



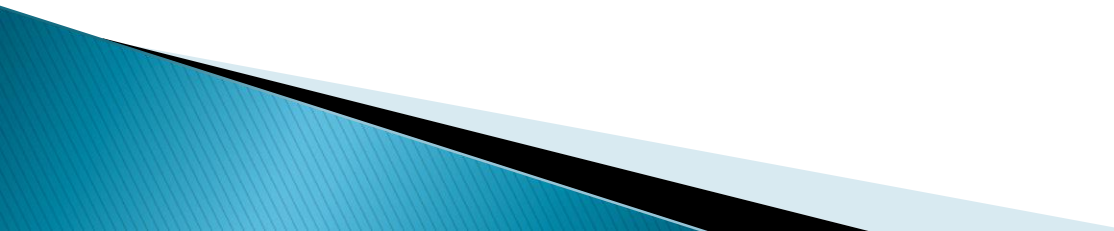
Pharmacokinetics II: Bioavailability and Distribution

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

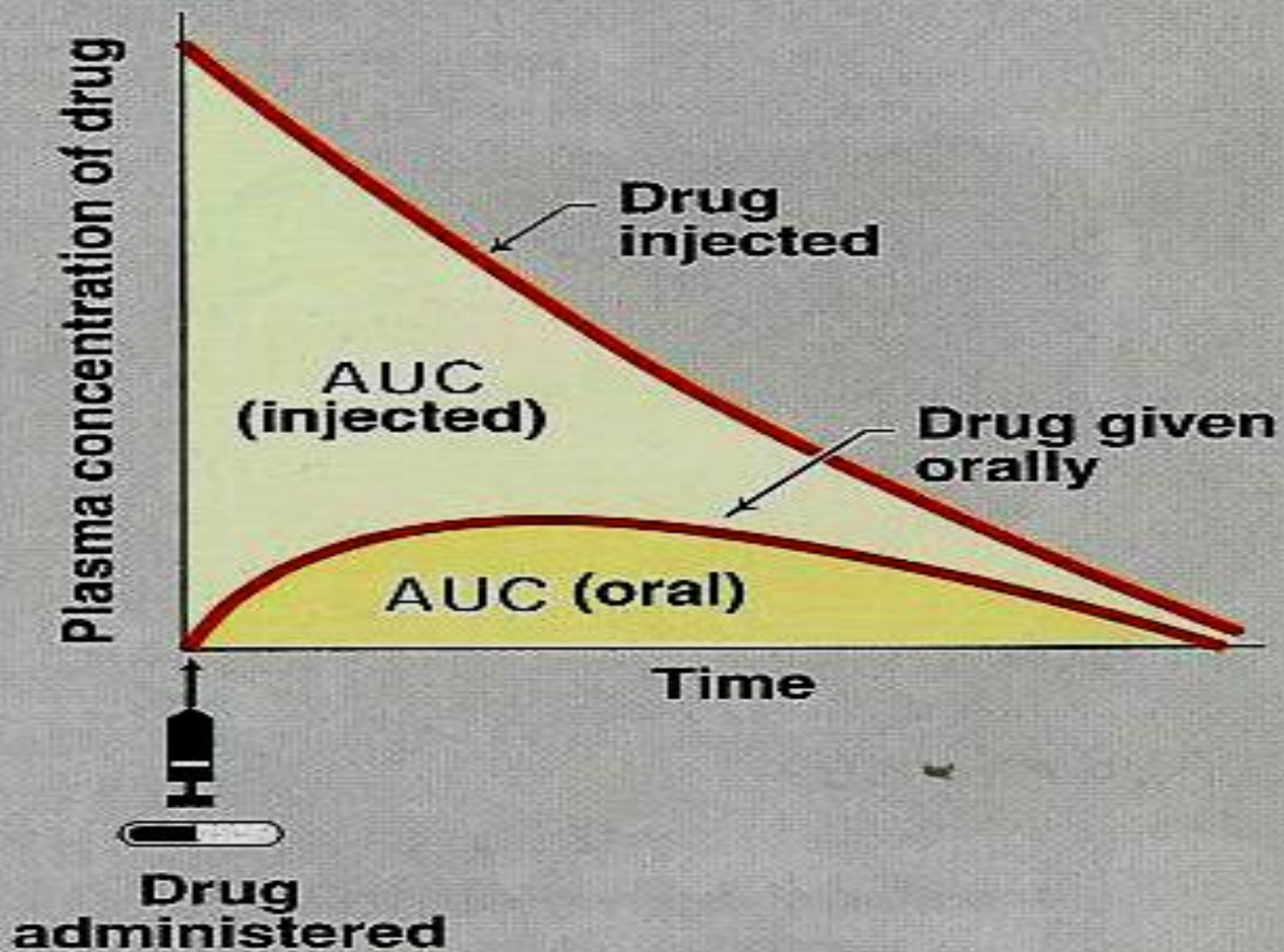
- ▶ **Major body fluid compartments**
 - ▶ **Concept of compartments.**
 - ▶ **Apparent volume of distribution (vd).**
 - ▶ **Plasma protein binding.**
 - ▶ **Tissue binding.**
- 

Bioavailability

▶ Is the amount of unchanged drug that enters systemic circulation after administration and becomes available to produce pharmacological actions (rate and extent of active reaching systemic circulation)

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

$$\text{Bioavailability} = \frac{\text{AUC oral}}{\text{AUC injected}} \times 100$$



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

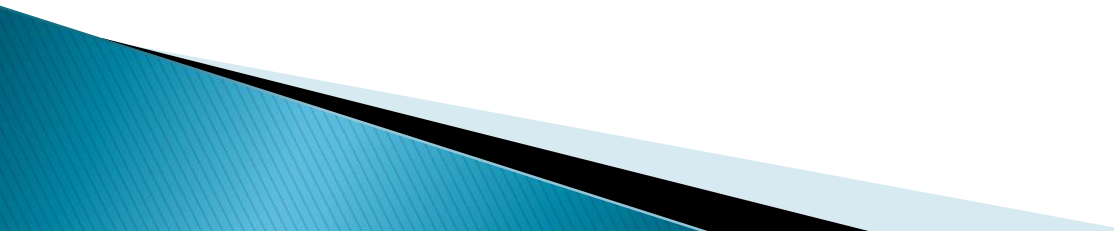
Factors affecting bioavailability:

- are the same factors controlling drug absorption
- First pass effect

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



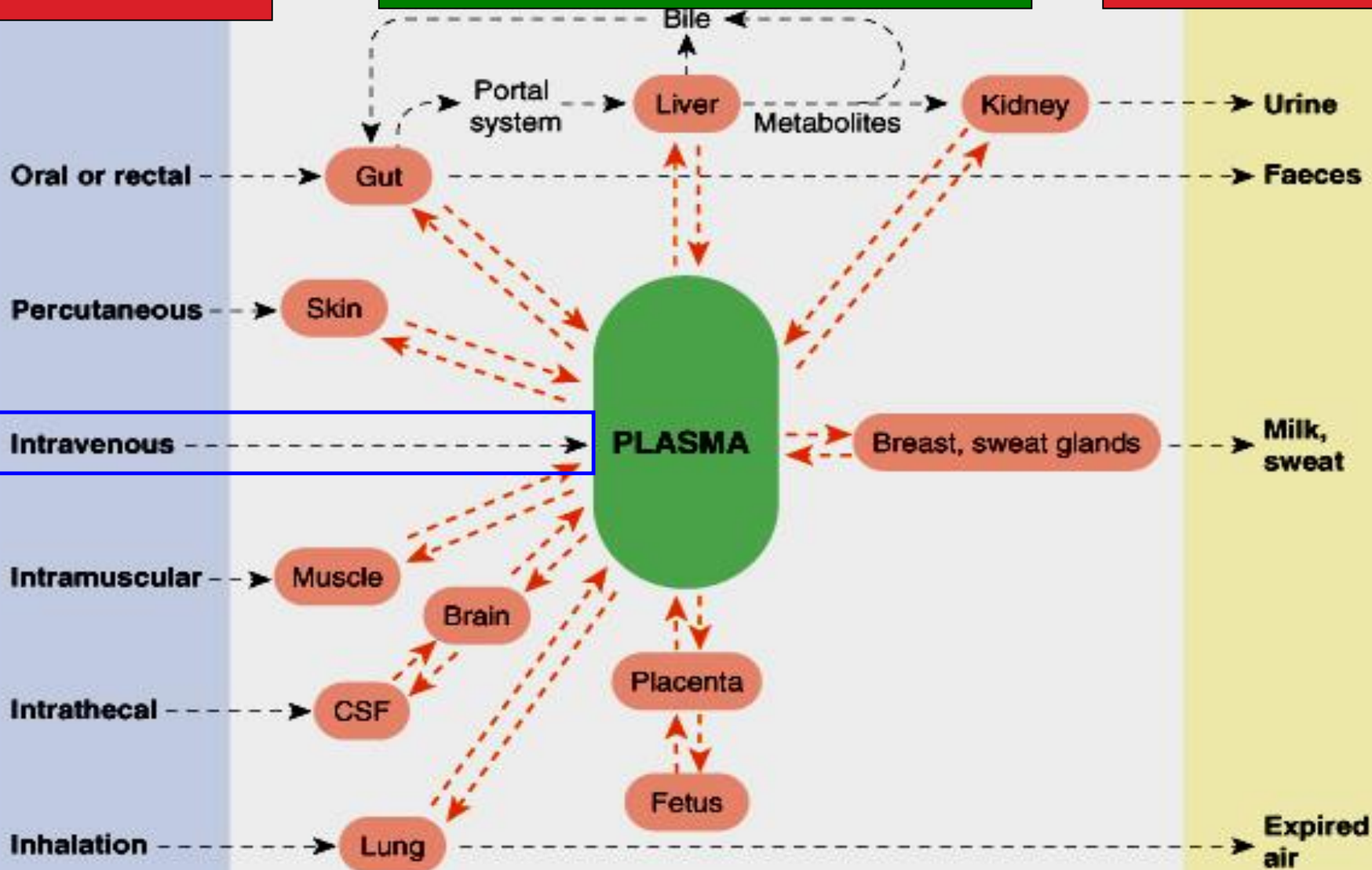
Extracellular

Intracellular

Sites of Administration

Absorption & distribution

Elimination



Apparent Volume of Distribution (Vd)

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

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

Why is Vd important?

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

The major body fluid compartments are

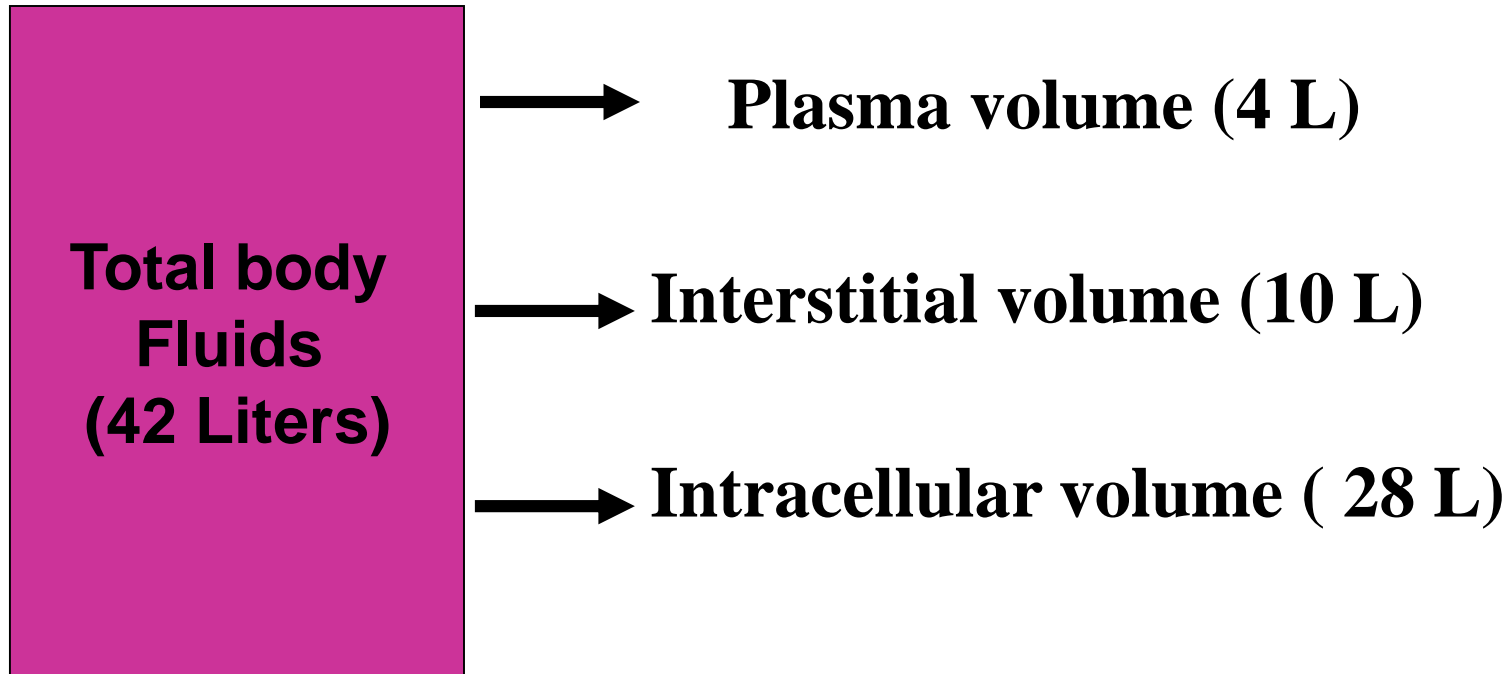
Extracellular fluid (21%)

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

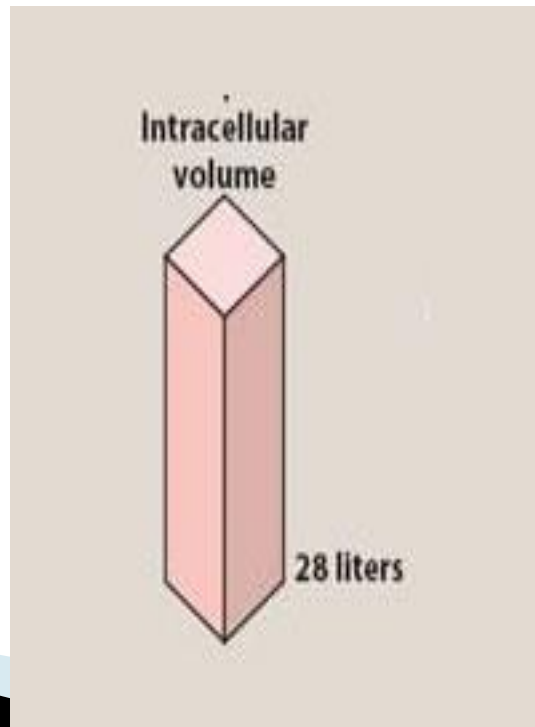
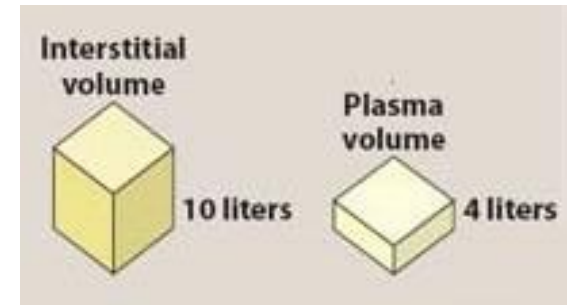
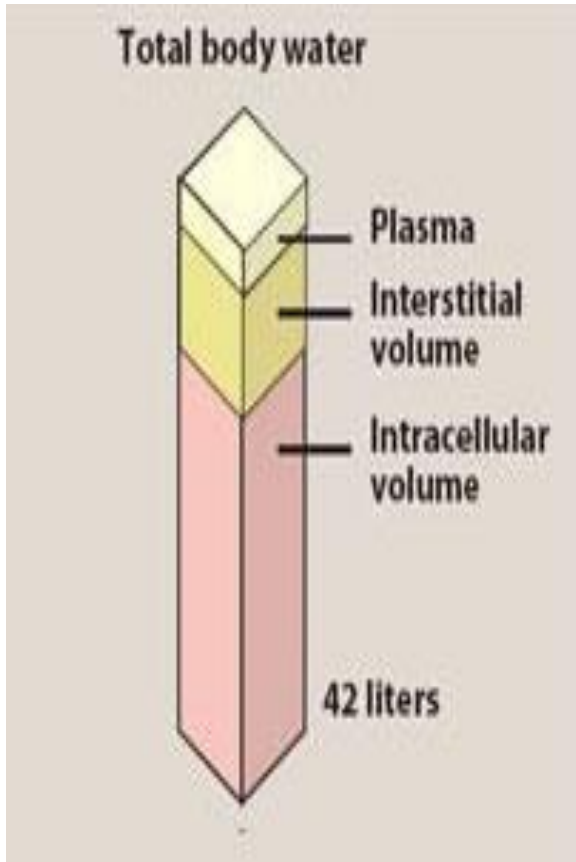
Intracellular fluid (35 %)

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

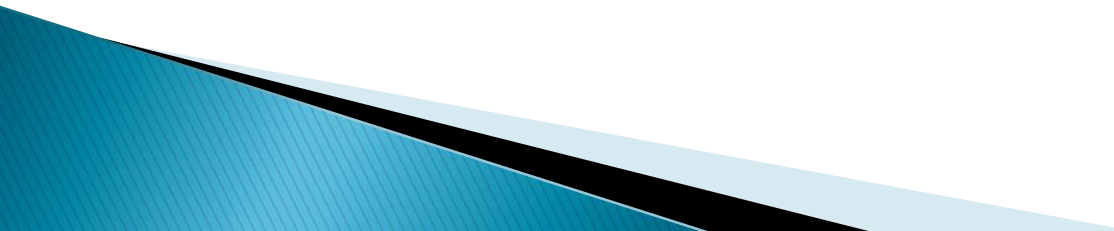
Total body fluids (70% of body weight in 70-kg individual)



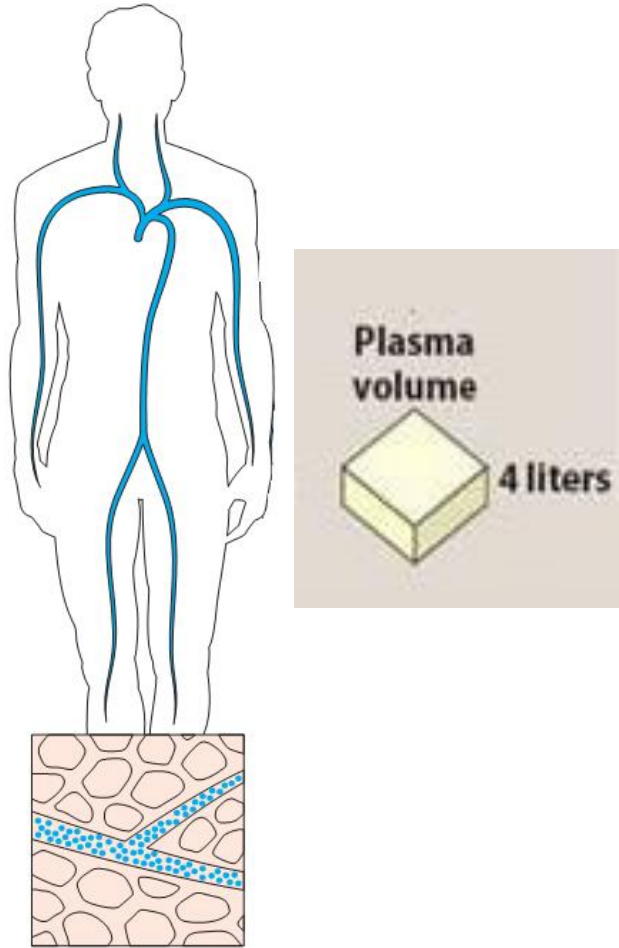
Volume of distribution



Drugs may distribute through:

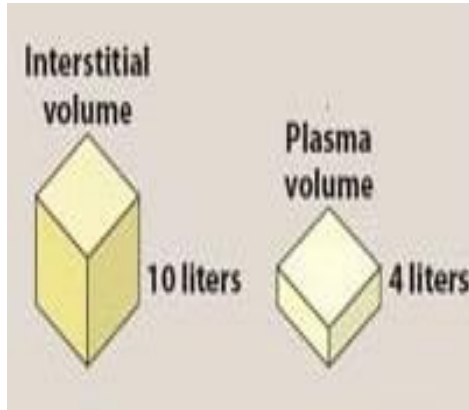
- ▶ One compartment
 - ▶ Two compartments
 - ▶ Multi-compartments
- 

Plasma compartment



- ▶ V_d : around 4 L.
- ▶ Very high molecular weight drugs, or drugs that bind to plasma proteins
- ▶ Can not moves across endothelial 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 intracellular 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 (V_d)

Drugs with low V_d

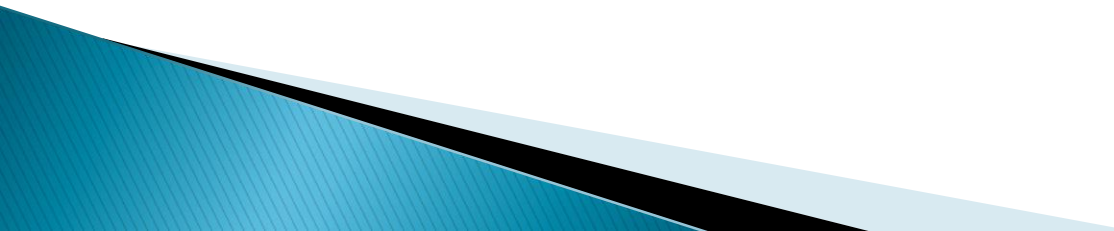
- ▶ **distributed in extracellular compartments (plasma & interstitial fluid).**
- ▶ **Polar comp or lipid insoluble drugs. e.g. gentamycin, atracurium**
- ▶ **High MW e.g. heparin – insulin.**
- ▶ **High plasma protein binding e.g. warfarin (anticoagulant).**
- ▶ **Do not cross BBB or placental barriers.**

Volume of Distribution (Vd)

Drugs with high Vd

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

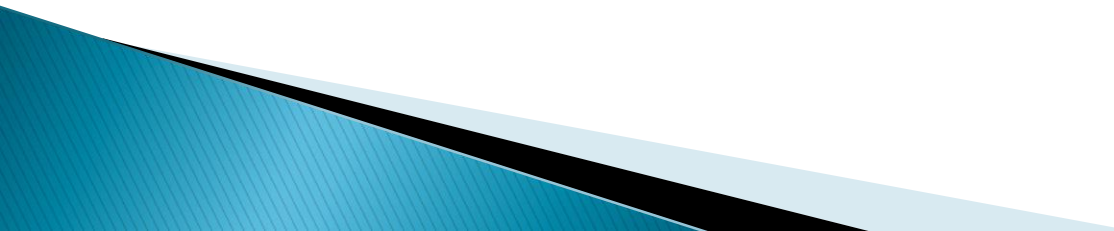
FACTORS AFFECTING DISTRIBUTION

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

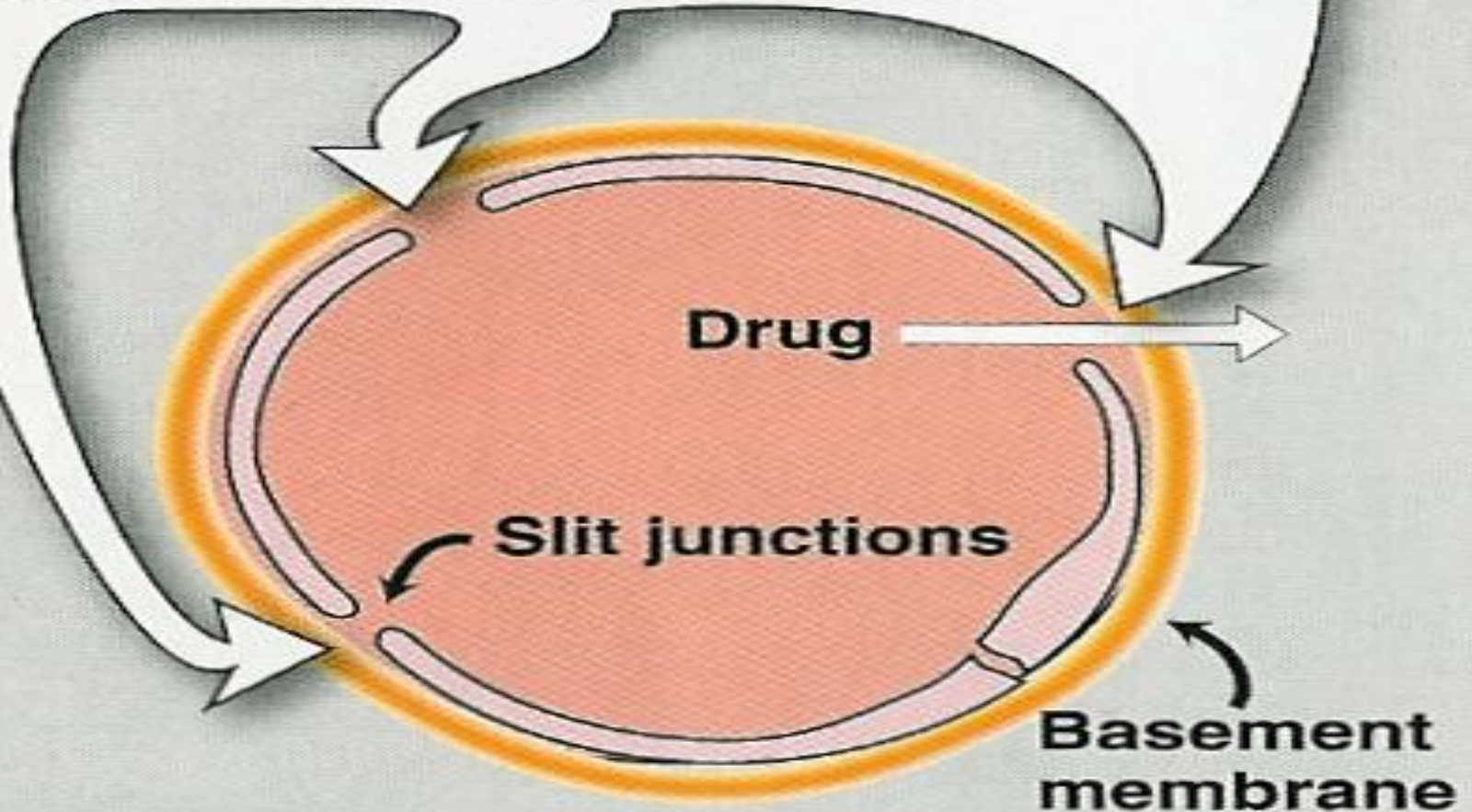
Placental barrier

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

A

Structure of endothelial cells in the liver

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



B

Structure of a brain capillary

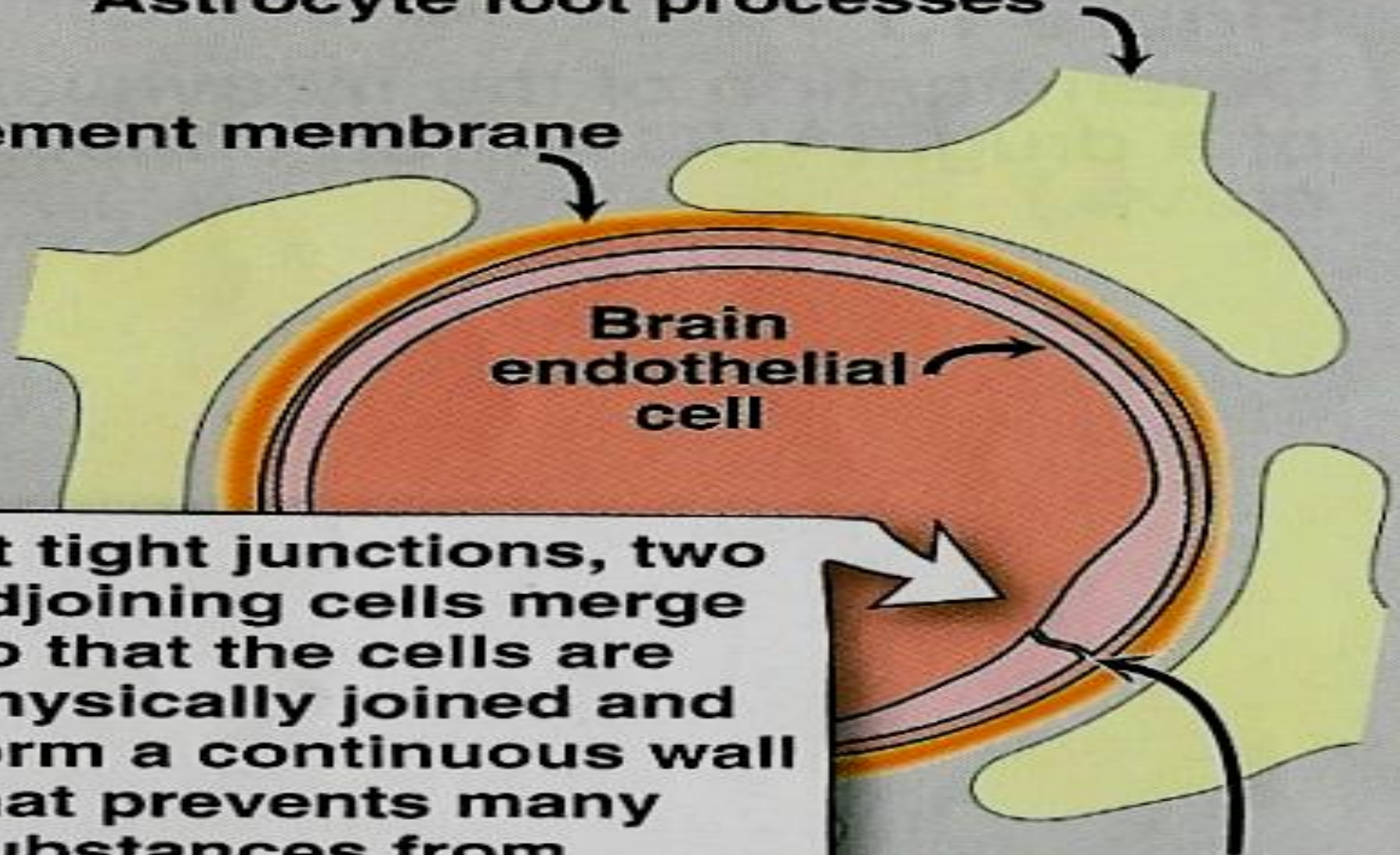
Astrocyte foot processes

Basement membrane

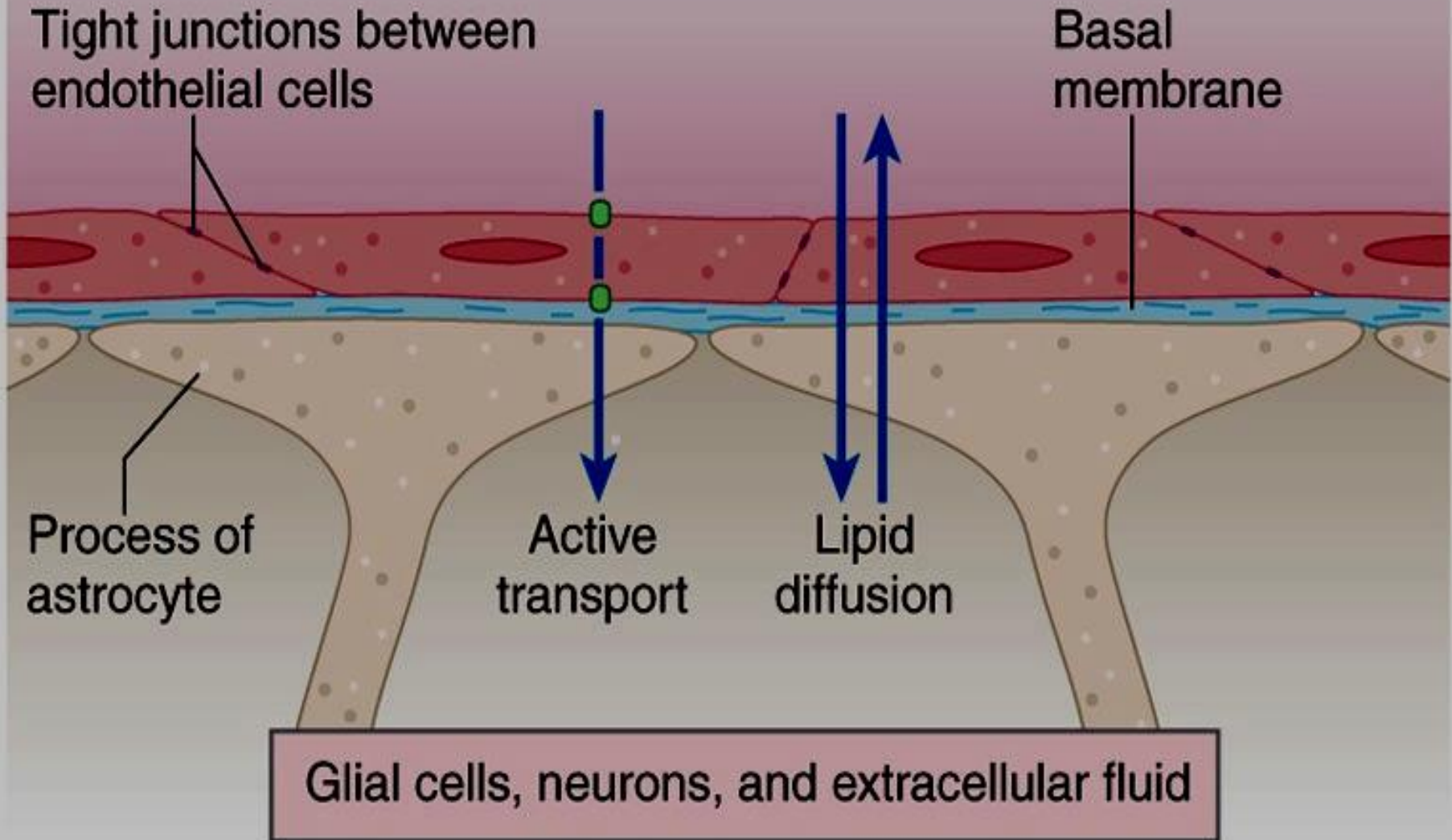
Brain endothelial cell

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

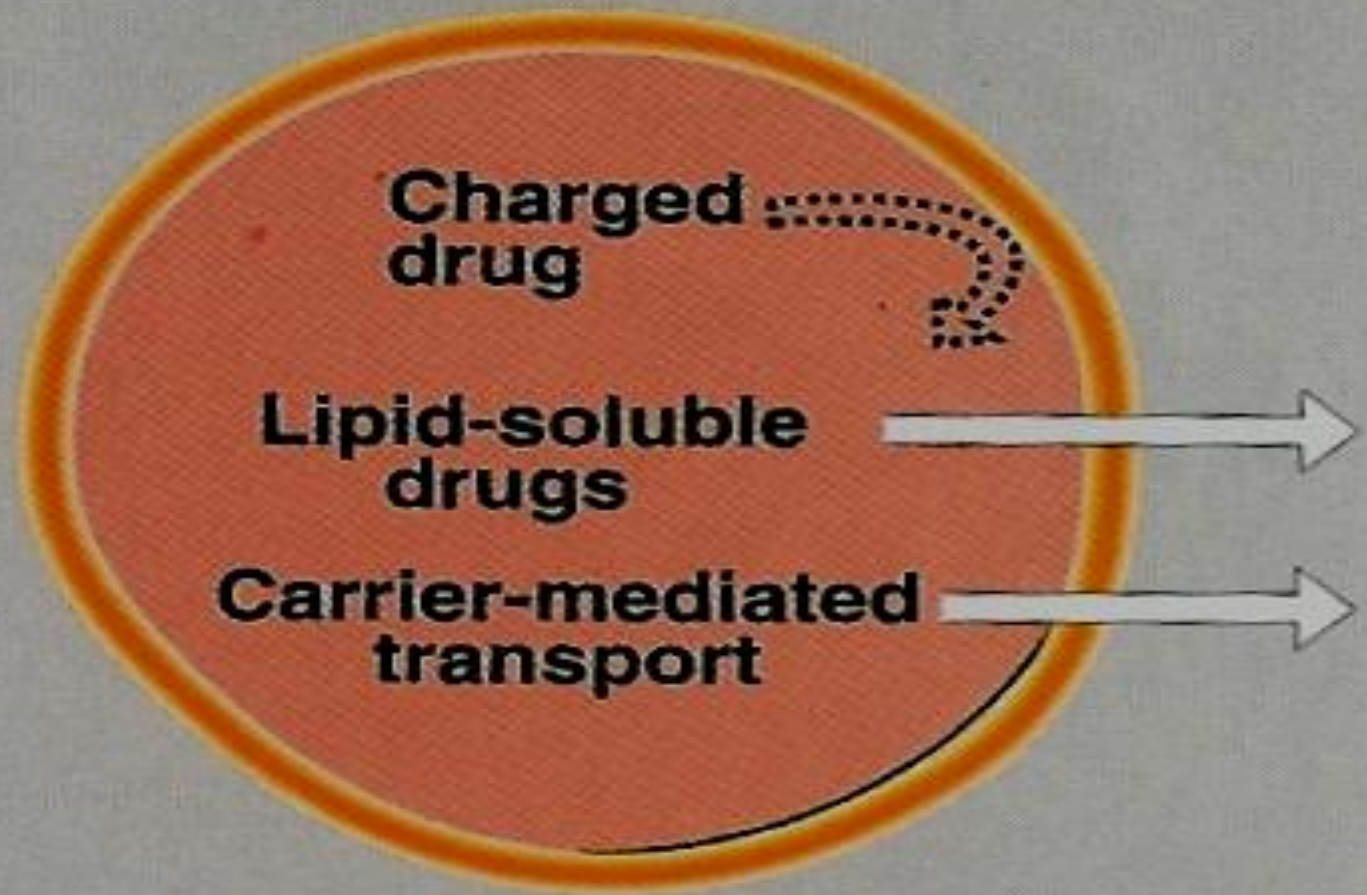


Blood capillary in central nervous system



C

Permeability of a brain capillary



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 (V_d).

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 (V_d).
- ▶ In blood, drugs exist in two forms bound and unbound forms in equilibrium



Tissues Binding

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

Tetracycline bind to bone

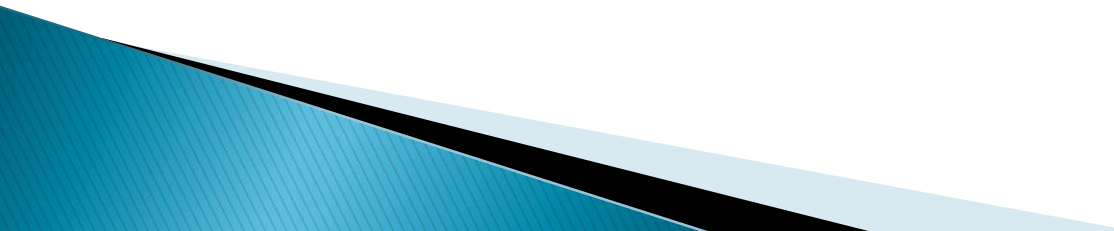
Bound form of drug

- **non diffusible form**
- **can not cross endothelial barrier**
- **can not combine with receptors**
- **inactive**
- **not available for metabolism & excretion**
- **has long duration of action ($t_{1/2}$).**

Unbound form of drug

- **diffusible form**
- **cross endothelial barrier**
- **combine with receptors**
- **active**
- **available for metabolism & excretion**
- **has short duration of action ($t_{1/2}$).**

Characters & consequences of Binding

- ▶ **Usually reversible.**
 - ▶ **determines volume of distribution (v_d)**
 - ▶ **Slows drug metabolism & excretion.**
 - ▶ **Prolongs duration of drug action ($t_{1/2}$).**
 - ▶ **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.