Absorption and Distribution of drugs

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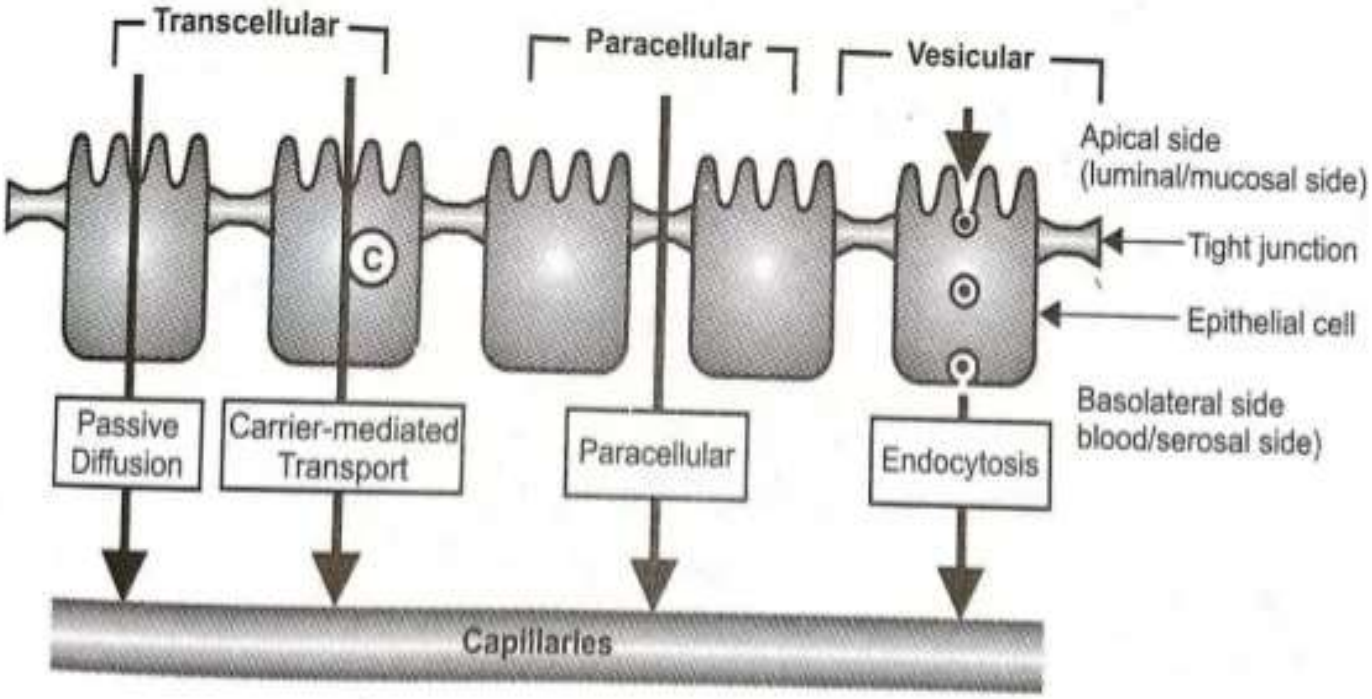
Overview

- Absorption
  1) Definition
  2) Factors affecting it
  3) Bioavailability
  4) Bioequivalence
- Distribution
  1) Definition
  2) Factors affecting it
  3) Volume of distribution
  4) Redistribution

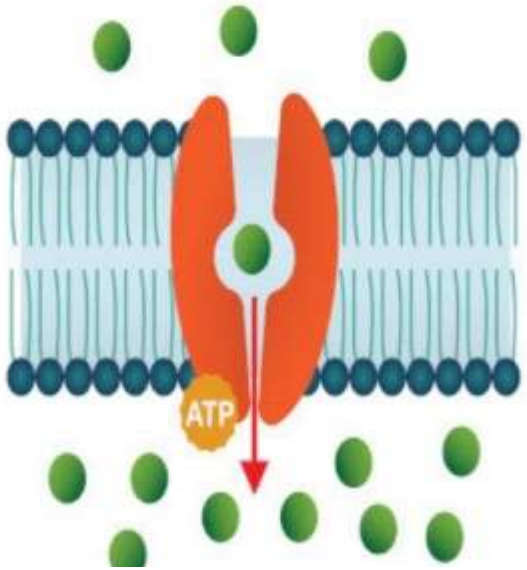
- Absorption is the movement of a drug from its site of administration into the central compartment (e.g., bloodstream)

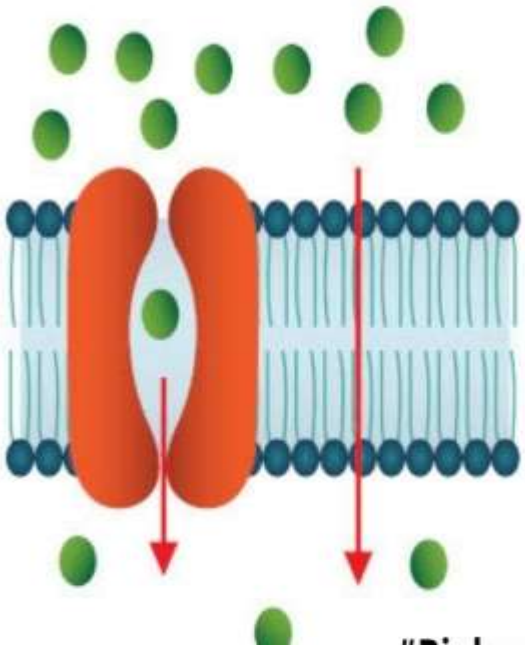
Compares the transcellular, paracellular and vesicular transport mechanism



Difference Between

Active Transport VS Passive Transport





Mechanisms of drug absorption

- There three broad categories are
- **1. Transcellular / intracellular transport**

A. Passive Transport Processes - Not require energy Further classified into following types

I. Passive diffusion

II. Pore transport

III. Ion- pair transport

IV. Facilitated or mediated diffusion

B. Active transport processes

I. Primary

II. Secondary

a. Symport (Co-transport)

b. Antiport (Counter transport)

- **2. Paracellular / Intercellular Transport**

  A. Permeation through tight junctions of epithelial cells

  B. Persorption

- **3. Vesicular or Corpuscular Transport (Endocytosis)**

  A. Pinocytosis

  B. Phagocytosis

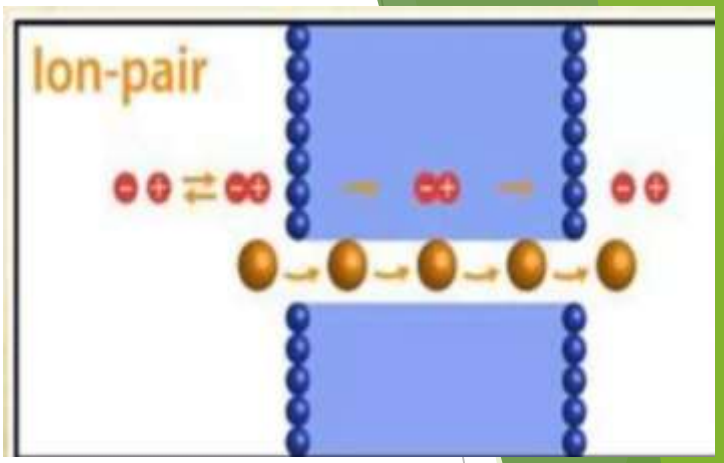
Passive Diffusion

- Also called non-ionic diffusion, it is the major process for absorption of more than 90% of the drugs.
- The driving force is concentration gradient.
- Passive diffusion is best expressed by Fick's first law of diffusion, which states that the drug molecules diffuse from a region of higher concentration to one of lower concentration until equilibrium is attained.

Pore Transport

- It is also called as convective transport, bulk flow or filtration.
- The driving force is hydrostatic pressure differences across the membrane.
- The process is important in the absorption of low molecular weight, generally water-soluble drugs.
- eg: urea, water and sugars.

Ion-pair transport



- Strong electrolyte drugs are highly lonized or charged molecules, such as sulfonic acid , quaternary nitrogen compounds.
- These drugs penetrate membranes poorly. When linked up with an oppositely charged ion, an ion pair is formed in which the overall charge of the pair is neutral. This neutral complex diffuses more easily across the membrane.
- e.g. the formation of an ion pair for propranolol (basic drug) with oleic acid.

Facilitated diffusion

- Facilitated diffusion (also known as facilitated transport or passive-mediated transport) is the process of molecules or ions across a biological membrane via specific transmembrane integral proteins.
- Carrier mediated transport operates down the concentration gradient (downhill transport).
- Driving force - Concentration gradient.
- No energy required.

Active transport

- Requires energy in form of ATP
- **Primary active transport**

  Requires direct energy

- **Types**

  1} Ion transporters

  Transporting ion in or outside cell

  Eg - ATP driven ion pump is proton pump

- **2} ABC [ATP binding cassette] transporters**

Responsible for transporting small foreign molecules out of cells.

Eg - ABC transporters in brain capillaries

Secondary active transport

- No direct energy requirement
- In secondary active transport, the transport across a biological membrane of a solute S1 , against its concentration gradient is energetically driven by the transport of another solute S2 , in accordance with its electrochemical gradient.

- **1] Symport (co - transport)**

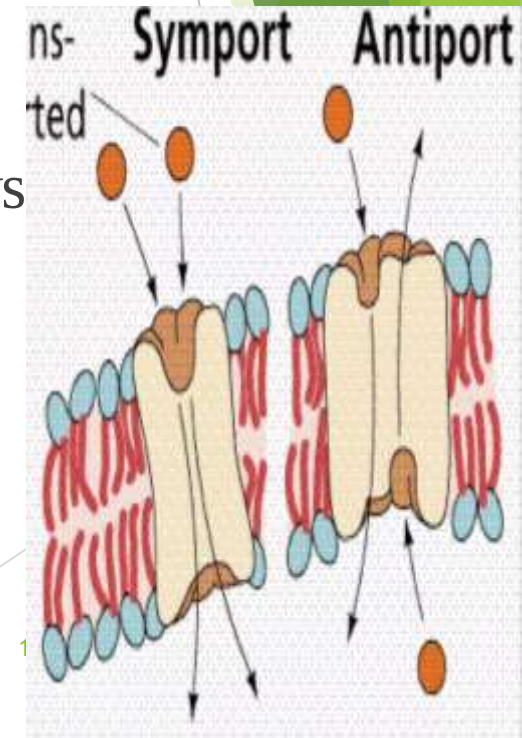
  Transport of both molecules in same direction

  Eg- As for glucose transport into the body from the lumen of the small intestine by the Na+-glucose transporter SGLT1.

- **2] Antiport (counter - transport)**

  Movement of molecules in opposite direction

  Eg - expulsion H+ using Na+ gradient in kidneys



2. Paracellular/Intercellular Transport

- Transport of drugs through the junctions between the epithelial cells. This pathway is of minor importance in drug absorption.
- The two paracellular transport mechanisms involved in drug absorption are –

(1) Permeation through tight junctions of epithelial cells. This process basically occurs through openings which are little bigger than the aqueous pores. such as insulin and cardiac glycosides are taken up this mechanism.

(2) Persorption is permeation of drug through temporary openings formed by shedding of two neighbouring epithelial cells into the lumen.

3. Vesicular or Corpuscular Transport (Endocytosis)

- Like active transport, these are also energy dependent process but involve transport of substances within vesicles into a cell. Vesicular transport of drugs can be classed into two categories

(1) Phagocytosis (cell eating): absorptive uptake of solid particulates

(2) Pinocytosis (cell drinking): uptake of fluid solute.

Absorption

- Absorption is the transfer of a drug from its site of administration to blood stream
- Factors affecting drug absorption:
  1. Rate of Dissolution
  2. Particle size
  3. Physical states
  4. Lipid solubility
  5. Formulation

6. pH & Ionization
7. Gastrointestinal transit time
8. Area of the absorbing surface
9. Blood flow
10. Metabolism of drugs
11. Disease states

- 1. Rate of Dissolution:

    1. Drugs in formulation that allow rapid dissolution have faster onset than drugs formulated for slow dissolution.

- 2. Particle size:

    1. Smaller the particles size has greater rate of absorption.

- 3. Physical states:

    1. Liquids are better absorbed than solid

- 4. Lipid solubility:

1.Highly lipid soluble unionized drugs are absorbed more rapidly than those drugs which lipid solubility is low

2. Eg - fat soluble Vit A, D, E, K are better absorbed

- 5.Formulation:

Sustained release dosage- delay absorption

- 6. pH & Ionization

Acidic drugs(aspirin) are better absorbed in stomach, Basic drugs (morphine) better absorbed in intestine

- 7. Gastrointestinal emptying time (GET)

The presence of food, volume & gastric contents can influence drug absorption by altering the GET

Rapid absorption occurs if the drug is given before meals E.g: GET is retarded by drug like atropine.

- 8. Area of the absorbing surface

Larger the surface area, faster absorption will be.

So orally administered drugs are usually absorbed from small intestine rather than stomach because of large surface area.

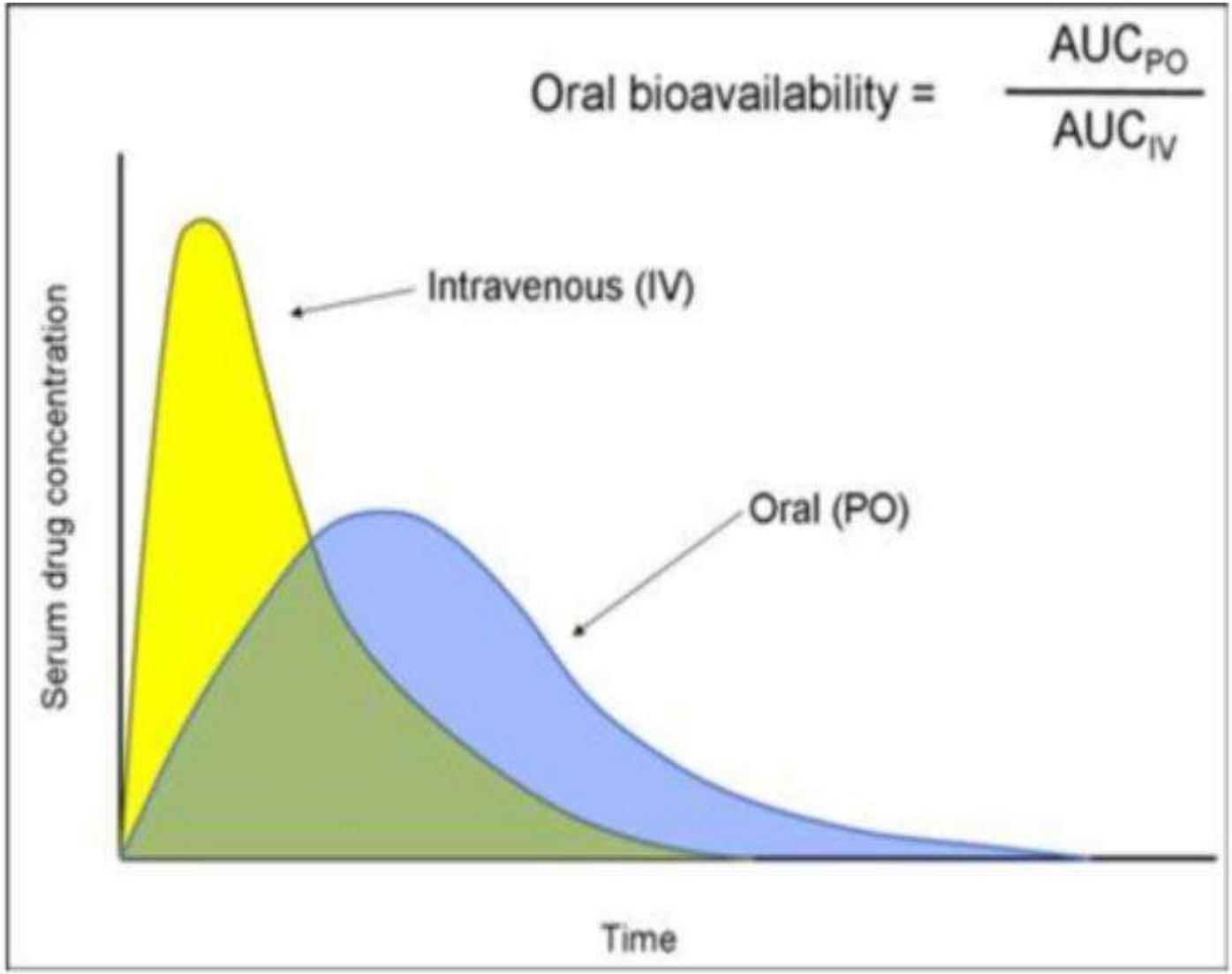
9. Blood flow: Drugs are absorbed most rapidly from sites where blood flow is high

- 10. Metabolism of drugs: Rapid degradation of a drugs by liver during first pass metabolism affect absorption & bioavailability.

- 11. Disease states: Absorption can be affected in condition like thyrotoxicosis,liver cirrhosis.

BIOAVAILABILITY

- Pharmacokinetic parameter governed by absorption is BIOAVAILABILITY.
- BIOAVAILABILITY ---It measures the fraction (F) of administered dose of a drug that reaches the systemic circulation in unchanged form.
- If BA is 100% → I.V parenteral dose
- BA is calculated by AUC (Area Under Curve)


Oral bioavailability = $\frac{AUC_{PO}}{AUC_{IV}}$
Intravenous (IV)
Oral (PO)
Serum drug concentration
Time

Bioequivalence

- Drug products are considered to be pharmaceutical equivalents if they contain the same active ingredients and are identical in strength or concentration, dosage form, and route of administration but desired outcome for patients.

Drug Distribution

- Drug distribution is the process by which a drug reversibly leaves the blood stream and enter the interstitial and cell of the tissues.
- Rate and extent being dependent on

(1) Capillary permeability

(2) Lipid solubility

(3) Extent of binding to plasma and tissue protein

(4) Blood flow

- **1.Blood flow:**

Blood flow to the brain, liver and kidney is greater than that to the skeletal muscles, whereas adipose tissue has a lower rate of blood flow.

- **2.Capillary permeability:**

Capillary permeability is determined by capillary structure and by the chemical nature of the drug.

- In the brain, the capillary structure is continuous, and there are no slit junctions. This contrasts with the liver and spleen, where a large part of the basement membrane is exposed due to large, discontinuous capillaries through which large plasma proteins can pass.

Blood-brain barrier:

- To enter the brain, drugs must pass through the endothelial cells of the capillaries of the CNS.
- Lipid-soluble drugs easily penetrate into the CNS because they can dissolve in the membrane of the endothelial cells.
- Ionized or polar drugs generally fail to enter the CNS because they are unable to pass through the endothelial cells of the CNS, which have no slit junctions.

- The capillary boundary that is present between the blood and brain is called BBB
- In the brain capillaries, the endothelial cells are joined by tight junctions.
- Only the lipid soluble and unionized form of drugs can pass through BBB and reach the brain, e.g. barbiturates, diazepam, etc.
- Lipid insoluble and ionized particles do not cross the BBB e.g. dopamine, aminoglycosides

- Pathological states like meningitis, encephalitis increase the permeability of the BBB and allow the normally impermeable substance to enter the brain.
- For example penicillin in normal condition has poor penetration through BBB but its penetration increase during meningitis.

Placenta barrier

- The lipid membrane between the mother and foetus is called placenta barrier.
- Unionized and lipid soluble drugs can freely pass the placenta barrier e.g anaesthetic, alcohol, morphine
- Certain drugs when given during pregnancy may cross the placenta and cause various dangerous effects in the foetus. This is called teratogenesis

E.g ---Thalidomide --⟶ phocomelia

Tetracycline--⟶ yellowish teeth

Drug structure

- The chemical nature of a drug strongly influences its ability to cross cell membranes.
- Hydrophobic drugs, which have a uniform distribution of electrons and no net charge, easily move across most biologic membranes.
- Hydrophilic drugs, which have either a nonuniform distribution of electrons or a positive or negative charge, do not easaily penetrate cell membranes, and therefore, must go through the slit junctions.

Binding of drugs to plasma proteins

- Reversible binding to plasma proteins sequesters drugs in a nondiffusible form and slows their transfer out of the vascular compartment.
- Plasma albumin is the major drug-binding protein and may act as a drug reservoir.
- As the concentration of the free drug decreases due to elimination by metabolism or excretion, the bound drug dissociates from the protein.
- This maintains the free-drug concentration as a constant fraction of the total drug in the plasma.

Plasma protein binding

- Many drugs bind to plasma proteins like albumin, αι acid glycoprotein .
- Clinical importance of PPB:

1. Drugs that are highly bound to plasma protein have a low volume of distribution

2. Plasma protein binding delay the metabolism of drugs

3.Highly protein bound drugs have longer duration of action e.g. sulphadoxine is highly plasma protein bound and has duration of 1 week.

4. In case of poisoning, highly PPB drugs are difficult to be removed.

5. Disease states like anemia, renal failure, chronic liver disease have low plasma albumin level so there will be increase in the free form of the drug which can lead to drug toxicity.

Volume of Distribution(Vd)

- The volume of distribution V relates the amount of drug in the body to the concentration of drug C in the blood or plasma, depending on the fluid measured.
- Vd = $\frac{\text{amount of drug in body}}{\text{plasma concentration}}$

- For drugs that are bound extensively to plasma proteins but are not bound to tissue components, the volume of distribution will approach that of the plasma volume because drug bound to plasma protein is measurable in the assay of most drugs.

- Effect of a large Vd on the half-life of a drug
- Delivery of drug to the organs of elimination depends not only on blood flow, but also on the fraction of the drug in the plasma.
- If the Vd 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 the volume of distribution can lead to an increase in the half-life and extend the duration of action of the drug.

Redistribution

- Highly lipid soluble drugs given i.v or by inhalation, initially get distributed to organs with high blood flow, e.g brain, heart, kidney etc.
- Later, less vascular but more bulky tissues (muscles, fat) take up the drug- plasma concentration falls and the drug is withdrawn from these sites.

- If the site of action of drug was in one of the highly perfused organs, redistribution results in termination of drug action.
- Anaesthetic action of thiopentone is terminated in few minutes due to redistribution. How ever, when the same drug is given repeatedly or continously over long periods, the low perfusion high capacity sites get progressively filled and the drug become long acting.

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THANK YOU!