Advanced Biopharmaceutics

Introduced by:

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Absorption

- Introduction
- Factors affecting absorption
- Mechanisms
- Applications

Introduction

- The amount of drug that enters the body from site of administration to the systemic circulation.
- The rate of absorption affects the onset, duration and intensity of drug action.
- The rate and efficiency of absorption depend on the route of administration.(Explain that?)

Factors affecting absorption:

- Physiological factors, may varied with variation of the route of administration.
- Physiochemical factors
- Pharmaceutical factors

Physiological factors

- Membrane thickness and surface area
- Pre-systemic metabolism
- pH of absorption media
- Presence of enzymes, food
- Integrity of membranes, Functional integrity (edema and diarrhea)
- Disease states like??
- Blood flow
- Movement, GET, Residence time

Q/ What is the meaning of Donnan effect??

Physiochemical factors

- Lipid solubility/ partition coefficient
- pka of drug/ ionization
- Solubility
- Molecular weight

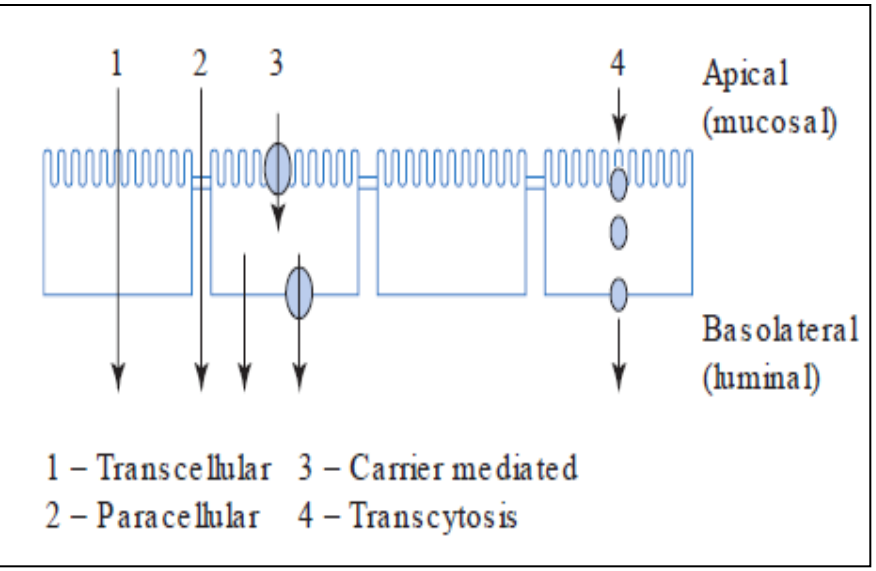
Pharmaceutical factors

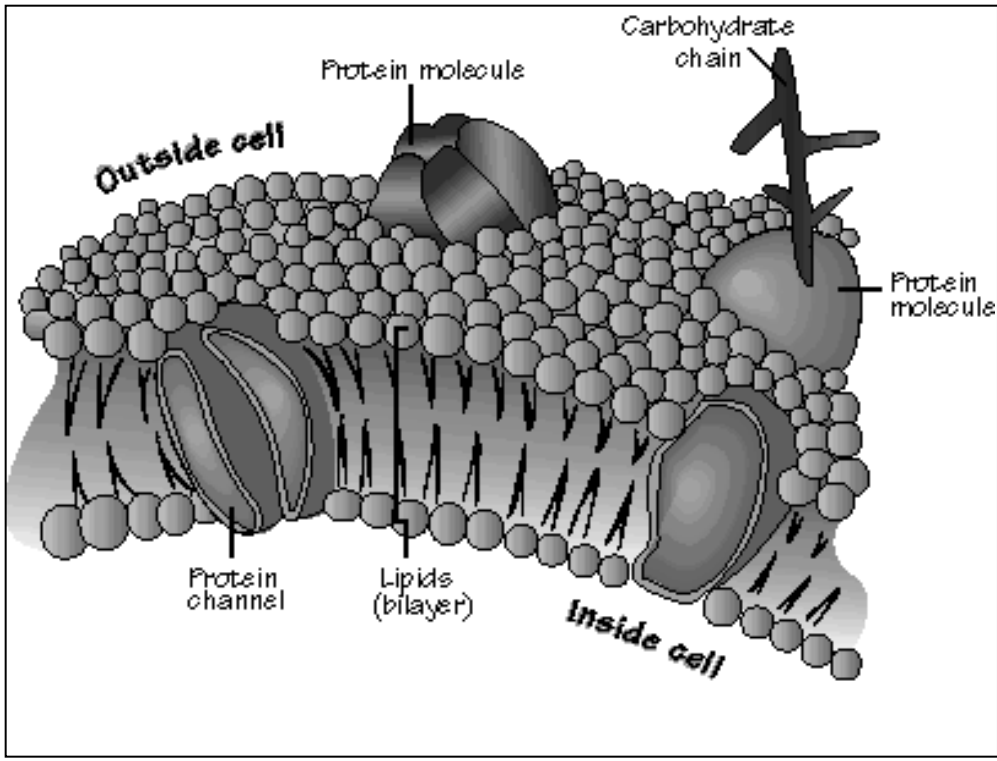
- Particle size
- Concentration of drug
- Dosage form
- Chemical nature of drug
- Formulation excipients
- Physical state

Mechanisms

Cell Membranes Structure:

Cell membrane consists of a phospholipid bilayer studded with proteins, poly-saccharides, lipids and the lipid bilayer.





- It is semipermeable to H_2O and some small, uncharged, molecules (O_2, CO_2) can pass through.
- Phospholipids have two parts

"Head": hydrophilic → attracts and mixes with H_2O, Two "fatty acid tails": hydrophobic.

Membrane proteins embedded in the bilayer serve as receptors, ion channels or transporters to transduce electrical or chemical signaling pathways and provide selective targets for drug actions.

Processes involved in the absorption of drug:

1) Passive membrane transport

a) Simple diffusion

b) Filtration/ aqueous diffusion

c) Osmosis

d) Bulk flow

2) Specialized transport

a) Active membrane transport (primary/secondary)

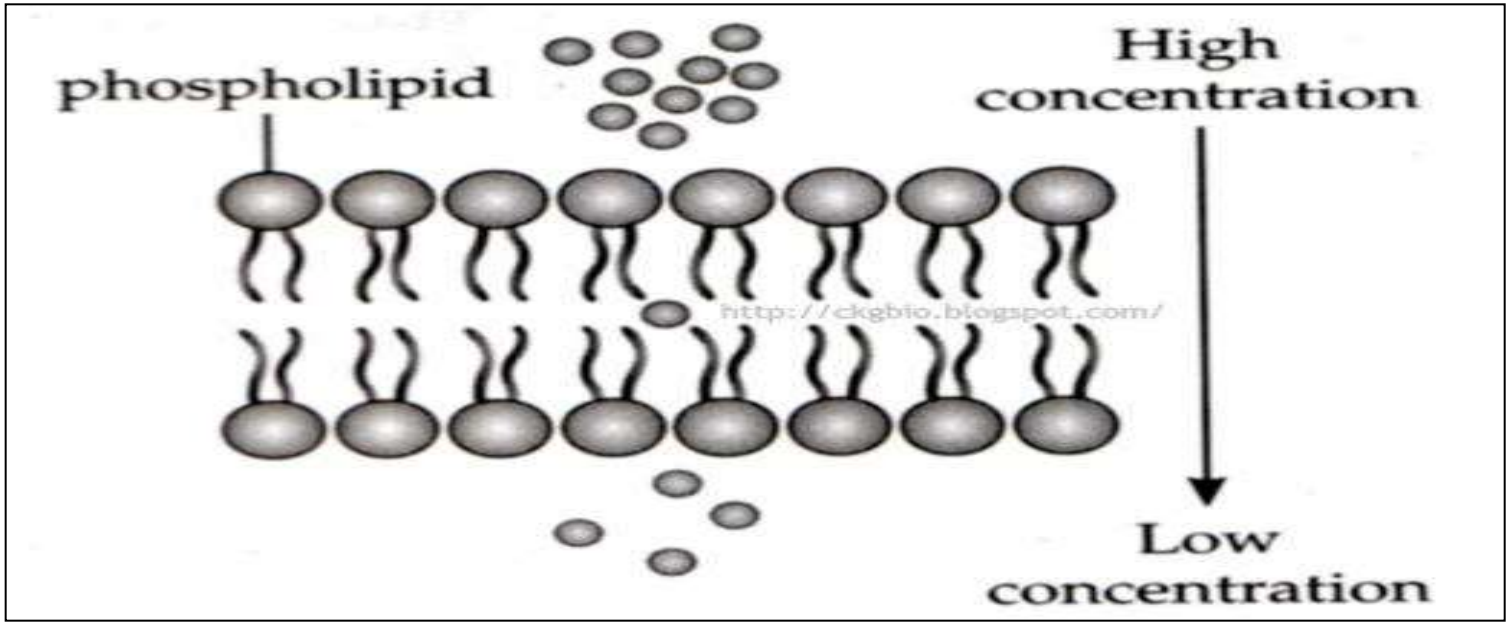
b) Facilitated diffusion

c) Endocytosis (phagocytosis/pinocytosis)

d) Exocytosis

1) Passive membrane transport:

In passive transport, the drug molecule penetrates in the lipid bilayer membrane from higher concentration to the lower concentration of solutes along the concentration gradient without expenditure of energy.

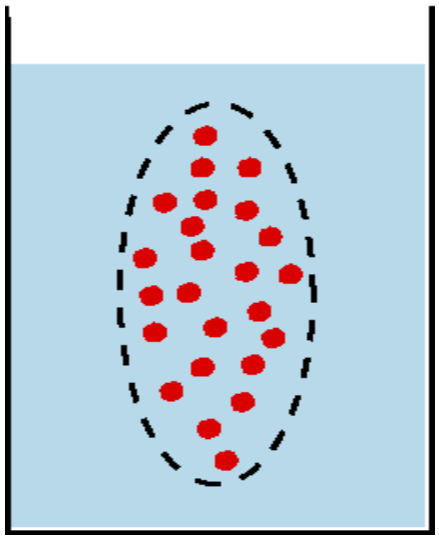


- So passive transport mechanism involves following processes.

a) Simple diffusion:

Direct movement of a solute through the semi permeable cell membrane from a phase of higher concentration to the phase of lower concentration without expenditure of energy until the equilibrium is achieved.

Fick's law of diffusion??

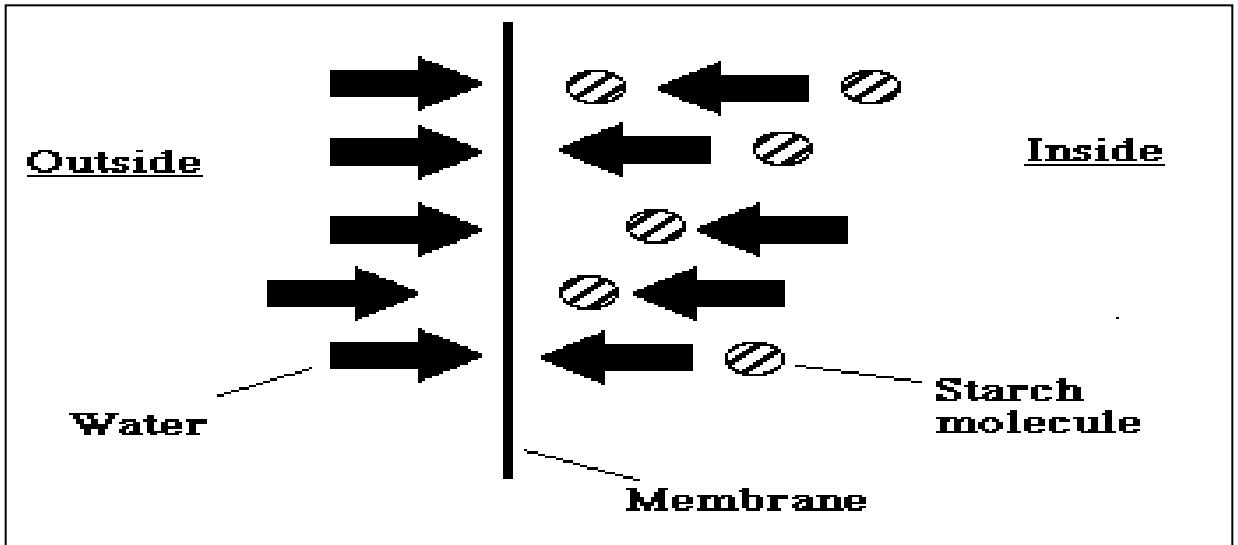


b) Filtration or aqueous diffusion:

It is the passage of a substance through pores in the cell membrane by means of their hydrostatic or osmotic pressure gradient.

Water, ions and some polar and non polar molecules of low molecular weight diffuse through membrane indicating the existence of pores or channels.

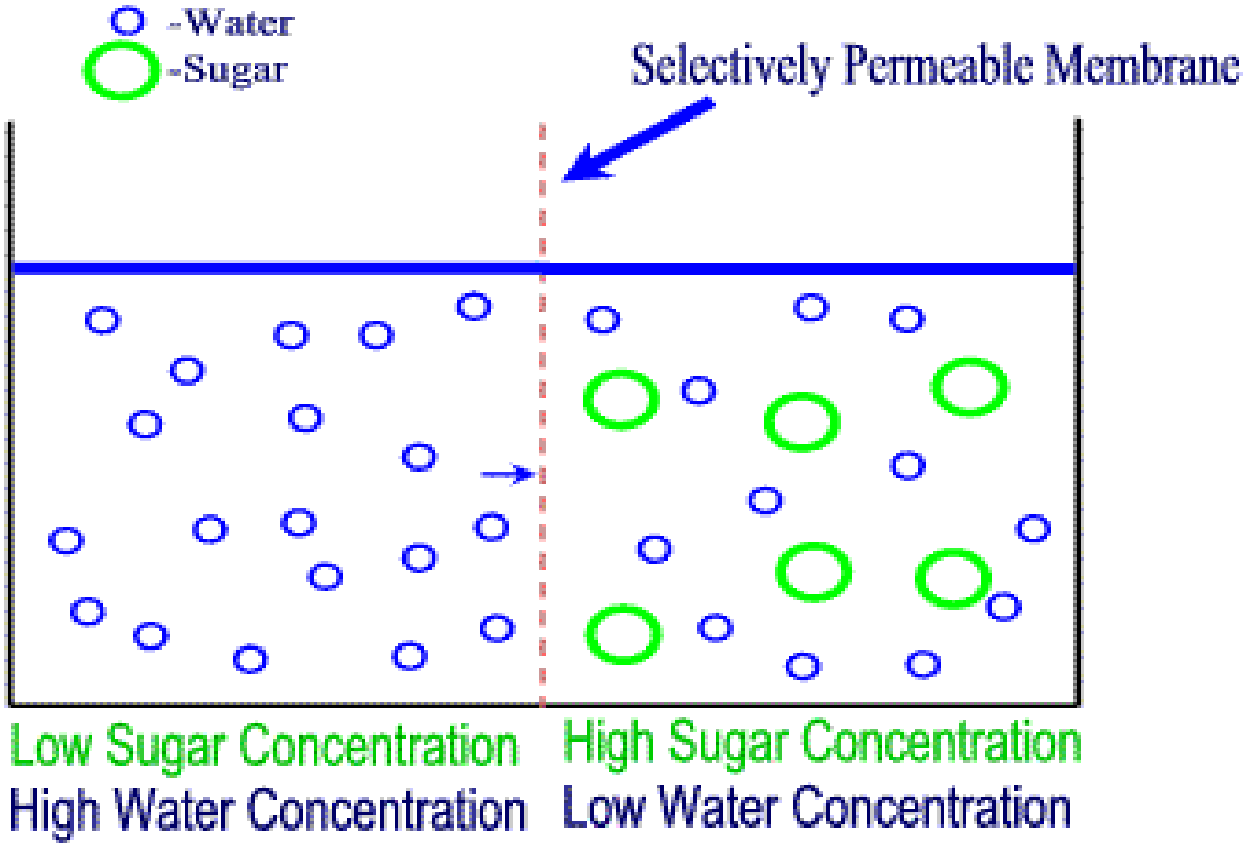
Glomerular membrane of kidney is a good example of filtration.



c) Osmosis:

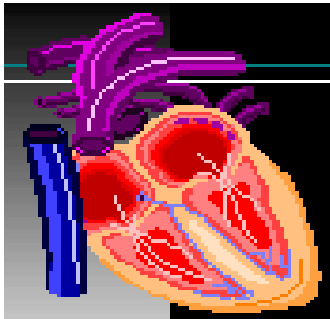
- Is a special case of diffusion.
- Here, a large molecule of drug like starch is dissolved in water. The starch molecule is too large to pass through the pores in the cell membrane, so it cannot diffuse from one side of the membrane to the other. The water molecules can do, pass through the membrane.
- Hence the membrane is said to be semi permeable, since it allows some molecules to pass through but not others.

Osmosis


-Water
-Sugar
Selectively Permeable Membrane
Low Sugar Concentration
High Water Concentration
High Sugar Concentration
Low Water Concentration

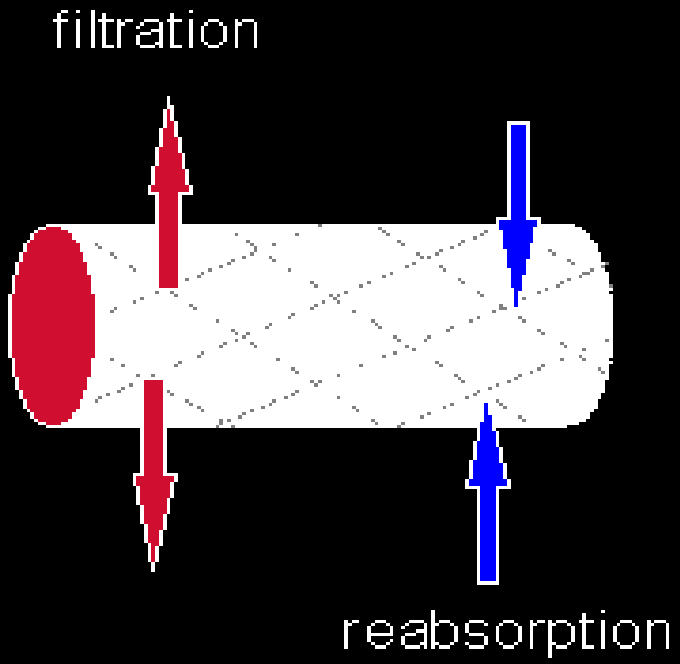
d) Bulk flow:

- It is the movement of drug molecules across the membrane by pores between capillaries endothelial cells.
- It is important in regulating the distribution of fluids between the plasma and interstitial fluid, that is important in maintain the blood pressure.

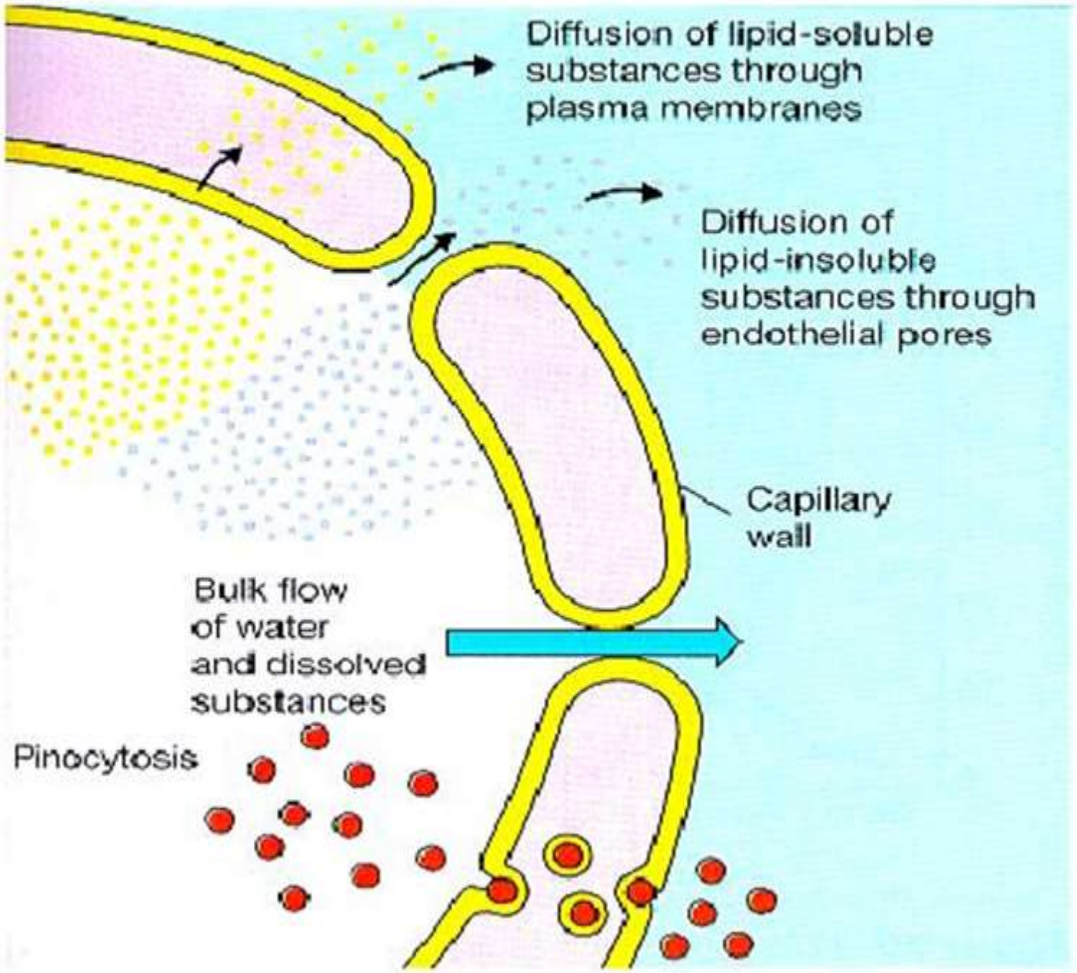


Capillaries: Bulk Flow

- Passive movement through **pores:**
  - water & solutes
- Balances the **extracellular fluid:**
  - plasma
  - interstitial fluid
- **Filtration** generally exceeds **reabsorption**



Capillaries



2) Specialized transport mechanism

- Specialized transport of drug across the cell membrane requires transport mechanisms or carrier protein. It involves various processes of mechanisms.
- In these mechanism drug forms a complex with the carrier proteins or transporters at the outer surface of the cell membrane and then transported across the cell membrane to the inner surface when the drug is released from the carrier complex.

a) Active transport mechanism

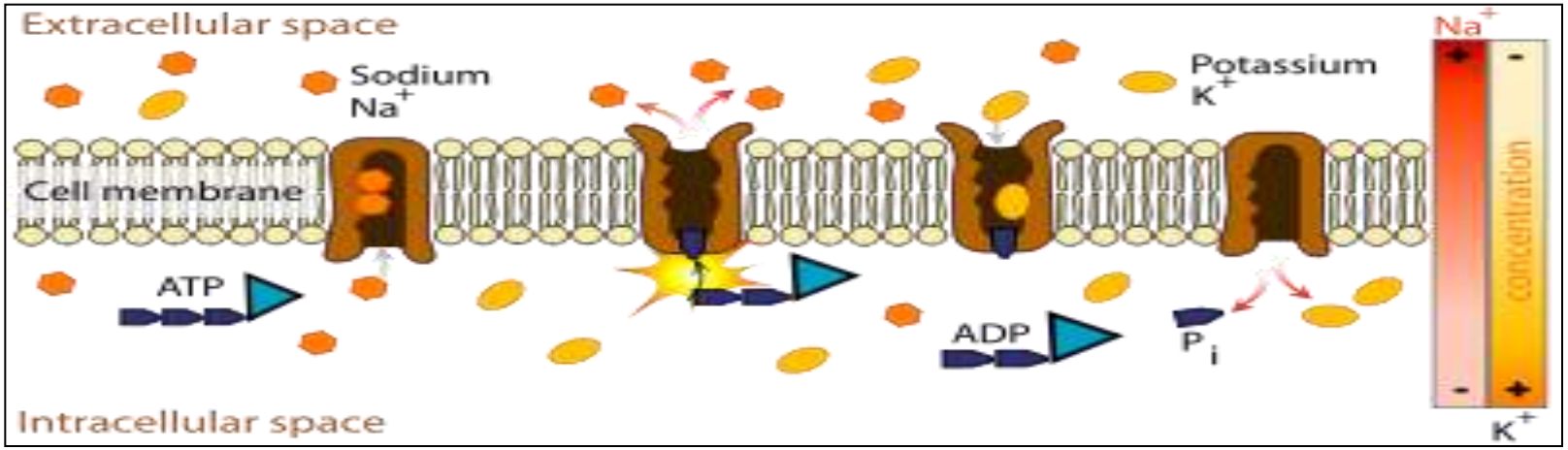
- In active transport, the drug molecule penetrates in the lipid bilayer membrane from lower concentration to the higher concentration of solutes against the concentration gradient with the expenditure of energy and with the help of special carrier proteins.
- This process has two types of energy dependent mechanisms.

i. Primary active transport

ii. Secondary active transport

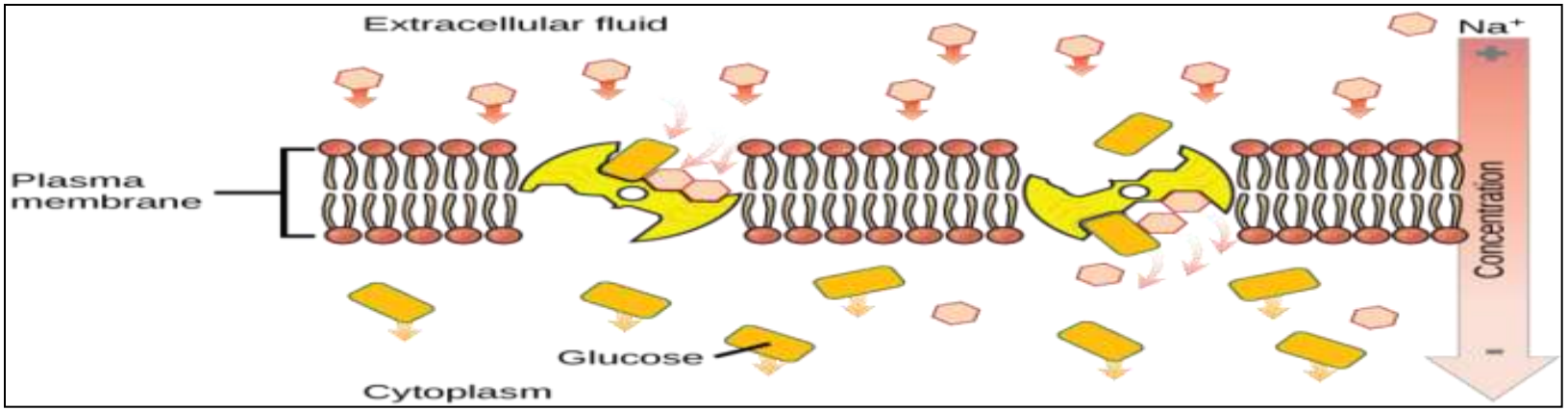
i. Primary active transport:

- Or direct active transport, directly uses energy to transport molecules across a membrane.
- The energy used in this type of active transport is ATP. The only substances transported by carriers that directly hydrolyze ATP. These include positively charged ions like Na^+, K^+, Ca^{++} or H^+.



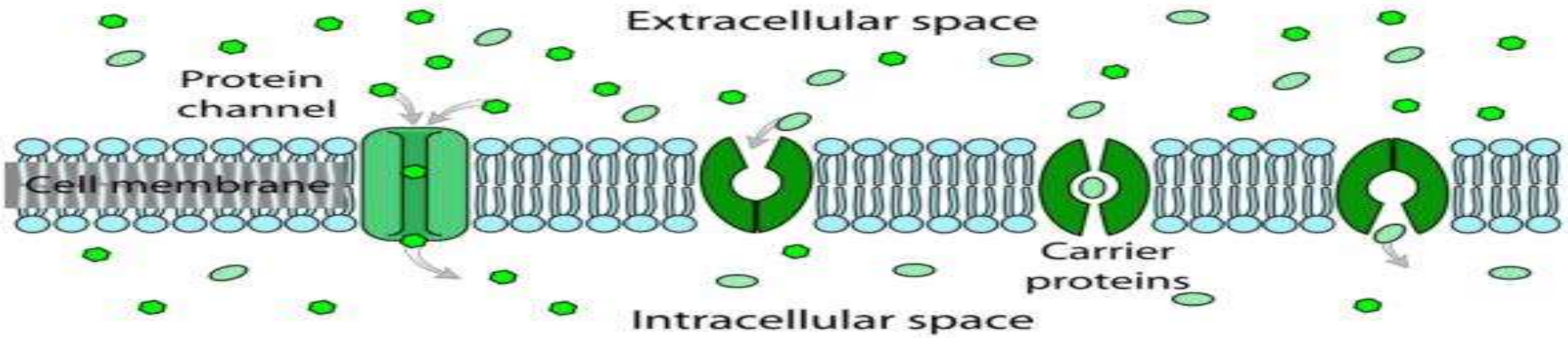
ii. Secondary active transport

- Or co-transport, electrochemical potential difference created by pumping ions out of the cell is used to transport molecules across a membrane but there is no direct coupling of ATP.
- Sodium-proton or Sodium-calcium co transport mechanism involved in this type of absorption mechanism.



b) Facilitated diffusion:

- It is a special form of carrier mediated transport in which the movement across cell membrane occurs along with the concentration gradient but with the help of special transporters or carrier proteins without the expenditure of energy.



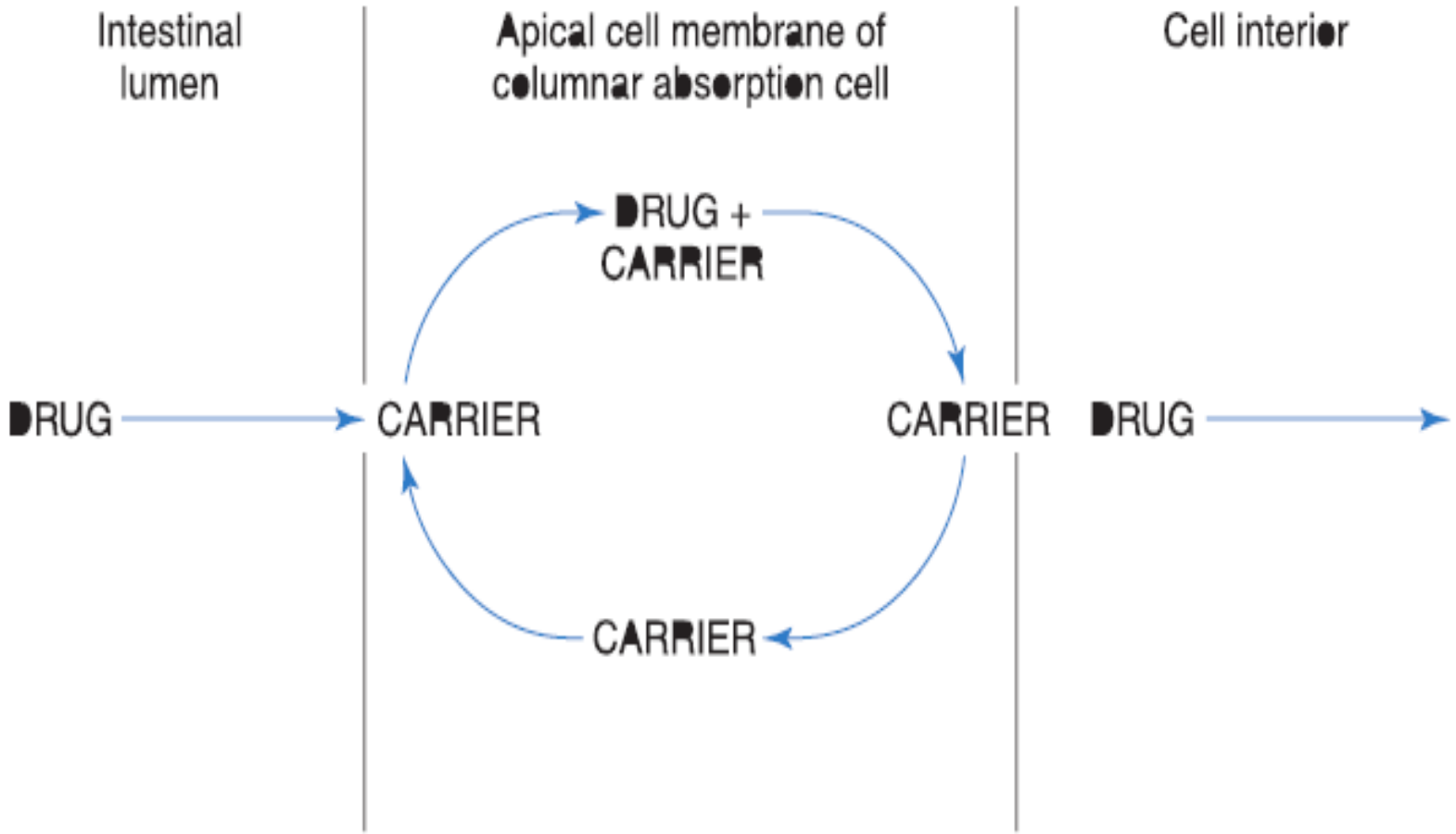


Fig. 19.11 • Diagrammatic representation of active transport of a drug across a cell membrane.

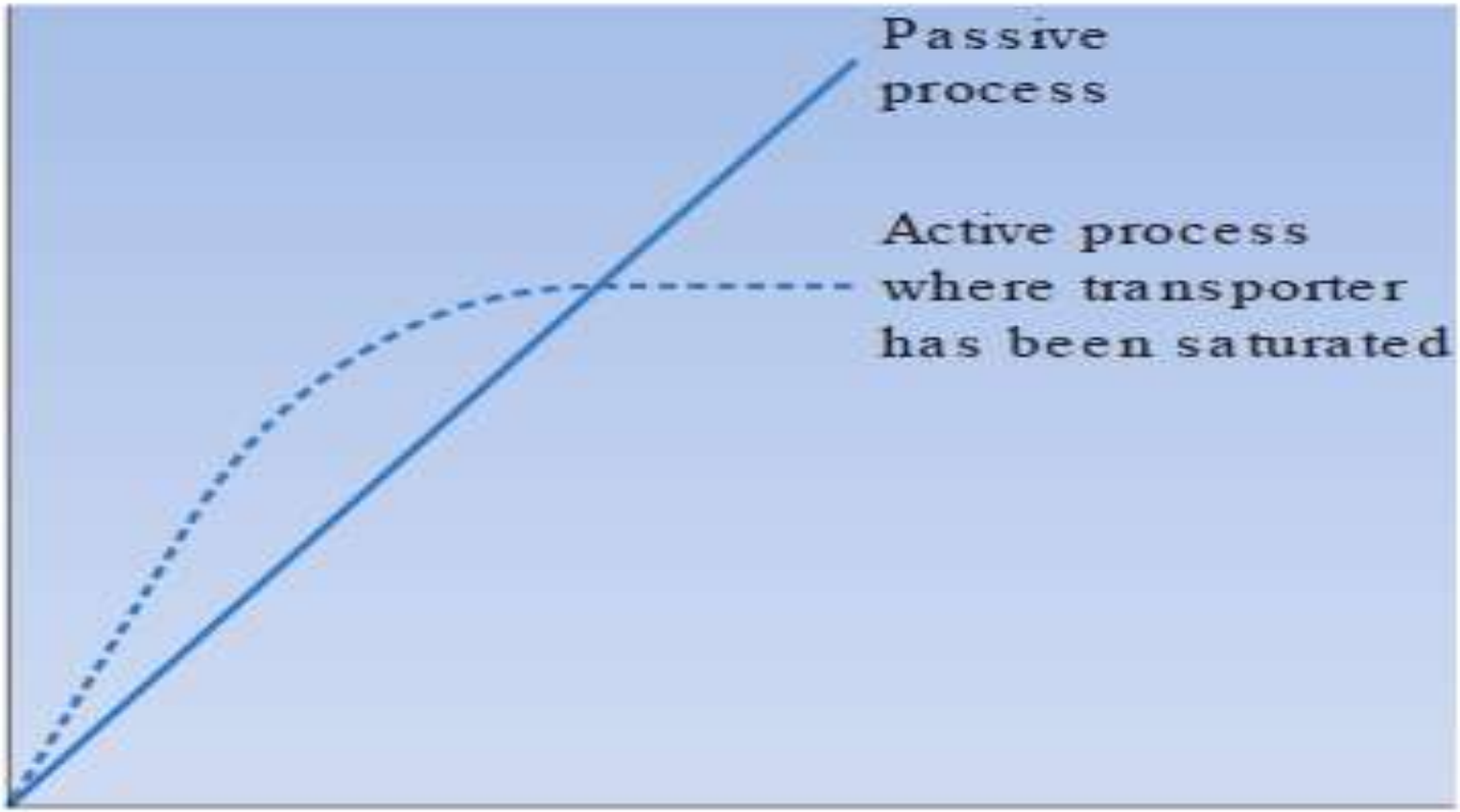


Fig. 19.12 • Relationship between rate of absorption and concentration at the absorption site for active and passive processes.

c) Endocytosis:

- Endocytosis is a process in which a substance gains entry into a cell by formation of intracellular vesicle by virtue of invagination of plasma membrane and membrane fusion takes place.

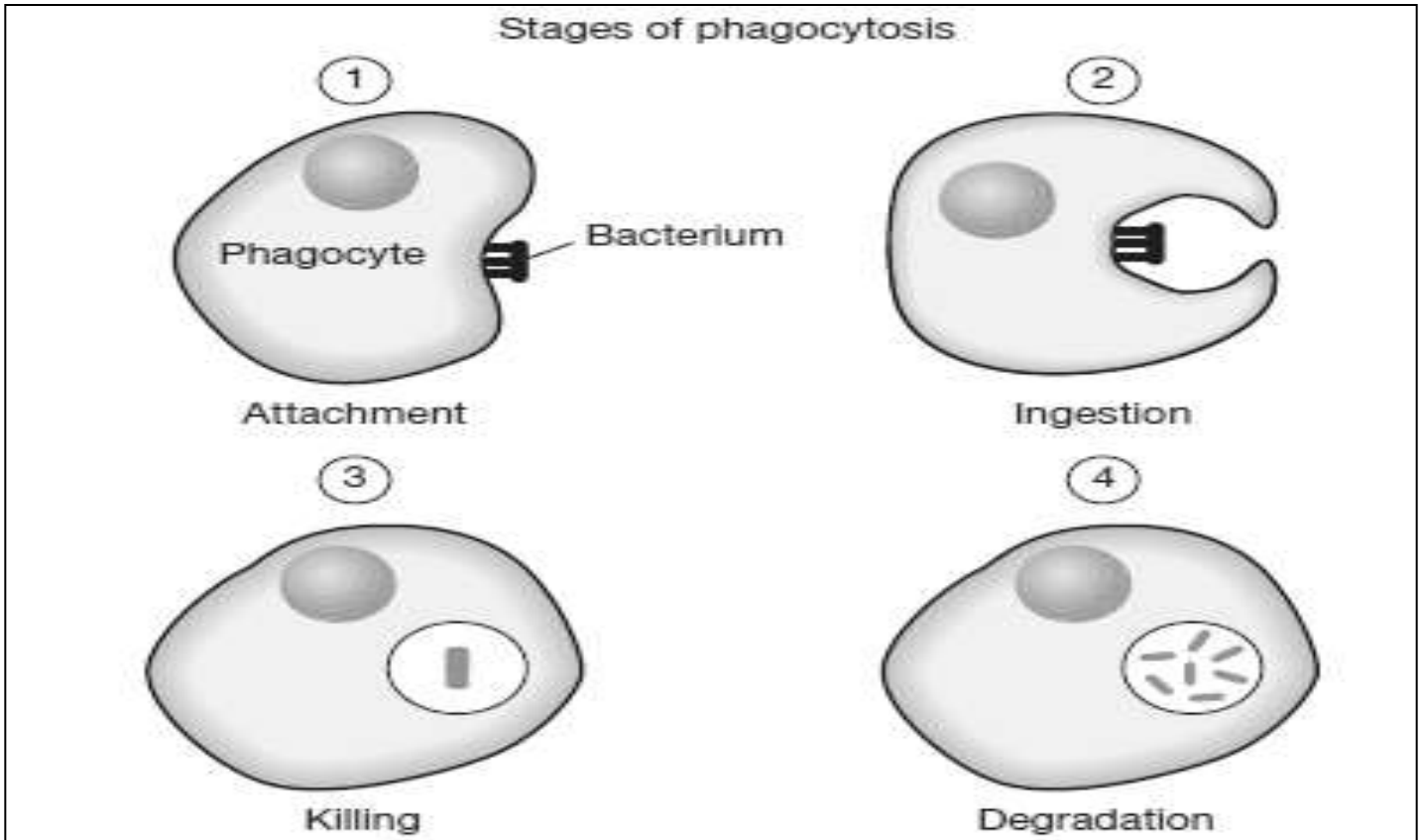
i. Phagocytosis

ii. Pinocytosis

iii. Receptor mediated endocytosis

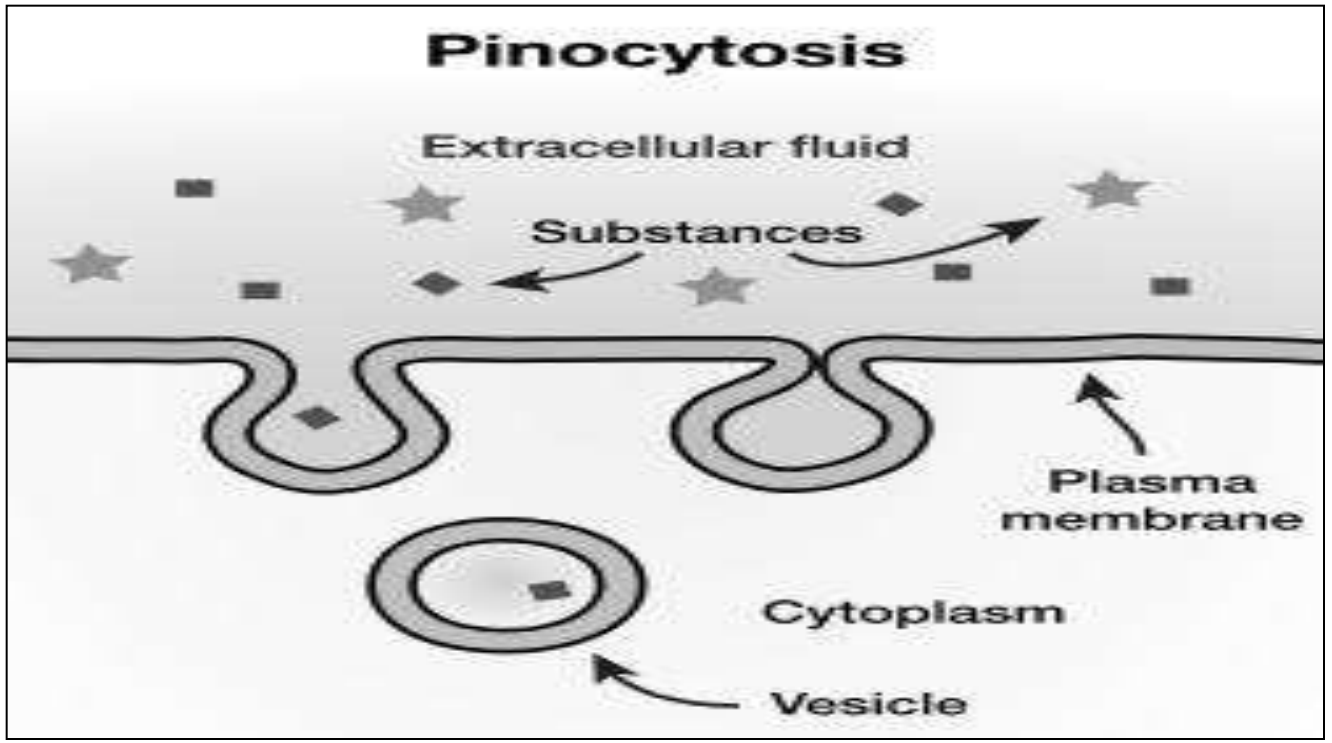
i. **Phagocytosis:**

- The cellular process of engulfing the solid particles e.g bacterium by vesicular internalization by the cell membrane itself to form the internal phagosome is known as phagocytosis.



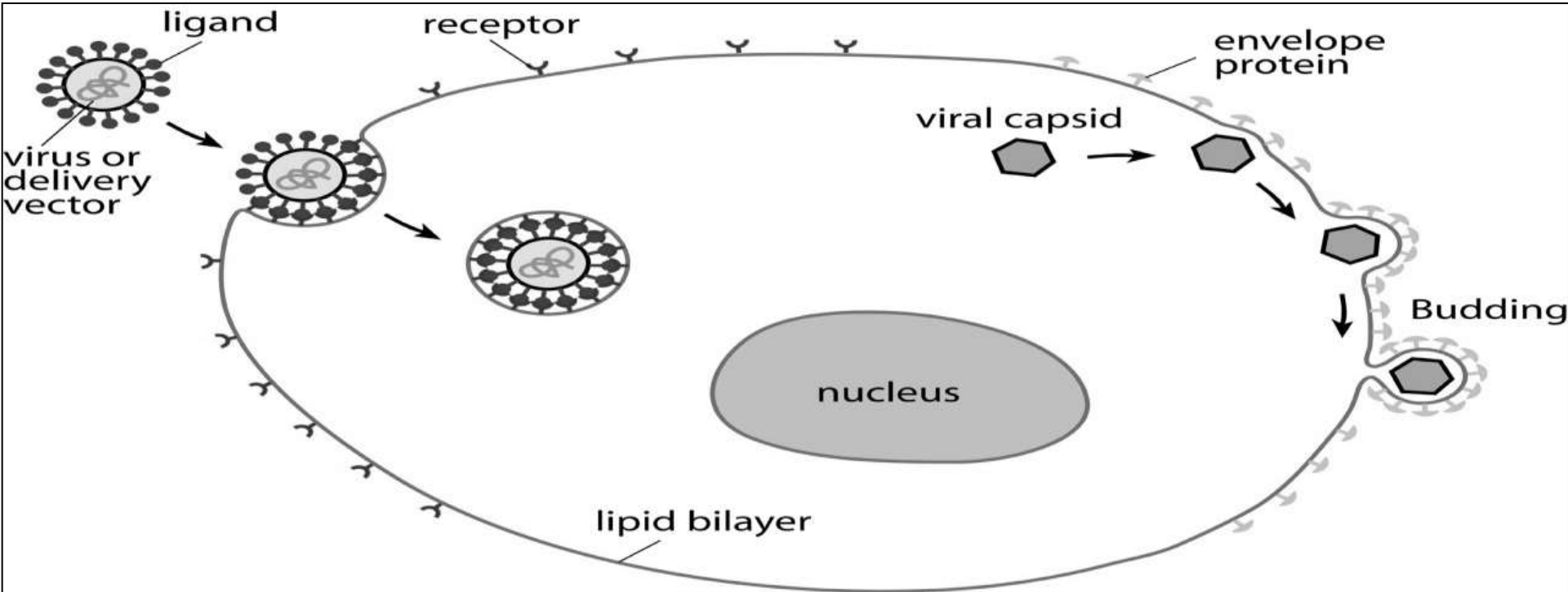
ii. **Pinocytosis:**

- The endocytosis in which small particle or liquid material is brought into the cell by forming an invagination or vesicle called lysozomes, is known as pinocytosis. This process requires a lot of energy in the form of ATP.



iii. Receptor-mediated endocytosis:

- Or called clathrin-dependent endocytosis, is a process by which cells internalize molecules (endocytosis) by the inward budding of plasma membrane vesicles containing proteins with receptor sites specific to the molecules being internalized.



d) Exocytosis:

- A process in which a substance removes from the cell by formation of extracellular vesicle by virtue of invagination of plasma membrane itself. Finally the vesicle is discharged with its contents into extracellular space.

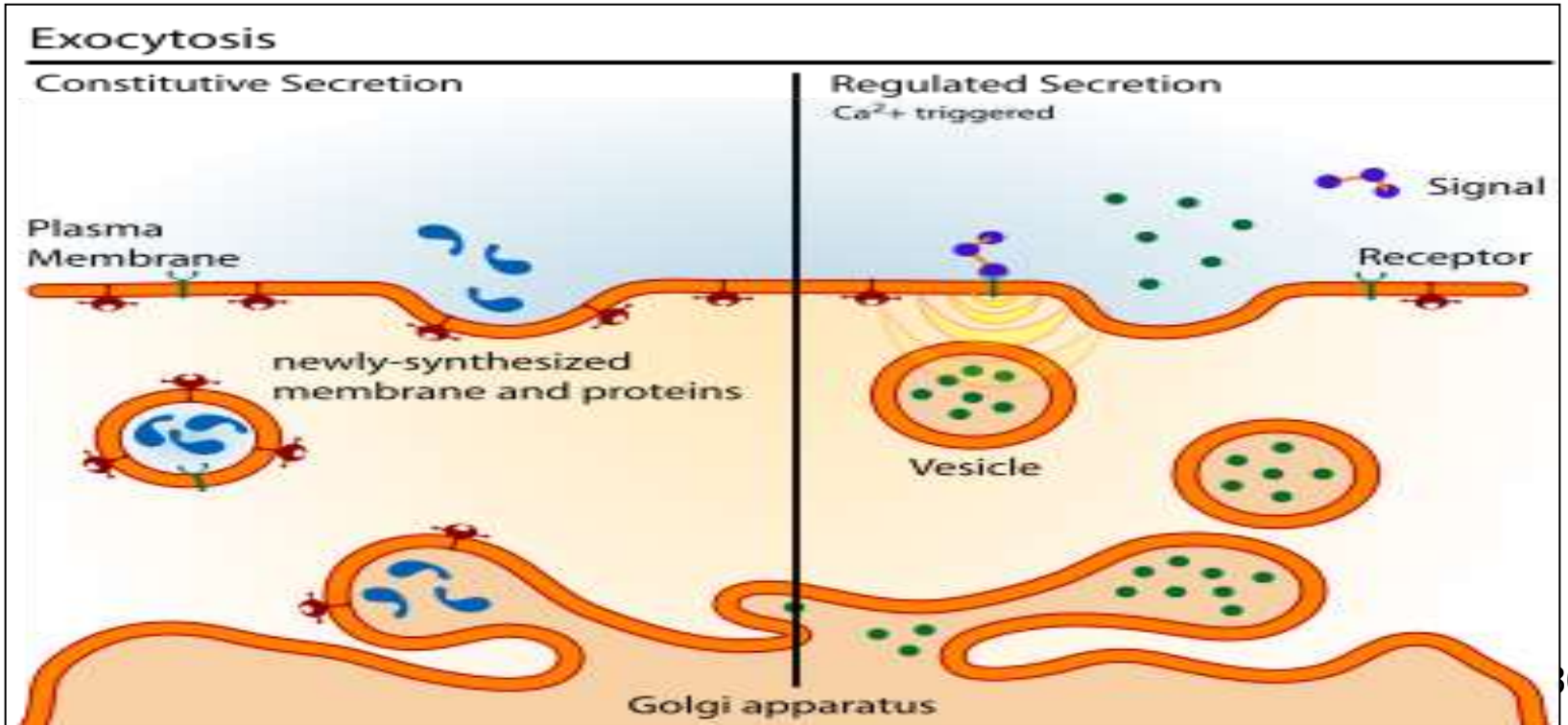


Table 19.2 Examples of transport mechanisms of commonly used drugs across the gastrointestinal absorptive epithelia

Route	Examples	Therapeutic class
Transcellular passive diffusion	Propranalol	β-blocker
	Testosterone	Steroid
	Ketoprofen	Non-steroidal anti-inflammatory
	Oestradiol	Sex hormone
	Naproxen	Non-steroidal anti-inflammatory
Paracellular	Cimetidine	H_2 antagonist
	Loperamide	Antidiarrhoeal
	Atenolol	β-blocker
	Mannitol	Sugar used as paracellular marker
	Tiludronate	Bisphosphonate
Carrier mediated	Cefalexin	Antibacterial
	Captopril	ACE inhibitor
	Levodopa	Dopaminergic
	Foscarnet	Antiviral
Transcellular diffusion subject to P-glycoprotein efflux	Ciclosporin	Immunosuppressant
	Nifedipine	Calcium channel blocker
	Verapamil	Calcium channel blocker
	Paclitaxel	Anticancer
	Digoxin	Cardiac glycoside