Pharmacokinetics II: Bioavailability and Distribution

Pharmacology Department

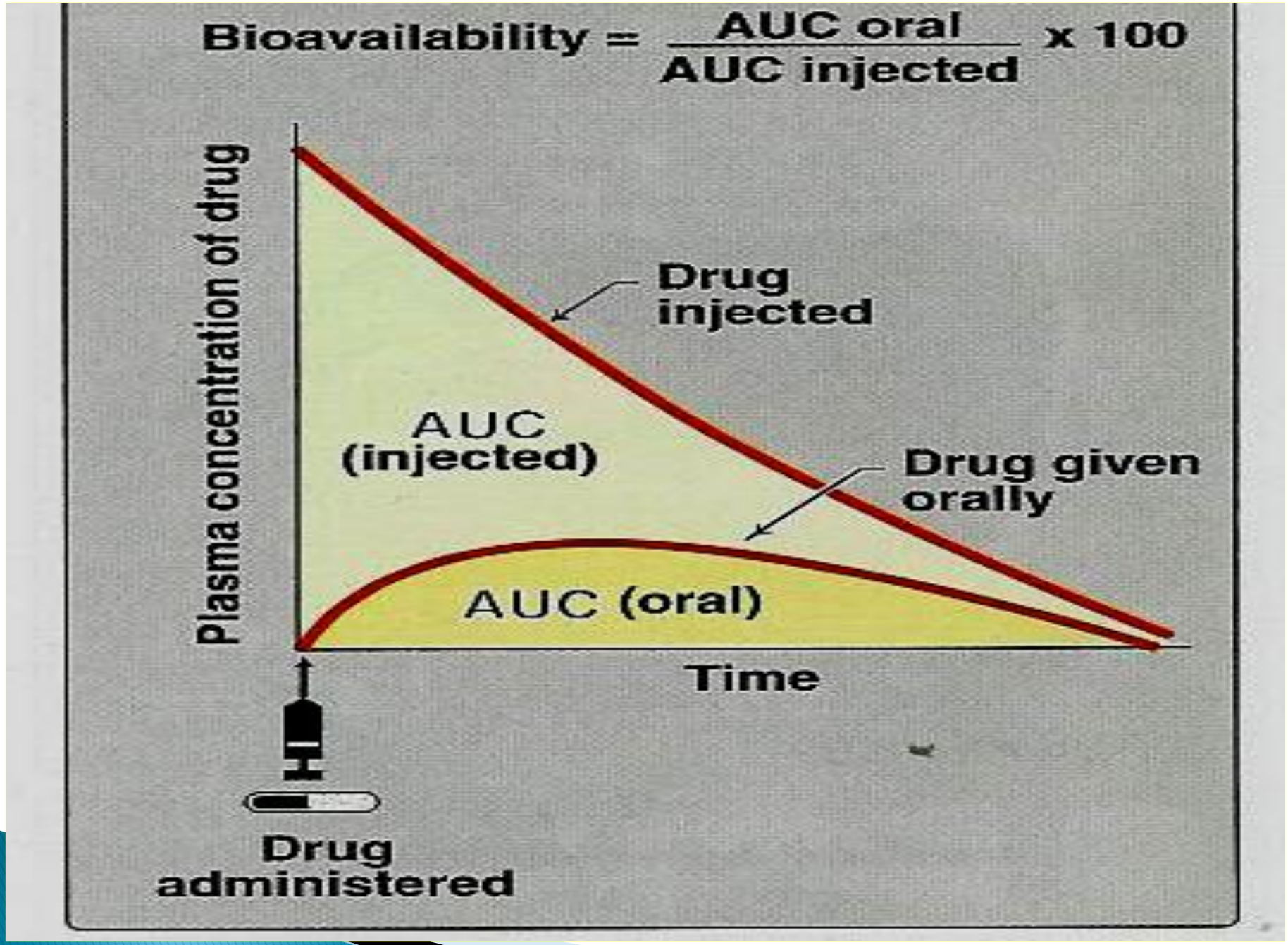
By the end of the lectures, students should be able to define the following:

- **Major body fluid compartments**
- **Concept of compartments.**
- **Apparent volume of distribution (vd).**
- **Plasma protein binding.**
- **Tissue binding.**

Bioavailability

- Is the amount of unchanged drug that enters systemic circulation after administration and becomes available to produce pharmacological actions

- **Bioavailability (F) = $\frac{\text{AUC (oral)}}{\text{AUC (I.V.)}} \times 100$**


Bioavailability = AUC oral / AUC injected x 100
Plasma concentration of drug
Drug injected
AUC (injected)
Drug given orally
AUC (oral)
Time
Drug administered

Bioavailability

- **I.V. provides 100% bioavailability i.e. F= 1.**
- Subcutaneous, intramuscular, oral, rectal, and other extra vascular routes of administration require that the drug be absorbed first, which can reduce bioavailability.

Absolute bioavailability

- The bioavailability of a drug after administration by any route is compared to its intravenous standard formulation.

Relative bioavailability

- is determined when two products are compared to each other, not to an intravenous standard.
- This is commonly calculated in the drug industry to determine that the generic formulation is bioequivalent to another formulation.
- e.g Tylenol (paracetamol 500 mg) compared to Panadol (paracetamol 500 mg).

Relative bioavailability

- is important to get an idea of how **different formulations** or **routes of administration** differ in their bioavailability.

- dosage adjustment is required when changing formulations or routes of administration.

Bioequivalence

- Two pharmaceutical products are **bioequivalent** when the rate and extent of bioavailability of active ingredients in two products are the same.

Factors affecting bioavailability:

- Factors controlling drug absorption
- First pass effect

Factors affecting absorption :

- **Route of administration.**
- **Dosage forms** (depending on particle size and disintegration, ease of dissolution).

(suspension > capsule > tablet)

- **Molecular weight of drug.**
- **Lipid solubility**
- **Degree of ionization**
- **Drug solubility (aqueous preparation better than oily, suspension preparations)**
- **Chemical instability in gastric pH**

(Penicillin & insulin)

Factors affecting absorption :

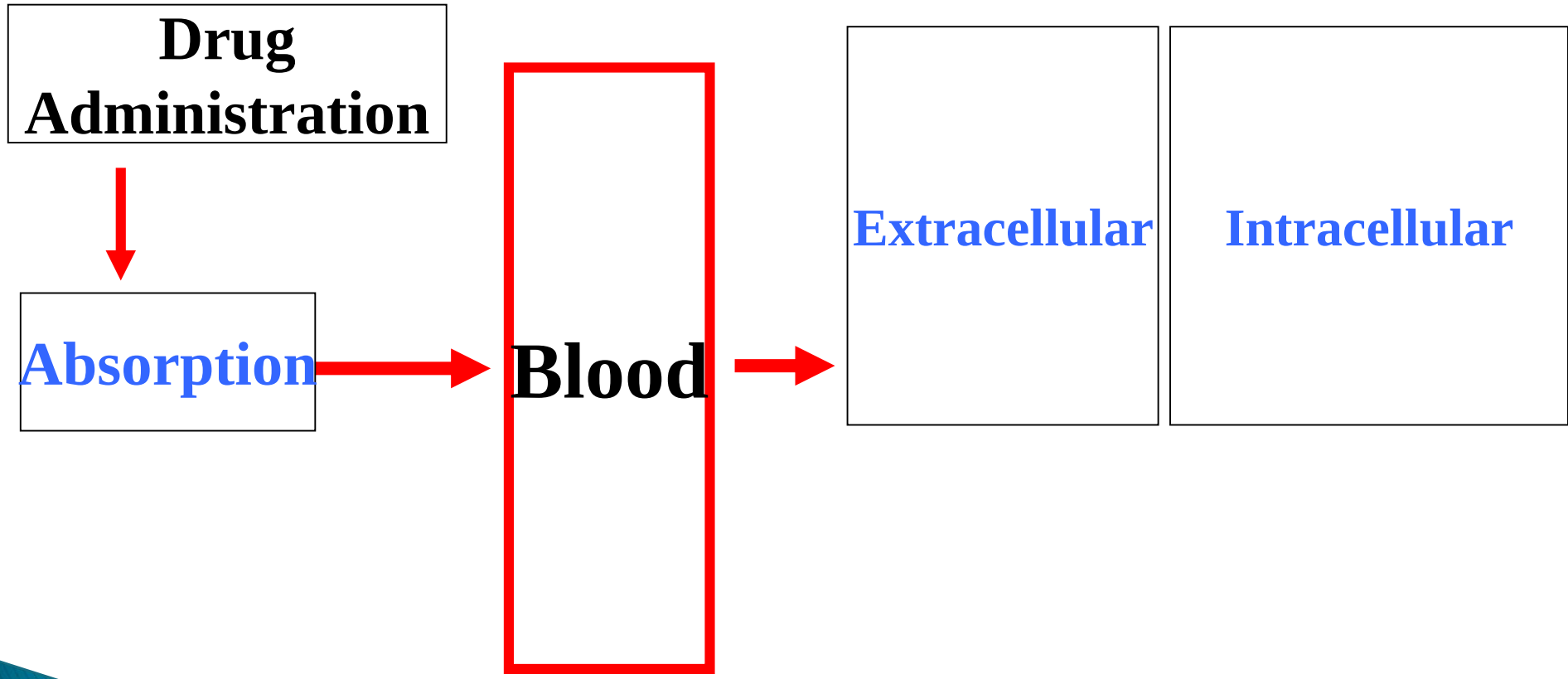
- **Surface area available for absorption.**
  - small intestine has large surface area than stomach due to intestinal microvilli.
- **Blood flow to absorptive site**
  - **greater** blood flow increases bioavailability
  - Intestine has greater blood flow than stomach
- **Intestinal motility (transit time)**
  - Diarrhea reduce absorption

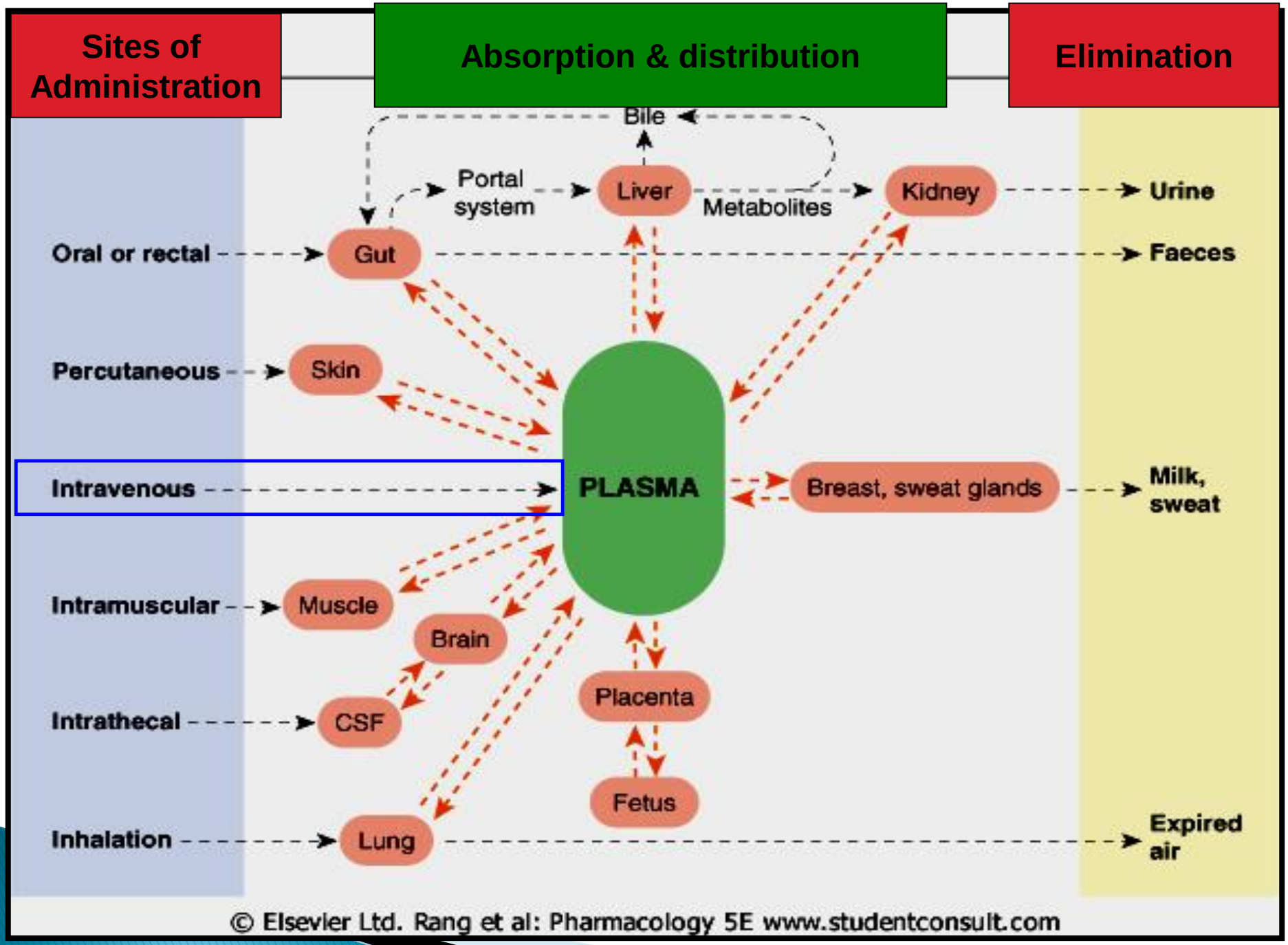
- **Gastric emptying**
  - drugs that increase gastric emptying enhances absorption (metoclopramide).
- **Drug interactions**
- **Food**
  - **Slow** gastric emptying
  - generally slow absorption
  - Tetracycline, aspirin, penicillin V
  - **A fatty meal** increase the absorption of fat soluble antifungal drug (e.g. griseofulvin)

Distribution

Distribution

Is the process by which drugs leave blood circulation and enters the interstitium and/or the cells of the tissues.


Drug Administration
Absorption
Blood
Extracellular
Intracellular


Sites of Administration
Absorption & distribution
Elimination
Bile
Portal system
Liver
Kidney
Urine
Oral or rectal
Gut
Faeces
Metabolites
Percutaneous
Skin
Intravenous
PLASMA
Breast, sweat glands
Milk, sweat
Intramuscular
Muscle
Brain
Placenta
Intrathecal
CSF
Fetus
Inhalation
Lung
Expired air
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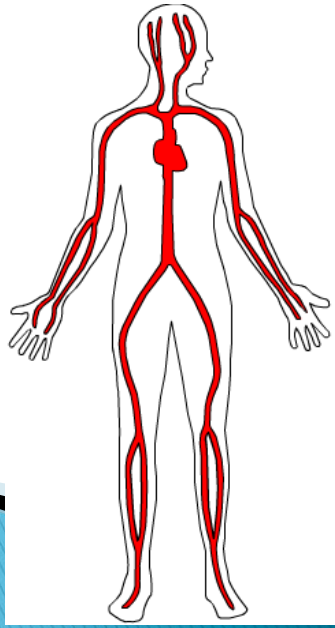
Dose of drug administered

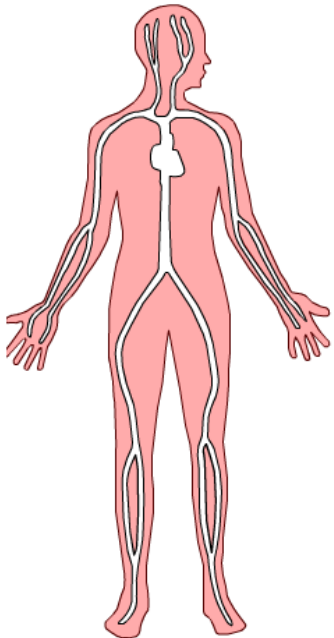
ABSORPTION

Drug concentration in systemic circulation

DISTRIBUTION

Drug in tissues of distribution





Apparent Volume of Distribution (Vd)

is the ratio of drug amount in the body (dose) to the concentration of drug in blood.

$$Vd\ (L) = \frac{\text{Dose (mg)}}{\text{plasma concentration (mg/L)}}$$

Why is Vd important?

- **To calculate loading dose**
- **Large Vd = means long duration of action**

The major body fluid compartments are

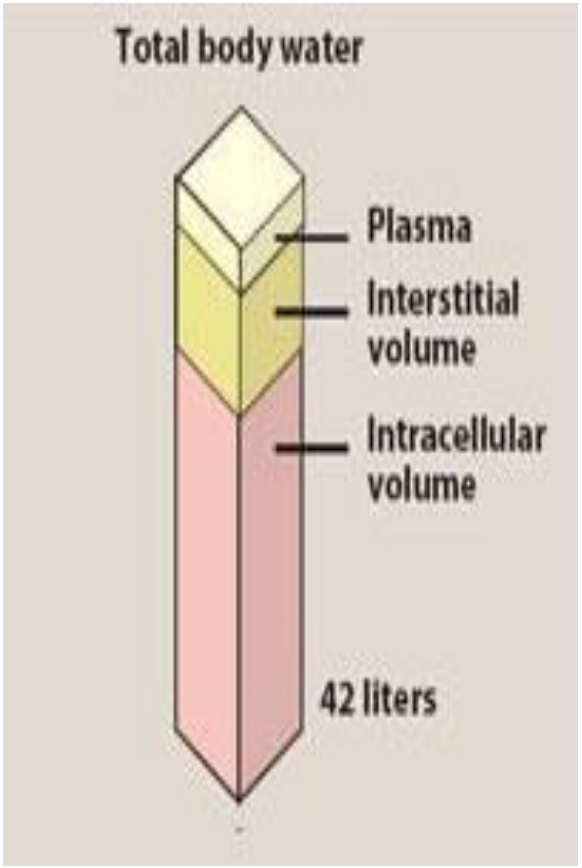
Extracellular fluid (22%)

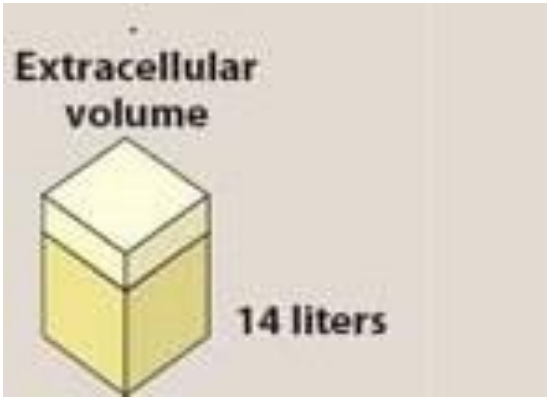
- Plasma (5 % of body weight = 4 liters).
- Interstitial fluid (16 % = 10 liters).

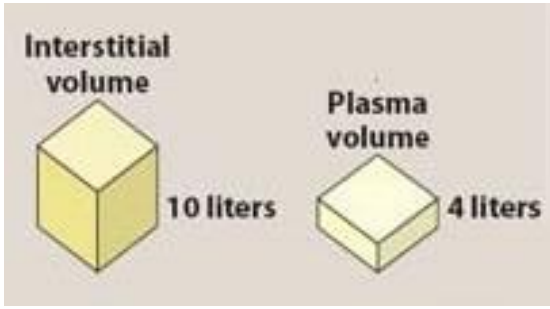
Intracellular fluid (35 %)

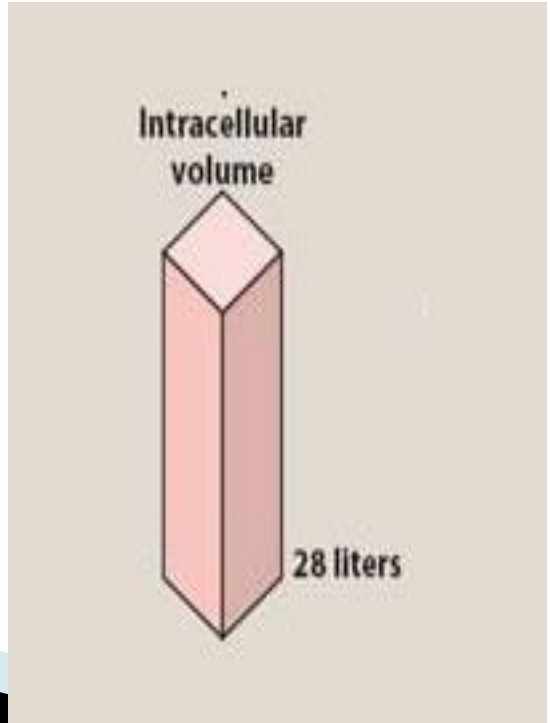
fluid present inside all cells in the body (28 L).

Volume of distribution





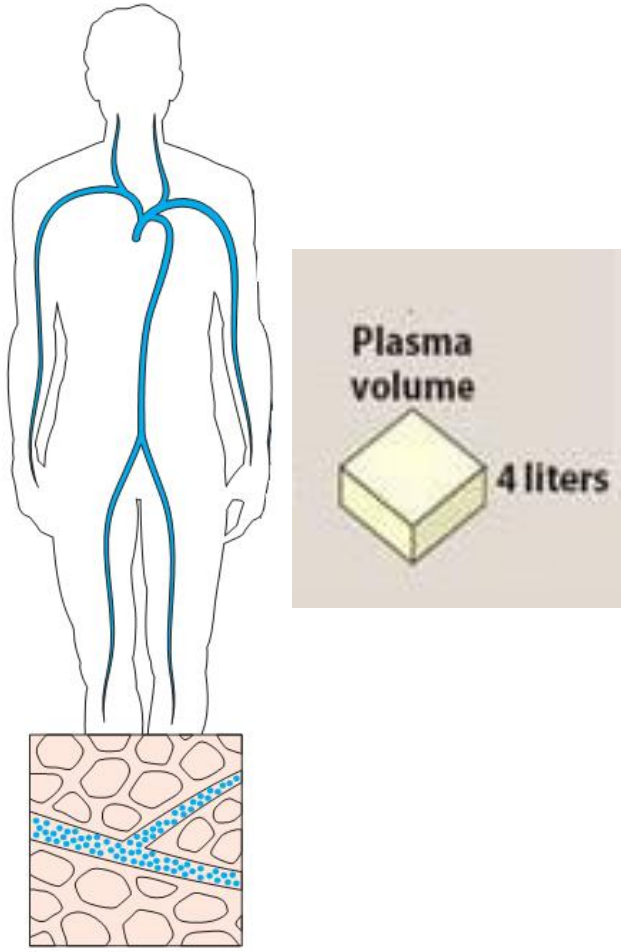




Drugs may distribute through:

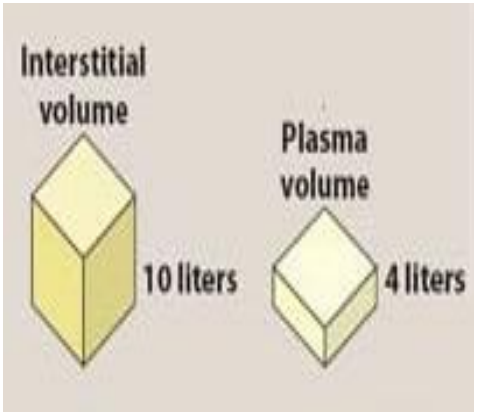
- One compartment
- Two compartments
- Multi-compartments

Plasma compartment



- Vd: around 4 L.
- Very high molecular weight drugs, or drugs that bind to plasma proteins
- Can not moves across endotelial cells of capillaries
- Drugs are trapped in blood
- Example: heparin 4L

Extracellular fluid



- Distribute through extracellular fluids.
- Pass endothelium into interstitial fluids BUT can not cross cell membranes to intracellular fluids.
- Drugs that have a low molecular weight but are hydrophilic.
- Vd: between 4 and 14 L.
  - E.g. atracuronium 11 L

Total body water (extracellular and intracellular)

- Diffusion to intracelullar fluid
- For lipid soluble drugs
- Vd equal to total body water.
  - Ethanol 38 L (34-41)
- Drug that binds strongly to tissues. Vd higher than total body water.
  - Digoxin:385 L

Volume of Distribution (Vd)

Drugs with low Vd

- **distributed in extracellular compartments (plasma & interstitial fluid).**
- **Polar comp or lipid insoluble drugs. e.g. gentamycin, atracurium**
- **High MW e.g. heparin – insulin.**
- **High plasma protein binding e.g. warfarin (anticoagulant).**
- **Do not cross BBB or placental barriers.**

Volume of Distribution (Vd)

Drugs with high Vd

- Have higher concentrations in tissues than in plasma.
- Lipid soluble.
- Distributed intracellularly
- e.g. digoxin, phenytion, morphine

FACTORS AFFECTING DISTRIBUTION

1.Cardiac output and blood flow.

2. **Physical and chemical properties of the drug**.

- Molecular weight
- Pka.
- Lipid solubility.

3. Capillary Permeability

4. Plasma protein binding

5. Tissue binding.

Blood flow to organs

- The greater the blood flow to tissues, the more distribution that occurs from plasma to interstitial fluids.

- Drugs distribute more rapidly to brain, liver and kidney > more than skeletal muscles & fat.

Physical and chemical properties of drug

- Most lipid soluble drugs (unionized, uncharged, nonpolar) cross biological membranes

- Hydrophilic drugs (ionized, charged, polar) do not readily cross membranes but go through slit junctions in endothelial cells of capillaries.

Capillary permeability

- Endothelial cells of capillaries in tissues other than brain have wide slit junctions allowing easy movement, permeation and distribution.

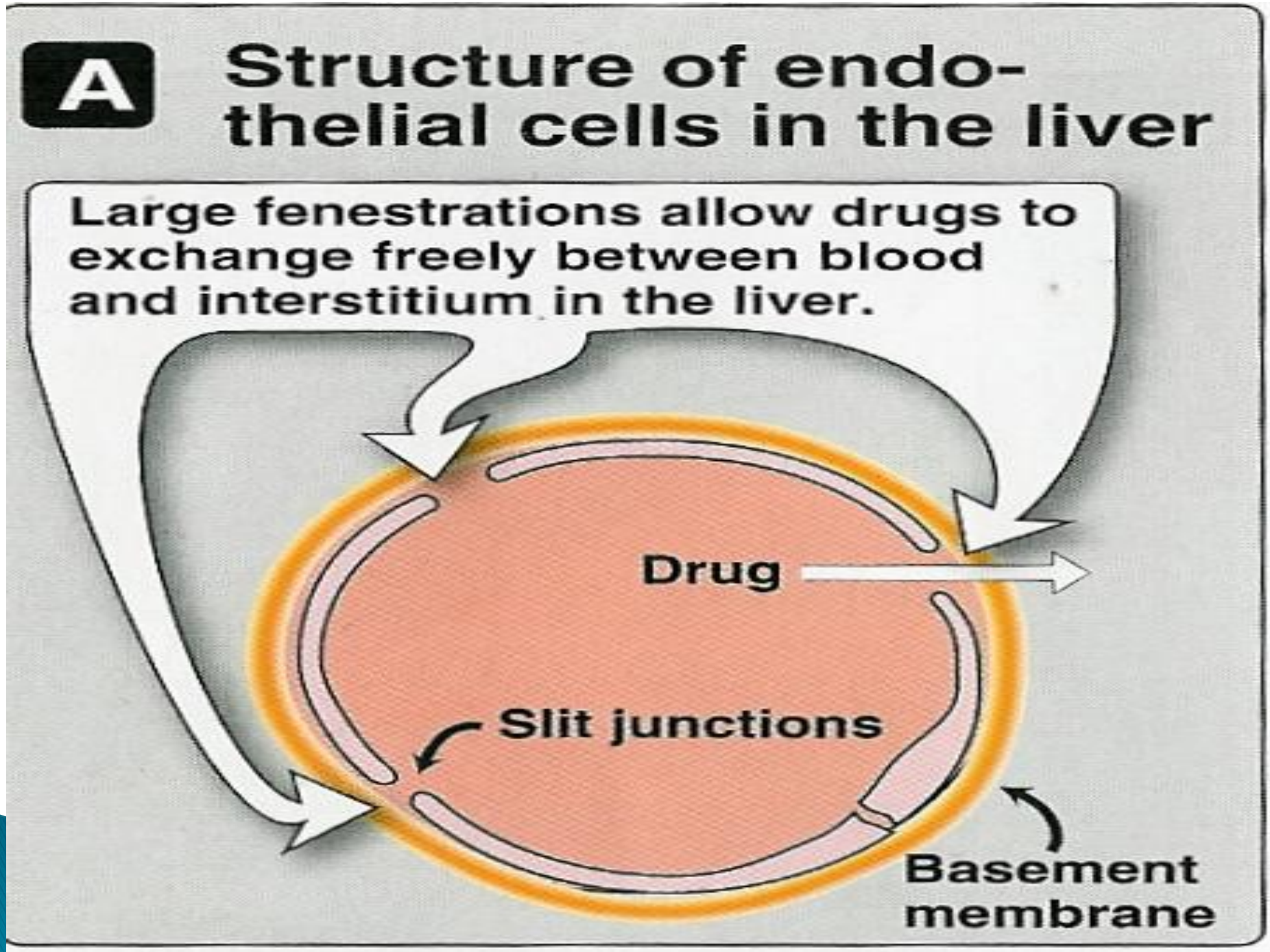
- Brain has tight junction Blood Brain Barrier (BBB).

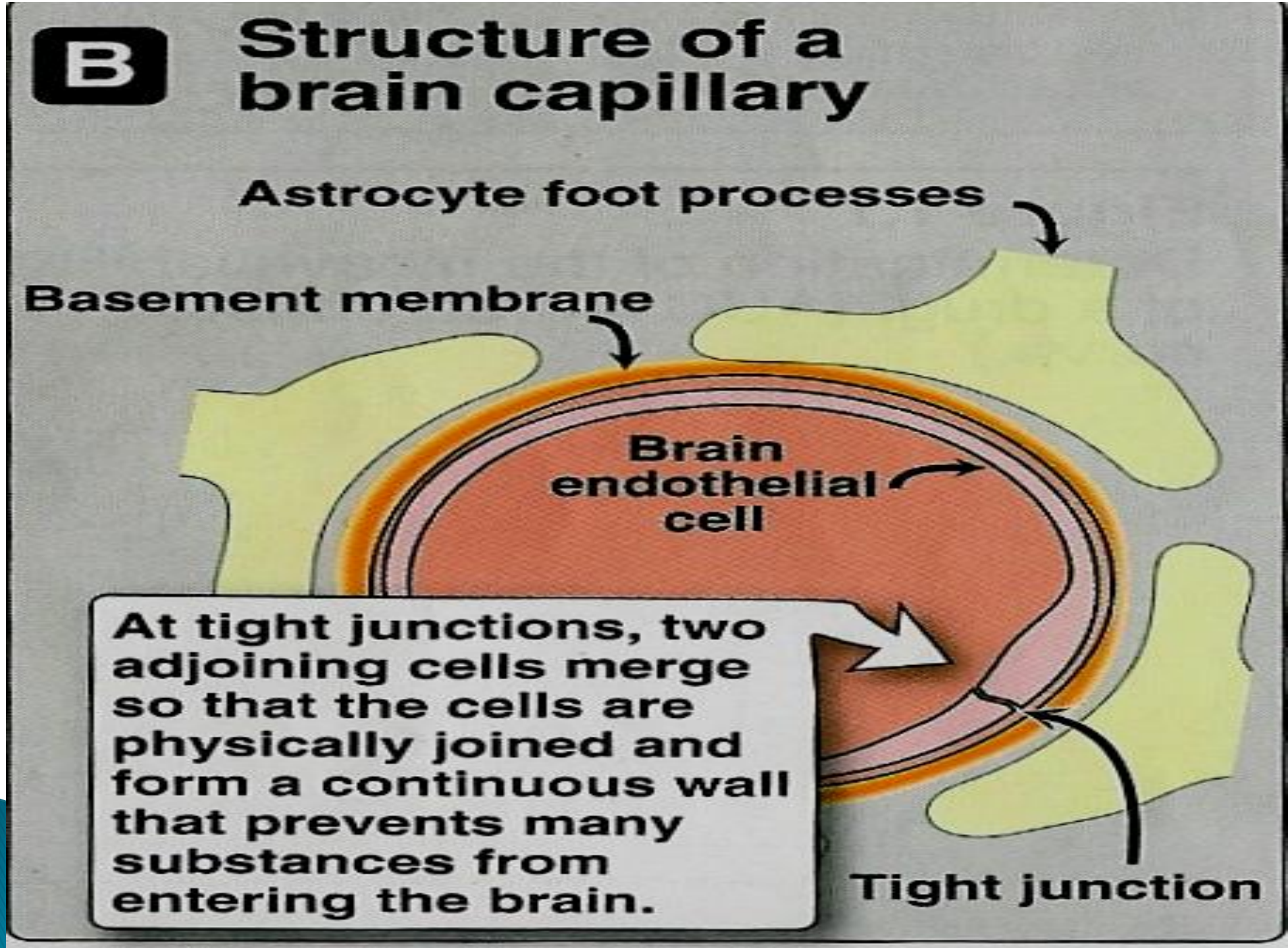
Blood brain barrier (BBB):

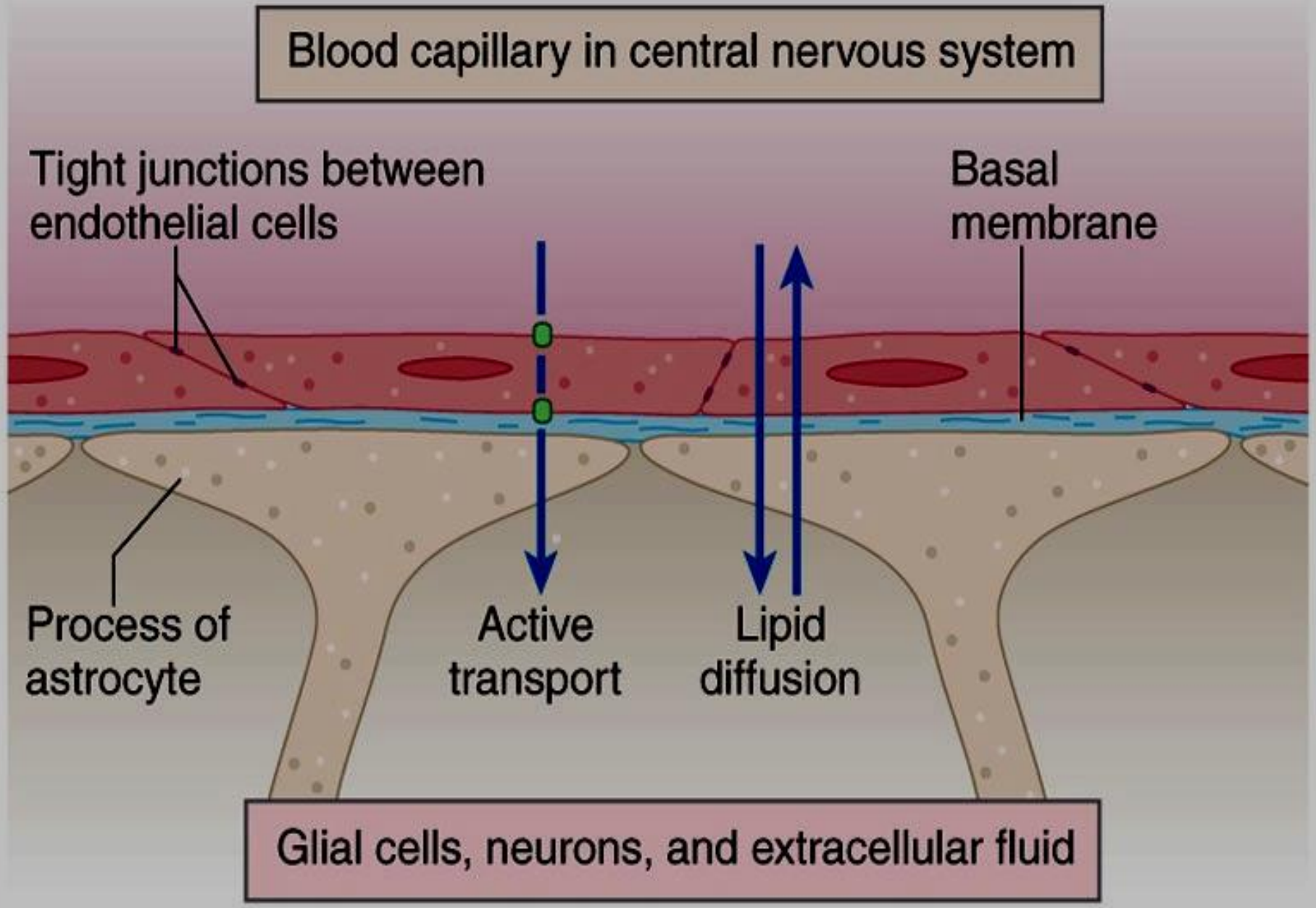
- Only lipid soluble drugs or actively transported drugs can cross BBB.
- Hydrophilic drugs (ionized or polar drugs) can not cross BBB.
- Inflammation as in **meningitis** increase permeability to hydrophilic drugs
- e.g. penicillin & gentamycin

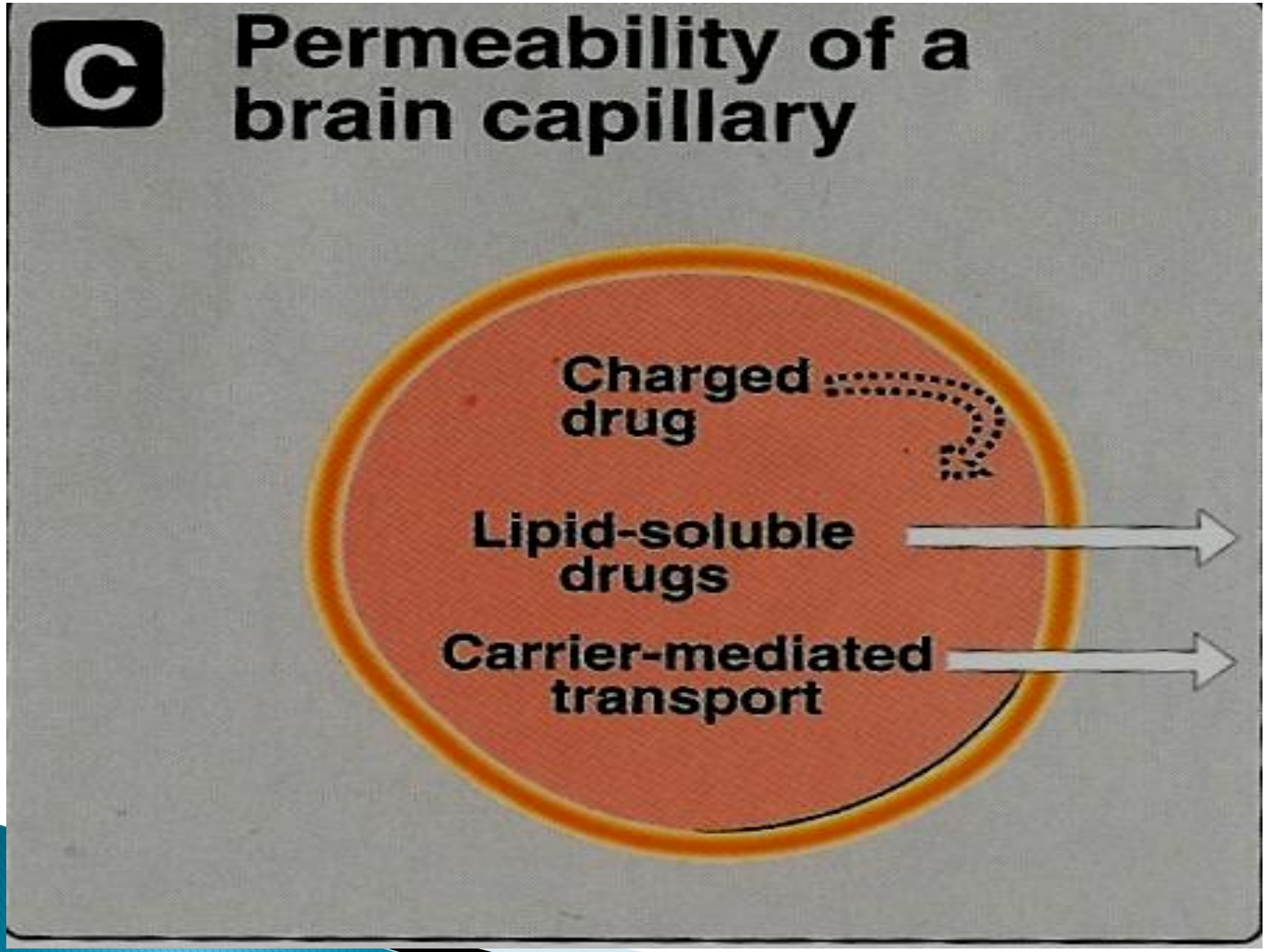
Placental barrier

- Lipid soluble drugs can cross placental barrier and enter the fetal blood.


A
Structure of endo-thelial cells in the liver
Large fenestrations allow drugs to exchange freely between blood and interstitium in the liver.
Drug
Slit junctions
Basement membrane


B
Structure of a brain capillary
Astrocyte foot processes
Basement membrane
Brain endothelial cell
At tight junctions, two adjoining cells merge so that the cells are physically joined and form a continuous wall that prevents many substances from entering the brain.
Tight junction




C
Permeability of a brain capillary
Charged drug
Lipid-soluble drugs
Carrier-mediated transport

Binding of Drugs

- **Plasma proteins binding.**
- **Tissue proteins binding.**

Plasma protein binding:

- Extensive plasma protein binding will cause more drug to stay in the blood compartment .

- Therefore, drugs which bind strongly to plasma protein tend to have lower distribution (Vd).

Plasma Proteins

Albumin

Has affinity for acidic drugs as warfarin, phenytoin, aspirin

alpha 1 -acid glycoproteins

Has affinity for basic drugs (cationic) as diazepam, quinidine.

Plasma protein binding

- drugs which bind strongly to plasma protein tend to have lower distribution (Vd).
- In blood, drugs exist in two forms bound and unbound forms in equilibrium

Unbound drug (free)  **bound drug**

Tissues Binding

Drugs can bind to specific tissues and will have high volume of distribution (Vd)

Tetracycline bind to bone

Bound form of drug

- non diffusible form
- can not cross endothelial barrier
- can not combine with receptors
- inactive
- not available for metabolism & excretion
- has long duration of action (t ½).

Unbound form of drug

- diffusible form
- cross endothelial barrier
- combine with receptors
- active
- available for metabolism & excretion
- has short duration of action (t ½).

Characters & consequences of Binding

- **Usually reversible.**
- **determines volume of distribution (vd)**
- **Slows drug metabolism & excretion.**
- **Prolongs duration of drug action (t1/2).**
- **Result in clinically important drug interactions**

Displacement

- Competition for the same binding site on the plasma proteins may occur between two drugs ⟶ displacement of one drug & increasing its concentrations & effects.

- Aspirin + Albumin–warfarin ⟶

Albumin–aspirin + free warfarin ⟶ bleeding.