Multi - compartment Model

(Delayed distribution Models).

→ 1- compt - models → pharmacokinetics of many drugs

→ Instantaneous distⁿ eg. decline in the amount of drug in the body ē time expressed by mono - exponential term (i.e - elimination).

→ Instantaneous distⁿ. is not truly possible for larger no. of drugs & drug distⁿ. is not mono. exponential but bi (or) multi - Exponential.

→ Becoz, body is composed of a heterogenous group of tissues Each ē diff. degree of blood flow & affinity for drug, so diffⁿ. ratio of Equi.

→ Assumptions:

1. Blood / plasma & highly perfused tissues such as brain, heart, lung, liver & kidneys as Central - compartment -
2. Other tissues ē similar distⁿ → pooled in Peripheral compt.
3. Intravenous admn. medications → introduced directly into Central Compt.
4. Irreversible drug elimination, either by hepatic bio - transformation or renal - excretion, takes place only from the Central compt.
5. Reversible distⁿ. betⁿ. Central & Peripheral compt.
6. After Eq. betⁿ (C) & (P) compt → Elimination of drug follows 1-order kinetics.
7. All rate process involving passage of drug in and out of the individual compt are 1- order process.

8. The peripheral compartment is usually inaccessible to direct measurement & is not a site of drug Elm (or) clearance.

⇒ Multi-compartment characteristics of a drug are best understood by giving it as I.V. bolus & observing the manner in which plasma conc. declines with time.

→ Two-compartment Open Model:

→ In this model, body tissues are classified into 2 categories

1. Central-compartment or compartment-1:

Comprising of blood & highly perfused tissues like Liver, Lungs, Kidneys; that equilibrate with the drug rapidly.

→ Elimination usually occurs from this compt.

2. Peripheral (or) Tissue cmpt. (or) Compt-2:

→ comprising of Poorly Perfused and Slow Equilibrating tissues i.e. muscles, Skin, adipose etc.

⇒ classification of a particular tissue: Ex: Brain → depends on ph. ch. Properties of drug.

a) A highly lipophilic drug (alcohol, nicotine, caffeine) can cross BBB → Brain as central compt.

b) Polar drugs, (β-lactum Antibiotics, aminoglycosides) cannot penetrate the BBB → Brain as peripheral compt.

→ The plasma concn. for a drug that follows a 2-compt. model declines biexponentially as the sum of 2 first-order processes i.e. distⁿ. & Elmn.

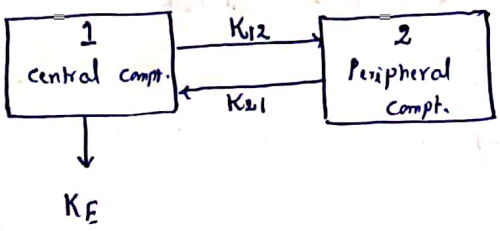
⇒ Depending upon the compt. from which the drug is Eliminated, the 2-compt. model is categorized into 3 types,

1. 2-compt model is Elimination from central compt.
2. " " " peripheral compt.
3. " " " both the compt.

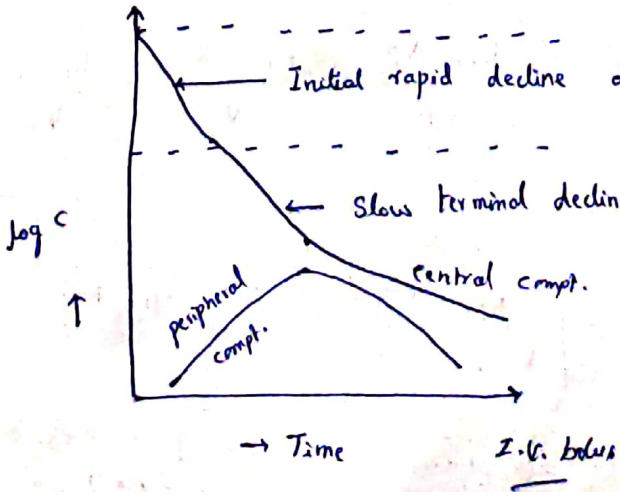
Two-compartment-Open Model:

Intravenous Bolus Administration:

Model:



→ After I.V. bolus → decline in plasma concn is biexponential indicating the presence of 2 disposition Process viz. distribution and elimination.



Central compt:

Initially, the concentration of drug in the central compartment declines rapidly, this is due to distⁿ. of drug from the central compt. to Peripheral compt. ⇒ Distribution Curve.

→ After some time, a Pseudo-distⁿ. Eq. betⁿ. 2 compts; Subsequent loss of drug from the Central compt. is slow, mainly due to Elimination. This second, slower rate-process is called as post-distribution (or) Elimination phase.

Peripheral compt:

(Drug conen, first increases (distⁿ) & reaches maximum and declines (post distⁿ / elm).

⇒ K_{12}, K_{21} → first-order distⁿ. rate constants.

⇒ rate of change in drug conen

$$\frac{dc}{dt} = \text{rate in} - \text{rate out}$$

⇒ rate of change in drug in central compt,

$$\frac{dc_c}{dt} = K_{21} \cdot C_p - K_{12} \cdot C_c - K_E \cdot C_c$$

⇒ $V_d = \frac{X}{C}$; $C = \frac{X}{V_d}$,

X_c, X_p → amt. of drug

V_c, V_p - apparent vol. of dist

$$\frac{dc_c}{dt} = \frac{K_{21} \cdot X_p}{V_p} - \frac{K_{12} \cdot X_c}{V_c} - \frac{K_E \cdot X_c}{V_c}$$

upon Integration.

$$C_c = \frac{X_0}{V_c} \left[\left(\frac{K_{21} - \alpha}{\beta - \alpha} \right) \cdot e^{-\alpha t} + \left(\frac{K_{21} - \beta}{\alpha - \beta} \right) \cdot e^{-\beta t} \right] \rightarrow \text{Eq - (1)}.$$

X_0 → I.V. bolus dose ; α, β → hybrid 1-order const. ↳ depends on K_{12}, K_{21}, K_E.

→ Rate of change in drug concn. in Peripheral compt.

$$\frac{dC_p}{dt} = K_{12} \cdot C_C - K_{21} \cdot C_p.$$

$$= \frac{K_{12} \cdot X_C}{V_C} - \frac{K_{21} \cdot X_p}{V_p}$$

upon Integration.

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

K_{12}, K_{21} → micro constants (or) transfer const.

→ Relation bet^n hybrid (or) micro-constants.

$$\alpha + \beta = K_{12} + K_{21} + K_E.$$

$$\alpha \cdot \beta = K_{21} \cdot K_E.$$

→ Eq ① in Simplified form.

$$C_C = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t}$$ A, B → hybrid constants.

C_C = distribution exponent + Elimination exponent.

$$A = \frac{X_0}{V_C} \left[\frac{K_{21} - \alpha}{\beta - \alpha} \right] \Rightarrow C_0 \left[\frac{K_{21} - \alpha}{\beta - \alpha} \right]$$

$$B = \frac{X_0}{V_C} \left[\frac{K_{21} - \beta}{\alpha - \beta} \right] \Rightarrow C_0 \left[\frac{K_{21} - \beta}{\alpha - \beta} \right].$$

C_0 → plasma drug concn. immediately after I.V. injection.

Method of Residuals: → To resolved into individual exponents.

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

→ Initial rapid distn >> terminal elimination.

$\alpha >> \beta$; hence $e^{-\alpha t}$ approaches zero much fast than $e^{-\beta t}$.

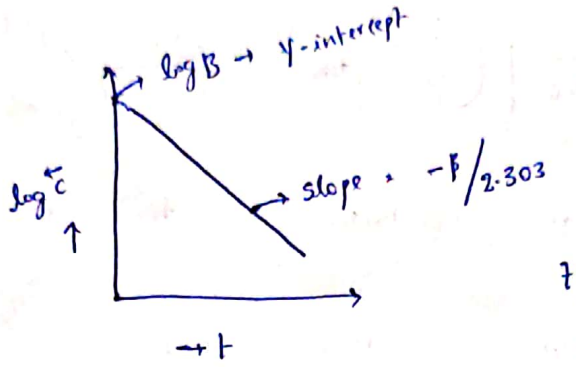
→ Equation reduces to

$$\overleftarrow{C} = B \cdot e^{-\beta t}$$

log form:

$$\log \overleftarrow{C} = \log B - \frac{\beta t}{2.303}$$

$\overleftarrow{C}$ → back Extrapolated plasma conen. values.



$t_{1/2} = 0.693/\beta$.

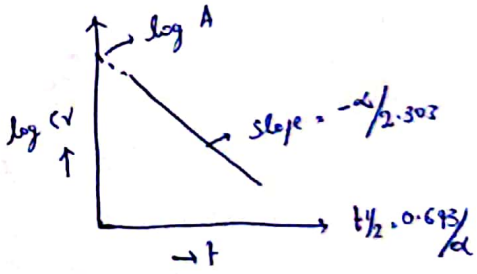
→ Substraction of Extrapolated plasma conen. values from true plasma conen. yields a residual conen. value C_r.

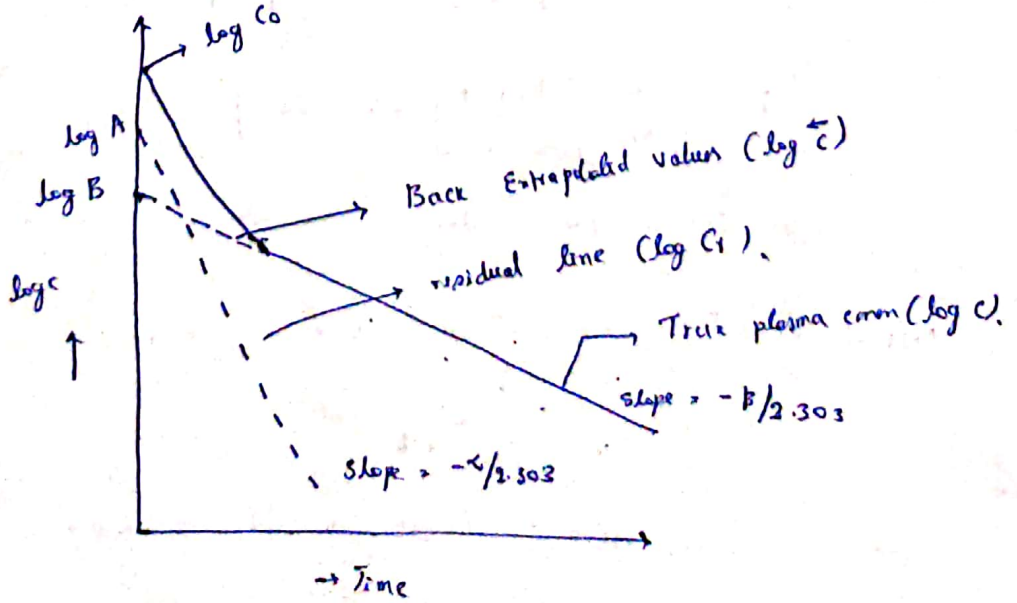
$$C_r = C - \overleftarrow{C}$$

$$C_r = A \cdot e^{-\alpha t}$$

log form:

$$\log C_r = \log A - \frac{\alpha t}{2.303}$$





→ Assessment of pharmacokinetic Parameters:

→ By method of residuals → A, B, α, β → values required.

→ other parameters → K_{12}, K_{21}, K_E (proper substitution).

$$C_0 = A + B$$

$$K_E = \frac{\alpha \cdot \beta \cdot C_0}{A\beta + B\alpha}$$

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

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

→ K_E → Elimination rate const from the central compt.

β → " " " - Entire Body.

over-all Elm. t½, calculated from β.

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

→ Apparent vol. of central compt V_c,

$$V_c = \frac{X_0}{C_0} = \frac{X_0}{K_E \cdot AUC}$$

→ Apparent vol. of peripheral compt, V_p,

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

→ At steady state

$$V_{d,ss} = V_c + V_p.$$

$$V_{d,area} = \frac{X_0}{\beta \cdot AUC}$$

→ Total Systemic clearance: $Cl_T = \beta \cdot V_d$.

Renal clearance, $Cl_R = K_e \cdot V_c$.

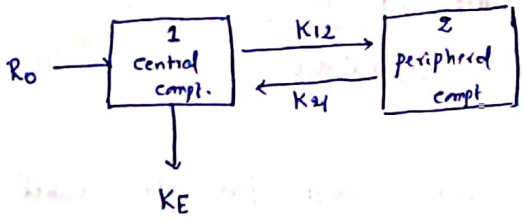
$\Rightarrow$ Pharmacokinetic parameters $\rightarrow$ calculated by urinary excretion data,

$$\frac{dX_u}{dt} = K_e \cdot V_c .$$

$\rightarrow$ rate of excretion,

$$\frac{dX_u}{dt} = K_e \cdot A \cdot e^{-\alpha t} + K_e \cdot B \cdot e^{-\beta t}.$$

B. Intravenous Infusion:



$\rightarrow$ The plasma (or) central compt. conc^n, I.V. infusion (Zero-order),

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

$\rightarrow$ At steady-state, the second & third term in bracket becomes Zero,

$$C_{SS} = \frac{R_0}{V_c \cdot K_E}$$

Now, $V_c \cdot K_E = V_d \cdot \beta$;

$$C_{SS} = \frac{R_0}{V_d \cdot \beta} = \frac{R_0}{Cl_T}.$$

$\rightarrow$ The loading dose $X_{0.L}$.

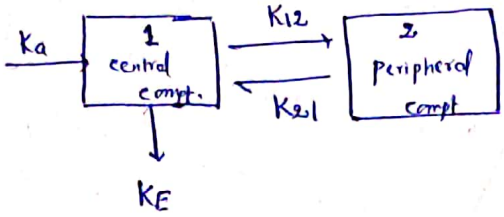
$$X_{0.L} = C_{SS} \cdot V_c = \frac{R_0}{V_c \cdot K_E} \cdot V_c$$

$$X_{0.L} = \frac{R_0}{K_E}.$$

→ Two - Compartment - Open Model:

Extra Vascular Administration: - First-order Absorption

Model:



→ The rate of change in drug conc. in central compt is described by

3 exponents → Absorption exponent

Distribution

Elimination

→ The plasma conc:

$$C = N \cdot e^{-ka \cdot t} + L \cdot e^{-\alpha t} + M \cdot e^{-\beta t}.$$

C : Abs Expt + Dist^n + Elm.

L, M, N — Co. efficients.

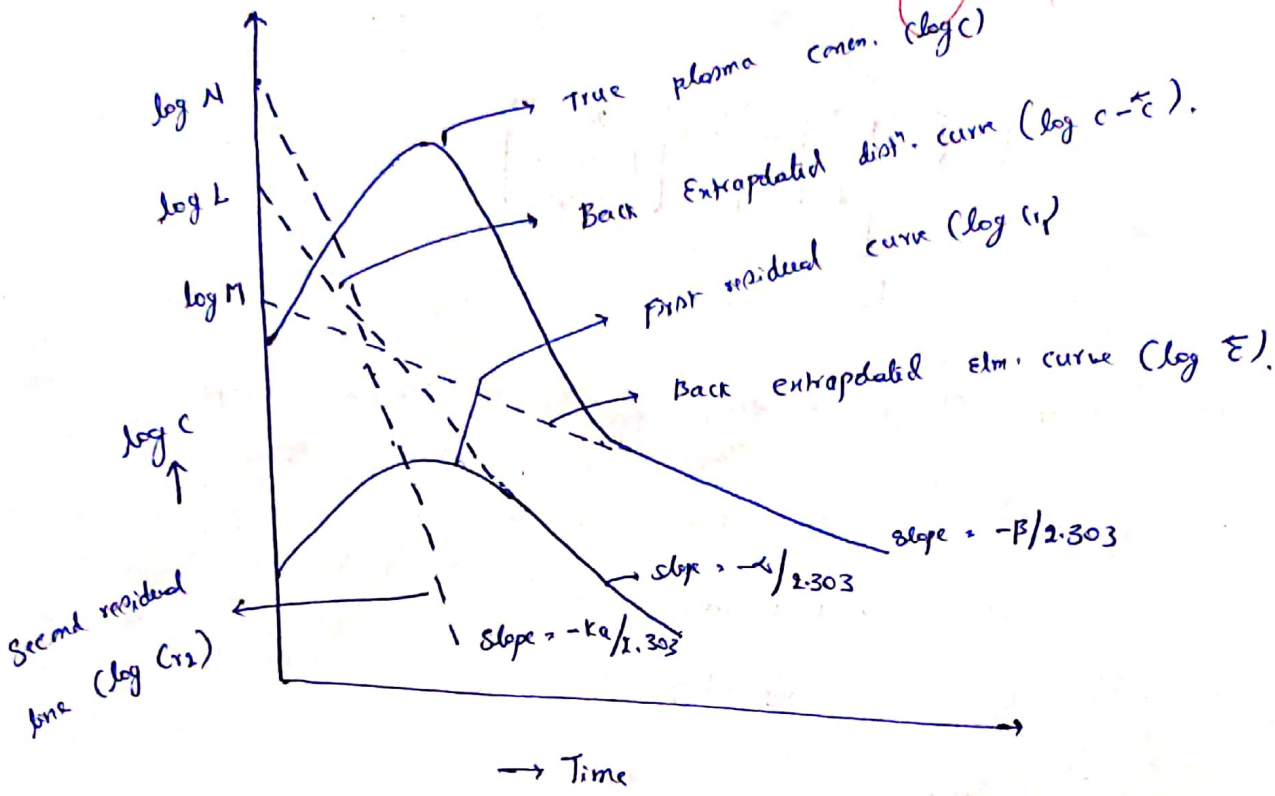
1) → method of residuals. $Ka > \alpha > \beta$.

2) Loo - Riegelman method → Ka estimation,

(contrast to wagner - nelson method).

→ Method requires plasma - time data profiles after oral and I.V. admn. of the drug to the same subject at diff times.

→ The method can be applied to drugs that distribute in any number of compartment.



Three- compartment model: