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UNIT I
Principles of Drug Therapy

Pharmacokinetics

Venkata Yellepeddi

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. Four pharmacokinetic properties determine the onset, intensity, and duration of drug action ([Figure 1.1](#)):

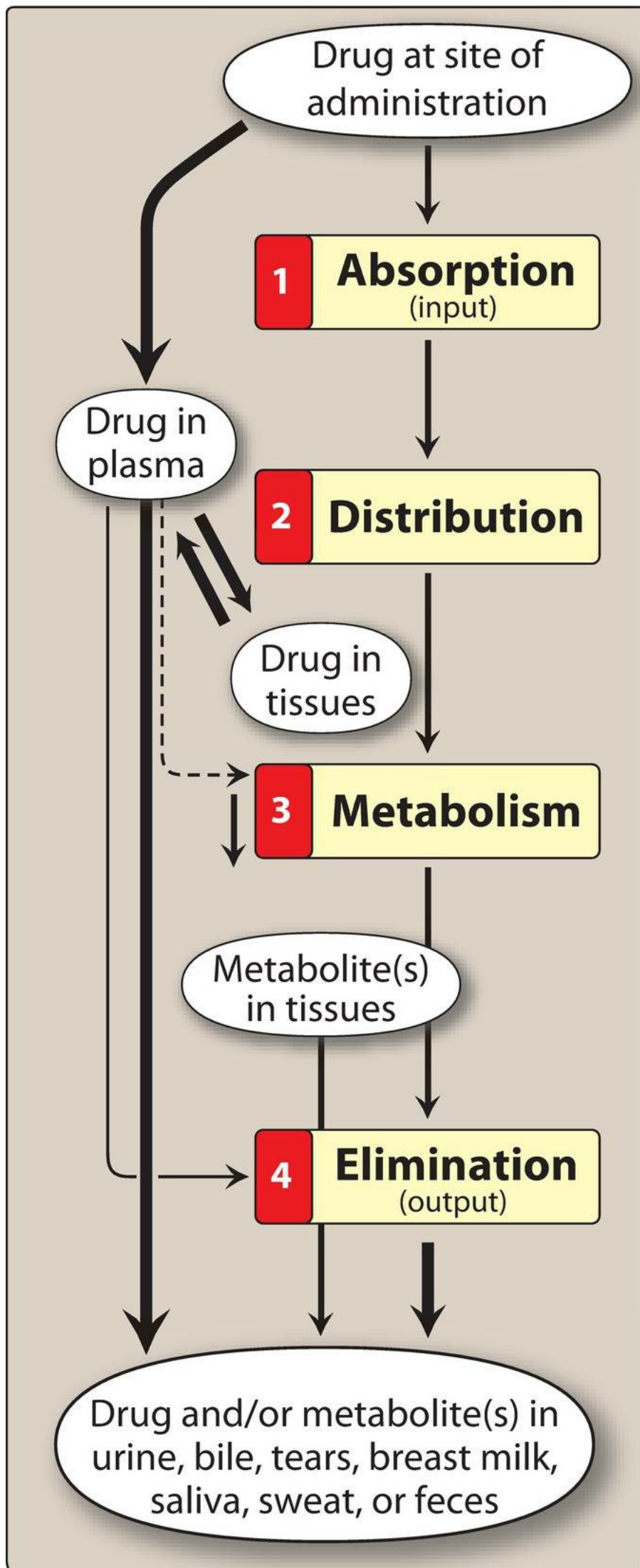


Figure 1.1 Schematic representation of drug absorption, distribution, metabolism, and elimination.

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

Using knowledge of pharmacokinetic parameters, clinicians can design optimal drug regimens, including the route of administration, dose, frequency, and duration of treatment.

II. Routes of Drug Administration

The route of administration is determined by properties of the drug (for example, water or lipid solubility, ionization) and by the therapeutic objectives (for example, the need for a rapid onset, 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).

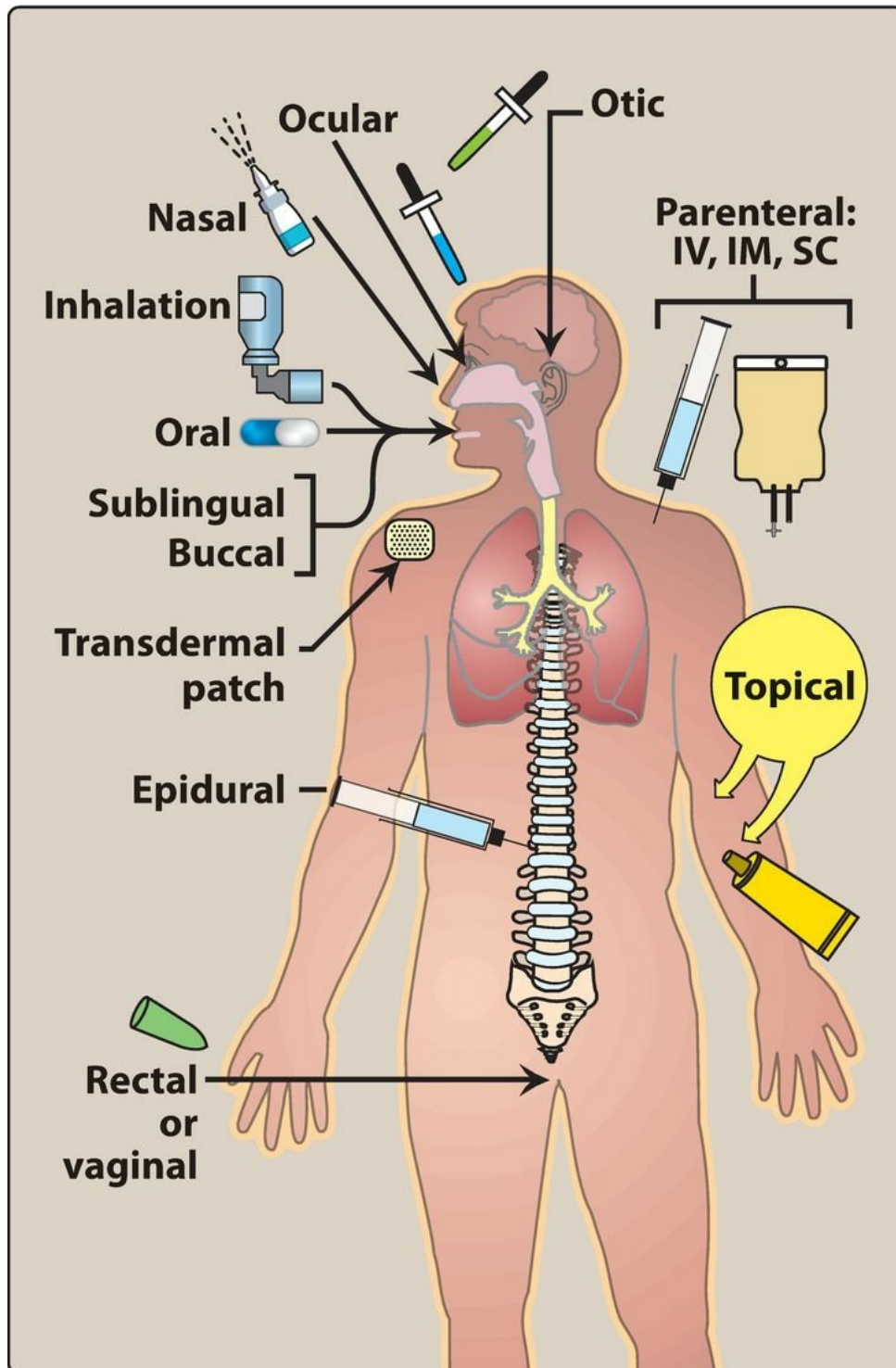


Figure 1.2 Commonly used routes of drug administration. IV = intravenous; IM = intramuscular; SC = subcutaneous.

A. Enteral

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

1. Oral

Oral administration provides many advantages. Oral drugs are easily self-administered, and toxicities and/or overdose of oral drugs may be overcome with antidotes, such as activated charcoal. However, the pathways involved in oral drug absorption are the most complicated, and the low gastric pH inactivates 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 protects the drug from stomach acid, delivering it instead to the less acidic intestine, where the coating dissolves and releases the drug. Enteric coating is useful for certain drugs (for example, *omeprazole*) that are acid labile, and for drugs that are irritating to the stomach, such as *aspirin*.

b. Extended-release preparations

Extended-release (abbreviated ER, XR, XL, SR, etc.) medications have special coatings or ingredients that control drug release, thereby allowing for slower absorption and prolonged duration of action. ER formulations can be dosed less frequently and may improve patient compliance. In addition, ER formulations may maintain concentrations within the therapeutic range over a longer duration, as opposed to immediate-release dosage forms, which may result in larger peaks and troughs in plasma concentration. ER formulations are advantageous for drugs with short half-lives. For example, the half-life of oral *morphine* is 2 to 4 hours, and it must be administered six times daily to provide continuous pain relief. However, only two doses are needed when extended-release tablets are used.

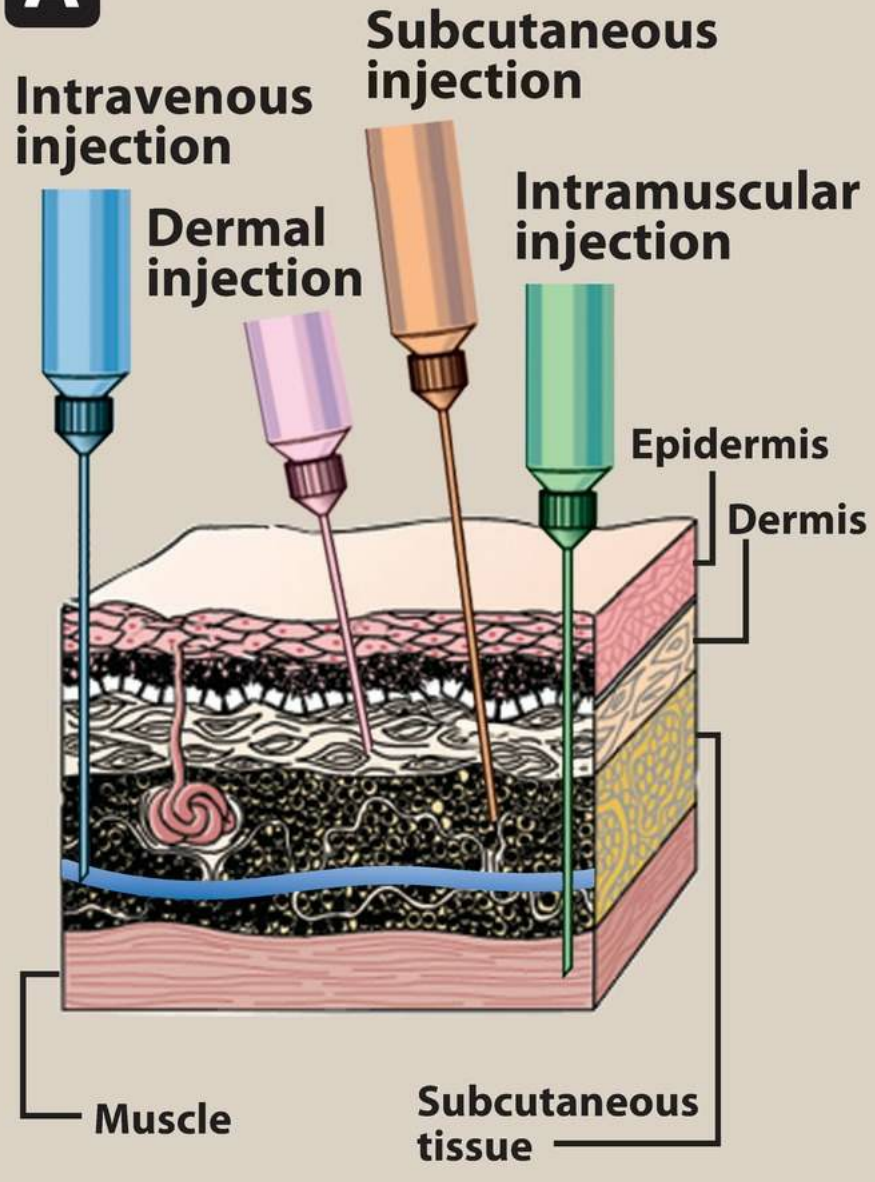
2. Sublingual/buccal

The sublingual route involves placement of drug under the tongue. The buccal route involves placement of drug between the cheek and gum. Both the sublingual and buccal routes of absorption have several advantages, including ease of administration, rapid absorption, bypass of the harsh gastrointestinal (GI) environment, and avoidance of first-pass metabolism (see discussion of first-pass metabolism below).

B. Parenteral

The parenteral route introduces drugs directly into the systemic circulation. Parenteral administration is used for drugs that are poorly absorbed from the GI tract (for example, *heparin*) or unstable in the GI tract (for example, *insulin*). Parenteral administration is also used for patients unable to take oral medications (unconscious patients) and in circumstances that require a rapid onset of action. Parenteral administration provides the most control over the dose of drug delivered to the body. However, this route of administration is irreversible and may cause pain, fear, local tissue damage, and infections. The four major parenteral routes are intravascular (intravenous or intra-arterial), intramuscular, subcutaneous, and intradermal ([Figure 1.3](#)).

A



B

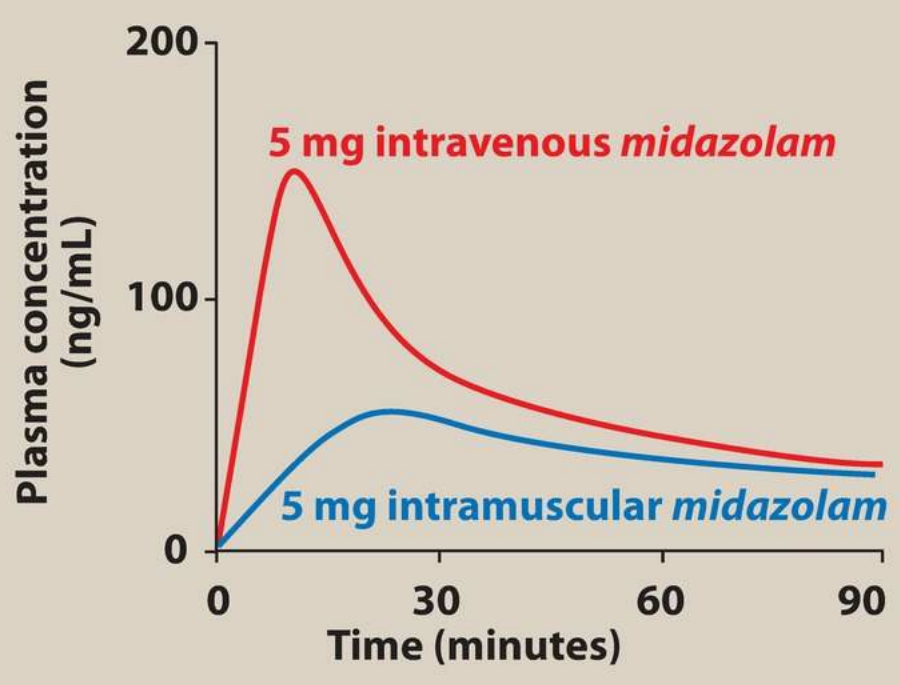


Figure 1.3 A. Schematic representation of subcutaneous and intramuscular injection. **B.** Plasma concentrations of *midazolam* after intravenous and intramuscular injection.

1. Intravenous (IV)

IV injection is the most common parenteral route. It is useful for drugs that are not absorbed orally, such as the neuromuscular blocker *rocuronium*. IV delivery permits a rapid effect and a maximum degree of control over the amount of drug delivered. When injected as a bolus, the full amount of drug is delivered to the systemic circulation almost immediately. If administered as an IV infusion, the drug is infused over a longer period, resulting in lower peak plasma concentrations and an increased duration of circulating drug.

2. Intramuscular (IM)

Drugs administered IM can be in aqueous solutions, which are absorbed rapidly, or in specialized depot preparations, which are absorbed slowly. Depot preparations often consist of a suspension of drug in a nonaqueous vehicle, such as polyethylene glycol. As the vehicle diffuses out of the muscle, drug precipitates at the site of injection. The drug then dissolves slowly, providing a sustained dose over an extended interval.

3. Subcutaneous (SC)

Like IM injection, SC injection provides absorption via simple diffusion and is 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.

4. Intradermal (ID)

The intradermal (ID) route involves injection into the dermis, the more vascular layer of skin under the epidermis. Agents for diagnostic determination and desensitization are usually administered by this route.

C. Other

1. Oral inhalation and nasal preparations

Both the oral inhalation and nasal routes of administration provide rapid delivery of drug across the large surface area of mucous membranes of the respiratory tract and pulmonary epithelium. Drug effects are almost as rapid as are those with IV bolus. Drugs that are gases (for example, some anesthetics) and those that can be dispersed in an aerosol are administered via inhalation. This route is effective and convenient for patients with respiratory disorders such as asthma or chronic obstructive pulmonary disease, because drug is delivered directly to the site of action, thereby minimizing systemic side effects. The nasal route involves topical administration of drugs directly into the nose, and it is often used for patients with allergic rhinitis.

2. Intrathecal/intraventricular

The blood–brain barrier 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.

3. Topical

Topical application is used when a local effect of the drug is desired.

4. 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.

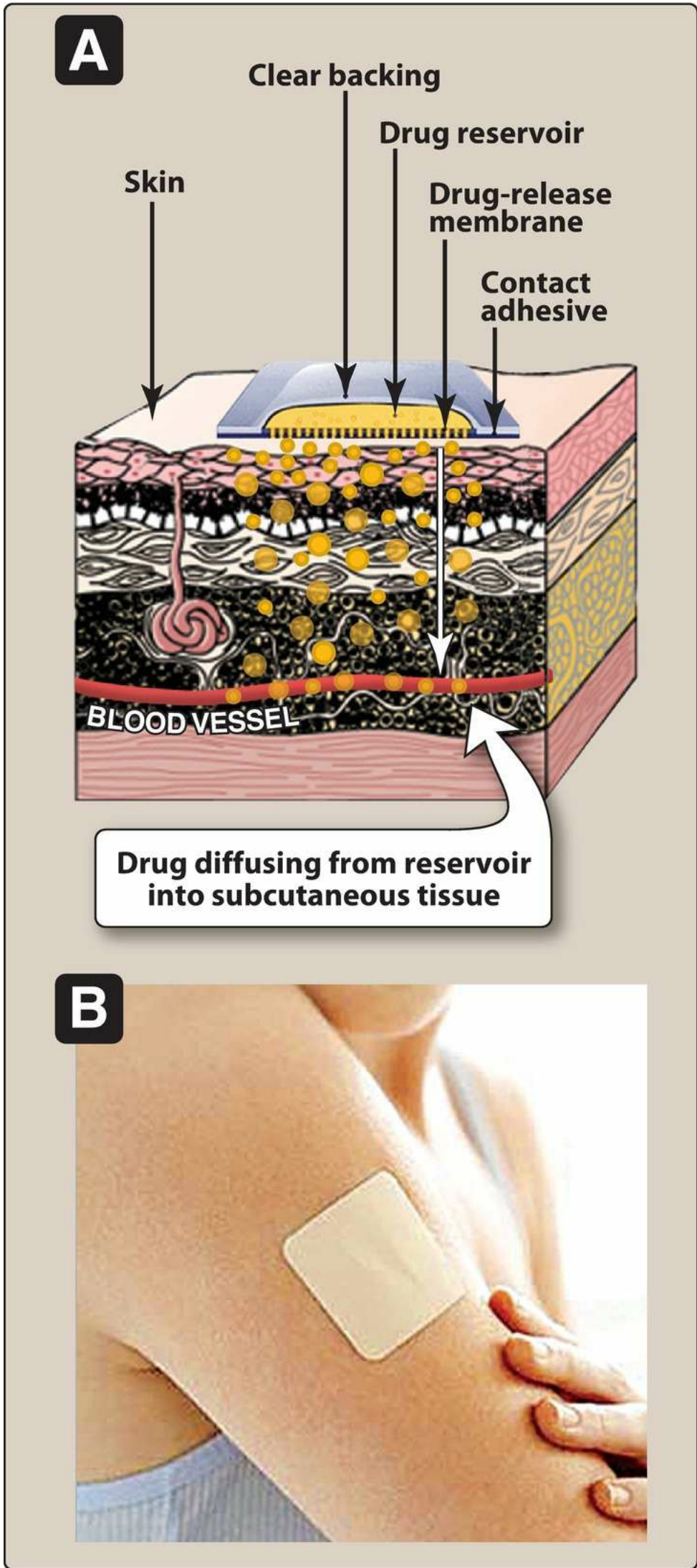


Figure 1.4 **A.** Schematic representation of a transdermal patch. **B.** Transdermal nicotine patch applied to the arm.

5. Rectal

Because 50% of the drainage of the rectal region bypasses the portal circulation, the biotransformation of drugs by the liver is minimized with rectal administration. The rectal route has the additional advantage of preventing destruction of the drug in the GI environment. This route is also useful if the drug induces vomiting when given orally, if the patient is already vomiting, or if the patient is unconscious. Rectal absorption is often erratic and incomplete, and many drugs irritate the rectal mucosa. Figure 1.5 summarizes characteristics of the common routes of administration, along with example drugs.

ROUTE OF ADMINISTRATION	ABSORPTION PATTERN	ADVANTAGES	DISADVANTAGES	EXAMPLES
Oral	<ul style="list-style-type: none"> Variable; affected by many factors 	<ul style="list-style-type: none"> Safest and most common, convenient, and economical route of administration 	<ul style="list-style-type: none"> Limited absorption of some drugs Food may affect absorption Patient compliance is necessary Drugs may be metabolized before systemic absorption 	<ul style="list-style-type: none"> Acetaminophen tablets Amoxicillin suspension
Sublingual	<ul style="list-style-type: none"> Depends on the drug: Few drugs (for example, nitroglycerin) have rapid, direct systemic absorption Most drugs erratically or incompletely absorbed 	<ul style="list-style-type: none"> Bypasses first-pass effect Bypasses destruction by stomach acid Drug stability maintained because the pH of saliva relatively neutral May cause immediate pharmacological effects 	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> Nitroglycerin Buprenorphine
Intravenous	<ul style="list-style-type: none"> Absorption not required 	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> Unsuitable for oily substances Bolus injection may result in adverse effects Most substances must be slowly injected Strict aseptic techniques needed 	<ul style="list-style-type: none"> Vancomycin Heparin
Intramuscular	<ul style="list-style-type: none"> Depends on drug diluents: Aqueous solution: prompt Depot preparations: slow and sustained 	<ul style="list-style-type: none"> Suitable if drug volume is moderate Suitable for oily vehicles and certain irritating substances Preferable to intravenous if patient must self-administer 	<ul style="list-style-type: none"> Affects certain lab tests (creatinase) Can be painful Can cause intramuscular hemorrhage (precluded during anticoagulation therapy) 	<ul style="list-style-type: none"> Haloperidol Depot medroxy-progesterone
Subcutaneous	<ul style="list-style-type: none"> Depends on drug diluents: Aqueous solution: prompt Depot preparations: slow and sustained 	<ul style="list-style-type: none"> Suitable for slow-release drugs Ideal for some poorly soluble suspensions 	<ul style="list-style-type: none"> Pain or necrosis if drug is irritating Unsuitable for drugs administered in large volumes 	<ul style="list-style-type: none"> Epinephrine Insulin Heparin
Inhalation	<ul style="list-style-type: none"> Systemic absorption may occur; this is not always desirable 	<ul style="list-style-type: none"> 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 parenteral administration Fewer systemic side effects 	<ul style="list-style-type: none"> Most addictive route (drug can enter the brain quickly) Patient may have difficulty regulating dose Some patients may have difficulty using inhalers 	<ul style="list-style-type: none"> Albuterol Fluticasone
Topical	<ul style="list-style-type: none"> Variable; affected by skin condition, area of skin, and other factors 	<ul style="list-style-type: none"> Suitable when local effect of drug is desired May be used for skin, eye, intravaginal, and intranasal products Minimizes systemic absorption Easy for patient 	<ul style="list-style-type: none"> Some systemic absorption can occur Unsuitable for drugs with high molecular weight or poor lipid solubility 	<ul style="list-style-type: none"> Clotrimazole cream Hydrocortisone cream Timolol eye drops
Transdermal (patch)	<ul style="list-style-type: none"> Slow and sustained 	<ul style="list-style-type: none"> Bypasses the first-pass effect Convenient and painless Ideal for drugs that are lipophilic and have poor oral bioavailability Ideal for drugs that are quickly eliminated from the body 	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> Nitroglycerin Nicotine Scopolamine
Rectal	<ul style="list-style-type: none"> Erratic and variable 	<ul style="list-style-type: none"> Partially bypasses first-pass effect Bypasses destruction by stomach acid Ideal if drug causes vomiting Ideal in patients who are vomiting, or comatose 	<ul style="list-style-type: none"> Drugs may irritate the rectal mucosa Not a well-accepted route 	<ul style="list-style-type: none"> Bisacodyl Promethazine

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

III. Absorption of Drugs

Absorption is the transfer of a drug from the site of administration to the bloodstream. The rate and extent of absorption depend on the environment where the drug is absorbed, chemical characteristics of the drug, and the route of administration (which influences bioavailability). Routes of administration other than intravenous may result in partial absorption and lower bioavailability.

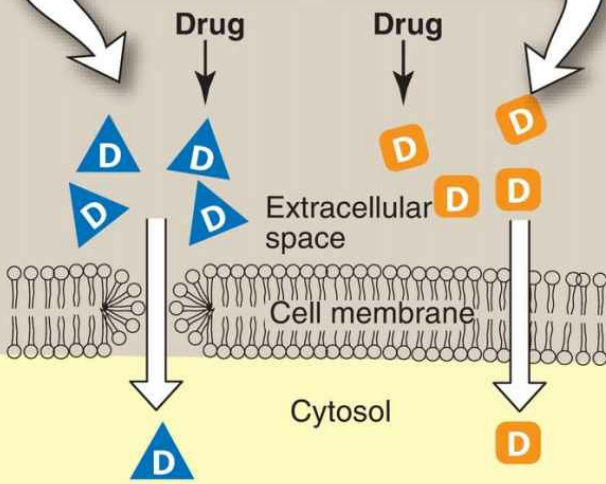
A. Mechanisms of absorption of drugs from the GI tract

Depending on their chemical properties, drugs may be absorbed from the GI tract by passive diffusion, facilitated diffusion, active transport, or endocytosis ([Figure 1.6](#)).

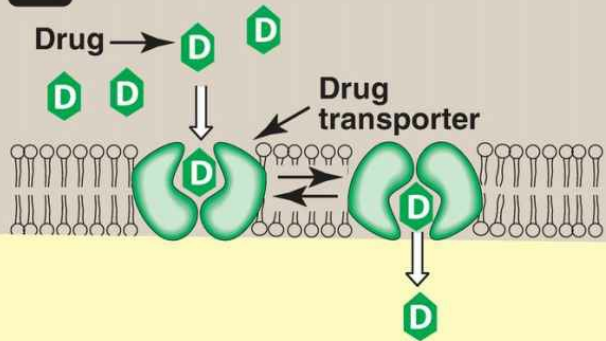
1 Passive diffusion

Passive diffusion of a water-soluble drug through an aqueous channel or pore

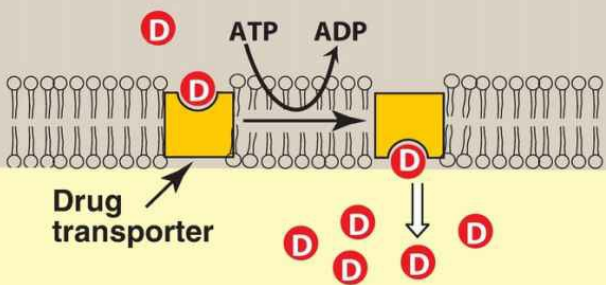
Passive diffusion of a lipid-soluble drug dissolved in a membrane



2 Facilitated diffusion



3 Active transport



4 Endocytosis

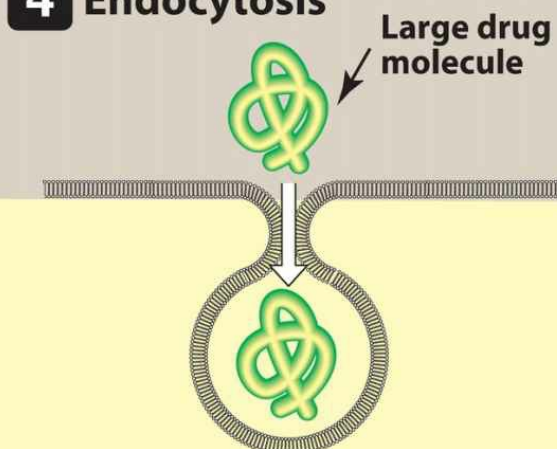


Figure 1.6 Schematic representation of drugs crossing a cell membrane. ATP = adenosine triphosphate; ADP = adenosine diphosphate.

1. Passive diffusion

The driving force for passive diffusion of a drug is the concentration gradient across a membrane separating two body compartments. In other words, the drug moves from an area of high concentration to one of lower concentration. Passive diffusion does not involve a carrier, is not saturable, and shows low structural specificity. The vast majority of drugs are absorbed 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 solubility in the membrane lipid bilayers.

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. 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.

3. Active transport

This mode of drug entry also involves specific carrier proteins that span the membrane. However, active transport is energy dependent, driven by the hydrolysis of adenosine triphosphate (ATP). It is capable of moving drugs against a concentration gradient, from a region of low drug concentration to one of higher concentration. The process is saturable. Active transport systems are selective and may be competitively inhibited by other cotransported substances.

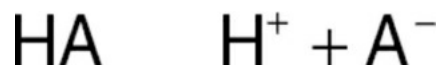
4. Endocytosis and exocytosis

This type of absorption is used to transport drugs of exceptionally large size across the cell membrane. Endocytosis involves engulfment of a drug by the cell membrane and transport into the cell by pinching off the drug-filled vesicle. Exocytosis is the reverse of endocytosis. Many cells use exocytosis to secrete substances out of the cell through a similar process of vesicle formation. Vitamin B₁₂ is transported across the gut wall by endocytosis, whereas certain neurotransmitters (for example, norepinephrine) are stored in intracellular vesicles in the nerve terminal and 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:

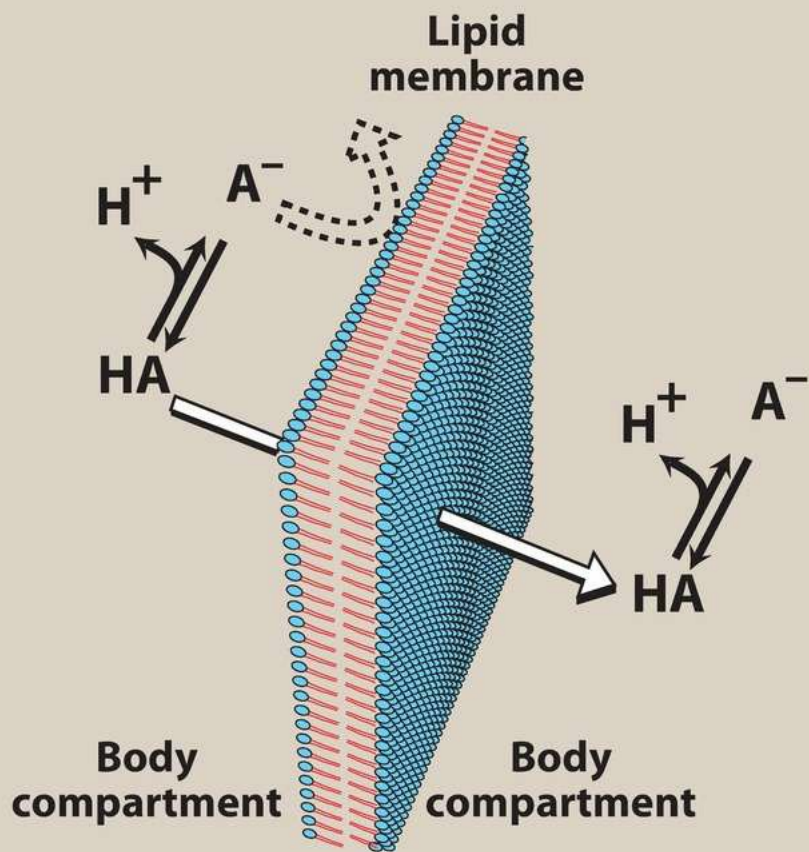


Weak bases (BH^+) can also release an H^+ . However, the protonated form of basic drugs is usually charged, and loss of a proton produces the uncharged base (B):



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 the protonated form BH^+ 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 drug achieves an equal concentration in all body water spaces.

A Weak acid



B Weak base

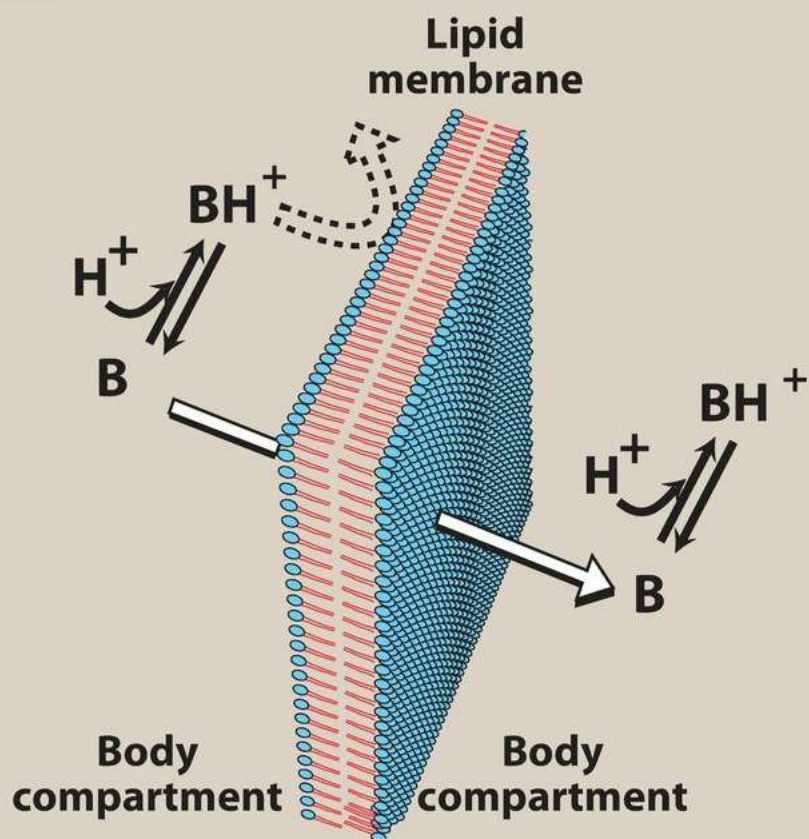


Figure 1.7 A. Diffusion of the nonionized form of a weak acid through a lipid membrane.
B. Diffusion of the nonionized form of a weak base through a lipid membrane.

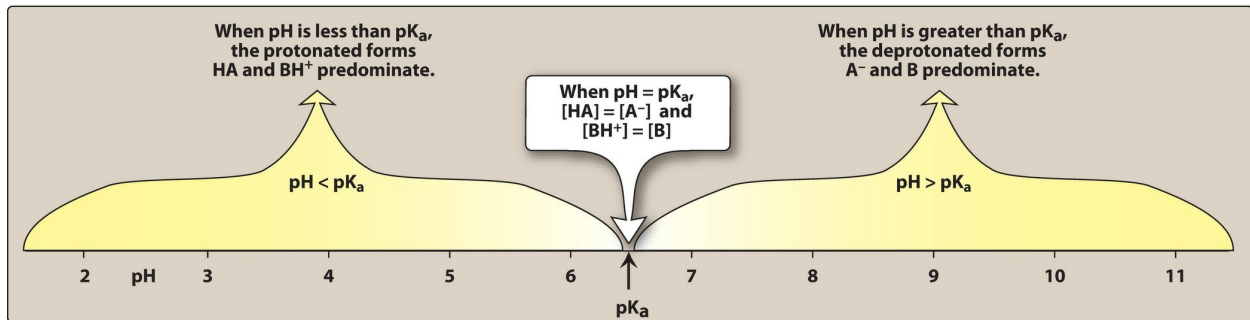


Figure 1.8 The distribution of a drug between its ionized and nonionized forms depends on the ambient pH and pK_a of the drug. For illustrative purposes, the drug has been assigned a pK_a of 6.5.

2. Blood flow to the absorption site

The intestines receive much more blood flow than does the stomach, so absorption from the intestine is favored over the stomach. [Note: Shock severely reduces blood flow to cutaneous tissues, thereby minimizing 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. [Note: 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 transmembrane transporter protein responsible for transporting various molecules, including drugs, across cell membranes (Figure 1.9). It is expressed in tissues throughout the body, including the liver, kidneys, placenta, intestines, and brain capillaries, and is involved in transportation of drugs from tissues to blood. That is, it “pumps” drugs out of cells. 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.

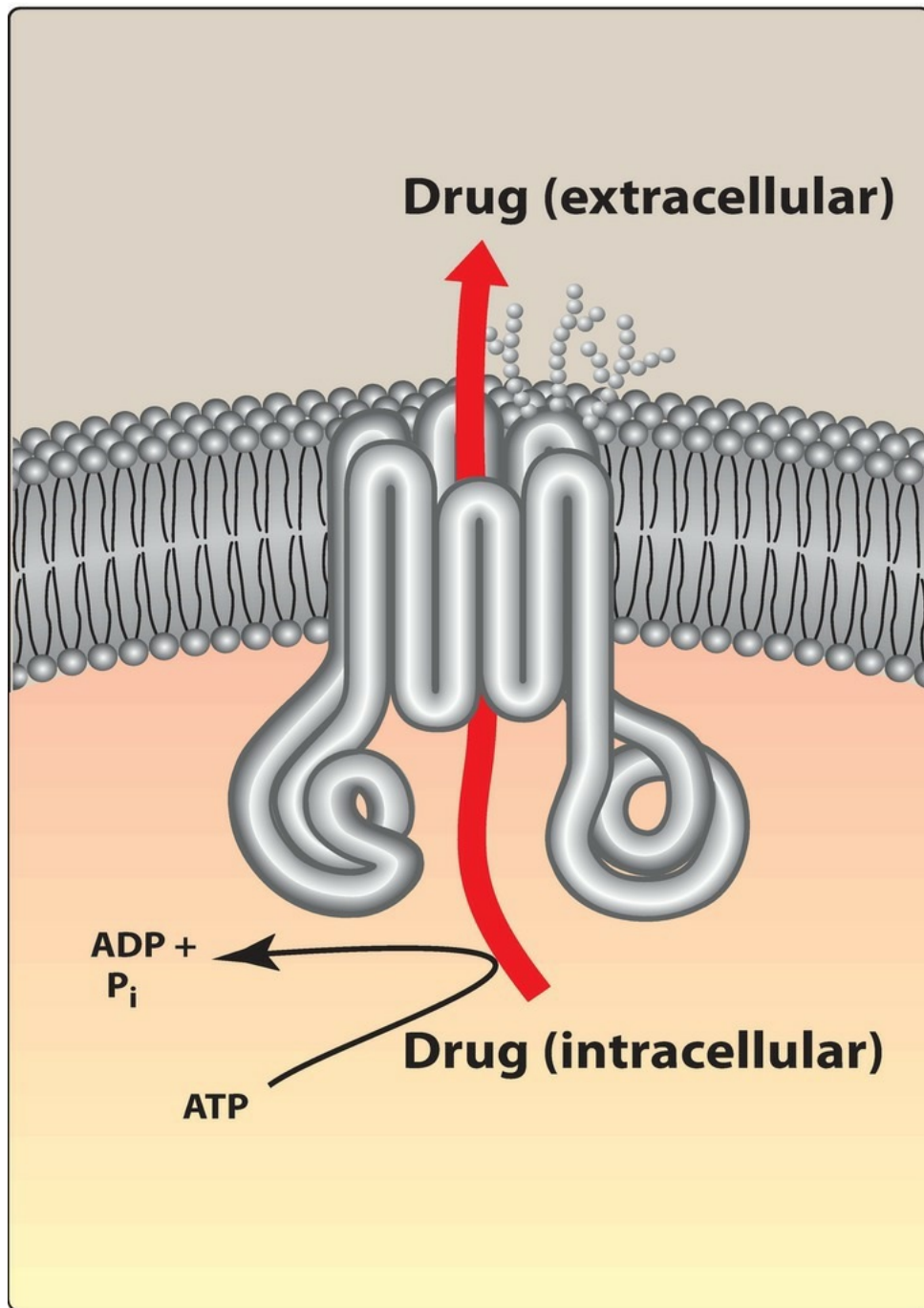


Figure 1.9 The six membrane-spanning loops of the P-glycoprotein form a central channel for the ATP-dependent pumping of drugs from the cell.

C. Bioavailability

Bioavailability is the rate and extent to which an administered drug reaches the systemic circulation. For example, if 100 mg of a drug is administered orally and 70 mg is absorbed unchanged, the bioavailability is 0.7 or 70%. Determining bioavailability is important for calculating drug dosages for nonintravenous routes of administration.

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 levels achieved by IV administration. After IV administration, 100% of the drug 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. A schematic depiction of determination of bioavailability is provided in [Figure 1.10](#).

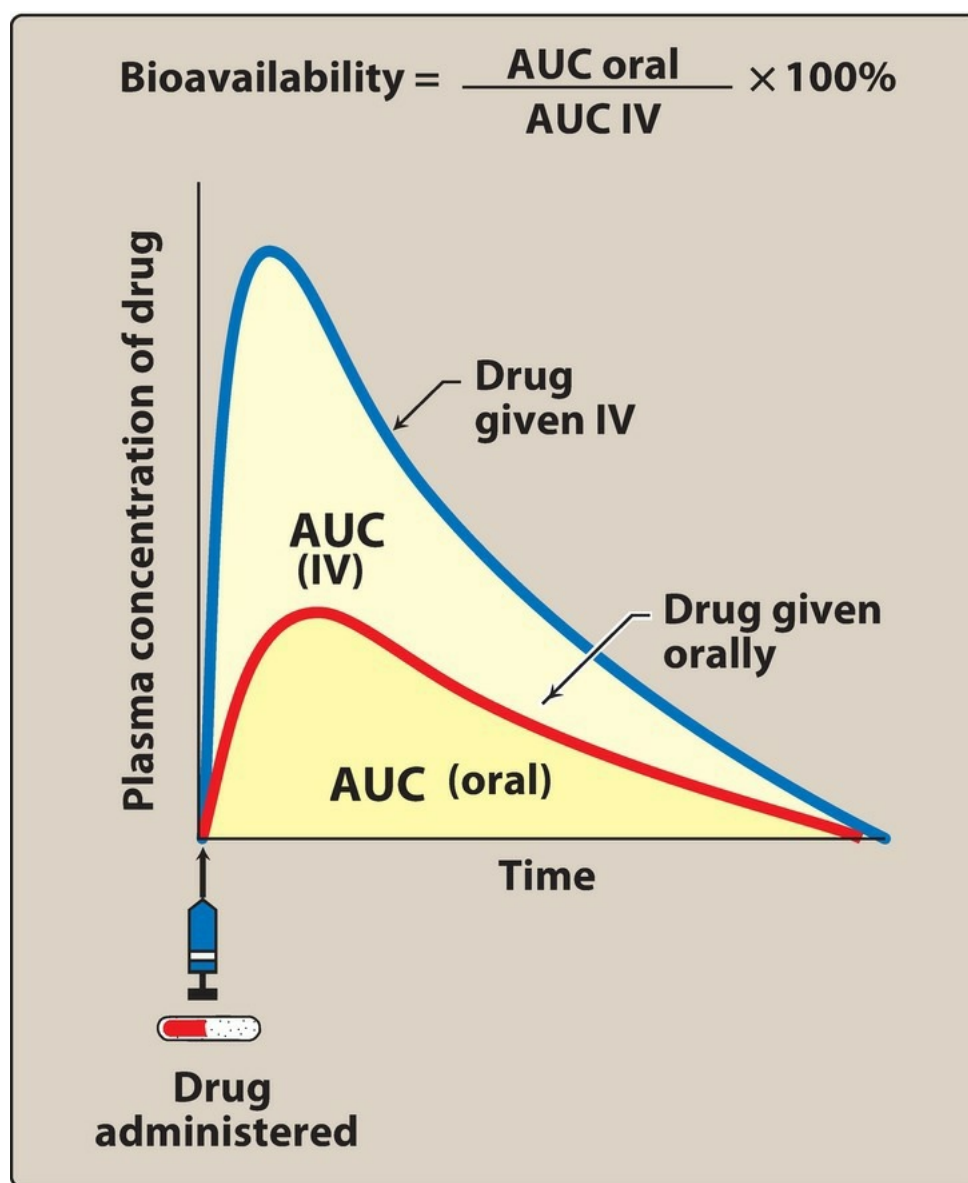


Figure 1.10 Determination of the bioavailability of a drug. AUC = area under curve; IV = intravenous.

2. Factors that influence bioavailability

In contrast to IV administration, which confers 100% bioavailability, orally administered drugs often undergo first-pass metabolism. This biotransformation, in addition to chemical and physical characteristics of the drug, determines the rate and extent to which the agent reaches the systemic circulation.

a. First-pass hepatic metabolism

When a drug is absorbed from the GI tract, it 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 entering the systemic circulation is decreased. This is referred to as first-pass metabolism. [Note: First-pass metabolism by the intestine or liver limits the efficacy of many oral medications. For example, more than 90% of *nitroglycerin* is cleared during first-pass metabolism. Hence, it is primarily administered via the sublingual, transdermal, or intravenous route.] Drugs with high first-pass metabolism should be given in doses sufficient to ensure that enough active drug reaches the desired site of action.

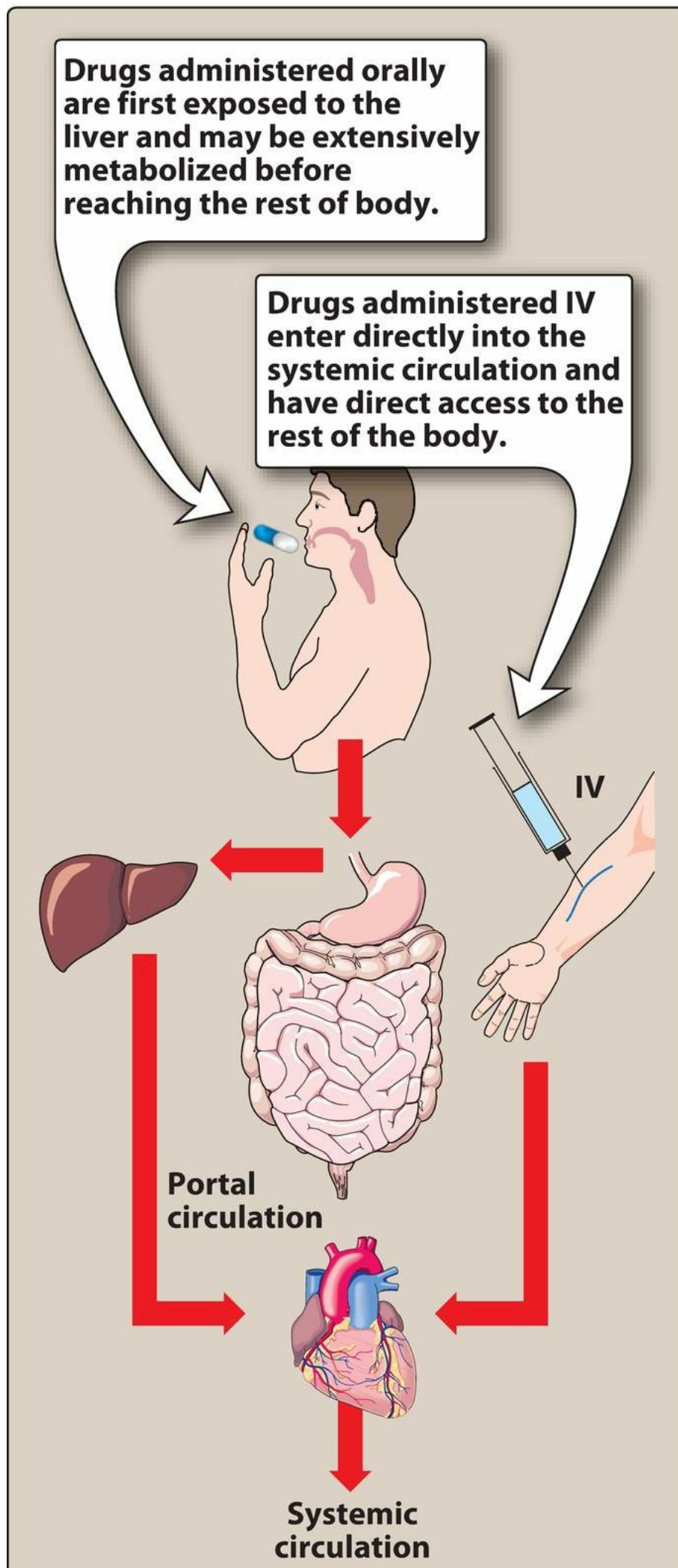


Figure 1.11 First-pass metabolism can occur with orally administered drugs. IV = intravenous.

b. Solubility of the drug

Very hydrophilic drugs are poorly absorbed because of the inability to cross lipid-rich cell membranes. Paradoxically, drugs that are extremely lipophilic are also poorly absorbed, because they are 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 lipophilic, 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 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 and other types of equivalence

Two drug formulations are bioequivalent if they show comparable bioavailability and similar times to achieve peak blood concentrations. Two drug formulations are therapeutically equivalent if they are pharmaceutically equivalent (that is, they have the same dosage form, contain the same active ingredient at the same strength, and use the same route of administration) with similar clinical and safety profiles. Thus, therapeutic equivalence requires that drug products are bioequivalent and pharmaceutically equivalent.

IV. Drug Distribution

Drug distribution is the process by which a drug reversibly leaves the bloodstream and enters the extracellular fluid and tissues. For drugs administered IV, absorption is not a factor, and the initial phase immediately following administration represents the distribution phase, during which the drug rapidly leaves the circulation and enters the tissues (Figure 1.12). The distribution of a drug from the plasma to the interstitium depends on cardiac output and local blood flow, capillary permeability, tissue volume, degree of binding of the drug to plasma and tissue proteins, and relative lipophilicity of the drug.

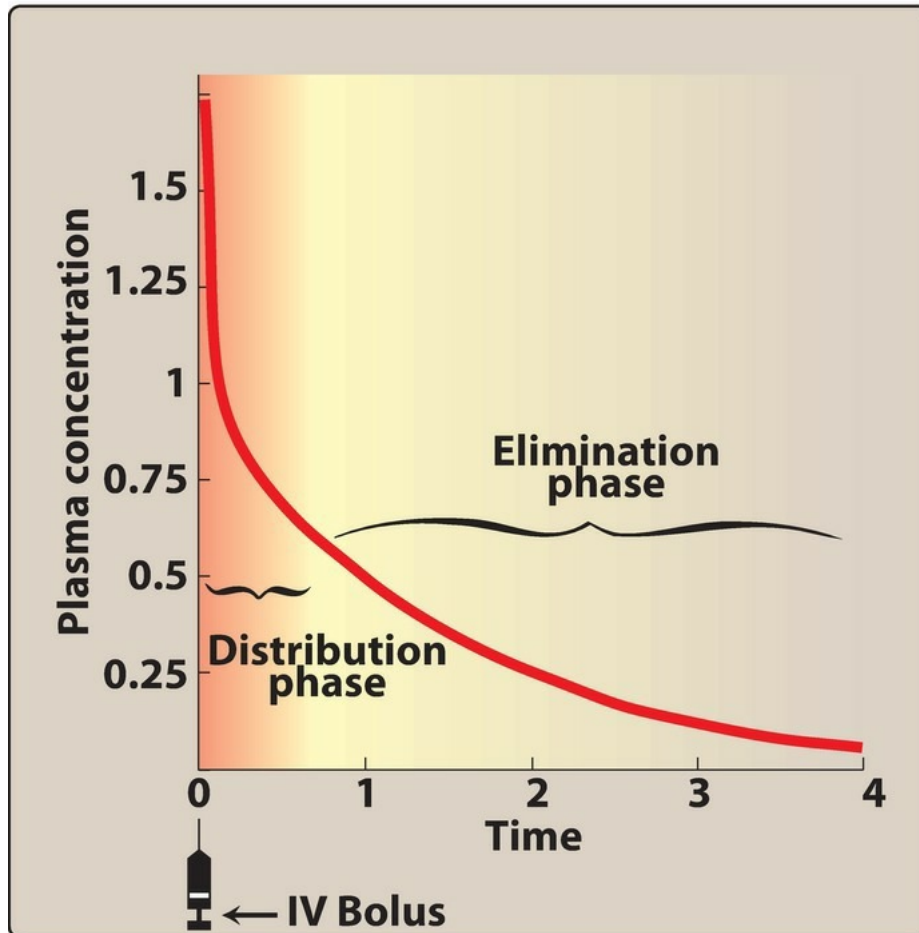


Figure 1.12 Drug concentrations in serum after a single injection of drug. Assume that the drug distributes and is subsequently eliminated.

A. Blood flow

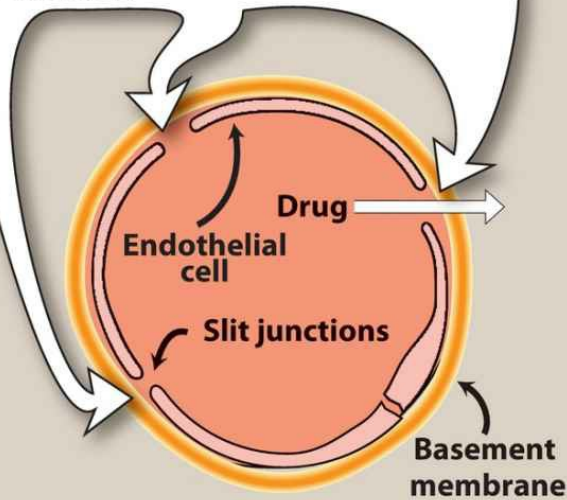
The rate of blood flow to the tissue capillaries varies widely. For instance, blood flow to “vessel-rich organs” (brain, liver, and kidney) is greater than that to the skeletal muscles. Adipose tissue, skin, and viscera have still lower rates of blood flow. Variation in blood flow partly explains the short duration of hypnosis produced by an IV bolus of *propofol* (see Chapter 13). High blood flow, together with high lipophilicity of *propofol*, permits rapid distribution into the CNS and produces anesthesia. A subsequent slower distribution to skeletal muscle and adipose tissue lowers the plasma concentration so that the drug diffuses out of the CNS, down the concentration gradient, and consciousness is regained.

B. Capillary permeability

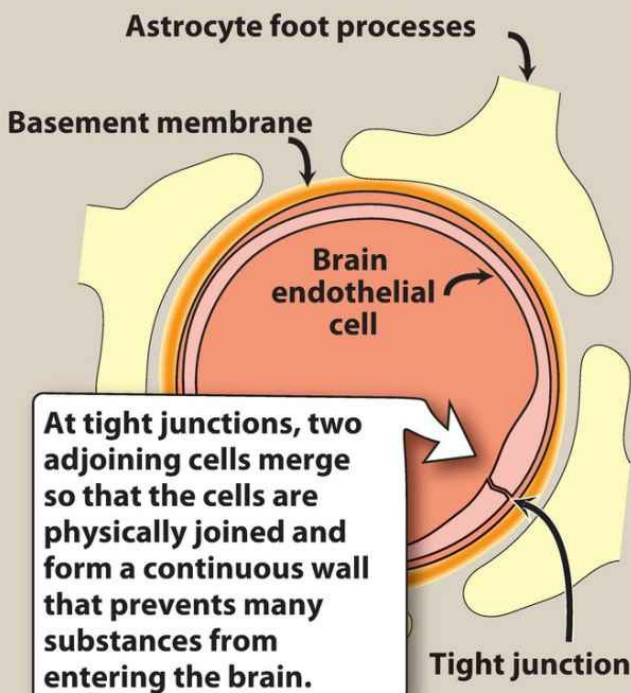
Capillary permeability is determined by capillary structure and by the chemical nature of the drug. Capillary structure varies in terms of the fraction of the basement membrane exposed by slit junctions between endothelial cells. In the liver and spleen, a significant portion of the basement membrane is exposed due to large, discontinuous capillaries through which large plasma proteins can pass (Figure 1.13A). In the brain, the capillary structure is continuous, and there are no slit junctions (Figure 1.13B). To enter the brain, drugs must pass through the endothelial cells of the CNS capillaries or undergo active transport. For example, a specific transporter carries *levodopa* into the brain. Lipid-soluble drugs readily penetrate the CNS because they dissolve in the endothelial cell membrane. By contrast, ionized or polar drugs generally fail to enter the CNS because they cannot pass through the endothelial cells that have no slit junctions (Figure 1.13C). These closely juxtaposed cells form tight junctions that constitute the blood–brain barrier.

A Structure of liver capillary

Large fenestrations allow drugs to move between blood and interstitium in the liver.



B Structure of a brain capillary



C Permeability of a brain capillary

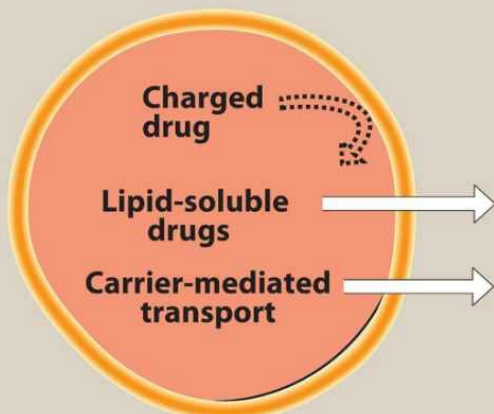


Figure 1.13 Cross section of liver and brain capillaries.

C. Binding of drugs to plasma proteins and tissues

1. Binding to plasma proteins

Reversible binding to plasma proteins sequesters drugs in a nondiffusible form and slows transfer out of the vascular compartment. Albumin is the major drug-binding protein, and it may act as a drug reservoir. As the concentration of free drug decreases due to elimination, the bound drug dissociates from albumin. This maintains the free-drug concentration as a constant fraction of the total drug in the plasma.

2. Binding to tissue proteins

Many drugs accumulate in tissues, leading to higher concentrations in tissues than in interstitial fluid and blood. Drugs may accumulate because of binding to lipids, proteins, or nucleic acids. Drugs may also undergo active transport into tissues. Tissue reservoirs may serve as a major source of the drug and prolong its actions or cause local drug toxicity. (For example, acrolein, the metabolite of *cyclophosphamide*, can cause hemorrhagic cystitis because it accumulates in the bladder.)

D. Lipophilicity

The chemical nature of a drug strongly influences its ability to cross cell membranes. Lipophilic drugs readily move across most biologic membranes. These drugs dissolve in the lipid membranes and penetrate the entire cell surface. The major factor influencing the distribution of lipophilic drugs is blood flow to the area. By contrast, hydrophilic drugs do not readily penetrate cell membranes and must pass through slit junctions.

E. Volume of distribution

The apparent volume of distribution, V_d , is defined as the fluid volume that is required to contain the entire drug in the body at the same concentration measured in the plasma. It is calculated by dividing the dose that ultimately gets into the systemic circulation by the plasma concentration at time zero (C_0).

$$V_d = \frac{\text{Amount of drug in the body}}{C_0}$$

Although V_d has no physiologic or physical basis, it can be useful to compare the distribution of a drug with the volumes of the water compartments in the body.

1. Distribution into the water compartments in the body

Once a drug enters the body, it has the potential to distribute into any one of the three functionally distinct compartments of body water or to become sequestered in a cellular site.

a. Plasma compartment

If a drug has a high molecular weight or is extensively protein bound, it is too large to pass through the slit junctions of the capillaries and, thus, is effectively trapped within the plasma (vascular) compartment. As a result, it has a low V_d that approximates the plasma volume, or about 4 L in a 70-kg individual. *Heparin* (see Chapter 21) shows this type of distribution.

b. Extracellular fluid

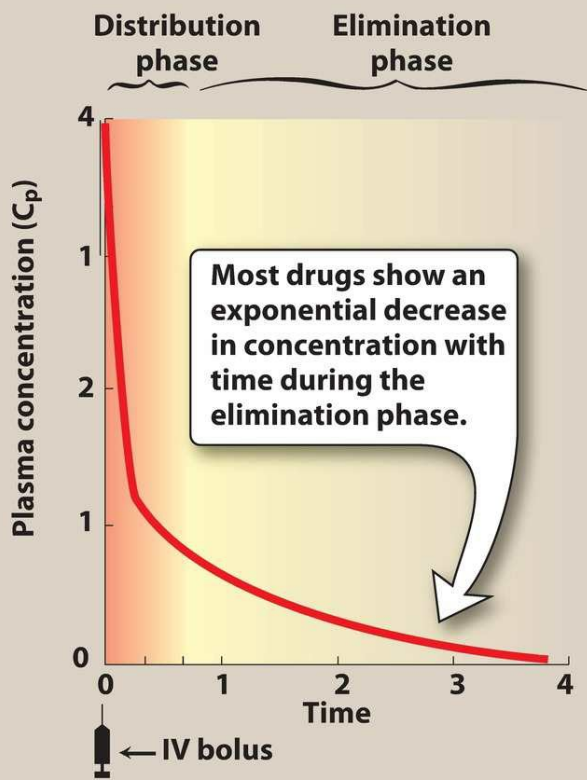
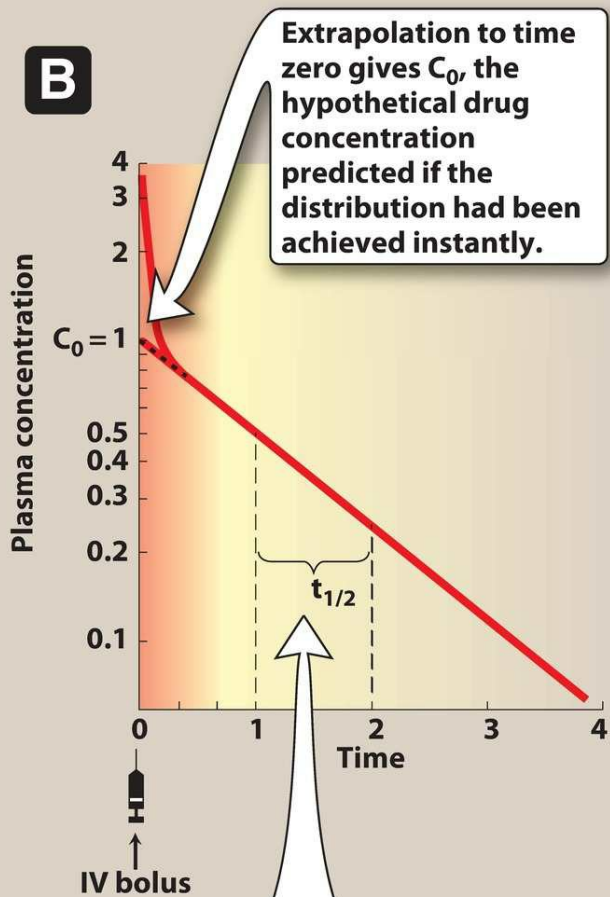
If a drug has a low molecular weight but is hydrophilic, it can pass through the endothelial slit junctions of the capillaries into the interstitial fluid. However, hydrophilic drugs cannot move across the lipid membranes of cells to enter the intracellular fluid. Therefore, these drugs distribute into a volume that is the sum of the plasma volume and the interstitial fluid, which together constitute the extracellular fluid (about 20% of body weight or 14 L in a 70-kg individual). Aminoglycoside antibiotics (see Chapter 30) show this type of distribution.

Total body water

If a drug has a low molecular weight and has enough lipophilicity, it can move into the interstitium through the slit junctions and pass through the cell membranes into the intracellular fluid. These drugs distribute into a volume of about 60% of body weight or about 42 L in a 70-kg individual. *Ethanol* exhibits this apparent V_d . [Note: In general, a larger V_d indicates greater distribution into tissues; a smaller V_d suggests confinement to plasma or extracellular fluid.]

2. Determination of V_d

The fact that drug clearance is usually a first-order process allows calculation of V_d . First order means that a constant fraction of the drug is eliminated per unit of time. This process can be most easily analyzed by plotting the log of the plasma drug concentration (C_p) versus time (Figure 1.14). The concentration of drug in the plasma can be extrapolated back to time zero (the time of IV bolus) on the Y axis to determine C_0 , which is the concentration of drug that would have been achieved if the distribution phase had occurred instantly. This allows calculation of V_d as

A**B**

The half-life (the time it takes to reduce the plasma drug concentration by half) is equal to $0.693 V_d/CL$.

Figure 1.14 Drug concentrations in plasma after a single injection of drug at time = 0. **A.** Concentration data are plotted on a linear scale. **B.** Concentration data are plotted on a log scale.

$$V_d = \frac{\text{Dose}}{C_0}$$

For example, if 10 mg of drug is injected into a patient and the plasma concentration is extrapolated back to time zero, and $C_0 = 1 \text{ mg/L}$ (from the graph in [Figure 1.14B](#)), then $V_d = 10 \text{ mg}/1 \text{ mg/L} = 10 \text{ L}$.

3. Effect of V_d on drug half-life

V_d has an important influence on the half-life of a drug, because drug elimination depends on the amount of drug delivered to the liver or kidney (or other organs where metabolism occurs) per unit of time. Delivery of drug to the organs of elimination depends not only on blood flow but also on the fraction of drug in the plasma. If a drug has a large V_d , most of the drug is in the extraplasmaic space and is unavailable to the excretory organs. Therefore, any factor that increases V_d can increase the half-life and extend the duration of action of the drug. [Note: An exceptionally large V_d indicates considerable sequestration of the drug in some tissues or compartments.]

V. Drug Clearance Through Metabolism

Once a drug enters the body, the process of elimination begins. The three major routes of elimination are hepatic metabolism, biliary elimination, and urinary excretion. [Note: Elimination is irreversible removal of drug from the body. It involves biotransformation (drug metabolism) and excretion. Excretion is removal of intact drug from the body.] Together, these elimination processes decrease the plasma concentration exponentially. That is, a constant fraction of the drug is eliminated in a given unit of time (Figure 1.14A). Metabolism results in products with increased polarity, which allows the drug to be eliminated. Clearance (CL) estimates the volume of blood from which the drug is cleared per unit of time. Total CL is a composite estimate reflecting all mechanisms of drug elimination and is calculated as follows:

$$CL = 0.693 \times V_d / t_{1/2}$$

where $t_{1/2}$ is the elimination half-life, V_d is the apparent volume of distribution, and 0.693 is the natural log constant. Drug half-life is often used as a measure of drug CL, because, for many drugs, V_d is a constant.

A. Kinetics of metabolism

1. First-order kinetics

The metabolic transformation of drugs is catalyzed by enzymes, and most of the reactions obey Michaelis-Menten kinetics, where K_m is Michaelis constant (the substrate concentration at half maximal velocity).

$$v = \text{Rate of drug metabolism} = \frac{V_{\max} [C]}{K_m + [C]}$$

In most clinical situations, the concentration of the drug, $[C]$, is much less than the Michaelis constant, K_m , and the Michaelis-Menten equation reduces to

$$v = \text{Rate of drug metabolism} = \frac{V_{\max} [C]}{K_m}$$

That is, the rate of drug metabolism and elimination is directly proportional to the concentration of free drug, and first-order kinetics is observed (Figure 1.15). This means that a constant fraction of drug is metabolized per unit of time (that is, with each half-life, the concentration decreases by 50%). First-order kinetics is also referred to as linear kinetics.

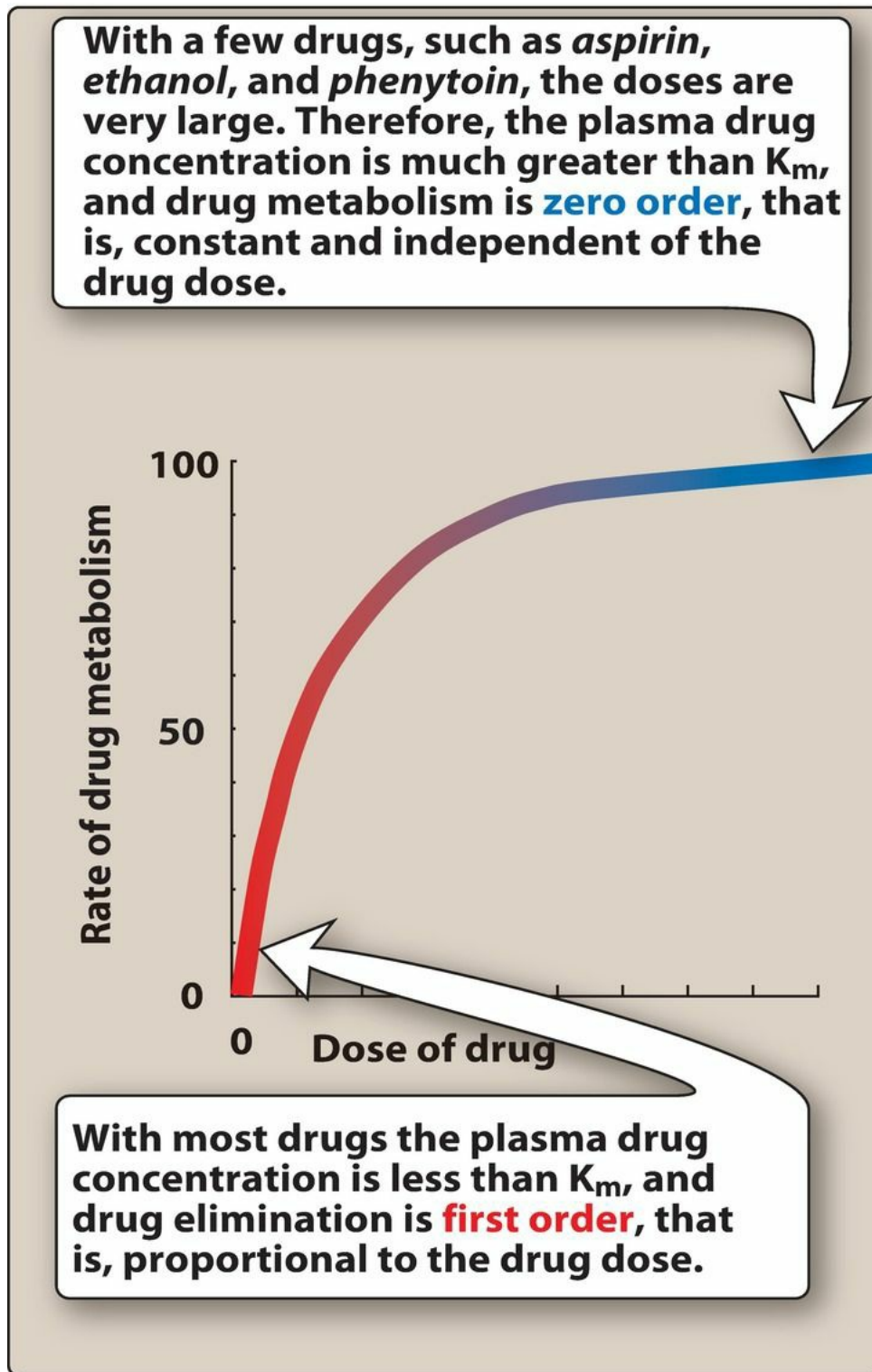


Figure 1.15 Effect of drug dose on the rate of metabolism.

2. Zero-order kinetics

With a few drugs, such as *aspirin*, *ethanol*, and *phenytoin*, the doses are very large. Therefore, $[C]$ is much greater than K_m , and the velocity equation becomes

$$v = \text{Rate of drug metabolism} = \frac{V_{\max} [C]}{[C]} = V_{\max}$$

The enzyme is saturated by a high free drug concentration, and the rate of metabolism remains constant over time. This is called zero-order kinetics (also called nonlinear kinetics). A constant amount of drug is metabolized per unit of time. The rate of elimination is constant and does not depend on the drug concentration.

B. Reactions of drug metabolism

The kidney cannot efficiently excrete lipophilic drugs that readily cross cell membranes and are reabsorbed in the distal convoluted tubules. Therefore, lipid-soluble agents are first metabolized into more polar (hydrophilic) substances in the liver via two general sets of reactions, called phase I and phase II (Figure 1.16).

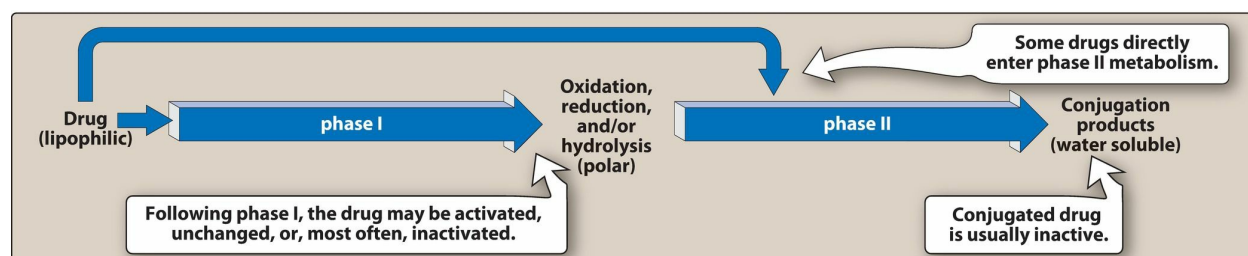


Figure 1.16 The biotransformation of drugs.

1. Phase I

Phase I reactions convert lipophilic drugs into more polar molecules by introducing or unmasking a polar functional group, such as $-OH$ or $-NH_2$. Phase I reactions usually involve reduction, oxidation, or hydrolysis. Phase I metabolism may increase, decrease, or have no effect on pharmacologic activity.

a. Phase I reactions utilizing the P450 system

The phase I reactions most frequently involved in drug metabolism are catalyzed by the cytochrome P450 (CYP) system. The P450 system is important for the metabolism of many endogenous compounds (such as steroids, lipids) and for the biotransformation of exogenous substances (drugs, carcinogens, and environmental pollutants). CYP is a superfamily of heme-containing isozymes located in most cells, but primarily in the liver and GI tract.

[1] Nomenclature

The family name is indicated by the Arabic number that follows CYP, and the capital letter designates the subfamily, for example, CYP3A (Figure 1.17). A second number indicates the specific isozyme, as in CYP3A4.