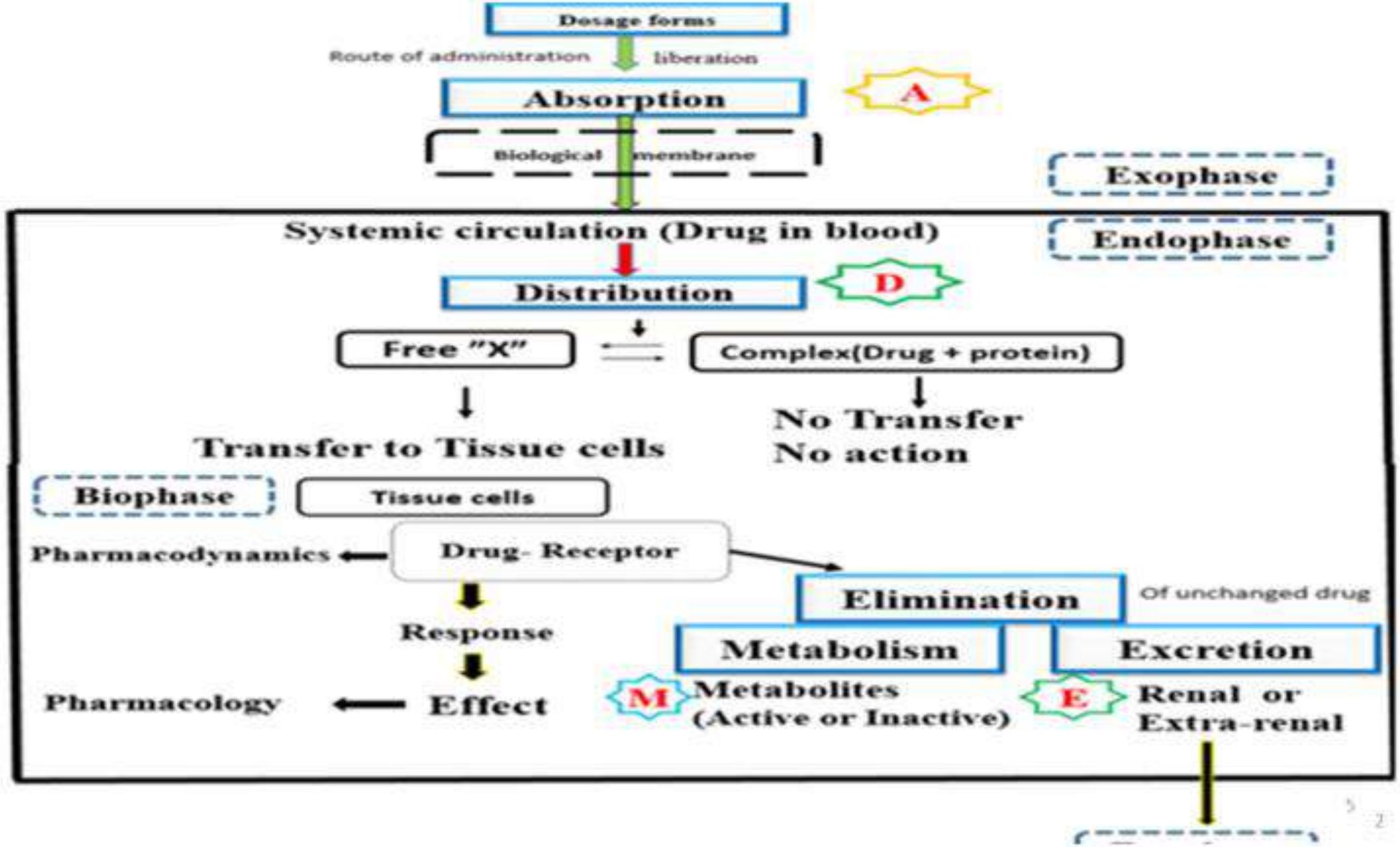
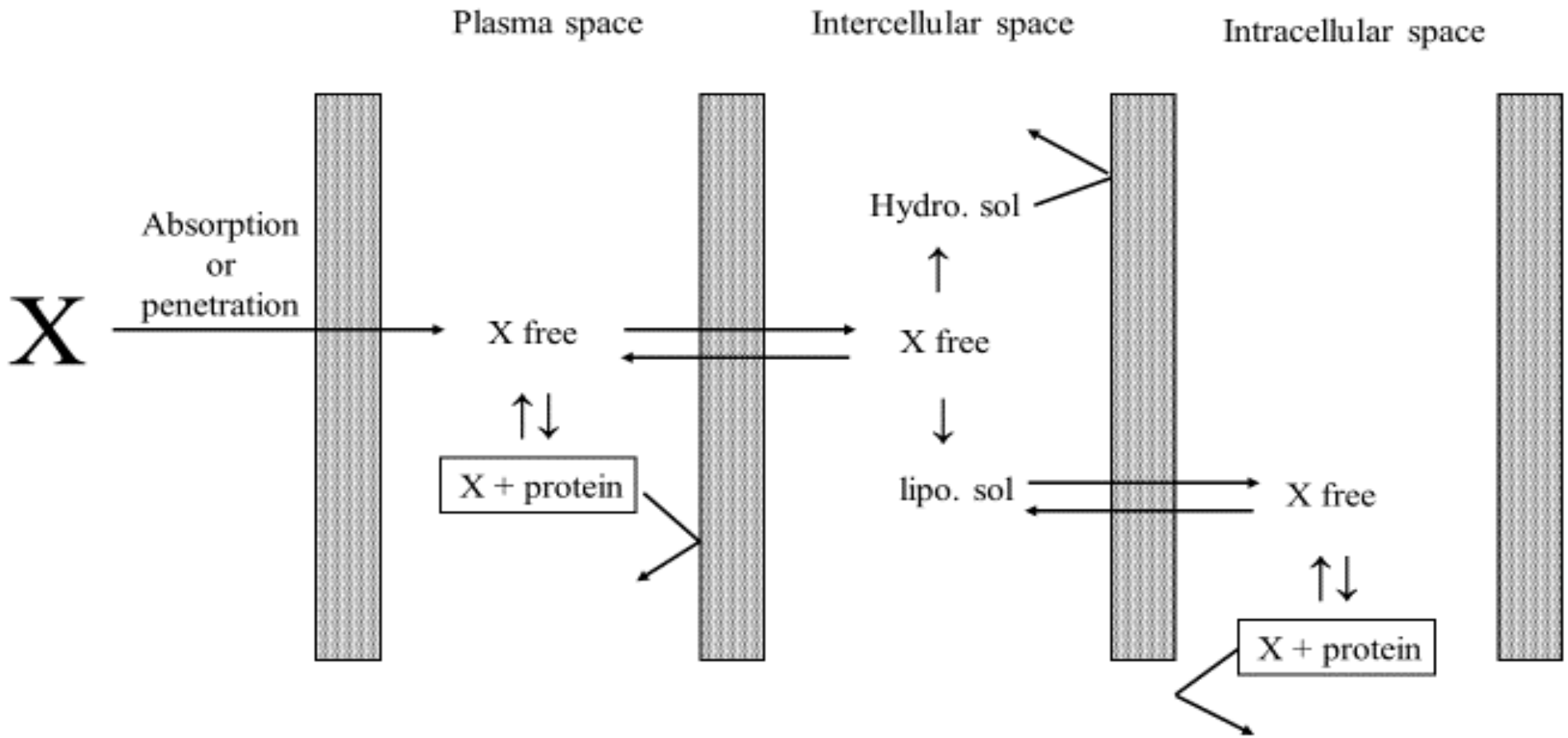
Drugs distribution and protein-plasma binding


Dosage forms
Route of administration
liberation
Absorption
A
Biological membrane
Exophase
Endophase
Systemic circulation (Drug in blood)
Distribution
D
Free "X"
Complex(Drug + protein)
No Transfer
No action
Transfer to Tissue cells
Biophase
Tissue cells
Pharmacodynamics
Drug- Receptor
Elimination
Of unchanged drug
Response
Metabolism
Excretion
Pharmacology
Effect
M
Metabolites
(Active or Inactive)
E
Renal or
Extra-renal

Volume of distribution



Distribution

- Drug distribution: Is the process by which the drug reversibly leaves the blood stream and enters the interstitium (extracellular fluid) and/ or the cells of the tissues.

Volume of distribution

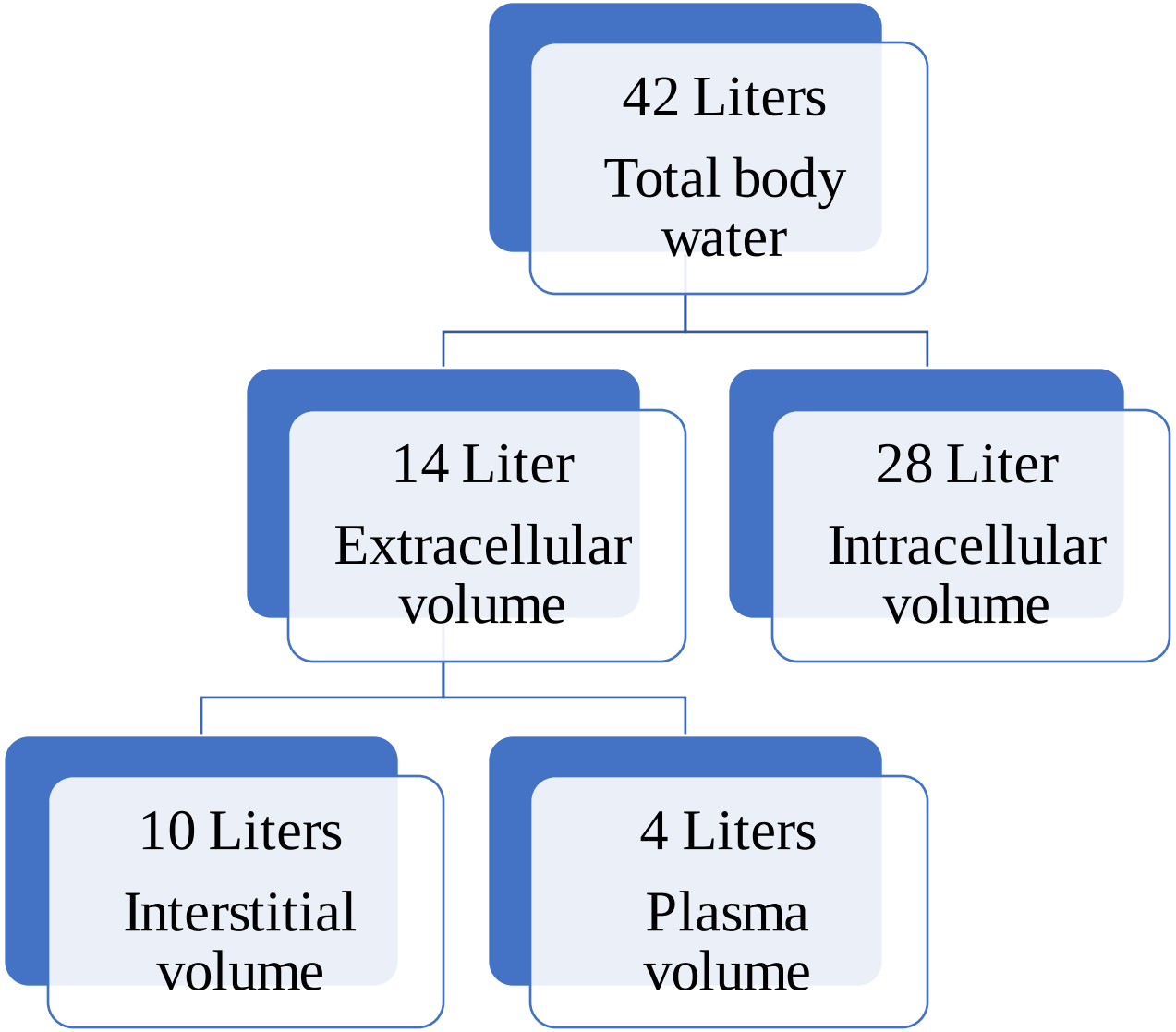
- Is a hypothetical volume of fluid into which the drug is disseminated. [distributed]

$$V_d = \frac{X_t}{Cp_t} \qquad \text{amount/concentration}$$

V_d : Volume of distribution

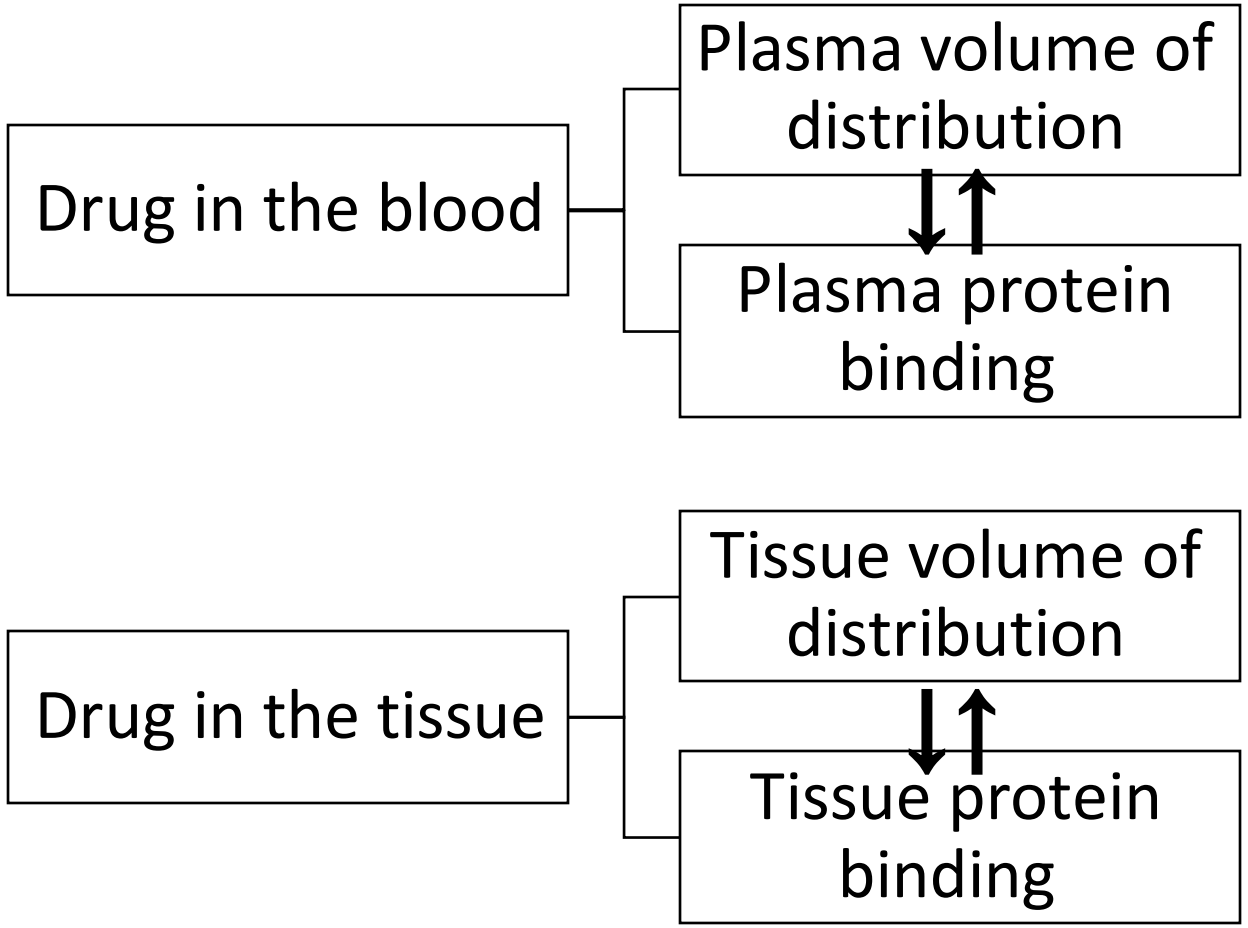
X_t: Amount of drug at time t (total amount in the body), described the weight of the dose.

Cp_t: Plasma concentration at the same time (unit: µg/ml or mg/L)

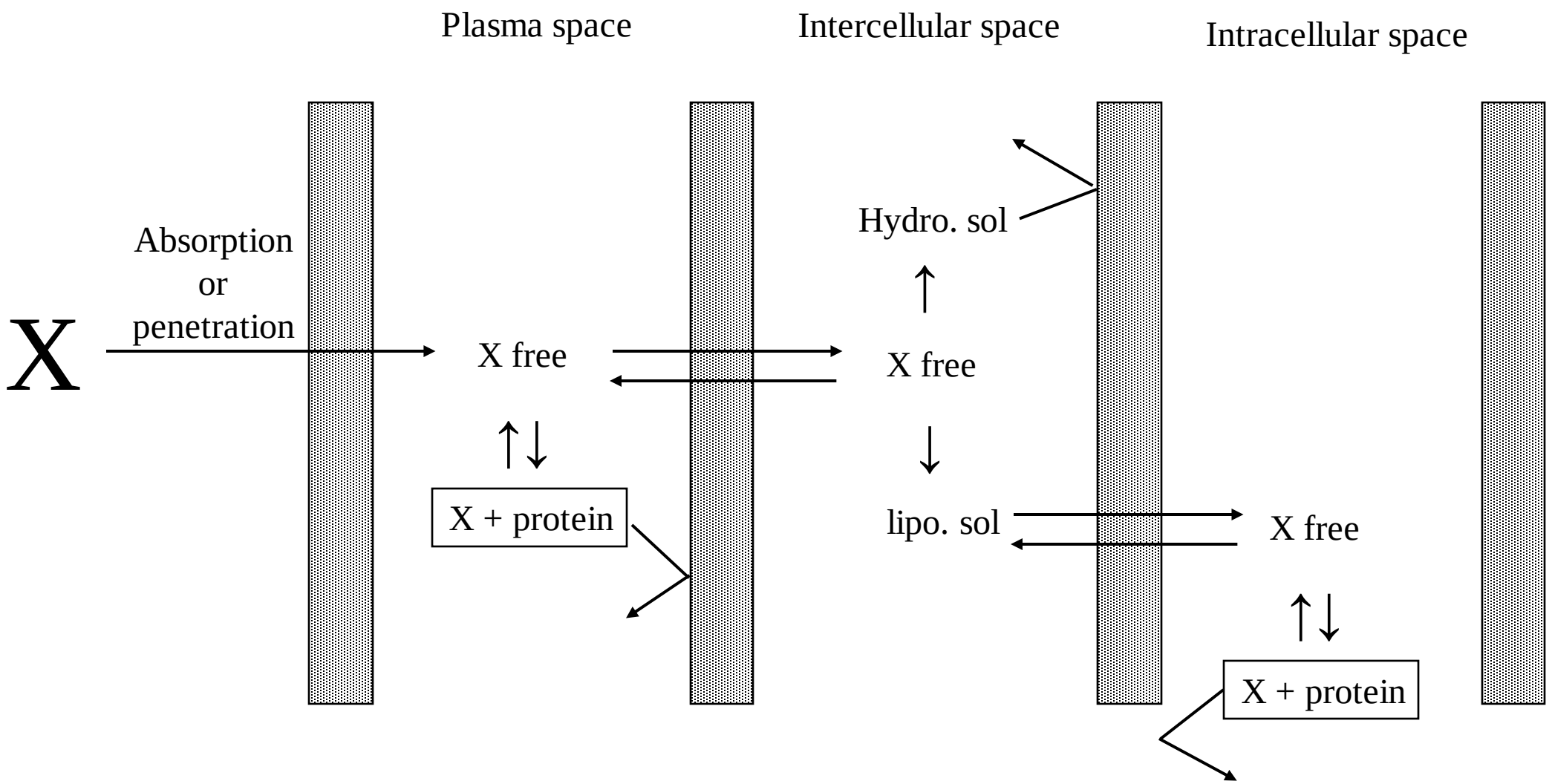


- Total water = 0.55 [weight (kg) + 0.5]

Drug distribution in the organism



Volume of distribution



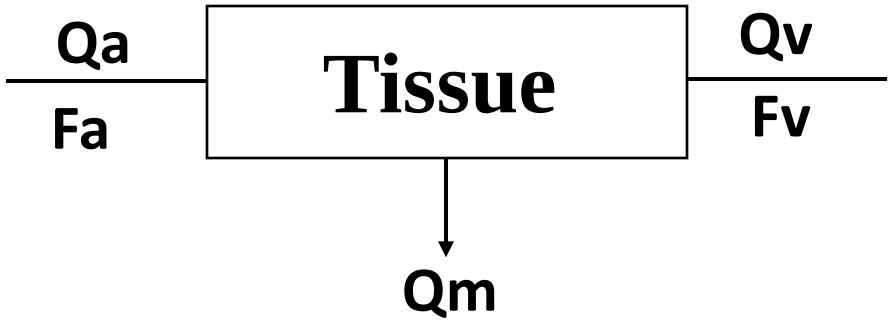
Distribution

- Drug distribution: Is the process by which the drug reversibly leaves the blood stream and enters the interstitium (extracellular fluid) and/ or the cells of the tissues.
- The delivery of a drug from the plasma to the interstitium primarily depends on:

1. **Blood flow**
2. **Capillary permeability**
3. **Binding of drugs to protiens**
4. **Relative hydrophobicity.**

Drugs distribution and protein-plasma binding

Ketty's theory



- Where:
- Qa = amount of drug in blood artery
- Qv = amount of drug in blood vein
- Qm = amount of drug metabolized
- Fa = artery blood flow
- Fv = vein blood flow

Drugs distribution is influenced by:

1) Amount of accumulated drug in tissue XT

$\frac{dxT}{dt}$ = Qa – (Qm + Qv) ,When Qm = 0

$\frac{dxT}{dt}$ = Qa – Qv

Qa = Fa . Ca ,, Qv = Fv . Cv ,, Fa = Fv = F

$\frac{dxT}{dt}$ = F (Ca – Cv) ……. first Ketty's theory

- Factors affecting the accumulation rate: F , Ca , Cv

2) Tissue volume VT

$$XT = CT \cdot VT$$

XT: amount in the tissue

CT: concentration in the tissue

VT: the volume of the tissue in which the drug is distributed

And $\frac{dxT}{dt} = F\ (Ca - Cv)$

$\frac{d(CT.VT)}{dt} = F\ (Ca - Cv)$

$\frac{dCT}{dt} = \frac{F}{VT}\ (Ca - Cv)$ ……. Seconed Ketty's theory

3) Partition coefficient Tissue/Blood

$$\lambda = \frac{CT}{Cv} \quad , \quad Cv = \frac{CT}{\lambda}$$

CT: the concentration of the drug in the tissue

Cv: the concentration of the drug in the blood

2nd Ketty's theory : $\frac{dCT}{dt} = \frac{F}{VT}(Ca - Cv)$, $Cv = \frac{CT}{\lambda}$

$$\frac{dCT}{dt} = \frac{F}{VT}\left(Ca - \frac{\boldsymbol{CT}}{\boldsymbol{\lambda}}\right) = \frac{\boldsymbol{Fm}}{\boldsymbol{VT}.\lambda}(Ca.\lambda - CT)$$

Where:

m: diffusion coefficient ≈ diffusability

$\frac{dCT}{dt}$: accumulation rate in tissue

If m = 0 $\rightarrow \frac{dCT}{dt} = 0$

If m = 1 $\rightarrow \frac{dCT}{dt} = \frac{\boldsymbol{F}}{\boldsymbol{VT}.\lambda}(Ca.\lambda - CT)$

- Factors affecting the accumulation rate in tissue:

F = ?? λ = ?? CT = ??

VT = ?? Ca = ?? m = ??

How the dCT changes with the time?

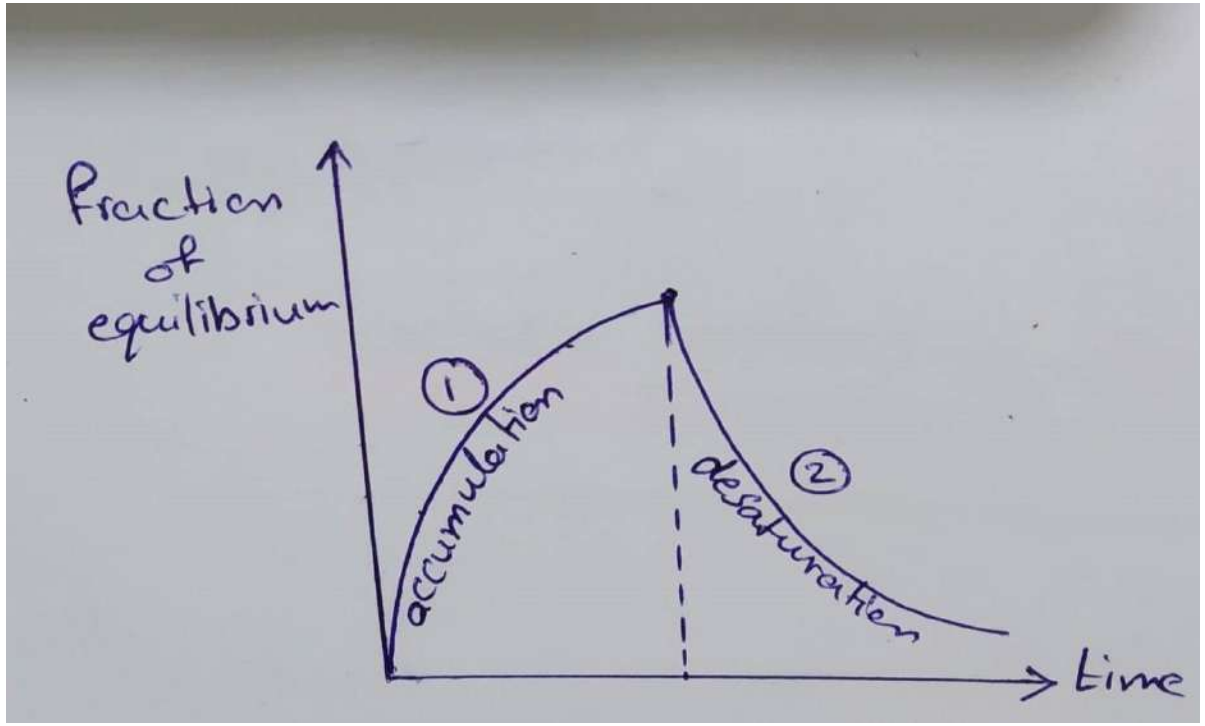
$$\frac{dCT}{dt} = \frac{F}{VT\,.\lambda}\,(\mathrm{Ca}.\lambda - \mathrm{CT})$$

$$\frac{dCT}{(\mathrm{Ca}.\lambda - \mathrm{CT})} = \frac{F}{VT\,.\lambda}\,dt \quad \ldots\ldots\ldots \text{ by integration, where } \mathrm{K} = \frac{F}{VT\,.\lambda}$$

$$\int_0^t \frac{dCT}{(\mathrm{Ca}.\lambda - \mathrm{CT})} = \mathrm{K} \int_0^t dt$$

$$\mathrm{CT} = \mathrm{Ca}.\lambda\,(1 - e^{Kt})$$

Graphically:



- At the saturation point (1)
Ca = constant, CT = 0, t = 0

- At the desaturation (2)
Ca = 0, CT = CTmax

After integration:

$$CTt = CT_0 \,.\, e^{-Ke.t}$$

CT0 = CTmax : concentration of the drug in the tissue at initial time

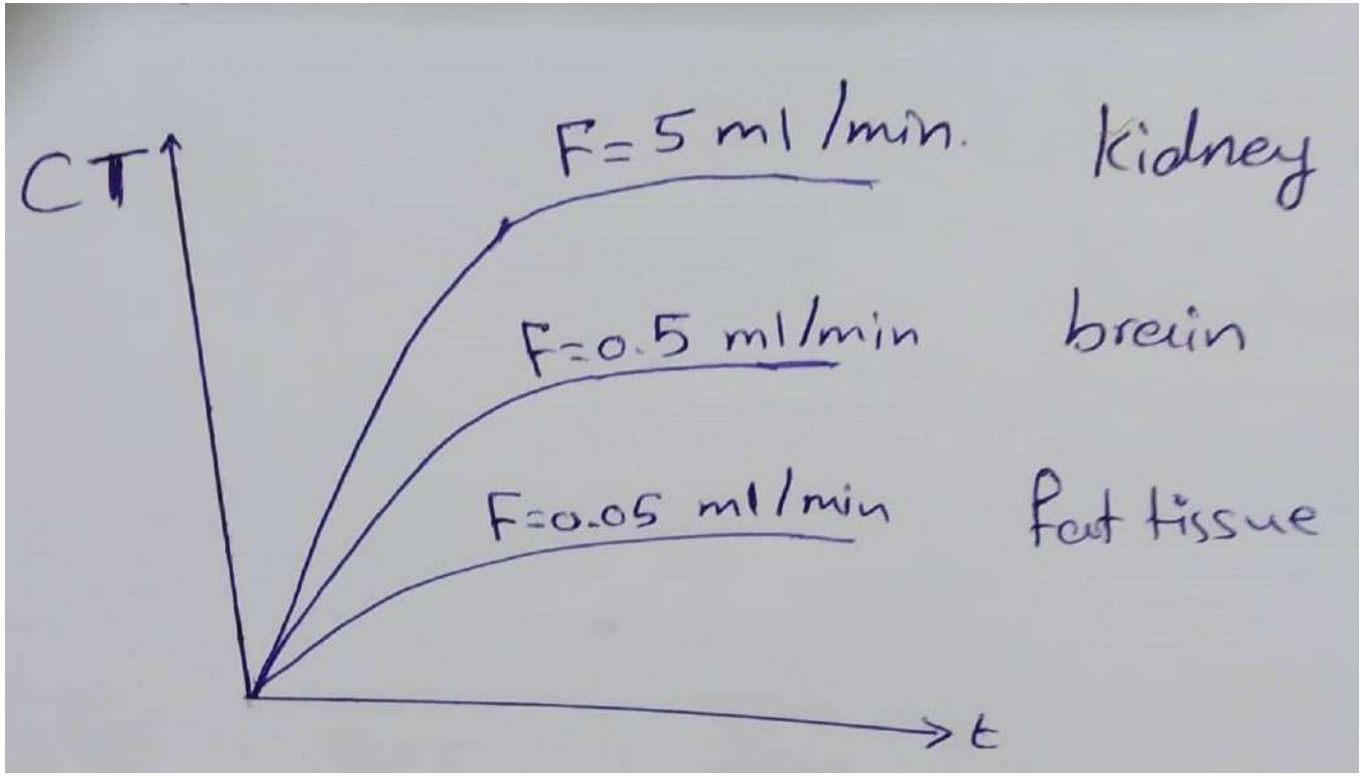
t : time

CTt : concentration of the drug in the tissue at time t

Ke : constant rate of elimination from the tissue to the blood

Summery

- Factors affecting the drugs distribution:
- 1- blood perfusion of organs



2- diffusability of drug in tissue (m)

m = diffusion coefficient

a) Permeability of the membrane.
b) Properties of the drug

- ✓ λ tissue/blood ??
- ✓ pka of drug and pH of the medium ??
- ✓ molecular weight

3- individual factors:

a) Age.
b) Pathological factors: inflammation
c) Physiological factors: pregnancy

4- Capacity for binding with plasma and for tissue proteins:

$$\alpha T = \frac{CTL}{CTT}$$

$$\alpha p = \frac{CpL}{CpT}$$

- αT= free fraction of drug in tissue
- CTL = free concentration of drug in tissue
- CTT = total concentration of drug in tissue

- αp = free fraction of drug in plasma
- CpL = free concentration of drug in plasma
- CpT = total concentration of drug in plasma

- When the equilibrium is taking place (between plasma and tissue volume), we can then establish:

$$CpL = CTL$$

$$\lambda = \frac{\alpha\, p}{\alpha\, T} = \frac{CpL}{CpT} \cdot \frac{CTT}{CTL} = \frac{CTT}{CpT}$$

5- other factors:

1) Qm ??
2) Passage of drug to other tissue??
3) Active transport??

Apparent volume of distribution

- Is an abstract volume or space which is calculated from the ration of the amount of drug in the body (X) to the concentration in plasma (Cp) once partition is stabilized

$$Vd = \frac{Xt}{Cpt} \quad ,, \quad \frac{w}{w/v} = v$$

- Is the hypothetical volume of body space (blood, fluids, membranes, tissues…etc) in which the drug appears to distribute with a concentration equals to that in plasma.

- Acidic drugs has small Vd (0.1 – 1.0 L/kg) due to high plasma protein binding while basic drugs has a large Vd (1 – 5 L/kg)

Calculation of Vd

- $Vd = \frac{Xp}{Cp}$, $Xp = Vd \cdot Cp$ $X = Xp + \Sigma XT$
  - Xp: the amount of drug in plasma
  - Σ XT: summation of amount of drug in tissues

- $XT = VT \cdot CT$, $X = Xp + \Sigma(VT.CT)$
- $\lambda = \frac{CT}{Cp}$, $CT = \lambda.Cp$
- $X = Xp + \Sigma(VT \cdot Cp \cdot \lambda) = Xp + Cp \cdot \Sigma(VT \cdot \lambda)$

- $Vd = \frac{Xp}{Cp} = \frac{Xp + Cp \cdot \Sigma(VT \cdot \lambda)}{Cp} = \frac{Xp}{Cp} + \Sigma(VT \cdot \lambda)$

- $Vd = Vp + \Sigma(VT \cdot \lambda)$

- $Vd = Vp + \Sigma(VT_1 . \lambda_1 + VT_2 . \lambda_2 + VT_3 . \lambda_3 + \ldots..)$
- $Vd = Vp + \Sigma(VT . \lambda)$

- Vd : apparent volume of distribution
- Vp : volume of blood (plasma)
- VT : tissular volume
- λ : permeability of the drug (tissue/blood)

- If:
- $\lambda = 0 \rightarrow Vd = Vp$
- $\lambda = 1 \rightarrow Vd = Vp + H_2O$ (intercellular)
- $\lambda >> 1 \rightarrow Vd = Vp + H_2O$ (intercellular) + H_2O (intracellular)

- The apparent volume of distribution may be also calculated from knowledge of the dose (X_0), Ke and AUC from t=0 to t=∞

- $Vd = \frac{X_0}{Ke \,.[AUC]}$

- $Cp = Ke \,.\, [AUC]$

Significance of the apparent Vd

1- Vd reflects the degree of distribution of the drug in the body.

2- Vd is dependent on Cp, a small Cp results in large Vd.

3- drugs with a large Vd are more concentrated in the extracellular tissue.

4- Vd is a useful indicator for the amount of drug outside the sampling compartment.

5- given the Vd for a particular drug, the total amount of drug in the body at any time after administration may be determined by the measurement of drug concentration in the blood at the same time

$$X_t = Vd \cdot Cp_t$$

6- for each drug, the apparent Vd is constant. In certain cases, Vd may be altered.

7- given the Vd, the total body clearance TBCl may be determined when given the Ke.

TBCl = Vd . Ke ; $\quad$ Vd = $\frac{TBCl}{Ke} = \frac{X_0}{Ke\,.[AUC]}$

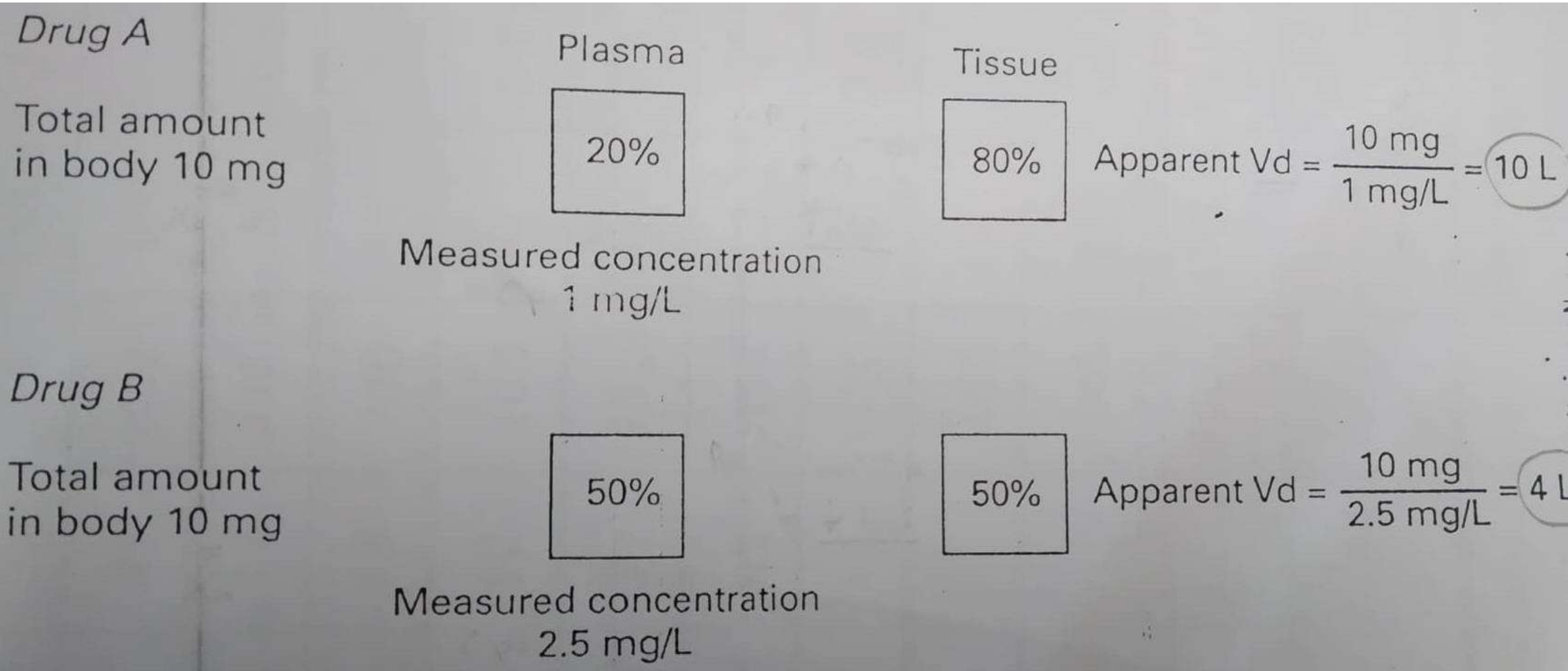
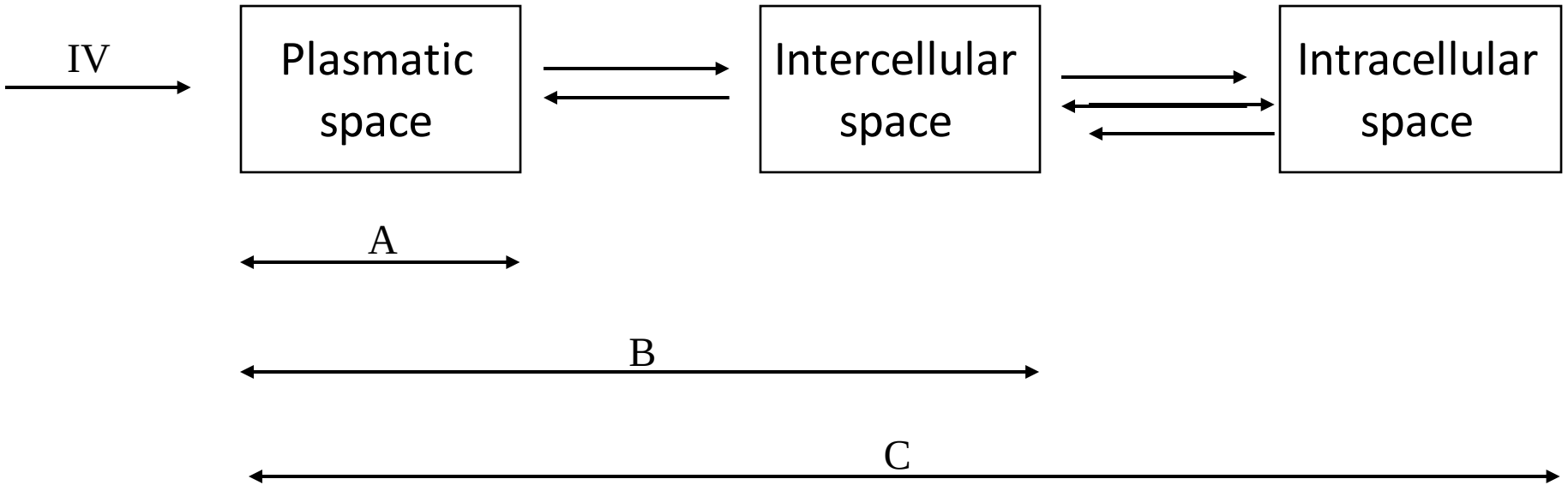


Figure 1.2 Distribution: more of drug A is distributed in the tissue compartment resulting in a higher apparent volume of distribution than drug B, where more remains in the plasma.

Determination of the water in the different spaces:



A: Evans Blue

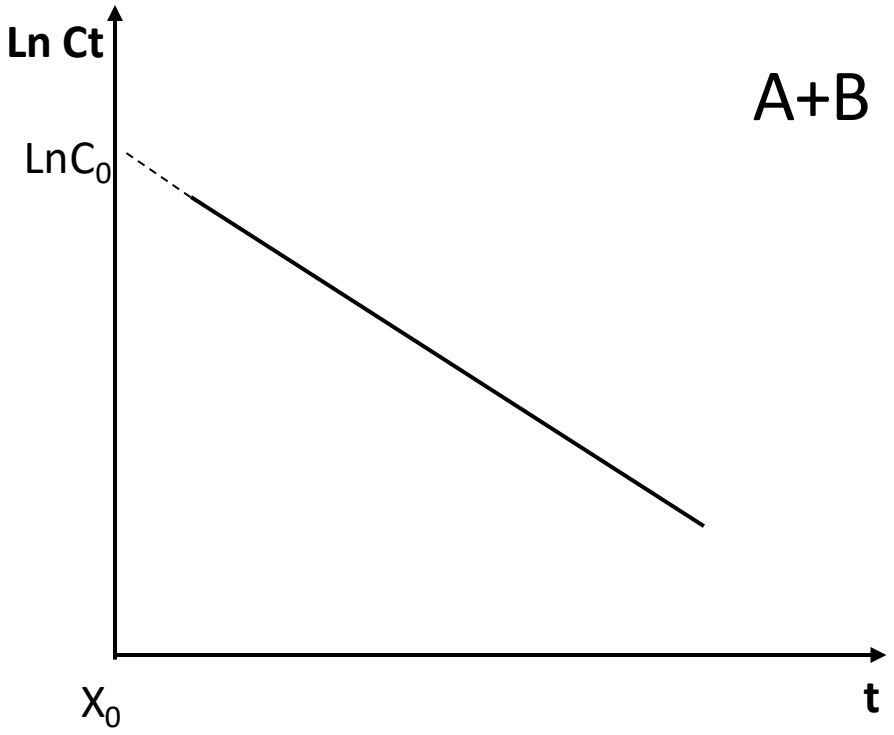
$$Vd = Vp = \frac{X_0}{Cpt}$$

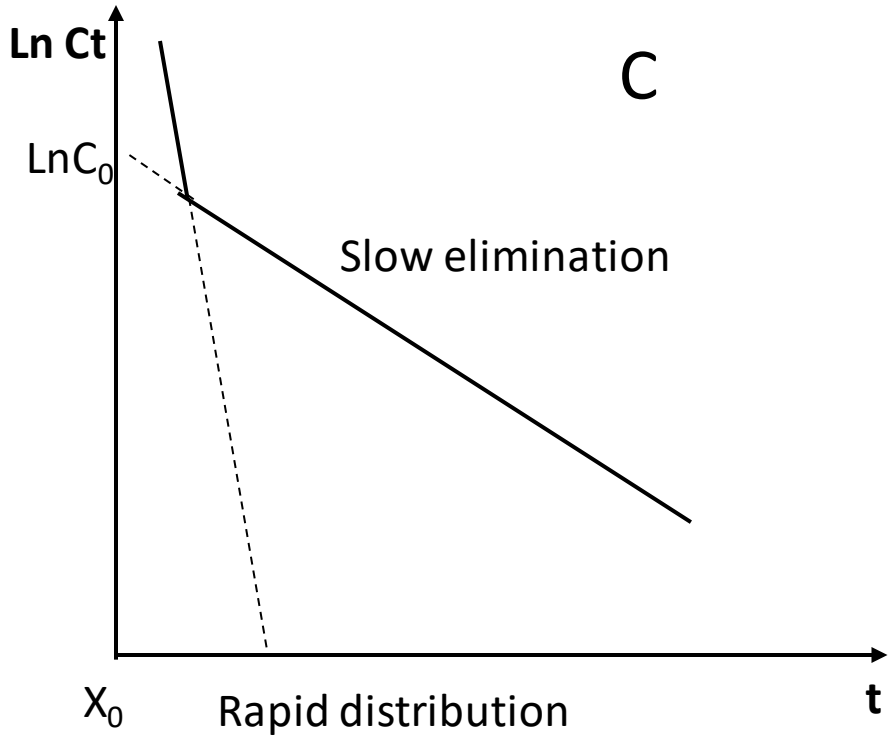
B: NaCl (marked)

$$Vd = Vp + V_{intercellular}$$

C: heavy water (deuterium)

$$Vd = Vp + V_{intercellular} + V_{intracellular}$$


Ln Ct
LnC0
A+B
X0
t


Ln Ct
LnC0
C
Slow elimination
X0
Rapid distribution
t

Effect of Vd on the $t_{1/2}$ of a drug

- If the Vd is large, most of drug is in the extraplasmatic space and unavailable to the excretory organs.
- So, any factor that increases the Vd can lead to an increase in the $t_{1/2}$ and extend the duration of action of the drug.
- $\uparrow t_{1/2} \rightarrow \uparrow$ Vd
- $\uparrow t_{1/2} \rightarrow \downarrow$ Ke
- $\uparrow$ Vd $\rightarrow \downarrow$ Ke

Protein plasma binding

1. Nature of binding.
2. Parameters of binding and its determination.
3. Evaluation methods of protein plasma binding.
4. Consequences of binding.

Nature of binding:

Types of plasma proteins are:

1- Globulin : α, β, γ, ….

2- Complex protein : lipoprotein, metalloprotein, …

3- Albumin : ↑Mwt=65000-69000

Presents 50% of total proteins (Binds approximately with 95% of drugs)

- Kinds of albumin:
  - Types I,II: frequently albumin that binds with drugs
  - Types III, IV: rarely bind with drugs

- Types of bonds:
  - Hydrophobic bonds
  - Hydrogen bonds
  - VanderWals
  - Electrostatical bonds

Binding capacity of albumin

- Millions of albumin molecules X no. of binging sites

1. **Low capacity**: One drug molecule per albumin molecule
2. **High capacity**: A number of drug molecules binding to a single albumin molecule

- Albumin has the strongest affinity for anionic drugs (weak acids) and hydrophobic drugs

- Most of hydrophilic drugs and neutral drugs do not bind to adbumin

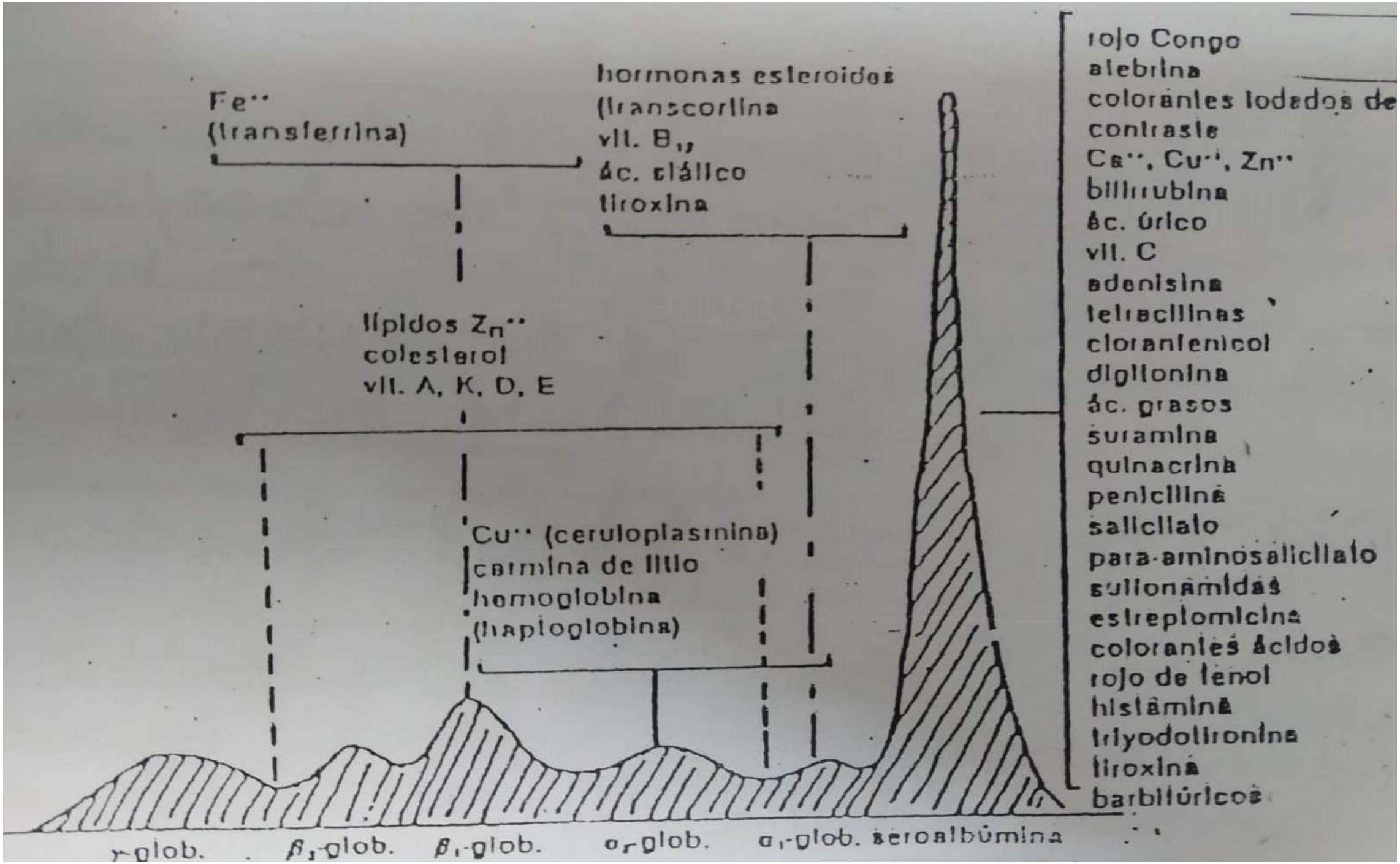
- Case A: [drugs class I], if the dose is < binding capacity, the dose/binding capacity ratio is low → binding sites are in excess of the available drug and the drug fraction bound is high.

- Case B: [drugs class II], if the dose is >> no. binding sites, the dose/binding capacity ratio is high → relatively high proportion of drug exists in the free state, not bound to albumin.

- Case C: administration of class I and II simultaneously → class II displace class I ?????? importance

Relationship between lyposolubility and Plasmaprotein (Albumin) binding in Barbiturics

Drug	%P.A.B.	
- Thiopental	65	very lyposoluble
- Secobarbital	45	+
- Pentobarbital	40	Lyposolubility
- Phenobarbital	20	−
- Barbital	5	few lyposolubility


Fe++
(transferrina)
hormonas esteroideas
(transcortina
vit. B12
ác. fólico
tiroxina
lípidos Zn++
colesterol
vit. A, K, D, E
Cu++ (ceruloplasmina)
carmina de litio
hemoglobina
(haptoglobina)
rojo Congo
albúmina
colorantes iodados de contraste
Ca++, Cu++, Zn++
bilirrubina
ác. úrico
vit. C
adenosina
tetraciclinas
cloranfenicol
digitonina
ác. grasos
suramina
quinacrina
penicilina
salicilato
para-aminosalicilato
sulfonamidas
estreptomicina
colorantes ácidos
rojo de fenol
histamina
triyodotironina
tiroxina
barbitúricos
γ-glob.
β2-glob.
β1-glob.
α2-glob.
α1-glob.
seroalbúmina

Plasma Protein Binding of Drugs

%Binding	Acidic Drugs	Basic Drugs
100-98	Glibenclamide, Ibuprofen, Oxyphenbutazone, Phenyl butazone	Diazepam
...98-95	Indomethacin, Tolbutamide, Warfarine	———
95-85	Chlorpropramide, Dicumarol, Probenecid, Oxacyllin, Sulfamethoxy-diacine	Amitryptilline, chlorpromacine Haloperidol, Hydralazine, Methadone, Nitrazepan, propranolol, Quinidine
85-70	Aspirin, Thiopentone, Phenoxy methylpenicillin, Sulfameracin	Diphenyldramine, Erythromycine, Gentamycin
70-50	Pentobarbitone, Phenobarbitone, Aminosalicylic acid, Nitrofurantoine, Sulfadiacine Sulfamethoxazol	Chlormetiazol, Chloroquine, Petidine, Pindolol, Tetracyline
<50	Ampicillin, Cephalotine, Metotrexate, Pirimidone	———
50-30		Atropine, Morphine, Streptomcin, Pyracynamine
<30		Clonidine, Kanamycine, Orciprenalin, Practolol, Theophylline

Parameters of the binding and its determination

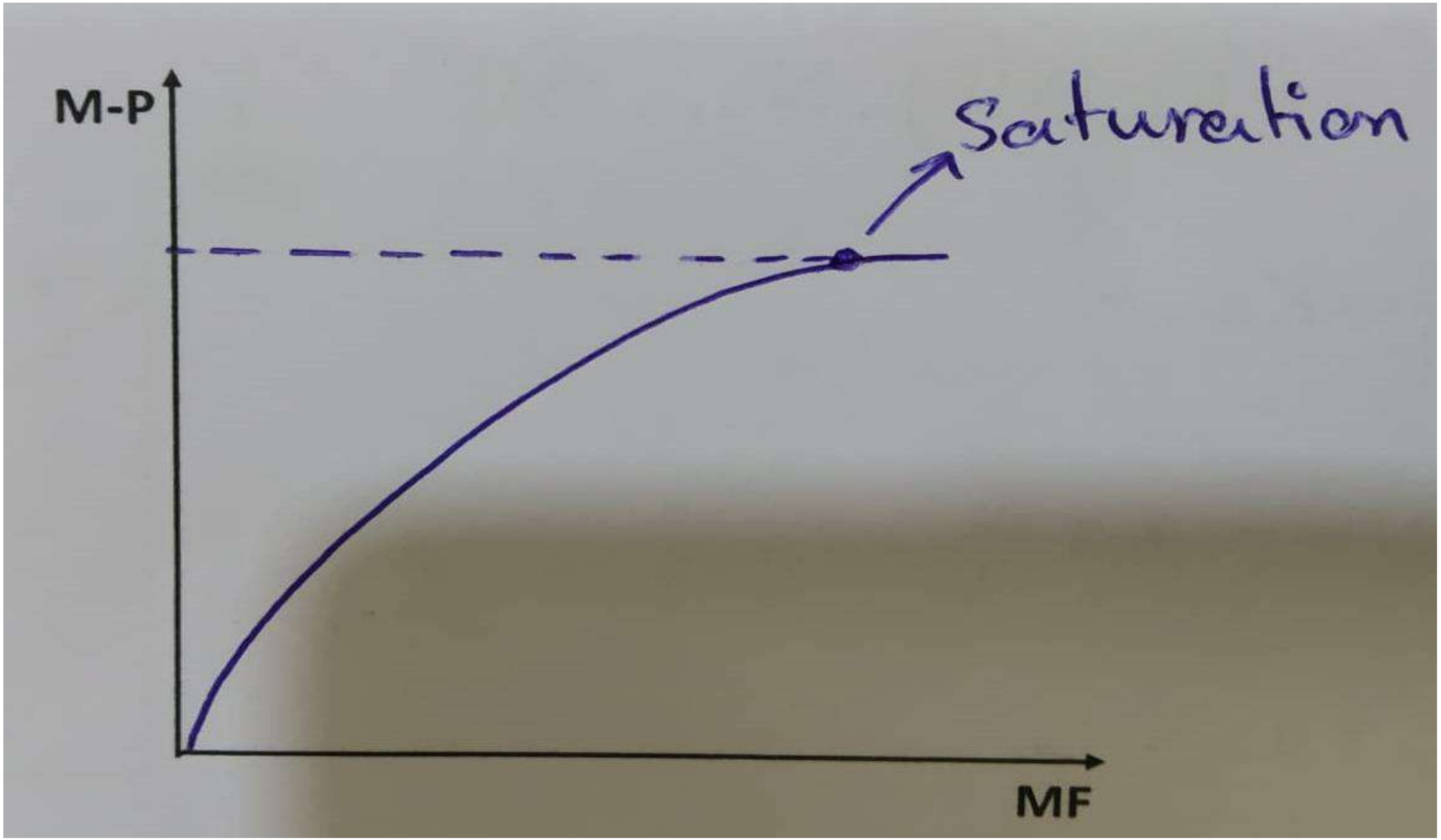
- $[M] + [P] \underset{Kd}{\overset{Ka}{\rightleftharpoons}} [MP]$

- [M] : concentration of free drug
- [P] : concentration of free protein
- Ka : constant of association
- [PT] : total protein

- $r = \frac{[MP]}{[PT]}$

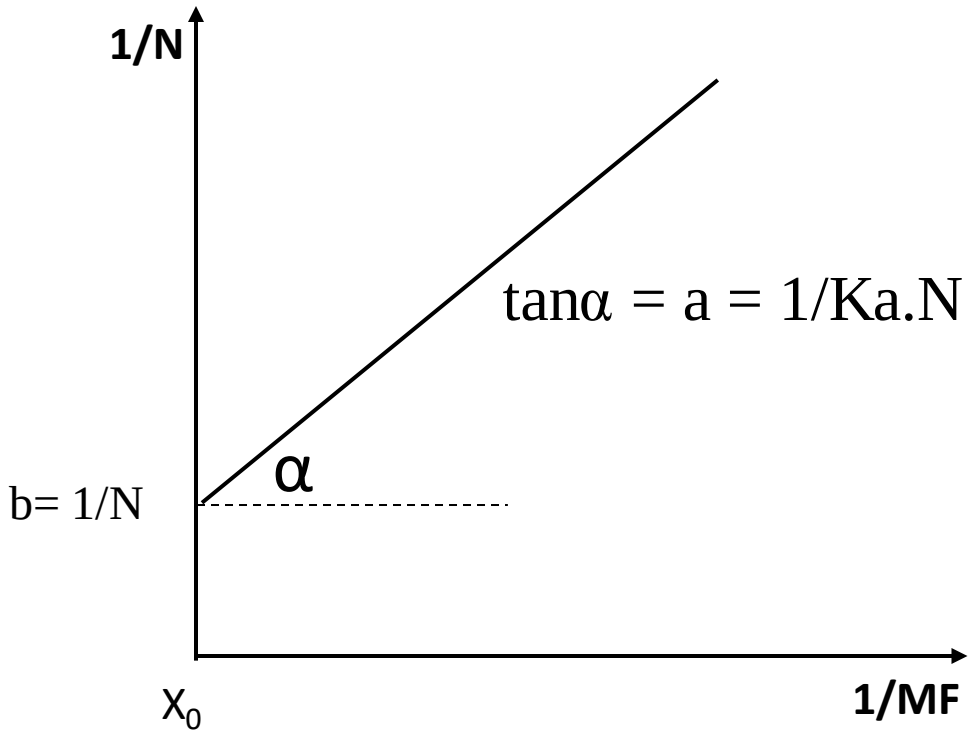
Parameters of the union and its determination

- MF + PF $\underset{Kd}{\overset{Ka}{\rightleftharpoons}}$ MP $\qquad Ka = \frac{[MP]}{[MF][PF]}$
- PT = PF + MP $\qquad [MP] = Ka\,[MF]\,[PF]$
- $r = \frac{[MP]}{[MP][PF]} = \frac{Ka.[MF][PF]}{[PF]+[MF][PF]Ka} = \frac{Ka.[MF]}{1+Ka[MF]}$ for one point of union
- $r = \frac{Ka.[MF]}{1+Ka[MF]} . N$,,, N= no. of points


M-P
Saturation
MF

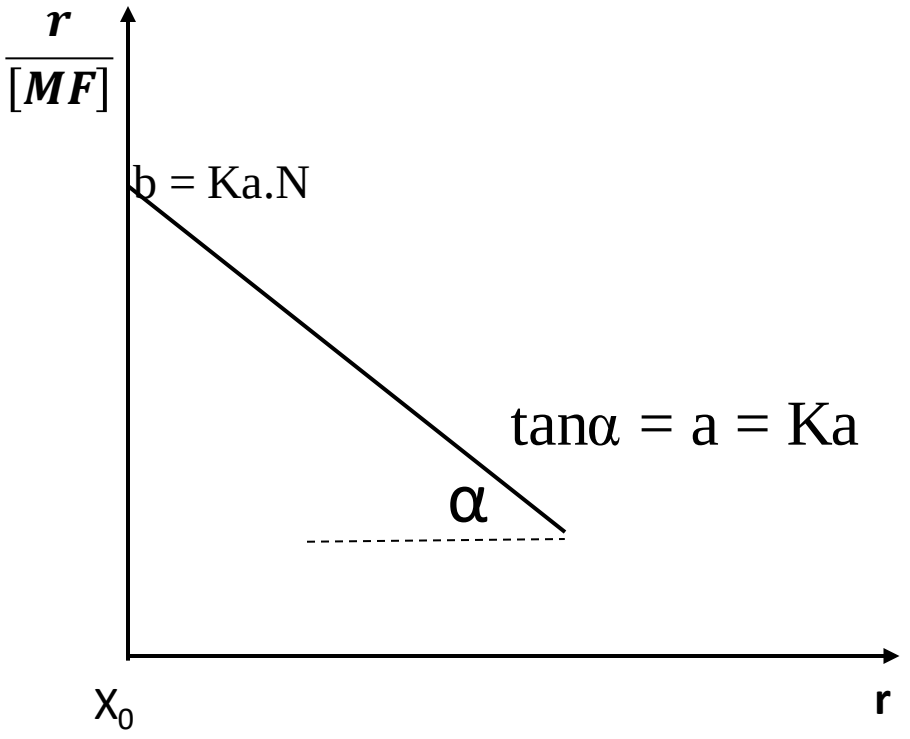
A- Representation of lineweaver-Burk

- $\frac{1}{r} = \frac{Ka.[MF]}{Ka.[MF].N} + \frac{1}{Ka.[MF].N}$
- $\frac{1}{r} = \frac{1}{N} + \frac{1}{Ka.N} \cdot \frac{1}{[MF]}$
- Y= b + a . X



B- Scachard representation

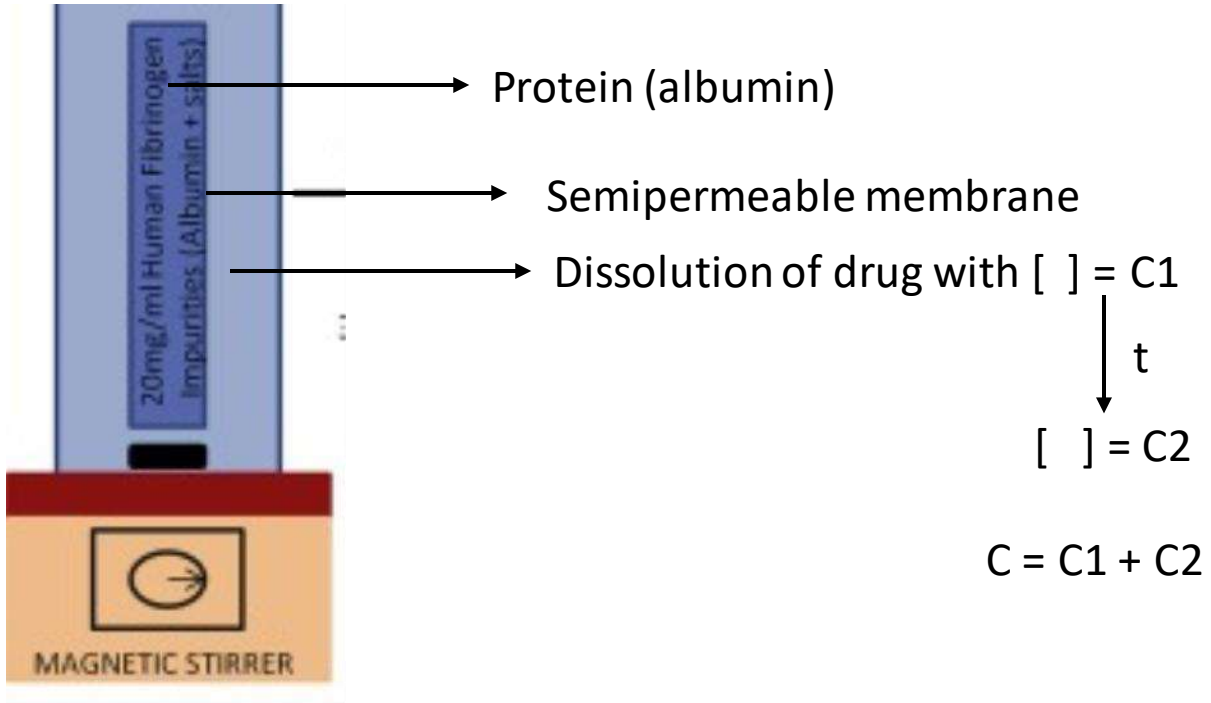
- r . Ka [MF] + r = Ka [MF] . N …. /MF
- r . Ka + $\frac{r}{[MF]}$ = Ka . N
- $\frac{r}{[MF]}$ = Ka . N – r . Ka
- Y = b + a . X



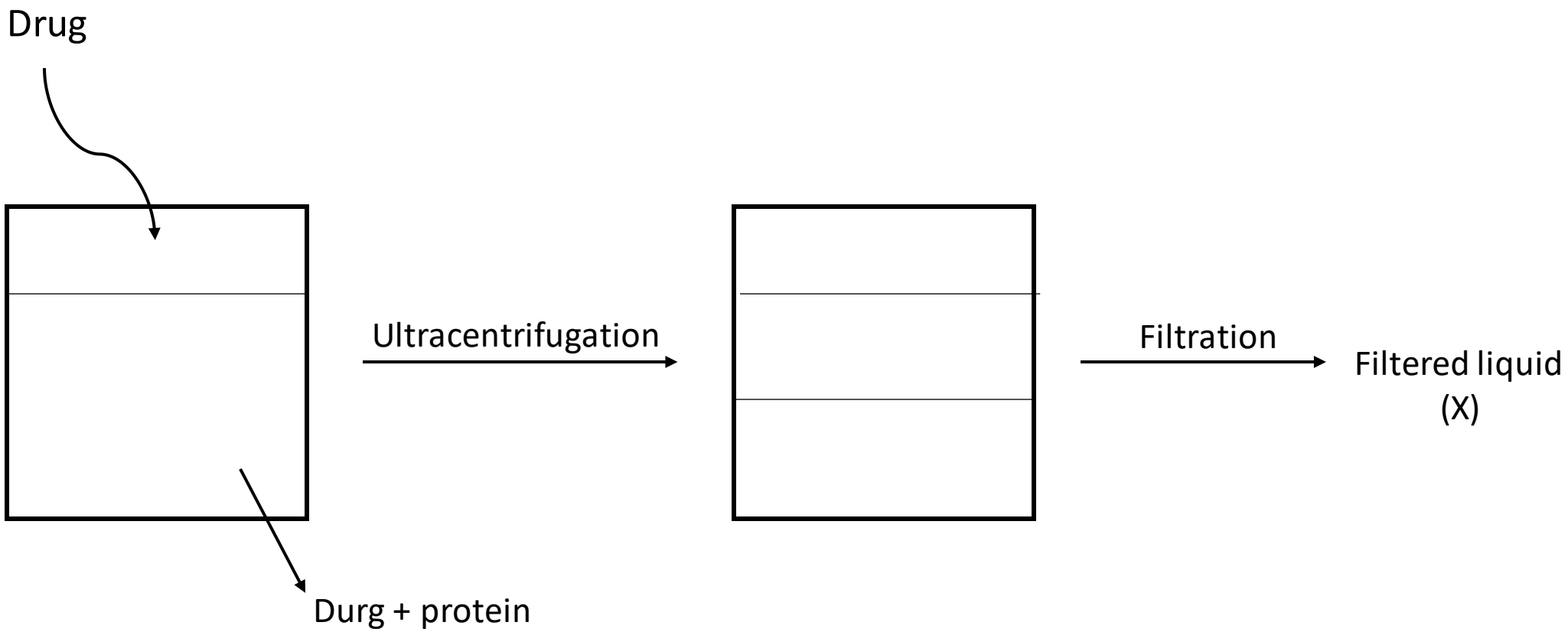
3- Evaluation methods

1. Electrophoresis (**Proteinogram**)
2. Dialysis
3. Ultracentrifugation and ultrafiltration

1- Dialysis



2- Ultracentrifugation and ultrafiltration



Factors affecting the determination of protein binding

1. The drug:
   - ✓Physicochemical properties of the drug.
   - ✓Total concentration of the drug in the body.
2. The protein
   - ✓Quantity of protein available for drug-protein binding.
   - ✓Quality of physicochemical nature of the protein synthesized.
3. The affinity between drug and protein
   - ✓Includes the magnitude of the association constant.
4. Drug interactions
   - ✓Competition for the drug by other substances at a protein binding site.
   - ✓Alteration of the protein by a substances that modifies the affinity of the drug for the protein; aspirin acetylates lysine residues of albumin.
5. The pathophysiologic condition of the patient
   - ✓For example, drug-protein binding may be reduced in ruemic patient and in patients with hepatic disease.

Consequences of binding (union)

I. Modification of pharmacokinetic parameters

We will show the effect of binding on some pharmacokinetic parameters:

1) Half life ($t_{1/2}$)

If the drug has high affinity for binding with plasma protein, its half life will be long.

2) Constant of absorption (K_a)

K_a of a drug is affected by plasma protein binding in direct.

↑protein binding →↑$K_a$way

3) **Constant of elimination (K_e)**

If the drug binds with plasma protein strongly and in large extent, the K_e will has a very small value.

4) **Volume of distribution (V_d)**

In general: There is a direct relationship between (V_d) and the percent of binding.

If the drug has a high affinity to bind with protein, it will has a large (V_d).

II. Advantages and disadvantages of binding

1) The binding of drug with plasma protein is advantage if the drug is toxic.
2) This binding a disadvantages in some drug especially in chemotherapeutic or antibacterial drugs. This property of binding is frequently seen in this types of drugs because all the bacterial infection occurs in extracellular spaces. The concentration of antibacterial drug at the site of infection is very important.

An antibiotic that is largely restricted to the blood because of extensive binding in this compartment will be present in very low concentration at the site of infection. A second antibiotic of similar potency, which is not bound to the plasma protein and is free to be distributed, may be present at the site of infection in high concentration.

The second drug would be the more effective in the clinical situation.

III. Competency of drug with plasma protein

1) Phenylbutazone (percent of binding = 80-90%, Ka is very high). competes with coumarine (oral anticoagulant agent, percent of binding = 95 – 99%, but chemical bond of union is weak) at the site of plasma protein binding.
2) Sulfonamides competes with bilirubin in neonate (at the site of protein binding) causing syndrome kernicterus which means toxic encephalitis.

IV. Basic drugs are less bounded to plasma protein than the acidic drug

V. Selective distribution

Some drugs have affinity to bind with tissue protein more than the plasma protein.

- Examples:

a) Vit A: Has a high affinity to bind with retina protein in eyes.

b) Digitalis drugs: these drugs have high affinity to bind with myocardial protein (heart).

VI. All iodide derivatives bind strongly with plasma protein.

This binding is called permanent binding.

VII. As the liposolubility of drug increases, the percent of binding with plasma protein will increase.

VIII. Plasma protein act as physiological solubilizer

For some drugs as: Bihydroxy Coumarin, phenobarbital.

Factors can modify the protein binding

I. Variation in protein concentration

I. Synthesis alteration.
II. Catabolism alteration.
III. Distribution between the vascular and extravascular spaces.

A. Physiological factors affecting the concentration of plasma proteins

- **Age**: *in new born*: decrease the concentration of plasma protein, and endogenous substances as bilirubin and free fatty acids can display some drugs.

in old people (elderly): decrease the concentration of plasma albumin, but increased glycoprotein.

- Pregnancy: When the state of pregnancy increases, the protein conc.of plasma decrease progressively. (albumin and γ-globulin)but α-1-glycoprotein increases at the end of pregnancy

- Life style: habits as tobacco produces decreasing in the concentration of plasma albumin.

B. Pathological factors

- In acute processes, it is found that the albumin is decreased, and the γ-globulin is increased.
- Myocardial infarction, pneumonia, rheumatic fever, peritonitis → ↓ level of albumin, also malignant tumor process causing decrease of albumin (↓synthesis of albumin).

- Surgery and burns cause the decreasing in extra vascular protein (hypoalbuminemia): ↑ capillary permeability for the intravascular albumin.
- Hepatic and renal deficiency: ↓ albumin
- Schizophrenia and psychosis: ↑ albumin

II- Structural alterations in the proteins molecule → changing in affinity

III- Interactions with endogenous substances or other drugs

- Fatty acids displaces: bilirubin, hydroxiphenilazobenzoic acid, salycilates, phenibutazone, thiopental and triptophane
- Sulfonamides in neonates displaces bilirubin (kernecterous).