BIOPHARMACEUTICS

Presented By

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INTRODUCTION

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

Bioavailability is defined as the rate and extent (amount) of drug absorption. Any alteration in the drug's bioavailability is reflected in its pharmacological effects.

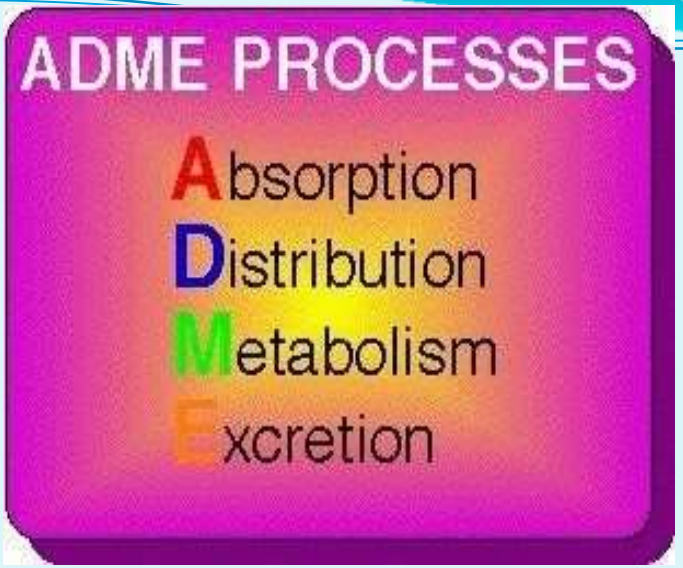
The process of movement of drug from its site of administration to systemic circulation is called as **absorption.**

The movement of drug between one compartment and the other (generally blood and the extravascular tissues) is referred to as **drug distribution**.

Elimination is defined as the process that tends to remove the drug from the body and terminate its action. Elimination occurs by two processes—**biotransformation** (metabolism), which usually inactivates the drug, and **excretion** which is responsible for the exit of drug/metabolites from the body.

Pharmacokinetics is defined as the study of time course of drug ADME and their relationship with its therapeutic and toxic effects of the drug

The use of pharmacokinetic principles in optimising the drug dosage to suit individual patient needs and achieving maximum therapeutic utility is called as **clinical pharmacokinetics.**

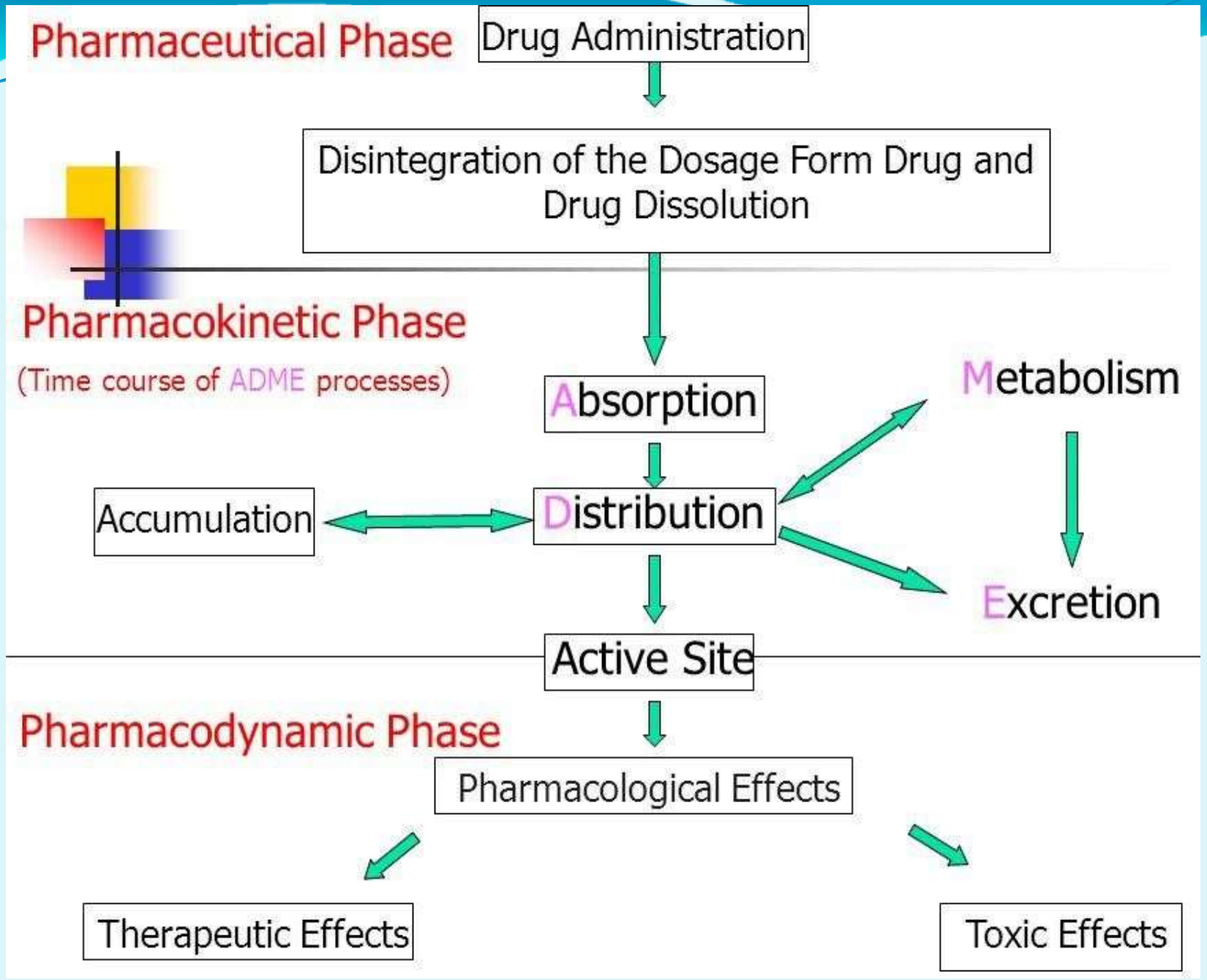


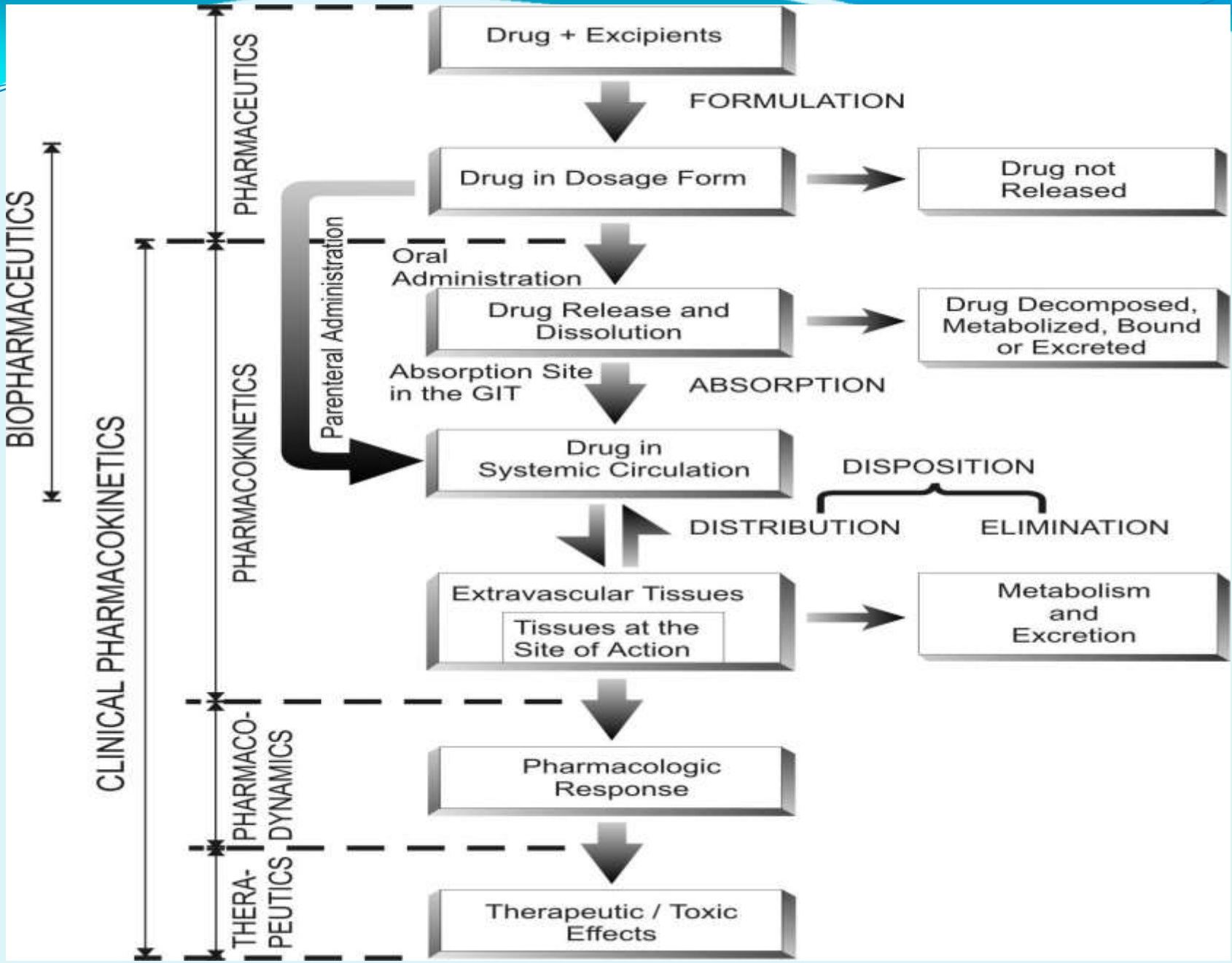
Absorption :Process by which drug enters the body.

Distribution :Dispersion of drugs throughout the fluids and tissues of the body.

Metabolism : Irreversible transformation of parent drug compounds into daughter metabolites.

Excretion :Elimination of drug metabolites from the body.

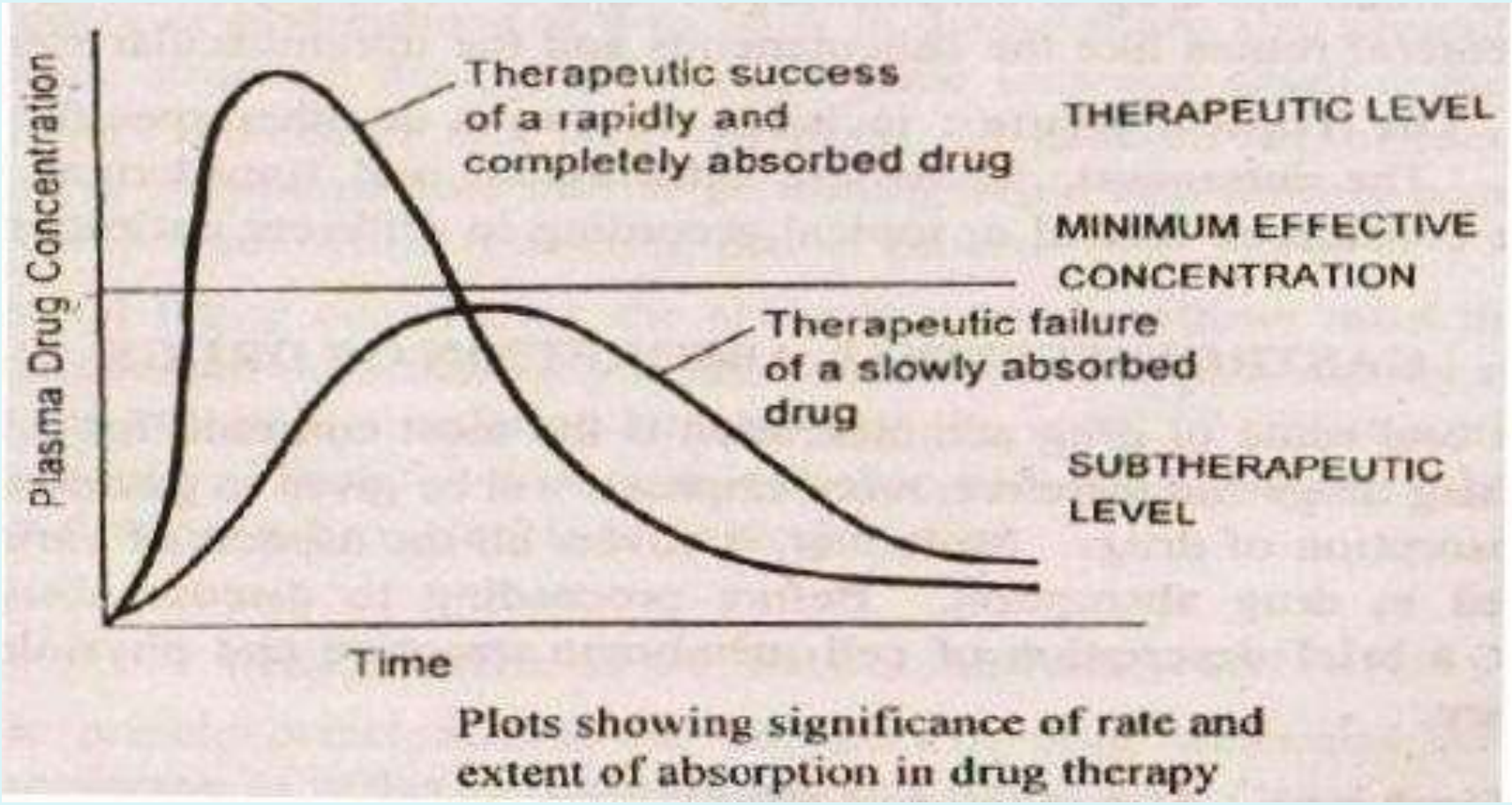

Pharmaceutical Phase
Drug Administration
Disintegration of the Dosage Form Drug and Drug Dissolution
Pharmacokinetic Phase
(Time course of ADME processes)
Absorption
Metabolism
Accumulation
Distribution
Excretion
Active Site
Pharmacodynamic Phase
Pharmacological Effects
Therapeutic Effects
Toxic Effects



Schematic representation of the processes involved in drug therapeutics

ABSORPTION OF DRUG

"The process of movement of drug from its site of administration to systemic circulation" is called as **absorption.**



Plots showing significance of rate and extent of absorption in drug therapy

Drug Absorption

- Definition:

  The process of movement of unchanged drug from the site of administration to systemic circulation.

- There always exist a correlation between the plasma concentration of a drug and the therapeutic response.

- So **absorption** can also be defined as the process of movement of unchanged drug from the site of administration to the site of measurement i.e. **Plasma.**

MECHANISMS OF DRUG ABSORPTION

There three broad categories are

1. **Transcellular / intracellular transport**
   - **A. Passive Transport Processes**
     - **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**

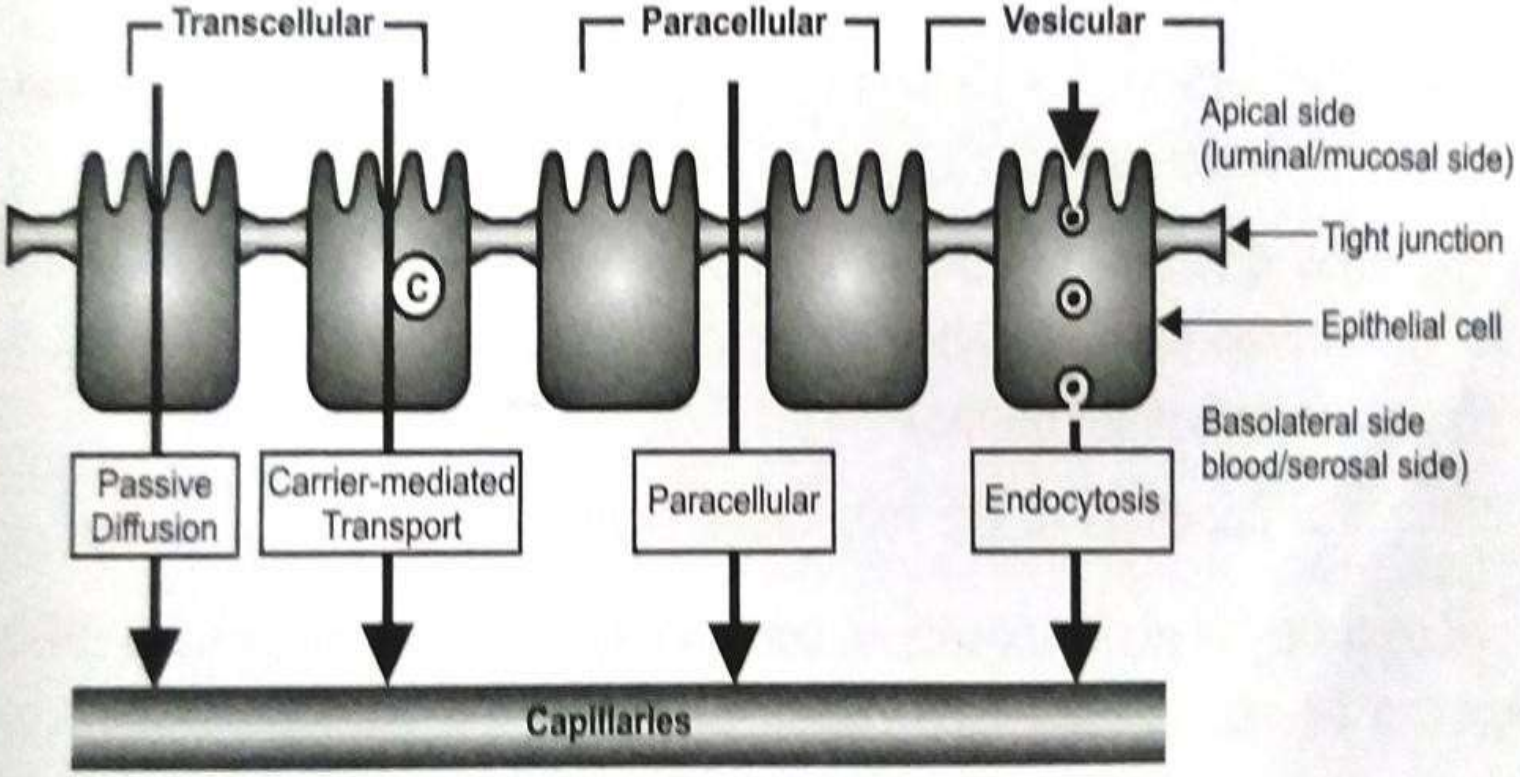


Fig. 2.3 Illustrative comparison of transcellular, paracellular and vesicular transport mechanisms.

The three broad categories are

1. **Transcellular/intracellular transport :** is defined as the passage of drugs across the GI epithelium. 3 steps involved
   - Permeation of GI epithelial cell membrane
   - Movement across the intracellular space (cytosol).
   - Permeation of the lateral or basolateral membrane.

The various transcellular transport processes involved in drug absorption are –

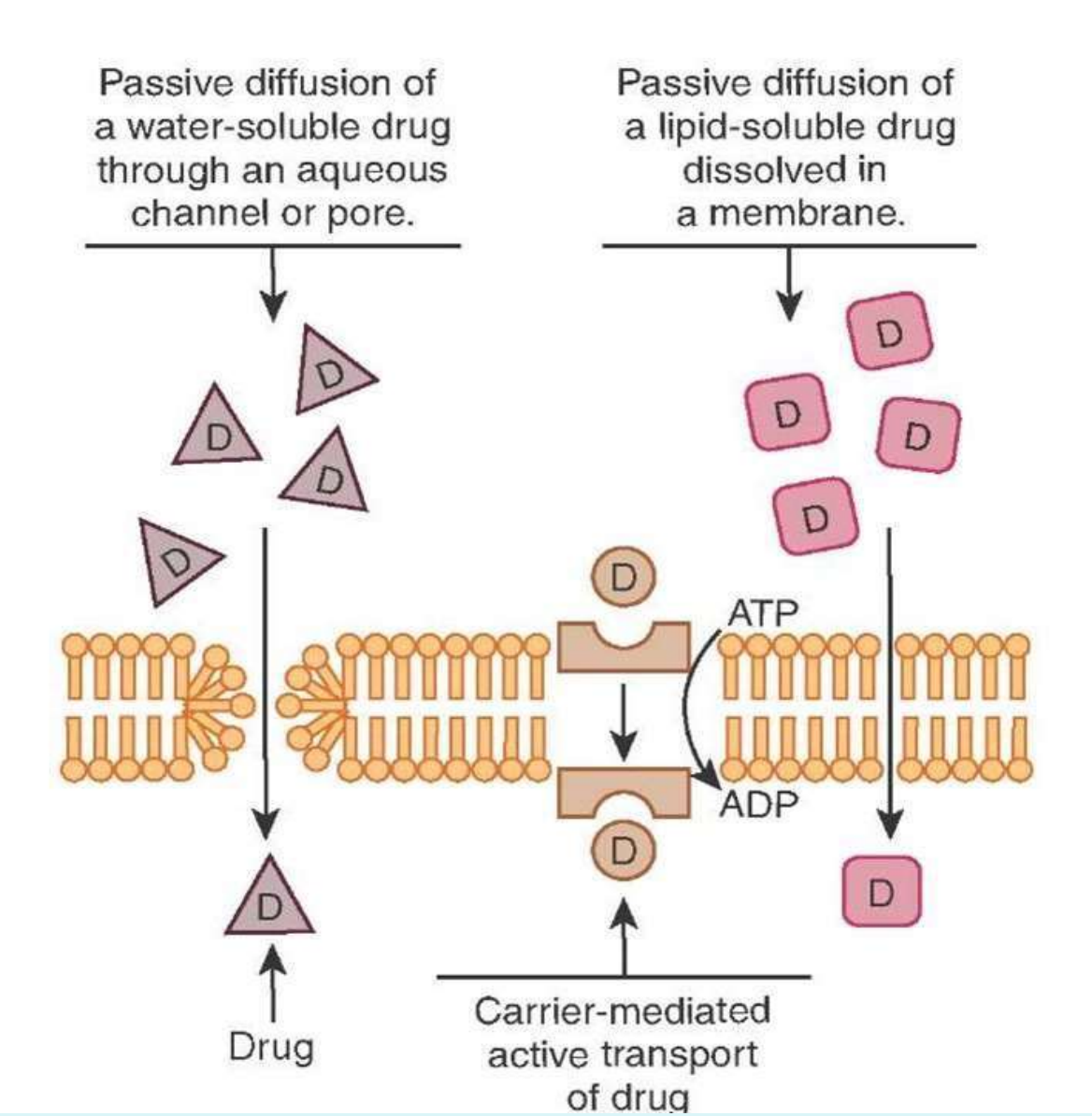
A.Passive Transport Processes –Not require energy Further classified into following types –

- Passive diffusion.
- Pore transport.
- Ion-pair transport.
- Facilitated- or mediated-diffusion.

Passive Diffusion

- Also called as Non-ionic diffusion.
- Major process for absorption of more than 90% of the drugs.
- Driving force: concentration or electrochemical gradient.
- It is defined as the difference in the drug concentration on either side of the membrane.

Drug movement is a result of the kinetic energy of molecules. Since no energy source is required, the process is called as passive diffusion.



•no energy source required.

•No carrier is needed.

•Water soluble drug (ionized or Polar): readily absorbed via aqueous channels or pores in the cell membrane.

•Lipid soluble drug (non-ionized or non polar): readily absorbed via cell membrane itself.

•Depends on lipid solubility.

•Depends on pka of drug-pH of medium.

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

Mathematically

$$\frac{dQ}{dt} = \frac{D\,A\,K_{m/w}\,(C_{GIT} - C)}{h}$$

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

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

A = surface area of the absorbing membrane for drug diffusion (area)

Km/w = partition coefficient of the drug between membrane and the aqueous GI fluids

(CGIT – C) = difference in the concentration of drug in GI fluid & the plasma, called as the concentration gradient.

h = thickness of the membrane (length)

Certain characteristics of passive diffusion:

- Downhill transport.
- Process is energy independent and non saturable.
- Greater the surface area & lesser the thickness of the membrane= faster the diffusion & more rapid the rate of drug absorption from intestine than from stomach.
- Equlibrium is attained when the concentration on either side of the membrane becomes equal.
- Greater the membrane/ water partition coefficient of drug = faster the absorption

Certain characteristics of passive diffusion contd..

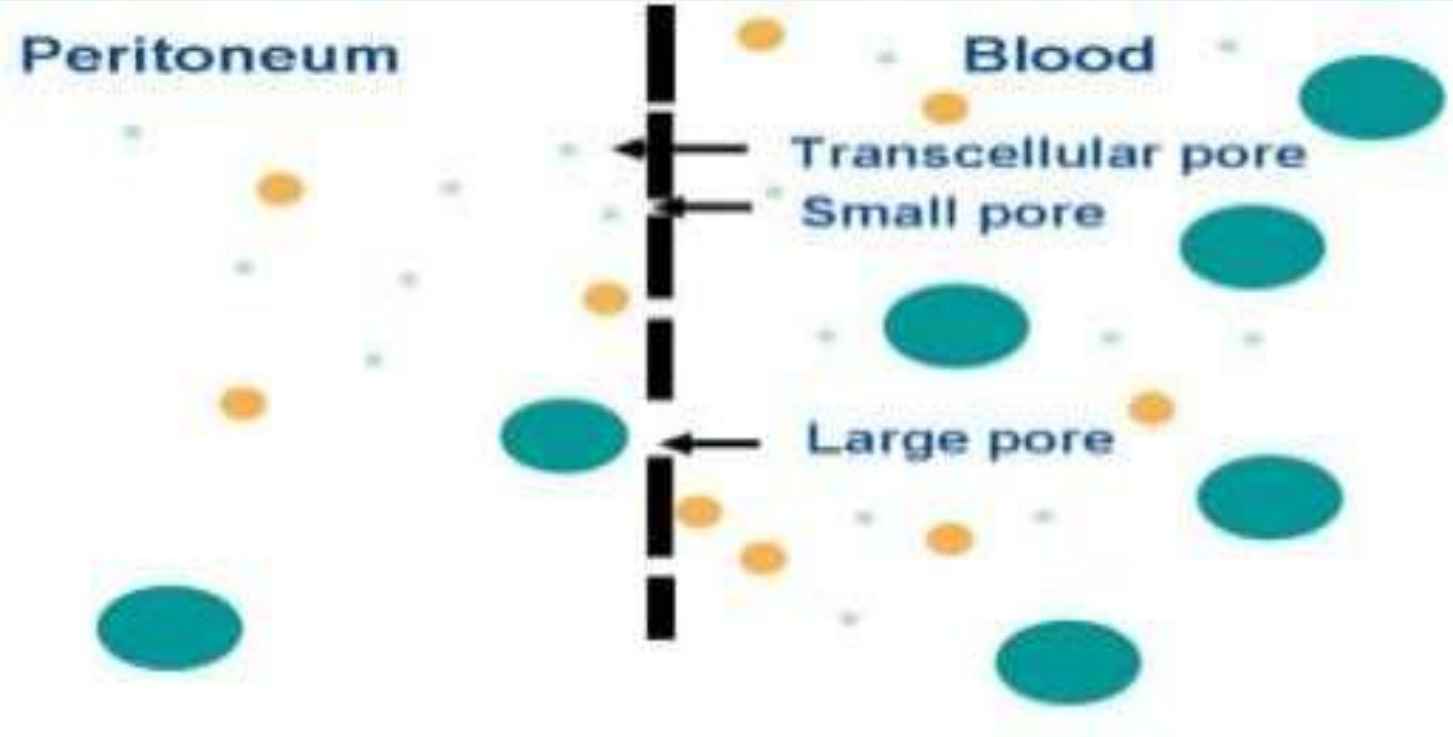
- Only non-ionised form is absorbable. The rate of transfer of unionised species is 3 -4 times the rate for ionised drugs.

[Example- Degree of Ionization (Polarity)
Lipid Soluble= Non-ionized molecule (NaCl)
Hydrophilic= Ionized molecules (Na+, Cl-)
So,
The more lipid soluble of drug----More absorption
The more water soluble of drug---- Less absorption

Drugs which are lipophilic easily cross membrane as compare to hydrophilic drug. This is the major source of variation in drug diffusion or absorption]

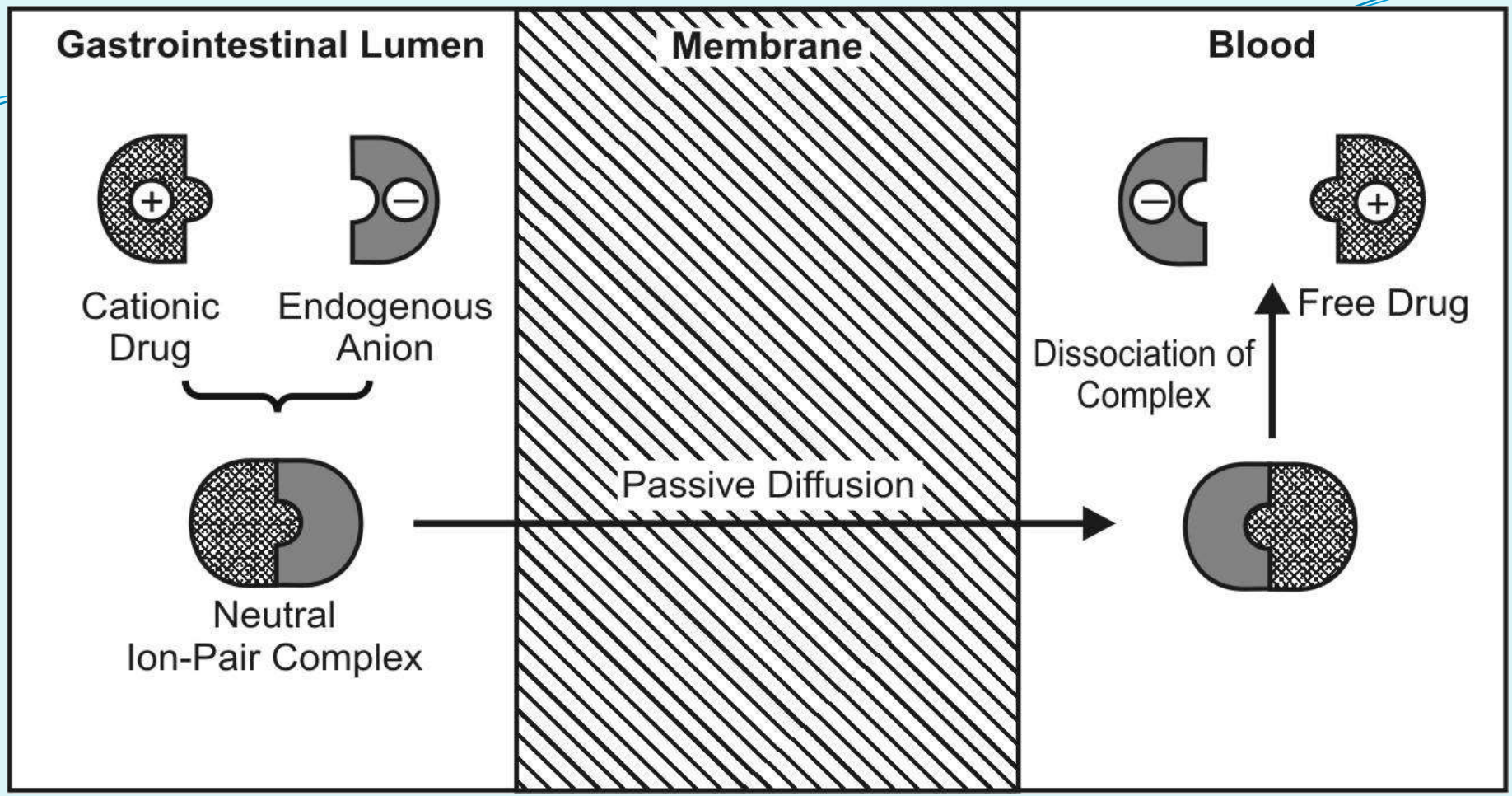
Pore Transport

- It is also called as **convective transport**, **bulk flow** or **filtration**.
- The driving force is hydrostatic pressure or the osmotic differences across the membrane.
- The process is important in the absorption of low molecular weight (less than 100), generally water-soluble drugs through narrow, aqueous-filled channels ex: urea, water and sugars.
- Chain-like or linear compounds of molecular weight up to 400 Daltons can be absorbed by filtration. For **example**, the straight-**chain** alkanes.
- Drug permeation through water-filled channels is importance in renal excretion, removal of drug from the cerebrospinal fluid and entry of drugs into the liver.


Peritoneum
Blood
Transcellular pore
Small pore
Large pore

Ion-Pair Transport

- Absorption of drugs like quaternary ammonium compounds (**Examples** are benzalkonium chloride, benzethonium chloride) and sulphonic acids (**sulfonic acid**), which ionise under all pH conditions, is ion-pair transport.
- **Despite their low o/w partition coefficient values, such agents penetrate the membrane by forming reversible neutral complexes with endogenous ions of the GIT like mucin.**
- Such neutral complexes have both the required lipophilicity as well as aqueous solubility for passive diffusion. Such a phenomenon is called as **ion-pair transport**.
- Propranolol, a basic drug that forms an ion pair with oleic acid, is absorbed by this mechanism.

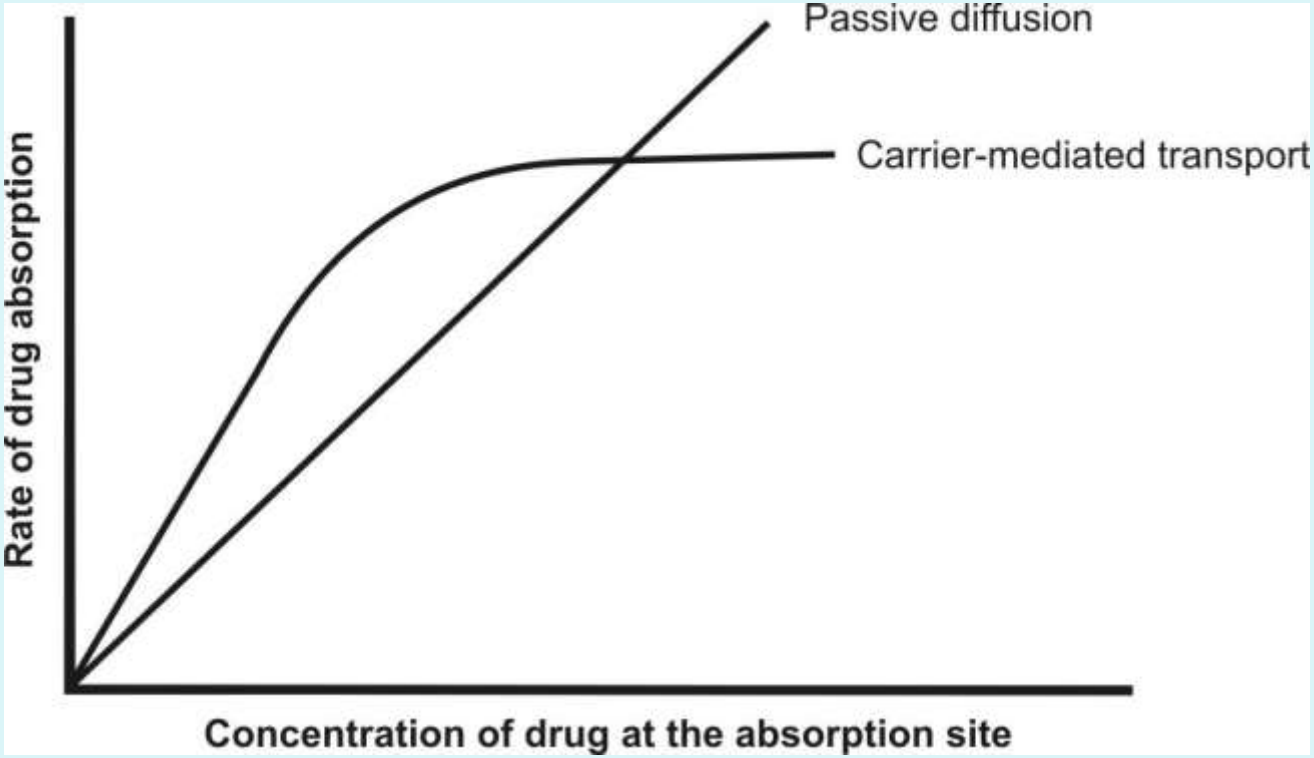


Ion-pair transport of a cationic drug

Carrier-Mediated Transport

- Some polar drugs cross the membrane more readily than can be predicted from their concentration gradient and partition coefficient values. Like monosaccharides, amino acids and vitamins will be poorly absorbed.
- The mechanism is involved is *carrier* that binds reversibly or non-covalently with the solute molecules to be transported. This carrier-solute complex traverses across the membrane to the other side where it dissociates and discharges the solute molecule.
- The carrier then returns to its original site to complete the cycle by accepting a fresh molecule of solute. Carriers in membranes are proteins (transport proteins) and may be an enzyme or some other component of the membrane.

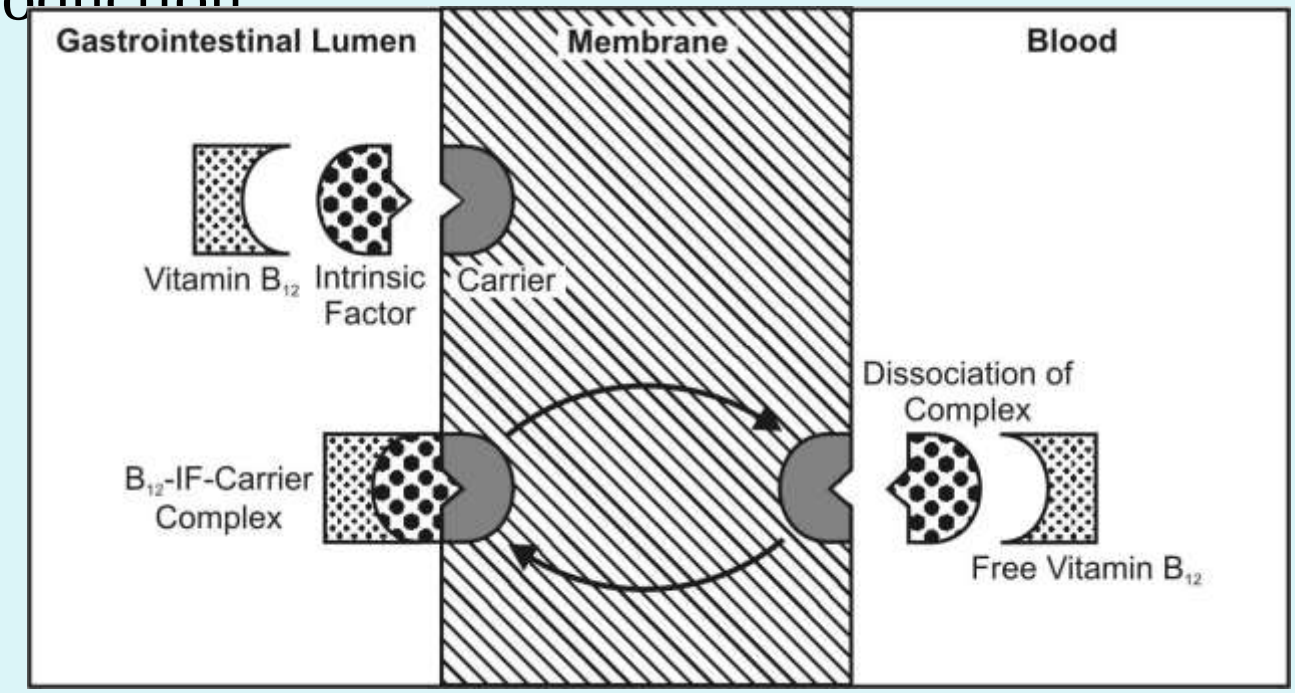
- Since the system is structure-specific, drugs having structure similar to essential nutrients, called as *false nutrients*, are absorbed by the same carriersystem.



Drug absorbed by passive diffusion, the rate of absorption increases linearly with the concentration but in case of carrier-mediated processes, the drug absorption increases linearly with concentration until the carriers become saturated after which it becomes curvilinear and approach a constant value at higher doses.

Facilitated Diffusion

- It is a carrier-mediated transport system that operates down the concentration gradient (***downhill transport***) but at a much a faster rate than can be accounted by simple passive diffusion. The **driving force is concentration gradient** (hence a passive process). Since **no energy expenditure** is involved, the process is not inhibited by metabolic poisons that interfere with energy production.



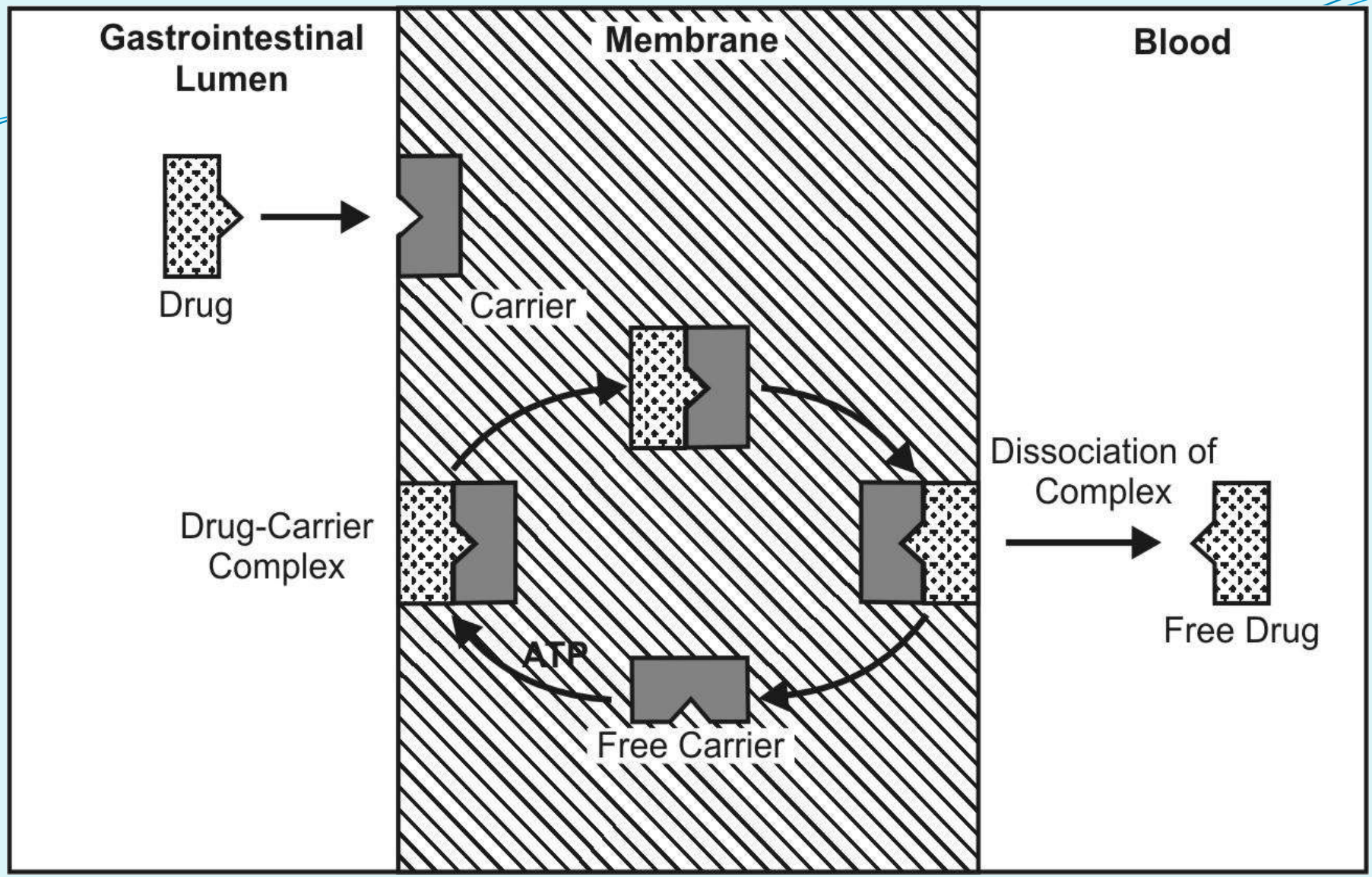
Facilitated diffusion of vitamin B12

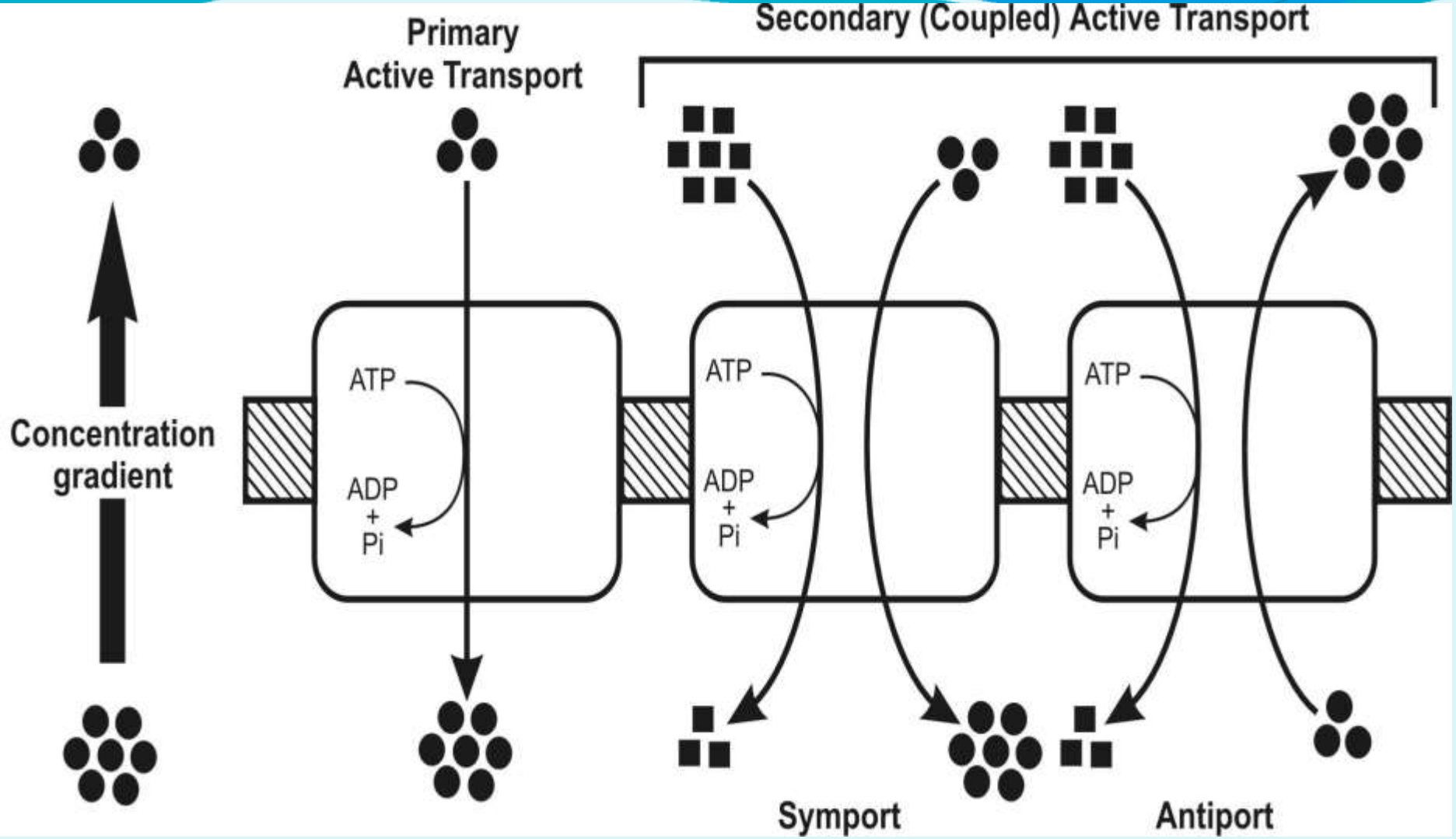
B. Active Transport Processes – This transport process requires energy from ATP to move drug molecules from extracellular to intracellular milieu. These are of two types –

- Primary active transport.
- Secondary active transport – this process is further subdivided into two –
  - Symport (co-transport).
  - Antiport (counter-transport).

Active Transport

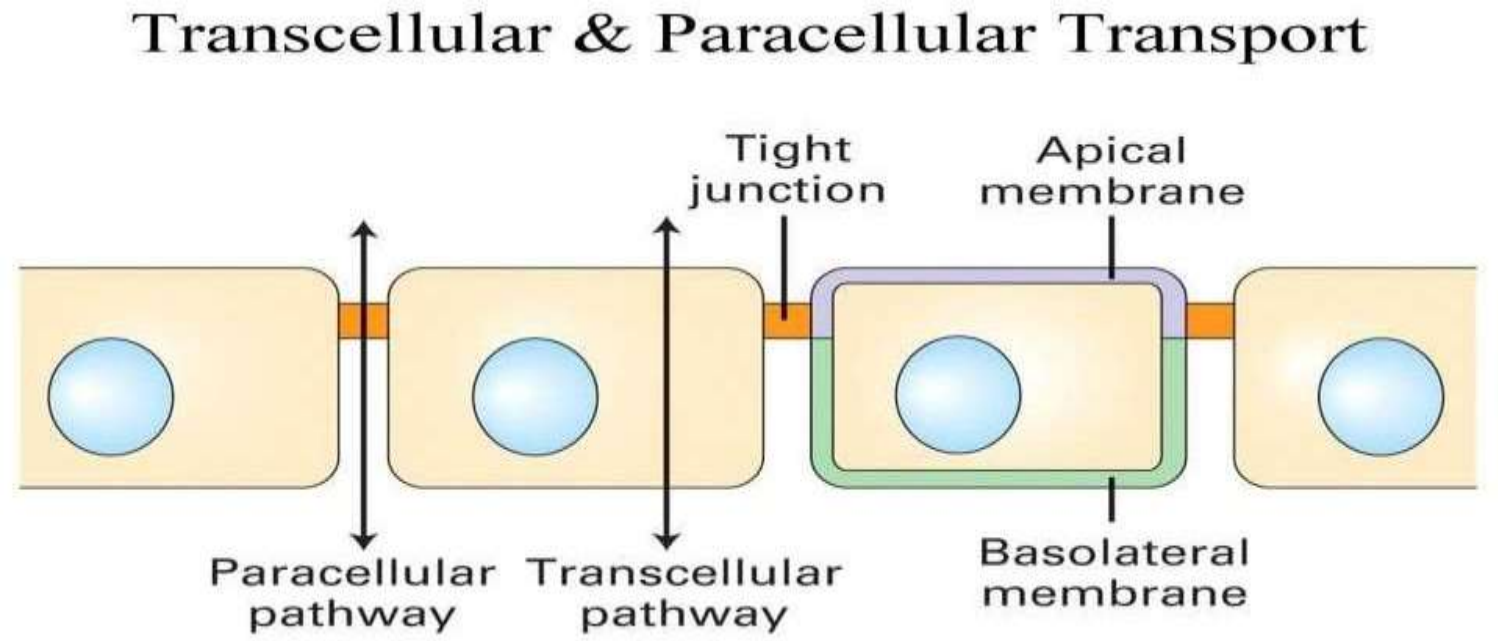
- This transport mechanism requires energy in the form ATP. Active transport mechanisms are further subdivided into -
- **Primary active transport** – In this process, there is direct ATP requirement. Moreover, the process transfers only one ion or molecule and in only one direction, and hence called as uniporter e.g. absorption of glucose.
- ***Secondary active transport*** – In these processes, there is no direct requirement of ATP i.e. it takes advantage of previously existing concentration gradient. The energy required in transporting an ion aids transport of another ion or molecule (co-transport or coupled transport) either in the same direction or in the opposite direction. Accordingly this process is further subdivided into –
  - *symport (co-transport)* – involves movement of both molecules in the same direction e.g. *Na^+-glucose symporter*
  - *Antiport (counter-transport)* – involves movement of molecules in the opposite direction e.g. H^+ ions using the Na^+ gradient in the kidneys.


Gastrointestinal Lumen
Membrane
Blood
Drug
Carrier
Drug-Carrier Complex
Dissociation of Complex
Free Drug
ATP
Free Carrier


Primary
Active Transport
Secondary (Coupled) Active Transport
Concentration
gradient
ATP
ADP
+
Pi
ATP
ADP
+
Pi
ATP
ADP
+
Pi
Symport
Antiport

2. *Paracellular/Intercellular Transport* – *is defined as the tra_n_sport of drugs through the jun_ctions between the GI epithelial cells*. This pathway is of minor importance in drug absorption. The two paracellular transport mechanisms involved in drug absorption are–

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

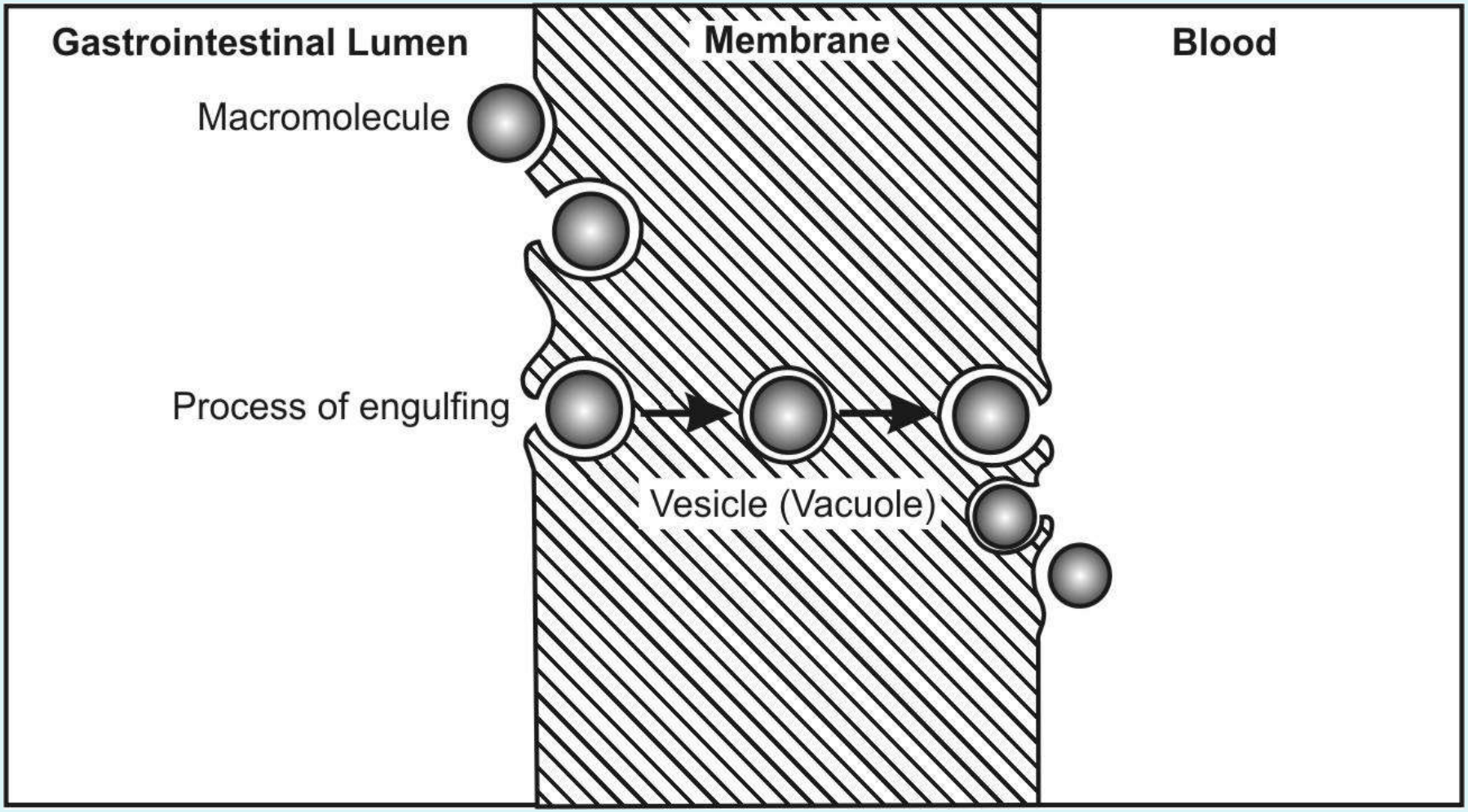

Transcellular & Paracellular Transport
Tight junction
Apical membrane
Paracellular pathway
Transcellular pathway
Basolateral membrane

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

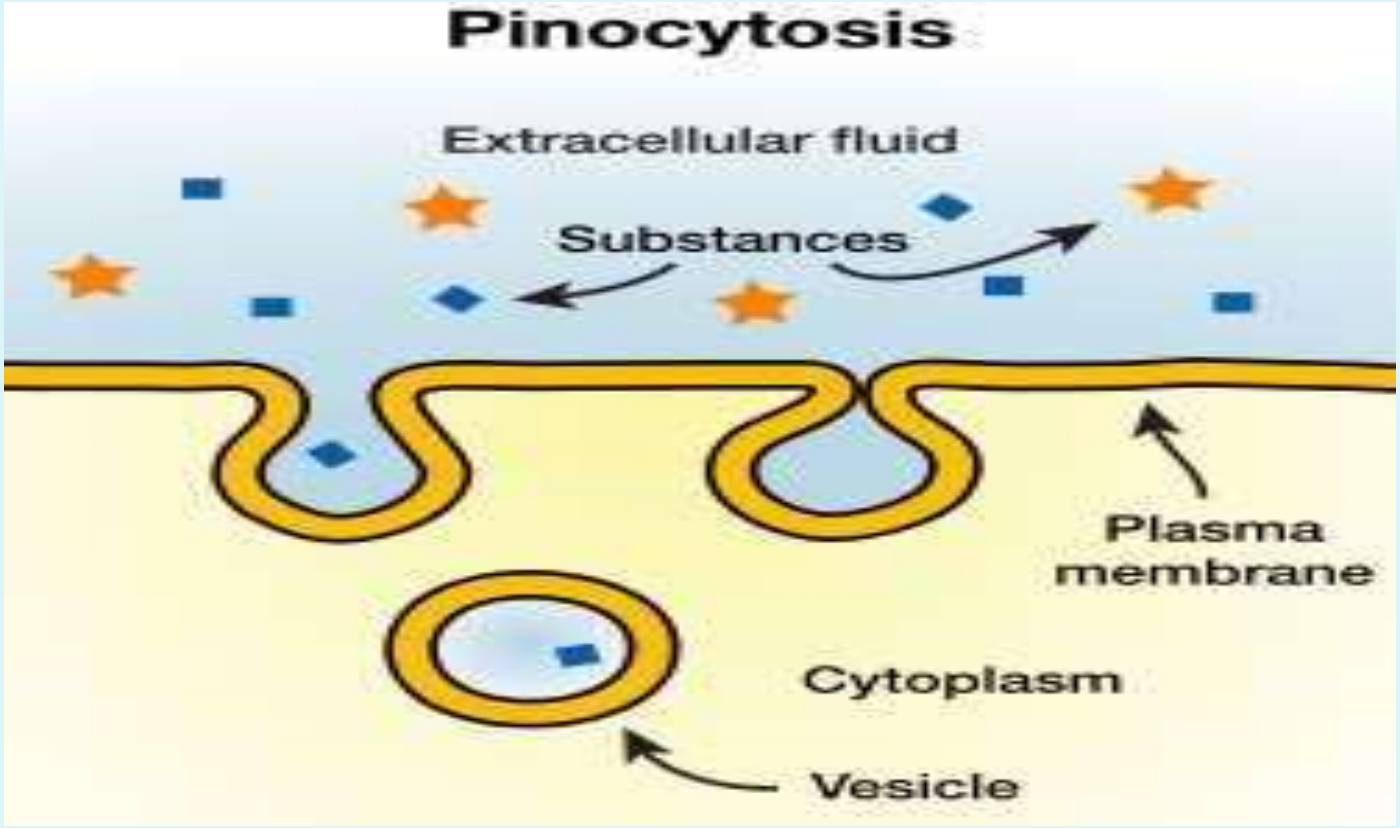
Like active transport, these are also energy dependent processes but involve transport of substances within vesicles into a cell. Since the mechanism involves transport across the cell membrane, the process can also be classified as transcellular. Vesicular transport of drugs can be classed into twocategories –

- Pinocytosis.
- Phagocytosis.

- This phenomenon is responsible for the cellular uptake of macromolecular nutrients like fats and starch, oil soluble vitamins like A, D, E and K, water soluble vitamin like B_{12} and drugs such as insulin. Another significance of such a process is that the drug is absorbed into the lymphatic circulation thereby bypassing first-pass hepatic metabolism.
- Endocytosis includes two types of processes:
- **Phagocytosis** (*cell eating*)**:** adsorptive uptake of solid particulates, and
- **Pinocytosis** (*cell drinking*)**:** uptake of fluid solute.


Gastrointestinal Lumen
Membrane
Blood
Macromolecule
Process of engulfing
Vesicle (Vacuole)

- **Pinocytosis (cell drinking):**
  - Uptake of fluid solute.
  - Orally administered Sabin Polio vaccine, lagre protein molecules, botulism toxin, oil, soluble vitamins etc absorbed by this mechanism



Conclusion

- **Passive diffusion:** most drugs having high lipophilicity & MW in the range 100-400 dalton are absorbed.
- **Pore transport:** water soluble drugs of MW less than 100 dalton are absorbed.
- **Ion-pair transport:** drugs that ionise at all pH conditions absorbed after complexing with oppositely charged ions are absorbed.
- **Carrier-mediated transport:** structure-specific drugs with affinity for carriers transported from specific sites are absorbed.
- **Endocytosis:** macromolecular nutrients and drugs as solid particles or oily droplets are absorbed.


Thank
you!!