

Basic Principles in Pharmacology

Pharmacology

- ▶ **Pharmacology:** is the study of drugs, their uses and how they affect organisms
 - **Pharmacokinetics:** describes what the body does to a drug.
 - **Pharmacodynamics:** describes what the drug does to the body.

Pharmacokinetics

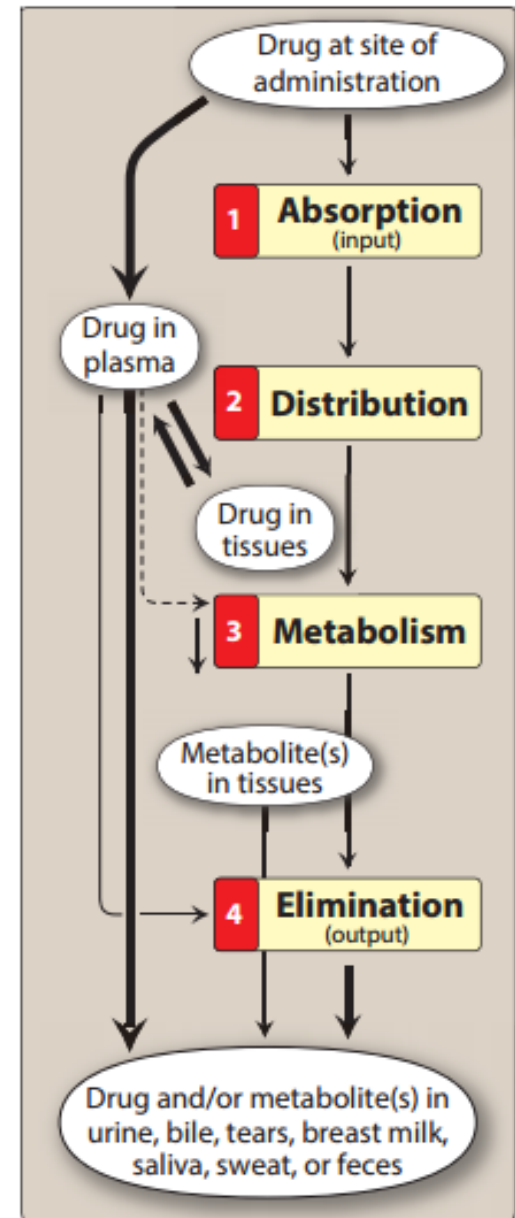
Pharmacokinetics

► ADME

- Absorption
- Distribution
- Metabolism
- Elimination

► ADME determine:

- The speed of onset of drug action
- The intensity of the drug effect
- The duration of drug action



ADME

Absorption: The drug absorption from the site of administration which permits the entry of the therapeutic agent into the plasma

Distribution: Reversible process, the drug leaves the bloodstream and distributes into the interstitial and intracellular fluids

Metabolism: Biotransformation of the drug into metabolites by the liver or other tissues

Elimination: The drug and its metabolites are eliminated into urine, bile or feces

Routes of Drug Administration

▶ Enteral

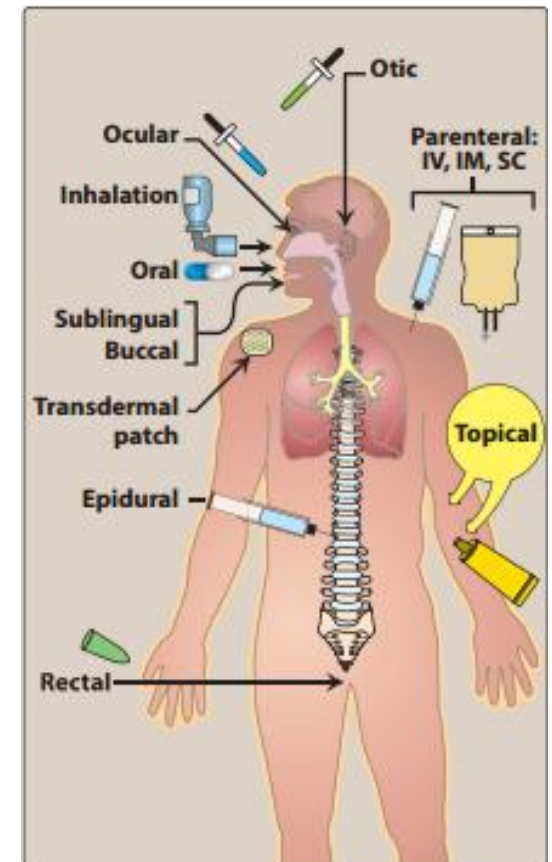
- Oral
- Sublingual

▶ Parenteral

- Intravenous (IV)
- Intramuscular (IM)
- Subcutaneous (SC)

▶ Other routes

- Inhalation
- Intrathecal/Intraventricular
- Topical
- Transdermal
- Rectal



Lippincott's Illustrated Reviews 6th edition

Routes of Administration

- ▶ Determined by
 - Properties of the drug
 - Water or lipid solubility
 - Ionization
 - Therapeutic objective
 - Rapid onset
 - Prolonged effect
 - Local effect

Enteral Route

► Oral administration:

◦ Advantages

- Easily self-administered
- Low risk of systemic infections (compared to parenteral)
- Easier to manage toxicity

◦ Disadvantages

- Inactivation of drugs due to first pass effect or stomach acidity

◦ Enteric coated

- To protect the stomach (e.g. Aspirin)
- To protect the drug from stomach acidity

◦ Extended release

- To control how fast the drug is released from the pill to the body

Enteral Route

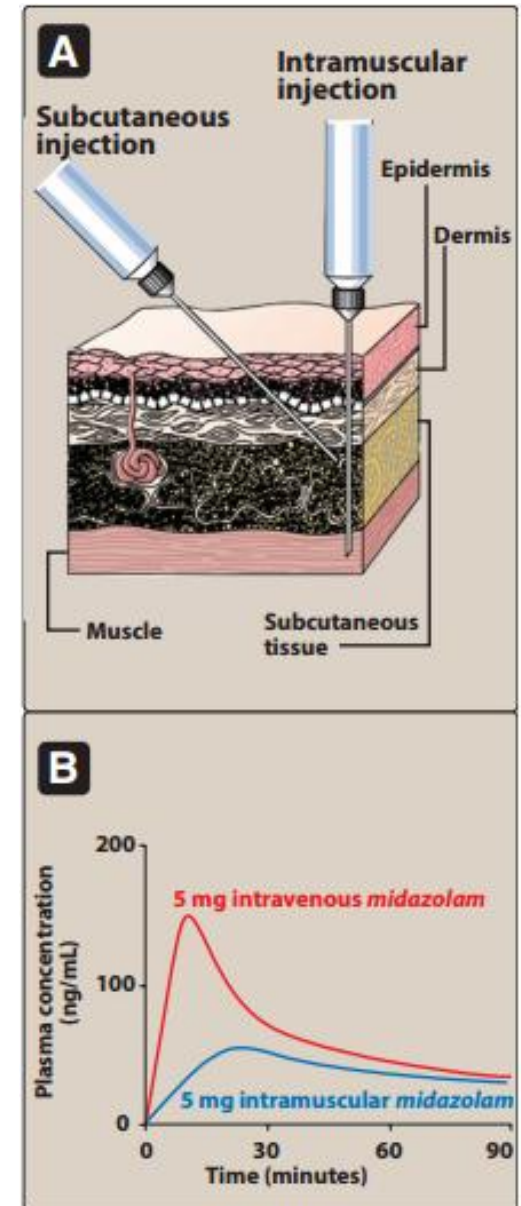
- ▶ Sublingual: Drug diffuses into the capillary network to the systemic circulation
 - Advantages
 - Rapid absorption
 - Convenience
 - Low incidence of infection
 - Bypass GI
 - Bypass first pass effect

Parenteral Route

- ▶ Direct administration of the drug across body barriers into the systemic circulation
 - Used for:
 1. Drugs with poor GI absorption (e.g. heparin)
 2. Drugs unstable in GI (e.g. insulin)
 3. Unconscious patients
 4. Rapid onset of action
 5. High bioavailability
 - Advantage: no first pass metabolism
 - Disadvantages: Risk of infection
 - Can be irreversible

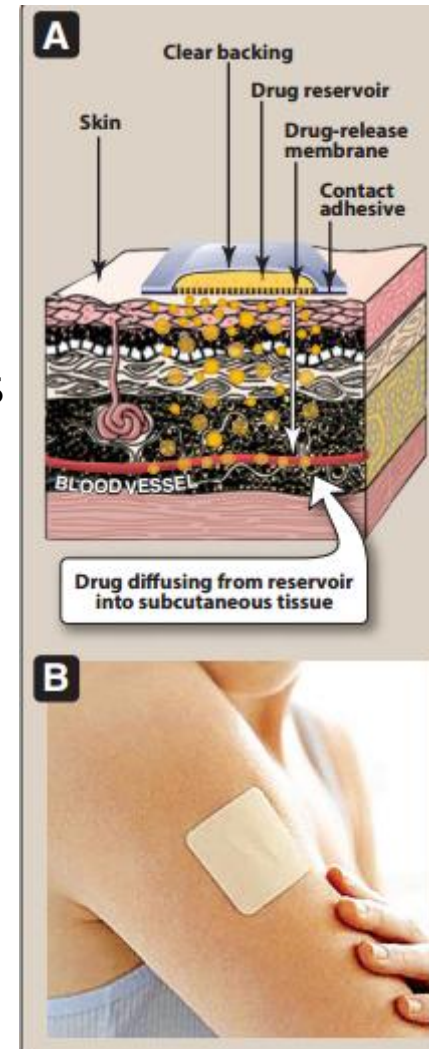
Parenteral Routes

- ▶ Intravenous (IV)
 - Bolus: Immediate delivery of full amount
 - Infusion: Delivery over a longer time
- ▶ Intramuscular
 - Aqueous solution (Rapid absorption)
 - Depot preparation in nonaqueous vehicle
- ▶ Subcutaneous
 - Less risk of hemolysis
 - May provide sustained slow effect



Additional Routes

- ▶ Inhalation
 - Oral or nasal
 - Rapid delivery across the large surface area of mucous membranes
- ▶ Intrathecal/intraventricular
 - Direct injection into the cerebrospinal fluid
 - Rapid delivery
 - To avoid the blood brain barrier
- ▶ Topical: application
 - Skin, for local effect.
- ▶ Transdermal
 - Sustained delivery of drugs (e.g. nicotine patches)
- ▶ Rectal
 - Avoids first pass metabolism
 - Rapid delivery
 - Used when oral administration is not possible (antiemetics)



Drug Absorption

Absorption of Drugs

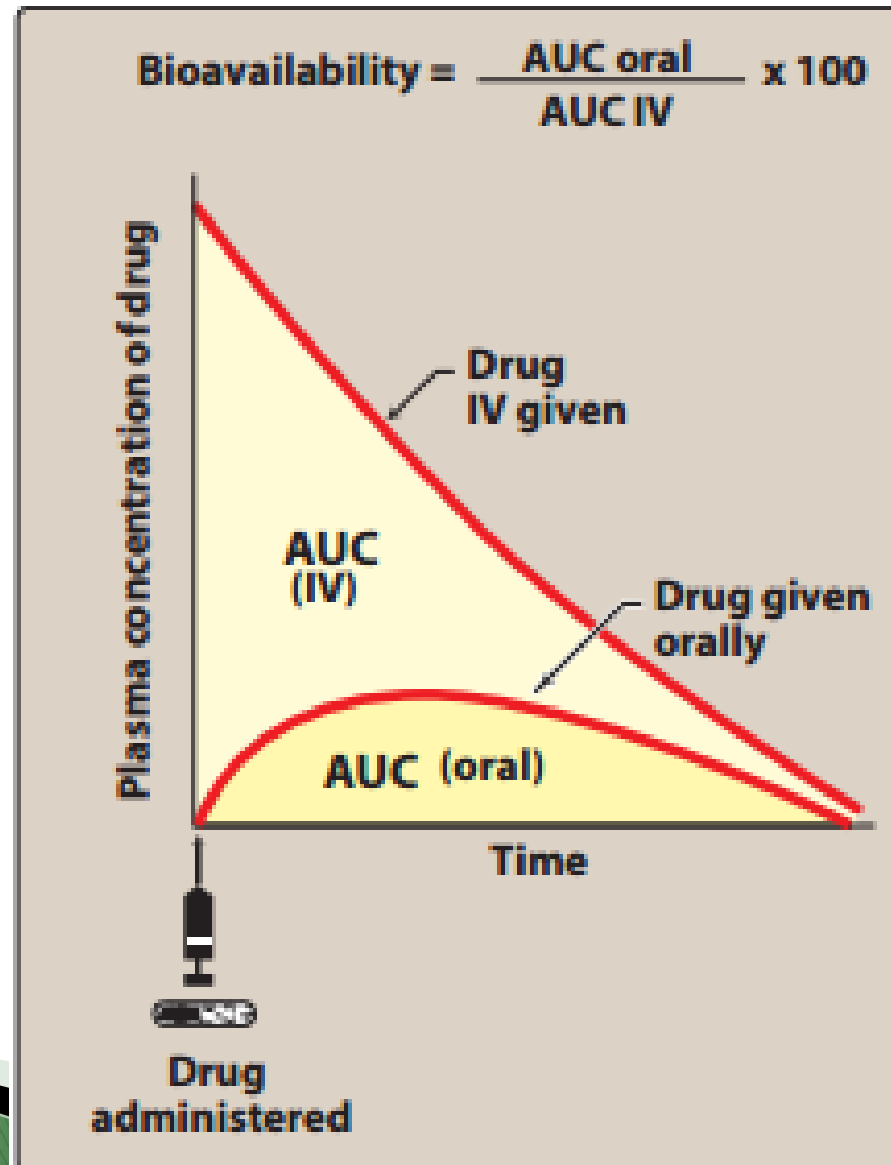
- ▶ Absorption is the transfer of a drug from the site of administration to the bloodstream via one of several mechanisms
- ▶ Rate and efficiency of absorption of a drug depend on:
 - The environment where the drug is absorbed
 - Chemical characteristics of the drug
 - Route of administration

- ▶ Absorption Rate: how rapidly does the drug get from its site of administration to the general circulation ?
- ▶ Absorption Extent: How much of the administered dose enters the general circulation ? (% bioavailability = F)

Bioavailability

- ▶ Bioavailability: The fraction of administered drug that reaches the systemic circulation
- ▶ Example 100 mg of a drug were administered orally, 70 mg of the drug were absorbed unchanged.
 - The bioavailability of this drug is 0.7 or 70%
- ▶ For IV drugs, absorption is complete
 - (100% bioavailability)
- ▶ Drug administration by other routes may result in partial absorption and lower bioavailability

Bioavailability

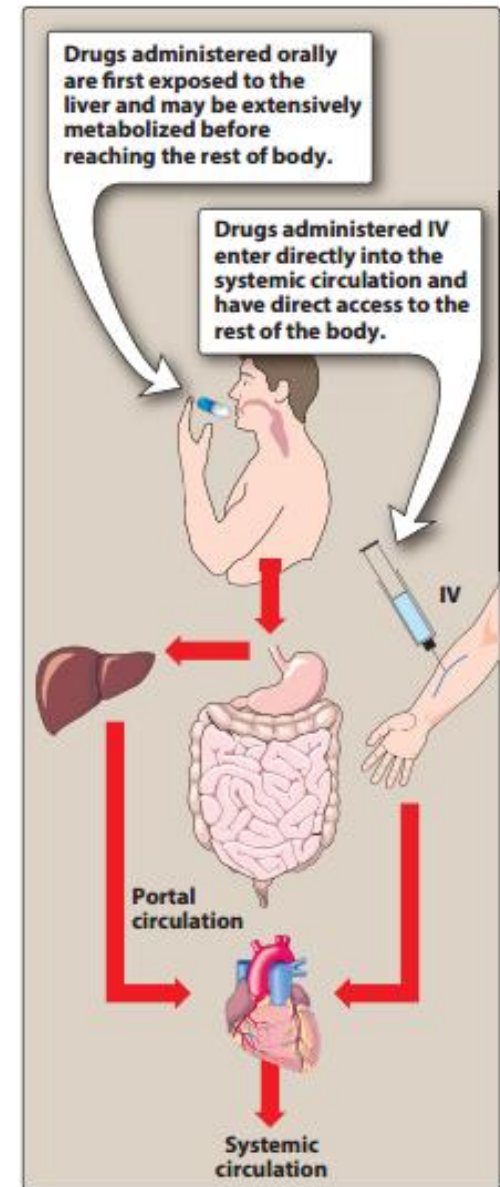


Factors that influence oral bioavailability

- First-pass hepatic metabolism
(Metabolism by liver enzymes prior to reaching the systemic circulation)
- Nature of the drug formulation
- Solubility of the drug
- Chemical instability
- Decomposition in acidic gastric juices
- Decomposition by hydrolytic gut enzymes (eg, proteases, lipases)
- Degradation by gut microorganisms
- Food in the gut may alter absorption rate and amount (eg. interact or form a complex)
- Metabolism by gut wall enzymes

First-pass metabolism

- ▶ When an oral drug is absorbed across the GI tract, it first enters the portal circulation before the systemic circulation
- ▶ If the drug is rapidly metabolized, less of the active ingredient will reach the systemic circulation
- ▶ Example: nitroglycerine (90% is cleared through passage through the liver)
 - It is Given sublingually



► Solubility of the drug

- Very hydrophilic drugs can not cross lipid-rich cell membranes, and so they are poorly absorbed
- Extremely hydrophobic drugs are poorly absorbed because they're insoluble in aqueous body fluids
- For good absorption the drug needs to be hydrophobic with some water solubility
- Most drugs are weak acids or bases

▶ Chemical instability

- Insulin is destroyed in the stomach by degradative enzymes
- Penicillin G. is instable in gastric pH

▶ Nature of the drug formulation

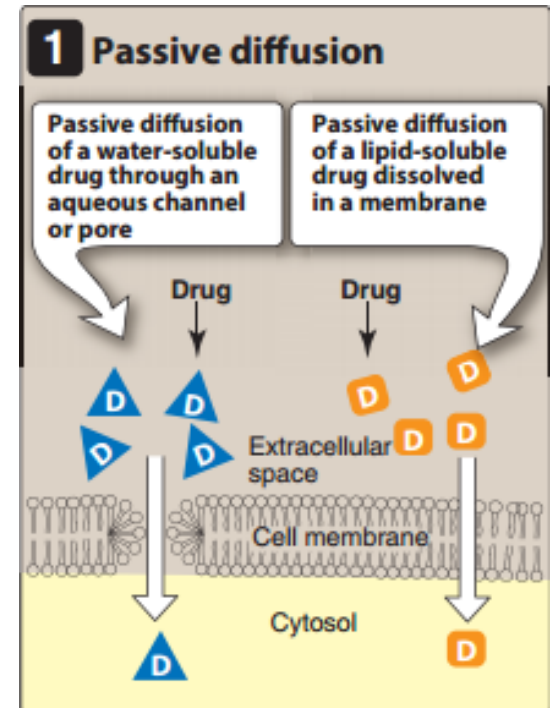
- Presence of excipients alter the rate of absorption

Mechanisms of drug absorption from GI tract

- ▶ Passive diffusion:
- ▶ Facilitated diffusion
- ▶ Active transport
- ▶ Endocytosis and exocytosis

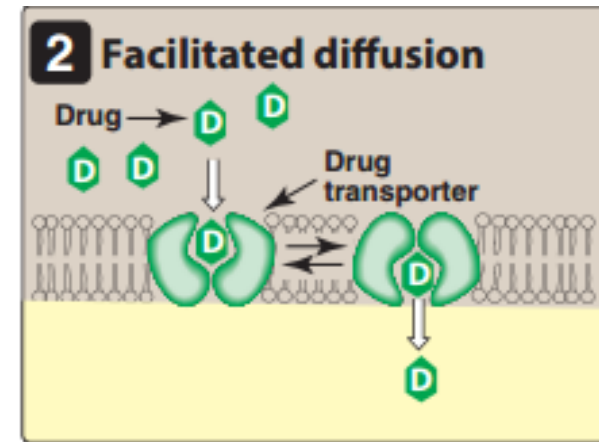
Passive diffusion

- ▶ Movement of drug molecules across membranes from a region of high concentration to a region of lower concentration
- ▶ Most drugs are absorbed through this mechanism
- ▶ No carrier involved
- ▶ Non saturable



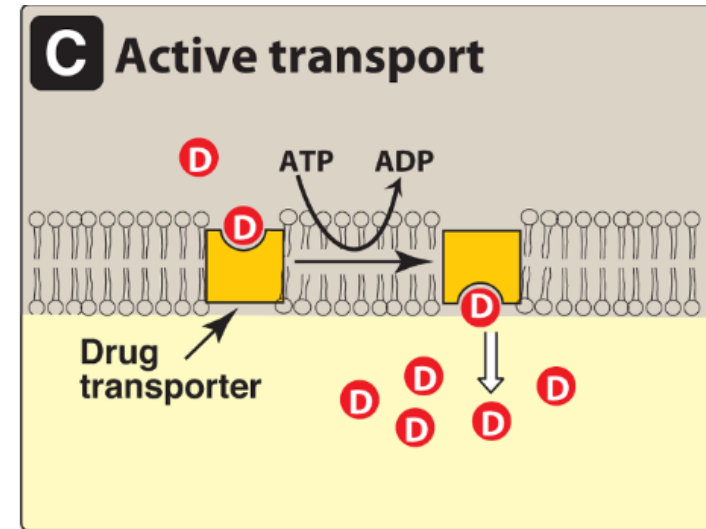
Facilitated diffusion

- ▶ Entry to the cell through specialized transmembrane carrier proteins
- ▶ Movement occurs from the area of the high concentration to the area of low concentration
- ▶ Does not require energy
- ▶ Can be saturated and inhibited by compounds that compete for the carrier



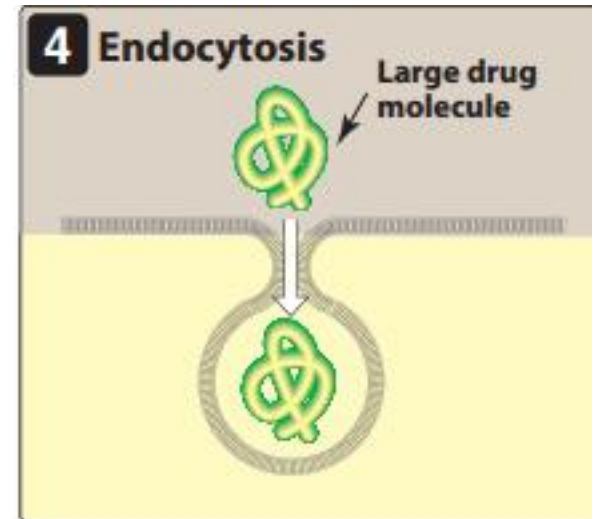
Active transport

- ▶ Involves specific carrier proteins
- ▶ Requires energy
- ▶ Moves the drugs against the concentration gradient (from low concentration to high concentration regions)
- ▶ Selective
- ▶ Saturable, can be inhibited by cotransported substances



Endocytosis and exocytosis

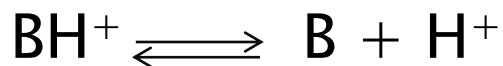
- ▶ Transport of exceptionally large drugs
- ▶ Endocytosis: engulfment of a molecule by the cell membrane
- ▶ Exocytosis: the reverse process that leads to the release of molecules
- ▶ Example: Vitamin B12 transport across the gut wall by endocytosis



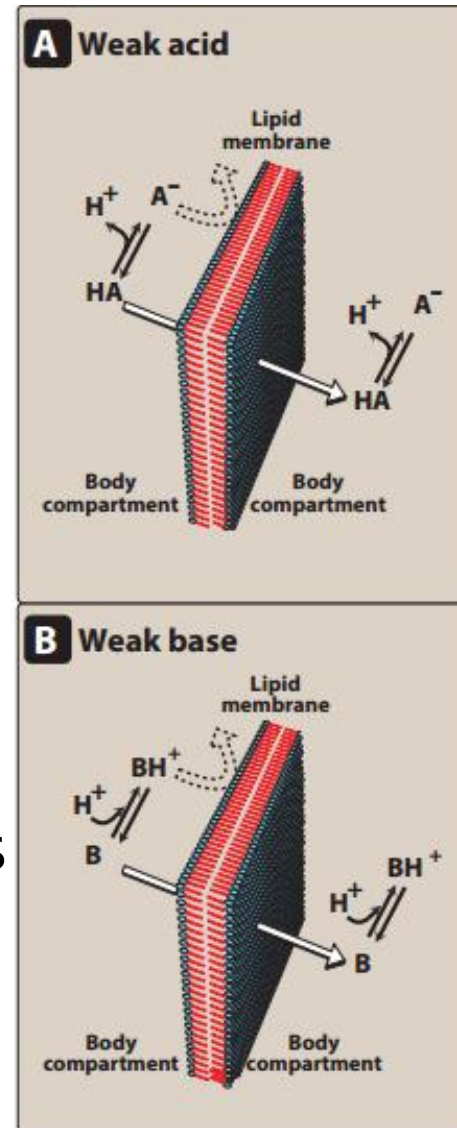
Factors influencing absorption

1. pH

- Most drugs are weak acids or weak bases



- Drugs pass through membranes easier when uncharged
- $\text{pH} < \text{pK}_a$ protonated form predominates
- $\text{pH} > \text{pK}_a$ deprotonated form predominates



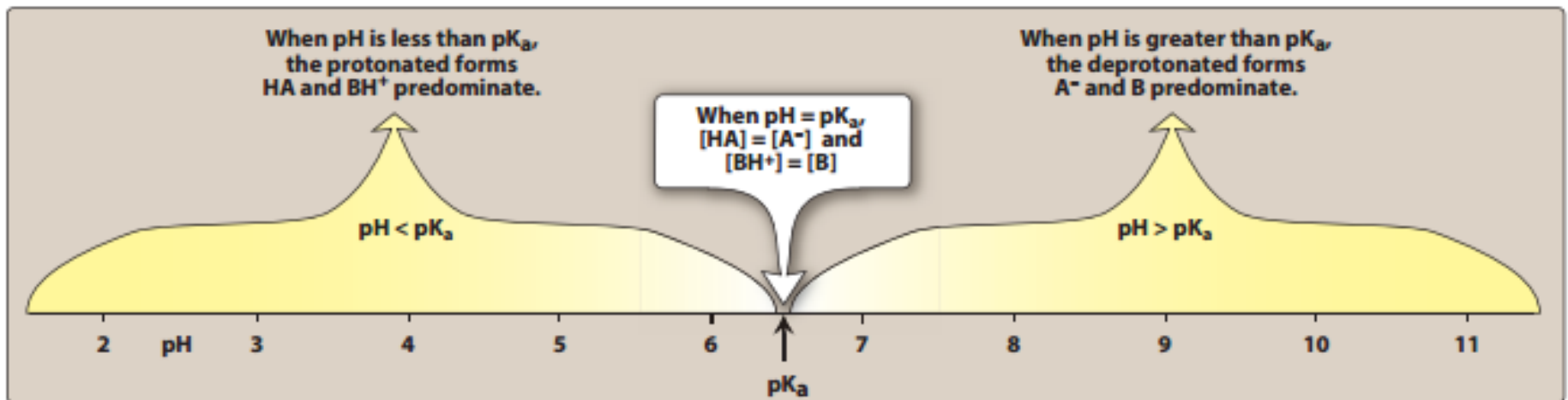


Figure 1.8

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.

Factors influencing absorption

2. Blood flow to the absorption site

- Because blood flow is much greater in the intestines than the stomach, absorption is greater in the intestines.

3. Total surface area available for absorption

- Intestines have large surface area

4. Contact time at the absorption surface

- Absorption is affected by changes in gastric motility (e.g. diarrhea)

5. Expression of P-glycoprotein

- Drug transporter (reduces absorption)
- In liver, kidney, brain, intestines

P-glycoproteins (P-gp)

- ▶ 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
- ▶ High expression of p-gp reduces absorption

▶ Bioequivalence

Two related drug preparations are bioequivalent if they show

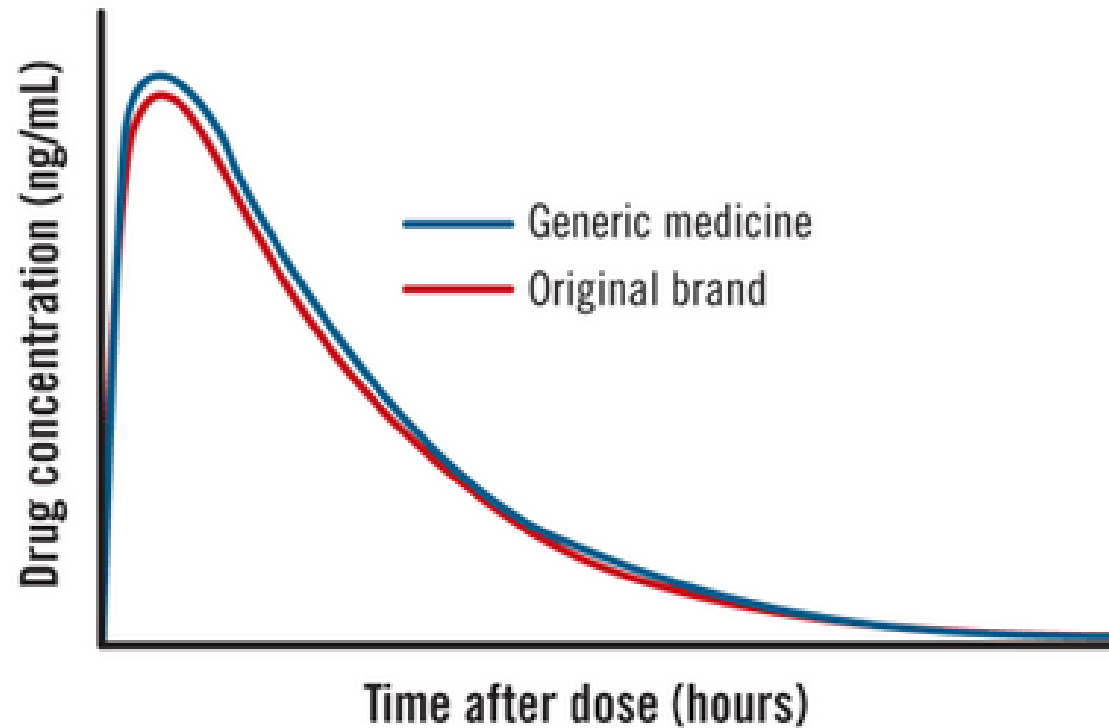
- Comparable bioavailability
- Similar times to achieve peak blood concentrations.

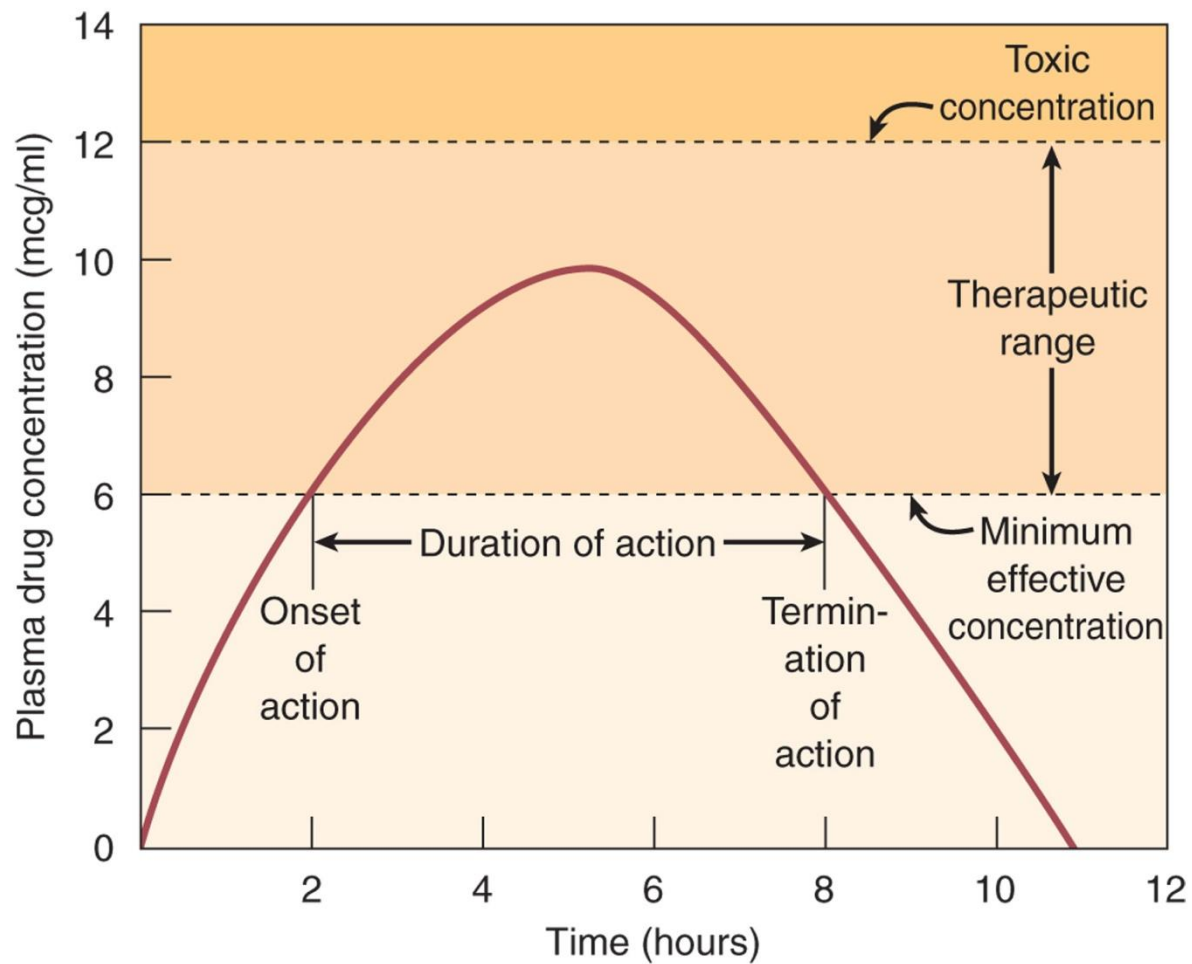
▶ Therapeutic equivalence

Two similar drug products are therapeutically equal if they are pharmaceutically equivalent with similar clinical and safety profiles

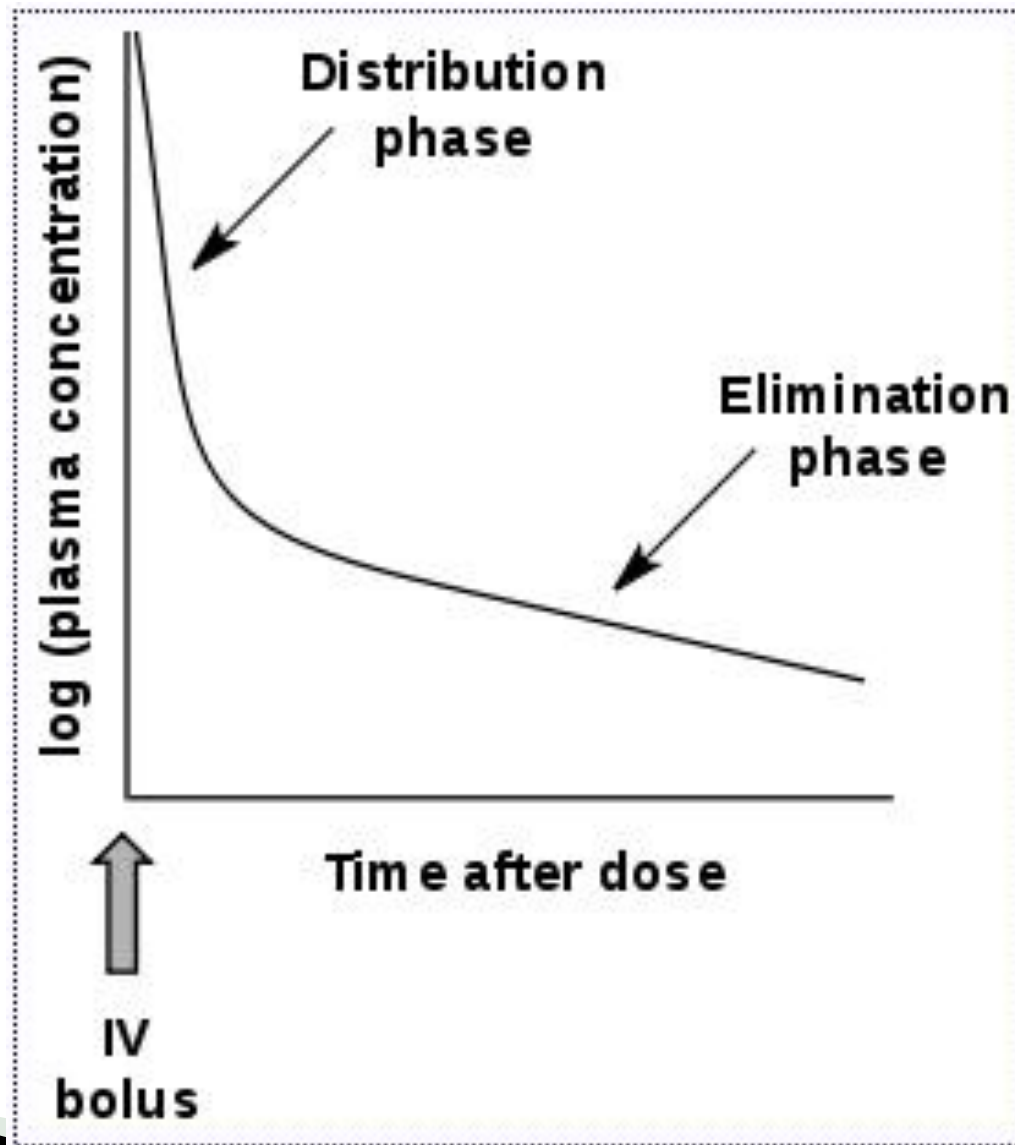
FIGURE

Bioequivalence analysis: *a hypothetical bioequivalence study*⁶





Adams et al. 2008



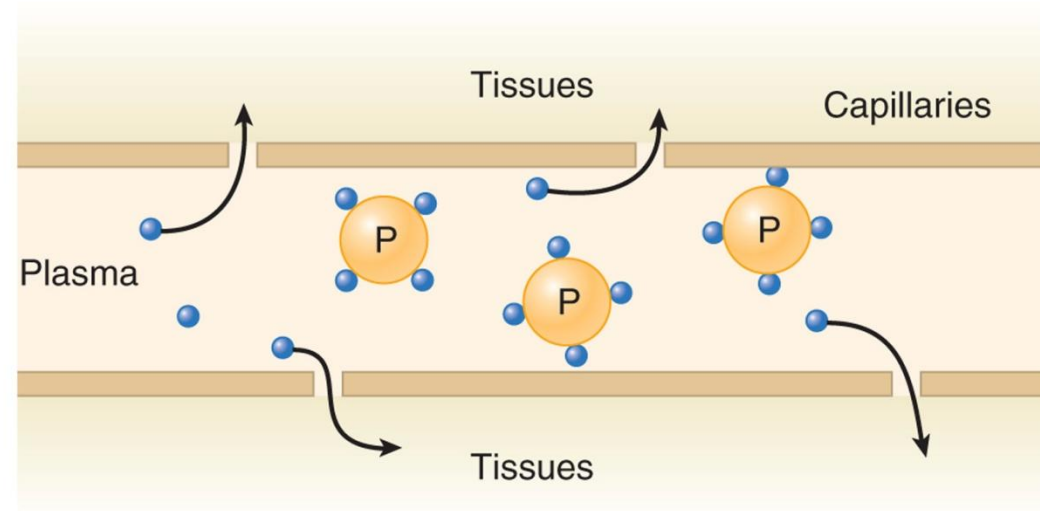
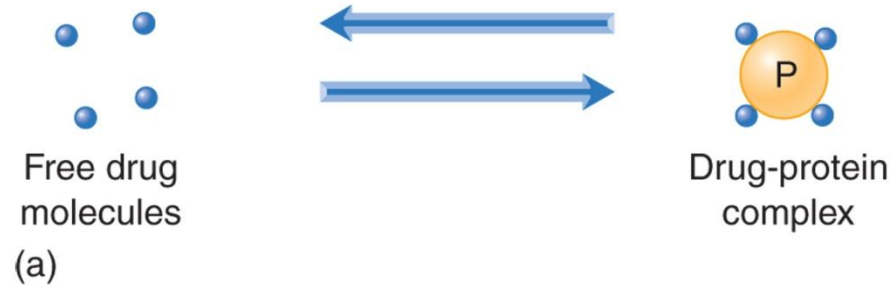
Drug Distribution

- ▶ Distribution: the process by which a drug reversibly leaves the blood stream and enters the interstitium and then cells
- ▶ For an IV drug; No absorption occurs
Distribution occurs immediately after administration

Drug Distribution

Distribution depends on

1. Cardiac output and regional blood flow
2. Capillary permeability
3. Tissue volume
4. Drug-protein binding in plasma and tissues
5. Hydrophobicity of the drug



(b)

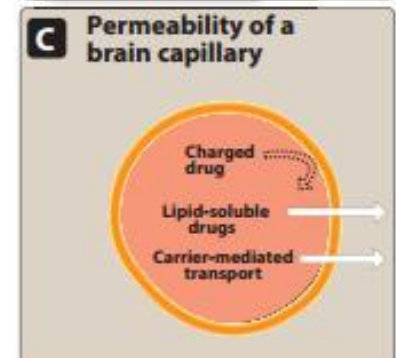
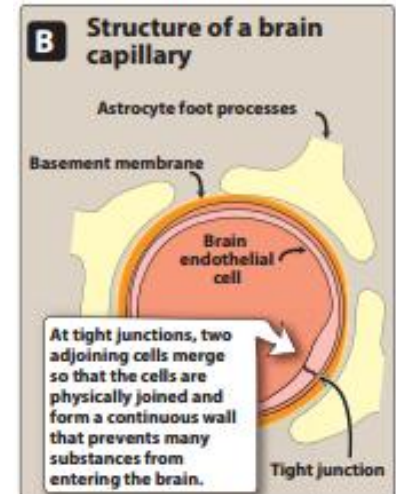
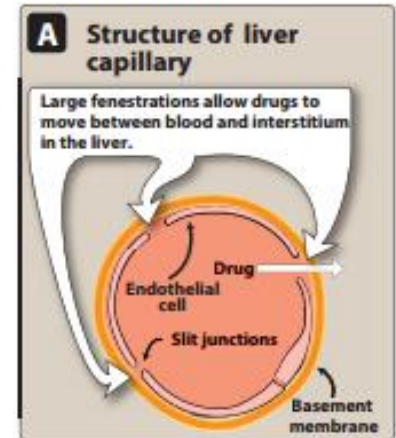
1. Blood Flow

- ▶ Due to unequal distribution of cardiac output, the rate of blood flow to tissue capillaries is variable
- ▶ Blood flow to the brain, liver and kidney is greater than that to skeletal muscles
- ▶ Adipose tissue, skin and viscera have lower rates of blood flow

- ▶ Example: thiopental, highly lipid soluble
 - Initially rapidly moves into the brain due to high blood flow and produces anesthesia
 - A slower distribution into skeletal muscles and adipose tissues lowers plasma concentration, and CNS concentration
 - Consciousness is regained

2. Capillary permeability

- ▶ Depends on
 - Capillary structure
 - Chemical nature of the drug



Drug-Protein binding

▶ Binding to plasma proteins

- Nonselective
- Albumin

◦ Protein bound drug $\rightleftharpoons$ Free drug  Distribution
Metabolism
Excretion

▶ Binding to tissue proteins

- Drugs can accumulate in tissues due to tissue protein binding extending their effects or causing local toxicity

▶ Hydrophobicity

- Hydrophobic drugs cross cell membranes
- Hydrophilic drugs need to pass through the slit junction

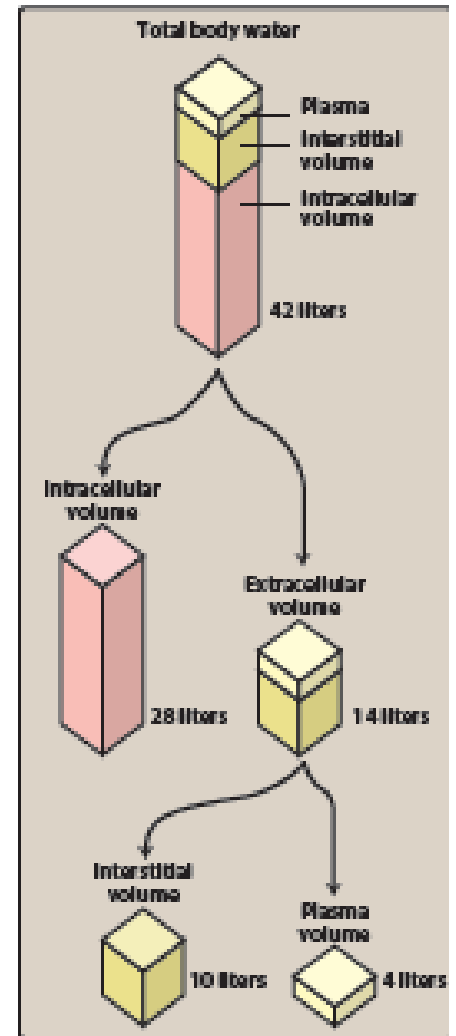
Volume of Distribution

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

V_d : Apparent volume of distribution

C_0 : Plasma concentration at time zero

- ▶ Vd has no physiologic basis
It can be used to compare the distribution of a drug in the water compartments of the body
 - Plasma (4L)large molecular weight or highly protein bound drugs
e.g. Heparin
 - Extracellular fluid (14L)Low molecular weight but hydrophilic and can not cross cell membranes
 - Total body water (42 L)Low molecular weight and hydrophobic

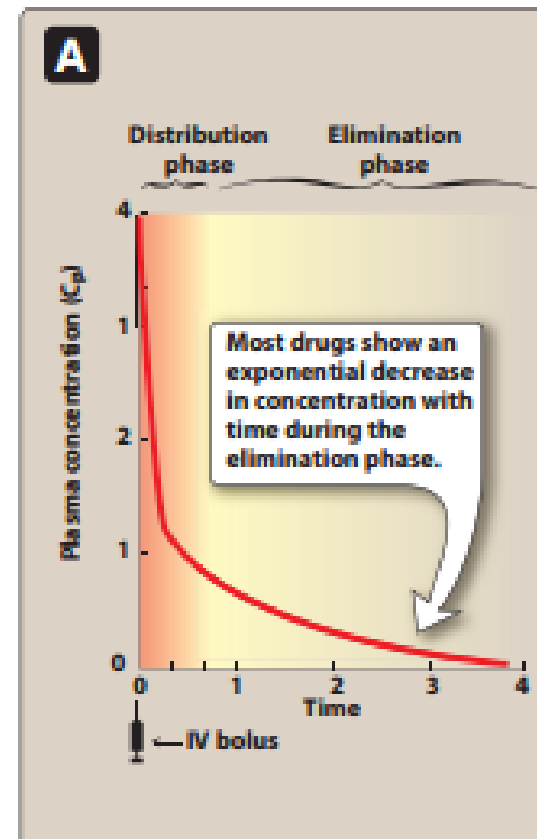


- ▶ **Apparent volume of distribution (V_d)**
 - A drug rarely associates with one water compartment
 - Usually drugs are bound to cellular compartments like
 - Proteins in plasma and cells
 - Lipids in adipocytes and cell membranes
 - Nucleic acids in nuclei of cells
- ▶ V_d is useful for calculating the loading dose of a drug

► Example:

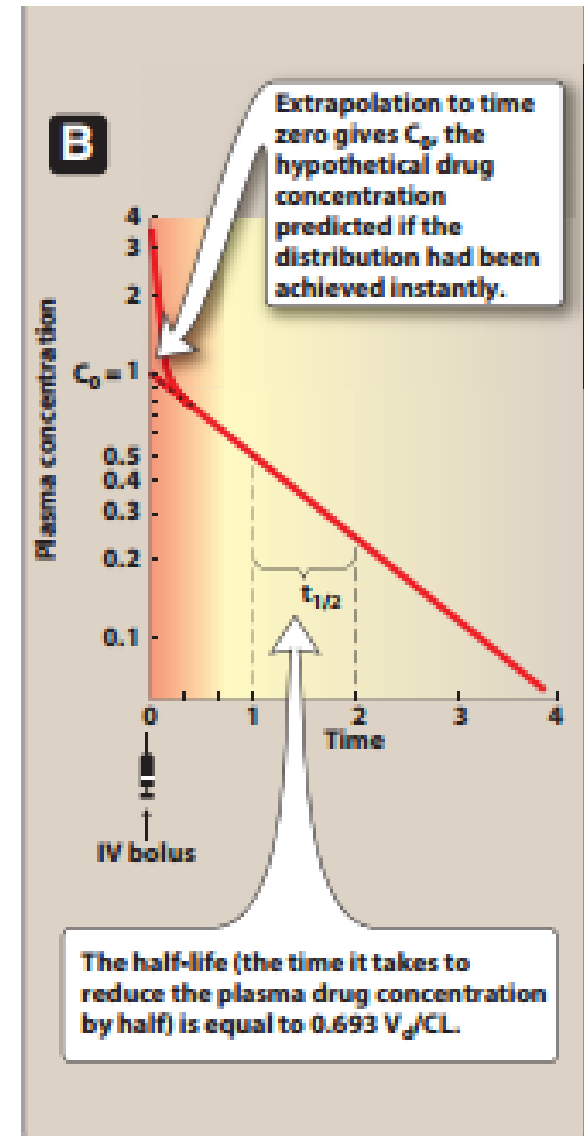
If 10 mg of a drug are injected and the plasma concentration is 1 mg/L what is V_d ?

$$V_d = \frac{\text{Dose}}{C_0} = \frac{10}{1} = 10 \text{ L}$$



Plasma Half-Life ($t_{1/2}$) of Drugs

- ▶ Length of time needed to decrease drug plasma concentration by one half
- ▶ The greater the half-life of the drug, the longer it takes to excrete
- ▶ Determines frequency and dosages



- ▶ Elimination depends on the amount of the drug delivered to the liver or the kidney per time unit
- ▶ The greater the V_d the less drug that is available to the excretory organ
- ▶ The greater the V_d the higher the half life of the drug, and the longer the duration of action
- ▶ An exceptionally high V_d indicates the sequestration of the drug in tissues

Metabolism

Drug clearance through metabolism

- ▶ Once the drug enters the body, elimination begins
- ▶ Routes of elimination include:
 1. Hepatic metabolism
 2. Elimination in bile
 3. Elimination in urine
- ▶ Metabolism leads to products with increased polarity which allows drug elimination

- ▶ Clearance (CL) the amount of drug cleared from the body per unit time
 - $CL = 0.693 \times V_d / t_{1/2}$
 - $t_{1/2}$: elimination half life for the drug
 - V_d : apparent volume of distribution

Metabolism Kinetics

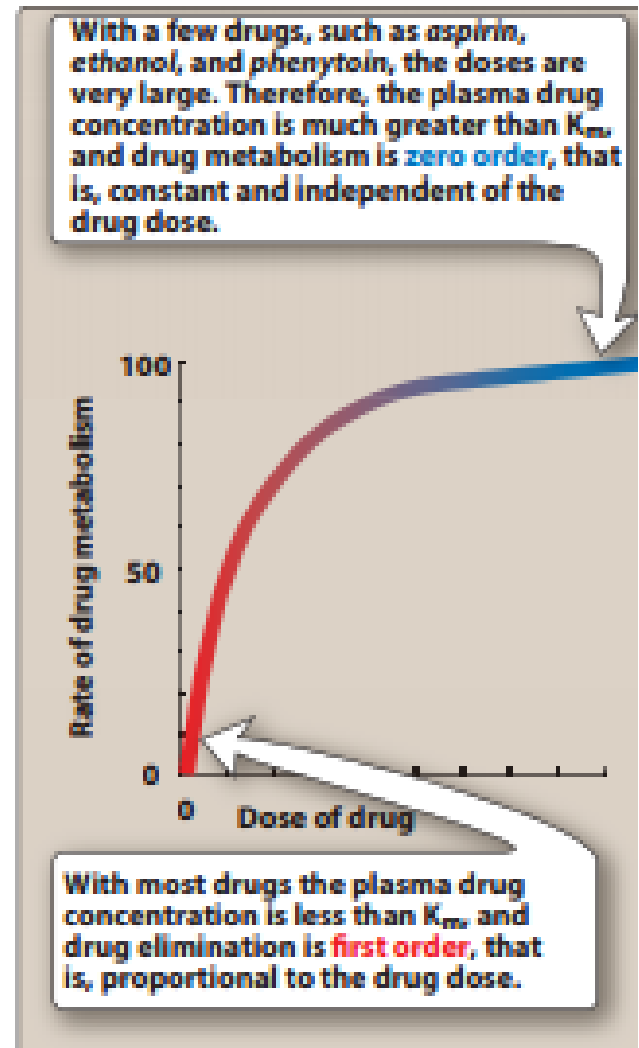
1. First-order kinetics

The rate of drug metabolism and elimination is directly proportional to the drug concentration

2. Zero-order kinetics (nonlinear kinetics)

e.g. aspirin, ethanol, phenytoin

The rate of metabolism or elimination is constant and does not depend on drug concentration.



► Michaelis–Menten Enzyme Kinetics

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

- First-order kinetics ($C \ll K_m$)

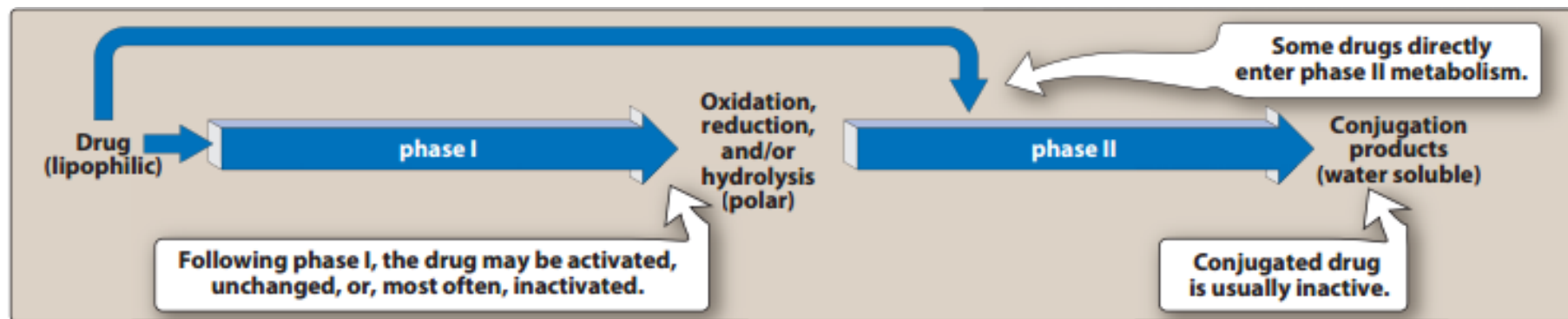
$$V = \text{rate of drug metabolism} = \frac{V_{\max} [C]}{K_m}$$

- Zero-order kinetics ($C \gg K_m$)

$$V = \text{rate of drug metabolism} = \frac{V_{\max}}{[C]} =$$

Reactions of Drug Metabolism

- ▶ Kidney cannot efficiently eliminate lipophilic drugs as they get reabsorbed in distal convoluted tubules.
- ▶ Lipid soluble agents must be metabolized into more polar (hydrophilic) substances in the liver
 1. Phase I reactions
Oxidation, Reduction, Hydrolysis
 2. Phase II reactions
Conjugation



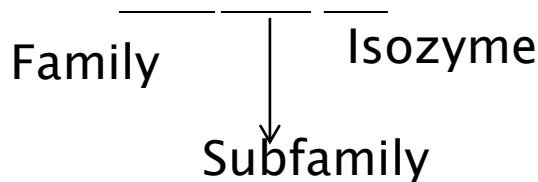
- ▶ Not all drugs undergo Phase I and Phase II metabolism in that order, sometimes the order is reversed.

Phase I Metabolism

- ▶ Conversion of lipophilic molecules into more polar molecules by unmasking or adding a polar group like $-OH$ or $-NH_2$
 - Involve P450 enzymes
(most frequent for Phase I drug metabolism)
 - Not involving P450: e.g. Esterases and Hydrolysis

P450

► Example: CYP3A4

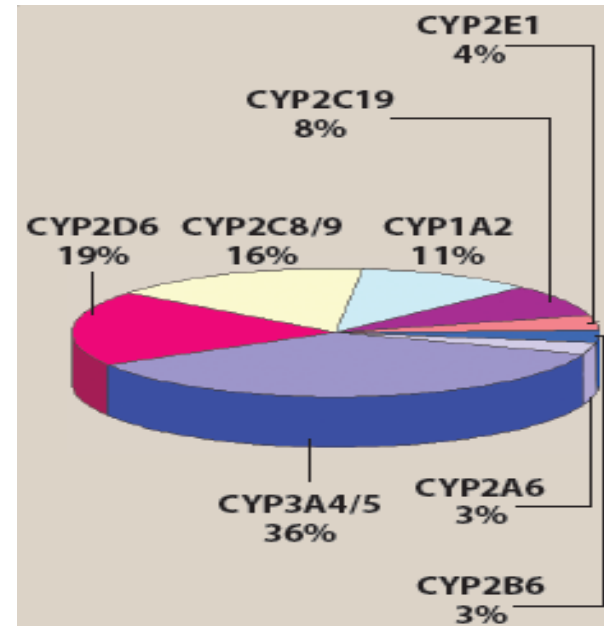


► Genetically variable

- Altered drug efficacy
- Altered toxicity risk
 - CYP2D6

► Inducers (increase metabolism) (Drug Interactions)

- Decrease plasma concentration
- Decrease therapeutic effect
- Decrease drug activity if metabolite is inactive
- Increase drug activity if metabolite is active



Isozyme: CYP3A4/5

COMMON SUBSTRATES	INDUCERS
Carbamazepine	Carbamazepine
Cyclosporine	Dexamethasone
Erythromycin	Phenobarbital
Nifedipine	Phenytoin
Verapamil	Rifampin

P450

► Inhibitors:

- P450 inhibitors cause drug interactions
- Can cause adverse reactions
- Example: Grapefruit and its juice can inhibit CYP3A4 leading to increased levels of drugs metabolized by this enzyme causing higher therapeutic or toxic effects

Phase II Metabolism

- ▶ Conjugation reactions
- ▶ If Phase I metabolite are still too lipophilic then they undergo conjugation reactions with endogenous substrates like:
 - Glucuronic acid (most common)
 - Sulfuric acid
 - Acetic acid
 - Amino acid

Excretion

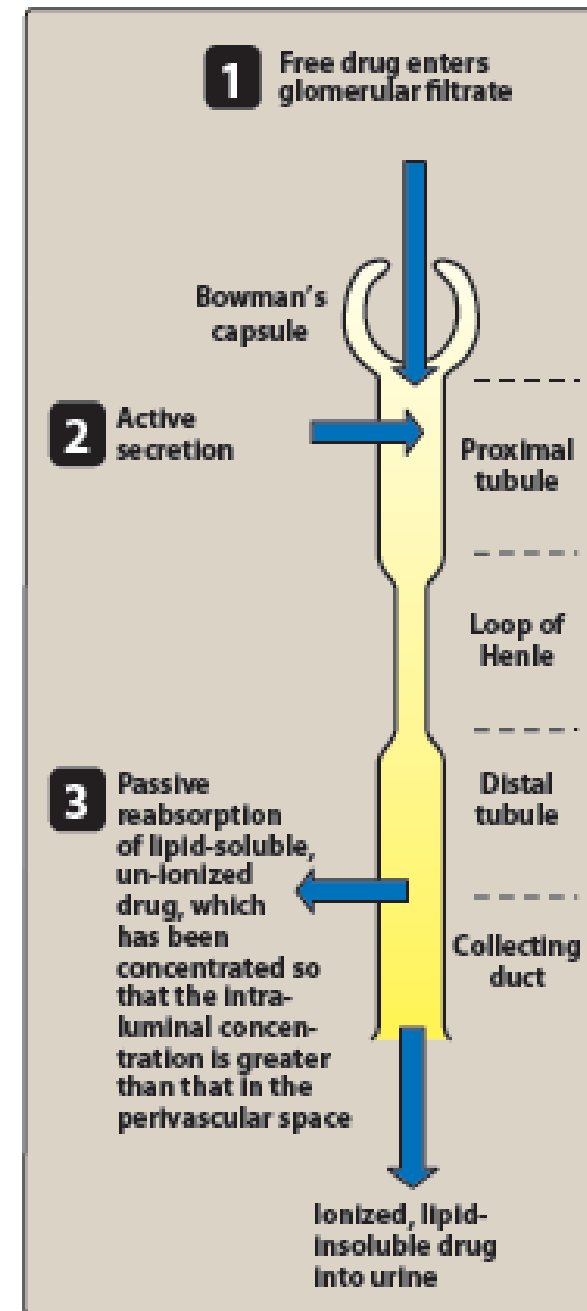
Drug excretion by the kidney

- ▶ The most important route for drug removal from the body is through the kidney into the urine
- ▶ Drugs need to be polar enough for efficient excretion

Renal elimination

- ▶ Elimination of drugs into the urine involves 3 processes:

1. Glomerular filtration
2. Proximal tubular secretion
3. Distal tubular reabsorption



Glomerular filtration

- ▶ Drugs enter the kidney through renal arteries which divide to form a glomerular capillary plexus
- ▶ Free drug (non-protein bound) flows into Bowman's space as part of the glomerular filtrate
- ▶ Glomerular filtration rate is 125mL/min
- ▶ Lipid solubility and pH do not influence glomerular filtration rate

Proximal tubular secretion

- ▶ Secretion occurs in the proximal tubules by 2 energy requiring active transport systems
 - One for anions (deprotonated forms of weak acids)
 - One for cations (protonated forms of weak bases)
- ▶ Competition between drugs on the transport systems can occur

Distal tubular reabsorption

- ▶ As a drug moves toward DTC its concentration becomes higher than in the perivascular space
- ▶ Uncharged drugs will diffuse out of the nephric lumen to the systemic circulation

Distal tubule reabsorption

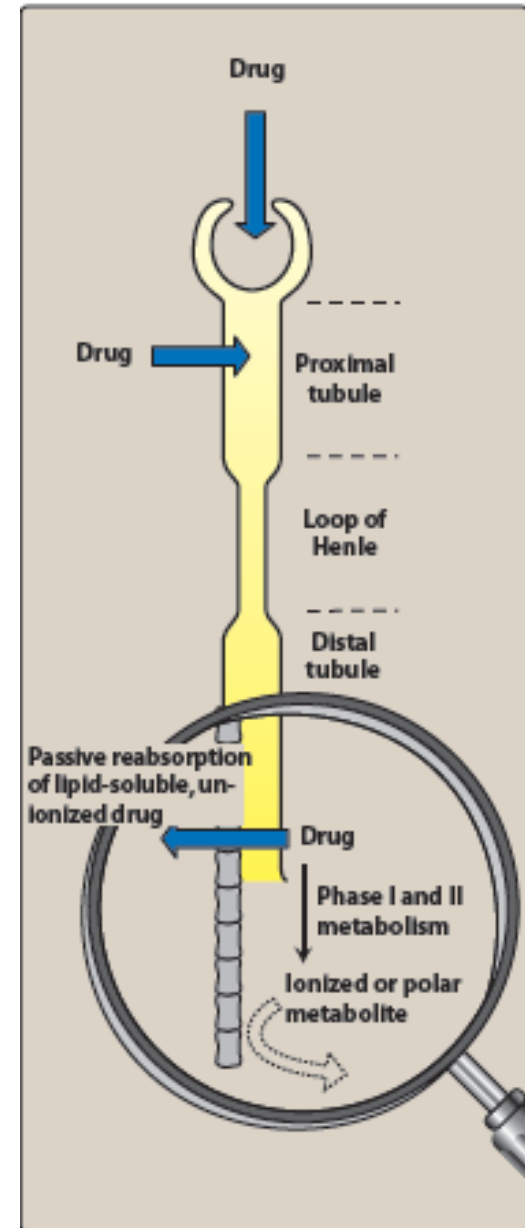
- ▶ Increasing the ionized form of the drug in the lumen by changing the pH of the urine can minimize the back-diffusion and increase clearance

{Ion Trapping}

- Elimination of weak acids can be increased by alkalization of the urine
 - e.g. phenobarbital (weak acid) overdose
- ➡ Alkalization of urine with bicarbonate keeps the drug ionized
- Elimination of weak bases can be enhanced by acidification of the urine
 - e.g. overdose of amphetamine (weak base)
- ➡ Acidification of urine with NH_4Cl causes the protonation of the drug and enhancement of its excretion

Role of drug metabolism in elimination

- ▶ Most drugs are lipid soluble
- ▶ Without chemical modification drugs would diffuse back from the kidney lumen when their concentration is higher there
- ▶ To minimize reabsorption drugs are modified (mainly in liver) to more polar compounds



Clearance by other routes

- ▶ Liver
- ▶ Intestine
- ▶ Bile
- ▶ Lungs
- ▶ Milk in nursing mothers
- ▶ To a small extent in sweat, tears saliva, hair and skin

▶ Liver

- contributes to drug loss through metabolism and/or excretion into the bile
- patients with renal failure may benefit from drugs excreted through this route

▶ Feces

- Elimination of unabsorbed orally ingested drugs
- Elimination of drugs that are secreted directly into the intestines or bile

▶ Lungs

- Elimination of anesthetic gases

▶ Breast milk

- Source of undesired effects to the infant

► Total body clearance

$$CL_{\text{total}} = CL_{\text{hepatic}} + CL_{\text{renal}} + CL_{\text{pulmonary}} + CL_{\text{other}}$$

where $CL_{\text{hepatic}} + CL_{\text{renal}}$ are typically the most important.

► $t_{1/2}$ of drugs can be altered by

- Diminished renal or hepatic flow (↑ $t_{1/2}$)
(e.g. cardiogenic shock, heart failure, hemorrhage)
- Decreased ability to extract drug from plasma (↑ $t_{1/2}$)
(e.g. renal disease)
- Decreased metabolism (↑ $t_{1/2}$)
- Increased hepatic blood flow (↓ $t_{1/2}$)
- Decreased protein binding (↓ $t_{1/2}$)
- Increased metabolism (↓ $t_{1/2}$)