BIOPHARMACEUTICS

WHAT IS BIOPHARMACEUTICS?

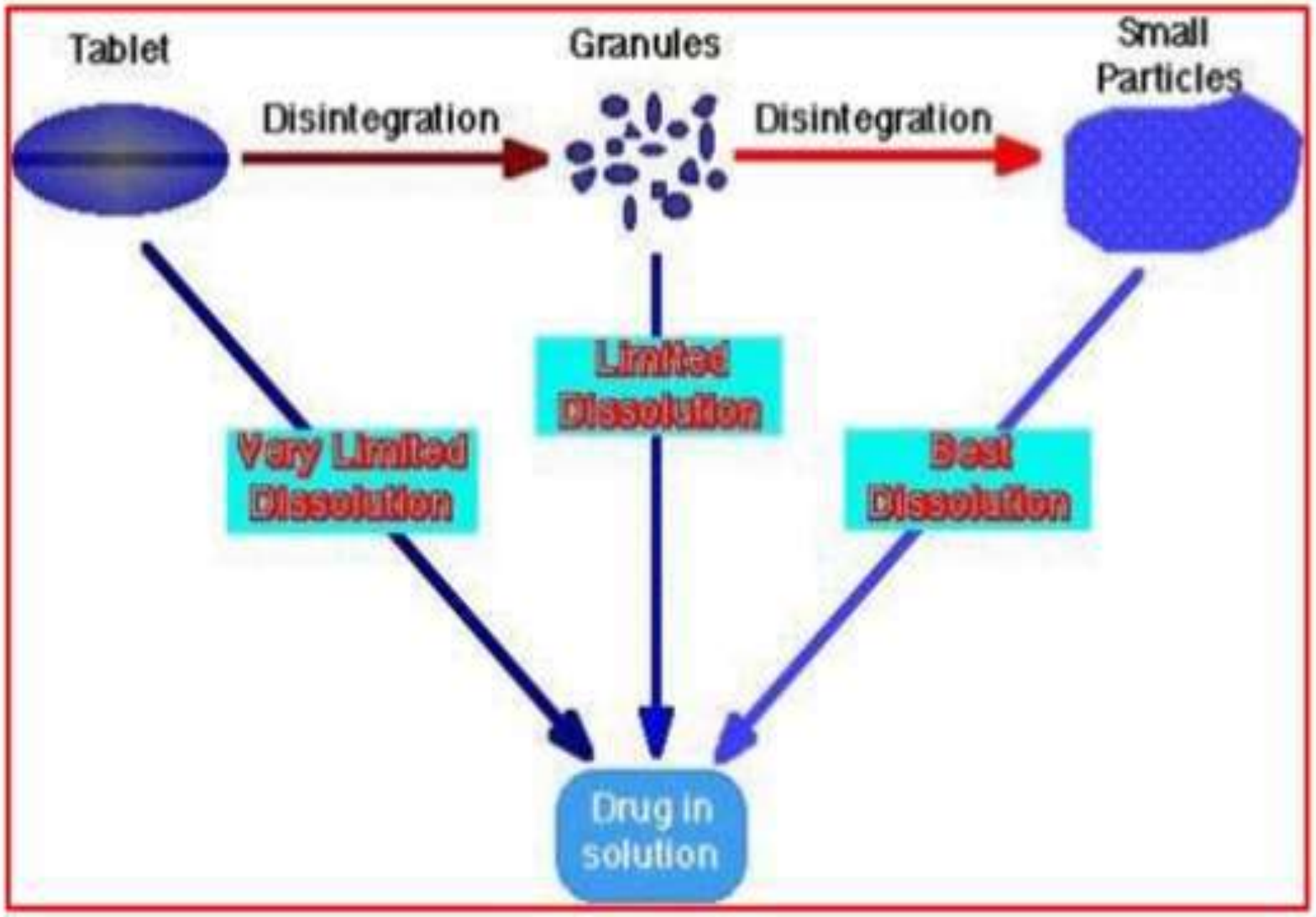
Biopharmaceutics can be defined as the study of how

- **the physicochemical properties of drugs,**
- **dosage forms and**
- **routes of administration**

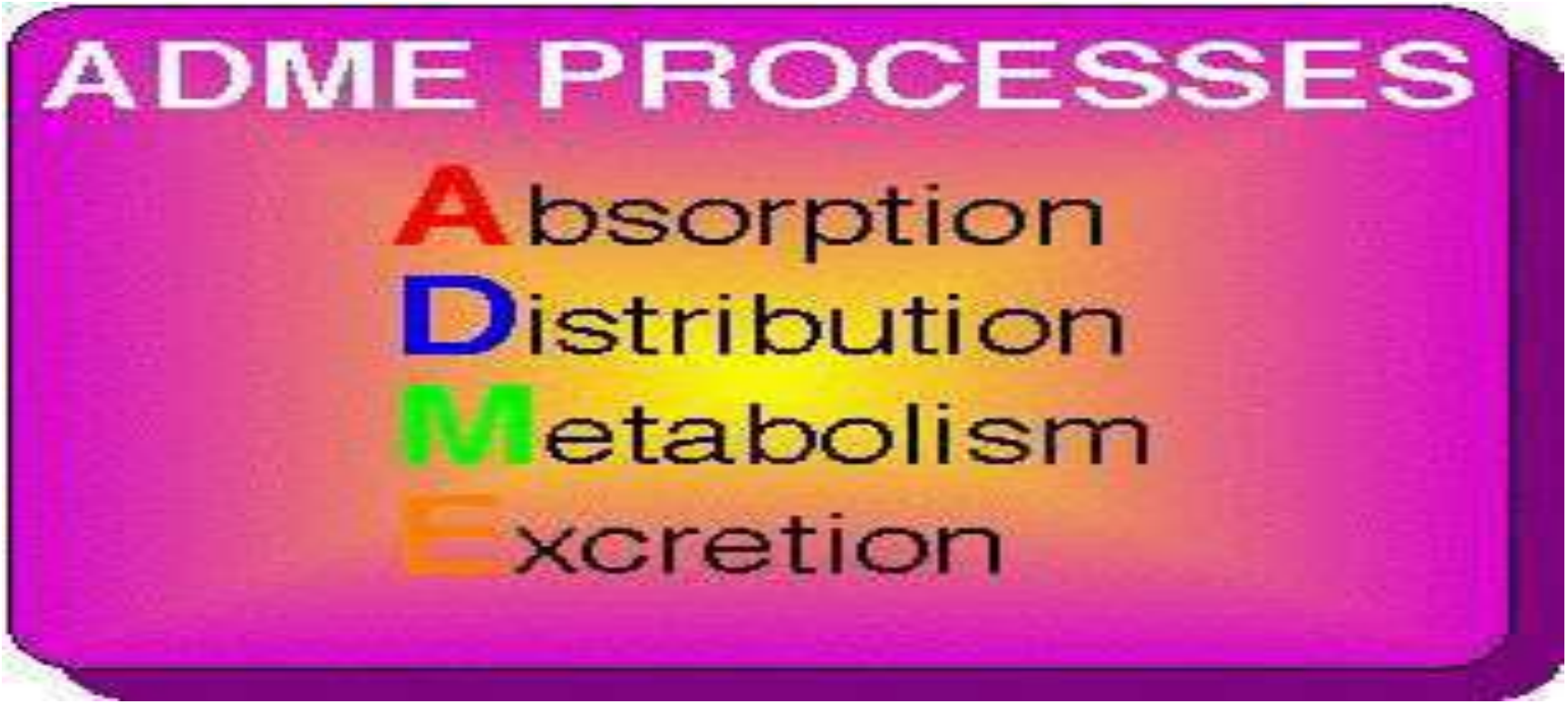
affect the rate and extent of drug absorption.

Bioavailability:

The rate and extent of drug absorption


Tablet
Granules
Small Particles
Disintegration
Disintegration
Limited Dissolution
Very Limited Dissolution
Best Dissolution
Drug in solution

- **Pharmacokinetics: The study and characterization of time course (kinetics) of drug absorption, distribution, metabolism and elimination (ADME).**



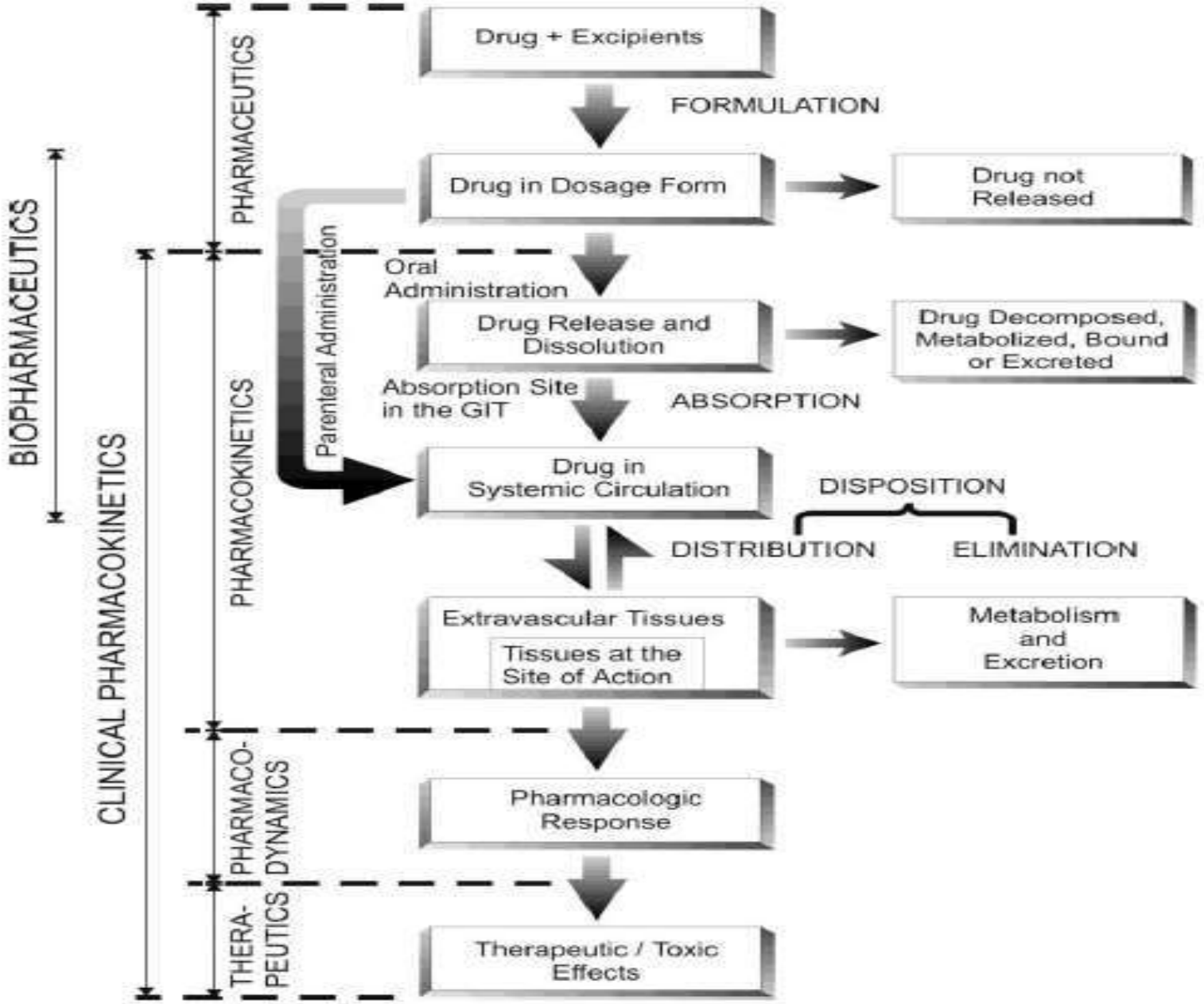


Figure: Schematic representation of the processes involved in drug therapeutics

- **The concentration of the drug in blood plasma depends on LADME**

- **L = Liberation**

the release of the drug from it's dosage form.

- **A = Absorption**

the movement of drug from the site of administration to the blood circulation.

- **D = Distribution**

the process by which drug diffuses or is transferred from intravascular space to extravascular space (body tissues).

- **M = Metabolism**

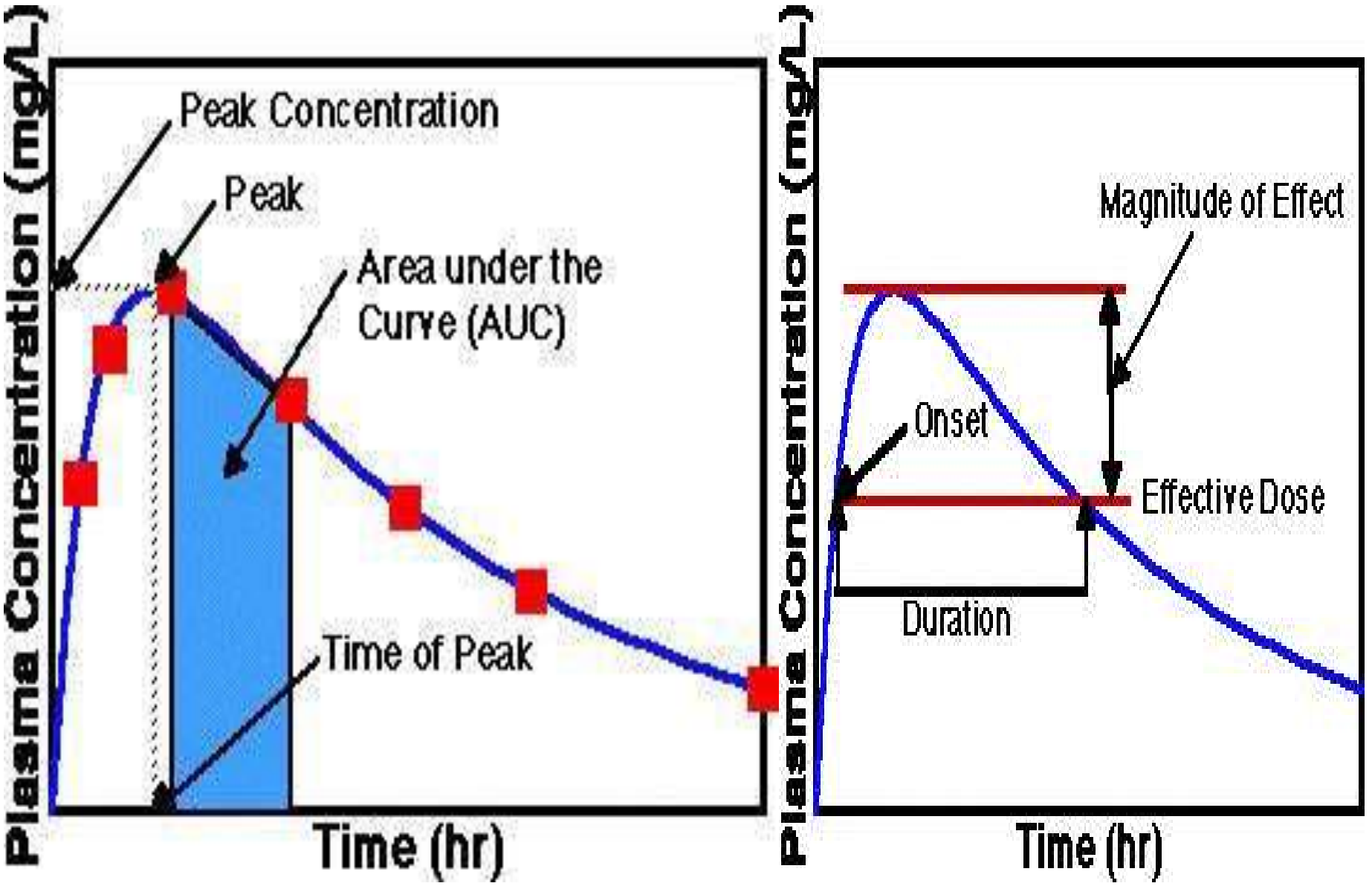
the chemical conversion or transformation of drugs into compounds which are easier to eliminate.

- **E = Excretion**

the elimination of unchanged drug or metabolite from the body via renal, biliary, or pulmonary processes.

- **Bioavailability:** The rate and extent of drug absorption.
- **Bioavailable dose:** The fraction of administered dose of a particular drug that reaches the systemic circulation intact.
- **Plasma level-time curve:**
- Plasma level-time curve is generated by measuring the drug concentration in plasma taking samples at predetermined time intervals after the administration of drug.

- Drug concentration in each plasma sample is plotted against the corresponding time at which the plasma sample was withdrawn.


Plasma Concentration (mg/L)
Peak Concentration
Peak
Area under the Curve (AUC)
Time of Peak
Time (hr)
Plasma Concentration (mg/L)
Magnitude of Effect
Onset
Effective Dose
Duration
Time (hr)

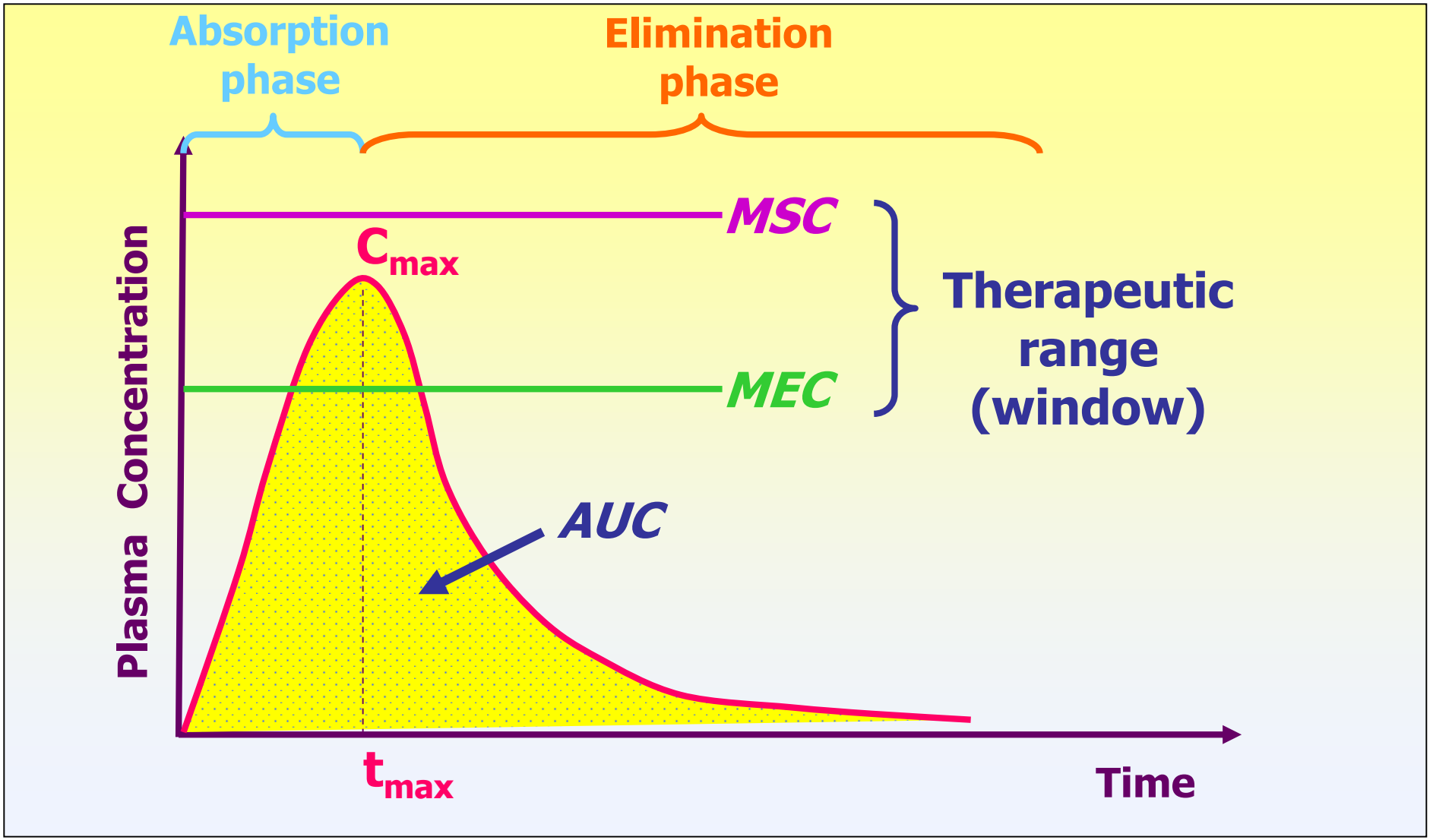


Figure: A typical blood plasma concentration-time curve obtained following the peroral administration of a single dose of a drug in a tablet.

- **Drug Product Performance Parameters:**

1) Minimum effective concentration (MEC): Minimum conc. of drug needed at the receptor site to produce the desired pharmacologic effect.

2) Minimum toxic concentration (MTC): Minimum drug conc. needed to produce a toxic effect.

3) Onset time: The time required for the drug to reach the MEC.

4) Duration of action: The difference between onset time and the time for the drug to decline back to the MEC.

5) Tmax: The time at which maximum drug conc. observed in plasma. It is proportional to the rate of drug absorption.

6) Cmax: The maximum drug conc. observed in plasma at a particular time.

7) AUC: It is related to the amount of drug absorbed systemically.

❖ **Routes of Administration:**

1. The Enteral Route:

- Includes ***per-oral*** i.e. gastrointestinal, sublingual/buccal and rectal routes.
- The GI route is the most common for administration of majority of drugs.

2. **The Parenteral Route:**

- Includes all routes of administration through or under one or more layers of skin.
- IV (No Absorption).
- Extravascular parenteral :SC & IM (Absorption).

3. **The Topical Route:**

- Includes skin, eyes or other specific membranes.
- The intranasal, inhalation, intra-vaginal and transdermal routes may be considered enteral or topical according to different definitions.

ABSORPTION

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

- **Main factors affecting oral absorption:**

1. Physiological factors:

1) Membrane physiology.

2) Passage of drugs across membranes.

3) Gastrointestinal physiology.

2. Physical-chemical factors of drugs.

3. Formulation factors.

❑ Physiological Factors:

I. Membrane physiology

- **Membrane structure (Fluid Mosaic Model)**

- **The biologic membrane consists mainly of a lipid bilayer containing primarily phospholipids and cholesterol, with imbedded proteins.**

- **The membrane contains also small aqueous channels or pores.**

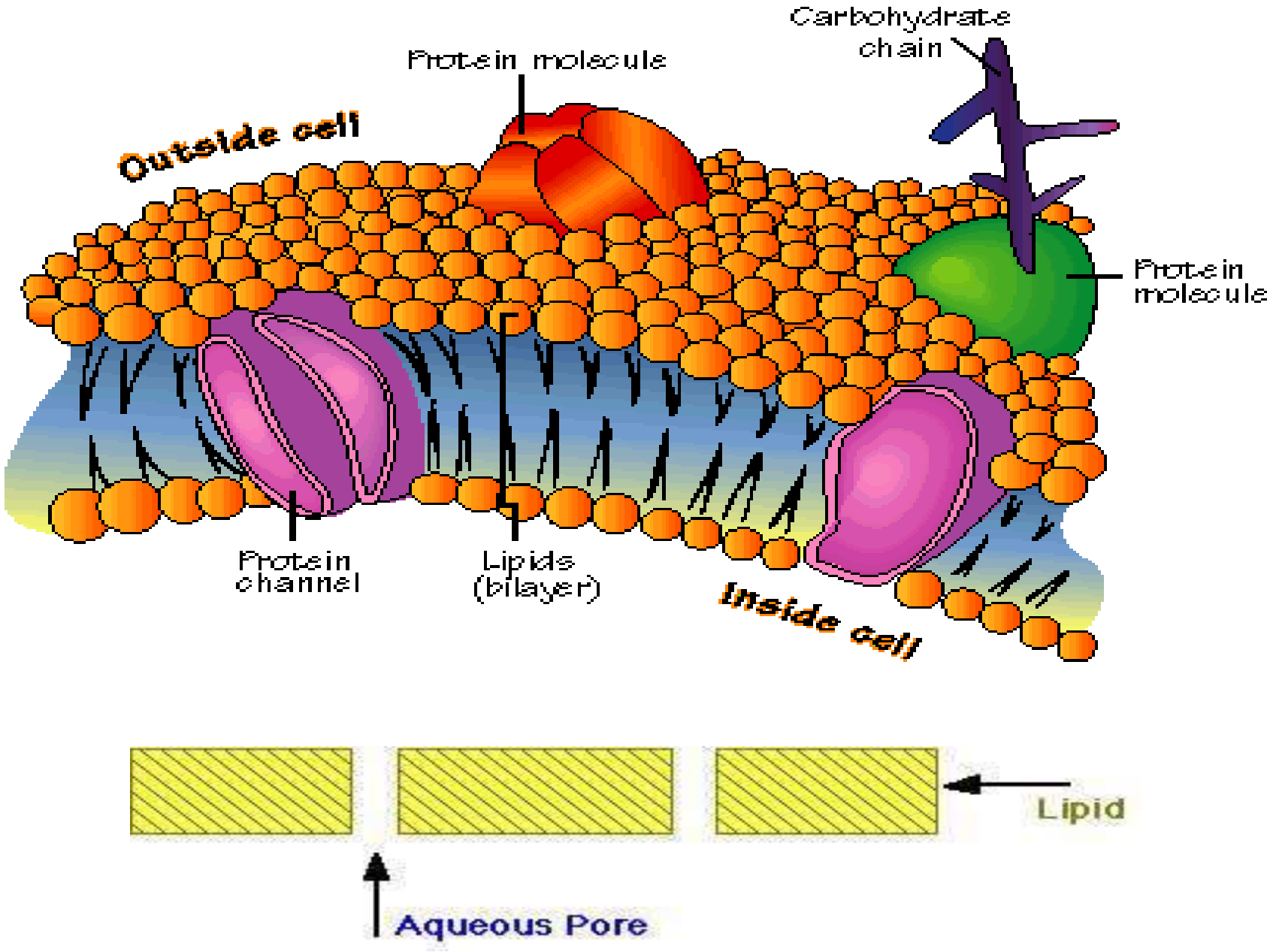


Figure: Simplified Model of Membrane

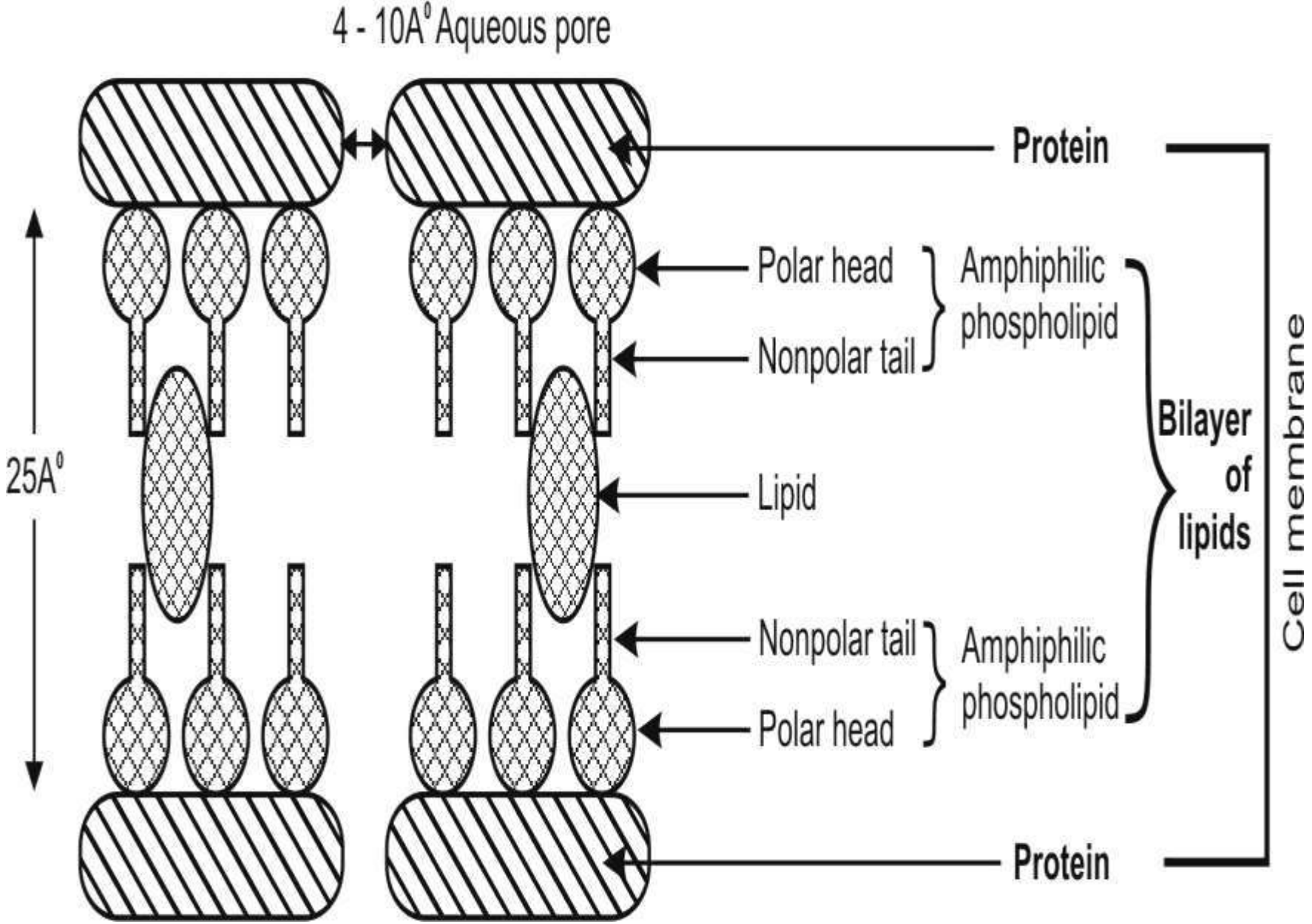


Figure:Basic structure of functional cell membrane

• Examples of Bio-membranes

- ✓ **Blood-brain barrier**
  - Has effectively no pores to prevent many polar materials (often toxic) from entering the brain.
  - Smaller lipid or lipid soluble materials, such as diethyl ether, halothane (used as general anesthetics) can easily enter the brain.
- ✓ **Renal tubules**
  - Relatively non-porous; lipid compounds or non-ionized species (dependent of pH and pKa) are reabsorbed.
- ✓ **Blood capillaries and renal glomerular membranes**
  - Quite porous, allowing non-polar and polar molecules (up to a fairly large size, just below that of albumin, (M.Wt. 69,000) to pass through.
  - Especially useful in the kidneys as it allows for excretion of polar (drug and waste compounds) substances.

II. Passage of drugs across the biological membranes

a *movement of drug across the membrane* is called **drug transport.**

- **MECHANISMS OF GASTROINTESTINAL ABSORPTION OF DRUGS :**

The three broad categories of drug transport mechanisms involved in absorption are :

A. Trans-cellular/intracellular transport.

B. Para-cellular/intrecellular transport.

C. Vesicular transport.

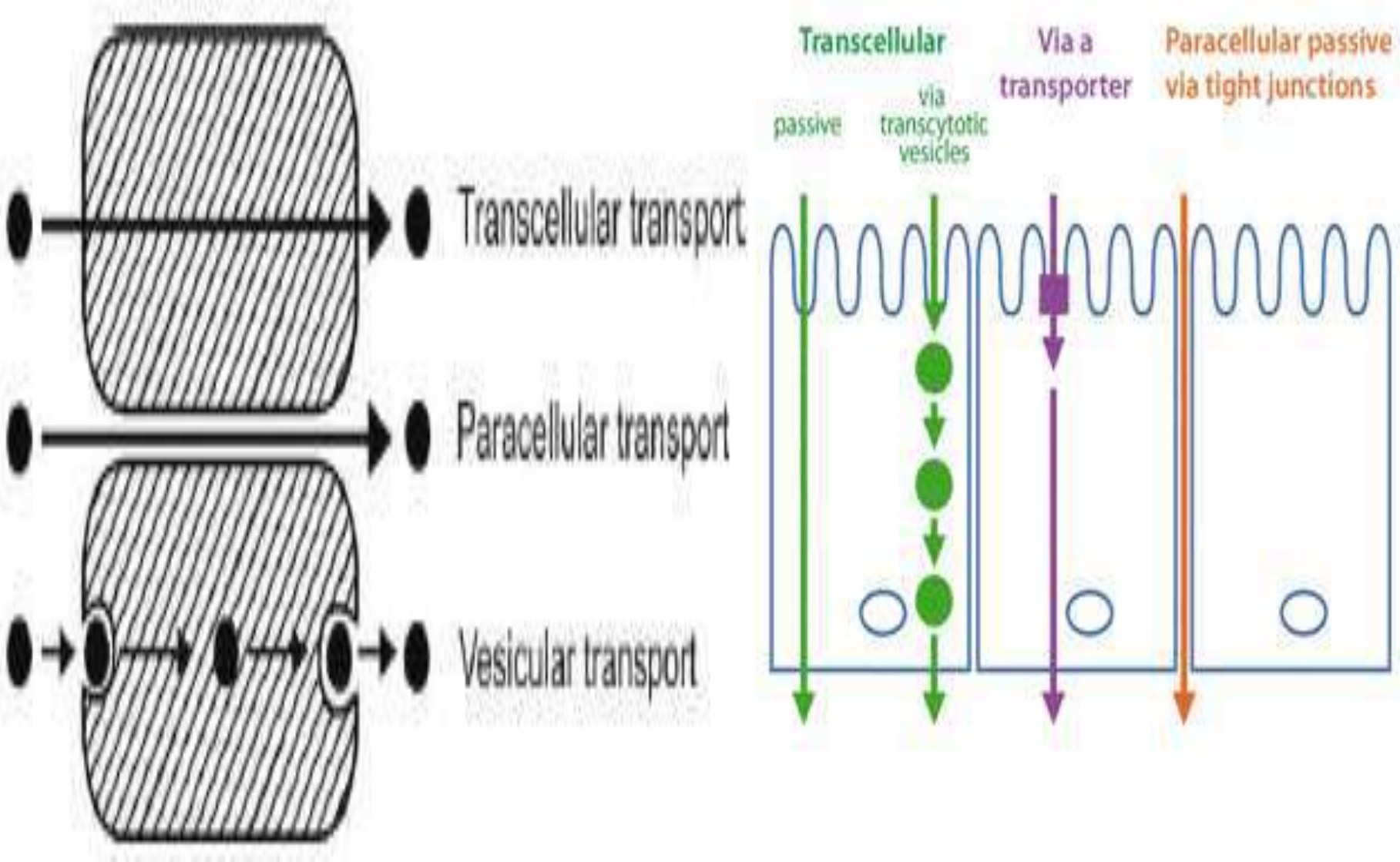


Figure: Illustrative comparison of transcellular, paracellular and vesicular transport.

A. Trans-cellular/Intracellular Transport:

- *The passage of drugs across the GI epithelium*
- The most common pathway for drug transport.
- involved:

1. Passive Transport Processes :

- do not require energy
- further classified into following types:

a. Passive diffusion **b. Pore transport**

c. Ion-pair transport **d. Facilitated- or mediated-diffusion.**

A. Transcellular/Intracellular Transport: (continued)

2. Active Transport Processes :

- requires energy from ATP to move drug molecules from extracellular to intracellular milieu.
- These are of two types –

a. Primary active transport.

b. Secondary active transport :subdivided into:

i. Symport (co-transport).

ii. Antiport (counter-transport).

B. Paracellular/Intercellular Transport:

- *through the junctions between the GI epithelial cells*.
- minor importance in drug absorption.
- Involved:

1. Permeation through tight junctions of epithelial cells

through openings which are little bigger than the aqueous pores. Compounds such as insulin and cardiac glycosides are taken up this mechanism.

2. ***Persorption:***

through temporary openings formed by shedding of two neighboring epithelial cells into the lumen.

C. Vesicular or Corpuscular Transport (Endocytosis):

- Energy dependent processes
- 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.
- Classified into two categories

1. **Pinocytosis.**
2. **Phagocytosis**.

▪ Passive diffusion:

- Also called **non-ionic diffusion**, it is the major process for absorption of more than 90% of the drugs.
- The driving force is **concentration** or **electrochemical gradient**. It is defined as the difference in the drug concentration on either side of the membrane.
- Passive diffusion is best expressed by **Fick's first law of diffusion**, which 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.

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

dQ/dt = rate of drug diffusion

D = diffusion coefficient of the drug

A = surface area of the absorbing membrane

$K_{m/w}$ = partition coefficient of the drug between membrane and the aqueous phase

(C_{GIT} – C) = difference in the concentration of drug in GI fluid & the plasma

h = thickness of the membrane.

- The parameters of this equation are:
  - **D, Diffusion coefficient:** 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 dQ/dt also increases.

  - **A, Surface area:** As the surface area increases the rate of

  diffusion also increase.

  The surface of the intestinal lining (with villae and microvillae) is much larger than the stomach. This is one reason absorption is generally faster from the intestine compared with absorption from the stomach.

- **Km/w, Partition co-efficient**: Partition co-efficient of the drug between the lipoidal membrane and aqueous GI fluids
- **dQ/dt**: Rate of drug diffusion: It represents the appearance of drug in the blood. The unit is (amount/time).
- **h, Membrane thickness:** The smaller the membrane thickness the quicker the diffusion process.
- As an example, membrane of the lung is quite thin thus inhalation absorption can be quite rapid.
- **(C_{GIT} - C), Concentration difference:** The drug conc. in blood or plasma will be quite low compared with the conc. in the GI tract.
- This conc. gradient allows the rapid complete absorption of many drug substances.
- Initially, when drug is ingested, $C_{GIT} >> C$, and large conc. gradient exist acting as driving force for absorption.

- **Sink Condition:**
  - Once passively absorbed drug enters blood, it is rapidly swept away and distributed into a much larger vol. of body fluids and hence, conc. of drug at the absorption site, CGIT, is maintained greater than the conc. of drug in plasma. Such condition is called sink condition.
  - Due to sink condition, C is very small compared to C_{GIT}.

- Factors affecting the passive diffusion according to Fick's Second Law
- $\frac{-dc}{dt} = \frac{D.A}{L}$ (C1α' 1 – C2α' 2)

Where:

α' 1 = Partition coefficient o/w (membrane/water)

α' 2 = Partition coefficient w/o (Blood/membrane)

Permeabilty of substances through the membranes:

Liposoluble> Unionized>Anions>Cations.

▪ 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.

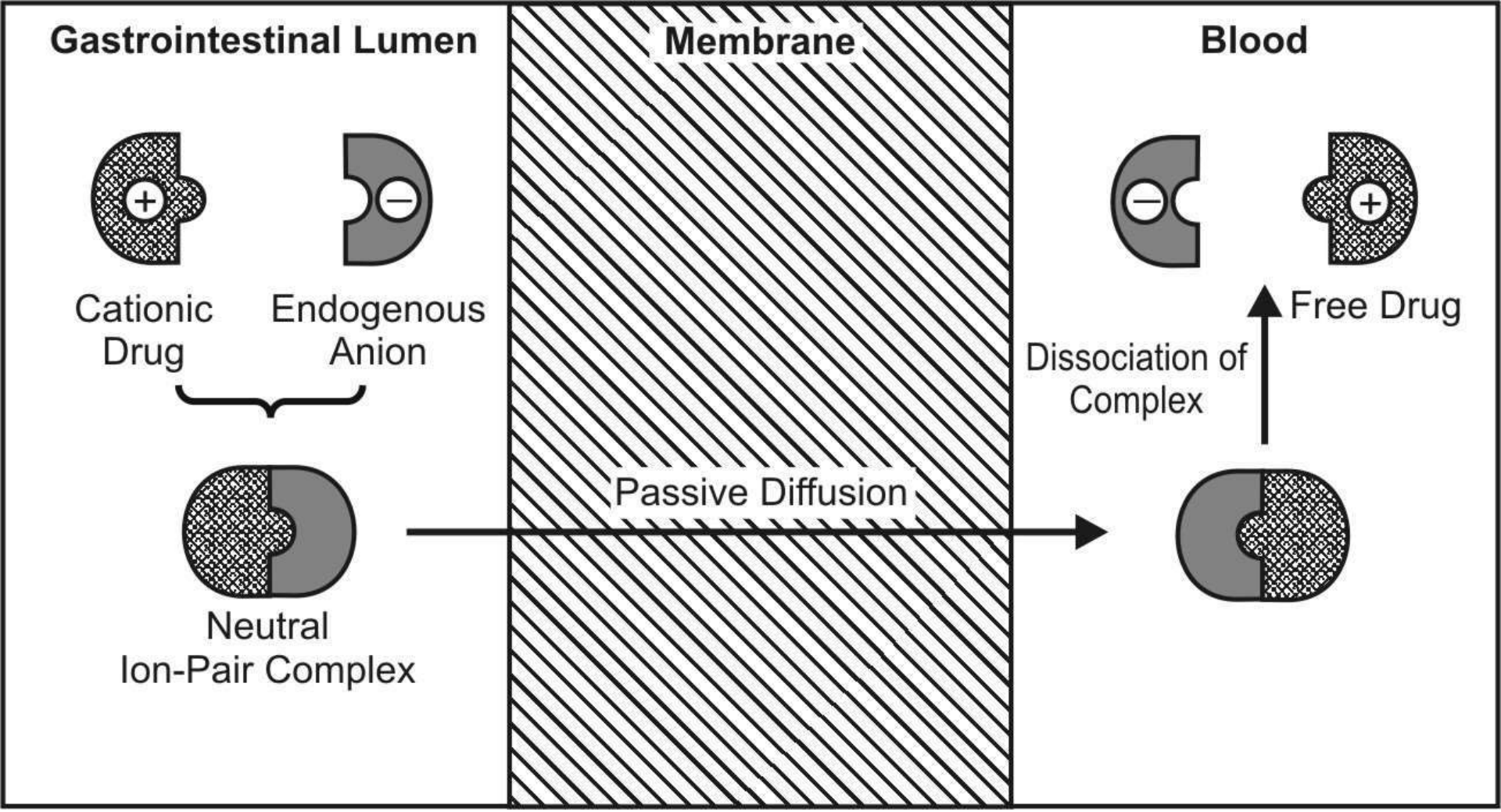
- The process is important in the absorption of low molecular weight (less than 100), generally water-soluble drugs through narrow, aqueous-filled channels ex: urea, water and sugars

- Chain-like or linear compounds of molecular weight up to 400 Daltons can be absorbed by filtration.

- Drug permeation through water-filled channels is important in renal excretion, removal of drug from the cerebrospinal fluid and entry of drugs into the liver.

▪ Ion-Pair Transport

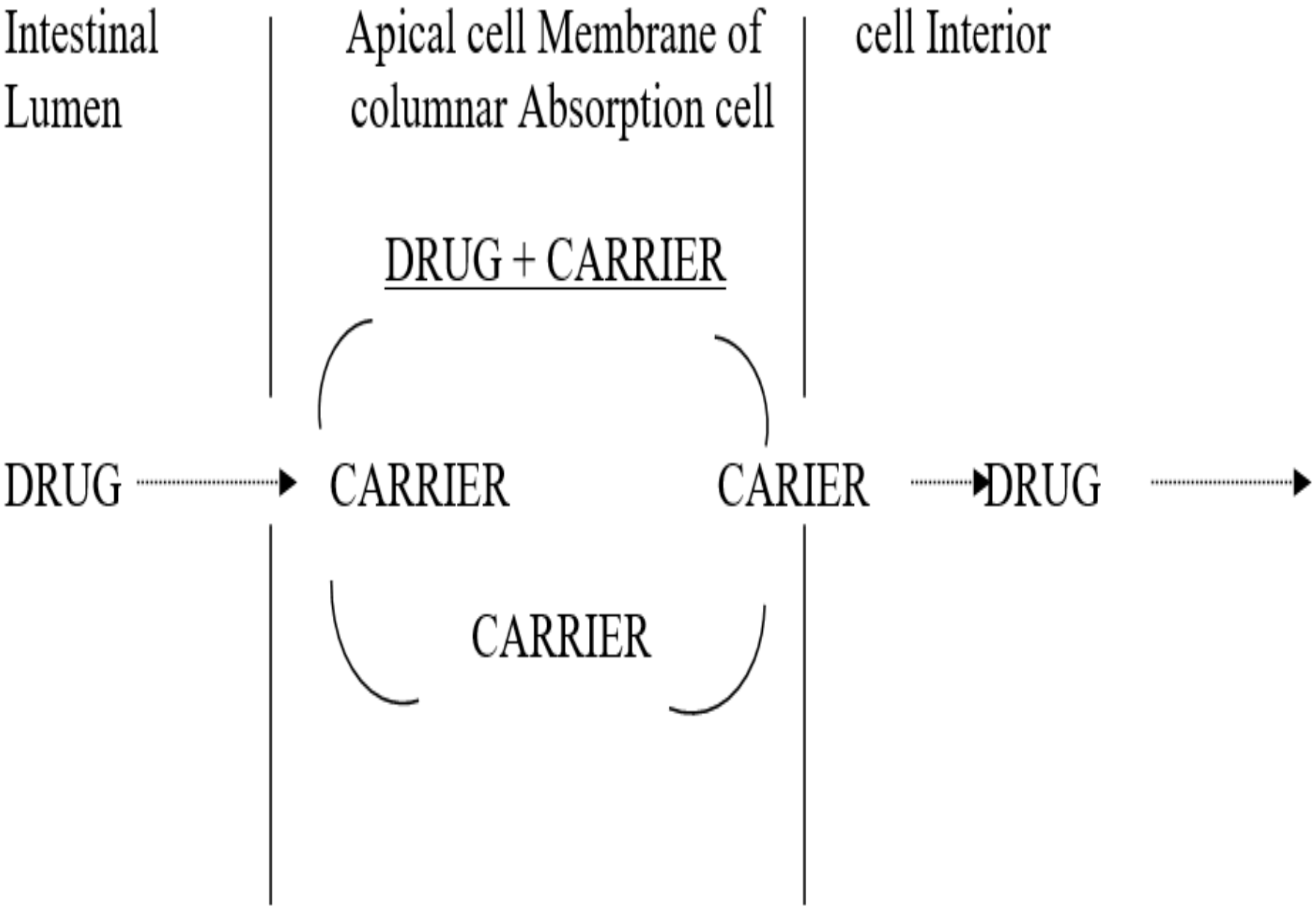
- Absorption of drugs like quaternary ammonium compounds and sulphonic acids, which ionise under all pH conditions, is ion-pair transport.
- Despite their low o/w partition coefficient values, such agents penetrate the membrane by forming reversible neutral complexes with endogenous ions of the GIT like 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.

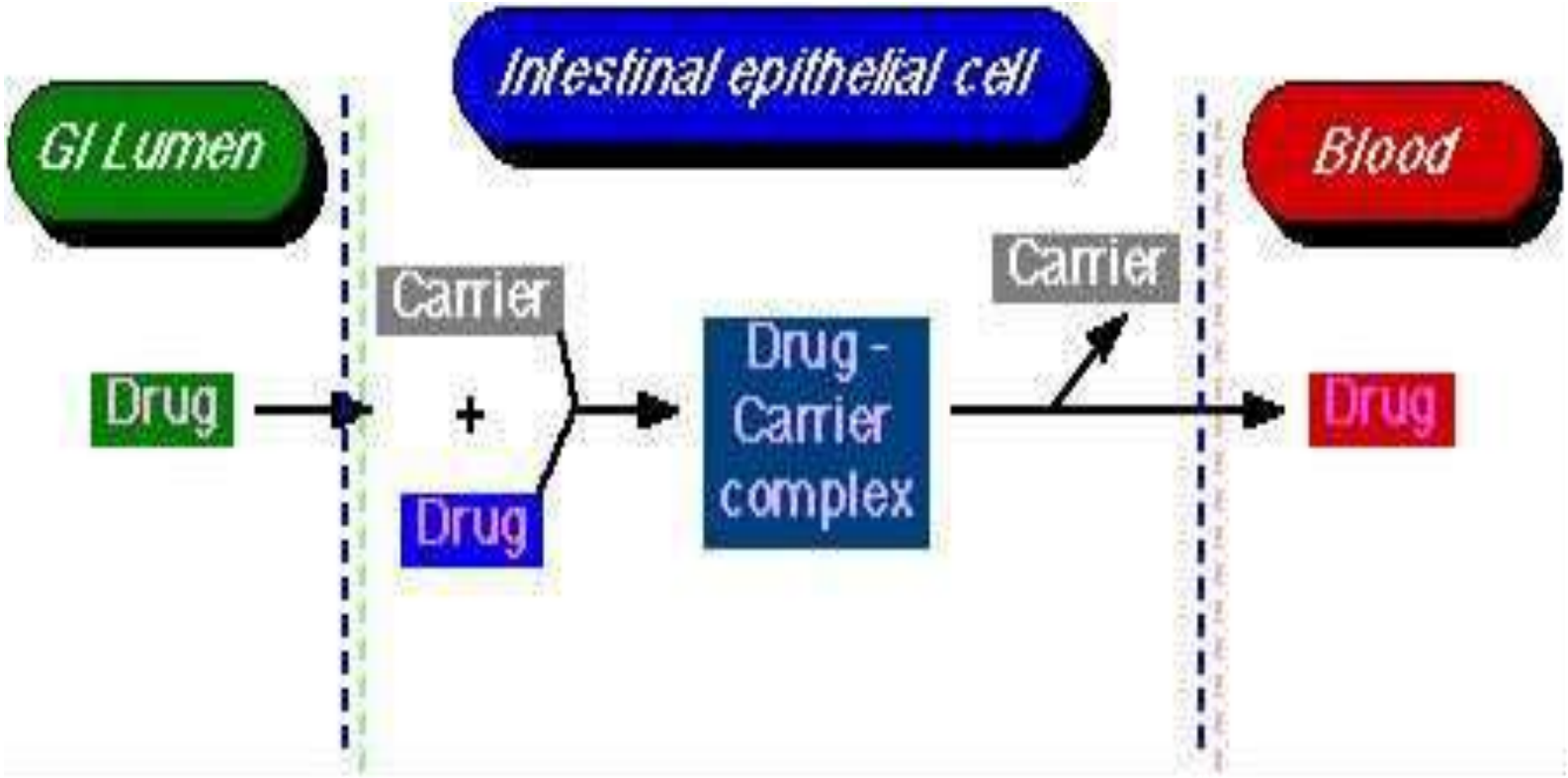


Ion-pair transport of a cationic drug

▪ Carrier-Mediated Transport

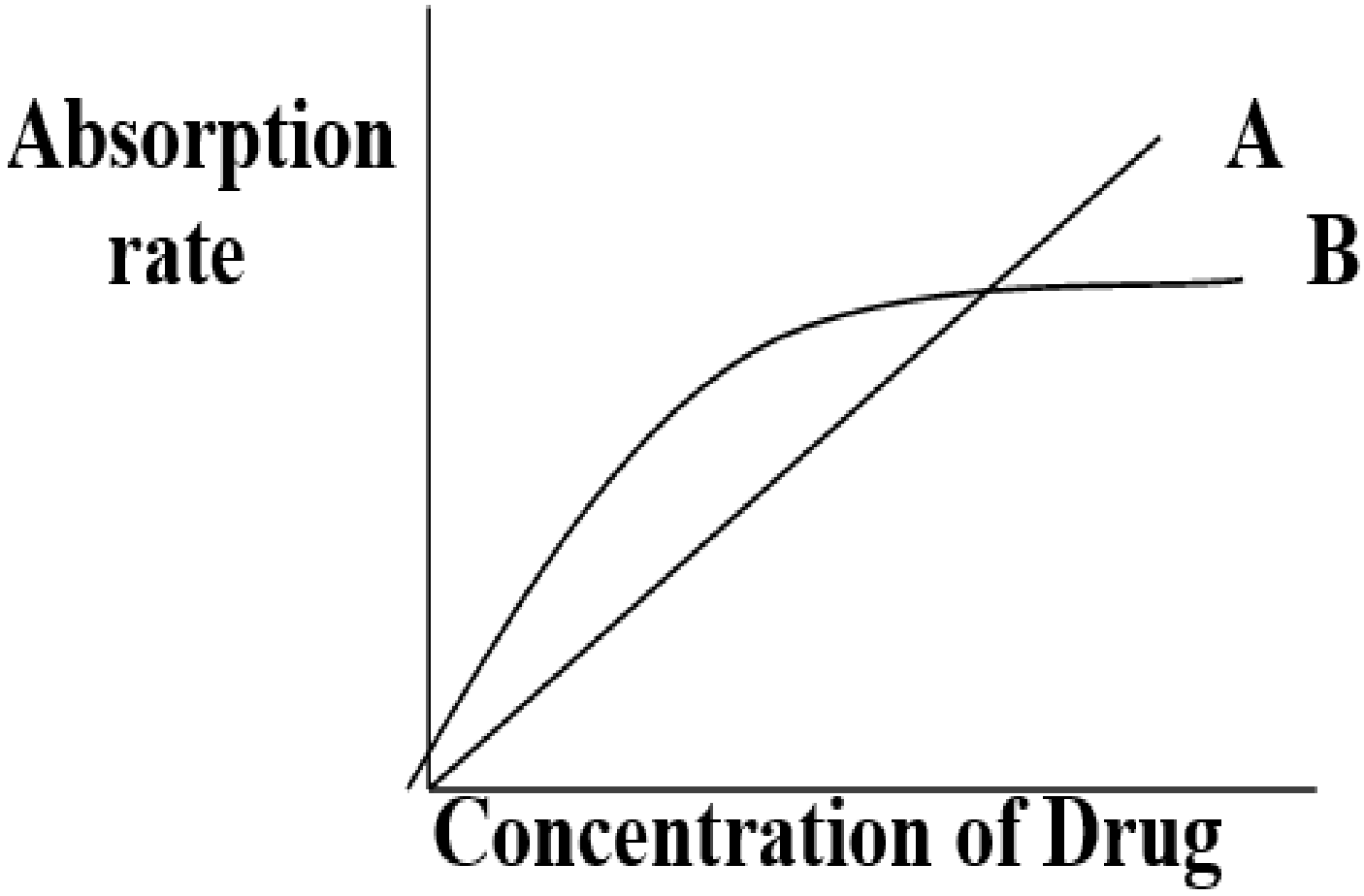
- Some polar drugs cross the membrane more readily than can be predicted from their concentration gradient and partition coefficient values. Like monosaccharides, amino acids and vitamins will be poorly absorbed.
- The mechanism is involved is *carrier* that binds reversibly or non-covalently with the 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.


Intestinal Lumen
Apical cell Membrane of columnar Absorption cell
cell Interior
DRUG + CARRIER
DRUG
CARRIER
CARIER
DRUG
CARRIER



1. Selectivity
2. Number of transporters
3. Affinity
4. Saturation?

- Comparison of the Diffusion Rate in the passive diffusion (Line A) and the active Transport (Line B)



- **Carrier-Mediated Transport Process:**
- **Mechanism:**

1- Binding of Drug with the Carrier.

2- Conformational Changing of the Carrier .

3- Dissociation of the Drug from the Complex : Drug – Carrier.

- **According to Michaelis Menten equation :**

$$-\frac{dA}{dt} = \frac{V_m \cdot A}{K_m + A}$$

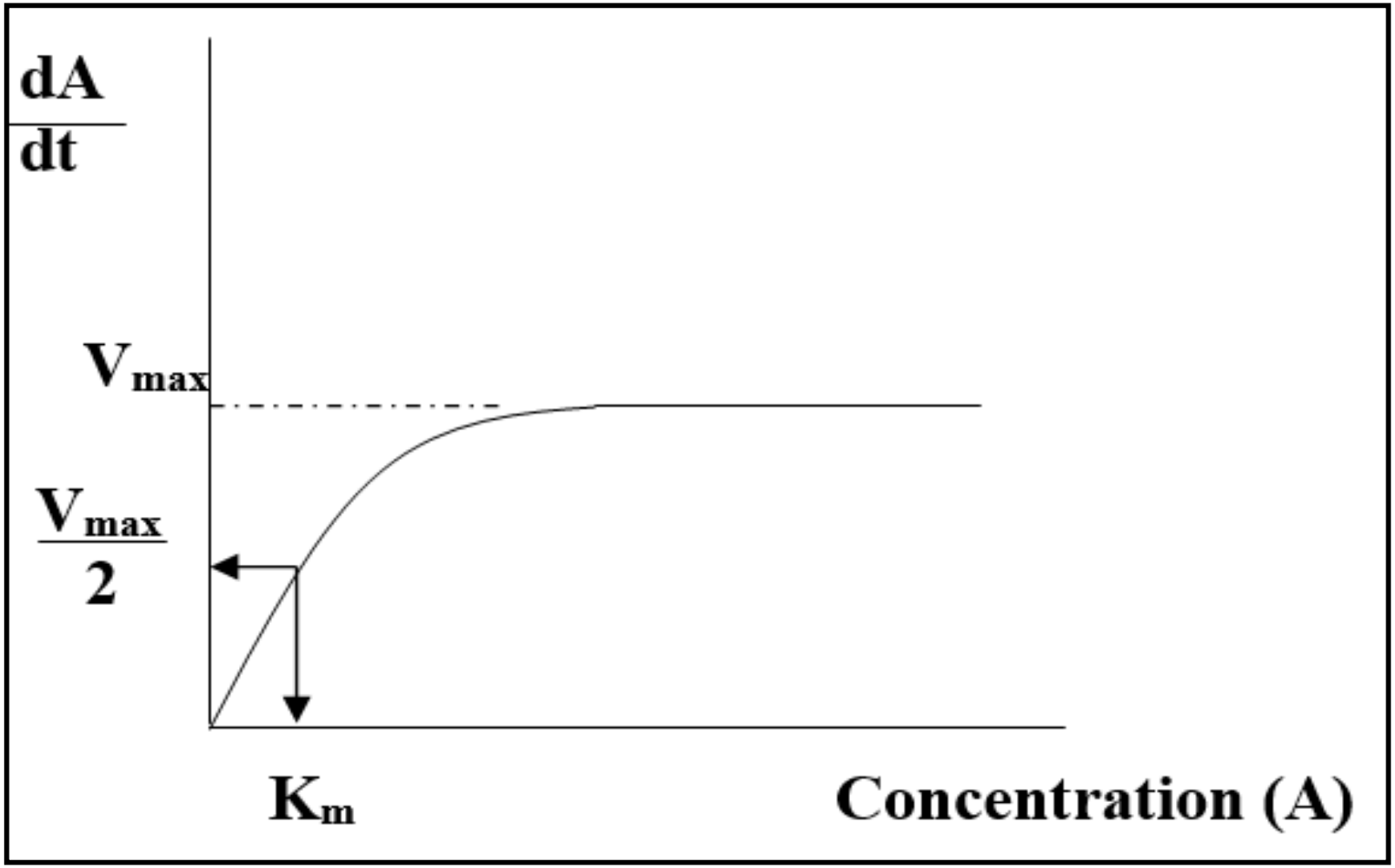
Where:

$\frac{dA}{dt}$: Absorption rate

V_m : Maximum Velocity of transport.

K_m : Constant of Michaelis Menten : Concentration of substrate in which the Velocity of transport is the half (V_m) exactly (mg/Cm^3).

A : Concentration of the substrate (Drug) in the site of absorption (mg/Cm3)



K_m , V_m are constants of Drug and Carrier. (K_{ap})

$$-\frac{dA}{dt} = \frac{V_m \cdot A}{K_m + A}$$

If $K_m >> A$

$$-\frac{dA}{dt} = K_{ap} \cdot A$$

First Order Kinetic
(Dose independent)
Linear

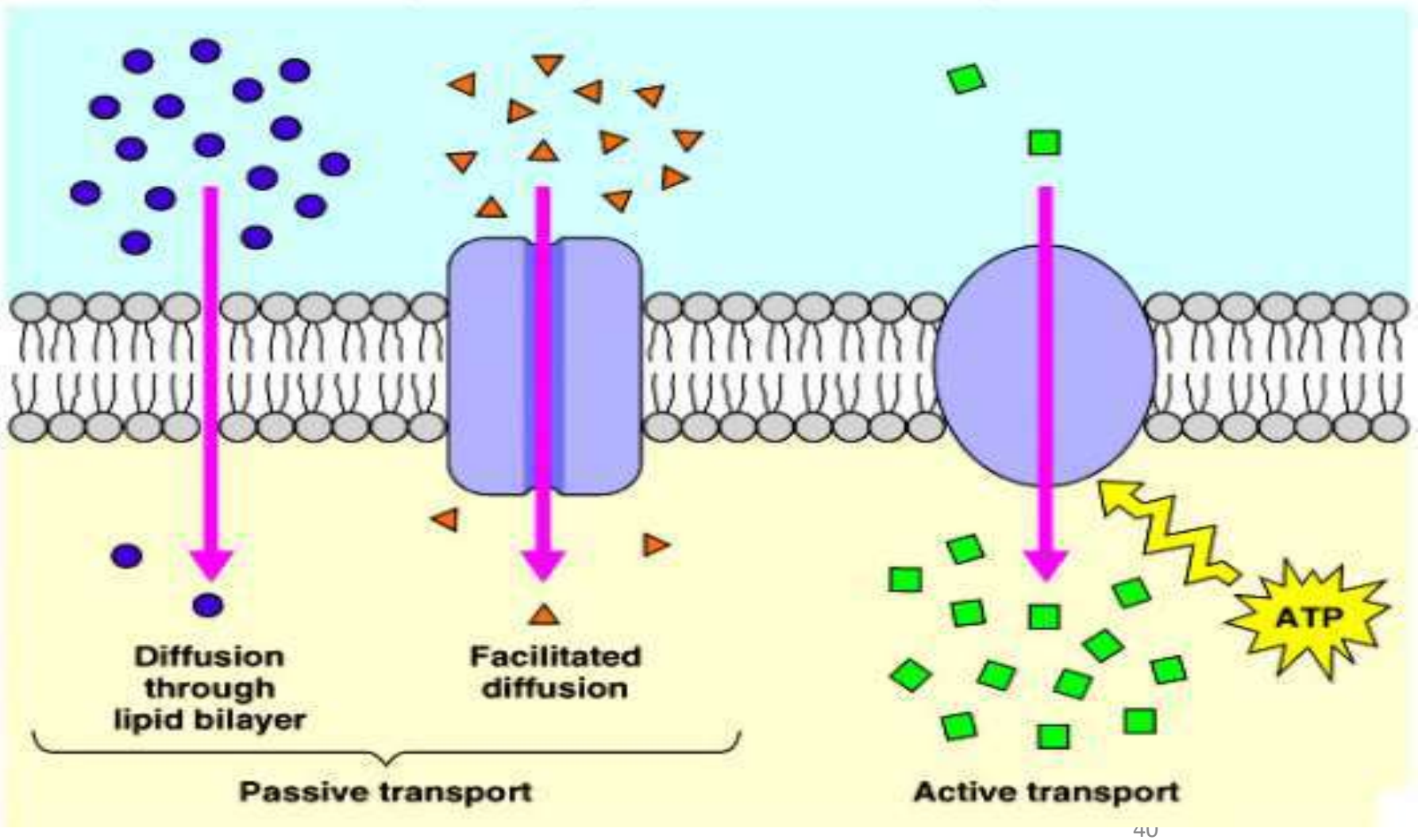
if $K_m << A$

$$-\frac{dA}{dt} = V_m$$

Zero Order Kinetic
(Dose dependent)
Non-linear

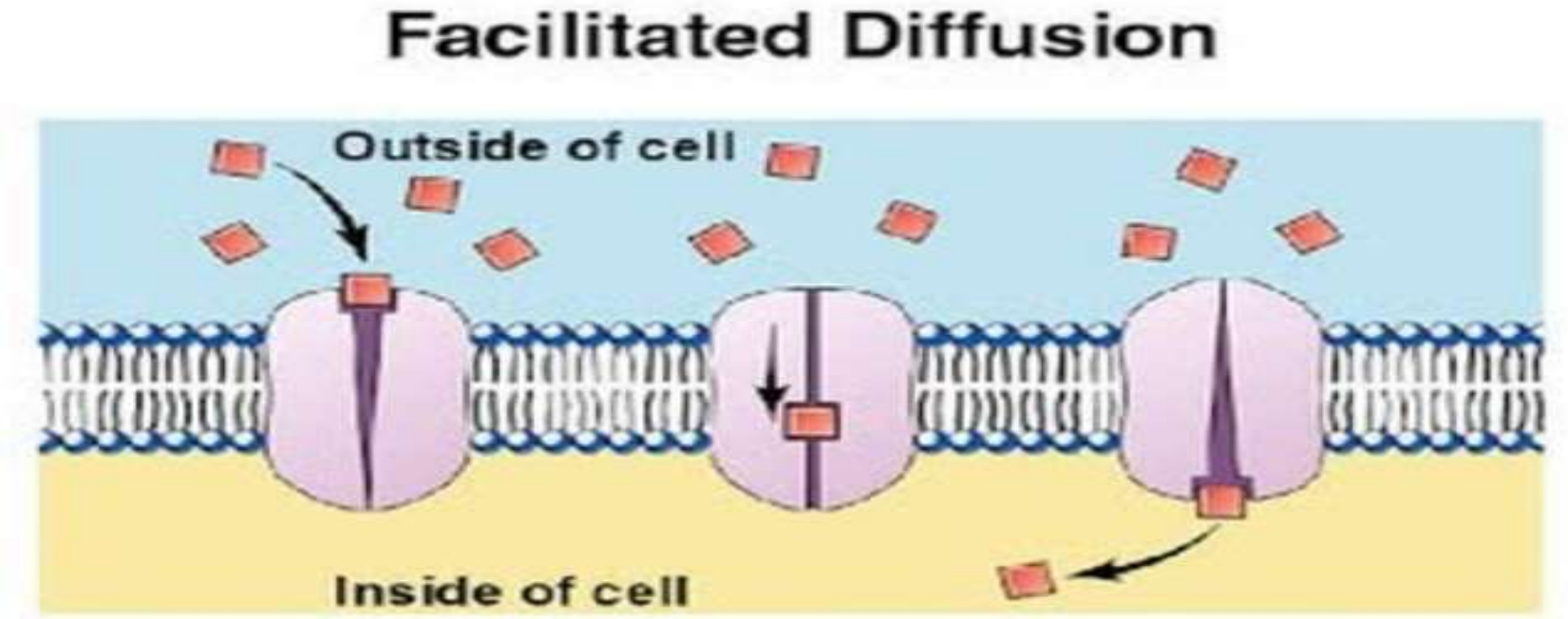
Some drugs are absorbed by passive diffusion and mediated system:

$$\frac{-dA}{dt} = \frac{Vm \,.\, A}{Km + A} + \mathrm{Ka} \,.\, \mathrm{A}$$



B. FACILITED TRANSPORT OR DIFFUSION:

It is a carrier mediated transport system similar to • active transport, however Facilitated diffusion occurs **with a concentration gradient** and **does not Require energy** for transport.



▪ *Active Transport Processes*

- Requires energy from ATP to move drug molecules from extracellular to intracellular milieu.
- Two types:

1.Primary active transport.

2.Secondary active transport

subdivided into two:

2.1. Symport (co-transport).

2.2. Antiport (counter-transport).

- **Primary active transport**:

- Direct ATP requirement.
- Transfers only one **ion** or **molecule** and in only one direction, and hence called as **uniporter** e.g. absorption of glucose.

- ***Secondary active transport***:

- 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)***: Movement of both molecules in the same direction e.g. *Na^+-glucose symporter*
  - ***Antiport (counter-transport):*** Movement of molecules in the opposite direction e.g. H^+ ions using the Na^+ gradient in the kidneys.

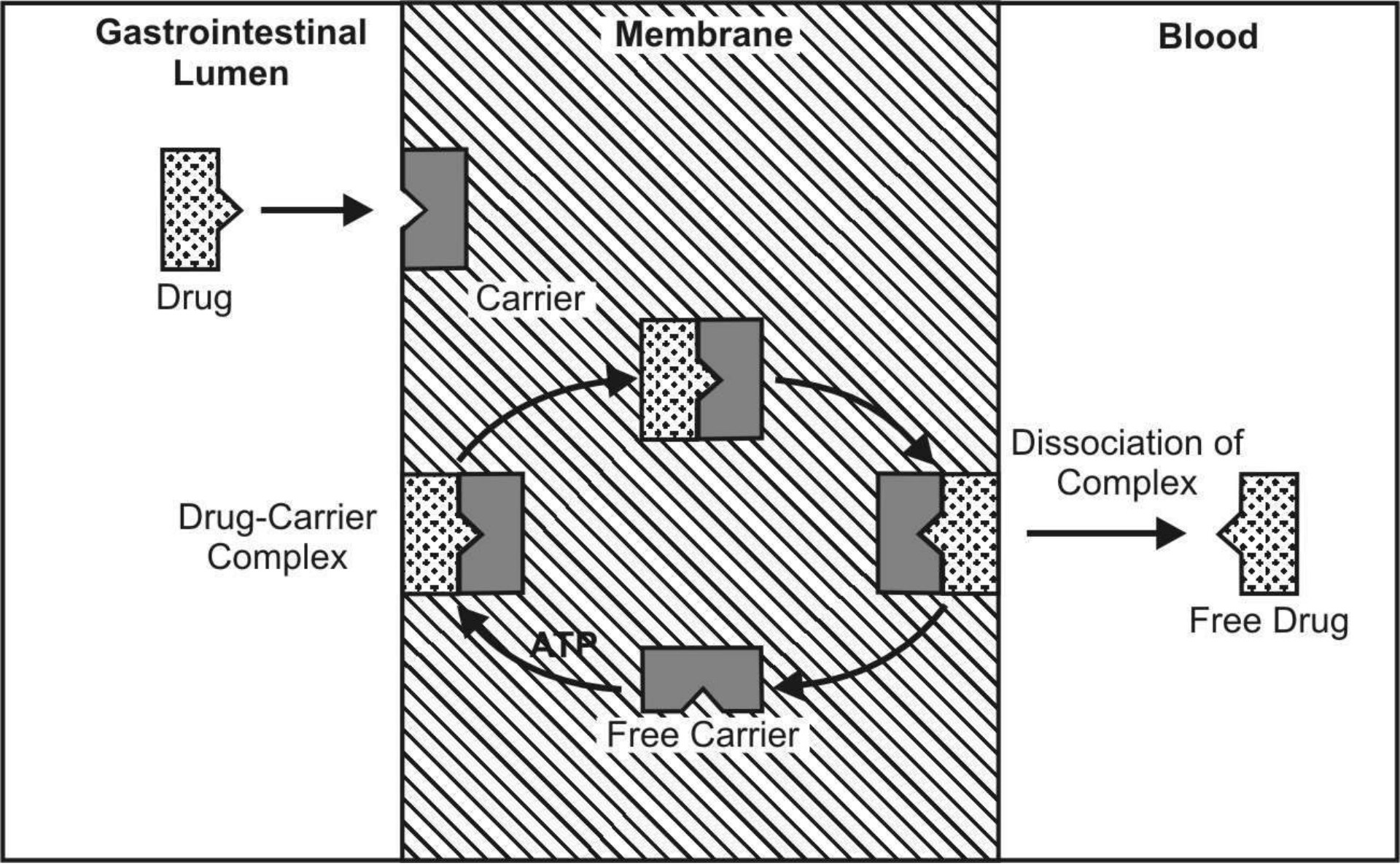


Figure: Active absorption of a drug

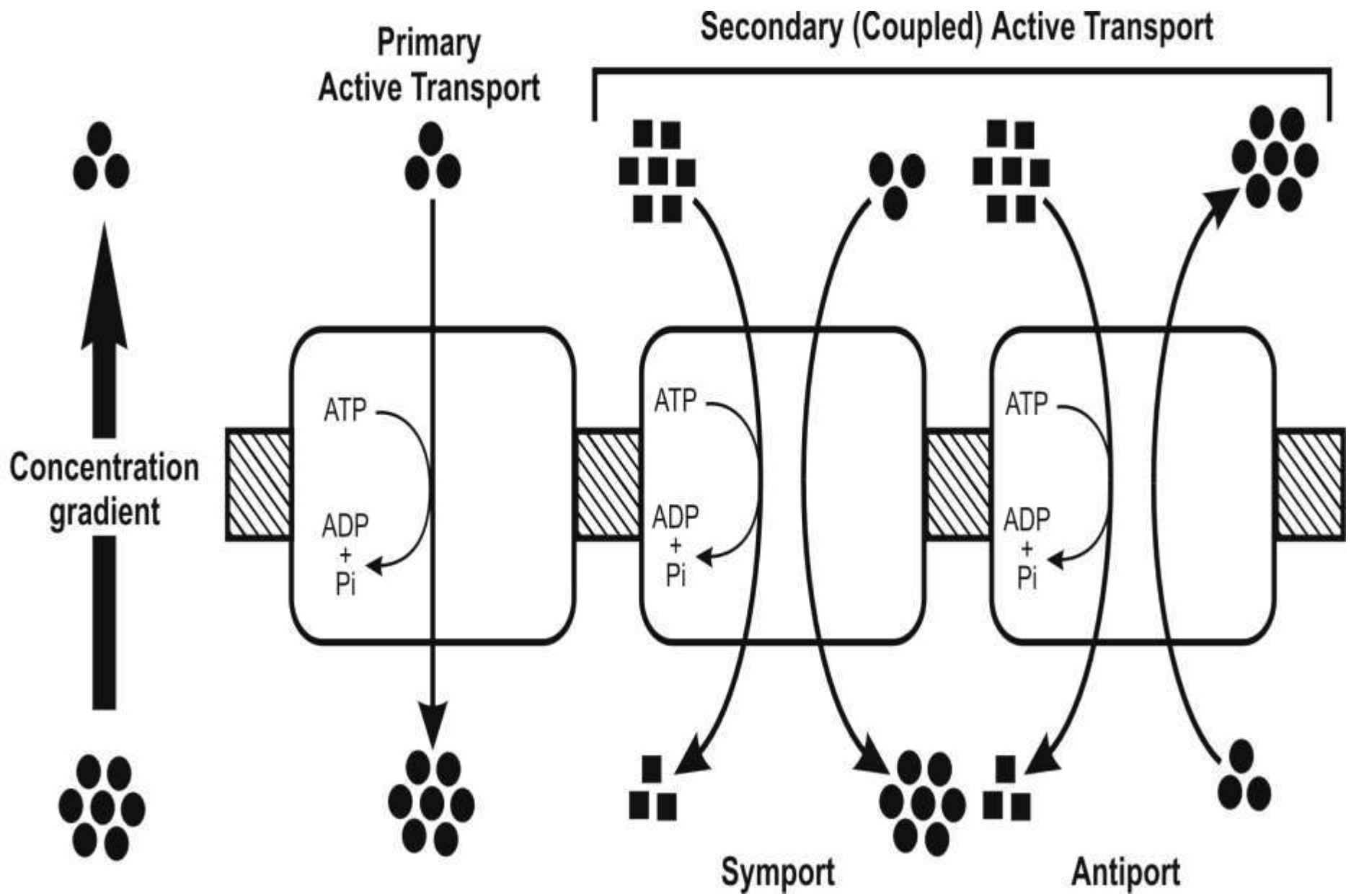


Figure: Types of active transport

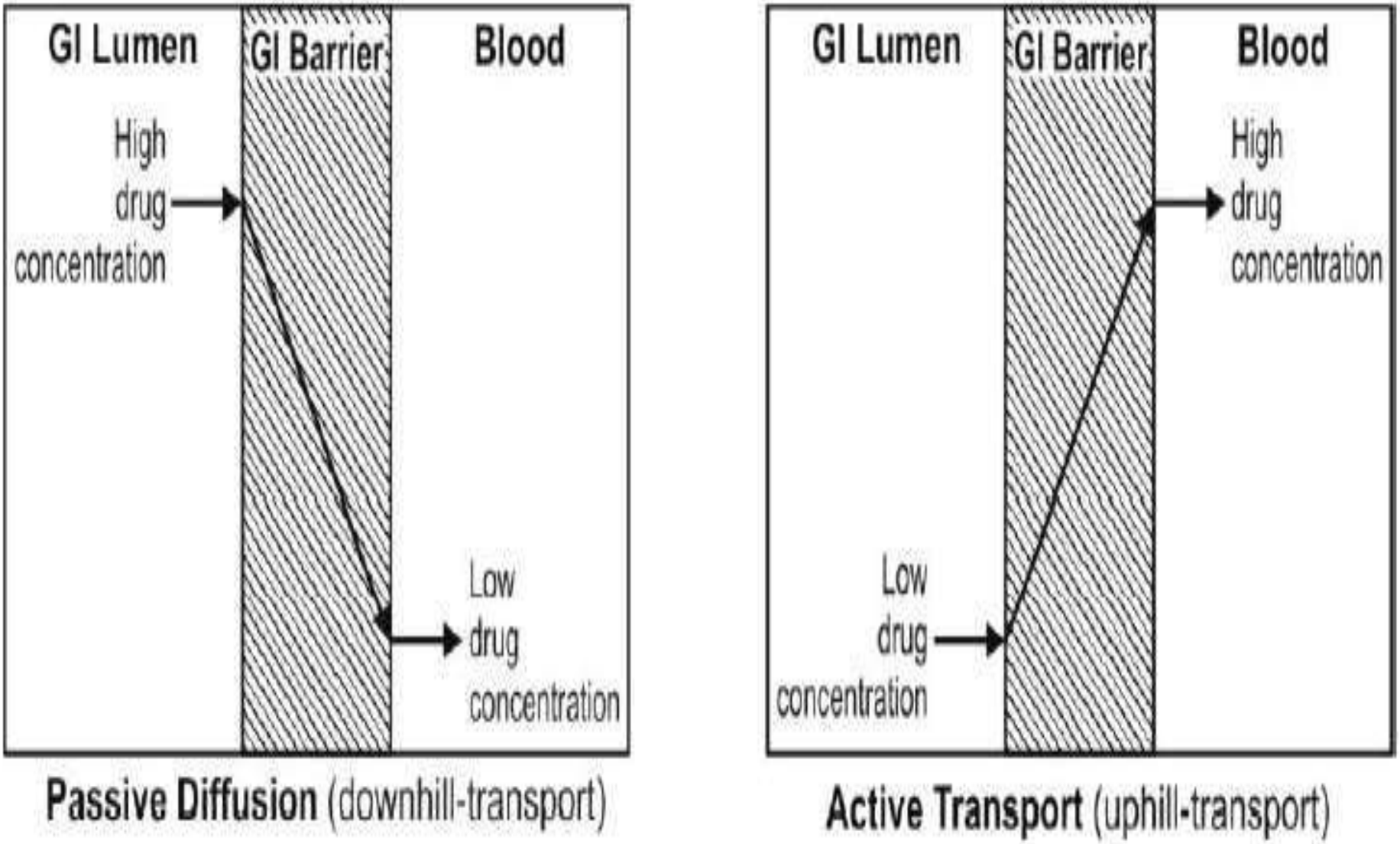


Figure: Comparison between active and passive transport

B. Paracellular/Intercellular Transport:

- *Through the junctions between the GI epithelial cells*.
- Minor importance in drug absorption.
- Involved:

1. Permeation through tight junctions of epithelial cells

Through openings which are little bigger than the aqueous pores. Compounds such as insulin and cardiac glycosides are taken up this mechanism.

2. ***Persorption:***

Through temporary openings formed by shedding of two neighboring epithelial cells into the lumen.

C. Vesicular or Corpuscular Transport (Endocytosis):

- 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.
- Only transport mechanism whereby a drug or compound does not have to be in an aqueous solution in order to be absorbed.

- Vesicular transport of drugs can be classed into two categories –
  - 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 by passing 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.

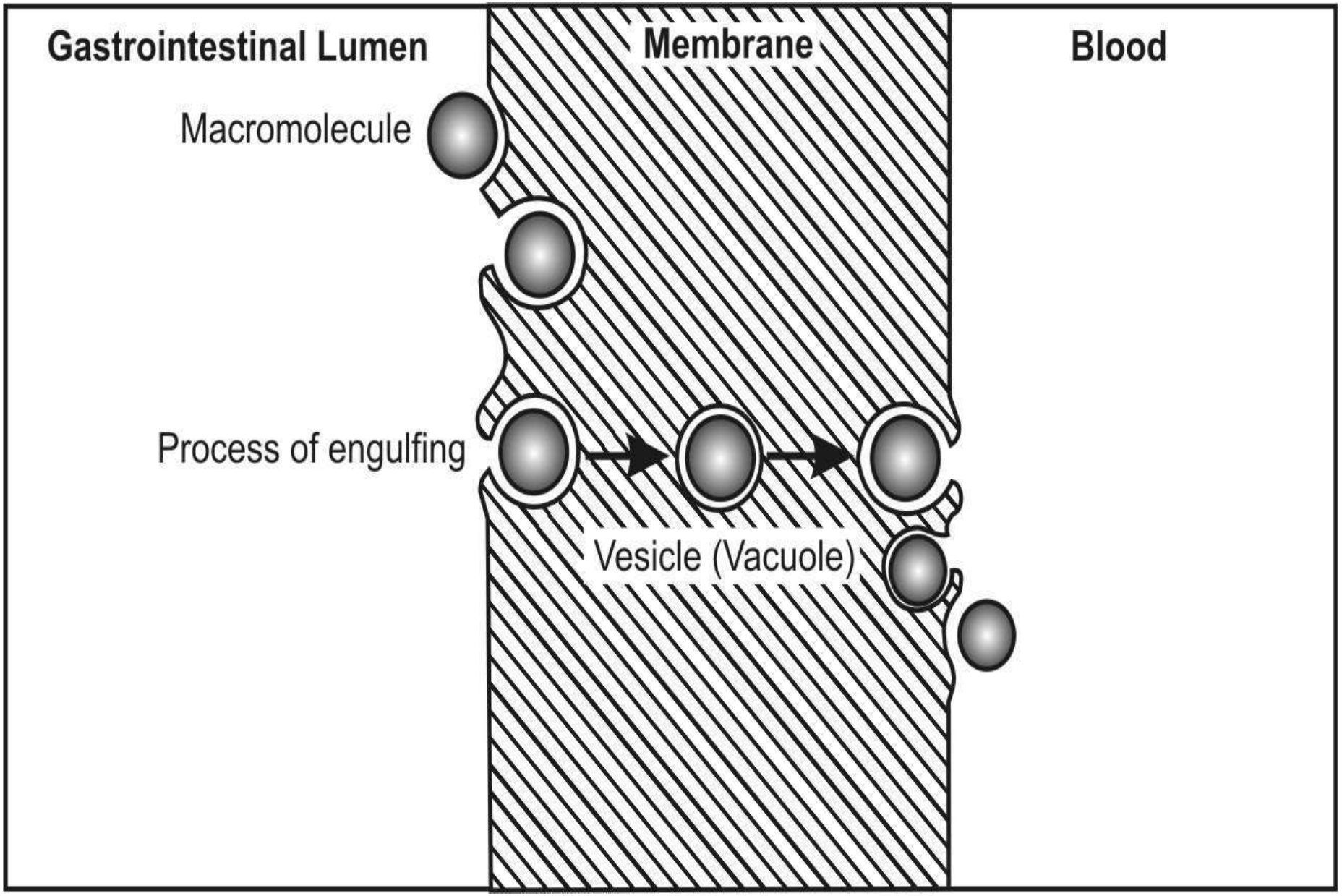


Figure: Endocytic uptake of macromolecule

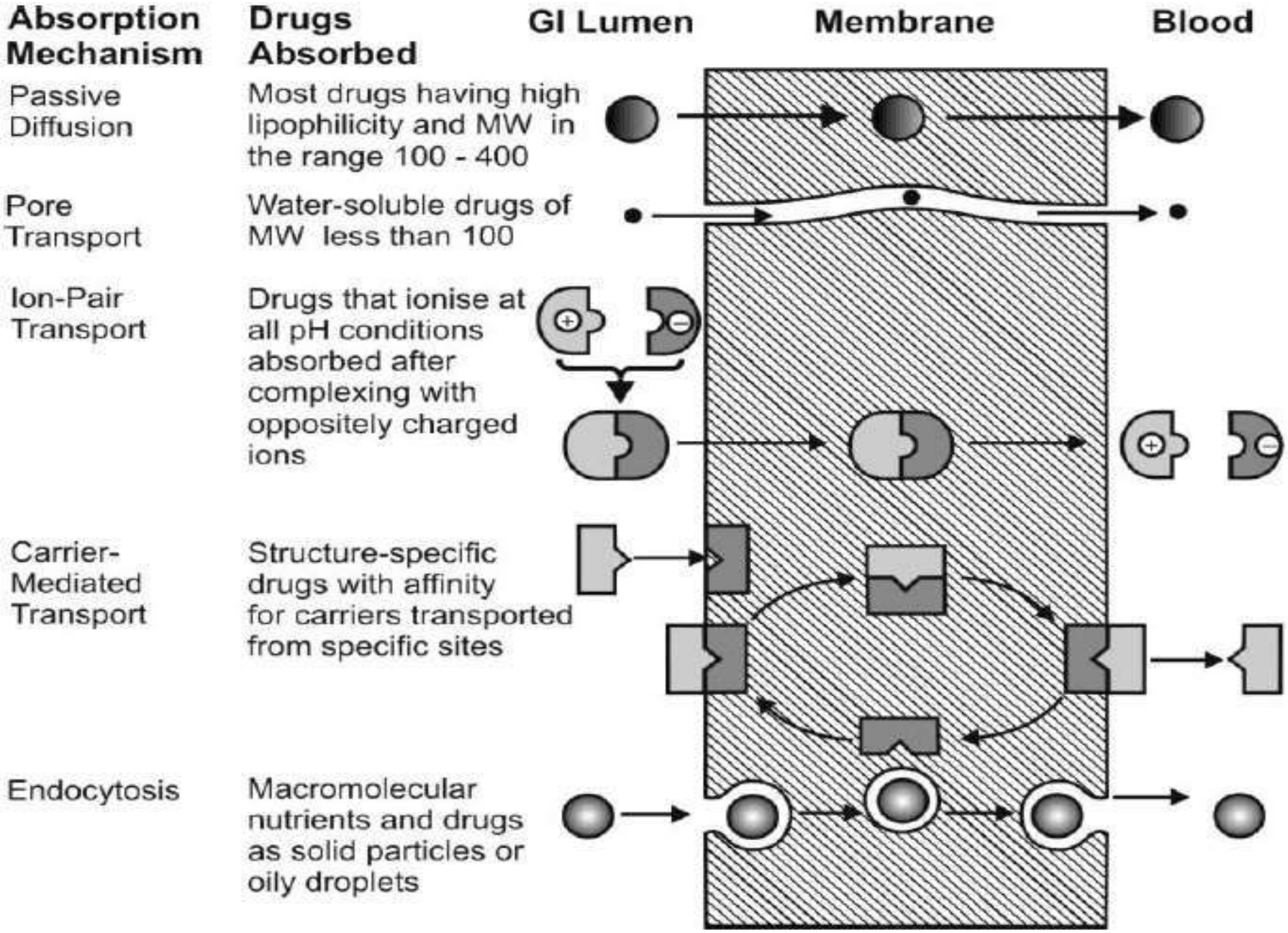


Figure: Summary of important transport processes and drugs absorbed through them

*MECANISMS OF ABSORPTION IN EXTRAVASCULAR ROUTES

- I. m; S. c → Crosse the Capillary endothelium by passive diffusion (Pores).

- Gastric mucosa → passive diffusion and some active transport.

- Small Intestine → All mechanisms.

- Large Intestine → Rectum → passive diffusion and some Pinocytosis

- (Bucal, sublingual, Nasal, Skin Ocular, and Respiratory): passive diffusion