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APPLIED PHYSICAL PHARMACY

Second Edition

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Preface

In the spirit of understanding how drugs work, this textbook explores the fundamental physicochemical attributes and processes important for understanding how a drug, usually in the form of a crystal, is transformed into a usable product that is administered to a patient to reach its pharmacological target, and then leaves the body. This is the discipline of physical pharmacy—the study of the physical and chemical properties of drugs and their dosage forms. When integrated with other critical knowledge of how drugs work, such as their pharmacologic effects, physical pharmacy forms part of the scientific foundation for the clinical sciences and, therefore, for clinical practice. A distinguishing feature of physical pharmacy is that, unlike pharmacology, which is learned to different degrees by other healthcare practitioners, physical pharmacy is a body of knowledge unique to the education of student pharmacists, for whom this textbook is written. It provides the physicochemical basis for rational formulation, manufacturing, compounding, drug delivery, product selection, and product usage. Therefore, it is knowledge indispensable for the ability of the pharmacist to comprehensively understand and explain how drugs work, in a manner and to an extent that is unparalleled by any other healthcare practitioner. In other words, it's a part of the body of knowledge that equips pharmacists with unique perspectives and insights in the provision of pharmaceutical care.

Significant revisions have been made from the first edition of *Applied Physical Pharmacy* published in 2003, including addition of clinical examples and applications that are relevant in contemporary pharmacy practice. Each chapter includes a set of *Learning Objectives* to guide the student's focus in learning, *Key Points* to delineate the critical concepts discussed in the chapters, *Problems* to apply and assess the understanding of chapter concepts, and *Clinical Questions* to apply the chapter concepts in a clinical context.

An overarching goal in the writing and editing of this edition was to improve its focus on the critical knowledge needed for the education of the student pharmacist. The number of chapters was reduced from 13 to 11. Chapters with conceptually common material were blended into new chapters. Each chapter was examined for relevance to pharmacy education, and was accordingly edited to help achieve this goal. Some of the material from the first edition that was considered important but more relevant to graduate work in physical pharmacy was moved to chapter appendices. This was done to improve the flow of material within the chapter, again to make it more conducive for learning by student pharmacists.

The textbook begins with a review of the key biopharmaceutics concepts of drug liberation, absorption, distribution, metabolism, and excretion. These concepts and others set the framework for subsequent chapters that describe physicochemical properties and processes related to the fate of the drug. These include states of matter (Chapter 2), solutions, (Chapter 3), ionization (Chapter 4), dissolution and partitioning (Chapter 5), mass transport (Chapter 6), and complexation and protein binding (Chapter 7). Concepts in these chapters are important not only for understanding a drug's fate in the body but also for providing the scientific basis for rational drug formulation. Other physical pharmacy topics

important to drug formulation and usage are discussed in the three chapters that follow, which describe dispersed systems (Chapter 8), interfacial phenomena (Chapter 9), and rheology (Chapter 10). The textbook concludes with an overview of the principles of kinetics (Chapter 11) that are important for understanding the rates at which many of the processes discussed in previous chapters occur. We are very grateful to all of the contributing authors who shared with us their expertise in important physical pharmacy knowledge and skills. A special thanks goes to Michael Weitz, the McGraw-Hill Executive Editor for Medical, Pharmacy & Allied Health Textbooks, for his enormous patience in accommodating our busy schedules, while guiding us to this textbook's conclusion. Thanks also to all of the McGraw-Hill editors, including Karen G. Edmonson. We also thank our pharmacy students who continuously inspire us to improve our craft of teaching. Most importantly, we are each grateful to our families, whose love, support, and patience helped make the writing and editing of this textbook possible and worthwhile.

The Editors

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1 Introduction to Biopharmaceutics

W. Cary Mobley

Learning Objectives

After completing this chapter, the reader should be able to:

- List the types and locations of drug targets.
- List common dosage forms and the nature of the drug within the listed dosage forms.
- Describe common routes of drug administration, including the administration locations and the absorption sites.
- Define bioavailability and describe important physiological and physicochemical factors that influence a drug's bioavailability.
- Describe the following physicochemical factors that can influence the fate of the drug in the body: solid state properties, ionization, solubility and dissolution, partition coefficient, mass transport and membrane passage, complexation and protein binding.
- Briefly describe each parameter in the LADME acronym.
- Describe the general roles of drug transporters (with examples) in the ADME processes of a drug's disposition in the body.

INTRODUCTION

Biopharmaceutics can be defined as the study of the physical and chemical properties of drugs and their proper dosage as related to the onset, duration, and intensity of drug action, or it can be defined as the study of the effects of physicochemical properties of the drug and the drug product, *in vitro,* on the bioavailability of the drug, *in vivo,* to produce a desired therapeutic effect. Both definitions imply the relationship between the physicochemical properties of the drug, the drug's biological fate in the body after its administration, and the resulting pharmacological action of the drug. Most of this textbook is focused on the details of important physicochemical properties. This chapter introduces fundamental concepts and processes related to the fate of the drug in the body in order to help provide a framework for many of the concepts in subsequent chapters. As a background to discussing the fate (or disposition) of drugs, a brief review of their targets, their dosage forms, and their routes of administration is given next.

Drug Targets

Most drugs exert their effects by interacting with targets, which are molecules or structures that are linked to a particular disease.[1,2] Most often the target is a macromolecule, such as a protein or nucleic acid. Protein targets dominate, and they include enzymes, ion channels, nuclear hormone receptors, structural proteins, membrane transport proteins, and G protein-coupled receptors. These targets have important biochemical or physiological roles, and drugs interact with them, either blocking, inhibiting, or activating them, with biochemical and physiological consequences. These consequences are desired to help make the patient well, but they can also be manifested as adverse effects in the patient. The targets are found in various areas of the body, and they may be within cells, embedded in cell membranes, or outside of cells in various body fluids.

Some targets can be accessed by the nonsystemic administration of the drug (i.e., without reaching the systemic circulation),

- Describe, in general, how drugs are liberated from their dosage forms.
- Describe gastrointestinal drug absorption into the systemic circulation, including the influences of a drug's physicochemical properties, and the steps taken by a dissolved drug in the small intestines to its entry into enteroctytes, hepatocytes, and finally the bloodstream.
- Describe enterohepatic cycling, possible rate-limiting steps in drug absorption, and first-pass metabolism.
- Describe the distribution of a drug from the plasma to the interstitia of tissues, including the influences of a drug's physicochemical properties, and of binding to plasma proteins and to tissue components.
- List other distribution sites, including the CNS, fat, and placenta.
- Define the apparent volume of drug distribution and relate it to the distribution of body water.
- Give an overview of the necessity, phases, and locations of drug metabolism.
- Describe renal drug excretion, including the influences of a drug's physicochemical properties.
- List nonrenal excretory pathways.
- Define and describe clearance and half-life, and briefly relate them to their importance for drug dosing.

such as targets in the intestinal lumen (reached from oral drug administration),[3] the dermis (reached from topical drug administration), and the bronchioles (reached from oral inhalation). However, in most cases, drug targets are reached by the drug after it enters the systemic circulation and distributes to the specific areas or cells that contain them. A drug's entry into the systemic circulation and distribution to its target(s) will be under the influence of many factors, including anatomical and physiological factors based on the route of the drug's administration (e.g., gastric emptying for the oral route) and blood flow to the various tissues. Drug entry and distribution are also under the influence of the physiochemical properties of the drug, such as size, charge, and lipophilicity. The roles of physicochemical factors are the main focus of this chapter.

Dosage Forms

A drug is administered to a patient as a specific *drug product,* which is a particular *dosage form* that is most often a formulation of the drug with various excipients. Excipients can be present for a variety of purposes, such as for improving stability, dissolution, manufacturing speed and quality, and flavoring. Dosage forms include the familiar tablets, capsules, and suspensions, as well as many others described in Table 1-1. When the

TABLE 1-1 Examples of Drug Dosage Forms and the Common State of the Drug Within Them

Dosage Form	Common State of the Drug in the Dosage Form
Tablet	Crystals in a compressed powder
Capsules, powder-filled	Crystals in a noncompressed powder
Capsules, liquid-filled	Molecules or crystals in vegetable oil
Suppository	Crystals in waxy, water-miscible or water-immiscible base
Solution	Molecules
Suspension	Crystals in an aqueous or nonaqueous liquid (see Chapter 8)
Ointment	Crystals or molecules in a semisolid oleaginous base
Cream	Crystals or molecules in water-miscible or immiscible semisolid cream base
Gel	Crystals or molecules in water-miscible semisolid gel base
Aerosol	Crystals or molecules in a gas, liquid, or semisolid

drug is formulated into its dosage form, it may be present in different physical forms, with the two most common being crystals and molecules. An important concept, described below, is that the drug must be released, or *liberated*, from its dosage form for it to begin the process of its journey to its receptor, with the first step of that process (for an undissolved drug) being its dissolution in the fluid of its route of administration.

Routes of Drug Administration

In addition to the variety of drug products in which a drug may be formulated, it's also important to understand that there are a variety of anatomical pathways, or routes of administration, through which a drug product may be administered. Table 1-2 describes many of the common routes of administration. These include routes for which it is intended that the drug be localized to a specific area, such as the eye for an ophthalmic application, the lungs for an oral inhalation, the central nervous system for an intrathecal injection, or a joint for an intrasynovial injection. For many administration routes, the drug is intended to pass into the systemic circulation for distribution throughout the body. In these cases, the drug may be administered directly into a vein, or indirectly by a number of other routes, with the oral route being the most common. For the indirect routes, the drug must pass through membranes of various types and it may be subject to metabolism before it reaches the systemic circulation. Therefore, drugs administered via indirect routes may not be completely bioavailable to the systemic circulation.

Bioavailability

Bioavailability can be defined as the proportion (percent or fraction) of an administered dose of unchanged drug that reaches the systemic circulation. An intravenous drug is administered directly into the systemic circulation, so is 100% bioavailable. For other routes, the bioavailability can be decreased by incomplete dissolution, incomplete absorption through epithelia, and presystemic metabolism. These will be described later. In some cases, the bioavailability can also be reduced if the drug chemically degrades in the body. For example, the proton pump inhibitor omeprazole can degrade in the acidic environment of the stomach, so it must be formulated with a buffer that raises gastric pH or in a way (e.g., enteric coating) that allows it to bypass the stomach before dissolving. Membrane and metabolic barriers can differ significantly from one route of administration to another (see Table 1-2). These barriers in combination with properties of the drug, drug product, and other physiological phenomena (e.g., gastric emptying) can reduce the drug's bioavailability. Bioavailability is a fundamental component of drug product performance that is assessed in the drug development process.

DRUG DISPOSITION—THE FATE OF THE DRUG AFTER ADMINISTRATION

As mentioned, once the intact drug reaches the systemic circulation it will distribute to various regions of the body, including those where its target is found. It will also be subject to metabolism and will be excreted from the body as intact drug or as drug metabolite. Figure 1-1 illustrates different processes that can affect the fate of an administered drug product, before and after the drug's entry into the systemic circulation. These processes are embodied in the acronym LADME, which stands for liberation (release of the drug from its dosage form), absorption (into the bloodstream), distribution (to various parts of the body), metabolism (by enzymes), and excretion (through the kidneys or other routes). The net effects of all of these processes yield a profile of plasma drug concentration versus time exemplified in Figure 1-2 for an extravascular (e.g., nonintravenous) drug administration. The curve depicts the minimum effective concentration needed for the desired therapeutic effect, the minimum toxic concentration for toxicity to manifest, and the duration of being at or above the minimum effective

TABLE 1-2 Common Routes of Drug Administration

Route	Administration Site	Primary Absorption Site(s)/ Purpose	Common Dosage Forms
Oral	Mouth (swallowed)	Epithelia of the upper small intestine, stomach; for a systemic effect	Tablet, capsule, solution, suspension, emulsion
Sublingual	Under the tongue	Epithelium under the tongue; for a systemic effect	Tablet
Buccal	Between the cheek and gums	Epithelial of the lining of the cheek or local action; for a local or systemic effect	Tablet, lozenge
Rectal	Rectum	Rectal epithelium or local action; for a local or systemic effect	Suppository, gel, foam aerosol
Vaginal	Vagina	Vaginal epithelium; mainly for a local effect	Suppository, tablet, ointment, cream
Intranasal	Nasal cavity	Nasal epithelium; mainly for a local effect	Solution, suspension
Pulmonary	Mouth (inhaled)	Bronchiolar epithelium; mainly for a local effect	Liquid solution or suspension
Ophthalmic	Eye surface	Corneal epithelium; for a local effect	Liquid solution or suspension
Topical	Epidermal surface	Stratum corneum; for a local effect	Powder, liquid solution or suspension, ointment, cream, gel
Transdermal	Epidermal surface	Stratum corneum, capillaries; mainly for a systemic effect	Ointment, cream, gel
Intravenous injection or infusion	Veins	None; for a systemic effect	Solution, emulsion (if nano-sized)
Intramuscular injection	Striated muscles (e.g., deltoid, thigh, buttocks)	Blood capillaries; for a systemic effect	Aqueous or nonaqueous solution or suspension
Subcutaneous injection	Subcutaneous fat	Blood and lymphatic capillaries; for a systemic effect	Aqueous solution or suspension
Intraperitoneal infusion	Peritoneal cavity	Peritoneum; mainly for organs of the peritoneal cavity (e.g., for ovarian cancer)	Aqueous solution
Intrathecal injection or infusion	Spinal cord (into the cerebrospinal fluid)	None; for local action in the CNS	Aqueous solution
Epidural injection or infusion	Outside of the dura mater of the spinal cord	Dura mater; for local action in the CNS	Aqueous solution
Intrasynovial injection	Synovial space of joints	None; for local action in the joints	Aqueous solution or suspension
Intraosseous injection or infusion	Bone marrow (e.g., of the tibia)	Sinusoidal capillaries; for systemic action (e.g., in emergencies)	Aqueous solution
Intravitreal injection	Vitreous humor of the eyeball	None; for local action within the eye	Aqueous solution

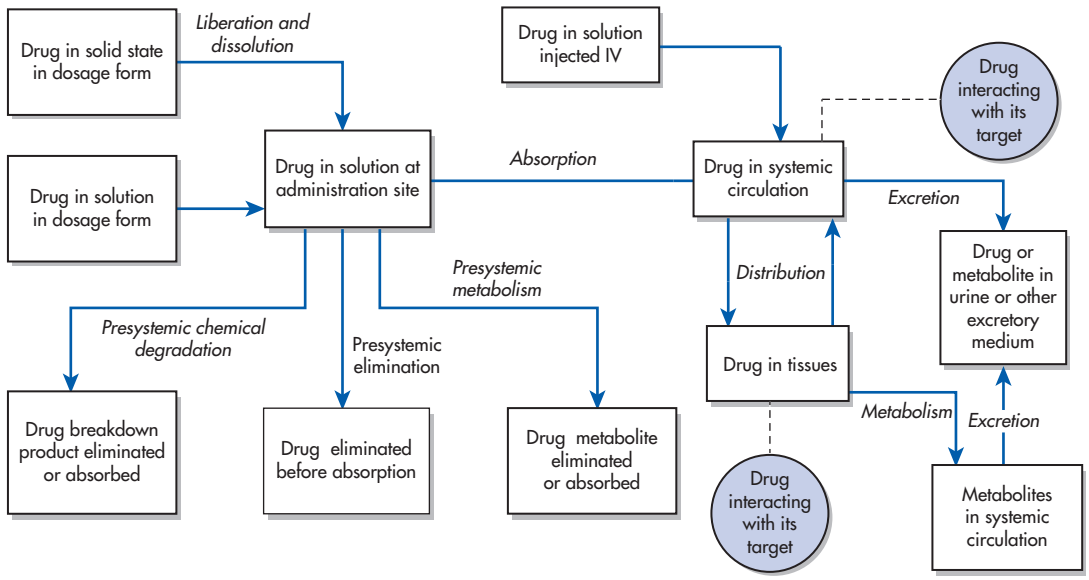

FIGURE 1-1 Common processes that affect the fate of a drug product for drugs intended to enter the systemic circulation.

concentration. The exact shape of a concentration versus time profile for a particular drug product, for example, how quickly and how high the plasma levels rise, depends on many factors including the dosage form (and the nature of the drug's release), the route of administration, the physicochemical properties of the drug, and the ADME processes, which are described next.

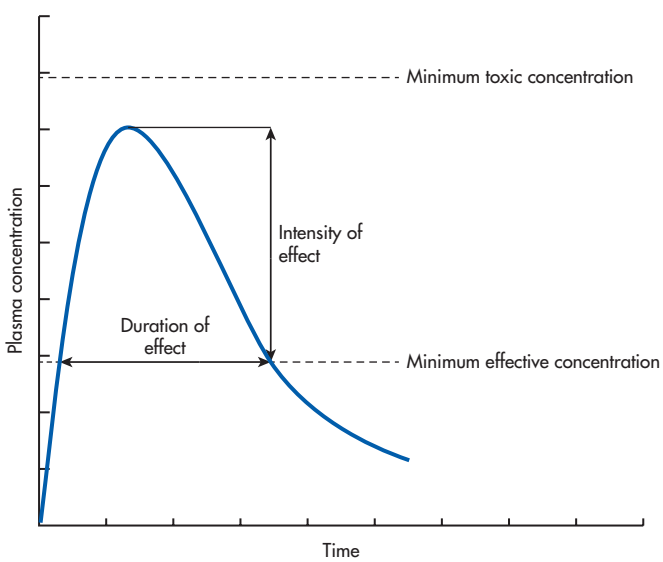

FIGURE 1-2 Plot of plasma concentration versus time for a single dose of a hypothetical drug administered by a nonintravenous route.

Physicochemical Factors Related to the Fate of the Drug in the Body

As mentioned, there are many physicochemical properties of a drug, which along with physiological factors will affect the fate of the drug in the body through their effects on the various LADME processes. Some of these properties are discussed in detail in different chapters of the textbook and are introduced here.[4]

Solid State Properties

Nearly all drugs reach the formulator in the solid state, most often as crystals. Many drugs can exist in different crystalline forms, or polymorphs, largely depending on crystallization conditions. The different polymorphs of a drug reflect the arrangement and interactions of the drug molecules within the crystal, and therefore different crystalline forms of the same drug will dissolve at different rates: Crystalline forms with weaker molecular interactions (within the crystal) will generally dissolve more quickly than forms with stronger interactions. In addition to crystalline forms, a solid drug may be amorphous (without crystalline form), with drug molecules generally exhibiting weaker interactions than crystalline forms. Therefore, amorphous forms of a particular drug generally dissolve faster than crystalline forms. Solid state properties are discussed in Chapter 2.

Ionization

Most drugs are weak acids or weak bases and therefore can exist in the ionized and/or the nonionized form, depending on the pH of the medium. The degree of a drug's ionization can be important for many biopharmaceutical properties, including water solubility, absorption, distribution, and excretion. This is largely because the two forms have different polarities, with the ionized form being the more polar form, which is the form that dissolves better in body fluids but will generally not pass through membranes as well as the less polar, nonionized form. Ionization and its implications are discussed in Chapter 4.

Solubility and Dissolution

Drugs must be in their molecular form to be absorbed through membranes, to be distributed throughout the circulation, to interact with their targets, and to be metabolized and excreted. Therefore, the *solubility* of the drug is a fundamental physicochemical property and its dissolution is a fundamental physicochemical process. Factors that tend to affect a drug's solubility in body fluids include its molecular nature (e.g., presence of polar functional groups), its state of ionization at the pH of the body fluid (with the ionized form being more water-soluble), and its crystallinity (with the weaker polymorph being more water-soluble). *Dissolution* rates in the body can be affected by the drug's water solubility and particle size (with smaller particles generally dissolving more quickly). Particle dissolution is discussed in Chapter 5.

Partition Coefficient

A drug's *partition coefficient* is a measure of its concentration in a nonpolar organic phase relative to that in a polar aqueous phase. The drug partitions between the two phases, largely based on its polarity. Therefore, the partition coefficient can be useful for predicting the passive diffusion of a drug across a lipid bilayer. Lipophilic drugs have higher partition coefficients and tend to have a better ability to pass through the cell membranes that they encounter during their passage through the body. Since most drugs are weak acids and weak bases, pH can play a significant role in passive diffusion. According to the pH-partition hypothesis, for ionizable drugs, the more lipid soluble nonionized form is the form that most readily crosses a lipid bilayer. Therefore, as the pH determines the extent of a drug's ionization, the pH at absorption or permeation sites plays a large role in determining the passive diffusion of a drug across a lipid bilayer and can be used, along with knowledge of a drug's p*Ka*, to predict drug absorption at different administration sites and the transport of drugs into different body fluids. Drug partitioning is discussed in Chapter 5.

Mass Transport and Membrane Passage

Mass transport refers to the movement of molecules of solutes (e.g., dissolved drug) or solvents from one region to another, and so it is a fundamental determinant of the drug's fate in the body. From their absorption to their elimination, drugs enter different regions of the body, largely by passing through membranes, a term that can be interpreted in different ways: It can refer to multiple layers of cells (e.g., the skin and eyeball), to single cell layers (e.g., intestinal and bronchial epithelia), and to the lipid bilayer of individual cells. Drugs cross membranes by passive mechanisms (where the membrane does not actively participate in drug passage) or by active mechanisms (where a membrane component actively participates in the transfer). *Passive diffusion* through cellular lipid bilayers is the most common way drugs cross biological membranes, and as mentioned, it favors drugs with sufficient lipophilicity. In addition, drugs may diffuse to various regions *between* cells, which is the typical way drugs pass through fenestrated capillary endothelia, such as with drug passage into many tissues and into the kidney glomerulus. In these passive processes, drugs will move down their concentration gradient (i.e., from a region of high concentration to a region of low concentration). Some drugs are actively transferred into and out of cells with the aid of drug transporters, which are membrane-bound proteins. If the active transfer is against the drug's concentration gradient the process is called *active transport*, and if it's with the concentration gradient, it is called *facilitated diffusion*. The processes of mass transport and membrane passage are discussed in Chapter 6.

Roles of drug transporters. Transporters are biologically critical to cellular homeostasis as they control the influx and efflux of many compounds, including nutrients, ions, and xenobiotics (i.e., foreign chemicals, including drugs). Their importance is supported by the fact that about 7% of the human genome codes for transporter-related proteins.[5] For many drugs, drug transporters are critical for determining the drug's fate, and can affect all ADME processes, as they are located in intestinal, renal, and hepatic epithelial cells, and in barrier endothelia of various organs, including the brain. Not only can they be important to a drug's fate in the body, transporters can also play roles in the resistance to drugs (e.g., some cancers and viral infections), and they can play a role in adverse drug effects. Transporters are classified into two superfamilies: ABC (ATP binding cassette) transporters, which are active transporters that utilize ATP for their energy; and SLC (solute carrier) transporters, which include facilitated transporters and ion-coupled active transporters, which require coupling with the transport of a second solute for their energy. P-glycoprotein, an ABC transporter, and organic anion transporting peptides (OATPs), SLC family members, are well-known examples of transporters that can be involved in the ADME processes. Their roles will be discussed further in subsequent sections of this chapter.

Complexation and Protein Binding

The binding of a drug to different molecules or macromolecules can be important for its fate in the body. For example, some drugs (such as tetracycline) can complex to calcium in the gastrointestinal tract, thereby limiting their absorption. In the bloodstream, drugs can bind to circulating plasma proteins, including albumin, which mainly binds acidic and neutral drugs, and alpha1-acid glycoprotein, which mainly binds basic drugs. Plasma protein binding can be an important factor for a drug's distribution, metabolism, excretion, and pharmacological activity. This is due to the fact that, generally, only free (unbound) drug can transfer from the bloodstream into the interstitial fluid that surrounds cells of a given tissue; only free drug can cross cell membranes and interact with other molecules, such as metabolic enzymes and drug targets; and only free drug can be renally excreted. In most cases, protein binding is a reversible equilibrium process, so as free drug is removed from an area, protein-bound drug is released to reestablish equilibrium. Details on drug binding are discussed in Chapter 7.

LADME

As mentioned, the discipline of biopharmaceutics encompasses an understanding of the factors that dictate a drug's fate in the body. *Pharmacokinetics* is a related discipline that can be described as the science of the kinetics of drug absorption, distribution, and elimination. It mathematically relates the ADME processes to parameters that are used to calculate and adjust dosing regimens for patients. Some of the mathematics of pharmacokinetics are described in Chapter 11 so will not be discussed here. However, some of the important pharmacokinetic concepts (such as bioavailability, volume of distribution, and clearance) will be introduced in the following review of LADME processes.[6]

Liberation

For most drug products, the drug is dispersed within its formulation, either in its molecular form or as solid particles (see Table 1-1). For it to be absorbed through biological membranes, it must be released (liberated) from its dosage form and, if it is in the solid state, it must dissolve in body fluids (i.e., it must be in its molecular form). (Drugs administered as aqueous solutions are ready to be absorbed.) Depending on the dosage form, there are different ways a drug can be released. If the drug is in an oily phase, such as an ointment that has been applied to the skin, an oil that has been injected into a muscle, or a fatty acid suppository base that has melted in the rectum, the drug, if undissolved, must partition to the aqueous biological fluid and dissolve. If the drug is an aqueous suspension, the suspended crystals must dissolve in the body fluid. If the drug is in a compressed tablet, the drug crystals are released and must dissolve, during and after a process of tablet disintegration, which functions to fully expose the drug crystals to the gastrointestinal fluids for dissolution. This process is depicted in Figure 1-3.

Absorption

Depending on the route of a drug product's administration, once the drug is dissolved in the fluid of the route, it faces different membrane barriers on its transfer into the fluid that will either contain the target or transport it to the target location (see Table 1-2). The transporting fluid is the bloodstream for most drug routes. A drug dissolved on the skin or eyeball must traverse several cell layers. A drug delivered epidurally (outside the spinal cord) must pass through the dura. Drugs injected intramuscularly and subcutaneously enter through blood capillaries and through lymphatic capillaries for subcutaneous injections. Drugs administered to the mucosal sites of the lungs, nasal cavity, mouth, and rectum must cross varying types of epithelia. This section will focus on drug absorption after oral administration, which is the most common route.

After oral administration and drug dissolution, absorption primarily occurs through the single layer of columnar cells that line the stomach and through the enterocytes of the upper small intestine (duodenum and jejunum). Of these absorptive pathways, absorption through the upper small intestines is usually far greater than through the stomach, primarily because of the larger small intestinal surface area (owing to the number of epithelial villi and enterocyte microvilli).

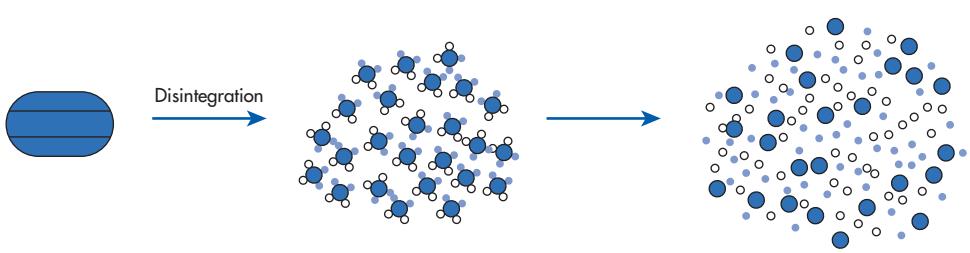

FIGURE 1-3 Depiction of the general process for tablet disintegration to release the drug for dissolution.

The most common pathway for drugs to cross the enterocyte lipid bilayers is by passive diffusion, although as discussed previously and below, transporters can play a significant role. Since passive diffusion dominates in most cases, and since most drugs are ionizable, gastrointestinal pH can play a critical role in drug absorption. The less polar, nonionized form of the drug is the form that can most readily traverse the enterocyte lipid bilayer. So, for example, a weak acid drug will be protonated and therefore predominantly nonionized at low gastric pH. The extent of ionization will depend on the actual pH and the drug's p*Ka*. Based on pH alone, a weak acid would be expected to be absorbed more in the stomach, but again, because of greater surface area, the small intestines will ordinarily be where most absorption occurs, whether the drug is a weak acid or a weak base. Another factor affecting the intestinal absorption of some drugs into the bloodstream will be the presence of drug transporters in the various cellular membranes encountered by the drug. Following is a general description of the intestinal absorptive pathway into the bloodstream, along with a brief introduction of the roles of drug transporters.

Until about the mid-1990s, a drug's oral bioavailability was considered to depend almost exclusively on its physicochemical properties of solubility and membrane permeability along with its susceptibility to hepatic first-pass metabolism. Since that time, it has become increasingly understood that for many drugs, the role of membrane-bound transporters can be significant.[6,7] These include *efflux* transporters, which as the name implies, move substances out of cells, and *uptake* (or *influx*) transporters, which move substances into cells. These transporters are also located in membranes in many other regions of the body, including the kidney and the blood–brain barrier, where they can serve roles on the disposition of drugs. In the typical sequence of cell membranes that a drug in intestinal fluids passes on its way into the bloodstream, the first encountered are the membranes of the enterocyte; first will be the apical membrane facing the intestinal lumen, and then the basolateral membrane facing the interstitium. On the apical membrane of the enterocyte is located P-glycoprotein, a major efflux transporter. It is believed that a role of this transporter is to move xenobiotics (foreign molecules) back into the intestinal lumen, followed by their reabsorption into the enterocyte. Repeated cycles of this process maximize the exposure of the xenobiotics to the metabolic enzymes that reside inside the cell. This interplay between efflux and metabolism can coordinate to reduce the amount of intact drug that enters the bloodstream, thereby decreasing its bioavailability. Drug that leaves the enterocyte through the basolateral membrane enters the interstitium, followed by its entry into the hepatic portal system, which transports the drug to the liver sinusoids where portal blood mixes with blood from the hepatic artery. The blood percolates through the large gaps in the sinusoidal endothelial cells to reach the hepatocytes. Drugs enter the hepatocyte on the basolateral side that faces the sinusoids. They will either enter by passive diffusion (e.g., if they are lipophilic enough) or with the aid of uptake transporters, such as organic anion transporting peptide (OATP), if, for example, it is charged or too hydrophilic to passively diffuse across the lipid bilayer. Metabolism occurs within the cell through the action of the metabolic enzymes that are located primarily on the endoplasmic reticulum. Drug and metabolites will leave the cell, again by passive diffusion or with the aid of transporters. Drug and metabolites that leave the cell through the basolateral side of the hepatocyte ultimately enter the hepatic veins, which drain into the inferior vena cava, followed by their distribution into the systemic circulation. Some drugs or metabolites may leave the hepatocyte through the apical side, which like the enterocyte, contains P-glycoprotein, which now functions to pump drug into the biliary canaliculi (bile capillaries), which eventually merge to form the hepatic bile duct that empties into the gall bladder, which ultimately deposits its contents into the intestinal lumen. Drugs that leave through the apical side of the hepatocyte are usually large (MW 300–500) and polar (such as glucouronide metabolites of some drugs).

Enterohepatic Circulation

If a drug (or metabolite) reenters the intestinal lumen by biliary excretion, some will be excreted in feces and some may be reabsorbed back into the enterocytes

in a cycling process known as *enterohepatic circulation* or *enterohepatic cycling*. This process is favored for drugs with molecular weights greater than approximately 300 and can occur for some hydrophilic metabolites, such as glucuronide metabolites that can be restored to their parent drug by the metabolic activity of intestinal bacteria. The parent drug can then be reabsorbed and the cycle can be repeated. For a drug that experiences enterohepatic cycling, the process can prolong the time that it is in the body and therefore its duration of action. The process can also contribute to its elimination in the feces.

Rate-Limiting Step in Drug Absorption

The rate and extent of drug absorption into the systemic circulation are the net effects of processes that follow the administration of the drug product. Using an orally administered tablet as an example, the main processes are: (1) tablet disintegration, (2) dissolution of the solid drug particles in gastrointestinal fluids, (3) gastric emptying into the small intestine, and (4) absorption into the systemic circulation. The rate of each of these processes will differ, and the step with the slowest rate will be the *rate-limiting step* that will dictate how quickly a drug will enter the bloodstream. Note that for other routes and dosage forms, there may be different processes that will affect the drug's absorption. Usually, it will be the rate of dissolution or rate of absorption that will be rate-limiting. For example, a polar drug may dissolve quickly but have difficulty passing through enterocyte lipid bilayers. This would make absorption rate-limiting. A nonpolar drug may have the opposite problem, making dissolution rate-limiting. Gastric emptying (of the drug) can be rate-limiting for drugs that are very soluble (and dissolve quickly) and have high intestinal permeability. Having this information about a drug's solubility, dissolution rate, and intestinal permeability is critical basic information that is obtained during the drug development process. It has value for the development of formulations and for the design of clinical studies.

First-Pass Metabolism

For drugs given orally, following their absorption they are subject to metabolism, first in the enterocytes that make up the intestinal epithelium, and then in hepatocytes after being transported to the liver via the hepatic portal vein. This presystemic metabolism is called *first-pass metabolism*, because it occurs on the first pass of the drug from the intestinal lumen and through the liver, before it enters the systemic circulation. It can significantly limit the amount of active drug that enters the systemic circulation and therefore can significantly limit an oral drug's bioavailability. Although *hepatic* first-pass metabolism is the major type of first-pass metabolism, other drug absorption sites, such as the skin and lungs, can also exhibit first-pass metabolism, but usually to a much lesser degree.

Distribution

Once a drug is in the bloodstream, it will distribute fairly rapidly throughout the body. However, distribution is not equal to all parts of the body, both in terms of speed and extent.[8] Distribution is generally fastest to well-perfused organs, such as the liver, kidney, and brain, and slower to other tissues such as the muscle, fat, and skin. Upon reaching capillary beds of various tissues and organs, most drug molecules are able to traverse the capillaries into the interstitium, and if they have sufficient lipophilicity they can passively diffuse into the cells that are bathed by the interstitial fluid.

Plasma Protein Binding and Tissue Binding

An important point mentioned before is that only free drug is able to leave the vasculature. Because of this, the binding of drugs to plasma proteins, such as albumin and alpha1-acid glycoprotein, can play a critical role in drug distribution. In most cases, the binding of drugs to plasma proteins is reversible, so when free drug leaves the plasma during distribution to tissues or by excretion, protein-bound drug dissociates to maintain the equilibrium.

Upon reaching the tissues, drugs can also bind to tissue components, such as cell membrane phospholipids and proteins, which, along with active transport processes, can lead to tissue accumulation of the drug. This tissue-bound drug can act as a drug reservoir that can slowly release the drug and prolong its action, but it can also lead to adverse effects if the drug is toxic to the particular tissue.

Other Distribution Sites

Central nervous system. A notable exception to easy passage into interstitial fluid is found with the central nervous system (CNS), where the endothelial cells of the capillaries supplying the brain and spinal cord are held together by tight junctions, which cause the capillaries to restrict the easy passage of drugs into the CNS interstitium, unless they are small and lipophilic enough to pass through the membranes of the capillary endothelial cells. In some cases, even small lipophilic drugs may show poor penetration into the CNS, because like the enterocytes and hepatocytes discussed previously, the capillary endothelial cells in the CNS possess efflux transporters, such as P-glycoprotein, that function to limit the entry of xenobiotics (including drugs) that are their substrate. On the other hand, there are also uptake transporters that facilitate the entry of certain hydrophilic substances. Examples are glucose, which utilizes glucose transporter 1 (GLUT1) for its facilitated entry into the brain, and large neutral amino acids, which utilize the L-type amino acid transporter 1 (LAT1).

Fat. Some lipophilic drugs, such as certain general anesthetics, can accumulate in adipose tissue. In these cases, the distribution of the drug may be significantly affected in obese patients and must be accounted for in drug dosing. Note that it is important for the practitioner to be aware that many lipophilic drugs do not accumulate in fat, so any assumptions should be made with caution.[9]

Placenta. Drugs can cross the human placenta by passive diffusion, in which case, blood flow, protein binding, and the pH of maternal and fetal blood and their effects on the drug's ionization state can be important for placental drug transfer. Additionally, as with many other sites of distribution, there are numerous efflux transporters (including P-glycoprotein) and uptake transporters that are important for controlling transport of their substrates to the developing fetus.[10]

Apparent Volume of Distribution

Each drug has a unique, and typically uneven, pattern of distribution in the body based on its physicochemical properties, such as ionization and lipophilicity, its binding to plasma proteins and tissue sites, its affinity to transporters, and the differences in perfusion of different tissues. However, knowing that the distribution pattern of the drug in the body is typically uneven, it is often useful for the pharmacist to know what dose is required to produce a desired plasma or blood level to achieve the desired effect. The apparent volume of distribution, or Vd, is a key pharmacokinetic parameter that enables that calculation. In essence, the volume of distribution is a proportionality factor that relates the total amount of drug in the body to the plasma or blood level. Different equations can be used to calculate Vd, but one that reflects this proportional relationship is:

$$Vd = Dose/Cp_o$$

where Cp_o is the initial plasma concentration achieved after an intravenous dose.

The volume of distribution is a hypothetical rather than an actual physiological volume, thus the term "apparent" is used. Although Vd doesn't indicate the volume of a specific body compartment, it can be used to rationalize the distribution behavior of the drug, based on its properties mentioned previously and on the approximate distribution of total body water in a patient. Figure 1-4 shows an approximate distribution of total body water, which is divided between intracellular and extracellular body water, the latter of which is further divided into plasma and interstitial body water. (Note that volumes in actual patients can vary.) A drug that is highly protein-bound may exhibit a low volume of distribution, approximating the plasma volume, because of the

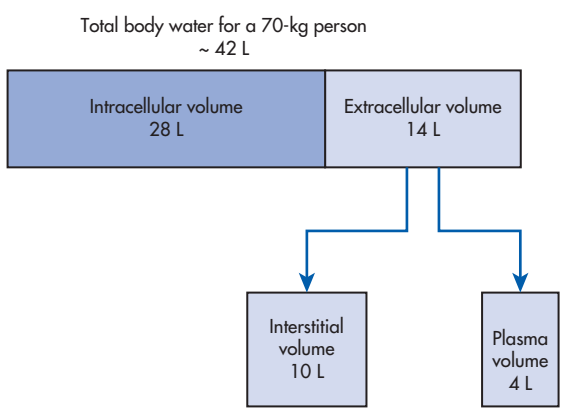

FIGURE 1-4 Approximate body water distribution for an individual with 42 L of total body water.

inability of the protein to pass into the interstitial fluid. On the other hand, a drug that has high interstitial tissue binding will have a relatively low plasma concentration, and therefore the calculated Vd can even exceed the total body water volume. Drugs with low protein and tissue binding and good ability to penetrate cell membranes will have an intermediate Vd closer to total body water, a reflection of their ability to distribute to total body water.

Metabolism

Most drugs are too lipophilic to be excreted unchanged in the urine. Though they will most often undergo glomerular filtration, their lipophilicity, which favored their passage through membranes elsewhere in the body, also favors their passive reabsorption from the filtrate (see "Excretion" section). The primary function of metabolism, of which the liver is the primary location, is to transform these compounds into more hydrophilic, and therefore more excretable metabolites.[11,12,13] The processes by which these metabolic biotransformations occur fall under two main types of enzymatic pathways, *phase 1* and *phase 2*.

Phase 1 reactions, also called *functionalization reactions,* either add or uncover a polar functional group—such as a hydroxyl, amine, or sulfhydryl group—on the parent compound. The most well known and most important enzyme family for phase 1 reactions is the cytochrome P450 (CYP) superfamily of enzymes, which catalyze the oxidation of organic compounds. Other possible reactive pathways in phase 1 reactions include hydrolysis and reduction. With the newly created or exposed polar functional group, the product of these phase 1 reactions may be hydrophilic enough to be rapidly excreted, but in many cases they may not be.

Phase 2 reactions, also called conjugation reactions, involve the covalent conjugation of a polar functional group on the parent compound or on a phase 1 metabolite, with endogenous polar compounds such as glucuronic acid, sulfuric acid, acetic acid, or amino acids. Of these, conjugation with glucuronic acid to form a glucuronide is the most common phase 2 reaction. The resulting conjugate in phase 2 reactions is usually hydrophilic enough to be rapidly excreted.

The products of drug metabolism usually have reduced or no pharmacological activity, but in some cases, the metabolites can have significant pharmacological effects or toxic effects. Pharmaceutical manufacturers may also create pharmacologically inert *prodrugs* that undergo metabolism to the pharmacologically active metabolite. Often, in these cases, the prodrug is more lipophilic and therefore better absorbed than its active metabolite.

Major Metabolic Sites

As mentioned, the liver is the primary metabolic organ. The most important extrahepatic metabolic site is the epithelium of the intestines, described in the section on absorption. Other important metabolic locations include the kidney, lungs, skin, and placenta.

Excretion

The kidneys are the major excretory organ for drugs or their metabolites. Renal excretion involves three major processes: (1) glomerular filtration, (2) secretion, and (3) reabsorption. Most drugs can be readily filtered through the fenestrated capillaries of glomeruli, regardless of their polarity or state of ionization. However, protein-bound drug cannot be filtered because the proteins (e.g., albumin) are too large to pass through the fenestrations. Those compounds that are polar or ionized tend to remain in the filtrate and are subsequently excreted in the urine. However, drugs that are nonpolar and relatively lipophilic can undergo extensive passive reabsorption in the distal tubules and will consequently be less readily excreted in the urine. Since reabsorption by passive diffusion of weak acid and weak base drugs favors the nonionized state, there can be significant variability in passive reabsorption for these drugs, depending on the urinary pH. Additionally, many compounds can be actively secreted into the proximal tubules by various efflux transporters, such as certain organic anion transporters (OAT) and organic cation transporters (OCT). Also, some compounds can be actively reabsorbed by uptake transporters in the proximal tubules.

Other Excretion Sites

Biliary/fecal. Though the kidney is the major excretory organ for drugs, other excretory pathways can be important, including biliary excretion. As discussed in the section on drug absorption, biliary secretion of drugs can be aided by efflux transporters and the process favors larger molecules. As also discussed, once drugs (or their metabolites) are secreted into the

biliary canaliculi and ultimately reach the intestines, some will be eliminated in the feces and some may be reabsorbed back into the body through the intestines via the process of *enterohepatic recycling.*

Others: Saliva, sweat, tears, breath, breast milk. Drugs may also be excreted by other routes including saliva, tears, breath, sweat, and breast milk. Excretion by these routes is mainly by passive diffusion, thus it favors the nonionized forms of weak acid and weak base drugs (see Chapter 6). Though drug excretion by these routes is usually quantitatively insignificant for the patient, they can still be clinically important. For example, saliva can be used to assay some drugs when it is difficult to obtain plasma samples, and for many drugs, breast-feeding may be inadvisable because of the drug's effect on the child.

Clearance—The Primary Measure of Drug Elimination

The primary pharmacokinetic parameter that is used as a measure of drug elimination from the body is *clearance* (CLp), which can be defined as the volume of plasma that is completely cleared of drug per unit time (e.g., mL/min).[14] It describes the relationship between the rate of drug elimination from the plasma and its plasma concentration.

Clearance may also be defined with respect to other concentrations measured, for example, clearance from the blood (CLb) or clearance of unbound drug (CLu). It is also important to note the total body clearance or systemic clearance is a composite of the clearance from each of the drug elimination pathways, including the renal clearance of unchanged drug in the urine (CLren), the clearance by drug metabolism and/or biliary secretion in the liver (CLhep), and the clearance by the other elimination pathways (CLother), including those mentioned previously. The total systemic clearance (CLsystemic) for a drug is a composite of the contributing elimination processes. For drugs that are eliminated predominantly by one organ (e.g., renal excretion or liver metabolism), a reduced capacity of that organ can affect the systemic clearance and would require dosing adjustment. Whereas knowledge of the volume of distribution enables calculation of the drug dose required to reach a certain plasma concentration, knowledge of a drug's clearance allows calculation of the *dose rate* required to maintain a *target steady state plasma concentration* (Cp_{ss}). For example, dose rate (mg/hr) = Cp_{ss} (mg/L) × CL (L/hr). (Note: Steady state concentration is the concentration when the rate of drug administration equals the rate of drug elimination, which occurs when the drug stops accumulating with dosing at regular intervals or with continuous intravenous infusion.)

Elimination Half-life

The elimination half-life of a drug in the plasma is the time required for the plasma concentration to decrease by 50%. So, after one half-life 50% of the drug will be eliminated, 75% will be eliminated after two half-lives, and 97% will be eliminated after five half-lives. The half-life is a derived parameter that is dependent on the drug's clearance and volume of distribution at steady state and can be calculated from these parameters according to the following equation:

$$t_{1/2} = V_{ss} / \mathrm{CL}$$

Knowing the drug's half-life can be useful for estimating appropriate dosing intervals and for estimating the time to reach steady state with multiple dosing, which requires about four to five half-lives. The concept of half-life is further discussed in Chapter 11.

CONCLUSION

This chapter discussed many of the important biopharmaceutical factors that determine a drug's fate after the administration of a drug product to a patient. Understanding these factors, integrated with a thorough knowledge of the principles and mathematics of pharmacokinetics, will enable pharmacist practitioners to competently initiate and modify dosing regimens for their patients. The discipline of pharmacokinetics will be touched on again in Chapter 11 but not fully covered. The reader is referred to the many excellent textbooks on pharmacokinetics. The remainder of this textbook is largely dedicated to elucidating the physicochemical drug properties that are not only important to a drug's fate in the body but are also important for a full understanding of other areas of a pharmacist's knowledge base, including dosage formulations and pharmacodynamics.

KEY POINTS

- Drug targets are generally macromolecules that are located in tissues and fluids throughout the body. Some of these targets can be accessed without drug absorption into the bloodstream. For most drug products, however, the targets are in tissues and cells that are accessed from the bloodstream.
- There are a variety of routes and dosage forms that can be used for drug administration to a patient, depending on the dosage form and route. The drug may have to first be released (liberated) from the dosage form, then cross membranes to enter the systemic circulation.
- Biopharmaceuticals relate the physicochemical properties of a drug to its disposition, or fate, in the body, to its pharmacological effect.
- The fate of the drug after it is administered to the patient is embodied in the acronym LADME, which stands for liberation (release of the drug from its dosage form), absorption (into the bloodstream), distribution (to various parts of the body), metabolism (by enzymes), and excretion (through the kidneys or other routes).
- Important physicochemical properties related to the drug's fate in the body, and discussed in this textbook, include solid state properties, ionization, solubility and dissolution, partition coefficient, mass transport and membrane passage, complexation, and protein binding.
- Drug transporters can play significant roles in drug disposition.
- Absorption after a drug is administered orally, mostly occurs through intestinal epithelial cells (enterocytes) by passive diffusion and can be under the influence of p-glycoprotein, which moves some drugs back into the intestinal lumen.
- Some drugs can be metabolized within enterocytes.
- After drugs leave the enterocytes, they enter the portal system, which transports them to the sinusoids that enable drug access to the hepatocytes where they can be absorbed, again mostly by passive diffusion, then metabolized.
- Drugs (and metabolites) leave the hepatocytes, and depending on where they leave the hepatocyte, they will enter the systemic circulation or the bile.
- Once in the bloodstream, the drug will distribute in the body, usually unevenly, based on its physicochemical properties, affinity to transporters, and on its binding to different components, such as plasma proteins. The volume of distribution is an important pharmacokinetic parameter that reflects a drug's distribution.
- Drug metabolism occurs at different sites, with the liver being the primary site. The general role of metabolism is to increase the hydrophilicity of a drug, making it more easily excreted in the urine.
- The kidney is the major excretory pathway, but other pathways, including the biliary pathway, can be important.
- Clearance is a primary pharmacokinetic parameter used as a measure of drug elimination.

CLINICAL QUESTIONS

1. The ingestion of grapefruit juice and grapefruits are known to increase the plasma levels of many drugs taken orally. The increase is due to the effects of certain furanocoumarins (present in grapefruit) on metabolizing enzymes in enterocytes and hepatocytes, and possibly on p-glycoprotein. Explain the likely effects of grapefruit on these proteins and how these effects can lead to increased plasma levels.
2. It has been demonstrated in many critically ill patients that plasma albumin concentrations can decrease. Explain why this may require dosage reductions for some highly albumin-bound drugs in critically ill patients.