UNIT-1

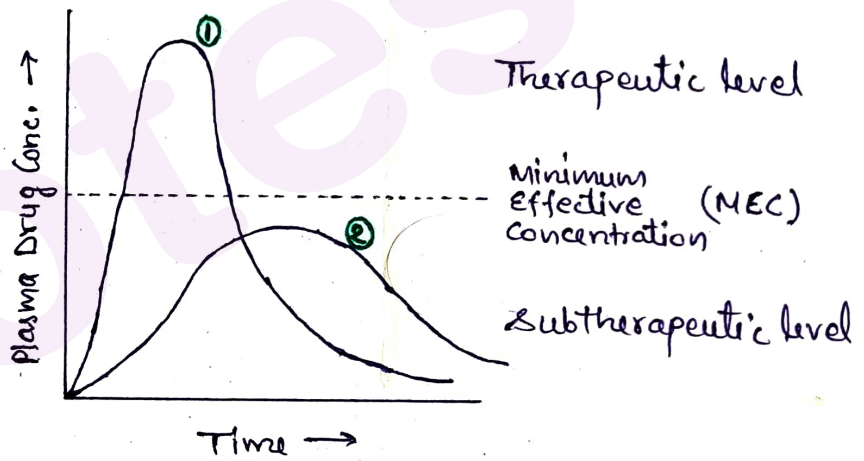
Biopharmaceutics → It is the study of factors influencing the rate and amount of drug that reaches the systemic circulation and use of this information to optimise the therapeutic efficacy of drug products.

Pharmacokinetics → It is the division of Pharmacology in which we study about the absorption, distribution, metabolism, and excretion of drugs.

Absorption

Drug absorption is defined as the process of movement of un-changed drug from the site of administration to systemic circulation.
The level of drug concentration in blood plasma decides the drug concentration at the site of action.

* Plots showing significance of rate and extent of absorption



Plot-1 → It shows a rapid and complete absorption of drug, hence its a therapeutic success.

Plot-2 → The drug is absorbed slowly and does not even reach the level when it can show its therapeutic activity. Hence, it is a therapeutic failure.

Routes of drug administration

Drugs enter systemic circulation by three major routes:

1) The enteral route
2) The Parenteral route
3) The topical route

1) Enteral Route → includes gastrointestinal (GI), sub-lingual / buccal and rectal routes. GI is most common route.

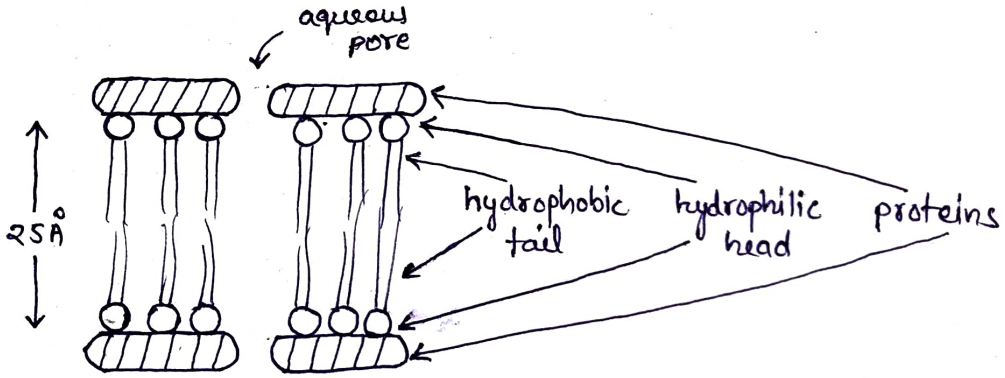
2) Parenteral Route → It includes all routes of administration through or under the layers of skin. When the drug is administered intravenously (I.V.), no absorption is required. Absorption is necessary for extravascular parenteral routes like the sub-cutaneous and the intramuscular routes.

3) Topical Routes → includes skin, eyes or other specific membranes.

Cell Membrane : structure and Physiology

Before proceeding to discuss absorption aspects, a brief discreption of cell membrane structure and physiology is necessary.

For a drug to be absorbed and distributed into organs and tissues and eliminated from the body, it passes through one or more biological membranes/ barriers at various locations. This movement of drug across the membrane is called as drug transport.



Basic structure of cell membrane

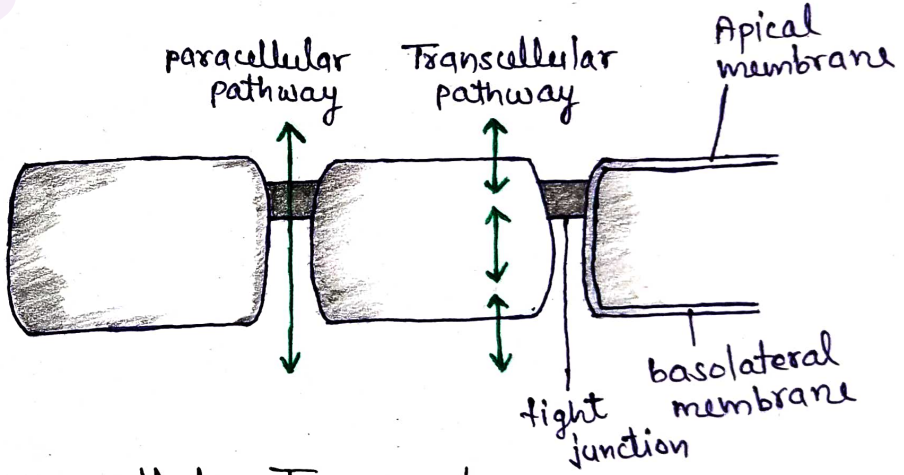
The cellular membrane consists of a double layer of phospholipids molecules arranged in such a fashion that their hydrophobic tails are oriented inwards and hydrophilic heads form the outer boundaries of the cellular membrane. Globular protein molecules are associated on both sides of these hydrophilic head boundaries and also embedded within the membrane structure. The hydrophobic core (tail) of the membrane is responsible for the relative impermeability of polar molecules. Aqueous pores of 4-10 Å in diameter are responsible for the passage of inorganic ions and water-soluble molecules like urea through the plasma membrane.

Cell membrane is a semi-permeable barrier that allows some compounds to pass through it and restricts others.

Mechanisms of Drug absorption

Mechanism of drug absorption involves the transport of drug molecules across various biological membranes. The three broad categories of drug transport mechanisms are:

A. Transcellular / Intracellular Transport
B. Paracellular / Intercellular Transport
C. Vesicular Transport.



A. Transcellular Transport

It is defined as the passage of drugs across the GI epithelium. It is the most common pathway for drug transport. It completes in three steps.

(i) permeation of GI epithelial cell membrane.
(ii) Movement across the intercellular space (cytosol).
(iii) Permeation of the lateral or basolateral membrane.

Transport by transcellular pathway types

1. Passive Transport Processes → These transport processes do not require energy to pass through the lipid bilayer.

Passive transport can be further classified:

a. Passive Diffusion
b. Pore Transport
c. Ion-pair Transport
d. Facilitated or mediated transport

2. Active Transport → These processes require energy. Further of two types:

a. Primary active transport
b. secondary active transport → Further divided
   (i) Symport (co-transport)
   (ii) Anti-port (counter-transport)

B. Paracellular Transport

It is defined as the transport of drugs through the junctions between the GI epithelial cells.

The two paracellular transport mechanisms are:

1. Permeation through tight junctions of epithelial cells:- this process basically occurs through opening which are little bigger than the aqueous pores. Compounds such as insulin and cardiac glycosides are taken up by this.
2. Persorption:- is the permeation of drug through temperary openings formed by shedding of two neighbouring epithelial cells into lumen.

C. Vesicular Transport (Endocytosis)

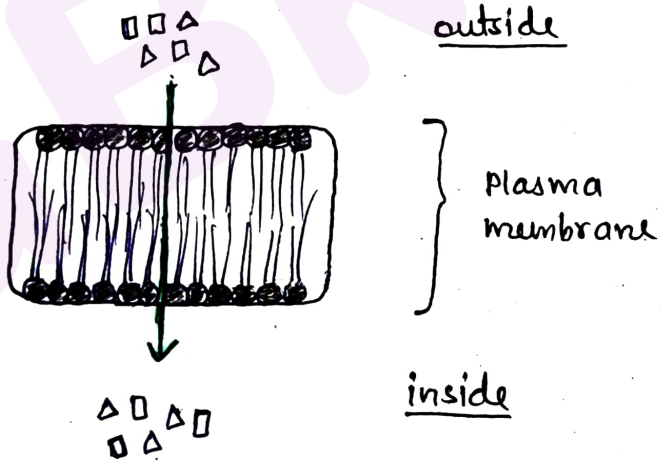
Like active transport, these are also energy dependent processes but involve transport of substances within vesicles into a cell.

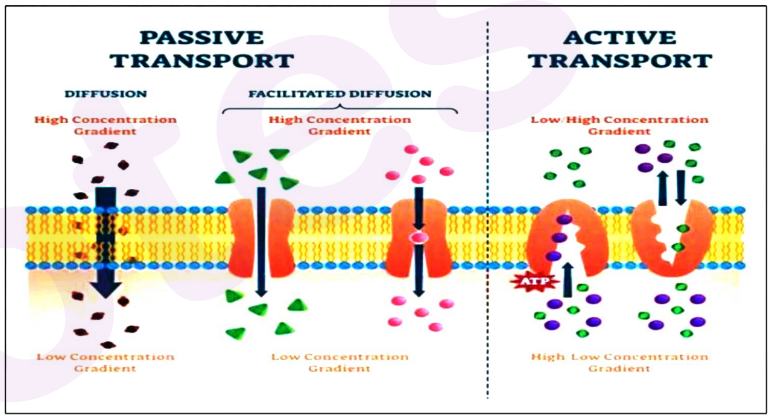
Endocytosis is of two types:

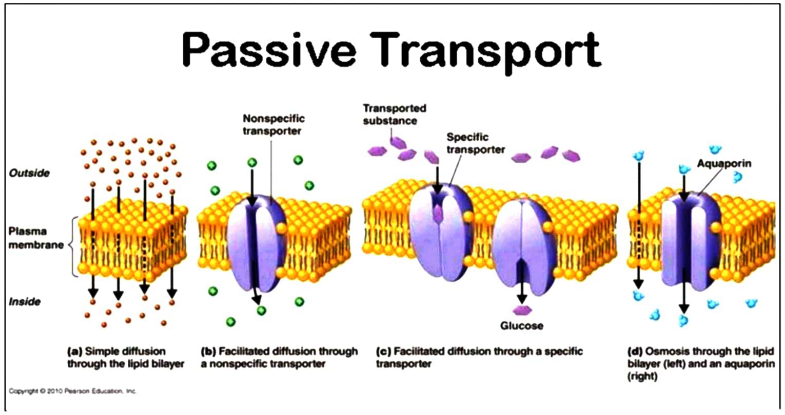
1. Pinocytosis
2. Phagocytosis

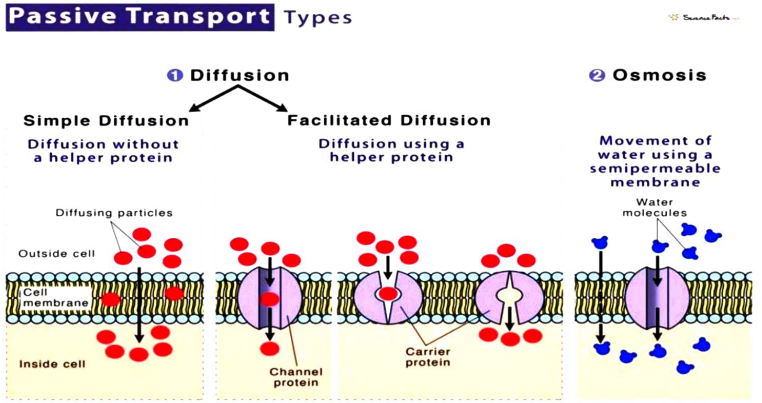
Passive Diffusion

Also called non-ionic diffusion, it is the major process of absorption for more than 90% of the drugs. The driving force is concentration gradient in this process. Passive diffusion occurs due to the difference in the drug concentration on either side of membrane. Since, no energy is consumed in diffusion, drug movement occurs due to the kinetic energy of molecules.









Passive diffusion is expressed by Fick's first law of diffusion which states that the drug molecules diffuse from a region of higher concentration to the one of lower concentration until equillibrium is attained and that the rate of diffusion is directly proportional to the concentration gradient across the membrane.

$$\frac{dQ}{dt} = \frac{DAK_{m/w}}{h} (C_{GIT} - C)$$

where,

dQ/dt = rate of drug diffusion (amount/time). It also represents the rate of appearance of drug in blood.

D = diffusion coefficient of the drug through the membrane (area/time).

A = surface area for absorbing membrane

$K_{m/w}$ = partition coefficient of the drug b/w the lipoidal membrane (cell membrane) and the aqueous GI fluids.

$(C_{GIT} - C)$ = difference in concentration of drug in the GI fluids and the blood plasma, called as concentration gradient (amount/volume).

h = thickness of membrane.

What do we know from Fick's First Law ?

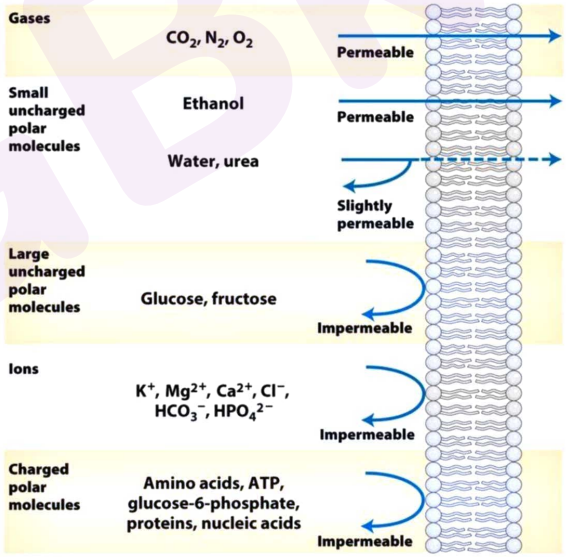
1) Drug moves down the concentration gradient indicating downhill transport.
2) The process is energy-independent.
3) The rate of drug transfer is directly proportional to the concentration gradient b/w GI fluids and the blood compartment.
4) The process of diffusion is rapid over short distances and slow over long distances.
5) Greater the area and lesser the thickness of the membrane, faster is the diffusion.
6) Equillibrium is attained when the concentration on either side of the membrane becomes equal.

7) The rate of transfer of unionised drugs is 3 to 4 times the rate of ionised drugs.

8) Since the membrane is lipoidal in nature, the lipophilic drug diffuses at a faster rate by solubilising in the lipid layer of membrane.

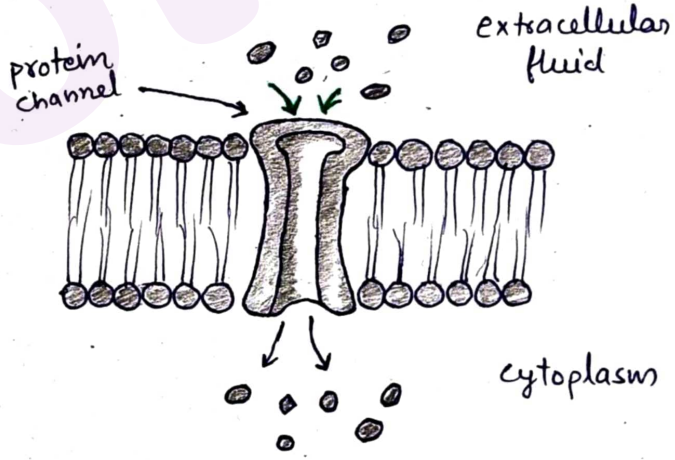
9) The diffusion generally decrease with increase in molecular weight of the compound. Drugs having molecular weights between 100 to 400 Daltons are effectively absorbed passively.

The relative permeability of different molecules to lipid bilayer can be understood by this figure.



Pore Transport

It is also called as convective transport, bulk flow or filtration. This mechanism is responsible for transport of molecules into the cell through the protein channels present in the cell membrane.

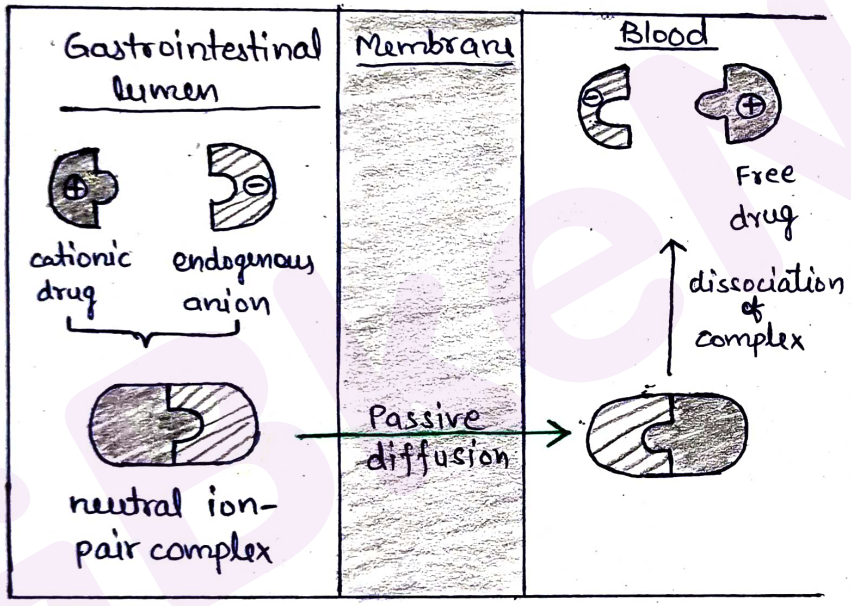


→ The process is important for low molecular wt. (≤100), low molecular size and water-soluble drugs through the narrow channels. For example, urea, water, sugars

→ Osmotic differences across the membrane causes bulk flow of water alongwith solid molecules through aqueous channels (pore).

Ion-Pair Transport

Ion-pair transport explains the absorption of drugs like quaternary ammonium compounds and sulphonic acids which ionise under all pH conditions.



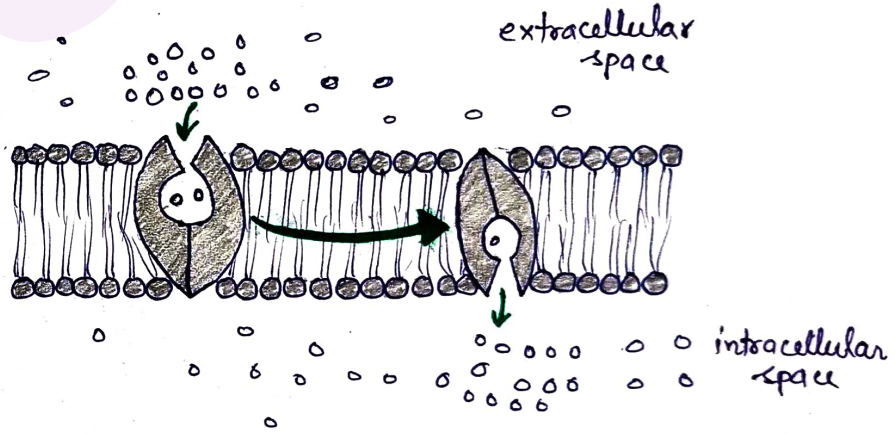
→ Such agents penetrate membrane by forming reversible neutral complexes with endogenous ions of the GIT like mucin.

→ Propranolol, a basic drug that forms an ion-pair with oleic acid is absorbed by this mechanism.

Facilitated Diffusion

It is a carrier-mediated transport system that operates down the concentration gradient but at a much faster rate than the simple passive diffusion.

Carriers usually proteins help drug molecules pass the cell membrane.



Examples include entry of glucose into RBCs and intestinal absorption of vitamin B_1 and B_2.

Active Transport

Active transport mechanisms utilise energy and are further classified as:

a. Primary active transport → In this process, there is direct ATP requirement.

The process transfers only one ion or molecule and in only one direction and hence called as uniporter e.g. absorption of glucose.

Carrier proteins involved in primary active transport are of two types.

(i) Ion transporters → are responsible for transporting ions in or out of cells. e.g. proton pump.

(ii) ABC transporters → are responsible for transporting small foreign molecules like drugs and toxins.

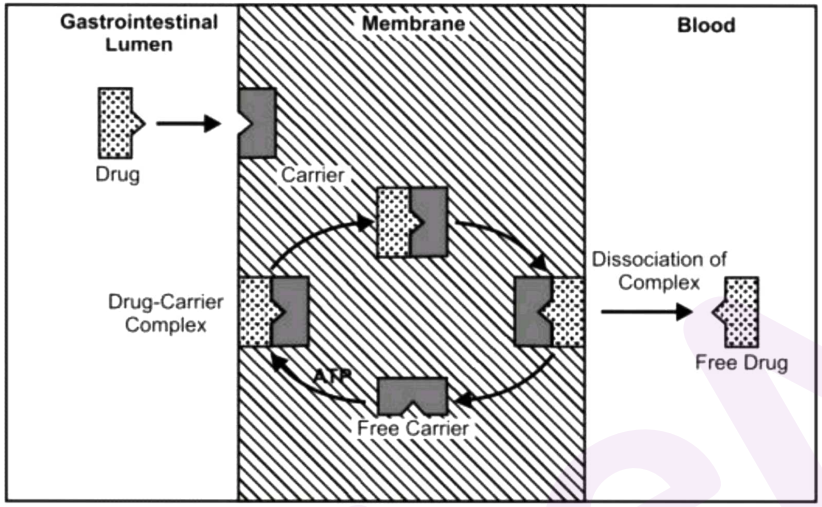
Example of ABC transporter is P-glycoprotein.

b. Secondary active transport → In these processes, there is no direct use of energy. It uses energy stored in the concentration gradients of ions. The energy required to transport an ion aids in transport of another ion or molecule either in same or in opposite direction

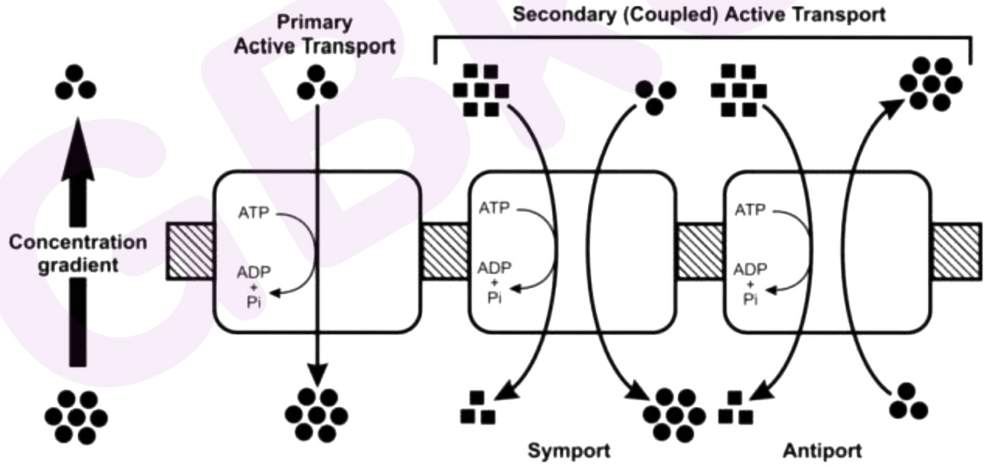
Further division:

(i) Symport (Co-transport) → involves movement of both molecules in the same direction.

(ii) Antiport (counter-transport) → involves movement of molecules in the opposite direction. e.g. H^+ and Na^+ ions in kidneys.



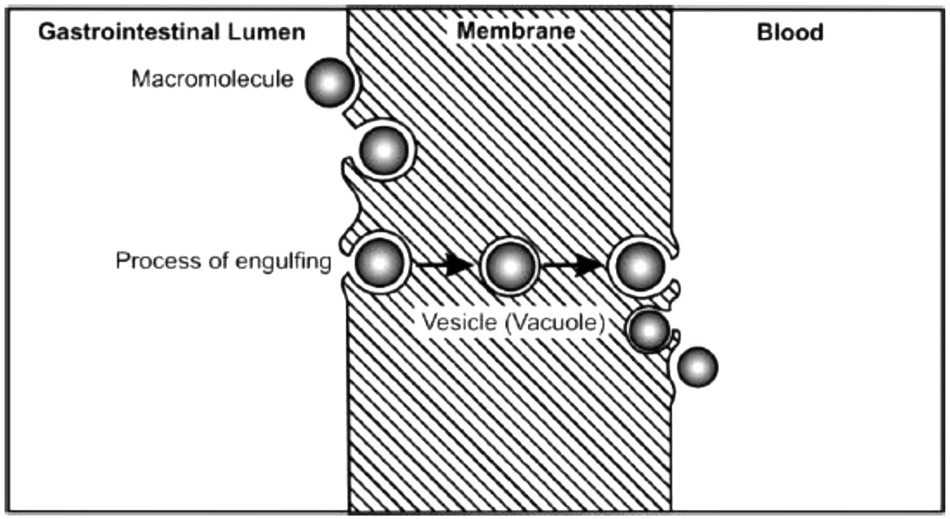
Active absorption of a drug



Types of active transport

Endocytosis

In endocytosis, cells engulf extracellular materials within a segment of the cell membrane to form a vesicle (hence called vesicular transport) which is then pinched off intracellularly. This is the only transport mechanism whereby a drug or a compound does not have to be in an aqueous solution in order to be absorbed.



Endocytosis includes two types of processes:

(i) Phagocytosis → cell eating : uptake of solid particles.

(ii) Pinocytosis → cell drinking : uptake of fluid droplets.

Factors Influencing GI absorption of Drug

A. Physicochemical Factors → These factors include the physical and chemical properties of drug.

1) Drug solubility
2) Particle size and effective surface area
3) Polymorphism and amorphism
4) Salt form of the drug
5) Lipophilicity of drug
6) pKa of drug and GI pH
7) Drug stability

B. Pharmaceutical Factors → include factors relating to the dosage form characteristics and pharmaceutical ingredients.

1) Disintegration time
2) Dissolution time
3) Pharmaceutical ingredients (excipients/adjuvants)
4) Nature and type of dosage form
5) Product age and storage condition

C. Patient-related factors → include factors relating to the anatomical, physiological, and pathological characteristics of the patient.

1) Age and disease states
2) Gastric emptying time
3) Intestinal transit time
4) GI pH
5) Blood flow through GIT
6) GI contents:
   a) Food
   b) Fluids
   c) other drugs and normal GI contents.

Drug absorption from non-per os extra-vascular routes

Drug absorption from non-oral extravascular sites is governed by same factors as the absorption from GIT because the barrier to transport of drugs from all such sites is the lipoidal membrane (cell membrane) similar to the GI barrier.

The routes:

A) Buccal / Sublingual Administration

buccal → the medicament is placed between the cheek and the gum.

sublingual → the drug is placed under the tongue and allowed to dissolve.

advantages

→ rapid absorption
→ No first-pass metabolism
→ No degradation as happens in GIT

B. Rectal Administration

The drugs may be administered as solutions (microenemas) or suppositories in the rectum.

→ No hepatic metabolism (first-pass).
→ Drug examples include aspirin, paracetamol, et.

C. Topical Administration

Drug is absorbed through skin. Majority of drugs applied topically are meant to exert their effect locally

There are three pathways for diffusion of solutes through the skin:

1. Transcellular (passive diffusion)
2. Intercellular (paracellular)
3. Transappendageal :- drug diffusion through
   - Hair follicles
   - sweat glands
   - Sebaceous glands

D. Intramuscular Administration

Absorption of drugs from intramuscular sites is relatively rapid but much slower in when compared to intravenous injections.

Deciding factors of rate of absorption from I.M.:

1) Vascularity of injection site :- flow of blood
2) Lipid solubility and ionisation of drug
3) Molecular size of the drug
4) Volume of injection and drug concentration
5) pH, composition and viscosity of injection vehicle.

E. Subcutaneous Administration

All factors that influence I.M. drug absorption are also applicable to absorption from subcutaneous site but slower than I.M.

The rate of absorption of drug from subcutaneous site can be increased by 2 ways.

1) Enhancing blood flow to the injection site :- by massage, application of heat or by exercise.
2) Increasing the drug-tissue contact area.

F. Pulmonary Administration

The drugs administered by inhalation are absorbed rapidly because of large surface area of alveoli, high permeability of alveolar epithelium.

The drugs administered by inhalation are generally gases (volatile / gaseous anaesthetics) or aerosol.

G. Intranasal Administration → nasal mucosa

Drug absorption from nasal mucosa is as rapid as observed after parenteral administration because of its rich vasculature and high permeability. This route is generally used to treat local symptoms like nasal congestion, etc.

H. Intraocular Administration

Topical application of drugs to the eyes is mainly used for local effects such as mydriasis, miosis, anaesthesia or treatment of infections, glaucoma.

The barrier to intraocular penetration of drugs is the cornea which possess both hydrophilic

and lipophilic characteristics. Thus, for good intraocular permeation, the drugs should possess biphasic solubility.

I. Vaginal Administration

Drugs are generally intended to act locally in the treatment of bacterial or fungal infections or prevent pregnancy.

→ The drug directly absorbed to systemic circulation with no first-pass metabolism

→ Factors that may influence drug absorption from intravaginal sites include pH of lumen fluids, vaginal secretions and microorganisms present in the vaginal lumen which may metabolise the drug.