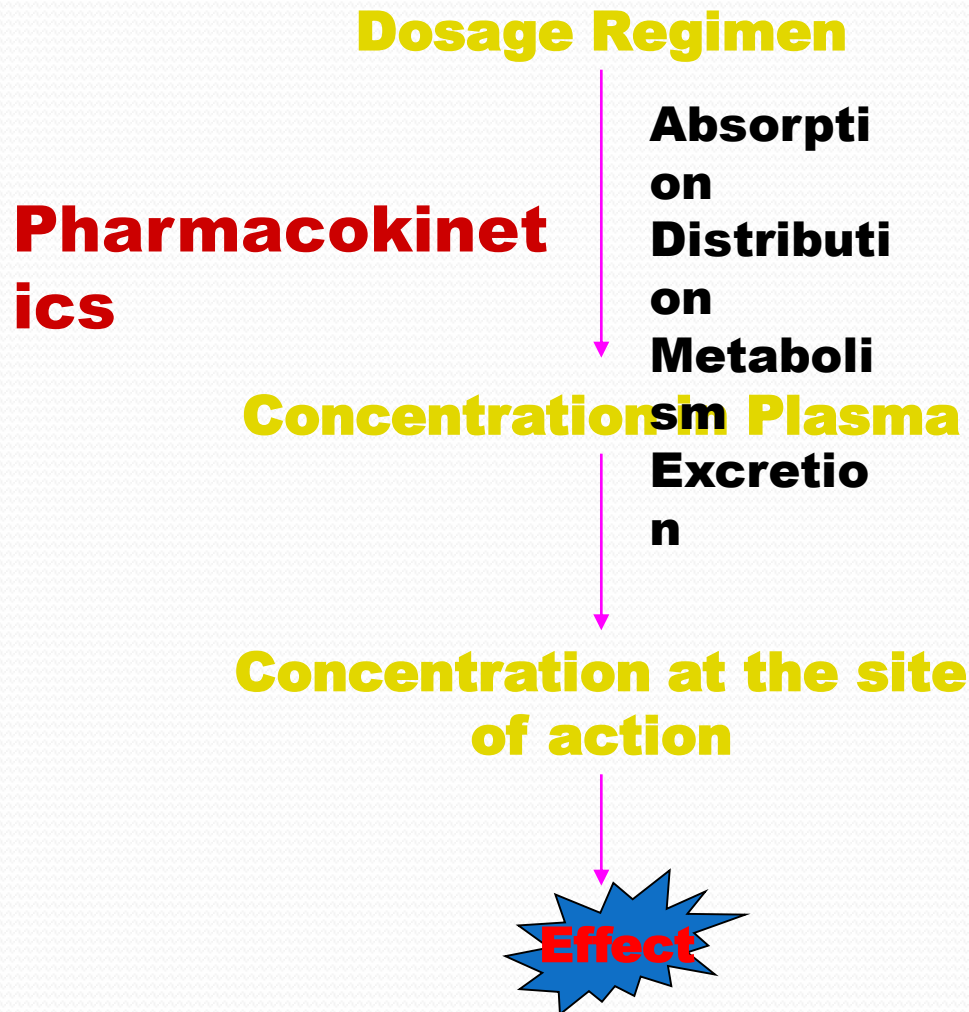


Pharmacokinetics

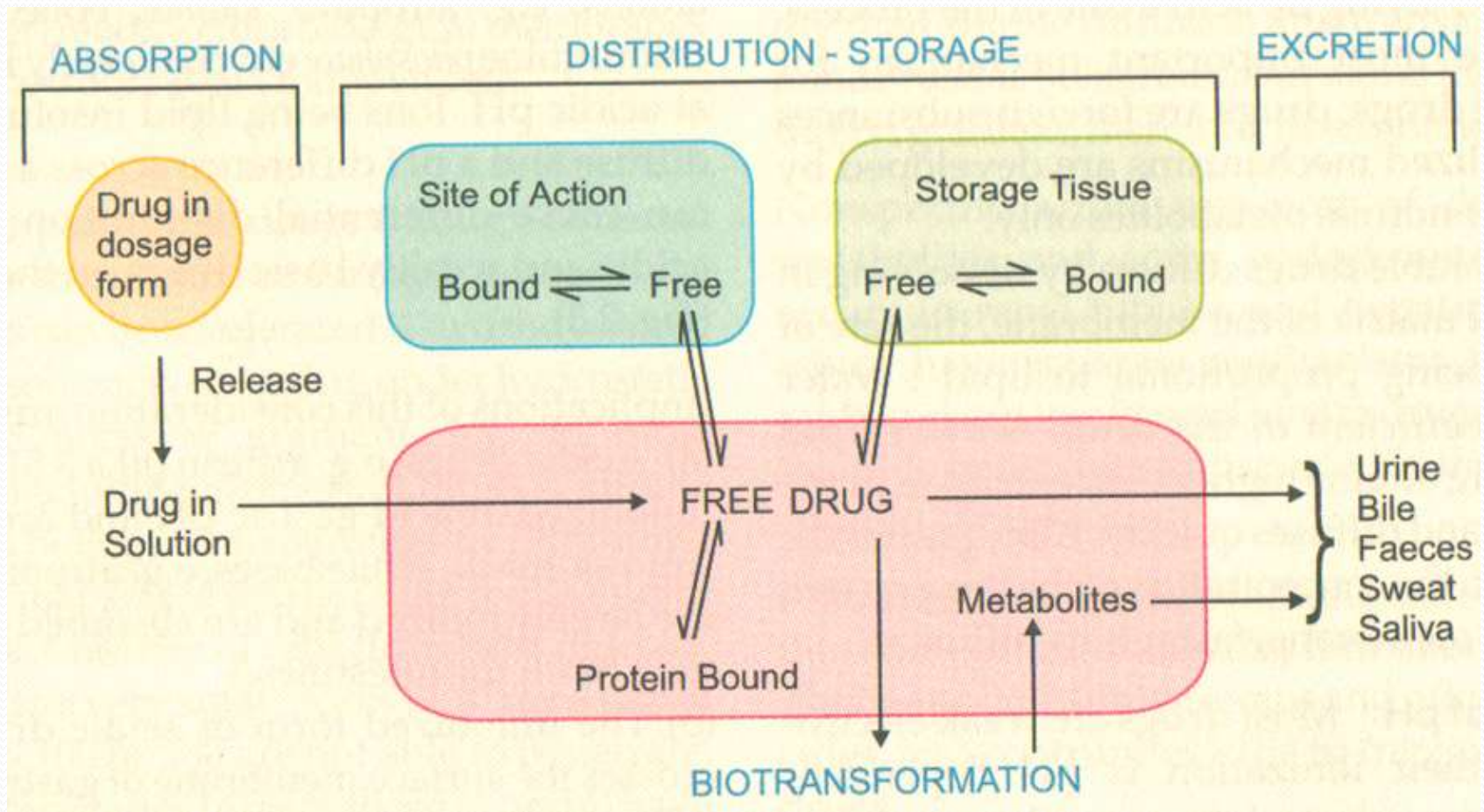
What is Pharmacokinetics

- *how the human body act on the drugs?*
- Pharmacokinetics is the quantitative study of drug movement in, through and out of the body. Intensity of effect is related to concentration of the drug at the site of action, which depends on its pharmacokinetic properties
- Pharmacokinetic properties of particular drug is important to determine the route of administration, dose, onset of action, peak action time, duration of action and frequency of dosing

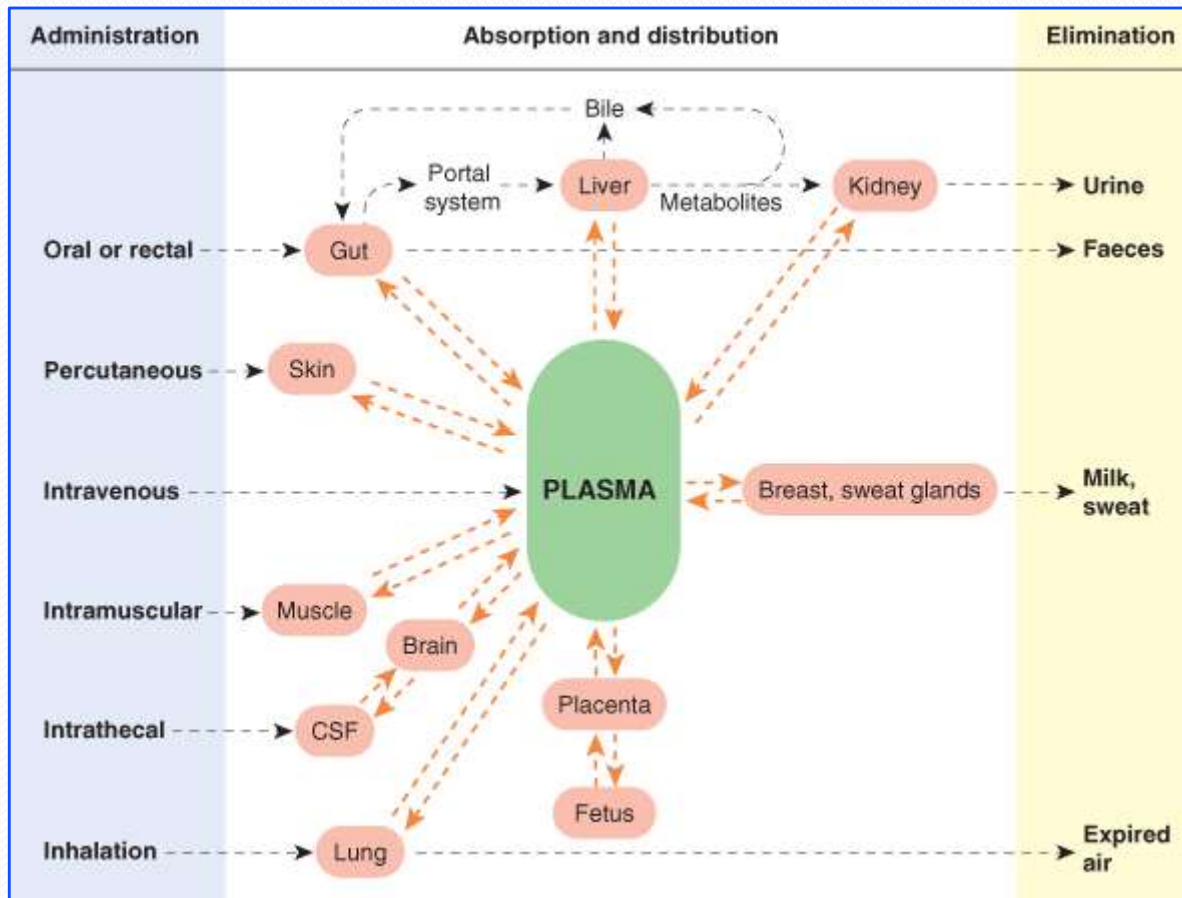
Relationship – Dynamics and Kinetics



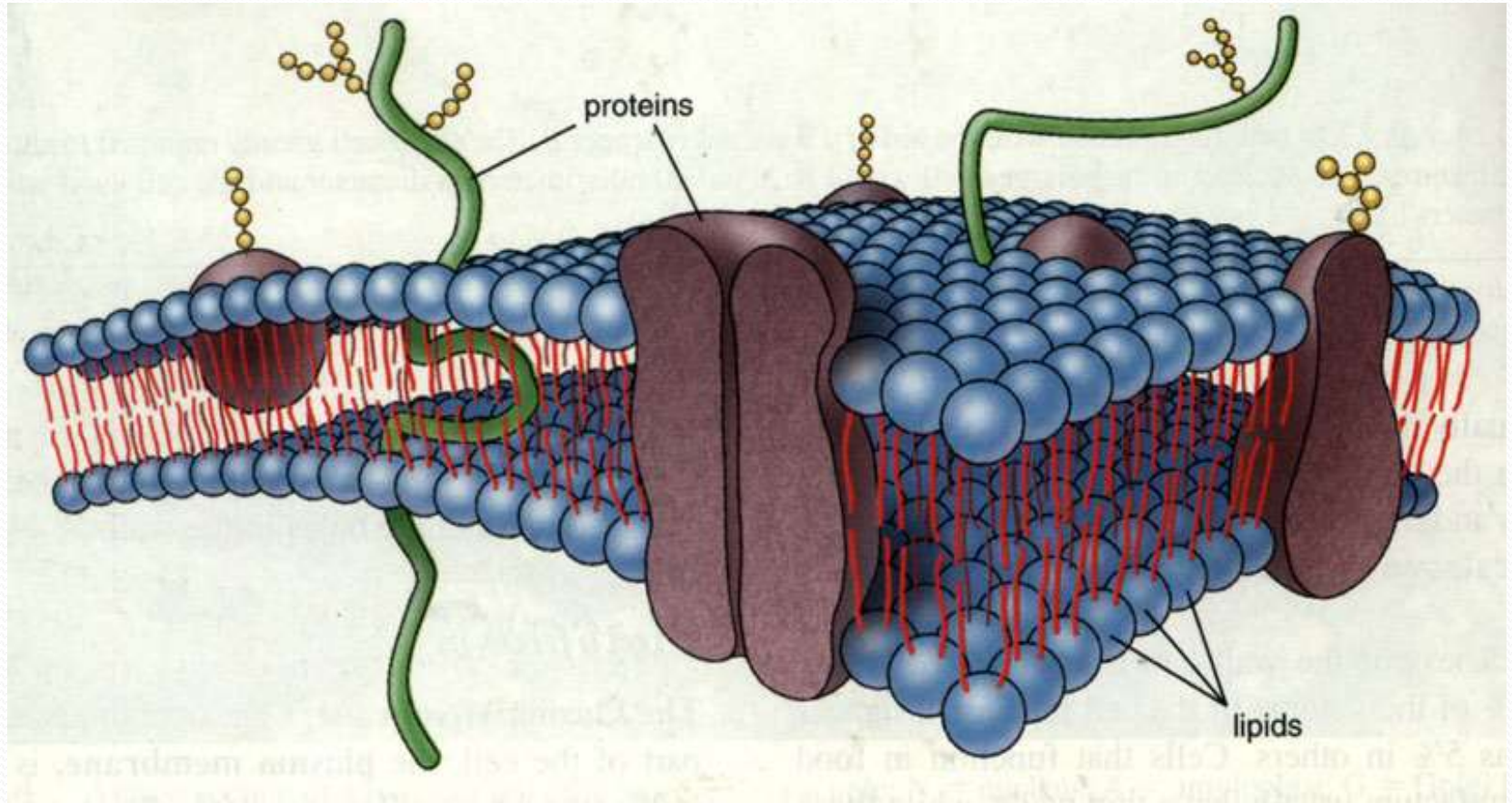
The Pharmacokinetic Process



The Pharmacokinetic Process



Biological Membrane - image



Drug Transportation

- Drug molecules can cross cell membrane by:
 - **Passive Diffusion**
 - **Protein – mediated transport** (carrier mediated)
 - Facilitated Transport
 - Active transport
 - Primary
 - Secondary

Passive transport (down hill movement)

- Most important Mechanism for most of the Drugs
- Majority of **drugs** diffuses across the membrane in the direction of concentration gradient
- No active role of the membrane
- Proportional to lipid : water partition coefficient
- Lipid soluble drugs diffuse by dissolving in the lipoidal matrix of the membrane
- Characteristics
 - Not requiring energy
 - Having no saturation
 - Having no carriers
 - Not resisting competitive inhibition

Passive transport

Affecting factors :

the size of molecule

lipid solubility

polarity

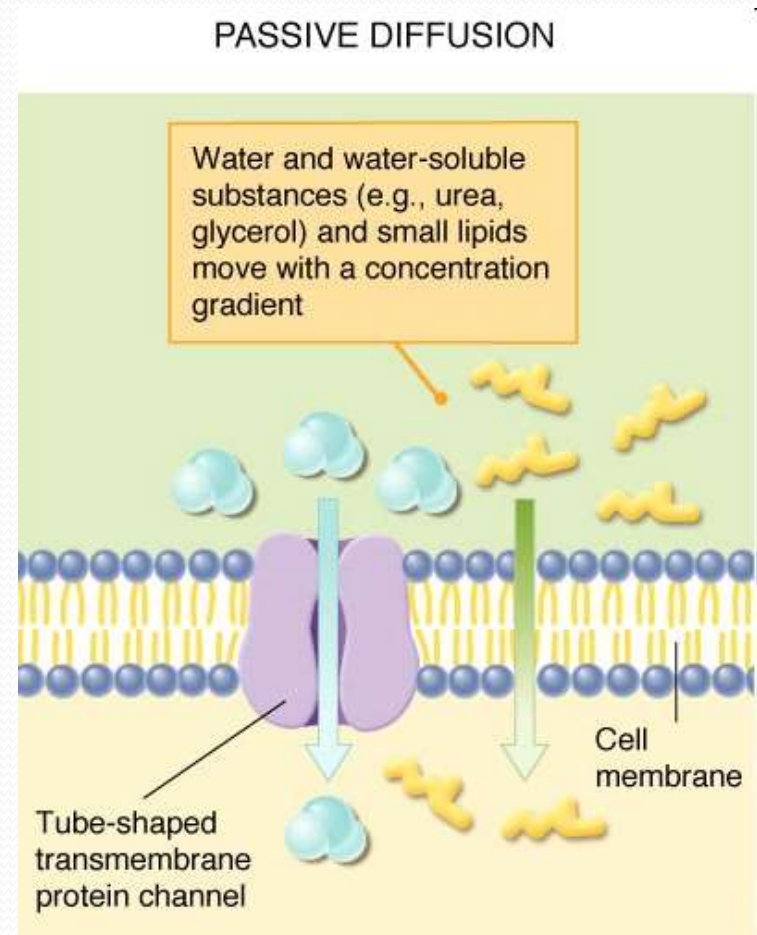
degree of ionization

the PH of the environment

such as: fluid of body

fluid in cell

blood, urine



Remember

- The drugs which are Unionized, low polarity and higher lipid solubility are easy to permeate membrane.
- The drugs which are ionized, high polarity and lower lipid solubility are difficult to permeate membrane.

pH Effect

- Most of drugs are weak acids or weak bases.
- The ionization of drugs may markedly reduce their ability to permeate membranes.
- The degree of ionization of drugs is determined by the surrounding pH and their pKa (negative logarithm of acidic dissociation constant of electrolyte)

Henderson–Hasselbalch Equation

$$\text{pH} = \text{pK}_a + \log \frac{[\text{A}^-]}{[\text{HA}]}$$

pKa = negative logarithm of acid dissociation constant

[A⁻] = ionized Drug

[HA] = unionized drug

Implications

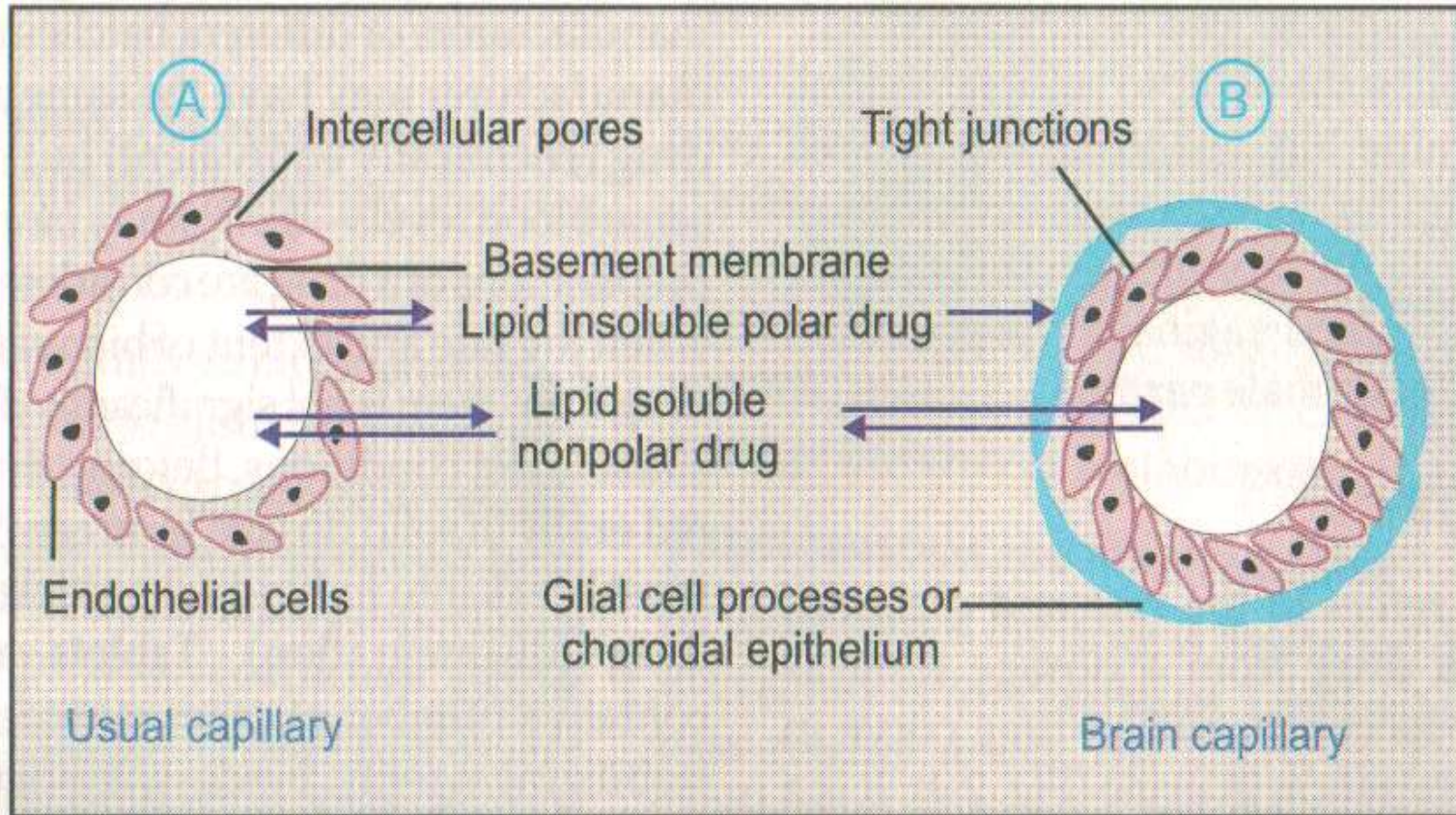
- Acidic drugs re absorbed are largely unionized in stomach and absorbed faster while basic drugs are absorbed faster in intestines
- Ion trapping
- Acidic drugs are excreted faster in alkaline urine – urinary alkalizers
- Basic drugs are excreted faster in acidic urine – urinary acidifiers

Filtration

- Passage of Drugs through aqueous pores in membrane or through Para cellular space
- Lipid insoluble drugs can cross – if the molecular size is small
- Majority of intestinal mucosa and RBCs have small pores and drugs cannot cross
- But, capillaries have large paracellular space and most drugs can filter through this



Filtration

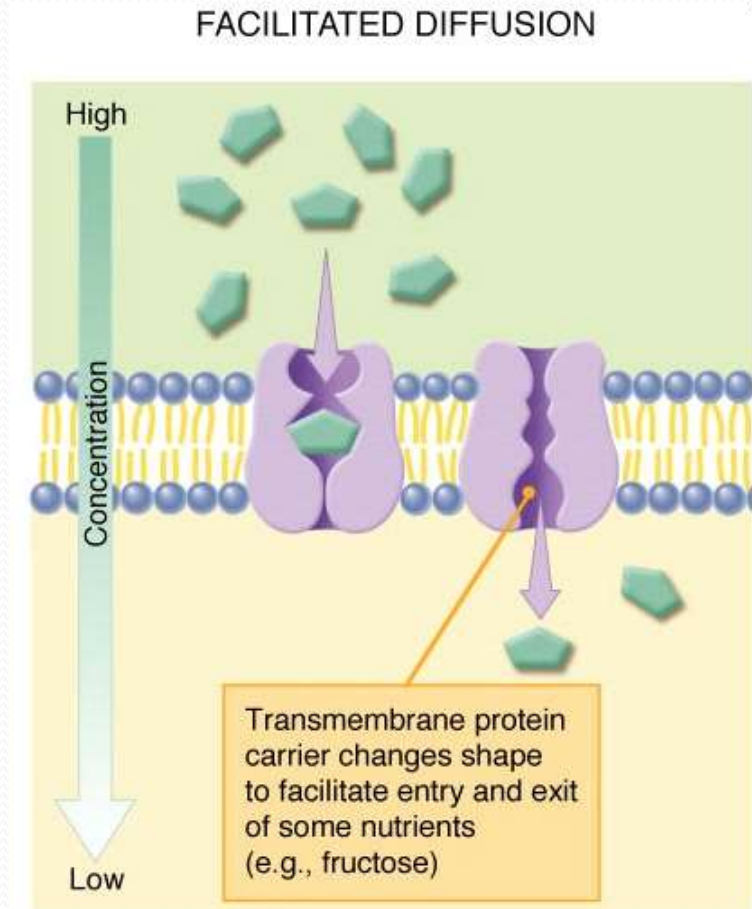


Carrier Mediated Transport

- Involve specific membrane transport proteins known as drug transporters or carriers – specific for the substrate
- Drug molecules bind to the transporter, translocated across the membrane, and then released on the other side of the membrane.
- Specific, saturable and inhibitable
- Depending on Energy requirement - Can be either **Facilitated (passive)** or **Active Transport**

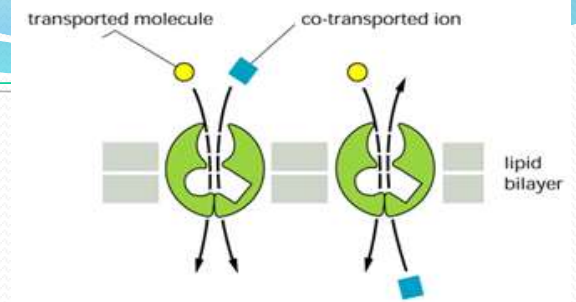
Facilitative transporters

- Move substrate of a single class (uniporters) down a concentration gradient
- No energy dependent
- Similar to entry of glucose into muscle (GLUT 4)



Active Transport – energy dependent

- Active (concentrative) transporters
 - can move solutes against a concentration gradient
 - energy dependent
- **Primary active transporters** - generate energy themselves (e.g. ATP hydrolysis)
- **Secondary transporters** - utilize energy stored in voltage and ion gradients generated by a primary active transporter (e.g. Na⁺/K⁺-ATPase)
 - **Symporters** (Co-transporters)
 - **Antiporters** (Exchangers)

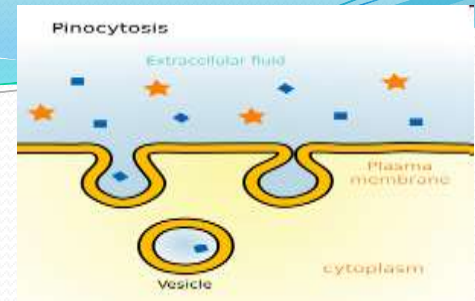


Major Drug Transporters

- ATP-Binding Cassette Transporters (ABC) Super family – Primary active transport
 - P-glycoprotein (P-gp)
 - Intestinal mucosa, renal tubules and blood brain barrier etc.
 - Mediate only efflux of solute from cytoplasm - detoxification
- Solute Carrier (SLC) transporters – Secondary active transport
 - Organic anion transporting polypeptides (OATPs)
 - Organic cation transporters (OCTs)
 - Expressed in liver and renal tubules – metabolism and excretion of drugs

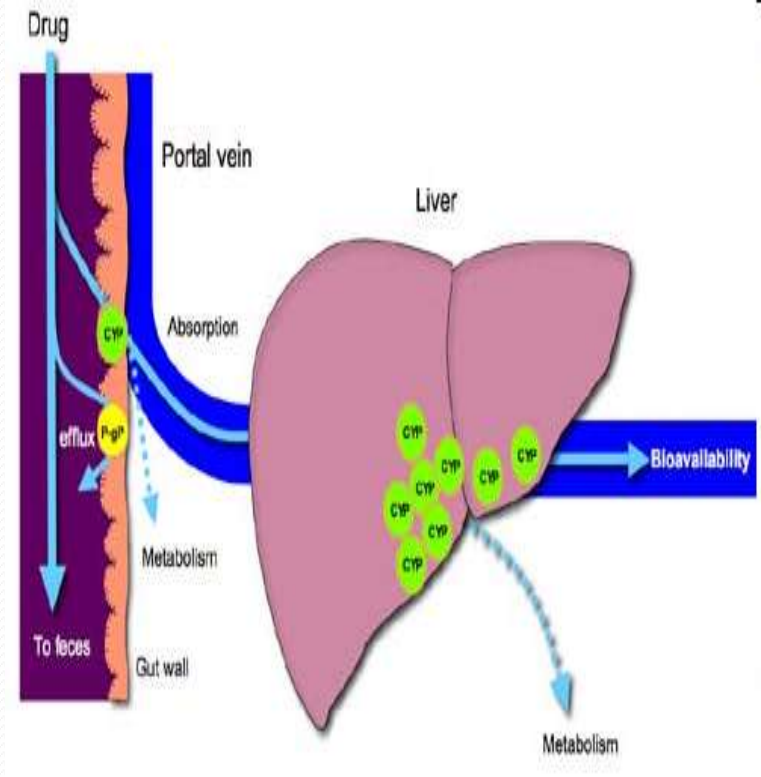
Pinocytosis

- It involves the invagination of a part of the cell membrane and trapping within the cell of a small vesicle containing extra cellular constituents. The vesicle contents can then be released within the cell, or extruded from the other side of the cell. Pinocytosis is important for the transport of some macromolecules (e.g. insulin through BBB).



1. Absorption of Drugs

- ❖ Absorption is the transfer of a drug from its site of administration to the blood stream
- ❖ Most of drugs are absorbed by the way of passive transport
- ❖ Intravenous administration has no absorption
- ❖ Fraction of administered dose and rate of absorption are important



Factors affecting absorption

➤ Drug properties:

lipid solubility, molecular weight, and polarity etc

- Blood flow to the absorption site
- Total surface area available for absorption
- Contact time at the absorption surface
- Affinity with special tissue

Routes of Administration (important):

Factors affecting absorption – contd.

Route of administration:

- Topical:
 - Depends on lipid solubility – only lipid soluble drugs are penetrate intact skin – only few drugs are used therapeutically
 - Examples – GTN, Hyoscine, Fentanyl, Nicotine, testosterone and estradiol
 - Organophosphorous compounds – systemic toxicity
 - Abraded skin: tannic acid – hepatic necrosis
 - Cornea permeable to lipid soluble drugs
 - Mucus membranes of mouth, rectum, vagina etc, are permeable to lipophilic drugs

Factors affecting absorption – contd.

Route of administration:

- Subcutaneous and Intramuscular:
 - Drugs directly reach the vicinity of capillaries – passes capillary endothelium and reach circulation
 - Passes through the large paracellular pores
 - Faster and more predictable than oral absorption
 - Exercise and heat – increase absorption
 - Adrenaline – decrease absorption

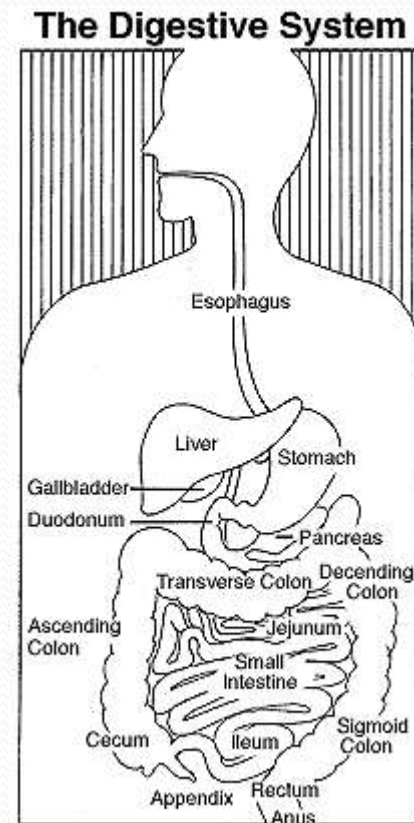
Factors affecting absorption – contd.

Route of administration: Oral Route

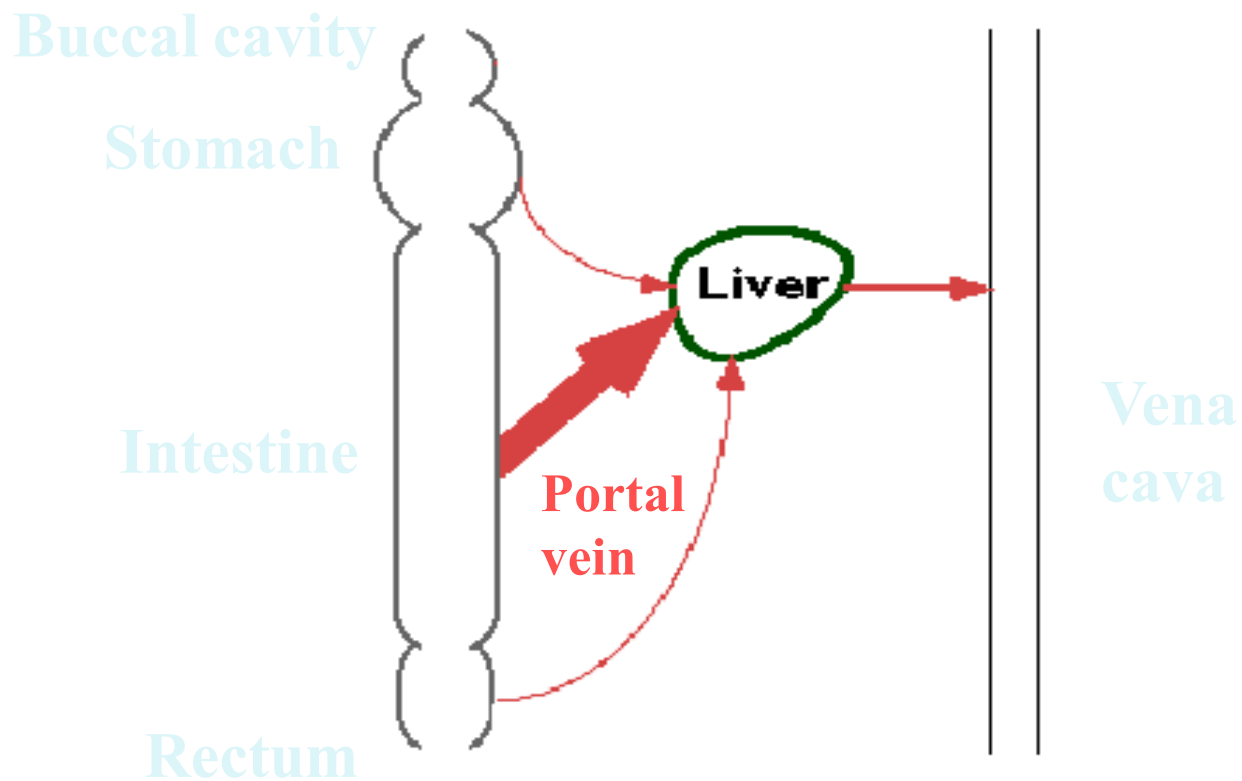
- Physical properties – Physical state, lipid or water solubility
- Dosage forms:
 - Particle size
 - Disintegration time and Dissolution Rate
- Physiological factors:
 - Ionization, pH effect
 - Presence of Food
 - Presence of Other agents

Oral Administration – 1st pass metabolism

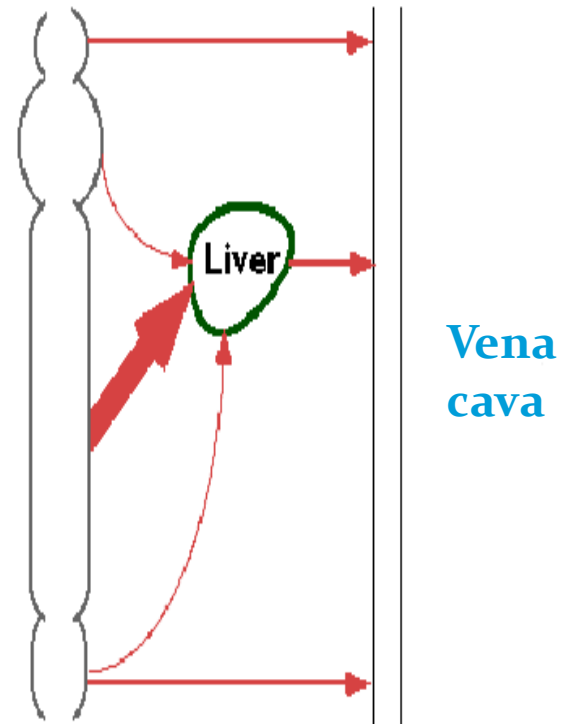
- Before the drug reaches the systemic circulation, the drug can be metabolized in the liver or intestine. As a Result, the concentration of drug in the systemic circulation will be reduced.



1st pass Elimination – Metabolism in liver



Buccal and Rectal – bypasses liver



Absorption – contd.

- Intravenous administration has no absorption phase
- According to the rate of absorption:

Inhalation → Sublingual → Rectal → intramuscular → subcutaneous → oral → transdermal

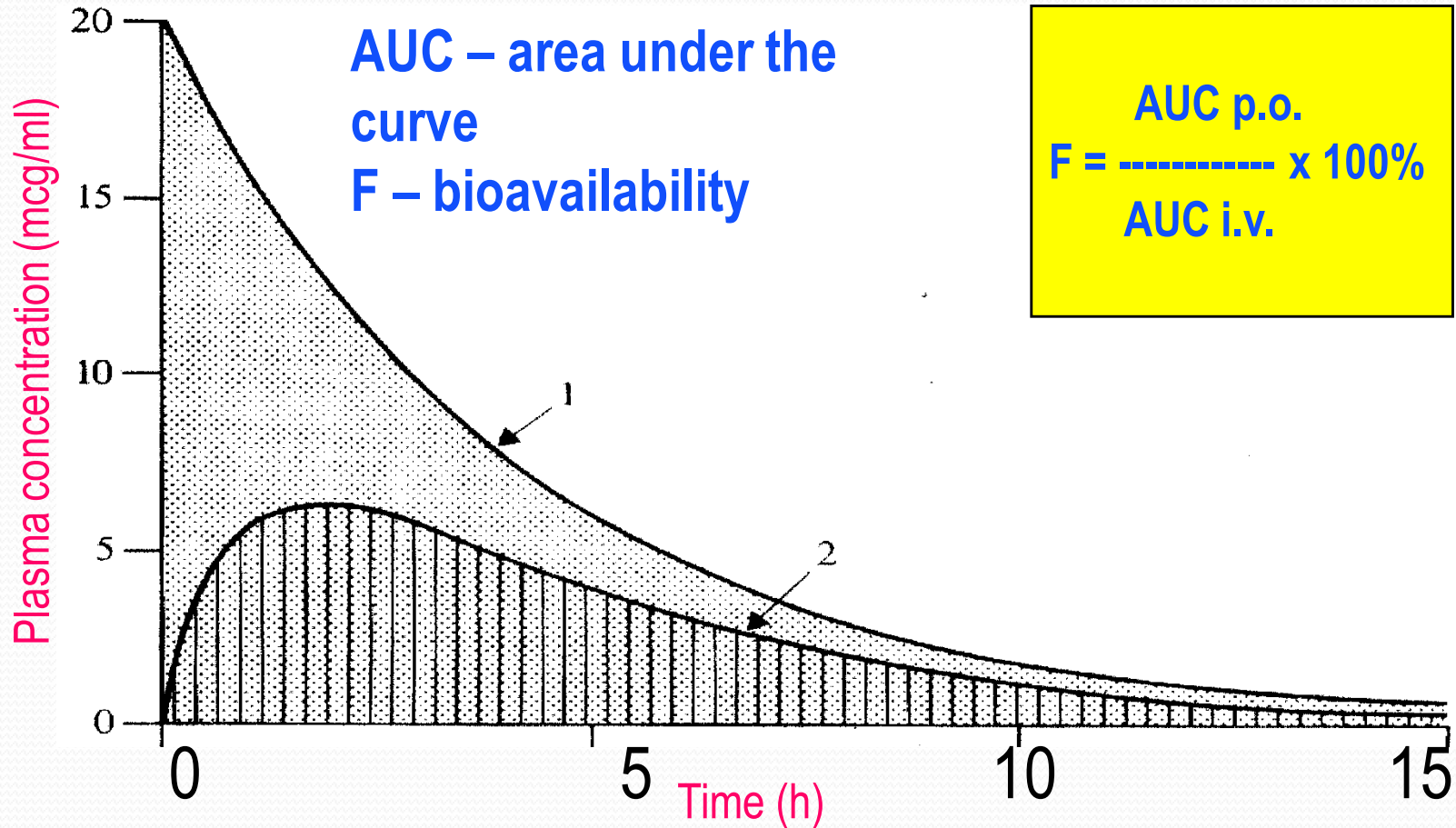
Example – Nitroglycerine:

IV effect – immediate, SL – 1 to 3 min and per rectal – 40 to 60 minute

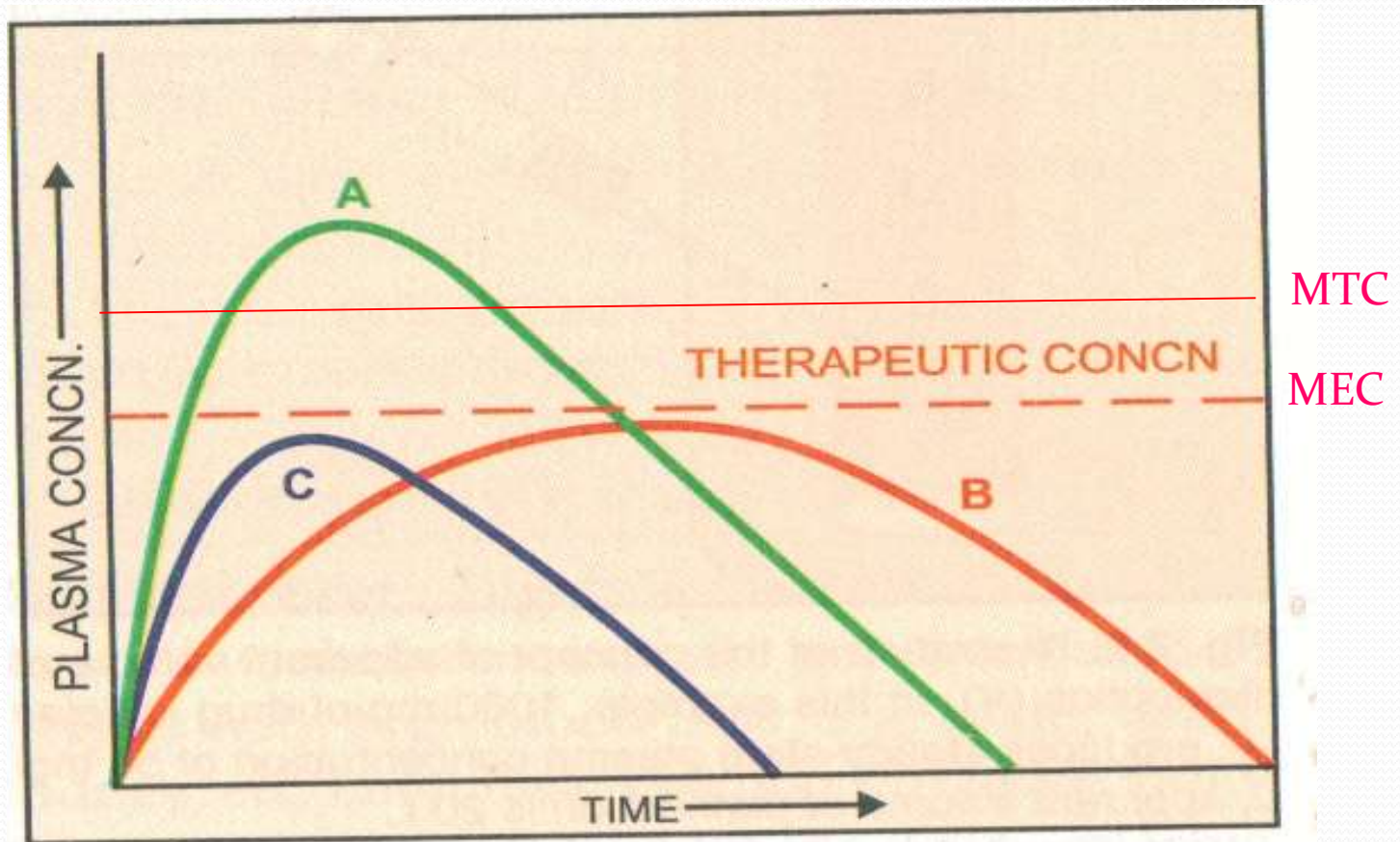
Bioavailability

- **Bioavailability** refers to the rate and extent of absorption of a drug from dosage form as determined by its concentration-time curve in blood or by its excretion in urine. It is a measure of the fraction (F) of administered dose of a drug that reaches the systemic circulation in the unchanged form
- Bioavailability of drug injected i.v. is 100%, but is frequently lower after oral ingestion, because:
 - The drug may be incompletely absorbed
 - The absorbed drug may undergo first pass metabolism in intestinal wall and/or liver or be excreted in bile.
- Practical Significance – low safety margin drugs

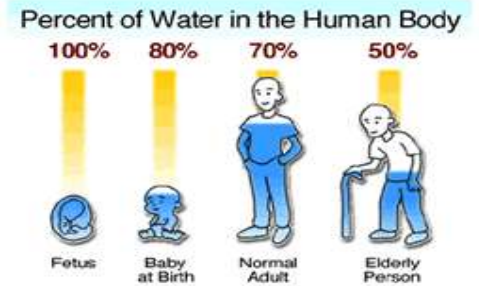
Bioavailability - AUC



Bioavailability – contd.



2. Distribution of Drugs

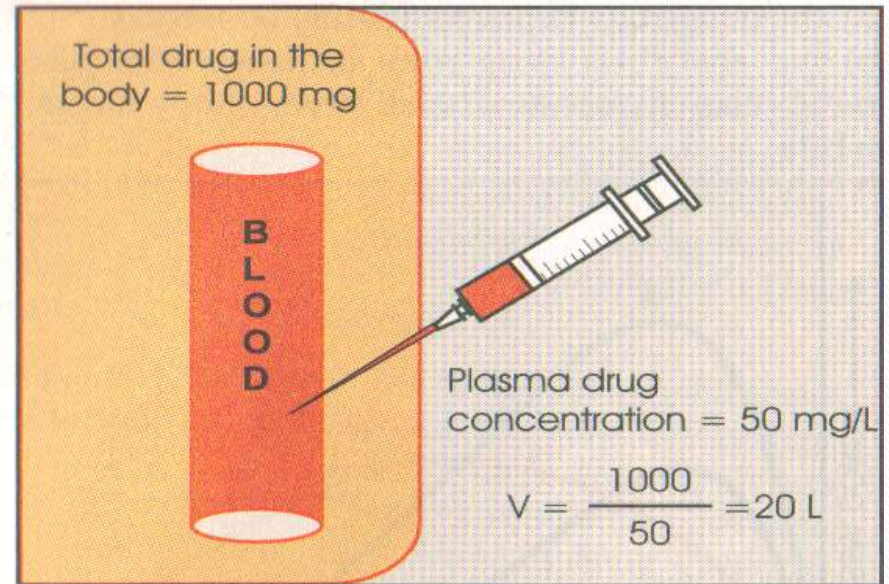


- It is the passage of drug from the circulation to the tissue and site of its action.
- The extent of distribution of drug depends on its lipid solubility, ionization at physiological pH (dependent on pKa), extent of binding to plasma and tissue proteins and differences in regional blood flow, disease like CHF, uremia, cirrhosis
- Movement of drug - until equilibration between unbound drug in plasma and tissue fluids

Volume of Distribution (V)

- Definition: Apparent Volume of distribution is defined as the volume that would accommodate all the drugs in the body, if the concentration was the same as in plasma
- Expressed as: in Liters

$$V = \frac{\text{Dose administered IV}}{\text{Plasma concentration}}$$

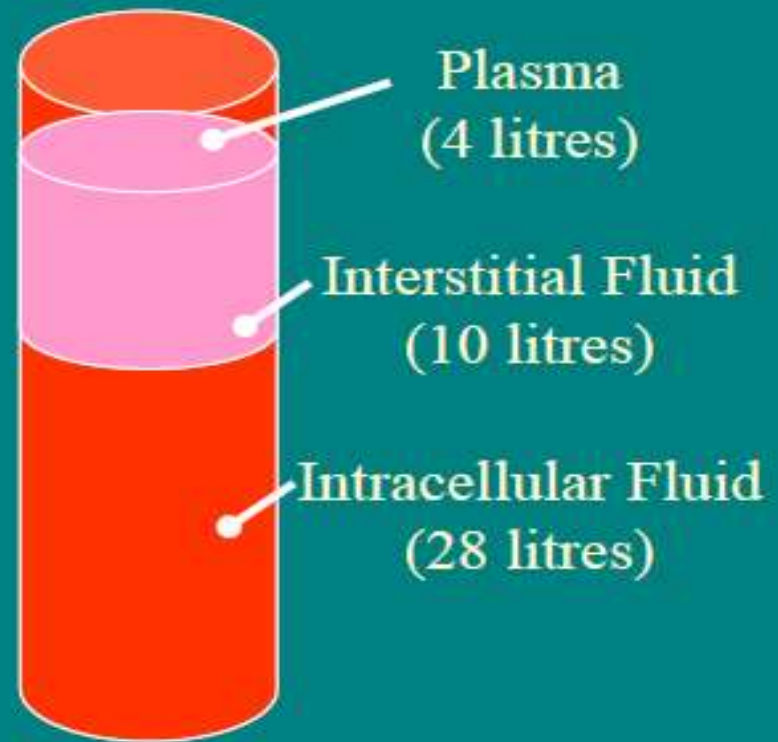


Volume of Distribution (V)

Drugs may distribute into any or all of the following compartments:

- **Plasma**
- **Interstitial Fluid**
- **Intracellular Fluid**

Total Body Fluid = 42 L (approx.)



Volume of Distribution (V)

(WHY ?)

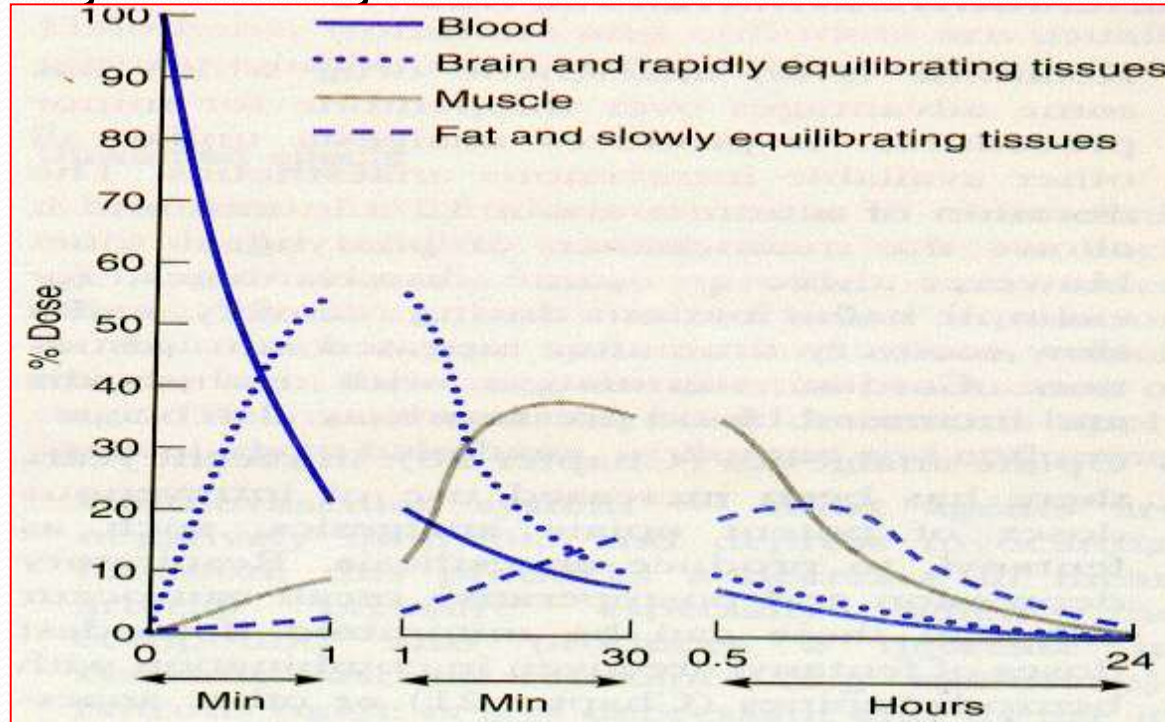
'Vd' is an imaginary Volume of Fluid which will accommodate the entire quantity of the drug in the body, if the concentration throughout this imaginary volume were same as that in plasma

Factors influencing Vd

- Lipid solubility (lipid : water partition coefficient)
- pKa of the drug
- Affinity for different tissues
- Blood flow – Brain Vs Fat
- Disease states
- Plasma protein Binding

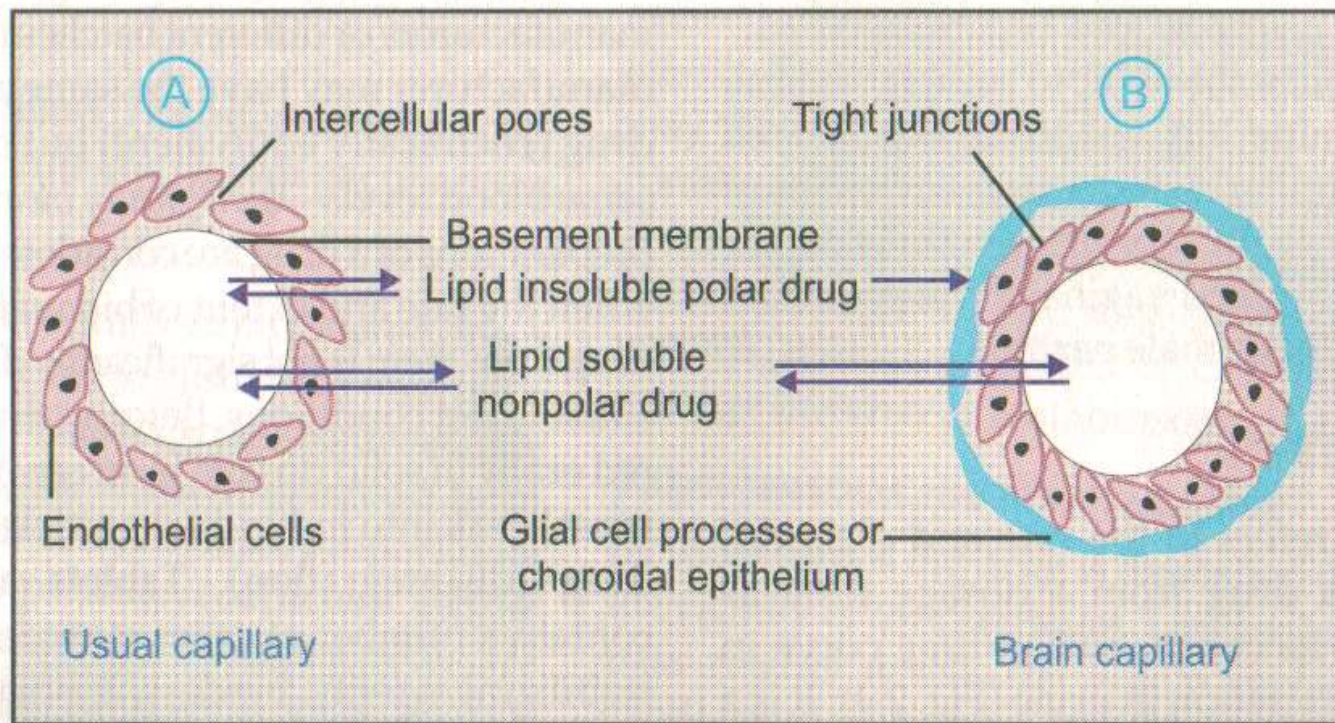
Redistribution

- Highly lipid soluble drugs – distribute to brain, heart and kidney etc. immediately followed by muscle and Fats



Brain and CSF Penetration

Blood brain barrier (BBB): includes the capillary endothelial cells (which have tight junctions and lack large intracellular pores) and an investment of glial tissue, over the capillaries. A similar barrier is located in the choroid plexus



Brain and CSF Penetration – contd.

- BBB is lipoidal and limits the entry of non-lipid soluble drugs (amikacin, gentamicin, neostigmine etc.).

(Only lipid soluble unionized drugs penetrate and have action on the CNS)

- Efflux carriers like P-gp (glycoprotein) present in brain capillary endothelial cell (also in intestinal mucosal, renal tubular, hepatic canalicular, placental and testicular cells) extrude drugs that enter brain by other processes.

(Inflammation of meninges of brain increases permeability of BBB)

- Dopamine (DA) does not enter brain, but its precursor levodopa does. This is used latter in parkinsonism.

Placental Transfer

- Only lipid soluble Drugs can penetrate – limitation of hydrophilic drugs
- Placental P-gp serves as limiting factor
- But, REMEMBER, its an **incomplete barrier** – some influx transporters operate
- Thalidomide

Plasma Protein Binding

- **Plasma protein binding (PPB):** Most drugs possess physicochemical affinity for plasma proteins. **Acidic drugs bind to plasma albumin and basic drugs to α 1-glycoprotein**
- Extent of binding depends on the individual compound. Increasing concentration of drug can progressively saturate the binding sites

The clinical significant implications of PPB are:

- a) Highly PPB drugs are largely restricted to the vascular compartment and tend to have lower Vd.
- b) The PPB fraction is not available for action.
- c) There is an equilibration between PPB fraction of drug and free molecules of drug.

Plasma Protein Binding – contd.

- d) The drugs with high physicochemical affinity for plasma proteins (e.g. aspirin, sulfonamides, chloramphenicol) can replace the other drugs (e.g. acenocoumarol, warfarin) or endogenous compounds (bilirubin) with lower affinity.
- e) High degree of protein binding makes the drug long acting, because bound fraction is not available for metabolism, unless it is actively excreted by liver or kidney tubules.
- f) Generally expressed plasma concentrations of the drug refer to bound as well as free drug.
- g) In hypoalbuminemia, binding may be reduced and high concentration of free drug may be attained (e.g. phenytoin).

Tissue storage

Drugs may also accumulate in specific organs or get bound to specific tissue constituents, e.g.:

- **Heart and skeletal muscles** – digoxin (to muscle proteins)
- **Liver** – chloroquine, tetracyclines, digoxin
- **Kidney** – digoxin, chloroquine
- **Thyroid gland** – iodine
- **Brain** – chlorpromazine, isoniazid, acetazolamide
- **Retina** – chloroquine
- **Iris** – ephedrine, atropine (to melanin)
- **Bones and teeth** – tetracyclines, heavy metals (to mucopolysaccharide of connective tissue)
- **Adipose tissues** – thiopental, ether, minocycline, DDT



Thank You