22 Oral Solid Dosage Forms

Chapter Objectives

At the conclusion of this chapter the student should be able to:

1. Understand the basic concepts and challenges associated with the development of an oral solid dosage form.
2. Describe the Biopharmaceutics Classification System (BCS) for drugs and understand how it may be applied to oral dosage form development.
3. Understand the importance of solubility and permeability in oral drug delivery.
4. Describe preformulation development activities and their importance in developing a drug product.
5. Apply basic physicochemical principles to active pharmaceutical ingredients.
6. Identify the roles that pharmaceutical excipients play in product development.
7. Understand the important physical, chemical, and mechanical properties of pharmaceutical materials and their relevance in formulation development.
8. Describe the common unit processes used to manufacture oral solid dosage forms.
9. Understand the importance and role of oral dosage form performance tests in ensuring product quality and performance.

Introduction

This chapter, in many ways, is the culmination of those that preceded it. Physical pharmacy and pharmaceutical science is the science of the delivery of active pharmaceutical ingredients (APIs) to the target site to achieve the desired pharmacological effect. For the drug to exert its biological effect, it must be released from the dosage form, permeate through biological membranes, and reach the site of action. Successful design and delivery of APIs requires a sound fundamental understanding of the diverse array of scientific topics presented in this text. The goal of this chapter is to provide an introduction to how these topics are integrated into dosage form design, product development, and manufacturing activities. The focus of this chapter is on oral drug delivery, and in particular solid dosage forms. Table 22-1 shows that a majority of pharmaceutical products, 60% or more, are offered as solid dosage forms. However, many of the basic principles apply to the design and manufacture of all types of pharmaceutical dosage forms. The pharmaceutical industry is, after all, a drug product industry, not a drug industry.

Gastrointestinal Absorption

As the focus of this chapter is on oral dosage forms, a brief review and understanding of the gastrointestinal tract and drug absorption is beneficial. Additional discussion of details of the physiology and absorption of drugs from the gastrointestinal (GI) tract has been presented in chapters on Biopharmaceutics (Chapter 12) and Drug Delivery Systems (Chapter 23).

The gastrointestinal tract is depicted in Figure 22-1 and some details of the dimensions and volumes and residence time are shown in Table 22-2. The oral cavity provides the first contact with biological fluids where mastication and mixing with saliva takes place and digestion begins. As ingested components are swallowed, they move through the esophagus into the stomach. The stomach provides several major functions. It processes food into chyme with vigorous contractions that mix the ingested contents with gastric secretions that continue digestion. It also regulates the input of these liquefied components into the intestinal tract and serves as a major site of chemical and enzymatic breakdown. As stomach contents empty, the chyme enters the small intestine where the absorption of a majority of drugs and nutrients takes place.

Absorption of drugs and nutrients can occur from each section of the small intestine and colon. The small intestine is partitioned into three sections: the duodenum, the jejunum, and the ileum. For most drugs, the duodenum and the proximal jejunum are the best sites of absorption as they have the highest absorptive surface area and often the highest concentration of dissolved drug is achieved in the lumen

of this region. Small intestinal absorption is now understood to be dramatically affected by regional differences in the distribution of transporters, enzymes, and greater detail is provided on these aspects in Chapter 12 on Biopharmaceutics. Significant drug absorption from the colon may also occur although the absorptive surface area is substantially less than that of the small intestine.[1,2] However, drug may remain in the colon for 12 to 72 hr and this longer residence time makes the colon an effective site of drug absorption in some cases. Drug absorption may also occur from the oral cavity[3,4,5] or, rarely, the stomach depending upon the drug and dosage form properties, which must be conducive to absorption from these sites.[6] The low absorptive surface area and typically short residence time of the stomach limits absorption from this site.

Biopharmaceutics Classification System

An important goal of pharmaceutical formulation development is to "facilitate" drug absorption and ensure that an

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adequate amount of drug reaches the systemic circulation. Many orally administered drugs enter systemic circulation via a passive diffusion process through the small intestine, although paracellular and transport-mediated absorption also occurs and our understanding of these absorption mechanisms continuous to grow. The Biopharmaceutics Classification System (BCS) is a tool to categorize compounds according to two key parameters: solubility and permeability.[7] Although the BCS does not address other important factors such as the drug absorption mechanism and presystemic degradation, it nonetheless provides a useful framework for identifying potential drug delivery challenges. It also facilitates the identification of appropriate oral dosage forms and strategies to consider that provide opportunities to overcome physicochemical limitations. According to the BCS, compounds are grouped into four classes according to their solubility and permeability as shown in Table 22-3. A detailed analysis of the transport and absorption of drugs is described earlier in this book and the student is directed there for a detailed discussion of the various aspects to relate to intestinal absorption.

Key Concept

Biopharmaceutics Classification System

The Biopharmaceutics Classification System (BCS) is a scientific framework for classifying drug substances based on their intestinal permeability and aqueous solubility. When combined with drug product dissolution, the BCS takes into account three of the most important factors that influence the rate and extent of drug absorption for immediate release dosage forms: intestinal permeability, solubility, and dissolution. The framework of the BCS may be used as a drug development tool to improve product development efficiency, identify necessary clinical testing, and establish useful in vitro evaluation strategies.

The basis of the BCS is rooted in the understanding that two very critical parameters affecting drug absorption are solubility and permeability. The importance of these two properties in determining oral absorption can be seen from the following equations describing the flux of drug across the intestinal membrane.

Table 22-1 Most Commonly Available Pharmaceutical Dosage Forms[1,2]

Dosage Form	WHO List of Essential Medicines (2007)	Top 100 Best Selling Drugs in 2007
Tablet	48%	63%
Capsule	11%	3%
Injection	38%	27%
Oral liquid	13%	2%
Topical	4%	3%

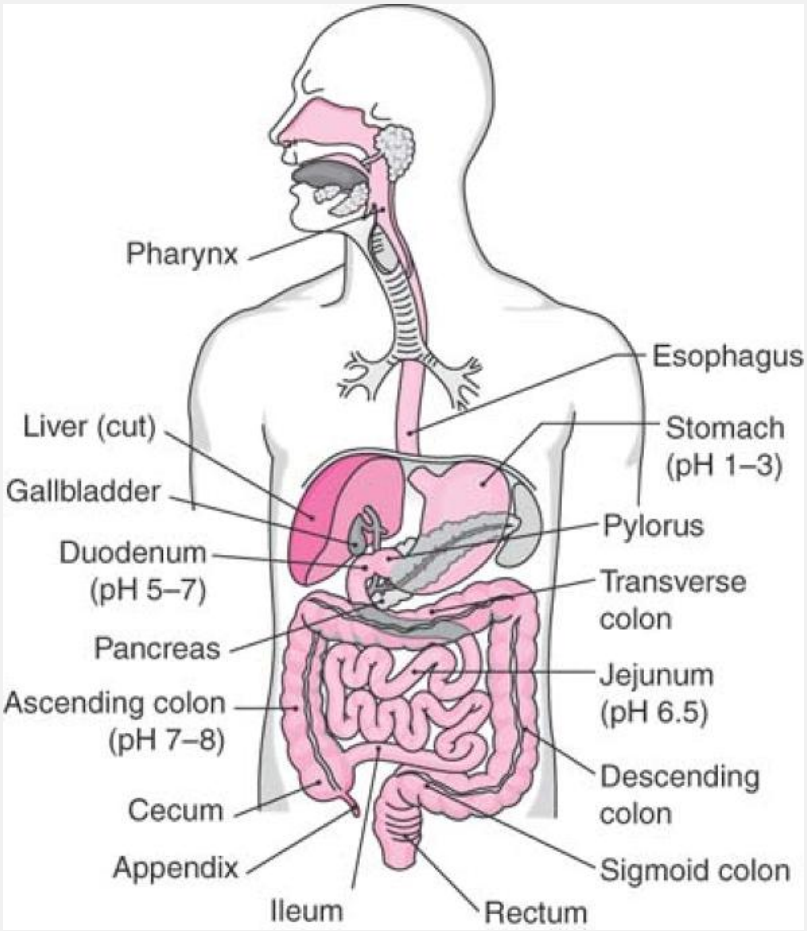

Fig. 22-1. Human digestive system.

From Fick's first law (also see equation 11-2), the flux of drug through a unit cross section (in other words, a cm^2 surface area) of intestinal membrane can be described by the following equation:

$$\text{Flux} = -D\frac{dC}{dx} = -D_m\left(\frac{C_2 - C_1}{x_2 - x_1}\right) \qquad \textbf{(22–1)}$$

where D_m is the diffusion coefficient of the drug, C is the concentration on the luminal side (1) and serosal side (2) of the membrane, and x is the distance of movement perpendicular to the membrane surface. This equation can be simplified further as (see also equation 11-11):

$$\text{Flux} = D_m\frac{C_1 - C_2}{h_m} \qquad \textbf{(22–2)}$$

Table 22-2 Approximate Volume, Residence Time, and Dimensions of the Human Gastrointestinal Tract[8,9,10,11,12]

	Fluid Volume (mL)	Residence Time (hr)	Diameter (cm)	Length (cm)
Oral cavity	1			
Stomach	15–250	0.25–3		15 × 30
Duodenum			3–4	25–30
Jejunum	22–300	2–4	3–4	200–250
Ilium			2–3.5	300–350
Cecum			7–9	9–12
Colon	2–100	12–72	5–6	85

Table 22-3 The Biopharmaceutics Classification System[7]

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

where h_m is the membrane thickness (also see equation 12-11).

Note that C_1 and C_2 are the concentrations of drug inside the membrane, but since these are very rarely known or measured, a distribution coefficient, K, is typically introduced into this equation to transform the concentrations to the respective aqueous concentrations on the bulk aqueous donor, C_d, and receiver, C_r, sides. The distribution coefficient reflects the tendency of the drug to partition into the membrane and is the ratio of the drug concentration in the membrane (C_1, C_2) to that in the aqueous phase immediately adjacent to the membrane (C_d, C_r). A lipophilic drug would have a distribution coefficient greater than 1 since biological membranes tend to be lipophilic.

$$K = \frac{C_1}{C_d} = \frac{C_2}{C_r} \qquad \textbf{(22–3)}$$

Equation **(**22-2**)** can then be rewritten as:

$$\text{Flux} = \frac{KD_m}{h_m} \cdot (C_d - C_r) = P_m(C_d - C_r) \qquad \textbf{(22–4)}$$

where P_m is the permeability of the biological membrane, and $C_d$and C_r are the aqueous concentrations of drug in the intestinal lumen (donor side) and serosal side (e.g., blood), respectively.

Finally, if the drug concentration is much lower on the serosal side of the intestinal membrane as is usually the case (often referred to as sink condition), equation **(**22-4**)** can be approximated by the following:

$$\text{Flux} \approx P_m(C_d) \qquad \textbf{(22–5)}$$

Equation **(**22-5**)** represents the essential point of the BCS that drug absorption (i.e., the flux) is determined by two factors, the membrane permeability, P_m, and the concentration of drug in the lumen of the intestine, C_d.

With the presence of solid drug in the intestine, the concentration of drug dissolved in the intestinal tract, C_d, may approach or equal its aqueous solubility if dissolution of drug from the dosage form is sufficiently rapid that it is not rate limiting. From equation **(**22-5**)**, it is apparent that the flux of drug across the intestine is proportional to the aqueous solubility in the lumen, C_d. For drugs that have high intestinal membrane permeability, P_m, the aqueous solubility may be the limiting factor for adequate drug flux (BCS Class II). Where the membrane permeability is low, it may be the factor limiting drug absorption (BCS Class III). BCS Class I compounds are the least problematic; both dissolution and oral absorption are generally not major challenges. Finally, Class IV compounds with poor solubility and poor permeability are very difficult compounds to develop using conventional oral dosage form strategies.

Utilization of BCS has led to extensive evaluation of drugs and drug products that now impact regulatory decisions on the type and level of testing necessary as, for example, to ensure equivalence of dosage forms. The BCS has evolved over the past decade to provide additional guidance on classification of products with respect to solubility, permeability, and even dissolution. In recent guidelines issued by the

Food and Drug Administration (FDA), a drug substance is considered highly soluble when the highest dose strength is soluble in <250 mL water (e.g., a glass of water) over a pH range of 1–7.5. Since dissolution rate is closely tied to solubility, FDA also provides additional guidance on dissolution criteria: a drug product is considered to be rapidly dissolving when >85% of the labeled amount of drug substance dissolves within 30 min using United States Pharmacopeia (USP) apparatus I or II in a volume of ≤900 mL. Finally, a drug 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.13 Early in product development the extent of human absorption may not be known and alternative methods of characterizing intestinal permeability may be considered. These include in vivo intestinal perfusion studies in humans, in vivo or in situ intestinal perfusion studies in animals, in vitro permeation experiments with excised human or animal intestinal tissue, or in vitro permeation experiments across epithelial cell monolayers.7,13,14,15,16,17

Even though the BCS was designed to guide decisions with respect to in vivo and in vitro correlations and the need for bioequivalence studies13 (see Chapter 12), it can also be used to categorize the types of formulation strategies that might be pursued.18 Table 22-4summarizes some dosage form options that may be considered for each biopharmaceutics class. Each class of compound, and especially Classes II, III, and IV, requires different dosage forms to deal with the challenges associated with solubility or permeability limitations. Characterizing the properties of the drug, also known as preformulation characterization, provides the information necessary to classify drugs and identify suitable dosage forms to address drug delivery issues. Back in an era when local pharmacies offered a delivery service, drug delivery was described as “a boy on a bicycle.” (J. Robinson, Oral Communication, 1995) In a way, drug delivery has not changed much. The goal of drug delivery today is still to efficiently and

effectively provide the medicine where it is needed and when it is needed.

Table 22-4 Oral Dosage form Options Based on Biopharmaceutics Classification System18

Class I: High Solubility, High Permeability	Class II: Low Solubility, High Permeability
• No major challenges for immediate-release dosage forms • Controlled release dosage forms may be needed to slow drug release from the dosage form and reduce absorption rate.	Formulations designed to overcome solubility or dissolution rate problems • Particle size reduction • Salt formation • Precipitation inhibitors • Metastable forms • Solid dispersion • Complexation • Lipid technologies • Cocrystals

Class III: High Solubility, Low Permeability	Class IV: Low Solubility, Low Permeability
Approaches to improve permeability • Prodrugs • Permeation enhancers • Ion pairing • Bioadhesives • Lipid technologies	• Formulations often use a combination of approaches identified in Class II and Class III to overcome dissolution and permeability problems. • Strategies for oral administration are not often feasible. • Often use alternative delivery methods, such as intravenous administration.

Example 22-1

Chloroquine phosphate has the following physicochemical and biological properties.19 Although the FDA has required in vivo documentation of bioavailability (BA) and bioequivalence (BE) for many drug products, in some cases FDA has allowed the use of in vitro methods for documenting BA and BE. Obtaining a biowaiver for a drug product based on in vitro BA and BE very often simplifies the application process and shortens the time to market. An FDA guidance describes recommendations for requesting waivers of in vivo BA/BE studies on the basis of the solubility and intestinal permeability of the drug substance and dissolution characteristics of the drug product, based on the biopharmaceutics classification system.13

Using chloroquine phosphate as an example, is it a BCS Class I compound and therefore a suitable candidate for a BCS Biowaiver?

- Aqueous solubility: Greater than 100 mg/mL in water
- Dose: 150 mg
- Human oral absorption: Rapid and almost complete. Bioavailability = 89% with high variability (67%–114%)

The aqueous solubility is high, although data over the entire pH range of interest (pH = 1–7.5) are lacking. One dose of 150 mg will dissolve in less than 2 mL of water. This suggests that chloroquine phosphate can be classified as a BCS high-solubility compound. The human absorption data from commercially available products indicate that the drug is well absorbed since the bioavailability is 89%. The FDA guidance defines “high permeability” as not less than 90% absorbed. While this falls slightly below the FDA guidance criteria, recent discussions have indicated that a minimum value of bioavailability can be lowered to 85%.17,20 This information supports the classification of chloroquine phosphate as a BCS Class I compound with high solubility and permeability and it would be a suitable candidate for a Biowaiver.

An oral solid dosage form of chloroquine phosphate should conform to the following:19

- Utilize standard excipients.
- Comply with the requirements for “rapidly dissolving” at pH 1.0, pH 4.5, and pH 6.8.13
- Comply with the similarity requirements for comparative dissolution testing versus the reference product at pH 1.0, pH 4.5, and pH 6.8.13

Preformulation Characterization

While hundreds of thousands of compounds are synthesized and evaluated every year in the pharmaceutical industry, very few make it to clinical testing and fewer still make it to the market. There are many reasons for failure. Because of the challenges associated with drug discovery and development, the opportunity to identify and develop a safe and effective product benefits greatly from the integration of pharmacology, chemistry, toxicology, metabolism, clinical research, thorough physicochemical characterization and, very importantly, dosage form development. The ability to identify a suitable dosage form is critical to success. The dosage form must deliver the drug to the desired site at the desired concentration (often considered the blood) for the desired duration. Finally, the dosage form must be robust and manufacturable!

To initiate formulation development activities, that is, the identification of an effective drug delivery system—important physical, chemical, and even mechanical properties (physicochemical or physicomechanical properties) as

well as drug absorption (permeability) properties need to be determined.

Key Concept

The Pharmaceutical Industry

The pharmaceutical industry is a drug product industry, not a drug industry. The pharmaceutical industry is highly regulated and much of that regulation is focused on ensuring a safe, effective, high quality, and consistently performing product. The active ingredient (the drug) is obviously critically important, but it is only in the context of a drug product (a dosage form) that the drug can be safely administered to the patient with the confidence that it will have the desired performance. It is the drug product that is of true value to the patient.

Evaluation of these properties during the drug discovery and development process, known as preformulation, help identify the most promising molecules for development and also provide key information for scientific dosage form design and development. Dosage forms that make sense to consider are dictated to a large extent by the molecular, particle, and bulk powder properties.

Typically, for oral dosage forms, crystalline drug forms are preferred. Common solid forms include crystalline polymorphs, hydrates, and crystalline salts of the active ingredient. This is especially true for solid dosage forms such as tablets and capsules since the solid form of the active ingredient may be a significant component in the dosage form and will impact manufacturing, dosage form performance and stability. Ideally, the most thermodynamically stable form is chosen as it will generally provide the greatest physical and chemical stability. Therefore, early identification and selection of the solid form to be used in development becomes paramount as it has a direct impact on physicochemical and drug delivery attributes.

Many of the physicochemical properties that have been discussed in this text are, in fact, dependent on the solid form. Aqueous solubility, hygroscopicity, and chemical stability are three obvious examples where very large differences may exist between solid forms of the same drug molecule. It is therefore important to rigorously characterize solid forms early in the discovery/development process. Selection of the right solid form can allow the pharmaceutical scientist to design the dosage form with optimal physicochemical, manufacturing, and dosage form performance properties. A thorough understanding of solid forms maximizes the opportunity to understand, control, and predict the behavior of a compound in the solid state, identify the appropriate dosage forms to consider, and develop a marketable product.

The reader is directed to Chapter 2*: States of Matter* and the literature for additional discussion of crystalline solids and polymorphism.[21,22,23,24]

Key Concept

Preformulation characterization

Preformulation characterization is the evaluation of those properties of the drug substance, and the solid forms in which it exists, that can impact drug delivery and drug product performance. Every form of a drug substance has unique physical and chemical properties that must be evaluated and understood to ensure the successful development of a safe and effective drug product with consistent drug delivery performance.

Example 22-2

An antiviral compound, ritonavir, marketed in a semisolid capsule as Norvir (Abbott) began to demonstrate physical instability and dissolution failures in 1998.[21,25] Upon investigation, the failures were shown to be caused by the crystallization of a new and previously unknown polymorph (Form II) in the semisolid capsule matrix that was approximately half the solubility of the original polymorphic form (Form I). The new form II, with lower solubility, was supersaturated in the formulation and upon storage, precipitated out in the capsule. The formation of this new polymorph was surprising since the semisolid dosage form using Form I showed no evidence of Form II formation on stability even after 24 months.25 The lower solubility polymorph exhibited slower dissolution which compromised dosage form performance. The semisolid capsule was withdrawn from the market and an alternative dosage form, a soft-gel capsule formulation with adequate stability, was developed and marketed.

The physicochemical characterization described in this chapter and indeed throughout this text can be applied to each of the forms that have been identified and isolated as each solid form will have a unique set of physicochemical and mechanical properties. Careful consideration of these properties will inevitably lead to the identification of better lead compounds and forms with which to enter development. Some of the key physical, chemical, mechanical, and biological properties that should be of interest to the development team and the pharmaceutical scientist are listed in Table 22-5. Each of these physical, chemical, mechanical, and biological properties can have a significant effect on the final dosage form design, performance, manufacturing, or stability and these are discussed in greater detail in the following sections. It should be kept in mind that many of these properties are dependent on the solid form and complete characterization of each of the most relevant solid forms is needed to

provide a complete physicochemical picture. Because of its importance in product development, extensive discussion of physicochemical characterization to support product development is available in many reference books.26

Table 22-5 Important Physical, Chemical, Mechanical, and Biological Properties for Oral Drug Delivery

Physical properties	*Chemical properties*
Polymorphic form(s) Crystallinity Melting point Particle size, shape, surface area Density Hygroscopicity Aqueous solubility as a function of pH Solubility in organic solvents	Ionization constant (pK_a) Solubility product (K_{sp}) of salt forms Chemical stability in solution Chemical stability in solid state Photolytic stability Oxidative stability Incompatibility with formulation additives Complexation with formulation additives Solubility in presence of surfactants (e.g., bile acids) Dissolution rate Wettability Partition coefficient (octanol–water)
Mechanical properties	*Biological properties*
Elasticity Plasticity (hardness) Bonding Brittleness Viscoelasticity	Membrane permeability Absorption, distribution, metabolism, excretion (ADME) Metabolism: Gut, first pass, systemic

Physical Properties

Melting Point

Melting point is defined as the temperature at which the solid phase exists in equilibrium with its liquid phase. As such, the melting point is a measure of the "energy" required to overcome the attractive forces that hold the crystal together. Melting point determination is of great value and can successfully be accomplished by any of several commonly used methods including visual observation of the melting of material packed in a capillary tube (Thiele arrangement), by hot-stage microscopy, or other thermal analysis methods such as differential scanning calorimetry. Careful characterization of thermal properties such as that possible with differential scanning calorimetry provides an opportunity to assess and quantify the presence of impurities as well as the presence or interconversion of polymorphs and pseudopolymorphs. Melting points and the energetics of desolvation can also be evaluated, as can the enthalpies of fusion for different solid forms. Chapter 2, States of Matter, provides additional discussion of melting point and thermal analysis.

As a practical matter, low melting materials tend to be more difficult to handle in conventional solid dosage forms. Melting points below about 60°C are generally considered to be problematic and melting points above 100°C are considered desirable. Temperatures in conventional manufacturing equipment such as high shear granulation and conventional tablet machine equipment may exceed 40°C, whereas fluid bed granulation and drying can involve temperatures approaching or exceeding 80°C. While amorphous solids do not have a distinct melting point, they undergo softening as temperatures

approach the glass transition temperature. Furthermore, common handling procedures (e.g., weighing, processing) can be difficult for low melting materials. Alternative dosage forms (liquid type) may be required for liquid or low melting materials. A comparison of melting points of polymorphs also provides a perspective on the relative stability of polymorphic forms.24

Aqueous Solubility

The importance of aqueous solubility in determining oral absorption can be seen from equation (22-5). From this equation it is apparent that the flux of drug across the intestinal membrane is proportional to the concentration of drug in solution, and more specifically, the nonionized drug concentration in solution. The aqueous solubility reflects this and an understanding of aqueous solubility, pH dependence, and the impact of biological fluid components is important in the physicochemical characterization of APIs.

Drug solubility may be determined experimentally by adding excess solid drug to well-defined aqueous media and agitating until equilibrium is achieved. Appropriate temperature control, solute purity, agitation rate, and time as well as monitoring of solid phase at equilibration are needed to ensure high-quality solubility data is obtained.27 A wide variety of techniques have been proposed for estimating aqueous

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solubility. They can broadly be classified as (*a*) methods based on group contributions, (*b*) techniques based on experimental or predicted physicochemical properties (e.g., partition coefficient, melting point), (*c*) methods based on molecular structure (e.g., molar volume, molecular surface area, topological indices), and (*d*) methods which use a combination of approaches.27,28,29 While all of the methods have some theoretical basis, their use in predicting aqueous solubility is largely empirical. Detailed discussions on solubility predictions may be found in the literature and in Chapter 9of this book. Each predictive approach has advantages and has been successfully applied to a variety of classes of compounds to develop and test the accuracy of solubility predictions. Usually, approaches that are developed from structurally related analogues yield more accurate predictions.29

Aqueous solubility is, in a simple sense, determined by the interaction of solute molecules in the crystal lattice, interactions in solution, and the entropy changes that occur as solute passes from the solid phase to the solution phase. For example, the pioneering work of Yalkowsky and Valvani30 illustrates the importance of two physical properties (melting point and lipophilicity) on solubility. They successfully estimated the solubility of rigid short-chain nonelectrolytes with the following equation:

$$\text{Log(S)} = -\log(\text{P}) - 0.01 \times (\text{MP}) + 1.05 \qquad \textbf{(22–6)}$$

where S is the molar solubility, P is the octanol–water partition coefficient, and MP is the melting point of the compound. Equation(22-6) provides insight into the relative importance of crystal energy (melting point) and lipophilicity (partition coefficient). Increasing either lipophilicity, P, or melting point, MP, results in decreased predicted aqueous solubility, S. This semiempirical approach has been applied and refined for a variety of solutes and classes of compounds.31,32,33,34,35 From equation (22-6), one can see that the octanol–water partition coefficient is a significant predictor of aqueous solubility. A 1-log unit change in aqueous solubility can be expected for each log unit change in partition coefficient. By comparison, a melting point change of 100°C is required to have the same 1-log unit change on solubility. The Yalkowsky–Valvani and similar equations can be used to predict aqueous solubility often within a factor of 2, using physical, chemical, and molecular properties.

Example 22-3

Caffeine (log *P* = -0.2, MP = 238°C) and cortisone (log *P* = 1.47, MP = 222°C) have similar melting points but substantially different log *P* values. Use equation (22-6) to estimate the molar aqueous solubility of each.

$$\text{For caffeine: Log(S)} = -(-0.2) - 0.01 \times (238) + 1.05 = -1.13$$
$$\text{and S} = 0.074 \text{ mol/L}$$
$$\text{For cortisone: Log(S)} = -(1.47) - 0.01 \times (222) + 1.05 = -2.64$$
$$\text{and S} = 0.0023 \text{ mol/L}$$

These two compounds illustrate the impact of partition coefficient on aqueous solubility.

Example 22-4

Triazolam (log *P* = 2.42, MP = 224°C) and ethyl-p-hydroxybenzoate (log *P* = 2.47, MP = 116°C) have similar log *P* values but substantially different melting points. Use equation (22-6) to estimate the molar aqueous solubility of each.

$$\text{For triazolam: Log(S)} = -(2.42) - 0.01 \times (224) + 1.05 = -3.61$$
$$\text{and S} = 0.00025 \text{ mol/L}$$
$$\text{For cortisone: Log(S)} = -(2.47) - 0.01 \times (116) + 1.05 = -2.58$$
$$\text{and S} = 0.0026 \text{ mol/L}$$

These two compounds illustrate the impact of melting point on aqueous solubility.

Aqueous solubility prediction continues to be an active area of research with a wide variety of approaches being applied to this important and challenging area and additional discussion of solubility can be found in Chapter 9 of this book.

Dissolution Rate

Aqueous solubility can also play a critical role in the rate of dissolution of drug and release from dosage forms. The rate at which a solute dissolves was described in quantitative terms by Noyes and Whitney in 189736 and the equation can be written in the following way (see also equation 13-2):

$$\text{Dissolution Rate} = \frac{dM}{dt} = \frac{D \cdot S}{h} \cdot (C_s - C) \qquad \textbf{(22–7)}$$

where *M* is the mass of solute dissolved in time *t*, *dM*/*dt* is the rate of dissolution, *D* is the aqueous diffusion coefficient, *S* is the surface area of the exposed solid, *h* is the aqueous diffusion layer thickness which is dependent on viscosity and agitation rate, C_s is the aqueous drug solubility at the surface of the dissolving solid, and *C*is the concentration of drug in the bulk aqueous phase. When $C \sim 0$, this is commonly referred to as sink conditions and equation **(**22-7**)**can be simplified to the following (see also equation 13-7).

$$\text{Dissolution Rate} = \frac{D \cdot S}{h} \cdot C_s \qquad \textbf{(22–8)}$$

From the Noyes Whitney equation, dissolution rate is seen to be directly proportional to the aqueous solubility, C_s, as well as the surface area, *S*, of drug exposed to the dissolution medium. It is common practice, especially for low-solubility drugs, to increase dissolution rate by increasing the surface area of a drug. This can be done through particle size reduction. If drug surface area is too low, the dissolution rate may be too slow and absorption can become dissolution rate limited. For high-solubility drugs, the dissolution rate is generally fast enough that a high drug concentration is achieved in the lumen and extensive particle size reduction is not needed. Use of high-solubility salts is commonly undertaken to facilitate rapid dissolution in the GI tract.

Although the mathematics becomes somewhat more complicated, dissolution of particles may also be modeled and this provides greater insight into the interplay of solubility and drug particle size on dissolution rate. For a drug powder consisting of uniformly sized, spherical particles, it is possible

to derive an equation that expresses the rate of dissolution. A detailed discussion and derivation of the following equation is provided in Chapter 13 (equation **13–20**) and will not be repeated here. The resulting equation that predicts the change in particle radius with time is:

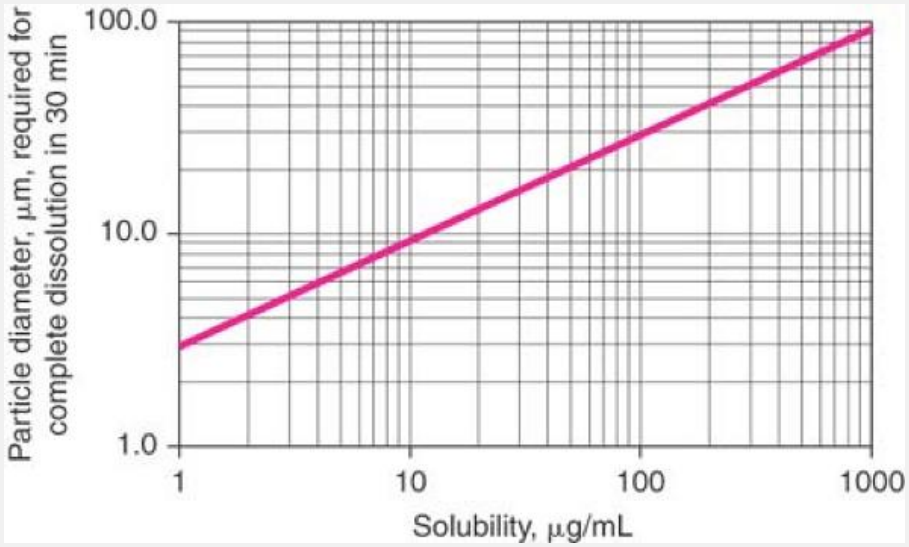

Fig. 22-2. Relationship between aqueous solubility and maximum spherical particle diameter that will dissolve in 30 min.

$$r^2 = r_0^2 - \frac{2DC_s t}{\rho} \qquad \textbf{(22–9)}$$

where r is the radius of the dissolving particle at time t, r_0 is the initial radius of the particle, D is the aqueous diffusion coefficient, C_s is the aqueous solubility, and ρ is the particle density.

The time for complete dissolution, τ, is the time it takes for the initial particle radius to be reduced to zero (i.e., set r = 0 in equation **22–9**) and is given by:

$$\tau = \frac{\rho \cdot r_0^2}{2DC_s} \qquad \textbf{(22–10)}$$

These equations may be used to make useful predictions about dissolution and the relationship between particle size (diameter) and solubility is shown in Figure 22-2. Based on these considerations, the need for particle size reduction to achieve adequate dissolution can be made.

Because pharmaceutical powders are not monodispersed, that is, not all the same size, it is important to consider the particle size distribution as well. A few large particles may seriously affect the dosage form dissolution rate of a material under some circumstances and more sophisticated mathematical models have been developed to address these issues.[37,38] As a rough "rule of thumb," if the particle diameter in μm is greater than the solubility in μg/mL, further particle size reduction may be needed to achieve adequate dissolution for an immediate release dosage form.

Example 22-5

A new drug is under development and the pharmaceutical scientist responsible for designing the first clinical formulation must identify the particle size necessary to achieve an acceptable rate of dissolution (e.g., complete dissolution in 30 min or less). Based on the physicochemical data available, the drug has a constant aqueous solubility of 10 μg/mL in the physiological pH range of 1 to 7. Additional information available includes the density of the crystalline drug (ρ = 1.52 g/cm^3) and the aqueous diffusion coefficient (estimated $D = 9 \times 10^{-6}$ cm^2/sec).

Estimate the time it would take for particles of 1 μm, 10 μm, and 100 μm in diameter to dissolve.

Use equation (22-10). Note: use consistent units for mass, time, and volume.

For 1 μm diameter particle $\tau = (1.52 \times (0.5 \times 10^{-4})2)/(2 \times (9 \times 10^{-6}) \times (10 \times 10^{-6})) = 21$ sec

For 10 μm diameter particle $\tau = 2211$ sec = 35.2 min

For 100 μm diameter particle $\tau = 2.1 \times 10^5$ sec = 3518 min
Based on these calculations, the particle size of the drug should be 10 μm or less to achieve rapid dissolution. Certainly, a particle size of 100 μm would be too large to achieve rapid dissolution.

Ionization Constant

Knowledge of acid–base ionization properties is essential to an understanding of solubility properties, partitioning, complexation, chemical stability, and drug absorption, and an extensive discussion of ionic equilibria is given in Chapter 7. The ionized molecule exhibits markedly different properties from the nonionized form. For weak acids, the equilibrium between the free acid, HA, and its conjugate base, A^-, is described by the following equilibrium equation (see also equation 7-10):

$$HAc = H_3O^+ + Ac^- \qquad \textbf{(22–11)}$$

and the corresponding acid dissociation constant is given by:

$$K_a = \frac{[H_3O^+][Ac^-]}{HAc} \qquad \textbf{(22–12)}$$

The equation for a weak base, B, and its conjugate acid, BH^+, is described by (also see equation 7-21):

$$K_a = \frac{[H_3O^+][B]}{[BH^+]} \qquad \textbf{(22–13)}$$

Of particular interest to the pharmaceutical scientist is the impact of pK_a on aqueous solubility and partitioning (see Chapter 9). Taking a weak acid as an example, the total aqueous solubility, S_T, is equal to the sum of the ionized and nonionized species concentrations in solution. Assuming that the solution is saturated with respect to free acid, the total solubility, S_T, can be written (see also equation **10-61**):

$$S_T = S_a(1 + (K_a/[H^+])) \qquad \textbf{(22–14)}$$

where the intrinsic solubility of the free acid is S_a. The solubility equation for a weak base is given by:

$$S_T = S_b(1 + ([H^+]/K_a)) \qquad \textbf{(22–15)}$$

These equations can be written in log form respectively as:

$$(S_T) = (S_a)(1 + 10^{(pH - pK_a)}) \qquad \textbf{(22–16)}$$

$$(S_T) = (S_b)(1 + 10^{(pK_a - pH)}) \qquad \textbf{(22–17)}$$

Based on these equations, typical solubility curves are shown inFigure 22-3 for a weak acid and a weak base and

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several significant conclusions and implications are worth pointing out. Taking the free base as an example, at pH greater than the pK_a, the predominant form present in solution is the nonionized form (free base) and the total solubility is essentially equal to the intrinsic solubility, that is, the free-base solubility. As the pH decreases below the pK_a, a rapid increase in total solubility is observed since the ionized form, BH^+, is dramatically increasing. In fact, for each unit decrease in pH, the total aqueous solubility will increase 10-fold in this region as shown in Figure 22-3. The total solubility will continue to increase as long as the ionized form continues to be soluble. Such dramatic increases in solubility as a function of pH demonstrate the importance of understanding and controlling solution pH and also offer the pharmaceutical scientist a number of possible opportunities to modify the dosage form and factors leading to oral absorption properties. It is important to recall, however, that often only the nonionized drug is well absorbed.

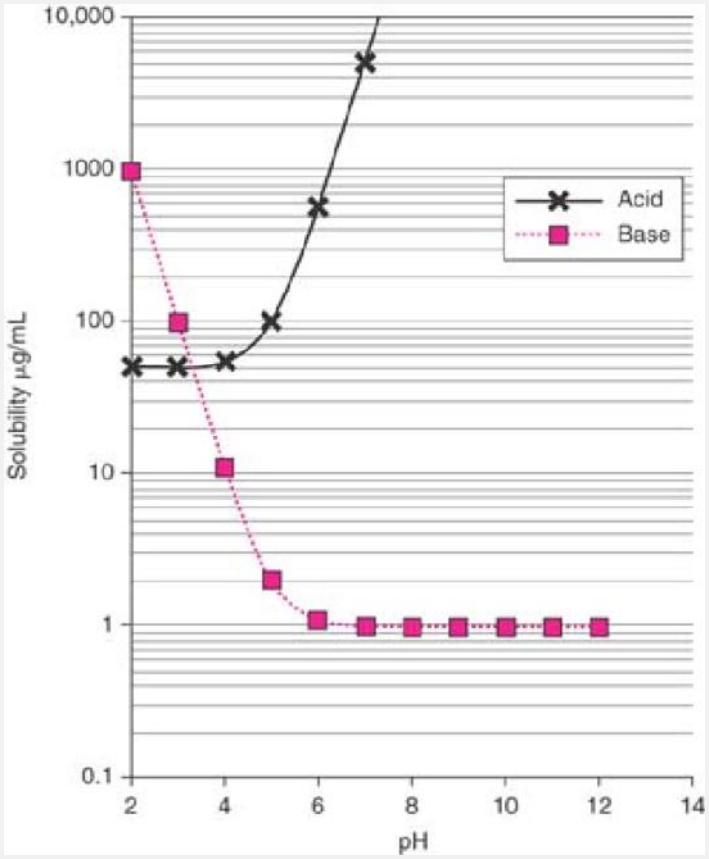

Fig. 22-3. Solubility (µg/mL) versus pH for an acid (intrinsic solubility = 50 (µg/mL) and base (intrinsic solubility = 1 (µg/mL) with pK_a = 5.0.

For weak acids, one will observe a rapid increase in total solubility as the pH exceeds the pK_a (Fig. 22-3) since the ionized species concentration, Ac^-, will increase with increasing pH. The pharmaceutical scientist must understand the solubility properties of both the nonionized species and its corresponding conjugate, ionized, form(s) since each may limit solubility.

From the solubility curves, one can draw conclusions regarding which solid form will exist at equilibrium as a function of pH. This basic principle is of significance in vivo since one might imagine dosing patients with a soluble salt of a base, which could rapidly dissolve in the low pH of the stomach, but as drug in the gastric contents enters the intestine where solution pH approaches neutral, precipitation of the insoluble free base could occur. Such changes have been proposed as an explanation for the poor bioavailability of highly soluble salts of weak bases.

Example 22-6

Kramer and Flynn39 investigated the aqueous solubility of 2-ethyl-2-phenyl-4-(2′-piperidyl)-1,3-dioxolane and its hydrochloride salt as a function of pH at 30°C in 0.05 M succinate buffer. The pK_a of the amine functional group was determined to be 8.5, the intrinsic solubility of the free base was 2.87 mg/mL, and the solubility of the hydrochloride salt corresponded to 60 mg/mL. Calculate the solubility of the free base and the hydrochloride salt at pH = 4, 6, 8, and 10.

Using equation (22-17), the solubility of the free base is:

$$(S_T) = (2.87)(1 + 10^{(8.5-4)}) = 90760 \text{ mg/mL at pH} = 4$$
$$(S_T) = (2.87)(1 + 10^{(8.5-6)}) = 910 \text{ mg/mL at pH} = 6$$
$$(S_T) = (2.87)(1 + 10^{(8.5-8)}) = 11.9 \text{ mg/mL at pH} = 8$$
$$(S_T) = (2.87)(1 + 10^{(8.5-10)}) = 2.96 \text{ mg/mL at pH} = 10$$

Using equation (22-16), the solubility of the hydrochloride salt is:

$$(S_T) = (60)(1 + 10^{(4-8.5)}) = 60 \text{ mg/mL at pH} = 4$$
$$(S_T) = (60)(1 + 10^{(6-8.5)}) = 60.1 \text{ mg/mL at pH} = 6$$
$$(S_T) = (60)(1 + 10^{(8-8.5)}) = 79 \text{ mg/mL at pH} = 8$$
$$(S_T) = (60)(1 + 10^{(10-8.5)}) = 1957 \text{ mg/mL at pH} = 10$$

Hygroscopicity

Moisture uptake or sorption is a significant concern for pharmaceutical powders. The extent of sorption of water depends on the chemical nature of the drug. Two types of moisture sorption are generally recognized: physical sorption and chemical sorption. Physical asorption is that which is associated with van der Waals forces and is reversible. A graph of the amount of water that is physically sorbed to the surface of a solid material as a function of equilibrium water vapor pressure yields an sorption isotherm. Greater detail on physical and chemical sorption is provided inChapter 15. In addition to surface sorption, water may condense in pores and the reader is referred to Chapter 18 for additional discussion of this topic.

Moisture has been shown to have a significant impact on the physical, chemical, and manufacturing properties of drugs, excipients, and formulations. It is also a key factor in decisions related to packaging, storage, handling, and shelf life, and successful development requires a sound understanding of hygroscopic properties. Moisture sorption isotherms can yield an abundance of information regarding the physical state of the solid and the conditions under which significant changes may occur. Conversion from an anhydrous form to a hydrated form may be observed when the relative humidity exceeds a critical level and moisture content rapidly increases in the solid. Quantitative measurement of

moisture content also provides valuable information on the type of hydrate that has formed.

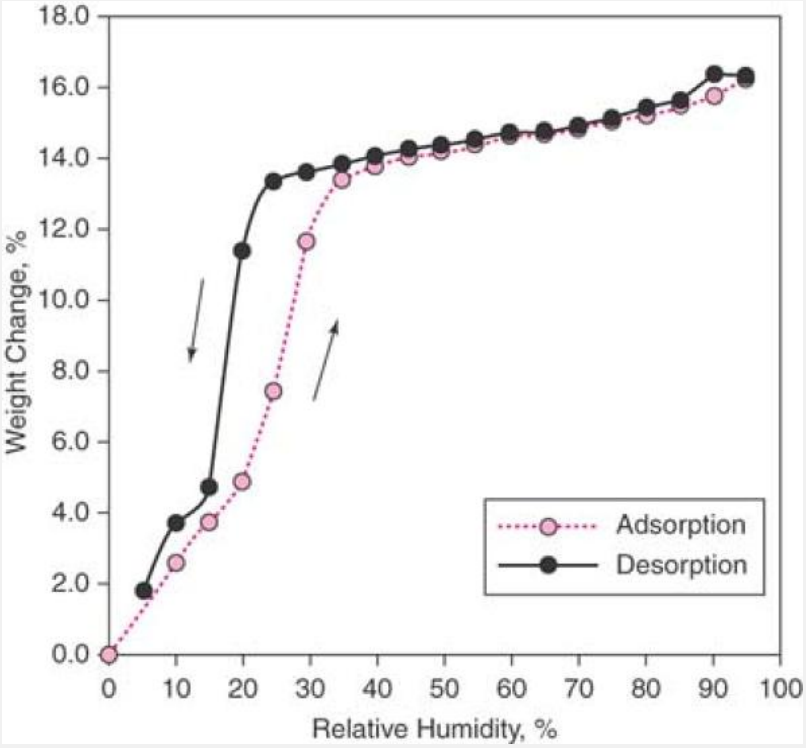

Fig. 22-4. Moisture sorption (% weight change) as a function of % Relative Humidity for an active pharmaceutical ingredient (API).

Measurement of moisture uptake is typically done by either of two general methods. The classical approach involves equilibration of solid at several different humidities and the subsequent determination of water content either by gravimetric or by analytical methods such as Karl Fischer titration or loss on drying. Moisture adsorption or desorption may be measured using this method and the process is effective but tedious and time-consuming. An automated controlled atmosphere system in conjunction with an electronic microbalance is now commonly used.[40,41,42] Such systems can generate an atmosphere with well-controlled humidity passing over a sample (often only a few milligrams are needed) and weight change is monitored and can be programmed to carry out a series of humidity increments to generate the adsorption and desorption curves. In this way, hysteresis may be observed as well as phase or form changes that are associated with moisture sorption. Examples of a moisture sorption curve are shown in Figure 22-4 and Figure 22-5.

In general, water adsorption to only the surface of crystalline materials will result in very limited moisture uptake. Only 0.1% water uptake is predicted to be needed to achieve monolayer coverage of a crystalline material with an average particle size of 1 μm.[31]Amorphous phases tend to be much more prone to moisture sorption and high moisture uptake by a solid is likely to reflect either the presence of significant amorphous regions or a change in solid form such as the formation of a hydrate. Moisture sorption has, in fact, been used to quantitate the amorphous content of predominantly crystalline materials.

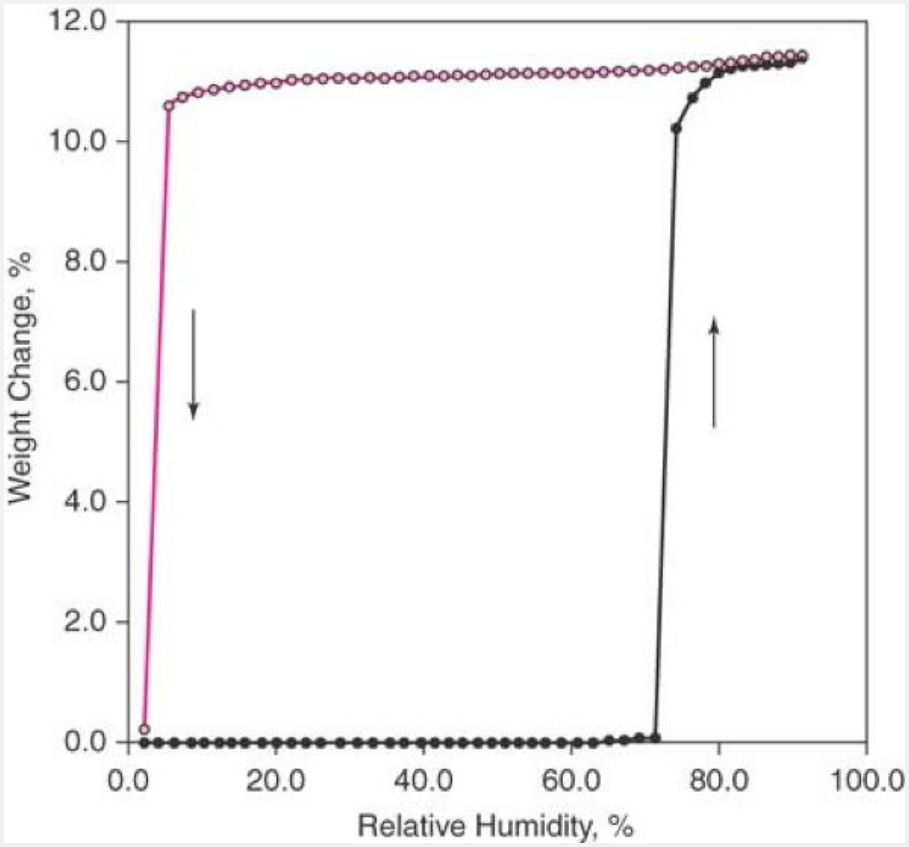

Fig. 22-5. Moisture sorption (% weight change) as a function of % Relative Humidity for an API demonstrating hydrate formation above 70% Relative humidity.

Example 22-7

Dynamic moisture sorption, in particular, provides an excellent opportunity to study solid form conversion andFigure 22-5 depicts a typical sorption curve of an antiarrhythmic compound that shows the conversion of an anhydrous form to a hydrate. Moisture uptake by the anhydrous form is very small on the moisture uptake curve until a critical humidity of about 70% is achieved. At this point, rapid moisture uptake occurs and a hydrate form containing about 10% moisture is formed.

Subsequent reduction in the humidity (desorption) shows the hydrate to remain until approximately 5% RH when it spontaneously converts to the anhydrous form. It is important to recognize, however, that conversion between solid forms is very time dependent. The relative humidities at which conversion was seen in Figure 22-5 are very dependent upon the length of time the solid material was equilibrated. For the material shown, conversion from the anhydrous to the hydrate “at equilibrium” will occur somewhere between 10% and 70% RH.

Particle Size

Understanding a pharmaceutical powder's particle size, shape, and distribution is an important component of formulation development. When working with the API, a few large or small particles in a batch can alter the final tablet's content uniformity (potency, segregation), dissolution profile, and/or processing (e.g., flow, compression pressure profile, granulating properties). Yalkowsky, Bolton, and others have developed a model to estimate the API particle size needed to pass United States Pharmacopeia (USP) content uniformity criteria.[32,33] A plot of the particle size needed to pass content

uniformity as a function of particle size and size distribution is shown in Figure 22-6. It is useful for estimating particle size requirements and determining whether additional drug

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particle size processing, such as milling, is necessary. Drug particle size and size distribution information can also help decide whether a direct compression formulation or dry granulation approach is more appropriate. Examination of drug particle size can also reveal inter and intrabatch differences or trends. If the particle size distribution has changed from one batch of API to the next, this could significantly impact the processing properties of the final formulation, as well as dissolution, leading to inconsistent dosage form performance.

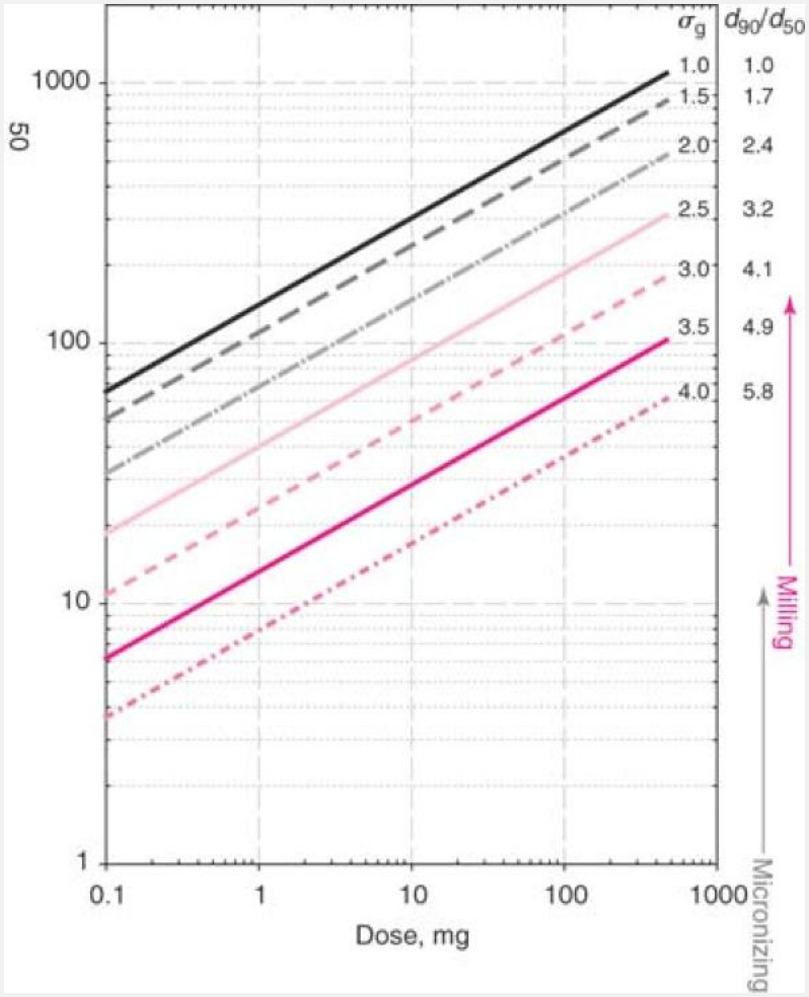

Fig. 22-6. Predicted maximum geometric mean volume particle diameter needed to pass USP content uniformity requirements as a function of dose (mg) and geometric standard deviation (σ_g) assuming log normal particle size distribution of active pharmaceutical ingredient.33

Key Concept

Shelf life

The shelf life of a pharmaceutical product is the time period during which the product is expected to remain within the acceptance criteria established by the manufacturer for the critical physical, chemical, and aesthetic properties when stored according to the

manufacturer's recommendations. The shelf life depends on the drug molecule, the dosage form, packaging, and the environmental conditions to which the dosage form is exposed. According to the FDA,43 there shall be a written testing program designed to assess the stability characteristics of drug products. The results of such stability testing must be used in determining appropriate storage conditions and expiration dates and include the following: sample size and test intervals based on statistical criteria for each attribute; storage conditions of samples; reliable, meaningful, and specific test methods; testing of the drug product in the same container-closure system as that in which the drug product is marketed; and testing of drug products for reconstitution at the time of dispensing (as directed in the labeling) as well as after they are reconstituted. An adequate number of batches of each drug product must be tested to determine an appropriate expiration date.

Particle size and size distribution are also important as they are critical parameters in assuring that the desired dissolution rate is achieved. Several theoretical models for dissolution of powders have been developed and discussed in previous chapters of this book. Flow characteristics of formulations are also influenced by particle shape, size, and size distribution.

Example 22-8

The drug molecule described in *Example* 22–5 will be manufactured as a tablet dosage form for Phase I clinical testing. Using Figure 22-6, identify the particle size necessary to achieve acceptable content uniformity for tablet strengths of 1 mg, 3 mg, and 10 mg assuming a monodispersed particle size distribution (i.e., all particles are the same size, $\sigma_g = 1.0$).

From Figure 22-6, for a 1-mg dose approximately a 130-μm particle size is needed to achieve content uniformity. For a 3-mg dose, approximately a 200-μm particle size is needed, whereas the high dose of 10 mg would require approximately 300 μm particle size. For this particular drug molecule, achieving the particle size needed to obtain adequate dissolution (Example 22-5, approximately 10 μm) will ensure that content uniformity can be achieved. Following milling of the drug to achieve a mean particle size diameter of 10 μm for clinical supply manufacture, the drug is found to have an extremely wide particle size distribution which is log normal with a geometric standard deviation, σ_g, of 4.0. Will content uniformity likely be achieved with the 1-mg dose tablet?

From Figure 22-6, the particle size necessary to achieve content uniformity for this extremely wide particle size distribution is estimated to be approximately 8 μm. These theoretical estimates indicate that content uniformity could be a problem during clinical supply manufacture of the low-dose tablet. Further processing the drug may be appropriate to better ensure success in clinical manufacturing.

Chemical Properties

Stability

Both solution and solid-state stability are key considerations for oral delivery. Chemical stability is addressed in detail in Chapter 15. The drug molecule must be adequately stable in the dosage form to ensure a satisfactory shelf life. For oral dosage forms, it is generally considered that 2 years is an acceptable shelf life. This allows sufficient time for the manufacture and storage of the active ingredient, the manufacture of the dosage form, shipping, storage, and finally sale

to and use by the consumer. Loss of potency is an obvious consideration and, generally, stability guidelines require that at least 90% of the drug remains at the end of the shelf life. More often though, shelf life is determined by the appearance of relatively low levels of degradation products. While perhaps a 5% loss of drug may be considered acceptable, the appearance of a degradation product or impurity of unknown toxicity at a level of 0.1% to 1% will likely require identification or qualification. Detailed guidance regarding stability has been provided by regulatory agencies such as those in the FDA Guidance for Industry and the International Conference on Harmonization.[34,35,43]

Solution Stability

Solution stability is important for oral products because the drug generally has to dissolve in the gastric or intestinal fluids prior to absorption. Residence time in the stomach varies between 15 min and a couple of hours depending on fasting/fed state. In addition, the stomach is generally acidic in a majority of subjects but may depend on disease state. In this context, stability under acidic conditions over a period of a couple of hours at 37°C may be satisfactory. Residence time in the small intestine is approximately 3 hr where the pH may range from approximately 5 to 7, whereas residence in the large intestine ranges up to 24 hr or more. Stability studies for up to 24 hr in the pH range of 5 to 7 at 37°C with no significant appearance of degradation products of unknown toxicity generally indicates that significant decomposition in the intestine will not occur. Other intestinal components such as microorganisms, enzymes, and surfactants can dramatically alter in vivo solution stability however. Buffered aqueous solution stability studies are typically done at pH of 1.2 to 2 and in the range of 5 to 7. A complete degradation rate profile can provide valuable information regarding the degradation mechanism and degradation products. A complete study and understanding of solution stability is particularly critical for aqueous and cosolvent solution formulations which may be developed for pediatric or geriatric populations.

Solid-State Stability

Adequate solid-state stability is often critical for many drugs since solid dosage forms (tablets, capsules) are generally the preferred delivery system. Stability of the drug in the dosage form for several years at room temperature is desirable. Unstable drugs may be developed, but the time and resources needed are generally greater and the chances of failure also greater. Accelerated stability studies are often carried out early in development on pure drug to assess stability and identify degradation products and mechanism. Testing at 50°C, 60°C, or even 70°C under dry and humid conditions (75% RH) for 1 month is often sufficient to provide an initial assessment. More quantitative assessments of drug and formulation stability are carried out to support regulatory filings and generally follow regulatory guidances.[34,35,44]

The field of solution and solid-state stability is large, varied, and beyond the scope of this chapter. Stability studies described above at a variety of conditions provide the perspective and understanding needed to make meaningful predictions of long-term stability and shelf life. Typically, solid-state decomposition occurs either by zero-order or first-order processes and additional discussion is provided in Chapter 14. Arrhenius analysis and extrapolation to room temperature provide additional confidence that the dosage form will have acceptable stability. Generally though, regulatory guidance allows for New Drug Applications to project shelf life based on accelerated conditions but data at the recommended storage temperature is required to support the actual shelf life of marketed products.

Mechanical Properties

Many investigations have demonstrated the importance and impact of the physical and chemical properties of materials on powder processing, oral dosage form design, and manufacturing. Physical properties such as particle size and shape clearly influence powder flow, for example. The previous sections of this chapter provide some perspective on characterization. However, mechanical properties (i.e., properties of a material under the influence of an applied stress) are also of great importance for oral dosage form development and manufacturing—particularly for solid dosage forms such as tablets. This section describes the importance of the mechanical properties of materials. For the purposes of this discussion, physical properties are considered to be those properties that are “perceptible especially through the senses”[45](i.e., properties such as particle size and shape). In contrast, mechanical properties are those properties of a material under an applied load: for example, elasticity, plasticity, viscoelasticity, bonding, and brittleness.

Table 22-5 lists some of the physical and mechanical properties that influence powder properties and compaction. For example, surface energy and elastic deformation properties influence individual particle true areas of contact as particles are compressed together. Plastic deformation likely occurs to some extent in powders and depends on the applied load and almost certainly it occurs during the compaction of powders into tablets. At asperities, local regions of high pressure can lead to localized plastic yielding.

Electrostatic forces can also play a role in powder flow depending on the insulating characteristics of the material and environmental conditions. Particle size, shape, and size distribution have all been shown to influence flow and compaction as well. A number of environmental factors such as humidity, adsorbed impurities (air, water, etc.), consolidation load and time, direction and rate of shear, and storage container properties are also important. With so many variables, it is not surprising that a wide variety of methods have been developed to characterize materials.

What holds particles together in a tablet? A detailed discussion is beyond the scope of this chapter and excellent references are available in the literature.[46,47] However, it is important to realize that the forces that hold particles together

in a tablet are the very same forces discussed in detail in introductory physical chemistry texts and in this book. There is nothing magical about particle–particle interactions; the forces involved are London dispersion forces, dipole interactions, surface energy considerations, and hydrogen bonding. The compression of powders into tablets brings particles into close proximity and these fundamental forces can then act effectively to produce strong particle–particle interactions and bonding. Particle rearrangement, elastic, and plastic deformation of material can establish large areas of true contact between particles; if the resulting particle–particle bonds are strong, a strong and intact tablet is produced.

Table 22-6 Mechanical Properties of Compacts of Selected Excipients Determined at A Compact Solid Fraction of 0.9

Excipient	Compression Pressure (MPa)	Tensile Strength (MPa)	Permanent Deformation Pressure (MPa)	Brittle Fracture Index	Bonding Index
Calcium phosphate, dibasic dihydrate[48]	395	5.6	667	0.10	
Microcrystalline cellulose[48]	98	8.7	153	0.08	0.06
Croscarmellose, sodium[48]	200	13.6	300	0.10	0.05
Lactose, anhydrous[48]	178	2.6	520	0.04	0.005
Lactose, monohydrate[48]	191	2.5	485	0.09	0.005
Lactose,	155	2.4	543	0.17	0.004

monohydrate, spray process48					
Sucrose46	180	2.0	473	0.68	0.004
Corn starch46	–	0.8	105	0.8	0.008
Sorbitol46	–	1.9	410	0.03	0.005
Calcium sulfate, dihydrate46	–	1.9	235	0.08	0.008

Materials used in the pharmaceutical industry can be elastic, plastic, viscoelastic, hard, or brittle in the same sense that metals, plastics, or wood are. The same concepts that mechanical engineers use to explain or characterize tensile, compressive, or shear strength are relevant to pharmaceutical materials. These mechanical properties of materials can have a profound effect on solids processing.

The mechanical properties of a material play an important role in powder flow and compaction by influencing particle–particle interaction, cohesion, and adhesion. They are critical properties that influence the true areas of contact between particles. Therefore, it is essential to be able to quantitatively characterize them. Table 22-6provides some mechanical property information for a number of pharmaceutical excipients. One can see that there are a wide range of values and it is important to take these material properties into consideration when developing tablet dosage forms since these mechanical properties determine how the formulation will behave during tablet compaction. There are a wide range of methodologies available for mechanical property characterization and it is important to realize that experimental results are very dependent on the methods used. The reader is directed to comprehensive reviews of this branch of science for additional information.[18,49,50,51,52,53,54,55,56]

Reliable mechanical property information can be useful in helping choose a processing method such as granulation or direct compression, selecting excipients with properties that will mask the poor mechanical properties of the drug, or helping document what went wrong, for example, when a tableting process is being scaled up or when a new bulk drug process is being tested. Since all of these can influence the quality of the final product, it is to the pharmaceutical scientist's advantage to understand the importance of mechanical properties of the active and inactive ingredients and quantitate them.

Elastic Deformation

In general, during the initial stages of compression, a material will be deformed elastically and a change in shape caused by an applied pressure is completely reversible and the specimen will return to its original shape on release of the pressure. During elastic deformation, the stress–strain relationship for a specimen is described by Hooke's law:

$$\sigma = E \cdot \varepsilon \qquad (22\text{–}18)$$

where

$$\varepsilon = \frac{l - l_o}{l_o} \qquad (22\text{–}19)$$

E is referred to as Young's modulus of elasticity, σ is the applied pressure, and ε is strain where l_o is the initial length of the specimen and l is the final length. The region of elastic deformation of a specimen is shown graphically in Figure 22-7. As long as the elastic limit is not exceeded, only elastic deformation

occurs. The elastic properties of materials can be understood by considering the attractive and repulsive forces between atoms and molecules. Elastic strain results from a change in the intermolecular spacing and, at least for small deformations, is reversible.

Plastic Deformation

Plastic deformation is the permanent change in shape of a specimen due to applied stress. The onset of plastic deformation is seen as the change of curvature in the stress–strain curve shown inFigure 22-7. Plastic deformation is important

because it permits pharmaceutical excipients and drugs to establish large true areas of contact during compaction. In this way, strong tablets can be prepared.

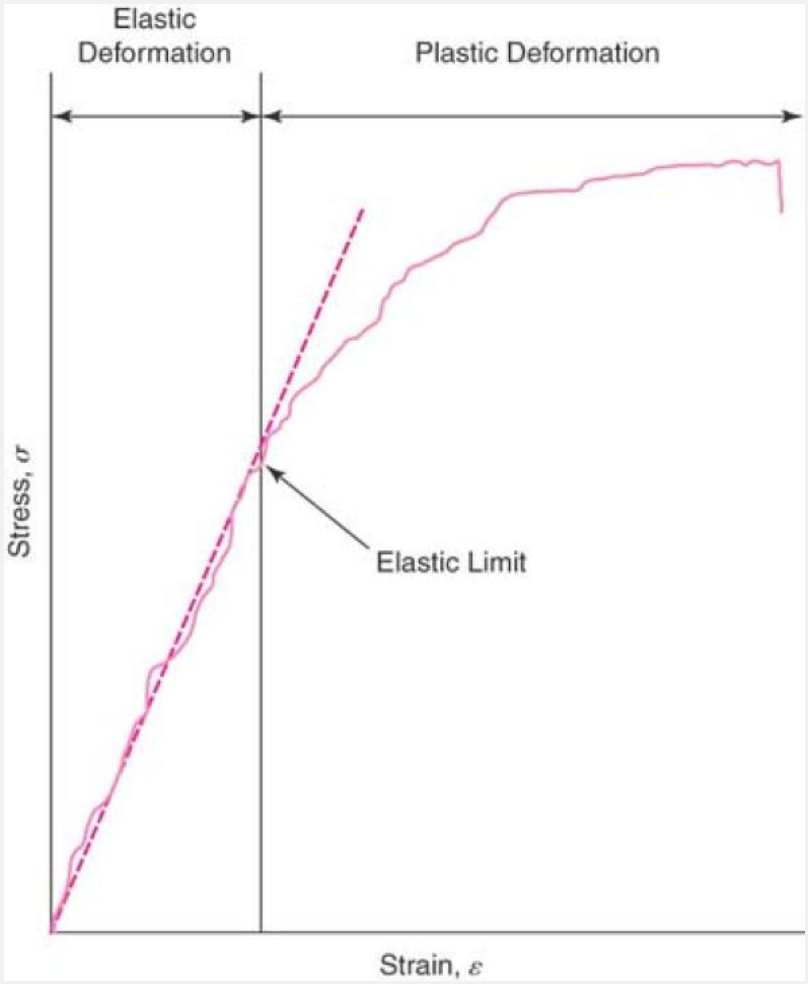

Fig. 22-7. Stress–strain curve depicting elastic and plastic deformation regions.

Plastic deformation, unlike elastic deformation, is generally not accurately predicted from atomic or molecular properties. Rather, plastic deformation is often determined by the presence of crystal defects such as dislocations, grain boundaries, and slip planes within crystals. The formation of dislocations and grain boundaries, and hence the mechanical properties of materials, is influenced by factors such as the rate of crystallization, particle size, the presence of impurities, and the type of crystallization solvent used. Slip planes may exist within crystals due to molecular packing arrangements that result in weak interplanar forces. Processes that influence these (e.g., crystallization rate, solvent, temperature) can be expected to influence the plastic deformation properties of materials and processing properties.

Brittle and Ductile Fracture

In addition to plastic deformation, materials may fail by either brittle fracture or ductile fracture; fracture being the separation of a body into two or more parts. Brittle fracture occurs by the rapid propagation of a crack throughout the specimen. Conversely, ductile fracture is characterized by extensive plastic deformation followed by fracture. Ductile failure is not typically seen with compacts of pharmaceutical materials. The characteristic snap of a tablet when pressed between the fingers as it breaks in half is indicative of brittle fracture. Brittle fracture of tablets experienced during normal processing and handling is not acceptable and selection of formulation components can allow pharmaceutical scientists to obtain tablets with acceptable properties.

Viscoelastic Properties

Viscoelastic properties can be important; viscoelasticity reflects the time-dependent nature of stress–strain. A basic understanding of viscoelasticity can be gained by considering processes that occur at a molecular level when a material is under stress. An applied stress, even when in the elastic region, effectively moves atoms or molecules from their equilibrium energy state. With time, the permanent rearrangement of atoms or molecules can occur.

The stress–strain relationship can therefore depend on the time frame over which the test is conducted. In compacting tablets, for example, it is frequently noted that higher compaction forces are required to make a tablet when the compaction speed is fast. All pharmaceutical materials are viscoelastic; the degree to which their mechanical properties are influenced by the rate of application of stress depends on the material. Appropriate selection of additional pharmaceutical ingredients is needed to address these problems.

Biological Properties

Partition Coefficient

The basic principle of the distribution of solute between immiscible solvents has been described in some detail in Chapter 9. The partition coefficient is defined for dilute solutions as the molar concentration ratio of a single, neutral species between two phases at equilibrium:

$$P = \frac{[A]_o}{[A]_w} \qquad (22\text{–}20)$$

Usually the logarithm (base 10) of the partition coefficient (logP) is used because partition coefficient values may range over 8 to 10 orders or magnitude. Indeed, the partition coefficient, typically the octanol–water partition coefficient, has become a widely used and studied physicochemical parameter in a variety of fields including medicinal chemistry, physical chemistry, pharmaceutics, environmental science, and toxicology. While *P* is the partition coefficient notation generally used in the pharmaceutical and medicinal chemistry literature, environmental and toxicological sciences have more traditionally used the term *K* or K_{ow}. One of the earliest applications of oil/water partitioning to explain pharmacological activity was the work of Overton57 and Meyer58over a century ago, which demonstrated that narcotic potency tended to increase with oil/water partition coefficient. The estimation and application of partition coefficient data to drug delivery began to grow rapidly in the 1960s to become one of the most widely used and studied physicochemical parameters in medicinal chemistry and pharmaceutics.59

Selection of the octanol–water system is often justified in part because, like biological membrane components, octanol

is flexible and contains a polar head and a nonpolar tail. Hence, the tendency of a drug molecule to leave the aqueous phase and partition into octanol is viewed as a measure of how efficiently drug will partition into and diffuse across biological barriers such as the intestinal membrane. While the octanol–water partition coefficient is, by far, most commonly used, other solvent systems such as cyclohexane–water and chloroform–water systems offer additional insight into partitioning phenomena. Partition coefficients are relatively simple, at least in principle, to measure. However, the devil is in the details and

certain aspects demand sufficient attention that rapid throughput methodologies have not yet been successfully developed.[60,61]

As mentioned above, partition coefficient refers to the distribution of the neutral species. For ionizable drugs where the ionized species does not partition into the organic phase, the apparent partition coefficient, *D*, can be calculated from the following:

$$\text{Acids: } \log D = \log P - \log(1 + 10^{(\text{pH}-\text{p}K_a)}) \quad \textbf{(22–21)}$$

$$\text{Bases: } \log D = \log P - \log(1 + 10^{(\text{p}K_a-\text{pH})}) \quad \textbf{(22–22)}$$

Permeability

New chemical compounds generated in today's pharmaceutical research environment often have unfavorable biopharmaceutical properties. These compounds are generally more lipophilic, less soluble, and are of higher molecular weight.[62] Indeed, permeability, solubility, and dose have been referred to as the "triad" that determines whether a drug molecule can be developed into a commercially viable product with the desired properties. As seen in equation **(**22-5**)** above, intestinal permeability can be critically important in controlling the rate and extent of absorption and to achieving desired plasma levels.

With the difficulties associated with accurate estimation of permeability based only on physicochemical properties, a variety of methods of measuring permeability have been developed and used. Among them are (*a*) cultured monolayer cell systems such as Caco-2 or MDCK, (*b*) diffusion cell systems which utilize small sections of intestinal mucosa between two chambers, (*c*) in situ intestinal perfusion experiments performed in anesthetized animals such as rats, and (*d*) intestinal perfusion studies performed in humans. All of these methods offer opportunities to study transport of drug across biological membranes under well-controlled conditions.

Key Concept

Formulation Development

Formulation development is the process of identifying the materials and methods necessary to manufacture a stable dosage form that consistently meets specified performance requirements throughout the product's shelf life. Dosage form efficacy, safety, quality, and manufacturability must be ensured. Chemical stability considerations, drug release characteristics, physical stability, absence of undesirable impurities or degradation products, aesthetic considerations, and the ability to consistently manufacture the dosage form in an environment that meets product supply demand are important factors that must be addressed in formulation development.

Oral Solid Dosage Forms

Oral administration is the most frequently utilized route of drug delivery and solid dosage forms are the most commonly available (see Table 22-1). To successfully develop oral solid formulations, the important physical, chemical, biological, and mechanical properties of the API need to be assessed and integrated into a suitable strategy that will lead to a dosage form that meets the necessary drug delivery requirements. The focus of this section is to provide an overview of the most commonly available oral solid dosage forms and manufacturing technologies used today. The principles of formulation development and manufacturing apply to any pharmaceutical dosage form though. Often, the decision to manufacture a product is influenced by the cost of manufacturing, packaging, storage, and shipping as well as the drug delivery requirements of the active ingredient. The properties of the drug may require alternative dosage form technologies such as liquid preparations (oral solutions, suspensions), liquid-filled soft gelatin capsules, and so on. Preformulation characterization influences the proper selection of the dosage form technology needed and a wide range of options exist (Table 22-4). Every dosage form requires a thorough characterization and understanding of formulation components, manufacturing processes, and product performance requirements. What follows is a discussion of these considerations focusing on the two most common oral dosage forms: tablets and capsules. The reader is also referred to the extensive literature available on this topic.[63,64,65,66]

Drug Release From Oral Dosage Forms

Drug release is the process by which a drug leaves the drug product and is available for absorption, distribution, metabolism, and excretion (ADME), eventually becoming available for pharmacologic action (Fig. 22-8). The selection of the appropriate drug release profile is dependent upon the drug ADME properties and the desired pharmacological effect. Proper selection of excipients and manufacturing methods for the dosage form permits a wide range of drug release profiles to be achieved when properly matched with drug properties. Some of the more common drug release profiles for solid oral dosage forms are immediate release, modified release, delayed release, extended release, and pulsatile

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release. Immediate-release drug products allow drugs to dissolve with no intention of delaying or prolonging dissolution or absorption of the drug. Delayed-release is defined as the release of a drug at a time other than immediately following administration. An excellent example of a delayed release dosage form is an enteric-coated tablet. Enteric-coated tablets protect the dosage form from the very acidic environment of the stomach and prevent tablet disintegration until it enters the upper GI tract where the less acidic intestinal fluid can dissolve the enteric polymer and facilitate the disintegration and dissolution of the tablet. Extended-release products are formulated to make the drug available over an extended period after administration. Typically, extended-release products reduce the dosing frequency required. Modified-release dosage forms is a term that applies to both delayed- and extended-release drug products and describes dosage forms whose drug-release characteristics are chosen to accomplish therapeutic or convenience objectives that are not offered by immediate release dosage forms. Pulsatile release involves the release of finite amounts (or pulses) of drug at distinct time intervals that are programmed into the drug product. Finally, controlled-release dosage forms is an inclusive term that includes extended-release and pulsatile-release products. Additional details on these topics and the relevant scientific principles are presented in chapters on “Drug Release and Dissolution” and “Drug Delivery Systems.”

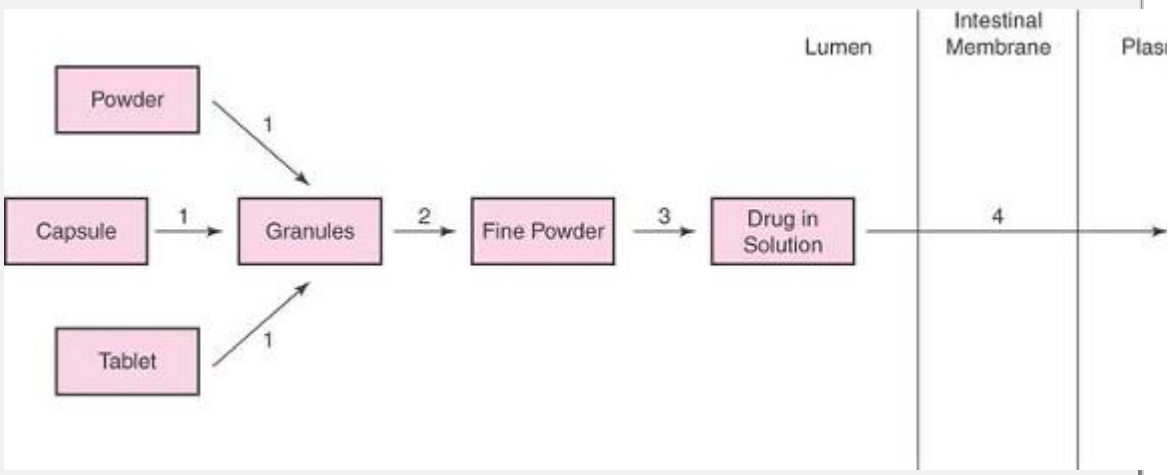

Fig. 22-8. Summary of processes associated with the administration of an immediate-release oral solid dosage form: (1) wetting and disintegration, (2) deagglomeration, (3) dissolution, and (4) absorption across the intestinal membrane.

Tablets

A wide variety of tablet dosage forms are available. Compressed tablets as a dosage form originated in the mid-19th century and are still the most commonly available dosage form. The technology and the science of tablet compression has advanced substantially making it a convenient and effective manufacturing approach for a wide variety of drugs. Compressed tablets are manufactured by

mechanically compressing the pharmaceutical formulation using a tablet punch and die system as shown in Figure 22-9. In a production environment, high-speed tablet presses can produce tablets at a very high rate, often at a rate that exceeds several thousand tablets per minute. Excipients are incorporated into a formulation with the API using a variety of manufacturing processes to ensure satisfactory manufacturing, stability, and dosage form performance. Tablets are compacted sufficiently hard to ensure that they will withstand normal handling during manufacturing, transport, and patient use but will perform as required to deliver the active ingredient when administered. For immediate release tablets, this involves the rapid disintegration of the compressed tablet into particulate material with subsequent dissolution of the drug substance in the gastrointestinal tract. Tablets are the most frequently prescribed dosage form and can provide the patient with a stable, elegant, effective, and convenient dosage form. However,

tablets are available only in fixed dosage strengths and offer a limited range of doses for the patients. Tablets may be scored to facilitate breaking them to provide fractional doses. Although uncommon, tablets may be formed using molding methods and it is now possible for compound pharmacies to prepare small quantities of compressed or molded tablets for patients. Tablets must be uniform in weight and appearance, contain the proper amount of active ingredient, and consistently achieve the overall drug release properties required to ensure effective administration of the drug for the entire shelf life of the product. For tablet dosage forms, the shelf life is often 2 years or more.

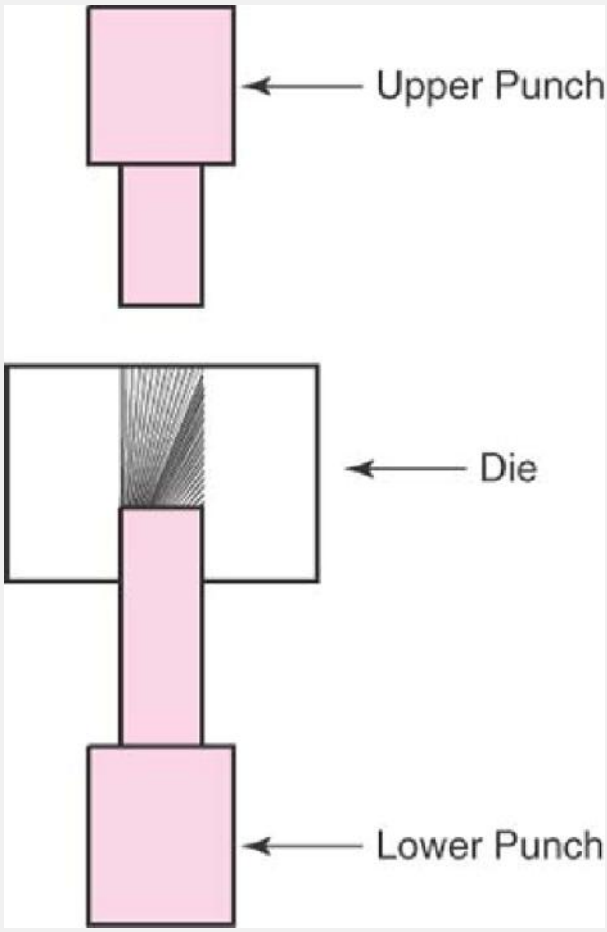

Fig. 22-9. Schematic drawing of typical punch and die system for tablet compaction.

Capsules

Capsule products have also been used for well over a century and they continue to be used in today's high-speed product manufacturing environment. They have an important role in drug delivery as they are quite flexible, relatively easy to manufacture, and they are amenable to small-scale manufacturing by the compounding pharmacist. Capsule shells consist of two parts: the base, or body, which is longer and has a smaller diameter, and the cap which is shorter and has a slightly larger diameter allowing it to slide over the base portion and form a snug seal. Capsule products are generally prepared by filling formulated material into the base and slipping the cap over the base to seal it. Capsule manufacturing can be done by manual, semimanual, or fully automatic methods. In today's large manufacturing environment, capsule products can be manufactured at high speed, though not as fast as compressed tablets. For this reason, tablets are generally a more cost-effective dosage form. Capsule products are generally dosed in their entirety.

Like tablets, capsules must be uniform in weight and appearance, contain the proper amount of active ingredient, and consistently achieve the overall drug release properties required to ensure effective administration of the drug. Gelatin is still the most common material used to manufacture capsule shells though newer polymeric materials such as hypromellose (HPMC) (hydroxypropyl methylcellulose) are becoming more commonly available and used.

Powders

Historically, powders have been used for both oral and external applications. Unlike standard tablets and capsules, powders enable physicians and pharmacists to more easily alter the quantity of active ingredient that is administered in a dose. Powders can also be useful in clinical studies because of the flexibility in dosing. Powders are not often made in mass quantities, however, and the application of powdered dosage forms is now largely limited to small clinical studies and compounding pharmacy practices. Powder formulations must contain the proper amount of active ingredient in each dose (e.g., that portion of the powder that is to be dosed) and consistently achieve the overall drug release property requirements.

Formulation Development

In addition to the APIs, dosage forms contain a number of other pharmaceutical additives called excipients. A formulation is a combination of excipients and active ingredient processed using one or more manufacturing processes to yield a pharmaceutical dosage form. According to USP, “Excipients are substances, other than the active drug substance or finished dosage form, that have been appropriately evaluated for safety and are included in drug delivery systems: 1) to aid in the processing of the drug delivery system during its manufacture; 2) to protect, support, or enhance stability, bioavailability, or patient acceptability; 3) to assist in product identification; or 4) to enhance any other attribute of the overall safety, effectiveness, or delivery of the drug during storage or use.”67Excipients are used for a reason and they play critical roles in a dosage form. A number of common excipient functions are listed inTable 22-7. Some of the more important excipients are described below. All excipients used in approved products are well studied and shown to be safe for human and veterinary use.

There are a number of pharmacopeias worldwide such as United States Pharmacopeia, the European Pharmacopeia, and the Japanese Pharmacopeia, that provide public standards for excipients.

As our understanding of drug absorption and intestinal physiology has increased, it has become clear that some excipients may serve a more active role of enhancing drug absorption by influencing intestinal transporters or other membrane properties. Such “active” excipients are the topic of a number of research investigations as a way to improve the oral delivery of what has traditionally been considered “difficult to deliver” drugs. These active excipients offer new opportunities for pharmaceutical scientists but caution is also warranted as indiscriminate permeability enhancement can lead to unwanted consequences.68,69,70

Table 22-7 Common Pharmaceutical Tablet and Capsule Excipient Functional Categories

Anticaking agent
Antioxidant
Binder (for wet granulation)
Coating agent
Coloring agent
Diluent
Disintegrant
Dissolution retardant (polymers)
Flavoring agent
Glidant
Lubricant
Preservative
Solubilizing agent
Sweetening agent
Wetting agent

Table 22-8 Common Pharmaceutical Tablet and Capsule Diluents

Calcium carbonate
Dicalcium phosphate
Lactose anhydrous
Lactose monohydrate
Lactose spray process
Mannitol
Microcrystalline cellulose
Sorbitol
Starch
Sucrose

Diluents

Diluents are ingredients incorporated into formulations to increase dosage form volume or weight. They are sometimes referred to as fillers and they often comprise a significant proportion of the dosage form. The quantity and type of diluent selected depends upon its physical and chemical properties and it must be matched to the active ingredient to ensure satisfactory stability and performance. Because the diluent may comprise a large portion of the dosage form, successful and robust manufacturing and dosage form performance is very dependent upon its properties. Among the most important functional roles diluents play is to impart desirable manufacturing properties such as good powder flow, tablet compaction strength, and desired performance including content uniformity, disintegration, dissolution, tablet integrity, friability, and physical and chemical stability. A number of commonly used solid dosage form diluents are listed in Table 22-8. Among the most commonly used diluents are lactose, dicalcium phosphate, and microcrystalline cellulose.

Binder

Tablet binders (Table 22-9) are incorporated into formulations to facilitate the agglomeration of powder into granules during mixing with a granulating fluid such as water, hydroalcoholic mixture, or other solvent. In a wet granulation process, the binder may be either dissolved or dispersed in the granulation liquid or blended in a dry state with other components and the granulation liquid added separately during agitation. Following evaporation of the granulation liquid, binders typically produce dry granules that achieve desirable manufacturing properties such as granule size and size distribution, shape, content, mass, active ingredient content, and compaction properties. Wet granulation facilitates the further processing of the granules by improving one or more granule properties such as flow, handling,

strength, resistance to segregation, dustiness, appearance, solubility, compaction, or drug release. Tablet binders are soluble or partially soluble in the granulating solvent. Upon addition of liquid, binders typically facilitate the production of moist granules (agglomerates) by altering interparticle adhesion. During drying, solid bridges are produced that result in significant granule strength.

Table 22-9 Common Pharmaceutical Tablet and Capsule Binders

Hypromellose (HPMC)
Povidone
Pregelatinized starch
Sodium carboxymethylcellulose
Starch

Table 22-10 Common Pharmaceutical Tablet and Capsule Disintegrants

Alginic acid
Crospovidone
Microcrystalline cellulose
Pregelatinized starch
Sodium croscarmellose
Sodium starch glycolate
Starch

Disintegrant

For most tablets and capsules, it is necessary to incorporate a disintegrant to overcome the cohesive strength of the tablet that was generated during compression. Disintegrants (Table 22-10) facilitate the uptake of water into the tablet or swell in contact with water producing an expansion of the tablet and the breakup of the bonds that hold the tablet together. So-called superdisintegrates perform both of these functions and cause tablets to disintegrate very rapidly upon exposure to water.

Lubricant

Lubricants typically are used to reduce frictional forces between formulation components and metal contact surfaces of manufacturing equipment such as tablet punches and dies (Table 22-11). The most commonly used lubricant in solid dosage forms is magnesium stearate. It is a solid powder that can be blended with other formulation components. Lubricants adhere to solid surfaces (formulation components and equipment parts)
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and reduce the particle–particle friction or the particle–equipment surface friction.

Table 22-11 Common Pharmaceutical Tablet and Capsule Lubricants

Magnesium stearate
Calcium stearate
Stearic acid
Sodium steryl fumerate
Polyethylene glycol
Sodium lauryl sulfate
Starch

Table 22-12 Common Pharmaceutical Tablet and Capsule Glidants and Anticaking Agents

Colloidal silicon dioxide
Calcium silicate
Magnesium silicate
Talc

Lubricants are typically incorporated in very low levels—often 1% w/w or less. Caution is required, however, because excessive lubricant levels may retard tablet disintegration or dissolution by creating large hydrophobic surfaces that will not wet or dissolve.

Glidants and Anticaking Agents

Glidants and anticaking agents (Table 22-12) are used to promote powder flow and to reduce the caking or clumping that can occur when powders are stored in bulk. Glidants and anticaking agents can also reduce the incidence of bridging during the emptying of powder hoppers and during powder processing. Glidants likely work through a combination of adsorption onto the surfaces of larger particles to help reduce particle–particle adhesive and cohesive forces and also by being dispersed between the larger particles and acting to reduce the friction between those particles. Anticaking agents generally work by absorbing free moisture that may otherwise permit the formation of particle–particle bridges that can cause caking.

Wetting and Solubilizing Agents

Surfactants, or surface-active agents, are amphiphilic molecules that contain both a polar and nonpolar region that can function as emulsifying, wetting, and solubilizing agents (see Table 22-13). The amphiphilic nature of surfactants is responsible for two important properties of these compounds that account for a variety of interfacial phenomena. One is the ability of surfactant molecules to adsorb at gas–liquid, liquid–liquid, and solid–liquid interfaces to reduce interfacial tension. They also have a tendency to self-associate and form aggregates or micelles once the critical micelle concentration is exceeded. The ability of surfactants to reduce interfacial tension is critical to emulsification and wetting while micelle formation enables the solubilization of water-insoluble compounds. These excipients are added to formulations to facilitate the wetting or solubilization of the drug substance.

Table 22-13 Common Pharmaceutical Tablet and Capsule Wetting and Solubilizing Agents

Sodium lauryl sulfate
Docusate sodium
Lecithin
Poloxamer
Polysorbate 80

Table 22-14 Common Pharmaceutical Tablet and Capsule Coating Agents

Hypromellose
Ethylcellulose
Methylcellulose
Ammonio methacrylate copolymer
Cellulose acetate
Cellulose acetate phthalate
Methacrylic acid copolymer
Sucrose

Coating Agents

Pharmaceuticals may be coated for several reasons including taste masking, improving ingestion, improving appearance, ease of identification, protecting active ingredients from the environment, and controlling drug release in the GI tract. The materials used in coating systems (Table 22-14) include natural and synthetic or semisynthetic materials. Although more popular decades ago, sugarcoating tablets is still performed. Some coating materials are used as colloidal dispersions. Titanium dioxide, an inorganic compound, is used in coatings as an opacifier. The coating system forms a layer on the tablet and changes appearance (nonfunctional coat) or performance (functional coat). Coating materials that are used must have the ability to form a film or coating system around the tablet that is complete and stable. The coating material must be applied uniformly to ensure proper performance by spreading over the surface of the dosage form and coalescing to form a smooth film. One important functional tablet coating is enteric coating. Enteric coating polymers are insoluble in the acidic environment of the stomach and protect the drug. Once the enteric-coated dosage form enters the intestine where the pH is higher, the polymer dissolves and allows the dosage form to disintegrate and the drug to dissolve.

Drug Release Modifying Agents

A variety of excipients, typically polymeric, may be used to delay the release of drug from a dosage form (Table 22-15). Common technologies used for this purpose include: matrix tablets, multiparticulate–coated particles, and osmotically controlled dosage forms. Selection of the release-modifying agent is dependent upon the drug properties and the drug release profile that is needed to optimize dosage form performance. In comparing the tables of excipients provided here, it is clear that excipients may serve different functions depending on how they are used in a formulation. For example,

hypromellose (HPMC) may be used as a tablet binder, a delayed release agent, or a tablet-coating agent depending on the quantity and processing methods used.

Table 22-15 Common Pharmaceutical Tablet and Capsule Drug Release

Modifying Agents
Hypromellose
Hydroxypropyl methylcellulose—acetate succinate
Ethylcellulose
Ammonio methacrylate copolymer
Cellulose acetate
Cellulose acetate phthalate
Methacrylic acid copolymer
Polymethacrylate
Carboxymethylcellulse
Polyvinylchloride
Polyvinylacetate

Other Excipients

There are a variety of other excipients that are utilized in solid dosage forms that are not enumerated here. All excipients in a dosage form are there for a reason and current regulatory filings require a dosage form manufacturer to indicate the function of each ingredient and ensure that they meet standards for safety, efficacy, and quality. The United States Pharmacopeia (USP/NF), the European Pharmacopeia, and the Japanese Pharmacopeia provide publically available standards for these purposes. The USP,71 the Handbook of Pharmaceutical Excipients,72 and other standard textbooks identify the functional categories of excipients and their typical uses.

Example 22-9

A commercially available tablet dosage form for the treatment of Parkinson disease lists the following excipients in its list of inactive ingredients: mannitol, starch, colloidal silicon dioxide, povidone, and magnesium stearate. Identify the functional purpose of each excipient:

- Mannitol: diluent
- Starch: diluent, binder, and/or disintegrant
- Colloidal silicon dioxide: glidant and/or anticaking agent
- Povidone: binder

- Magnesium Stearate: lubricant

Note that starch and colloidal silicon dioxide may serve more than one purpose in this formulation and it is sometimes difficult to know exactly what an excipient function is without knowing more about the formulation. The function of an excipient is dependent upon the formulation, the manufacturing process, and the dosage form performance requirements.

 **Key Concept**

Current Good Manufacturing Practices

Current Good Manufacturing Practices (cGMPs) are a set of regulations established by the US Food and Drug Administration that contain the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, manufacturing, processing, packing, or holding of a drug to ensure that the drug meets the requirements for safety, identity, strength, and the necessary quality and purity requirements. Failure to comply with cGMPs in the manufacturing, processing, packing, or holding of a drug renders it to be adulterated and subject to regulatory action.

Manufacturing

Regulatory Environment

The FDA regulates the new drug approval process in the United States and other countries have similar regulatory bodies to ensure that pharmaceutical products are manufactured and distributed in a way that ensures safety, efficacy, and quality. In 1906, President Theodore Roosevelt signed into law the Food and Drug Act that, in effect, established what is now known as the FDA. The responsibilities of the FDA were substantially expanded when President Franklin Roosevelt signed the Food, Drug, and Cosmetic (FD&C) Act into law in 1938. These changes came about as a result of the 1937 sulfanilamide elixir tragedy in which more than 100 people died after using the drug formulated in the toxic solvent ethylene glycol. The 1938 act required predistribution clearance for the safety of new drugs, authorized factory inspections, and expanded the legal authority of the FDA. Further revisions and expansion of the FDA responsibilities occurred in 1962 when the Kefauver–Harris Amendment to the FD&C Act established the requirement that all new drug applications demonstrate, for the first time, substantial evidence of efficacy for marketed claims in addition to the previous requirements of demonstrated safety.

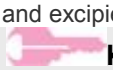
Today's pharmaceutical industry is highly regulated and global in nature and the impact of regulatory requirements is far reaching. Regulatory agencies, including the FDA, have established good laboratory practices, good manufacturing practices, good clinical practices, good distribution practices, good regulatory practices, guidelines for new drug applications, limits on advertising, postmarketing surveillance and clinical monitoring, and a host of other guidelines and requirements to ensure product quality, safety, and efficacy. The FDA's stated mission is to protect “the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and affordable; and helping

the public get the accurate, science-based information they need to use medicines and foods to improve their health.”73

With respect to pharmaceutical manufacturing, current Good Manufacturing Practices (cGMPs) play a pivotal role. Originally established in 1963 and expanded upon in 1979, cGMPs present the minimum requirements for manufacturing, packaging, and storage of human and veterinary products. These cGMPs provide guidance on organization and personnel, buildings and facilities, equipment, production and process controls, packaging and labeling, holding and distribution, and laboratory controls as well as records and reports. In effect, virtually every aspect of the manufacturing, packaging, and storage of a pharmaceutical product is carefully assessed, analyzed, and controlled to ensure product quality.74,75

Manufacturing

Pharmaceutical manufacturing on a large scale is carried out in facilities that conform to good manufacturing practices. In comparison, pharmaceutical compounding (medications made by a pharmacist or other healthcare provider in response to a valid prescription) comprises approximately 1% of prescriptions filled, totaling approximately 30 million prescriptions and $1 billion annually.76 Following physical, chemical, and mechanical property characterization of the API, initial formulation development activities are undertaken to design a formulation with the desired stability, drug release, and manufacturing properties. A general outline of the overall formulation development process is provided in Table 22-16. Different approaches may be taken. The “plan for success” approach often front-loads formulation development activities where extensive work is done to identify robust, manufacturable formulations very early in development. If the drug being studied moves successfully through early clinical studies, product manufacturing will not be on the critical path and the development process can move as quickly as possible. An alternate approach being taken these days is a material and resource sparing one, in which only enough time and effort is expended to identify and manufacture a formulation that meets the clinical and regulatory requirements of the project. In the former approach, the formulations utilized in early clinical testing are often very representative of what the final dosage form will look and behave like. With the latter approach, extensive formulation and process development is postponed until the drug successfully passes the early clinical testing milestones. With either approach, as the drug moves through development, a wide range of studies are conducted to identify the components and quantities of the formulation that are required to achieve the desired dosage form performance. Following formulation design activities, additional effort goes into identifying the manufacturing processes and specific processing conditions that will be necessary to combine the drug and excipients into a manufacturable product.



Key Concept

Pharmaceutical Quality by Design

Pharmaceutical Quality by Design (QbD) is a systematic, scientific, risk-based, and proactive approach to pharmaceutical development that begins with predefined objectives and emphasizes product and process understanding and process control. This includes designing and developing formulations and manufacturing processes to ensure that predefined product quality objectives are consistently met. QbD identifies characteristics that are critical to quality and translates them into the attributes that the drug product should possess and establishes how the critical process parameters can be varied to consistently produce a drug product with the desired characteristics. The specifications of a drug product under QbD should be clinically relevant and generally determined by product performance. Under QbD, consistency comes from the design and control of the manufacturing process.

Table 22-16 Formulation Design and Development

Preliminary Formulation Development
Physical, chemical and mechanical property characterization of the API
Preliminary formulation design (preliminary selection of excipients, processing)
Preliminary formulation process selection
Initiate Marketed Product Formulation Development
Excipient range-finding studies
Identify and assess manufacturing process variables
Final Formulation Development
Final process characterization
Product Appearance
Tablet coating process characterization
Tablet tooling evaluation
Scale Up Activities
Prepare large-scale lots
Stability
Establish final packaging and stability
Regulatory Filings

File NDA

File regulatory documents worldwide

Unit Processes

Most pharmaceutical manufacturing today consists of a series of separate and distinct manufacturing steps called unit processes. Typically, each of these discrete steps can be viewed as an individual activity and each can be evaluated and optimized to produce a consistent material. Several examples of a series of manufacturing steps (sometimes referred to as a manufacturing or process train) are shown in Figure 22-10. Among the most common unit processes for oral solid dosage forms are milling, blending, granulation, tablet

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compression or capsule filling, and tablet coating. Each of these unit processes offers challenges and opportunities to the pharmaceutical scientist. The physical, chemical, and mechanical properties of the materials (active ingredient, excipients, intermediate materials) that are introduced into equipment may influence the properties of the material that is obtained after processing. Those properties that have a significant and important impact on the manufacturing or performance of the product can be considered critical material attributes. Those processing parameters that have a significant and important impact on manufacturing or performance are referred to as critical process parameters. A recent paradigm shift within the regulatory agencies has pharmaceutical manufacturers moving toward a Quality by Design or QbD approach in which well designed, controlled, and studied materials and manufacturing processes identify the critical material attributes and critical process parameters needed to achieve a final product that consistently meets the performance requirements.[75,77] Each unit process is often studied in some detail using appropriate experimental methods (e.g., design of experiments).

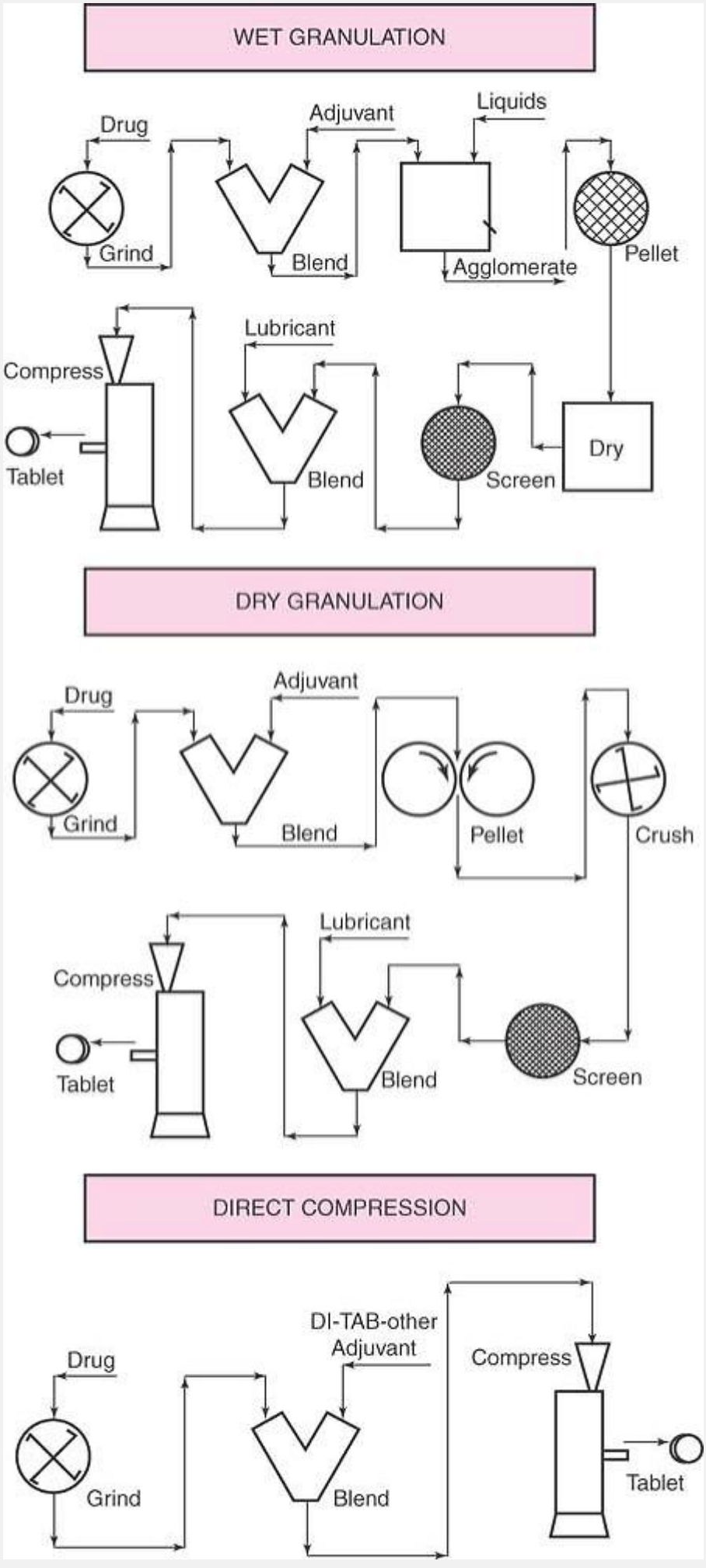
WET GRANULATION
Drug
Adjuvant
Liquids
Grind
Blend
Agglomerate
Pellet
Lubricant
Compress
Tablet
Blend
Screen
Dry
DRY GRANULATION
Drug
Adjuvant
Grind
Blend
Pellet
Crush
Lubricant
Compress
Tablet
Blend
Screen
DIRECT COMPRESSION
DI-TAB-other
Adjuvant
Drug
Compress
Grind
Blend
Tablet

Fig. 22-10. The three main methods for the preparation of tablets. (Courtesy of Stauffer Chemical Co. Tarpon Springs, FL.)

Milling

The particle size of pharmaceutical materials is often a critical material attribute that can impact processing and performance. Particle size has been shown to influence processes like blending, granulation, and compaction. Particle size also influences dosage form performance characteristics such as dissolution and content uniformity. For this reason particle size is often carefully studied and controlled. Where particle size, shape, and size distribution can be controlled by crystallization, crystal-engineering strategies are desirable. Where this is not possible, materials may be milled to achieve the desired particle size, shape, and size distribution (micromeritic properties, Chapter 18). A variety of mill types are available to the pharmaceutical scientist and some of these are shown in Table 22-17. Proper selection of mill type and process conditions can be used to tailor micromeritic properties. Milling is most often applied to the API since pharmaceutical grade excipients may be purchased in a range of particle sizes that usually meet development scientist's needs.

Blending or Mixing

The blending of solid particles in the dry state is one of the oldest industrial processes known to man. Blending or mixing is a unit process that is used at some point in virtually every oral solid dosage form manufacturing process train. Science and technology have advanced our understanding of blending and a variety of methods are available to carry out this process. Blending is a process that results in the randomization of particles within a powder system and achieves an assembly of particles that are more or less thoroughly dispersed. Blending can be described as proceeding in the following steps. A static powder must first expand before particle–particle movement is possible. Once expansion of a powder occurs, particles are able to move; shear forces are necessary to produce movement between particles. Movement of particles relative to one another requires adequate three-dimensional stresses that result in essentially random particle movement and mixing.

Diffusion mixers operate by facilitating the reorientation of particles relative to one another due to powder bed expansion and random motion of particles. Diffusion type mixers are commonly used in the pharmaceutical industry and include V-blenders, double-cone blenders, bin blenders, and drum blenders. Convection mixers facilitate mixing by

reorienting particles relative to one another due to mechanical movement using paddles. Examples of convective mixers are ribbon blenders, screw blenders, planetary blenders, and high-intensity mixers.

Table 22-17 Mill Types and Approximate Particle Size Achieved

Type	Coarse	Medium Fine	Fine	Very Fine	Super Fine	Ultra Fine
Range of particle size, μm	1000–5000	500–1000	150–500	50–150	25–50	2–10
Screening mills	X	X	X			
Impact mills		X	X	X		
Air swept impact mill		X	X	X		
Fluid energy mill				X	X	X

Granulation

If a simple blend of excipients and active ingredients does not have the physical, chemical, or mechanical properties needed to achieve the manufacturing and performance requirements, the blended powders may be further processed using granulation methods. A direct blend, often referred to as a direct compression formulation, is advantageous and often preferred over granulated powders because it requires fewer steps for manufacturing and is therefore more cost-effective. Granulation is the process of particle agglomeration and size enlargement of powdered ingredients to achieve desirable processing properties such as improved powder flow or compression. Within the pharmaceutical industry dry granulation and wet granulation methodologies are most often used if a direct blend is not suitable.

Wet granulation is achieved by mixing a granulating fluid, often water, together with other blended components to achieve a wet mass that forms larger agglomerates called granules. Once the desired granule growth has been achieved, commonly referred to as a granulation endpoint, the wet massing process is stopped and the granules are then dried. As the drying occurs, ingredients which were dissolved in the granulation fluid form solid bridges that hold the particles together. Generally, a pharmaceutical binder (see Table 22-9 for examples) is added to the blend or granulating liquid which acts as the glue to permanently hold the particles together. The dried granules may then be milled to achieve the final desired particle size. The wet granulation process has a number of advantages related to improved processability but its disadvantages include exposure of the formulation components to granulating liquid and exposure to the elevated temperatures necessary to dry the wet granules. Wet granulation may be carried out in high shear equipment or alternatively utilize fluid bed technology. The properties of the granules formed depend on the properties of the individual materials used and the process and the process parameters that are used in granulation.

Dry granulation is achieved by compressing powdered materials into dense, cohesive compacts which are then milled and screened to produce a granular form of material with desirable particle size characteristics. The compaction process in dry granulation may be achieved in a continuous fashion using what is known as roller compaction. Roller compaction is the process of compressing powder blend to produce a solid ribbon between two rollers. An alternative and less commonly used method is

to compress powders into large tablets, called slugs, which are then milled and screened. Among the advantages of dry granulation is that the materials are not exposed to granulation fluid or the high temperatures required to dry the granulated material.

Drying

In the manufacture of solid dosage forms, it is sometimes necessary to include a wet granulation step in the manufacturing process as described above. Drying is undertaken to remove excess water (or other granulation liquid) from the solid granules by evaporation. The drying process is designed to reduce the moisture content to an acceptable value. The final value depends upon the material being dried. There are a wide variety of drying methods. Among the most commonly used in the pharmaceutical industry are direct heating methods where heat transfer is accomplished by direct contact between the wet solid mass and heated air. An example of a static method of drying is tray-drying where the granulation is placed on a tray that is then placed in an oven and drying takes place. An alternative and more common method that is conducive to large-scale manufacturing is to physically move the moist granulation with heating to cause evaporation. The most commonly used method of drying is fluidized bed drying where the granulation is fluidized in heated air.

Lubrication

A separate blending step, called the lubrication step, is described here because it is a very frequently used unit process. The lubrication step involves a separate mixing step where a lubricant (Table 22-11) is incorporated into the formulation. It is very often the last step before tablet compression or capsule filling. As with the other unit processes, the properties of the lubricant and the process parameters must be carefully assessed and characterized because an inappropriately performed lubrication step can have a significant negative impact on dosage form performance. The commonly used lubricants magnesium stearate or stearic acid are very water insoluble. Incorporation of an excessive amount of one of these ingredients or excessive mixing has been shown to decrease the dissolution rate of the final dosage form. Appropriate characterization and control of the lubricant as well as

an understanding and control of this unit process is very often important in ensuring consistent dosage form performance.

Table 22-18 Common Pharmaceutical Compressed Tablet Dosage Forms

Immediate-release tablet controlled release tablet
Bilayer tablet
Multilayer tablet
Osmotic tablet
Sugarcoated tablet
Film-coated tablet

Enteric-coated tablet
Gelatin-coated tablet
Buccal tablet
Sublingual tablet
Chewable tablet
Effervescent tablet
Molded tablet
Rapidly disintegrating tablet
Mucoadhesive tablet
Gastroretentive tablet

Compression

Following the blending, granulation, and lubrication steps, the formulation is ready for compression into a tablet. Tablet dosage forms are manufactured using a compression process. A wide variety of tablet dosage forms with a remarkable range of performance characteristics can be prepared with the proper selection of formulation ingredients and processing. The seeming simplicity of the tablet dosage form belies the remarkable flexibility and creativity this technology offers as a sophisticated drug delivery device. Many of the available tablet dosage forms are listed in Table 22-18.

Powder compression into tablets is the application of pressure to the formulated powder to achieve a reduction in volume and the generation of strength within the compacted material to form an intact tablet. Tablet tooling consists of a lower punch which snugly fits into the tablet die from below and an upper punch which can enter the die from above (Fig. 22-9). The die serves to hold the formulated powder in place when the lower punch is in place, and the upper and lower punches are forced together to compress the powder. Powder compaction can be done using a small, hand-operated press but, of course, in a large-scale manufacturing environment, high-speed tableting machines are used to produce thousands of tablets per minute. An example of a large-scale tableting machine is shown in Fig. 22-11.

The process of powder compaction into tablets can be described as a six-step process as shown schematically in Figure 22-12. The first step (Stage 1) is the die filling step in which powder is moved into the die. The powder in this state is loosely aggregated in the die. The lower punch position holds the powder in the die and determines the amount of powder that the die will hold. The compression process begins in the second step (Stage 2) as the upper punch is pressed into the die; the applied force results in rearrangement and consolidation of the powder. In the third stage of compression (Stage 3),

significant particle deformation and possibly particle fracture occur as the powder further consolidates into a cohesive mass. In this stage of compression, significant areas of contact are established between particles as they are pressed closer together and this can result in significant particle–particle bonding. The decompression stage (Stage 4) begins as the upper punch force is reduced and the upper punch is removed. During the decompression stage some of the elastic deformation that occurred during compression results in some tablet expansion. (Stage 5) involves the lower punch being pushed upward as the compacted tablet is pushed upward. If the formulation is properly designed, the final stage (Stage 6) results in the ejection of an intact tablet that has the desired strength and performance characteristics. On rotary tablet machines, multiple punches and dies are located around the outside of a circular die table and the compression process described above occurs as they are rotated under circular compression rolls that force the upper and lower punches together and punch guides pull them apart with precise timing. The entire process described above can occur on a production tablet press in less than 100 milliseconds.

Fig. 22-11. Example of a production tablet press. (Courtesy of Korsch Tableting, Korsch AG, Berlin.)

The compression process has been studied in detail by a number of investigators and a variety of equations to describe the relationship between compression pressure and tablet density have been

developed.[78,79,80,81,82,83] One of the most commonly utilized equations was developed by Heckel.[81,82] He proposed that there was a relationship between the yield

strength of the material and the pressure necessary to cause compaction. The yield strength of a material is a measure of its ability to permanently or plastically deform as discussed in the previous section on mechanical properties. A high-yield pressure indicates that a material is hard; a low-yield pressure indicates a soft material. From this, he derived an equation referred to as the Heckel equation (equation **22–25**), expressing the relationship between the relative density of the compact and the compression pressure applied.

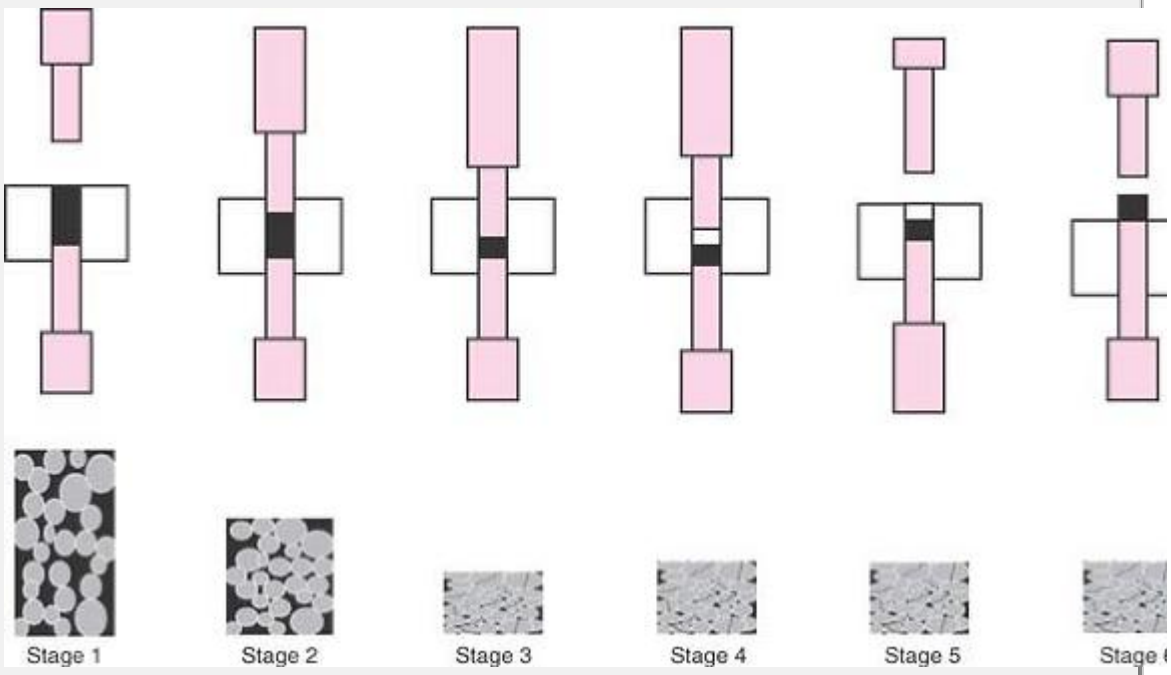

Fig. 22-12. Stages of tablet compaction.

In tablet compaction, an important concept is that of relative density. The relative density, *D*, of a material is given by the following equation:

$$D = \frac{\rho_S}{\rho_A} \qquad \textbf{(22–23)}$$

where ρ_S is the density of the powder or compact in g/cm^3 and ρ_A is the absolute or true density of the material in g/cm^3. The true density of a material is its density in the absence of pores, meaning that the material contains absolutely no void space between particles. The reader is directed to Chapter 18 on Micromeritics for further discussion of density and methods of measurement.

From equation **(**22-23**)**, the relative density, *D*, has a maximum value of 1.0 and this occurs when all of the void space is compressed out of the compressed powder and only solid material with no pores remains. Ranges of *D* are between 0.4 and 0.95 for loose powders and highly compacted tablets, respectively. Virtually all pharmaceutical tablets have some porous structure though, and typical values for relative density are in the range of 0.7 to 0.9, meaning that between 30% and 10% of the volume of the tablet consists of pores. The relationship between relative density and porosity, ε, is given by:

$$\varepsilon = 1 - D \qquad \textbf{(22–24)}$$

The Heckel relationship is based on the assumption that the decreasing void space within the tablet follows a first-order rate process.[82]

$$\frac{dD}{dP} = K \cdot (1 - D) \qquad \textbf{(22–25)}$$

where *D* is the tablet relative density, *P* is the applied pressure, and*K* is a constant that reflects the ability of the powder to consolidate into a coherent mass.
Integrating equation (22-26), the Heckel equation is:

$$\ln\left(\frac{1}{1-D}\right) = K \cdot P + A \qquad \textbf{(22–26)}$$

K is the slope of the Heckel equation and is a measure of the plasticity of the material. *A* greater slope indicates that the material has greater plasticity and is more easily permanently deformed. *A*Heckel plot obtained by plotting ln(1/1 - *D*) versus *P* is shown inFigure 22-13 for three different pharmaceutical excipients. As seen in this figure, only the terminal portion of the plot is linear and conforms to equation (22-26). The different terminal slopes indicate that these three materials have significantly different deformation properties. The initial nonlinear region of the plot is the region in which the Heckel equation does not apply and reflects the initial stage of consolidation where significant particle rearrangement is occurring.
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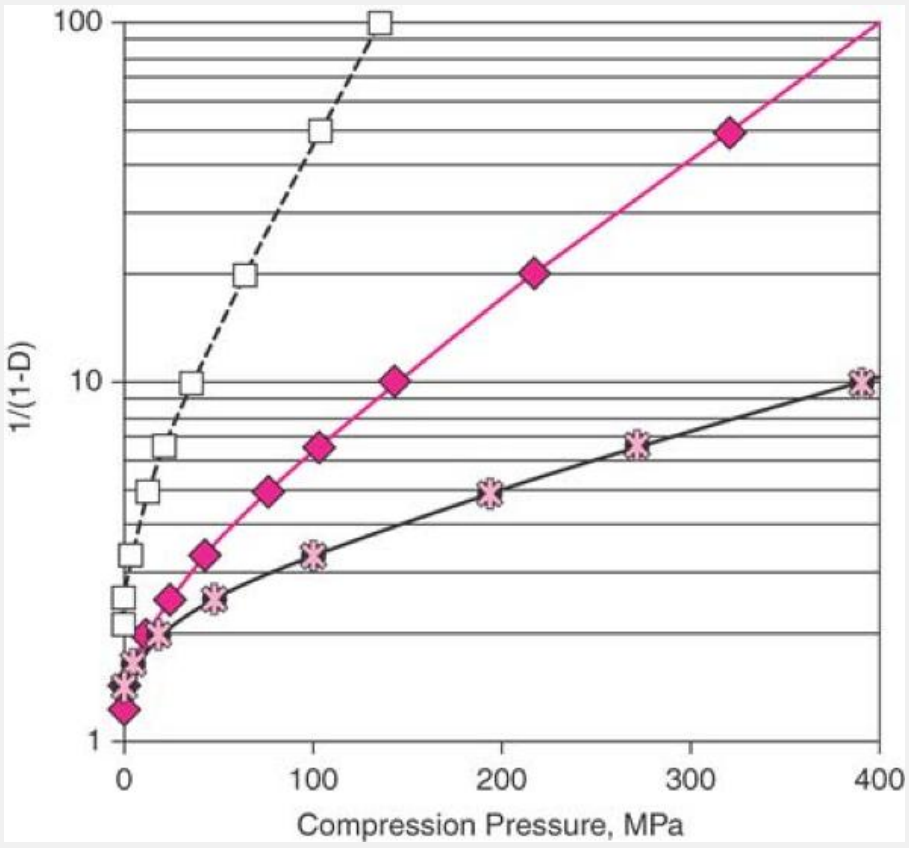


Fig. 22-13. Heckel plot of three pharmaceutical excipients.

Heckel and other equations have been used to interpret and predict the compaction properties of pharmaceutical materials and formulations. Because of the critical importance of the compaction process in forming tablet dosage forms, a great deal of research has revolved around understanding and modeling this process. The reader is directed to other comprehensive discussions of powder compaction for further information.[84,85]
There are several significant challenges to developing and successfully manufacturing compressed tablets in a production environment. The formulation must have the necessary properties to ensure

consistent powder flow properties that allow it to move through the manufacturing equipment, including movement from any intermediate storage containers to the tablet press hopper and feeder system that directs the powder down into the tablet die. Following compression, the tablet must have acceptable aesthetic properties such as a smooth, elegant appearance without cracks or chips. It must also be robust enough to handle any remaining processing that is required such as coating and packaging, yet consistently meet all the performance characteristics that ensure satisfactory performance such as disintegration and dissolution.

Tablet Coating

Some tablet dosage forms may be coated. Coatings may be described as either functional or nonfunctional. Although more popular decades ago, sugarcoating tablets are still performed. The sugarcoating process seals and protects the tablet dosage form and, with the incorporation of color, adds a distinctive look and taste to the tablet. Many tablets are film-coated today as it is a more cost-efficient process than sugarcoating. A thin polymeric layer with a color added is sprayed onto the surface of the tablets to provide a distinctive appearance. Both sugarcoating and film coating may also serve to prevent the patient from experiencing the undesirable taste that some active ingredients have. An example of a functional coat is enteric coating. The enteric-coating material is insoluble in the acidic fluid of the stomach but dissolves in the relatively neutral pH of the intestine. Enteric coating is therefore a way of protecting acid labile drugs from being exposed to the harsh acidic stomach media that can degrade some active ingredients. Controlled release polymers may also be applied to dosage forms to control the rate at which drug enters the intestinal tract and is absorbed.

Capsule Filling

Capsules are solid dosage forms in which the medicinal agent and excipients are enclosed in a small shell of gelatin. The capsule shells may be hard two-piece capsules or a soft gelatin film. Two-piece capsules consist of a capsule body into which the formulated material can be filled and the slightly larger diameter cap that slips over the body to seal the capsule. Soft gelatin capsules are sometimes referred to as soft elastic capsules. Soft gelatin capsules may be filled with liquids or semisolid ingredients, whereas the two-piece capsules are very often filled with dried powders. Recent advancements in two-piece capsule technology now allow for liquid and semisolid fills. The vast majority of capsules are intended to be swallowed whole by the patient. While a majority of capsules are manufactured from gelatin, new polymeric, two-piece capsules prepared from HPMC and pullulan (a water-soluble polysaccharide) are now available and additional materials such as starches are being investigated. Capsule machine equipment is designed to move the formulation into the capsule body followed by positioning and closing the cap to produce the final product. One of the main advantages of capsule formulations is that they do not have to undergo the compaction process as tablets do. This can simplify the formulation process. Industrial capsule machines are capable of fast manufacturing speeds though capsule machines do not currently reach the dosage form output of tablet machines.

Continuous Processing

While the previous sections have covered some of the details of current pharmaceutical manufacturing processes which are done in batch mode, the future of pharmaceutical manufacturing is moving toward continuous processing. Continuous processing often combines one or more pharmaceutical processes utilizing equipment designed to allow for continuous input of starting materials, material processing, and continuous exit of final processed material. There are a variety of benefits to continuous processing. A continuous process inherently provides an opportunity for improved quality and consistency as it involves processing a much smaller quantity of material at any one time. For example, in a typical batch wet granulation unit operation involving a batch size of 300 Kg, the entire quantity is processed simultaneously. For a continuous operation with reasonable material throughput, the quantity of material being processed at any given time may be only about 400 g.

Continuous processing involves operating equipment at steady state and this makes process control strategies

including online measurement of critical process parameters as well as product quality attributes more feasible. Process and statistical modeling can be used to develop control strategies consistent with the Quality by design (Qbd) initiative. These advantages provide the opportunity for simple scale-up. In many instances, it is possible to make large-scale lots with the same equipment used during small-scale development activities by running the process longer. Finally, as the unit operations are integrated into a continuous process, there may be considerable material and resource savings.

Among the commonly used unit operations in solid oral dosage form development, milling, roller compaction (dry granulation), compression (tableting), encapsulation, and packaging are inherently continuous processes. Wet granulation, drying, blending and coating are inherently batch processes. Over the last decade, a concerted effort from industry and equipment manufacturers has resulted in significant progress being done to make these unit operations continuous. As an example, for wet granulation, a modified twin screw extruder and other similar equipment have been designed for use. For drying, fluid bed and dielectric drying have been used. Several designs of low and high shear continuous dry blending equipment are also being marketed. For coating, there are several large-scale continuous coaters in use. With active research and development activities underway, significant advancement is expected to occur in the equipment engineering as well as overall process integration to make this approach for solid oral dosage from development a success in the next 5 to 10 years.

Final Dosage Form Finishing and Packaging

Following the manufacture of tablets or capsules, final finishing of the dosage forms takes place. Two-piece capsules, for example, may be polished to remove small amounts of powder that may adhere to the outside of the capsules during filling. On a large scale, many capsule and tablet machines are affixed to a cleaning vacuum that removes extraneous material from the tablets or capsules as they leave the machine. Following manufacture, the tablets and capsules may be stored in bulk containers until they are packaged. The final dosage form packaging plays a critical part in ensuring and maintaining product quality. Drugs that are adversely affected by light will be packaged in light-resistant containers, whereas moisture-sensitive drugs may be packaged with a desiccant to ensure that the dosage forms are not exposed to high moisture levels that could cause physical or chemical degradation. Properly stored dosage forms will remain stable and effective throughout the entire labeled shelf life of the product.

Dosage form Testing

Tablet Hardness

The mechanical strength of tablet dosage forms is an important property and it plays a significant role in product development and manufacturing control. The mechanical strength of tablet dosage forms is sometimes referred to as tablet hardness or tablet crushing strength. Pharmaceutical ingredients which bond well together are capable of forming tablets with high strength. An old rule of thumb for tablet hardness was that the tablet should break with a sharp snap when squeezed between the fingers and thumb. Commercially available tablet hardness testers are available to provide quantitative data on tablet hardness. Tablet hardness is the force necessary to cause a tablet to fracture when compressed between two rigid platens. Tablet strength is influenced by the formulation components, the processing used to make the formulation, and the process of forming the compressed tablet. The resistance of tablets to chipping, abrasion, and breakage depends on tablet hardness. Tablet hardness is used as a manufacturing control tool and hardness values are often determined throughout a tablet manufacturing lot. If tablet hardness values vary, adjustments to the tablet machine can be made to ensure that the tablet hardness remains within the accepted range. Tablet hardness values should be high enough to ensure satisfactory appearance and tablet strength to withstand further tablet processing and handling but not so high that the dosage form will fail performance criteria such as disintegration or dissolution.

Friability

Tablets must be hard enough to withstand the agitation and stresses that occur during manufacturing, coating, packaging, shipping, and patient use. However, tablets must also be friable enough to break up when swallowed. The pharmaceutical scientist's responsibility in developing a robust tablet formulation

is to produce a dosage form that has adequate hardness and tablet strength to withstand the stresses but, when necessary, will break up and release the drug in a consistent fashion when administered to the patient. Tablet friability is a measure of the ability of the tablets to withstand stresses. The USP describes friabilator apparatus and test methodologies to evaluate tablet resistance to abrasion. Tablets are placed in a 12-inch diameter drum which rotates for a set period of revolutions, typically 100. A shaped arm lifts the tablets and drops them half the height of the drum with each revolution. At the end of this operation, tablets are removed, dedusted, and reweighed. The percent weight change is calculated and is used as a measure of friability. Tablets that remain intact without cracking or chipping (e.g., <1% weight change) typically have sufficient strength to withstand further processing and packaging.

Disintegration

One simple measure of the ability of a compressed tablet or capsule to release drug is the disintegration test. The disintegration time is the time it takes for a dosage form to break apart upon exposure to water with mild agitation. Pharmacopeia's worldwide, including USP, provide details for carrying out standardized disintegration testing that specify the disintegration liquid, the apparatus, the number of dosage units to test, and disintegration endpoint determination. Disintegration tests, official in the USP since 1950, are only indirectly related to drug bioavailability and product performance.

For conventional immediate release tablets, disintegration times may range from less than 1 min to as much as 5 to 15 min. The disintegration time is markedly affected by formulation ingredients and processing. However, disintegration time does not necessarily bear a direct relationship to in vivo release of drug from a dosage form. To be absorbed, the drug substance must be in solution and the disintegration test only measures the time required for the tablet to break up into particles or for a capsule to disperse its contents. The test is useful as a quality assurance tool and is still used today for this purpose.

Dissolution

Dissolution refers to the process by which a solid phase (e.g., a tablet or powder) goes into a solution phase such as water or gastrointestinal fluid. If the dosage form is intended to disintegrate, the tablet or capsule disintegrates into granules and these granules deaggregate, in turn, into fine particles that disperse in the dissolution medium. The individual particles then separate and dissolve (e.g., mix molecule by molecule) with the liquid. Disintegration, deaggregation, and dissolution may occur simultaneously with the release of a drug from its delivery form. Some kinds of controlled release dosage forms are not intended to fully disintegrate on exposure to fluid but rather to slowly release drug from the dosage form over a period of time. Drug dissolution is therefore the process by which drug molecules are liberated from a solid phase and enter into solution. If particles remain in the solid phase once they are introduced into a solution, a pharmaceutical suspension results. Suspensions are covered in Chapters 16 and17. In the vast majority of circumstances, only drugs in solution can be absorbed, distributed, metabolized, excreted, or even produce a pharmacologic action. Thus, dissolution is an important process.

The effectiveness of a tablet in releasing its drug for systemic absorption is influenced by the rate of disintegration and the deaggregation of the granules. Ordinarily of more importance, however, is the dissolution rate of the solid drug. Dissolution is the limiting or rate-controlling step in the absorption of drugs with low solubility (see BCS discussion) when it is the slowest of the steps involved in the release of the drug from a dosage form and passage into systemic circulation.

Although there are many customized and unique dissolution testing devices reported in the literature, the United States Pharmacopeia (USP) and other pharmacopeias worldwide have established standard methodologies and equipment to perform testing of immediate- and modified-release oral dosage forms. The most commonly used methods for evaluating dissolution first appeared in the USP in the early 1970s. The two most common methods are known as the USP basket (method I) and paddle (method II) methods. The reader is referred to Chapter 13 for additional discussion of dissolution testing methods.

In practice, a rotating basket or paddle provides a steady stirring motion in a large vessel with 500 to 1000 mL of fluid controlled to 37°C. The devices are relatively simple and standardized. The USP basket and paddle methods are the methods of choice for dissolution testing of immediate-release oral solid dosage forms. Although water is one of the most commonly listed dissolution media found in USP monographs, it may not be physiologically relevant due to the lack of buffering capacity or other biological components. Biorelevant dissolution media are sometimes used instead of buffered aqueous solutions to more precisely simulate in vivo conditions and these are discussed in greater detail in Chapter 13.

Modified-release delivery systems are similar in size and shape to conventional immediate-release dosage forms but the mechanism of drug release is very different and depends upon the design. The mechanisms for controlling the release of the drugs is becoming very sophisticated and special consideration must be given to how drug release is evaluated. For this reason there are several alternative dissolution apparatuses that may be used for modified-release dosage forms.

Stability

One of the most important activities of formulation development is to evaluate both the physical and chemical stability of the drug substance in the dosage form. It is essential that the drug substance have known purity (typically 97% or greater) and sufficiently low levels of impurities to ensure safety and efficacy. The presence of impurities, or the generation of degradation products as a result of decomposition on storage, must be carefully characterized and controlled and where possible, eliminated with appropriate product design, packaging, and storage. Chemical decomposition of medicinal agents may take on many forms; among the most common decomposition processes are those of hydrolysis and oxidation. Additional details on the various aspects of chemical stability are described in previous sections of this book.

Stability is defined as the extent to which a product retains the same properties and characteristics that it possessed at the time of manufacture. A stable dosage form is one that retains all of its critical physical, chemical, and dosage form performance characteristics such as chemical stability, potency, disintegration, dissolution, and drug release. Pharmaceutical scientists are interested not only in chemical stability, that is, the extent to which the active ingredient retains its chemical integrity and potency but also in physical stability. Physical stability considerations include appearance, tablet hardness or capsule integrity, disintegration, and dissolution profiles. Appropriate characterization and control of physical and chemical stability of dosage forms generally will ensure therapeutic performance. Both physical and chemical stability considerations are important in selecting storage conditions and containers. Temperature, exposure to light, and humidity often are the critical parameters that influence dosage form physicochemical stability. Stability and expiration dating are based on reaction kinetics, that is, the study of the rate of chemical and physical change and the way the rate is influenced by storage conditions. The FDA and other regulatory bodies

worldwide have provided guidance and regulations regarding stability and stability testing of pharmaceutical ingredients and products.[44,74,77,87] Stability testing during each stage of development provides the information needed to optimize product stability and performance. Table 22-19 provides International Conference on Harmonization guidelines and working recommendations to support regulatory filings regarding the presence of impurities and degradation products. Each commercially available pharmaceutical product has a well-defined shelf life and use of the product within its shelf life assures the patient that the product will be safe and effective when stored as directed. Typically oral solid dosage forms such as tablets and capsules have shelf lives of 2 years or more from the date of manufacture when stored at room temperature in appropriate containers, which may be necessary to protect them from light and humidity. In general, kinetic studies are performed to characterize stability of the active ingredient alone (bulk drug stability study) as well as the product. Accelerated stability is done to stress the drug in the dosage form to help define the limits and critical parameters that impact stability. Accelerated stability studies may be used to extrapolate or estimate shelf life at room

temperature. Accelerated stability studies are very often done in the early stages of product development and may be used to support establishing the product shelf life. In addition to the accelerated stabilities, long-term stability studies carried out under the usual conditions of transport and storage are done. Consideration of the different climate zones to which the product may be shipped must be considered as the different climate zones experience different temperature and humidity conditions throughout the year. While the details of all that is necessary to characterize the stability of a pharmaceutical product are beyond the scope of this section, regulatory guidance is available and Chapter 14 provides additional details.

Table 22-19 Thresholds for Degradation Products in New Drug Products[86]*

Maximum Daily Dose	Threshold
Reporting Thresholds	
≤1 g	0.1%
>1 g	0.05%
Identification Thresholds	
<1 mg	1.0% or 5 µg TDI, whichever is lower
1 mg–10 mg	0.5% or 20 µg TDI, whichever is lower
>10 mg–2 g	0.2% or 2 mg TDI, whichever is lower
>2 g	0.10%
Qualification Thresholds	
<10 mg	1.0% or 50 µg TDI, whichever is lower
10 mg–100 mg	0.5% or 200 µg TDI, whichever is lower
>100 mg–2 g	0.2% or 3 mg TDI, whichever is lower
>2 g	0.15%

*The maximum daily dose is the amount of drug substance administered per

day. Thresholds for degradation products are expressed either as a percentage of the drug substance or as total daily intake (TDI) of the degradation product. Lower thresholds can be appropriate if the degradation product is unusually toxic. Higher thresholds should be scientifically justified.

Example 22-10

An antihypertensive drug underdevelopment was placed on stability and the potency was measured over a 36-month period. Graph the following data and determine the first-order decomposition rate, the half-life, and the shelf life (time to 90% of label):

% Potency	Time (months)
100	0
98.5	3
97.0	6
94.6	12
92.0	18
90.4	24
85.0	36

Calculate logarithm of A/A_0 at each timepoint and plot as a function of time. Calculate the slope of the line using linear regression.

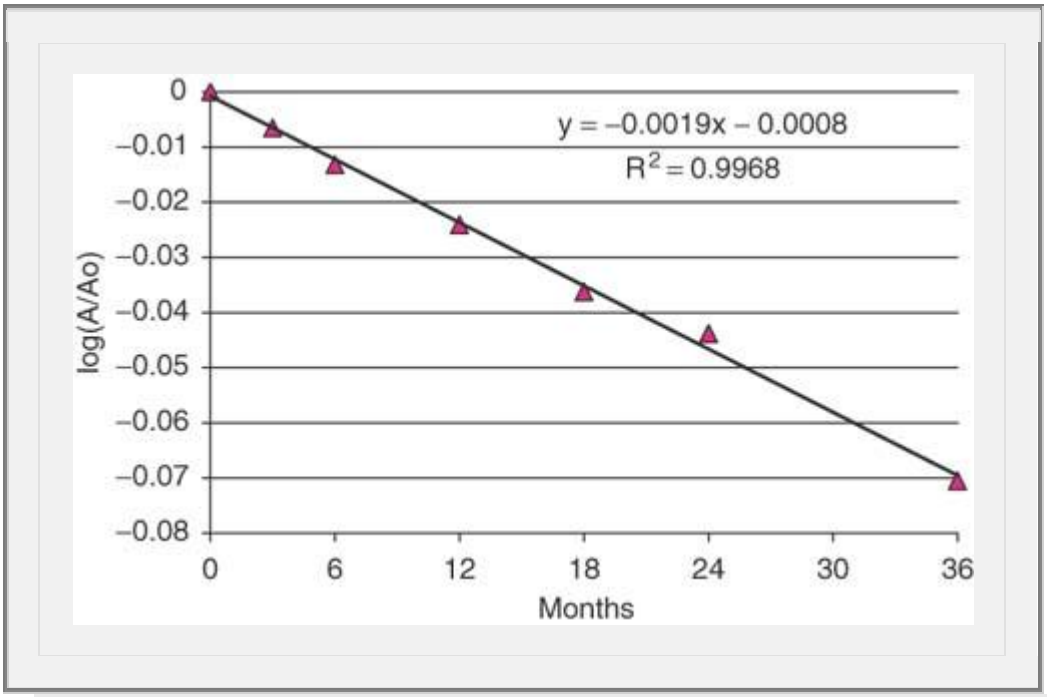
The linear regression line for the plot of $\log(A/A_0) = -0.0019t - 0.0008$ with $R^2 = 0.997$

The rate constant from equation (14-13) related to the slope of the line: k = -slope × 2.303 = 0.0044 mo^{-1}

Using equation (14-18), $t_{1/2} = 0.693/k = 158$ months

The shelf life is defined as the time required for 10% of the drug to disappear.

$t_{90\%} = 0.105/k = 23.9$ months.



$\ln (A/A_0) = -0.058t - 0.0001$

The first-order rate constant is the slope of the linear regression line: $k = 0.058$ months^{-1}

The half-life can be calculated using equation (15-18) as:

$t_{1/2} = 0.693/k = 11.9$ months

The shelf life (time to reach 90% of initial potency) can be calculated using equation (15-14) as:

$t_{90\%} = (2.303/k) \times \log(100/90) = 0.105/k = 8.3$ months

Chapter Summary

Physical pharmacy and pharmaceutical science is the science of the delivery of APIs to the target site to achieve the

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desired pharmacological effect. For a drug to exert its biological effect, it must be released from the dosage form into the body, permeate through biological membranes, and reach the site of action. Successful delivery of APIs requires a sound understanding of a diverse array of scientific topics including physical and chemical properties, particle and powder properties, excipient properties and selection, dosage form manufacturing, drug absorption and transport, dosage form performance, and stability.

Practice problems for this chapter can be found at thePoint.lww.com/Sinko6e.

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Chapter Legacy

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