (Fig. 5.1). The point at which increasing concentration of surfactant leads to micelle formation is called the **critical micelle concentration (CMC)**. Surfactants can solubilize drugs by acting as a co-solvent or through uptake of the drug molecules into these micelles. Examples of surfactants can be found in Table 5.6.

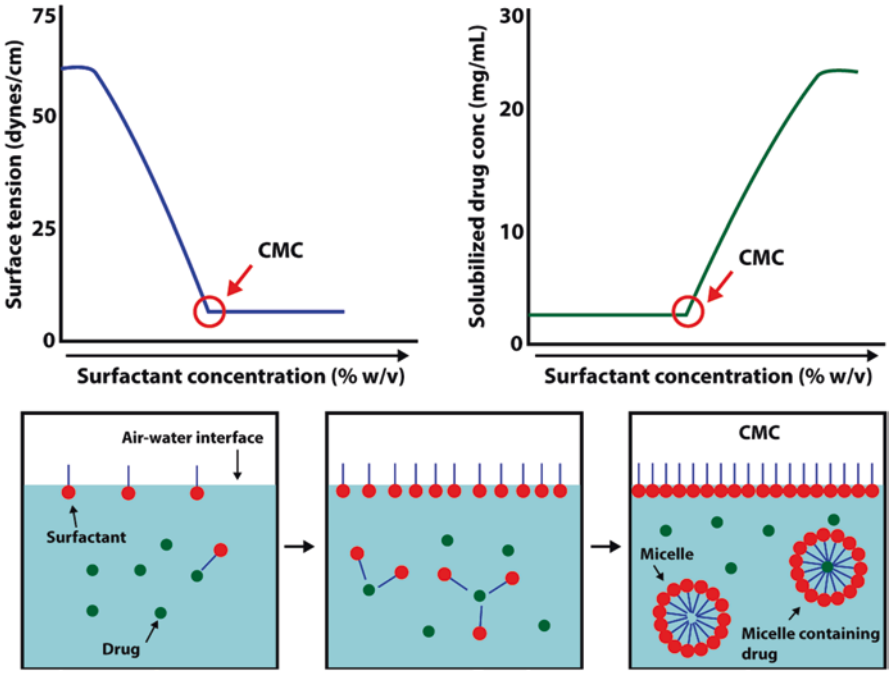

Fig. 5.1 Surfactants adsorb at the interface of a system to decrease surface tension. At a certain concentration (the critical micelle concentration), surfactant molecules self-assemble to form aggregates called micelles

Table 5.6 Examples of surfactants used in pharmaceutical formulations

Category	Examples
Anionic	Potassium laurate Sodium dodecyl sulfate (i.e., sodium lauryl sulfate) Docusate sodium Lauric acid
Cationic	Cetrimonium bromide Benzalkonium chloride
Nonionic	Poloxamer 407 Polysorbate (Tween®) 20, 40, 60, 80 Sorbitan esters (Span®) 40, 60, 80 Polyoxyethylene castor oil (Cremophor® RH) Polyoxyl 15 hydroxystearate (Solutol® HS 15)

5.4 The Parenteral Route and Injectable Dosage Forms

Parenteral drug delivery refers to the delivery of a drug to the site of action through bypassing of the oral route of administration. Injectable drugs are an important subgroup of parenteral dosage forms.

Injectable administration refers to the delivery of sterile drug preparations directly to the blood or tissue. To ensure long-term stability, injectable products can be formulated as a dry powder that requires further reconstitution prior to administration with a suitable solvent. Injectable formulations are further divided into single-dose or multi-dose, depending on the presence of preservatives in the formulation.

Drugs formulated for injection into the body require special consideration, as the formulation must be isotonic, sterile, free of fever-causing agents known as pyrogens, and free of particulate matter if formulated as a solution. Excipients should be non-toxic, sterile, and compatible. A list of example excipients utilized in injectable dosage forms can be found in Table 5.7.

5.4.1 Routes of Administration

Injectable dosage forms are administered via many routes including the intravenous route, the intramuscular route, or subcutaneous route. Each has its own advantages and disadvantages.

Intravenous (IV) administration refers to the injection of a drug directly into a vein. The advantage of the intravenous route is the rapid onset of therapeutic action, but in the case of adverse reactions, the drug cannot be retrieved once it is administered. While there is generally not a volume limitation for the IV route, larger volumes require longer infusion times.

Intramuscular (IM) administration refers to the injection of a drug into a muscle tissue. The volume that can be administered IM is generally limited to

Table 5.7 Exemplary excipients used in injectable formulations

Excipient category	Examples
Solvents	Sterile water for injection, USP Bacteriostatic water for injection, USP Vegetable oils • Castor oil • Cottonseed oil • Medium chain triglycerides • Sesame oil • Soybean oil • Safflower oil
Co-solvents	Ethanol Propylene glycol Polyethylene glycol Glycerin
Buffers	Acetic acid/acetate Citric acid/citrate Phosphoric acid/phosphate Histidine
Tonicity adjusters	Sodium chloride Mannitol Glycerin
Preservatives	Benzalkonium chloride Benzyl alcohol Methylparaben Phenol Propylparaben
Antioxidants	Ascorbic acid Sodium ascorbate Sodium bisulfate Sodium metabisulfite Cysteine
Surfactants	Polysorbate 80 Lecithin
Complexing agents	Hydroxypropyl-β-cyclodextrin Sulfobutylether-β-cyclodextrin
Chelating agents	EDTA Citric acid

3–5 mL. This route also provides rapid onset of action due to extensive vascularization of the muscle.

Subcutaneous (SC) administration refers to the injection of a drug beneath the skin between the dermis and muscle. The volume that can be administered SC is generally limited to 1–2 mL.

5.4.2 Isotonicity

An injectable formulation should be as close to isotonic as possible to reduce the risk of cellular damage and irritation with administration. The term **isotonic** refers to a solution with the same osmotic pressure as the body fluid into which it will be administered. For blood, this value is approximately 290 mOsm/L, although it may range from 285 to 310 mOsm/L. Normal saline (0.9% sodium chloride) is considered an isotonic solution. The tonicity of a drug formulation can be adjusted by the addition of sodium chloride, sucrose, mannitol, or dextrose, or through further dilution.

5.4.3 pH

The pH of injectables should be studied to achieve drug stability, solubility, and tissue compatibility. Often, injectables are formulated at a pH close to physiological pH (pH 7.4), although small volume doses are less stringent in the required pH of the formulation. Administration of a formulation that is not near physiological pH can lead to irritation, pain, and **phlebitis** (inflammation of the vein).

To maintain the intended pH of the product throughout its shelf-life, buffer systems are often added to parenteral products. The buffer concentration and/or buffer strength must be kept at a low enough concentration so as not to alter the pH of the blood or cause tissue irritation.

5.4.4 Syringeability and Injectability

Syringeability refers to the ability to withdraw a homogenous dose through a hypodermic needle from a vial. Factors that are assessed when determining an injectable product's syringeability include the ease of withdrawal from the vial, clogging or foaming tendencies of the liquid product, and the accuracy of the dose measurements.

Injectability refers to the ability to eject the liquid formulation from a needle into a patient. Factors that are assessed include pressure or force needed for a successful injection, the evenness of flow of the product from the syringe, clogging, and accuracy of the dose. Needle geometry and surface finish of the syringe may affect syringeability and injectability.

5.4.5 Long-Acting Injectable Formulations

To ensure sustained administration of drug over time, long-acting injectable formulations have been developed. They are especially useful in the treatment of diseases in which patient compliance is poor, such as schizophrenia. Examples include sterile implants that are placed under the skin, or IM or SC injection formulations that upon administration create a depot from which drug is released over time (e.g., **depot injections**).

Mechanisms of long-acting injections include:

(a) Formulation of a drug solution in an oil-based solvent, from which the drug is slowly absorbed into the surrounding tissue.
(b) Incorporation of the drug into a biodegradable polymer microsphere, such as poly(lactide-co-glycolide) (PLGA).
(c) Formulation of a drug suspension in a liquid vehicle, from which the drug slowly dissolves and diffuses into the surrounding tissue.

5.5 Lyophilization

The long-term storage of a drug formulation in dry powder form is useful if a drug is prone to degradation when formulated as an aqueous solution. **Lyophilization**, also known as freeze-drying, is a process used to create a dry powder product from a liquid that can be reconstituted with the addition of a solvent. Lyophilization works by the process of **sublimation,** which is the direct conversion of a solid water (ice) to a vapor. Sublimation of ice (water) requires low pressure.

The three stages of the lyophilization process are freezing, primary drying, and secondary drying, as described below.

(a) In the freezing stage, the drug formulation in solution is frozen at atmospheric pressure. For crystalline drugs, freezing should occur below the eutectic (freezing/melting point) temperature, and for amorphous drugs, it should occur below the glass transition temperature.
(b) In the primary drying stage, a vacuum is applied to the frozen solution, causing sublimation and removal of the ice from the frozen system. A powder remains at this point, though it will still have residual frozen water present.
(c) In the secondary drying stage, heat is introduced into the system under vacuum, and any remaining water is removed from the formulation.

Ideally, the end product of the lyophilization process will be a porous solid structure (known as a **"cake"** or a "plug") consisting of the originally dissolved solids. The cake must be of sufficient strength, dryness, and porosity to ensure stability and quick reconstitution time. If the reconstituted drug product will be used parenterally, it is also important that the lyophilized cake is sterile and free of pyrogens.

Table 5.8 Exemplary excipients for lyophilization

Excipient category	Examples
Bulking agent	Mannitol Lactose Sucrose Trehalose Glycine
Cryoprotectant	Albumin Sucrose Polyethylene glycol Lactose Mannitol
Lyoprotectant	Sucrose Trehalose Dextran Amino acids Lactose Mannitol

A lyophilized formulation can contain a **bulking agent** to increase the solid contents of the formulation, a **cryoprotectant** to protect the drug during the freezing process, and a **lyoprotectant** to protect the drug during the sublimation process. As with other solution formulations, buffering agents, antioxidants, and preservatives may be included to maintain stability. Often, excipients serve multiple functions in the formulation. Examples of excipients used in lyophilization are described in Table 5.8.

5.6 Sterilization of Pharmaceutical Products

There are several ways to sterilize drug products, the choice of which will depend on the physicochemical properties of the drug.

5.6.1 Heat Sterilization

Heat sterilization can be achieved by using steam or dry heat. An autoclave is used for steam sterilization. In this process, pressure is used to increase the temperature of the system to a point at which microbial proteins are denatured and coagulated. This method requires that the drug containing formulations undergoing sterilization can withstand temperatures of 121 °C and are also not sensitive to moisture. It is often used for aqueous solutions in sealed containers, glassware, and surgical dressings. Steam sterilization should be avoided for oils and fats.

Alternatively, an oven can be used to achieve dry heat sterilization. This process requires higher temperatures (>160 °C) and longer exposure times than steam sterilization and is used to sterilize dry chemicals, oils, glycerin, or petroleum products.

5.6.2 Sterilization of Heat-Sensitive Drugs

If the drug is sensitive to heat (i.e., thermally labile), sterilization can be achieved through sterile filtration of the drug solution. As the solution is pushed through the filter, microorganisms are trapped onto a filter. The disadvantage with this type of sterilization, however, is that the drug itself may also be adsorbed onto the filter.

Gas sterilization is also an option for heat-sensitive or moisture-sensitive drugs. Ethylene oxide or propylene oxide is the typical gas used, and exposure occurs in a device similar to an autoclave. Gas sterilization process is affected by concentration of the gas, length of exposure, temperature, and humidity of the system. Caution must be taken when working with these gases, as they are flammable and explosive.

5.6.3 Pyrogen Testing

Pyrogens are the lipopolysaccharide by-products of microorganisms. In mammals, pyrogens produce fever, and their presence can lead to other toxic immune responses in the body, such as septic shock. Because pyrogens are water soluble and heat stable, they may remain in the product even after sterilization, which necessitates the need for careful prevention of contamination and thorough testing of the product.

The recognized USP standard method to determine the presence of pyrogens is the Limulus amebocyte lysate (LAL) test. This test utilizes blood from the horseshoe crab, which coagulates in the presence of low levels of lipopolysaccharides.

5.7 Packaging of Sterile Injections

In order to maintain a sterile product, the type of container used requires careful consideration. Injections may be stored in single-dose or multi-dose vials. Single-dose containers do not remain sterile upon opening; however, multi-dose vials may be entered repeatedly without compromising the integrity of the product. Single-dose containers include single-dose vials and ampoules. Product from ampoules must be withdrawn using a filter needle, due to the possible presence of glass particulates.

It is important that the container must not react with the sterile drug product and that the container allows for easy inspection of the product to check for the presence of particulates.

USP further defines parenteral products as small volume or large volume. **Small-volume parenterals** are packaged in containers that contain 100 mL or less, while **large-volume parenterals** are packaged in containers that contain more than 100 mL.

5.7.1 Labeling Requirements

If liquid, the label of a parenteral product must state the percent content of drug or the amount of drug in the specified volume and, if dry, the amount of active ingredient present and volume of liquid to be added. The label should also include the name of the drug, the route of administration, storage conditions and expiration date, name of manufacturer and distributor, and lot number.

Further Reading

Suggested readings for the student include the following texts:

1. Fricker G, Kromp T, Wendel A, Blume A, Zirkel J, Rebmann H, Setzer C, Quinkert RO, Martin F, Müller-Goymann C. Phospholipids and lipid-based formulations in oral drug delivery. Pharm Res. 2010;27(8):1469–86.
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3. Surasarang SH, Williams RO. Co-solvent and complexation systems. In: Formulating poorly water soluble drugs. 2nd ed. New York: Springer; 2016. p. 215–56.

Chapter 6
Disperse Systems: Suspensions

Abstract This chapter covers crucial aspects of the formulation of pharmaceutical suspensions. Properties relevant to suspension stability and drug delivery are discussed, including particle settling, flocculation, particle aggregation, viscosity, zeta potential, and Ostwald ripening are discussed. Methods of particle size reduction are introduced, including those to produce nanoparticles. An extensive discussion of relevant excipients is also included.

Keywords Suspension · Dispersion · Viscosity · Particle settling · Suspension stability · Particle size reduction · Colloidal dispersion · Nanoparticles · Suspending agents · Surfactant

Learning Objectives

- Describe a pharmaceutical suspension.
- Explain the desired features of a pharmaceutical suspension.
- Explain how Stokes' equation describes the rate of settling of particles of a suspension.
- Compare and contrast flocculated and deflocculated suspensions.
- Describe rheology and viscosity as it relates to pharmaceutical suspensions.
- Compare and contrast the five different types of non-Newtonian flow.
- Explain how the stability of a suspension is characterized.
- Describe how aggregation of suspended particles is prevented.
- Explain the concept of instability due to particle growth by Ostwald ripening.
- Describe three different methods of particle size reduction.
- Explain Brownian motion as it relates to colloidal dispersions.
- Compare and contrast the different technologies used to produce drug nanocrystals.
- Explain how nanocrystal delivery achieves increased solubility and dissolution rate of a poorly water-soluble drug substance.
- Explain why nanoparticles can be more unstable than microparticles when formulated as a suspension.
- Explain the function of surface active agents (i.e., surfactant) as used in pharmaceutical dosage forms.

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- Explain the concept of critical micelle concentration.
- Explain how the contact angle relates to wetting and wetting agent.
- Compare and contrast the four classes of pharmaceutical surfactants.
- Describe the different excipients that are included in suspension formulations.

Key Concepts

Students should know and be able to describe each of the following concepts as they review this chapter:

- Association colloids
- Bingham/plastic flow
- Brownian motion
- Coarse dispersion
- Colloidal dispersion
- Comminution
- Contact angle
- Deflocculated suspension
- Disperse system
- Electrostatic stabilization
- Fick's first law
- Flocculation
- Floccule
- High-pressure homogenization
- Lyophilic colloids
- Lyophobic colloids
- Newtonian flow
- Non-Newtonian flow
- Ostwald ripening
- Rheology
- Shear rate
- Shear stress
- Shear-thickening/dilatant flow
- Shear-thinning/pseudoplastic flow
- Steric stabilization
- Stokes–Einstein equation
- Structured vehicle
- Surface free energy
- Surfactant
- Suspension
- Thixotropic flow
- Tyndall effect
- Viscoplastic flow
- Viscosity
- Wet ball milling
- Wetting agent
- Zeta potential

6.1 Introduction

A **disperse system** is defined as a two-phase system in which an insoluble or immiscible dispersed phase (e.g., solid particles or liquid droplets) is distributed through a continuous phase**.** Disperse systems are typically classified based upon the size of the dispersed phase (i.e., particles or droplets).

(a) **Colloidal dispersions** are generally defined as disperse systems in which the particles/droplets (dispersed phase) are smaller than 0.5 μm.
(b) **Coarse dispersions** are generally defined as disperse systems in which the particles/droplets (dispersed phase) are larger than 0.5 μm.

Dispersions can also be categorized as suspensions (a solid dispersed in a liquid) or emulsions (liquid dispersed in a liquid), depending on the properties of the dispersed phase.

A **suspension** is a liquid disperse system consisting of particles distributed uniformly within a liquid vehicle (also called the suspending medium) in which the particles have minimum solubility. Suspensions may be formulated for various routes of administration, including oral, ophthalmic, otic, inhalation, nasal, and injectable routes. Suspension formulations may be utilized when:

(a) There is not a suitable solvent available to dissolve a drug.
(b) To mask the taste of drugs.
(c) To control the release of drugs. For example, drugs intended for injection may be formulated as a suspension for intramuscular injection utilizing an oily or aqueous vehicle in order to create a depot that the drug is slowly released from over time.

6.2 Properties of Suspensions

To ensure a uniform dose of a medication, a pharmaceutical suspension should have the following properties:

(a) Particles settle slowly
(b) Particles are readily and uniformly redispersed upon shaking
(c) Particle size remains consistent over time
(d) Viscosity is high enough to ensure a uniform dose, but not so viscous that the suspension cannot be easily poured/measured from the bottle or injected

6.2.1 Particle Settling

Stokes' law describes the particle settling rate for coarse dispersions and is described by the following equation:

$$v = d^2 \left(\rho_s - \rho_v \right) g \,/\, 18\eta$$

where,

v = Sedimentation rate (cm/s),
d = Particle diameter (cm)
ρ_s = Particle density (g/cm^3)
ρ_v = Vehicle density (g/cm^3)
g = Force of gravity (981 cm/s^2)
η = Vehicle viscosity (P)

Stokes' law assumes that the particles are spherical, the suspension is dilute (less than 2% w/v), the particles do not flocculate, there is no **Brownian motion** (random motion resulting from collisions of the drug particles as a result of being continuously bombarded by molecules of the liquid vehicle), and there are no electrical effects.

As described by Stokes' equation, the settling rate is directly proportional to the size of the suspended particles. The rate of settling for a larger particle will be greater than that of a smaller particle. Therefore, reducing particle size is one method of reducing the settling rate. Likewise, higher density particles will settle at a faster rate than lower density particles. The rate of sedimentation can also be reduced by increasing the viscosity of the suspending medium.

For example, consider a drug particle with a density of 1.3 g/cm^3 and diameter of 20 μm, suspended in two different vehicles: glycerin, with a viscosity = 950 cP at 25 °C and density of 1.262 g/cm^3, or water with a viscosity = 0.89 cP at 25 °C and density of 1 g/cm^3. Glycerin is much more viscous than water, so suspending a particle in this vehicle will result in a settling rate of 8.7×10^{-9} cm/s, while the same particle suspended in water will have a settling rate of 7.3×10^{-3} cm/s. In other words, the particle will sediment more than 6.5 cm in water after 900 s (15 min), whereas in glycerin the particle will have sedimented less than 80 nm over the same time period.

6.2.2 Flocculation, Deflocculation, and Aggregation

Particles dispersed in a liquid vehicle can exhibit Van der Waals attractive and electrostatic repulsion forces. As a result of these forces, particles may be deflocculated, flocculated, or aggregated. Forces at the surface of the particle (i.e., attractive or electrostatic repulsive forces) determine the degree of flocculation and aggregation.

A **deflocculated suspension** refers to a system in which particles are individually and uniformly dispersed throughout the liquid medium. A system will remain deflocculated when repulsive energy between the suspended particles is high, as this repulsion opposes direct collision and contact of the particles. Deflocculated particles may settle slowly however, and over time a layer of particle sediment will form at the bottom of the suspension that will be difficult to resuspend. This happens because as settling occurs, small particles fill in the gaps between larger sedimented particles resulting in the formation of a closely packed arrangement at the bottom of the suspension. In addition, the particles at the bottom of this arrangement are further compressed by the weight of particles settling above them. Even though the particles have repulsive energy barrier, this compression allows the particles to come into closer contact and repulsion is overcome and particles may also form crystal bridges. The result is a compact cake of irreversibly aggregated particles that is not dispersed upon shaking, due to the high energy required to resuspend the particles.

A **flocculated suspension** refers to a system in which suspended particles are formed into **floccules** (i.e., weakly attracted or weakly bonded aggregates of particles) rather than separate particles. In pharmaceutical formulations, controlled flocculation is a mechanism to prevent particle caking in suspension formulations. Floccules are held together by weak particle-to-particle bonds (i.e., Van der Waal forces), but the particles still remain a small distance apart from one another. Flocculation occurs when attractive forces between particles are slightly greater than repulsive forces. When included in a suspension, flocculated particles settle more rapidly than individual particles. However, they do not settle completely, which makes them less prone to compaction and formation of a cake that is difficult to resuspend at the bottom of the bottle. This allows for easier resuspension of the particles compared to deflocculated particles. Reducing the surface charge of particles, also known as the zeta potential, is one means of inducing flocculation. This can be achieved through the addition of electrolytes or surface-active agents.

6.2.3 Rheology

Fluid materials flow when subjected to stress. **Rheology** refers to the study of this flow, and **viscosity** refers to the resistance of a material against flow or the measure of its internal friction. The higher the viscosity, the more resistant the material to flow. Viscosity is a function of shear rate and temperature. **Shear rate** is defined as the speed of the movement of the layers of liquid with respect to one another when force is applied, while **shear stress** is defined as the force per unit area required to bring about flow.

Materials may exhibit Newtonian or non-Newtonian flow behavior. If a material has **Newtonian flow** (Fig. 6.1), viscosity remains constant regardless of shear stress applied. In other words, Newtonian fluids have a linear relationship between applied stress and flow. An example of a Newtonian fluid is water.

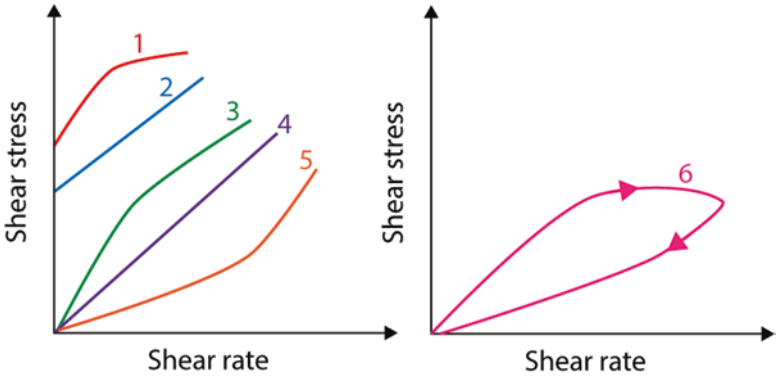

Fig. 6.1 Flow curves of various fluids are shown. (*1*) A viscoplastic fluid, (*2*) a plastic fluid (Bingham), (*3*) a pseudoplastic fluid, (*4*) a Newtonian fluid, (*5*) a dilatant fluid, and (*6*) an exemplary thixotropic fluid

Systems that do not follow Newton's law of flow are referred to as exhibiting **non-Newtonian flow** (Fig. 6.1). These systems do not consistently show a linear relationship between applied stress and flow, although a linear relationship may exist for a certain period of time. Suspensions are an example of a system that typically exhibits non-Newtonian flow.

Non-Newtonian flow can be further subdivided into

(a) **Shear-thinning or pseudoplastic flow:** These systems show a decrease in viscosity with increasing shear rates. At very low shear-stress values and very high shear-stress values, the viscosity reaches a constant value. These regions are referred to as the lower and upper Newtonian regions. This type of flow occurs in solutions that contain celluloses or polymers. When stress is applied, these macromolecules tend to orient in the same direction and exhibit a reduced resistance to flow and decreased viscosity.

(b) **Bingham or plastic flow:** In these systems, a critical level of stress (called the "yield stress") is necessary to initiate flow, after which the material exhibits Newtonian flow.

(c) **Viscoplastic flow:** A critical level of stress (called the "yield stress") is necessary to initiate flow, after which the material exhibits shear-thinning behavior until reaching a plateau.

(d) **Shear-thickening or dilatant flow:** These systems show an increase in viscosity with increasing shear-strain rate, due to structural rearrangement of the material. Shear-thickening behavior typically occurs only over a short range of shear strain rate. Shear-thickening flow is more likely to occur in suspensions with high concentrations of particles.

(e) **Thixotropic flow:** In these systems, application of shear results in gradual decrease in viscosity followed by a recovery. This can be thought of as a reversible transition between an elastic solid state and a liquid state. These systems can flow like a liquid when exposed to high shear rates (such as the shaking of

a bottle). When the shear stress is removed, the system reverts back to the elastic solid state over time due to rebuilding of internal network structures of the material. This type of system is useful because when the formulation is in the elastic solid state, the particles have reduced tendency to settle due to the viscosity of the vehicle.

6.2.4 Electrical Charge and Zeta Potential

At the interface between the dispersed particles and aqueous medium, electrical charge develops as a result of ionization of surface functional groups and adsorption of ions onto the particle. A double layer of electrical charge develops consisting of the surface charge and surrounding counterions, and an electrical potential develops between the surface and the bulk phases of the interface. This electrical potential between the tightly bound surface liquid layer on a particle and bulk phase of the vehicle is defined as the **zeta potential** (Fig. 6.2). The zeta potential can be thought of as the effective charge of the particle, and it influences the repulsive and attractive forces between suspended particles. The zeta potential is measured by applying an electrical field to the particle and observing its motion.

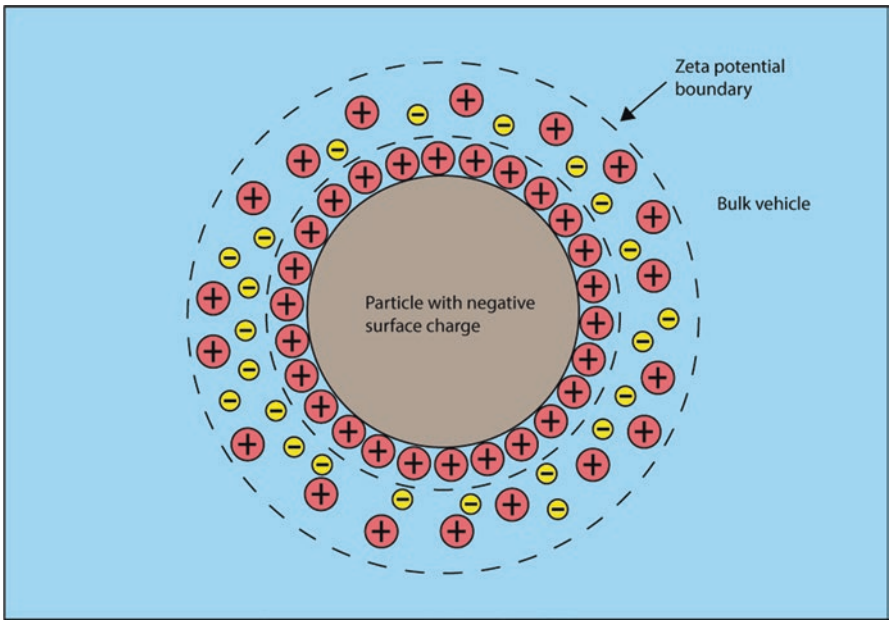

Fig. 6.2 Suspended particles develop a double layer of electrical charge. The electrical potential between tightly bound surface liquid layer on particle and bulk phase of the vehicle is defined as the zeta potential

6.3 Stability of Suspensions

Both chemical and physical stability must be carefully considered for suspension formulations.

As with all pharmaceutical formulations, drug degradation in suspension must be assessed. To ensure chemical stability, in some cases suspensions are stored in powder form and reconstituted immediately before use.

Physical stability can be characterized by particle settling, particle growth (known as Ostwald ripening), and aggregation. These are assessed by determining the settling rate and volume, as well as the uniformity of the suspension after agitation. Changes in particle size distribution can be assessed using a microscope or light-scattering techniques.

6.3.1 Particle Settling

Settling can be reduced through the use of a **structured vehicle**, which is a viscous aqueous solution containing natural and/or synthetic polymers (e.g., gums) that are designed to slow particle settling and reduce sedimentation by providing more viscosity to the continuous phase of the liquid vehicle.

6.3.2 Particle Aggregation

Suspensions are thermodynamically unstable because the relatively large surface area of particles created from the **comminution** process (particle size reduction or milling process) is associated with an increased surface free energy. Generally, **surface free energy** refers to the work done by the force that creates the new surface. It can also be thought of as the energy input required to disrupt intermolecular bonds and create new surfaces. Dispersion of the particles within a liquid vehicle in which they have low solubility also requires a significant amount of energy input, as a result of the increased area of the liquid–solid interface and the interfacial surface tension.

Micronized solid particles are highly energetic and tend to regroup or aggregate to decrease exposed surface area and thereby decrease surface free energy. In some cases, irreversible particle–particle aggregation will occur as a result of strong attractive forces between the particles, and as a result, a suspension may no longer be uniformly dispersed.

Surfactants stabilize suspensions by decreasing interfacial tension, which reduces the surface energy of the system. Surfactants may also have a steric stabilization effect, in which particles are repulsed from one another by the adsorbed surfactant layer on the surface of the particles.

Particle charge can also have an effect on dispersion stability. Particles can acquire charge as a result of ionizable groups present on the molecule or by the adsorption of ions onto the particle surface. Attraction of particles of opposite charge leads to an increased tendency for the particles to aggregate. If the particles within a dispersion have the same surface charge, electrostatic repulsion can result in the dispersion having greater stability against particle aggregation. The zeta potential (i.e., the effective charge of the particle in suspension) influences these attractive and repulsive forces. As the zeta potential increases in magnitude (i.e., either more negative or more positive), the degree of repulsion between particles also increases. At low zeta potential (i.e., closer to neutral charge), there may be insufficient repulsive forces to prevent particles from coming together, resulting in aggregation and instability of the dispersion. It therefore may be advantageous to alter the zeta potential through the introduction of ionic surfactants and electrolytes.

6.3.3 Particle Growth (Ostwald Ripening)

Ostwald ripening is a phenomenon where particles within a suspension tend to grow in size over time and during storage. Fluctuations in temperature during storage of a suspension may result in small changes in drug solubility. Small increases in temperature can result in the dissolution of the smallest particles within a suspension, and when temperature returns to lower values, the dissolved drug preferentially recrystallizes on the surface of larger particles that remain in suspension (Fig. 6.3). This leads to an overall shift in the particle size distribution of a suspension toward larger particles. Ostwald ripening is reduced in suspensions with a narrow particle size distributions, as all particles demonstrate similar solubility.

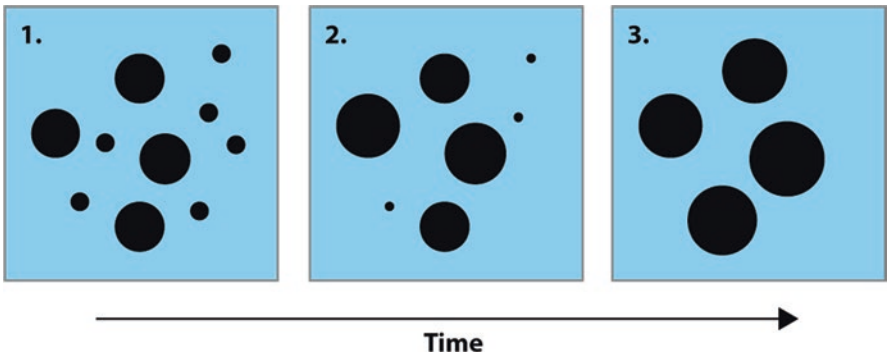

Fig. 6.3 Ostwald ripening occurs when small particles dissolve in a suspension and recrystallize onto larger particles. This results in a shift in the particle size distribution toward larger particles

Large fluctuations in temperature of the system should likewise be avoided, as a drug might be soluble at a higher temperature but then crystallize out when the temperature is lowered, resulting in a change in the particle size distribution or conversion to a different polymorph.

6.4 Methods of Particle Size Reduction for Suspensions

The size of particles within a suspension can affect the sedimentation rate as well as the ability to resuspend the particles. If the absorption of a drug when administered to a patient is dissolution rate limited, decreasing the particle size can also increase the bioavailability of the drug by increasing the dissolution rate. In addition, if the particles are too large in a suspension, the formulation will have gritty texture which can be unpleasant and unacceptable for ophthalmic or topical administration.

On a small scale, particle size can be reduced through mechanical grinding of particles using a mortar and pestle. A wetting agent or the suspension vehicle is added to the particles to make a smooth paste, which is then incorporated in the final suspension formulation. On the larger manufacturing scale, microfluidization and homogenization are useful techniques for the reduction of particle size.

In the context of pharmaceutical dispersed systems, **homogenization** is the mechanical size reduction of particles through high energy shear forces, cavitation, and collisions. Piston gap homogenization is a process in which drug particles are suspended in an aqueous surfactant solution and stirred at high speeds. The suspension is then passed through a homogenizer where it must move through an opening that is much narrower than the original reservoir. This rapid change in volume causes an increase in pressure that is then quickly relieved when suspension flows into another wide reservoir. These rapid changes in pressure result in a bubble implosion that creates cavitation force and particle breakage.

Similar to homogenization, **microfluidization** reduces particle size by shear forces. The suspension is passed through a chamber at a high velocity. In this chamber, the particles undergo collisions that lead to particle breakage and size reduction.

6.5 Colloidal Dispersions

Colloidal dispersions consist of particles or droplets less than 0.5 μm in diameter that are dispersed within a liquid phase. Examples include liposomes and nanoparticles.

Colloidal dispersions are generally classified based on the affinity between the dispersed phase and the continuous phase. These include:

(a) **Lyophilic (solvent-loving) colloids**, in which there is attraction between the dispersed phase and the vehicle. If the vehicle is aqueous, these are known as hydrophilic colloids. They are generally thermodynamically stable.

(b) **Lyophobic (solvent-hating) colloids**, in which there is little attraction between the dispersed phase and the vehicle. If the vehicle is aqueous, these are known as hydrophobic colloids. They are generally thermodynamically unstable.
(c) **Association colloids**, in which the dispersed particles are considered amphiphilic. These particles have a tendency to associate into larger agglomerates when placed in oil or water vehicles. An example of this is micelles formed by surfactants. They are generally thermodynamically stable.

Colloidal dispersions have special properties, including

(a) Light scattering (Tyndall effect)
(b) Brownian motion

6.5.1 Light Scattering Properties of Colloids

Colloid dispersions scatter light when a narrow beam of light is passed through the dispersion. This is known as the **Tyndall effect**. It provides a means of measuring the concentration of droplets within the dispersion through the relationship between turbidity and Beer's law.

6.5.2 Kinetic Movement of Colloids

Due to the particle size range of colloidal dispersions (1 nm up to 0.5 μm), the particles do not undergo sedimentation due to gravity. Instead, the particles are subject to the phenomenon of **Brownian motion**, which is defined as the random motion of particles that occurs as a result of particle collisions with molecules of the surrounding medium. The result of Brownian motion is that particles in the colloidal range remain suspended without sedimentation indefinitely. As particle size increases, the tendency for particles to sediment increases.

Particles in a colloidal dispersion will diffuse from an area of high concentration to an area of lower concentration according to **Fick's first law** (shown below).

$$J = -D\frac{dC}{dx}$$

where

J = Mass flux
D = Diffusion coefficient
dC/dx = Concentration gradient

The diffusion coefficient is described by the **Stokes–Einstein equation**:

$$D = \frac{kT}{6\pi\eta R}$$

where

D = Diffusion coefficient
k = Boltzmann constant
T = Absolute temperature
η = Viscosity of the medium
R = Hydrodynamic radius of the particle, droplet, or phase

As demonstrated by the two equations, the magnitude of the diffusion is inversely proportional to the size of the particle (dispersed phase) and the viscosity of the medium. Smaller particles (or droplets) will exhibit faster diffusion, while a more viscous medium will result in slower diffusion.

6.5.3 Nanoparticles in Suspensions

Delivery of particles within the nanometer range can increase the dissolution rate of poorly water-soluble drug substance in the GI fluids, thereby improving bioavailability in many cases. Reduction in particle size results in increases in particle surface areas and also decreases the diffusion layer thickness, resulting in a higher dissolution rate. However, this reduction in particle size also leads to a more unstable suspension due to the increase in surface free energy as a result of the increased surface energy created through particle size reduction methods. Particles will thus have a tendency toward agglomeration in order to reduce the surface area and free energy. The inclusion of a physical stabilizing agent, e.g., a surfactant, is necessary to prevent the particles from agglomerating; however, there must be a balance as too little stabilizer allows agglomeration while too much stabilizer may promote Ostwald ripening through solubility changes.

Stabilization of nanocrystals may be achieved through:

(a) Thermodynamic stabilization, which utilizes a coating of surfactant or polymer around the particles or
(b) Kinetic stabilization, which utilizes additional energy input to compensate for the increased free energy in the system

Several technologies are used to manufacture drug nanoparticles. In particular, stable nanosuspension formulations have been achieved using wet ball milling and high pressure homogenization.

Wet ball milling is a process in which coarse drug particles are fed into a suitable container and filled with milling media (i.e., grinding media) and a stabilizing agent (e.g., surfactant) to reduce particle aggregation (Fig. 6.4). High shear forces fracture the drug crystals into nanometer-size particles. The benefit of wet ball milling is that it results in a stable aqueous suspension when properly formulated.

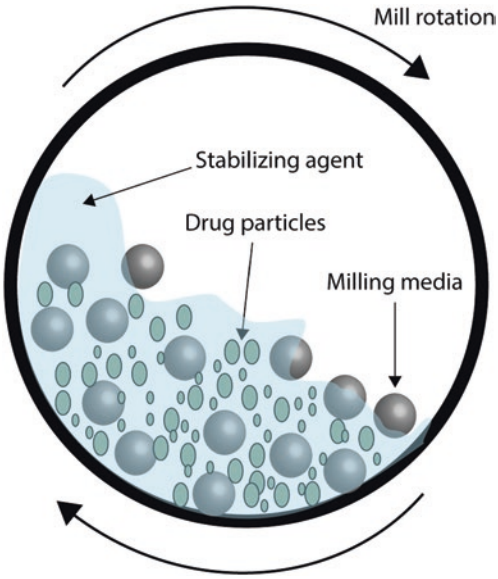

Fig. 6.4 Horizontal cross section of a wet ball mill

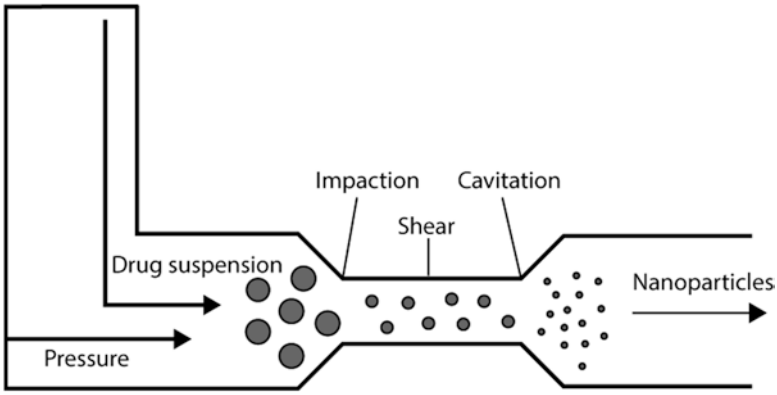

Fig. 6.5 Schematic of a high-pressure homogenizer

High pressure homogenization uses jet-stream homogenization by pumping drug, dispersion medium, surfactants, and stabilizers under high pressure through a micro fluidizing nozzle (Fig. 6.5). Particle size reduction in this case is caused by cavitation forces, shear forces, and collision.

6.6 Excipients Used in Suspension Formulations

Excipient selection will depend on the route of administration, properties of the drug, and the target patient population. For example, in formulations intended for neonates, preservatives, colorings, flavorings, or alcohol should be avoided as they may cause toxicity. Particularly for suspension formulations, the effect of excipients on vehicle viscosity, particle aggregation, and drug solubility must be considered, as this can affect the stability of the dosage form.

6.6.1 Suspending Agents

Suspending agents may be added to the suspension formulation to increase viscosity and reduce particle settling. Examples of suspending agents are provided in Table 6.1.

Table 6.1 Examples of suspending agents

Classification	Examples
Cellulose derivatives	Sodium carboxymethylcellulose Microcrystalline cellulose Hydroxyethyl cellulose Hydroxypropyl methylcellulose (HPMC, also known as hypromellose) Hydroxypropyl cellulose Hydroxypropyl ethylcellulose Carboxymethylcellulose
Clays	Bentonite Magnesium aluminum silicate (Veegum) Silicon dioxides
Gums and derivatives	Acacia Gellan gum Pectin Tragacanth Xanthan gum Locust bean gum Guar gum
Natural polymers	Agar Alginate Carrageenan
Synthetic polymers	Carbomer (Carbopol) Polyvinyl alcohol (PVA) Povidone (also known as Polyvinylpyrrolidone) Polyethylene oxide

Table 6.2 Selected examples of viscosity-increasing agents

Alginic acid
Agar
Acacia
Bentonite
Carbomer
Carboxymethylcellulose
Hypromellose
Methylcellulose
Povidone
Sodium alginate
Tragacanth

6.6.2 Viscosity-Increasing Agents

Viscosity-increasing agents are included in suspension formulation to render the preparation more resistant to flow and deter sedimentation. Examples of suspending agents are provided in Table 6.2.

6.6.3 Surfactants

A **surfactant** is an amphiphilic molecule (contains both hydrophilic and lipophilic components) that, due to its amphiphilic nature, preferentially adsorbs at the interface of two immiscible phases. Generally, the surfactant molecules can replace the molecules at the original (higher energy) interface and thus minimize the surface free energy.

The surfactant molecule will orient itself according to the interface that is present (e.g., drug particle surface and liquid vehicle). At a solid–liquid interface, such as a hydrophobic particle in water, the hydrophobic end will be oriented toward the solid and the hydrophilic end toward the liquid which increases wettability (Fig. 6.6). At a liquid–liquid interface, such as in the case of two immiscible liquids, the hydrophilic end of the surfactant will be oriented toward the more polar liquid while the hydrophobic end will point toward the less polar liquid.

Surfactants are included in suspension formulations to aid in the dispersion of the particles, especially if the powder is not wettable. They may also be incorporated in order to achieve a process of "controlled flocculation" via their electrostatic attraction and bridging between particles.

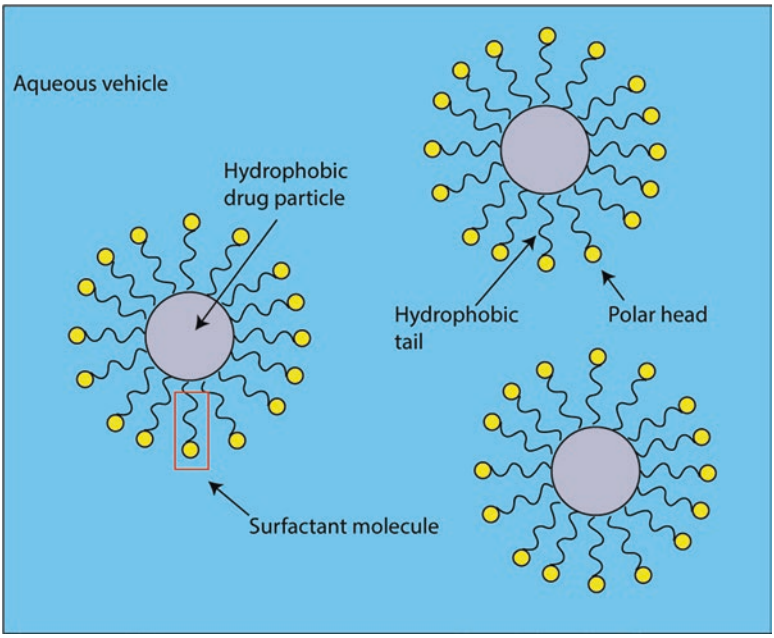

Fig. 6.6 Surfactant molecules surround a hydrophobic drug suspended in an aqueous vehicle. Surfactants enhance wettability and dispersion by reducing the interfacial tension and lowering the contact angle between the solid and liquid surfaces

6.6.3.1 Surfactants as Wetting Agents

It can be difficult to disperse particles within a suspension due to the layer of adsorbed gas molecules upon the surface of the particle. This results in clumping of particles or floating of particles on the surface of the vehicle. A **wetting agent** is a surfactant that lowers the contact angle and aids in displacing the air phase at the surface, replacing it with a liquid phase.

The term **contact angle** refers to the angle between the surface of a solid and a liquid (Fig. 6.7). The size of the contact angle predicts the wetting of a substance by a liquid. If the contact angle is less than 90°, wetting of the solvent by the liquid will take place. If the contact angle is greater than 90°, wetting will not take place. Ideally the contact angle should be as close as possible to zero to ensure that wetting occurs.

6.6.3.2 Surfactants as Stabilizing Agents

Surfactants can increase the physical stability of suspensions through electrostatic or steric means. **Electrostatic stabilization** occurs through an increase in the electrostatic repulsion between particles as a result of adsorption of surface active ions.

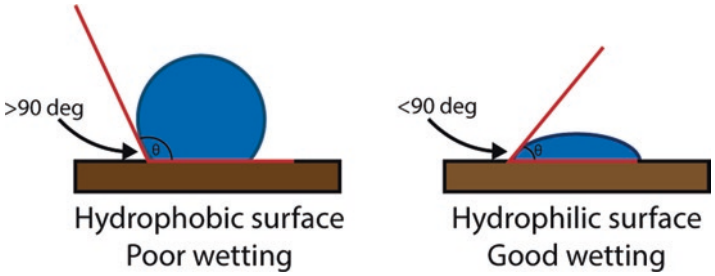

Fig. 6.7 The contact angle is used to assess the wetting of a substance by a liquid

This results in a decreased tendency of the particles to coagulate. **Steric stabilization** is a process in which surfactants form a hydrophilic shell around a particle, preventing close contact between particles. **Electrosteric stabilization** is a combination of the two.

6.6.3.3 Micelles

As the surfactant concentration increases, all the interfacial surfaces becomes saturated with surfactant molecules. In order to shield the hydrophobic component of the surfactant molecules from the aqueous phase, an aggregation of surfactant molecules known as micelles are formed. The point at which increasing concentration of surfactant leads to micelle formation is called the critical micelle concentration (CMC) (Fig. 6.8). The CMC is important to consider in a suspension formulation, as the tendency of a surfactant to adsorb onto the solid–liquid interface and act as a wetting agent is in competition with the surfactants tendency to form micelles.

6.6.3.4 Categories of Surfactants

Surfactants are generally classified into four categories: anionic, cationic, amopholytic, and nonionic. Anionic surfactants possess a hydrophilic group that carries a negative charge, while cationic surfactant possess a hydrophilic group that carries a positive charge. Ampholytic, also known as zwitterionic, contains groups with both negative and positive charges. Nonionic surfactants have no charge, and instead derive their water solubility from highly polar groups. Examples of surfactants are listed in Table 6.3.

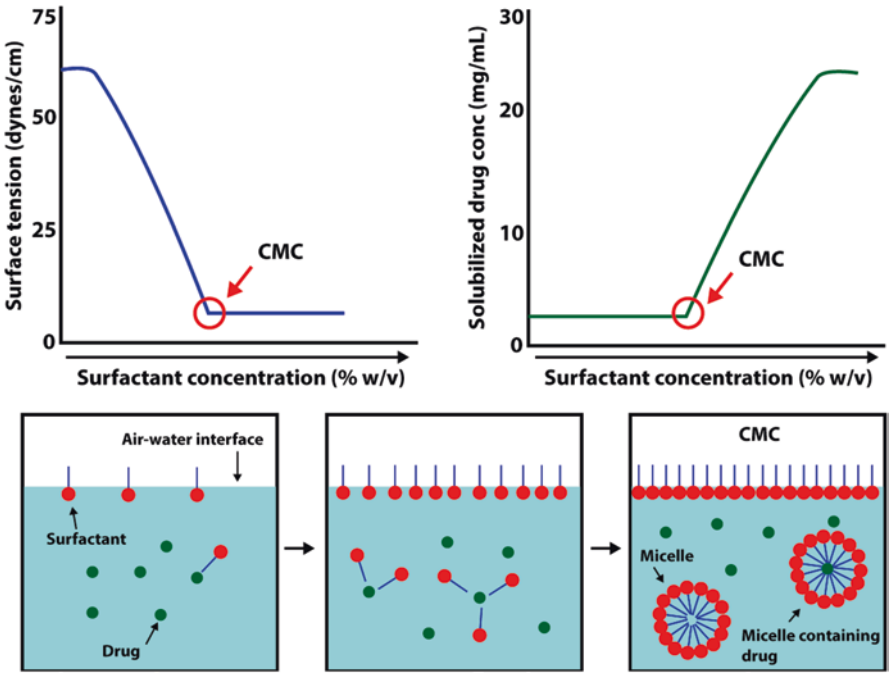

Fig. 6.8 The point at which increasing concentration of surfactant leads to micelle formation is called the critical micelle concentration (CMC). For exemplary purposes, if drug solubility is increased by the presence of micelles, then the figure represents graphically what happens to drug solubility as surfactant concentration is increased and more micelles are formed

Table 6.3 Examples of surfactants

Category	Examples
Anionic	Potassium laurate Sodium dodecyl sulfate (i.e., sodium lauryl sulfate)
Cationic	Cetrimide Benzalkonium chloride Benzethonium chloride
Nonionic	Poloxamer 407 Polysorbate (Tween®) 20, 40, 60, 80 Sorbitan esters (Span®) 40, 60, 80 Polyoxyethylene castor oil (Cremophor® RH) Polyoxyl 15 Hydroxystearate (Solutol® HS 15)

6.6.4 Flocculating Agents

Flocculating agents are included in suspension formulations to induce weakly bonded conglomerates of particles (flocs). They include surfactants, electrolytes, and hydrophilic polymers.

Table 6.4 Examples of flocculating agents

Category	Examples
Surfactant	Docusate sodium Polysorbate 80 Sodium lauryl sulfate Sorbitan monolaurate
Hydrophilic polymer	Carboxymethylcellulose sodium Methylcellulose Polyethylene glycol Tragacanth Xanthan gum
Electrolyte	Aluminum chloride Potassium dihydrogen phosphate Sodium chloride

Electrolytes such as potassium chloride, sodium chloride, citrates, or phosphates contribute to flocculation by reducing the surface charge of suspended particles close to zero. Upon addition of electrolytes, the particles will adsorb the positively charged cations or negatively charged anions in a tight layer on their surface. Zeta potential is defined as the difference in electric potential between this tightly bound layer and the electroneutral region of the solution. A large zeta potential (positive or negative) is indicative of particle repulsion and a deflocculated system. Controlled flocculation is achieved by lowering the zeta potential through the careful addition of electrolytes, which results in compression of the electrical layer surrounding the particle. However, if too much electrolyte is added to the system, the particle surfaces can be neutralized, and aggregation and caking may occur. The flocculating power of electrolytes increases with increasing valency of the ions.

Both surfactants and hydrophilic polymers may act as flocculating agents by adsorbing suspended particles and creating a repulsive electric layer around the particles, preventing irreversible agglomeration. Just beyond this repulsive layer; however, a weak attraction layer exists allowing for flocculation to occur between particles through weak interactions and crosslinking of surfactant or polymer molecules between particles. If too high a concentration of surfactant or polymer is added, deflocculation will occur and particles will remain separated. Examples of flocculating agents are listed in Table 6.4.

6.6.5 Sweetening Agents and Flavors

Sweetening agents and flavors are often added to suspensions to enhance palatability. Examples of sweetening agents are listed in Table 6.5.

Table 6.5 Examples of sweetening agents

Aspartame
Alitame
Acesulfame potassium
Dextrose
Erythritol
Fructose
Glucose, liquid
Glycerin
Inulin
Isomalt
Lactitol
Maltose
Mannitol
Saccharin sodium
Sorbitol
Trehalose
Xylitol
Sucrose

6.6.6 Other Excipients

Suspensions may additionally include excipients such as buffering agents, flavors, colorants, and preservatives.

Further Reading

Suggested readings for the student include the following texts:

1. Iyer AK, et al. Exploiting the enhanced permeability and retention effect for tumor targeting. Drug Discov Today. 2006;11(17):812–8.
2. Jermain SV, Brough C, Williams RO III. Amorphous solid dispersions and nanocrystal technologies for poorly water-soluble drug delivery–an update. Int J Pharm. 2018;535(1–2):379–92.
3. Leleux J, Williams RO III. Recent advances in mechanical reduction methods: particulate systems. Drug Dev Ind Pharm. 2014;40(3):289–300.
4. Wong J, et al. Suspensions for intravenous (IV) injection: a review of development, preclinical and clinical aspects. Adv Drug Deliv Rev. 2008;60:939–54.

Chapter 7
Disperse Systems: Emulsions

Abstract This chapter provides an overview of emulsion types, their methods for manufacture, and their suitability for various routes of administration. Excipients and their function in promoting emulsion stability are discussed. A review of microemulsions and liposomes is also provided.

Keywords Emulsion · Dispersion · Liposomes · Emulsion stability · Emulsifying agents · Hydrophile–lipophile balance system · Surface active agent · Surfactant · Colloidal dispersion

Learning Objectives
- Describe an emulsion.
- Define the different types of emulsions.
- Describe the role of the emulsifying agent in preparing an emulsion.
- Describe the HLB system of categorizing emulsifying or surface-active agents.
- Describe the different types of emulsifying agents and provide an example for each.
- Explain how colloidal delivery systems are used in the following: microemulsions and liposomes.
- Explain aggregation and coalescence of emulsion droplets as related to emulsion stability, and describe how this relates to Stoke's law.

Key Concepts
Students should know and be able to describe each of the following concepts as they review this chapter:

- Aggregation
- Coalescence
- Dry gum method
- Emulsifying agent (emulsifier)
- Emulsion
- Emulsion cracking/breaking
- Emulsion creaming

A. D. Brunaugh et al., *Essential Pharmaceutics*, AAPS Introductions in the Pharmaceutical Sciences, https://doi.org/10.1007/978-3-030-31745-4_7

- Emulsion settling
- Hydrophile–lipophile balance (HLB) system
- Liposomes
- Microemulsions
- Oil-in-water (O/W) emulsion
- Oleaginous
- Phase inversion
- Plastic or interfacial film theory
- Surface tension theory
- Water-in-oil (W/O) emulsion
- Wet gum method

7.1 Introduction

An **emulsion** is a type of dispersion in which a liquid phase composed of small droplets or globules is distributed homogeneously throughout a liquid vehicle in which it is immiscible using an emulsifying agent. The liquid phase consisting of small droplets is referred to as the dispersed or internal phase, while the vehicle in which these are dispersed is referred to as the continuous or external phase. The appearance and consistency of the final emulsion formulation may be liquid-like or semisolid, thus allowing emulsions to be utilized for the delivery of drugs through a variety of routes of administration.

7.2 Emulsion Types

Emulsions can be further classified as oil-in-water (O/W) or water-in-oil (W/O) depending on which components make up the internal and external phases (Fig. 7.1). **O/W** refers to an emulsion with an **oleaginous** (i.e., oil) internal phase and an aqueous external phase, while **W/O** describes an emulsion with an aqueous internal phase and an oleaginous external phase. It is also possible to make more complicated emulsion systems, such as oil-in-water-in-oil (O/W/O) or water-in-oil-in-water (W/O/W), by re-emulsifying an existing emulsion within another external phase.

The type of emulsion formed (whether oil or water will be present as the continuous phase) is generally dependent upon which component coalesces more. This is primarily dependent upon the type of interfacial film/barrier produced by adsorption of one or more emulsifying agents (emulsifiers) at the interface and the polar/nonpolar nature and solubility characteristics of the emulsifying agent(s). An **emulsifying agent (emulsifier)** is an inactive ingredient that is added to stabilize the dispersion and prevent two immiscible phases from separating (Fig. 7.2). Emulsifying agents can be surfactants and polymers.

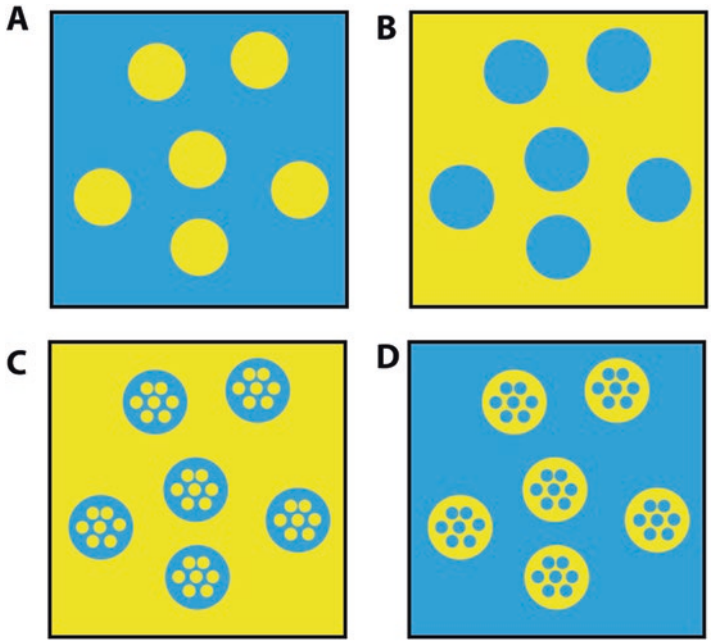

Fig. 7.1 Depending on the composition of the internal and external phases, emulsions may be classified as (**a**) oil-in-water, (**b**) water-in-oil, (**c**) oil-in-water-in-oil, (**d**) water-in-oil-in-water (yellow denotes oil phase and blue denotes water phase)

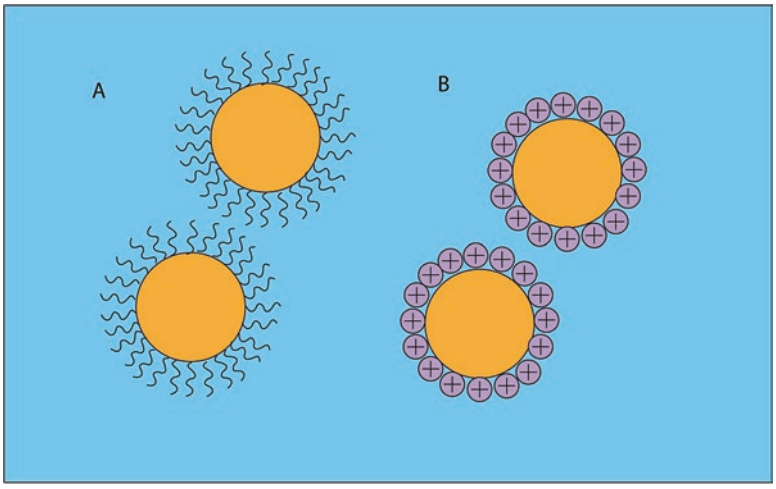

Fig. 7.2 Molecules of the emulsifying agent surround dispersed globules and provide a stabilizing effect. The interfacial barrier may result from (**a**) steric hindrance or (**b**) electrostatic repulsion

For oil droplets dispersed in an aqueous phase, an interfacial barrier is often created as a result of electrically charged surface groups producing repulsion between oil droplets or as a result of steric repulsion from hydrated polymers. In general, for dispersed water droplets in an oil phase, the longer the hydrocarbon chain length of the emulsifier, the greater the barrier for the water droplet coalescence.

7.3 Routes of Administration

Like suspensions, emulsion-based formulations can be developed for various administration routes, including oral, injection, ophthalmic, or topical. The intended route of administration plays a factor in deciding what type of emulsion should be created and what excipients should be used.

7.3.1 Oral Route

Often, O/W or W/O/W emulsions are used for oral delivery as these systems allow for the administration of poorly water soluble drugs in which the drug is dissolved in the oil-based dispersed phase, while also providing taste-masking of the oil component through dispersion in a sweetened aqueous vehicles.

7.3.2 Topical Route

Semisolid emulsions are often preferred for topical application, as this allows the therapeutic agent to remain in contact with the skin because of preferable rheological characteristics. Depending on the drug and disease state, the emulsion may be formulated as an O/W or W/O. In general, W/O emulsions spread more easily on the skin, while O/W emulsions are more conveniently removed from the skin. Drugs known to be irritating may be placed in the internal phase of the emulsion to reduce irritation.

7.4 Emulsifying Agents

Dispersions of immiscible liquids are thermodynamically unstable and will revert back to their separate, non-dispersed phases without the inclusion of a stabilizing agent, e.g., emulsifying agent. It is therefore necessary to include an emulsifying agent as a component in the emulsion system. An emulsifying agent is typically a surface-active excipient that is adsorbed around the surface of the internal phase

droplets of an emulsion in order to reduce interfacial tension between the two phases. The emulsifying agent must not only promote emulsification and stability of the system such that the two immiscible liquids do not separate, but it must also be compatible with other emulsion ingredients and not cause adverse effects. The minimum concentration to achieve stabilization should be targeted, as surfactants can be irritating (e.g., hemolytic and irritating to the skin and mucosal membranes).

7.4.1 Stabilization Theory

Upon mixing of two immiscible liquids, one of the phases will divide into small droplets. This results in a large increase in interfacial area and, therefore, interfacial tension of the system. To reduce the interfacial area between the two immiscible phases, the dispersed droplets will have a tendency to coalesce in order to reduce the surface free energy.

There are several theories regarding how emulsifying agents promote stability, which include the following:

(a) **Surface tension theory.** The surface tension theory considers that the addition of a surfactant increases stability of an emulsion through reduction of the interfacial tension between two immiscible liquid phases.
(b) **Plastic or interfacial film theory**. In the plastic or interfacial film theory, it is hypothesized that the emulsifying agent collects at the interface of the oil and water liquids, leading to a formation of a thin film of emulsifying agent around droplets of the internal phase. This film prevents contact and coalescence of the internal phase, and a stronger film results in a more stable emulsion.

7.4.2 Hydrophile–Lipophile Balance

The **hydrophile–lipophile balance (HLB) system** provides a method of categorizing surfactants based upon the balance in size and strength of their lipophilic and hydrophilic characteristics.

In general:

1. The typical range in the system is 1–20, though a surfactant can be given a value as high as 40.
2. Molecules that have a higher polarity and greater hydrophilicity are assigned a higher value in the system, while lipophilic molecules are assigned a lower value.
3. The HLB value of the surfactant can help determine what type of emulsion will form.
4. Surfactants with an HLB < 10 are considered lipophilic (water insoluble) and produce W/O emulsions.

Table 7.1 General guide for HLB values of various surface active agents

Type of surface active agent	HLB
Antifoaming agent	1–3
W/O emulsifying agents	3–6
Wetting agents	7–9
O/W emulsifying agents	8–18
Solubilizers	15–20
Detergents	13–16

5. Surfactants with an HLB > 10 are hydrophilic (lipid insoluble) and produce O/W emulsions.
6. The HLB system is also used to categorize oil and oil-like substances.
7. When selecting an emulsifying agent, it should be considered what the HLB value of the dispersed phase is, and the HLB of the emulsifying agent should be as close as possible to it.
8. Multiple emulsifying agents can be combined to reach the desired HLB.

The typical values of various surface-active agents and their functions are listed in Table 7.1.

Two types of surfactants that are often utilized in pharmaceutical products are sorbitan monostearate (Span®) and polysorbate (Tween®).

1. The HLB for Span® surfactants range from 2.1 to 6.7, depending on the type, and thus are lipophilic and will produce W/O emulsions.
2. The HLB value for Tween® surfactants range from 15 to 17 and thus are hydrophilic and will produce O/W emulsions.

7.4.3 Types of Emulsifying Agents

Various types of emulsifying agents may be utilized in pharmaceutical preparations, including macromolecules, high molecular weight alcohols, surfactants, and finely divided solid particles.

Hydrophilic colloids (e.g., proteins, acacia, cellulose derivatives, and alginate) stabilize emulsions by adsorbing at the oil/water interface and forming viscoelastic multilayers that provide a mechanical or steric barrier to coalescence. If the colloid has an ionizable group (as in the case of a protein), electrical repulsion can also prevent coalescence. Polymeric emulsifiers such as Pemulen® stabilize emulsions by forming an adsorbed aqueous gel layer around the dispersed oil droplets.

In general, nonionic surfactants are less toxic and less sensitive to electrolyte and pH variation as compared to ionic surfactants. The method of stabilization for nonionic surfactants is likely to be steric stabilization since there is little electrical

repulsive force contributing to stability. Anionic surfactants are generally efficient emulsifiers above pH 7 and are incompatible with cationic surfactants and cations particularly if they are polycationic. Cationic surfactants are generally efficient emulsifiers below pH 7 and are incompatible with anionic surfactants and anions particularly if they are polyvalent.

Finely divided solid particles (e.g., clays, inorganic particles, etc.) can be used to stabilize emulsions if they are preferentially wetted by one phase and are able to adhere to one another to form a film around the dispersed droplets. If the solid particles are preferentially wetted by water, an O/W emulsion will form. If the finely divided solid particles are preferentially wetted by oil, then a W/O emulsion will form.

Examples of emulsifying agents are listed in Table 7.2.

Table 7.2 Examples of emulsifying agents

Classification	Examples	Type of emulsion formed
Macromolecules/ hydrophilic colloids	Acacia	O/W
	Tragacanth	
	Agar	
	Alginate	
	Chondrus	
	Pectin	
	Gelatin	
	Casein	
	Pemulen® (high molecular weight polyacrylic acid polymers)	
High molecular weight alcohols	Stearyl alcohol	O/W
	Cetyl alcohol	
	Glyceryl monostearate	
Anionic surfactants	Triethanolamine oleate	O/W
	Lauric acid	
Cationic surfactants	Benzalkonium chloride	O/W
	Hexadecyl pyridinium chloride	
	Cetrimide	
Nonionic surfactants	Sorbitan esters	W/O Sorbitan monolaurate HLB: 8.6 Sorbitan monooleate (span® 80) HLB: 4.3 Sorbitan monopalmitate HLB: 6.7 Sorbitan trioleate HLB: 1.8
	Polysorbate	O/W Polysorbate 20 HLB: 16.7 Polysorbate 40 HLB: 15.6 Polysorbate 60 HLB: 14.9 Polysorbate 80 HLB: 15.0
	Glyceryl laurate	W/O HLB = 5.2
Finely divided solids	Bentonite	Formation of O/W or W/O phase is dependent upon the volume of each phase.
	Magnesium hydroxide	
	Aluminum hydroxide	

7.5 Other Excipients

An aqueous external phase of O/W emulsions can promote microbial growth. Preservatives may be included in the formulation, or the product can be sterilized or prepared by aseptic processing. Antioxidants may also be included to ensure long-term stability.

7.6 Preparation of Emulsions

The preparation of an emulsion requires the application of mechanical energy through agitation of the system in order to disperse droplets. Methods to achieve this include handheld or industrial mixers, homogenizers, mills, or ultrasonication devices.

On small scale of production, such as in a compounding pharmacy, emulsions can be prepared using a mortar and pestle, mechanical blender or mixer, and hand homogenizers. Methods of preparation include the **dry gum method**, in which the emulsifying agent is mixed with oil phase before the addition of the aqueous phase followed by other excipients, or the **wet gum method**, in which the emulsifying agent is mixed with the aqueous phase, followed by slow incorporation of the oil phase and other excipients. After preparation, the emulsion may be passed through a hand homogenizer in order to reduce the internal phase droplet size.

The rheological properties of emulsions can be altered by changing the volume of the dispersed phase component as well as the amount and type of emulsifying agent. In general, if the volume of the internal phase is low, then the properties of the emulsion will be more matched with those of the external phase. W/O emulsions will generally have higher viscosity than O/W emulsions.

7.7 Colloidal Dispersions: Microemulsions

Microemulsions are type of colloidal dispersion consisting of oil and water phases that have been rendered homogenous, transparent, and physically stable by the addition of large amounts of surfactants. Unlike emulsions, microemulsions are thermodynamically stable. The size of microemulsion droplets is much smaller than that of coarse emulsions and ranges from 6 to 100 nm with a narrow size distribution.

In order to sufficiently reduce the interfacial tension between the water and oil phases and form a microemulsion, it is generally necessary to include an additional surfactant (i.e., co-surfactant).

7.7.1 Liposomes

A **liposome** is a synthetic vesicle in which an aqueous core is surrounded by a bilayer lipid membrane. Liposomes allow for protective and targeted delivery of various drugs and nucleic acid or protein-based therapies. To form the bilayer, a double-chained lipid such as phosphatidylcholine is used. The presence of the lipid bilayer allows for the incorporation of both hydrophilic and hydrophobic molecules into the liposome, with hydrophilic molecules sequestering in the center of the liposome and hydrophobic molecules incorporating into the lipid bilayer. Different molecules can be added to the surface of liposomes to enhance targeting. Depending upon the size of the vesicle, liposomes are further classified as small unilamellar vesicles (single bilayer, 25–100 nm in size), large unilamellar vesicles (single bilayer, greater than 100 nm in size), and large multilamellar vesicles (multiple bilayers, 100 nm to several micrometers in size) (Fig. 7.3).

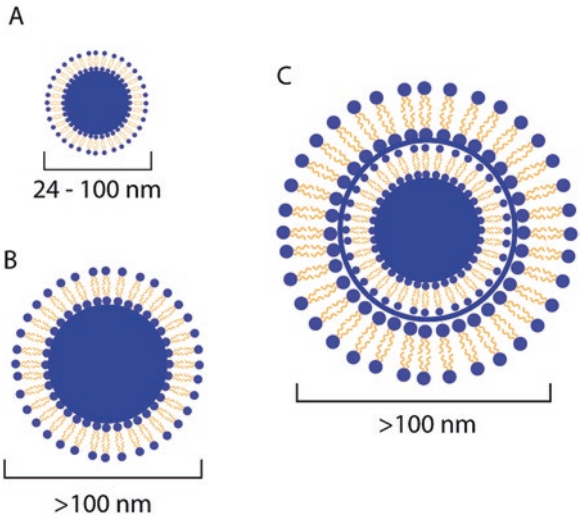

Fig. 7.3 Liposomes may vary in size and number of bilayers. (**a**) Small unilamellar vesicles consist of a single bilayer and are 25–100 nm in size; (**b**) large unilamellar vesicles consist of a single bilayer and are greater than 100 nm in size; (**c**) large multilamellar vesicles consist of multiple bilayers and may be greater than 100 nm in size

7.8 Emulsion Stability

7.8.1 Aggregation and Coalescence

Aggregation and coalescence occur in order to reduce the Gibbs' free energy of the system by minimizing the surface area of the internal phase droplets. **Aggregation** refers to the grouping together of droplets without fusion as a result of attractive forces. **Coalescence** refers to fusion of smaller droplets to form larger droplets. If the interactions are weak enough, aggregation can be a reversible process in which the internal phase droplets are redispersed upon shaking of the emulsion; however, coalescence refers to an irreversible process.

7.8.2 Phase Separation

Due to density differences between the internal and external phases, aggregated droplets have a tendency to rise to the top (described as "**creaming**") or fall to the bottom (described as "**settling**") of the emulsion. In some cases this can be reversed through agitation (e.g., shaking of the container prior to administration to the patient) of the emulsion; however, if the aggregates are strongly bound or the emulsion is not sufficiently agitated, incorrect dosing can occur. The creaming and settling processes of emulsions can be minimized by considering the Stoke's equation.

With regard to emulsions, the Stoke's equation relates the rate of separation of the dispersed phase to droplet size, density difference between the phases, and the viscosity of the external phase. As seen in the equation below, the rate of separation is increased by increased droplet size of the internal phase, increased density difference between the two phases, and decreased viscosity of the external phase.

$$v = d^2 \left(\rho_s - \rho_v \right) g \,/\, 18\eta$$

where,

v = Sedimentation rate
d = Droplet diameter
ρ_s = Droplet density
ρ_v = Vehicle density
g = Force of gravity
η = Vehicle viscosity

Cracking or breaking refers to the separation of an emulsion back into its original two immiscible liquid phases. This can occur due to compromising of the interfacial film surrounding internal phase droplets, which may be induced by the addition of an excipient that is incompatible with the emulsifying agent, bacterial growth, or temperature change. Unlike creaming, cracking is an irreversible process.

7.8.3 Phase Inversion

Phase inversion, which refers to the conversion from an O/W emulsion to a W/O emulsion and vice versa, can occur as a result of an excessive amount of the dispersed phase present in the system (>70%) or as a result of excipient incompatibilities that alter the HLB of the emulsifying agent.

Further Reading

Suggested readings for the student include the following texts:

1. Jiao J. Polyoxyethylated nonionic surfactants and their applications in topical ocular drug delivery. Adv Drug Deliv Rev. 2008;60(15):1663–73.
2. Torchilin VP. Recent advances with liposomes as pharmaceutical carriers. Nat Rev. Drug Discov. 2005;4(2):145.

Chapter 8
Ophthalmic and Otic Drug Delivery

Abstract This chapter introduces special considerations and formulation techniques for ophthalmic and otic drug delivery. Types of ophthalmic dosage forms are reviewed and placed in clinically relevant context. Commonly used excipients and their functions are also reviewed.

Keywords Ophthalmic drug delivery · Otic drug delivery · Ophthalmic dosage forms · Ocular bioavailability

Learning Objectives

- Explain the sterility and preservation considerations as they apply to ophthalmic products. List examples of preservatives used in these products and their typical range.
- Explain isotonicity as it relates to ophthalmic products.
- Explain the use of buffers as related to ophthalmic products. List examples of these excipients.
- Explain the use of viscosity and thickening agents as related to ophthalmic products. List examples of these excipients.
- Describe the concept of ocular bioavailability and factors that can affect a drug's ocular bioavailability.
- Compare and contrast ophthalmic solutions, gels, suspensions, ointments, and emulsions.
- Explain the proper administration technique for ophthalmic liquid products.
- Describe the advantages of nonionic surfactants used in ophthalmic delivery systems based on their compatibility, stability, and toxicity.
- Describe the concept of otic drug delivery.
- Explain the barriers to otic drug delivery.
- Describe formulation considerations of otic dosage forms.

Key Concepts

Students should know and be able to describe each of the following concepts as they review this chapter:

A. D. Brunaugh et al., *Essential Pharmaceutics*, AAPS Introductions in the Pharmaceutical Sciences, https://doi.org/10.1007/978-3-030-31745-4_8

- Ophthalmic delivery
- Ophthalmic emulsions
- Ophthalmic gels
- Ophthalmic ointments
- Ophthalmic solutions
- Ophthalmic suspensions
- Otic delivery

8.1 Introduction

This chapter focuses on the essentials of ophthalmic and otic delivery systems.

Ophthalmic delivery is defined as the delivery of drugs topically or intraocularly to the eye. This dosage form is primarily used to treat local conditions of the eye such as infections, allergies, inflammation, glaucoma, and dryness, with the benefit of having limited risk of systemic side effects. Ophthalmic preparations may be delivered in a number of ways, including via solutions, suspensions, gels, ointments, or emulsions.

Otic delivery is concerned with the local administration to the ear. Similar to the eye, the ear is a delicate and anatomically/physiologically protected organ that requires special formulation approaches to achieve therapeutic delivery. There are several barriers to be overcome to allow drug delivery to the target site within the ear.

8.2 Special Considerations in Ophthalmic Dosage Forms

The volume capacity of the front of the eye is limited. The average tear volume is about 7 μL, while the maximum volume that can be held in the conjunctival cul-de-sac of the lower lid is 30 μL. The drainage rate from the cul-de-sac (Fig. 8.1) adjusts with increased volume; therefore, a higher drug concentration in a smaller volume is ideal, as a low volume dose will reduce the amount of drainage and medication wastage. This also leads to an important patient counseling point: administration of two separate eye drops should be separated by a period of time, as the administration of the second drug may dilute the first. Commercial eye drops typically range from 25 to 70 μL.

In addition to considerations regarding dosage volume, ophthalmic products have similar formulation design requirements to injectable and nasal formulations regarding sterility, tonicity, and pH.

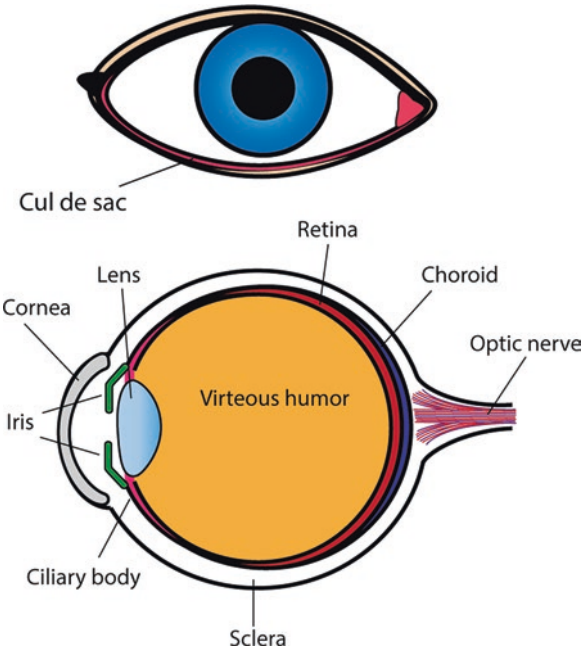

Fig. 8.1 Anatomy of eye

Table 8.1 Exemplary preservatives for ophthalmic dosage forms

Preservative	Concentration (%)
Benzalkonium chloride	0.004–0.01
Benzethonium chloride	0.01
Chlorobutanol	0.5
Phenylmercuric acetate	0.004
Phenylmercuric nitrite	0.004
Thimerosal	0.005–0.01

8.2.1 Sterility

Sterility is a compendial requirement for ophthalmic dosage forms, and maintaining sterility of ophthalmic drugs is paramount for patient safety. Preparations may be sterilized through autoclaving or filtration. Often, preservatives are also included in the formulation to prevent microbial growth, particularly for multi-dose products. If no preservative is present, then the product is typically dispensed in a single-use container. Recently, preservative free multi-dose bottle packaging has been commercialized. Typically used preservatives and their ranges are listed in Table 8.1.

Of note, mixtures of benzalkonium chloride and polymyxin B or disodium ethylenediaminetetraacetate (EDTA) (0.01–0.1%), a chelating agent, are effective against most strains of *Pseudomonas aeruginosa*, a bacterium that can cause ulceration of the eye and blindness.

8.2.2 Tonicity

Tonicity of ophthalmic products should generally be adjusted to match physiological conditions. Ophthalmic products with an osmotic pressure equivalent to that of 0.6–2% sodium chloride solution have been reported to avoid causing discomfort to the eye.

8.2.3 pH

The pH of an ophthalmic formulation may be buffered to enhance patient comfort and increase stability, solubility, and bioavailability of the drug. Ideally, the pH should be similar to that of tears; however, the eye does have buffering capacity and can typically neutralize administered products, except in cases of large deviation or when the formulation itself is strongly buffered.

8.2.4 Ocular Bioavailability

Bioavailability of drugs administered via the topical ophthalmic route is affected by a multitude of factors. Absorption of drugs often occurs primarily through the cornea (Fig. 8.1). The cornea features a multilayer barrier to absorption. The most anterior layer, the hydrophobic squamous epithelium, acts as a barrier to hydrophilic molecules while the stroma, the thickest layer of the cornea, is hydrophilic and acts as a barrier to hydrophobic molecules. Therefore, molecules that have both hydrophilic and lipophilic properties will typically be able to penetrate most readily. Binding of the drug by proteins found in the tears can also reduce bioavailability, as protein-bound drugs are too large to penetrate the corneal epithelium.

The retention time of the medication on the eye is another absorption-limiting factor. A longer retention time on the eye is desirable, as it leads to increased opportunity for the drug to diffuse and be absorbed before being cleared. Viscosity and thickening agents may be used in ophthalmic preparations to increase the time the drug is in contact with the ocular tissue. It has been reported that the optimal viscosity range for an ophthalmic product is between 15 and 25 cP. Commonly used thickening agents in ophthalmic preparations are listed in Table 8.2.

Table 8.2 Exemplary thickening agents for ophthalmic dosage forms

Thickening agent	Exemplary concentration (% w/v)
Methylcellulose 4000 cP	0.25
Methylcellulose 25 cP	1
Hydroxypropyl methylcellulose (hypromellose) 3 cP	0.5
Polyvinyl alcohol	1.4

Table 8.3 Example of patient counseling steps for administration of ophthalmic products

Step 1	Prior to administration, the patient or caregiver's hands should be washed thoroughly
Step 2	To instill the eye drops, the patient's head should be tilted back. Often it is recommended to pull the lower eyelid of the eye down to create a pocket to which the drop is administered. In the case of an ointment or a gel, a thin ribbon can be applied
Step 3	Application of gentle pressure applied to the inner corner of the eye near the nose may also be recommended as this prevents a significant proportion of lacrimal drainage
Step 4	The cap must be replaced on the container immediately after administration to reduce the risk of contamination

8.2.5 Packaging

The preferred packaging for a topical ophthalmic preparation is a soft plastic container with a built-in dropper, which protects the product from outside contamination and makes it easier for the patient to use. The patients must be counseled not to touch the tip of the dropper directly on the eye, to reduce the risk of infection and corneal damage. If the container is single-use, it must be disposed of immediately after administration regardless if there is medication remaining in the packaging, due to the lack of preservatives in the formulation.

8.2.6 Administration

It is important to counsel patients on the correct administration of ophthalmic products both to ensure that therapeutic effect is achieved and to prevent infection. Table 8.3 outlines an example of patient counseling steps for ophthalmic products.

8.3 Types of Ophthalmic Dosage Forms

Ophthalmic solutions contain active ingredients that are completely soluble in the liquid vehicle. The benefit of this type of dosage form is that dose uniformity is ensured, and the application of the drug typically does not cause blurry vision.

The disadvantage is that there is very little contact time between the drug and the cornea before the solution is drained away, which can lead to low levels of absorption.

Ophthalmic suspensions consist of particles of insoluble drug in an aqueous vehicle that also contains suspending agents. To be absorbed, the particles must dissolve sufficiently during the residence time on the eye which makes the intrinsic solubility of the drug an important factor to consider. In order to ensure dose uniformity, patients should be counseled to shake the formulation each time before administration, as settling of the drug particles may occur. Particle size of the suspended drug particles is of critical importance due to the potential for irritation and drug dissolution.

Ophthalmic ointments may consist of drug incorporated into mineral oil and white petrolatum base. Since the ointment base is anhydrous, it can be used to carry moisture-sensitive medication. The ointment stays in place after application, and this longer contact time results in greater bioavailability. The disadvantage, however, is that the time to onset of action may be slower. The application of the ointment will cause blurry vision, and an important patient counseling point is to administer the ophthalmic ointment at bedtime when possible.

Ophthalmic gels contain polymers, such as carbomer, that form an aqueous semisolid dosage form that is applied to the eye in a similar manner to an ointment. In some cases, ophthalmic gels are formulated as a solution in which included polymers form a gel upon contact with tear fluid. This transition can occur due to a change in temperature, pH, or the presence of proteins within the tear fluid.

The advantage of ophthalmic gels is that they provide increased contact time with the eye tissue before clearance and thus increased drug absorbance and prolonged duration of therapeutic effect. Similar to ointments, the disadvantage of gels is that they can cause blurring of vision.

Ophthalmic emulsions consist of a drug dissolved in a nonaqueous vehicle that is then emulsified with water using a surfactant. This allows for the delivery of poorly water soluble drugs in an aqueous form. The key component of the emulsion is the inclusion of a surface-active agent (surfactant). Surfactants are molecules that contain both hydrophobic and hydrophilic components. When placed in a system containing hydrophilic and hydrophobic phases, the surfactant accumulates at the interphase of the phases and slows aggregation and coalescence of the two materials. This ensures that the phases do not separate out.

Surfactants are generally classified based upon the polar subgroups in their chemical structures. Categories include amphoteric, cationic, anionic, and nonionic. Compared to the other types of surfactants, nonionic surfactants are preferred in ophthalmic delivery systems because they are generally less toxic, less hemolytic, and less irritating to the surface of the eye. They also tend to maintain near physiological pH in solution. Polyoxyethylated nonionic surfactants are widely used in ophthalmic preparations. These surfactants are amphiphilic in that they have a hydrophilic polyethylene oxide or polyethylene glycol side chain, while the remainder of the molecule possesses lipophilic properties. The extent of the water solubility of these molecules is determined by the length of the alkyl side chain and the number of ethylene oxide units in the molecule. An alkyl side chain of 12 or less

Table 8.4 Exemplary polyoxyethylated nonionic surfactants for ophthalmic products

Polysorbates
Poloxamers
Tyloxapol

carbons with five or more ethylene oxide units is indicative of solubility in water at room temperature. The higher the percentage weight of polyethylene oxide in the molecule, the higher the hydrophile–lipophile balance (HLB) will be, meaning that the surfactant molecule will have greater solubility in the aqueous solution. Examples of commonly used polyoxyethylated nonionic surfactants are outlined in Table 8.4.

8.4 Special Considerations in Otic Dosage Forms

Anatomically, the ear consists of three major regions: the outer ear, the middle ear, and the inner ear. The outer ear consists of the ear canal to the ear drum (tympanic membrane). The middle ear includes the delicate ear structures including the ossicle and is also known as the auris media. The inner ear consists of the eustachian tube which connects the middle air and upper airways.

The first major barrier to administration of therapeutic agents is the tympanic membrane which is thin (around 100 nm thick) but impermeable to most drugs except small molecular weight lipophilic molecules as it is structurally similar to the skin barrier (see Chap. 9). The second major barrier is membranes that are located in the middle ear and are semipermeable membranes which are around 70 μm thick. Lastly, a barrier exists between the blood vessels of the ear that prevents systemically absorbed drugs from entering the cochlea.

8.5 Types of Otic Dosage Forms

Commonly used topical medications include topical antibiotic and antifungal drugs in the form of drops, gels, or foams. Applying these formulations topically enables administration of high local concentrations compared to systemic administration. The limitation of topical administration is the potential for toxicity locally in the ear.

Formulations can incorporate the drug in solution or as a suspension in vehicles based on water, glycerol, diluted alcohol, propylene glycol, and mixtures of these. The vehicle selection largely depends on the solubility of the drug, the drug dose, and the desired volume of formulation to be administered to the limited capacity of the ear (e.g., a few drops).

Products may have excipients included to increase the viscosity of the formulation to enhance retention of the therapeutic within the ear. Otic foams can be used to improve drug retention in the ear canal.

Traditionally, topical otic preparations are formulated as solutions or suspensions with a pH of around 3 or 4 to help limit microbial growth.

Further Reading

Suggested readings for the student include the following texts:

1. Jiao J. Polyoxyethylated nonionic surfactants and their applications in topical ocular drug delivery. Adv Drug Deliv Rev. 2008;60:1663–73.
2. Liu X, Li M, Smyth H, Zhang F. Otic drug delivery systems: formulation principles and recent developments. Drug Dev Ind Pharm. 2018;44(9):1395–408. https://doi.org/10.1080/03639045.2018.1464022.

Chapter 9
Topical and Transdermal Drug Delivery

Abstract This chapter reviews numerous concepts relevant to drug delivery topically and transdermally. Topics covered include the skin's function barrier, mechanisms for drug transport through the skin, in vitro analytical techniques, and methods to increase drug permeation. Commonly used formulation approaches such as semisolid dosage forms and transdermal patches are also discussed.

Keywords Topical drug delivery · Transdermal drug delivery · Percutaneous absorption · Fick's law of diffusion · Permeation enhancement · Semisolid dosage forms · Transdermal patches

Learning Objectives

- Compare and contrast topical and transdermal drug delivery.
- Describe how the anatomy of the skin contributes to its barrier function.
- Describe how Fick's law of diffusion can be applied to drug diffusion through the skin.
- Discuss the factors affecting drug absorption across the skin.
- Compare and contrast the routes of passive diffusion of drugs through the skin.
- Describe how percutaneous absorption is assessed in vitro.
- Explain the different approaches to enhance percutaneous absorption of drugs.
- Discuss the types and uses of percutaneous absorption enhancers including chemical and physical methods used for transdermal products.
- Explain the differences between an ointment, cream, and gel as dosage forms intended for topical application.
- Explain the use and properties of transdermal patches to deliver drugs into the systemic circulation.
- Understand what general clinical information the pharmacist should advise the patient when using transdermal drug delivery systems.

Key Concepts

Students should know and be able to describe each of the following concepts as they review this chapter:

A. D. Brunaugh et al., *Essential Pharmaceutics*, AAPS Introductions in the Pharmaceutical Sciences, https://doi.org/10.1007/978-3-030-31745-4_9

- Absorption base
- Cream
- Dermis
- Diffusion cell
- Diffusion coefficient
- Epidermis
- Fusion method (ointment preparation)
- Gel
- Hydrocarbon base
- Hydrogel
- Incorporation method (ointment preparation)
- Intercellular route (passive diffusion)
- Iontophoresis
- Lotion
- Matrix-type patch
- Microneedles
- Ointment
- Organogel
- Paste
- Percutaneous absorption
- Permeation enhancer
- Reservoir-type patch
- Sink condition
- Sonophoresis
- Stratum corneum
- Topical drug delivery
- Transcellular route (passive diffusion)
- Transdermal drug delivery
- Water-removable base
- Water-soluble base

9.1 Introduction

One of the primary physiological functions of the skin is to act as a barrier to toxins present in the environment and to minimize water loss from the body. This function of the skin, however, also serves as a barrier to the permeation of drugs applied to the skin for absorption and therapeutic effect. The ability of a drug to diffuse out of a formulation that is applied to the skin, and then across the skin, is dependent upon several factors, including:

(a) The intrinsic properties of a drug
(b) The formulation composition
(c) The excipients in the formulation that may interact/disrupt the skin barrier

Topical drug delivery (also known as dermal delivery) refers to the delivery of a drug to the skin for local therapeutic action, with the objective of only minimal systemic absorption. Topical dosage forms are designed to treat dermatological conditions, e.g., acne, inflammation, itching, and local infections.

The term **transdermal drug delivery** refers to the delivery of a drug across the skin with the intent for the drug to be absorbed through the skin layers and exert a systemic effect. **Percutaneous absorption** (often used interchangeably with transdermal drug delivery) refers to the absorption of a drug through the skin into the systemic circulation.

9.2 Anatomy of the Skin: A Brief Review

The anatomy of the skin is key to its barrier function and can be divided into two distinct parts: the epidermis and the dermis.

Epidermis (Fig. 9.1) is the outermost part of the skin (made up of different layers itself) and consists of stratified squamous epithelial cells. The outermost layer of the epidermis is made up of dead, keratinized cells known as corneocytes. This outer layer of the skin is known as the **stratum corneum**. The keratin-filled corneocytes are embedded within a lipid matrix composed of cholesterol, ceramides, free fatty acids, and phospholipids. This leads to what is commonly described as a "brick-and-mortar"-type structure and serves as a primary barrier to chemical and physical penetration through the skin.

Beneath the epidermis lies the **dermis**, which contains collagen in a mucopolysaccharide matrix. It has been thought that the dermis provides little barrier function

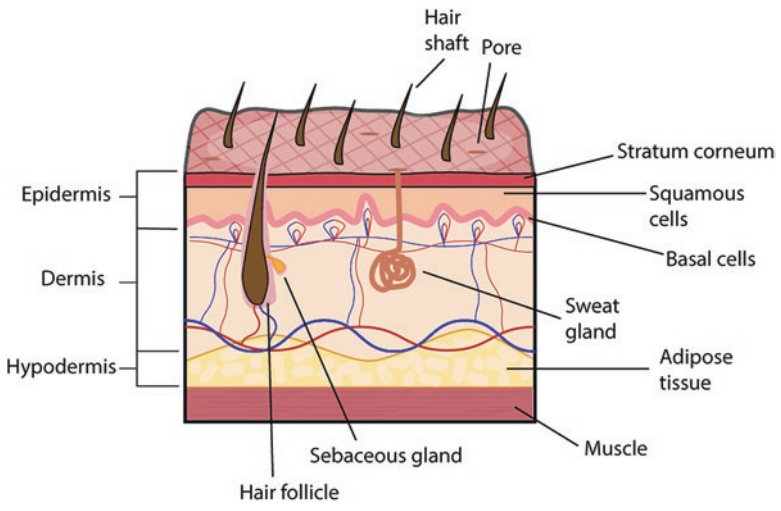

Fig. 9.1 Structure of the skin

to the permeation of most drugs, but this may depend on the drug properties. Hair follicles and sweat glands extend down into the dermis and provide a "shunt" or bypass pathway from the outside of the body to the dermis avoiding the epidermal barrier; however, these openings only make up around 0.1% of the skin surface.

9.3 Diffusion of Drug Through the Skin

Drug contained in a pharmaceutical composition can be applied onto the skin to achieve a local therapeutic effect or to obtain a systemic effect. For a systemic effect to occur, the drug must be transported through the skin layers into the vasculature.

9.3.1 Application of Fick's Law of Diffusion

When considering drug diffusion through the skin (e.g., from a vehicle applied to the skin), the stratum corneum can be thought of as a semipermeable membrane separating two compartments. In this way, drug diffusion through the skin at steady state can be described using Fick's first law, shown as:

$$J = \frac{DP\left(C_1 - C_2\right)}{h}$$

where:

J is the permeation, or flux, of a drug through the membrane (e.g., skin).
D is the diffusion coefficient of the drug in the membrane (e.g., skin). It represents the resistance of a drug molecule's movement through the skin.
h is the thickness of the membrane, also referred to as the diffusional path length.
P is the drug partition coefficient between the membrane and the drug vehicle.
C_1 and C_2 are the concentrations in the two compartments. C_2 may be neglected if assuming **sink condition** is met, which is defined by the USP as having a volume of medium at least three times the volume that is required to form a saturated solution of the drug.

Thus, four factors influence the transport of drugs across the skin:

(a) The drug concentration gradient
(b) The partition coefficient
(c) The diffusion coefficient of the molecule
(d) The length of the pathway through skin

It is important to note that the concentration gradient and the partition coefficient will be greatly influenced by the formulation. Because of this, a pharmacist may change permeability by changing the design of the formulation.

9.3.2 *Transport Through the Skin Layers*

Transport through the skin often consists of partitioning of the drug from the topically applied vehicle into the intercellular lipid matrix of the stratum corneum, followed by diffusion through skin layers.

Each layer of the skin may exhibit diffusional resistance, the largest of which is often attributed to the stratum corneum. As such, this is often the rate-limiting step in absorption of a drug applied to the skin surface. For successful transdermal delivery to occur, it is necessary for the drug to be relatively potent as only a small amount of drug may actually reach the systemic circulation.

There are three suggested pathways for passive diffusion of drugs through the stratum corneum:

(a) **Transcellular route**, defined as a pathway through the corneocytes. This requires transport through alternating layers of lipophilic domains and polar domains.
(b) **Intercellular route**, defined as a pathway around the corneocytes.
(c) **Transappendageal route,** in which generally hydrophilic drugs diffuse through the epidermis to the dermis through the shunt pathways formed by the hair follicles and sweat ducts (Fig. 9.2).

The intercellular pathway is thought to be the predominant pathway of diffusion. It has been suggested that diffusion through the intercellular lipid matrix requires that the drug possesses a degree of lipophilicity, with a $\log P_{o/w}$ of 2–3 considered ideal. If the drug is too lipophilic, however, it will have a tendency to remain in the stratum corneum, rather than partitioning into the more aqueous environments of the viable epidermis and dermis.

The tightly packed nature of the stratum corneum cells can often exclude the diffusion of large molecules like peptides and proteins without additional delivery technologies (e.g., permeation enhancers). The ideal molecular weight for a drug intended for transdermal delivery is about 500 Daltons or less. The lipophilicity and hydrophilicity of the drug will also affect diffusion through the skin.

In some cases, the epidermis may be the target for drug penetration following application to the skin. The stratum corneum is extremely hygroscopic, and is thus a useful site to achieve skin softening. Likewise, keratolytic agents function by sloughing the keratinized cells within the stratum corneum. As drug diffuses through the stratum corneum, it can bind to the skin components, thus limiting subsequent migration and providing a type of drug depot.

While it is difficult to achieve drug penetration through the stratum corneum, diffusion may occur more easily through the dermis layer, depending on the physicochemical properties of the drug. If a systemic effect is not desired, the drug must be formulated to limit continued diffusion.

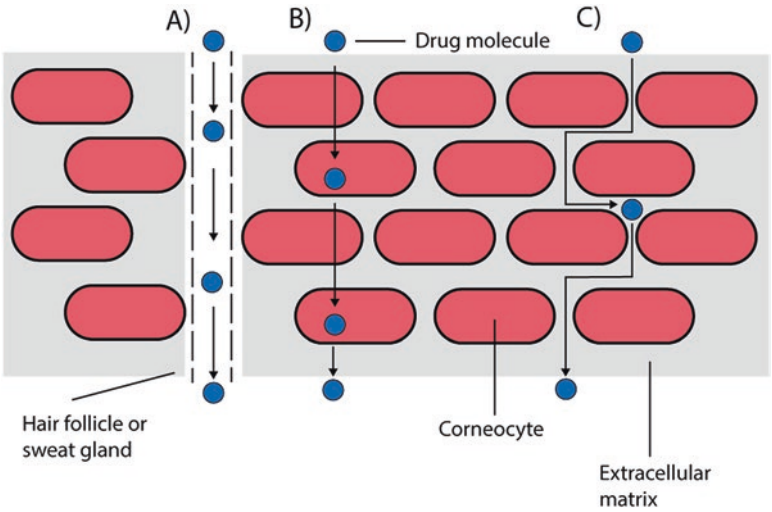

Fig. 9.2 Passive drug diffusion through the stratum corneum is theorized to occur via three pathways: (**a**) transappendageal route, (**b**) transcellular route, and (**c**) intercellular route

9.3.3 In Vitro Analysis

To test percutaneous absorption of a drug in vitro, a **diffusion cell** is often used in which intact skin acts as a semipermeable membrane between two compartments containing fluid media (Fig. 9.3). Drug is added to one compartment (donor compartment) and drug perfusion through the semipermeable membrane is evaluated by measuring drug concentration in the receptor compartment over time.

9.4 Mechanisms of Enhancing Drug Penetration Through Skin

Various approaches may be used to enhance percutaneous absorption of drugs that are not ideal candidates for transdermal effect based on their properties.

Fick's first law equation describes how percutaneous absorption can be enhanced. Three main mechanisms for enhancing diffusion include:

(a) Increase the diffusion coefficient
(b) Increase drug partitioning into the skin
(c) Increase the degree of drug saturation in the vehicle

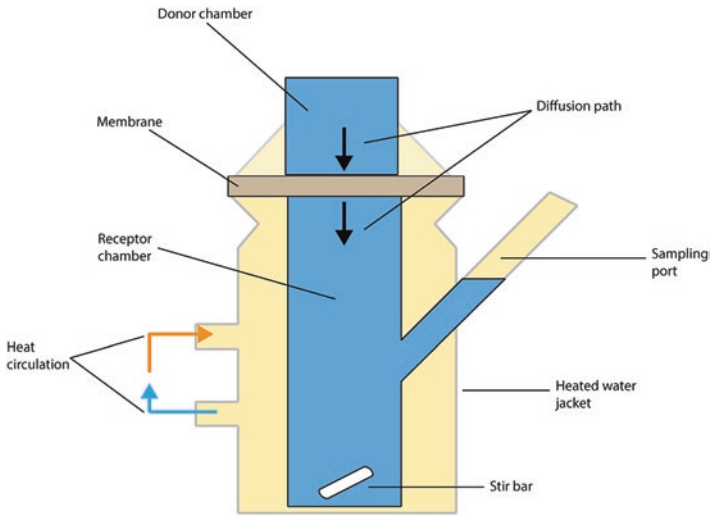

Fig. 9.3 A Franz diffusion cell used for the in vitro analysis of drug permeation through skin. Often intact skin is used as the membrane

9.4.1 Diffusion Coefficient

Mechanisms to alter the **diffusion coefficient** (i.e., the resistance of drug movement through the skin) and enhancing percutaneous absorption include:

(a) Occlusion of the skin
(b) Increasing skin temperature
(c) Use of chemical penetration enhancers

Occluding the skin prevents loss of water and increases the hydration of the stratum corneum, which increases the skin permeability.

Increased temperature increases skin permeation and systemic uptake through changes in blood flow. The diffusion coefficient is directly proportional to temperature. Thus, as the temperature increases so does diffusion and therefore permeation/flux through the skin. An important patient counseling point for transdermal/topical delivery forms is that application of heat (e.g., heating pad or hot bath) can lead to undesired increases in drug release and overdose.

Permeation enhancers are defined as substances typically added to the formulation that increase drug absorption through the skin. Permeation enhancers may have a direct effect on the permeability of the skin by increasing skin hydration or by disordering the lipid matrix, such as in the case of solvents or surfactants.

Chemical permeation enhancers include:

(a) Surfactants (such as polysorbates)
(b) Fatty acids/esters (such as oleic acid)
(c) Terpenes (such as limonene)
(d) Solvents (DMSO and ethanol)

Surfactants can increase the diffusion coefficient by solubilizing or extracting lipids from the stratum corneum and denaturing keratin. Fatty acids can increase lipid bilayer fluidity. Skin uptake of solvents such as propylene glycol, ethanol, transcutol, and *N*-methyl pyrrolidone can increase permeation by increasing drug solubility in the skin.

Examples can also be found in Table 9.3 in Sect. 9.7. Permeation enhancers may be used individually or in combination. The amount of the permeation enhancer that can be used is often limited, as these chemicals can cause irritation of the skin.

9.4.2 Partition Coefficient

The choice of vehicle can affect the extent of drug absorption in the skin layer. The drug should have a greater physicochemical attraction to the skin than the vehicle, to ensure that the drug exits the vehicle.

9.4.3 Degree of Drug Saturation in the Formulation

Degree of saturation can be increased by increasing the drug concentration in the vehicle or by decreasing the solubility of the drug in the vehicle. In particular, the creation of a supersaturated solution of the drug in the vehicle is desirable, as this will generate a thermodynamic drive for the drug to diffuse out of the vehicle and into the skin.

Supersaturation, however, is a thermodynamically unstable state and drug crystallization can occur over time. Addition of anti-nucleating polymers can delay crystallization. An alternative method is to create a supersaturated system directly before or during the application of the formulation to the skin. One method to achieve this is the incorporation of a volatile component into the topically applied formulation. The volatile component will evaporate upon the application of the composition to the skin, which concentrates the drug into remaining fraction of the vehicle and leads to the creation of a saturated or supersaturated solution.

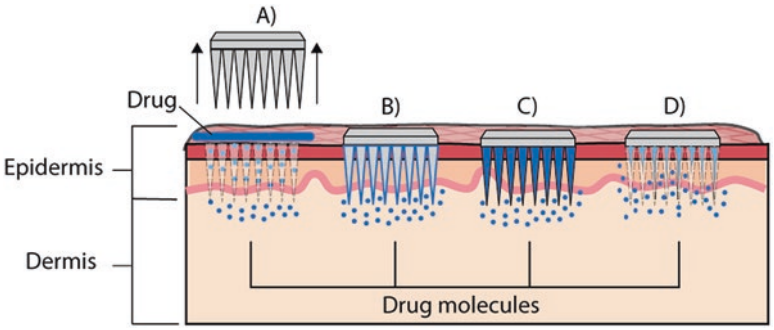

Fig. 9.4 Microneedles are a mechanical-based method for enhancing drug absorption through the epidermis. Designs under investigation include (**a**) solid microneedles, (**b**) drug-coated microneedles, (**c**) hollow microneedles, and (**d**) dissolvable microneedles

9.4.4 Electrical and Mechanical Methods of Increasing Drug Transport

The permeability of the skin to a drug may be enhanced through mechanical disruption of the stratum corneum. Mechanical methods to increase drug transport are promising approaches for the delivery of hydrophilic drugs or macromolecules through the skin.

Iontophoresis and sonophoresis are two examples of this approach. **Iontophoresis** is the delivery of charged particles across the skin through the application of a low-level electrical current. Few products have been FDA approved and marketed using this approach. **Sonophoresis** is a method of enhancing absorption through high-frequency ultrasound, which increases drug diffusion through formation of cavities within the intercellular lipids.

Microneedles (Fig. 9.4) are another mechanical-based method for enhancing absorption. In this system, needles are designed to be at a length of 50–200 μm, where they do not encounter the nerve endings in the skin, but still allow for the increased diffusion of topically applied drugs through the epidermis into the dermis. The intent of this approach is to avoid administration pain and damage to the skin. Currently no FDA-approved drug products contain microneedles, although many are in development.

9.5 Topical Semisolid Formulations

Semisolid topical dosage forms include ointments, creams, lotions, gels, and pastes. These dosage forms are defined by the USP as follows:

(a) **Ointments** are defined as semisolid base intended for external application to the skin or mucosal membranes. According to the USP, they usually contain less than 20% water and more than 50% hydrocarbons, waxes, or polyols.
(b) **Creams** are defined as semisolid dosage forms but contain drugs dispersed as either an O/W or W/O emulsion in a water-washable base. Creams are easier to spread on the skin and remove than ointments.
(c) **Lotions** are defined as fluid, viscid emulsions that are intended for external application.
(d) **Gels** are defined as semisolid, jelly-like systems that consist of either small inorganic particles or large organic particles dispersed within a liquid vehicle.
(e) **Pastes** are defined as semisolid dosage forms that contain >50% solids. They have a stiff consistency and are typically used as protective coatings for the skin.

9.5.1 Ointment Bases

When selecting a base for a topical dosage form, several factors must be considered such as:

(a) Release of the drug from the base
(b) Effect of the drug on consistency of the base
(c) Stability/shelf-life of the formulation
(d) The characteristics of the skin surface and the desired effect on the skin

Hydrocarbon bases (also known as oleaginous bases) are water-immiscible bases that have an emollient (softening) effect, which can be beneficial for dry, scaly skin. They are primarily used as occlusive dressings, which are designed to protect wounds from the air and retain moisture and body fluids. Hydrocarbon bases are also useful for keeping drugs in prolonged contact with the skin.

Absorption bases also have an emollient effect and are not easily removed by water. Aqueous solutions can be incorporated into these bases.

Water-removable bases are O/W emulsions that can be easily washed off skin with water. The USP defines these bases as creams.

Water-soluble bases are comprised of only water-soluble components and no oleaginous compounds. They are also known as “greaseless ointment bases” by the USP. These bases can also be washed off with water.

Table 9.1 lists examples and relevant properties of different types of bases utilized in topically applied formulations.

Table 9.1 Examples of bases for semisolid topical dosage forms

Type of base	Examples	Properties
Hydrocarbon (oleaginous) bases	Petrolatum, USP (Vaseline®)	Yellow color, 38–60°C melting point
	White petrolatum, USP (white Vaseline®)	Petrolatum that has been decolorized
	Yellow ointment, USP	Yellow wax added to petrolatum to increase viscosity
	White ointment, USP	White wax added to petrolatum
Absorption bases	Hydrophilic petrolatum, USP	Mixture of cholesterol, stearyl alcohol, white wax, white petrolatum that is used to incorporate hydrophilic drugs
	Lanolin, USP	Derived from sheep's wool
	Aquaphor®	Contains petrolatum, mineral oil, ceresin, lanolin alcohol, glycerin, panthenol, and bisabolol
Water-removable bases (also known as creams by USP)	Hydrophilic ointment, USP	Contains stearyl alcohol, white petrolatum, methylparaben, propylparaben, sodium lauryl sulfate, propylene glycol, and purified water
	Vanishing cream	O/W emulsion Rubbing cream into skin removes visibility of cream
	Cold cream	W/O emulsion Contains mineral oil, alcohol, glycerin, and lanolin
	Hydrous lanolin	Lanolin USP and purified water
	Rose water ointment	Contains cetyl esters wax, white wax, almond oil, sodium borate, rose water, purified water, and rose oil
Water-soluble bases (also known as greaseless ointment bases by USP)	Polyethylene glycol ointment NF	Mostly used for incorporation of solid substances since it softens with addition of water

9.5.2 Ointment Manufacture/Preparation

Ointments can be prepared by incorporation or fusion. In the **incorporation method**, the components of the ointment are mixed together until fully incorporated and homogeneous. In the **fusion method**, all or some of the components are combined by melting together. The mixture is then cooled to room temperature while constantly being stirred until it is congealed.

Table 9.2 Examples of gelling agents

Gelling agent	Example properties
Aluminum monostearate	Practically insoluble in water
Bentonite	Alkaline pH may make it unsuitable for certain drugs Loses suspending capacity at pH <7
Carbomer	Rapidly wetting, but has a tendency to clump. Very small particle size Viscosity is reduced at pH < 3 or >12 or in the presence of strong electrolytes
Gelatin	Soluble in water above 40 °C, forming a colloidal solution, which gels on cooling to 35–40 °C Forms a thixotropic and heat-reversible system
Glyceryl monooleate	Bioadhesive properties
Glyceryl palmitostearate	Practically insoluble in water
Methylcellulose	High concentration of electrolytes will cause the polymer to precipitate
Pectin	Gelling properties are dependent upon esterification with methoxy groups. Gelation of high-methoxy pectin occurs at pH <3.5. Low-methoxy pectin gelation is not dependent on acid
Povidone	Compatible with wide range of inorganic salts, resins, and other chemicals. Can be used to increase solubility of poorly soluble drug
Sodium carboxymethylcellulose	pH must be between pH 5 and 10 to maintain viscosity. Soluble in water at all temperatures
Tragacanth gum	Forms gel most stable at pH 4–8. Must add preservative
Xanthan gum	Can be used in combination with guar gum, locust bean gum, and cassia gum to create high-viscosity gel

9.5.3 Gels

The intermediate solid–liquid properties of gels are derived from the formation of a three-dimensional network formed by the solid component, which immobilizes the liquid component.

Gels are further classified as **hydrogels**, which have an aqueous continuous phase, or **organogels**, which have an organic solvent as the continuous phase.

Examples of gelling agents can be found in Table 9.2.

9.6 Transdermal Patches

Patches are used to deliver a drug transdermally (i.e., percutaneously). Delivery of drug intended to exert a systemic effect via a drug formulated in a patch allows for:

(a) Avoidance of first-pass metabolism

(b) Avoidance of enzymes within the gastrointestinal tract
(c) Long duration of drug delivery (can result in improved patient compliance)
(d) Decreased fluctuations of drug levels in the blood through controlled release

A number of patch formulations are on the market, including those for clonidine, fentanyl, lidocaine, nicotine, nitroglycerin, estradiol, testosterone, oxybutynin, and scopolamine. In general, the delivery of drugs transdermally is limited to those with:

(a) A low molecular mass (less than 500 Daltons)
(b) High lipophilicity
(c) Low therapeutic dose

However, the delivery of high molecular weight, hydrophilic drugs is an area of research interest.

9.6.1 Patch Design

Transdermal patches can be classified into two categories, based upon their design:

(a) Reservoir-type patches
(b) Matrix-type patches

A **reservoir-type patches** typically contains four layers: an impermeable backing layer, a solution or gel drug-reservoir layer, a semipermeable membrane that acts as a rate-limiting barrier for drug diffusion, and an adhesive layer that contacts the skin.

A **matrix-type patch** typically does not contain a rate-controlling membrane and instead consists of an impermeable backing layer, a solid drug-polymer matrix layer, and an adhesive layer. In some cases, the adhesive may be combined with the drug-polymer matrix (Fig. 9.5).

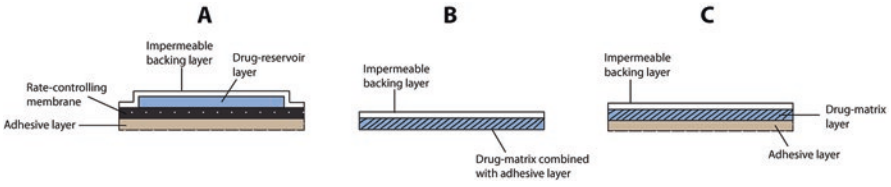

Fig. 9.5 Designs of different transdermal patches. (**a**) A reservoir-type patch, (**b**) a matrix-type patch with the drug-polymer matrix combined with the adhesive, and (**c**) a matrix-type patch with a separate adhesive layer

9.6.2 Drug Release from Transdermal Patches

In the case of a reservoir-type transdermal patch, the release of drug from the patch is controlled by a rate-limiting membrane, which is typically designed to impart a continuous release of drug. Prior to administration, drug will diffuse and saturate the adhesive layer with drug, which provides an initial bolus effect. The advantage of this type of system is that drug release is less susceptible to changes in the skin integrity (since the rate is controlled by a membrane within the patch).

In the case of a matrix-type transdermal system, flux (J) relies on Fick's law for diffusion of drug out of the adhesive polymer matrix. This is not rate-controlled by the patch, rather it is controlled by the skin barrier. If the matrix is formulated without an excess of drug, the transport of the drug from the patch to skin will decrease as the concentration of drug decreases in the patch. However, if the matrix is formulated with an excess of drug, the flux of drug into the skin will remain constant (zero-order release) for the duration of the patch use. The advantage of this type of systems is that they tend to be simpler in design compared to reservoir-type patches and carry less risk of dose-dumping due to manipulation of the patch. However, if the permeability of the drug across the skin is increased, as in the case of damaged or compromised skin, then the release of drug from the polymer matrix will also be increased.

9.6.3 Patient Counseling: Transdermal Systems

It is important to provide patients with the clinical information needed to ensure effective and safe use of transdermal delivery systems. This is especially true for patch systems which contain an amount of drug intended to last for several days, as alteration of the drug release mechanisms can result in a dangerous overdose.

Due to differences in the thickness of the epidermal layer, percutaneous absorption can vary with the site of application. Patients should therefore be advised on which areas of the body that the patch can be applied. The patient should apply the patch to clean, dry skin that is relatively free of hair. To prevent increased levels of absorption, the skin should be unbroken. If the skin is broken, drug will diffuse quickly into the capillary network, bypassing the mechanism of diffusion of the transdermal system and potentially increasing systemic exposure to a dangerous level. Skin that is calloused may reduce the level of absorption, so these areas should be avoided as well.

Reservoir-type patches should not be cut, as this may disrupt the rate-control mechanism and can result in dose dumping. Matrix-type patches generally can be cut without disruption of the rate-control mechanism. For example, in the case of lidocaine patches, the patch is cut in order to adjust the size to the area of treatment.

However, in most cases, the prescribing information will advise that the patch should not be cut as this makes it difficult to accurately dose potent medications, such as fentanyl.

9.7 Additional Excipients Utilized in Topical and Transdermal Dosage Forms

Additional excipients may be utilized in topical and transdermal dosage forms. These are described in Table 9.3.

Table 9.3 Additional excipients utilized in topical and transdermal dosage forms

Excipient	Function	Examples
Humectants	Used to prevent drying of preparations, particularly ointments and creams	Glycerin Ammonium alginate butylene glycol Cyclomethicone polydextrose Propylene glycol Sodium hyaluronate trehalose Triacetin Xylitol Sorbitol
Stiffening agent	Increase viscosity of preparation	Cetyl alcohol Cetyl esters wax Dextrin Microcrystalline wax Paraffin Stearyl alcohol White wax Yellow wax
Permeation enhancers	Enhance permeation of drug through the epidermis	Alcohol Azone Dimethyl sulfoxide (DMSO) Isopropyl myristate Isopropyl palmitate Lauric acid Myristic acid Oleic acid Palmitic acid Propylene glycol Pyrrolidones Sodium lauryl sulfate Terpenes Thymol Urea

(continued)

Table 9.3 (continued)

Excipient	Function	Examples
Antimicrobial preservative	Prevent microbial growth	Ethanol Benzalkonium chloride Benzethonium chloride Benzoic acid Benzyl alcohol Boric acid Bronopol Butylene glycol Calcium acetate Calcium chloride Calcium lactate Cetrimide Cetylpyridinium chloride Chlorhexidine Chlorobutanol Chlorocresol Chloroxylenol Cresol Glycerin Hexetidine Imidurea Monothioglycerol Pentetic acid Phenol Phenoxyethanol Phenylethyl alcohol Phenylmercuric acetate Phenylmercuric borate Phenylmercuric nitrate Potassium benzoate Potassium metabisulfite Propionic acid Propylene glycol Sodium acetate Sodium borate Sodium lactate Sodium metabisulfite Sodium sulfite Sulfur dioxide Thimerosal

Further Reading

Suggested readings for the student include the following texts:

1. Kim YC, Park JH, Prausnitz MR. Microneedles for drug and vaccine delivery. Adv Drug Deliv Rev. 2012;64(14):1547–68.
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Chapter 10
Rectal and Vaginal Drug Delivery

Abstract This chapter provides an overview of dosage forms relevant to rectal and vaginal drug delivery. Barriers to drug absorption are discussed and frequently used excipients are covered. The manufacturing and special formulation considerations for drug delivery using suppository formulations are also reviewed.

Keywords Rectal drug delivery · Vaginal drug delivery · Suppositories · Vaginal dosage forms · Suppository excipients · Suppository manufacturing

Learning Objectives

- Describe the advantages the rectal route for systemic absorption of drugs.
- Describe how the rectal environment and physiology affect systemic absorption of drugs.
- Describe the different types of rectal dosage forms.
- Describe how the vaginal environment and physiology affect systemic absorption of drugs.
- Describe the different types of vaginal dosage forms.
- Describe the ideal characteristics of a suppository formulation.
- Describe the desirable properties of a suppository base.
- Describe the effect of the suppository base on drug release.
- Compare and contrast the mechanism of drug release of oleaginous and water-soluble suppository bases.
- Describe the consequences of polymorph transformation of cocoa butter.
- Describe the relationship between melting point and molecular weight of polyethylene glycol (PEG).
- Describe the different excipients that can be incorporated in suppository formulations.
- Explain the proper storage conditions for suppositories.
- Describe the different production methods for suppositories.

Key Concepts

Students should know and be able to describe each of the following concepts as they review this chapter:

A. D. Brunaugh et al., *Essential Pharmaceutics*, AAPS Introductions in the Pharmaceutical Sciences, https://doi.org/10.1007/978-3-030-31745-4_10

- Cocoa butter, NF
- Compression molding
- Enemas
- Glycerinated gelatin
- Hydrogenated fatty bases
- Hydroxyl value
- Intrauterine devices
- Matrix system (vaginal rings)
- Melt molding
- Reservoir system (vaginal rings)
- Suppositories

10.1 Introduction

Drug delivery to the rectal and vaginal mucosal membranes may be useful for achieving local or systemic drug effects. For local action, the drug is often formulated to remain in the area where it will have a therapeutic effect (e.g., relieve constipation or hemorrhoid pain). To achieve systemic action, the drug should be absorbed through the mucous membranes of the rectum or vagina.

Suppositories are the most recognizable dosage form for the rectal and vaginal administration routes, but foams, inserts, and semisolid dosage forms are also used.

10.2 Rectal Route

Locally applied (also referred to as topically applied in the rectum) rectal dosage forms may be indicated to treat hemorrhoids and other diseases of the rectum. Locally acting drugs include steroids, anesthetics, and pain relievers.

The rectum epithelia can also be well suited for systemic absorption of drug and may permit rapid absorption of drugs. Absorption from the lower rectum bypasses portal circulation through the liver and thus has the important advantage of avoiding first-pass metabolism. Administration of dosage forms via the rectal route is thus useful for drugs for which systemic delivery is desired and in the following scenarios:

1. The patient is unable to swallow
2. The drug is inactivated in the stomach acid or is unstable to proteolytic enzymes
3. The drug undergoes high first-pass metabolism
4. The drug possesses limited absorption in the upper gastrointestinal tract
5. The drug may cause irritation to the gastric mucosa
6. The drug requires high doses and cannot be easily formulated as oral solid dosage forms

Examples of systemically acting drugs that are delivered rectally include indomethacin (pain relief), ondansetron (antiemetic), prochlorperazine (sedation, antiemetic), and aspirin (pain, anti-inflammatory).

10.2.1 Rectum Physiology

The systemic absorption of a drug administered rectally may differ from the absorption observed when the same drug is administered orally. The physiological state of the rectum as well as the physicochemical properties of the drug both affect rectal absorption.

The surface area available for absorption in the rectum is about 200–400 cm^3. The rectum contains 2–4 mL of mucous that has a neutral pH of about 7 and practically no buffering capacity. The pH can be affected by colonic contents which may lead to variations in drug absorption. The small amount of fluid in the rectum can result in low absorption of poorly water soluble drugs, and adjustments in the formulation may need to be made.

The rectal wall is composed of a single layer of epithelium, endocrine, and goblet cells. The rectum lacks villi and digestive enzymes. Passive transport through the epithelium cells is the primary mode of drug absorption. To passively diffuse through the cell membrane, a certain degree of drug lipophilicity is necessary. For absorption to occur, the drug must be in contact with the rectum surface, which may be affected by the colonic contents.

There are three means of blood supply to the liver: the superior, the middle, and the inferior veins. The superior vein from the rectum enters into mesenteric veins, then into the hepatic portal vein into the liver, while the middle and inferior veins move into the vena cava. First-pass metabolism of a systemically absorbed drug from the rectum is therefore reduced compared to an orally administered drug. Thus, the positioning of a suppository can affect the degree of bioavailability of the drug being delivered within. Drugs absorbed higher in the rectum will be drained by the superior vein and undergo first pass metabolism, while drugs absorbed lower in the rectum will be drained by the middle and inferior veins and avoid first-pass metabolism.

10.2.2 Rectal Dosage Forms

Examples of rectal dosage forms include:

(a) Suppositories
(b) Enemas
(c) Semisolid dosage forms (gels, foams, and ointments)

Table 10.1 Examples of commercially available rectal suppositories

Drug	Indication	Systemic or locally acting?
Aspirin	Analgesia	Systemic
Acetaminophen	Analgesia Antipyretic	Systemic
Indomethacin	Analgesia Inflammation	Systemic
Ondansetron	Nausea/vomiting	Systemic
Prochlorperazine	Nausea/vomiting	Systemic
Promethazine	Nausea/vomiting Allergic reaction	Systemic
Bisacodyl	Constipation	Local
Glycerin	Constipation	Local
Mesalamine	Ulcerative proctitis	Local
Hydrocortisone	Hemorrhoids	Local

Suppositories are defined as solid dosage forms intended for insertion into a body orifice (e.g., rectum, vagina, or urethra) for local or systemic action. They consist of drug dispersed (e.g., dissolved or suspended) within a rigid solid base. They may be administered rectally and can be used to treat both local and systemic conditions. Examples of commercially available rectal suppositories can be found in Table 10.1.

Enemas are solutions or dispersions that are injected (e.g., inserted) into the rectum and contain drug within a small volume of water or oil. The aqueous solution can be buffered with phosphate salt. To enhance retention within the rectum, the viscosity of the formulation may be adjusted through the addition of cellulose polymer derivatives and other viscosity enhancing agents.

Gels, foams, or ointments may be administered by insertion into the rectum to treat local diseases such as hemorrhoids or inflammatory bowel disease. These dosage forms tend to be better retained as compared to enemas. Thermoreversible rectal gel formulations have also been developed (e.g., diazepam rectal gel) to improve retention of the dosage form in the rectum.

10.3 Vaginal Route

Typically, drugs delivered via the vaginal route are intended to treat local gynecological conditions. Locally acting drugs include contraceptives, antifungals, antimicrobials, moisturizers, or hormones to alleviate postmenopausal symptoms.

Systemic delivery of drugs via the vaginal route is a focus of research, as it carries the potential to provide a noninvasive method of avoiding first-pass metabolism. As is the case with many other delivery routes, systemic absorption of drugs from the vaginal route is dependent upon molecular weight, lipophilicity, and degree of ionization of the drug but is also affected by the thickness of the vaginal wall,

which changes during the course of the menstrual cycle or pregnancy, and residence time of the dosage form. Menopausal changes in the pH and volume of vaginal fluid can also affect drug absorption. Vaginal administration of formulations containing estrogens or progesterone may lead to systemic absorption of these hormones.

10.3.1 Vaginal Physiology

The vaginal wall is coated with an aqueous fluid that can allow for dissolution of drugs. Typically, the vaginal fluid is acidic due to the presence of microbial flora. Its pH ranges between about pH 4 and 5, while cervical mucus has a pH of about 6.5. Changes in the pH and volume of the vaginal fluid occur with patient age and the menstrual cycle.

Various enzymes and microbes are present in the vaginal cavity, though intravaginal enzymatic activity is lower than that in the gastrointestinal system.

The vaginal wall is vascularized. The vaginal veins pass into the uterine artery, which can mediate delivery of drugs to the uterus while avoiding systemic effects.

10.3.2 Vaginal Dosage Forms

Vaginal dosage forms include:

- Intravaginal rings
- Tablets
- Suppositories (also known as pessaries)
- Semisolid dosage forms (e.g., gels, creams, and foams)
- Intrauterine devices (IUDs)

Intravaginal rings can provide controlled release of drug(s) over a prolonged period of time after insertion. This can be useful for contraceptives, where maintenance of patient compliance is critical for efficacy. Typically intravaginal rings consist of an extruded, elastic carrier ring that is made up of silicone or ethylene vinyl acetate copolymers. The ring may be formulated as a **matrix system**, in which drug is distributed throughout the polymer, or as a **reservoir system**, in which drug is contained in a reservoir core surrounded by a rate-controlling outer membrane.

Suppositories dissolve or melt in the vaginal cavity to gradually release drug. They are often used to administer drugs to treat fungal infections, induce labor, or provide hormone replacement therapy. Examples of commercially available vaginal suppositories can be found in Table 10.2.

Vaginal tablets can be manufactured using techniques described in Chap. 3: Capsule and Tablet Dosage. They are typically inserted into the vaginal cavity using an applicator. Examples of drugs formulated as vaginal tablets include antifungal agents and estrogens.

Table 10.2 Examples of commercially available vaginal suppositories

Drug	Indication	Systemic or locally acting?
Miconazole	Vulvovaginal candidiasis	Local
Terconazole	Vulvovaginal candidiasis	Local
Progesterone	Amenorrhea Hormone replacement therapy	Systemic

Semisolid dosage forms (gels, creams, and foams) are available for vaginal administration, typically with an applicator. Examples include spermicidal contraceptive, anti-infective agents, drugs for labor induction, and hormonal replacement therapies. Retention of these dosage forms can be an issue. Incorporation of bioadhesive polymers may help to prolong residence time, and this is an area of research interest.

Intrauterine devices (IUDs) are contraceptive devices inserted into the uterus through the vaginal route. This procedure is performed by a healthcare professional. IUDs may be constructed of copper to provide non-hormonal contraception or may release progestin to provide hormonal contraception.

10.4 Suppository Formulation

For a drug to come into contact with the mucosal membrane of the rectum or vagina, the drug must first be released from the suppository base. This requires that the suppository melts, softens, or dissolves in the body orifice.

Beyond the typical pharmaceutical considerations (e.g., stability, compatibility, drug solubility), a suppository dosage form ideally has the following characteristics:

(a) Facilitates easy insertion
(b) Facilitates retention for the intended time period
(c) Ensures appropriate release drug from the formulation
(d) Ensures compatibility with local tissues
(e) Does not cause discomfort for the patient

The size and shape of a suppository are important considerations for patient comfort and will be unique to the body orifice intended for administration. Adult rectal suppositories are about 2 g in weight, generally 1.5 in. (32 mm) long, cylindrically shaped, and have a tapered end to allow for easy insertion though some debate exists around how the shape and insertion orientation influences performance of the suppository. Rectal suppositories intended for pediatrics are about half this size.

Vaginal suppositories may be more ovular or cone-shaped, as these types of suppositories are typically supplied with an applicator. They are about 2–5 g in weight.

10.4.1 Suppository Base Considerations

Desirable properties of a suppository base include:

(a) Non-irritating. If the base irritates the rectal membrane, it can initiate a colonic response and cause evacuation of the suppository
(b) Chemically and physiologically inert
(c) Firm enough to be inserted (dependent upon melting point), but melts or dissolves in the orifice to release the drug

Suppository bases are classified into two categories based upon their lipophilicity or hydrophilicity:

(a) Fatty or oleaginous bases, which include cocoa butter, Fattibase™, Wecobee® bases, and Witepsol® bases.
(b) Water-soluble bases, which include glycerinated gelatin and polyethylene glycols.
(c) It is also possible to formulate bases that possess both lipophilic and hydrophilic properties. This base typically contains an emulsifying agent or surfactant.

The base chosen for the suppository will have a significant effect on the rate of drug release. The choice of base will often depend upon the lipid-water partition coefficient of the drug and the miscibility of the base with the body fluids. To ensure maximum release of drug from the base, typically a hydrophilic drug will be incorporated into a fatty base while a lipophilic drug will be incorporated into a water soluble base. A lipophilic drug contained in a fatty base will have reduced tendency to migrate into the aqueous fluid of the rectum compared to a hydrophilic drug.

The effect of the drug on the melting point of the base must also be considered. In some cases, the drug may lower the melting point of the base, rendering it too soft for insertion. A higher melting point suppository base, however, may not melt or dissolve in the body cavity and thus prevents the release of the drug.

10.4.2 Oleaginous Bases

Oleaginous (i.e., fatty) suppository bases melt quickly at body temperature; however, since the fatty base is not miscible with the aqueous bodily fluids, a drug with a high degree of lipophilicity will tend to remain in the base. Water-soluble drugs will release from the base quickly due to the attraction toward the aqueous fluids.

One example of an oleaginous base is **cocoa butter, NF** (also known as theobroma oil), which is a mixture of triglycerides derived from the roasted seeds of *Theobroma cacao*. Cocoa butter, NF melts just below body temperature (30–36 °C) which makes it ideal for use as a suppository base.

Table 10.3 Polymorphs of cocoa butter

Polymorphic form	Melting point (°C)
Gamma	18
Alpha	22–28
Beta'	28
Beta	35

However, due to the triglyceride content, cocoa butter has multiple polymorphs which can cause difficulty in processing. If the cocoa butter is heated to a temperature much greater than its melting point and then quickly cooled, it can be transformed into the metastable alpha crystalline polymorphic form that has a much lower melting point. The consequence of this is that the base may never solidify at room temperature. With time (about 2–3 days) and storage at a cold temperature (~10 °C), the alpha polymorphic form will convert to the higher melting point and more stable beta polymorphic form. Thus, when manufacturing a suppository with cocoa butter, the base must not be heated to higher than 35 °C to prevent conversion to the alpha polymorph upon cooling (Table 10.3).

The addition of certain compounds (i.e., volatile oils, phenolic drugs) act as eutectics to cocoa butter. This has the effect of the mixture having a lower melting point compared to the individual components. To counteract this, solidifying agents may be added. Solidifying agents include Cetyl Esters Wax NF and White Wax NF. However, the concentration of solidifying agent may alter the release of drug from the dosage form. Also, it was found that if less than 3% of the solidifying agent is incorporated, the formation of a eutectic mixture can result in the melting point being lowered further. The amount of drug and the type of drug will determine the amount of solidifying agent that is needed.

Other bases in the oleaginous category include **hydrogenated fatty bases**. These are referred to by the USP as "Hard Fat NF" bases. These bases consist of triglycerides derived from plant oils. Examples include Fattibase™ and the Witepsol® and Wecobee® series of bases. These bases perform similarly to cocoa butter but have good stability, since they do not exhibit polymorphism; and these bases release well from molds. Additionally, because the amount of unsaturated fatty acids is reduced, these bases are less prone to oxidation as compared to cocoa butter.

Witepsol® bases are mixtures of synthetic triglycerides of various molecular weights. They are divided into four classes (H, W, S, E) depending on the melting point and **hydroxyl value** (the number of free hydroxyl groups in the base). Within each series, the bases are given specific numbers to delineate differences in melting point and hydroxyl value. The use of a lower hydroxyl value base can help minimize the risk of chemical reaction between the base and other formulation components; however, low hydroxyl bases tend to be less elastic than bases with higher hydroxyl values which can lead to brittleness.

(a) The Witepsol® H series is characterized by small gap between melting and solidification temperatures, and have hydroxyl values below 15.

Table 10.4 Examples of commercially available Hard Fat, NF bases for suppositories

Trade name	Composition	Melting point (°C)	Solidification point (°C)
Fattibase™	Triglycerides from palm oil, palm kernel oil, coconut oil, with glyceryl monostearate, and polyoxyl stearate (act as emulsifiers)	32–36.5	27–31
Witepsol® H32	Triglycerides of saturated fatty acids C12–18 with variable amounts of partial glycerides	31–33	30–32.5
Witepsol® H12		32–33.5	29–33
Witepsol® H35		33.5–35.5	32–35
Witepsol® H5		34–36	33–35
Witepsol® H15		33.5–35.5	32.5–34.5
Witepsol® H37		36–38	35–37
Witepsol® H185		38–39	34–37
Witepsol® W32		32–33.5	25–30
Witepsol® W25		33.5–35.5	29–33
Witepsol® W35		33.5–35.5	27–32
Witepsol® W45		33.5–35.5	27–32
Witepsol® W31		35–37	30–33
Witepsol® S51	Additionally contain ethoxylated cetostearyl alcohol (nonionic surfactant)	30–32	25–27
Witepsol® S55		33.5–35.5	28–33
Witepsol® S58		31.5–33.5	27–29
Witepsol® E75	Additionally contain beeswax	38	32–36
Witepsol® E76		37–39	31–35
Witepsol® E85		42–44	37–42
Wecobee® FS	Coconut oil triglycerides	39.8	
Wecobee® M		35	
Wecobee® R		34–37	
Wecobee® S		43.9	

(b) The Witepsol® W series is characterized by a larger gap between the melting and solidification points and have a hydroxyl values between 20 and 50.
(c) The Witepsol® S series additionally contains a nonionic surfactant (ethoxylated cetostearyl alcohol) to aid in dispersibility and absorption of drugs. The hydroxyl values range from 55 to 70.
(d) The Witepsol® E series is characterized by a melting point above body temperature, which makes them useful in cases where the addition of a drug lowers the melting point of the base.

Examples of commercially available Hard Fat, NF bases are found in Table 10.4.

10.4.3 Water-Soluble Bases

Glycerinated gelatin and polyethylene glycol are typically used water-soluble suppository bases. Rather than melting, these bases release drug by dissolving in the body fluids.

Glycerinated gelatin consists of 20% glycerin dissolved in gelatin, with an added suspension or solution containing the drug. Glycerinated gelatin dissolves slowly in mucus, allowing for prolonged drug release. This base is typically utilized in formulation of vaginal suppositories, as it provides prolonged local action as the glycerinated gelatin softens more slowly than the fatty bases. Due to the hygroscopic nature of glycerin, the suppository may cause dryness and irritation with insertion as water will be drawn from the mucosal layer. During storage and handling, adequate protection must be provided from moisture in the environment, otherwise distortion in its shape may occur. Glycerinated gelatin base is typically not used rectally, as it has an osmotic effect and can stimulate evacuation. Glycerin suppositories are used, however, in the treatment of constipation.

Polyethylene glycol (PEG) is available in varying molecular weight ranges, which are designated by the number that follows PEG. Increasing the molecular weight of PEG increases its melting point and decreases its water solubility and hygroscopicity. Increasing the molecular weight also increases its viscosity. For example, a base composed of PEG 20 K is more viscous and shows slower drug dissolution than a base composed of PEG 3350.

PEG has the following properties:

(a) PEG 200–400 is liquid at room temperature, clear, and colorless.
(b) PEG 1000–1500 is semisolid, wax-like, and white with a melting point from 37 to 40 °C.
(c) PEG 1540–20K is solid, wax-like, and white. PEG 1540 has a melting point of 40–48 °C. PEG 20K has a melting point of 60–63 °C.

PEG does not melt at body temperature, but instead can dissolve. This allows for control over the release of drug via controlled dissolution of PEG/PEG mixtures. For water soluble drugs, the release rate is proportional to the molecular weight of the PEG. Two or more PEGs may be combined to reach the desired hardness and dissolution time. The addition of surfactants or plasticizing agents to the PEG base may be necessary to decrease brittleness of the final product.

PEG bases can be more irritating to the mucosal membranes than fatty bases. To reduce irritation, PEG bases should contain at least 20% water; if not, patients should be instructed to dip the suppository in water prior to use to reduce stinging sensation upon insertion into the orifice.

Nonionic surfactants such as sorbitan esters (Span®), polyoxyethylene stearates (Polyoxyl®), or polysorbates can be incorporated with PEG to adjust the melting point, vehicle consistency, and improve drug absorption. An example is Polybase™, which is a mixture of PEGs and polysorbate 80. It is a water miscible base that dissolves upon insertion, rather than melting (e.g., its melting point is 60–71 °C), and exhibits good stability at room temperature.

Table 10.5 Examples of excipients utilized in suppository formulations

Excipient	Function	Examples
Antioxidant	Prevent oxidation of base or drug	Alpha-tocopherol
Suspending agent	Prevents settling of particles in molten base	1–10% silica gel
Toughening agents	Used for high melting point bases, which are prone to brittleness and fracture	Polysorbate 80 Propylene glycol Castor oil Sweet almond oil
Mold lubricant	Prevents sticking of suppositories to the mold	Mineral oil (for water-soluble bases) Glycerin or propylene glycol (for oleaginous bases)
Viscosity-enhancing agents	Sustains release of drug from suppository base	Methyl cellulose Colloidal silicon oxide Aluminum monostearate
Surfactants/ emulsifying agents	Wet drug powder and reduce agglomeration Enhance spreading of base on mucosal surface Can also increase rate of drug release from base	Lecithin Sorbitan esters (Span®), Polyoxyethylene stearates (Polyoxyl®) Polysorbates (Tween®)
Eutectic agent	Lowers melting point	Sweet almond oil Liquid paraffin
Solidifying agent	Raises melting point	White wax Cetyl esters wax Beeswax

10.4.4 Other Excipients for Suppository Dosage Forms

Depending upon the characteristics of the drug and the base, various other excipients may be incorporated into suppository formulations. Examples of these can be found in Table 10.5.

10.4.5 Particle Size and Particle Settling During the Preparation of Suppositories

Particle size of the drug is an important consideration in suspension suppository formulations. A reduced particle size is desirable to prevent sedimentation of the drug in the molten suppository base before it has solidified during manufacture in accordance with Stokes' law (below). Likewise, particle sedimentation may also be reduced by increasing the viscosity of suppository base and reducing the density difference between the drug particles and the base.

$$v = d^2 \left(\rho_s - \rho_v \right) g / 18\eta$$

where,

v = Sedimentation rate (cm/s)
d = Particle diameter (cm)
ρ_s = Particle density (g/cm^3)
ρ_v = Base density (g/cm^3)
g = Force of gravity (981 cm/s^2)
η = Base viscosity (P)

A reduced drug particle size may also be used to ensure an adequate dissolution rate, especially in the case of poorly water soluble drugs.

10.4.6 Drug Release from a Suppository Base and Absorption

Drug release from a suppository base is dependent upon:

(a) Melting or dissolution of the suppository base
(b) Diffusion of the drug from the suppository base
(c) Dissolution of the drug in the bodily fluids

Lipophilic drugs can be slowly released from an oily base and moderately released from a water-soluble base. The lipophilic drug will dissolve slowly once in the aqueous compartment of the body orifice.

Hydrophilic drugs can be released rapidly from an oily base. Release from a water-soluble base is dependent on the rate of dissolution of the base and the rate of diffusion of the drug out of the base.

Increased viscosity of the base decreases drug release. The viscosity of the base can be increased by adding greater amounts of fat or wax, or in the case of PEG bases, by using a higher molecular weight PEG.

10.4.7 Storage and Handling

Environmental storage concerns include humidity. In high humidity conditions, the suppository can absorb moisture from the atmosphere (e.g., glycerinated gelatin suppositories should be stored in a sealed glass container to prevent the uptake of moisture, as glycerin is hygroscopic). In low humidity conditions, the suppository can lose water to the atmosphere and become brittle.

In general, suppositories should be stored at cool temperatures to prevent softening of the base (less than 30 °C for cocoa butter bases, and less than 35 °C for glycerinated gelatin bases). Suppositories containing PEG bases can withstand higher temperatures due to their higher melting points.

In many cases, suppositories are either individually wrapped in foil or plastic, or packaged as a continuous plastic strip. It is an important patient counseling point to remind patients to unwrap the suppository prior to insertion.

10.5 Suppository Manufacture/Production

Suppositories are generally produced through melt-molding or compression-molding. Disposable molds can be used which eliminates the need for cleaning and removal of the suppositories. The molds serve as packaging to the patients.

In **melt molding,** the components of the suppository are melted together, poured into a mold, and allowed to cool and congeal. On an industrial scale, the principles of injection molding may be applied to melt molding to extrude melted base into molds under pressure.

In **compression molding**, a paste-like mixture of base and drug is forced into a mold under pressure, without the use of additional heat. Compression is a useful method for heat labile drugs and allows for the incorporation of a higher drug loading of substances that are insoluble in the base.

For compounded suppositories, it is important to calculate the amount of volume that the loaded drug displaces such that the correct proportion of base and drugs are used for the desired dose.

Further Reading

Suggested readings for the student include the following texts:

1. Lang B, McGinity JW, Williams RO. Hot melt extrusion—basic principles and pharmaceutical applications. Drug Dev Ind Pharm. 2014;40(9):1133–55.. (see page 1150; “Implants” section)
2. Shin S, Byun S. Controlled release of ethinylestradiol from ethylene-vinyl acetate membrane. Int J Pharm. 1996;137(21):95–102.
3. Anderson GD, Saneto RP. Current oral and non-oral routes of antiepileptic drug delivery. Adv Drug Deliv Rev. 2012;64(10):911–8.

Chapter 11
Pulmonary Drug Delivery

Abstract This chapter provides an introductory overview on concepts related to drug delivery to the lungs. Physiological barriers to lung delivery are examined, as are the mechanisms for overcoming these barriers through delivery device and formulation design. A review is provided of delivery mechanisms and design of the three major classes of pulmonary drug delivery devices (pressurized metered dose inhalers, nebulizers, and dry powder inhalers). For each class of device, appropriate formulation approaches are discussed.

Keywords Nebulizer · Pressurized metered dose inhaler · Dry powder inhaler · Orally inhaled drug products · Pulmonary drug delivery · Pulmonary device design · Powder dispersion · Lung deposition

Learning Objectives

- Describe the advantages of local drug delivery to the lungs.
- Describe the advantages of systemic drug delivery via the lungs.
- Describe how the physiology of the lung differs between lung regions.
- Describe the three primary mechanisms of particle deposition in the lungs.
- Describe how particle aerodynamic diameter influences deposition in the lungs.
- Explain how particles are cleared from the lungs.
- Describe the advantages, disadvantages, and drug delivery mechanism of each class of pulmonary delivery devices.
- Compare and contrast jet nebulizers, ultrasonic nebulizers, and vibrating mesh nebulizers.
- Describe the design of pMDIs and the function of each device component.
- Explain the importance of drug solubility in the formulation of pMDIs.
- Explain the role of carrier particles (e.g., lactose) in DPI formulations.
- Describe the different mechanisms of particle de-agglomeration found in DPIs.
- Explain the concept of device resistance in DPI devices.
- Describe how performance of pulmonary delivery devices is assessed.

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Key Concepts
Students should know and be able to describe each of the following concepts as they review this chapter:

- Aerodynamic diameter
- Active dry powder inhalers
- Air jet milling
- Atomization
- Carrier-based systems (DPIs)
- Conducting airway
- Dead volume
- Device metered (DPIs)
- Diffusion (particle deposition)
- Dry powder inhalers
- Factory metered/pre-metered (DPIs)
- Fine particle fraction (FPF)
- Inertial impaction (particle deposition)
- Jet nebulizers
- Macrophage phagocytosis
- Mass median aerodynamic diameter (MMAD)
- Mucociliary escalator
- Nebulizers
- Orally inhaled drugs
- Passive dry powder inhalers
- Pressurized metered dose inhalers
- Respirable fraction (RF)
- Respiratory airway
- Scintigraphic studies
- Sedimentation (particle deposition)
- Spacers
- Spray drying
- Turbulent flow
- Ultrasonic nebulizers
- Vibrating mesh nebulizers

11.1 Introduction

Inhaled drugs are typically administered through the mouth (often referred to as **orally inhaled drug products**). The inhalation route is frequently utilized for local delivery of drugs to the lungs. A variety of pulmonary diseases can be treated through the targeted delivery of drugs that allows for:

(a) More concentrated drug/higher dose at the site of action
(b) Reduced systemic exposure and associated side effects

(c) Rapid onset of therapeutic effect

Examples of pulmonary diseases that may benefit from local therapeutic delivery include asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, pulmonary hypertension, and infections such as pneumonia or tuberculosis.

The airways are also an attractive route for systemic administration of drugs for several reasons, including:

(a) Large surface area for absorption
(b) Rich blood supply
(c) Thin barrier to systemic circulation

This allows for the delivery of drugs to the systemic circulation in cases where:

(a) Therapeutic drugs are degraded in the stomach, such as insulin or other biologics
(b) A noninvasive alternative to injections or infusions is desired
(c) Rapid onset of action is desired
(d) First-pass metabolism must be avoided

A challenge of successful pulmonary delivery is that the lung anatomy and physiology generally prevents easy inhalation of exogenous particles that may occur in ambient inhaled air. Thus, inhaler devices are often inefficient, in some cases only delivering about 10–20% of the loaded dose to the lungs. Because drugs are often inhaled through the mouth, administration may result in oropharyngeal irritation or unpleasant taste.

Several classes of devices have been developed for respiratory drug administration. Because the mechanisms for drug aerosolization differ for each type of device, each device class has specific advantages and disadvantages. The main device classes (Fig. 11.1) used to administer drugs to the lungs include the following:

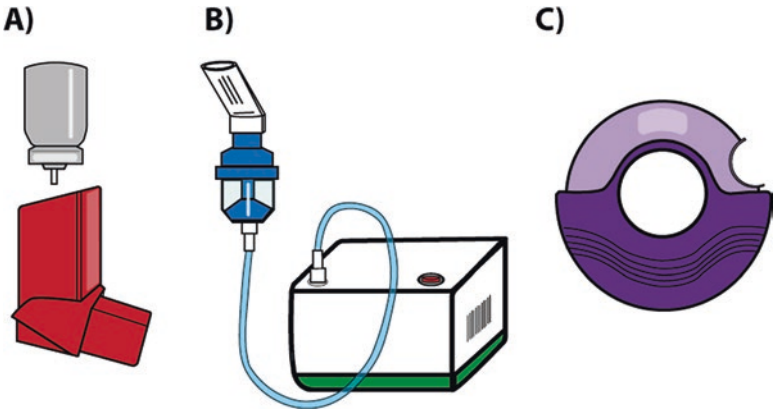

Fig. 11.1 An exemplary pressurized metered dose inhaler (**a**), nebulizer (**b**), and dry powder inhaler (**c**)

(a) Pressurized metered dose inhalers (pMDIs), which are propellant driven.
(b) Nebulizers, which are aqueous liquid spray systems.
(c) Dry powder inhalers (DPIs), which aerosolize drug powder by energy input from the patient or the device itself.

In addition to these classes, a propellant-free, multi-dose inhaler called the Respimat® Soft Mist Inhaler (SMI) has been developed that utilizes mechanical power from a spring to generate an aerosol cloud.

11.2 Lung Physiology

The airways serve two main purposes:

(a) Gas exchange and respiration
(b) Prevent the entry of exogenous substances into the body

The lung can be thought of as a tube that bifurcates (i.e., branches) sequentially as the airways progress from the central to the peripheral areas of the lungs. The series of bifurcation occurs for approximately 23 generations from the trachea to the alveolar sacs. Thus, the surface area of the airways increases dramatically moving from the trachea to the deep lungs, with the greatest surface area occurring in the alveolar region (approximately equivalent surface area to half a tennis court). Depending on the disease state being treated, different areas may be targeted by the aerosol to reach the desired receptors.

The lungs can be divided into two distinct zones, the conducting airway and the respiratory airway. The **conducting airway** functions to filter and condition the inhaled air and consists of:

(a) Oropharynx or nasopharynx (for nose breathing)
(b) Trachea
(c) Bronchi
(d) Terminal bronchioles

The **respiratory airway**, which is the site of gas exchange in the lungs, consists of:

(a) Respiratory bronchioles
(b) Alveolar ducts
(c) Alveolar sacs

The epithelium layer of the alveoli is much thinner (for more efficient gas exchange) than the conducting airways, and the branching nature of the lungs results in a large alveolar surface area. Therefore, the deep lung region is ideally suited for drug absorption and systemic delivery.

Differences in airflow velocity exist between the different regions of the lungs during breathing. Higher up in the airways, airflow occurs through a narrower cross-sectional area and must navigate larger changes in direction around various

anatomical features than in the deep lung that has more linear flow and overall larger cross-sectional area. These features contribute to the filtering function of the upper airways that can capture inhaled particles or droplets before entering the lungs.

The nasal passages and oropharyngeal (i.e., mouth and throat) regions act as a filter for the body during respiration. Moving deeper into the airways, the mucociliary escalator and alveolar macrophages provide particle clearance.

11.3 Mechanisms of Particle Deposition

The primary factor affecting aerosol deposition in the airways is the aerodynamic diameter of the particle. **Aerodynamic diameter** is defined as the diameter of a unit density sphere having the same settling velocity as the particle (or droplet) of interest. Aerodynamic diameter takes into consideration the geometric diameter of a particle as well as its density and shape. Aerodynamic diameter can be calculated from the equation below:

$$D_{ae} = D_{eq}\sqrt{\frac{\rho_p}{\rho_i X}}$$

where,

D_{ae} is the aerodynamic diameter of the particle.
D_{eq} is the geometric diameter of the particle.
ρ_p is the particle density.
ρ_i is the reference density, typically water.
χ is the shape factor, which is equal to 1 for a spherical particle and changes as the particle shape deviates from spherical.

Other particle characteristics affecting lung deposition include:

(a) Particle density, which contributes to inertia
(b) Particle charge, which can lead to aggregation of particles
(c) Particle shape
(d) Solubility and hygroscopicity of the particle, as the lungs are a high humidity environment
(e) Patient-dependent factors like airflow velocity and airway structure

The primary mechanisms of particle deposition include:

(a) Inertial impaction
(b) Sedimentation
(c) Diffusion

Particle deposition via **inertial impaction** relies on particle size, density, and velocity. The rapid airflow, high particle velocity, and abrupt airflow directional changes that occur in the upper airways lead to the predominant particle deposition

method of inertial impaction in the upper airways and for particles or droplets with an aerodynamic diameter greater than 5 μm.

Particle deposition via **sedimentation** occurs as a result of gravitational forces on the particle. As airflow velocity and directional changes decrease in the bronchial and bronchiolar regions of the lung, sedimentation likely becomes the dominant mechanism of particle deposition and will lead to deposition of particles between 1 and 5 μm.

For particles less than 1 μm, the primary mechanism of deposition will be **diffusion** (Brownian motion) due to the low airflow rate in the deep lung. These particles (i.e., those within the nanometer range) are also subjected to significant removal via exhalation.

In general, larger particles (i.e., those greater than 5 μm) tend to have significant deposition in the upper airways, while particles less than 1 μm are predominantly deposited in the lower airways. However, because particles smaller than 1 μm are subject to removal by exhalation, the optimum particle size range for respiratory delivery is from 1 to 5 μm.

11.3.1 Particle Clearance and Dissolution

Clearance mechanisms of particles from the lungs include mucociliary and cough clearance as well as macrophage uptake. Termed the **mucociliary escalator**, the epithelium of the upper airway is covered with cilia that move forward an overlying layer of mucus that is eventually swallowed. Insoluble or slowly dissolving particles that deposit in the conducting airways are cleared via the mucociliary escalator.

Insoluble or slowly dissolving particles deposited into the alveolar region of the lungs are primarily cleared by **macrophage phagocytosis**. Macrophage phagocytosis is dependent upon the size of the particles, with most efficient uptake occurring for particles between 1.5 and 3 μm in size. While the conducting airways contain mucus-secreting cells, the alveoli are devoid of mucous and are lined with a fluid contain phospholipids (i.e., lung surfactant). The surface active nature of this fluid may contribute to particle wetting and dissolution in the deep lung.

11.3.2 Influence of Disease

Disease may alter pulmonary drug deposition and clearance. For example, in chronic bronchitis, emphysema, and pulmonary fibrosis, the airway diameter is reduced, which increases the velocity of the air flow and results in a greater tendency for particles to undergo inertial impaction. This results in an increase in large airway deposition of particles compared to healthy lungs. In asthma, chronic obstructive pulmonary disease (COPD) and cystic fibrosis (CF), the changes in mucus viscosity, mucus acidity, and cilia damage secondary to chronic inflamma-

tion and infection result in impairment of mucociliary clearance of particles. The viscous, sticky mucus present in the lungs of CF patients also reduces particle diffusion to the epithelium layer.

11.4 Nebulizers

Nebulizers generally deliver liquid drug formulations to the lungs through **atomization**, which is defined as the breakup of the bulk liquid into fine droplets. The extent of lung deposition of aerosolized drug from nebulizers is dependent upon the droplet size, in addition to other aerosol characteristics such as droplet density and charge, and patient-dependent factors such as airway anatomy and inhalation patterns. Both solution and suspension formulations have been delivered from nebulizers.

Nebulizer therapy is beneficial for patients who are too young or too ill to use pMDIs or DPIs, as effective utilization of the nebulizer device is not critically reliant upon patient coordination (pMDIs) or sufficient inspiratory flow (DPIs). However, the disadvantages of nebulizers are that the design of the devices is often bulky and lack portability, and administration times can be lengthy. However, recent device design efforts have sought to improve the portability of nebulizers and shorten administration time. Administration times can also be lengthy, though nebulizers have been developed with a reduction in administration time. Performance efficiency of different types of nebulizers may also depend on the formulation, and thus a certain drug formulation may not be compatible with different types of devices.

There are several different types of nebulizers (Fig. 11.2), including:

(a) Jet nebulizers
(b) Ultrasonic nebulizers
(c) Vibrating mesh nebulizers

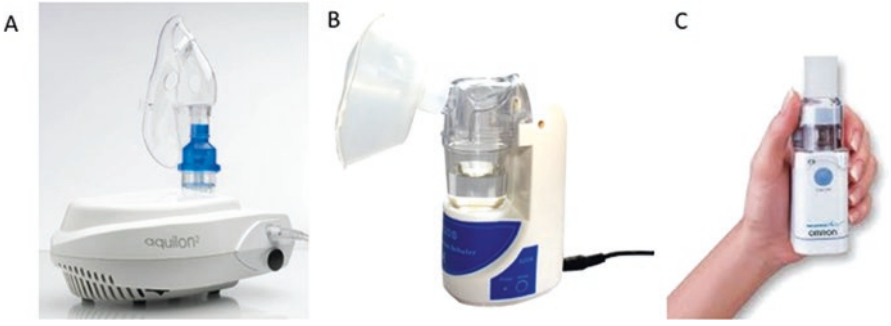

Fig. 11.2 Nebulizers can be divided into three categories. (**a**) Jet nebulizer, (**b**) Ultrasonic nebulizer, (**c**) Vibrating mesh nebulizer

11.4.1 Jet Nebulizers

Jet nebulizers atomize liquid formulations, solutions, or suspensions, through the application of compressed air through a narrow orifice. This results in the creation of negative pressure as a result of Bernoulli's principle and draws liquid up through a feeder tube (Venturi effect). This liquid stream is then broken up into droplets by turbulence within the air stream and/or by impaction with baffles included in the device design. Droplets that are small enough to remain entrained (i.e., suspended) within the air stream exit the nebulizer in the form of a liquid aerosol cloud, while droplets that are too large will fall back (via gravitational sedimentation) into the liquid reservoir to be atomized again. The presence of the baffles helps slow the velocity of the air stream and reduce droplet impaction onto the throat region of the patient.

Liquid viscosity, reservoir volume, humidity, and temperature can affect the performance of jet nebulizers. When the liquid falls below a certain volume within the jet nebulizer, atomization performance can be negatively affected and sputtering may occur. Changes in temperature and humidity can affect droplet size distribution or result in precipitation of the drug within the formulation. Generally, an increase in the viscosity of the liquid formulation results in an increase in the atomized droplet size.

The major disadvantage of jet nebulizers is the high amount of drug wastage, due to the portion of the liquid in the nebulizer that remains unavailable for use (known as the "**dead volume**"). Liquid adhesion to the walls of the device may also occur, which can be alleviated by the operator (patient) tapping the device or by designing the device so that the surface area available for adhesion within the reservoir is minimized. Loss of droplets during administration may be minimized through the use of a vent and valves in the device. Not all drug formulations may be appropriate for administration via jet nebulizer, particularly proteins due to the repeated stress of atomization and exposure of the protein at the air–liquid interface. Some proteins, however, have been successfully administered via jet nebulizer. Recombinant DNase (Pulmozyme®) is administered via jet nebulizer to reduce mucus viscosity in cystic fibrosis.

11.4.2 Ultrasonic Nebulizers

Ultrasonic nebulizers atomize liquid formulations through the utilization of a piezoelectric crystal that vibrates at high frequencies (Fig. 11.3). Droplet formation occurs as a result of capillary wave and cavitation formation in the liquid formulation as the piezoelectric crystal oscillates.

Compared to jet nebulizers, ultrasonic nebulizers can be less bulky and feature shorter drug administration times. Ultrasonic nebulizers also have drug waste because there is a dead volume that remains. A disadvantage of ultrasonic nebulizers is that the oscillation of the piezoelectric crystal results in the production of heat, which can be a concern for heat-labile drugs.

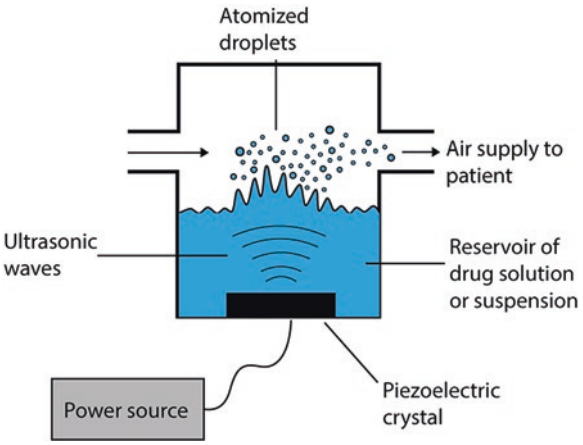

Fig. 11.3 Ultrasonic nebulizers generate aerosols through oscillation of a piezoelectric crystal

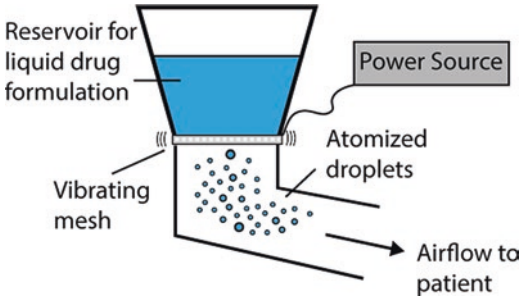

Fig. 11.4 Vibrating mesh nebulizers induce droplet atomization through vibration of a mesh membrane. In this example, the mesh is connected directly to a piezoelectric element to induce vibrations

11.4.3 Vibrating Mesh Nebulizers

Vibrating mesh nebulizers use oscillation and a mesh membrane to induce droplet production through cavitation and wave formation in the liquid below the mesh (Fig. 11.4).

The advantage of vibrating mesh nebulizers compared to ultrasonic nebulizers is that a lower amount of energy is utilized and thus less heat is produced. However, based on the fact that a lower amount of energy is employed, the performance of these devices is more affected by the viscosity of the liquid formulation. Also suspension systems may be difficult to atomize due to the size limitations of the mesh.

11.4.4 Nebulizer Formulations

Drugs intended for administration by nebulization are formulated as sterile solutions or suspensions, similar to those prepared for parenteral use. The formulation can be adjusted to achieve isotonicity and the formulation pH of between 3 and 8.5 has been used.

All aqueous-based oral inhalation solutions, suspensions, and spray drug products must be sterile in order to comply with the FDA requirements found in 21 CFR 200.51. Testing methodology for oral inhalation solutions, suspensions, and sprays can be found in USP <71> Sterility Tests. The FDA recommends unit-dose packaging for these drug products to prevent microbial contamination during use.

The delivery of poorly water soluble drugs by nebulization presents a challenge but can be achieved in suspension systems. While ethanol may be utilized as a cosolvent and propylene glycol as a surfactant, the lungs have a low tolerability for these nonaqueous solvents and thus the quantities that may be included in the formulation is limited.

11.5 Pressurized Metered Dose Inhalers

Pressurized metered dose inhalers (pMDIs) (Fig. 11.5) are propellant driven, metered drug delivery devices. Their advantages include:

(a) Portability
(b) Rapid administration times
(c) Sterility and prevention of backflow
(d) Protection of the drug from light, oxygen, and water
(e) Patient familiarity

However, pMDIs have disadvantages including:

(a) Requiring coordination between actuation of the device and inhalation of the dose by the patient, which may be difficult for some patients to achieve because of the fast-moving aerosol plume.
(b) Formulation challenges because of the nonaqueous liquid propellant system.

The principle design of pMDIs is a propellant-containing drug formulation which is stored under pressure in a canister. The propellants used in pMDIs are gases at room temperature and atmospheric pressure, with boiling points less than 21 °C and vapor pressures between 14 and 85 PSI at room temperature. In the sealed, pressurized canister of a pMDI, the propellant is predominantly in the liquid state. However, above the liquid phase, part of the propellant will be in the gaseous state (Fig. 11.4). This equilibrium is important because the pressure within the canister remains constant throughout the use of the product, despite prior doses being

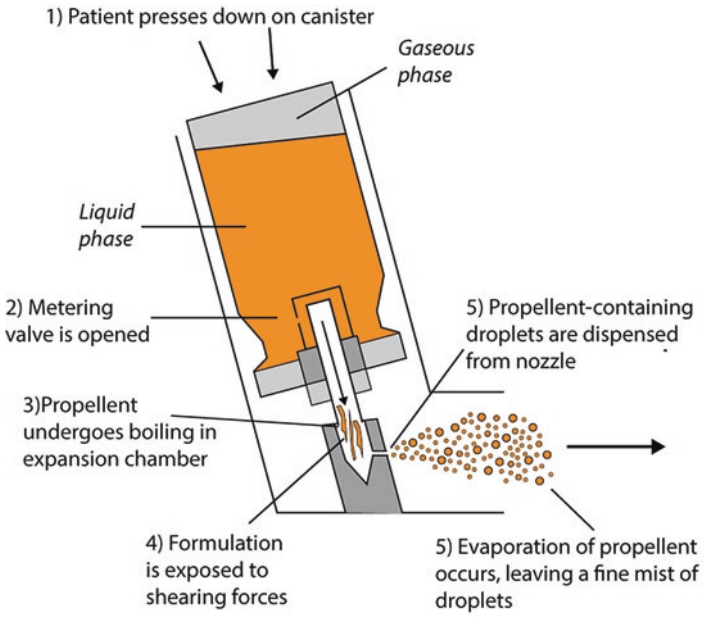

Fig. 11.5 Formation of an aerosol from a pMDI

dispensed from the canister. This is in contrast to nonliquefied compressed gas propellants where the pressure within the canister decreases as the gas is dispensed and results in changes in atomization as the product is used (and therefore, this system is not used for inhalation aerosols).

The propellant provides the energy to forcibly dispense the formulation from the pMDI device. Upon actuation, the liquid formulation is released from the metering valve and the propellant undergoes evaporation at a room temperature, atmospheric pressure environment. A fine mist of drug droplets results, depending upon the composition of the formulation (Fig. 11.5).

11.5.1 Device Design

The basic design of a pMDI incorporates the following components (Fig. 11.6):

(a) Pressurized, sealed canister containing the propellant/drug blend (in solution or suspension)
(b) Metering valve crimped onto the canister
(c) Actuator that connects the metering valve to an atomization nozzle
(d) Mouthpiece

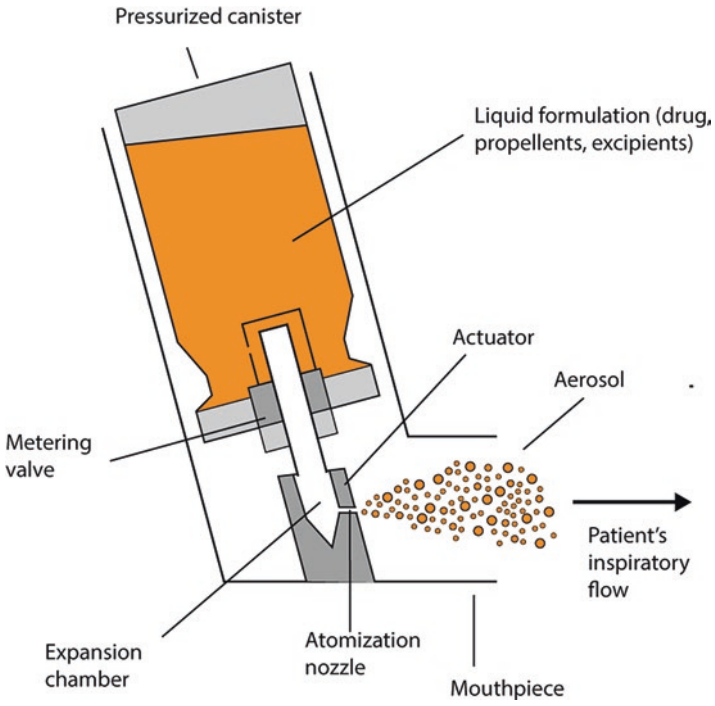

Fig. 11.6 Design of an exemplary pMDI device

The design of the device is important for performance of the aerosol:

(a) The metering valve is designed to release a fixed volume of the propellant/drug blend when triggered by the actuator and must be oriented downwards during use in order for the next dose to load.
(b) When the device is actuated, the formulation passes through an orifice in the actuator that results in the formation of an atomized aerosol plume.
(c) The actuator may be adjusted in order to change the plume characteristics. For example, the atomization orifice diameter may be changed.
(d) Inhalation airflow-activated actuators have also been used. An example of breath-triggered actuators is the Autohaler®, in which actuation occurs when the patient's inspiratory flow reaches 30 L/min. This helps improve the coordination between patient inspiration and device actuation.

Spacers are defined by the FDA as devices comprised of a reservoir (e.g., empty air volume) into which aerosol medication is dispensed. They are often utilized with pMDIs to extend the distance between the actuator and the mouth of the patient. They also enable the deacceleration of the emitted dose (thereby reducing oropharyngeal deposition) and provide longer evaporation times for the propellant. Overall, they are intended to minimize the delivery of large aerosolized particles which

would otherwise be deposited in the mouth. Spacers may also facilitate proper inhalation by providing sound cues to the patients if they are inhaling too quickly.

Valves holding chambers are similar to spacers, but function to hold the actuated aerosol cloud, increase the evaporation time for the propellant, and reduce oropharyngeal deposition to improve lung deposition.

11.5.2 Formulation Considerations of pMDIs

Drugs intended for delivery via a pMDI are formulated in nonaqueous propellants (e.g., hydrofluoroalkanes: HFA 134a and 227), sometimes with additional excipients. Important formulation factors for pMDIs include:

(a) Drug solubility in the propellant (determines whether a suspension or solution will be formulated)
(b) Vapor pressure
(c) Solubility of oxygen in the formulation
(d) Density of the suspending vehicle, in the case of suspension formulations

The active drug in a pMDI formulation may be suspended or dissolved in the propellant. The drug should either be completely soluble in the formulation or practically insoluble. This results in either a solution or a suspension being formed. Partial solubility is not desirable, as it can lead to Ostwald ripening, changes in the particle size distribution, and subsequent irregular dosing. Fluctuations in temperature can also lead to changes in drug solubility, which can in turn lead to precipitation, dissolution, and crystal growth. In order to formulate the drug as a solution, the drug should be soluble enough that the entire dose is emitted in one to two actuations.

Vapor pressure can affect particle size, droplet evaporation, and plume shape and velocity. Solubility of oxygen in the formulation can affect the stability of the drug. The density can affect the stability of the suspension. To prevent settling of the suspended particles, the density of the vehicle and the particles should be as close as possible.

11.5.3 Propellants

Originally, the propellants of choice for pMDIs were chlorofluorocarbons (CFCs). However, due to environmental concerns, phasing out of CFCs from pMDI formulations was required by the FDA.

Most drugs and excipients studied have poor solubility in HFAs. Cosolvents, such as ethanol, may be incorporated in the formulation to increase the solubility of the surfactants, but large concentrations of ethanol can negatively affect the aerosol performance by lowering the vapor pressure of the system as well as causing irritation to the lung tissue.

A mixture of propellants may be used to formulate pMDIs. The advantages of a mixture of propellants are that:

(a) Vapor pressure can be modulated, which in turn influences the particle size and aerosol plume
(b) Density can be adjusted to match that of suspended drug particles, which enhances suspension stability by reducing particle settling

11.5.4 Other Excipients

In suspension pMDI formulations, surfactants are often incorporated to stabilize the dispersion through the reduction of electrostatic charge of the micronized drug particles. For solution-based pMDIs, surfactants are often incorporated to prevent crystal growth and ensure solubilization of the drug. Surfactants may also be included for valve lubrication.

Cosolvents are less volatile than propellants and are incorporated in the pMDI formulation to facilitate dissolving the drug in the propellant system and lower the vapor pressure in order to modulate particle size. Ethanol is a commonly used cosolvent in pMDIs.

Other excipients that may be utilized include stabilizers, preservatives, antioxidants, and buffers.

11.6 Dry Powder Inhalers

Dry powder inhalers (DPIs) consist of a powdered drug formulation and device in which aerosolization of the powder is driven by patient inspiration through the device—i.e., they are considered "passive" or patient-driven (although none are currently marketed, some "active" DPIs have been developed that use an external energy source to aerosolize the powder). DPIs provide an alternative to propellant and aqueous-based aerosol drug delivery systems, while still retaining the portability and rapid administration times found in pMDIs. Unlike pMDIs, DPIs require little patient coordination between actuation and inhalation, as drug is not aerosolized until the patient breathes in, though sufficient inspiratory flow must be generated by the patient to properly aerosolize the powder dose. These devices are also useful for the delivery of drugs which may be unstable in liquid form and are thus promising for the pulmonary delivery of biological products.

To be deposited in the lungs, drug particles must generally fall within the size range of 0.5–5 μm aerodynamic diameter. The increased surface area-to-mass ratio found in particles of this size range, as well as the increased surface energy brought

about by manufacturing processes for these fine powders, generally results in highly cohesive particles and the formation of aggregates. These aggregates hinder complete redispersion and aerosolization of inhalable powder, thus making it a challenge to deliver accurate doses to the lungs. Cohesive forces also reduce the flowability of inhalable powders, which can lead to manufacturing difficulties due to the need to accurately fill powder doses.

11.6.1 Formulation

Drug particles must be manufactured in a particle size range suitable for inhalation (e.g., aerodynamic diameter less than 5 μm). Air jet milling and spray drying are typical manufacturing methods. In **air jet milling**, particle size is mechanically reduced through particle–particle and particle–equipment collisions that are induced through application of a high-velocity air stream. **Spray drying** involves atomization of a liquid containing the drug and subsequent rapid drying of drug solution, resulting in the formation of solid drug particles. The properties of these particles can be manipulated by adjusting processing parameters, such as atomization nozzle type, liquid feed rate, airflow rate, and surface tension and viscosity of the liquid drug formulation.

The particles resulting from these manufacturing processes are typically highly cohesive. To overcome cohesive forces and improve powder flow and dispersibility, the drug contained within a DPI can be blended with large carrier particles or formulated as an agglomerate-based system. **Carrier-based systems** utilize a mixture/blend of micronized drug particles with larger excipient particles, typically lactose. The micronized drug adheres to the larger lactose particles, which results in improved powder flow compared to the drug alone. Upon inhalation by the patient, the drug particles are intended to be separated from the carrier particles by the inhaler device. This approach is especially useful for low-potency drugs, where the dose may be so low that it requires a diluent for feasible delivery.

Agglomerate-based formulations may contain pure drug or a mixture of drug and excipient(s) which are intentionally formulated into agglomerates to improve powder flow. These agglomerates must be strong enough to withstand the manufacturing process, but can be deagglomerated upon inhalation by the patient. An example of an agglomerate-based DPI is the Pulmicort Flexhaler® (AstraZeneca).

Overall, the choice of excipients for dry powder formulations is relatively limited, with only a few excipients that are in FDA-approved products. To reduce the mass of excipients required in DPI formulations, efforts have been made to engineer particles (i.e., particle engineering) to exhibit properties that are suitable for aerosolization by manipulating factors such as shape, size, porosity, and surface properties.

11.6.2 Mechanisms of Aerosolization (Particle Fluidization and Re-dispersion)

As the airflow moves over the static powder bed, particles are fluidized. Fluidized powders must then be deaggregated by strong aerodynamic forces (turbulence) or particle collisions within the inhaler (re-dispersion). Fluidization and deaggregation of powder from DPI often dependent upon both particle size and attractive forces between particles. Potential adhesion forces at play include:

(a) Van der Waals forces
(b) Electrostatic forces
(c) Capillary forces
(d) Mechanical interlocking and solid bridging forces

11.6.3 Device Design

To overcome the cohesive forces between particles, breakup aggregates, and aerosolize the drug powder, sufficient energy must be supplied through the device. DPIs are categorized as passive or active devices depending on the manner by which this energy is supplied.

Passive DPIs are dependent upon the inhalation force of the patient to provide the energy needed to disperse the drug powder. The strength of the patient's airflow can therefore influence the amount of drug delivered to the lungs. While this eliminates the issues with coordinating device actuation with breathing maneuver found with pMDIs, some patients may not be able to exert the necessary inspiratory force to aerosolize the powder due to disease or age (i.e., pediatric or elderly patients).

Active DPIs utilize an external energy source to generate powder dispersion, rather than relying on the patient's inhalation efforts. Devices in development include those where powder fluidization is powered by electrical, pneumatic, or mechanical forces.

Other design components may be included to facilitate the breakup of aggregates. These design elements are intended to introduce turbulence within the device. **Turbulent flow** consists of highly irregular and rapid fluctuations of velocity in time and space. Turbulent flow subjects the drug aggregates and particles to shear forces as a result of acceleration in different directions. At forces of sufficient magnitude, particles are detached from aggregates and/or carrier particles. One method for inducing turbulence is the inclusion of spiraling flow channels that carry the dose as it exits the device. Another method is to include tangential air channels that open into a cylindrical chamber. This results in the creation of a high-energy vortex as the patient inhales through the device.

Mechanical forces are also utilized to deaggregate powder in DPIs. These may be mechanically driven, in the case of impellers, beads, and spring-driven hammers,

or provide a method for impaction, as is the case of baffles, in which the entrained powder impacts the baffle and subsequently deaggregates. Other deaggregation methods include the introduction of pneumatic forces to the powder bed or mechanical vibration through the use of specifically arranged capsules, flutter films, and piezoelectric crystals.

A mesh or screen is typically included in DPI device design, often for the purpose of preventing capsule fragments from being inhaled. The inclusion of a mesh also results in disruptions in the flow stream. For example, a mesh may suppress turbulence downstream by obtaining a spatially uniform air flow. Likewise, turbulence may be increased by the presence of a mesh in the flow stream through the use of large pores. The presence of the mesh can facilitate particle deaggregation; however, particles may remain trapped on the mesh, negating the overall effect.

DPIs can also be classified based upon whether the drug is stored in and metered out from a reservoir system present in the device itself (**device metered**) or dispensed from single, discrete dosing units such as capsules or blisters (**factory metered or pre-metered**). Factory-metered DPIs generally offer better protection of the drug from the environment and dose dispensing may be less prone to variability. However, depending on the device design, the patient may need to reload the dosage unit system, which can be inconvenient.

While device-metered DPIs can potentially administer multiple doses without requiring reloading, disadvantages include dose and dispensing variability. Protection of the drug powder from the environment (e.g., moisture) is also a concern that must be considered.

11.6.4 Device Resistance

An important parameter for pharmacists to understand when considering different inhaler devices is the resistance of the device to the inhalation effort of a patient. To deliver drug to the lungs of the patient, air must flow through the DPI device. Flow rate (Q) through the device is related to device resistance (R) and pressure drop (ΔP) across the device by the following equation:

$$\sqrt{\Delta P} = QR$$

When patients inhale, it is their diaphragm that generates a pressure drop that results in airflow. For a given pressure drop, a higher flow rate is achieved through a lower resistance device. Device resistance can be thought of as how the device restricts flow. Resistance is increased by constricting the flow of air through the use of narrowing inlets that can generate turbulence. By narrowing the cross-sectional area of the flow stream, the flow velocity within the device is increased and the greater kinetic energy is carried by the flow stream, which can lead to improvements in device performance. Though the performance of high-resistance DPIs may often

exceed that of low-resistance DPIs, pediatric or elderly patients may have difficulty generating sufficient inhalation flow rate through the devices. Additionally, the velocity of the flow must be reduced or the majority of the particles will end up impacting in the mouth or back of the throat. This may be accomplished by widening the flow path through the mouthpiece, which reduces the axial velocity of the flow stream exiting the device. Baffles or curved paths can also be designed to reduce flow velocity.

11.7 Analytical Methods for Pulmonary Drug Delivery Systems

Performance of pulmonary delivery devices may be assessed by in vivo or in vitro. In vivo, device performance is assessed by **scintigraphic studies**, which allow visualization of the regional lung deposition of the inhaled drug through incorporation of a gamma-radiating nuclide into the formulation (Fig. 11.7). Scintigraphic studies are used to quantify the amount and the area of drug deposition in the lungs and are thus useful for when drug targeting to specific areas of the lungs is desired.

In vitro, the aerodynamic size distribution of particles emitted from the device can be used as an estimate of aerosol deposition efficiency. The **mass median aerodynamic diameter (MMAD)**, which is a statistical measure of the aerodynamic size of the aerosol and represents the 50% point in the cumulative particle size distribution, is commonly used. The MMAD is determined using inertial impaction,

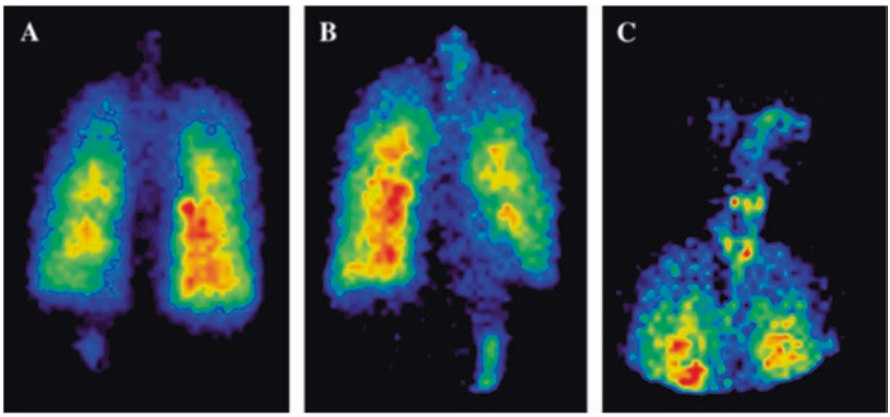

Fig. 11.7 Scintigraphic images show pulmonary deposition of technetium-99m-labeled albuterol particles. Reprinted with permission of the American Thoracic Society. Copyright © 2019 American Thoracic Society. Cite: Usmani OS, Biddiscombe MF, Barnes PJ/2005/Regional Lung Deposition and Bronchodilator Response as a Function of β2-Agonist Particle Size/The American Journal of Respiratory and Critical Care Medicine/172/1497–504. The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society

utilizing either cascade impaction or multistage liquid impingement devices. Particles with an MMAD of 1–3 μm often correlate with deposition in the deep lungs (alveoli), while particles with an MMAD of larger than 5 μm correlate with deposition in the upper airways (bronchioles).

Inertial impaction studies also give insight into lung deposition, by providing the geometric standard deviation (GSD) of the particles and **fine particle fraction (FPF)**. The fine particle fraction is defined as the percentage of the emitted dose that is within the respirable range (i.e., aerodynamic diameter less than 5 μm). The FPF is an important parameter for assessing the performance efficiency of a device. Similarly, device and formulation performance may be described in terms of **respirable fraction (RF)**, which is defined as the percentage of the loaded dose that is within the respirable range (i.e., aerodynamic diameter less than 5 μm). It is important to note that the FDA distinguishes between **metered dose from the device** (i.e., the standardized dose measured from the device or blister/capsule) and the **target delivered dose,** defined by the FDA as the amount of drug that is delivered from the mouthpiece under specific test conditions, such as flow rate or duration of flow.

For pMDIs, the USP requires additional tests such as spray pattern and geometry, plume velocity, spray temperature, and spray force, which are used to predict the lung deposition of the drug.

Further Reading

Suggested readings for the student include the following texts:

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Chapter 12
Nasal Drug Delivery

Abstract This chapter covers the fundamentals of nasal drug delivery. Anatomical barriers to drug delivery, examples and functions of commonly used excipients, and device design are reviewed. Analytical procedures relevant to testing the performance of nasal drug products are also introduced.

Keywords Nasal drug delivery · Nasal formulations · Nasal drug delivery devices · Nasal device performance testing · Nasal spray

Learning Objectives
- Explain the advantages of the nasal route for drug delivery.
- Describe the barriers related to nasal drug delivery.
- Explain the optimal droplet/particle size for nasal cavity retention.
- Describe the different excipients used in nasal formulations.
- Describe the methods of drug administration for the nasal route.
- Describe the FDA-recommended performance tests for nasal devices.

Key Concepts
Students should know and be able to describe each of the following concepts as they review this chapter:

- Metered dose
- Priming
- Nasal spray pump
- Nasal pressurized metered dose inhaler

12.1 Introduction

The nasal route of delivery has the advantages of easy access (for local delivery) and rapid onset of action (due to the rich vascularization of the nasal cavity) and is considered noninvasive (compared to the parenteral route). Both local and systemic

A. D. Brunaugh et al., *Essential Pharmaceutics*, AAPS Introductions in the Pharmaceutical Sciences, https://doi.org/10.1007/978-3-030-31745-4_12

acting drugs can be delivered via the nasal route. Examples of nasally administered drugs include corticosteroids, antihistamines, decongestants, calcitonin, triptans, and vaccines. Nasal formulations are most often liquid-based (solution or suspension) dosage forms, which may be administered via drops or sprays to the nasal cavity. Recently, nasal powder formulations have also been developed. Though not discussed in this text, the use of the nasal route for delivery of drugs to the brain is an area of intense research focus, as the nasal cavity is innervated and may potentially allow for bypass of the blood–brain barrier for drug delivery.

12.2 Barriers for Nasal Drug Delivery

The nasal cavity functions to warm, moisturize, and filter inspired air prior to its entry into the respiratory system. The anatomical structures that enable these functions to occur may also act as barriers for drug delivery and must be considered during the development of the formulation and design of the delivery device.

Similar to the lungs, the nasal cavity contains a mucociliary clearance system that functions to filter large particles. Ciliated epithelial cells move the mucus layer covering the nasal epithelium forward toward the nasopharynx. This can potentially lead to rapid clearance of deposited drug and may reduce drug absorption. To improve retention of deposited drug on the nasal epithelium, the use of gelling agents and bioadhesive polymers (i.e., a natural polymer with adhesive properties) is under investigation.

Additionally, the size and geometry of the nasal airway differ between individuals, with age, gender, and ethnicity contributing to variation. These anatomical differences may result in variability drug deposition in the nasal cavity, and thus deviations in drug absorption. Nasal casts based upon medical imaging have been used to study in vitro the effect of nasal geometry on drug delivery. This area of research is likely to become increasingly important as the use of the nasal route for drug brain delivery is explored.

Lastly, droplet or particle size distribution of the nasal spray or powder upon actuation from the device can affect the area of the nasal cavity in which the drug is deposited and subsequently the therapeutic effect of the delivered drug. In general, particles/droplets that are greater than 10 μm in diameter are retained in the nasal cavities and do not enter the lungs upon inspiration.

12.3 Excipients Used in Nasal Formulations

Depending on the physicochemical properties of the drug, it may be necessary to incorporate excipients into the formulation to enable successful nasal drug delivery and therapeutic effect. Relative to some other routes of administration, a limited number of excipients are contained in FDA-approved nasal products.

Table 12.1 Examples of excipients used in nasal solution formulations

Excipient category	Exemplary excipients and concentrations
Tonicity adjusting agent	Sodium chloride (0.65–0.9% w/v) Dextrose (5% w/w)
Buffering agent	Citric acid (0.17–0.28% w/v) Disodium phosphate (0.19–0.65% w/v)
Preservative	Benzyl alcohol (<0.5% w/v) Benzalkonium chloride (0.02–0.12% w/v) Methylparaben (<0.7% w/w) Propylparaben (<0.3% w/w)
Antioxidant	Butylated hydroxyanisole (<0.02% w/v) Butylated hydroxytoluene (<0.0001% w/w)
Complexing agent	Edetate disodium (EDTA) (0.01–0.2% w/v)
pH-adjusting agent	Sodium hydroxide (limits not specified by the FDA) Sulfuric acid (<1.88% w/v)
Viscosity-enhancing agents	Hydroxypropyl methylcellulose (HPMC) (<0.1% w/v) Microcrystalline cellulose (MCC) (<0.002% w/w)

If the drug has low aqueous solubility, the inclusion of cosolvents may be necessary in order to keep the drug dissolved. Suspending agents, such as carboxymethylcellulose sodium and microcrystalline cellulose, or surfactants, such as polysorbate and polyethylene glycol, may be required if the formulation is a suspension.

As with parenteral solutions, tonicity of the nasal formulation is adjusted through the inclusion of suitable tonicity agents such as dextrose or sodium chloride. Preservatives and antioxidants are also included in the formulation to ensure long-term stability. Preservatives in FDA-approved nasal products include benzyl alcohol, benzalkonium chloride, methylparaben, and propylparaben.

12.4 Methods of Nasal Administration

Liquid nasal formulations may be delivered via droppers, squeeze bottles, pressurized delivery systems, or mechanical spray pumps systems (Fig. 12.1).

Many over-the-counter nasal formulations are administered through droppers or squeeze bottles. Dosing accuracy and residence time are a challenge with nasal drops, as the drops only cover a small area of the nasal mucosa and quickly drip down the oropharynx where it is swallowed. This dosage form may be better suited for infants, who have a smaller nasal mucosa that is more easily covered by the drops. Squeeze bottles that deliver a spray formulation can reach a larger surface area of the nasal mucosa than drops, but dose control and variability remain an issue as the amount of pressure placed on the bottle (used to generate the dispensing of the formulation) can affect the spray and droplet/particle size distribution. In addition, squeeze bottles are not a closed system, and microbes can enter the container from the tip of the bottle and through backflow after administration.

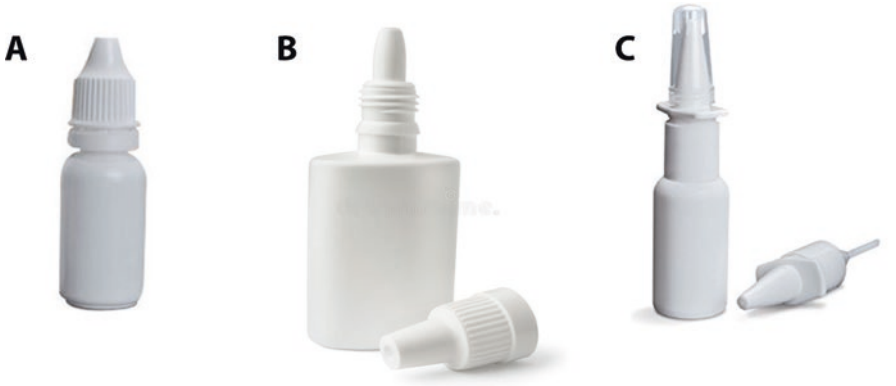

Fig. 12.1 Examples of nasal devices: (**a**) dropper, (**b**) squeeze bottle, (**c**) mechanical spray pump system. Many over-the-counter squeeze bottles can also function as dropper bottles when turned upside down

Alternative to droppers and squeeze bottles are metered-dose nasal spray pumps or nasal pressurized metered-dose inhalers. **Metered dose** is defined as the release of a specific amount of drug by the device upon each device actuation. **Nasal spray pumps**, which the FDA defines as all components of the container system that are responsible for metering, atomization, and delivery of the formulation to the patient, may generate a spray plume through mechanical or power-assisted forces. **Nasal pressurized metered-dose inhalers** generate a plume through the use of a propellant.

In general, these systems offer greater reproducibility of delivered dose, though the characteristics of the emitted spray are still dependent upon the properties of the pump, formulation, actuator orifice. Additionally, an important patient counseling point for metered nasal delivery systems is that they may require **priming** (i.e., repeated actuations of the device until a fine mist/spray appears) upon first use, or if the device has not been regularly used. Other unit dose or dual dose devices may be pre-primed.

12.5 Nasal Device Performance Testing

Performance of nasal delivery systems are affected by the dosage volume, the spray angle, spray/plume geometry, the size distribution of droplets in the spray, and in the case of a suspension formulation, the particle size distribution of suspended particles within the formulation. These device and formulation performance parameters vary depending upon the drug product and are influenced by the viscosity and surface tension of the liquid formulation as well as the dimensions and mechanics of the device. It is particularly important that these parameters remain consistent and

Table 12.2 FDA-recommended nasal device performance tests

Test	FDA-recommended acceptance criteria
Pump spray weight delivery	Weight of individual sprays should be within 15% of target weight and their mean weight within 10% of target weight
Spray content uniformity	$N = 10$ containers from the beginning and end of a batch should be tested. From each container, one to two sprays should be actuated, and the amount of active ingredient delivered from the actuation should not exceed 80–120% of the labeled claim for more than 2 of 20 determinations. Additional criteria are provided by the FDA if the drug product does not meet the initial acceptance criteria
Spray pattern and plume geometry	Acceptance criteria should include the shape of the spray pattern and the size of the pattern
Droplet-size distribution	Acceptance criteria should correspond to 3–4 cut-off values for the delivered plume. For example, the 10% diameter cut-off (D_{10}), the 50% diameter cut-off (D_{50}), the 90% diameter cut-off (D_{90}), and span [$(D_{90}–D_{10})/D_{50}$] can be used

reproducible throughout the lifetime of the drug product, as they affect the delivery of the drug to the therapeutic target. The FDA includes specific recommendations for nasal drug products in the "Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products."

Device-specific assays that are recommended by the FDA for nasal drug products are outlined in Table 12.2.

Additional tests may also be performed, including evaluation of the plume characteristics upon actuation of the device at different angles or under different inhalation flow-rate conditions.

Further Reading

Suggested readings for the student include the following texts:

1. Arora P, Sharma S, Garg S. Permeability issues in nasal drug delivery. Drug Discov Today. 2002;7(18):967–75.
2. Djupesland PG. Nasal drug delivery devices: characteristics and performance in a clinical perspective—a review. Drug Deliv Transl Res. 2013;3(1):42–62.
3. Warnken ZN, Smyth HD, Davis DA, Weitman S, Kuhn JG, Williams RO III. Personalized medicine in nasal delivery: the use of patient-specific administration parameters to improve nasal drug targeting using 3D-printed nasal replica casts. Mol Pharm. 2018;15(4):1392–402.
4. Warnken Z, Smyth HD, Williams RO. Route-specific challenges in the delivery of poorly water-soluble drugs. In: Formulating poorly water soluble drugs. Cham: Springer; 2016. p. 1–39.
5. Warnken Z, Kim Y, Mansour H, Williams RO III, Smyth HDC. Fundamentals in nasal drug delivery. In: Inhalation aerosols: physical and biological basis for therapy. 3rd ed. Boca Raton: CRC Press; 2019.

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A. D. Brunaugh et al., *Essential Pharmaceutics*, AAPS Introductions in the Pharmaceutical Sciences, https://doi.org/10.1007/978-3-030-31745-4