

Pharmacokinetics

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Readings

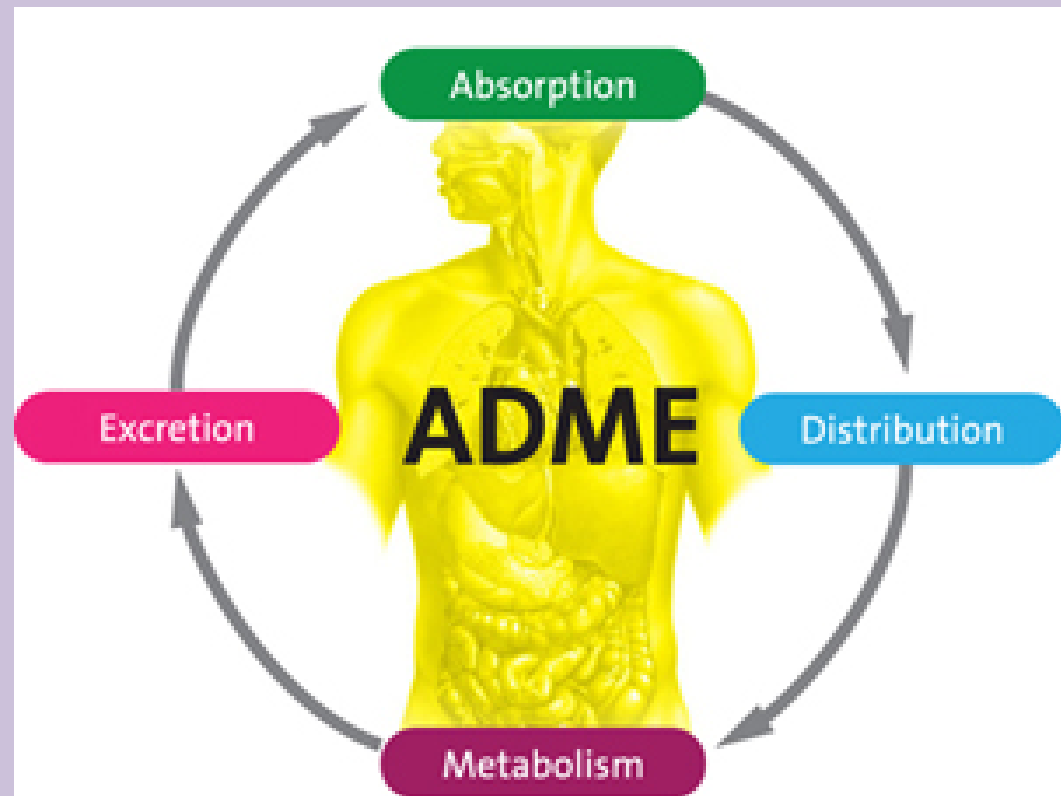
- Lippincott's Illustrated Reviews: Pharmacology , 6th ed. .
- Basic & Clinical Pharmacology , Bertram G. Katzung 12th ed. .
- Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th ed. .

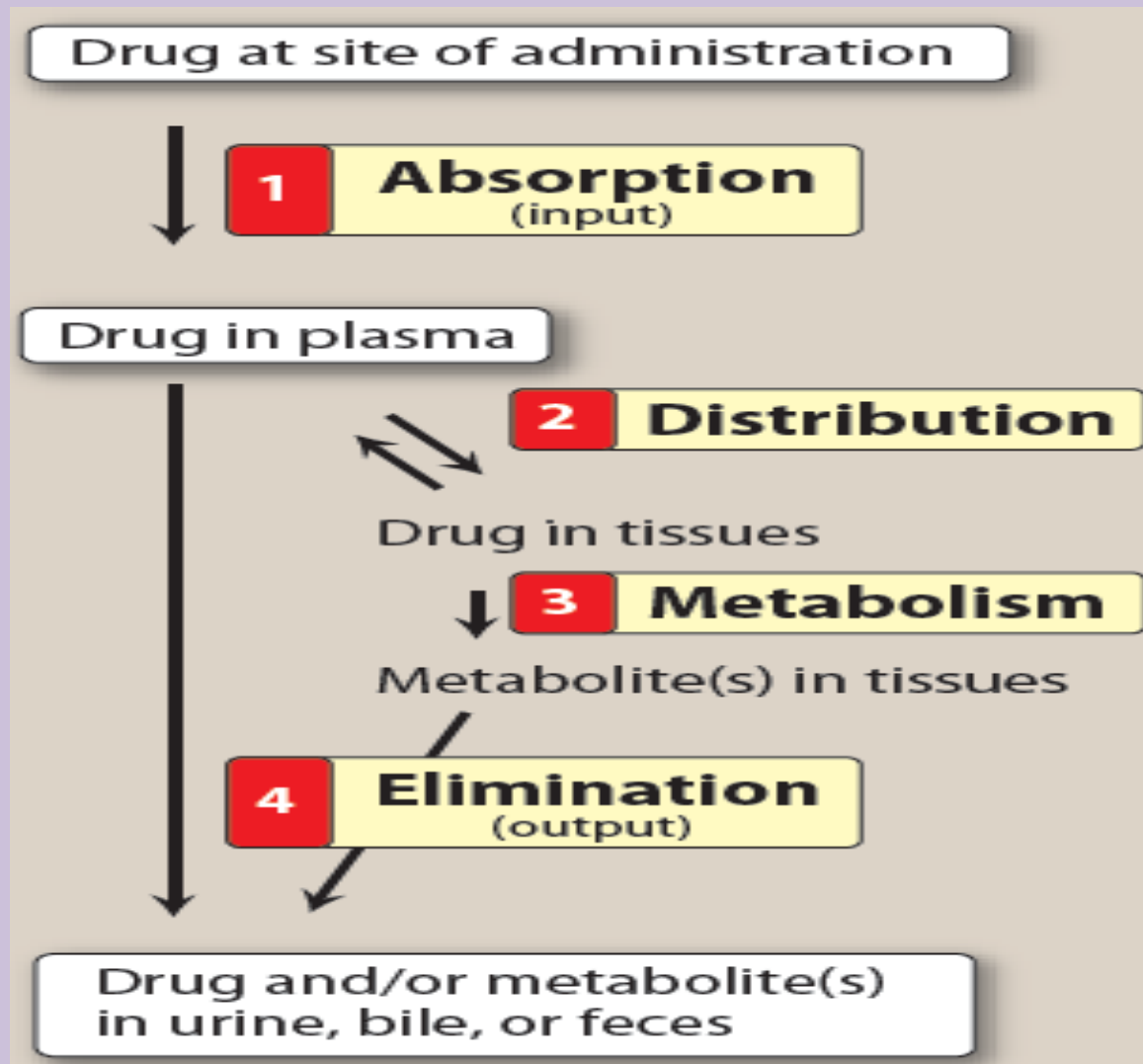
Pharmacokinetics (PK)

- Refers to what the body does to a drug, whereas pharmacodynamics describes what the drug does to the body.

PK parameters :-

- ✓ Absorption
- ✓ Distribution
- ✓ Metabolism
- ✓ Elimination





Absorption

The rate and efficiency of absorption depend on :-

- Route of administration (which affects bioavailability).
- Chemical structure of the drug.
- Dosage form.



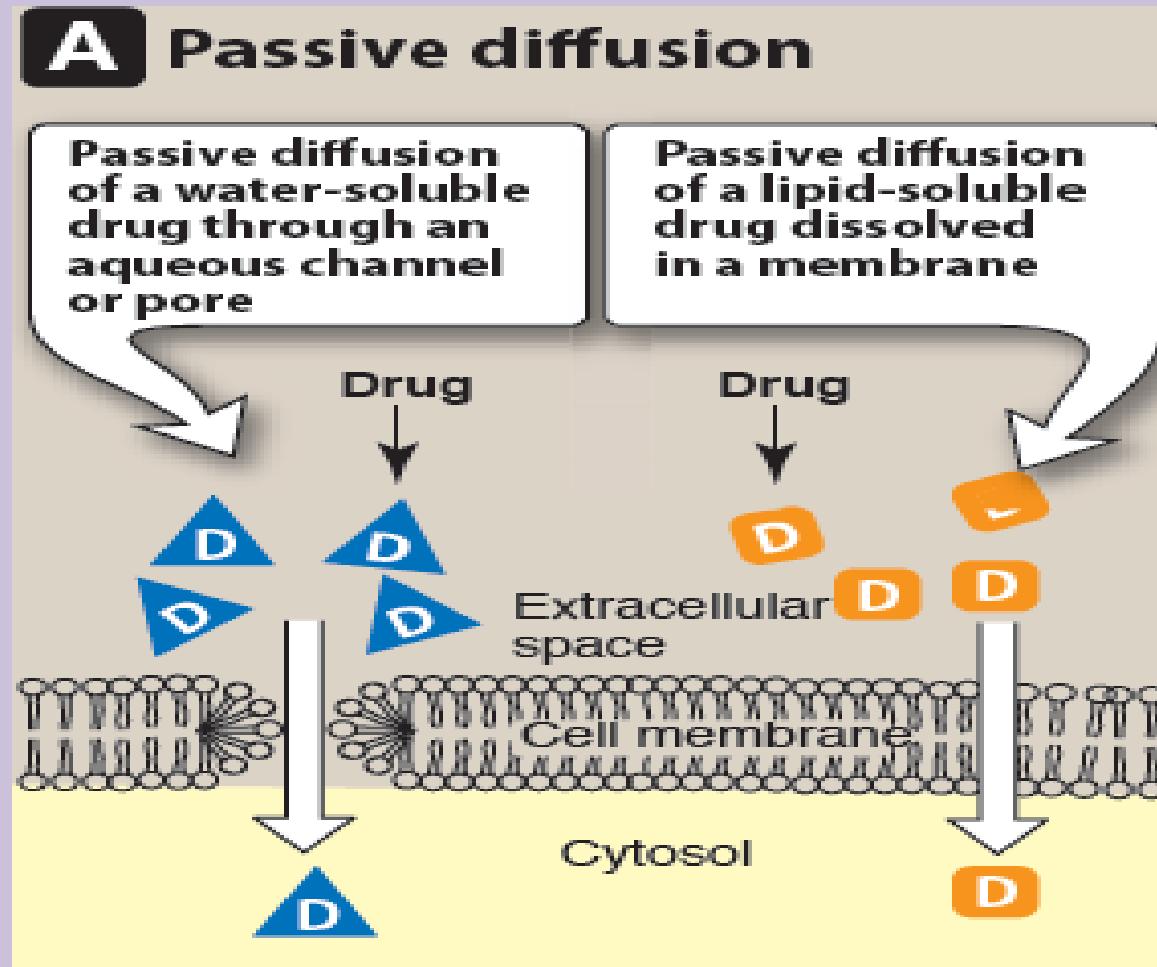
Mechanisms of absorption of drugs from the GIT

- A. Passive diffusion.
- B. Facilitated diffusion.
- C. Active transport.
- D. Endocytosis.

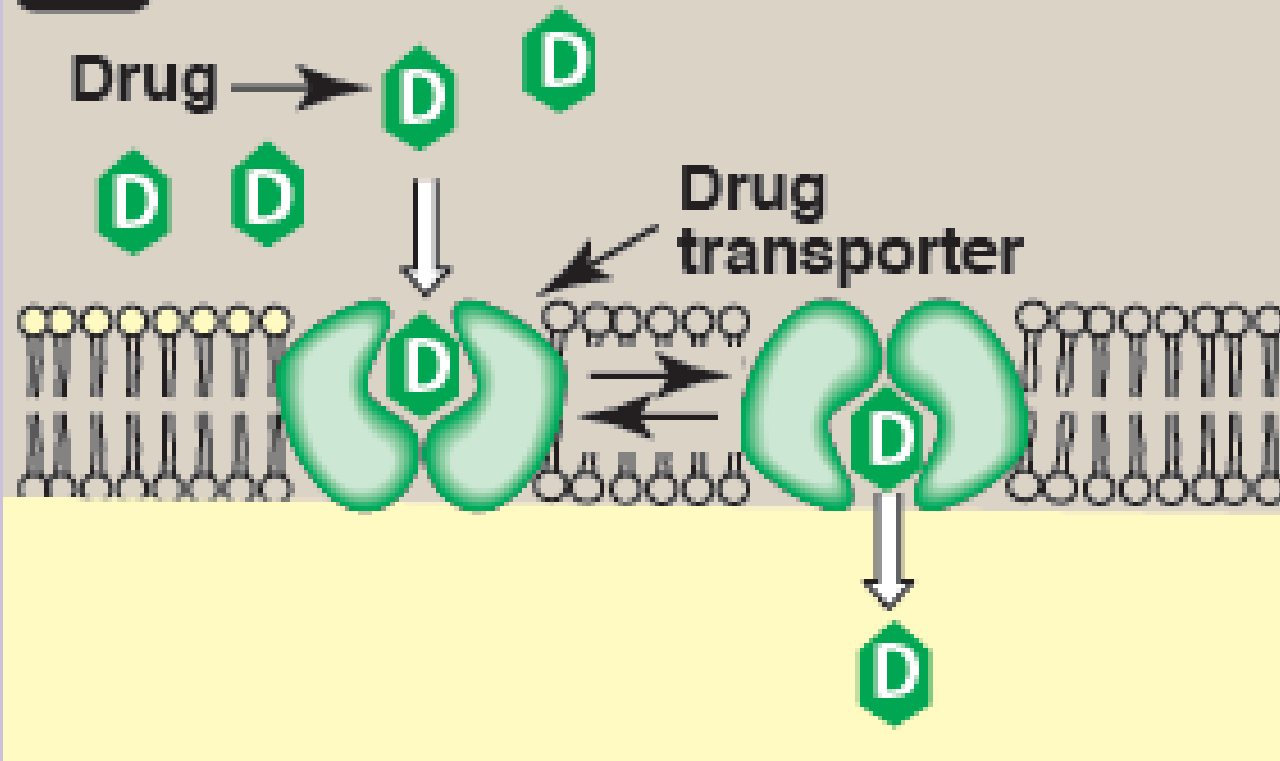
Mechanisms of absorption of drugs from the GIT

A. Passive diffusion

(driving force is conc. Gradient).



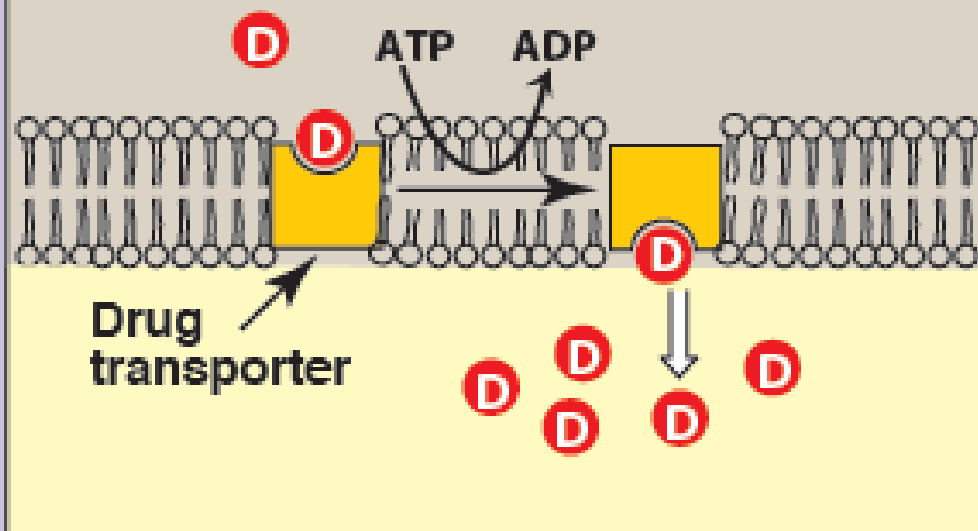
B Facilitated diffusion



B. Facilitated diffusion

- Drugs enter the cell through transmembrane carrier proteins from an area of high conc. to an area of low conc. .
- Facilitated diffusion does not require energy.
- It's saturable and inhibitable.

C Active transport



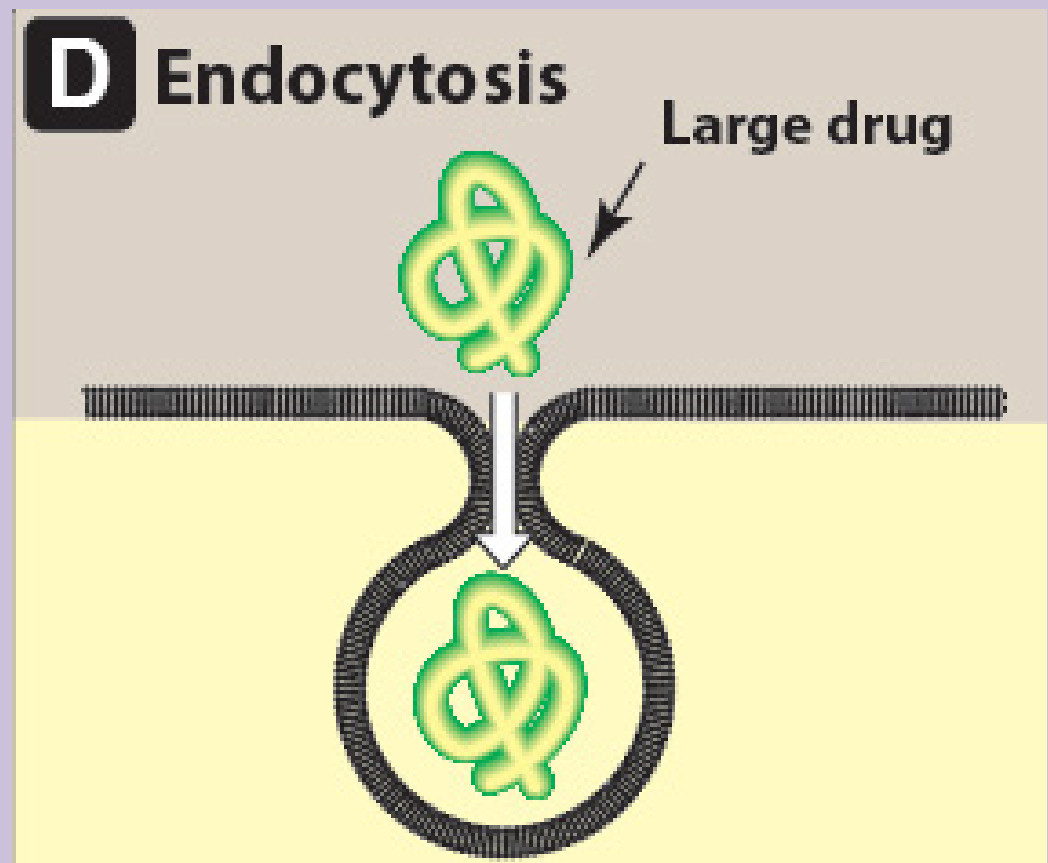
C. Active transport

This mode of transport is similar to facilitated diffusion, but some important differences are present between them which are :-

1. Active transport can act against conc. gradient.
2. Active transport requires energy (provided by ATP hydrolysis).

D. Endocytosis

-For drugs with large molecular size (e.g. B₁₂).





What is bioavailability ?

Bioavailability

is the percentage of *unchanged* drug reaching the systemic circulation following administration by any route.

Example

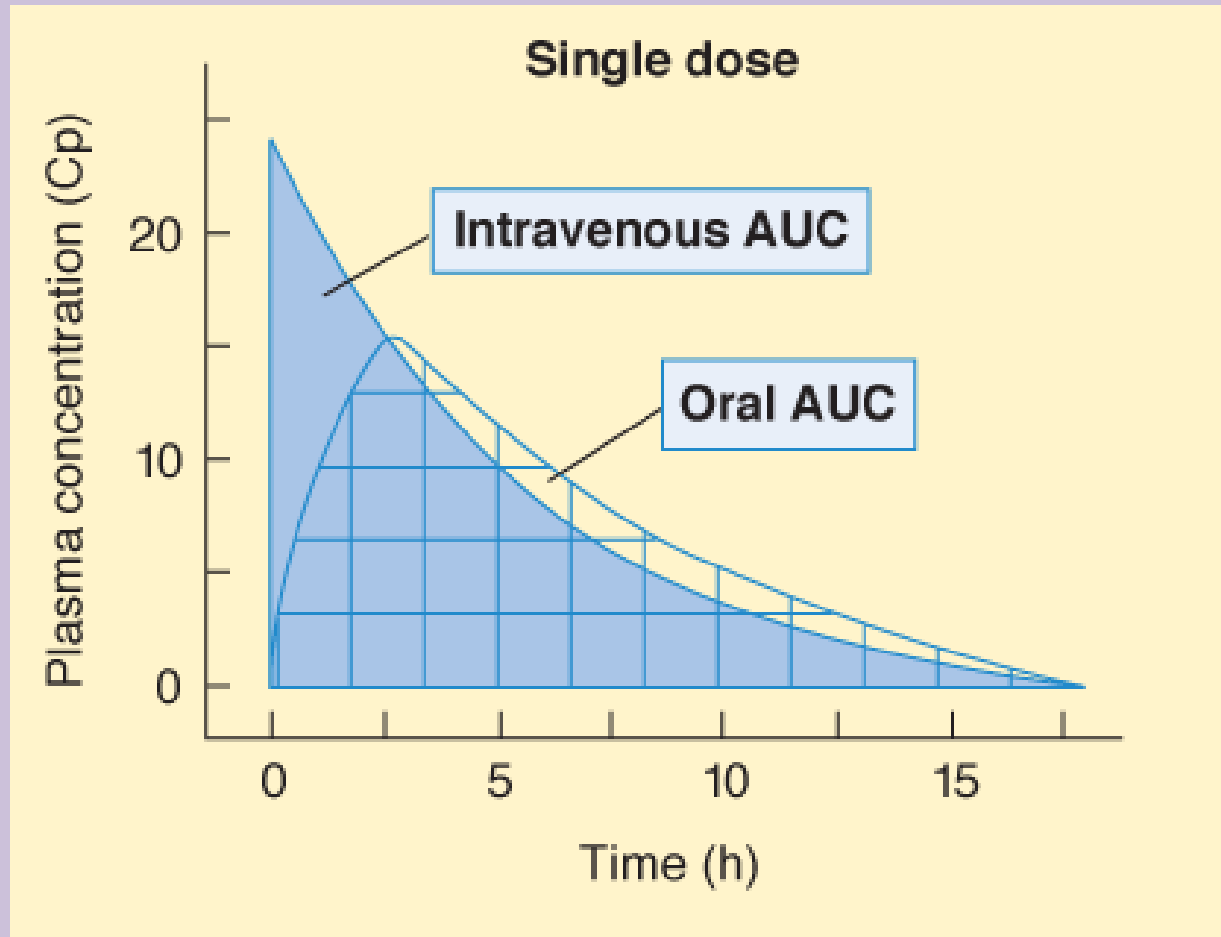
- If 100 mg of a drug are administered PO, and 90 mg of this drug are absorbed unchanged, the bioavailability is :

90 % (or 0.9)

- If 500 mg of a drug are administered PO, and 100 mg of this drug are absorbed unchanged, the bioavailability is

20 % (or 0.2).

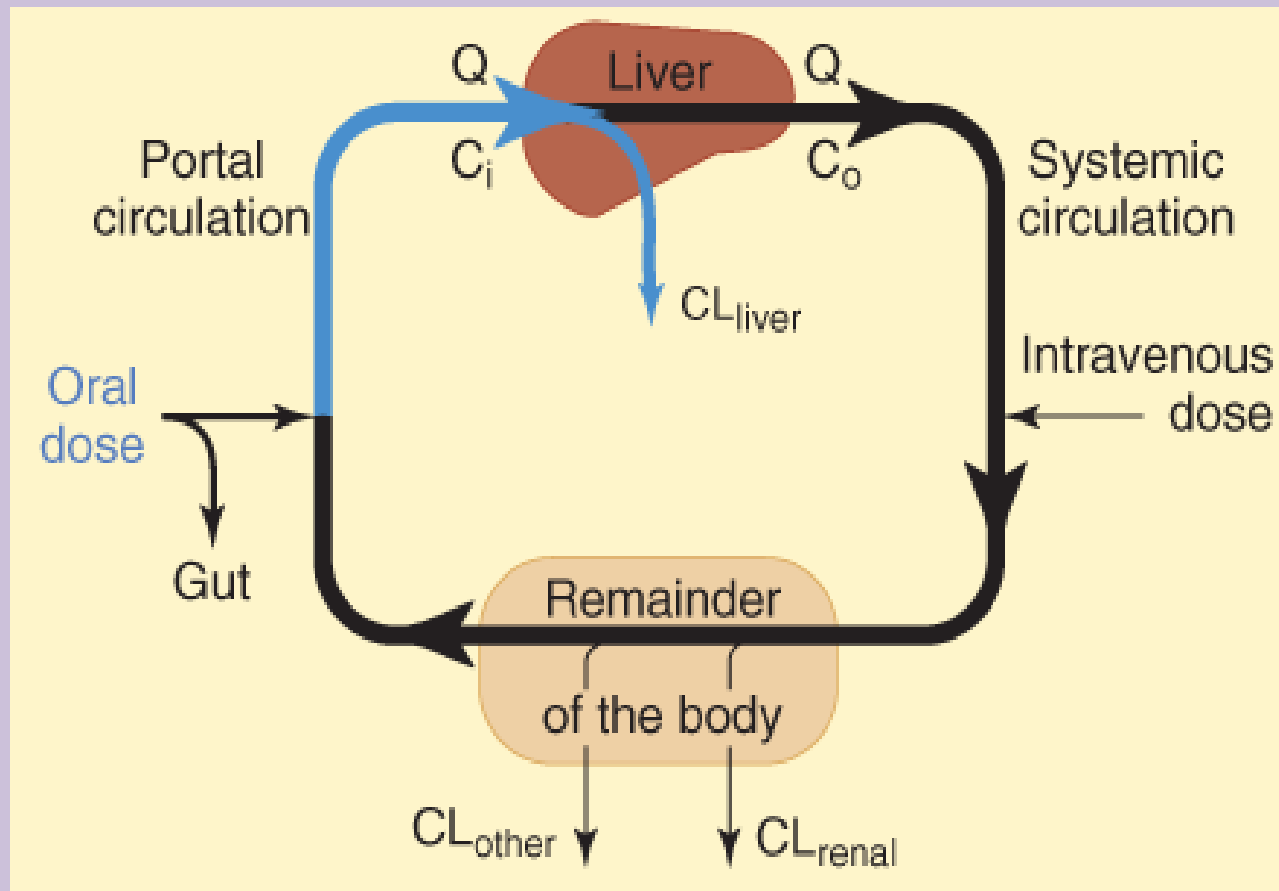
Calculation of bioavailability



$$\text{Bioavailability} = \text{AUC}_{\text{route}} / \text{AUC}_{\text{IV}}$$

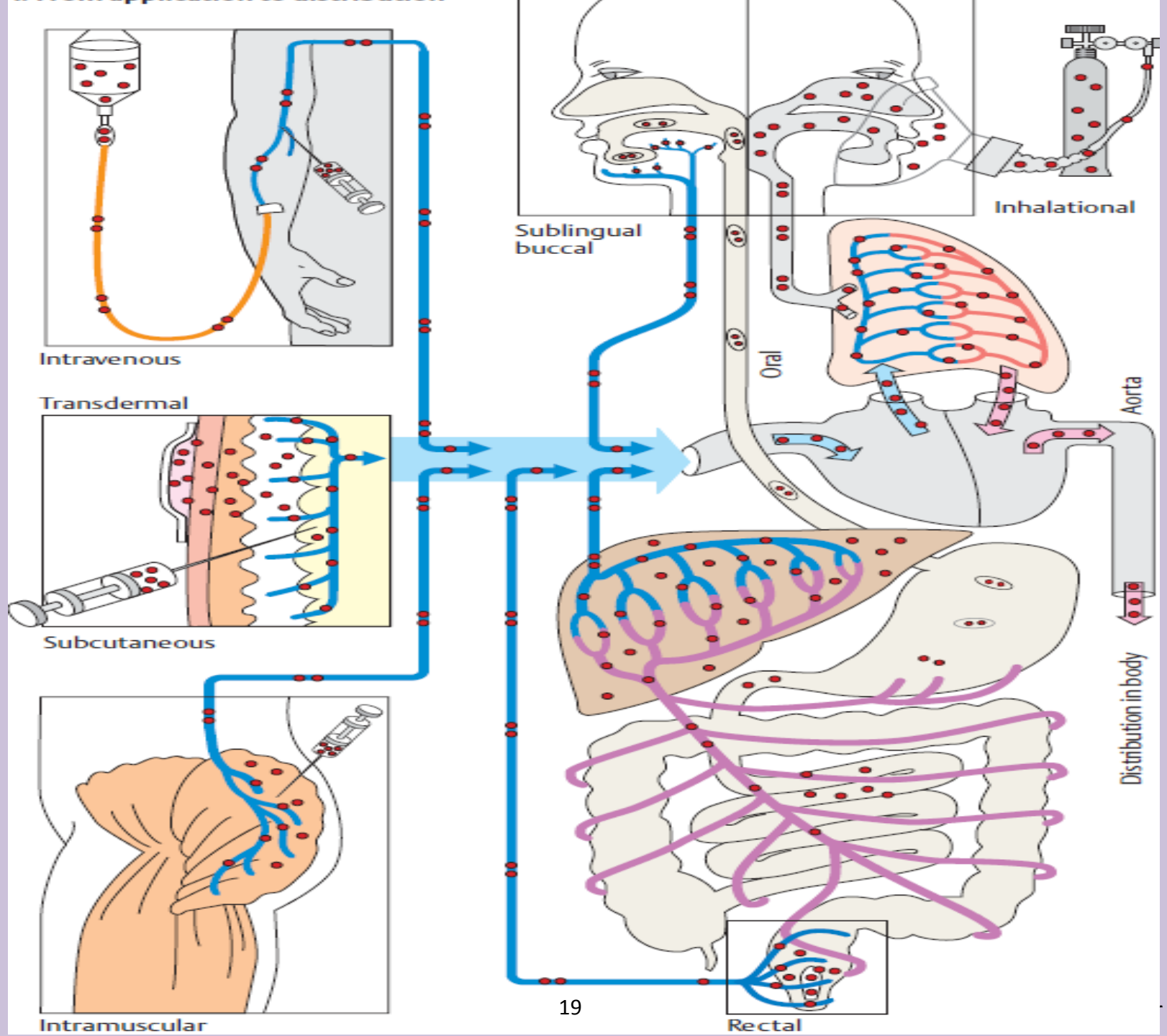
Factors that influence bioavailability

1. First-pass hepatic metabolism.



2. Route of administration.

Route	Bioavailability (%)
Intravenous (IV)	100 (by definition)
Intramuscular (IM)	75 to ≤ 100
Subcutaneous (SC)	75 to ≤ 100
Oral (PO)	5 to < 100
Rectal (PR)	30 to < 100
Inhalation	5 to < 100
Transdermal	80 to ≤ 100



3. Solubility of the drug :-

- ❑ Very hydrophilic drugs are poorly absorbed because of their inability to cross the lipid-rich cell membranes.
- ❑ Very hydrophobic drugs are also poorly absorbed, because they are totally insoluble in aqueous body fluids and, therefore, can not gain access to the surface of cells.
- ❑ For a drug to be absorbable, it must be largely hydrophobic, yet have some solubility in aqueous solutions.

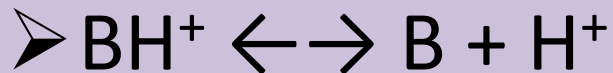
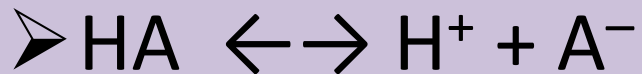
4. Chemical instability .

Insulin can not be given orally , why ?

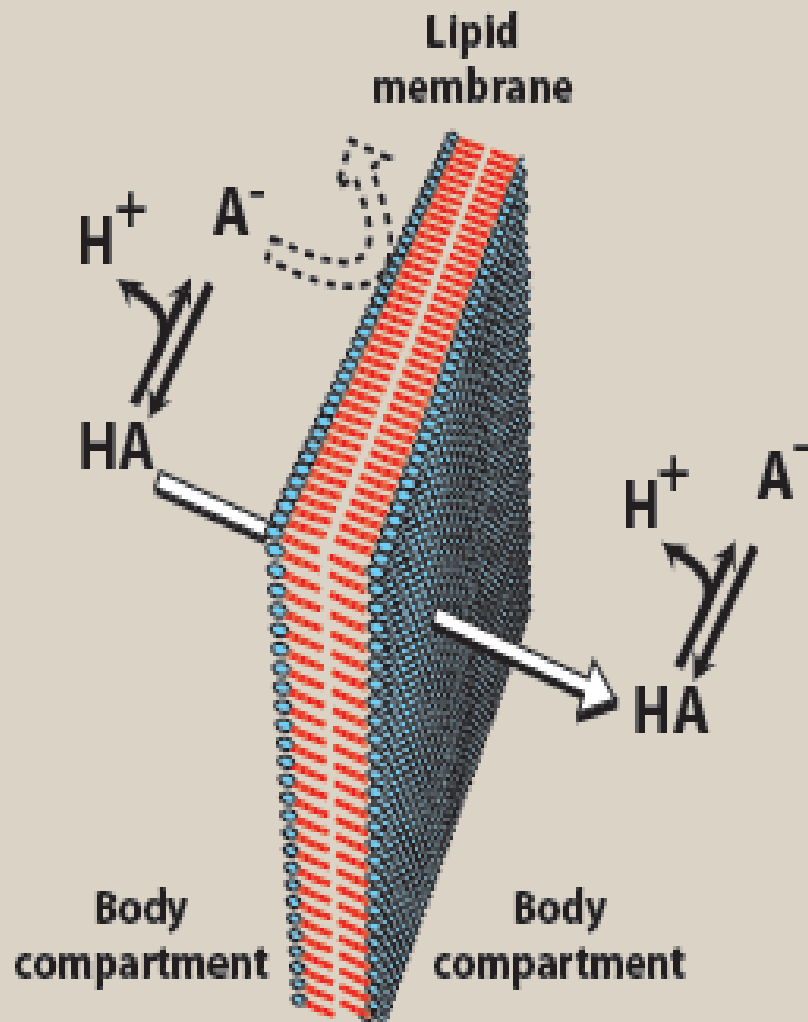
5. Dosage form.

Factors influencing absorption

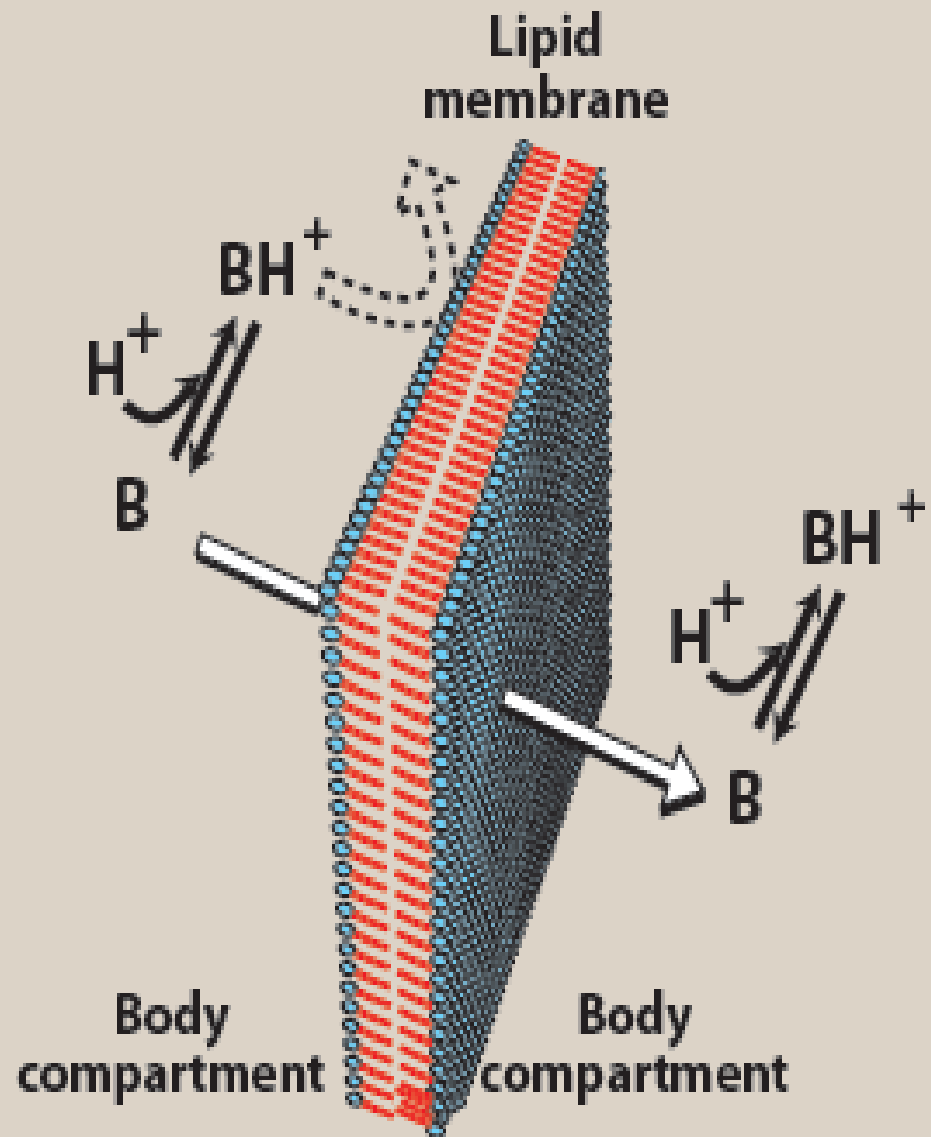
1. pH: Most drugs are either weak acids or weak bases.

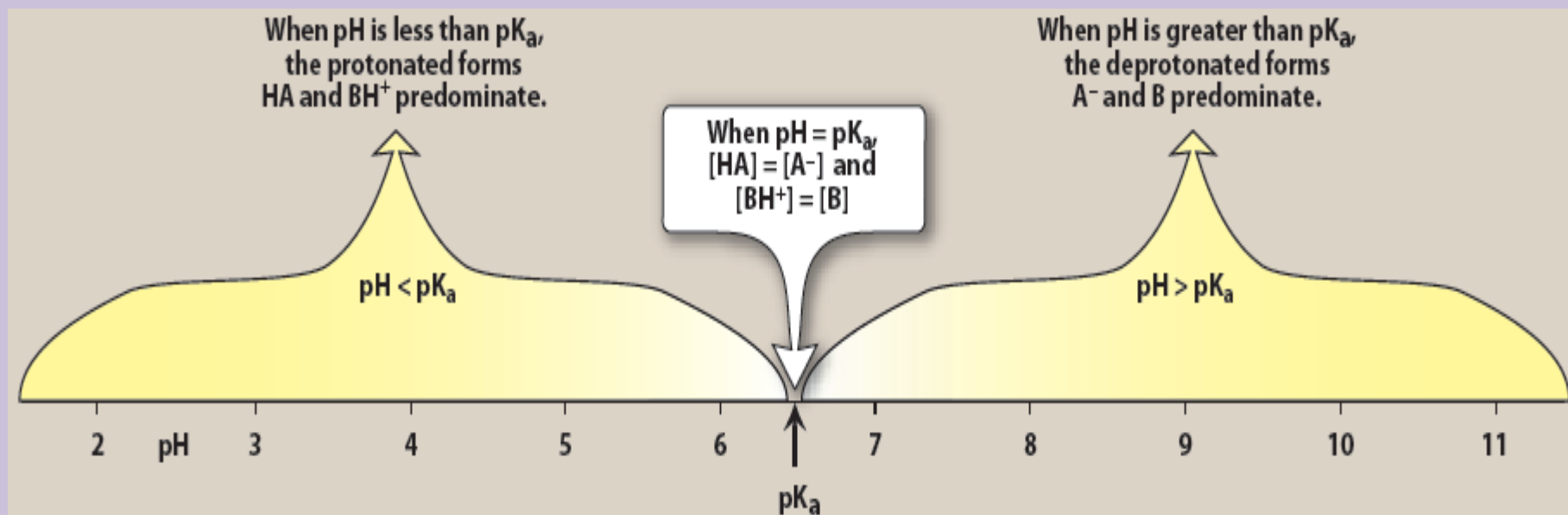


A Weak acid



B Weak base





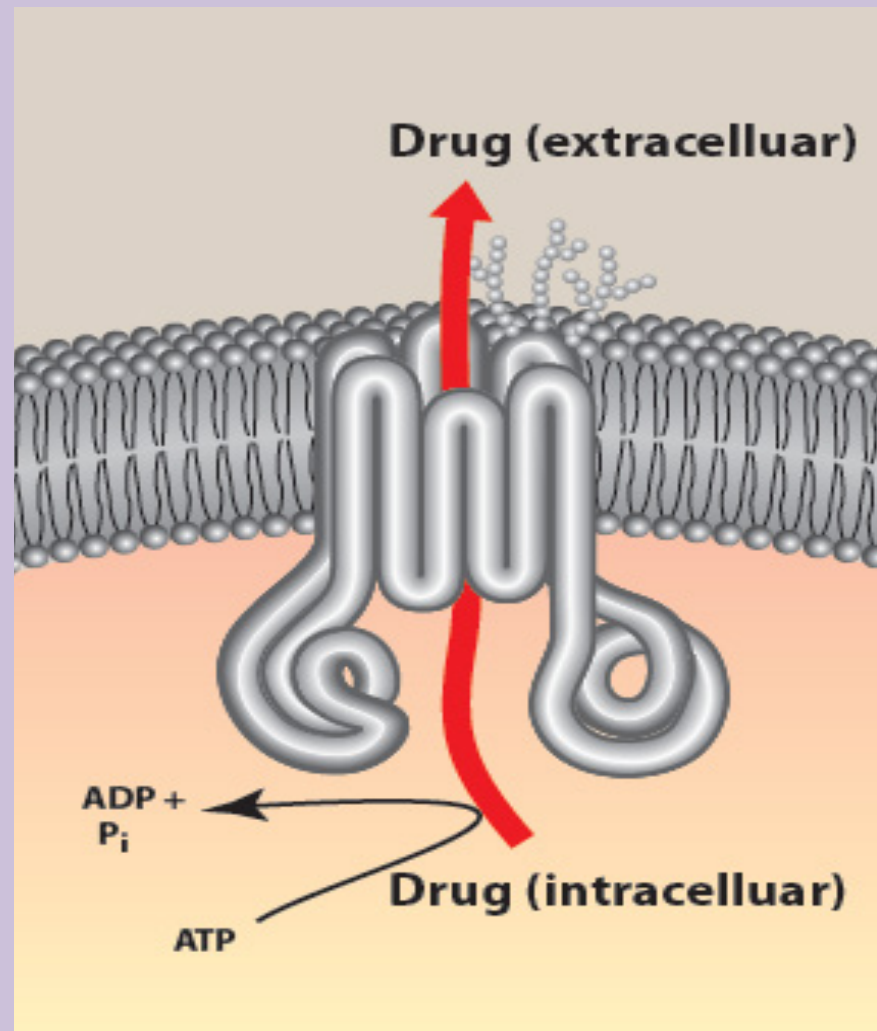
2. Blood flow to the absorption site

Q: The absorption of drugs is higher in the stomach as compared with small intestine

(True or False).

3. Contact time at the absorption surface & Total surface area available for absorption.

4. Expression of P-glycoprotein (MDR)

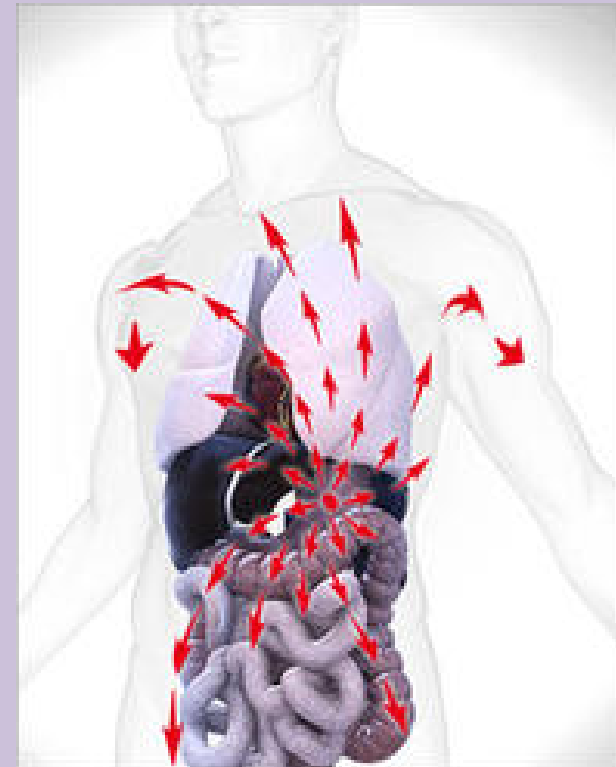


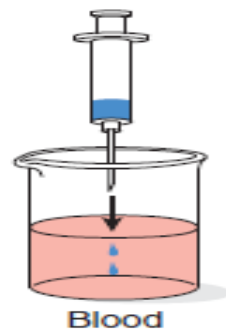
It is expressed throughout the body, and its function is to decrease the drug's conc. inside the body through transporting drug into:

Transport drug into	Organ
Bile	Liver
Urine	Kidneys
Intestinal lumen	Intestine
Back into the blood	Brain capillaries
Back into maternal blood	Placenta

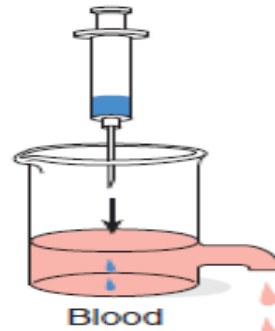
DISTRIBUTION

is the process by which a drug reversibly leaves the bloodstream and enters the interstitium (extracellular fluid) and then the cells of the tissues.

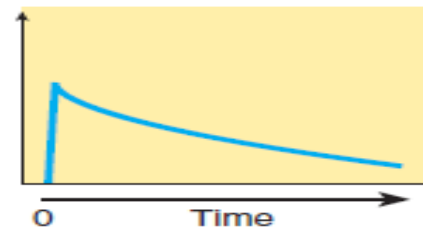
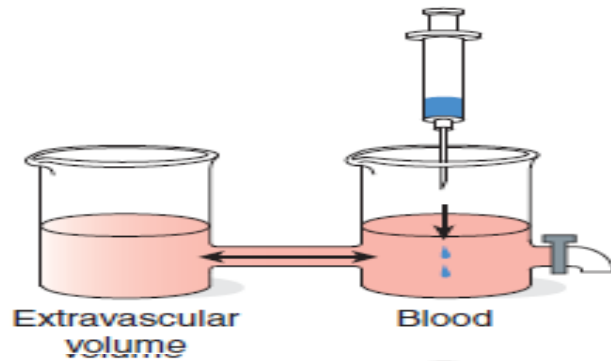


A

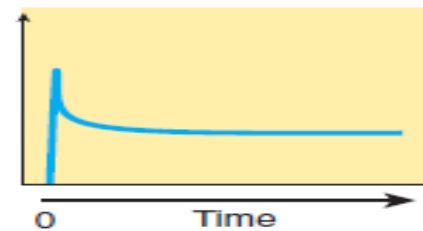
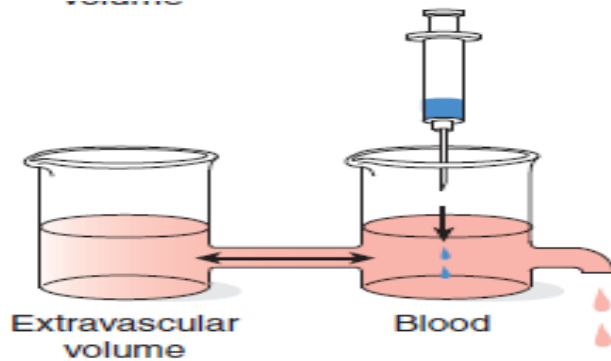
Amount
in blood

**B**

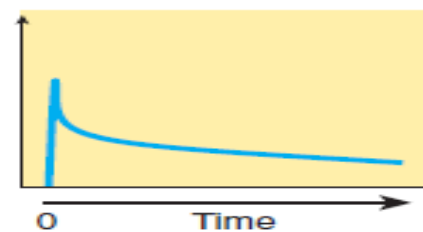
Amount
in blood

**C**

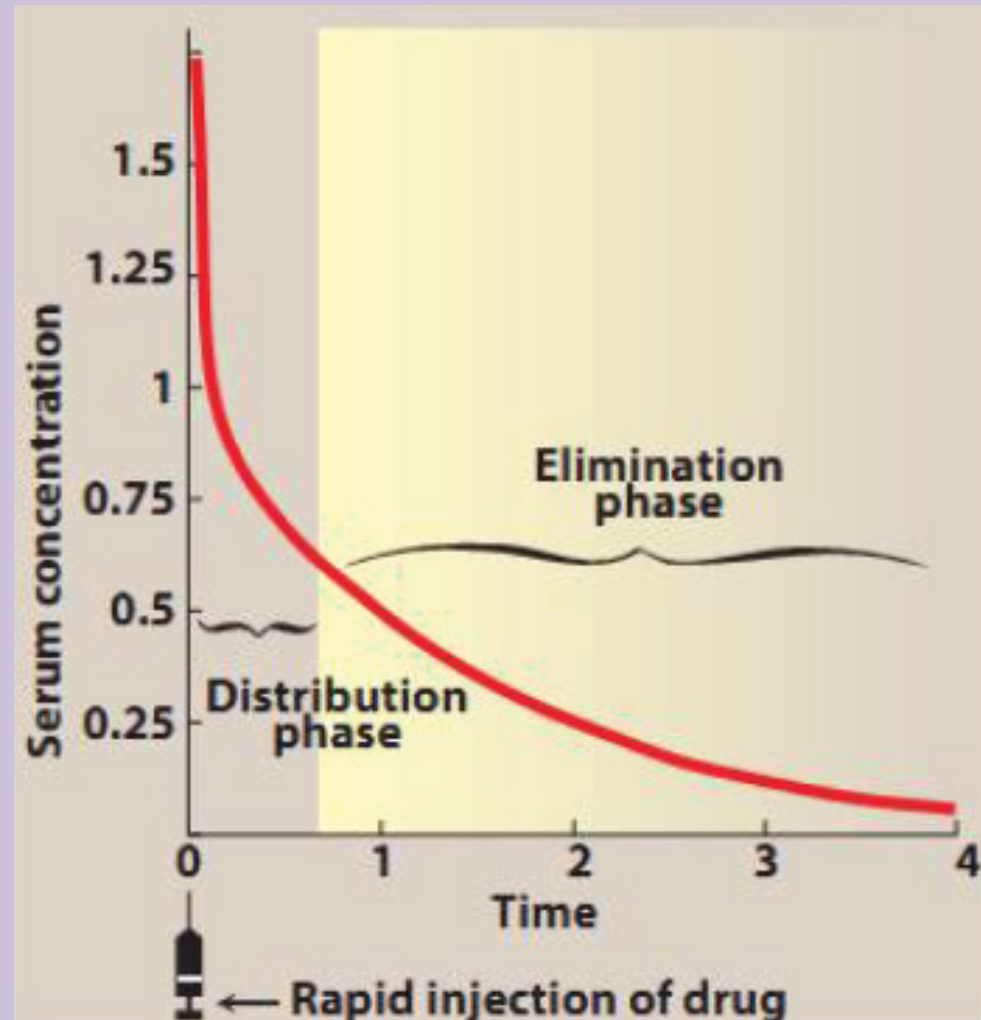
Amount
in blood

**D**

Amount
in blood



- For a drug administered IV, the initial phase (that is, from immediately after administration through the rapid fall in concentration) represents the distribution phase.
- This is followed by the elimination phase, when drug in the plasma is in equilibrium with drug in the tissues.

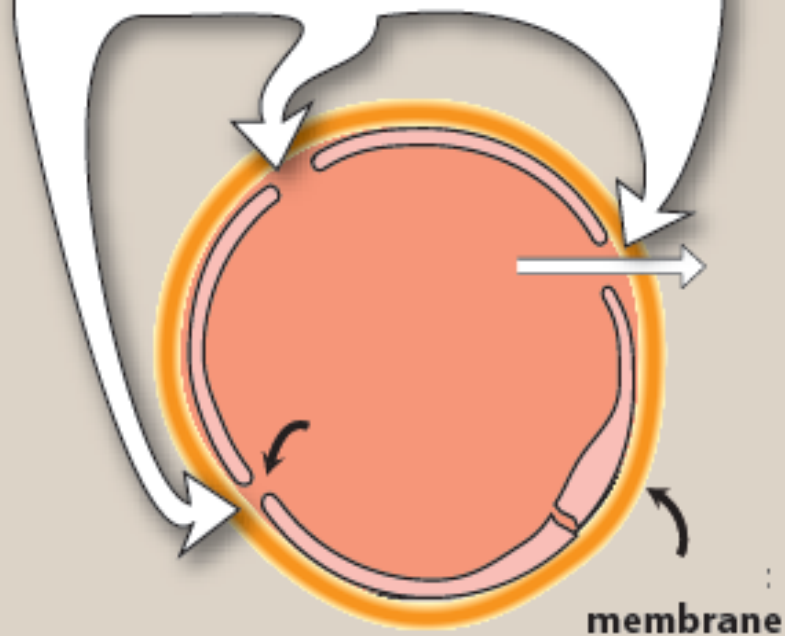


The distribution of a drug from the plasma to the interstitium primarily depends on:-

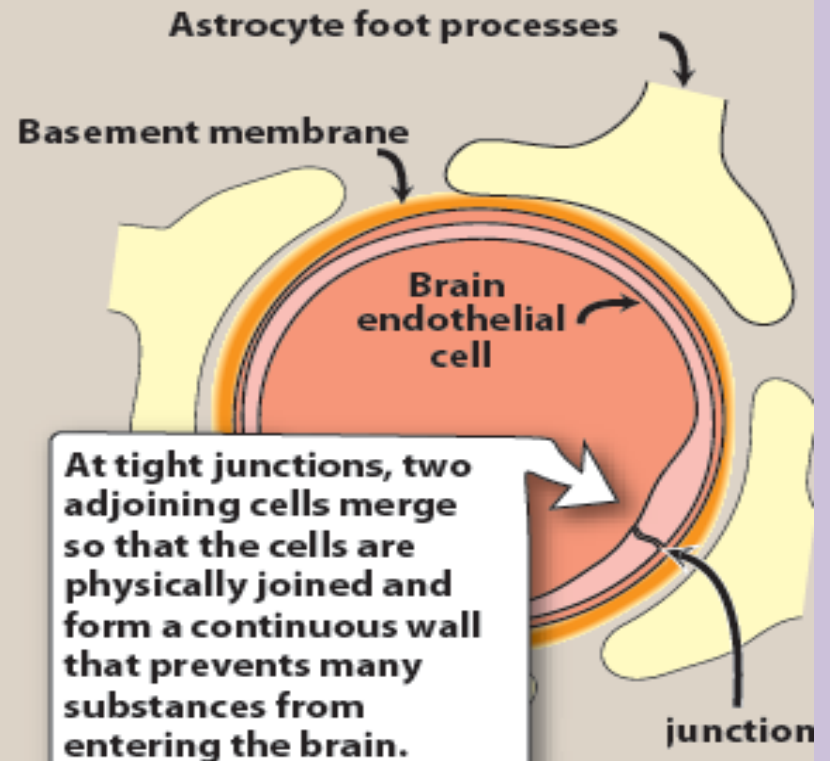
- Regional blood flow/Cardiac output.
- Plasma protein binding.
- Tissue volume.
- Relative hydrophobicity of the drug.
- Capillary permeability.

A Structure of endothelial cells in the liver

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



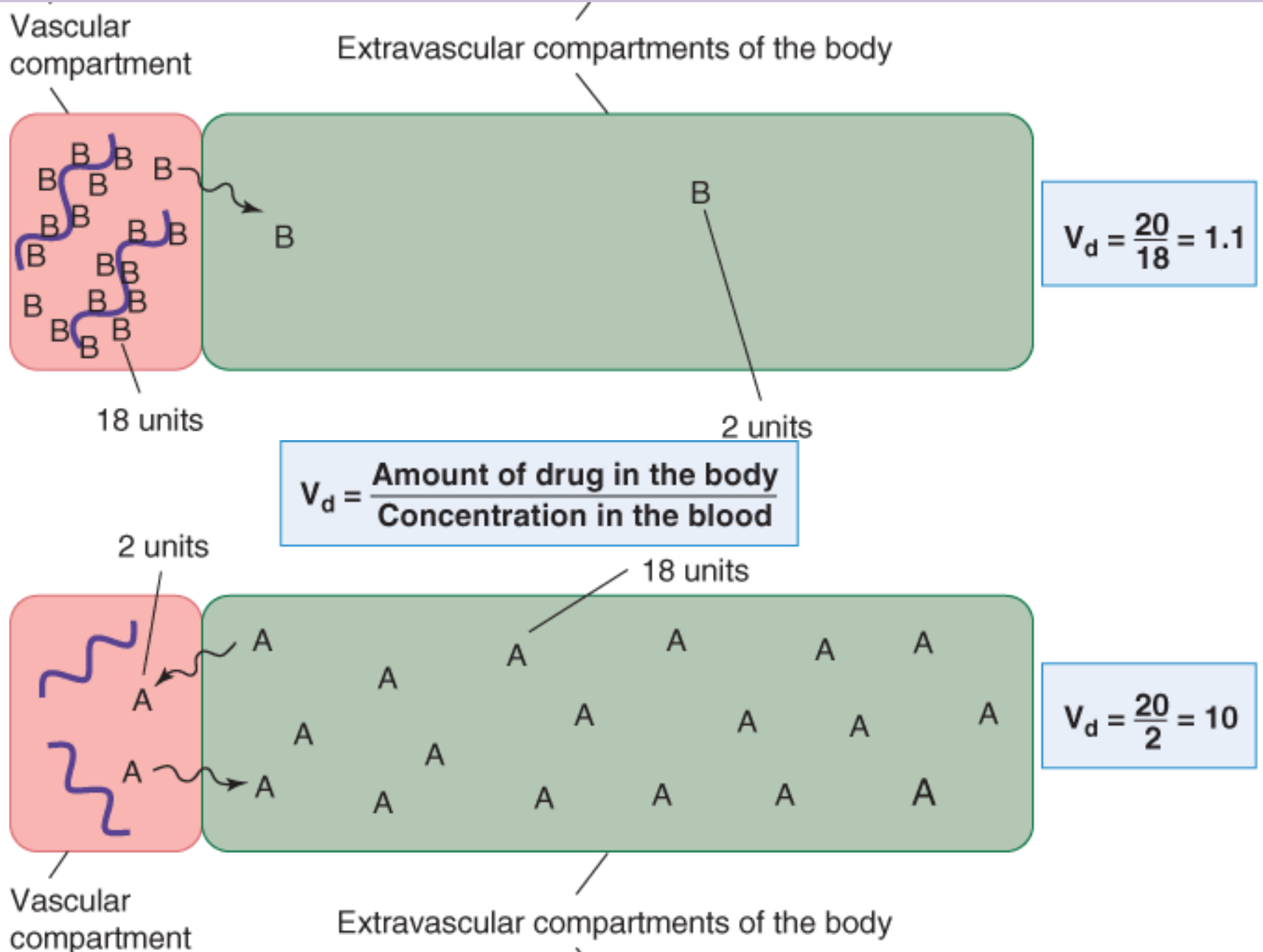
B Structure of a brain capillary



Volume of distribution (V_d)

- is the fluid volume that is required to contain the entire drug in the body at the same concentration measured in the plasma.

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



- V_d can vastly exceed any physical volume in the body because it is the volume apparently necessary to contain the amount of drug homogeneously at the concentration found in the blood, plasma, or water.
- E.g. Chloroquine 13000 L , Aspirin 11 L.

- If the V_d for a drug is large, most of the drug is in the extraplasmic space and is unavailable to the excretory organs.
- Therefore, any factor that increases V_d can lead to an increase in the half-life of the drug.

Half-life ($t_{1/2}$)

- is the time required to change the amount of drug in the body by one-half during elimination.
- $t_{1/2} = 0.7 V_d / CL$

Plasma protein binding

- Albumin is a major carrier for acidic drugs ; α_1 -acid glycoprotein binds basic drugs.
- Binding is reversible.
- Hypoalbuminemia secondary to severe liver disease or nephrotic syndrome results in reduced binding and an increase in the unbound fraction.

Binding of a drug to plasma proteins limits drug's :-

1. Concentration in tissues and at its site of action.
2. Glomerular filtration and renal elimination.
3. Transport and metabolism.

