
Bio Pharma
Lama Nofal

Drug Absorption

يعني امتصاص الدواء من الامعاء
حتى يوصل للدورة الدموية

Presented by Dr. Muna Oqal

drug absorption تتعلق بـ membrane physiology or transport of drug

وفي بعض الاحيان ممكن تتعلق بالـ GIT حسب نوع الطعام اذا كان خفيف او ثقيل عالمعدة

membrane >> phospholipid bilayer (contain : protein , macromolecule , carbohydrate)
hydrophobic>> tails
hydrophilic >> heads

in general the membrane : is physiological barrier separated the cytosol from the cytoplasm
(out side from the inside)

Absorption

Main factors affecting oral absorption:

I. **Physiological factors**

II. Physico-chemical factors

III. Formulation factors.

Absorption

I. Physiological factors affecting oral absorption:

1. **Membrane physiology**.
2. **Passage of drugs across membranes**.
3. **Gastrointestinal physiology**.

A. Characteristics of GIT physiology and drug absorption

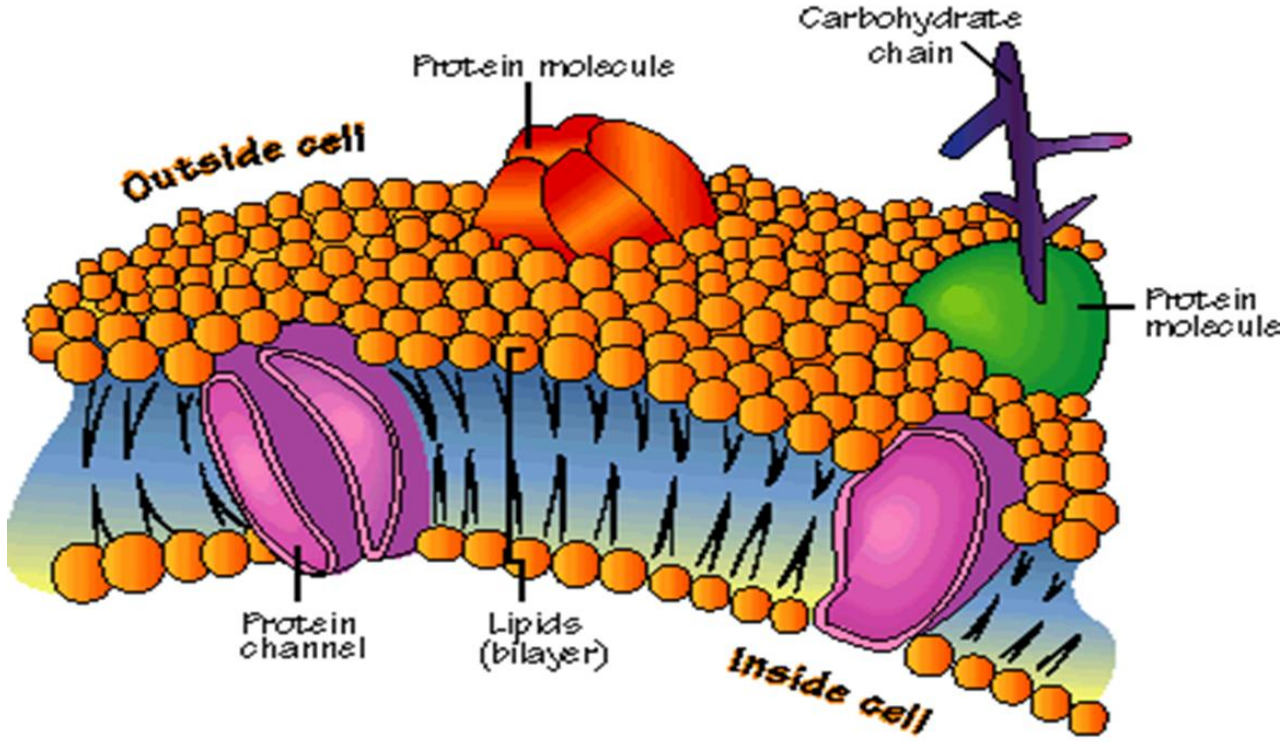
B. Gastric emptying time and motility

C. Effect of food on drug absorption

Physiological Factors Influencing Bioavailability

1. Membrane physiology:

- The cell membrane is the barrier that separates the inside of the cell from the outside.
- The cell membrane is made up of phospholipids, proteins, and other macromolecules.
- The phospholipids make up a bilayer. It contains hydrophilic and hydrophobic molecules.
- The proteins in the cell membrane are located within the phospholipid bilayer.
- So, the biologic membrane is mainly lipid in nature but contains small aqueous channels or pores.



Physiological factors affecting oral absorption

1. Membrane physiology

- Functionally, cell membranes are semipermeable partitions that act as selective barriers to the passage of molecules.

- For example: Water, some selected small molecules, and lipid-soluble molecules pass through such membranes, whereas highly charged molecules and large molecules, such as proteins and protein-bound drugs, do not.

2. Passage of drugs across cell membranes

1. **Carrier mediated transport:**
   A. Active transport
   B. Facilitated diffusion
   C. P-glycoprotein

2. **Passive diffusion**
3. **Vesicular transport**
4. **Pore (convective) transport**
5. **Ion pair formation**

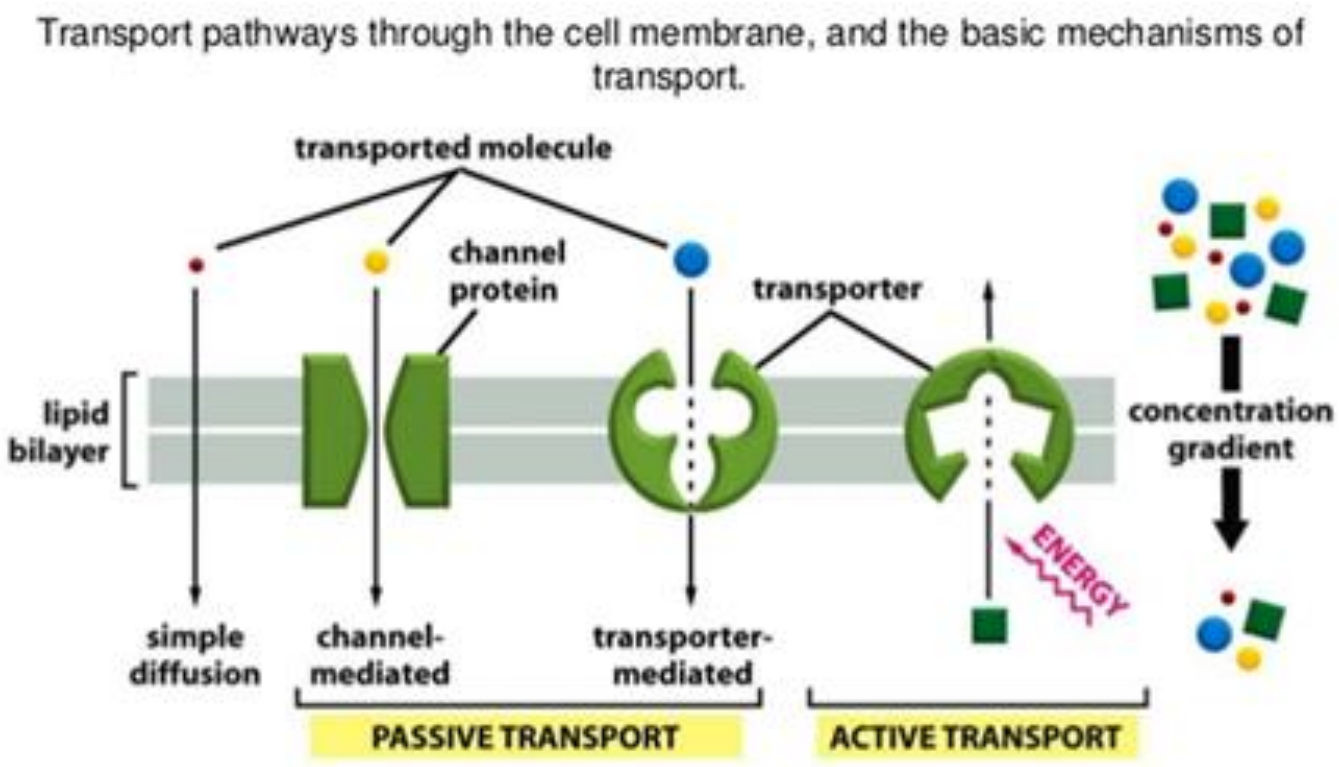
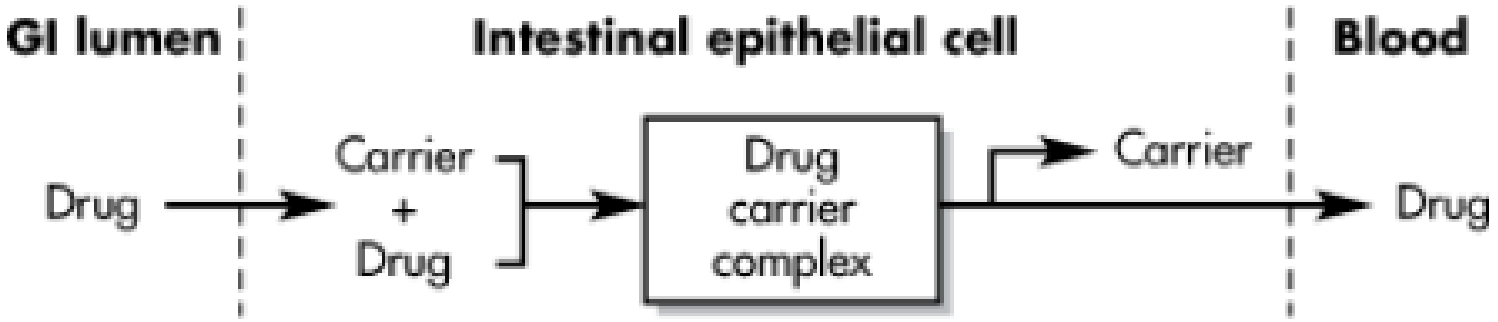


Illustration of different mechanisms of cell membrane transport

2. Transport across the membranes

1. Carrier mediated transport:

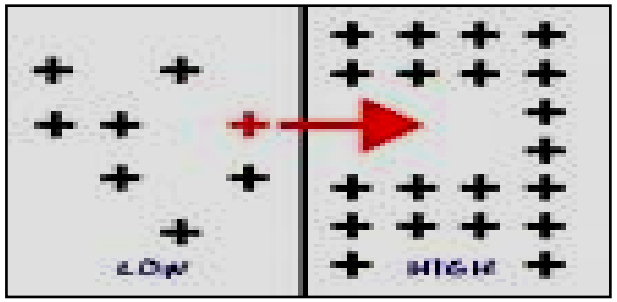


Scheme for the hypothetical carrier-mediated transport process

2. Transport across the membranes

need ATP

A. Active transport:



- A few lipid-insoluble drugs (e.g.5-flurouracil, L-dopa) that resemble natural physiologic metabolites (e.g. glucose, amino acids) are absorbed from the GIT by this process.

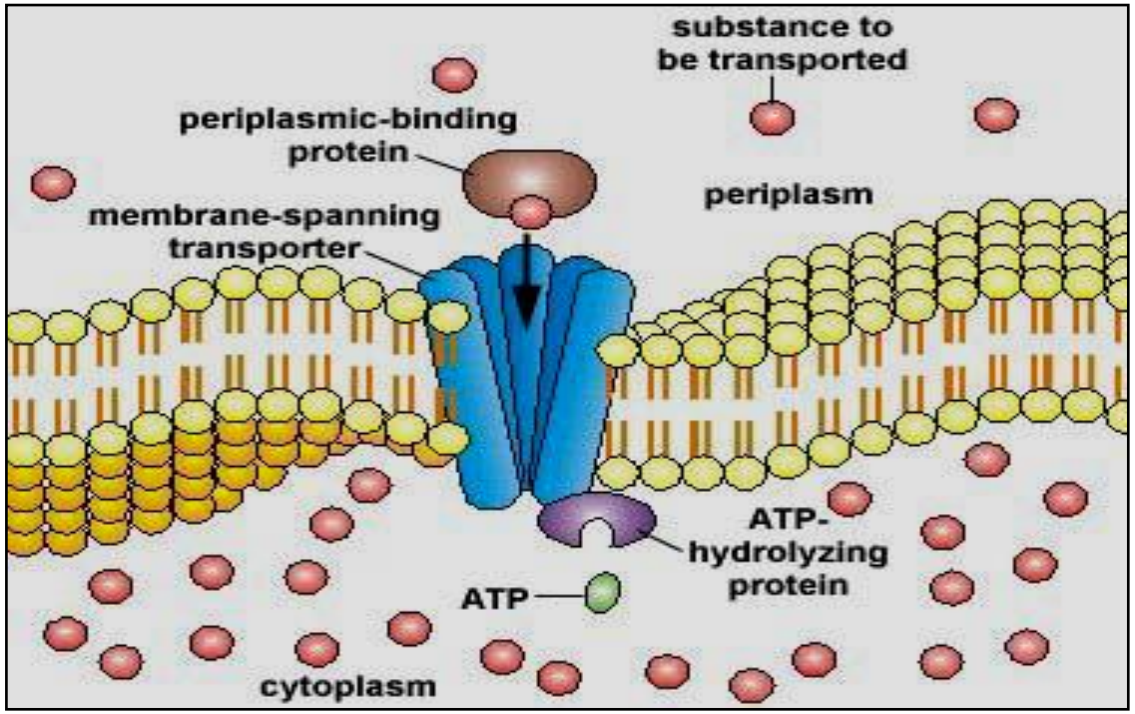
- Transport of a drug against concentration gradient (from regions of low drug concentrations to regions of high concentrations).

- It is an energy-consuming system.

بعض المشاكل التي تواجه هذه الطريقة

- The carrier molecule may be highly selective for the drug molecule, therefore, drugs of similar structure may compete for sites of adsorption on the carrier (competitive inhibition is possible)

- Because only a certain amount of carrier is available, all the adsorption sites on the carrier may become saturated if the drug concentration gets very high.

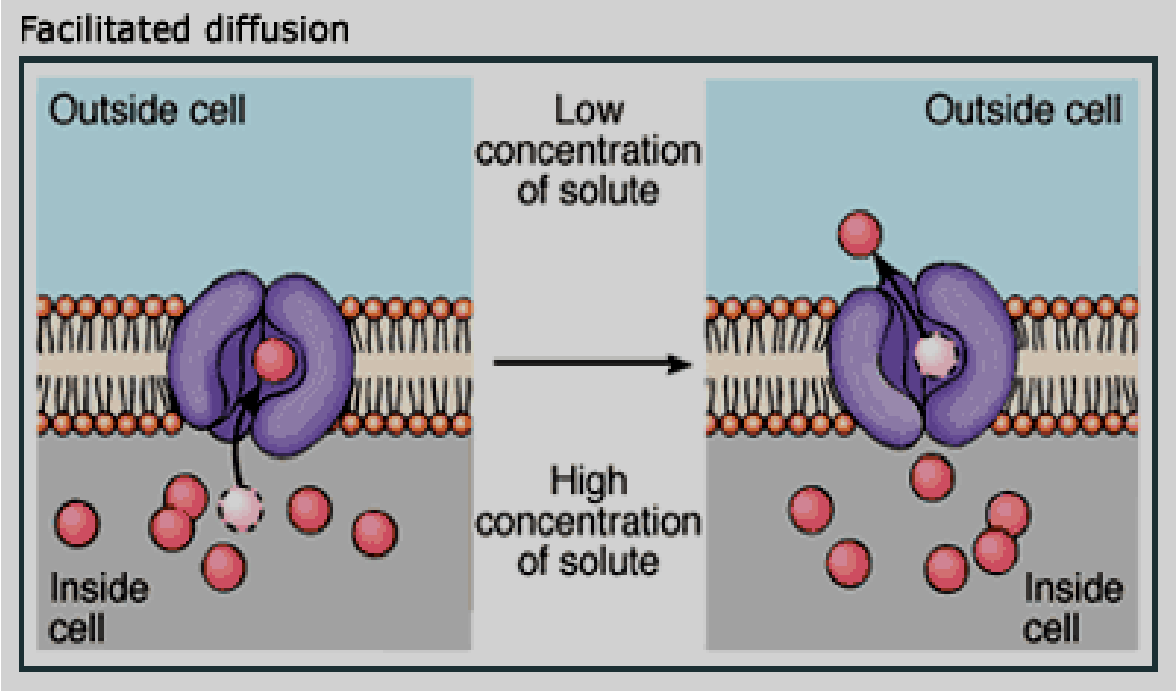


2. Transport across the membranes

no need ATP
have channel protein

B- Facilitated diffusion:

- Play a very minor role in absorption.
- A drug carrier is required but no energy is necessary. e.g. vitamin B12 transport.
- Saturable if not enough carrier and structurally selective for the drug and shows competition kinetics for drugs of similar structure. نفس المشاكل السابقة
- No transport against a concentration gradient only downhill but faster.



2. Transport across the membranes

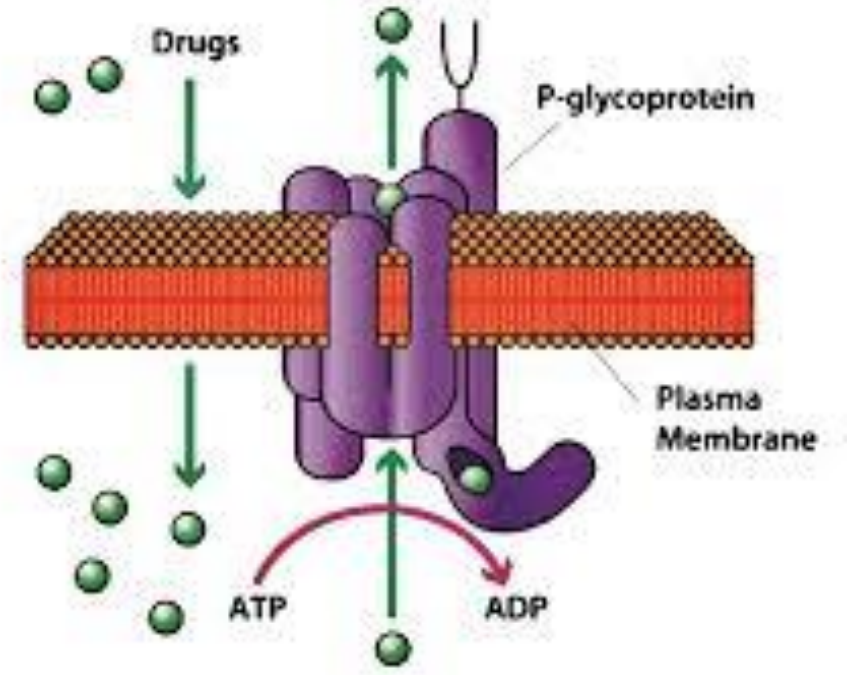
تتبع لعائلة ABC efflux

وهي غير مفيدة

C. P-glycoprotein (PGP) transporters :

- P-glycoprotein are transmembrane proteins present throughout the body including liver, brain, kidney and the intestinal tract epithelia.
- This is an active, ATP-dependent process.
- Act as reverse pump generally inhibiting absorption (actively exporting drugs out of the cell).
- It is known as multidrug resistance protein 1 (MDR1).

تعد احد وسائل ممناعة الخلية للدواء ومثال عليها الخلايا السرطانية



دخول الدواء من خارج الخلية الى داخلها تسمى infflux

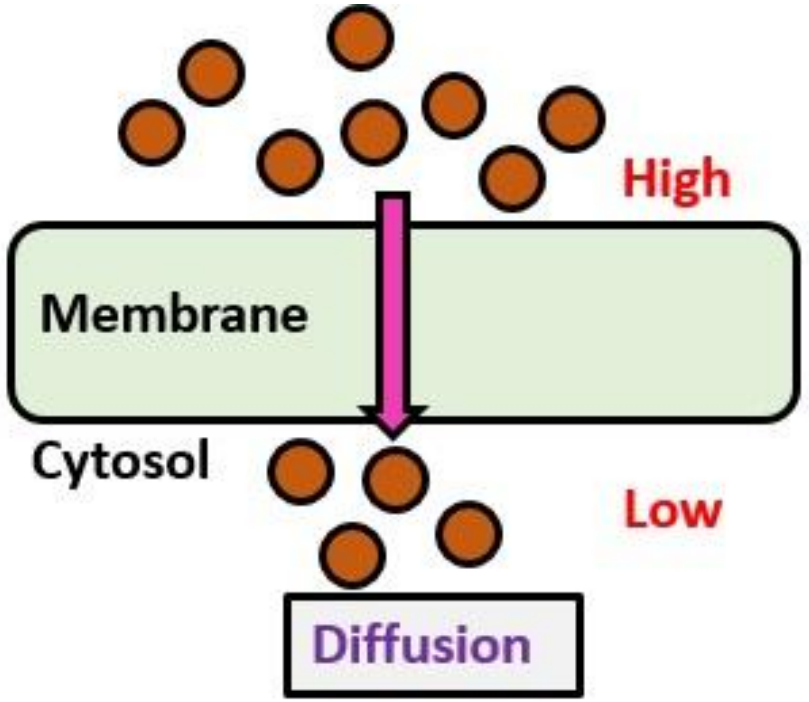
ذهاب الدواء من داخل الخلية الى خارجها تسمى efflux

2. Transport across the membranes

no need ATP

2- Passive diffusion:

- Most drugs cross biologic membranes by passive diffusion.
- Diffusion occurs when the drug concentration on one side of the membrane is higher than that on the other side.
- The process is passive because no external energy is expended.
- The driving force for passive diffusion is the difference in drug concentrations on either side of the cell membrane (higher drug concentrations on the mucosal side compared to the blood).
- So The rate of transport of drug across the membrane can be described by Fick's first law of diffusion. According to it, drug molecules diffuse from a region of high drug concentration to a region of low drug concentration.



2. Transport across the membranes

Fick's First Law, Rate of Diffusion

$$\text{Rate of diffusion} = \frac{dM}{dt} = -\frac{D \bullet A \bullet (Ch - Cl)}{x}$$

- The parameters of above equation are:

✓ D: diffusion coefficient. علاقة طردية

This parameter is related to the size and lipid solubility of the drug and the viscosity of the diffusion medium. As lipid solubility increases or molecular size decreases then D increases and thus dM/dt also increases.

✓ A: surface area. علاقة طردية

As the surface area increases the rate of diffusion also increase. The surface of the intestinal lining (with villi and microvilli) is much larger than the stomach. This is one reason absorption is generally faster from the intestine compared with absorption from the stomach.

2. Transport across the membranes

✓X: membrane thickness: علاقة عكسية

The smaller the membrane thickness the quicker the diffusion process. As one example, the membrane in the lung is quite thin thus inhalation absorption can be quite rapid.

✓(Ch -Cl): concentration difference.

The drug concentration in blood or plasma will be quite low compared with the concentration in the GI tract. It is this concentration gradient which allows the rapid complete absorption of many drug substances.

- Normally **Cl << Ch** then:-

$$\frac{dM}{dt} = -\frac{D \bullet A \bullet Ch}{x}$$

constant, ka

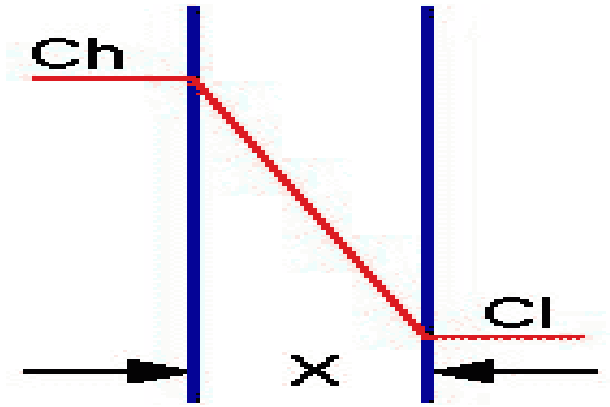
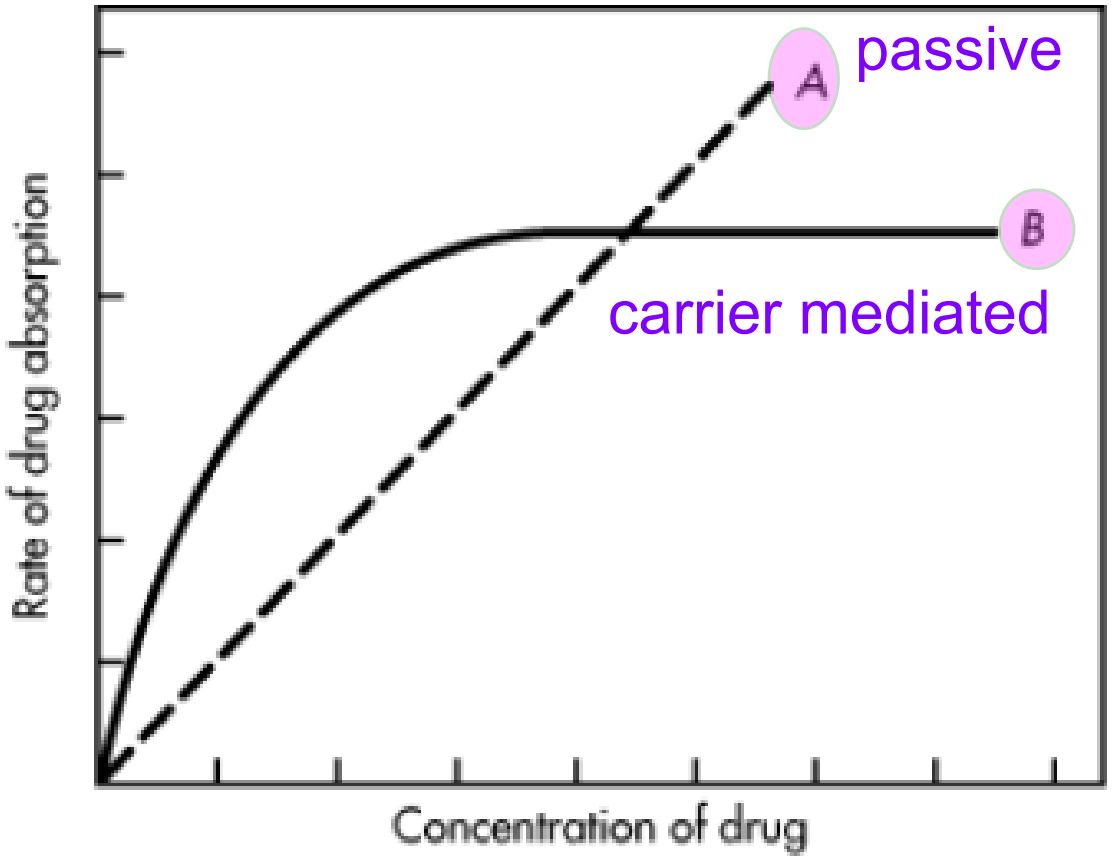


Diagram of Passive Transport with a Concentration Gradient

2. Transport across the membranes



Relationship between drug concentration and absorption rate For a passive process (Curve A) and for a carrier-mediated Process (Curve B).

2. Transport across the membranes

3. Vesicular transport:

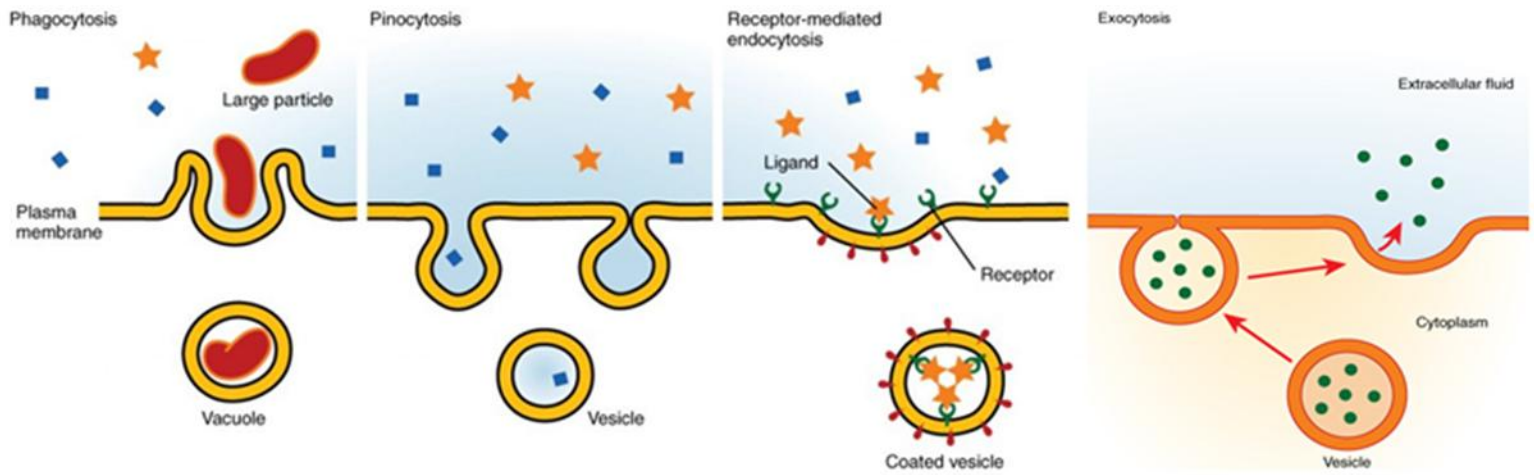
- It is the process of engulfing particles or dissolved materials by the cell.
- Vesicular transport is the proposed process for the absorption of Vitamin A, D, E, and K, peptides in new born.

- Pinocytosis and phagocytosis are forms of vesicular transport that differ by the type of material ingested.

➢ **Pinocytosis:** refers to the engulfment of small molecules or fluid.

➢ **Phagocytosis:** refers to the engulfment of larger particles or macromolecules.

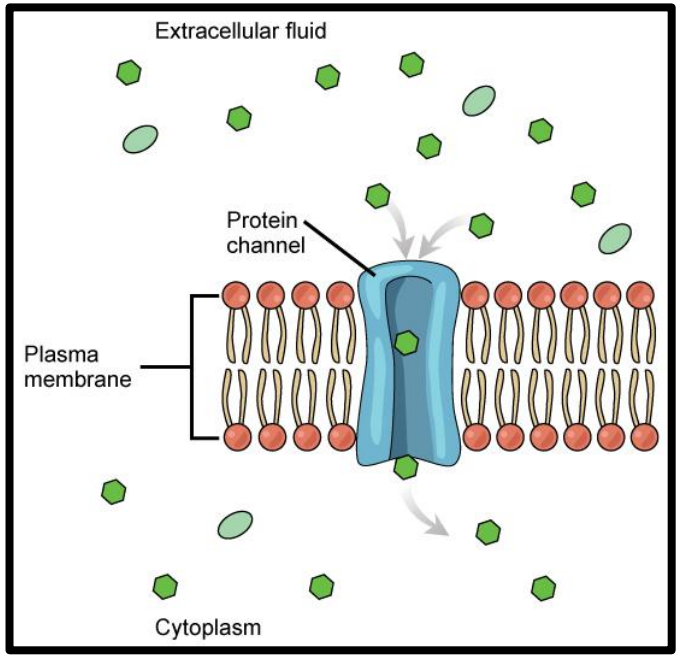
➢ During pinocytosis or phagocytosis, the cell membrane invaginates to surround the material, and then engulfs the material into the cell. Subsequently, the cell membrane containing the material forms a vesicle or vacuole within the cell. Endocytosis and exocytosis are the processes of moving specific macromolecules into and out of a cell, respectively.



2. Transport across the membranes

4. Pore (convective) transport:

- A certain type of protein called transport protein may form an open channel across the lipid membrane of the cell.
- Very small molecules, such as urea, water and sugars are able to rapidly cross the cell membrane through these pores.
- Small molecules including drugs move through the channel by diffusion more rapidly than at other parts of the membrane.



5. Ion pair formation:

- Strong electrolyte drugs are highly ionized or charged molecules, such as quaternary nitrogen compounds.
- These drugs penetrate membranes poorly. When linked up with an oppositely charged ion (counter 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.

الافضل ان تكون الادوية متاينة

weak acid >> aspirin