

PHARMACOKINETICS

-GENERAL PHARMACOLOGY

UNIT-II(PART-B)

BY- ASST.PROF Sucharita Babu

➤ **TRANSPORT SYSTEM**

➤ **ABSORPTION**

➤ **DISTRIBUTION**

➤ **BIOTRANSFORMATION**

➤ **ELIMINATION**

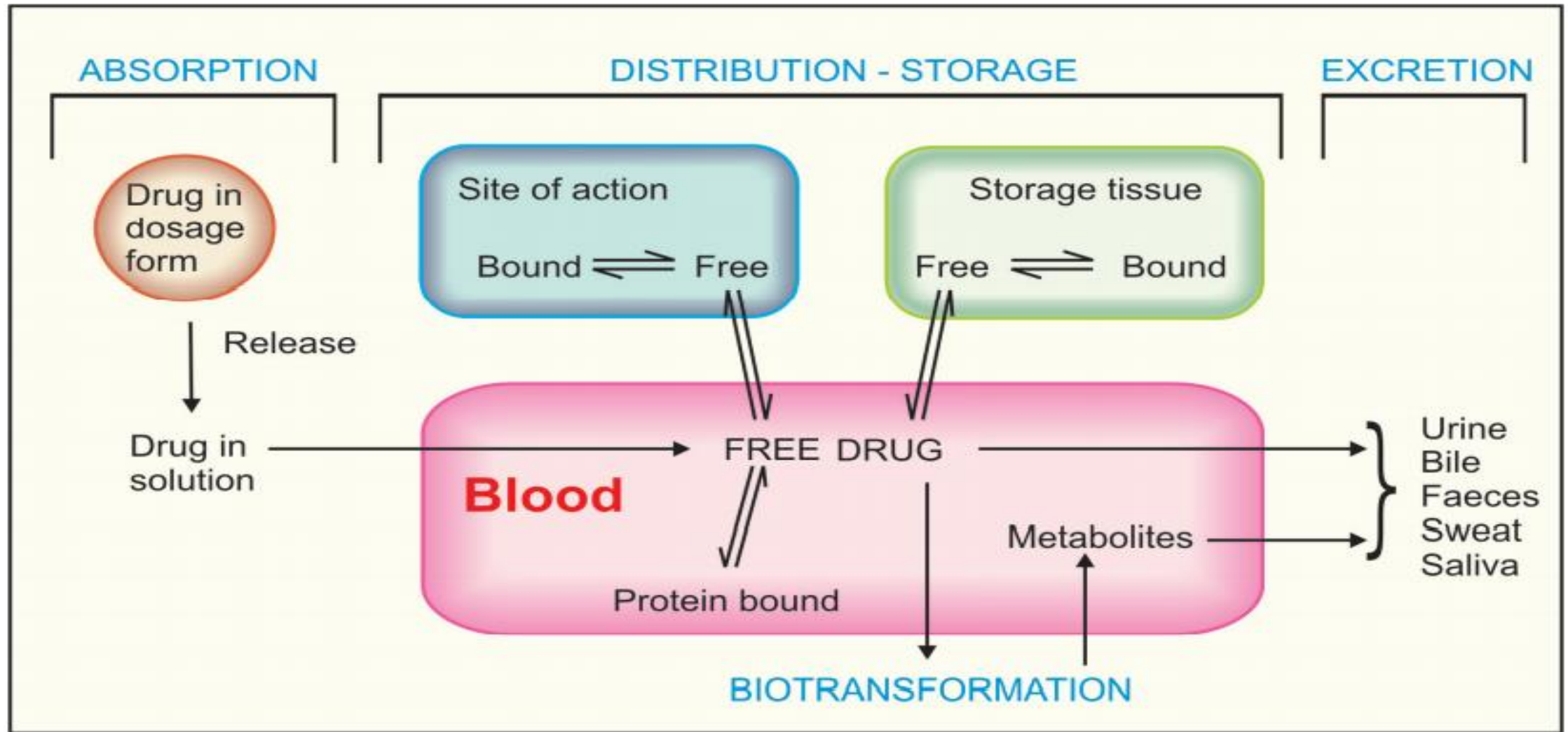


Fig. 2.1: Schematic depiction of pharmacokinetic processes

Biological Membrane

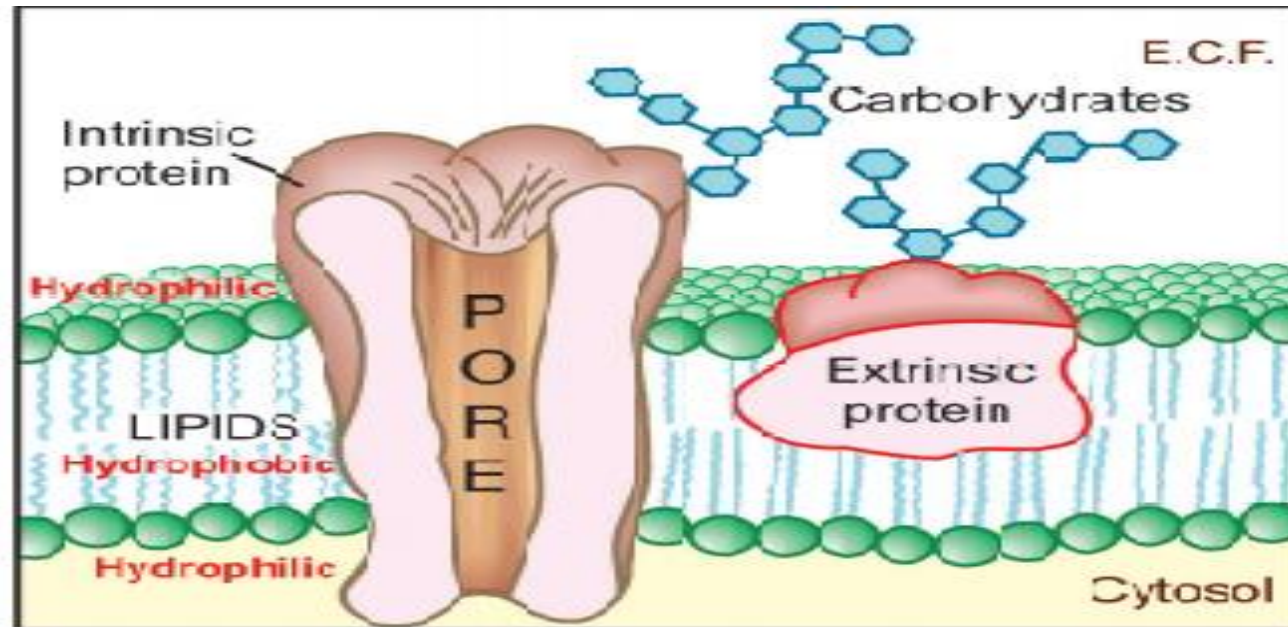


Fig. 2.2: Illustration of the organisation of biological membrane

- A biological membrane or bio-membrane is an enclosing or separating membrane that act as a selectively permeable barrier with in living things.
- Biological membranes are made up of 3 major component: lipid, protein & sugars.
- This is a bilayer of about 100 Å thick, in the form of cell membranes, consist of a phospholipid bilayer with embedded, integral & peripheral proteins used in communication & transportation of chemicals & ions.
- In all cells protein in plasma membrane selectively absorb nutrients, expel wastes & maintain proper intracellular ionic composition.

ABSORPTION:

Absorption is the transfer of a drug from its site of administration to the Bloodstream.

- The rate and efficiency of absorption depend on the route of administration. For IV delivery, absorption is complete, that is the total dose of drug reaches the systemic circulation.
- Drug delivery by other routes may result in only partial absorption and, thus, lower bioavailability.

Factors affecting Drug Absorption:

Pharmaceutical factors:

- I. Disintegration
- II. Dissolution
- III. Particle size

Drug Factors:

- I. Lipid Solubility
- II. P H
- III. Ionization

Biological Factors:

- I. Surface area
- II. Gastric Emptying time
- III. Presence of Food
- IV. Disease Condition
- V. First pass metabolism

Factors affecting Drug absorption related to patient:-

- Route of administration.
- Gastric pH.
- Content of the GIT

Factors affecting absorption in pediatric patients:-

- Gastrointestinal pH changes
- Gastric emptying
- Gastric enzymes
- Bile acids & biliary function
- Gastrointestinal flora
- Formula/food interaction

Bioavailability:

- Bioavailability is the fraction of administered drug that reaches the systemic circulation in a chemically unchanged form.
- For example, if 100 mg of a drug are administered orally and 70 mg of this drug are absorbed unchanged, the bioavailability is 0.7 or seventy percent.
- The bioavailability of drug injected i.v is 100 %.

Bioequivalence

- Two related drugs are bioequivalent if they show comparable bioavailability and similar times to achieve peak blood concentrations.
- Two related drugs with a significant difference in bioavailability are said to be bioinequivalent.

DISTRIBUTION:

The extent and pattern of distribution of a drug depends on its:

- Lipid solubility
- ionization at physiological pH (a function of its pK_a)
- extent of binding to plasma and tissue proteins
- presence of tissue-specific transporters
- differences in regional blood flow.

FACTORS AFFECTING DRUG DISTRIBUTION:

1. Physicochemical properties of drugs:

- Molecular size, degree of ionization, partition coefficient & stereochemical nature.
- Almost all drugs having molecular weight less than 500-600 daltons easily cross the capillary to diffuse into the extracellular interstitial fluid.
- Small water solubles molecule & ions of size below 50 daltons enter the cell through aqueous filled channels where as those of larger size are restricted unless a specialized transport system exist for them.

- .A drug that remains unionized (lipophilic) can penetrate the cells relatively more rapidly since the blood & ECF pH remain constant at 7.4
- Among the drugs that have same o/w partition-coefficient but differ in the extent of ionisation at blood pH, the one that ionises to a lesser extent will have greater penetrability than that which ionises to a larger extent.

2. Physiological barrier to distribution of Drugs :

a. Blood-brain barrier (BBB) & Blood-cerebrospinal fluid barrier (CSF):

- The brain capillaries consist of endothelial cells which are joined to one another by continuous tight intercellular junctions comprising what is called blood brain barrier.
- Blood CSF barrier is located choroid plexus, capillaries are lined by choroidal epithelium having tight junction.
- The barrier are Both lipoidal & limits the entry of nonlipid soluble drugs.
- Exit of drug from the CSF & brain is not dependent on lipid solubility.

Blood-placental barrier:

- Placental membrane are lipoidal & allow free passage of lipophilic drug while restricting hydrophilic drugs.
- When non-lipoidal soluble drugs present in high concentration or for long time in maternal circulation, gain access to the foetus.
- It is an incomplete barrier & almost any drug taken by the mother can affect the foetus or the new borne.
- Teratogenicity is defined as foetal abnormalities caused by administration of drugs during pregnancy.

3. Plasma protein binding:

- Drugs ordinarily bind to protein in a reversible form and in dynamic equilibrium.
- Those bound to protein are called bound drug, and those unbound to protein are called free drug.
- Only the unbound drugs can diffuse through the capillary wall, produce its systemic effects.
- Bound drugs lose pharmacological activity momentarily, and act as a drug reservoir.

- Patient with low plasma protein (uraemia, hepatic disease) or old age people with low albumin in plasma ,their percentage of protein binding may be changed, amount of unbound drug increases, effect precipitate.

Volume of Distribution : The apparent volume of distribution, V_d , is defined as the volume of fluid required to contain the total amount, Q of drug in the body at the same concentration as that present in the plasma, C_p

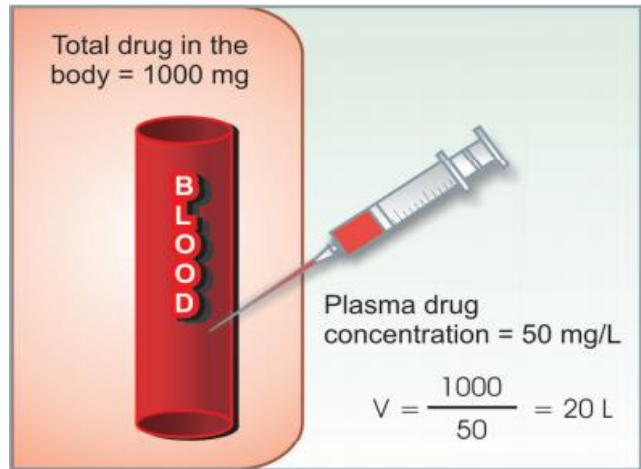


Fig. 2.7: Illustration of the concept of apparent volume of distribution (V).

$$V = \frac{\text{dose administered i.v.}}{\text{plasma concentration}}$$

- 1000mg of drug injected i.v. produces steady-state plasma concentration of 50mg/L, apparent volume of distribution is 20 L
- V_d is not a real volume, small volume indicates extensive plasma protein binding, but large volume indicates extensive tissue binding.
- V_d is increased by increased tissue binding, decreased plasma binding and increased lipid solubility.

ELIMINATION:

- Drugs are eliminated either in original form or as metabolites.
- Only the unbound or free drug is capable of being eliminated.
- This is because the drug protein complex can't penetrate into the metabolising organ (liver).
- The larger molecular size of complex also prevents it from getting filtered through the glomerulus.
- Thus, drug which are more than 90 % bound are eliminated slowly i.e they have long elimination half life.

Elimination can be affected by:

1. Drug half life: How long the drug will remain in the body, total amount of the drug is diminished by one-half.

The plasma half life ($t_{1/2}$) of a drug is the time taken for its plasma concentration to be reduced to half of its original value.

2. Accumulation: Time required to reach loading dose to reach desired therapeutic level. Loading dose: This is a single or few quickly repeated dose given in the beginning to attain target concentration rapidly.

$$\text{Loading dose} = \frac{\text{target } C_p \times V}{F}$$

3.Clearance: Removal of drug from the body.

Clearance is defined as the hypothetical volume of body fluids containing drug from which the drug is removed or cleared completely in a specific period of time.

It is expressed in ml/min

$$CL = \text{Rate of elimination} / C$$

where C is the plasma concentration.

4.Onset of action:

The time when a drug is sufficiently absorbed to reach an effective blood level & sufficiently distributed to its site of action to get a therapeutic response.

5. Peak concentration:

Concentration of drug rises in the blood, more drug reaches the site of action & therapeutic response increases.

6. Duration:

Once drugs begin to circulate, it begins to be eliminated, eventually drug level absorption falls behind elimination & therapeutic benefits declines or stop.