Basic Principles in Pharmacology

Pharmacology

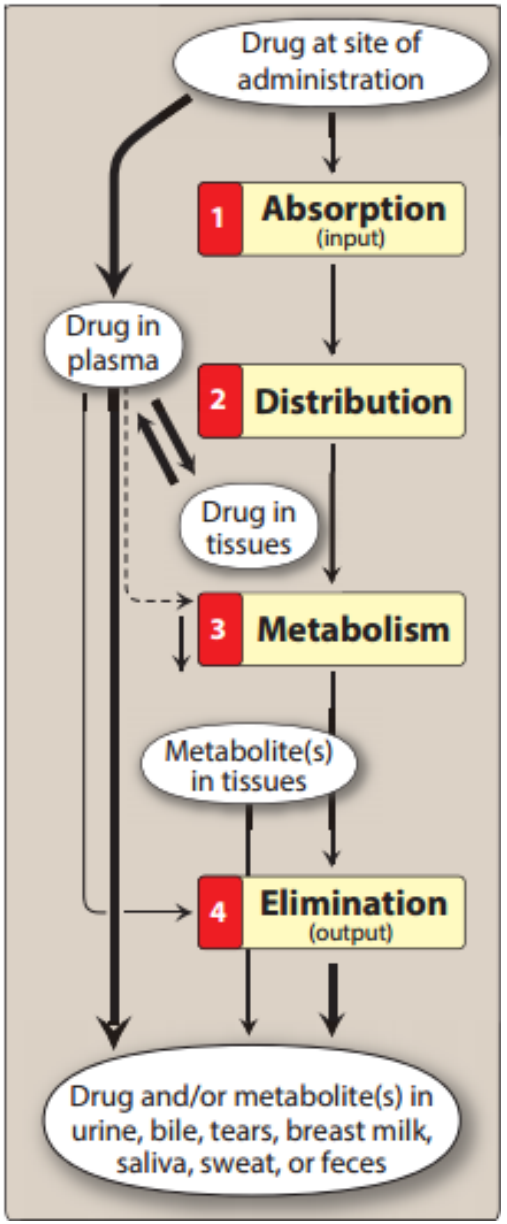
- **Pharmacology**: is the study of drugs, their uses and how they affect organisms
  - **Pharmacokinetics:** describes what the body does to a drug.
  - **Pharmacodynamics:** describes what the drug does to the body.

Pharmacokinetics

Pharmacokinetics

- ADME
  - **A**bsorption
  - **D**istribution
  - **M**etabolism
  - **E**limination

- ADME determine:
  - The speed of onset of drug action
  - The intensity of the drug effect
  - The duration of drug action



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ADME

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

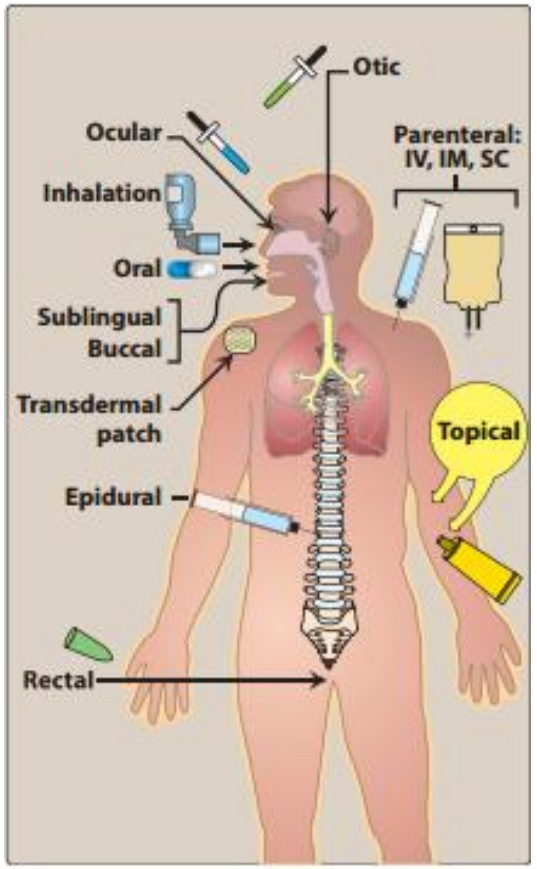
Distribution: Reversible process, the drug leaves the bloodstream and distributes into the interstitial and intracellular fluids

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



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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

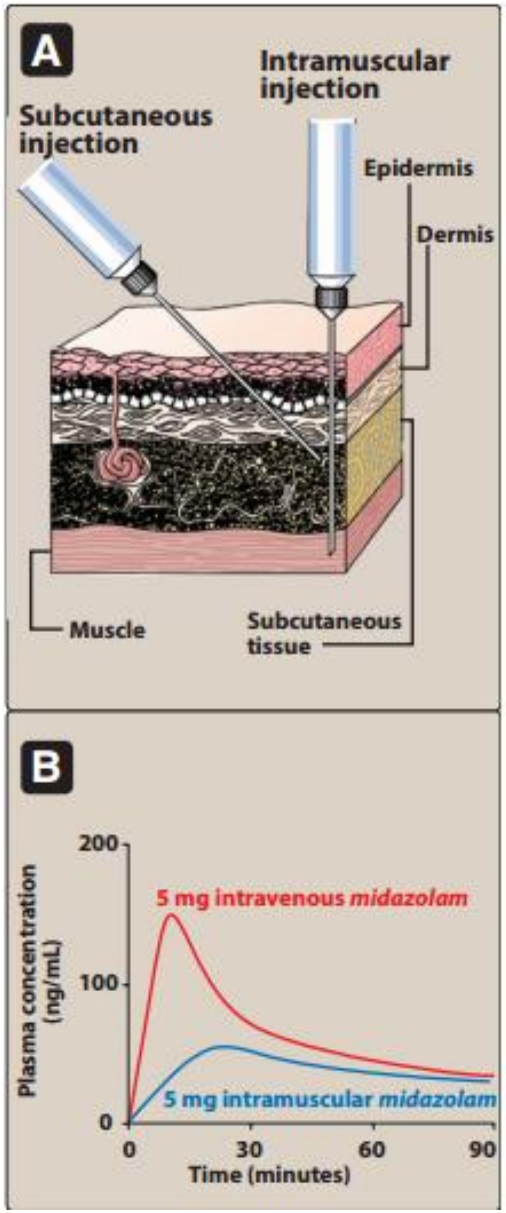
Parenteral Route

- 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

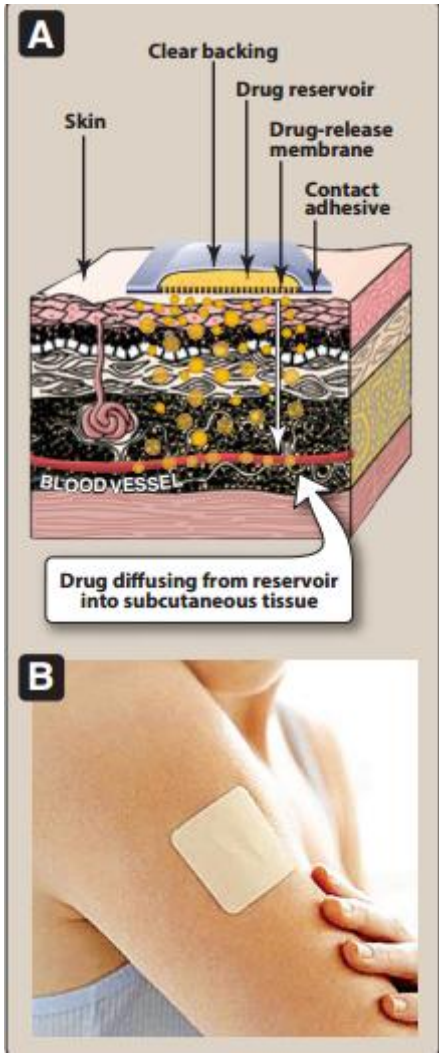
Parenteral Routes

- 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

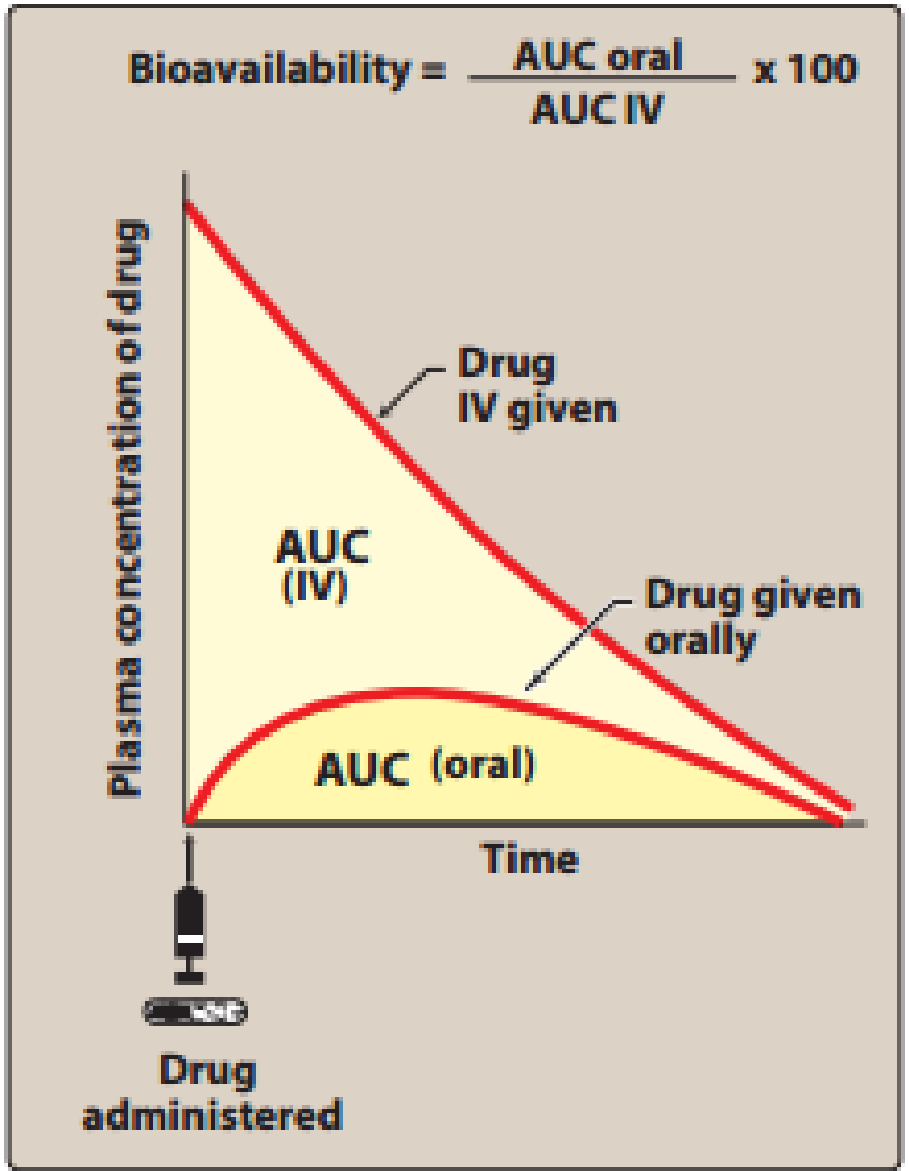
- Absorption Rate: how rapidly does the drug get from its site of administration to the general circulation ?

- 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

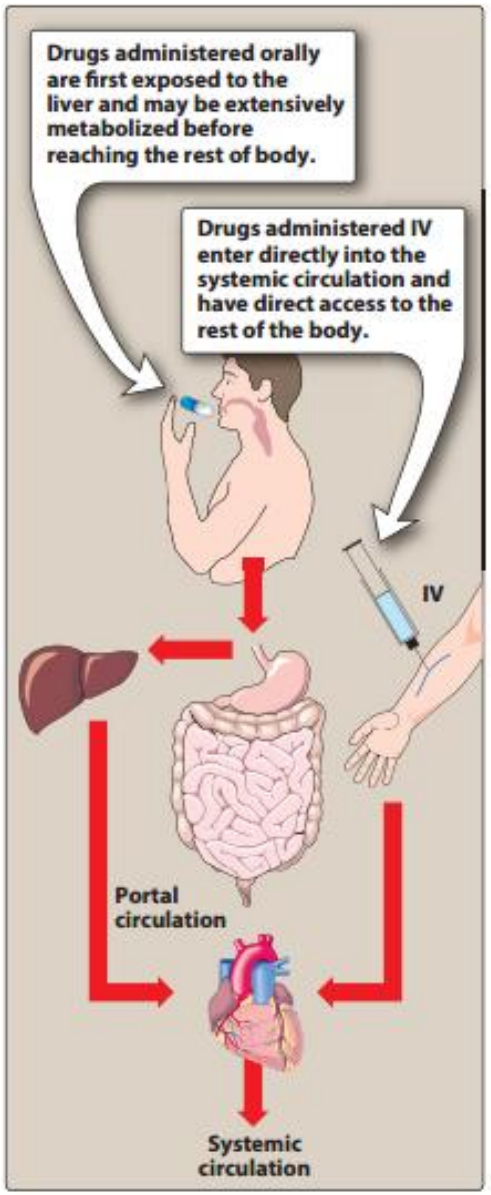


Factors that influence oral bioavailability

- 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

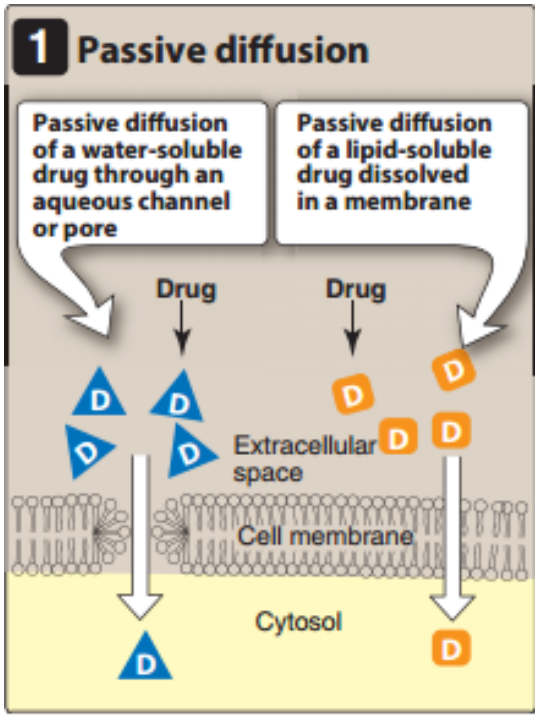
- Nature of the drug formulation
  - Presence of excipients alter the rate of absorption

Mechanisms of drug absorption from GI tract

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

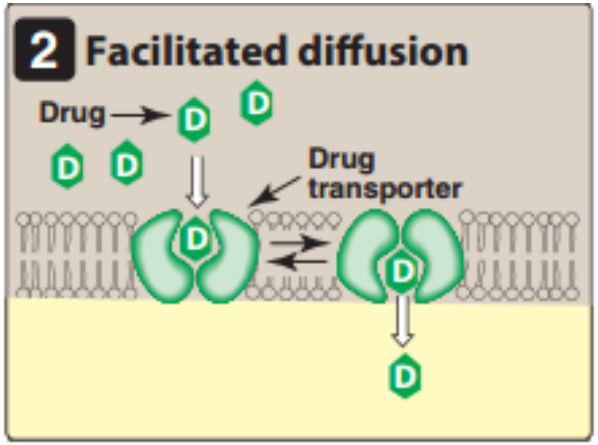
Passive diffusion

- 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



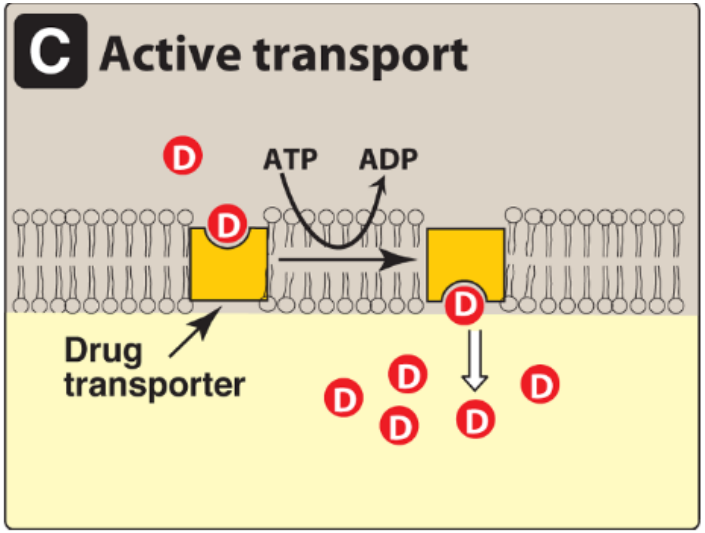
Facilitated diffusion

- 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



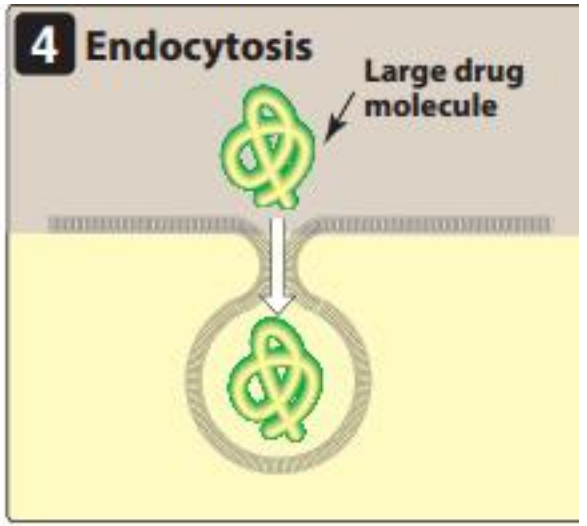
Active transport

- 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

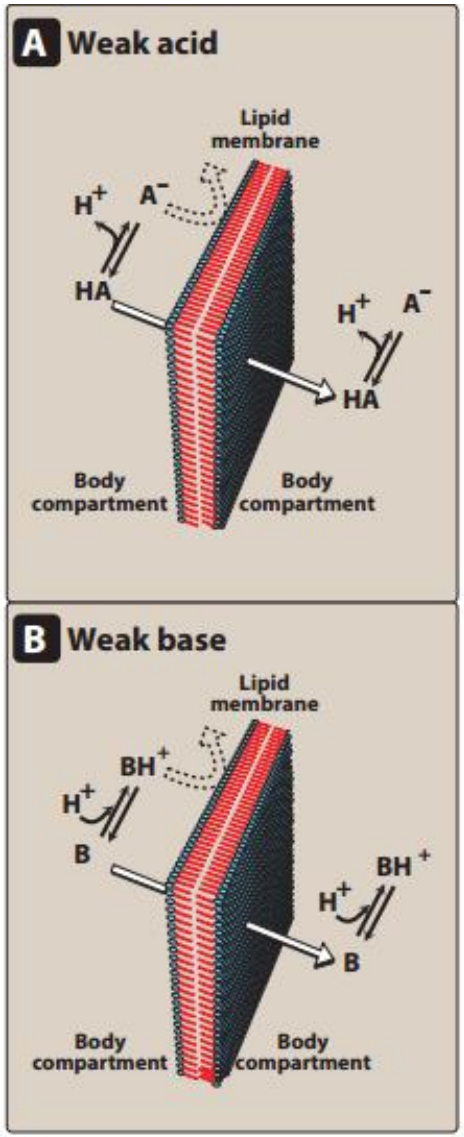
1. pH
   - Most drugs are weak acids or weak bases

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

     $BH^+ \rightleftharpoons B + H^+$

   - Drugs pass through membranes easier when uncharged

   - $pH < pK_a$ protonated form predominates
   - $pH > pK_a$ deprotonated form predominates



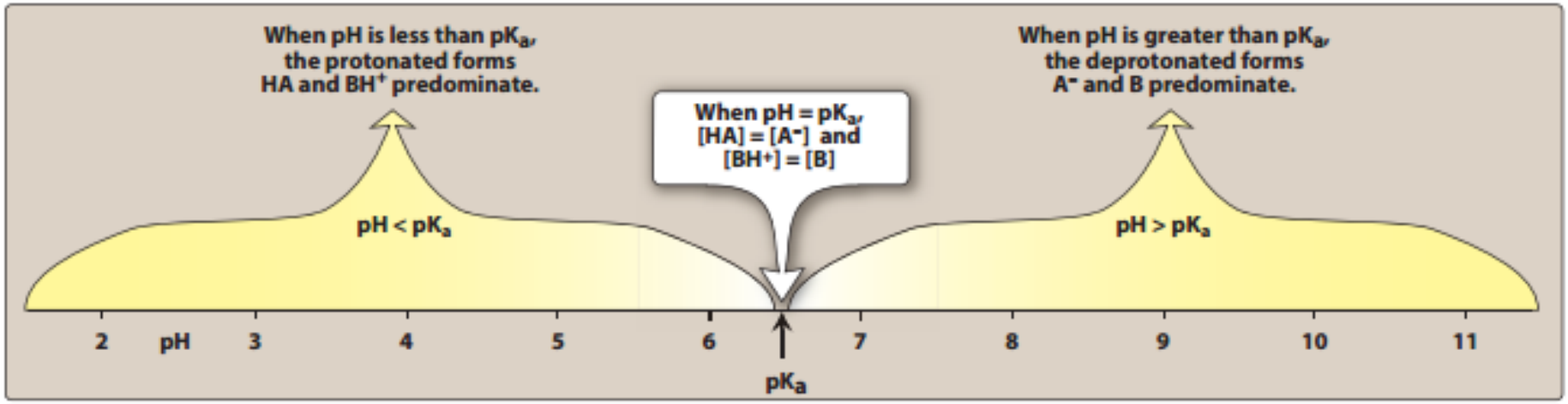


Figure 1.8

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

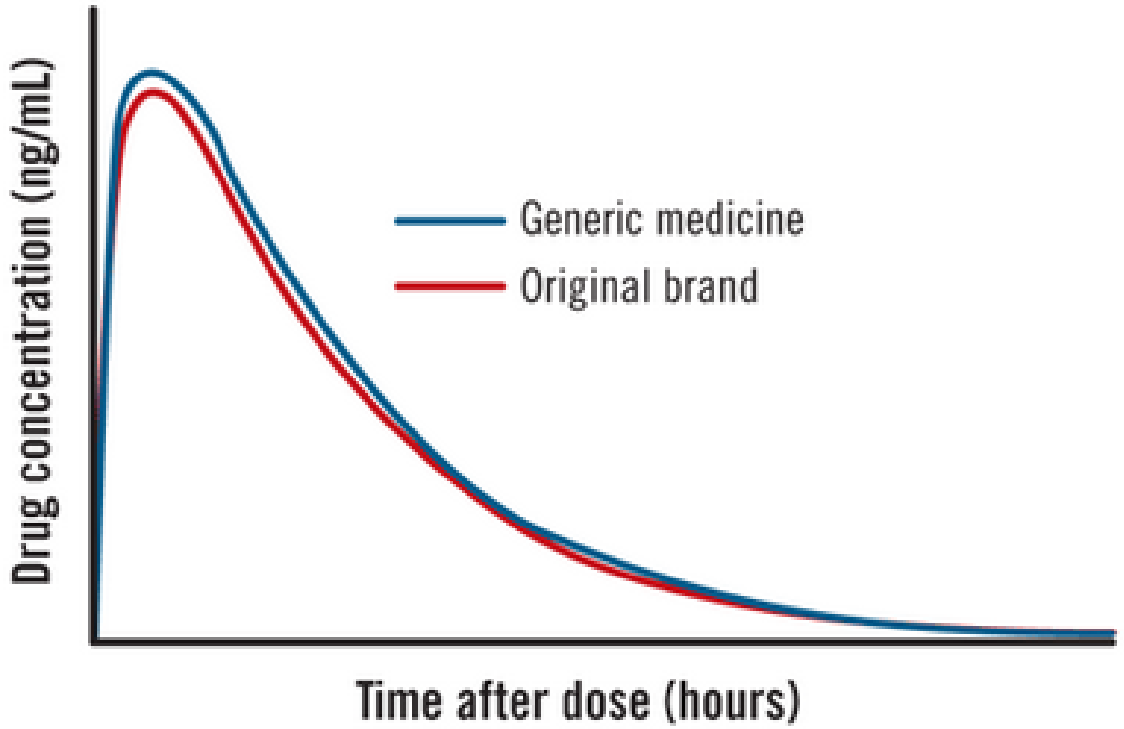
  Two related drug preparations are bioequivalent if they show
  - Comparable bioavailability
  - Similar times to achieve peak blood concentrations.

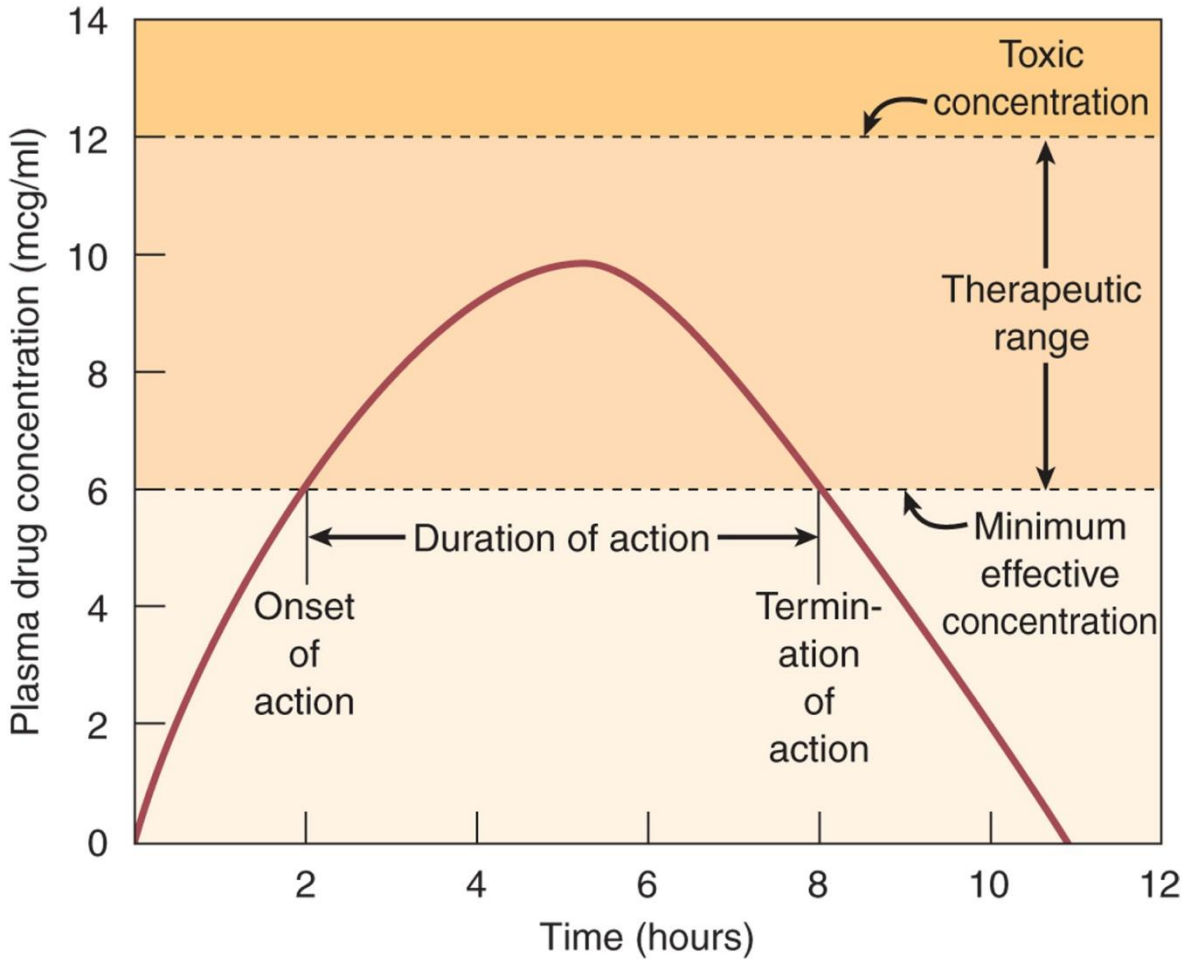
- Therapeutic equivalence

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

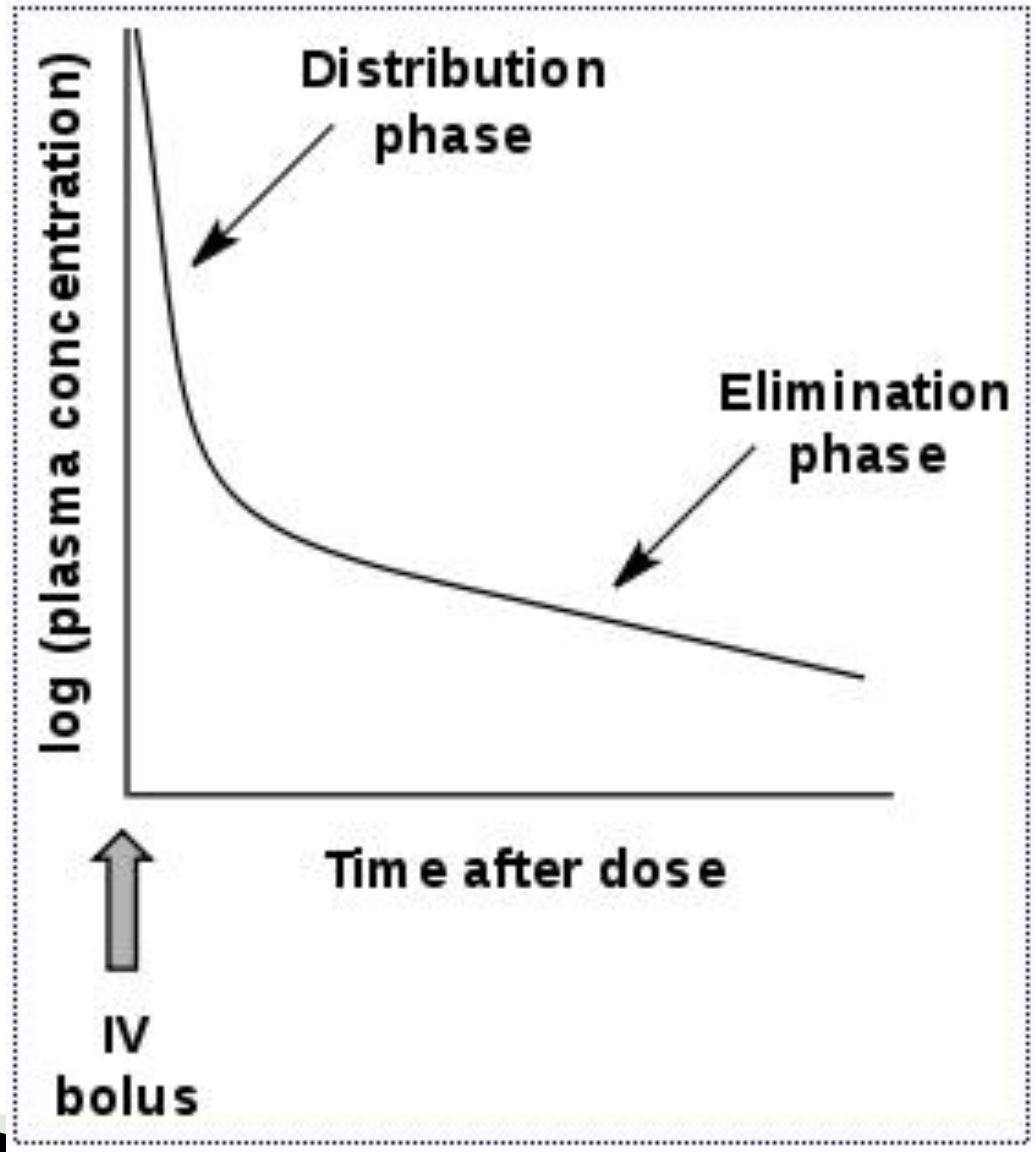
FIGURE

Bioequivalence analysis: *a hypothetical bioequivalence study*[6]





Adams et al. 2008


log (plasma concentration)
Distribution phase
Elimination phase
Time after dose
IV bolus

Drug Distribution

- Distribution: the process by which a drug reversibly leaves the blood stream and enters the interstitium and then cells

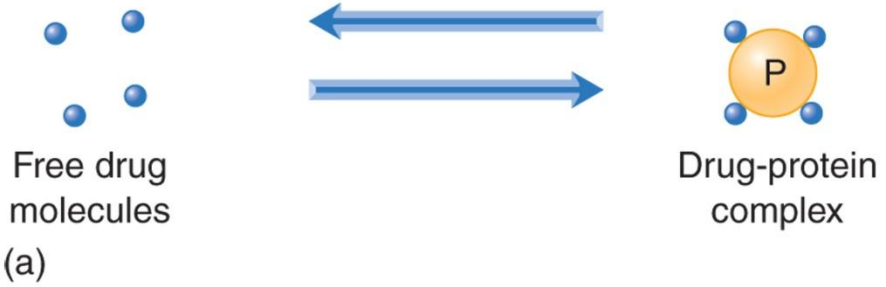
- For an IV drug; No absorption occurs

Distribution occurs immediately after administration

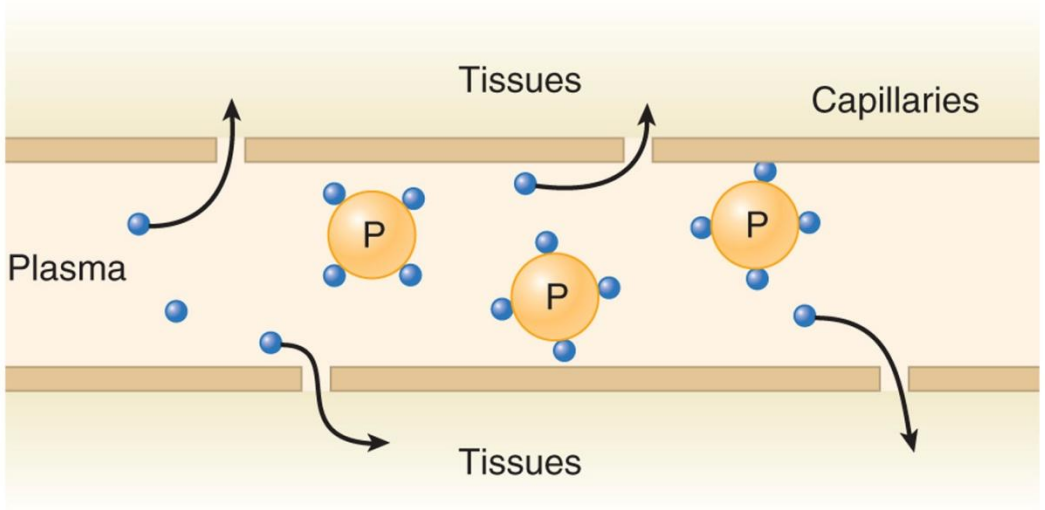
Drug Distribution

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



(a)



(b)

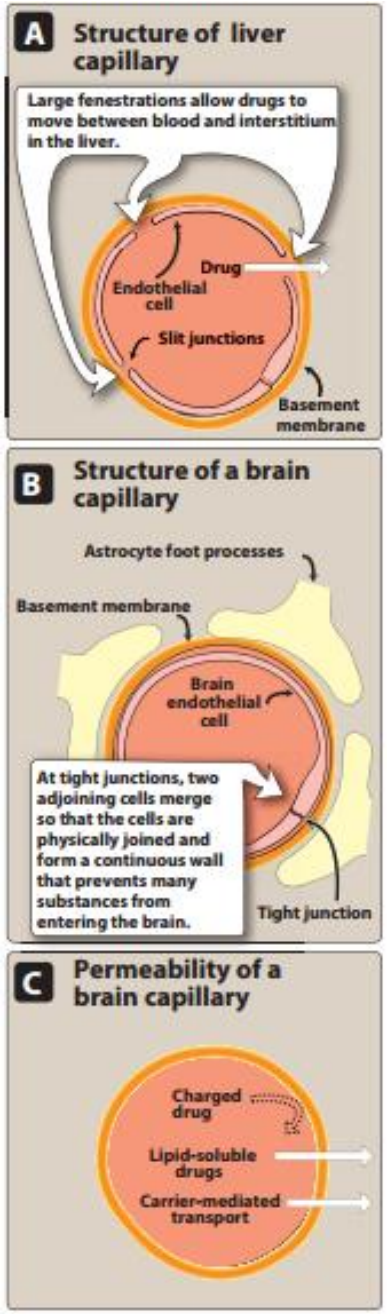
1. Blood Flow

- 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

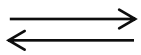
- Example: thiopental, highly lipid soluble
  - Initially rapidly moves into the brain due to high blood flow and produces anesthesia
  - A slower distribution into skeletal muscles and adipose tissues lowers plasma concentration, and CNS concentration
  - Consciousness is regained

2. Capillary permeability

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



Drug–Protein binding

- Binding to plasma proteins
  - Nonselective
  - Albumin
  - Protein bound drug  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

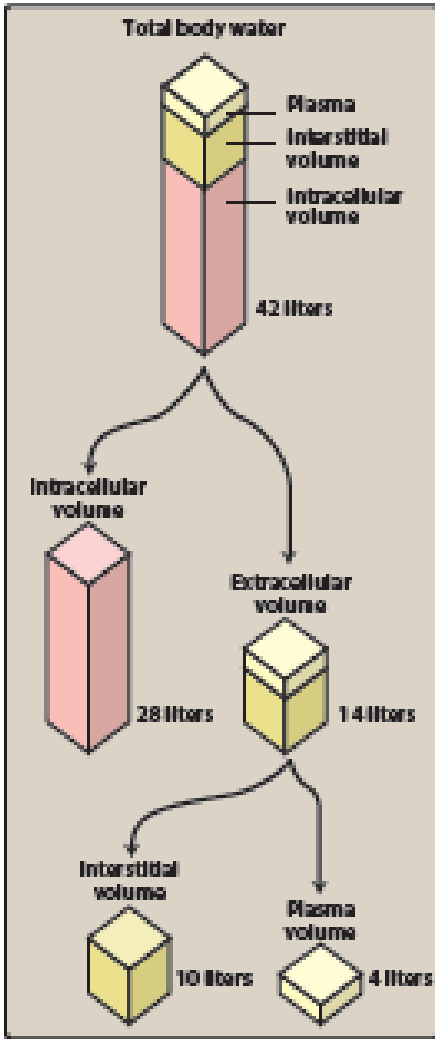
  It can be used to compare the distribution of a drug in the water compartments of the body
  - Plasma (4L)

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



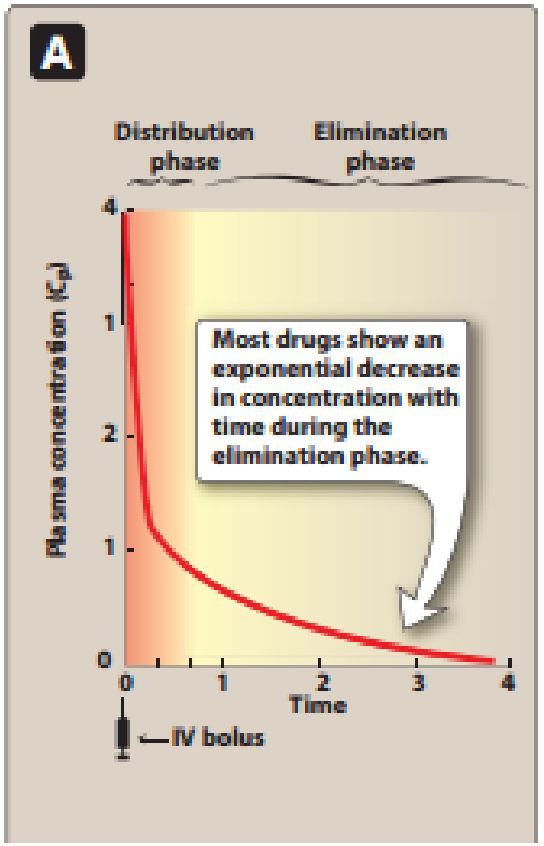
- Apparent volume of distribution (V_d)
  - A drug rarely associates with one water compartment
  - Usually drugs are bound to cellular compartments like
    - Proteins in plasma and cells
    - Lipids in adipocytes and cell membranes
    - Nucleic acids in nuclei of cells

- V_d is useful for calculating the loading dose of a drug

- Example:

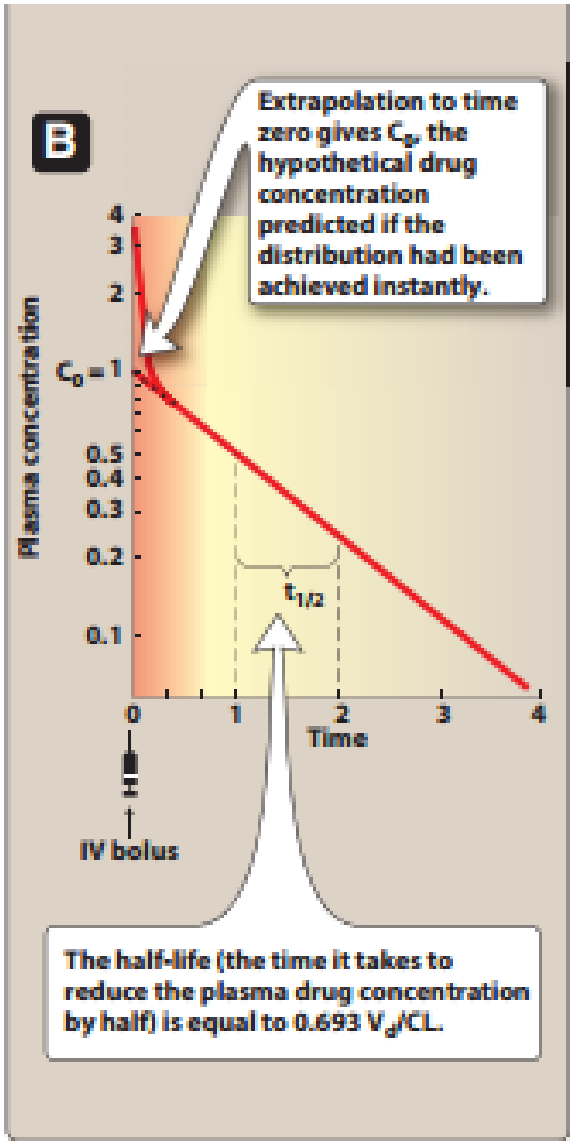
  If 10 mg of a drug are injected and the plasma concentration is 1 mg/L what is V_d?

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



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

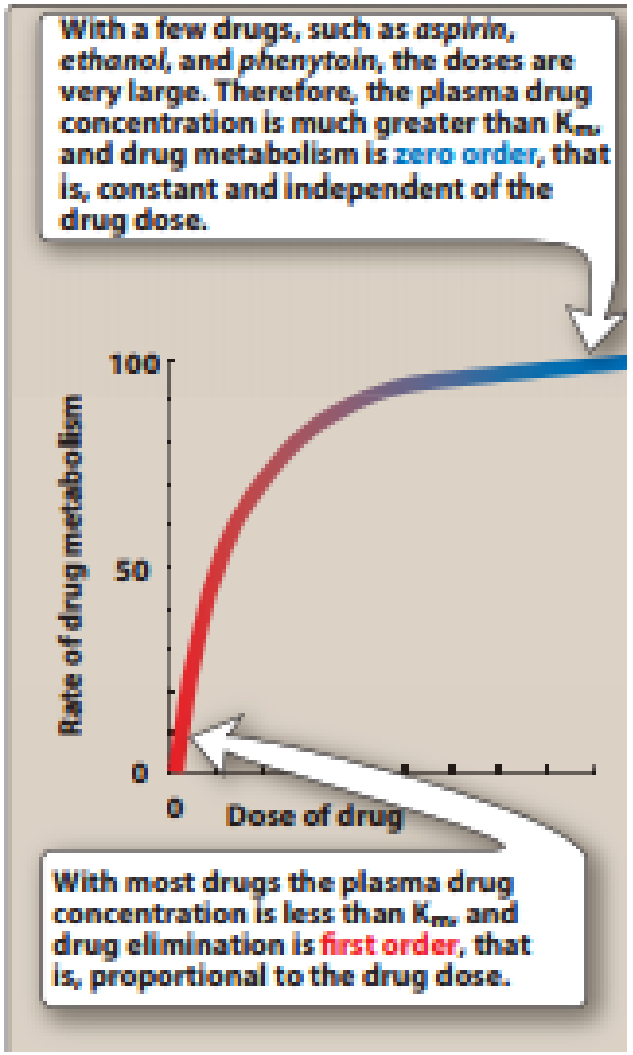
1. First-order kinetics

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 is <<<<Km)

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

  - Zero-order kinetics (C>>>>>Km)

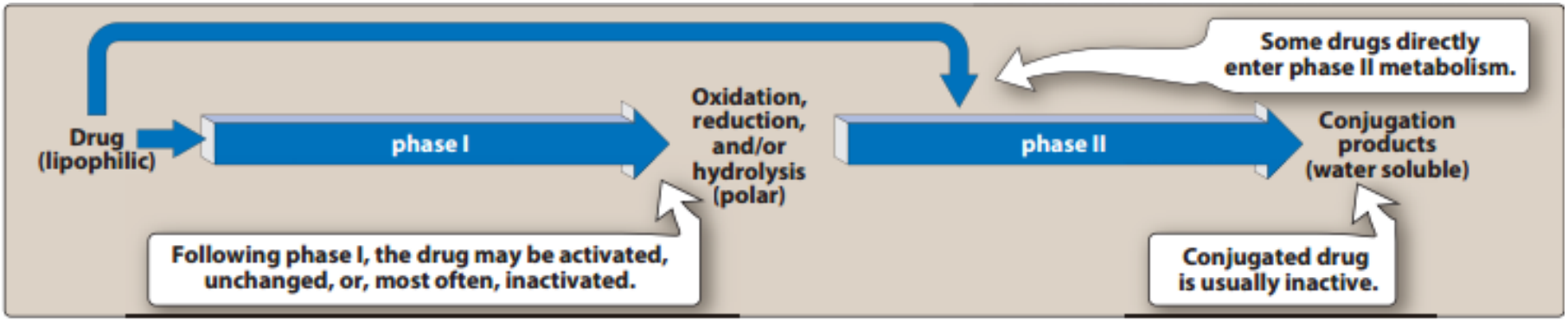
    $$V = \text{rate of drug metabolism} = \frac{V_{max}[C]}{[C]} = V_{max}$$

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

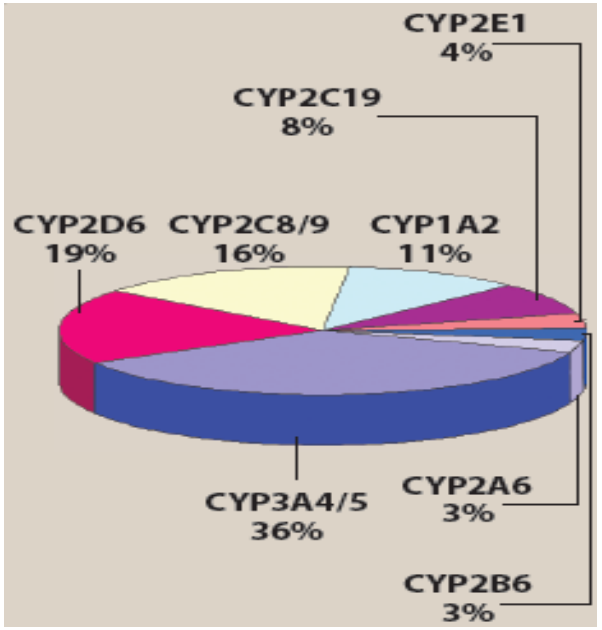
- Conversion of lipophilic molecules into more polar molecules by unmasking or adding a polar group like –OH or –NH_2
  - Involve P450 enzymes
    (most frequent for Phase I drug metabolism)
  - Not involving P450: e.g. Esterases and Hydrolysis

P450

- Example: CYP3A4

  Family — Subfamily — Isozyme

- 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 inac
  - Increase drug activity if metabolite is activ

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

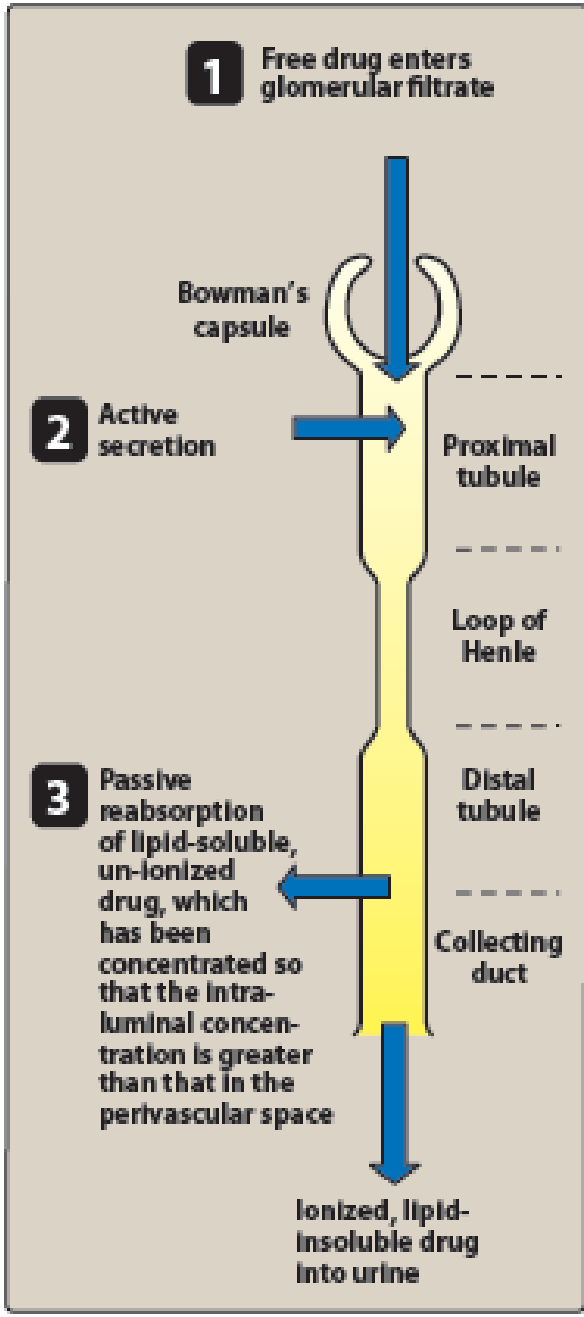
Drug excretion by the kidney

- 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 alkalinization of the urine
  - e.g. phenobarbital (weak acid) overdose

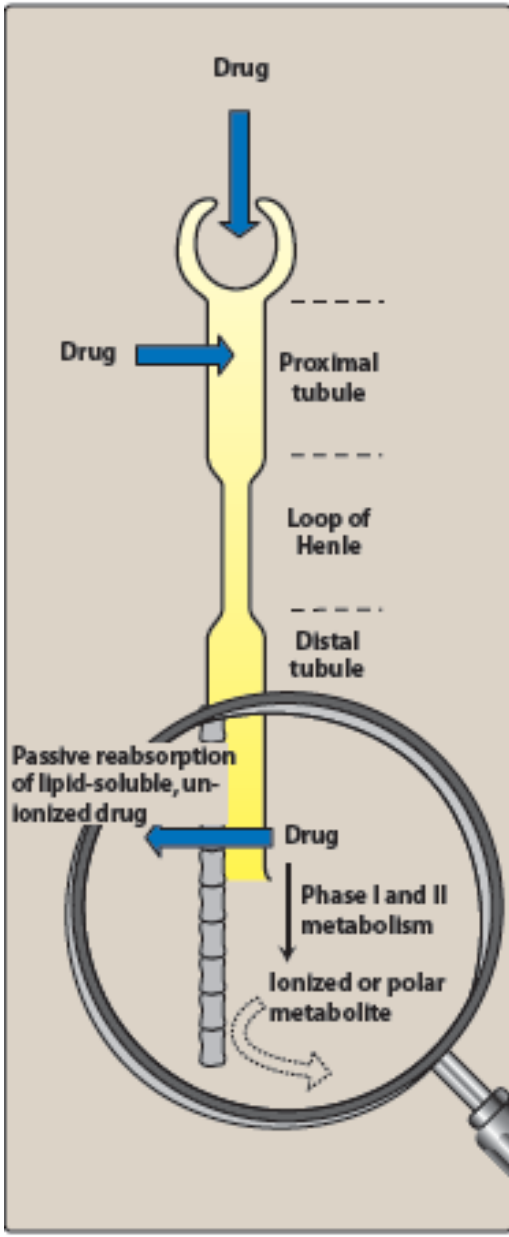
⇨ Alkalinization of urine with bicarbonate keeps the drug ionized

- 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

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

where $CL_{hepatic} + CL_{renal}$ 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 (↓ $t_{1/2}$)