

Pharmacokinetics: Absorption (Drug Transport across Biological Membranes)

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PHARMACOKINETICS

- ✓ Pharmacokinetics is the quantitative study of drug movement **in, through** and **out** of the body.
- ✓ It studies the processes of **absorption, distribution, metabolism** and **excretion** of drugs (how the body affects the drugs; **movement** or **disposition** of drugs in the body).
- ✓ It quantifies the **fate of a drug** by measurement of its concentration and metabolites in blood and urine over a period of time after its administration.

Pharmacokinetic (PK) processes

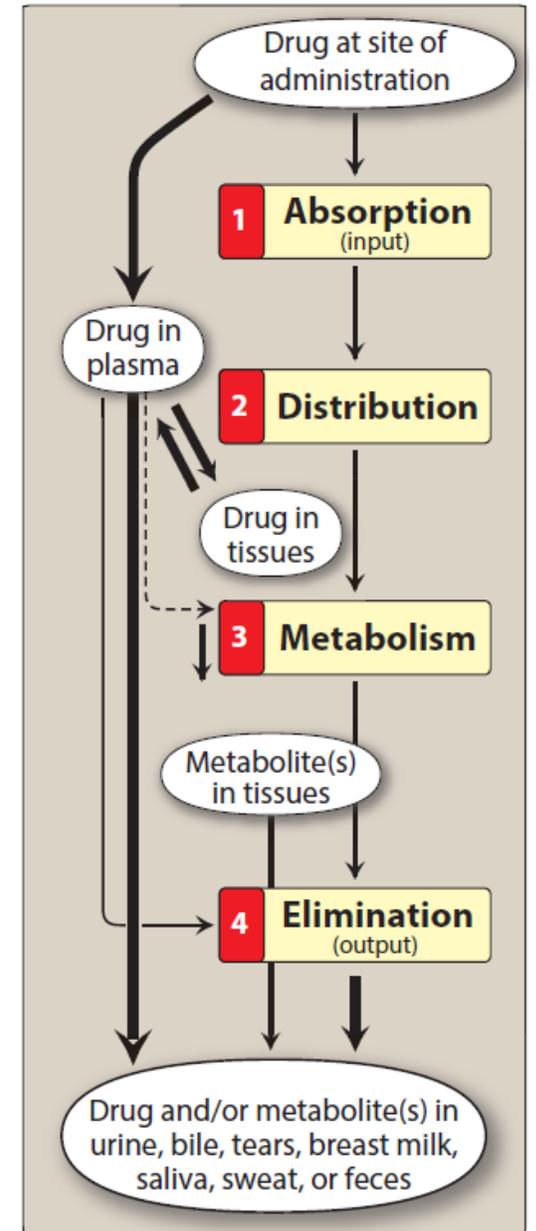
- ✓ Four pharmacokinetic properties determine the **onset, intensity**, and the **duration** of drug action.

Absorption: First, absorption from the site of administration **permits entry of the drug** (either directly or indirectly) **into plasma**.

Distribution: Second, the drug may then reversibly **leave the bloodstream** and **distribute into the interstitial and intracellular fluids**.

Metabolism: Third, the drug may be **biotransformed by metabolism** by the **liver or other tissues**.

Elimination: Finally, the drug and its metabolites are **eliminated from the body in urine, bile, or faeces**.



Source: Lippincott's Pharmacology (6th Edn.)

Pharmacokinetic (PK) processes

contd...

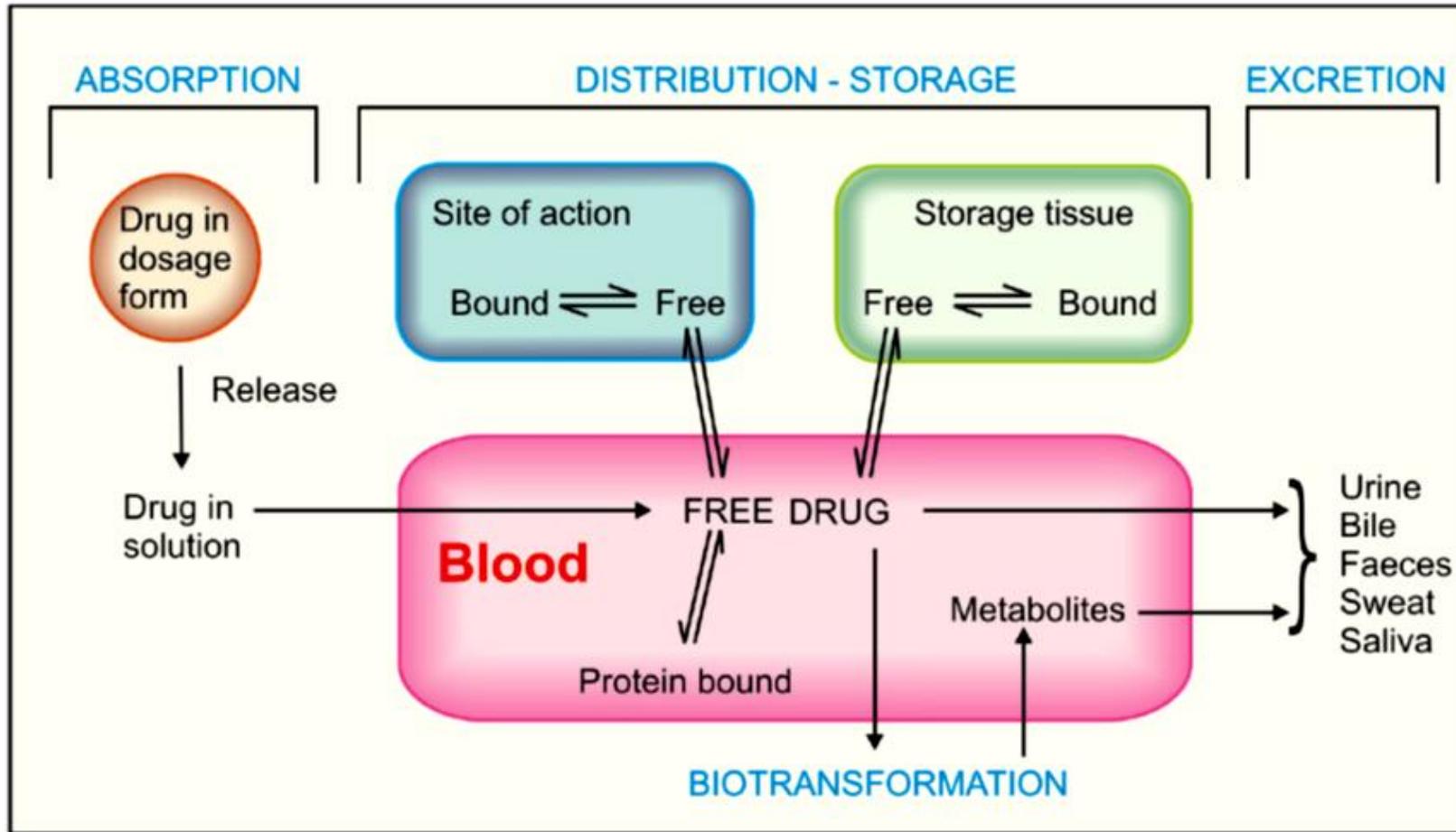


Figure:
Schematic depiction of pharmacokinetic processes

Source: Essentials of Medical Pharmacology - by KD Tripathi (8th Edn.)

Pharmacokinetic (PK) processes contd...

- ✓ **Intensity of response of a drug** is related to its concentration at the site of action, which in turn is dependent on its pharmacokinetic properties.
- ✓ Pharmacokinetic considerations, therefore, determine the **route (s) of administration, dose, latency of onset, time of peak action, duration of action - frequency of administration** of a drug.

ABSORPTION OF DRUGS

- ✓ Absorption is the transfer of a drug from the site of administration to the bloodstream.
- ✓ The rate and extent of absorption depend on the environment where the drug is absorbed, chemical characteristics of the drug, and the route of administration (which influences bioavailability).
- ✓ Routes of administration other than intravenous may result in partial absorption and lower bioavailability.

Nature of Biological membranes:

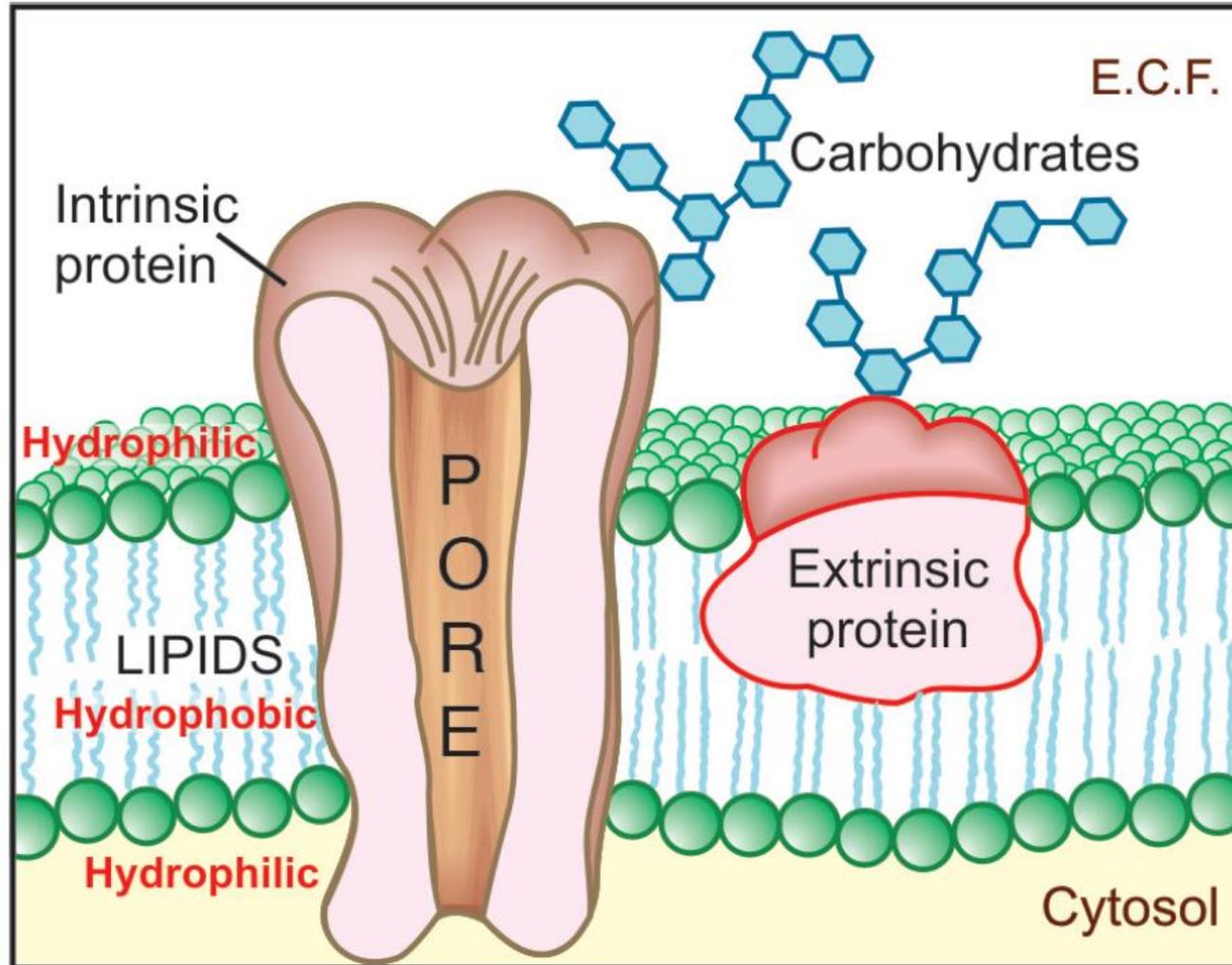


Figure:
Illustration of the organization of Biological Membrane

Biological membranes

- The **Plasma membrane** is the interface between a cell and the ECF.
- Possesses features and properties which **allow movement of solutes into and out of the cell.**
- **Cholesterol-containing, double layer of phospholipids molecules** arranged perpendicular to the surfaces.
- **Outer layer** has its polar groups directed to the ECF while the **inner layer** presents its polar groups towards the ICF.
- Individual lipids can move laterally, endowing the membrane with **fluidity, flexibility, imperviousness to polar molecules,** and high electrical resistance.
- The lipid molecules can even flip from one bilayer of the membrane to the other.

Biological membranes

contd...

Fluid mosaic model

- Proteins integral to the membrane are a heterogeneous set of globular molecules, each arranged in an amphipathic structure.
- Aqueous channels appear to be present in the core of the globular intrinsic (integral) proteins and may be gated (i.e. channels may open and close) by conformational changes in the proteins.
- Biological membranes behave as if they were lipoids punctured by aqueous pores and allow drugs and physiological materials to cross by passive or carrier mediated processes.

Drug Passage across Membranes

- ✓ Cell membranes form the barriers between aqueous compartments in the body.
- ✓ An epithelial barrier, such as the gastrointestinal mucosa or renal tubule, consists of **a layer of cells** tightly connected to each other so that molecules must traverse **at least two cell membranes** (inner and outer) to pass from one side to the other.
- ✓ Depending on chemical properties, drugs may be absorbed from the GI tract by **passive diffusion, facilitated diffusion, active transport, or endocytosis.**

Passive Diffusion

- The drug diffuses across the membrane in the **direction of its concentration gradient**, the membrane playing no active role in the process.
- **Most important mechanism** for majority of the drugs.
- **Lipid soluble drugs:** Diffuse by dissolving in the lipoidal matrix of the membrane, the rate of transport being proportional to lipid:water partition coefficient of the drug.
- **A more lipid soluble drug attains higher concentration** in the membrane and diffuses quickly.
- Also, greater the difference in the concentration of the drug on two sides of the membrane, faster is its diffusion.

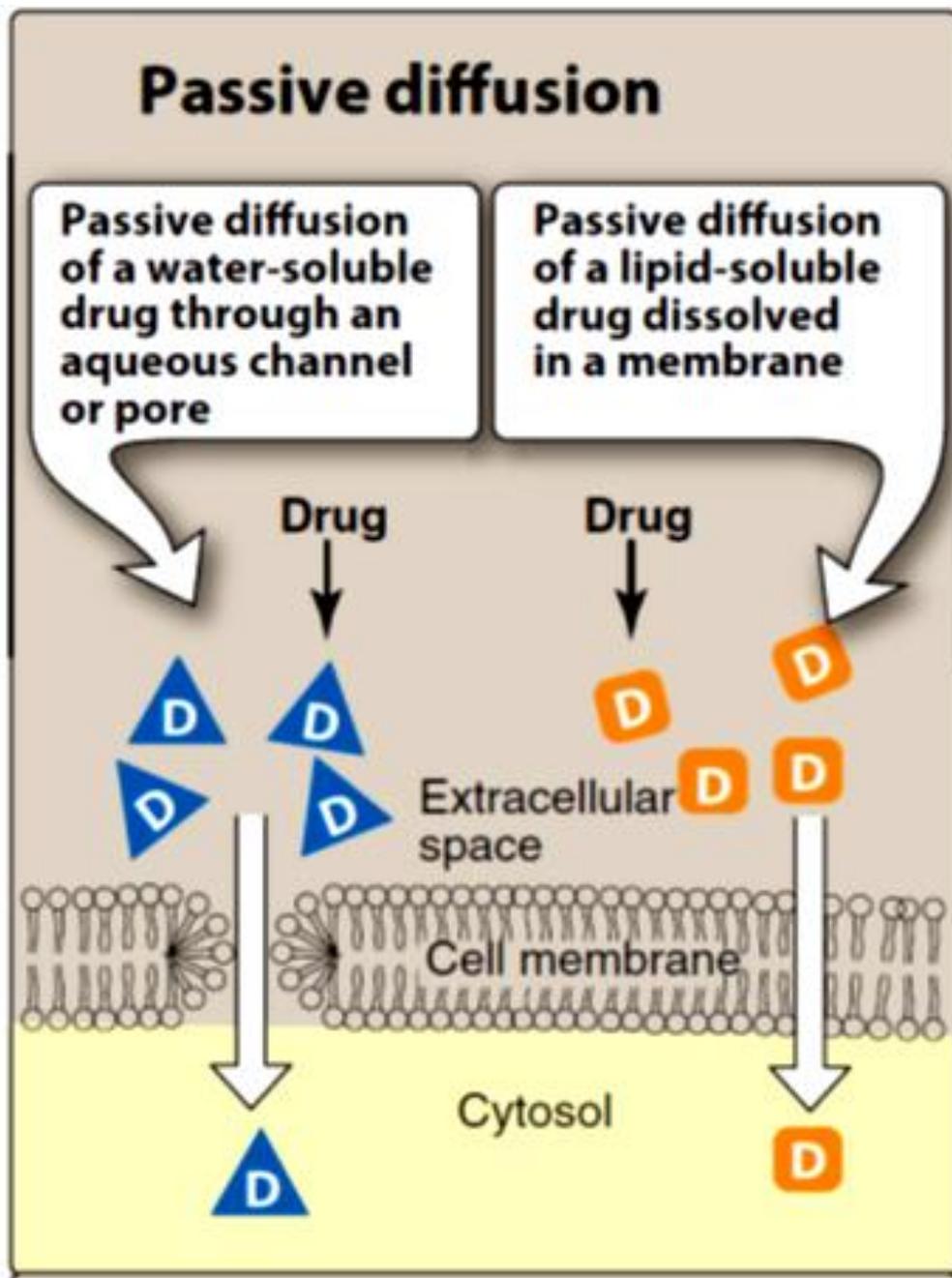
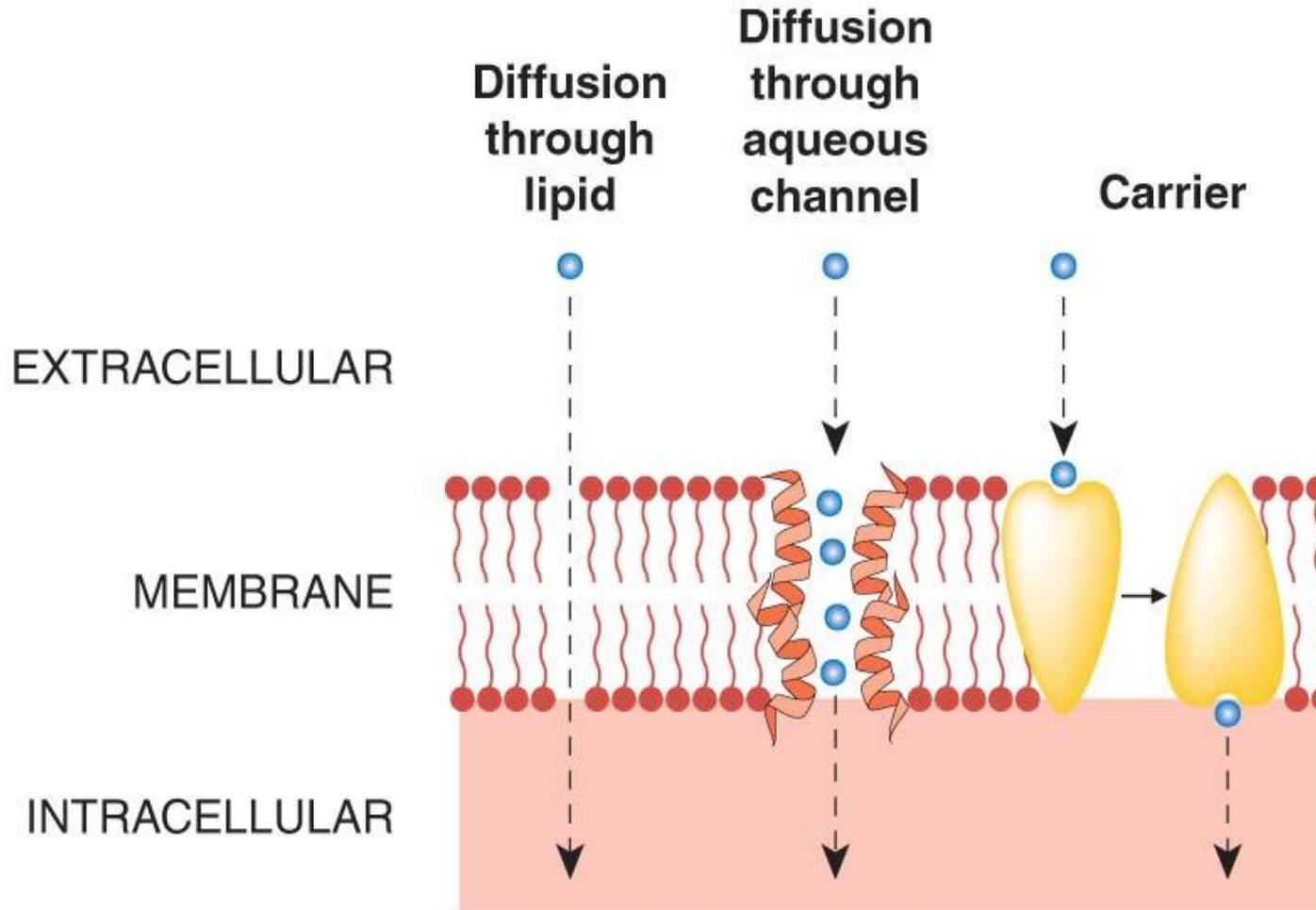


Figure:
Schematic representation of drugs crossing a cell membrane by passive diffusion

Filtration (Diffusion through aqueous channel)

- It is passage of drugs through aqueous pores in the membrane or through paracellular spaces.
- Lipid insoluble drugs cross biological membranes by filtration if their molecular size is smaller than the diameter of the pores.
- Majority of cells (intestinal mucosa, RBC etc.) have very small pores (4 Å) and drugs with MW > 100 or 200 are not able to penetrate.
- However, capillaries (except those in brain) have larger pores (40 Å) and most drugs (even albumin can filter through these).

Diffusion & Filtration



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Figure:
Routes by which solutes can traverse cell membranes (Molecules can also cross cellular barriers by pinocytosis)

Source: Rang & Dale's Pharmacology, Elsevier (9th Edn.)

Specialized Transport (Carrier mediated)

- When the rate of movement of molecules across a membrane is greater than can be accounted for by the operation of conventional laws of diffusion, the existence of a carrier-mediated transport system can be suspected.
- Such systems are well known in physiology, e.g. in **glucose uptake into erythrocytes** and **sodium ion expulsion from erythrocytes**.
- A rapidly reversible interaction between components of the membrane and the transported substance.
- The drug combines with a carrier present in the membrane and the complex then translocates from one face of the membrane to the other.

Specialized Transport (Carrier mediated)

contd...

- This kind of transport shows **relative selectivity** toward the chemical nature of the substance moved across the membrane.
- Since a carrier (membrane component) is involved in transport, the **process is saturable**, and substances of a similar chemical nature may compete for the carrier.
- **Competitive inhibition** is a characteristic of carrier-mediated transport.
- Substances permitting transit of ions across membranes are called **ionophores**.
- Carrier-mediated transport is of two types i.e. active transport and facilitated diffusion.

Active transport

- Movement occurs against the concentration gradient, needs energy.
- Inhibited by metabolic poisons.
- It results in selective accumulation of the substance on one side of the membrane.
- The rapid transfer into urine and bile of drugs that are strongly acidic or basic as well as most drug metabolites takes place by active transport.
- Generation of pH gradient across a biological membrane is also an active process.

Active transport

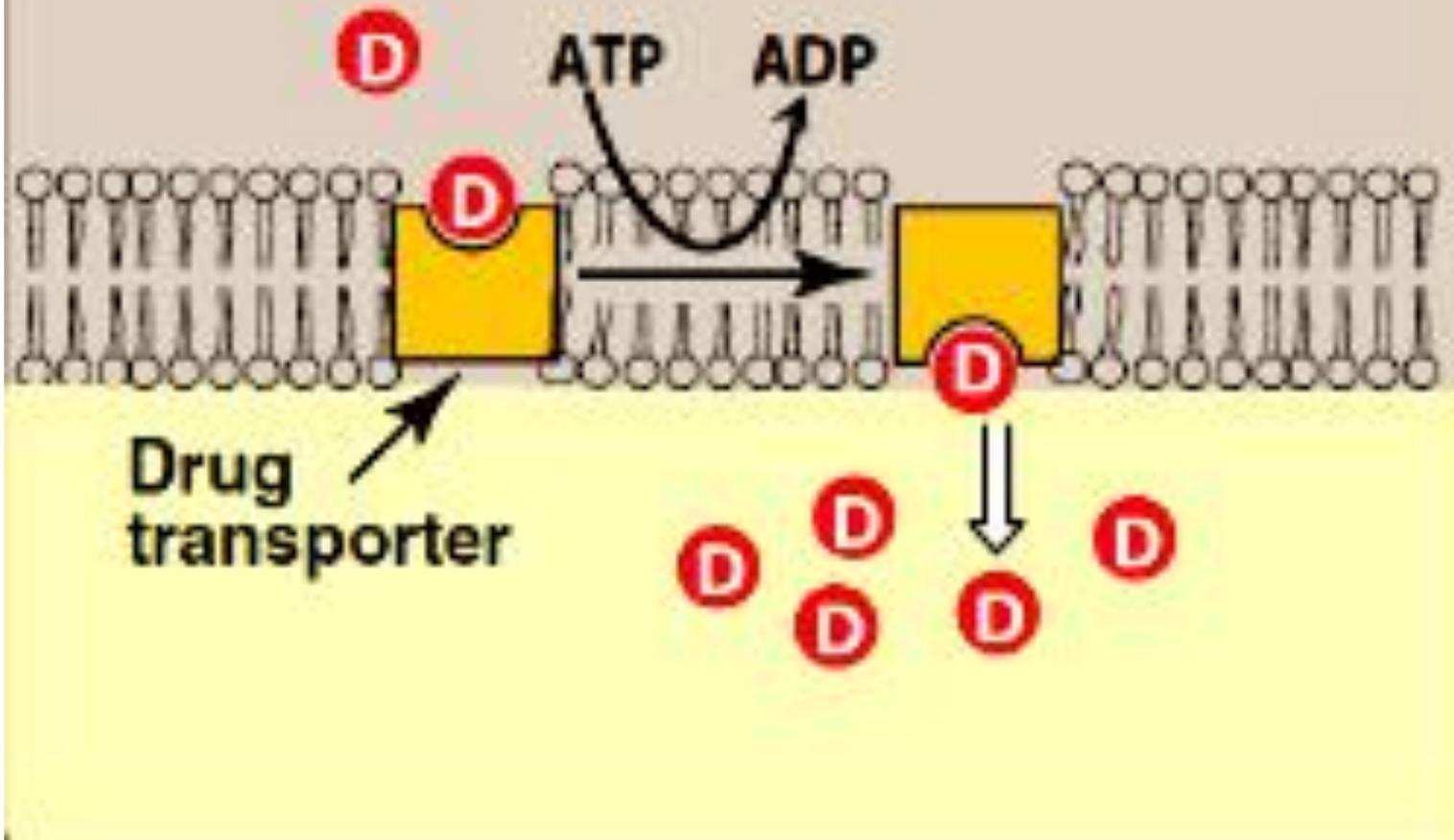


Figure:
Schematic representation of drugs crossing a cell membrane by active transport

Facilitated diffusion

- It is neither an energy-dependent process nor does it move substances against a concentration gradient.
- Transport is facilitated, however, by attachment to a carrier and is more rapid than simple diffusion and translocates even non-diffusible substrates.
- Entry of glucose into most cells takes place by facilitated diffusion (enhanced by insulin), but its passage across the GI mucosa and excretion by renal tubular cells are active processes.

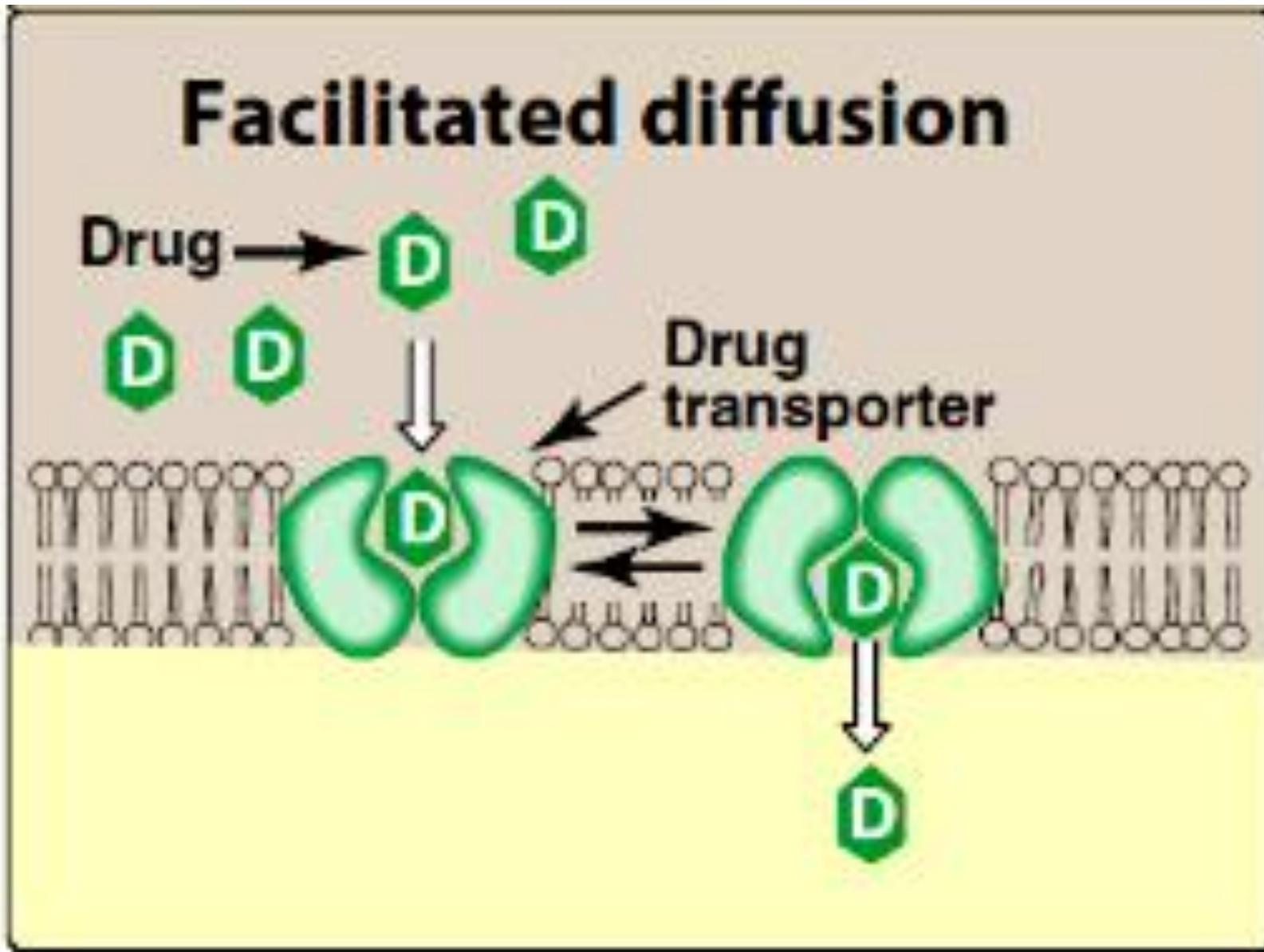


Figure:
Schematic representation of drugs crossing a cell membrane by facilitated diffusion

Phagocytosis and Pinocytosis of drugs

- Cells have the ability to engulf either particles (phagocytosis) or droplets (pinocytosis).
- If the engulfed material is not susceptible to enzyme degradation it will persist, e.g. particles of talc or droplets of liquid paraffin. In relation to drugs, this possibility is of more histopathological than pharmacological interest at present.
- The absorption of immunoglobulins through the gut mucosa of young calves depends on pinocytosis.

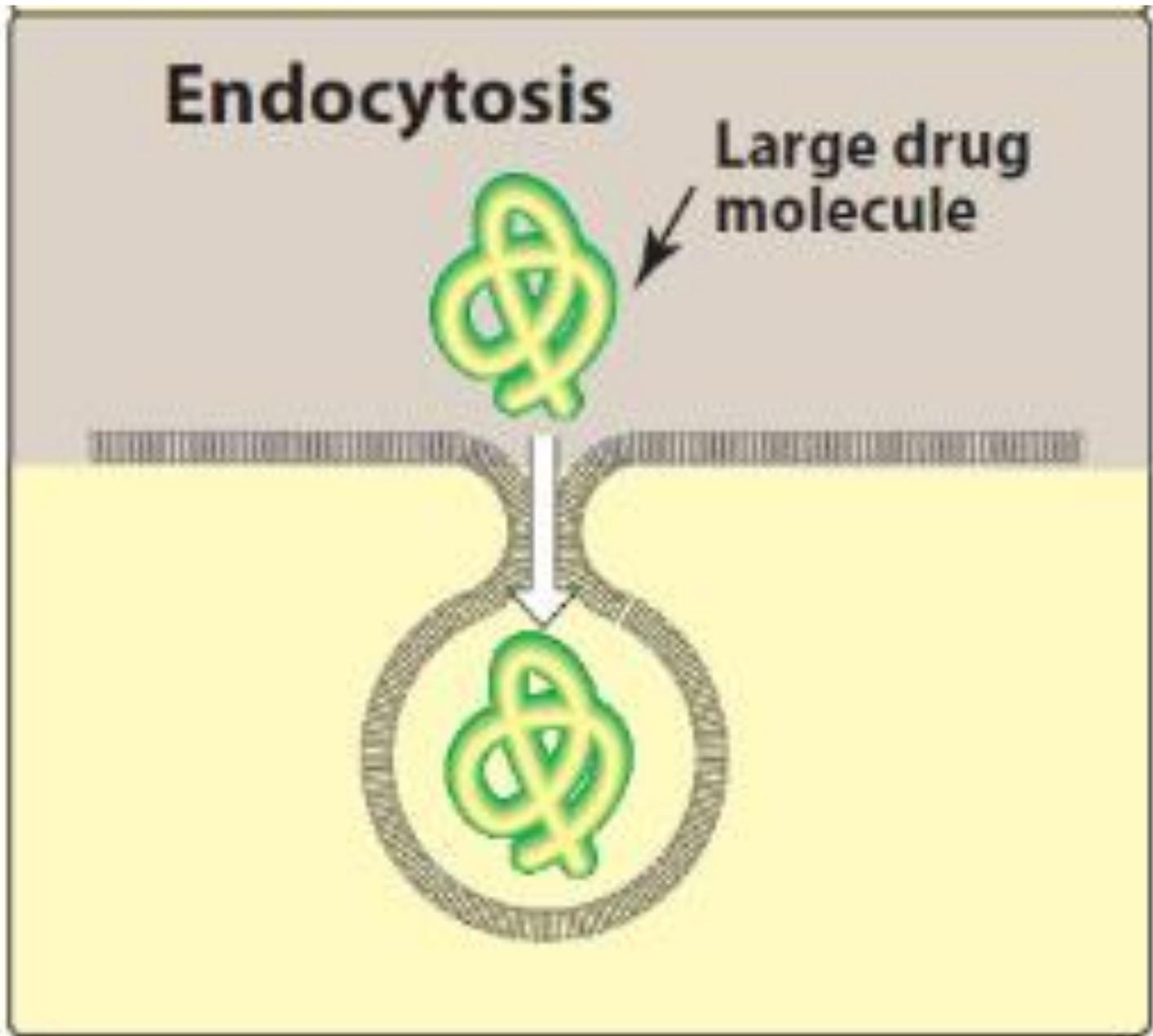


Figure:
Schematic representation of drugs crossing a cell membrane by Endocytosis

Thank You

