

DRUG DISTRIBUTION

Once a drug enters into the blood stream, the drug is subjected to a number of processes called as Disposition Processes that tend to lower the plasma concentration.

- 1. Distribution** which involves **reversible** transfer of a drug between compartments.
- 2. Elimination** which involves **irreversible loss** of drug from the body. It comprises of **biotransformation and excretion**.

DEFINITION

Drug Distribution is defined as the **Reversible** transfer of drug between one compartment (blood) to another (extra vascular tissue)

Significance :-

Pharmacological action of drug depends upon its concentration at the site of action

Thus distribution plays important role in

- Onset of Action
- Intensity of Action
- Duration of Action

STEPS IN DRUG DISTRIBUTION

- Permeation of Free Drug through capillary wall & entry in to ECF.
- Permeation of drugs from ECF to ICF through membrane of tissue cell.

Rate Limiting Steps

- ❖ Rate of Perfusion to the ECF
- ❖ Membrane Permeability of the Drug

DISTRIBUTION PROCESS

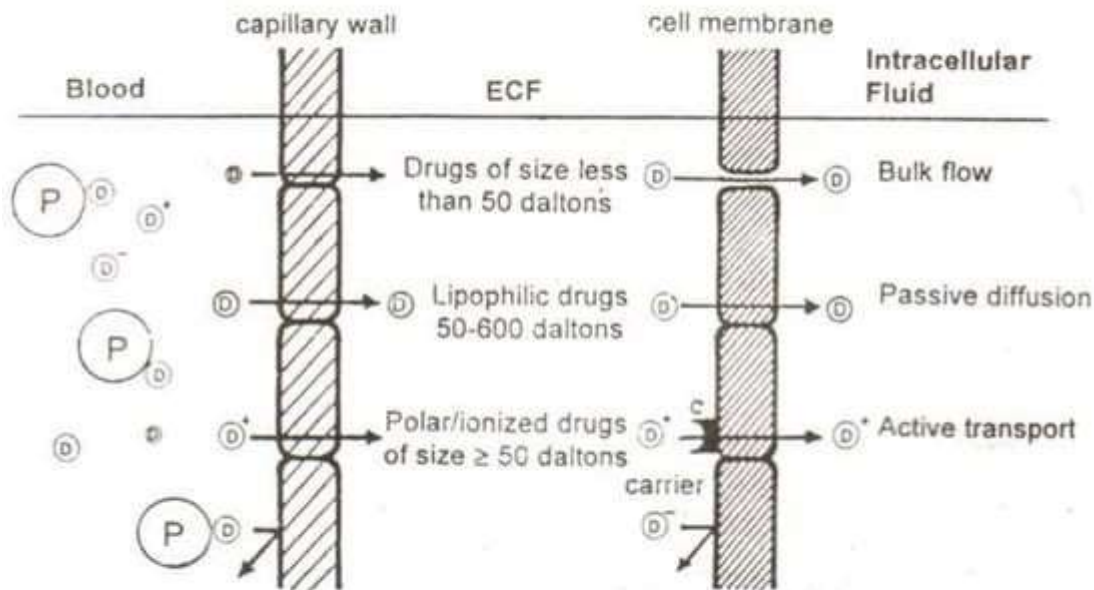


Fig. 3.3 Plasma membrane barrier and drug diffusion across it

Distribution is a Passive Process,
for which the
Driving Force is
the Conc. Gradient
between the Blood
and Extravascular
Tissues

- The Process occurs by the Diffusion of Free Drug until equilibrium is established

FACTORS AFFECTING DISTRIBUTION OF DRUGS

1. Tissue Permeability of Drugs

- ❖ Physicochemical Properties of drug like
Mol.size, pK_a , o/w Partition Coefficient
- ❖ Physiological barriers to diffusion of drugs

2. Organ/tissue size and perfusion rate

3. Binding of drugs to tissue components.

- ❖ binding of drug to blood components
- ❖ binding of drug to extra cellular components

4. Miscellaneous

TISSUE PERMEABILITY OF DRUGS

Physicochemical Properties of drug

- Molecular size,
- pKa
- o/w Partition Co Efficient.

Physiological barriers to Diffusion of Drugs

- Simple Capillary Endothelial Barrier
- Simple Cell Membrane Barrier
- Blood Brain Barrier
- Blood – CSF Barrier
- Blood Placental Barrier
- Blood Testis Barrier

1). TISSUE PERMEABILITY OF DRUG

a. physicochemical property:

1) Molecular Size;

Mol wt less than 500 to 600 Dalton easily pass capillary membrane to extra cellular fluid.

Penetration of drug from ECF to cells is function of Mol size, ionization constant & lipophilicity of drug

From extra cellular fluid to cross cell membrane through aqueous filled channels need particle size less than 50 Dalton (small) with hydrophilic property .

Large mol size restricted or require specialized transport system



1). TISSUE PERMEABILITY OF DRUG

a. Physicochemical Property

ii) Degree of Ionization (pKa)

♪ The pH at which half of a drug is unionized is called pKa

A weak acid becomes unionized in a strong acidic environment.

A weak acid becomes ionized in a neutral or basic environment.

&

A weak base becomes unionized in a strong basic environment.

A weak base becomes ionized in a neutral or acidic environment.

BUT

The PH of Blood plasma, extra cellular fluid and CSF is 7.4(constant)

Except in acidosis and alkalosis

All the drugs ionize at plasma pH (i.e. Polar , Hydrophilic Drugs)

Can not penetrate the Lipoidal cell membrane

1). TISSUE PERMEABILITY OF DRUG

a. Physicochemical Property

iii) o/w permeability

- ❑ Polar and hydrophilic drugs are less likely to cross the cell membrane

Where,,,,,,,,

- ❖ **Nonpolar and hydrophobic drugs are more likely to cross the cell membrane**

$$\text{EFFECTIVE } K_{o/w} = \text{Fraction unionized at pH 7.4} \times K_{o/w} \text{ of unionized drug}$$

In case of polar drugs where permeability is the rate-limiting step in the distribution, the driving force is the effective partition coefficient of drugthat can be calculated by above formula

➤ **Lipoidal drug** penetrate the tissue **rapidly**. Among Drugs with same K_o/w but diff in ionization of blood pH.

➤ One which has **less ionization** show **better distribution**.

E.g. Phenobarbital > salicylic acid

Both are having same K_o/w but phenobarbital have more unionized at blood pH

➤ highly specialized and less permeable to water soluble drugs.

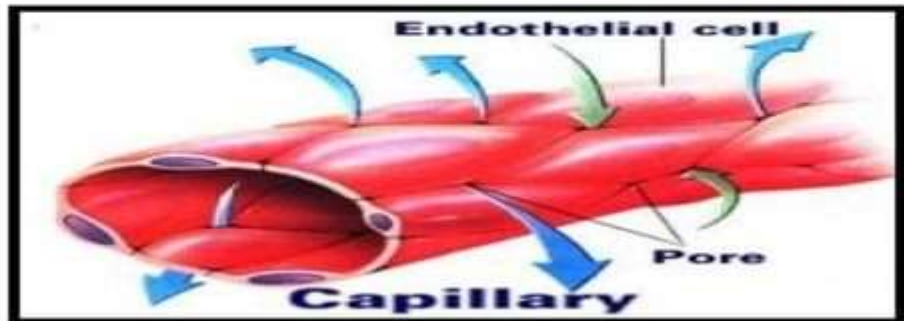
B. PHYSIOLOGICAL BARRIERS

1) The simple capillary endothelial barrier

Capillary supply the blood to the most inner tissue

All drugs **ionized** or **unionized** molecular size less than **600dalton** diffuse through the capillary endothelium to interstitial fluid

Only drugs that bound to that blood components can't pass through this barrier Because of larger size of complex



B. PHYSIOLOGICAL BARRIERS

2. Simple cell membrane barrier

once the drug diffuse through capillary to extracellular fluid ,its further entry in to cells of most tissue is **limited**.

Simple cell Membrane is similar to the lipoidal barrier (absorption)

Non polar & hydrophilic drugs will pass through it (passively).

Lipophilic drugs with 50–600 dalton mol size &

Hydrophilic, Polar drugs with <50dalton will **pass** this membrane

B. PHYSIOLOGICAL BARRIERS

3) Blood brain barrier

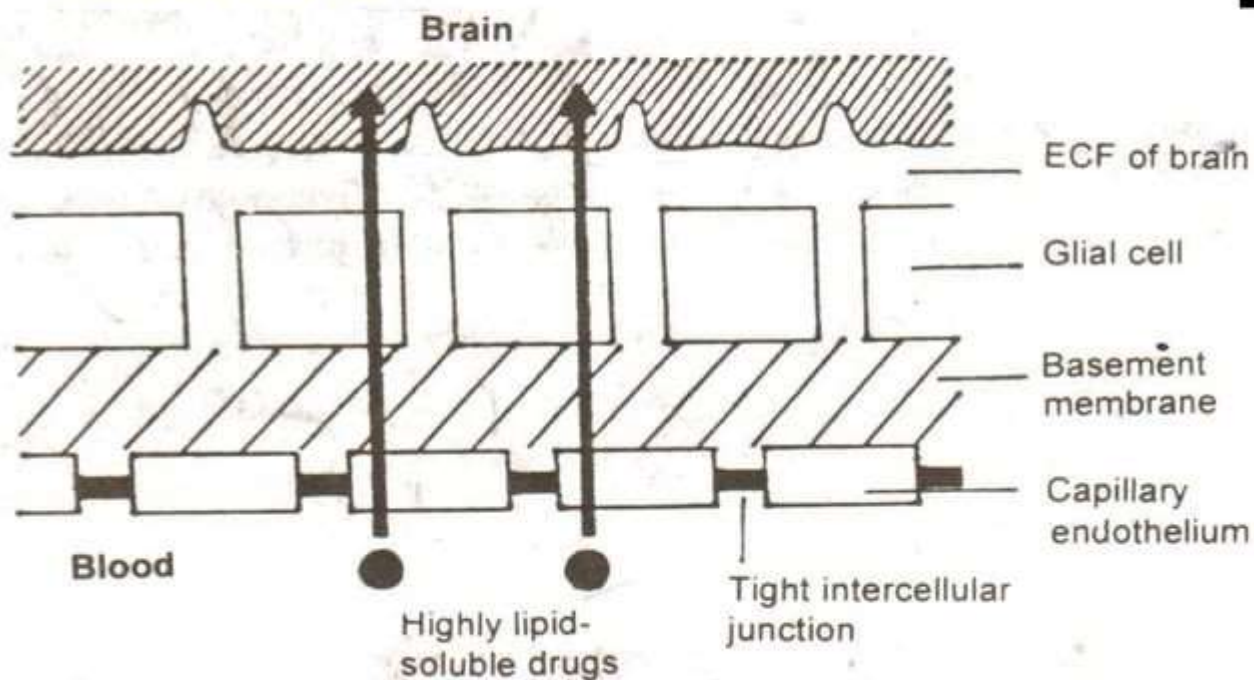


Fig. 3.4 Blood-brain barrier

B. PHYSIOLOGICAL BARRIERS

3) Blood brain barrier

Capillary in brain is highly specialized & much less permeable to water soluble drugs

ENDOTHELIAL CELLS ;- **Tightly bonded** with each other by **intracellular junctions**

ASTROCYTES :- present @ the base of endothelial tissue and act as **supporting materials**

& it **Form Envelop** around the capillary thus intercellular passage get blocked.

BBB is **lipoidal barrier**, thus drugs with **high o/w partition coefficient** diffuse **passively** others (**moderately lipid soluble** and **partially ionised molecules** passes slowly.

Polar natural substance (sugar & amino acid) transported to brain actively thus structurally similar drug can pass easily to BBB.

DIFFERENT APPROACHES TO CROSS BBB

A) Permeation Enhancers ; - **Dymethyl Sulfoxide**

B) Pro- Drug Approach ; - **Dopamine**----- **Levodopa**
(Parkinsonism)

and **osmotic disruption of the BBB** BY infusing
internal carotid artery with **mannitol**

C) carrier system ; - **Dihydropyridine** (Lipid soluble) **moiety**
redox system (highly lipophilic & cross the BBB)

Complex formation (DRUG-DHP). After entering in
brain DHP gets metabolize by **(CNS)** enzyme in brain and
drug gets **trapped** in side the brain.

Polar pyridinium ion can not diffuse back out of the brain.

Ex. Steroidal drug

B. PHYSIOLOGICAL BARRIERS

4) Cerebral spinal fluid barrier ;-

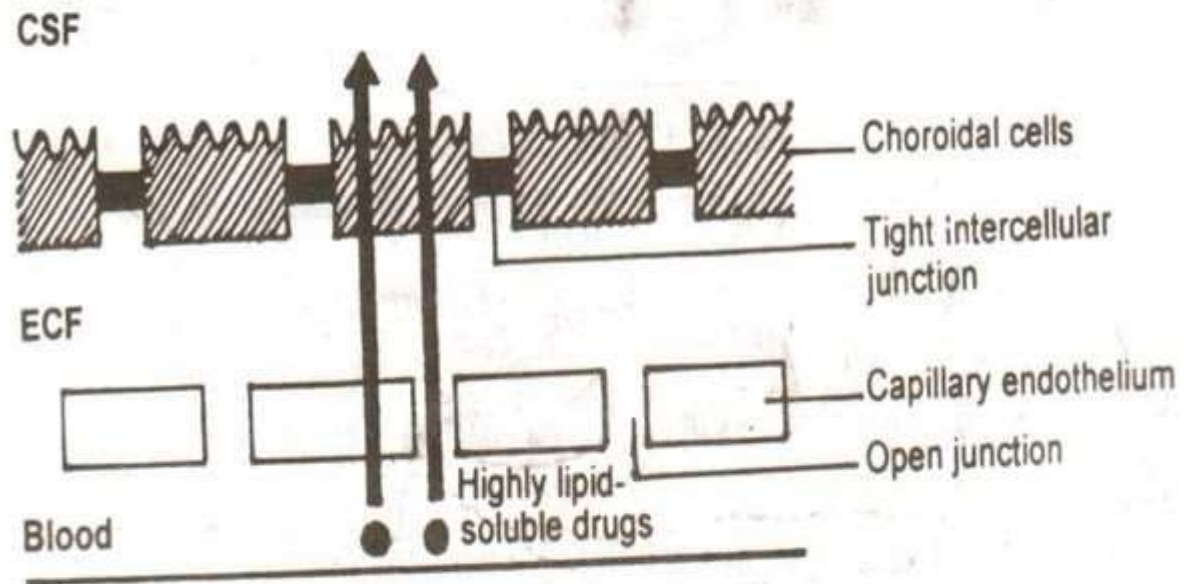


Fig. 3.5 The blood-CSF barrier

B. PHYSIOLOGICAL BARRIERS

4) Cerebral Spinal Fluid Barrier;-

Capillary endothelial cells;- have **open junction** or gaps so.... Drugs can **flow freely b/w capillary wall & choroidal cells**.

Choroids plexus;- major components of CSF barriers is choroidal cells which are joined with each other by **tight junctions forming the blood-CSF barrier** (similar permeability to BBB)

Highly lipid soluble drugs can easily cross the blood-CSF Barrier but moderately soluble & ionize drugs permeate slowly.

Mechanism of drug transport is **similar to CNS & CSF** but the Degree of uptake may vary significantly.

B. PHYSIOLOGICAL BARRIERS

5) Placenta barriers :-

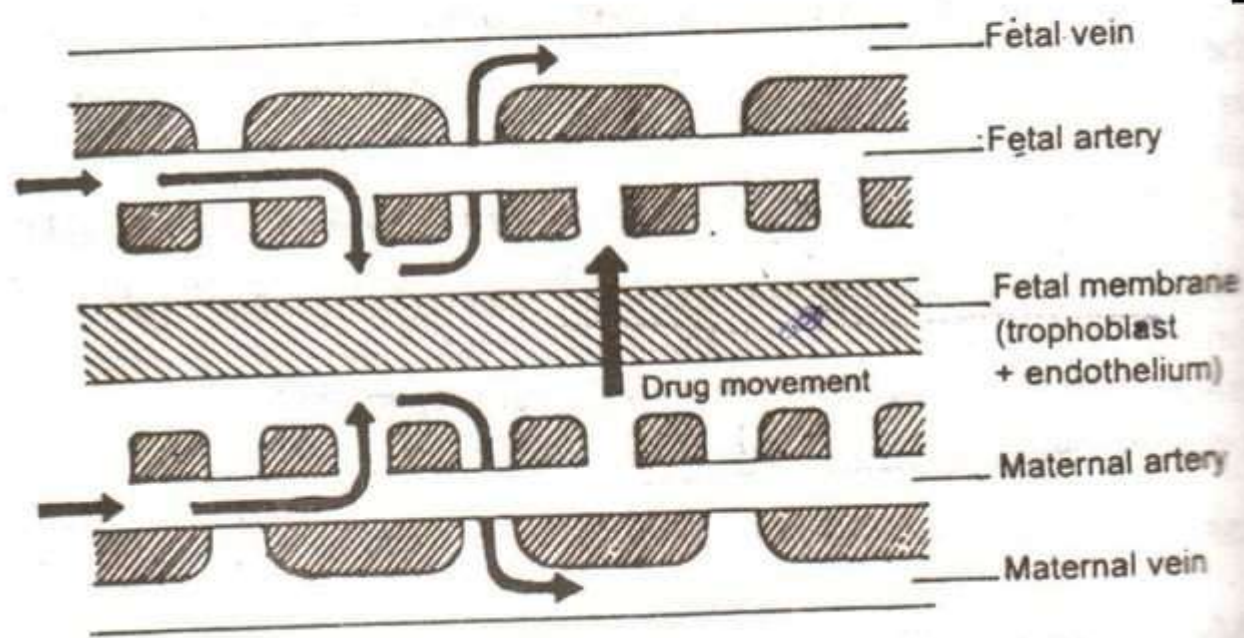


Fig. 3.6 Placental barrier and blood flow across it

B. PHYSIOLOGICAL BARRIERS

5) Placenta barriers :-

- It's the barrier b/w **Maternal** & **Fetal** blood vessels
- Both are **separated** by **fetal trofoblast** basement membrane & endothelium .
- Thickness 25μ @ *early pregnancy* later reduce up to 2μ (even its effectiveness remain unchanged)
- Mol wt **<1000** Dalton & moderate to high lipid solubility drugs like..... (Sulfonamides, Barbiturets, Steroids, Narcotic some Antibiotics) cross the barrier by **Simple Diffusion rapidly**
- Essential Nutrients for fetal growth transported by **carrier-mediated processes**.
- **Immunoglobulines** are transported by **endocytosis**.
- Drugs dangerous to fetus at **Two stages**
- Its advisable to avoid drugs during **1st trimester** (fetal organ development) some drugs produce **teratogenic effect**
ex. Phenytoin, methotrexate
- later stage pregnancy affect physiological functions like **respiratory depression** ex. morphine
- Better to restrict all drugs during pregnancy.

B. PHYSIOLOGICAL BARRIERS

6) Blood - Testis Barrier :-

This barrier not located @ capillary endothelium level.

But **at sertoli - sertoli cell junction.**

It is the tight junction / barrier **b/w neighboring** sertoli cells that **act as blood-testis barrier .**

This barrier restrict the passage of drugs to spermatocytes & spermatids.

2). 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 (ml/min/ml)

Perfusion rate - limited when.....

1) Drug is highly lipophilic

2) Membrane across which the drug is supposed to diffuse

Above both the cases *Greater* the blood flow, *Faster* the distribution

Organ perfused	Blood flow (mL/min)	Organ mass (kg)	Normalized blood flow (mL/min/kg)
Liver	1700	2.5	680
Kidney	1000	0.3	3333
CNS	800	1.3	615
Myocardium	250	0.3	833
Fat	250	10	25
Other (muscle...)	1400	55.6	25
total	5400	70	

- Distribution is **permeability** rate - limited in following cases
 - When the drug is ionic/polar/water soluble
 - Where the highly selective physiology barrier **restrict** the diffusion of such drugs to the inside of cell.
- Distribution will be **perfusion** rate - limited
 - When the drug is highly lipophilic
 - When the membrane is highly permeable.

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

Unit: ml/min/ml

(Distribution Rate Constant) $K_t = \text{perfusion rate} / K_{t/b}$

Distribution half life = $0.693/K_t$

$= 0.693K_{t/b} / \text{perfusion rate}$

$K_{t/b}$ tissue/blood partition coefficient

Highly lipophilic drugs can cross **most selective barrier** like BBB, ex. thiopental,

Highly permeable capillary wall permits passage of almost all drugs (**except those bound to plasma protein**).

Highly perfused tissues **Lungs, Kidneys, Liver, Heart, Brain** are rapidly equilibrated with **lipid soluble drugs**

Drug is distributed in a particular tissue or organ **depends** upon the **size of tissue** (Volume) & **Tissue/blood** partition coefficient

Ex. Thiopental i.v (lipophilic drug) & high tissue/blood partition coefficient towards brain & adipose tissue

But brain is **highly perfused organ** so drug is distributed **fast** and shows **rapid onset of action** than poorly perfused adipose tissue.

3) Binding of drug to blood and other tissue components

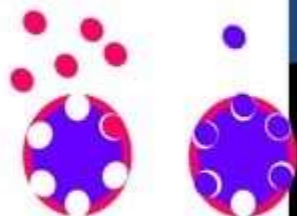
- Binding of drugs to blood components
 - Blood cells
 - Plasma proteins
- Binding of drugs to extra vascular tissues

3).BINDING OF DRUG TO TISSUE COMPONENTS

a) Binding of drug to blood components:-

i) Plasma protein bindings

- **Human serum albumin**:-all types drug
- **α_1 -acid glycoprotein** :-basic drugs(impr)
- **Lipoproteins** :-basic,lipophilic drugs(chlorpromazin)
- **α_1 -Globuline** :-steroids like corticosterone ,vit-B12
- **α_2 -Globuline** :-vit-A,D,E,K,cupric ions.
- **Hemoglobin** :-Phenytoin, phenothiazines.



ii) Blood cells bindings:-

- RBC** : 40% of blood comprise of blood cells
out of that 95% cells are RBC (RBC comprise of hemoglobin)
drugs like, phenytoin,phenobarbiton binds with **Hb**
,imipramine,chlorpromazine binds with **RBC Cell wall**

The major component of blood is RBC

The RBC comprises of **3** components each of which can bind to drugs:

- Hemoglobin
- Carbonic Anhydrase
- Cell Membrane

BINDING OF DRUGS TO PLASMA PROTEINS

- The binding of drug to plasma protein is **reversible**
- The **extent** or **order** of binding of drugs to various plasma proteins is:

Albumin > α_1 -Acid Glycoprotein > Lipoproteins > Globulins

Human Serum Albumin

- Most abundant plasma protein with **large** drug binding capacity
- Both **endogenous** compounds and **drugs** bind to **HSA**
- Four different sites on HSA:
 - Site I: warfarin and azapropazone binding site**
 - Site II: diazepam binding site**
 - Site III: digitoxin binding site**
 - Site IV: tamxifen binding site**

3).BINDING OF DRUG TO TISSUE COMPONENTS

B. Extra Vascular Tissue proteins

- 40% of total body weight comprise of **vascular tissues**
- Tissue–drug binding result in localization of drug at specific site in body and serve as **reservoir**
- As binding **increases** it also **increase** bio–logical half life.
- **Irreversible** binding leads to drug **toxicity**.
(carbamazepin–autoinduction)
- liver>kidney>lungs>muscle>skin>eye>bone>Hair,
nail

4). Miscellaneous Factors

➤ **Age:**

- a) **Total body water**
- b) **Fat content**
- c) **Skeletal muscles**
- d) **Organ composition**
- e) **Plasma protein content**

➤ **Pregnancy**

➤ **Obesity**

➤ **Diet**

➤ **Disease states**

4). MISCELLANEOUS FACTORS

a) AGE:-

Difference in distribution pattern is mainly due to

Total body water -(both ICF & ECF) **greater** in infants

Fat content - **higher** in infants & elderly

Skeletal muscle - **lesser** in infants & elderly

organ composition - BBB is **poorly** developed in infants & **myelin** content is **low** & cerebral blood flow is **high**, hence greater penetration of drug in brain

plasma protein content- low albumin in both infants & elderly

b) PREGNANCY:-

During Pregnancy, due to growth of UTERUS, PLECENTA, FETUS...

Increases the volume available for distribution drug.

fetus have separate compartment for drug distribution, plasma & ECF Volume also **increase** but albumin content is **low**.

C) OBECITY :-

In obese persons, high adipose (fatty acid) tissue so high distribution of lipophilic drugs

4). MISCELLANEOUS FACTORS

d) DIET:- A diet **high** in fats will **increases** free fatty acid levels in circulation thereby **affecting binding** of acidic drugs (NSAIDs to albumin)

e) DISEASE STATES:- mechanism involved in alteration of drug distribution in disease states.

i) Altered albumin & other drug-binding protein concentration.

ii) Alteration or reduced perfusion to organ or tissue

iii) Altered tissue pH.

iv) Alteration of permeability of physiological barrier (**BBB**)

EX- BBB (in **meningitis** & **encephalities**) BBB becomes more permeable polar antibiotics ampicilin, penicilin G. &

patient affect **CCF**, Perfusion rate to entire body **decreases** it affect distribution.

f) DRUG INTERACTION:- **Displacement interaction** occurs when two drugs administered which having similar binding site affinity.

Ex. **A.** Warfarin (Displaced Drug) & **B.** Phenylbutabutazone (Displacer) **HSA**

Apparent Volume Of Distribution

The apparent volume of distribution is a proportionality constant relating the plasma concentration to the total amount of drug in the body.

$$X = C \cdot V_d$$

$$X = V_d \cdot C$$

$$V_d = X / C$$

Apparent volume of distribution = amount of drug in the body / plasma drug concentration

Apparent volume of distribution is dependent on **concentration of drug in plasma**.

Drugs with a large apparent volume are more concentrated in **extra vascular tissues** and **less concentrated intravascular**.

In certain pathological cases, the V_d for the drug may be altered if the distribution of the drug is changed.

$$V_d = X/C$$

$$V_d = X_0 / C_0$$

= i.v. bolus dose / concentration of drug in plasma

for drugs given as **i.v. bolus**:

$$V_{d(\text{area})} = X_0 / K_E (\text{AUC})$$

For drugs administered **extravascularly**:

$$V_{d(\text{area})} = F X_0 / K_E (\text{AUC})$$