Biopharmaceutics

Lecture-4

Passive diffusion-continue

- Many drugs have both lipophilic and hydrophilic chemical substituents.
- Those drugs that are more lipid soluble tend to traverse cell membranes more easily than less lipid-soluble or more water-soluble molecules.
- For drugs that act as weak electrolytes, such as weak acids and bases, the extent of ionization influences the rate of drug transport.

- The ionized species of the drug contains a charge and is more water soluble than the nonionized species of the drug, which is more lipid soluble.
- The extent of ionization of a weak electrolyte will depend on both the pKa of the drug and the pH of the medium in which the drug is dissolved.

- *Henderson and Hasselbalch* used the following expressions pertaining to weak acids and weak bases to describe the relationship between pKa and pH:
- **For weak acids,**

Ratio = salt/acid

$= [A^-]/[HA] = 10^{(pH-pKa)}$ ---(13.4)

- **For weak base**

Ratio = base/salt

$= [RNH_2]/[RNH_3^+] = 10^{(pH-pKa)}$ ---- (13.5)

- With Equations 13.4 and 13.5, the proportion of free acid or free base existing as the nonionized species may be determined at any given pH, assuming the pKa for the drug is known.
- For example, at a plasma pH of 7.4, salicylic acid (pKa = 3.0) exists mostly in its ionized or water-soluble form, as shown below:

$$\text{Ratio} = [\text{salt}]/[\text{acid}] = 10^{(7.4-3)}$$

$$\log [\text{salt}]/[\text{acid}] = 7.4-3 = 4.4$$

$$[\text{salt}]/[\text{acid}] = 2.51 \times 10^{4}$$

- In a simple system, the total drug concentration on either side of a membrane should be the same at equilibrium, assuming Fick's law of diffusion is the only distribution factor involved.
- For diffusible drugs, such as nonelectrolyte drugs or drugs that do not ionize, the drug concentrations on either side of the membrane are the same at equilibrium.
- However, for electrolyte drugs or drugs that ionize, the total drug concentrations on either side of the membrane are not equal at equilibrium if the pH of the medium differs on respective sides of the membrane.

- For example, consider the concentration of salicylic acid (pKa = 3.0) in the stomach (pH 1.2) as opposed to its concentration in the plasma (pH 7.4) (Figure 13-4).
- According to the Henderson-Hasselbalch equation (Eq. 13.4) for weak acids, at pH 7.4 and at pH 1.2, salicylic acid exists in the ratios that follow.

- In the plasma, at pH 7.4:
- Ratio = $(RCOO^-)/(RCOOH) = 2.5 \times 10^4$
- In gastric juice, at pH 1.2:

  $$\text{Ratio} = (RCOO^-)/(RCOOH) = 10^{(1.2-3.0)}$$
  $$= 1.58 \times 10^{-2}$$
- The total drug concentration on either side of the membrane is determined as shown in table 13.2.

Model for the distribution of an orally administered weak electrolyte drug such as salicylic acid

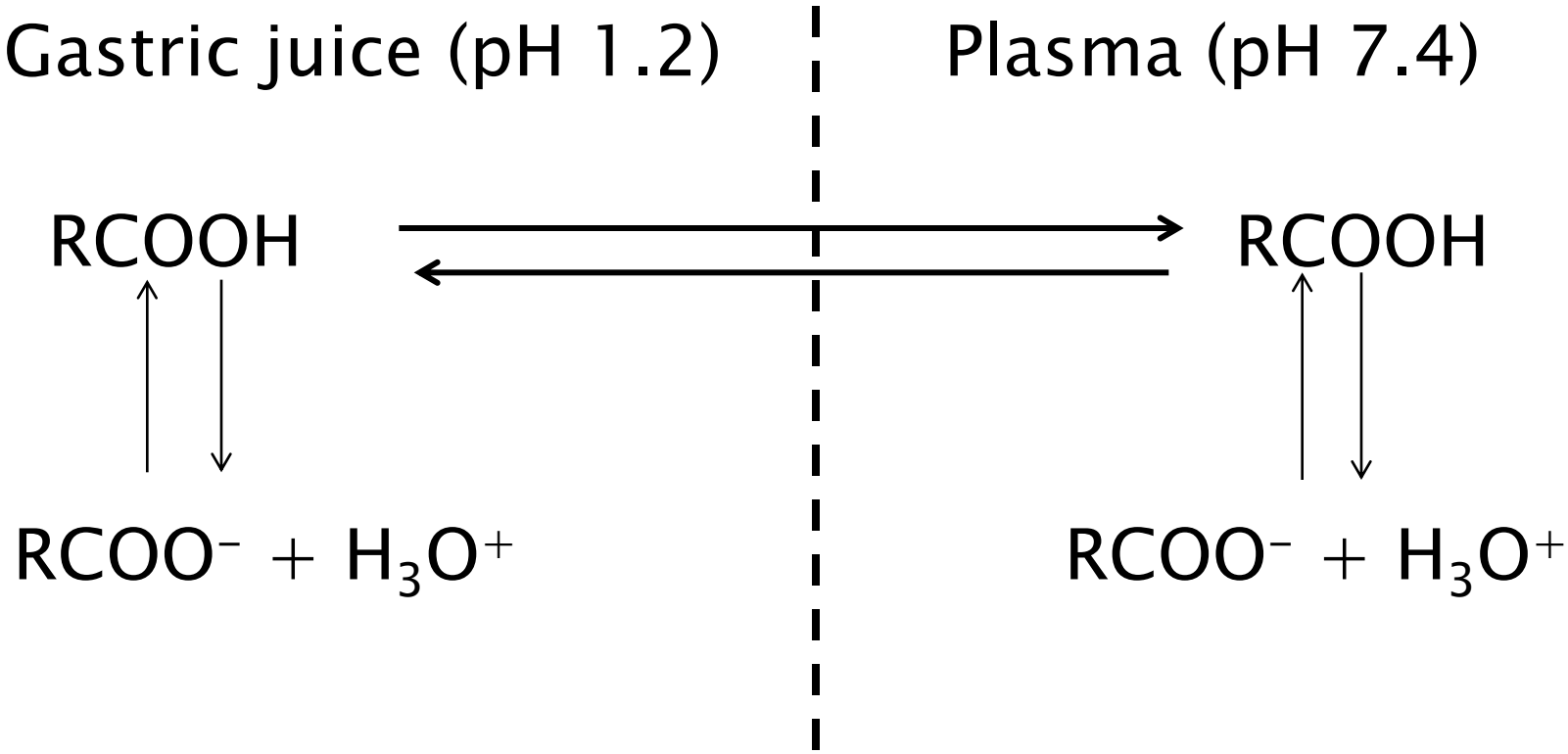


Table 13.2 Relative concentration of salicylic acid as affected by pH

Drug	Gastric juice (pH 1.2)	Plasma (pH 7.4)
RCOOH	1.0000	1
RCOO-	0.0158	25100
Total drug concentration	1.0158	25101

- Thus, the pH affects distribution of salicylic acid (RCOOH) and its salt ($RCOO^-$) across cell membranes. It is assumed that the acid, RCOOH, is freely permeable and the salt, $RCOO^-$, is not permeable across the cell membrane.
- In this example the total concentration of salicylic acid at equilibrium is approximately 25,000 times greater in the plasma than in the stomach (Table 13.2). These calculations can also be applied to weak bases, using Equation 13.5.

- According to the *pH–partition hypothesis* , if the pH on one side of a cell membrane differs from the pH on the other side of the membrane, then

1. the drug (weak acid or base) will ionize to different degrees on respective sides of the membrane;
2. the total drug concentrations (ionized plus nonionized drug) on either side of the membrane will be unequal; and
3. the compartment in which the drug is more highly ionized will contain the greater total drug concentration. For these reasons, a weak acid (such as salicylic acid) will be rapidly absorbed from the stomach (pH 1.2), whereas a weak base (such as quinidine) will be poorly absorbed from the stomach.

- Another factor that can influence drug concentrations on either side of a membrane is a particular ***affinity*** of the drug for a tissue component, which prevents the drug from moving freely back across the cell membrane.
- For example, a drug such as dicumarol binds to plasma protein, and digoxin binds to tissue protein. In each case, the protein-bound drug does not move freely across the cell membrane. Drugs such as chlordane are very lipid soluble and will partition into adipose (fat) tissue.

- In addition, a drug such as tetracycline might form a complex with calcium in the bones and teeth.
- Finally, a drug may concentrate in a tissue due to a specific uptake or active transport process. Such processes have been demonstrated for iodide in thyroid tissue, potassium in the intracellular water, and certain catecholamines into adrenergic storage sites.
- Such drugs may have a higher total drug concentration on the side where binding occurs, yet the free drug concentration that diffuses across cell membranes will be the same on both sides of the membrane.

- Instead of diffusing into the cell, drugs can also diffuse into the spaces around the cell as an absorption mechanism.
- In paracellular drug absorption, drug molecules smaller than 500 MW diffuse into the tight junctions, or spaces between intestinal epithelial cells.

Carrier-Mediated Transport

- Theoretically, a lipophilic drug may pass through the cell or go around it. If the drug has a low molecular weight and is lipophilic, the lipid cell membrane is not a barrier to drug diffusion and absorption.
- In the intestine, drugs and other molecules can go through the intestinal epithelial cells by either diffusion or a carrier-mediated mechanism.
- Numerous specialized carrier-mediated transport systems are present in the body, especially in the intestine for the absorption of ions and nutrients required by the body.

Active Transport

- Active transport is a carrier-mediated transmembrane process that plays an important role in the gastrointestinal absorption and in renal and biliary secretion of many drugs and metabolites.
- A few lipid-insoluble drugs that resemble natural physiologic metabolites (such as 5-fluorouracil) are absorbed from the gastrointestinal tract by this process.

- Active transport is characterized by the transport of drug against a concentration gradient-that is, from regions of low drug concentrations to regions of high concentrations. Therefore, this is an energy-consuming system.
- In addition, active transport is a specialized process requiring a carrier that binds the drug to form a carrier-drug complex that shuttles the drug across the membrane and then dissociates the drug on the other side of the membrane (Figure 13-5).

- The carrier molecule may be highly selective for the drug molecule. If the drug structurally resembles a natural substrate that is actively transported, then it is likely to be actively transported by the same carrier mechanism.
- Therefore, drugs of similar structure may compete for sites of adsorption on the carrier.
- Furthermore, because only a fixed number of carrier molecules are available, all the binding sites on the carrier may become saturated if the drug concentration gets very high.

- A comparison between the rate of drug absorption and the concentration of drug at the absorption site is shown in **Figure 13-6**. Notice that for a drug absorbed by passive diffusion, the rate of absorption increases in a linear relationship to drug concentration.
- In contrast, when a drug is absorbed by a carrier-mediated process, the rate of drug absorption increases with drug concentration until the carrier molecules are completely saturated.
- At higher drug concentrations, the rate of drug absorption remains constant, or zero order.

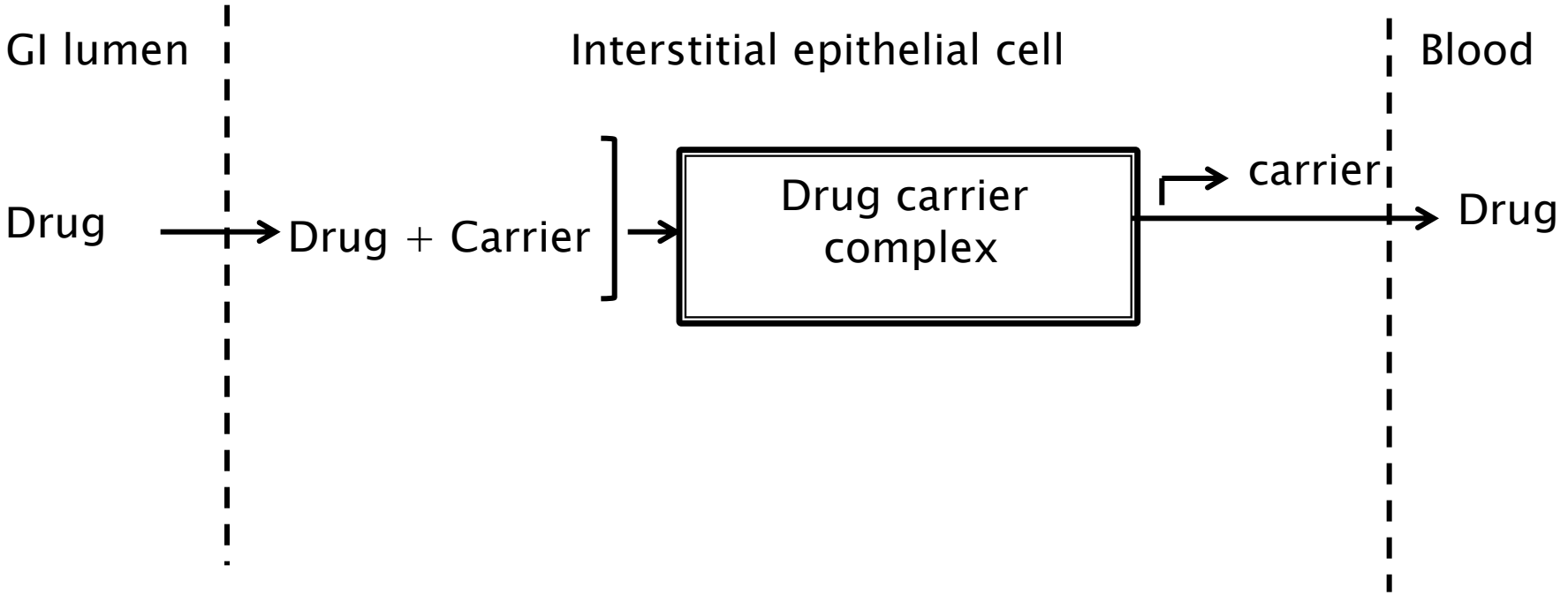


Figure 13-5. hypothetical carrier-mediated transport process

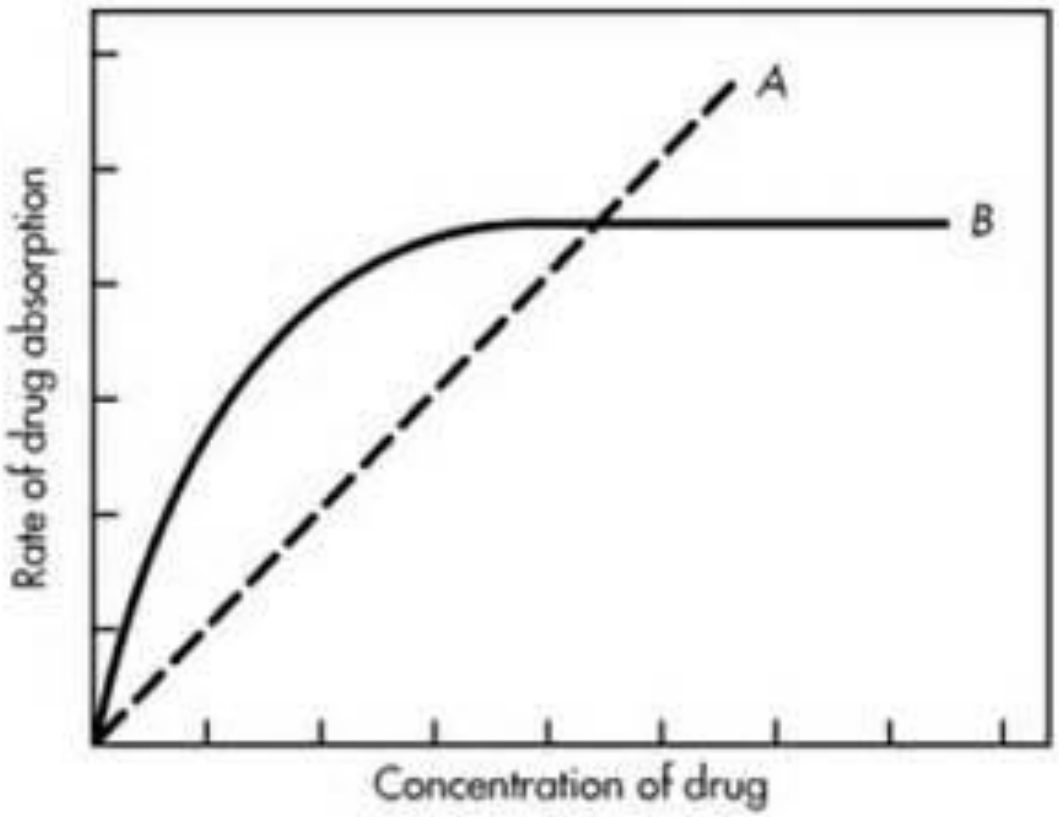
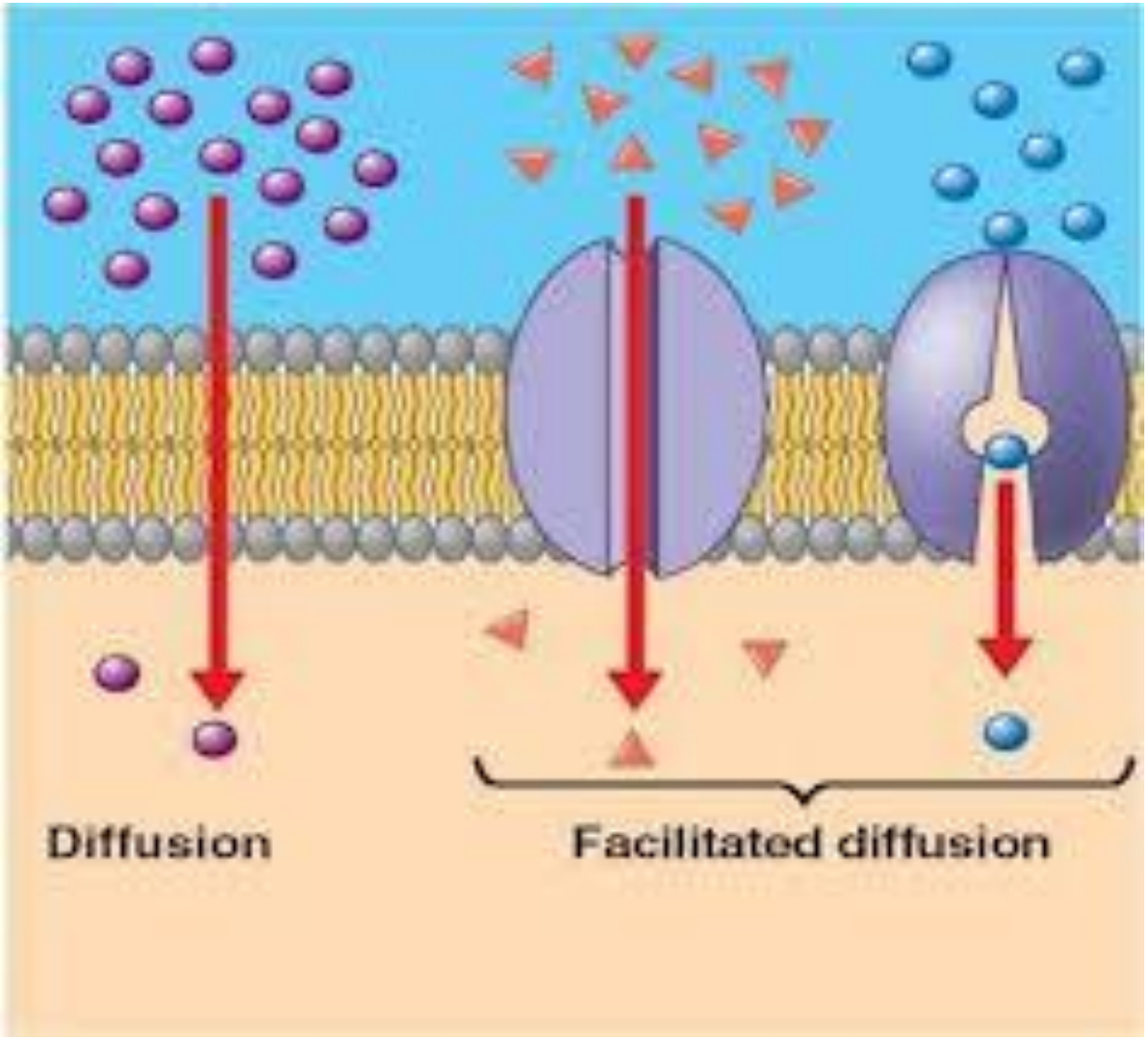


Figure 13-6. Comparison of the rates of drug absorption of a drug absorbed by passive diffusion (line A) and a drug absorbed by a carrier-mediated system (line B).

Facilitated Diffusion

- Facilitated diffusion is also a carrier-mediated transport system, differing from active transport in that the drug moves along a concentration gradient (i.e., move from a region of high drug concentration to a region of low drug concentration).
- Therefore, this system does not require input. However, because this system is carrier mediated, it is saturable and structurally selective for the drug and shows competition kinetics for drugs of similar structure.
- In terms of drug absorption, facilitated diffusion seems to play a very minor role.

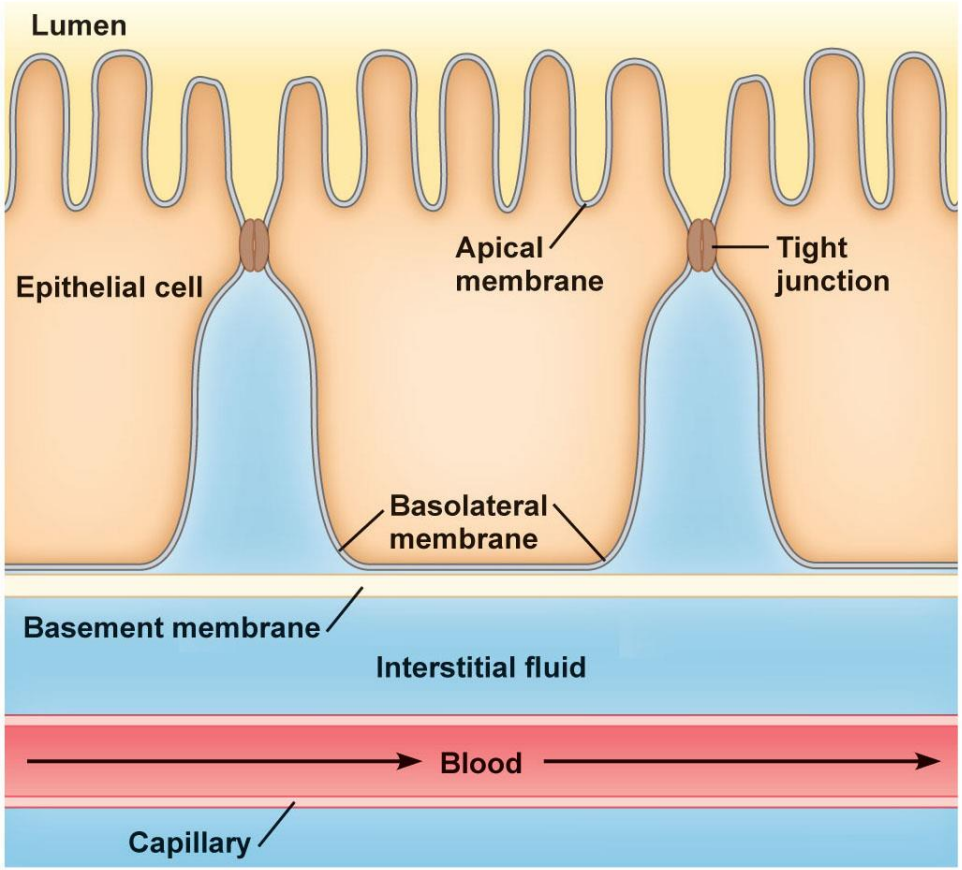

Diffusion
Facilitated diffusion

Carrier-Mediated Intestinal Transport

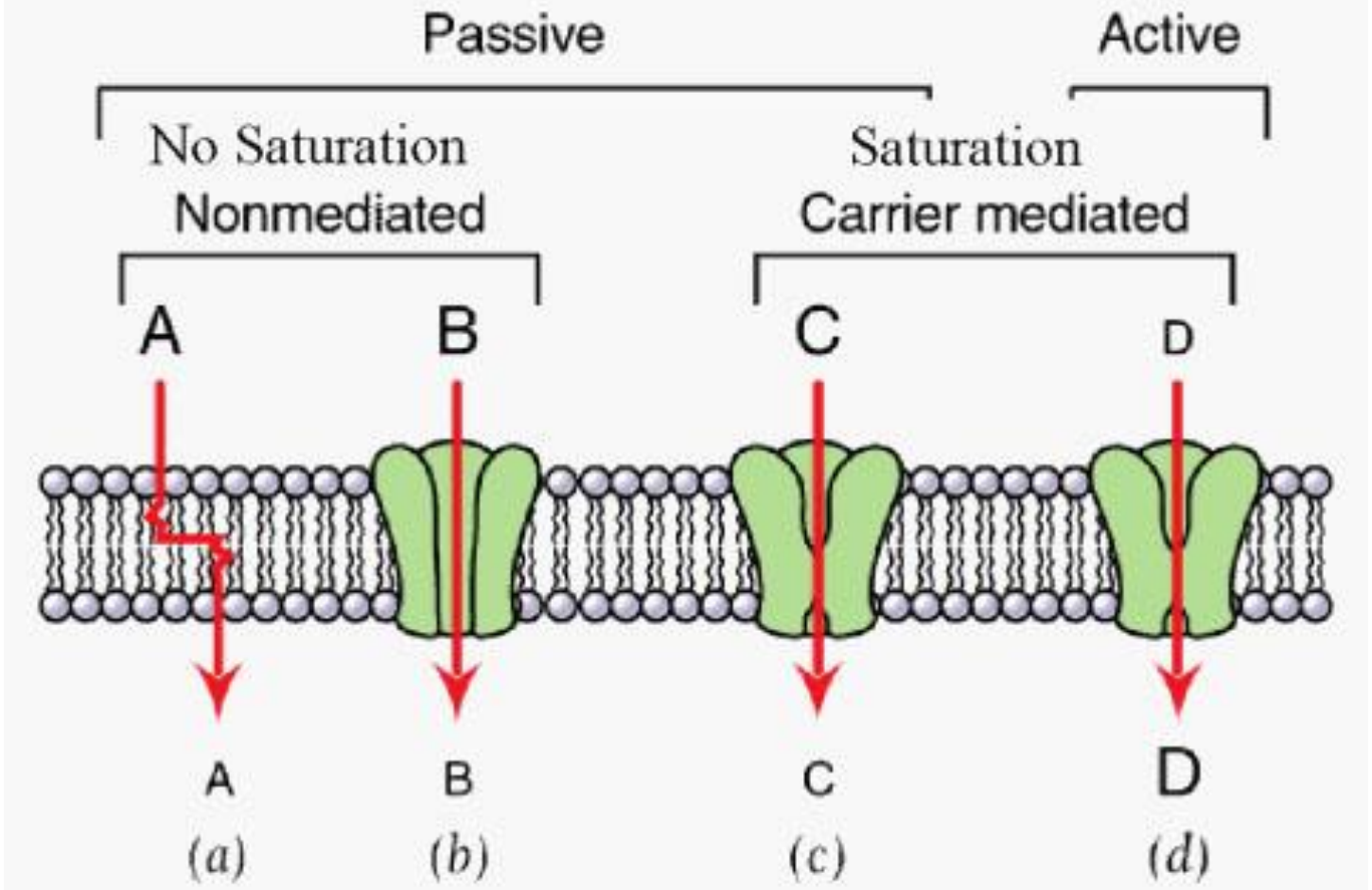
- Various carrier-mediated systems (transporters) are present at the intestinal brush border and basolateral membrane for the absorption of specific ions and nutrients essential for the body.
- Many drugs are absorbed by these carriers because of the structural similarity to natural substances (Table 13.3).
- A transmembrane protein, P-glycoprotein (Pgp), has been identified in the intestine.

- Pgp appears to reduce apparent intestinal epithelial cell permeability from lumen to blood for various lipophilic or cytotoxic drugs.
- Other transporters are also present in the intestines. For example, many oral cephalosporins are absorbed through the amino acid transporter.
- Cefazolin, a parenteral-only cephalosporin, is not available orally because it cannot be absorbed to a significant degree through this mechanism.

Intestinal brush border and basolateral membrane

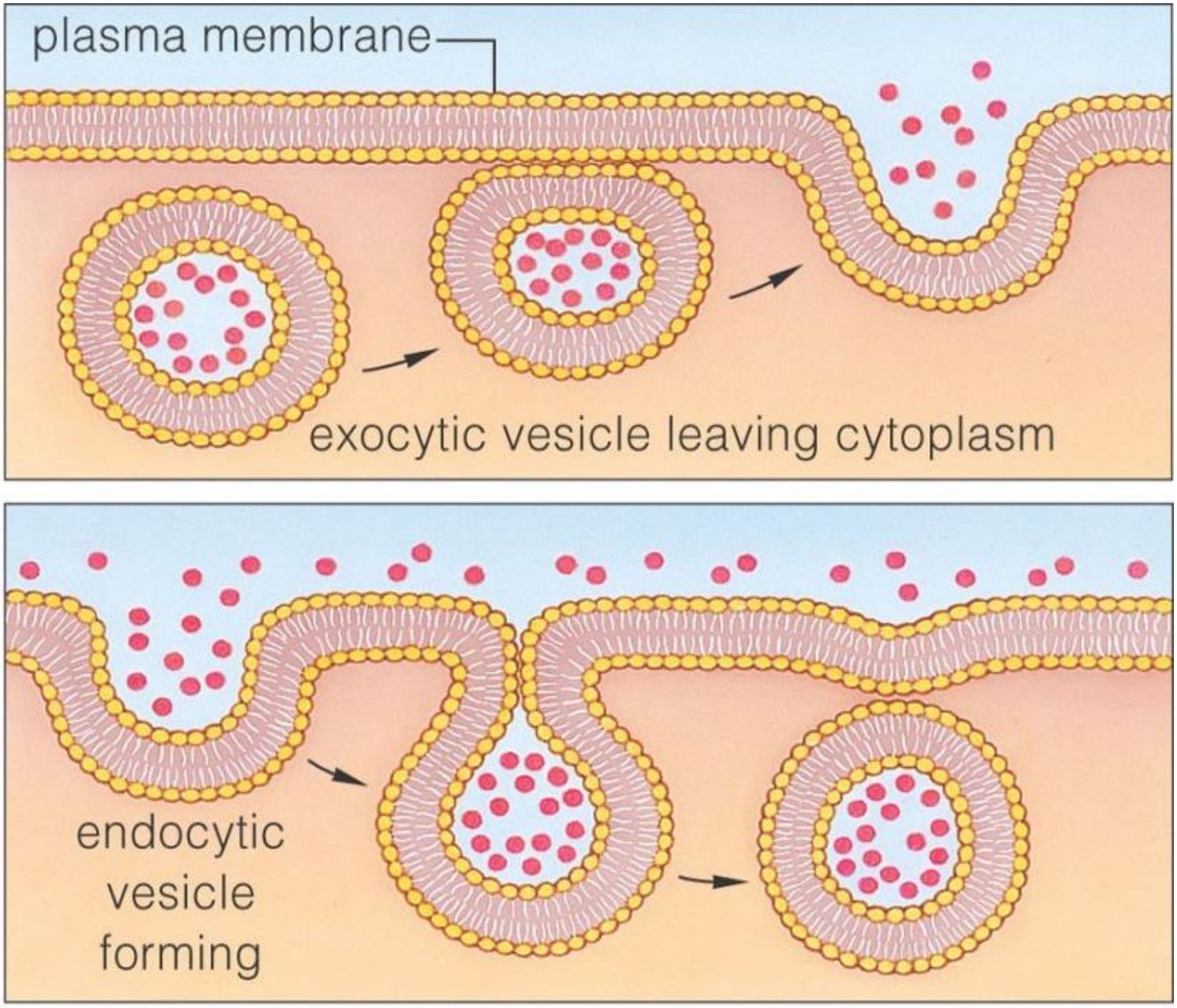


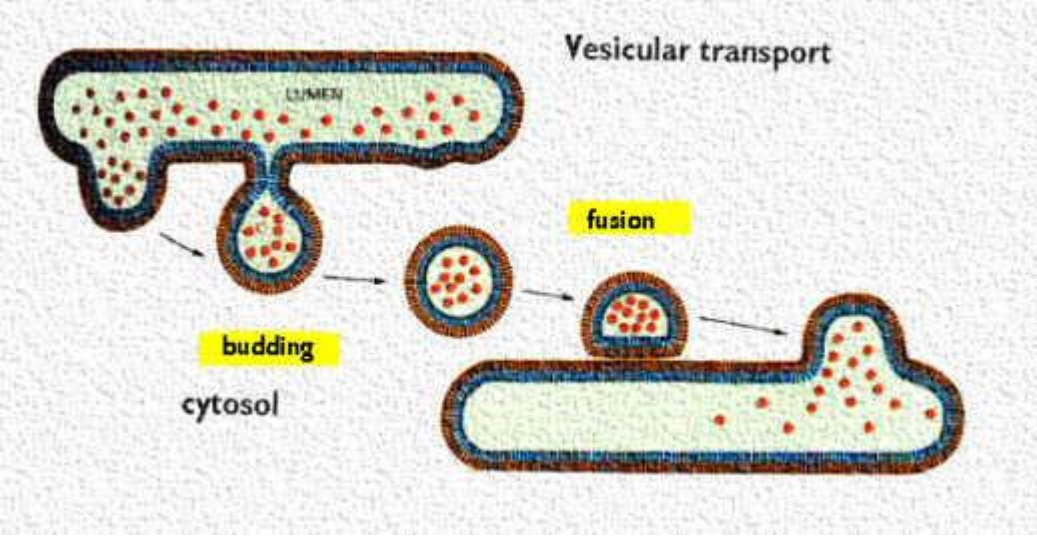
Comparison of Transport Types



Vesicular transport

- Vesicular transport is the process of engulfing particles or dissolved materials by the cell.
- Pinocytosis and phagocytosis are forms of vesicular transport that differ by the type of material ingested.
- Pinocytosis refers to the engulfment of small solutes or fluid, whereas phagocytosis refers to the engulfment of larger particles or macromolecules, generally by macrophages.
- Endocytosis and exocytosis are the processes of moving specific macromolecules into and out of a cell, respectively.

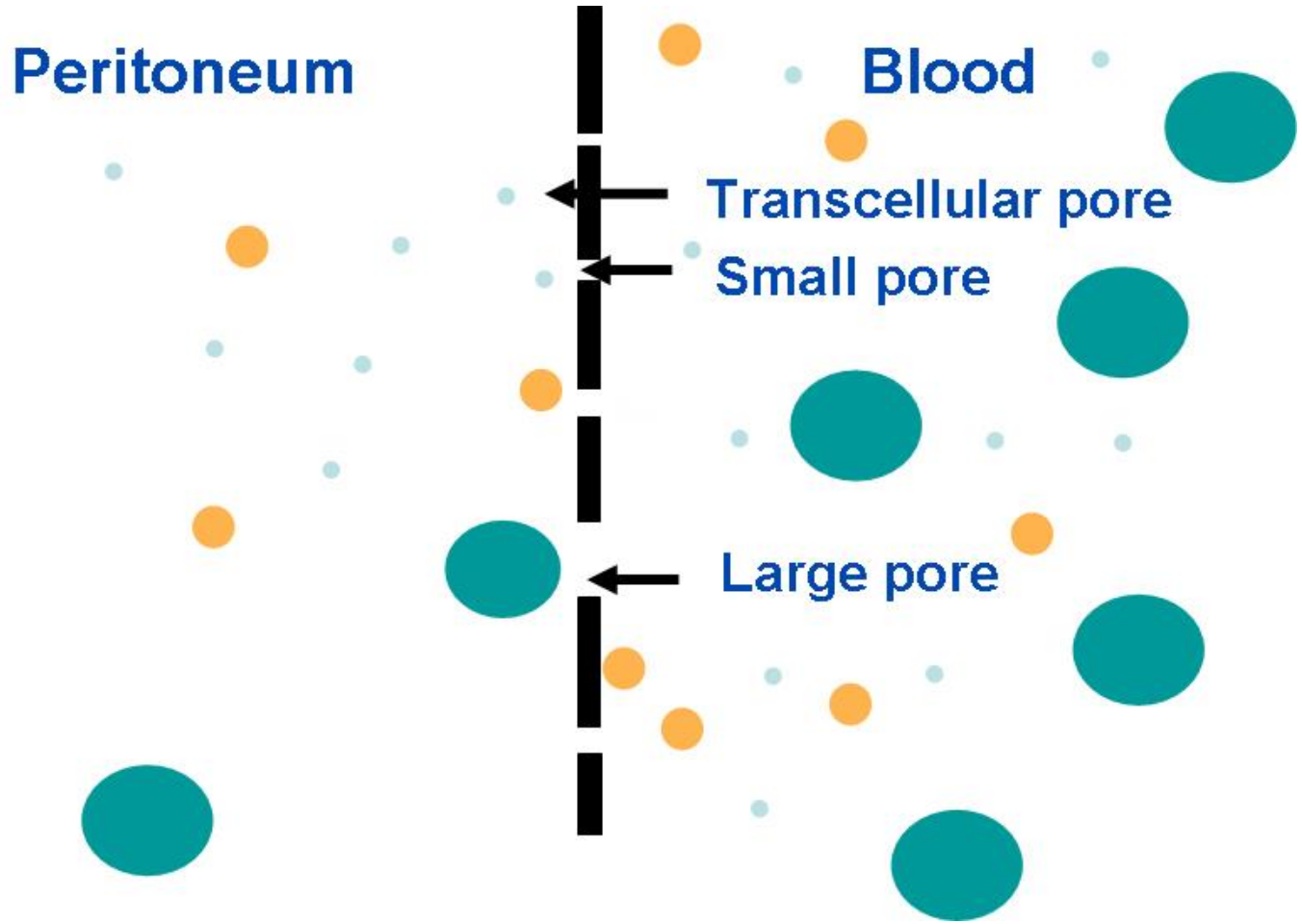

plasma membrane
exocytic vesicle leaving cytoplasm
endocytic vesicle forming

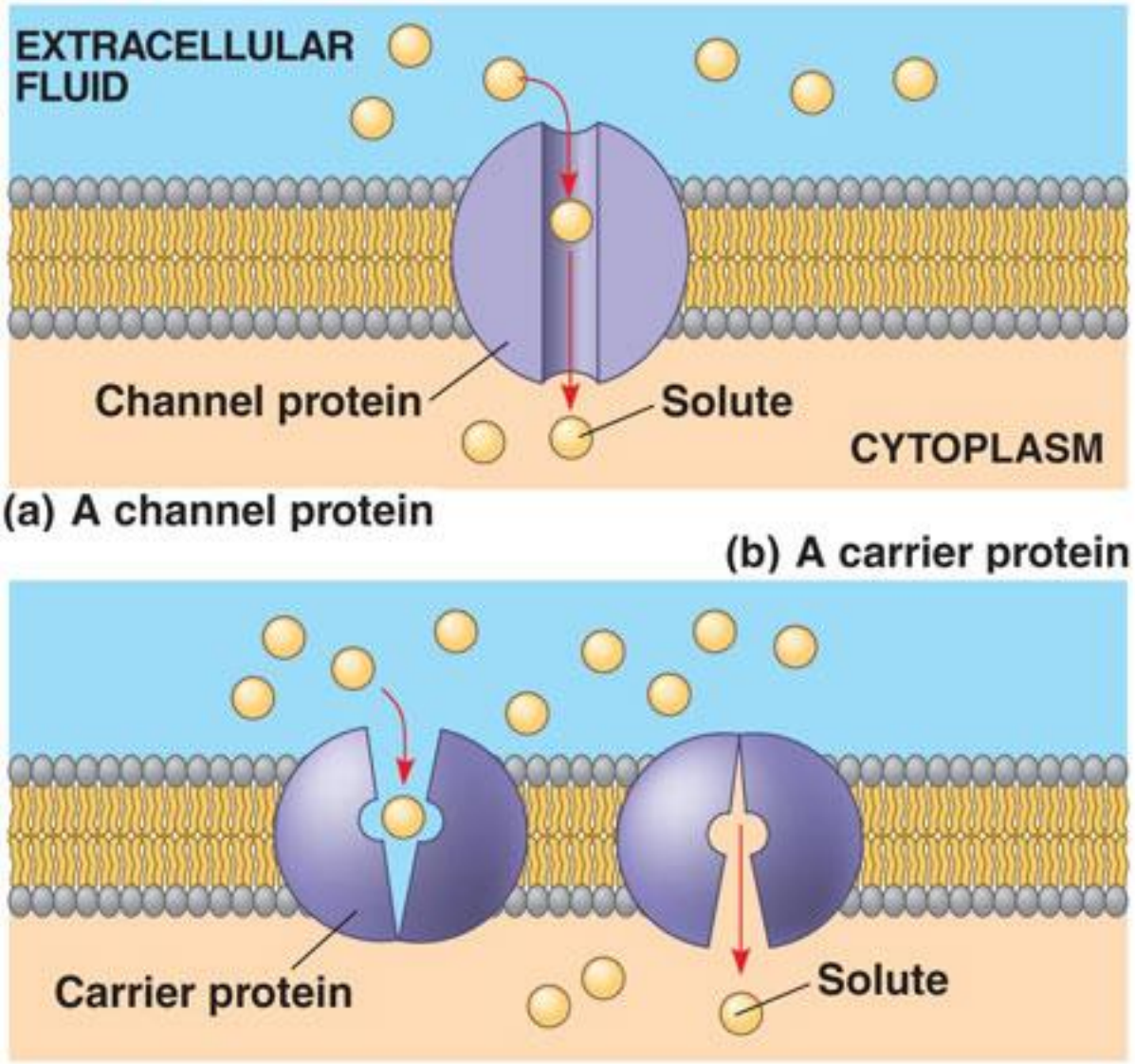

Vesicular transport
LUMEN
fusion
budding
cytosol

- During pinocytosis or phagocytosis, the cell membrane invaginates to surround the material and then engulfs the material, incorporating it into the cell (Fig. 13-7). Subsequently, the cell membrane containing the material forms vesicle or vacuole within the cell.
- Vesicular transport is the proposed process for the absorption of orally administered Sabin polio vaccine and various large proteins.
- An example of exocytosis is the transport of a protein such as insulin from insulin-producing cells of the pancreas into the extracellular space. The insulin molecules are first packaged into intracellular vesicles, which then fuse with the plasma membrane to release the insulin outside the cell.

Pore (convective) Transport

- Very small molecules (such as urea, water, and sugars) are able to cross cell membranes rapidly, as if the membrane contained channels or pores. Although such pores have never been directly observed by microscopy, the model of drug permeation through aqueous pores is used to explain renal excretion of drugs and the uptake of drugs into the liver.
- A certain type of protein called a transport protein may form an open channel across the lipid membrane of the cell. Small molecules including drugs move through the channel by diffusion more rapidly than at other parts of the membrane.


Peritoneum
Blood
Transcellular pore
Small pore
Large pore


EXTRACELLULAR FLUID
Channel protein
Solute
CYTOPLASM
(a) A channel protein
(b) A carrier protein
Carrier protein
Solute

Ion-Pair Formation

- Strong electrolyte drugs are highly ionized or charged molecules, such as quaternary nitrogen compounds with extreme pK_a values. Strong electrolyte drugs maintain their charge at all physiologic pH values and penetrate membrane poorly.
- When the ionized drug is linked up with an oppositely charged ion, an ion pair is formed in which the overall charge of the pair is neutral.
- This neutral drug complex diffused more easily across the membrane.
- For example, the formation of ion pairs to facilitate drug absorption has been demonstrated for propranolol, a basic drug that forms an ion pair with oleic acid, and quinine, which forms an ion pair with hexylsalicylate.

- An interesting application of ion pairs is the complexation of amphotericin B and DSPG (disteroylphosphatidylglycerol) in some amphotericin B/liposome products.
- Ion pairing may transiently alter distribution, reduce high plasma free drug concentration, and reduce renal toxicity.