FACTORS AFFECTING THE DRUG ABSORPTION

Dr. Afsheen Qamar

ABSORPTION

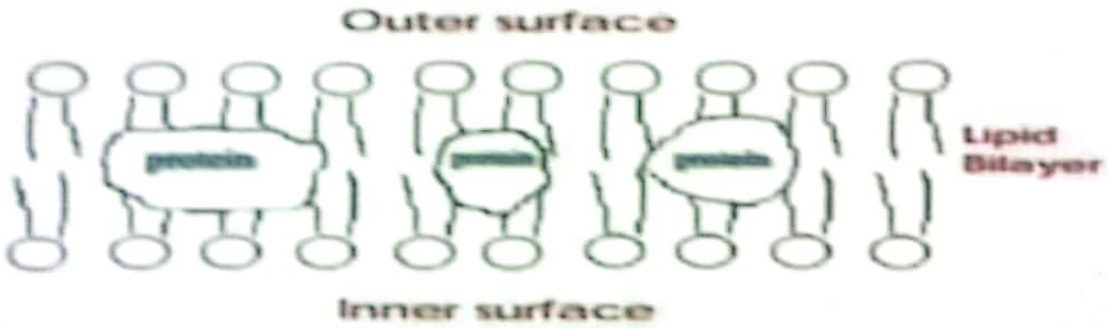
- It is the transfer of drug from site of administration to the blood stream.

- **Rate and extent of drugs absorption is depend upon:**
  - Environment from where drug is absorbed
  - Chemical nature of drug
  - Routes of drug administration

For intravenous route, absorption is 100% (complete) i-e total dose of drug reaches the circulation

Mechanism of drug absorption

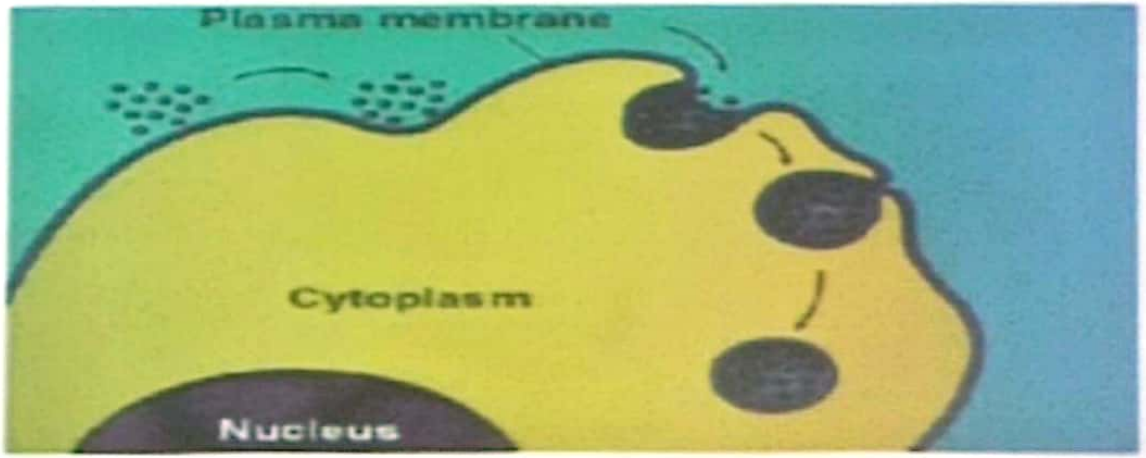
- **Passive diffusion:** Drugs diffuse across the cell membrane from a region of high concentration to low concentration due to concentration gradient.
- lipid-soluble drugs diffuse most rapidly through the lipid bilayer.
- Water soluble drugs penetrate through aqueous pore in cell membrane
- Small molecules tend to penetrate membranes more rapidly than larger ones.



- **Facilitated diffusion:** A carrier protein after conformational changes in the membrane combines reversibly with the drug , and the carrier-substrate complex rapidly cross the membrane, releasing the substrate inside or outside the cell under concentration gradient.

- **Active transport:** Carrier protein mediated transport of molecules against a concentration gradient. Active transport seems to be limited to drugs structurally similar to endogenous substances (eg, ions, vitamins, sugars, amino acids).it require energy in the form of ATP.

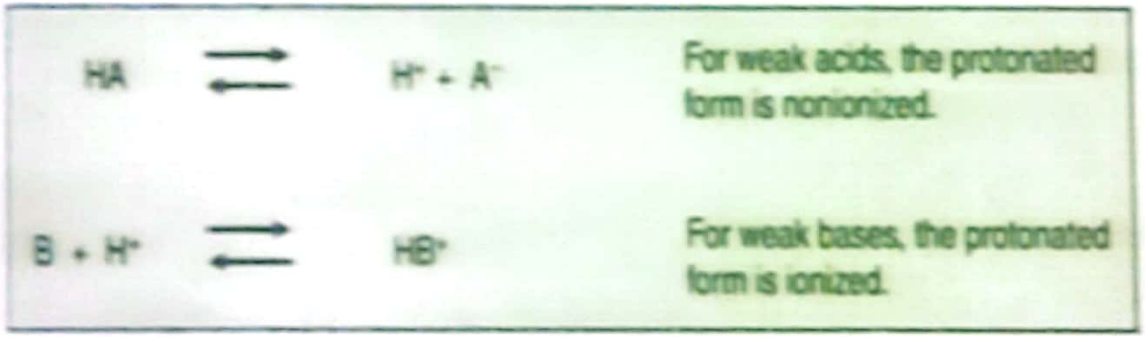
- **Pinocytosis:** large molecules are engulfed by a cell, forming a vesicle by cell membrane that moves to the cell interior. Energy expenditure is required.



Factors affecting the drug absorption

- pH
- Blood Flow
- Total surface area of absorption site
- Contact time with absorption site
- Expression of P-Glycoprotain

- **pH:** A drug passes through membrane more readily if it is uncharged.
- Mostly drugs are either weak acids or weak bases.



- For a weak acid uncharged protonated form and for a weak base uncharged B form more easily permeate through the membrane.
- In case of poisoning with basic drug, urine can be made more acidic (by administering ammonium chloride),
- by virtue of which the basic drug becomes ionized and is not reabsorbed
- Results that more of it is excreted out.

- **Blood flow:** Blood flow is a strong determinant of the rate of absorption. Reduced blood flow means reduced exposure to drug. Increase blood flow enhance the rate of absorption.
- Decreased blood flow (eg, in shock) may lower the concentration gradient across the intestinal mucosa and reduce absorption by passive diffusion.
- **Total surface area of absorption site:** a drug's absorption is enhanced if there is a large surface area available for absorption (e.g. villi/microvilli of intestinal tract)

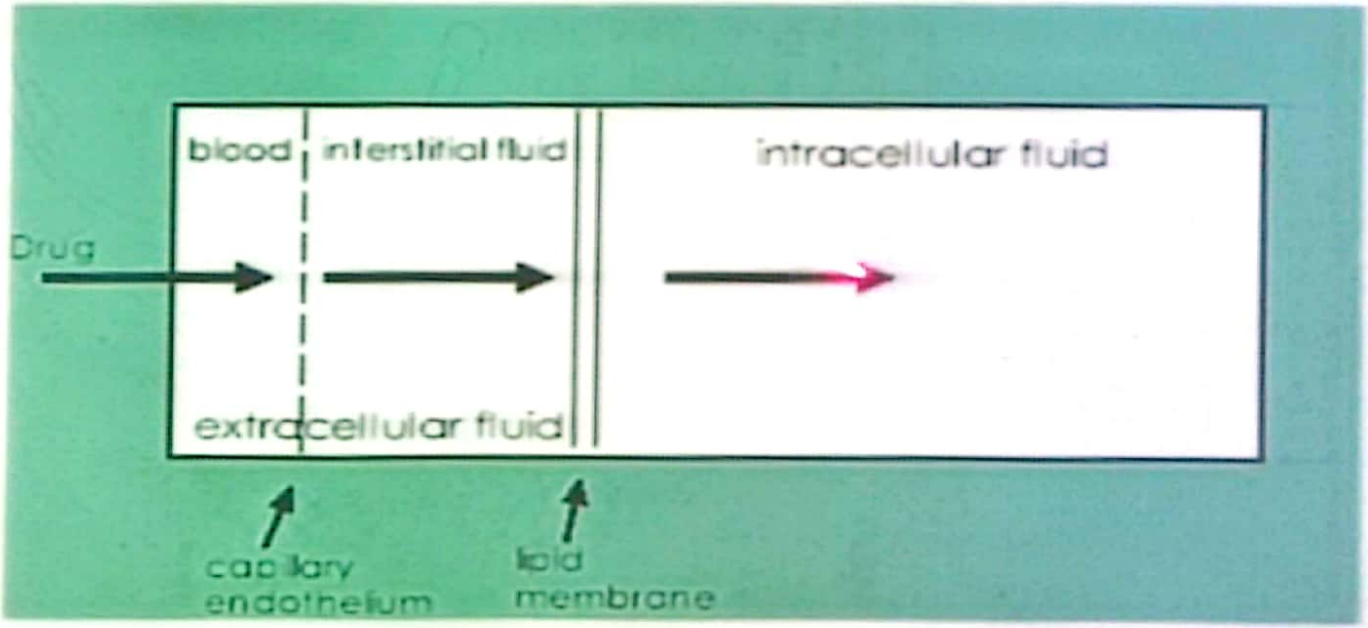
- **Contact time with absorption site:** The faster it moves through thus decreasing its contact time at the absorption surface and therefore less is absorbed like in diarrhea. Also the presents of food dilutes the drug and slows gastric emptying and thus the drug is generally absorbed slower.

- **P-Glycoprotein:** these are transmembrane transporter protein which involve in energy-dependent efflux mechanisms in the cell membranes. The area with high conc. Of p-glycoprotein reduce drug absorption. It involve in multidrug resistant.

Factors affecting the Drug distribution

Distribution

- The process by which drug reversibly move from the bloodstream to the interstitium and to the tissues



DISTRIBUTION

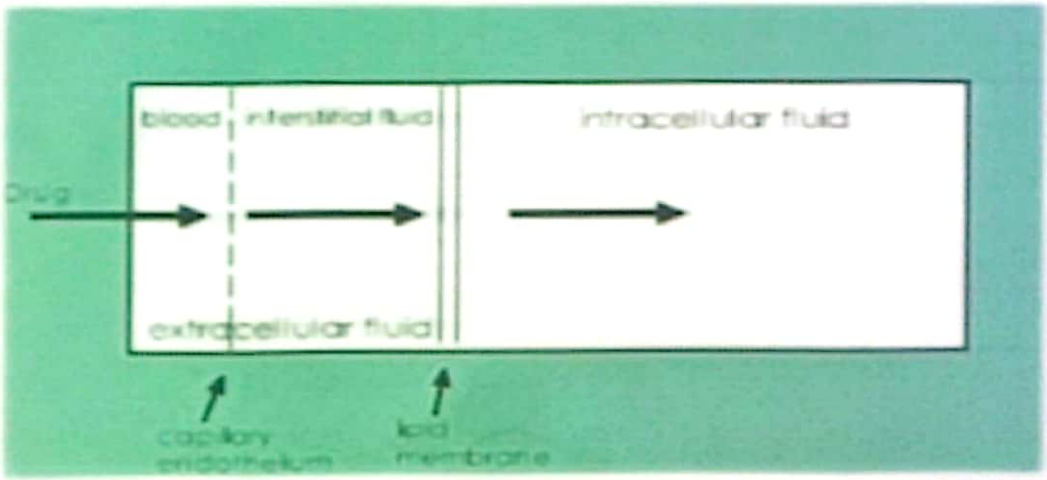
- All of the fluid in the body (referred to as the total body water), in which a drug can be dissolved, can be roughly divided into three compartments:

➢intravascular (blood plasma found within blood vessels)

➢interstitial/tissue (fluid surrounding cells)

➢ intracellular (fluid within cells, i.e. cytosol)

- The distribution of a drug into these compartments is dictated by it's physical and chemical properties



Factors affecting the Drug distribution

- **Blood flow:**
  - Drug distribution in the patient will depend on the blood flow to various sites in the body.
  - Organs like the brain, liver, kidney and the heart are highly perfused with blood. By contrast, the bone and the skeletal muscle, skin and adipose tissues experience less blood perfusion. Therefore, drugs are likely to distribute more rapidly to tissues/organs that are more richly perfused with blood.

Capillary permeability:

Drug distribution is also affected by capillary structure.

- Most capillaries are "leaky" / having pores and do not impede diffusion of drugs
- Blood-brain barrier formed by high level of tight junctions between cells for BBB.
- Blood brain Barrier is impermeable to most water-soluble drugs.

Lipophilicity of drug: the higher the lipophilicity of a drug, the easier with penetration through lipid bilayer of membrane and greater its distribution.

Protein Binding

- **Many drugs bind to plasma proteins** in the blood slower their transfer out of the vascular compartment. Plasma protein binding limits distribution. A drug that binds plasma protein diffuses less efficiently than a drug that doesn't.
- Binding of drug with plasma protein act as a reservoir for free drug as the drug concentration decreases with drug elimination.
- **Binding with tissue protein:** some drug accumulate in tissue by binding with protein, lipid or nucleic acid act as tissue reservoir and may contributes in local toxicity.
- Acroline causes hemorrhagic cystitis

Volume of distribution

- Vd is **defined as the total amount of drug in the body divided by its concentration in plasma**

Amt of drug in body/plasma drug conc

- The volume of distribution is amount of fluid into which drug is distributed and useful **in estimating the dose required to achieve a given plasma concentration**
- Vd reflects the degree to which the drug is present in extravascular tissues rather than in the plasma. A drug with a high Vd tends to leave the plasma and enter other compartments in the body, leading to low plasma concentrations. A drug with a low Vd tends to remain in the plasma, meaning a lower dose of a drug is required to achieve a given plasma concentration.
- Drug with high Vd has long half life and extended duration of action of drug.

TOTAL BODY WATER

Volumes of body fluids	
Fluid substances	**Volume (liter)**
Extra cellular Fluid	14
a) Plasma	3–4
b) Interstitial fluid	10
Intracellular fluids	28
Total body water	42

A drug has a high molecular weight or extensively protein bounded ,it is to large to pass through the slit junctions of capillaries will trap in plasma and has low Vd.
A hydrophilic drug with low molecular weight pass through the slit junctions and enter into the interstitium and distributed in plasma and interstitium (extracellular fluid)