# Biopharmaceutics & Pharmacokinetics

# Biopharmaceutics - The Study in which we know about time period and effect of drug on the basis of ADME Process

A Absorption - Process of movement of drug molecule from Stomach or Intestine to Blood Stream.

D - Distribution - Transfer or movement of drug substance to different body parts through blood flow.

M - Metabolism : Breakdown of drug from Active form to inactive form

E - Elimination - Removal of drug from the Body.

* On the Basis of ADME, we know about adverse effects of drug, efficacy and time period of action of drug.

* The drug effect is depends upon the ADME process rate and no. of receptors present on cell.

* Biopharmaceutics - also deals with Bioavailability

Bioavailability - the actual amount of drug produce effect in the Body.

# Aim of Biopharmaceutics :

→ The Aim is to produce better effect of drug on body with dose correction.

→ To serve better health welfare to public

→ To reduce side effects of drugs

→ To know the properties of different drugs.

# Pharmacokinetics :- The Study of how body interact with drug or other administrated substance for entire duration of action.

* It also involves other important factors like Bioavailability, half-life, clearance, Volume of distribution also.

Half life - The time it take the drug's concentration in Plasma reduced to half.

clearance - The rate at which drug is removed from Body.

Volume of distribution - The apparent volume in which drug is distributed.

# Aim of Pharmacokinetics :-

→ understand the drug's ADME processes.

→ Determine drug's bioavailability and half-life.

→ Predict Potential drug interaction and adverse effect.

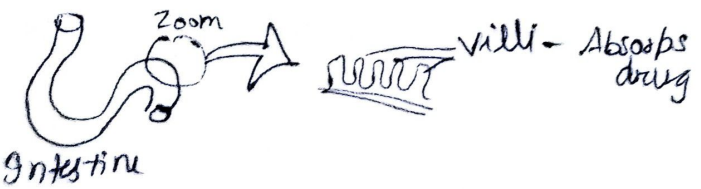
# Absorption

The travelling of drug from Stomach to Blood or from any Particular route called absorption.

→ 100% Absorption by Parenteral Route

→ Safe absorption considered in oral form

→ Small Intestine absorbs more amount of drug due to villi present in Intestine that enhances surface area.

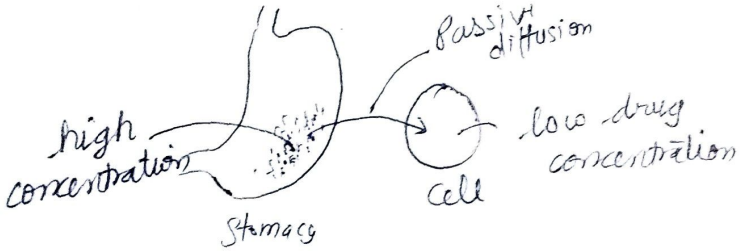


# Mechanism of Absorption through GIT :-

- Passive diffusion
- Filteration method / Pore Transport
- Carrier mediated Transport
- Ion Pair Transport
- Endocytosis

**Passive Diffusion** :- Movement of drug particle from high to low concentration.

→ No or less energy Required.




→ difference between concentrations of 2 Places called concentration gradient (D)

→ lipophilic (oily) drugs pass easily the cell membrane but hydrophilic (watery natured) drugs pass less.

**Passive Diffusion follows ficks law**

$$\frac{dC}{dt} = \frac{D A K_{o/w} D_c}{h}$$

Concentration of diffuse particle per unit time

D = Concentration gradient

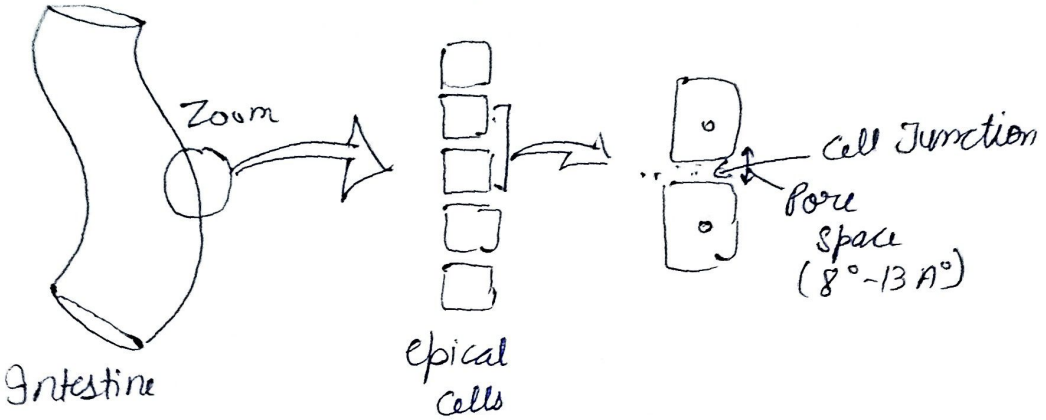
A = Area / Surface

K = Partition coefficient

$D_c$ = Concentration gradient

h = thickness of cell membrane

# Filteration Transport / Pore Transport :-




The drug can cross the cell Junction of Intestine due to very Small size.

→ diffusion principle

→ drug may be anionic (+ve), anionic (-ve) & Neutral.

→ Small molecule can Transport easily.

example - Atenolol, Ametine, Ranitidine, Furosemide etc.

→ Rate of Filteration depends upon tight Junction complex (Rate Limiting Step) and concentration.

→ Every drug cross by this space.

→ No First Pass Metabolism.

Factor affecting filteration :-

$$J = \frac{D \epsilon C}{h}$$

J = Amount of drug transfer from Intestine to Blood

D = Diffusion coefficient.

$\epsilon$ = fraction of surface Area

C = concentration of drug

h = thickness.

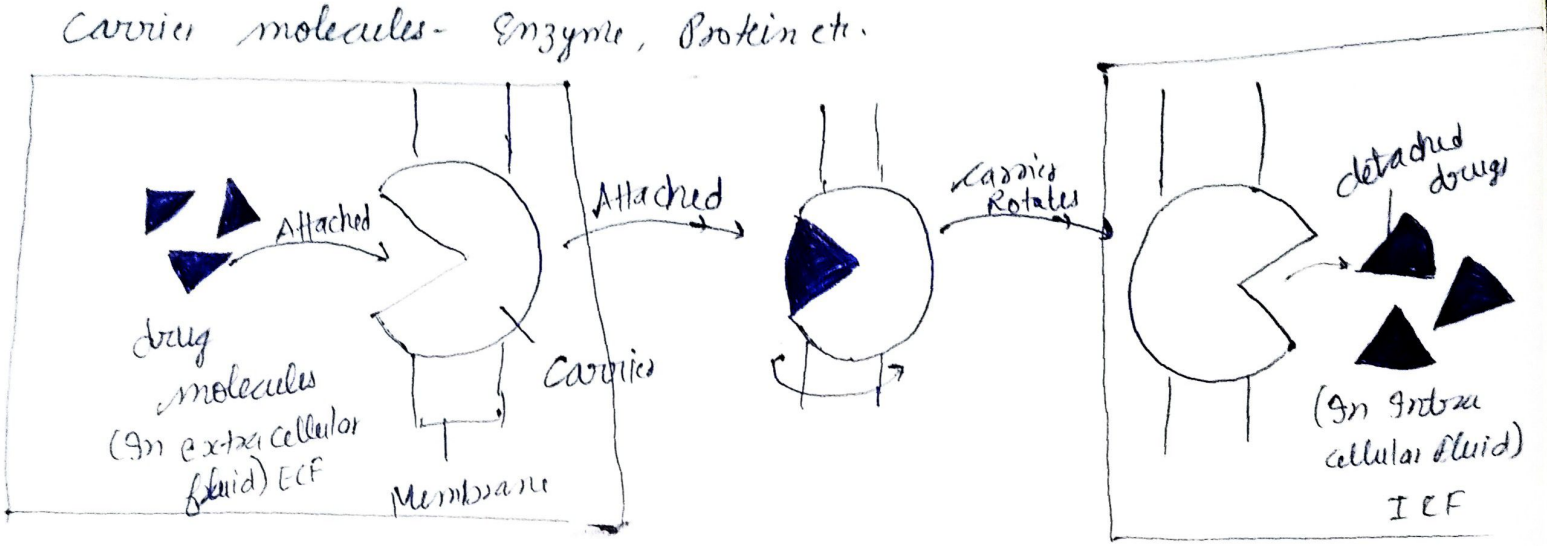
# Carrier Mediated Transport :-

The transportation is Transfer of drug through a carrier.

→ used due to Barriers (BBB, BPB etc)

→ Passive Transport Type

Carrier molecules - Enzyme, Protein etc.




Reversible Complex - when drug Release By Carrier.

Irreversible complex - when drug does not detached to carrier.

example - Pyrimidine, L-amino acid, Na, K, Fe, $B_3$ (vitamin), vitamin $B_6$

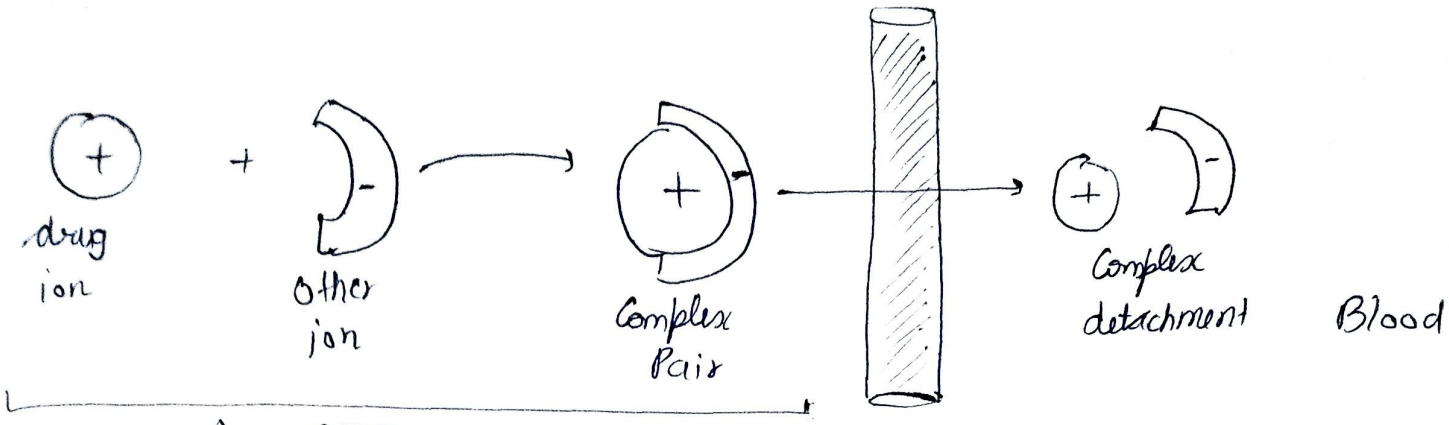
~~Carrier Mediated Transport~~:

Ion Pair Transport: Ionic Natured drug Transports through Ion Pairs.

drug - cationic or Anionic.

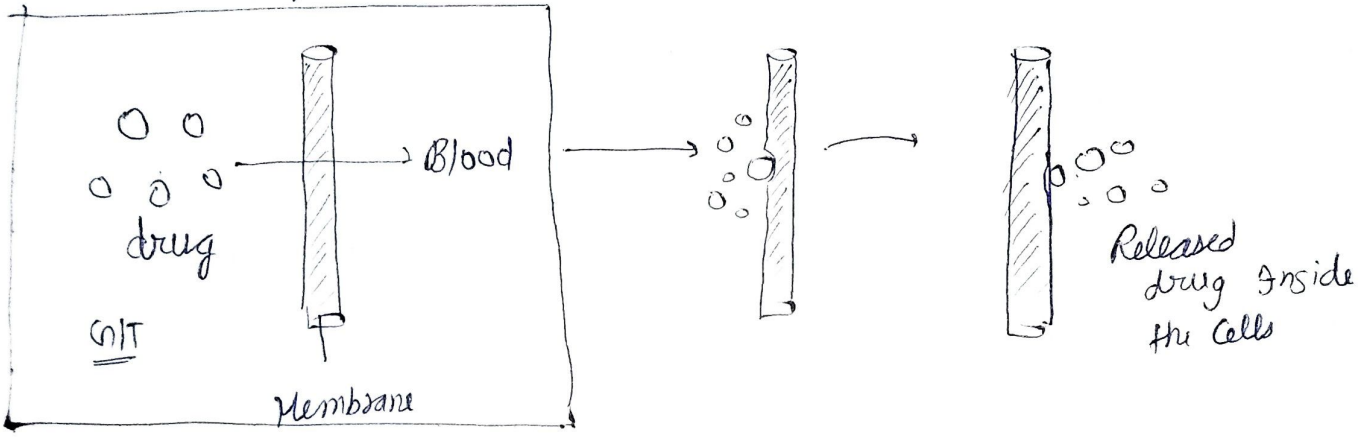
→ The ionic drug Binds to other (oppositely charged) ionic drug and forms Neutral Pair and easily cross the Membrane of Intestine to reach Blood

example - quinine, Quaternary Ammonium compound, Propanolol etc




Ion Pair Transport

Endocytosis : The engulfment of drug through fluidy natured cell membranes




example - oral Polio Vaccine, egg starch etc.

# Factor Affecting Absorption

⇒ Disintegration & Dissolution - Tablet disintgrate through HCl in Stomach (Breakdown)

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dissolution of drugs (dissolve)

Active constituents

↓

Affects absorption

- Small particles have Better Absorption.

⇒ Formulation - The defective amount of excipients in API with suitable method can affect disintegration and dissolution that affed absorption.

- Acidic drug dissolved in stomach
- Basic drug dissolved in Intestine

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Must be in unionised form

- Lipophilic drugs easily cross membrane

⇒ Biological Factor :- Small Intestine Absorbs more than stomach.

- Gastric emptying time - It refers to the time it takes for the stomach to empty its constituents into small Intestine.

Include
- Food type
- Volume and composition of meal
- Hormonal Regulation
- Medications
- Health conditions etc.

⇒ Dosage forms - diffsent dosage forms can affects absorption
exam - Tablet have more absorption time than liquid, Syrups etc.

⇒ Age and health status of Individuals :-

- Immature gut and different gastric PH in infants and children have low absorption
- adult persons have better absorption rate
- Improper health or disease condition can cause defective effect on absorption

⇒ Route of administration - different routes in body can cause effects on absorption.

example - • Oral administration have safe absorption and have more absorption time but have first Pass Metabolism
• IV (Parenteral) Route have 100% Absorption, 0 first Pass metabolism.

⇒ Presence of Food :- Absorption affected by particular time ~~of~~ of Food Intake and digestion.

- drug's intaked after Meal - PCM, Aspirin
- drug's intaked before Meal - Ranitidine

# Absorption From Non Per Oral Extra-Vascular Routes

Absorption other than Intestinal Routes.

Advantages of Non Per Oral Extra-Vascular Routes :

→ More action due to No First Pass metabolism
→ Follow by Pass Metabolism (No liver metabolism)
→ 100% efficacy.

## Routes

① Sublingual - Drug administer and absorbed under tongue through diffusion to Systemic Circulation

Disadvantage - May be uncomfortable
May be Irritable

② Buccal - Drug placed between cheek and Gum
- Lipid Soluble.

3. Rectal Route - Drug absorbed through Anal Route.
~~Insulin~~, Diazepam, PCM
e.g- ~~Insulin~~, ~~heparin~~ etc
but less drug can be administered.

4. Sub - Cutaneous - Drug placed and absorbed beneath the skin.
ex g- Insulin, ~~Diazepam~~ Heparin etc-

5. Inhalation - Drug absorbed by inhalation process through / from Nasal Cavity.
e g- general Anaesthetics, Asthma Pump.
→ Lungs have Blood Capillaries (fine Blood Vessels) - that transport drug to Body.

6. Nasal - Drug through Nose can be absorbed
e.g - GnRH in droplet form

7. IM (Intra - muscular) :- drug inserts to Triceps, to muscles.

8. IV (Intra - Venous) : drug absorbed through Veins.
→ Rapid action
- 100% Bioavailability.

9. Intra - Peritonial Cavity : drug introduced to Peritonial Cavity or large cavity

Peritoneal Cavity (B/w liver & stomach)

10. Intra - Articular - drug administered and Absorped in between Joints through Injection.

→ In case of Arthritis, GOUT etc.

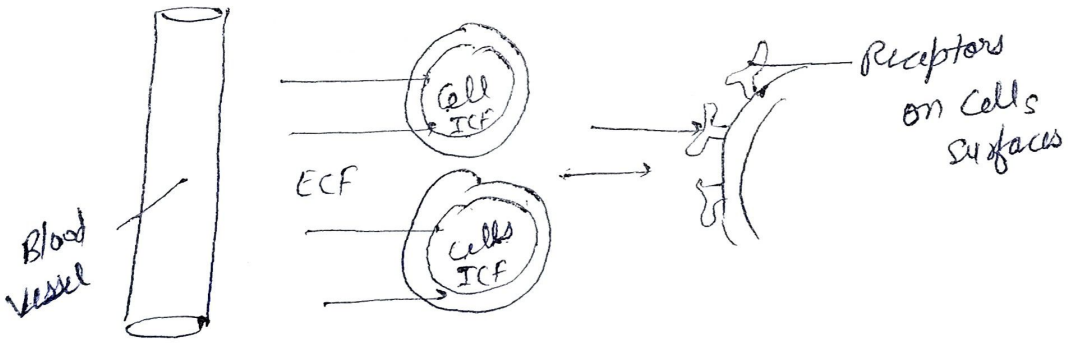
11. Intra Medullary - Drug administered in Medulla to Bone Marrow.

# Distribution

Process of movement of drug substance from Systemic circulation to ECF and enters to cell through carrier process.

## Tissue Permeability of Drug

Movement of drug from Blood to Extra cellular (ECF) fluid and from ECF, drug move to ICF with help of carriers, capillaries etc.




## Factors Affecting Permeability

(1) Physicochemical Properties - Exam. - Lipophilicity, Partition coeff., molecular weight.

→ Lipophilicity can be Identified theory Partition coefficient = $\frac{C \text{ in oil}}{C \text{ in water}}$

– Hydrophilic and Ionic drug have low membrane Transport

Partition coeff. ∝ Permeability.

2. Molecular Size :- If particle size is less than 500 the Permeability is Better.

3. Drug Transports :- carries through with drug Travels at their Site of Action
   - Suitable transporter helps the drug to Bind to suitable Size.
   - Transporter - Pumps, enzymes, Protein etc.

4. Physiological Barriers :-
   drug particle size less than 600 Dalton can easily Pass capillary wall.
   exam, - BBB, BCSF, BPB etc.

## Apparent Volume of Distribution ($V_d$)

It is the Volume of Body fluid in which drug distributed, also known as apparent volume of distribution
→ describes the theoretical volume in which drug distributed throughout Body.

High $V_d$ = Extensive tissue distribution
low $V_d$ = limited tissue distribution

$$V_d = \frac{\text{Amount of drug in Body}}{\text{Plasma drug concentration}} = \frac{X}{C}$$

$V_d$ = Amount of drug in Body
$X$ = Amount of drug in Body (whole)
$C$ = Plasma drug concentration.

# Factor affect $V_d$

→ **Lipophilicity** $\propto V_d$

More the Lipophilicity of drug, more will be the distribution volume.

→ **Protein Binding** - It is inversely proportional to the volume of distribution

→ Protein Binding $\propto \frac{1}{V_d}$

→ More is the protein binding, lesser is the volume of distribution because of high molecular weight and size.

→ **Tissue Binding** - when drug binds to the site tissue then, volume of distribution is more

Tissue Binding $\propto V_d$

→ **Other Factors**

- Age
- Pregnancy
- obesity
- Diet
- Disease State etc

# Binding of Drugs

drug binds to the protein present in Blood and tissues.

→ Drug binds to Proteins present in Blood but not activated

After absorption of drug from GIT to the System circulation

↓

Proteins Present in the Blood like Albumin, glycoproteins, Lipoproteins etc.

↓

drug bound to that Proteins (suitable) and travels to Site of Action

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After reaching Site of Action, drug get unbound to Blood protein to cross the capillary membrane

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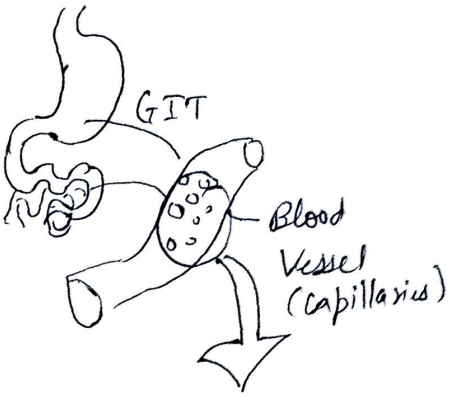
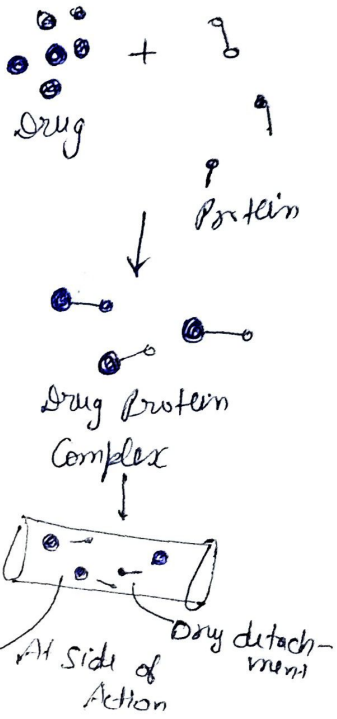
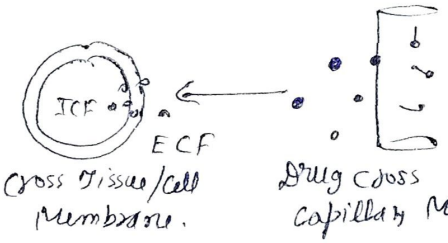
After unbounding, cross capillary to ECF and the to ICF




★ Blood Contain Proteins (Plasma Proteins) - human Serum Albumin
α- Acid glycoprotein
Lipoprotein

★ Drug Binding Types

- On Basis of Protein Attachment
  - Reversibly - drug unbound to Protein after Reaching to Site of Action due to weak forces attachment
  - Irreversibly - drug Non unbound due to attachment due to stronger bonds or forces.
- On Basis of Cellular Components Binding
  - Intracellular - drug Bind to Receptor & Shows Action. Called 1° (Primary) Receptor Binding (In tissues)
  - Extracellular - drug Binds to Plasma Protein, No Show Action called 2° Receptor Binding (In Blood)

Binding of drug
- In Blood → Bound to Plasma Protein
- In Blood → Blood cells
- Bind to ECF tissue, Protein Fats, Bones etc.

☆ Plasma Proteins

→ Albumin have affinity to bind with all drugs.
→ $\alpha_1$ - Acid glycoprotein – Binds to Basic Drugs
→ Lipoprotein binds with Basic and Lipophilic drugs
→ $\alpha_1$ - globulins - Steroids
→ $\alpha_2$ - globulins - Vitamin A, D, E, K

☆ Blood Cells

→ Phenytoin, Pentobarbital, Phenothiazine binds to hemoglobin
→ Acetazolamide, Chlorthalidon et binds to Carbonic Anhydrase (Present in Membrane of RBC)
→ Imipramine, Chlorpromazine binds to RBC's Cell Membrane.

☆ Tissue Binding :- drug binds to Tissue can enhance volume of distribution, may be reversible or Irreversible
eg. - PCM (Accessive) Cause hepatotoxicity

# Factor Affecting Drug Protein Binding :-

☆ Drug Related Factors :-

→ Lipophilicity - More the drug Lipophilic, more ability to binds with proteins (Lipoproteins) and cross cell Membrane
→ Concentration of drug - More the drug amount or concentration, more will be the drug protein complex formation.

Concentration of drug ∝ Protein Binding

→ Affinity of drug - Some drugs have same action but different affinity of Binding to Proteins

example - Lidocaine have more affinity of α-1 acid glycoprotein Compare to Albumin.

☆ Tissue Related Factors :-

→ Physicochemical Properties :- example - Molecular size of drug, PKa, Partition Coeff.

- More will be the Partition Coeff., more is the Binding & Permeability.
- Less the Molecular Size of drug, higher the distribution in Tissues.

→ Tissue Size and Perfusion Rate :-

- drug distribution is directly Proportional to the Blood flow. also, affects Protein Binding.

☆ Patient Related Factors :-

→ Age :- In Neonates, Albumin content is very low.

- In Adults, More affinity of Binding.

→ Disease state :- Albumin concentration vary with disease Results in affected Binding.

☆ Drug-Interaction :-

→ Sometimes, due to certain Reasons, drug fails to Binds to Protein that affect Bindings.

Reasons - Drug-Drug Interactions, etc.

☆ Sometimes, change in Protein Structure may also affect Binding.

# Kinetics of Protein Binding

Let Protein = P , Drug = D

Protein + Drug ⟶ Protein – Drug

[P] + [D] ⟶ P–D

Let Equilibrium Stability Constant = K

which is equal to Ratio of Product Concentration to the Concentration of Reactants.

Product – PD

Reactants – P & D

* Conc. Represents in Square Brackets

$$K = \frac{[PD]}{[P]\,[D]}$$

[PD] - Concentration of Protein drug complex

[P] - concentration of unbound Protein

[D] - Concentration of free drug.

$$K = \frac{[PD]}{[P]\,[D]}$$

$$K\,[P]\,[D] = [PD] \quad \text{—(1)}$$

* Some drug Molecules Binds to Protein, Some can't Binds, Some Protein is in free form.

[Pt] = Total Amount of Protein Available for Drug Binding

[P] - unbound Protein (Conc.)

[PD] - Drug Protein complex (Conc.)

then,

$$[P_t] = [P] + [PD]$$

$$[P_t] - [PD] = [P] \quad \text{—}$$

Put $([P] = [P_t] - [PD])$ in eqn (1)

eqn (1) is $K[P][D] = [PD]$

$K[[P_t] - [PD]][D] = [PD]$ $\quad ([P] = [P_t] - [PD])$

(Multiply)

$K[D][[P_t] - [PD]] = [PD]$

$K[D][P_t] - K[D][PD] = [PD]$

$K[D][P_t] = [PD] + K[D][PD]$ $\quad ([PD]$ – Take common)

$K[D][P_t] = [PD](1 + K[D])$

$$\frac{K[D][P_t]}{1 + K[D]} = [PD]$$

$$\frac{K[D]}{1 + K[D]} = \frac{[PD]}{[P_t]} = r$$

$$\boxed{r = \frac{K[D]}{1 + K[D]} = \frac{[PD]}{[P_t]}}$$

$r$ = Moles of drug Bound per mole of total Protein.

# Significance of Protein Binding

★ When drug Binding is irreversible, No Absorption, distribution, Metabolism and elimination occur

↓

due to increase in $t_{1/2}$ of complexed drug

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drug Accumulates in the tissues and cause toxicity

★ Molecular weight:

- Low Molecular weight and Size → high Volume of distribution
- High Molecular weight and Size → low Volume of distribution.

* Protein Binding helps in Diagnosis, when chlorine atom in chloroquinone replaced with Radiolabelled Iodine, it used to Diagnose Melanomas of eye.

* Target drug Therapy - drug Binds to Protein in such a mechism, that it Target at specific Site at which drug is Required.

* Drug Intaractions: Displacement of one drug by another drug by another Protein binding Sites can increase free drug concentration.

* Dosing and Toxicity: understanding protein binding helps in determining effective doses and minimizing toxicity risks.

* Predicting drug Behavior: Protein Binding data can inform predictions about drug distribution, efficacy and safety.