BP-604T.BIOPHARMACEUTICS AND PHARMACOKENICTS (Theory)

UNIT-ONE (Part 2)

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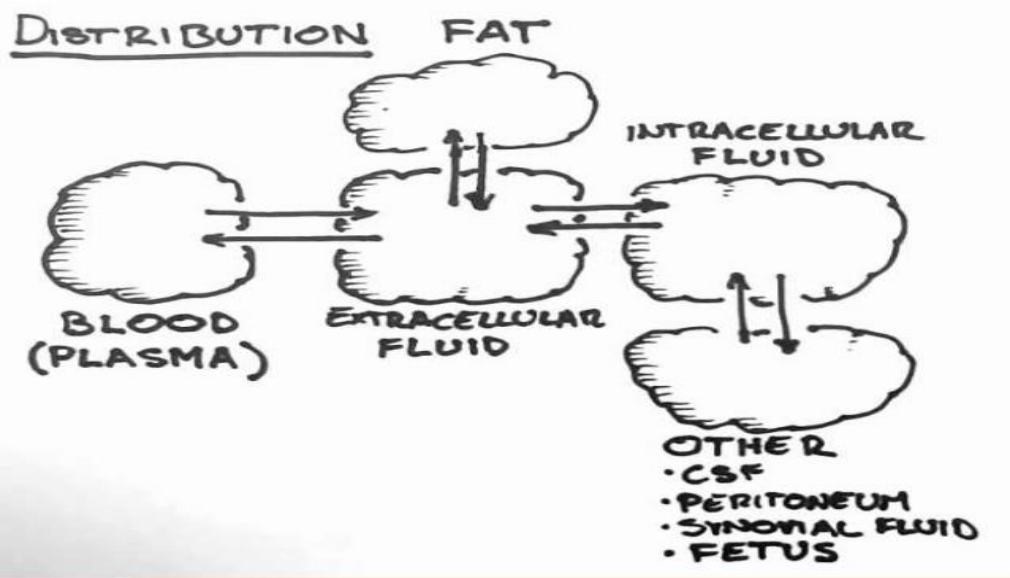
UNIT-ONE Part -2 **5 Horus**

Distribution Tissue permeability of drug ,binding of drug, apparent ,volume of drug distribution, plasma and tissue protein binding ,kinetics of protein binding clinical significances of protein binding of drugs

DRUG DISTRIBUTION IN THE BODY

Distribution: Distribution is the reversible transfer of a drug between one compartment and other.

Since the process is carried out by the circulation of blood, one compartment is always the blood or the plasma and the other represents extravascular fluids and other body tissues



- Distribution of a drug is not uniform through out the body because different tissues receive the drug form plasma at different rates and to different extents

Tissue permeability of the drugs

- Physicochemical properties like molecular size, pKa and o/w partition coefficient.
- Physiological barriers to diffusion of drugs.

Binding of drugs to tissue components

- Binding of drugs to blood components
- Binding of drugs to extravascular tissue proteins.

Miscellaneous factors

- Age
- Pregnancy
- Obesity
- Diet
- Disease states
- Drug interaction

➢ TISSUE PERMEABILITY OF DRUGS

Two major rate-determining steps in the distribution of drugs are:

- ✓ Rate of blood perfusion
- ✓ Rate of tissue permeability

If the blood perfusion to the tissues are high then the tissue permeability will be the rate determining step in the process of distribution.

The tissue permeability of a drug depends upon the physicochemical properties of the drug as well as the physiological barriers.

Physicochemical properties of the drugs:

Molecular size

Almost all drugs having molecular weight less than 500 to 600 daltons easily cross the capillary membrane to diffuse into the extracellular fluid (ECF).

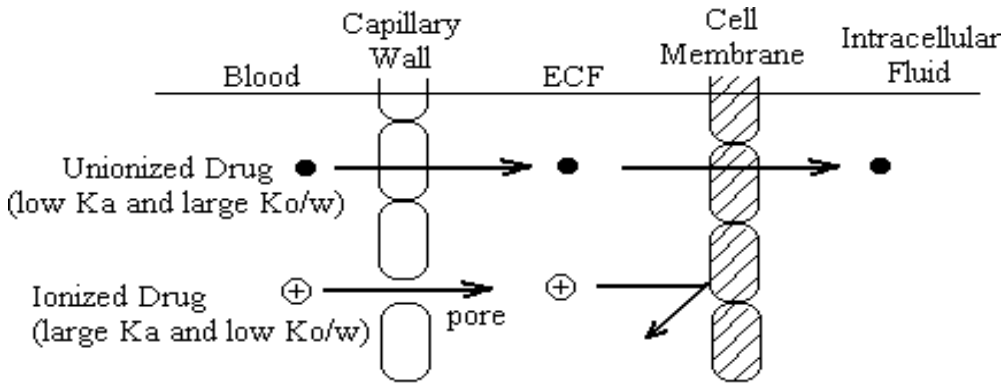


Fig. Permeation of unionized drugs across the capillary and cell membrane

- ✓ Only small, water-soluble molecules and ions of size below 50 daltons enter the cell through water channels.
- ✓ Larger molecules are transported through specialized transport system existing on the cell membrane.

➢ ***Degree of ionisation*** Most drugs are either weak acids or weak bases and their degree of ionization at plasma or ECF pH (i.e. 7.4) depends upon their pKa.

All the drugs that ionize are plasma pH (i.e. polar hydrophilic drugs) cannot penetrate the lipoidal cell membrane and tissue permeability is the rate determining step

Physiological barriers to distribution of drugs

Some of the important simple and specialized physiologic barriers are:

- ➢ Simple capillary endothelial barrier
- ➢ Simple cell membrane barrier
- ➢ Blood-Brain-Barrier (BBB)
- ➢ Cerebro Spinal Fluid Barrier (CSF Barrier)

- Placental Barrier
- Blood-Testis Barrier

- ***The simple capillary endothelial barrier:***

The membrane of capillary are unicellular in thickness; are practically no barrier for drugs having molecular weight under 600 daltons. Only drugs bound to blood components

e.g. plasma protein, blood corpuscles are restricted due to large molecular size of the complex.

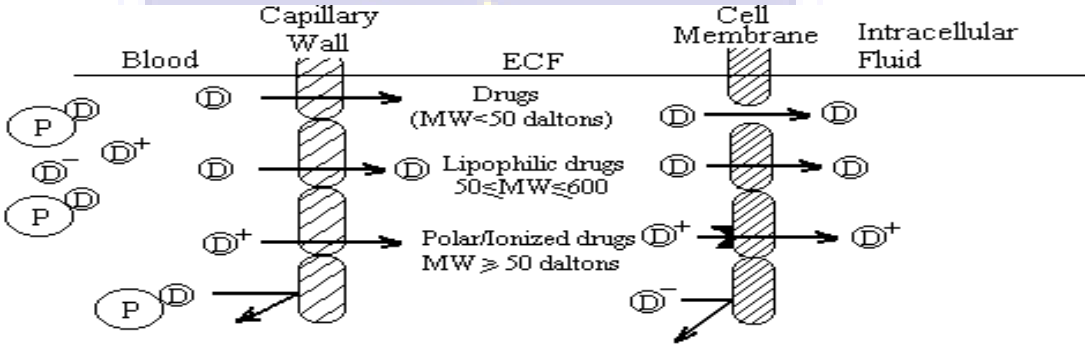


Fig. Plasma membrane barrier and drug diffusion across it

= Drug-protein complex

= Carrier

- **The simple cell membrane barrier**

Once a drug diffuses from the capillary wall into the extracellular fluid, its further entry into cells of most tissues is limited by its permeability through the cell membrane that lines such cells.

- **Blood Brain Barrier**

The brain capillaries consist of endothelial cells which are joined to one another by continuous, tightly intercellular junctions comprising what is called as the blood-brain-barrier.

the capillaries in the brain are highly specialized and much less permeable to hydrophilic molecules. More over the glial cells and basement membrane forms a solid envelope around the brain capillaries. As a result, the intercellular passage is blocked and for a drug to gain access from the capillaries circulation into the brain, it has to pass through cells rather than between them

- ✓ Since the BBB is a lipoidal barrier, it allows only the drugs having high Ko/w to diffuse passively.
- ✓ Moderately lipid soluble and partially ionized molecules penetrate at a slow rate

➢ Blood-cerebrospinal barrier

The cerebro-spinal fluid (CSF) is formed mainly by the choroidal plexus of the lateral, third and fourth ventricles and is similar in composition to the ECF of brain.

- ✓ A drug that enters the CSF slowly cannot achieve a high concentration as the bulk flow of CSF continuously removes the drug.

➢ **Placental barrier** The human placental barrier has a mean thickness of 25 μm in early pregnancy that reduces to 2 μm at full term. Many drugs having molecular weight less than 1000 daltons and moderate to high lipid solubility

ORGAN/TISSUE SIZE AND PERFUSION RATE

Perfusion rate is defined as the volume of blood that flows per unit time per unit volume of the tissue.

- ❖ It is expressed in ml (of blood)/min/ml (of the tissue).

Relative volume of different organs and tissues and their perfusion rates

Organ/Tissue	%k of Body volume	Perfusion rate (ml blood/min/ml of tissue)
I. Highly perfused tissue		
1. Lungs	0.7	10.2
2. Kidneys	0.4	4.5
3. Adrenals	0.03	1.2
4. Liver	2.3	0.8
5. Heart	0.5	0.6
6. Brain	2.0	0.5
II. Moderately perfused tissue		
7. Muscles	42.0	0.034
8. Skin	15.0	0.033
III. *Poorly perfused*		
9. Fat (adipose tissue)	10.0	0.03
10.Bone (skeleton)	16.0	0.02

➢ Age

Differences in distribution pattern of a drug in different age groups are mainly due to differences in –

- ✓ Total body water (both intracellular and extracellular) – is much greater in infants.
- ✓ Fat content – is also higher in infants and elderly.
- ✓ Skeletal muscles – are lesser in infants and in elderly.
- ✓ Organ composition – the blood brain barrier is poorly developed in infants, the myelin content is low and cerebralblood flow is high, hence greater penetration of drugs in the brain.
- ✓ Plasma protein content – low albumin content in both infants and in elderly.

➢ Pregnancy

- ✓ During pregnancy, the growth of uterus, placenta and fetus increases the volume available for distribution of drugs.
- ✓ The fetus represents a separate compartment in which a drug can distribute. The plasma and the extracellular fluid volume also increase but their is a fall in albumin content.

➢ Obesity

In obese persons, the high adipose tissue content can take up a large fraction of lipophilic drugs despite the

fact that perfusion through it is low. The high fatty acid levels in obese persons alter the binding characteristics ofacidic drugs.

➢ Diet

A diet high in fats will increase drugs such as NSAIDs to albumin.

➢ Disease states

A number of mechanisms may be involved in the alteration of drug distribution characteristics in disease states

- ✓ Altered albumin and other drug-binding protein concentration
- ✓ Altered or reduced perfusion to organs or tissues
- ✓ Altered tissue pH.

Example: An interesting example of altered permeability of the physiologic barrier is that of blood brain barrier (BBB). In meningitis and encephalitis, the BBB becomes more permeable and thus polar antibiotics such as penicillin G and ampicillin which do not normally cross it, gain access to the brain.

Drug interactions

Drug interactions that affect distribution are mainly due to differences in plasma protein or tissue binding of drugs

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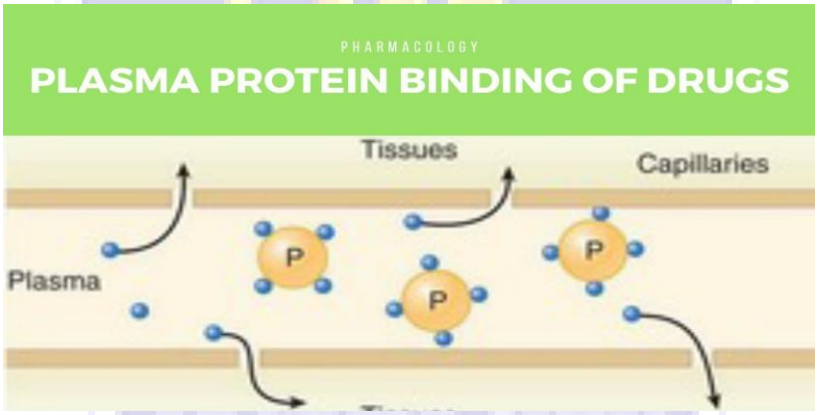
PROTEIN BINDING OF DRUGS

- Protein binding is define as the ability of protein to form bonds with other substance such as blood components plasma , blood cell
- A drug in the body can interact with several tissue components of which the two major categories are blood and extravascular tissues.
- The interacting molecules are generally the macromolecules such as proteins, DNS and adipose tissue.
- The phenomenon of complex formation with proteins is called **protein binding** of drugs.



- Protein-drug binding: Binding of drugs to various tissue components and its influence on deposition and clinical response. Only the unbound drug moves reversibly between the compartments.

Binding of drugs falls into two classes:

1.Binding of drugs to blood components like -

- Plasma proteins
- Blood cells

2.Binding of drugs to extravascular tissue proteins,

- fats,
- bones, etc

1. **Binding of drugs to blood components**

- **Plasma Protein Binding**

The extent or order of binding of drugs to various plasma proteins is:

albumin > α1Acid Glycoprotein > lipoproteins > globulins

Blood proteins to which drugs binds

Protein	Molecular weight	Concentration (g %)	Drugs that bind
Human serum albumin	65,000	3.5 - 5.0	large variety of all types of drugs
α1 - Acid glycoprotein	44,000	0.04 - 0.1	basic drugs such as imipramine, lidocaine, quinidine, etc.
Lipoproteins	200,000 to 3,400,000	variable	basic, lipophilic drugs like chlorpromazine
α1- Globulin	59,000	0.003-0.007	steroids like corticosterone, and thyroxine and cyanocobolamine (Vit. B12)
α2- Globulin	134,000	0.015-0.060	vitamins A, D, E and K and cupric ions
Hemoglobin	64,000	11-16	Phenytoin, pentobarbital and phenothiazines

- **Binding of drugs to blood cells**

More than 40% of the blood comprises of blood cells of which 95% is RBC. Thus significant RBC binding ofdrug is possible. The RBC comprises of 3 components:

- Haemoglobin: Phenytoin, pentobarbital and phenothiazines bind to haemoglobin.
- Carbonic anhydrase :Acetazolamide and chlorthalidone (carbonic anhydrase inhibitors)
- Cell membranes :Imipramine and chlorpromazine are reported to bind to RBC membrane

Binding of drugs to extravascular tissue proteins:

- **Tissue binding of drugs**

Tissue-drug binding is important from two point of views:

(i) It increase the *volume of distribution* (by reducing the concentration of free drug in the plasma)

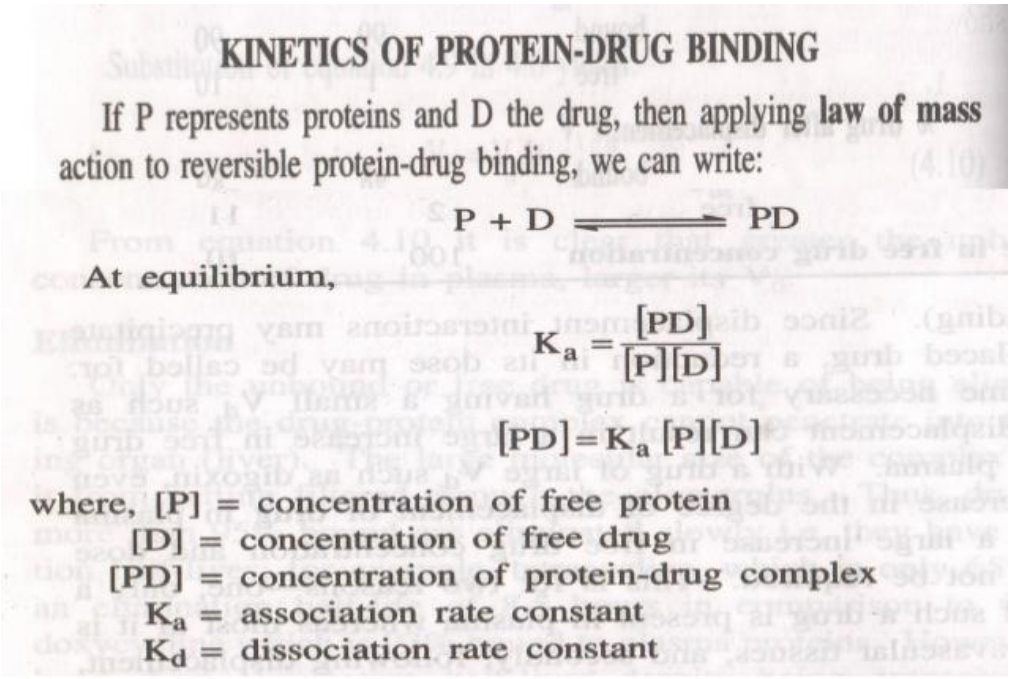
(ii) drug bound to tissue acts as a reservoir and hence *biological half life* increases.

- For majority of drugs that bind to extravascular tissues, the order of binding is :

liver > *kidney* > *lung* > *muscle*

- Liver: Oxidation products of carbon tetrachloride and paracetamol bind irreversibly with liver tissues resulting in hepatotoxicity.
- Kidneys: Metallothionin, a protein present in the kidneys, binds to heavy metals such as lead, mercury and cadmium.
- .Lungs : Basic drugs like imipramine, chlorpromazine and antihistamines accumulate in the lungs.
- Bones : Tetracycline bind to bones and tee

Kinetics Of Protein-Drug Binding



KINETICS OF PROTEIN-DRUG BINDING

If P represents proteins and D the drug, then applying **law of mass** action to reversible protein-drug binding, we can write:

$$P + D \rightleftharpoons PD$$

At equilibrium,

$$K_a = \frac{[PD]}{[P][D]}$$

$$[PD] = K_a [P][D]$$

where, [P] = concentration of free protein
[D] = concentration of free drug
[PD] = concentration of protein-drug complex
K_a = association rate constant
K_d = dissociation rate constant

Significance of protein binding

➢ Absorption

- ✓ From the absorption site the drug is absorbed to the blood. This absorption process will stop when free drug concentration at both sides become equal.
- ✓ If the drug is bound significantly to plasma protein then free drug in the plasma becomes less and hence the absorption process goes on. Thus much more amount of drug is absorbed.

➢ Systemic solubility of drugs

- ✓ Water insoluble drugs, neutral endogenous macromolecules (such as heparin, steroids and oil soluble vitamins) are circulated and distributed to tissues by binding to lipoproteins.

➢ Distribution

- ✓ Some drug may bind to a specific tissue and may produce toxic reaction to the tissue. Plasma protein binding restricts the entry of the drug into a tissue, thus saves

the tissue.

- ✓ A protein bound drug does not cross the blood brain barrier, the placental barrier and the glomerulus.

- **Tissue binding, apparent volume of distribution and drug storage**
  - ✓ A drug that is extensively bound to blood components remains confined to blood and very little amount of drug will be available for distribution in the tissues. In this case the apparent volume of distribution (Vd) will be decreased.
  - ✓ If the drug is bound to some tissue then the concentration of drug in the blood compartment will be less hence the Vd will be high.
  - ✓ In both the cases the drug-protein complex will act as drug reservoir

- **Elimination**
  - ✓ Only the unbound or free drug can be eliminated because the drug-protein complex cannot penetrate into the metabolising organ (e.g. liver).
  - ✓ The large molecular size of the complex prevents it from filtration through glomerulus. Thus drugs which are more than 95% bound to protein eliminates slowly and the elimination half life will be

- **Displacement interaction and toxicity**
  - ✓ If two drugs A and B, both have the same binding sites to plasma protein then one drug will displace the other.
  - ✓ Thus the free drug concentration of both the drug in the plasma will rise and may precipitate toxic reaction. e.g. warfarin and phenylbutazone.

- **Diagnosis**
  - ✓ Thyroid gland (tissue) has great affinity for iodine. So any disorder of thyroid gland can be detected by administering compounds with radioactive iodine (I^{131})

- **Therapy and drug targeting**

  The binding of drugs to lipoproteins can be used for site specific delivery of hydrophilic moieties. e.g. in cancer therapy tumour cells have great affinity for LDL (low density lipoprotein) than normal tissues. Hence binding of suitable neoplastic agent to LDL can be used as a therapeutic tool.