Lecture 2

Organic Pharm. Chemistry for Pharmacy Students

By

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DRUG DISTRIBUTION

- A drug is a chemical molecule.
- Following introduction into the body, a drug must pass through many barriers, survive alternate sites of attachment and storage, and avoid significant metabolic destruction before it reaches the site of action, usually a receptor on or in a cell .
- At the receptor, the following equilibrium usually holds:

$$\text{Drug} + \text{Receptor} \leftrightarrows \text{Drug} - \text{Receptor} - \text{Complex} \rightarrow \text{Pharmacologic Response}$$

$$\text{Drug} - \text{Receptor} - \text{Complex} \leftrightarrows \text{Drug excretion in the circulatory system}$$

- The ideal drug molecule will show favourable binding characteristics to the receptor, and the equilibrium will lie to the right.
- At the same time, the drug will be expected to dissociate from the receptor and re-enter the systemic circulation to be excreted.
- Major exceptions include :

1. the alkylating agents used in cancer chemotherapy.
2. a few inhibitors of the enzyme acetyl cholinesterase.
3. suicide inhibitors of monoamine oxidase.

- These pharmacological agents form covalent bonds with the receptor, usually an enzyme's active site.
- In these cases, the cell must destroy the receptor or enzyme, or, in the case of the alkylating agents, the cell would be replaced, ideally with a normal cell.

Oral Administration

- Assume that the drug is administered orally. The drug must go into solution to pass through the gastrointestinal mucosa.
- Even drugs administered as true solutions may not remain in solution as they enter the acidic stomach and then pass into the alkaline intestinal tract.

The ability of the drug to dissolve is governed by several factors, including:

- 1. its chemical structure,
- 2. variation in particle size and particle surface area,
- 3.nature of the crystal form,
- 4.type of tablet coating, and type of tablet matrix.

- By **varying the dosage form and physical characteristics of the drug**, it is possible to have a drug dissolve quickly or slowly, with the latter being the situation for many of the sustained-action products.
- An example is orally administered **sodium phenytoin**, with which variation of both the crystal form and tablet adjuvants can significantly alter the bioavailability of this drug widely used in the treatment of epilepsy.

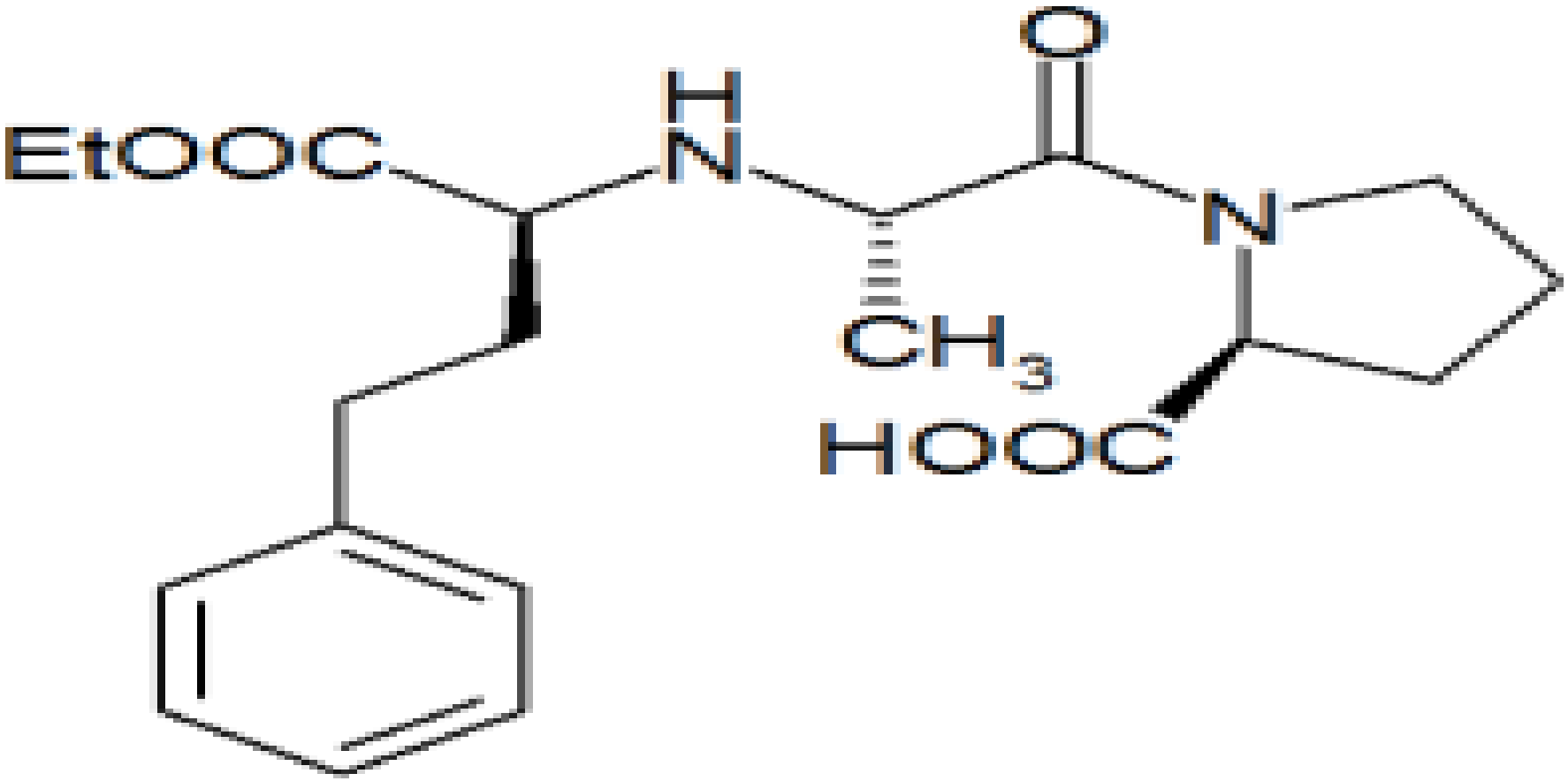
- **Chemical modification** is also used to a limited extent to facilitate a drug reaching its desired target.
- An example is **olsalazine**, used in the treatment of ulcerative colitis. This drug is a dimer of the pharmacologically active mesalamine (5-aminosalicylic acid). The latter is not effective orally because it is metabolized to inactive forms before reaching the colon. The dimeric form passes through a significant portion of the intestinal tract before being cleaved by the intestinal bacteria to two equivalents of mesalamine.

- As illustrated by olsalazine, any compound passing through the gastrointestinal tract will encounter a large number and variety of digestive and bacterial enzymes, which, in theory, can degrade the drug molecule.
- In practice, a new drug entity under investigation will likely be dropped from further consideration if it cannot survive in the intestinal tract or its oral bioavailability is low, necessitating parenteral dosage forms only.
- An exception would be a drug for which there is no effective alternative or which is more effective than existing products and can be administered by an alternate route, including parenteral, buccal, or transdermal. In contrast, these same digestive enzymes can be used to advantage.

- **Chloramphenicol** is water soluble enough (2.5 mg/mL) to come in contact with the taste receptors on the tongue, producing an unpalatable bitterness.
- To mask this intense bitter taste, the palmitic acid moiety is added as an ester of chloramphenicol's primary alcohol.
- This reduces the parent drug's water solubility (1.05 mg/mL), enough so that it can be formulated as a suspension that passes over the bitter taste receptors on the tongue.
- Once in the intestinal tract, the ester linkage is hydrolyzed by the digestive esterases to the active antibiotic chloramphenicol and the very common dietary fatty acid palmitic acid.

- Olsalazine and chloramphenicol palmitate are examples of " **Prodrugs** ".
- Most prodrugs are compounds that are inactive in their native form but are easily metabolized to the active agent.
- Occasionally, the prodrug approach is used to enhance the absorption of a drug that is poorly absorbed from the gastrointestinal tract.
- **Enalapril** is the ethyl ester of enalaprilic acid, an active inhibitor of angiotensin converting enzyme (ACE). The ester prodrug is much more readily absorbed orally than the pharmacologically active carboxylic acid.

Enlapril
enlaprilic acid



- Unless the drug is intended to act locally in the gastrointestinal tract, it will have to pass through the gastrointestinal mucosal barrier into venous circulation to reach the site of the receptor.
- The drug's route involves distribution or partitioning between the aqueous environment of the gastrointestinal tract, the lipid bilayer cell membrane of the mucosal cells, possibly the aqueous interior of the mucosal cells, the lipid bilayer membranes on the venous side of the gastrointestinal tract, and the aqueous environment of venous circulation.

Parenteral Administration

- Many times, there will be therapeutic advantages in bypassing the intestinal barrier by using parenteral (injectable) dosage forms.
- This is common in:
- 1.patients who, because of illness,
- 2. cannot tolerate or are incapable of accepting drugs orally.
- 3.Some drugs are so rapidly and completely metabolized to inactive products in the liver (first-pass effect) that oral administration is precluded.

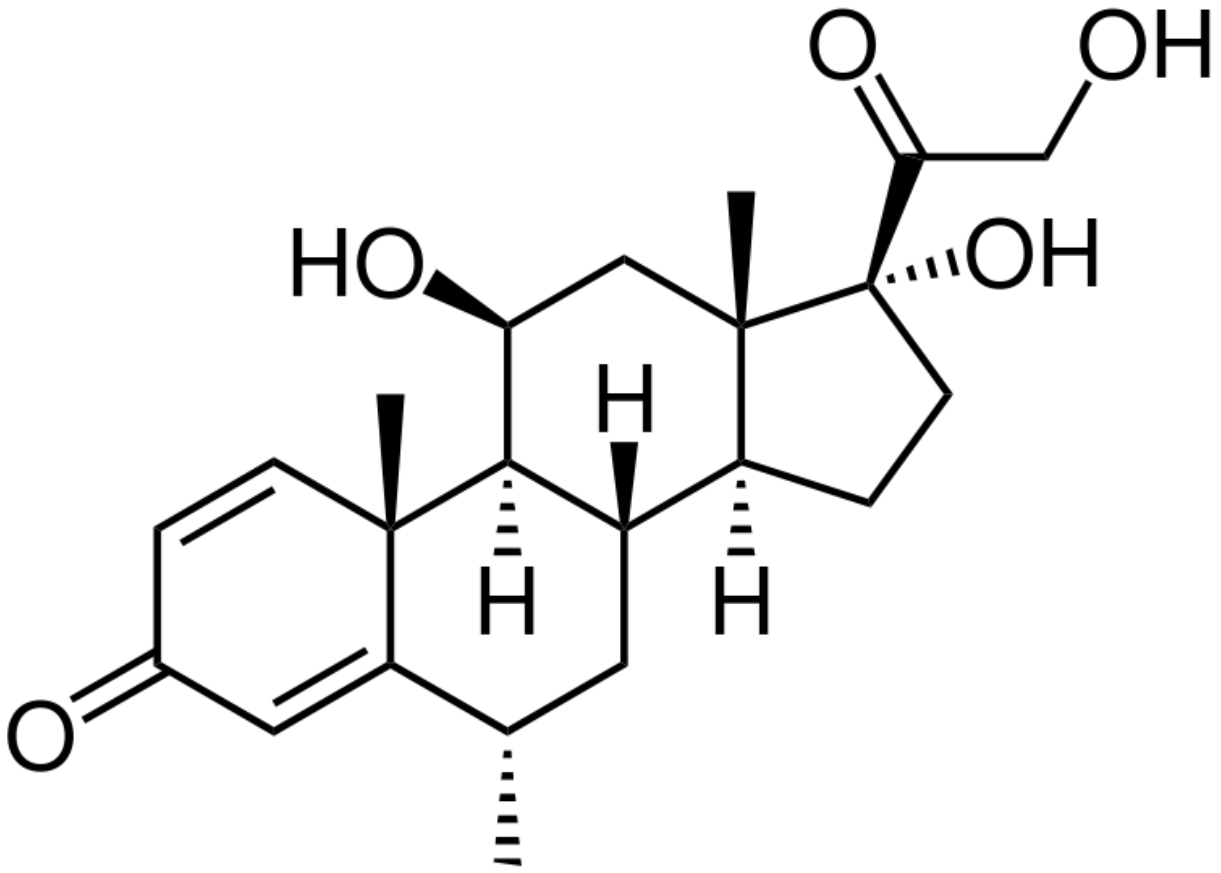
- **Intravenous administration** places the drug directly into the circulatory system, where it will be rapidly distributed throughout the body, including tissue depots and the liver, where most biotransformations occur , in addition to the receptors.
- **Subcutaneous and intramuscular injections** slow distribution of the drug, because it must diffuse from the site of injection into systemic circulation.
- **Intraspinal and intracerebral routes** will place the drug directly into the spinal fluid or brain, respectively. This bypasses a specialized epithelial tissue, the blood-brain barrier, which protects the brain from exposure to a large number of metabolites and chemicals.

- **Local anesthetics** are examples of administration of a drug directly onto the desired nerve.
- A spinal block is a form of anesthesia performed by injecting a local anesthetic directly into the spinal cord at a specific location to block transmission along specific neurons.
- These parenteral routes produce a depot in the tissues , from which the drug must reach the blood or lymph. Once in systemic circulation, the drug will undergo the same distributive phenomena as orally and intravenously administered agents before reaching the target receptor.

- In general, the same factors that control the drug's passage through the gastrointestinal mucosa will also determine the rate of movement out of the tissue depot.
- The **prodrug approach** can also be used to alter the solubility characteristics, which, in turn, can increase the flexibility in formulating dosage forms.
- The solubility of **methylprednisolone** can be altered from essentially water insoluble methylprednisolone acetate to slightly water-insoluble methylprednisolone to water-soluble methylprednisolone sodium succinate.

- The water-soluble sodium hemisuccinate salt is used in oral, intravenous, and intramuscular dosage forms.
- Methylprednisolone itself is normally found in tablets.
- The acetate ester is found in topical ointments and sterile aqueous suspensions for intramuscular injection.
- Both the succinate and acetate esters are hydrolyzed to the active methylprednisolone by the patient’s own systemic hydrolytic enzymes (esterases).

Methyl prednisolone



- **Protein Binding**
- Once the drug enters the systemic circulation , it can undergo several events.
- It may stay in solution, but many drugs will be bound to the serum proteins, usually albumin. Thus, a new equilibrium must be considered. Depending on the equilibrium constant, the drug can remain in systemic circulation bound to albumin for a considerable period and not be available to the sites of biotransformation, the pharmacological receptors, and excretion.

Protein binding can have a profound effect on:

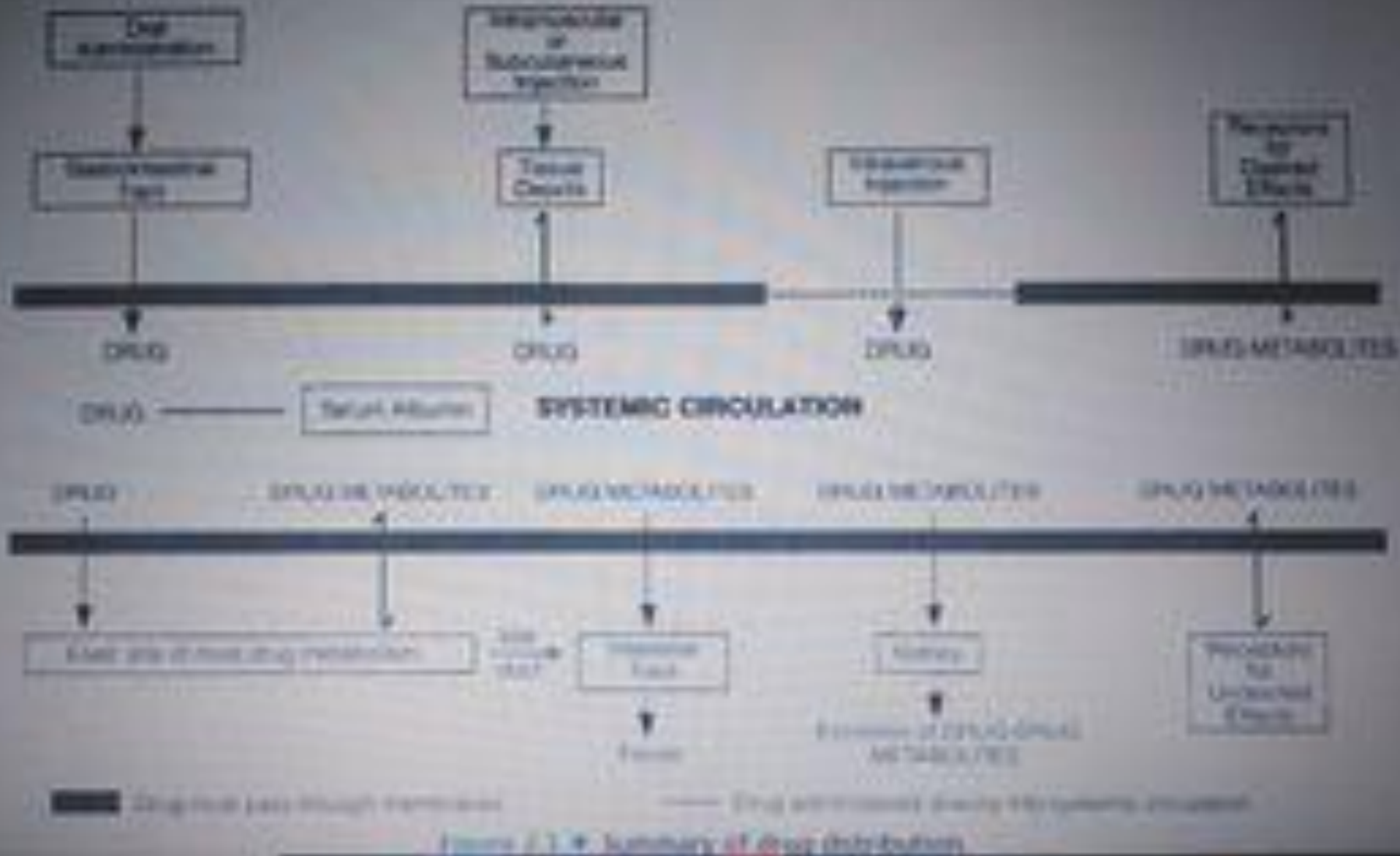
1. Biodistribution,
2. Half-life in the body also can prolong the drug's duration of action.

The drug– protein complex is too large to pass through the renal glomerular membranes, preventing rapid excretion of the drug.

- 3.The drug's effective solubility
- A drug with such poor water solubility that therapeutic concentrations of the unbound (active) drug normally cannot be maintained still can be a very effective agent.
- The albumin–drug complex acts as a reservoir by providing large enough concentrations of free drug to cause a pharmacological response at the receptor.

- 4. Protein binding may also limit access to certain body compartments.
- The placenta is able to block passage of proteins from maternal to fetal circulation. Thus, drugs that normally would be expected to cross the placental barrier and possibly harm the fetus are retained in the maternal circulation, bound to the mother's serum proteins.

- 5. Interaction with other drugs.
- The drug–protein binding phenomenon can lead to some clinically significant drug–drug interactions that result when one drug displaces another from the binding site on albumin.
- A large number of drugs can displace the anticoagulant warfarin from its albumin-binding sites. This increases the effective concentration of warfarin at the receptor, leading to an increased prothrombin time and potential haemorrhage .


DRUG
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DRUG METABOLITES
DRUG
SYSTEMIC CIRCULATION
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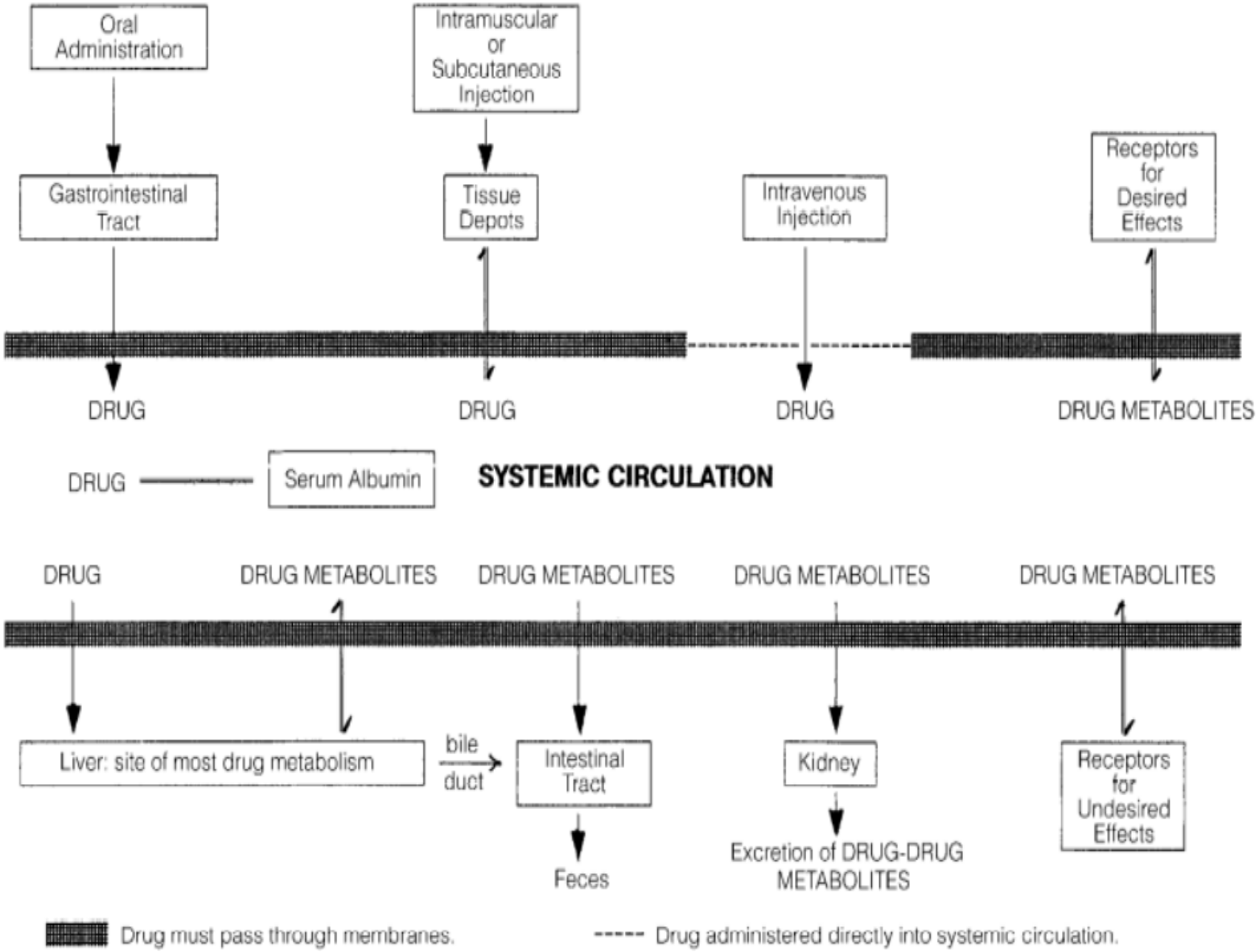

Figure 2.1 • Summary of drug distribution.

- **Questions :**

1.The drug is combine with cell at (receptors)

2. The drug absorbed from the stomach in form of (solution)

3. The factors that affect the absorption of a drug include ……,……,……,……

4. Sustained-action drugs usually dissolve ……

5. Parenteral dosage forms are used when ……

6. What are the alternate route of administration when a drug cannot taken orally ?

7. What is a prodrug ?
8. Give example of a prodrug .
9. What is the main uses of prodrugs ?
10. When parenteral administration is nesccary ?
11. What are the different parenteral routs ?
12. Biotransformations occur in the ……and……..?
13. Local anesthetics are examples of administration of a drug directly onto ……. ?
14. Many drugs will be bound to the serum proteins, usually …… ?
15. What are the effects of Protein binding ?