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Pharmacology

(Fifth Edition)

药理学

（第5版）

Michelle A. Clark
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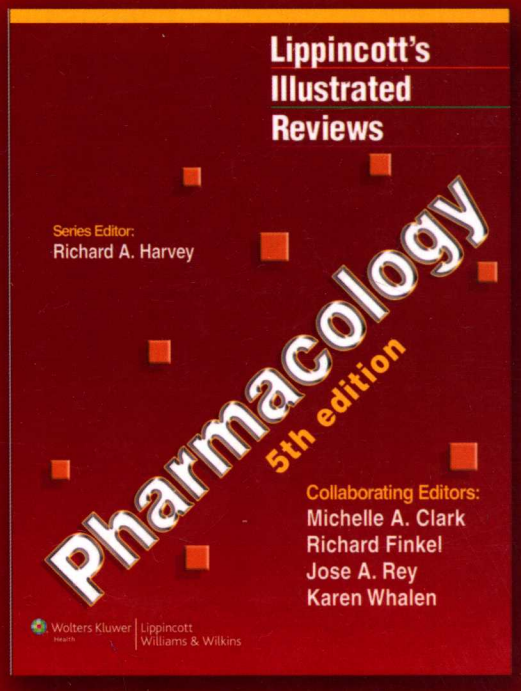

北京大学医学出版社

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UNIT I
Principles of Drug Therapy

1 Pharmacokinetics

I. OVERVIEW

Pharmacokinetics refers to what the body does to a drug, whereas pharmacodynamics (see Chapter 2) describes what the drug does to the body. Once administered through one of several available routes, four pharmacokinetic properties determine the speed of onset of drug action, the intensity of the drug's effect, and the duration of drug action (Figure 1.1):

- **Absorption:** First, drug absorption from the site of administration permits entry of the therapeutic agent (either directly or indirectly) into plasma.
- **Distribution:** Second, the drug may then reversibly leave the bloodstream and distribute into the interstitial and intracellular fluids.
- **Metabolism:** Third, the drug may be biotransformed by metabolism by the liver, or other tissues.
- **Elimination:** Finally, the drug and its metabolites are eliminated from the body in urine, bile, or feces.

Pharmacokinetic parameters allow the clinician to design and optimize treatment regimens, including decisions as to the route of administration for a specific drug, the amount and frequency of each dose, and the duration of treatment.

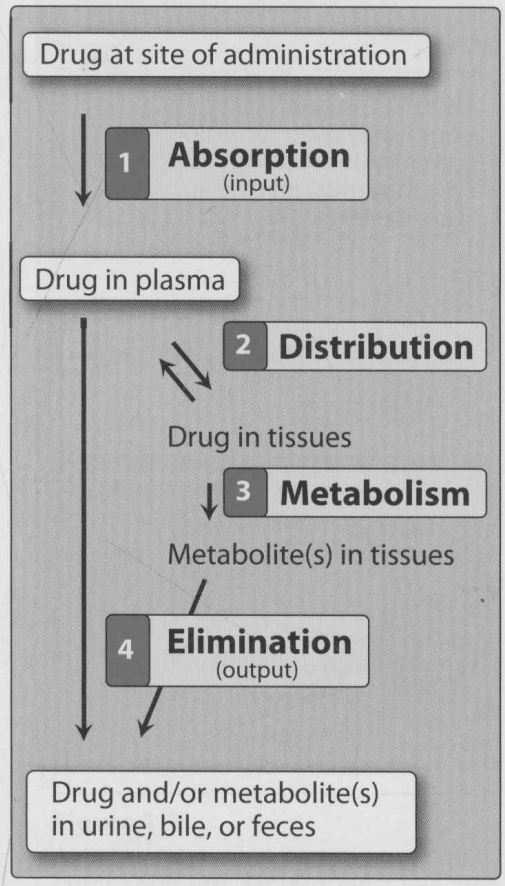


Figure 1.1
Schematic representation of drug absorption, distribution, metabolism, and elimination.

II. ROUTES OF DRUG ADMINISTRATION

The route of administration is determined primarily by the properties of the drug (for example, water or lipid solubility, ionization) and by the therapeutic objectives (for example, the desirability of a rapid onset of action, the need for long-term treatment, or restriction of delivery to a local site). Major routes of drug administration include enteral, parenteral, and topical among others. Figure 1.2 illustrates the subcategories of these routes as well as other methods of drug administration.

A. Enteral

Enteral administration, or administering a drug by mouth, is the safest and most common, convenient, and economical method of drug administration. When the drug is given in the mouth, it may be swallowed, allowing oral delivery, or it may be placed under the tongue (sublingual), facilitating direct absorption into the bloodstream.

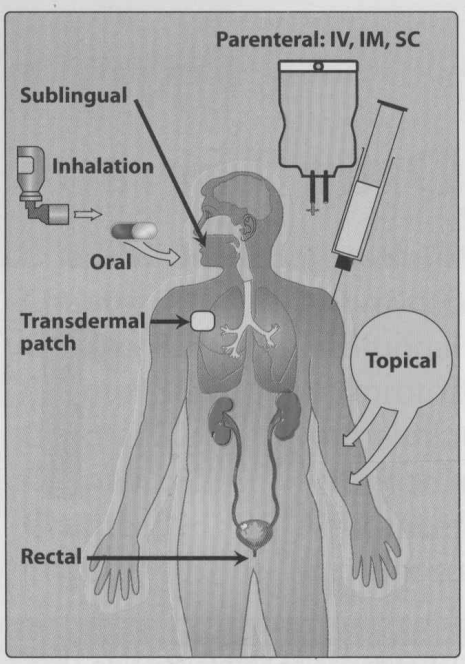


Figure 1.2
Commonly used routes of drug administration. IV = intravenous; IM = intramuscular; SC = subcutaneous.

1. **Oral:** Giving a drug by mouth provides many advantages to the patient. Oral drugs are easily self-administered and, compared to drugs given parenterally, have a low risk of systemic infections that could complicate treatment. Moreover, toxicities and overdose by the oral route may be overcome with antidotes, such as activated charcoal. On the other hand, the pathways involved in oral drug absorption are the most complicated, and the low pH of the stomach may inactivate some drugs. A wide range of oral preparations is available including enteric-coated and extended-release preparations.

   a. **Enteric-coated preparations:** An enteric coating is a chemical envelope that resists the action of the fluids and enzymes in the stomach but dissolves readily in the upper intestine. Such coating is useful for certain groups of drugs (for example, *omeprazole*) that are acid unstable. Enteric coatings protect the drug from stomach acid, delivering them instead to the less acidic intestine, where the coating dissolves and allows the drug to be released. Similarly, drugs that have an irritant effect on the stomach, such as *aspirin*, can be coated with a substance that will dissolve only in the small intestine, thereby protecting the stomach.

   b. **Extended-release preparations:** Extended-release medications have special coatings or ingredients that control how fast the drug is released from the pill into the body. Having a longer duration of action may improve patient compliance, because the medication does not have to be taken as often. Additionally, extended-release dosage forms may maintain concentrations within an acceptable therapeutic range over a long period of time, as opposed to immediate-release dosage forms, which may result in larger peaks and troughs in plasma concentrations. These extended-release formulations are advantageous for drugs with short half-lives. For example, the half-life of *morphine* is 2 to 4 hours in adults. Oral *morphine* must be administered six times in 24 hours to obtain a continuous analgesic effect. However, only two doses are needed when controlled-release tablets are used. Unfortunately, many of the extended release formulations may have been developed to create a marketing advantage over conventional-release products, rather than because of documented clinical advantage.

2. **Sublingual:** Placement under the tongue allows a drug to diffuse into the capillary network and, therefore, to enter the systemic circulation directly. Sublingual administration of an agent has several advantages, including rapid absorption, convenience of administration, low incidence of infection, bypass of the harsh gastrointestinal (GI) environment, and avoidance of first-pass metabolism (the drug is absorbed into the superior vena cava). The buccal route (between cheek and gum) is similar to the sublingual route.

B. Parenteral

The parenteral route introduces drugs directly across the body's barrier defenses into the systemic circulation. Parenteral administration is used for drugs that are poorly absorbed from the GI tract (for example, *heparin*) and for agents that are unstable in the GI tract (for example, *insulin*). Parenteral administration is also used for treatment

of unconscious patients and under circumstances that require a rapid onset of action. In addition, these routes have the highest bioavailability and are not subject to first-pass metabolism or harsh GI environments. Parenteral administration provides the most control over the actual dose of drug delivered to the body. However, these administrations are irreversible and may cause pain, fear, local tissue damage, and infections. The three major parenteral routes are intravascular (intravenous or intra-arterial), intramuscular, and subcutaneous (see Figure 1.2). Each route has advantages and drawbacks.

1. **Intravenous (IV):** IV injection is the most common parenteral route. For drugs that are not absorbed orally, such as the neuromuscular blocker *atracurium*, there is often no other choice. IV delivery permits a rapid effect and a maximum degree of control over the circulating levels of the drug. When injected as a bolus, the full amount of a drug is delivered to the systemic circulation almost immediately. The same dose also may be administered as an IV infusion during a longer time, resulting in a decrease in the peak plasma concentration and an increase in the time the drug is present in the circulation. IV injection is advantageous for administering chemicals that may cause irritation when administered via other routes, because the substance is rapidly diluted by the blood. However, unlike drugs in the GI tract, those that are injected cannot be recalled by strategies, such as by binding to activated charcoal. IV injection may inadvertently introduce bacteria and other infective particles through contamination at the site of injection. It may also precipitate blood constituents, induce hemolysis, or cause other adverse reactions by the too-rapid delivery of high concentrations of a drug to the plasma and tissues. Therefore, patients must be carefully monitored for unfavorable drug reactions, and the rate of infusion must be carefully controlled.

2. **Intramuscular (IM):** Drugs administered IM can be in aqueous solutions, which are absorbed rapidly (Figure 1.3), or in specialized depot preparations, which are absorbed slowly. Depot preparations often consist of a suspension of the drug in a nonaqueous vehicle such as polyethylene glycol. As the vehicle diffuses out of the muscle, the drug precipitates at the site of injection. The drug then dissolves slowly, providing a sustained dose over an extended period of time. Examples of sustained-release drugs are *haloperidol* (see p. 165) and depot *medroxyprogesterone* (see p. 323). These drugs produce extended neuroleptic and contraceptive effects, respectively.

3. **Subcutaneous (SC):** This route of administration, like IM injection, requires absorption via simple diffusion and is somewhat slower than the IV route. SC injection minimizes the risks of hemolysis or thrombosis associated with IV injection and may provide constant, slow, and sustained effects. This route should not be used with drugs that cause tissue irritation, because severe pain and necrosis may occur. [Note: Minute amounts of *epinephrine* are sometimes combined with a drug administered subcutaneously to restrict its area of action. *Epinephrine* acts as a local vasoconstrictor and decreases removal of a drug, such as *lidocaine*, from the site of administration.] Other examples of drugs given via SC administration include solids, such as a single rod containing the contraceptive *etonogestrel* that is implanted for long-term activity (see p. 325), and programmable mechanical pumps that can be implanted to deliver *insulin* in diabetic patients.

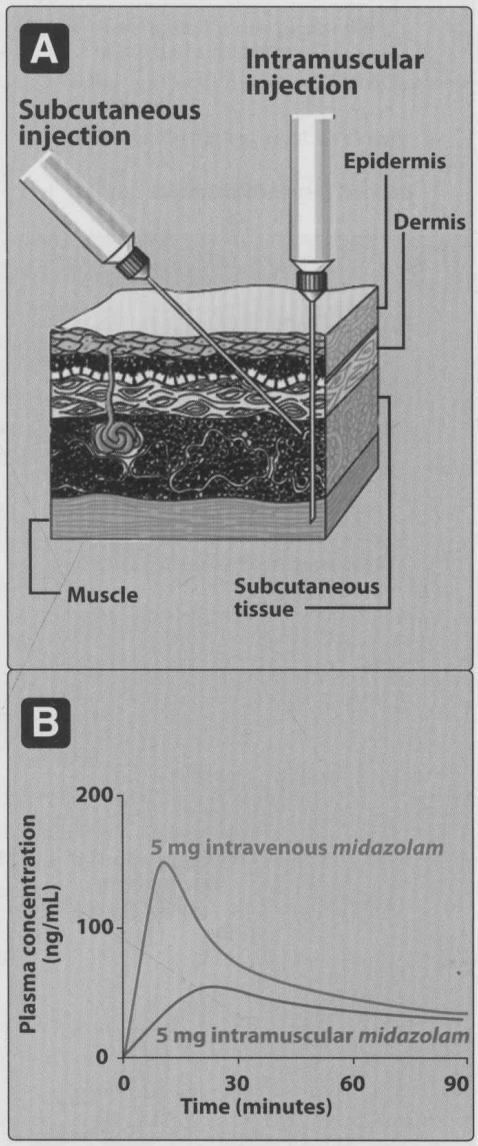


Figure 1.3
A. Schematic representation of subcutaneous and intramuscular injection. B. Plasma concentrations of *midazolam* after intravenous and intramuscular injection.

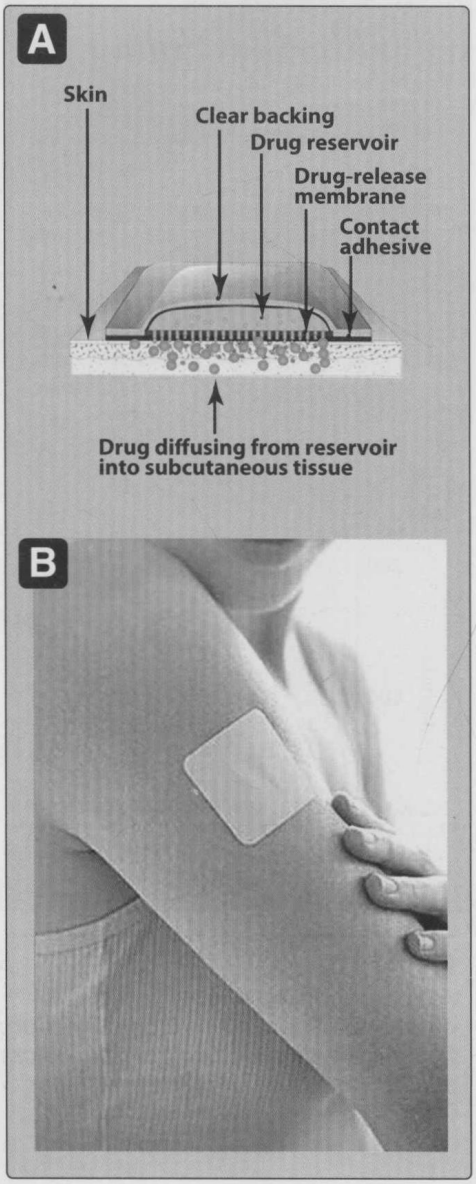


Figure 1.4
A. Schematic representation of a transdermal patch. B. Transdermal nicotine patch applied to arm.

C. Other

1. **Oral inhalation:** Inhalation routes, both oral and nasal (see below), provide rapid delivery of a drug across the large surface area of the mucous membranes of the respiratory tract and pulmonary epithelium, producing an effect almost as rapidly as does IV injection. This route of administration is used for drugs that are gases (for example, some anesthetics) and those that can be dispersed in an aerosol. This route is particularly effective and convenient for patients with respiratory complaints (such as asthma or chronic obstructive pulmonary disease), because the drug is delivered directly to the site of action, thereby minimizing systemic side effects. Examples of drugs administered via this route include bronchodilators, such as *albuterol*, and corticosteroids, such as *fluticasone*.

2. **Nasal inhalation:** This route involves administration of drugs directly into the nose. Agents include nasal decongestants, such as *oxymetazoline*, and anti-inflammatory corticosteroids such as *mometasone furoate*. *Desmopressin* is administered intranasally in the treatment of diabetes insipidus. Salmon *calcitonin*, a peptide hormone used in the treatment of osteoporosis, is also available as a nasal spray.

3. **Intrathecal/intraventricular:** The blood-brain barrier (see p. 10) typically delays or prevents the absorption of drugs into the central nervous system (CNS). When local, rapid effects are needed, it is necessary to introduce drugs directly into the cerebrospinal fluid. For example, intrathecal *amphotericin B* is used in treating cryptococcal meningitis (see p. 430).

4. **Topical:** Topical application is used when a local effect of the drug is desired. For example, *clotrimazole* is applied as a cream directly to the skin in the treatment of dermatophytosis.

5. **Transdermal:** This route of administration achieves systemic effects by application of drugs to the skin, usually via a transdermal patch (Figure 1.4). The rate of absorption can vary markedly, depending on the physical characteristics of the skin at the site of application as well as the lipid solubility of the drug. This route is most often used for the sustained delivery of drugs, such as the antianginal drug *nitroglycerin*, the antiemetic *scopolamine*, and nicotine transdermal patches, which are used to facilitate smoking cessation.

6. **Rectal:** Because 50 percent of the drainage of the rectal region bypasses the portal circulation, the biotransformation of drugs by the liver is minimized with rectal administration. Like the sublingual route of administration, the rectal route has the additional advantage of preventing the destruction of the drug by intestinal enzymes or by low pH in the stomach. The rectal route is also useful if the drug induces vomiting when given orally, if the patient is already vomiting, or if the patient is unconscious. [Note: The rectal route is commonly used to administer antiemetic agents.] On the other hand, rectal absorption is often erratic and incomplete, and many drugs irritate the rectal mucosa. Figure 1.5 summarizes the characteristics of the common routes of administration.

ROUTE OF ADMINISTRATION	ABSORPTION PATTERN	ADVANTAGES	DISADVANTAGES
Oral	• Variable; affected by many factors	• Safest and most common, convenient, and economical route of administration	• Limited absorption of some drugs • Food may affect absorption • Patient compliance is necessary • Drugs may be metabolized before systemic absorption
Intravenous	• Absorption not required	• Can have immediate effects • Ideal if dosed in large volumes • Suitable for irritating substances and complex mixtures • Valuable in emergency situations • Dosage titration permissible • Ideal for high-molecular-weight proteins and peptide drugs	• Unsuitable for oily or poorly absorbed substances • Bolus injection may result in adverse effects • Most substances must be slowly injected • Strict aseptic techniques needed
Subcutaneous	• Depends on drug diluents: Aqueous solution: prompt Depot preparations: slow and sustained	• Suitable for slow-release drugs • Ideal for some poorly soluble suspensions	• Pain or necrosis if drug is irritating • Unsuitable for drugs administered in large volumes
Intramuscular	• Depends on drug diluents: Aqueous solution: prompt Depot preparations: slow and sustained	• Suitable if drug volume is moderate • Suitable for oily vehicles and certain irritating substances • Preferable to intravenous if patient must self administer	• Affects certain lab tests (creatine kinase) • Can be painful • Can cause intramuscular hemorrhage (precluded during anticoagulation therapy)
Transdermal (patch)	• Slow and sustained	• Bypasses the first-pass effect • Convenient and painless • Ideal for drugs that are lipophilic, thus requiring prolonged administration • Ideal for drugs that are quickly eliminated from the body	• Some patients are allergic to patches, which can cause irritation • Drug must be highly lipophilic • May cause delayed delivery of drug to pharmacological site of action • Limited to drugs that can be taken in small daily doses
Rectal	• Erratic and variable	• Partially bypasses first-pass effect • Bypasses destruction by stomach acid • Ideal if drug causes vomiting • Ideal in patients who are vomiting, or comatose	• Drugs may irritate the rectal mucosa • Not a well-accepted route.
Inhalation	• Systemic absorption may occur. This is not always desirable	• Absorption is rapid; can have immediate effects • Ideal for gases • Effective for patients with respiratory problems • Dose can be titrated • Localized effect to target lungs: lower doses used compared to that with oral or parental administration • Fewer systemic side effects	• Most addictive route (drug can enter the brain quickly) • Patient may have difficulty regulating dose • Some patients may have difficulty using inhalers
Sublingual	• Depends on the drug: Few drugs (for example, *nitroglycerin*) have rapid, direct systemic absorption Most drugs erratically or incompletely absorbed	• Bypasses first-pass effect • Bypasses destruction by stomach acid • Drug stability maintained because the pH of saliva relatively neutral • May cause immediate pharmacological effects	• Limited to certain types of drugs • Limited to drugs that can be taken in small doses • May lose part of the drug dose if swallowed

Figure 1.5
The absorption pattern, advantages, and disadvantages of the most common routes of administration.

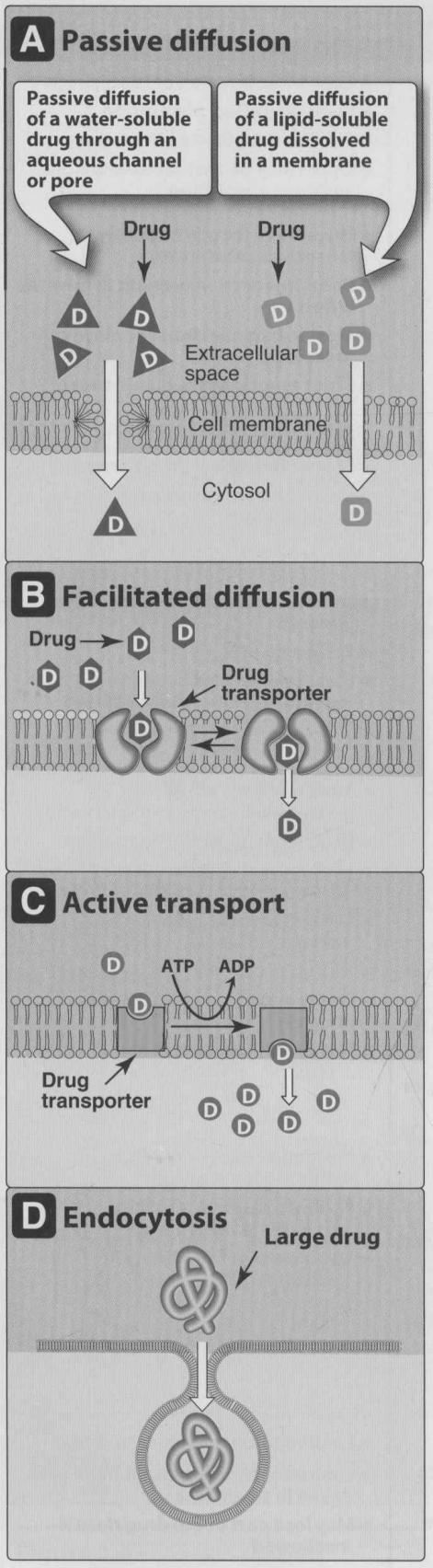


Figure 1.6
Schematic representation of drugs crossing a cell membrane. ATP = adenosine triphosphate; ADP = adenosine diphosphate.

III. ABSORPTION OF DRUGS

Absorption is the transfer of a drug from its site of administration to the bloodstream via one of several mechanisms. The rate and efficiency of absorption depend on both factors in the environment where the drug is absorbed and the drug's chemical characteristics and route of administration (which influence its bioavailability). For IV delivery, absorption is complete. That is, the total dose of drug administered reaches the systemic circulation (100% bioavailability). Drug delivery by other routes may result in only partial absorption and, thus, lower bioavailability.

A. Mechanisms of absorption of drugs from the GI tract

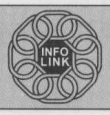
Depending on their chemical properties, drugs may be absorbed from the GI tract by passive diffusion, facilitated diffusion, active transport, or endocytosis.

1. **Passive diffusion:** The driving force for passive absorption of a drug is the concentration gradient across a membrane separating two body compartments. In other words, the drug moves from a region of high concentration to one of lower concentration. Passive diffusion does not involve a carrier, is not saturable, and shows a low structural specificity. The vast majority of drugs gain access to the body by this mechanism. Water-soluble drugs penetrate the cell membrane through aqueous channels or pores, whereas lipid-soluble drugs readily move across most biologic membranes due to their solubility in the membrane lipid bilayers (Figure 1.6A).

2. **Facilitated diffusion:** Other agents can enter the cell through specialized transmembrane carrier proteins that facilitate the passage of large molecules. These carrier proteins undergo conformational changes, allowing the passage of drugs or endogenous molecules into the interior of cells and moving them from an area of high concentration to an area of low concentration. This process is known as facilitated diffusion. It does not require energy, can be saturated, and may be inhibited by compounds that compete for the carrier (Figure 1.6B).

3. **Active transport:** This mode of drug entry also involves specific carrier proteins that span the membrane. A few drugs that closely resemble the structure of naturally occurring metabolites are actively transported across cell membranes using these specific carrier proteins. Energy-dependent active transport is driven by the hydrolysis of adenosine triphosphate (Figure 1.6C). It is capable of moving drugs against a concentration gradient, from a region of low drug concentration to one of higher drug concentration. The process shows saturation kinetics for the carrier, much in the same way that an enzyme-catalyzed reaction shows a maximal velocity at high substrate levels where all the active sites are filled with substrate.[1] Active transport systems are selective and may be competitively inhibited by other cotransported substances.

4. **Endocytosis and exocytosis:** These types of drug delivery systems transport drugs of exceptionally large size across the cell mem-



[1]See Chapter 5 in ***Lippincott's Illustrated Reviews: Biochemistry*** for a discussion of enzyme kinetics.

brane. Endocytosis involves engulfment of a drug molecule by the cell membrane and transport into the cell by pinching off the drug-filled vesicle (Figure 1.6D). Exocytosis is the reverse of endocytosis and is used by cells to secrete many substances by a similar vesicle formation process. Vitamin B_{12} is transported across the gut wall by endocytosis, whereas certain neurotransmitters (for example, norepinephrine) are stored in intracellular membrane-bound vesicles in the nerve terminal and are released by exocytosis.

B. Factors influencing absorption

1. **Effect of pH on drug absorption:** Most drugs are either weak acids or weak bases. Acidic drugs (HA) release a proton (H^+), causing a charged anion (A^-) to form:[2]

$$HA \rightleftarrows H^+ + A^-$$

Weak bases (BH^+) can also release an H^+. However, the protonated form of basic drugs is usually charged, and loss of a proton produces the uncharged base (B):

$$BH^+ \rightleftarrows B + H^+$$

A drug passes through membranes more readily if it is uncharged (Figure 1.7). Thus, for a weak acid, the uncharged, protonated HA can permeate through membranes, and A^- cannot. For a weak base, the uncharged form, B, penetrates through the cell membrane, but BH^+, the protonated form, does not. Therefore, the effective concentration of the permeable form of each drug at its absorption site is determined by the relative concentrations of the charged and uncharged forms. The ratio between the two forms is, in turn, determined by the pH at the site of absorption and by the strength of the weak acid or base, which is represented by the ionization constant, pK_a (Figure 1.8). [Note: The pK_a is a measure of the strength of the interaction of a compound with a proton. The lower the pK_a of a drug, the more acidic it is. Conversely, the higher the pK_a, the more basic is the drug.] Distribution equilibrium is achieved when the permeable form of a

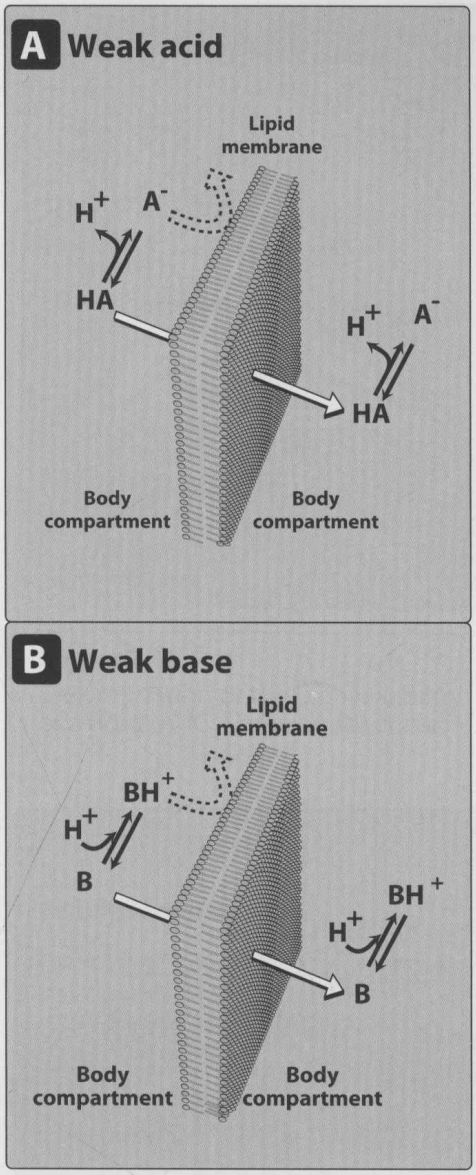


Figure 1.7
A. Diffusion of the non-ionized form of a weak acid through a lipid membrane. B. Diffusion of the non-ionized form of a weak base through a lipid membrane.

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[2]See Chapter 1 in ***Lippincott's Illustrated Reviews: Biochemistry*** for a discussion of acid-base chemistry.

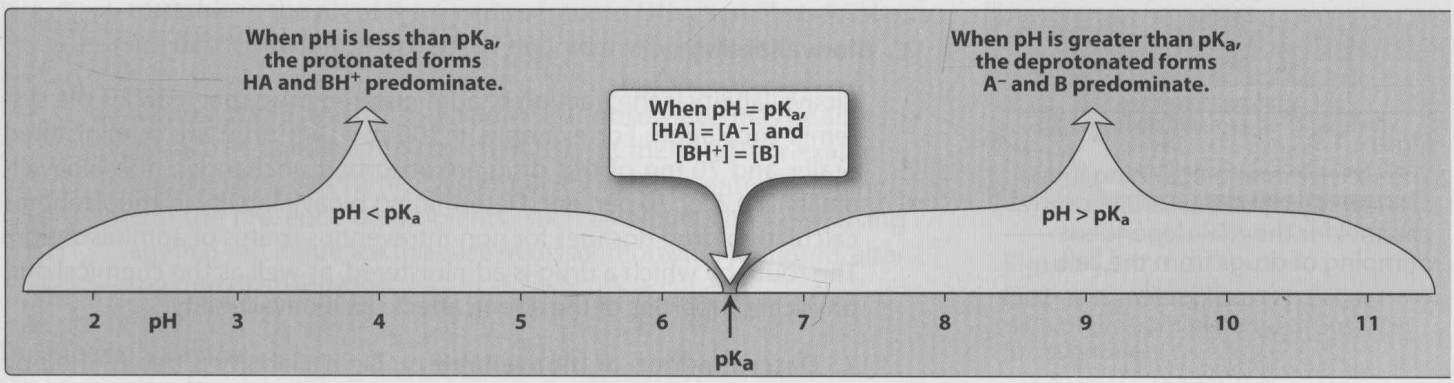

Figure 1.8
The distribution of a drug between its ionized and non-ionized forms depends on the ambient pH and pK_a of the drug. For illustrative purposes, the drug has been assigned a pK_a of 6.5.

drug achieves an equal concentration in all body water spaces. [Note: Highly lipid-soluble drugs rapidly cross membranes and often enter tissues at a rate determined by blood flow.]

2. **Blood flow to the absorption site:** Because blood flow to the intestine is much greater than the flow to the stomach, absorption from the intestine is favored over that from the stomach. [Note: Shock severely reduces blood flow to cutaneous tissues, thereby minimizing the absorption from SC administration.]

3. **Total surface area available for absorption:** With a surface rich in brush borders containing microvilli, the intestine has a surface area about 1000-fold that of the stomach, making absorption of the drug across the intestine more efficient.

4. **Contact time at the absorption surface:** If a drug moves through the GI tract very quickly, as can happen with severe diarrhea, it is not well absorbed. Conversely, anything that delays the transport of the drug from the stomach to the intestine delays the rate of absorption of the drug. [Note: Parasympathetic input increases the rate of gastric emptying, whereas sympathetic input (prompted, for example, by exercise or stressful emotions) as well as anticholinergics (for example, *dicyclomine*), delays gastric emptying. Also, the presence of food in the stomach both dilutes the drug and slows gastric emptying. Therefore, a drug taken with a meal is generally absorbed more slowly.]

5. **Expression of P-glycoprotein:** P-glycoprotein is a multidrug transmembrane transporter protein responsible for transporting various molecules, including drugs, across cell membranes (Figure 1.9). It is expressed throughout the body, and its functions include:
   - In the liver: transporting drugs into bile for elimination
   - In kidneys: pumping drugs into urine for excretion
   - In the placenta: transporting drugs back into maternal blood, thereby reducing fetal exposure to drugs
   - In the intestines: transporting drugs into the intestinal lumen and reducing drug absorption into the blood
   - In the brain capillaries: pumping drugs back into blood, limiting drug access to the brain

   Thus, in areas of high expression, P-glycoprotein reduces drug absorption. In addition to transporting many drugs out of cells, it is also associated with multidrug resistance (see p. 485).

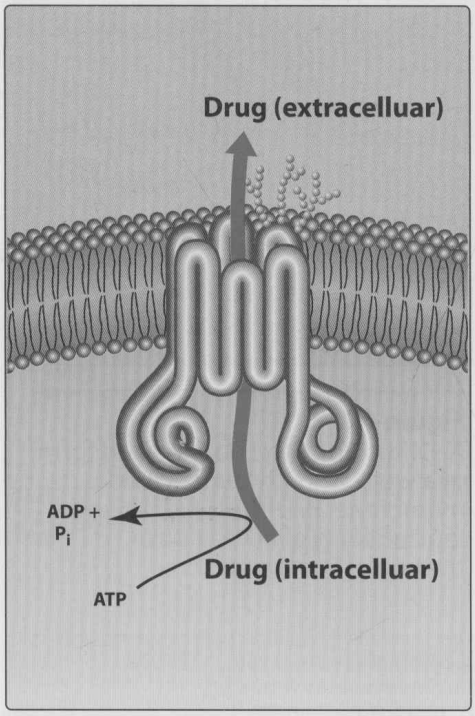

Figure 1.9
The six membrane-spanning loops of the P-glycoprotein form a central channel for the ATP-dependent pumping of drugs from the cell.

C. Bioavailability

Bioavailability is the fraction of administered drug that reaches the systemic circulation. For example, if 100 mg of a drug are administered orally, and 70 mg of this drug are absorbed unchanged, the bioavailability is 0.7, or 70 percent. Determining bioavailability is important for calculating drug dosages for non-intravenous routes of administration. The route by which a drug is administered, as well as the chemical and physical properties of the agent, affects its bioavailability.

1. **Determination of bioavailability:** Bioavailability is determined by comparing plasma levels of a drug after a particular route of administration (for example, oral administration) with plasma drug levels

achieved by IV injection, in which the total agent rapidly enters the circulation. When the drug is given orally, only part of the administered dose appears in the plasma. By plotting plasma concentrations of the drug versus time, the area under the curve (AUC) can be measured. This curve reflects the extent of absorption of the drug. [Note: By definition, this is 100 percent for drugs delivered intravenously.] Bioavailability of a drug administered orally is the ratio of the area calculated for oral administration compared with the area calculated for IV injection if doses are equivalent (Figure 1.10).

2. **Factors that influence bioavailability:** In contrast to IV administration, which confers 100% bioavailability, oral administration of a drug often involves first-pass metabolism. This biotransformation, in addition to the drug's chemical and physical characteristics, determines the amount of the agent that reaches the circulation and at what rate.

   a. **First-pass hepatic metabolism:** When a drug is absorbed across the GI tract, it first enters the portal circulation before entering the systemic circulation (Figure 1.11). If the drug is rapidly metabolized in the liver or gut wall during this initial passage, the amount of unchanged drug that gains access to the systemic circulation is decreased. [Note: First-pass metabolism by the intestine or liver limits the efficacy of many drugs when taken orally. For example, more than 90 percent of *nitroglycerin* is cleared during a single passage through the liver, which is the primary reason why this agent is administered via the sublingual route]. Drugs that exhibit high first-pass metabolism should be given in sufficient quantities to ensure that enough of the active drug reaches the target concentration.

   b. **Solubility of the drug:** Very hydrophilic drugs are poorly absorbed because of their inability to cross the lipid-rich cell membranes. Paradoxically, drugs that are extremely hydrophobic are also poorly absorbed, because they are totally insoluble in aqueous body fluids and, therefore, cannot gain access to the surface of cells. For a drug to be readily absorbed, it must be largely hydrophobic, yet have some solubility in aqueous solutions. This is one reason why many drugs are either weak acids or weak bases.

   c. **Chemical instability:** Some drugs, such as *penicillin G*, are unstable in the pH of the gastric contents. Others, such as *insulin*, are destroyed in the GI tract by degradative enzymes.

   d. **Nature of the drug formulation:** Drug absorption may be altered by factors unrelated to the chemistry of the drug. For example, particle size, salt form, crystal polymorphism, enteric coatings, and the presence of excipients (such as binders and dispersing agents) can influence the ease of dissolution and, therefore, alter the rate of absorption.

D. **Bioequivalence**:

Two related drug preparations are bioequivalent if they show comparable bioavailability and similar times to achieve peak blood concentrations.

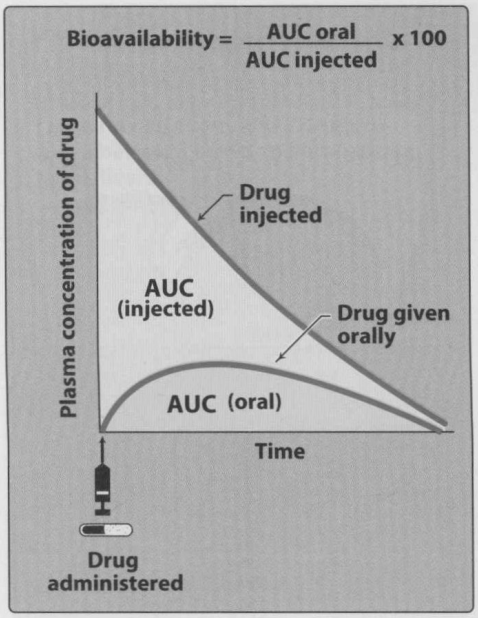

Figure 1.10
Determination of the bioavailability of a drug. AUC = area under curve.

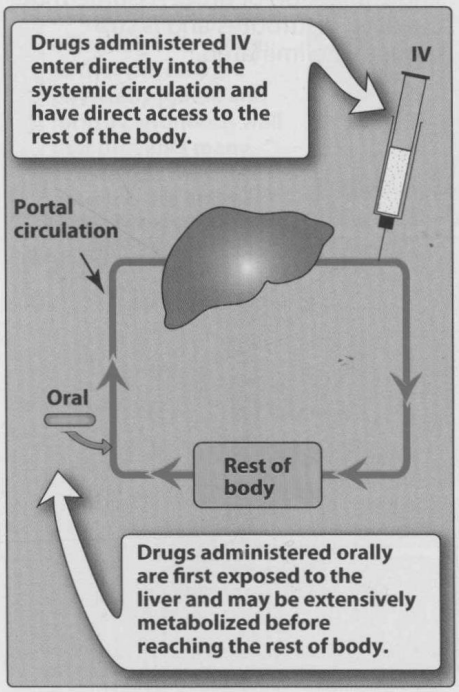

Figure 1.11
First-pass metabolism can occur with orally administered drugs. IV = intravenous.