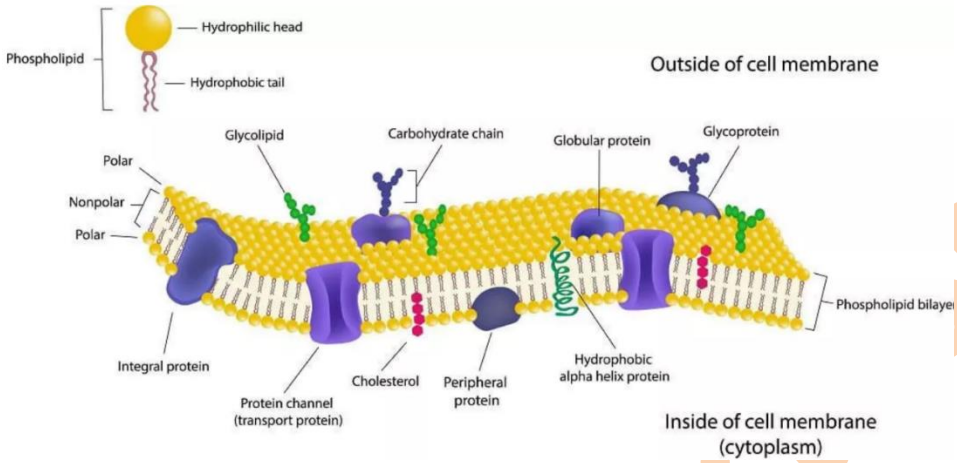
DRUG ABSORPTION

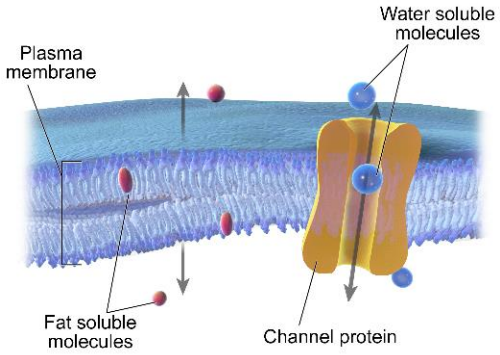
- **Definition**- Absorption is the transfer of a drug from the site of administration to the bloodstream(systemic circulation)
- Except when given i.v., the drug has to cross biological membranes (cell membrane)
- **Cell membrane**-



- This is a bilayer (about 100 Å thick) of phospholipid and cholesterol molecules, the polar groups of these are oriented at the two surfaces and the nonpolar hydrocarbon chains are embedded in the matrix to form a continuous sheet. This imparts high electrical resistance and semipermeability to the membrane.
- Extrinsic and intrinsic protein molecules are adsorbed on the lipid bilayer.
- Glycoproteins or glycolipids are formed on the surface by attachment to polymeric sugars.
- The specific lipid and protein composition of different membranes differs according to the cell or the organelle type.
- The proteins are able to freely float through the membrane.
- Some of the intrinsic ones, which extend through the full thickness of the membrane, surround fine aqueous pores.
- Paracellular spaces or channels also exist between certain epithelial/ endothelial cells.
- Other adsorbed proteins have enzymatic, carrier, receptor or signal transduction properties.
- Lipid molecules also are capable of lateral movement.
- Thus, biological membranes are highly dynamic structures.

❖ **Types of absorption or Mechanism of absorption**

- Drugs are transported across the membranes by:
  - (a) Passive diffusion and filtration
  - (b) Specialized transport



(a) Passive diffusion(No use of energy or ATP)

- The drug diffuses across the membrane in the direction of its concentration gradient (high to low).
- The vast majority of drugs are absorbed by this mechanism
- The membrane playing no active role in the process.
- This is the most important mechanism for majority of drugs
- Lipid soluble drugs diffuse by dissolving in the lipoidal matrix of the membrane,
- The rate of transport is proportional to the lipid : water partition coefficient of the drug. A more lipid-soluble drug attains higher concentration in the membrane and diffuses quickly. Also, greater the difference in the concentration of the drug on the two sides of the membrane, faster is its diffusion.
- Water-soluble drugs penetrate the cell membrane through aqueous channels or pores. It is also called pore transport or bulk flow or filtration

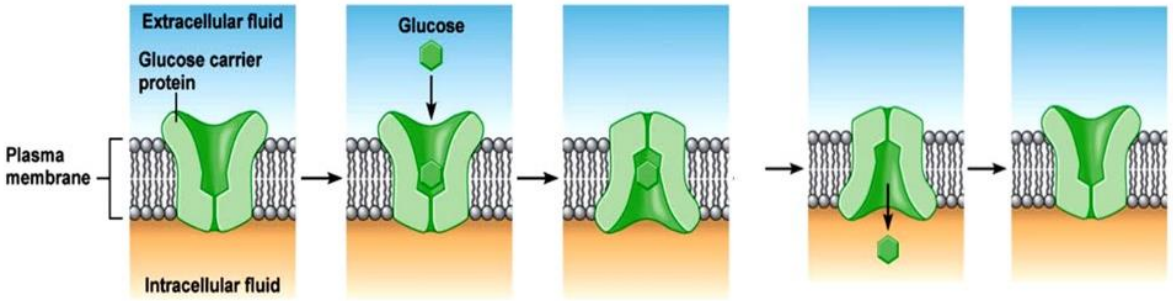
(b) Specialised transport- it is divided into two category

Some terms

- The two main transporter superfamilies are the ATP-binding cassette (ABC) superfamily and the **solute carrier (SLC) superfamily**.
- Solute carrier (SLC) transporters — a family of more than 300 membrane-bound proteins that facilitate the transport of a wide array of substrates across biological membranes
- ABC transporters harness energy from ATP hydrolysis and function as efflux transporters, whereas SLC transporters are primarily involved in the uptake of small molecules into cells.
- Specialised transport can be carrier mediated or by vesicular transport (endocytosis, exocytosis).

A. Carrier transport-

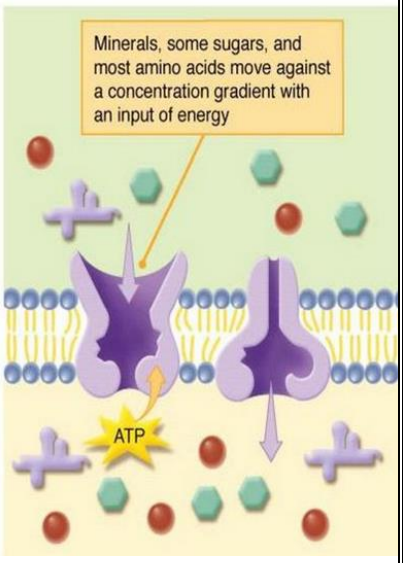
i) Facilitated diffusion(no use of energy)



- The transporter, belonging to the super-family of *solute carrier* (SLC) transporters, operates passively without needing energy and translocate the substrate in the direction of its electrochemical gradient, i.e. from higher to lower concentration.
- It facilitates permeation of a poorly diffusible substrate, e.g. the entry of glucose into muscle and fat cells by the glucose transporter GLUT 4.

ii) Active transport (use energy)-

- It requires energy for transportation
- It is inhibited by metabolic poisons
- It transports the solute against its concentration gradient (low to high), which result in selective accumulation of the substance on one side of the membrane.
- e.g. levodopa and methyl dopa are actively absorbed from the gut by the aromatic amino acid transporter.
- Active transport can be primary or secondary depending on the source of the driving force.

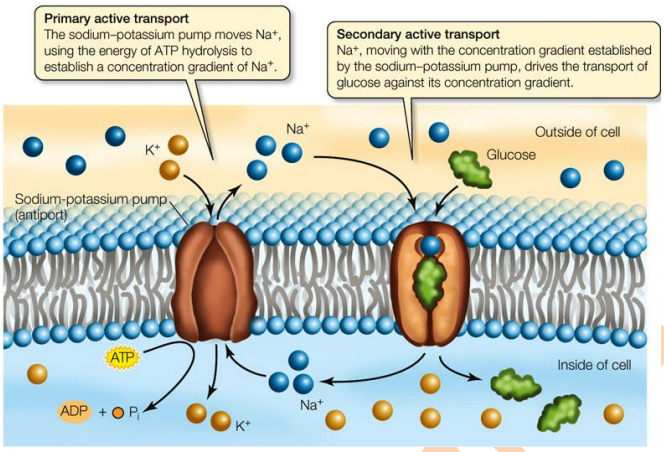


(a) Primary active transport-

Energy is obtained directly by the hydrolysis of ATP . The transporters belong to the superfamily of *ATP binding cassettee* (ABC) transporters whose intracellular loops have ATPase activity. They mediate only efflux of the solute from the cytoplasm, either to extracellular fluid or into an intracellular organelli (endoplasmic reticulum, mitochondria, etc.)

(b) Secondary active transport-

The energy required in transporting an ion aids transport of another ion/molecule
It can be further divided in two category-

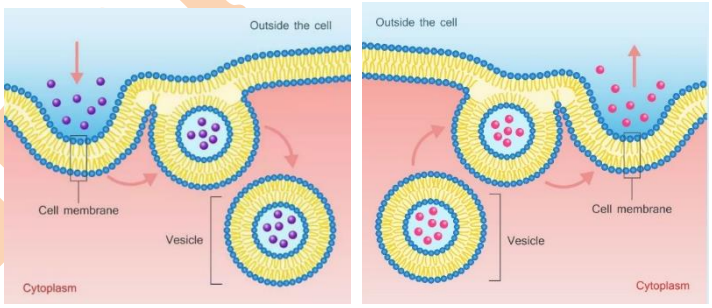


1. **Symport or cotransport-**
   - When the concentration gradients are such that both the solutes move in the same direction, it is called *symport* or *cotransport*,
2. **Anti-port or exchange transport**
   - When they move in opposite directions, it is termed *antiport* or *exchange transport*.
   - Metabolic energy (from hydrolysis of ATP) is spent in maintaining high transmembrane electrochemical gradient of the second solute (generally Na+).

Note-

- Carrier transport (both facilitated diffusion and active transport) is saturable.
- The maximum rate of transport is dependent on the density of the transporter in a particular membrane, and the substrate concentration
- Genetic polymorphism can alter both the density and affinity of the transporter protein for different substrates and thus affect the pharmacokinetics of drugs.
- Tissue specific drug distribution can occur due to the presence of specific transporters in certain cells.

B. Vesicular transport (endocytosis and exocytosis)



- Some molecules or particles are just too large to pass through the plasma membrane or to move through a transport protein. So cells use two other active transport processes to move these macromolecules (large molecules) into or out of the cell. Vesicles or other bodies in the cytoplasm move macromolecules or large particles across the plasma membrane. There are two types of vesicle transport, endocytosis and exocytosis

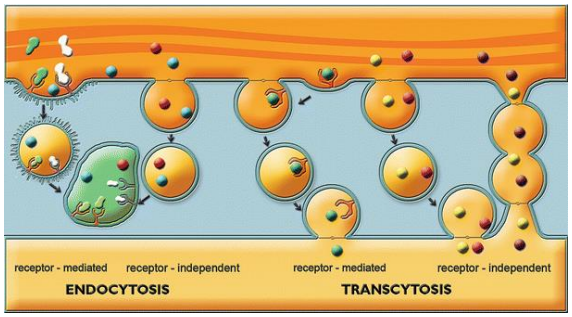
1. Endocytosis

- It is the process of capturing a substance or particle from outside the cell by engulfing it with the cell membrane.
- The membrane folds over the substance and it becomes completely enclosed by the membrane. At this point a membrane-bound sac, or vesicle, pinches off and moves the substance into the cytosol.
- Vitamin B12 is transported across the gut wall by endocytosis.
- There are three main kinds of endocytosis:

(a) **Phagocytosis**, or *cellular eating,* occurs when the dissolved materials enter the cell. The plasma membrane engulfs the solid material, forming a phagocytic vesicle.

(b) **Pinocytosis**, or *cellular drinking,* occurs when the plasma membrane folds inward to form a channel allowing dissolved substances to enter the cell. When the channel is closed, the liquid is encircled within a pinocytic vesicle.

(c) **Transcytosis**



- **Transcytosis** (also known as **cytopempsis**) is a type of transcellular transport in which various macromolecules are transported across the interior of a cell.
- Macromolecules are captured in vesicles on one side of the cell, drawn across the cell, and ejected on the other side.
- Examples of macromolecules transported include IgA, transferrin, and insulin.
- It is most commonly observed in epithelial cells.

2. **Exocytosis**
    - It is the reverse of endocytosis.
    - **Exocytosis** describes the process of vesicles fusing with the plasma membrane and releasing their contents to the outside of the cell. Exocytosis occurs when a cell produces substances for export, such as a protein, or when the cell is getting rid of a waste product or a toxin.
    - Most hormones (insulin, etc.) and neurotransmitters, like noradrenaline, are secreted/released from the cell/nerve ending by exocytosis.

❖ **FACTOR AFFECTING DRUG ABSORPTION**

1. **Aqueous solubility**
    - Drugs given in solid form must dissolve in the aqueous bio-phase before they are absorbed. For poorly water soluble drugs (aspirin, griseofulvin) rate of dissolution governs rate of absorption.
    - A drug given as watery solution is absorbed faster than when the same is given in solid form or as oily solution.
2. **Concentration**
    - Passive diffusion depends on concentration gradient therefore drug given as concentrated solution is absorbed faster than from dilute solution.
3. **Effect of pH**
    - Most drugs are either weak base or weak acids
    - Acidic drugs are present in two form- unionised(HA) or an ionised (charged) form(A^-) [HA $\rightleftharpoons$ A^- + H^+]
    - Basic drugs are present in two form- unionised(B) or an ionised (charged) form(BH^+) [BH^+ $\rightleftharpoons$ B + H^+]
    - A drug passes through membrane more readily if it is un-ionised(un-charged or non-polar)
    - Acidic drugs are unionised in acidic medium, that's why acidic drugs are absorbed from the stomach (pH-1.5 to 3.5)
    - Bases are unionised in basic medium that's why basic drugs are mainly absorbed from the intestine (pH- 6 to 7.4)
4. **Blood flow to the absorption site**
   The intestines receive much more blood flow than the stomach, so absorption of drug is also more from intestine than stomach
5. **Total surface area available for absorption**
   Intestine contain brush bordered microvilli which increases surface area about 1000 times than that of stomach, hence drug is more efficiently absorb in intestine.
6. **Contact time at the absorption site**
    - If a drug moves through the GI tract very quickly, as can happen with severe diarrhea, it is not well absorbed. Conversely, anything that delays the transport of the drug from the stomach to the intestine delays the rate of absorption.
    - The presence of food in the stomach both dilutes the drug and slows gastric emptying. Therefore, a drug taken with a meal is generally absorbed more slowly.
7. **Expression of P-glycoprotein**
    - P-glycoprotein is a transmembrane transporter protein responsible for transporting various molecules, including drugs, across cell membranes.
    - It is expressed in tissues throughout the body, including the liver, kidneys, placenta, intestines, and brain capillaries, and is involved in transportation of drugs from tissues to blood. That is, it "pumps" drugs out of cells.
    - Thus, in areas of high expression, P-glycoprotein reduces drug absorption.
    - In addition to transporting many drugs out of cells, it is also associated with multidrug resistance.

8. **Route of administration**

This affects drug absorption, because each route has its own peculiarities.

i) Oral –

- The effective barrier to orally administered drugs is the epithelial lining of the gastrointestinal tract, which is lipoidal
- Dissolution is a surface phenomenon, therefore, *particle size* of the drug in solid dosage form governs rate of dissolution and in turn rate of absorption.
- *Presence of food* dilutes the drug and retards absorption. Further, certain drugs form poorly absorbed complexes with food constituents
- Certain drugs are degraded in the gastrointestinal tract
- Absorption of a drug can be affected by other concurrently ingested drugs. This may be a *luminal effect*: formation of insoluble complexes
- Drugs can also alter absorption by *gut wall effects*: altering motility or causing mucosal damage

ii) Subcutaneous and intramuscular

- By these routes the drug is deposited directly in the vicinity of the capillaries. Lipid soluble drugs pass readily across the whole surface of the capillary endothelium
- Absorption from s.c. site is slower than that from i.m. site, but both are generally faster and more consistent/ predictable than oral absorption.
- Application of heat and muscular exercise accelerate drug absorption by increasing blood flow

iii) Topical sites (skin, cornea, mucous membranes

- Systemic absorption after topical application depends primarily on lipid solubility of drugs.

9. **Dosage form-**

Absorption also depends on dosage form in the following order

Solution > emulsion > suspension > capsule > tablets > coated tablets > enteric coated tablet > sustain release tablet

10. **Product age and storage condition-**

Aging and alteration in storage condition change the physiochemical properties of a drug which adversely affect its bioavailability.

11. **Patient related factors-**

Age-

i) In infants the gastric pH is high and intestinal surface area and blood flow to GIT is less. This result in altered absorption pattern

ii) Elderly patient has impaired gastric emptying, decreased intestinal surface area, decreased blood flow to GIT, higher incidence of achlorhydria and bacterial overgrowth in small intestine. These all factor affect drug absorption.

iii) Disease state-
it may affect the drug bioavailability as it affect the intestinal transit. Ex- GI disease, CVS disease, Hepatic disease.