

Pharmacokinetics: Absorption (Drug Transport across Biological Membranes)

VPT: Unit I; Lecture-11
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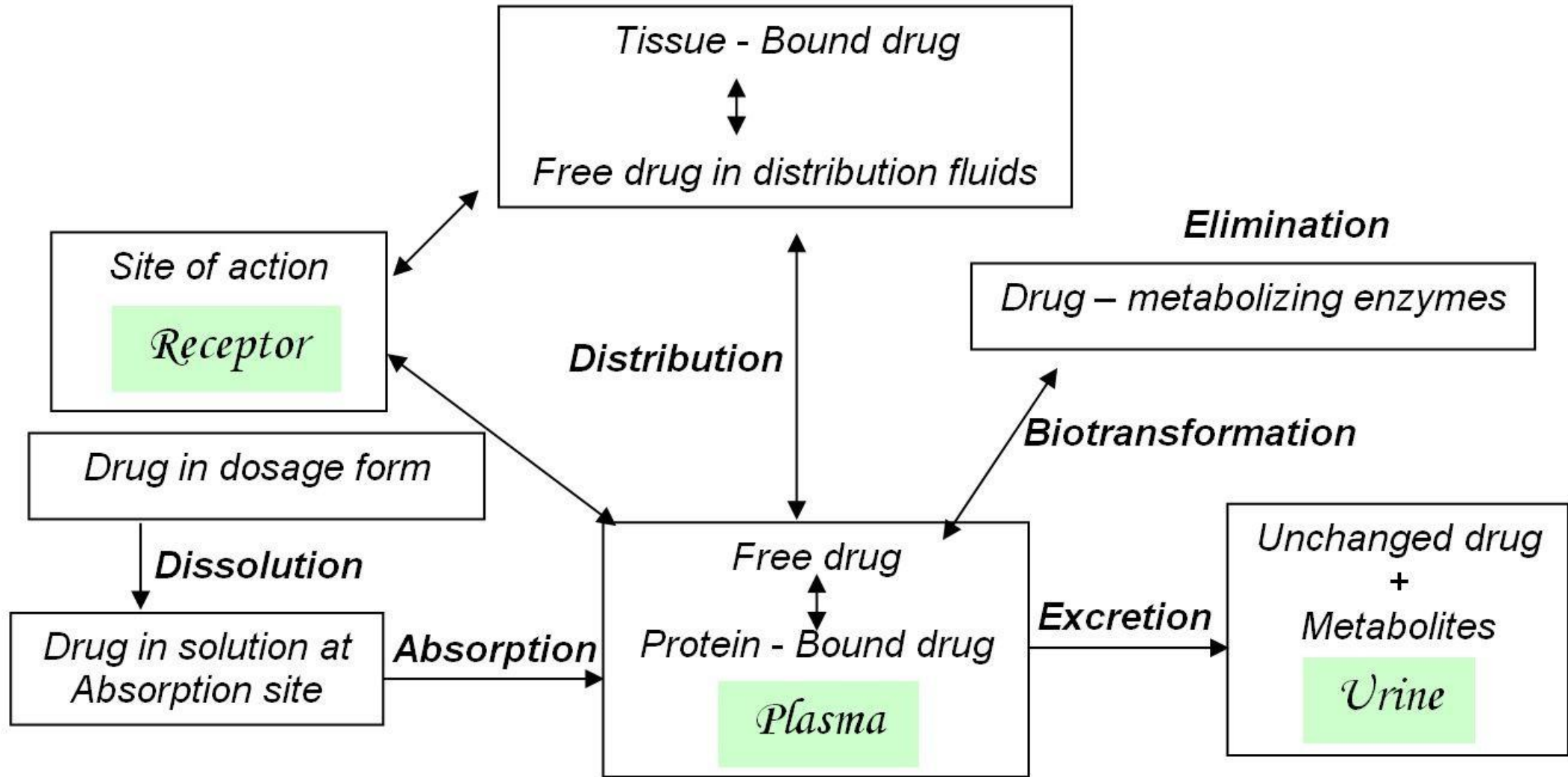


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Drug Passage across Membranes

- ✓ 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.**

Drug Movement (ADME processes)



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.

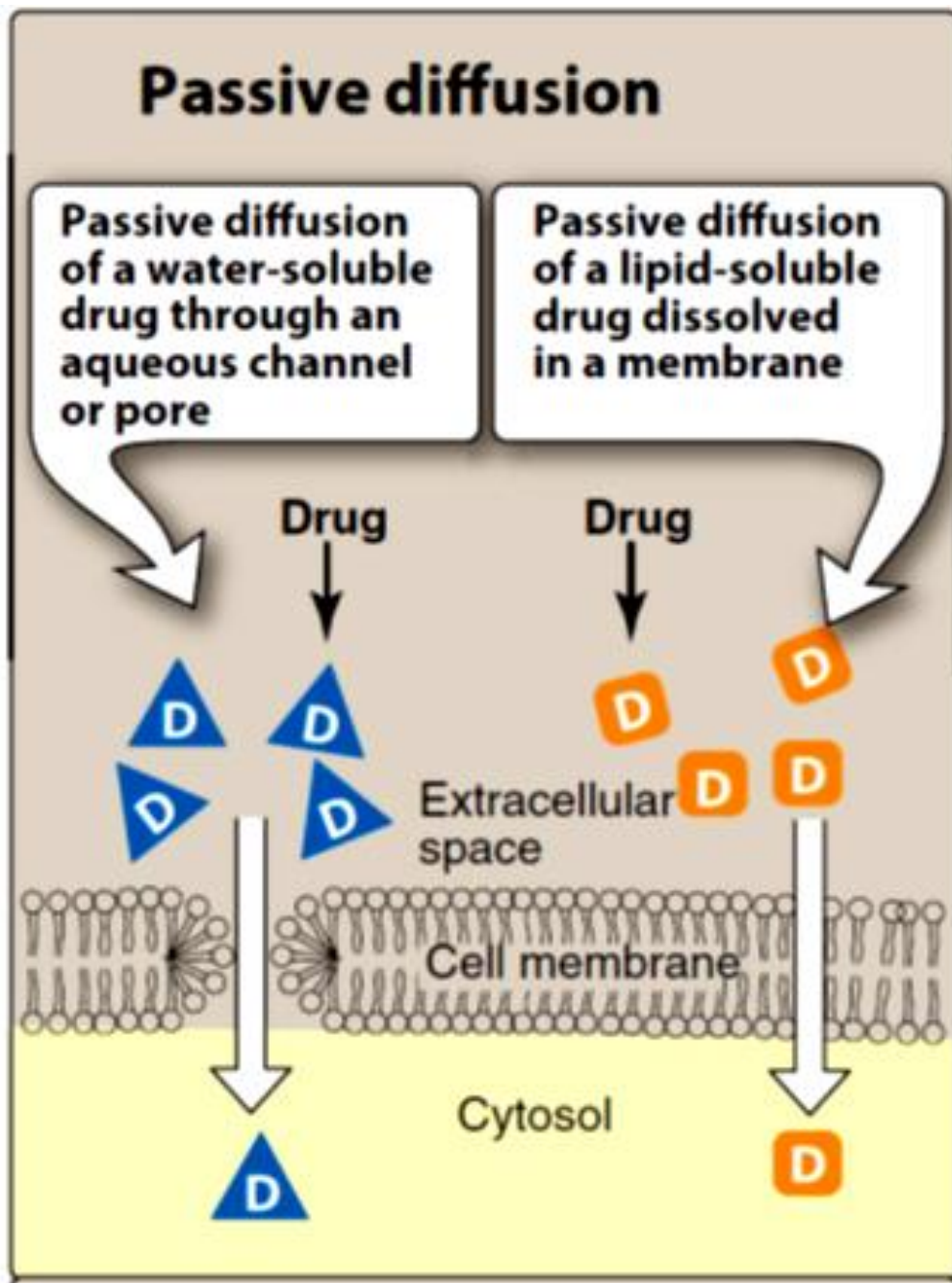
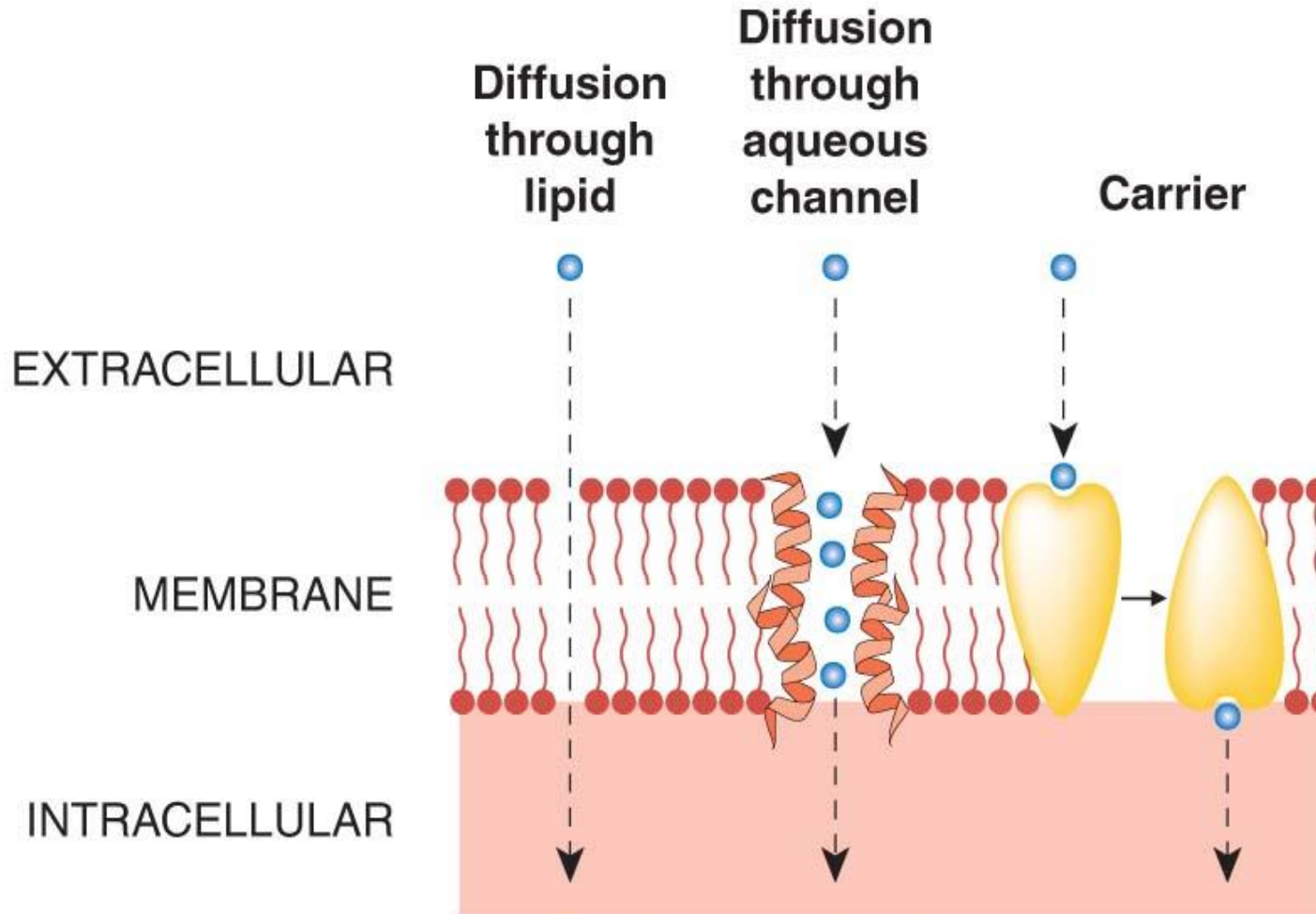


Figure:
Schematic representation of drugs crossing a cell membrane by passive diffusion

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



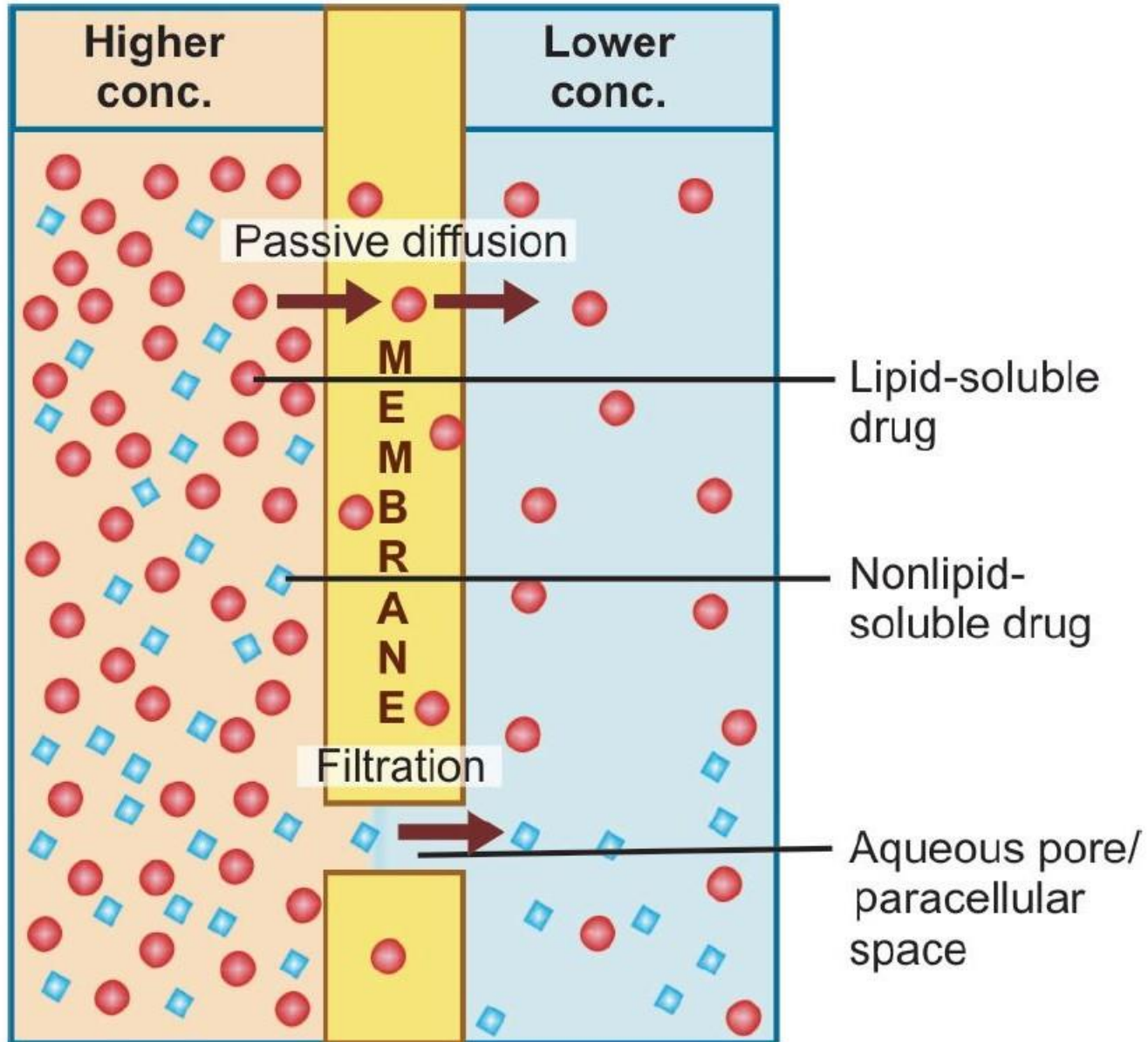
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Figure:
Routes by which solutes can traverse cell membranes (Molecules can also cross cellular barriers by pinocytosis)

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

Diffusion & Filtration

contd...



Source:
Essentials of
Medical
Pharmacology
(7th Edn.)
by K.D. Tripathi

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

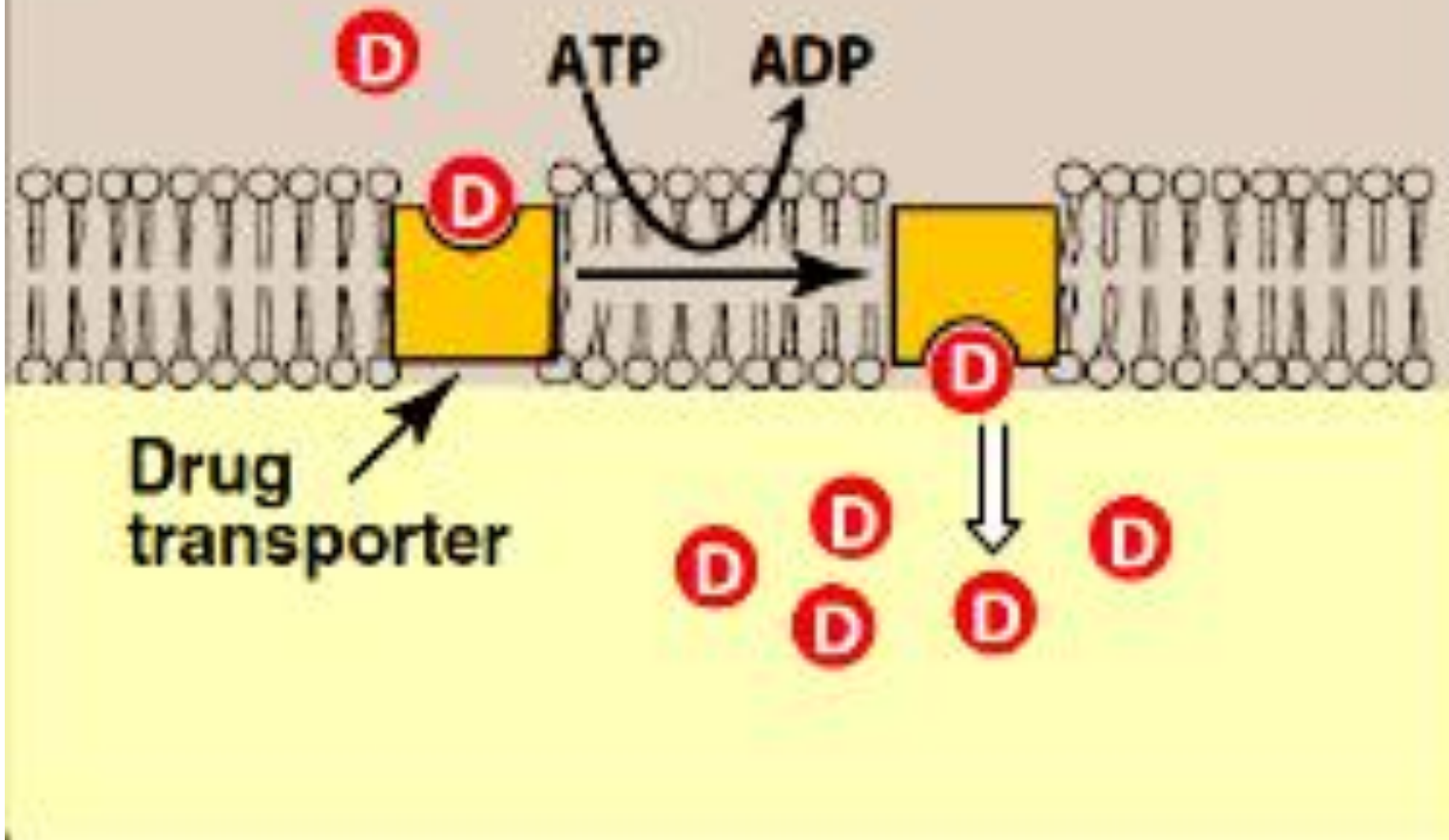


Figure:
Schematic representation of drugs crossing a cell membrane by active transport

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.

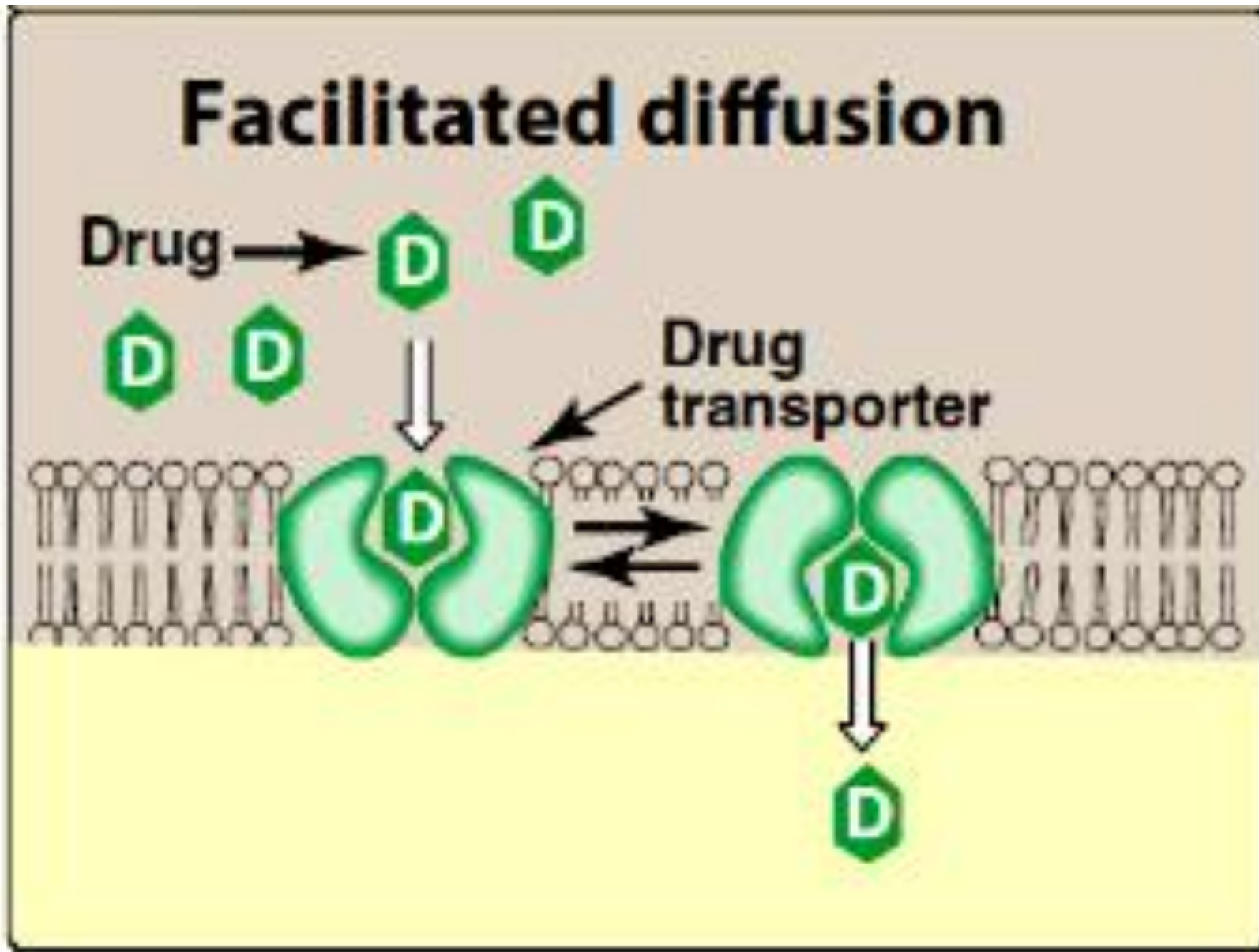


Figure:
Schematic representation of drugs crossing a cell membrane by facilitated diffusion

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.

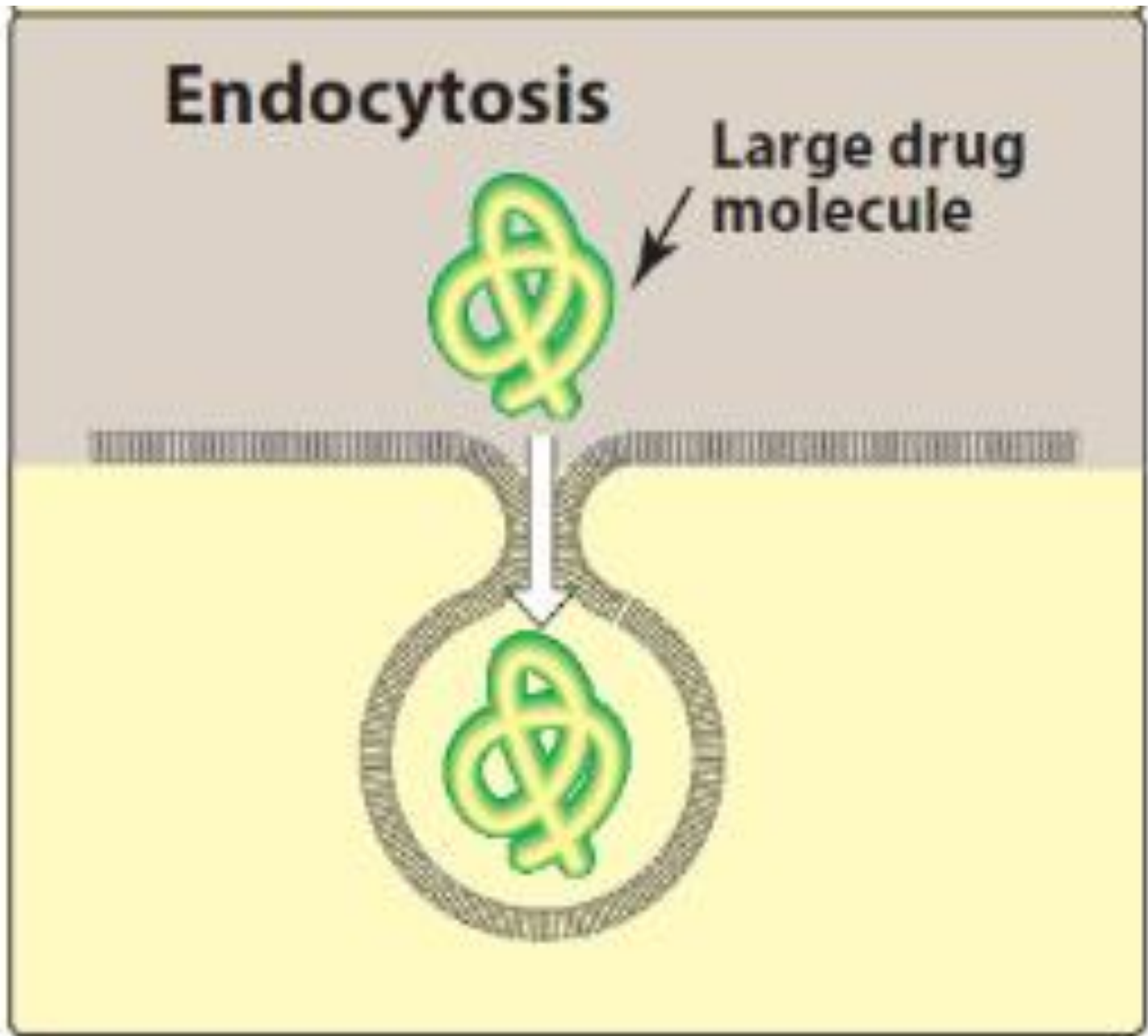


Figure:
Schematic representation of drugs crossing a cell membrane by Endocytosis

Thank You

