

UNIT - 4

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Multicompartment models -

Introduction — one-compartment model adequately describes pharmacokinetics of many drugs.

→ Instantaneous distribution equilibrium is assumed in such cases & decline in the amount of drug in the body with time is expressed by an equation with monoexponential term.

⇒ Ideally, a true pharmacokinetic model should be the one with a rate constant for each tissue undergoing equilibrium, which is difficult mathematically.

① Blood/plasma and the highly perfused tissues such as brain, heart, lung, liver & kidneys constitute the central compartment -

② Other tissues with similar distribution characteristics are pooled together to constitute peripheral compartment tissue on the basis of similarity in their distribution characteristics

③ Intravenously administered medications are introduced directly into the central compartment

④ Irreversible drug elimination, either by hepatic biotransformation or renal excretion, takes place

place only from the central compartment

- (5) Reversible distribution occurs b/w central & peripheral compartment with a finite time required for distribution equilibrium to be attained.
- (6) After drug equilibration b/w central & the peripheral compartment elimination of drug follows first-order kinetics
- (7) All rate processes involving passage of drug in and out of individual compartment are first order processes & plasma level-time curve is best described by sum of series of exponential terms each corresponding to first order rate processes associated with a given compartment
- (8) The peripheral compartment is usually inaccessible to direct measurement & is not a site of drug elimination or clearance.

Two compartment open model

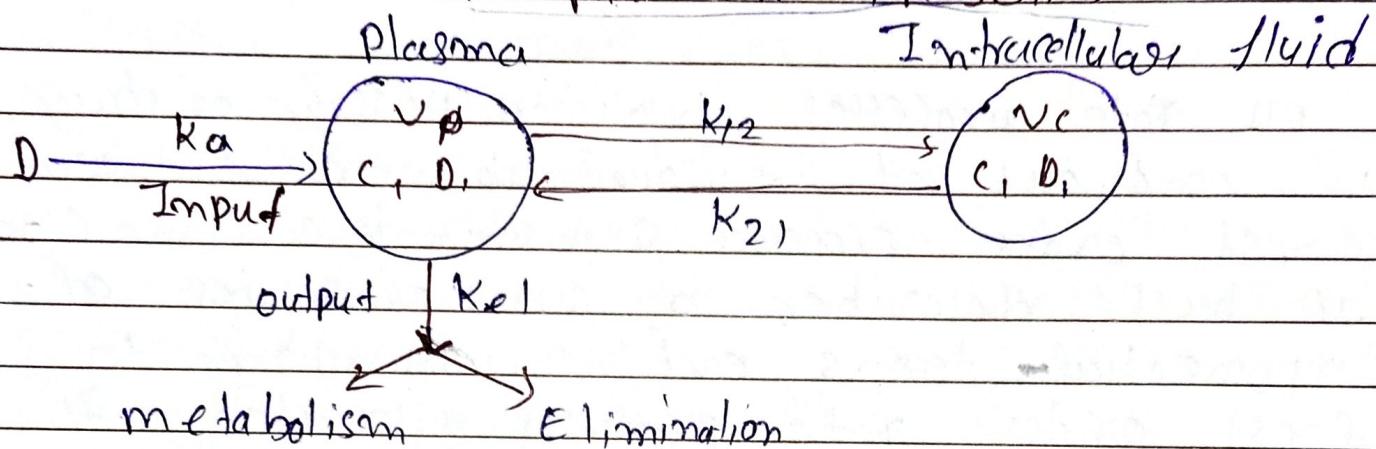
Two categories -

- (1) central compartment or compartment I- comprising of blood & highly perfused tissues like liver, lungs, kidneys etc. that

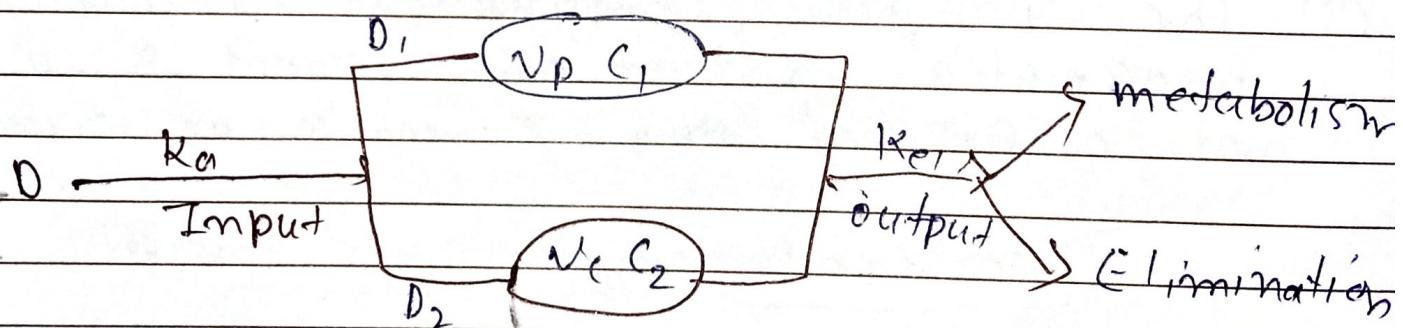
equilibrate with the drug rapidly.

- (2) Peripheral or Tissue compartment or compartment 2 - comprising of poorly perfused & slow equilibrating tissues such as muscles, skin, adipose etc. & considered as a hybrid of several functional physiological unit.

Compartment in series



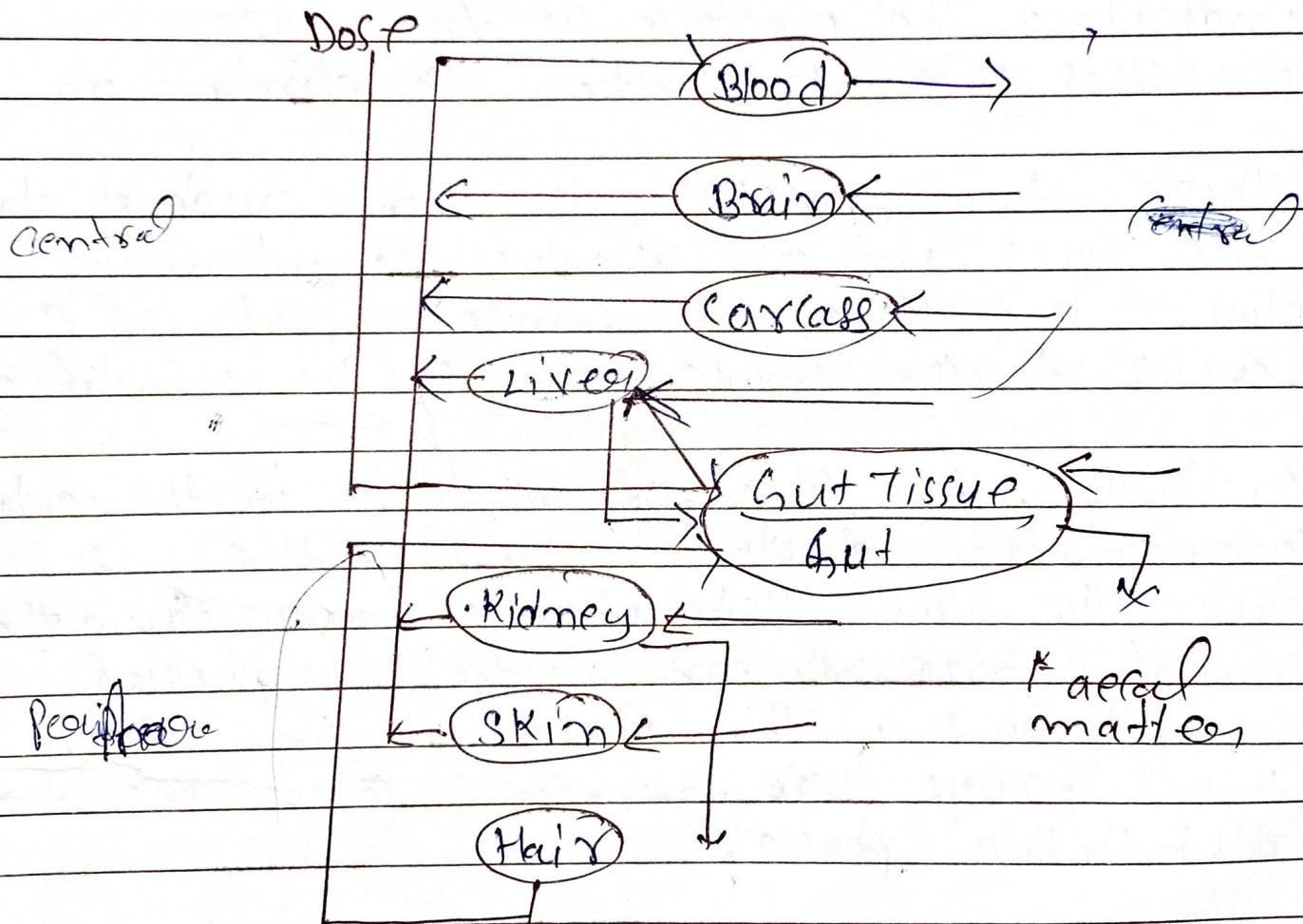
Compartment in parallel



→ Classification of a particular tissue for example brain into central or peripheral compartment depends upon the physicochemical properties of the drug.

Depending upon the compartment from which the drug is eliminated the two compartment model can be categorized into 3 types

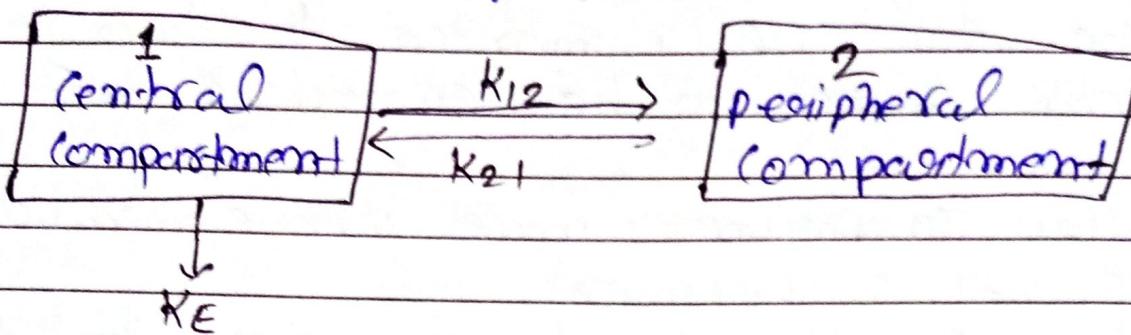
- ① Two compartment model with elimination from central compartment
- ② Two compartment model with elimination from peripheral compartment.
- ③ Two compartment model with elimination from both the compartments



Two compartment open model - IV. Bolus

The model can be depicted as shown

below with elimination from the central compartment.



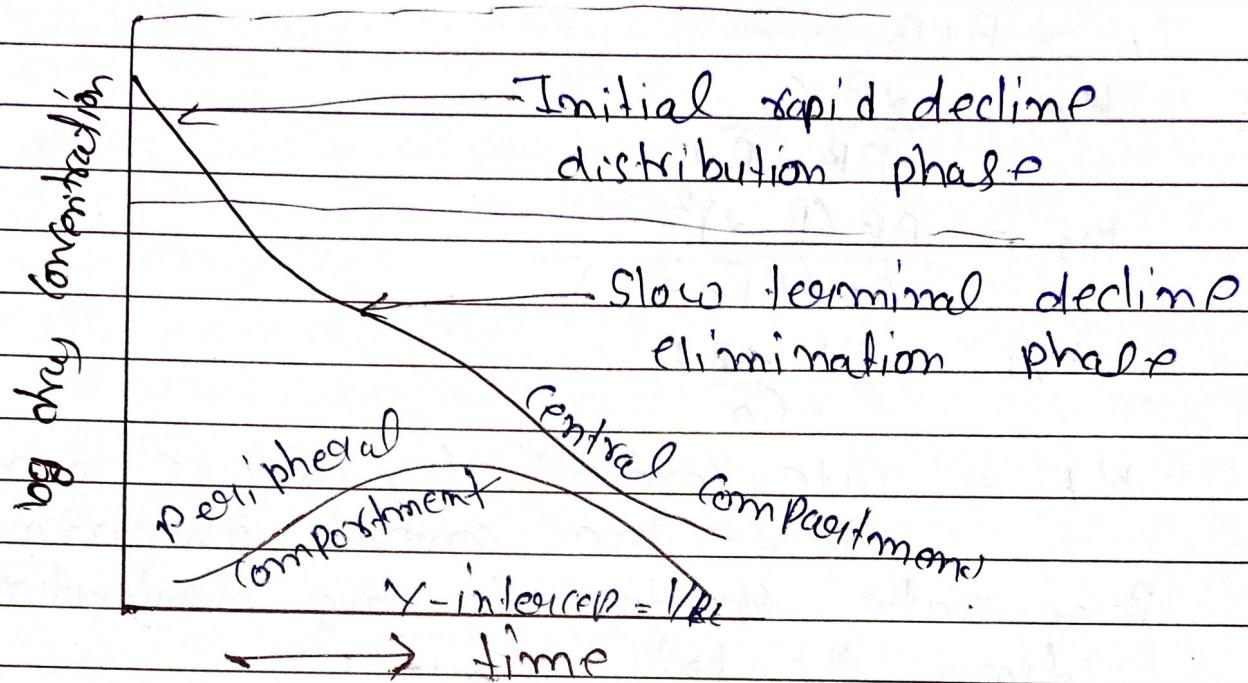
After the i.v. bolus of a drug that follows two compartment kinetics the decline in plasma concentration is biexponential indicating the presence of two disposition processes viz. distribution & elimination.

These two processes are not evident to the eyes in a regular arithmetic plot but when a Semilog plot of C versus t is made, they can be identified.

Initially, the conc of the drug in the central compartment declines rapidly this is due to the distribution of drug from the central compartment to the peripheral compartment. The phase during which this occurs is therefore called as its distributive phase.

After sometime a pseudo-distribution equilibrium is achieved b/w the Central 2 compartment following which the subsequent loss of drug from the Central compartment is slow & mainly due to elimination.

→ This second slower rate - process is called as the post distribution or elimination phase.



⇒ The constants k_{12} & k_{21} that depict reversible transfer of drug b/w compartment are called as micro constant or transfer constant.

- Relationship b/w hybrid & micro constants are given as

$$\alpha + \beta = k_{12} + k_{21} + k_E$$

$$\alpha \beta = k_{21} k_E$$

$$C_c = Ae^{-\alpha t} + Be^{-\beta t}$$

C_c = Distribution exponent + Elimination

$$A = \frac{X_0}{V_c} \left[\frac{k_{21} - \alpha}{\beta - \alpha} \right] = C_0 \left[\frac{k_{21} - \alpha}{\beta - \alpha} \right], \quad \text{exponent } B = \frac{X_0}{V_c} \left[\frac{-k_E - \beta}{\alpha - \beta} \right] = C_0 \left[\frac{k_E - \beta}{\alpha - \beta} \right]$$

Determination of pharmacokinetic parameters after I.V. Bolus -

$$C_0 = A + B$$

$$k_E = \frac{\alpha \beta C_0}{AB + \beta \alpha}$$

$$K_{12} = \frac{AB(\beta - \alpha)^2}{C_0(AB + \beta \alpha)}$$

$$K_{21} = \frac{\beta \alpha + B \alpha}{C_0}$$

k_E = rate constant for drug elimination from the central compartment

β = rate constant for drug elimination from the body

- Area under the plasma concentration time curve (AUC) can be obtained

$$AUC = \frac{A}{\alpha} + \frac{B}{\beta}$$

- The apparent Volume of central compartment (V_c) is given as

$$V_c = \frac{X_0}{C_0} = \frac{X_0}{k_E AUC}$$

- ⇒ The apparent volume of peripheral compartment (V_p) is given as

$$V_p = \frac{V_c K_{12}}{K_{21}}$$

Apparent Volume

$$V_{dss} = V_c + V_p$$

$$V_{diluted} = \frac{X_0}{\beta \text{ AUC}}$$

Total Systemic clearance

$$C_{IT} = \beta V_d$$

Urinary excretion

$$\frac{dx_u}{dt} = k_e V_c$$

Rate of excretion of unchanged drug in urine

$$\frac{dx_u}{dt} = k_e A e^{-\alpha t} + k_e B e^{-\beta t}$$

Renal clearance is given

$$C_{LR} = k_e V_c$$

Method of Residuals -

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

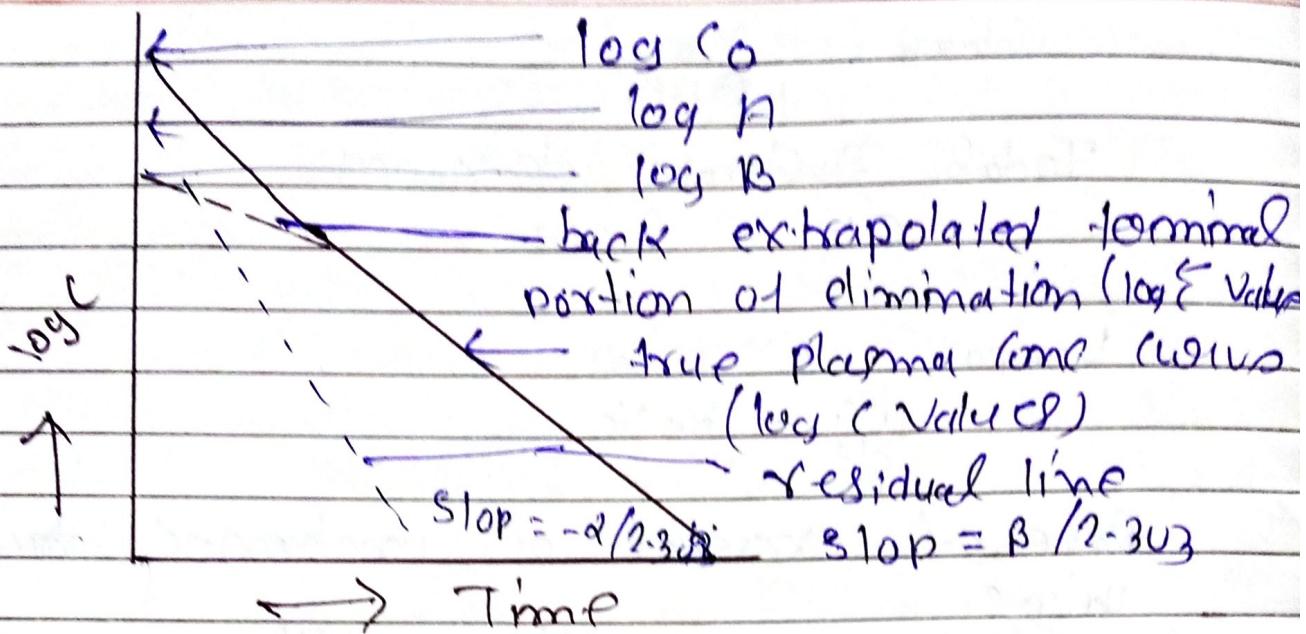
$$C_t = A e^{-\alpha t} + B e^{-\beta t}$$

The Rate constant $\alpha \gg \beta$ & hence the term $e^{-\alpha t}$ approaches zero much faster than does $e^{-\beta t}$.

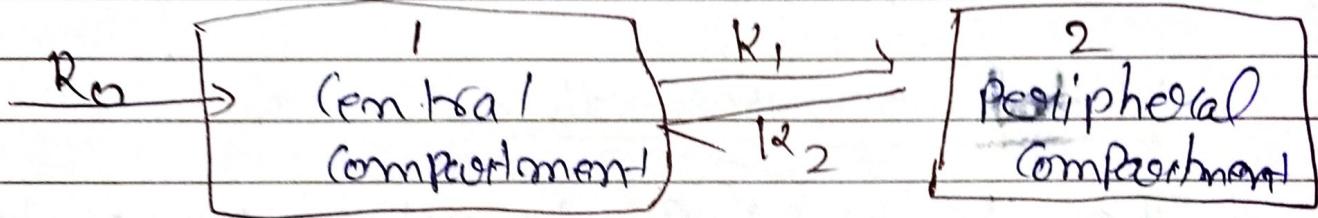
$$\leftarrow \Sigma = B e^{-\beta t}$$

log form

$$\log \underline{C} = \log B = \frac{\beta t}{2-303}$$



Two Compartment open model
I.V. infusion

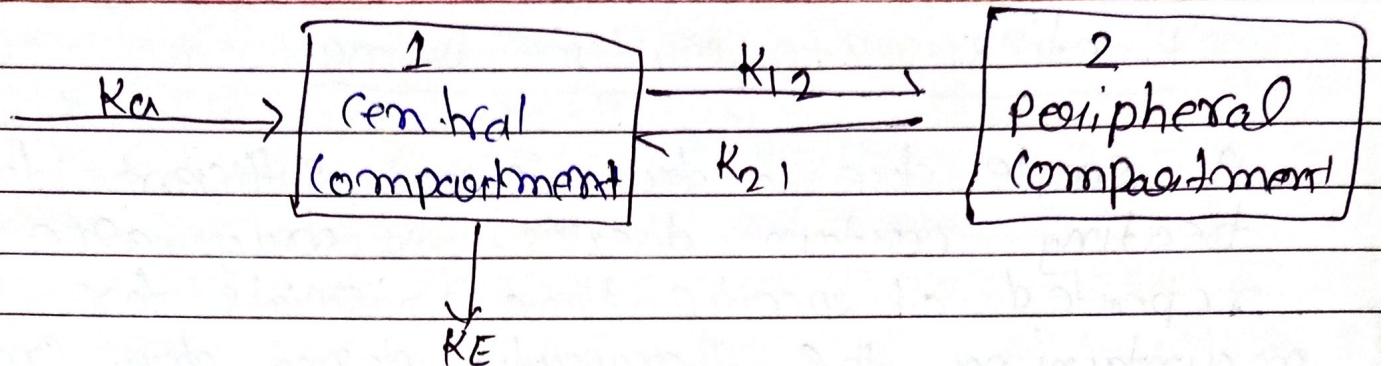


$$C = \frac{R_0}{V_c K_E} \left[1 + \left(\frac{K_E - \beta}{\beta - \alpha} \right) e^{-\alpha t} + \left(\frac{K_E - \alpha}{\alpha - \beta} \right) e^{-\beta t} \right]$$

$$C_{ss} = \frac{R_0}{V_d \beta} = \frac{R_0}{CIT}$$

~~$$X_{0,L} = C_{ss} V_c = \frac{R_0}{K_E}$$~~

Two Compartment open model -
Extravascular Administration



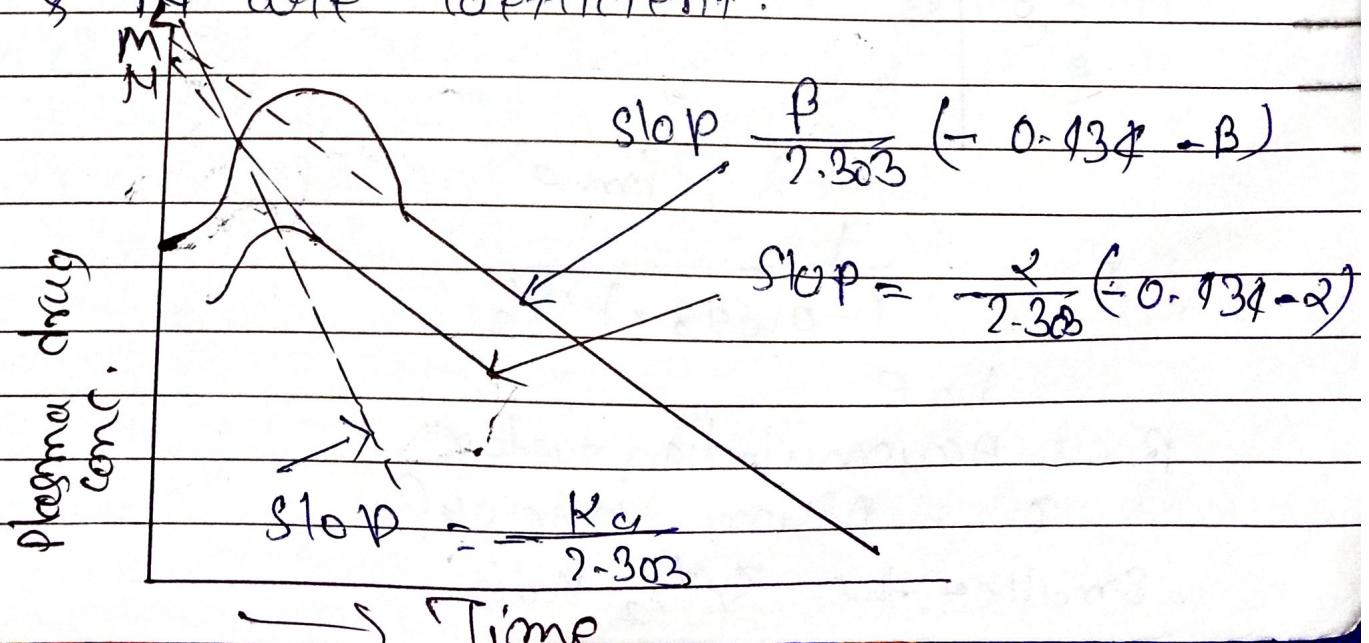
For a drug that enters the body by a first order absorption process and distributed according to two compartment model, the rate of change in drug conc in the central compartment is described by 3 exponents an absorption exponent, & the 2 usual exponents that describe drug disposition

The plasma conc. at any time t is given by equation

$$C = N e^{-K_a t} + L e^{-R t} + m e^{-B t}$$

C = Absorption exponent + Distribution exponent.
+ Elimination exponent.

Where K_a , R & B have usual meaning L, m
& M are coefficient.

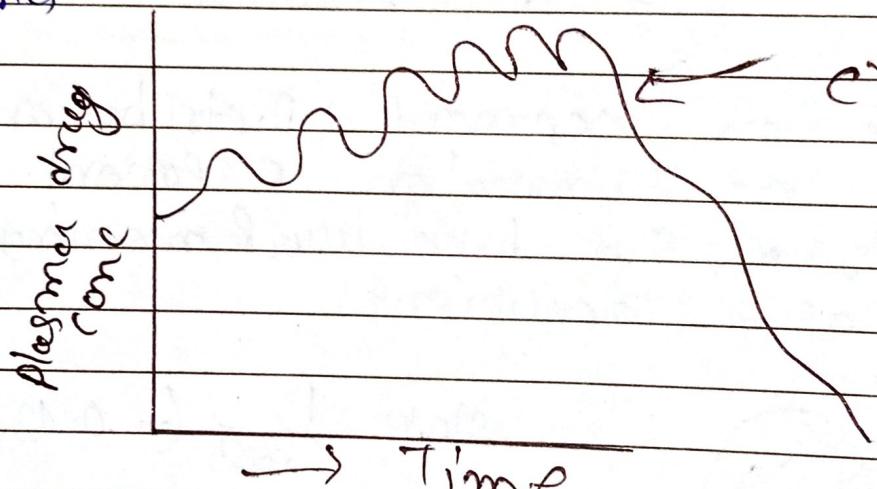


Kinetics of multiple Dosing -

A single dose of drug is not sufficient for treating certain diseases. So drug are repeated at specific time intervals for maintaining the therapeutic plasma drug conc throughout the treatment period.

The objective of drug treatment is to achieve & maintain plasma drug conc. within the therapeutic range with minimum fluctuations.

When the first dose is administered in an oral multiple dosing regimen the plasma drug conc rises & reaches the peak & then declines -



$$R = \frac{1}{(1 - e^{-\frac{\tau}{t_1}})^{\frac{1}{t_1}}}$$

R = Accumulation factor

τ = Dosing interval

Smaller the τ/t_1 ratio .

Average steady state plasma drug conc depends

- (1) Maintenance dose (X_0)
- (2) Fraction of the dose absorbed (F)
- (3) Dosing interval (T)
- (4) Clearance (Cl)

$$C = \frac{F \cdot X_0}{Cl \cdot T}$$

$$C = \frac{1.44 \cdot F \cdot X_0 \cdot t_{1/2}}{V_d \cdot T} = \frac{AUC}{t}$$

V_d = Volume of distribution

AUC = Area under the plasma drug conc. - time curve after single maintenance dose.

$$X_0 = \frac{C \cdot Cl \cdot T}{F} = \frac{C \cdot V_d \cdot T}{1.44 \cdot F + 1/2}$$

Steady state Drug levels

The time required to reach steady state depends on the drug's half-life. If $K_E > K_d$ the drug reaches the plateau in approximately five half-lives. This is called the plateau principle, which also means that K_E determines the rate at which the multiple dose steady state is reached.

maximum & minimum concentration during multiple dosing -

If n is the number of doses administered (max)

$C_{n\text{min}}$ obtained on multiple dosing after the n^{th} dose is given as

$$C_{n\text{min}} = C_0 \left[\frac{1 - e^{-nK_E T}}{1 - e^{-K_E T}} \right]$$

$$C_{n\text{min}} = C_0 \left[\frac{1 - e^{-nK_E T}}{1 - e^{-K_E T}} \right] e^{-K_E T} = C_{n\text{max}} e^{-K_E T}$$

\Rightarrow The min & max conc of drug in plasma at steady-state are given

$$C_{ss\text{max}} = \frac{C_0}{1 - e^{-K_E T}}$$

$$C_{ss\text{min}} = C_0 \frac{e^{-K_E T}}{1 - e^{-K_E T}} \cdot C_{ss\text{max}} e^{-K_E T}$$

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

- 1) Maintenance dose (X_0)
- 2) Fraction of dose absorbed (F)
- 3) Dosing interval (T)
- 4) Clearance (C_l) of drug

Calculation of loading & maintenance doses & their significance in clinical settings: —

A drug is therapeutically active when it attains the desired steady state in

five half-lives. However, if the drug is having a long half-life, it will take a longer time.

Such an initial dose or first dose intended to be therapeutic is termed priming or loading dose ($X_{0,L}$)

$$X_{0,L} = \frac{C_{ss} \cdot V_d}{F}$$

If V_d is not known the loading dose can be determined as

$$\frac{X_{0,L}}{X_0} = \frac{1}{(1 - e^{-K_a t}) (1 - e^{-K_E t})}$$

$$\frac{X_{0,L}}{X_0} = \frac{1}{1 - e^{-K_E t}} = R_{ar}$$

Loading Dose

The ratio of loading dose

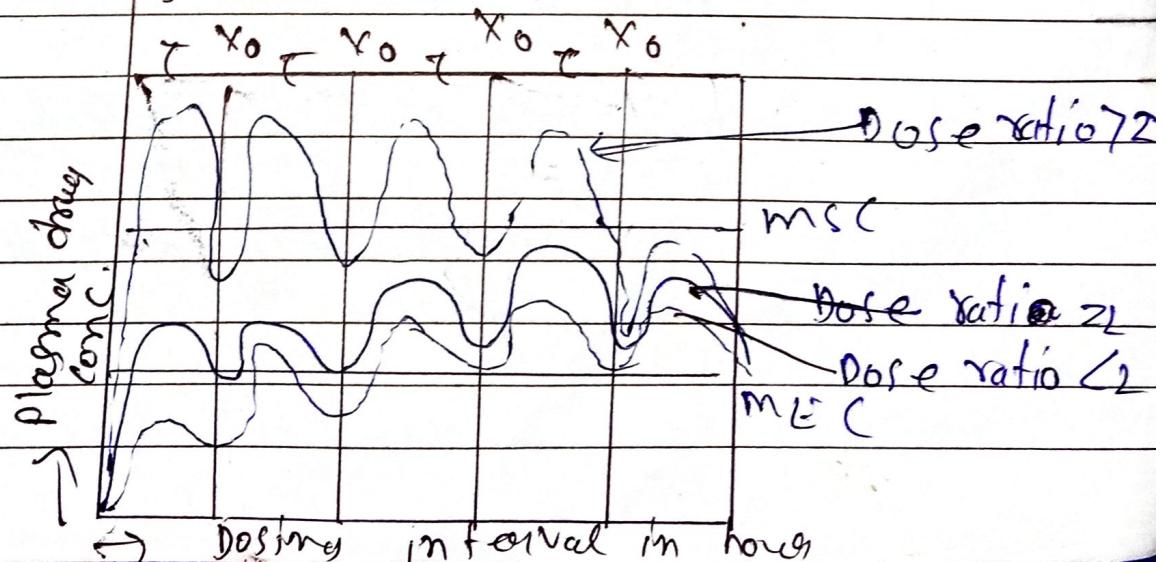
to maintenance dose ($X_{0,L}/X_0$) is termed dose ratio. As a rule when

1) $t = 1/2$ dose ratio = 2.0

2) $t > 1/2$ dose ratio < 2.0

3) $t < 1/2$ dose ratio > 2.0

loading dose $X_{0,L}$ maintenance dose X_0



maintainence of drug within therapeutic range

- 1) Drug therapeutic index
- 2) Drug half life &
- 3) Drug convenience

⇒ In drugs with short half-life (< 24 hours)
& narrow therapeutic index e.g.—
heparin, it is not easy to maintain

A drug with very long half-life
(> 24 hours e.g. Amlodipine, should be
given once in 24 hours.