Pharmacokinetics

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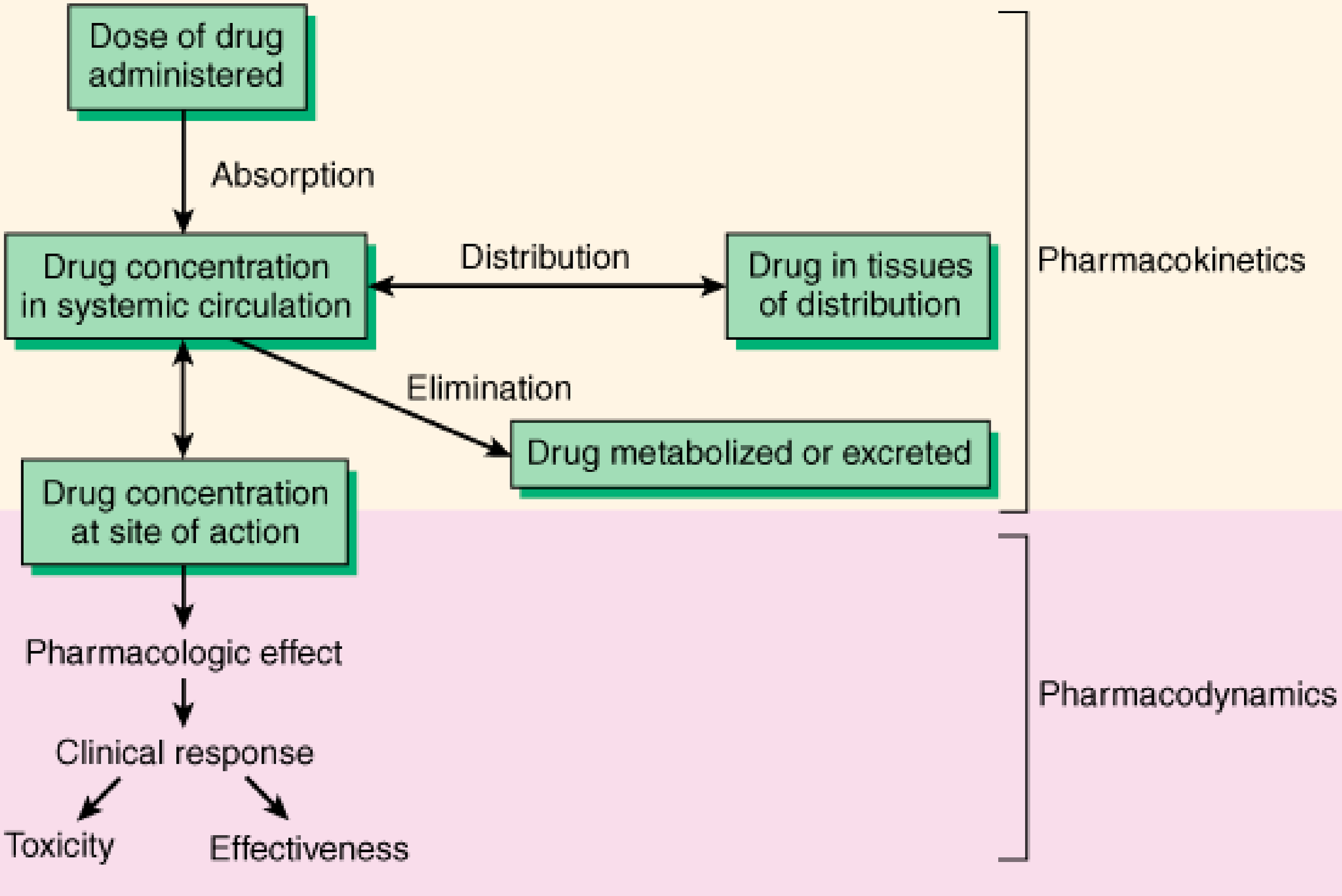
Pharmacokinetics

- May be simply defined as what the body does to the drug.
- The determination of the fate of substances administered from an exogenous source to a living organism.
- The study of the movement of drugs in the body, including the processes of absorption, distribution, localization in tissues, biotransformation and excretion.



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

Routes of Drug Administration

Determined by properties of the drug

- **Water solubility**
- **Lipid solubility**
- **Ionization**

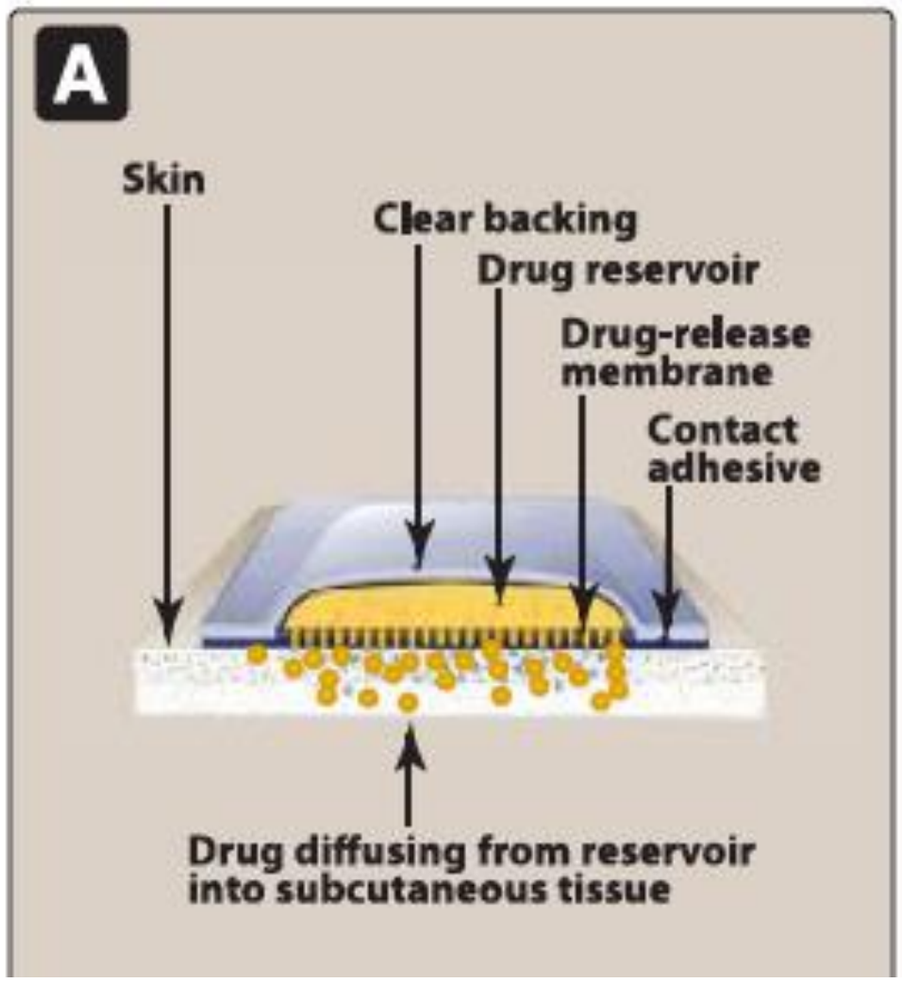
Determined by the therapeutic objective

- **Duration of treatment**
- **Desirability of rapid onset**
- **Restrictions**

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

Transdermal Patch



Mechanisms of absorption of drugs from the GI tract Dependi

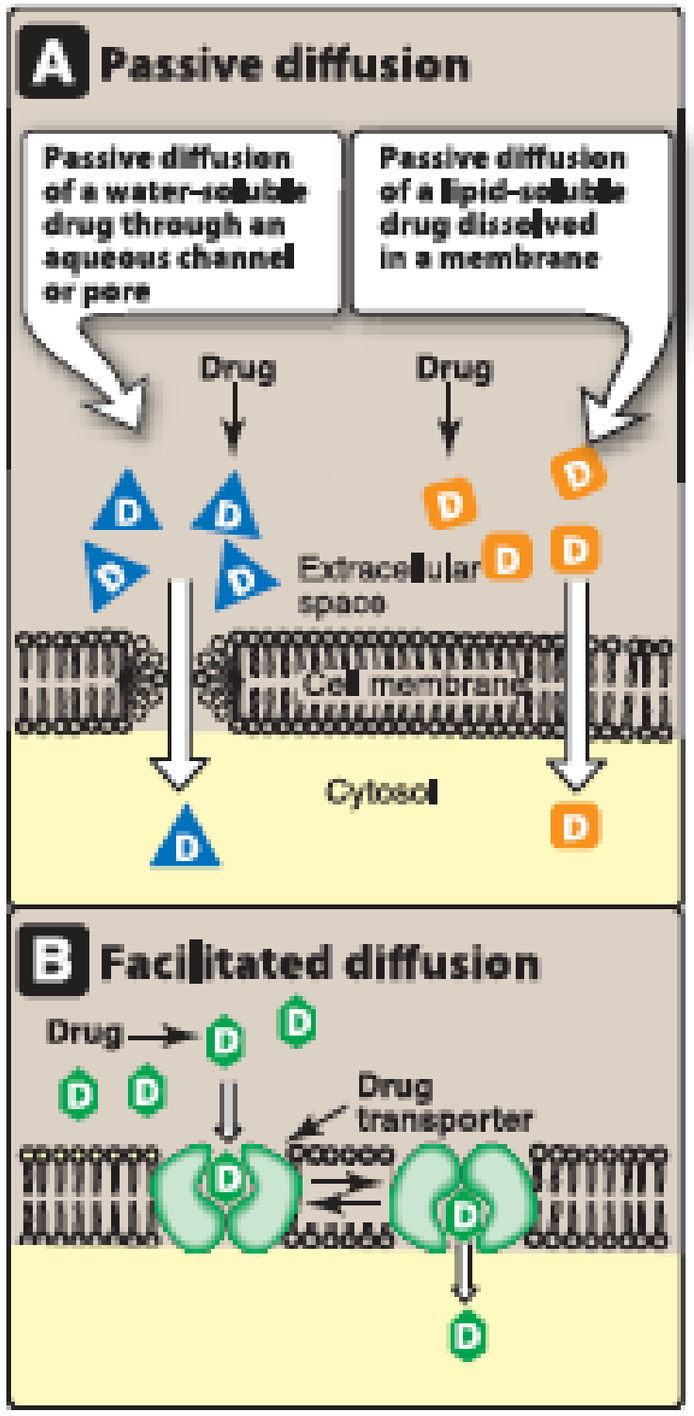
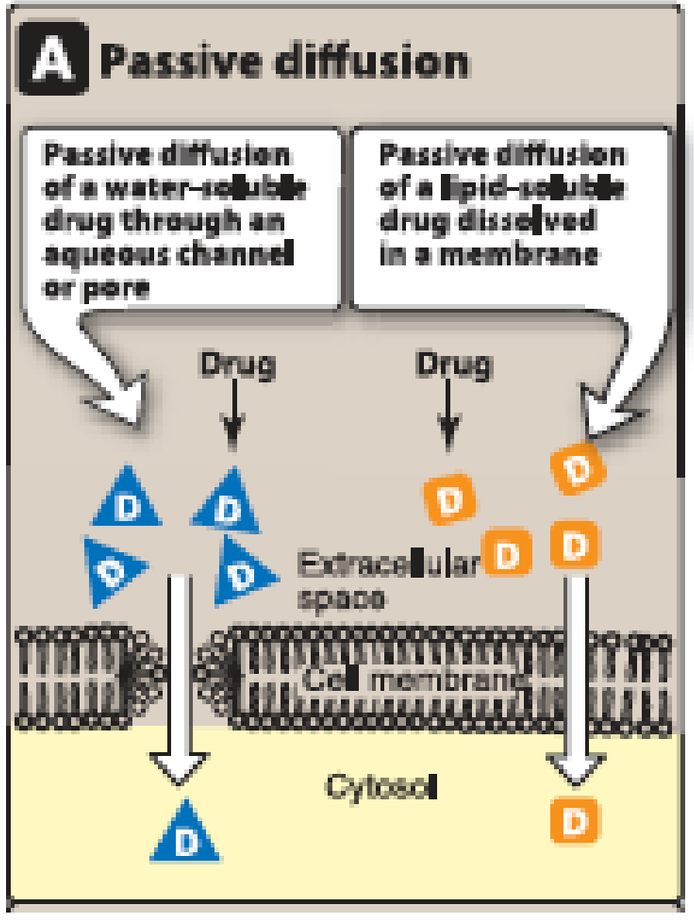


Figure 1.6
Schematic representation of drugs crossing a cell membrane. ATP = adenosine triphosphate; ADP = adenosine diphosphate.

Mechanisms of absorption of drugs from the GI tract

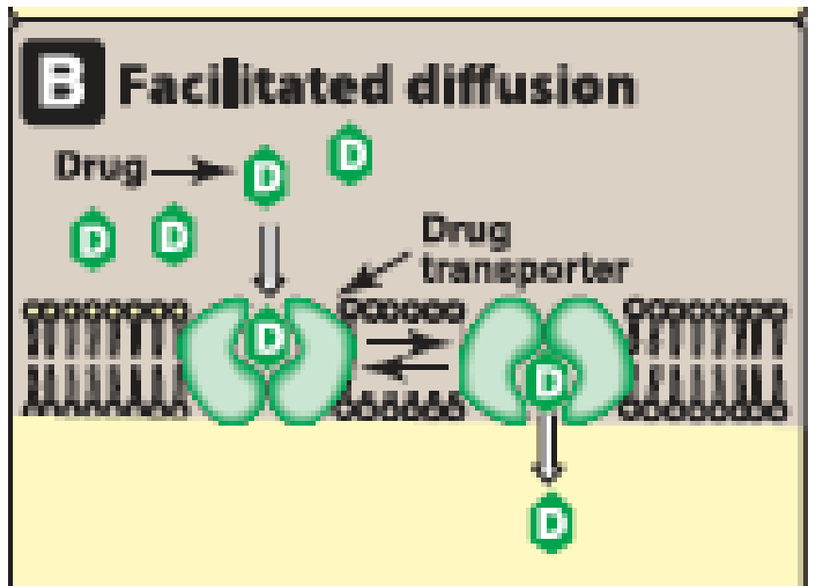
1. Passive diffusion: The driving force for passive absorption of a drug is the concentration gradient across a membrane separating two body compartments.
Passive diffusion does not involve a carrier, is not saturable, and shows a low structural specificity.

- 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.



2. Facilitated diffusion: Other agents can enter the cell through specialised 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.

It does not require energy, can be saturated,
and may be inhibited by compounds that compete for the carrier.
Example: Glucose transport



3. Active transport: This mode of drug entry also involves specific carrier proteins that span the membrane.

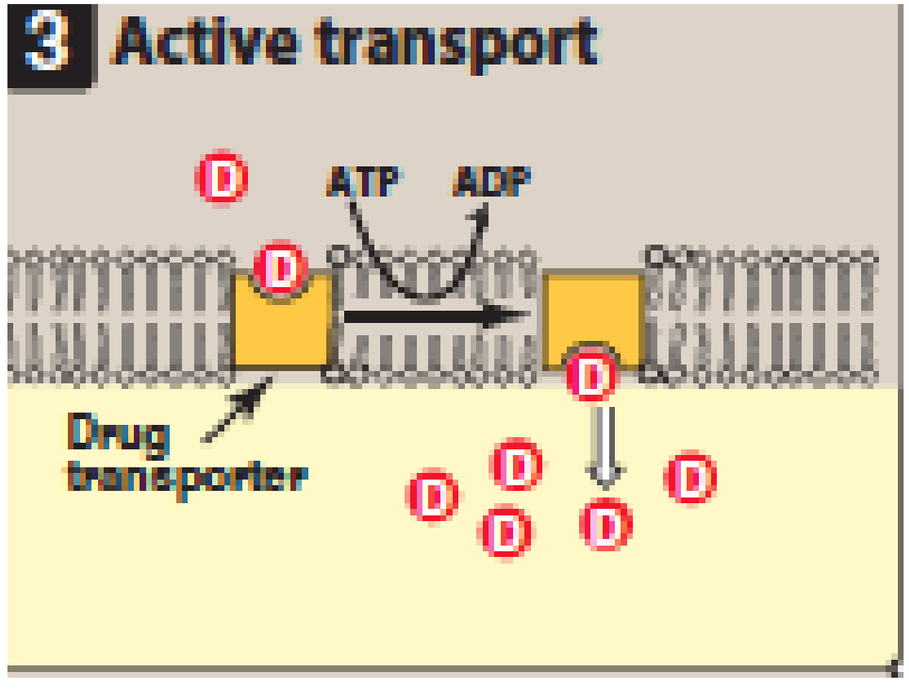
A few drugs that closely resemble the structure of naturally occurring metabolites are actively transported across cell membranes using specific carrier proteins.

Energy-dependent active transport is driven by the hydrolysis of ATP.

It is capable of moving drugs against a concentration gradient.

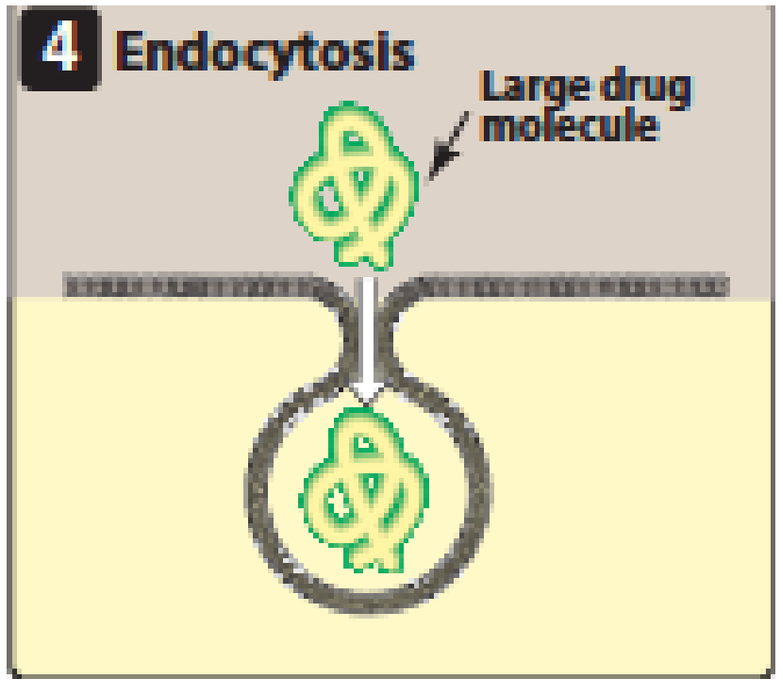
The process is saturable. Active transport systems are selective and may be competitively inhibited by other cotransported substances.

Example :The Sodium-Potassium pump



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**
- **norepinephrine is stored in intracellular vesicles in the nerve terminal and released by exocytosis.**



Absorption

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 and physical characteristics of the drug, and the route of administration (which influences bioavailability).**

- **Complete after IV**
- **Variable after all others (lower than IV)**

Factors influencing absorption

1. pH: Most drugs are either weak acids or weak bases. Acidic drugs (HA) release a proton (H+), causing a charged anion (A−) to form:

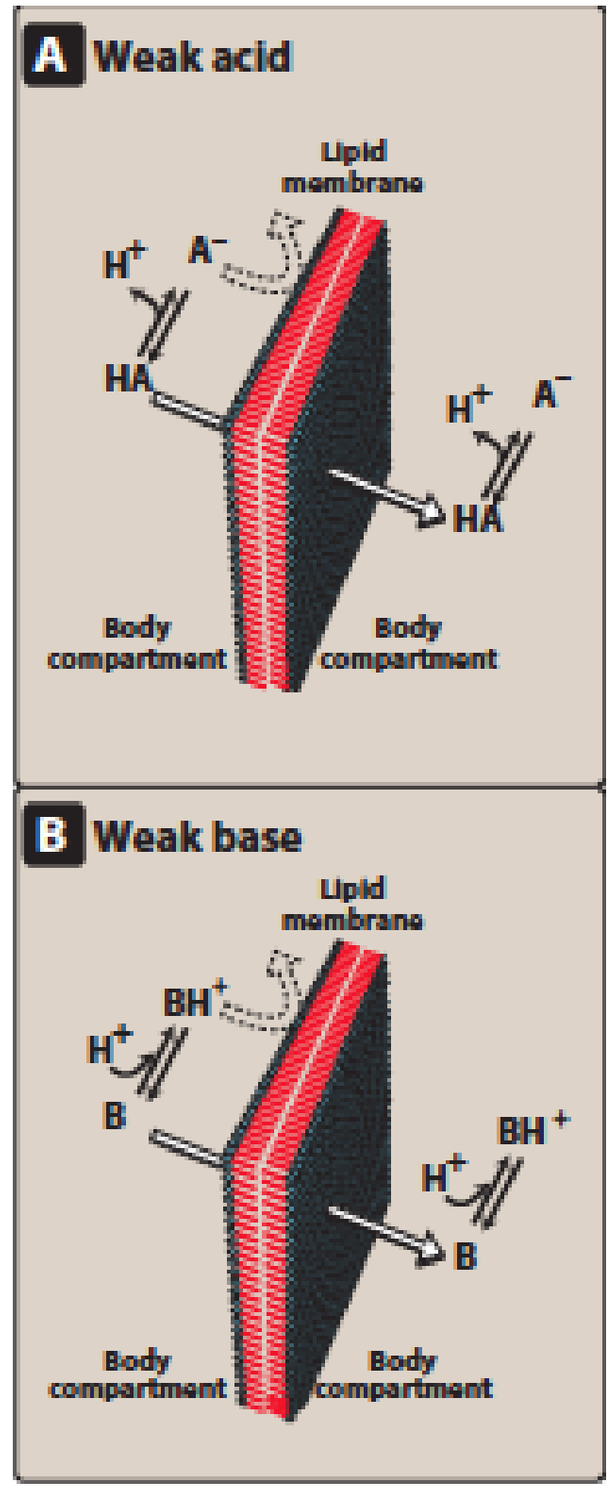
$$HA \rightleftarrows H^+ + A^-$$

Weak bases (BH+) can also release an H+.

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

A drug passes through membranes more readily if it is uncharged

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.



- **Weak acidic drugs are absorbed faster and more completely in the stomach (acidic medium).**
- **Weak basic drugs are absorbed faster and more completely in the intestines (alkaline medium).**

$$pH = pK_a + \log \frac{[\text{nonprotonated species}]}{[\text{protonated species}]}$$

For acids: $pH = pK_a + \log \frac{[A^-]}{[HA]}$

For bases: $pH = pK_a + \log \frac{[B]}{[BH^+]}$

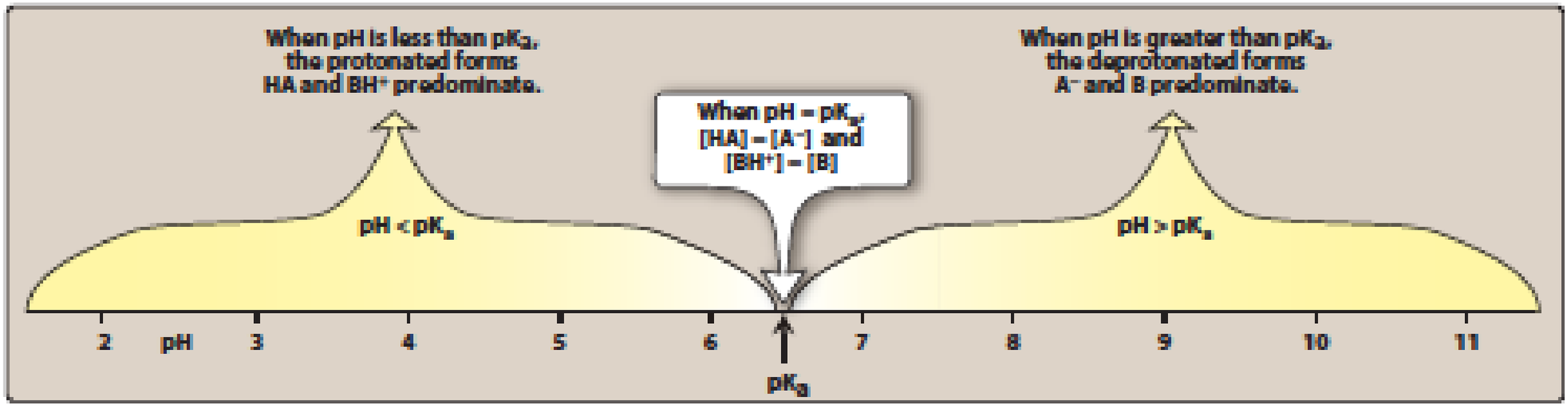


Figure 1.8
The distribution of a drug between its ionized and nonionized forms depends on the ambient pH and pK_a of the drug. For illustrative purposes, the drug has been assigned a pK_a of 6.5.

Factors influencing absorption

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, pKa .

The pKa is a measure of the strength of the interaction of a compound with a proton.

Distribution equilibrium is achieved when the permeable form of a drug achieves an equal concentration in all body water spaces.

Factors influencing absorption

2. Blood flow to the absorption site: The intestines receive much more blood flow than the stomach, so absorption from the intestine is favoured over the stomach.

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.

Factors influencing absorption

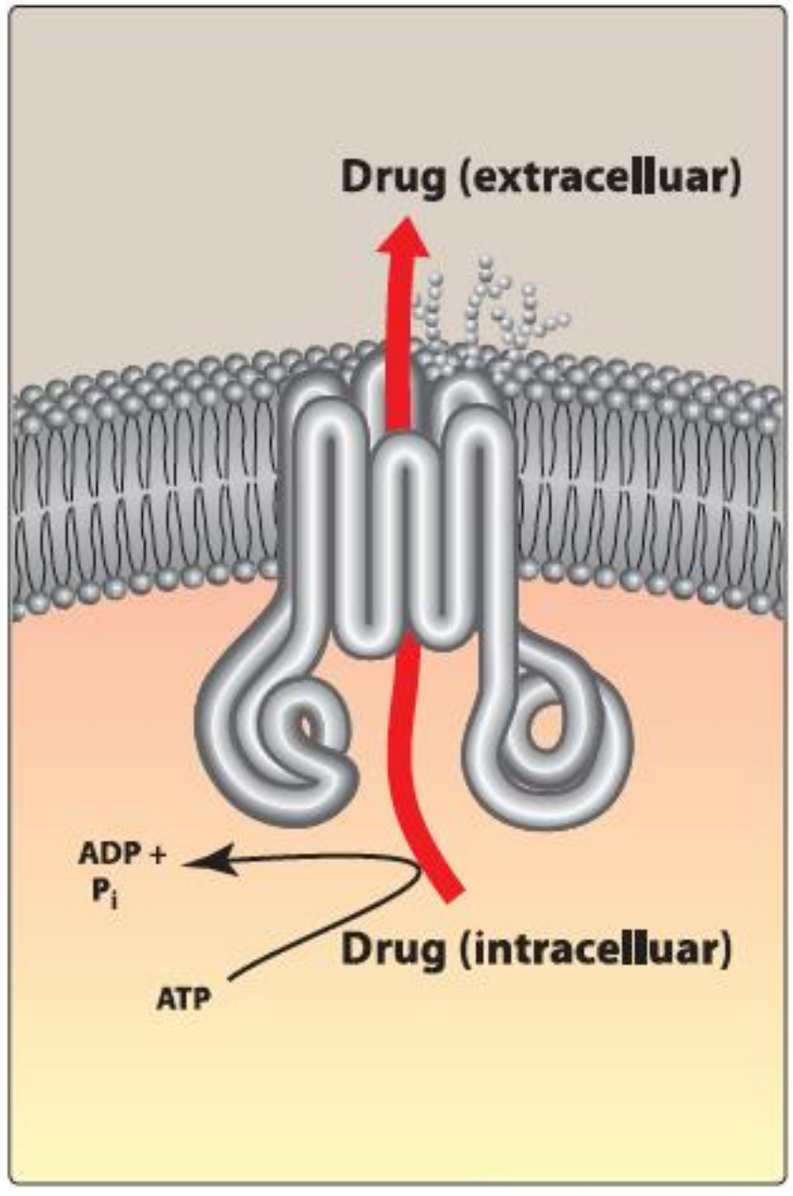
4. Contact time at the absorption surface: If a drug moves through the GI tract very quickly, as can happen with severe diarrhea, it is not well absorbed.

Anything that delays the transport of the drug from the stomach to the intestine delays the rate of absorption of the drug.

[Note: The presence of food in the stomach both dilutes the drug and slows gastric emptying. a drug taken with a meal is generally absorbed more slowly.

Factors influencing absorption

5. Expression of P-glycoprotein: P-glycoprotein is a transmembrane transporter protein responsible for transporting various molecules, including drugs, across cell membranes.



- **Where: liver, kidneys, placenta, intestines, and brain capillaries**
- **Involved in transportation of drugs from tissues to blood. “pumps” drugs out of the cells.**
- **Areas of high expression P-glycoprotein reduces drug absorption.**
- **Associated with multi drug resistance.**

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 non-intravenous routes of administration.

Determination of bioavailability

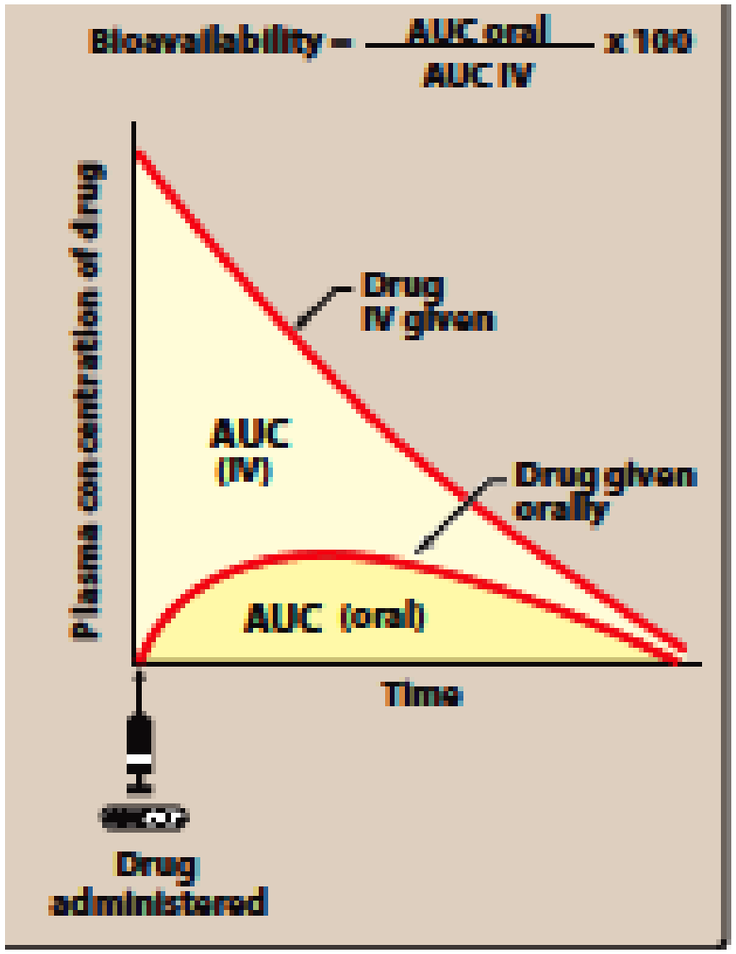
- Bioavailability is determined by comparing plasma levels of a drug after a particular route of administration with levels achieved by IV administration.

- 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.

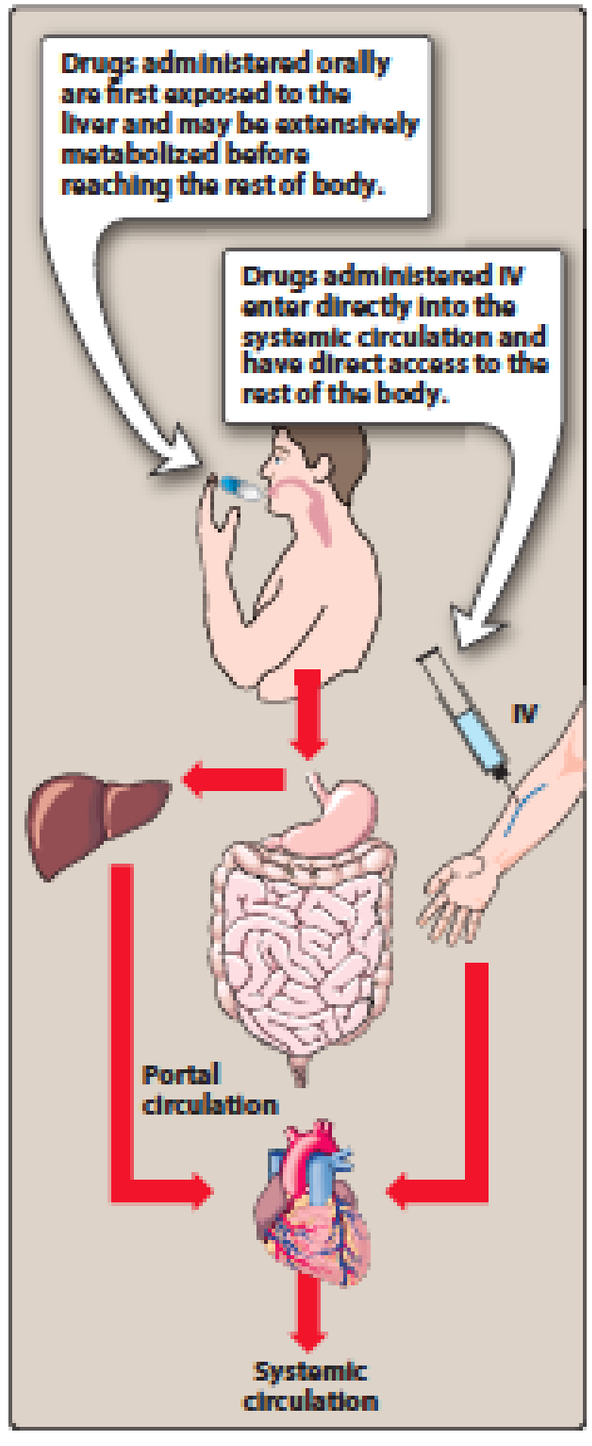
- By plotting plasma concentrations of the drug versus time, the area under the curve (AUC) can be measured.

- The total AUC reflects the extent of absorption of the drug. Bioavailability of a drug give orally is the ratio of the AUC following oral administration to the AUC following IV administration



Factors influencing bioavailability

First-pass metabolism: When a drug is absorbed from the GI tract, it enters the portal circulation before entering the systemic circulation. 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.



- First-pass metabolism by the intestine or liver limits the efficacy of many oral medications.
- Example:more than 90% of nitroglycerin is cleared during first-pass metabolism.
- Drugs with high first-pass metabolism should be given in doses sufficient to ensure that enough active drug reaches the desired site of action.

Factors influencing bioavailability

Solubility of the drug:

- Very hydrophilic drugs are poorly absorbed because of their inability to cross lipid-rich cell membranes.

- Drugs that are extremely lipophilic 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 lipophilic, yet have some solubility in aqueous solutions.

- This is one reason why many drugs are either weak acids or weak bases.

Factors influencing bioavailability

Chemical instability:

- Some drugs, such as penicillin G, are unstable in the pH of the gastric contents.

- Insulin is destroyed in the GI tract by degradative enzymes.

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.