DRUG ABSORPTION

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INTRODUCTION

- A drug injected intravascularly (intravenously and/or intra-arterially) directly enters the systemic circulation and exerts its pharmacological effects.

- If intended to act systemically, such drugs can exert their pharmacological actions only when they come into blood circulation from their site of application,

  for this, absorption is an important prerequisite step.

- **Drug absorption** is defined as the process of movement of unchanged drug from the site of administration to systemic circulation.

- Following absorption, the effectiveness of a drug can only be assessed by its concentration at the site of action.

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

- **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.

- A drug that is completely but slowly absorbed may fail to show therapeutic response as the plasma concentration for desired effect is never achieved.

- On the contrary, a rapidly absorbed drug attains the therapeutic level easily to elicit pharmacological effect.

- Thus, both the rate and the extent of drug absorption are important.

ABSORPTION PATTERN HAS SEVERAL ADVANTAGES:

- Lesser susceptibility of the drug for degradation or interaction due to rapid absorption.
- Higher blood levels and rapid onset of action.
- More uniform, greater and reproducible therapeutic response.

Drugs that have to enter the systemic circulation to exert their effect can be administered by three major routes:

- **The Enteral Route:** includes *peroral* i.e. gastrointestinal, sublingual/buccal and rectal routes. The GI route is the most common for administration of majority of drugs.

- **The Parenteral Route:** includes all routes of administration through or under one or more layers of skin. While no absorption is required when the drug is administered i.v., it is necessary for extravascular parenteral routes like the subcutaneous and the intramuscular routes.

- **The Topical Route:** includes skin, eyes or other specific membranes. The intranasal, inhalation, intravaginal and transdermal routes may be considered enteral or topical according to different definitions.

BIOAVAILABILITY/ABSORPTION OF DRUG FROM COMMON ROUTES OF DRUG ADMINISTRATION

PARENTERAL ROUTE

ROUTE	BIOAVAILABILITY	ADVANTAGES	DISADVANTAGES
Intravenous (IV)	· Complete (100%) systemic drug absorption.	· Drug is given for immediate or controlled effect.	· Increased chance for adverse reaction.
		· May inject large fluid volumes.	· Possible anaphylaxis.
		· Suitable for irritating drugs	· Requires skill in insertion of infusion set.
			· Tissue damage at site of injection (infiltration, necrosis, or sterile abscess).
Intramuscular injection (IM)	· Rapid absorption from aqueous solutions. · Slow absorption from non-aqueous (oily) solutions.	· Easier to inject than intravenous injection. · Larger volumes may be used compared to subcutaneous solution.	· Irritating drugs may be very painful. · Variable rates of absorption depending upon muscle group injected and blood flow.
Subcutaneous injection (SC)	· Rapid absorption from aqueous solution. · Slow absorption from depot formulations.	· Generally, used for vaccines and drugs not absorbed orally e.g. insulin.	· Rate of drug absorption depends upon blood flow and injection volume.

ENTERAL ROUTE

ROUTE	BIOAVAILABILITY	ADVANTAGES	DISADVANTAGES
Buccal or sublingual (SL)	· Rapid absorption of lipid-soluble drugs.	No presystemic metabolism.	· Some drug may be swallowed. Not for most drugs or drugs with high doses.
Oral (PO)	· Absorption may vary. Generally slower absorption rate compared to IV bolus or IM injection.	· Safest and easiest route of drug administration. · Suitable for both immediate-release and modified-release drug products.	· Some drugs are unstable in GIT, or undergo presystemic metabolism or show erratic absorption.
Rectal (PR)	· Absorption may vary from suppository.	· Useful when patient cannot swallow medication.	· Absorption may be erratic. Suppository may migrate to different position.
	· More reliable absorption from enema (solution).	· Used for local and systemic effects.	· Some patient discomfort.

OTHER ROUTES

ROUTE	BIOAVAILABILITY	ADVANTAGES	DISADVANTAGES
Transdermal	· Slow absorption, rate may vary. · Increased absorption with occlusive dressings.	· Transdermal delivery system (patch) is easy to use and withdraw. · Continuous release for a specified period. · Used for lipid-soluble drugs with low dose and low MW. · Low presystemic metabolism.	· Some irritation by patch or drug. · Permeability of skin variable with condition, anatomic site, age, and gender. · Type of cream or ointment base affects drug release and absorption.
Inhalation	· Rapid absorption.	· May be used for local or systemic effects.	· Particle size of drug determines anatomic placement in respiratory tract.

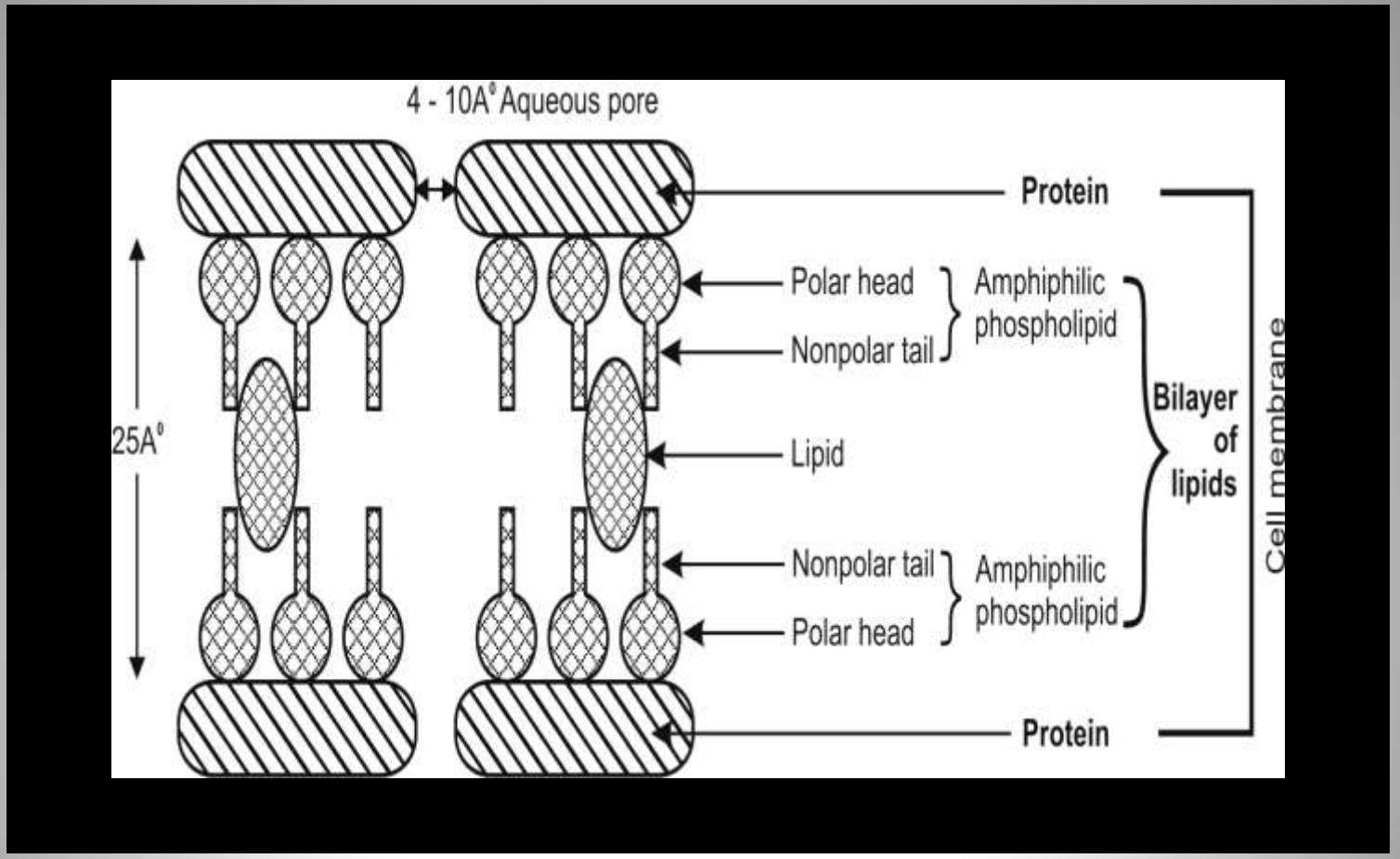
GASTROINTESTINAL ABSORPTION OF DRUGS

CELL MEMBRANE: STRUCTURE AND PHYSIOLOGY

- For a drug to be absorbed and distributed into organs and tissues and eliminated from the body, it must pass through one or more biological membranes/barriers at various locations.

- Such a *movement of drug across the membrane* is called as **Drug transport**.

BASIC STRUCTURE OF CELL MEMBRANE



MECHANISMS OF DRUG ABSORPTION

- The three broad categories of drug transport mechanisms involved in absorption are –
  - **Transcellular / intracellular transport**
  - **Paracellular / intercellular transport**
  - **Vesicular transport**

TRANSCELLULAR / INTRACELLULAR TRANSPORT

- ***Transcellular/Intracellular Transport*** *– is defined as the passage of drugs across the GI epithelium*. It is the most common pathway for drug transport.

- The 3 steps involved in transcellular transport of drugs are –

  - Permeation of GI epithelial cell membrane, a lipoidal barrier – this is the major obstacle to drug absorption.

  - Movement across the intracellular space (cytosol).

  - Permeation of the lateral or basolateral membrane- this is of secondary importance.

VARIOUS TRANSCELLULAR TRANSPORT PROCESSES

Passive Transport Processes –

- ✓ These transport processes do not require energy other than that of molecular motion (Brownian motion) to pass through the lipid bilayer.
- ✓ Passive transport processes can be further classified into following types –
  - Passive diffusion.
  - Pore transport.
  - Ion-pair transport.
  - Facilitated- or mediated-diffusion.

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).

PARACELLULAR / INTERCELLULAR TRANSPORT

- **Paracellular/Intercellular Transport** – is defined as the transport of drugs through the junctions between the GI epithelial cells.

- 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.

Paracellular transport differs from pore transport

- ✓ Paracellular transport involves transfer of drug across epithelium and through the cellular junctions

- ✓ In case of pore transport, the molecules are transferred from outside of the epithelial cell into the cell through pores present in the cell membrane.

VESICULAR OR CORPUSCULAR TRANSPORT

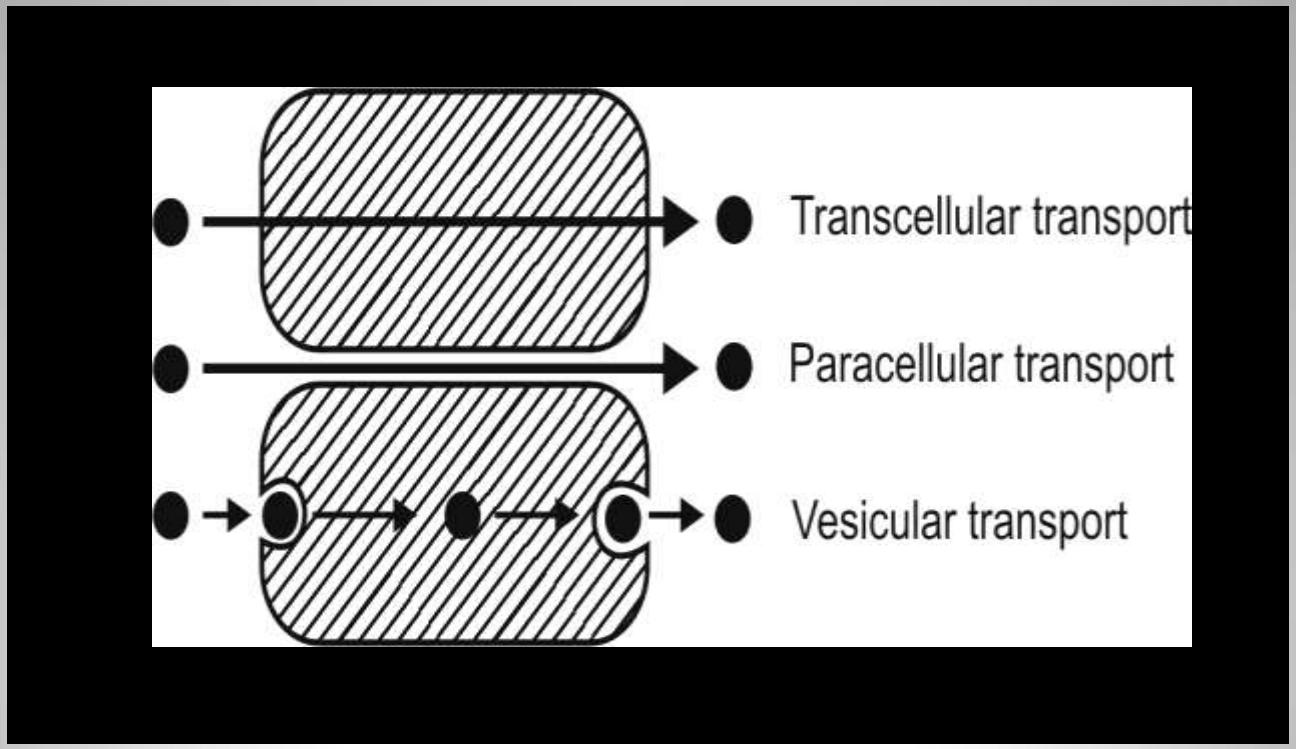
Vesicular or ***Corpuscular Transport (Endocytosis)***

- 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 two categories

  Pinocytosis.

  Phagocytosis.

ILLUSTRATIVE COMPARISON OF TRANSCELLULAR, PARACELLULAR AND VESICULAR TRANSPORT MECHANISMS



PASSIVE DIFFUSION

- Also called **non-ionic diffusion**
- It is the major process for absorption of more than 90% of the drugs.
- The driving force for this process is the **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.

- During passive diffusion, the drug present in the aqueous solution at the absorption site partitions and dissolves in the lipid material of the membrane and finally leaves it by dissolving again in an aqueous medium, this time at the inside of the membrane.

- Passive diffusion is best expressed by FICK'S FIRST LAW OF DIFFUSION,

  - ***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.***

- It can be mathematically expressed by the following equation:

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

- Where,
  - **dQ/dt = rate of drug diffusion (amount/time). It also represents 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 the lipoidal membrane and the aqueous GI fluids (no units)**
  - **(CGIT – C) = difference in the concentration of drug in the GI fluids and the plasma, called as the concentration gradient (amount/volume)**
  - **h = thickness of the membrane (length)**

CHARACTERISTICS OF PASSIVE DIFFUSION

- The drug moves down the concentration gradient indicating *downhill transport.*
- The process is energy-independent and non-saturable.
- The rate of drug transfer is directly proportional to the concentration gradient between GI fluids and the blood compartment.
- Greater the area and lesser the thickness of the membrane, faster the diffusion; thus, more rapid is the rate of drug absorption from the intestine than from the stomach.
- The process is rapid over short distances and slower over long distances.

- Equilibrium is attained when the concentration on either side of the membrane becomes equal.

- Drugs which can exist in both ionised and unionised forms approach equilibrium primarily by the transfer of the unionised species; the rate of transfer of unionised species is 3 to 4 times the rate for ionised drugs.

- Greater the membrane/water partition coefficient of drug, faster the absorption; since the membrane is lipoidal in nature, a lipophilic drug diffuses at a faster rate by solubilising in the lipid layer of the membrane.

- The drug diffuses rapidly when the volume of GI fluid is low; conversely, dilution of GI fluids decreases the drug concentration in these fluids (C_{GIT}) and lower the concentration gradient ($C_{GIT - C}$).

  This phenomenon is, however, made use of in treating cases of oral overdose or poisoning.

- The process is dependent, to a lesser extent, on the square root of the molecular size of the drug –

  Drugs having molecular weights between 100 to 400 Daltons are effectively absorbed passively.

- The diffusion generally decreases with increase in the molecular weight of the compound.

  Exceptions—for example, cyclosporine A, a peptide of molecular weight 1200, is absorbed orally much better than any other peptide.

- Initially, when the drug is ingested, CGIT >> C and a large concentration gradient exists thereby acting as the driving force for absorption.

- As equilibrium approaches, the drug diffusion should stop and consequently a large fraction of drug may remain unabsorbed.

- But this is not the case; once the passively absorbed drug enters blood, it is rapidly swept away and distributed into a much larger volume of body fluids

  hence, the concentration of drug at the absorption site, CGIT, is maintained greater than the concentration of drug in plasma.

- Such a condition is called as **sink condition** for drug absorption.

- As a result, equation may be simplified to

$$\frac{dQ}{dt} = PC_{GIT}$$

- It is an expression for a first-order process.
- Thus, passive diffusion follows first-order kinetics.
- Since a large concentration gradient always exists at the absorption site for passive diffusion, the rate of drug absorption is usually more rapid than the rate of elimination.
- Besides, dilution and distribution of the absorbed drug into a large pool of body fluids and its subsequent binding to various tissues are other reasons for elimination being slower than absorption.

RELATIVE PASSIVE DIFFUSION RATE OF DIFFERENT TYPES OF MOLECULES

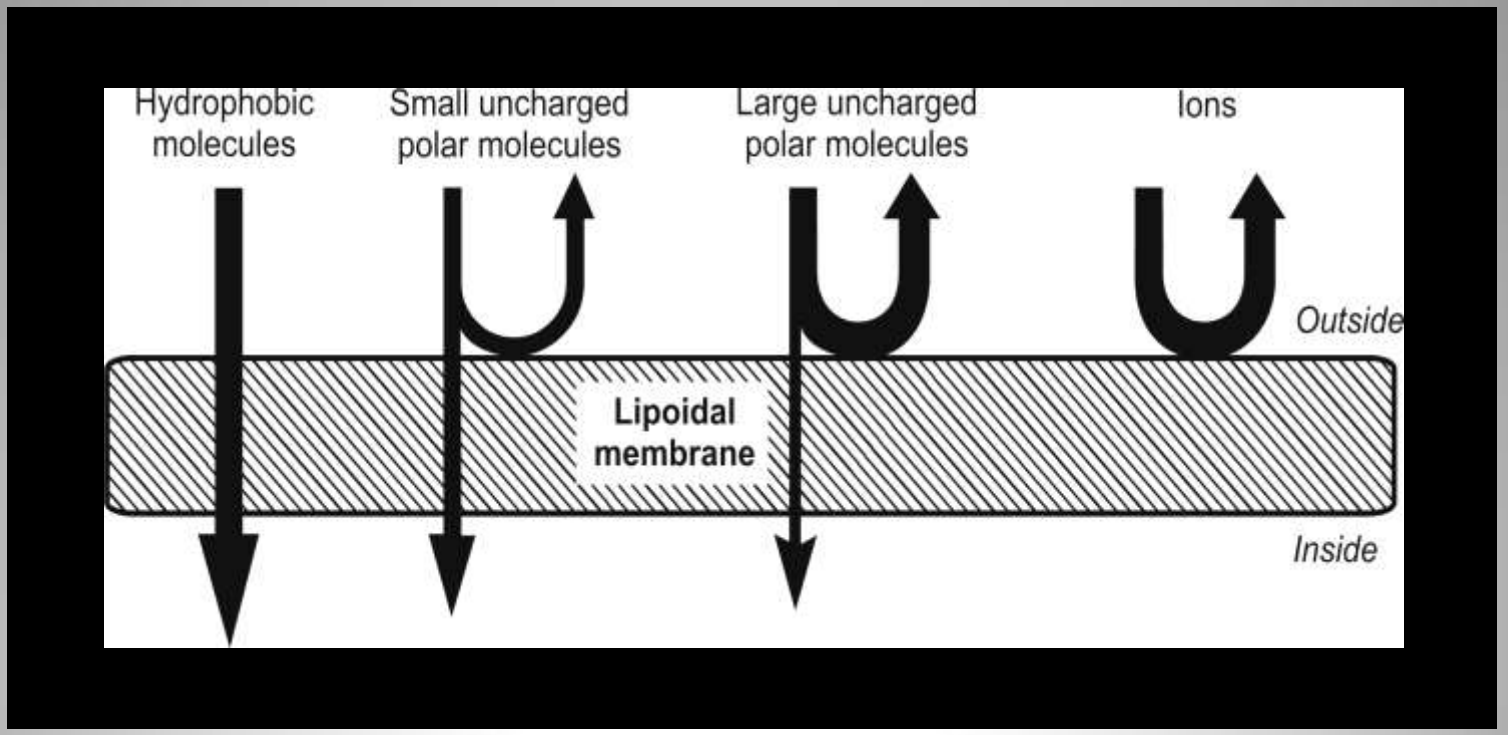


ILLUSTRATION OF THE RELATIVE PERMEABILITY OF DIFFERENT MOLECULES TO LIPID BILAYER.

PORE TRANSPORT

- It is also called as **convective transport**, **bulk flow** or **filtration**.

- This mechanism is responsible for transport of molecules into the cell through the protein channels present in the cell membrane.

CHARACTERISTICS OF PORE TRANSPORT

- The driving force is constituted by the hydrostatic pressure or the osmotic differences across the membrane due to which bulk flow of water along with small solid molecules occurs through such aqueous channels.

  Water flux that promotes such a transport is called as **solvent drag**.

- The process is important in the absorption of low molecular weight (less than 100), low molecular size (smaller than the diameter of the pore) and generally water-soluble drugs through narrow, aqueous-filled channels or pores in the membrane structure—for example, urea, water and sugars.

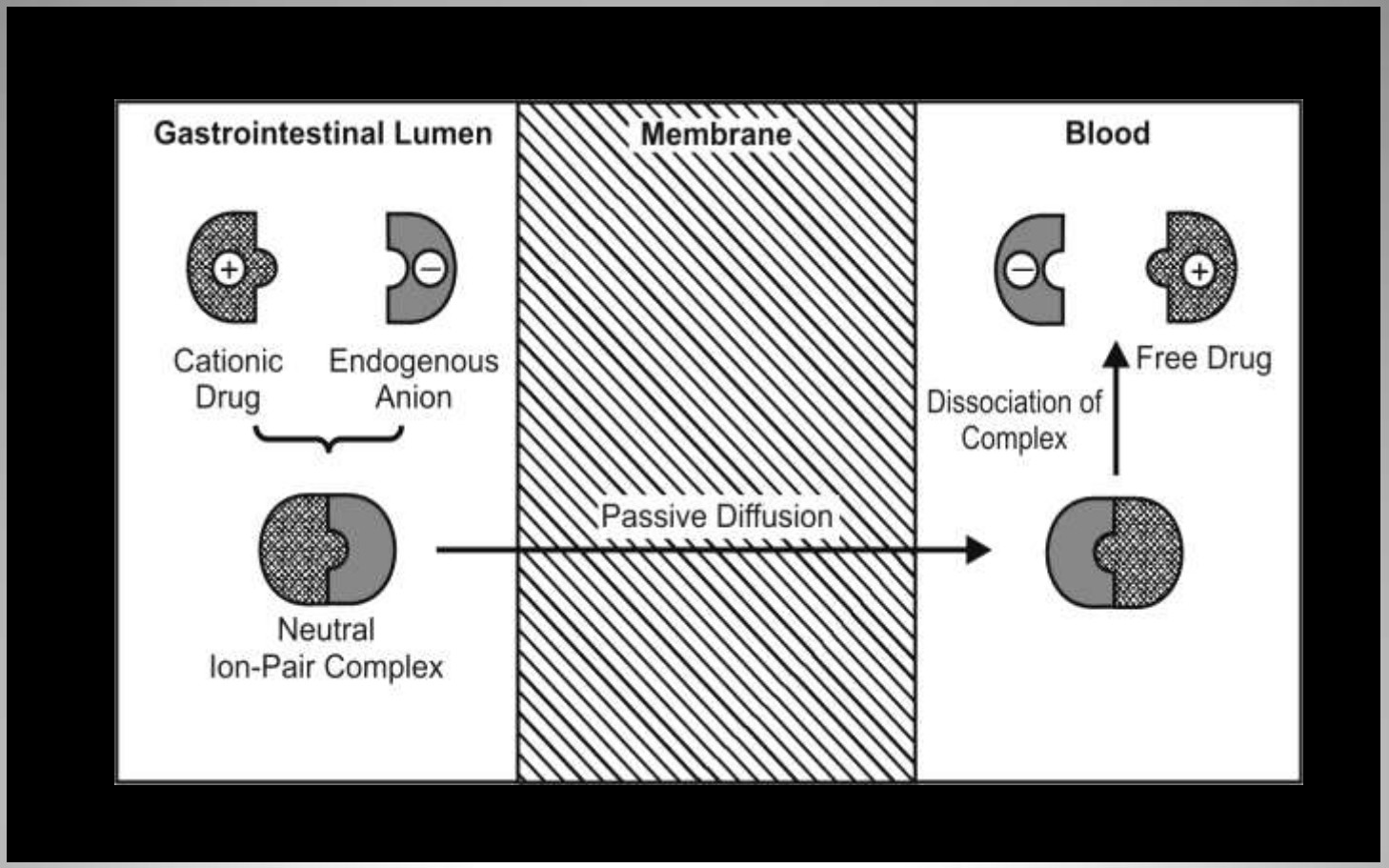
- Chain-like or linear compounds of molecular weight up to 400 Daltons can be absorbed by filtration.

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

ION-PAIR TRANSPORT

- Mechanism that explains the 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.

- This suggests presence of specialized transport mechanisms without which many essential water-soluble nutrients like monosaccharides, amino acids and vitamins will be poorly absorbed.

- The mechanism is thought to involve a component of the membrane called as the *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.
- They are numerous in all biological membranes and are found dissolved in the lipid bilayer of the membrane.

IMPORTANT CHARACTERISTICS OF CARRIER-MEDIATED TRANSPORT

- A carrier protein always has an uncharged (non-polar) outer surface which allows it to be soluble within the lipid of the membrane.
- The carriers have no directionality; they work with same efficiency in both directions.
- The transport process is structure-specific i.e. the carriers have special affinity for and transfer a drug of specific chemical structure only (i.e. lock and key arrangement); generally the carriers have special affinity for essential nutrients.

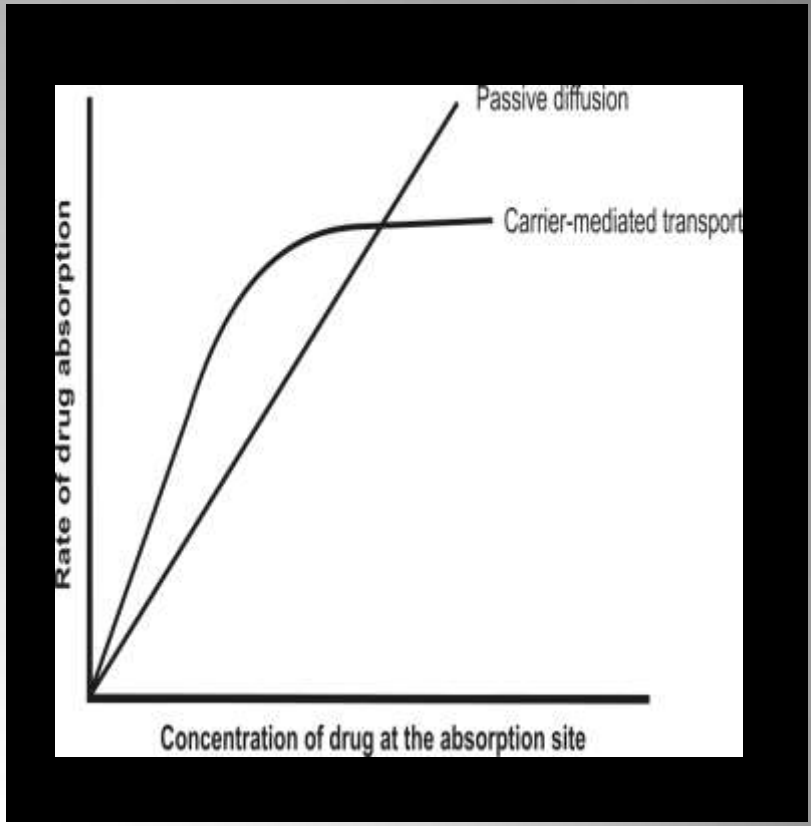
- Since the system is structure-specific, drugs having structure similar to essential nutrients, called as ***false nutrients***, are absorbed by the same carrier system.

  This mechanism is of particular importance in the absorption of several antineoplastic agents like **5-fluorouracil** and **5-bromouracil** which serve as false nutrients.

- As the number of carriers is limited, the transport system is subject to competition between agents having similar structure.

- Since the number of carriers is limited, the system is capacity-limited i.e. at higher drug concentration; the system becomes saturated and approaches an asymptote

- Such a capacity-limited process can be adequately described by **mixed order kinetics**, also called as **Michaelis-Menten, saturation** or **non-linear kinetics**



- Specialized absorption or carrier-mediated absorption generally occurs from specific sites of the intestinal tract which are rich in number of carriers.

  Such *an area in which the carrier system is most dense* is called as **absorption window**. Drugs absorbed through such absorption windows are poor candidates for controlled release formulations.

- Two types of carrier-mediated transport systems include

  - **Facilitated diffusion and**
  - **Active transport.**

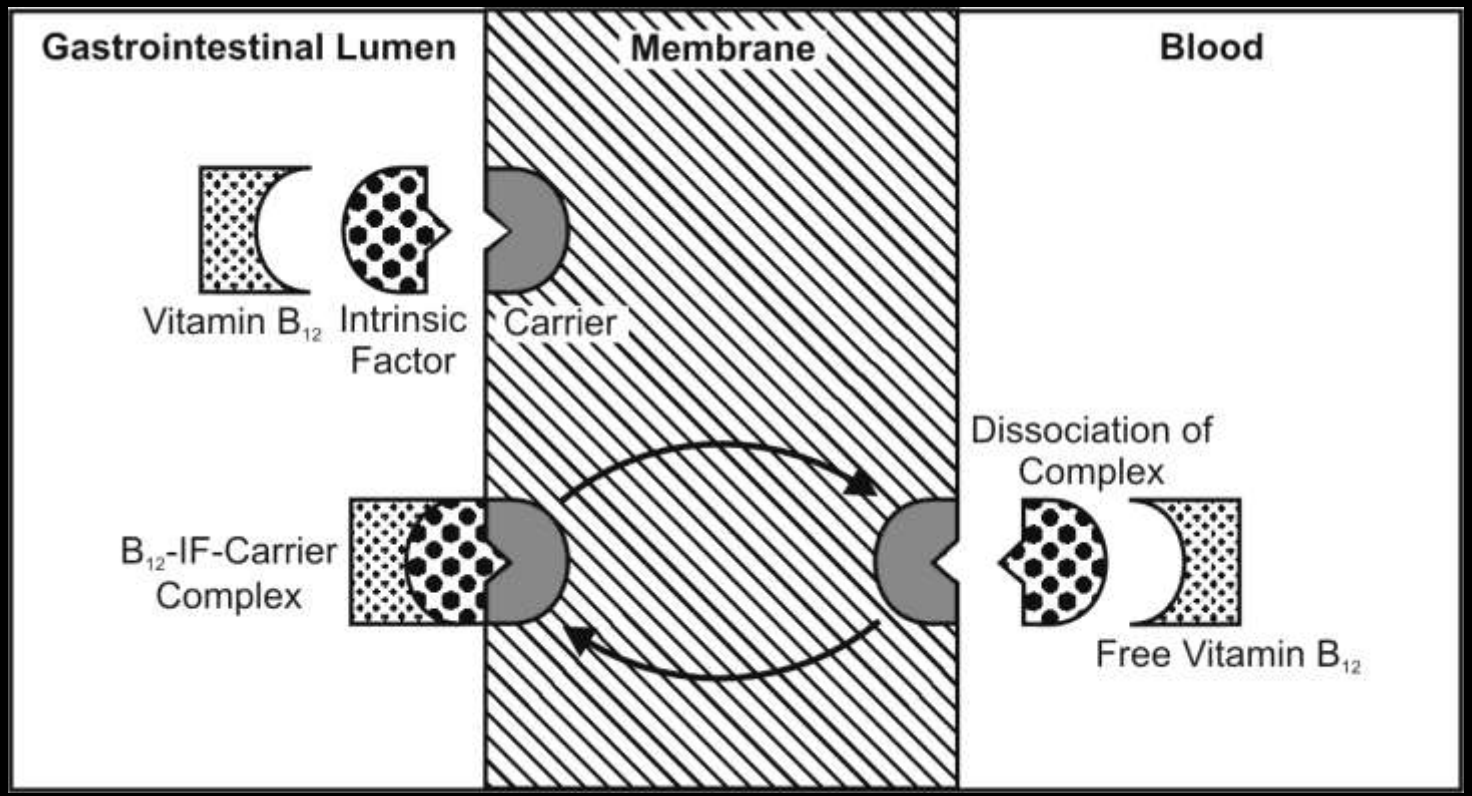
FACILITATED DIFFUSION

- 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

- Facilitated diffusion is of limited importance in the absorption of drugs.

- Examples of such a transport system include entry of glucose into RBCs and intestinal absorption of vitamins B1 and B2.
- A classic example of passive facilitated diffusion is the GI absorption of vitamin B12.
- An intrinsic factor (IF), a glycoprotein produced by the gastric parietal cells, forms a complex with vitamin B12 which is then transported across the intestinal membrane by a carrier system



FACILITATED DIFFUSION OF VITAMIN B12

ACTIVE TRANSPORT

- This transport mechanism requires energy in the form ATP. Active transport mechanisms are further subdivided into –
  - *Primary active transport*
  - *Secondary active transport*

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. Carrier proteins involved in primary active transport are of two types –
  - *Ion transporters*
  - *ABC (ATP-binding cassette) transporters*

ION TRANSPORTERS

- Responsible for transporting ions in or out of cells.
- A classic example of ATP-driven ion pump is *proton pump* which is implicated in acidification of intracellular compartments.
- Two types of ion transporters which play important role in the intestinal absorption of drugs have been identified –

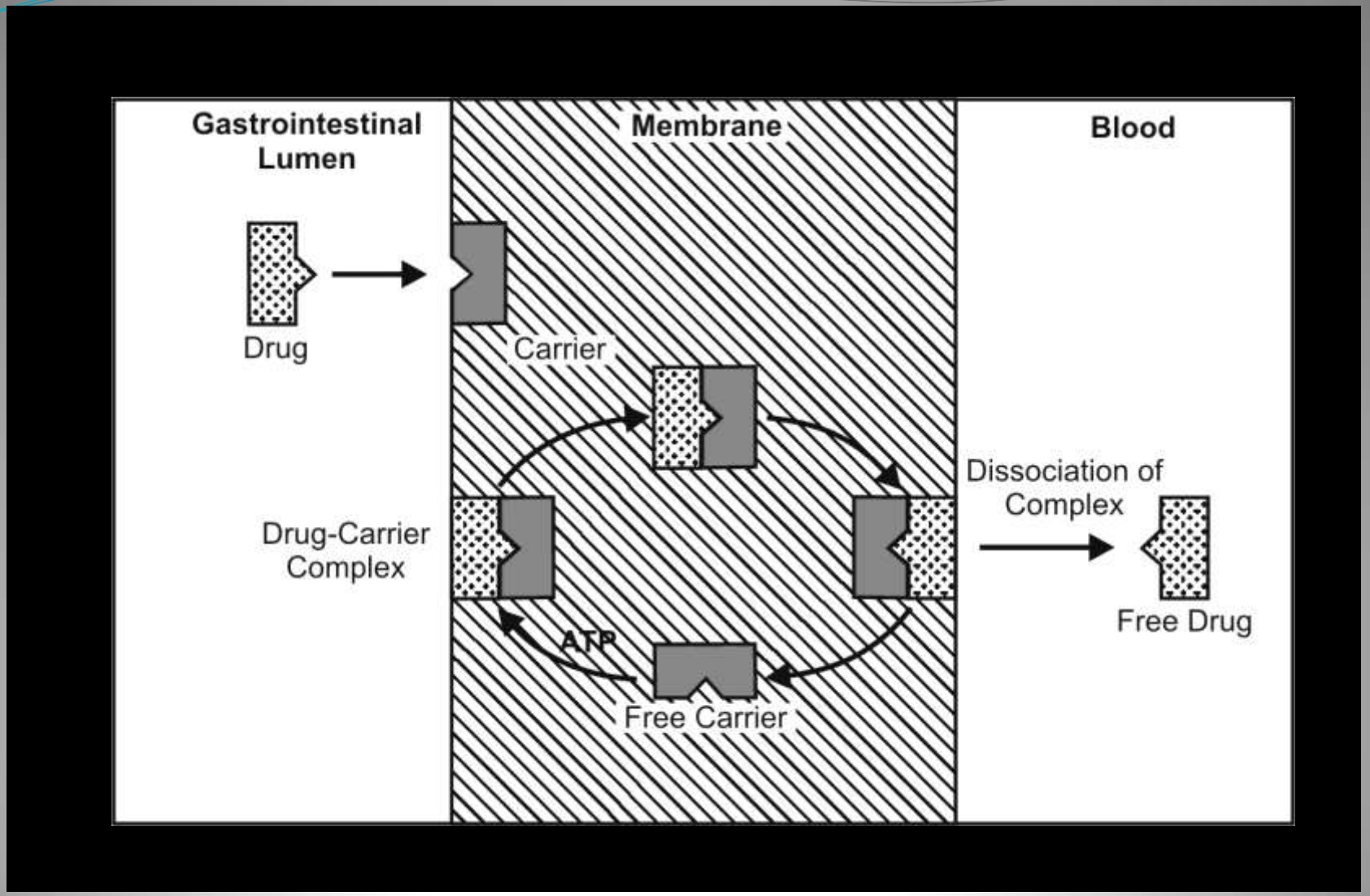
  - ***Organic anion transporter*** – which aids absorption of drugs such as pravastatin and atorvastatin.

  - ***Organic cation transporter*** – which aids absorption of drugs such as diphenhydramine.

ABC (ATP-binding cassette) transporters

- Responsible for transporting small foreign molecules (like drugs and toxins) especially out of cells (and thus called as *efflux pumps*) which make them clinically important.

- A classic example of ABC transporter is *P-glycoprotein* (P-gp).



Active absorption of a drug

Active transport is a more important process than facilitated diffusion in the absorption of nutrients and drugs and differs from it in several respects:

- The drug is transported from a region of lower to one of higher concentration i.e. against the concentration gradient (in the case of ions, against an electrochemical gradient) or *uphill transport*, without any regard for equilibrium.
- The process is faster than passive diffusion.
- Since the process is uphill, energy is required in the work done by the carrier.
- As the process requires expenditure of energy, it can be inhibited by metabolic poisons that interfere with energy production like fluorides, cyanide and dinitrophenol and lack of oxygen, etc.

- Endogenous substances that are transported actively include sodium, potassium, calcium, iron, glucose, certain amino acids and vitamins like niacin, pyridoxin and ascorbic acid.

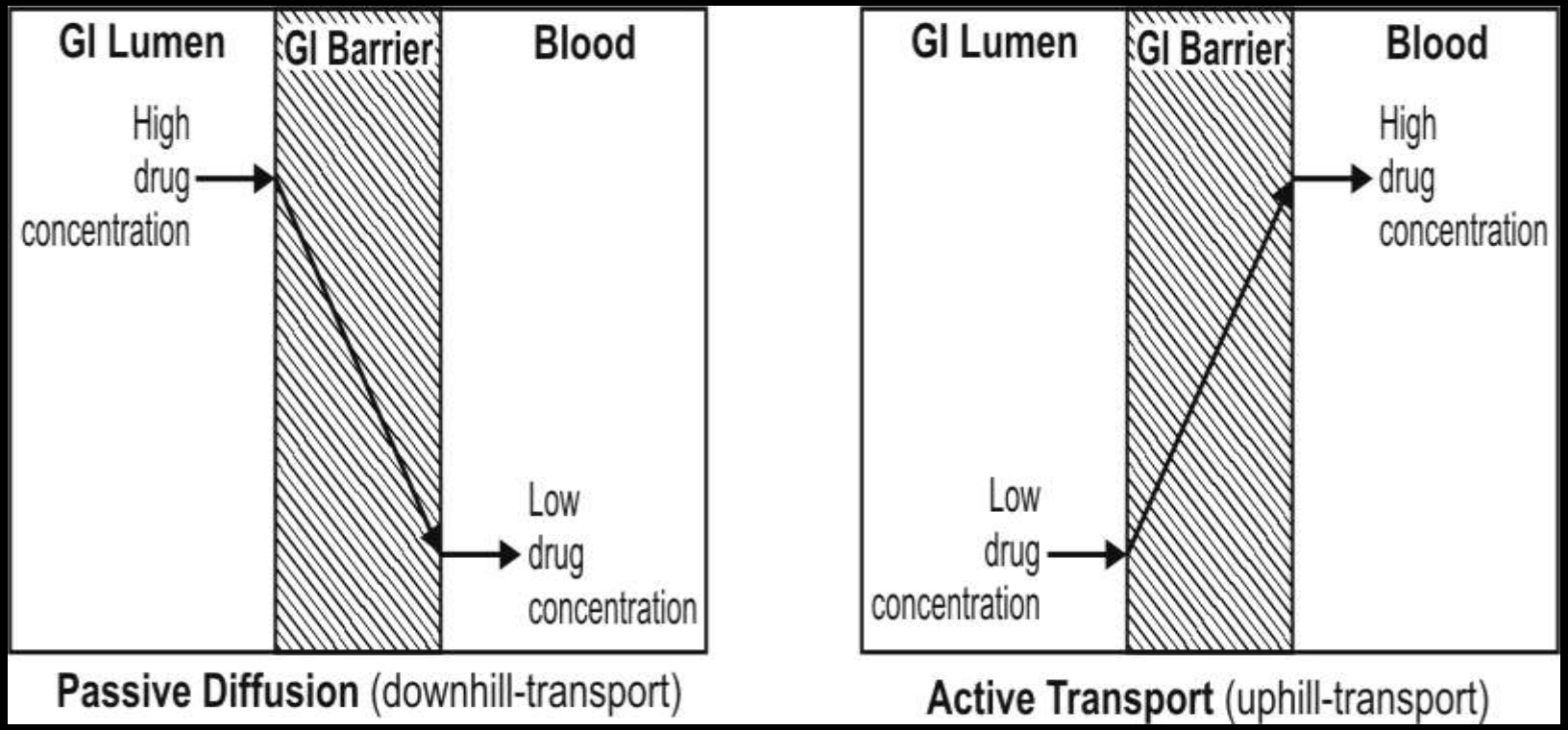
- Drugs having structural similarity to such agents are absorbed actively, particularly the agents useful in cancer chemotherapy.

- Examples include absorption of 5-fluorouracil and 5-bromouracil via the pyrimidine transport system, absorption of methyldopa and levodopa via an L-amino acid transport system and absorption of ACE inhibitor enalapril via the small peptide carrier system.

- A good example of competitive inhibition of drug absorption via active transport is the impaired absorption of levodopa when ingested with meals rich in proteins.

- Active transport is also important in renal and biliary excretion of many drugs and their metabolites and secretion of certain acids out of the CNS.

COMPARISON BETWEEN ACTIVE AND PASSIVE TRANSPORT

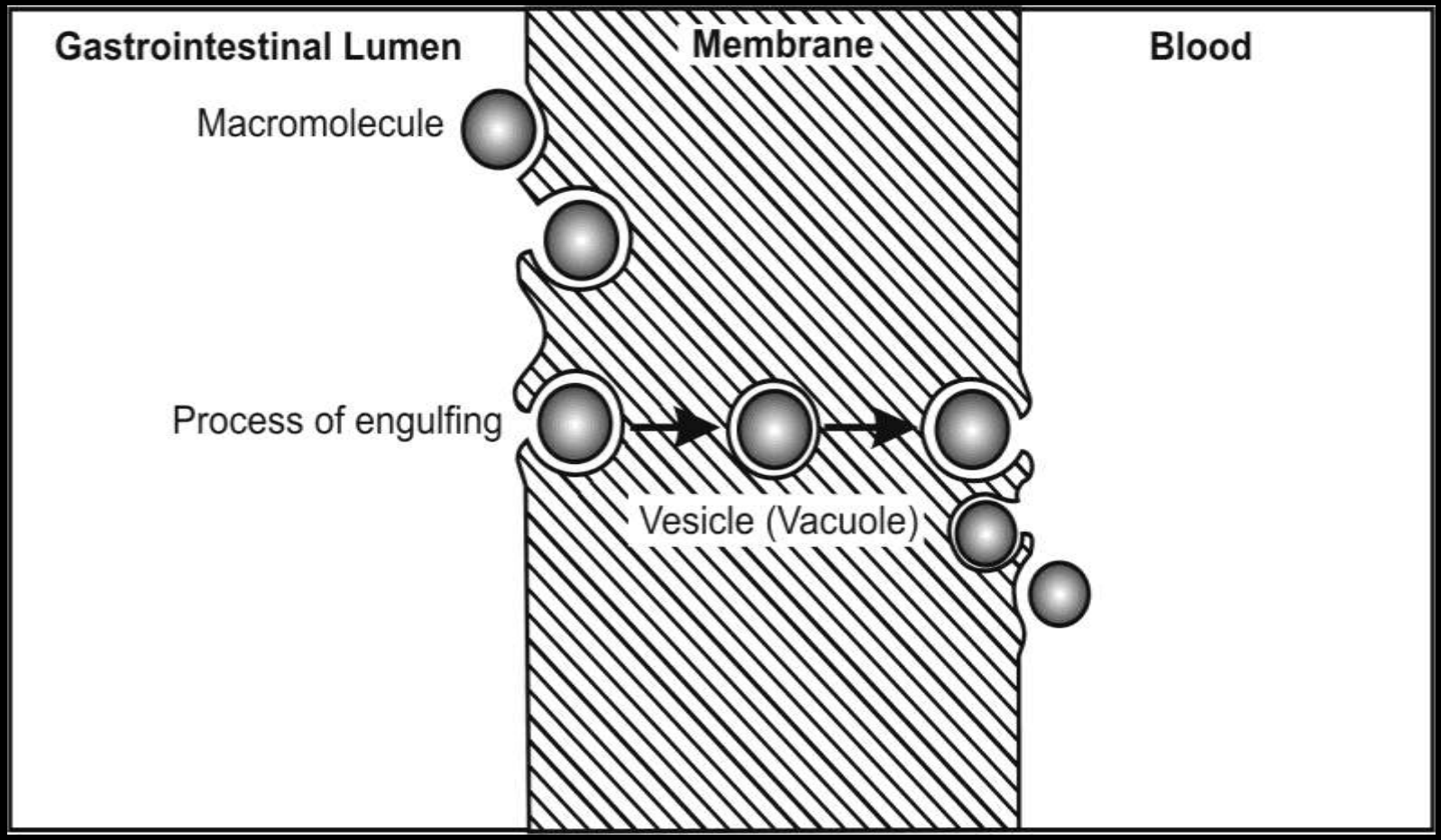


ENDOCYTOSIS

- It is a minor transport mechanism which involves engulfing extracellular materials within a segment of the cell membrane to form a saccule or a vesicle (hence also called as **corpuscular** or **vesicular transport)** which is then pinched-off intracellularly

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

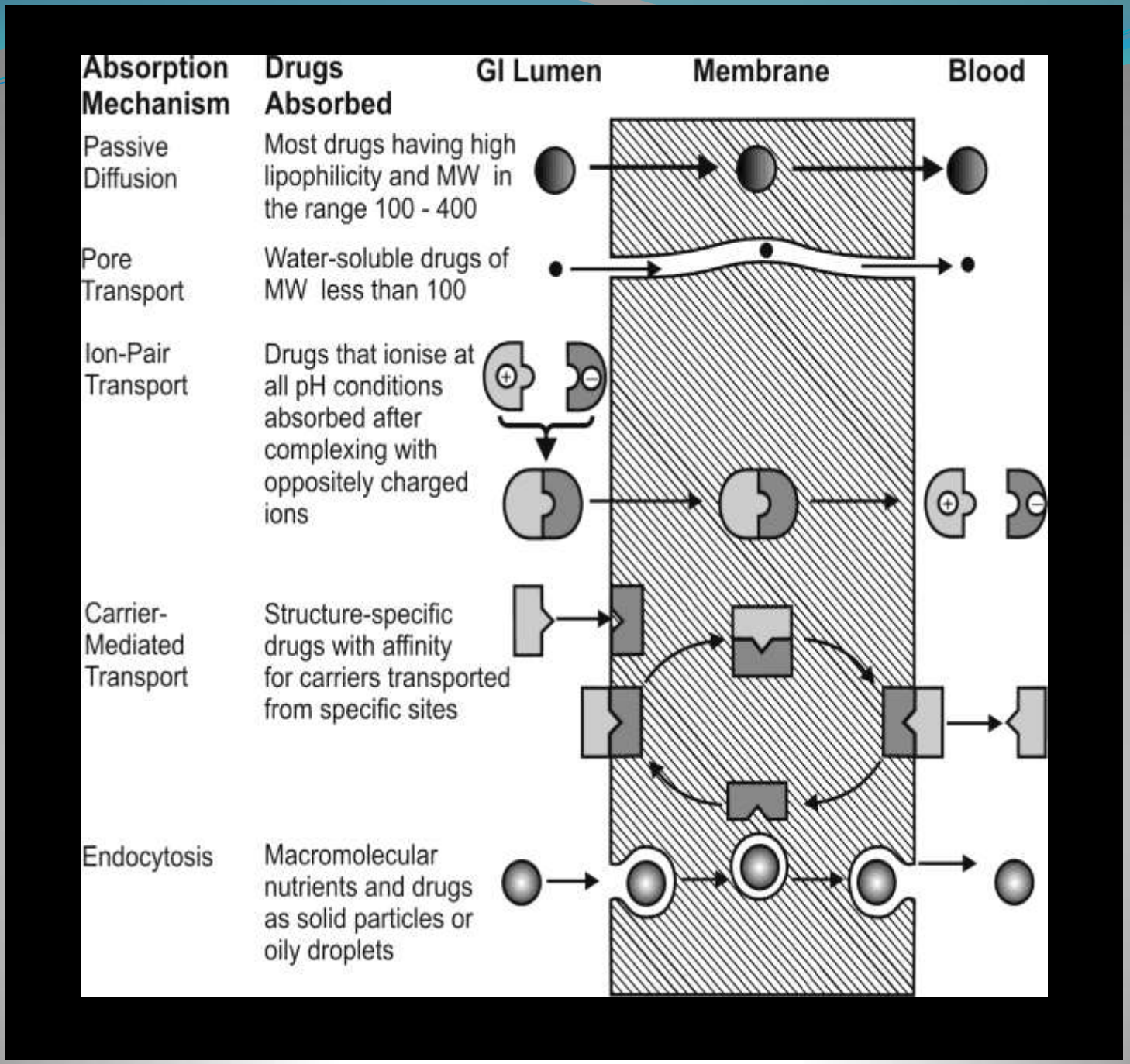
ENDOCYTIC UPTAKE OF MACROMOLECULES



- 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 B12 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.**
- Orally administered Sabin polio vaccine, large protein molecules and the botulism toxin (that causes food poisoning) are thought to be absorbed by **pinocytosis.**
- Sometimes, an endocytic vesicle is transferred from one extracellular compartment to another. Such a phenomenon is called as **transcytosis.**


Absorption Mechanism
Drugs Absorbed
GI Lumen
Membrane
Blood
Passive Diffusion
Most drugs having high lipophilicity and MW in the range 100 - 400
Pore Transport
Water-soluble drugs of MW less than 100
Ion-Pair Transport
Drugs that ionise at all pH conditions absorbed after complexing with oppositely charged ions
Carrier-Mediated Transport
Structure-specific drugs with affinity for carriers transported from specific sites
Endocytosis
Macromolecular nutrients and drugs as solid particles or oily droplets