9/4/2020

Unit-4

Multicompartments Models

Multicompartment models are based on following assumption -

(1) Blood / Plasma & the highly perfused tissues such as Brain, Heart, lung, liver & kidney constitute the central compartment.

(2) Other tissues with similar distribution characteristics are paralel together to constitute Peripheral compartment. tissues on the basis of similarity in their distribution.

(3) Intravenously (i.v.) administration medications are introduced directly into the Central Compartment.

Irreversible drug elimination either by hepatic biotransformation or renal excretion take place only from the Central Compartment.

(5) Reversible distribution occurs between Central & peripheral compartment.

(6) Elimination of drug follow first order kinetics.

(7) All rate processes involving passage of drug in & out of individual compartment are first-order process.

Two Compartment Open Model

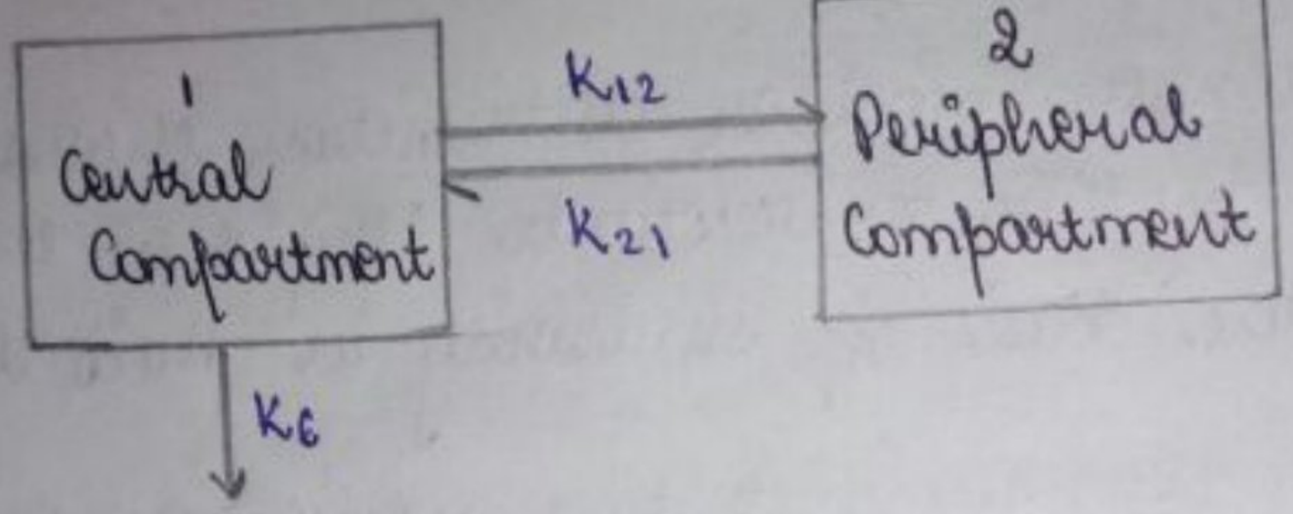
The Body tissues are broadly classified into 2 categories:

(1) Central Compartment or Compartment 1 -

It comprising of blood & highly perfused tissues like liver, lungs, kidney, etc that equilibrate with the Drug Capacity. Elimination usually occurs from this

Compartment.

(2) Peripheral or Tissue Compartment or Compartment 2 - It comprising of poorly perfused & slow equilibrating tissues such as muscles, skin, adipose tissue, etc & considered as a hybrid of several functional physiologic units.



Imp → Two Compartment open model I.V. Bolus Administration

After the i.v. bolus of a drug that follows two-compartment kinetics, the decline in plasma conc": is biexponential indicating the presence of two disposition processes i.e. distribution & elimination.

Imp "Initially, the conc" of drug in the central compartment declines rapidly, this is due to the distribution of drug from the central compartment to the peripheral compartment. This phase is called as Distributive phase".

Imp "After sometime, the loss of drug from the central compartment is slow & mainly due to elimination. This slower rate process is called as the Post-distributive or elimination phase".

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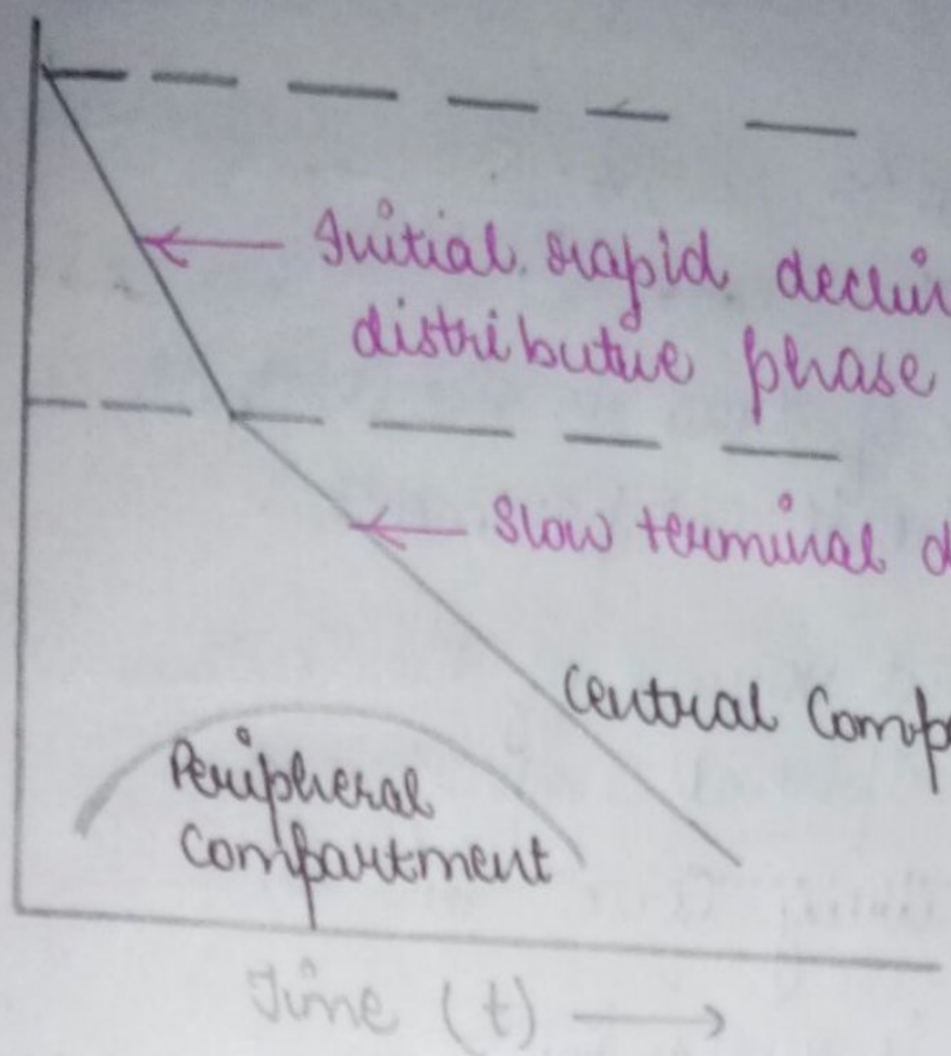


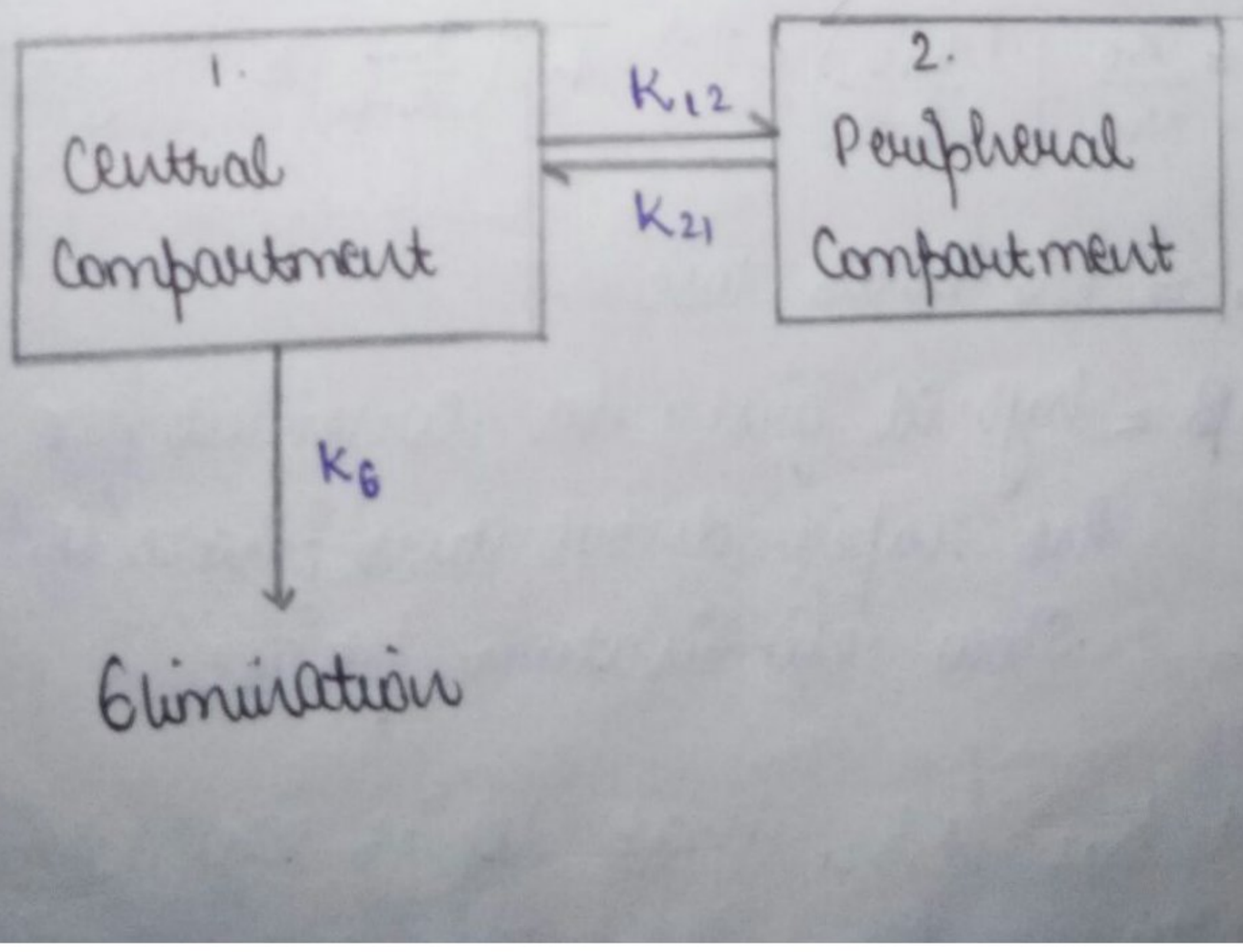
Let K_{12} & K_{21} be the first-order distribution rate Constant showing drug transfer between central & peripheral Compartments.

The rate of change in drug Conc^n in the Central Compartment -

$$\frac{dC_c}{dt} = K_{21}C_p - K_{12}C_c - K_6C_c \quad \text{— (1)}$$

where, C_p = Conc^n in peripheral compartment.

C_c = Conc^n in Central Compartment.



Put the value $X = V_d \cdot C$ in the above eqⁿ -

$$\frac{dC_c}{dt} = \frac{K_{21} X_p}{V_p} - \frac{K_{12} X_c}{V_c} - \frac{K_e X_c}{V_c} \quad -(2)$$

Where, X_c & X_p = amount of drug in the Central & peripheral compartment

V_c & V_p = Apparent volume of the Central & peripheral Compartment

The rate of change in drug Conc^n in the peripheral Compartment is given by -

$$\frac{dC_p}{dt} = K_{12} C_c - K_{21} C_p \quad -(3)$$

$$\frac{dC_p}{dt} = \frac{K_{12} X_c}{V_c} - \frac{K_{21} X_p}{V_p} \quad -(4)$$

On integration of eqⁿ (2) & (4) & Simplifying -

$$C_c = \frac{X_0}{V_c} \left[\left(\frac{K_{21} - \alpha}{\beta - \alpha} \right) e^{-\alpha t} + \left(\frac{K_{21} - \beta}{\alpha - \beta} \right) e^{-\beta t} \right] \quad -(5)$$

$$C_p = \frac{X_0}{V_p} \left[\left(\frac{K_{12}}{\beta - \alpha} \right) e^{-\alpha t} + \left(\frac{K_{12}}{\alpha - \beta} \right) e^{-\beta t} \right] \quad -(6)$$

where, X_0 = i.v bolus dose

α & β = hybrid first order constant for the rapid distribution phase & the slow elimination phase.

" The constant K_{12} & K_{21} that depict reversible transfer of drug between compartments are called microconstants or transfer constants."

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The mathematical relationship between hybrid & 153
microconstants are —

$$\alpha + \beta = K_{12} + K_{21} + K_e \quad -(7)$$

$$\alpha\beta = K_{21} K_e \quad -(8)$$

Eq^n: (5) is written as - exponential

$$C_t = A e^{-\alpha t} + B e^{-\beta t} \quad -(9)$$

C_t = Distribution + Elimination
exponent exponent.

From eq^n (5) & (6) -

$$A = \frac{X_0}{V_c}\left[\frac{K_{11} - \alpha}{\beta - \alpha}\right]$$

$$A = C_0\left[\frac{K_{11} - \alpha}{\beta - \alpha}\right] \quad ---- (10)$$

$$B = \frac{X_0}{V_c}\left[\frac{K_{21} - \beta}{\alpha - \beta}\right]$$

$$B = C_0\left[\frac{K_{21} - \beta}{\alpha - \beta}\right] \quad ---- (11)$$

$$\therefore X = V_d \cdot C \quad , \quad C = \frac{X}{V_d}$$

where, C_0 = Plasma drug conc^n immediately after
i.v. injection.

↓

It is also called initial conc^n.

The biexponential disposition curves obtained after i.v. bolus of a drug that fits two compartment model can be resolved into its individual exponents by the method of residuals.

$$C_c = Ae^{-\alpha t} + Be^{-\beta t} \quad -(9)$$

The initial decline due to distribution is more rapid than the terminal decline due to elimination i.e. the rate constant $\alpha >> \beta$, so, $Ae^{-\alpha t}$ is zero.

Above eq^n reduce to,

$$\overleftarrow{C} = Be^{-\beta t} \quad -(12)$$

In log form,

$$\log \overleftarrow{C} = \log B - \frac{\beta t}{2.303} \quad -(13)$$

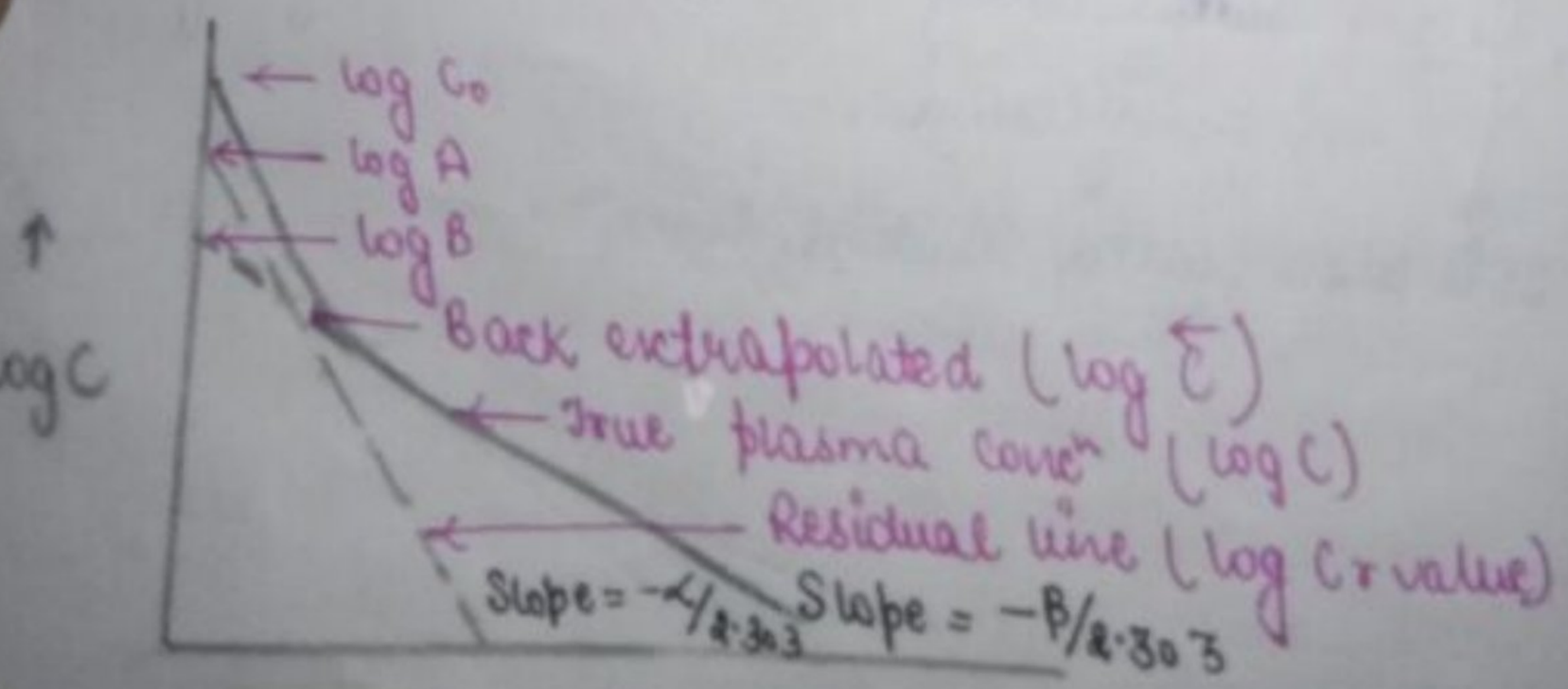
where $\overleftarrow{C}$ = back extrapolate plasma conc^n values.

A series of residual conc^n values C_r.

$$C_r = C - \overleftarrow{C} = Ae^{-\alpha t} \quad -(14)$$

In log form,

$$\log C_r = \log A - \frac{\alpha t}{2.303} \quad -(15)$$



A semilog plot of biexponential plasma conc^n-time curve by the method of residuals for a drug that follow two-compartment kinetics.

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Kinetics of Multiple Dosing

→ Design of Dosage Regimens -

"Dosage regimen is defined as the manner in which a drug is taken. For some drugs like analgesics, hypnotics, antiemetics, etc a single dose may provide effective treatment."

Imp.

If illness is longer than drugs are required to be taken on a repetitive basis over a period of long time so, successful therapy, design of an optimal multiple dosage regimen is necessary.

Imp.

An optimal multiple dosage regimen is the one in which the drug is administered in suitable doses with sufficient frequency that maintenance of plasma conc^n with in the therapeutic window.

Approaches to design of Dosage regimen :

(i) Empirical Design Regimen - It is designed by physical based on empirical clinical data & observation.

(ii) Individualized Dosage Regimen - It is most accurate approach & based on the pharmacokinetics of drug in the individual patient.

(iii) Dosage Regimen on Population average - Most used approach. This is 2 types -:

(a) Fixed model.

(b) Adaptive model.

Date :

→ Dose Size & Dose Frequency -

The two major parameters that can be adjusted in developing a dosage regimen are -

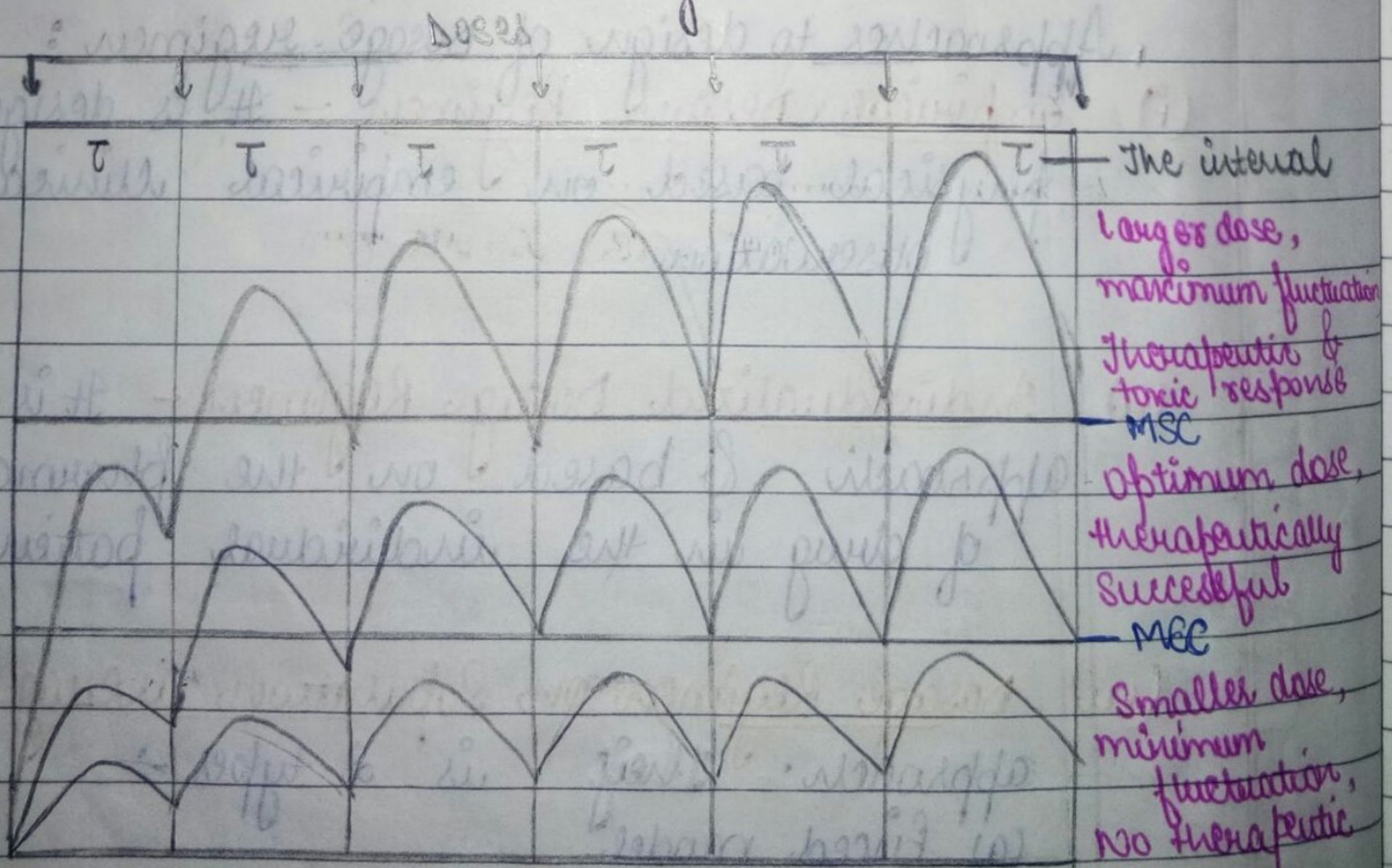
(1) The dose size - the quantity of drug administered each time

(2) The dosing frequency - the time interval between doses.

Dose Size :-

- The magnitude of both therapeutic & toxic responses depends upon dose size.
- Dose size calculation also requires the knowledge of amount of drug absorbed after administration of each dose.
- Greater the dose size, greater the fluctuation between $C_{ss,max}$ & $C_{ss,min}$ during each dosing interval.

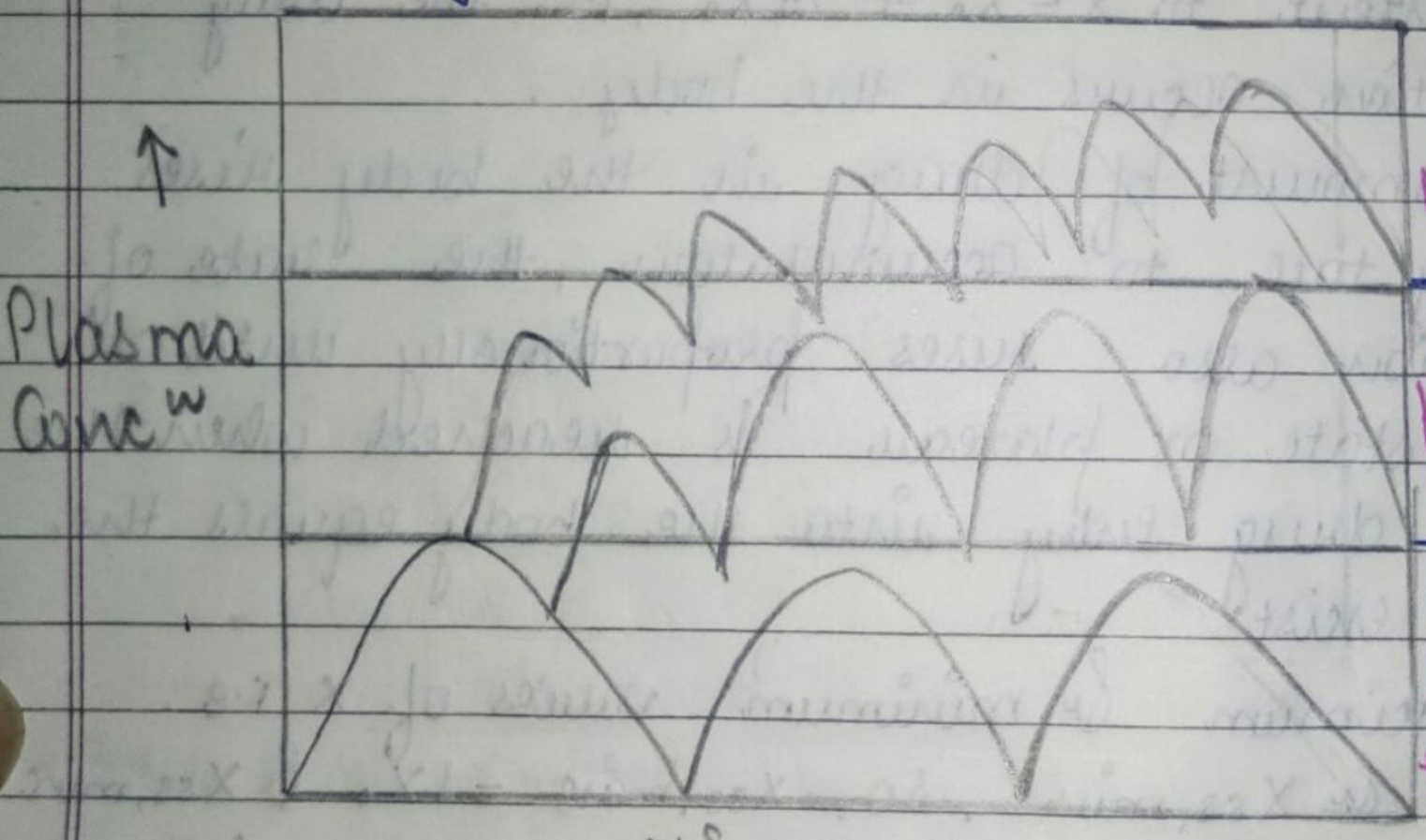
($C_{ss,max}$ → Conc^n at steady state maximum).
($C_{ss,min}$ → Conc^n at steady state minimum)



Dose size on plasma Conc^n-time profile after oral administration of a drug at a fixed interval of time -

Dosing Frequency :-

- The dose interval (inverse of dosing frequency) is calculate on the basis of half-life of the drug.
- If the interval is increased & the dose is unchanged, C_{max}, C_{min} & C_{av} decrease but the ratio C_{max}/C_{min} increases.
- Opposite is observed when dosing interval is reduced or dosing frequency increased.
- It also results in greater drug accumulation in the body & toxicity.



High dosing frequency ($\tau < t_{1/2}$) less fluctuation but show therapeutic & MSC toxic response.

optimum dosing frequency ($\tau = t_{1/2}$), therapeutically successfull. — MEC

less dosing frequency ($\tau > t_{1/2}$), large fluctuation, therapeutically unsuccessfull

Dosing frequency on plasma Conc^n - time profile obtained after oral administration of fixed dose of a drug.

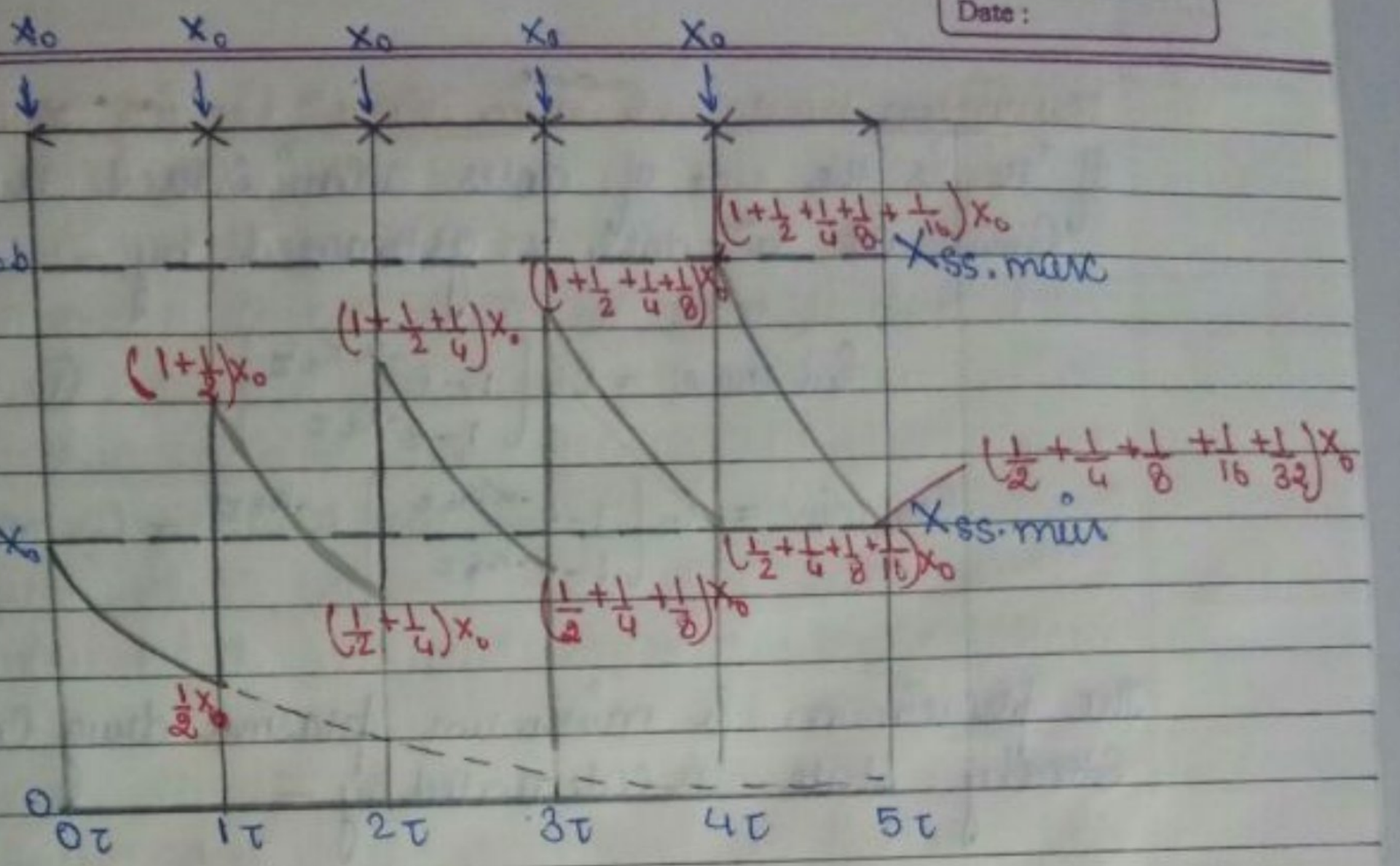
Imp NOTE :

A proper balance between both size & dosing frequency is desired to attain steady-state Conc^n. with minimum fluctuation & to ensure therapeutic efficacy & safety.

Ans ⇒ **Drug Accumulation During Multiple dosing** - Consider the amount of drug in the body - time profile obtained after i.v. multiple dosing with dosing interval τ equal to one $t_{1/2}$ half-life. (i.e $\tau = t_{1/2}$).

- After the administration of first dose X_0 at $\tau = 0$, the amount of drug in the body will be $X = 1X_0$.
- At the next dosing interval when $X = 1/2\, X_0$, the amount of drug remaining in the body, administration of the next i.v. dose raises the body content to $X = X_0 + 1/2\, X_0$, i.e. the drug accumulation occurs in the body.
- As the amount of drug in the body rises gradually due to accumulation, the rate of elimination also rises proportionally until a steady-state or plateau is reached when the rate of drug entry into the body equals the rate of excist.
- The maximum & minimum values of X i.e. $X_{ss,max}$ & $X_{ss,min}$, so, $X_{ss,min} = 1X_0$ & $X_{ss,max} = 2X_0$
- The extent to which a drug accumulation in the body during multiple dosing is independent of dose size & is a function of Dosing interval & elimination half-life ($t_{1/2}$).

$$\text{Accumulation Index } (R_{ac}) = \frac{1}{1 - e^{-k_e \tau}}$$



The graph shows the accumulation of drug in the body during multiple dose regimen of i.v. bolus with dosing interval (τ) equal to one half life ($t_{1/2}$) of the drug. Approximately 5 half-life are required for attainment of steady-state.

Steady-State Drug level —

- The time required to reach steady state depends upon the half-life of the drug.
- If $K_a >> K_e$, the plateau is reached in approximately 5 half-lives, this is called Plateau principle.
- The multiple dose steady-state is dependent only by K_e.
- The time taken to reach steady-state is independent of dose size, dosing interval & no. of doses.

Maximum and minimum Conc" During Multiple Dosing -
If 'n' is the no. of doses administered. Here Cmax &
Cmin at n^th dose is estimated by -

$$C_{n,max} = C_0 \left[\frac{1 - e^{-nK_0\tau}}{1 - e^{-K_0\tau}} \right] \quad \text{---- (1)}$$

$$C_{n,min} = C_0 \left[\frac{1 - e^{-nK_0\tau}}{1 - e^{-K_0\tau}} \right] e^{-K_0\tau} = C_{n,max} e^{-K_0\tau} \quad \text{(2)}$$

The maximum & minimum plasma drug Conc" at steady - state is calculated by -

$$C_{ss,max} = \frac{C_0}{1 - e^{-K_0\tau}} \quad \text{---- (3)}$$

$$C_{ss,min} = \frac{C_0 e^{-K_0\tau}}{1 - e^{-K_0\tau}} = C_{ss,max} e^{-K_0\tau} \quad \text{---- (4)}$$

where, C_0 = Conc" attained from instantaneous absorption & distribution.

Fluctuation.

"Fluctuation is defined as the ratio Cmax/Cmin."

- Greater the ratio, greater the fluctuation.
- It depends upon dosing frequency & half-life of the drug.
- It also depends upon the rate of absorption.
- The greatest fluctuation is observed when the drug is given as i.v. bolus.
- Fluctuation are small when the drug is given extravascularly because of continuous absorption.

Average Conc" & Body Content on Multiple dosing at Steady-State

The average drug conc" at steady-state ($C_{ss,av}$) depends on -

(a) Maintenance dose (X_0).
(b) Fraction of dose absorbed (f).
(c) Dosing interval (τ)
(d) Clearance (Cl_T) (or V_d & K_e or $t_{1/2}$) of the drug.

Average conc" & drug content on multiple dosing to steady state:

$$C_{ss,av} = \frac{f X_0}{Cl_T \tau} \quad \text{— (1)}$$

$$= \frac{1.44 f X_0}{V_d \tau} = \frac{AUC\ (single\ dose)}{\tau} \quad \text{— (2)}$$

Since, $X = V_d C$, the body content at steady state is given as:

$$X_{ss,av} = \frac{1.44 f X_0 t_{1/2}}{\tau} \quad \text{— (3)}$$

These average values are not arithmetic mean of $C_{ss,max}$ & $C_{ss,min}$ as the plasma drug conc" undergoes exponential decline.

Loading & Maintenance Doses —

A drug does not show therapeutic activity unless it reaches the desired steady-state. It takes about 5-half-lives to attain it & therefore the time taken will be too long if the drug has a long half-life.

Plateau can be reach immediately by administering a dose that gives the desired steady-state instantaneously before the commencement of maintenance doses X_0.

An initial or first dose intended to be therapeutic is called as Priming dose or loading dose $X_{0,L}$.

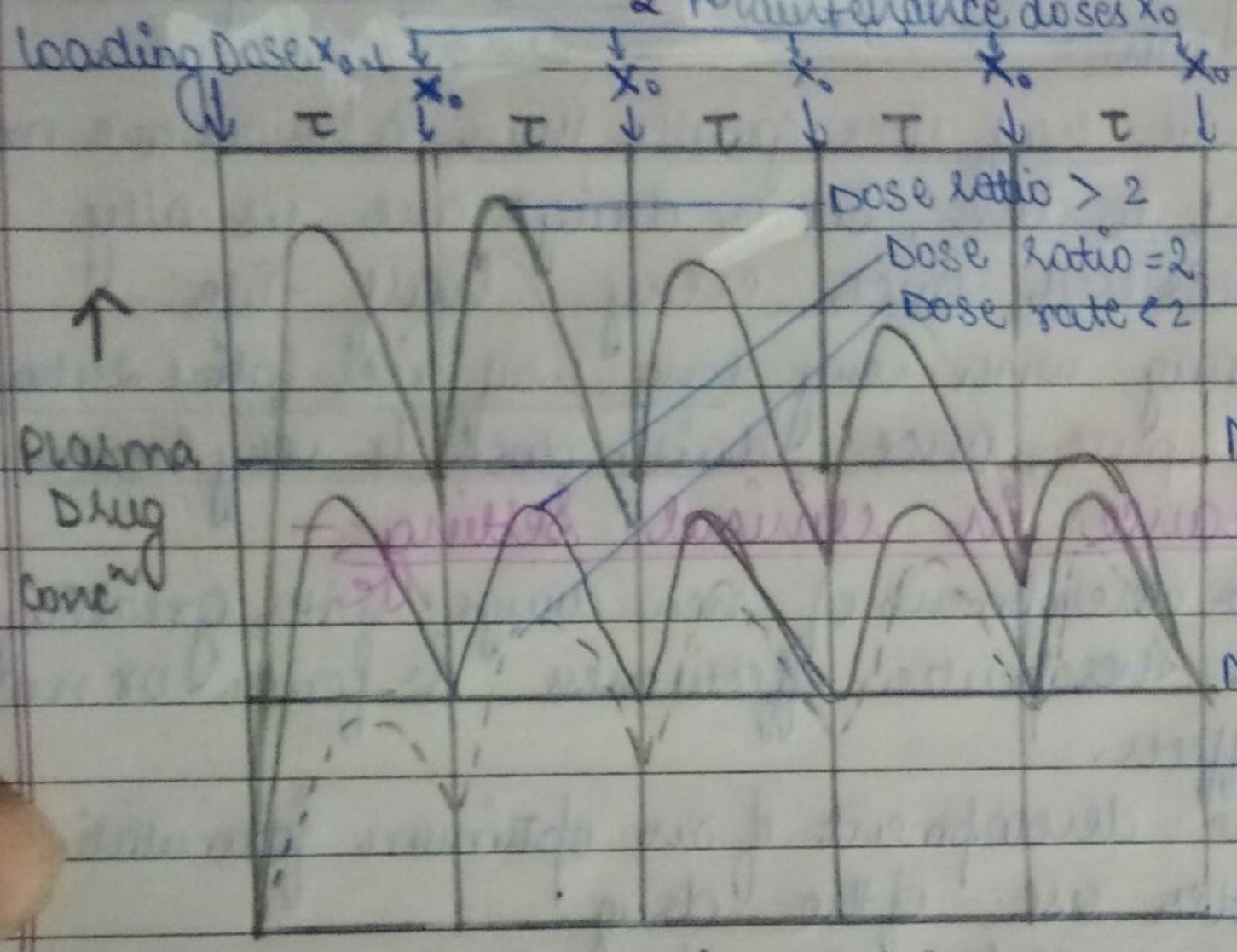
A simple eq^n for calculating loading dose is:

$$X_{0,L} = \frac{C_{ssav} V_d}{f}$$

where, f = fraction of dose absorb
V_d = volume of distribution

- After e.v. administration, Cmax is always smaller than that after i.v. administration & hence loading dose is proportionally smaller.
- For drugs having low therapeutic indices, the loading dose may be divided into smaller doses to be given at various intervals before the first maintenance dose.

• "The ratio of loading dose to maintenance dose $X_{0,L}/X_0$ is called as dose ratio."
As a rule, when
(1) $\tau = t_{1/2}$, dose ratio = 2.0
(2) τ $t_{1/2}$, dose ratio < 2.0
(3) $\tau < t_{1/2}$ Dose ratio > 2.0



loading & maintenance Doses at different dosing interval

Maintenance of Drug with in the Therapeutic Range -
• The maintaining drug Conc^ with in the therapeutic window depends upon -
(1) Therapeutic index of the drug
(2) Half life of the drug.
(3) Convenience of dosing.

• To maintenance of drug within the therapeutic range can be stated :
→ For a drug with short half life (less than 3 hours) & narrow therapeutic index eg - Heparin, dosing frequency has to be essentially less than $t_{1/2}$.

Date :

→ For a drug with short half life eg- Penicillin $t_{1/2}$ = 0.4 hours & high therapeutic index dosing frequency can be several times that of $t_{1/2}$ but the maintenance dose has to be larger.

→ A drug with intermediate $t_{1/2}$ (3 to 8 hours) may be given at interval $\tau \leq t_{1/2}$ if therapeutic index is low.

→ Drug with half lives greater than 8 hours are more convenient to dose. Such drugs are usually administered once every half-life.

→ For drug with very long half lives (above 24 hours) eg amlodipine, once daily dose is very convenient.

Significance in clinical Setting -

(1) Design & development of new drugs with greatly improved therapeutic effectiveness & fewer or no toxic effects.
(2) Design & development of an optimum formulation for better use of the drug.
(3) Design & development of Controlled / targeted release formulation.
(4) Select the appropriate route for drug administration.
(5) Select the right drug for a particular illness.
(6) Predict & explain drug-food & drug-drug interaction
(7) Design an appropriate multiple dosage regimen.
(8) Therapeutic drug monitoring in individual patients.
(9) Dosage adjustment in situation of altered physiology & drug interaction.

Clinically, the two most important application of pharmacokinetics principle are:
(a) Design of an optimal dosage regimen
(b) Clinical management of individual patient & therapeutic drug monitoring.

→ Salivary Excretion :
The pH of saliva varies from 5.8 to 8.4. Unionized lipid soluble drugs are excreted passively. The bitter after taste in the mouth of a patient on medication is an indication of drug excretion in saliva. Some basic drugs inhibit saliva secretion & are responsible for mouth dryness.
Compounds excreted in saliva are Caffeine, Phenytoin, Theophylline.

→ Mammary Excretion :
Milk consist of lactic secretion which is rich in fats & proteins. 0.5 - 1 litre of milk is secreted per day in lactating mothers. Excretion of drug in milk is important as it gains entry in breast feeding infants.
pH of milk varies from 6.4 to 7.6. Free, unionized & lipid soluble drug diffuse passively. Highly plasma bound drug like Warfarin is less secreted in milk. Since milk contains proteins ; Drugs excreted can bind to it.
Amount of drug excreted in milk is less than 1% & fraction consumed by infant is too less to produce toxic effects. Some potent drugs like barbiturates, morphine may induce toxicity.

Adverse effects -
- Discoloration of teeth with tetracycline & jaundice due to interaction of bilirubin with sulfonamides.
- Nicotine is secreted in the milk of mothers who smoke.

Group B - Compounds whose ratio > 1
eg. Bile salts, Bilirubin, Creatinine, etc.

Group C - Compounds whose ratio < 1
eg. Sucrose, insulin, Phosphates, Phospholipids.

Drugs can fall in any of the above categories.

⟹ Several factors influence secretion of drugs in bile :

(1) Physicochemical properties of the drug -

(a) Molecular weight :

Molecular weight of Drug	Excretion Pattern
Below 300 dalton	Excreted mainly in urine, less than 5% is excreted in bile
Above 500 daltons	Excreted mainly in bile, less than 5% is excreted in urine
Between 300 to 500 dalton	Excreted in both urine & bile.

(b) Polarity -
Greater the polarity, better the excretion. Thus, metabolities are more excreted in the bile than the parent drug because of their increased polarity.

(iii) Tubular Reabsorption :

Tubular reabsorption occurs after the glomerular filtration of drugs. Reabsorption of a drug is indicated, when the excretion rate values are less than GFR of 130 ml/min.

An agent such as glucose that is completely reabsorbed after filtration has a clearance value of zero.

Reabsorption increases the half-life of a drug in contrast to tubular secretion.

Tubular reabsorption can take place in either of the 2 ways :

(i) Active Tubular Reabsorption.
(ii) Passive Tubular Reabsorption.

Concept of Clearance :

The clearance concept was first introduced to describe renal excretion of endogenous compounds in order to measure the kidney function.

The term is now applied to all organs involved in drug elimination such as liver, lungs, the biliary system, etc and are referred to as hepatic clearance, pulmonary clearance, Biliary clearance & so on.

The sum of individual clearances by all eliminating organs is called as total body clearance or total systemic clearance."