2/9/2020

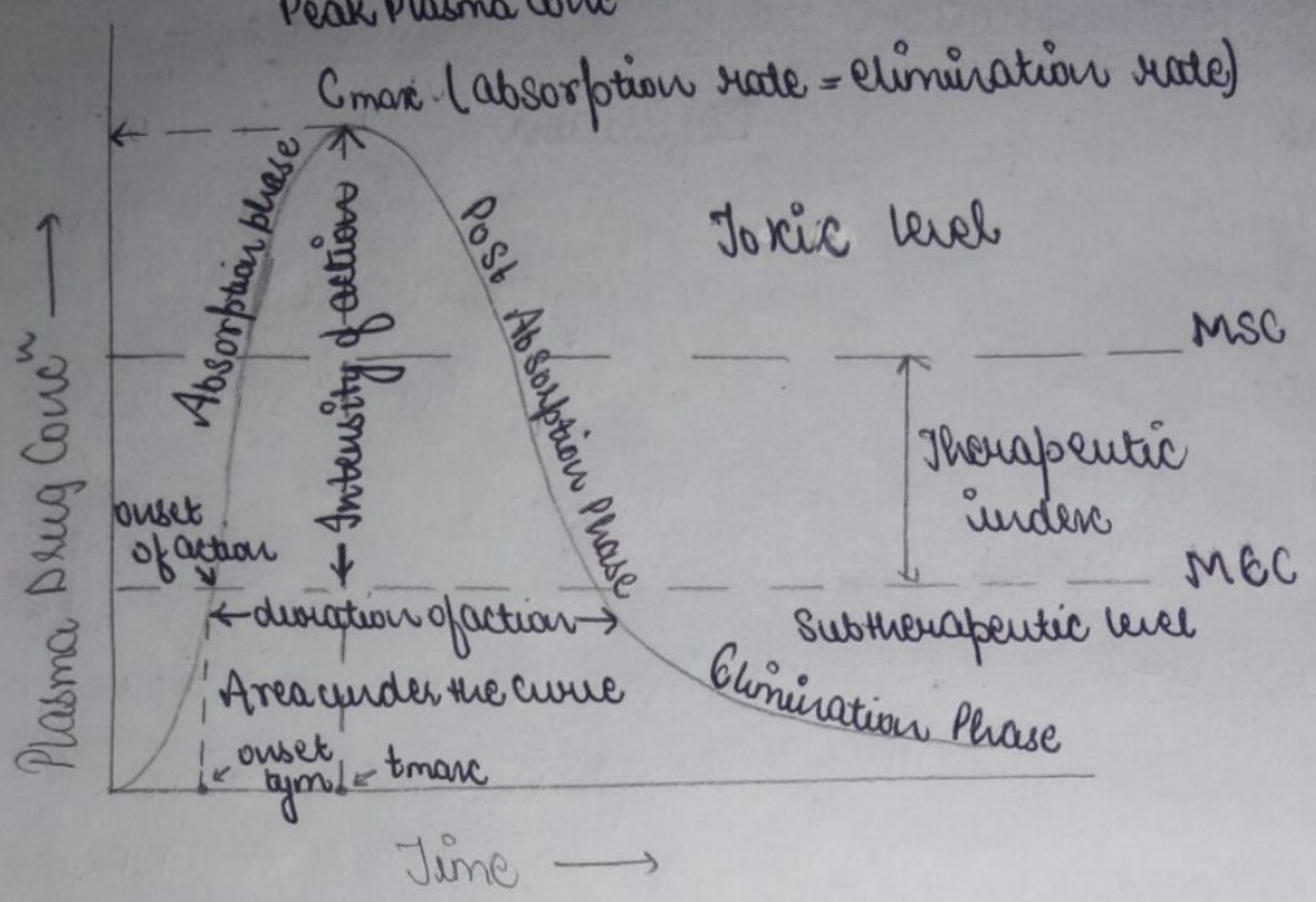
Unit-3
Pharmacokinetics

*: Definition & Introduction to Pharmacokinetics -

S.NO.	Terms	Definition
(1.)	Dosage Regimen	The frequency of administration of a drug in a particular dose.
(2.) V.V Imp	Therapeutic Conc" range or Therapeutic window	The "plasma drug conc" between the two limits.
(3.) V.V Imp	Pharmacokinetics	It is defined as the kinetics of drug absorption, distribution, metabolism & excretion (ADME) & their relationship with the pharmacological, therapeutic or toxicological response in human & animals.
(4.)	Clinical Pharmacokinetic	The application of pharmacokinetic principles in the safe & effective management of individual patients.
(5.)	Population Pharmacokinetic	The study of pharmacokinetic differences of drugs in various population groups.
(6.)	Toxicokinetics	The application of pharmacokinetic principles to the design, conduct & interpretation of drug safety evaluation studies.

Plasma Drug Conc" Time- profile -

A direct relationship exists between the conc" of drug at the biophase (site of action) & the conc" of drug in plasma.



Types of Parameters -

There are two types of parameters :

(1) Pharmacokinetic parameter.

(2) Pharmacodynamic parameter.

→ Pharmacokinetic Parameter -

The 3 important pharmacokinetic parameters are :

(1) Peak Plasma Conc" (Cmax)-

" • The point of maximum conc" of drug in plasma is called as the peak & the conc" of drug at is peak is known as Peak Plasma Conc". "

• It is also called Peak height conc" & maximum drug conc".

• Cmax is expressed in mcg/ml.

• The peak plasma level depends upon - • Dose administered.
• Rate of absorption.
• Rate of elimination.

- The portion of curve to the left of the peak represents absorption phase.
- The section of curve to the right of the peak generally represents elimination phase.
- Peak concentration is often related to the intensity of pharmacological response & should ideally be above Minimum Effective Concentration (MEC) but less than the Maximum Safe Conc". (MSC).

(2) Time of Peak Conc" (tmax)-

- "The time of drug to reach peak conc" in plasma (after extravascular administration) is called as the time of peak conc"."
- tmax is expressed in hours.

(3) Area under the Curve (AUC)-

- "It represents the total integrated area under the plasma level-time profile & expresses the total amount of drug that comes into the systemic circulation after its administration."
- AUC is expressed in mcg/ml X hours.

→ Pharmacodynamic Parameter -

The various pharmacodynamic parameters are :

(1) Minimum Effective Conc". (MEC) -

- "It is defined as the minimum conc" of drug in plasma required to produce the therapeutic effect."
- The conc" of drug below MEC is said to be in the subtherapeutic level
- In case of antibiotics, the term Minimum Inhibitory Conc" (MIC) is used. It describes the minimum conc" of antibiotic in plasma required to kill or inhibit the growth of microorganisms.

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(2) Maximum Safe Conc" (MSC) -

- It is also called Minimum toxic conc" (MTC).
- "It is the conc" of drug in plasma above which adverse or unwanted effects are precipitated."
- Conc" of drug above MSC is said to be in the Toxic level.

(3) Onset Tym -

"It is the time required for the drug to start producing pharmacologic response."

(4) Onset of Action -

"The beginning of pharmacologic response is called as onset of action".

(5) Duration of Action -

"The tym period for which the plasma conc" of drug remains above the MEC level is called as duration of drug action".

(6) Intensity of Action -

"It is the maximum pharmacological response produced by the peak plasma conc" of drug."

- It is also called the peak response.

(7) Therapeutic Range -

"The drug conc" between MEC & MSC represents the therapeutic range."

- It is also known as Therapeutic window.

(8) Therapeutic Index -

"The ratio of MSC to MEC is called as therapeutic index."

"It is also defined as the ratio of dose required to produce toxic or lethal effects to dose required to produce therapeutic effect."

∴ Rate, Rate Constants & Order of Reaction :-

The velocity with which a reaction or a process occurs is called as **rate**.

The manner in which the conc^{n} of drug influences the rate of reaction or process is called as **the order of reaction**.

Consider the following reaction -

$$\text{Drug A} \longrightarrow \text{Drug B} \quad -(1)$$

The rate of forward reaction :

$$\frac{-dA}{dt} \quad -(2)$$

Negative sign indicates that the conc^{n} of drug A decreases with time 't'.

(Note : The rate of reaction is determined by decreases in Conc^{n} of drug A with time 't')

If 'C' is the conc^{n} of drug A, the rate of decrease in of drug A as it is changed to B can be described by a eq^{n} -

$$\frac{dC}{dt} = -k\,C^{n} \quad -(3)$$

where, k = Rate Constant
n = Order of reaction
C = Conc^{n} of A

If, n = 0 Zero order reaction
n = 1 First order reaction
n = 2 Second order reaction
& so on - - - - -

Zero-order kinetics (Constant Rate process):

If $n=0$ then

$$\frac{dC}{dt} = -k_0 C^0 \quad -(4)$$

(where, C^0 = the conc^n of total zero)

$$\frac{dC}{dt} = -k_0 \quad -(5)$$

(where k_0 = zero order rate constant).

"Zero Order process can be defined as the one whose rate is independent of the conc^n of drug undergoing reaction i.e. the rate of reaction cannot be increased further by increasing the conc^n of reactants."

Rearranged the eq^n:

$$dC = -k_0 dt \quad -(6)$$

Integration the eq^n (6):

$$\int_{C_0}^{C} dC = -k_0 \int_0^t dt$$

on solving,

$$C - C_0 = -k_0 t \quad -(7)$$

$$C = C_0 - k_0 t \quad -(8)$$

(where, C_0 = Conc^n of drug at $t=0$,
C = Conc^n of drug yet to undergo rx^n at time 't')

Eq^n (8) shows that of a straight line eq^n & states that conc^n of reactant decreases linearly with time.

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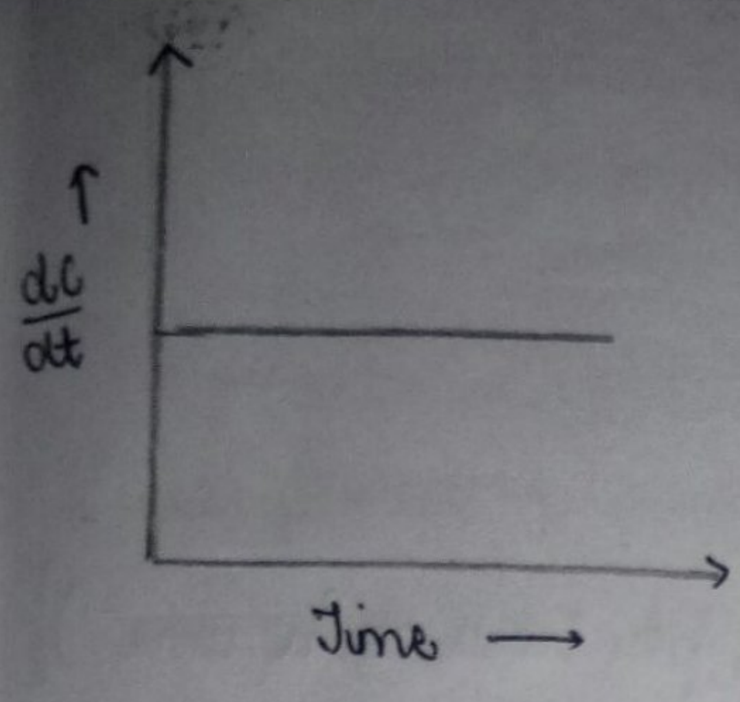
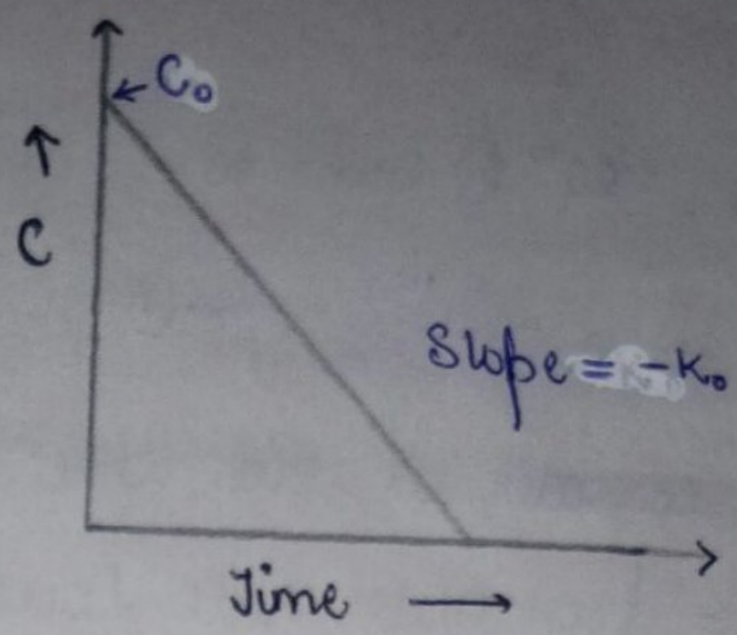




Graph of Zero order kinetic

Zero-order Half life ($t_{1/2}$):

"Half life ($t_{1/2}$) or Half-time is defined as the time period required for the Conc" of drug to decrease by one-half."

When $t = t_{1/2}$, $C = \frac{C_0}{2}$. Put the value in eq" (8)

$$C = C_0 - K_0 t \quad -(8)$$

$$\frac{C_0}{2} = C_0 - K_0 t_{1/2} \quad -(9)$$

on solving, $\frac{C_0}{2} - C_0 = -K_0 t_{1/2}$

$$-\frac{C_0}{2} = -K_0 t_{1/2}$$

$$t_{1/2} = \frac{C_0}{2K_0} \quad (10) \text{ (where 1/2 or 0.5)}$$

or $$t_{1/2} = \frac{0.5 C_0}{K_0} \quad \text{—— (11)}$$

Examples of Zero order :

(1) Metabolism, Protein drug binding / enzymes or Carrier mediated transport under saturated condition.

(2) Drug as constant rate i.v. infusion

(3) Controlled drug delivery i.e. implants, osmotic pressure, etc.

First Order Kinetics :

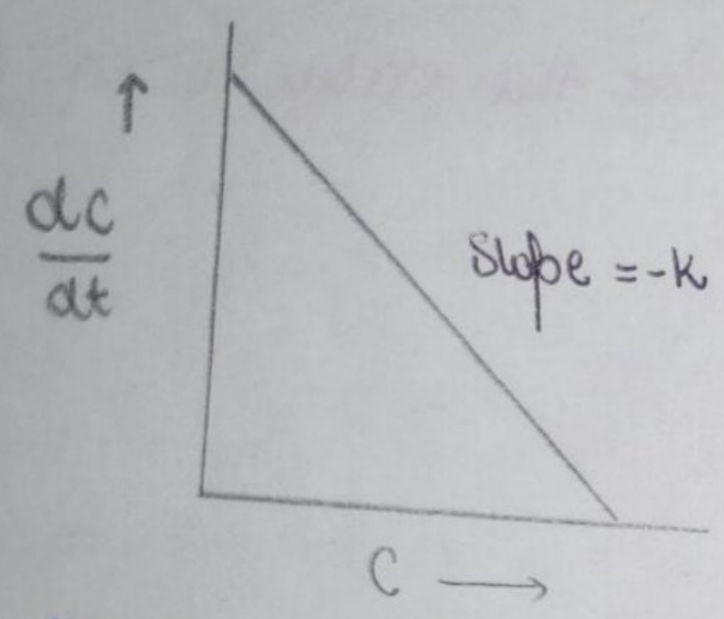
If $n=1$, eq^n ① Come to -

$$\frac{dC}{dt} = -kC^1 \quad -①$$

($n=1$ consider as one Conc^n).

[where, k = first order rate constant (per hour or in time^{-1})]

"first order process is the one whose rate is directly proportional to the Conc^n of the drug undergoing rx^n i.e. greater the Conc^n, faster the reaction."



Graph of first order kinetics

Rearranged the eq^n ① :

$$\frac{dC}{dt} = -kC$$

$$\frac{dC}{C} = -k\,dt \quad -②$$

Integrating the eq^n. ② :

$$\int_{C_0}^{C} \frac{dC}{C} = -k \int_0^t dt$$

$$C - C_0 = -kt$$

$$C = C_0 - kt$$

$$\ln C = \ln C_0 - kt \quad -③$$

Exponential form of eqⁿ ③

$$C = C_0 e^{-kt} \quad -④$$

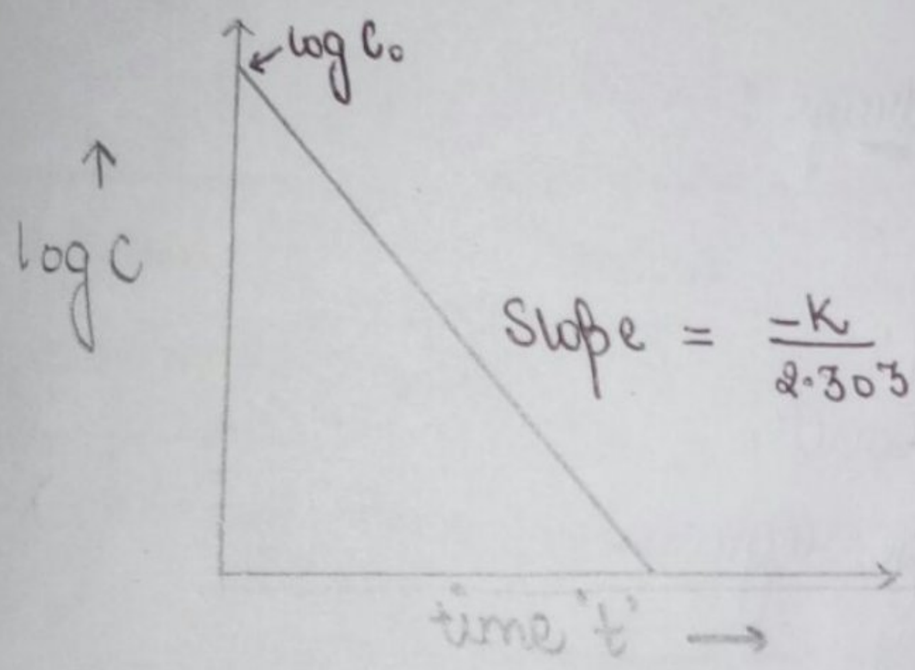
where, e = natural log base.

* First order process is also called as Monoexponential rate process.

Since, $\ln = 2.303 \log$, eqⁿ - ③ becomes -

$$\log C = \log C_0 - \frac{kt}{2.303} \quad -⑤$$

or $\log C = \log C_0 - 0.434 kt \quad -⑥$



Semilog graph of first-order kinetics

First-order Half life :

$$t = t_{1/2} \quad , \quad C = \frac{C_0}{2}$$

$$t_{1/2} = \frac{2.303}{k} \log \frac{C_0}{C}$$

$$= \frac{2.303}{k} \log \frac{C_0}{\frac{C_0}{2}}$$

$$= \frac{2.303}{k} \log 2 \quad (\text{where } \log 2 = 0.3010)$$

$$= \frac{2.303}{k} . 0.3010$$

$$t_{1/2} = \frac{0.693}{k} \quad — ⑦$$

Example -

Most pharmacokinetic parameter i.e. absorption, distribution & elimination.

∴ Pharmacokinetic Models -

Models are used to describe changes in drug conc" in the body with time.

"A model is a hypothesis that employes mathematical terms to concisely describe quantitative relationship."

"A pharmacokinetic Parameters provide concise means of expressing mathematically or quantitatively, the time course of drug throughout the body."

Application of Pharmacokinetic drugs :

(1) Behaviour of drugs in patient.
(2) Predicting the conc" of drug.
(3) Predicting the multiple dose conc".
(4) Calculating the optimum dosage regimen.
(5) Evaluating the risk of toxicity.
(6) Correlating plasma drug conc".
(7) Evaluating the bioequivalence / bioequivalence Studies.
(8) Explaining drug interaction.

Types of Pharmacokinetic Models :

The three different approaches to Pharmacokinetic analysis of experimental data are -

(i) Compartment Modeling
(ii) Non-compartment Modeling (Distributed parameter models).
(iii) Physiological Modeling

→ Compartment Model –

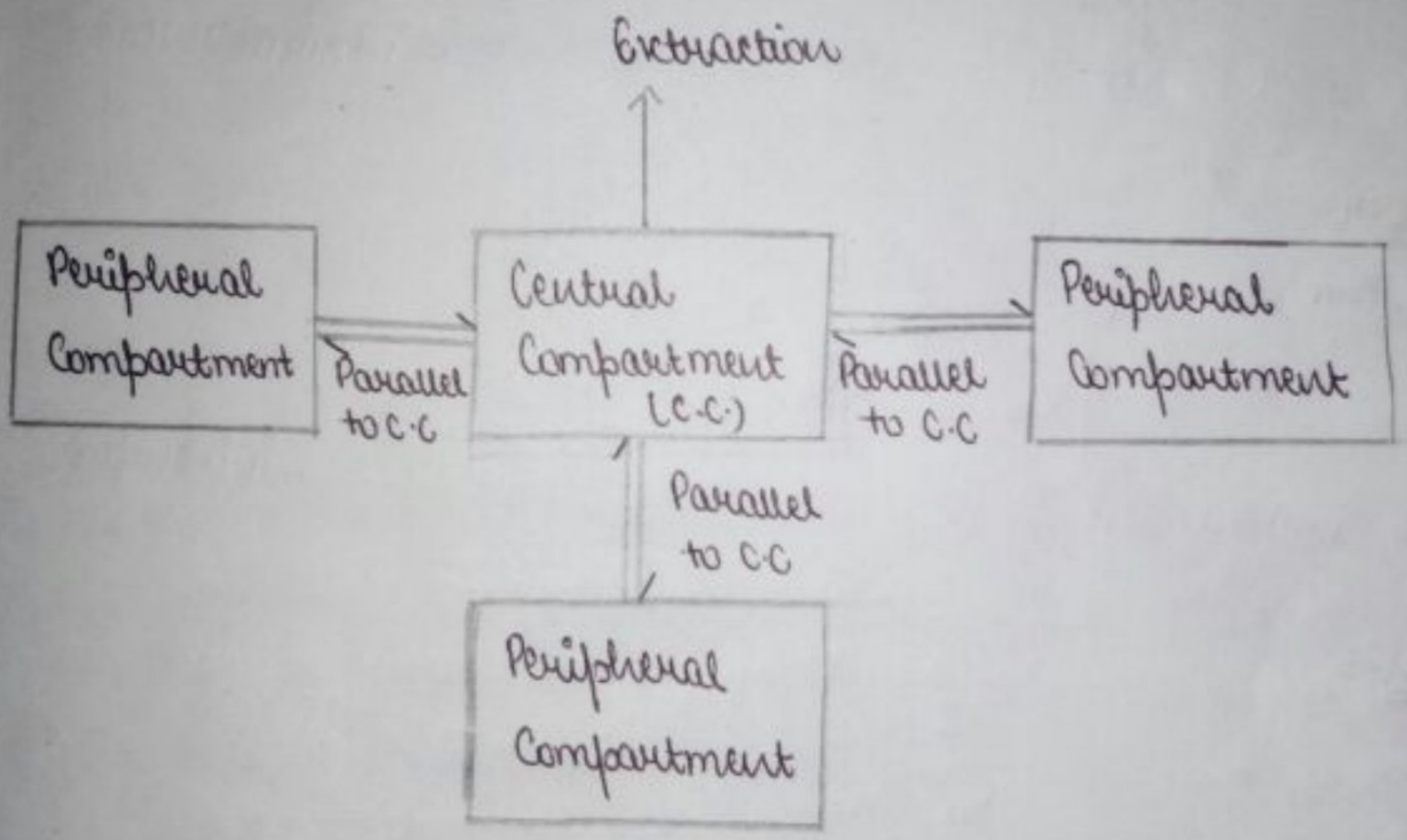
Compartmental analysis is the traditional & most commonly used approach to pharmacokinetic characterization of a drug.

Compartment Models are divided into two categories:

(a) Mammillary Model
(b) Catenary Model

⇒ Mammillary Model:–

It consist of one or more peripheral compartments connected to the central compartment.

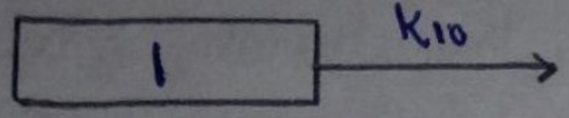


- Central Compartment comprises of plasma & highly perfused tissues such as lungs, liver, kidneys, etc.
- Peripheral Compartment or Tissue Compartments are those with low vascularity & poor perfusion. Distribution of drugs to these components is through blood.

Various Mammillary Compartment Models:

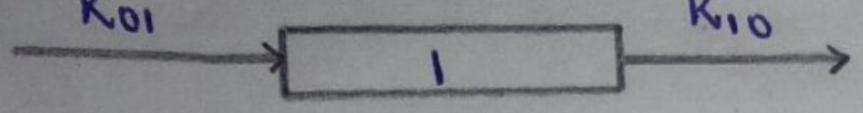
The rate Constant K_{01} is basically K_a, the first order absorption rate constant & K_{10} is K_E, the first order elimination rate Constant

Model-1



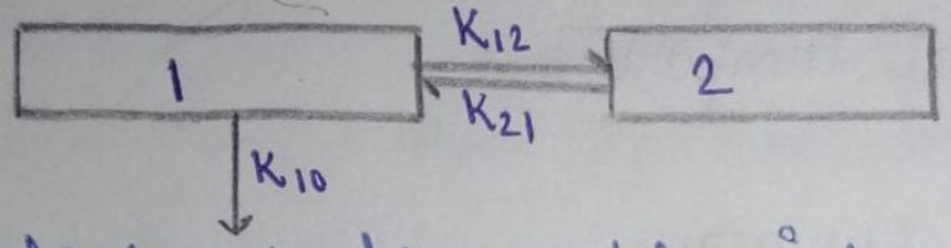
One compartment open model, intravenous administration

Model-2



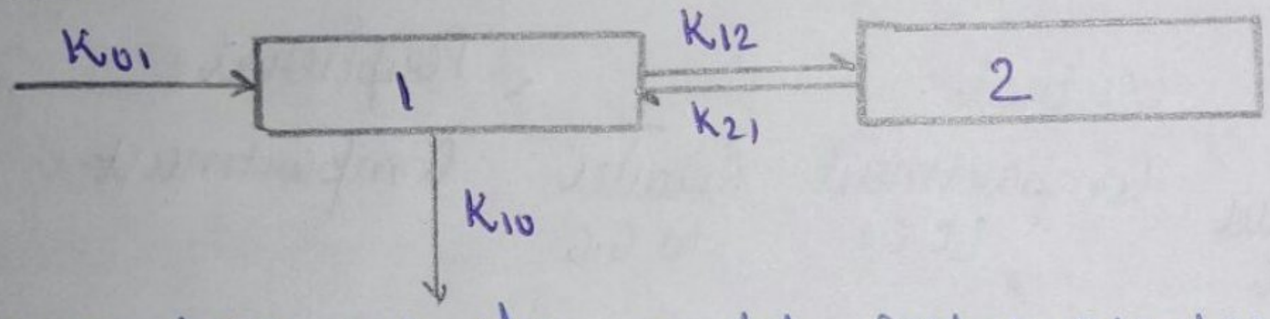
one-compartment open model, extravascular administration (oral, rectal, etc).

Model-3



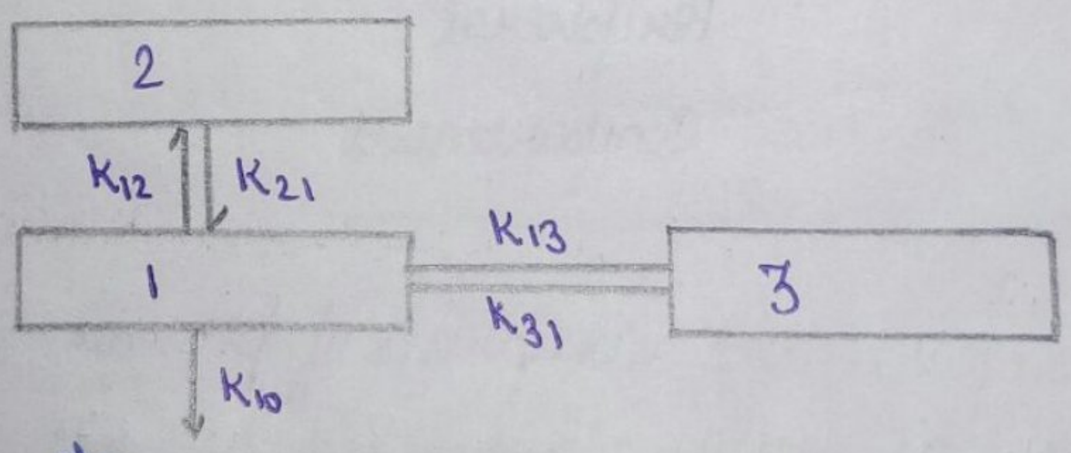
Two compartment open model, intravenous Administration

Model-4



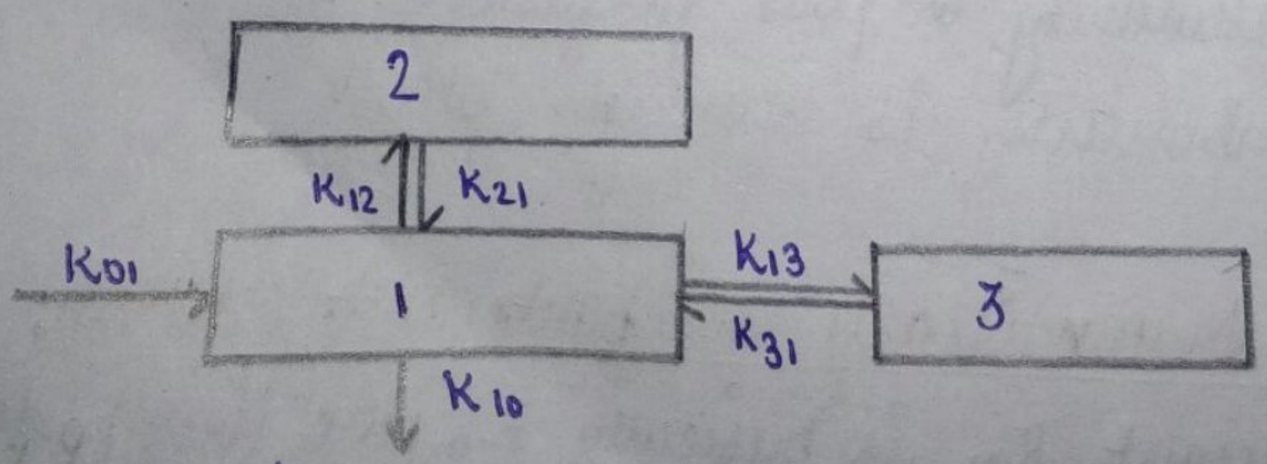
Two compartment open model, extravascular administration

Model-5



Three compartment open model, intravenous administration

Model-6



Three compartment open model, extravascular administration.

⇒ Catenu

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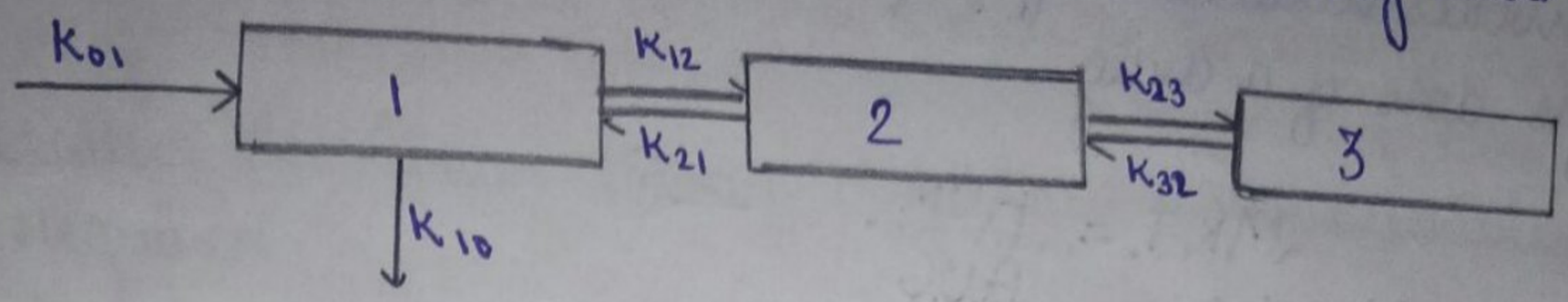
⇒ Catenuary Model :-

In this model, the compartments are joined to one another in a series like compartments of a train. It is rarely used.



Advantages -

(1) It is a simple & flexible approach & widely used.
(2) It gives a visual representation of various rate process.
(3) It shows many rate constants are necessary.
(4) It enables monitoring of drug Conc^n changes with time
(5) It is useful in predicting drug Conc^n- time profile.
(6) It is important in the development of dosage regimens.
(7) It is useful in relating plasma drug levels to therapeutics & toxic

Disadvantages -

(1) Extensive efforts are required.
(2) The model may vary within a study population.
(3) The approach can be applied only to a specific drug under study.
(4) Difficulties generally arise when using models.

→ Non-Compartment Model / Distributed Parameter Model -

- The distributed parameter model differ from physiological models in that the mathematical equation are more complex & collection of drug conc^n data is more difficult.
- The non-compartmental model as analysis, also called as the model independent method. It doesnot require the compartment model.
- This method is based on the drugs or metabolites follow linear kinetics & on the basis, this technique can be applied to any compartment model.

- The non-compartmental approach based on the statistical moments theory.

It involves collection of experimental data following a single dose of a drug.

$$MRT = \frac{AUMC}{AUC} \quad -(1)$$

where, MRT = Mean Residence Time
AUMC = Area under the first-moment curve.
AUC = Area under the zero-moment curve.

AUMC is obtained from a plot of product of plasma drug conc^n & time (i.e. C.t) versus time (t) from zero to infinity.

$$AUMC = \int_0^\infty C.t.dt \quad -(2)$$

AUC is obtained from a plot of plasma drug conc^n versus time from zero to infinity.

$$AUC = \int_0^\infty C\,dt \quad -(3)$$

Practically, the AUMC & AUC can be calculated from the respective graphs by the trapezoidal rule (the method dividing the curve by a series of vertical lines into a no. of trapezoids, calculating separately the area of each trapezoid & adding them together)

MRT is defined as the average amount of time spent by the drug in the body before being eliminated.

MRT is represent the time for 63.2% of the intravenous bolus dose to be eliminated.

Advantages -

(1) Ease of derivation of pharmacokinetic parameters by simple algebraic eqn.

(2) The same mathematical treatment can be applied to almost any drug.

(3) A detailed description of drug disposition characteristics is not required.

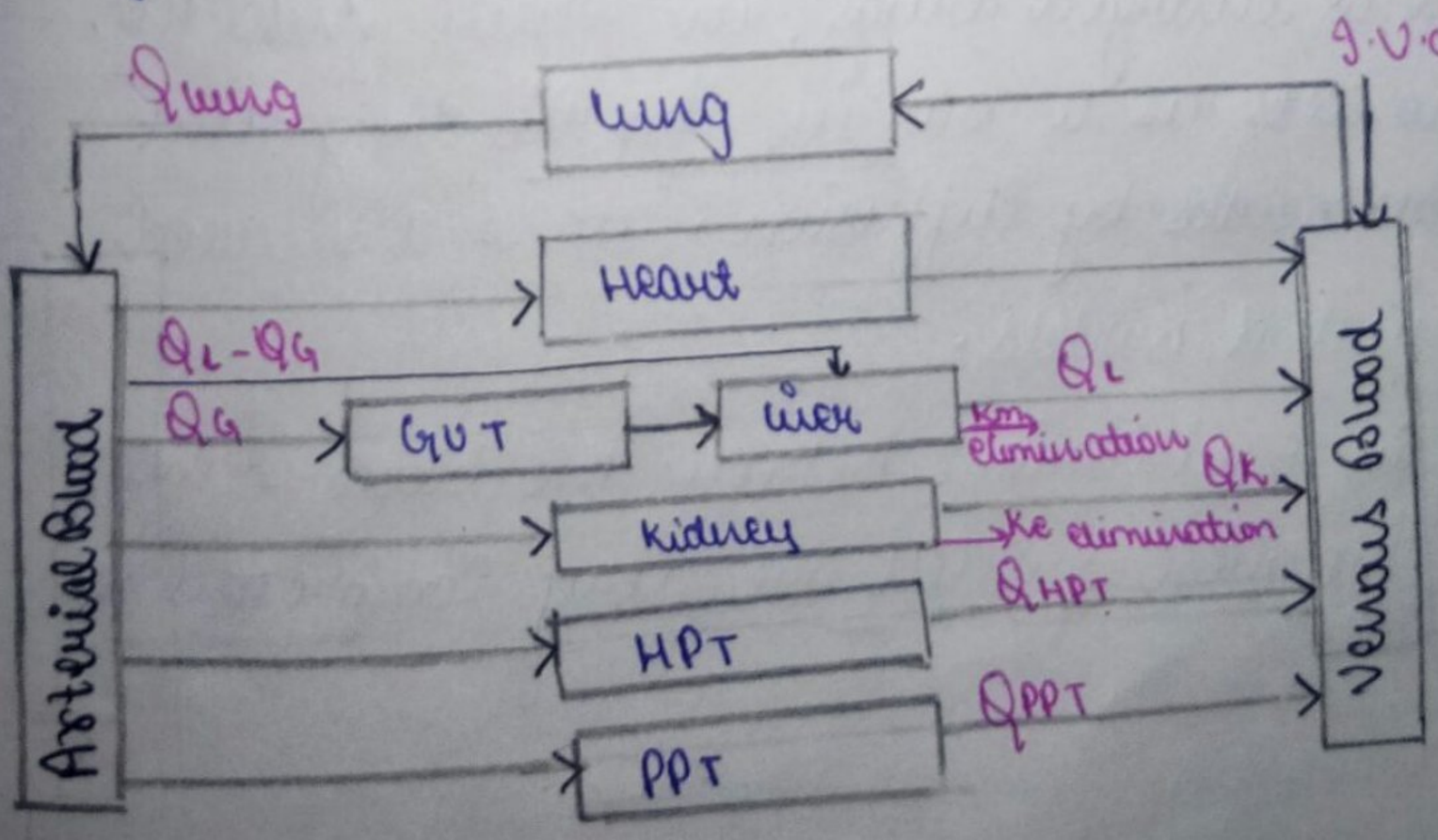
Disadvantages -

(1) It provides limited information regarding the plasma drug-conc^{n}-time profile.

(2) The method doesnot adequately treat non-linear case.

→ Physiological Models -

- These models are also known as Physiologically-based pharmacokinetics models (PB-PK models).
- The no. of compartments to be included in the model depends upon the disposition characteristics of the drug.
- Lungs, liver, Brain & kidney are grouped as Rapidly equilibrating tissue (RET) while muscles & adipose as Slowly equilibrating tissues (SET).
- The compartments are arranged in a series in a flow diagram in flow chart -



Q indicates blood flow rate to a body region.
HPT stands for Highly perfused tissues.
PPT stands for Poorly perfused tissues.
K_m is rate constant for hepatic elimination.
K_e is first order rate constant for Urinary excretion.

Types of Physiological Models -

They are two types of physiological models :

(1) Blood flow rate limited models :-

- These models are more popular & commonly used.
- The drug movement within a body region is much more rapid than its rate of delivery to that region by the perfusing blood. It is also called perfusion rate - limited models.
- It is applicable only to the highly membrane permeable drugs i.e. low molecular weight, poorly-ionised & highly lipophilic drugs.
- Ex - Thiopental, lidocaine, etc.

(2) Membrane Permeation rate - limited models :-

These models are more complex & applicable to highly polar, ionised & charged drugs, in which case the cell membrane acts as a barrier for the drug that gradually permeates by diffusion. It is also called diffusion - limited models.

The time lag in equilibrium between the blood & the tissues, eq^n for these models are very complicated.

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Advantages -

(1) Mathematical treatment is straight forward.
(2) Model is suitable where tissue drug conc^{n} & binding are known.
(3) Data fitting is not required since drug conc^{n} in various body regions can be predicted on the basis of organ or tissue size, perfusion rate.
(4) The model gives exact description of drug conc^{n}-time profile in any organ or tissues.
(5) The method is frequently used in animals.
(6) Correlation of data in several animals species is possible.
(7) Mechanism of ADME of drug can be easily explained by this model.

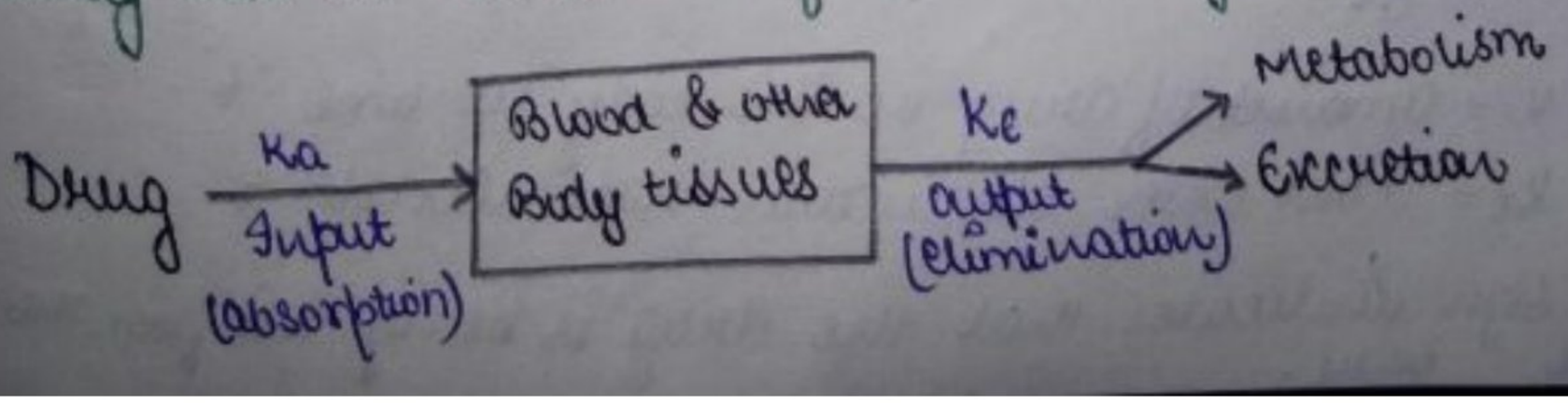
Disadvantages -

(1) Experimental data is a very exhausted process.
(2) Prediction of individualized dosing is difficult.
(3) The members of data point is less than the pharmacokinetics-parameters to be assessed.
(4) Monitoring of drug conc^{n} in body is difficult.

∴ One-Compartment Model -

- One-compartment model is the simplest model.
- The body is considered as a single, kinetically homogenous unit.
- Drugs moves dynamically in (absorption) & out (elimination) of the compartment.
- Rate of input (absorption) > rate of output (elimination).

∴ "The term open indicates that the input (absorption) & output (elimination) are unidirectional & that the drug can be eliminated from the body."



Types of One-Compartment Model -

It consists of 3 types :

(a) One compartment open model, i.v. bolus Administration
↑ (single dose of drug)

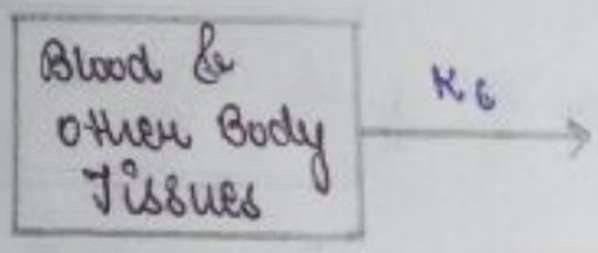
(b) One compartment open model, i.v. infusion administration
(Continuous dose like drip)

(c) One compartment open model, extravascular administration
↑ (oral, rectal, etc)

(a) One compartment open model, i.v. Bolus administration :

when a drug that distributes rapidly in the body is given in the form of a rapid intravenous injection (i.v. bolus).

The model can show :



∴ Rate of drug present to the body -

$$\frac{dx}{dt} = \text{Rate in (availability)} - \text{Rate out (Elimination)} \quad -(1)$$

Rate in or absorption is absent (because i.v. injection), the eq^n becomes :

$$\frac{dx}{dt} = -\text{Rate out} \quad -(2)$$

Rate out or elimination follows first order kinetics, then :

$$\frac{dx}{dt} = -K_e X \quad -(3)$$

where x = amount of drug in the body at time 't'.
K_e = First order elimination rate constant.

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- Negative sign indicates that the drug is being lost from the body.

(a) Elimination Rate Constant:

If drug that follows one-compartment kinetics & is administered as a rapid I.V. injection experiences decline in plasma drug conc^{n} due to elimination of drug from the body, this phase is called elimination phase.

Integrating of eq^{n} ③ -

$$\ln X = \ln X_0 - K_e t \quad -④$$

where, X_0 = amount of drug at time 't' = 0.

Eq^{n} ④ can also be written in the exponential form -

$$X = X_0 e^{-K_e t} \quad -⑤$$

Transforming eq^{n} ④ into common logarithms (log base 10)

$$\log X = \log X_0 - \frac{K_e t}{2.303} \quad -⑥$$

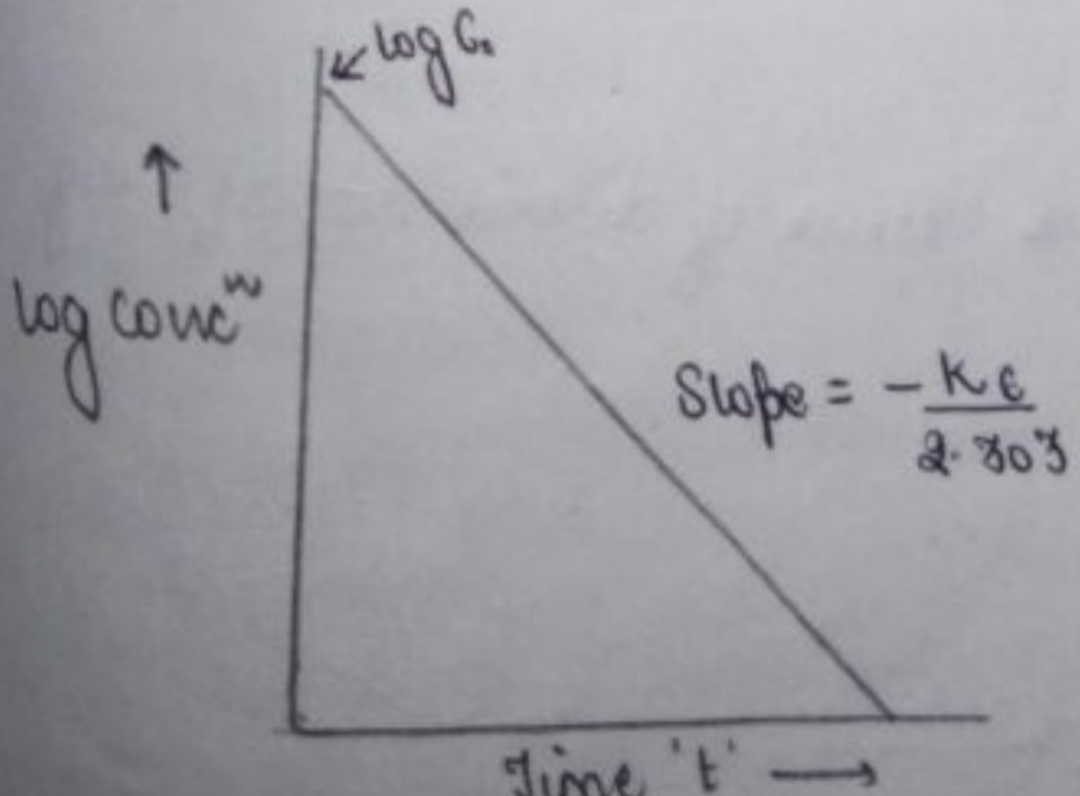
Amount 'X' convert into Conc^{n} 'C' form -

$$X = V_d \cdot C \quad -⑦$$

where, V_d = Apparent volume of distribution.

$$\log C = \log C_0 - \frac{K_e t}{2.303} \quad -⑧$$

where, C_0 = plasma drug conc^{n} immediately after i.v. injection.



"Elimination of drug from the body is the sum of urinary excretion, metabolism, biliary excretion & other involved mechanism. Thus, K_e is an additive property of rate constants for each of these processes & is called overall elimination rate constant".

$$K_e = k_e + k_m + k_b + k_1 + \dots \quad — (9)$$

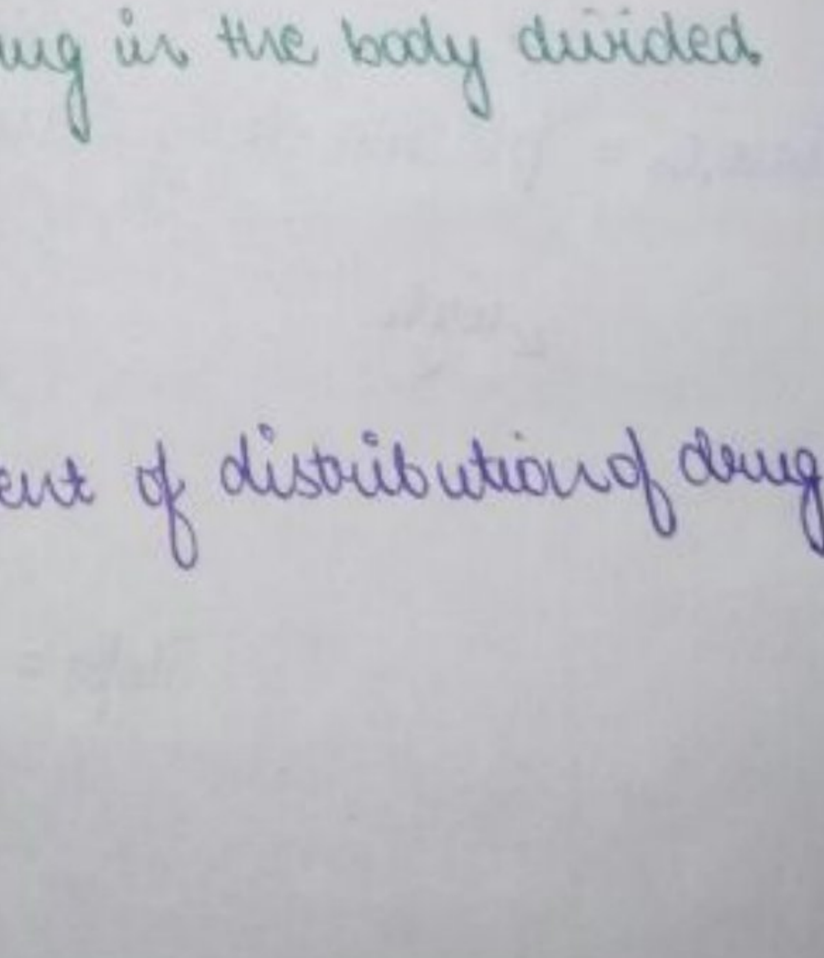
Sub:

(b) Elimination Half-life : ($t_{1/2}$)

- It is also called biological Half-life.
- It is defined as the time taken for the amount of drug in the body as well as plasma conc^n to decline by one-half or 50 % its initial value.
- It is expressed in hours or minutes.

$$t_{1/2} = \frac{0.693}{K_e}$$

or $$t_{1/2} = \frac{0.693\, V_d}{Cl_T}$$



(c) Apparent Volume of Distribution : (V_d)

- It is defined as the amount of drug in the body divided by plasma drug conc^n.

$$V_d = \frac{X}{C}$$

where, V_d = measure of the extent of distribution of drug.

- It is expressed in litres.

- By rapid i.v. injection –

$$V_d = \frac{X_0}{C_0} = \frac{\text{i.v. bolus dose}}{C_0}$$

Clearance : (Cl)

- It is defined as the theoretical volume of Body fluid containing drug from which the drug is completely removed in a given period of time.
- It is expressed in ml/min or litres/hour.

$$\text{Clearance} = \frac{\text{Rate of elimination}}{\text{Plasma drug conc}^{n}}$$

$$Cl = \frac{dx/dt}{C}$$

(c) Total Body clearance : (Cl_T)

- Elimination of a drug from the body involves processes occuring in kidney, liver, lungs & other eliminating organ.
- Clearance at an individual organ level is called as organ clearance.

$$\text{Renal clearance } (Cl_R) = \frac{\text{Rate of elimination by Kidney}}{C}$$

$$\text{Hepatic clearance } (Cl_H) = \frac{\text{Rate of elimination by liver}}{C}$$

$$\text{other organ clearance } (Cl_{other}) = \frac{\text{Rate of elimination by other organ}}{C}$$

Total Body clearance is also known as Total systemic clearance, is an additive property of individual organ clearance.

Hence, $Cl_T = Cl_R + Cl_H + Cl_{other}$.

(f) Organ clearance : Clorgan (Extraction Rate (ER).

At an organ level, the rate of elimination can be written as -

Rate of elimination By an organ = Rate of 'in' to the organ — Rate of 'out' from the organ —①

Rate of 'in' to the organ = organ blood flow × Entering conc" —②
⇒ Q·C·in

Rate of 'out' from the organ = organ blood flow × Existing conc" —③
⇒ Q·C·out

Rate of elimination = Q·C·in — Q·C·out
= Q (Cin − Cout) —④

Organ clearance ⇒ Clorgan = Rate of extraction / Cin
= Q(Cin − Cout) / Cin = Q·ER —⑤

Imp

Extraction Ratio, E·R = (Cin − Cout) / Cin

It has no unit & values from 0 to 1.

ER is an index of how efficiently the eliminating organ clears the blood flowing through it of drug.

(9) Renal Clearance : (Cl_R)

when using the plasma level-time data. It can also be used to estimate the renal clearance of unchanged drug according to eq^n -

$$\text{Renal Clearance} = \frac{\text{Rate of elimination by kidney}}{\text{Plasma drug Conc}^n}$$

$$Cl_R = \frac{dx/dt}{C}$$

$$\text{or } Cl_R = \frac{\text{Total amount of drug excreted unchanged}}{\text{Area under the plasma level-time Curve.}}$$

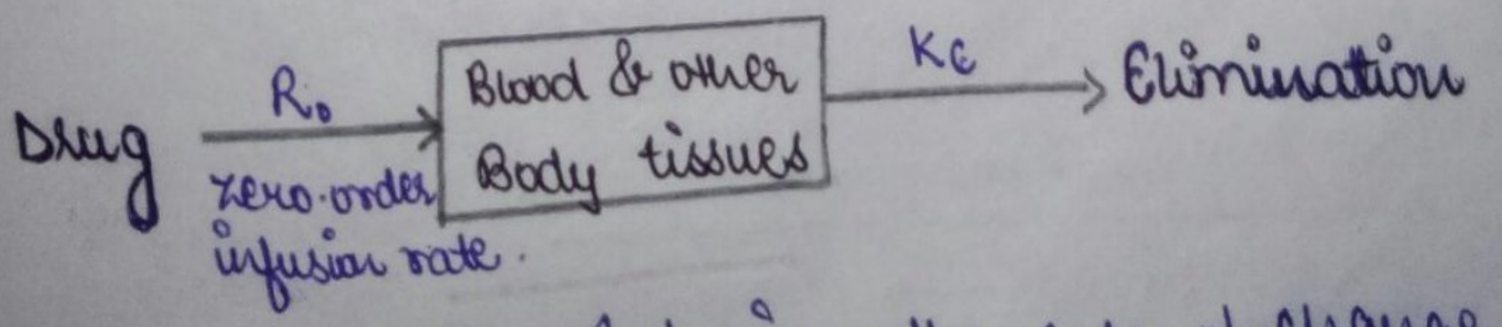
(b) One Compartment open model Intravenous infusion :

Rapid i.v. injection is unsuitable when the drug has potential to precipitate toxicity. In such a situation, the drug is administered at a constant rate (zero-order) by i.v. infusion (continuous or slow flow).

Advantages of such a zero-order infusion of drugs :

(1) Ease of Control of rate of infusion.
(2) Prevents fluctuating maxima & minima, plasma level.
(3) Electrolytes & nutrients can be administered.

The model can be represent -



At any time during Infusion, the rate of change in the amount of drug in the body, $\frac{dx}{dt}$ is the difference between the zero-order rate of drug infusion R_0 & first-order rate of elimination, $-K_E X$.

$$\frac{dX}{dt} = R_0 - K_e X \quad -①$$

Integration & rearrangement of above eq^n -

$$X = \frac{R_0}{K_e}\left(1 - e^{-K_e t}\right) \quad -②$$

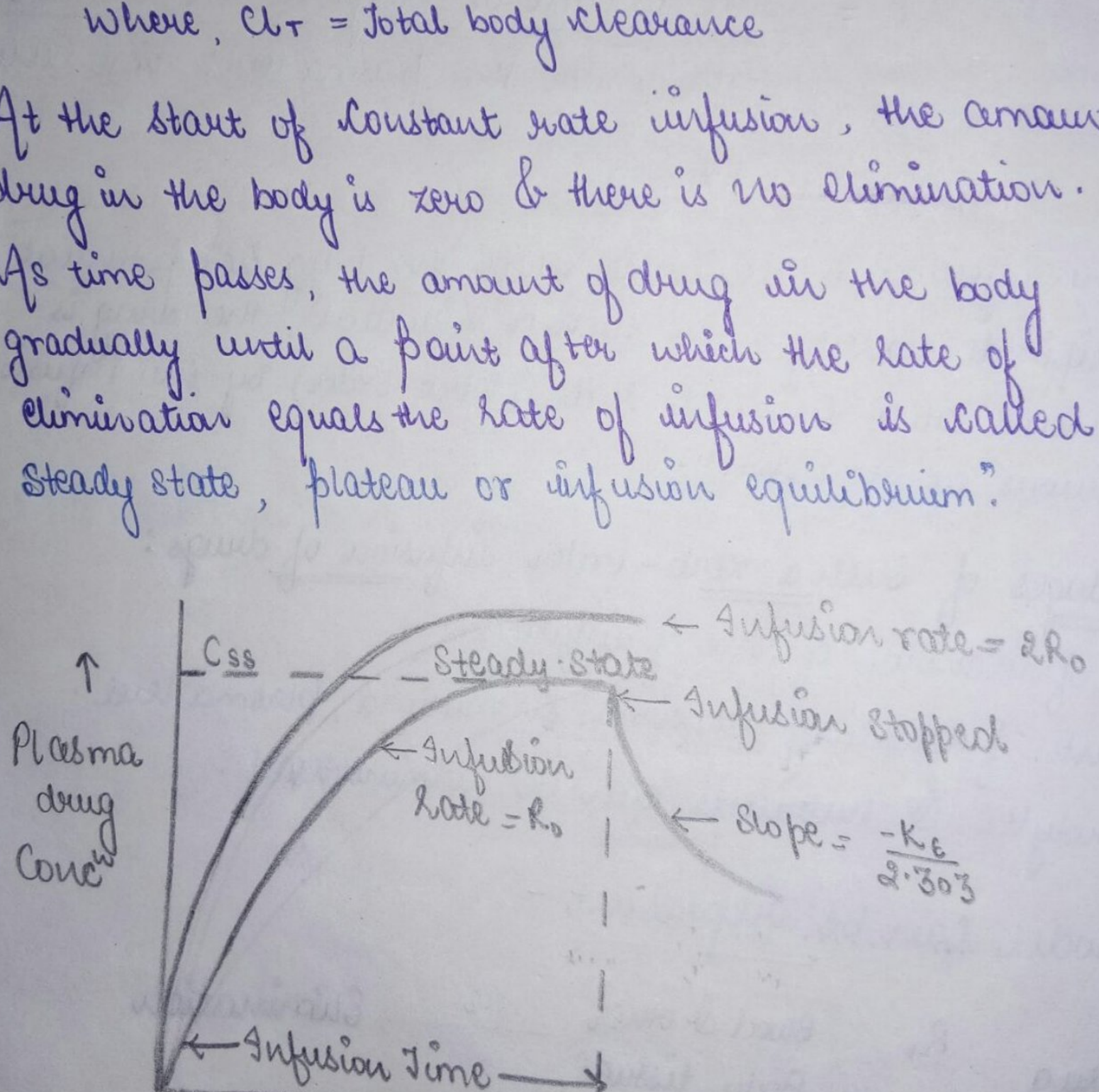
Since $X = V_d \cdot C$, the above eq^n convert into conc^n -

$$C = \frac{R_0}{K_e V_d}\left(1 - e^{-K_e t}\right)$$

$$C = \frac{R_0}{Cl_T}\left(1 - e^{-K_e t}\right) \quad — ③$$

Where, Cl_T = Total body clearance

- At the start of constant rate infusion, the amount of drug in the body is zero & there is no elimination.
- "As time passes, the amount of drug in the body gradually until a point after which the rate of elimination equals the rate of infusion is called steady state, plateau or infusion equilibrium".



Plasma Conc^n-Tym Profile (i.v. infusion)

At steady-state, the rate of change of amount of drug in the body is zero, the eq^{n} becomes:

$$Zero = R_0 - K_E X_{SS}$$

$$K_E X_{SS} = R_0 \quad \text{— (4)}$$

Transform the Conc^{n} terms & rearranging the eq^{n}:

$$C_{SS} = \frac{R_0}{K_E V_d} = \frac{R_0}{Cl_T} \quad \text{i.e. } \frac{\text{Infusion rate}}{\text{clearance}} \quad \text{— (5)}$$

Eq^{n} (5) Substituting in eq^{n} (3)

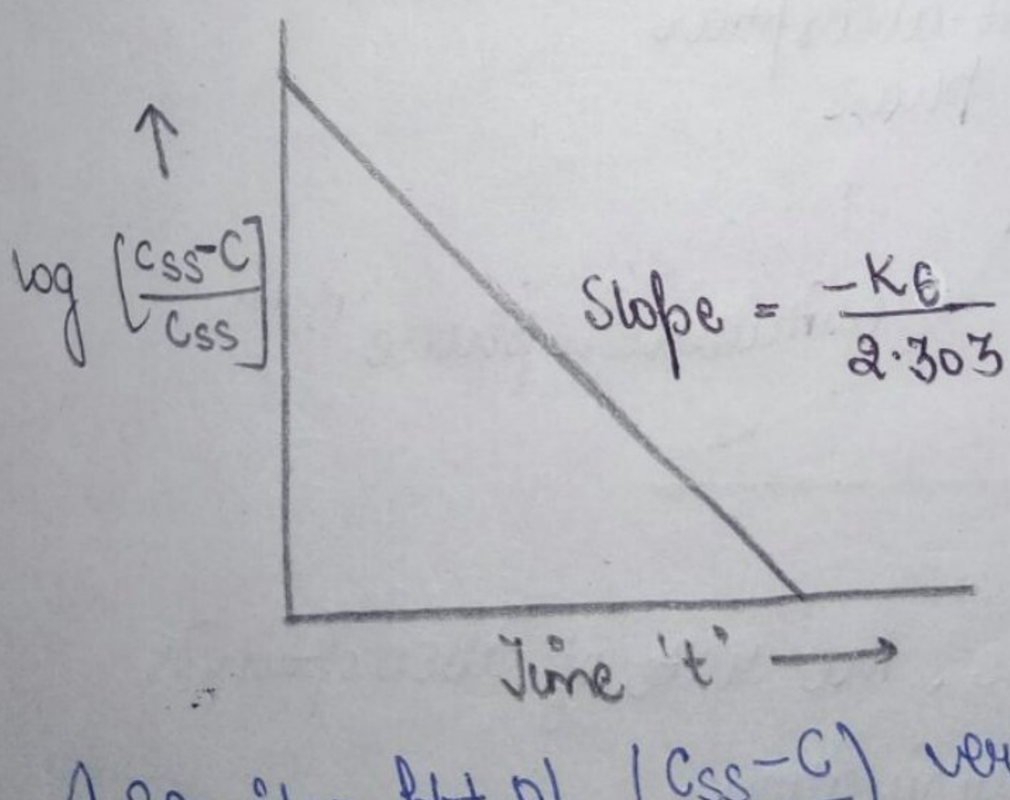
$$C = C_{SS}\ (1 - e^{-K_E t}) \quad \text{— (6)}$$

Rearrangement:

$$\left[\frac{C_{SS} - C}{C_{SS}}\right] = e^{-K_E t} \quad \text{— (7)}$$

Transforming into log form, the eq^{n} become -

$$\log\left[\frac{C_{SS} - C}{C_{SS}}\right] = \frac{-K_E t}{2.303} \quad \text{— (8)}$$



A semilog plot of $\left(\frac{C_{SS} - C}{C_{SS}}\right)$ versus t

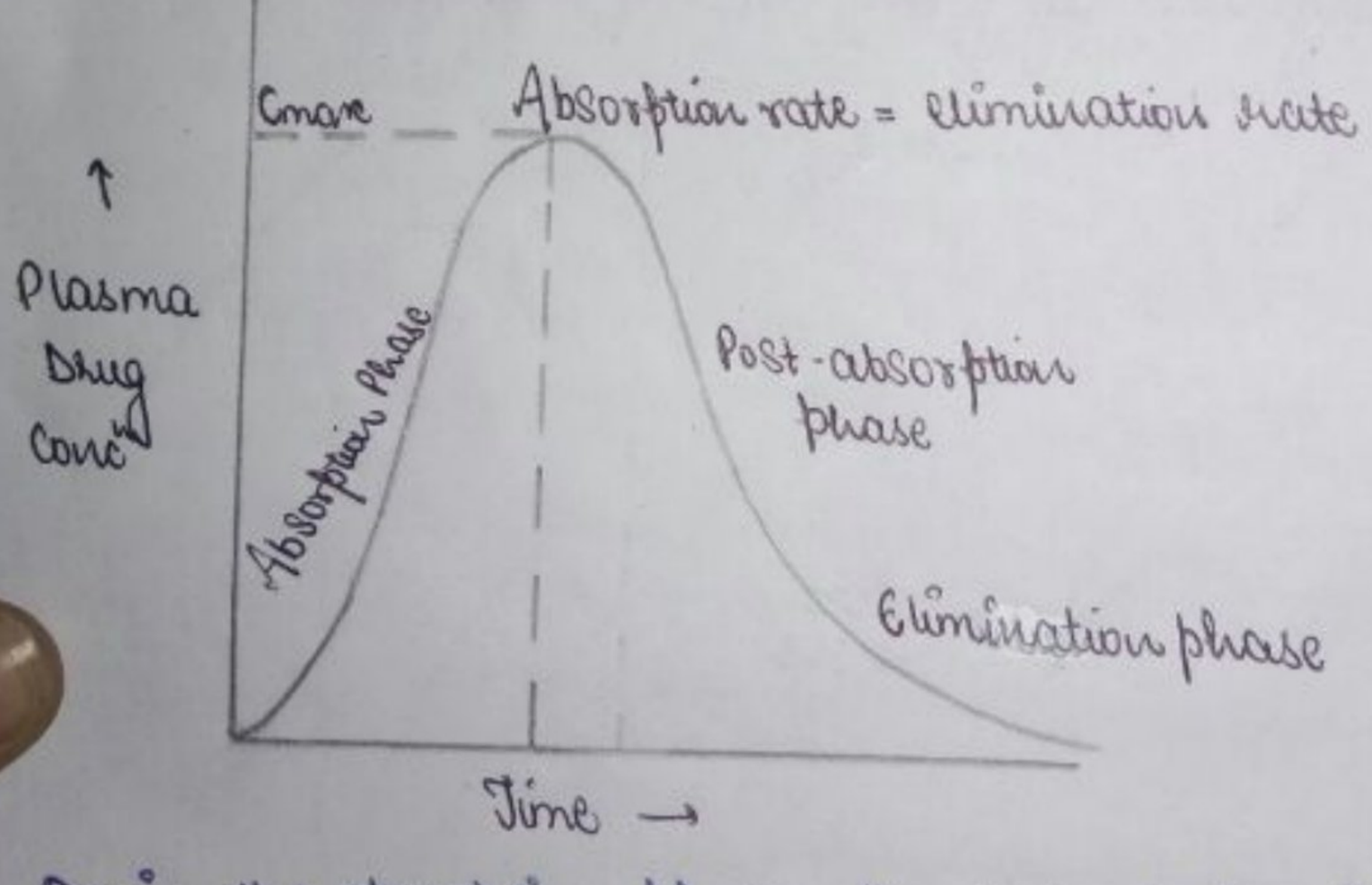
(C) One Compartment open model Extravascular administration:

After e.v. administration, the rate of change in the amount of drug in the body $\frac{dx}{dt}$ is the difference between the rate of input (absorption) $\frac{dx_{ev}}{dt}$ & rate of output (elimination) $\frac{dx_e}{dt}$.

$$\frac{dx}{dt} = \text{Rate of absorption} - \text{Rate of elimination}.$$

$$\frac{dx}{dt} = \frac{dx_{ev}}{dt} - \frac{dx_e}{dt} \quad —①$$

For a drug that follows one-compartment kinetics, the plasma Conc^n-time profile is characterized by absorption phase, post-absorption phase & elimination phase.



- During the absorption phase, the rate of absorption is greater than the rate of elimination.

$$\frac{dx_{ev}}{dt} > \frac{dx_e}{dt} \quad —(1a)$$

- At peak plasma Conc^n, the rate of absorption equals the rate of elimination.

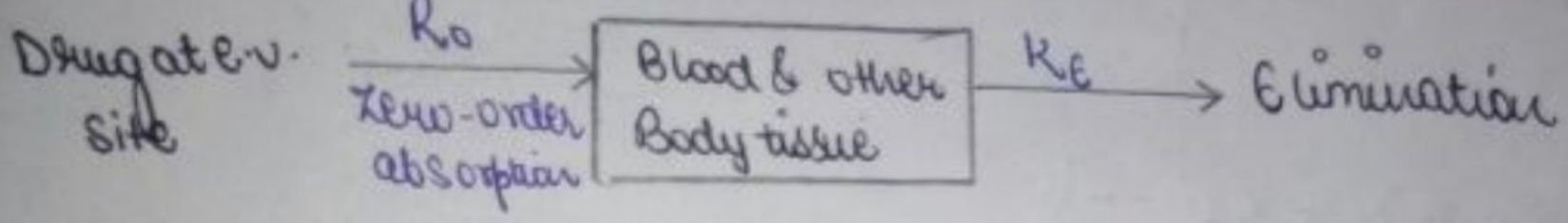
$$\frac{dx_{ev}}{dt} = \frac{dx_e}{dt} \quad —(1b)$$

. During the post-absorption phase, there is some drug at the extravascular site still remaining to be absorbed & the rate of elimination at this stage is greater than the absorption rate.

$$\frac{dX_{ev}}{dt} < \frac{dX_e}{dt} \quad -(1C)$$

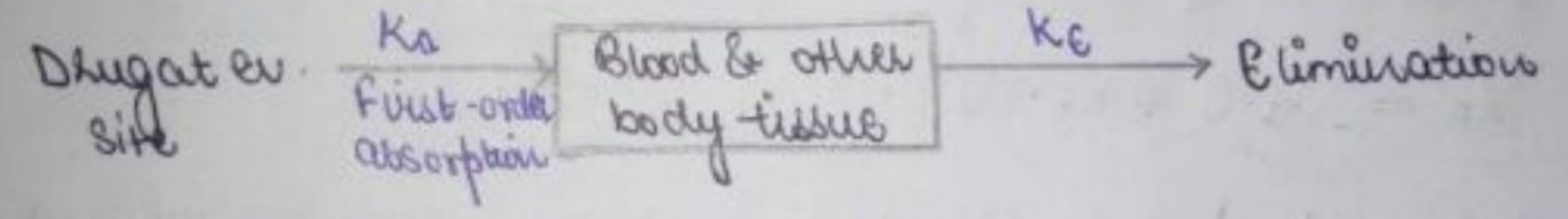
Zero-order Absorption Rate:

. This model is similar to that of constant rate infusion.



. The rate of absorption of controlled drug delivery is zero order.

First-order Absorption Rate:



Differential form of the eq^n ①

$$\frac{dX}{dt} = \frac{dX_{ev}}{dt} - \frac{dX_e}{dt} \quad -①$$

$$\frac{dX}{dt} = K_a X_a - K_e X \quad -②$$

where, K_a = first-order absorption rate constant

X_a = amount of drug at the absorption site.

On integrating the eq^n ②

$$X = \frac{K_a f X_0}{(K_a - K_e)} \left[e^{-K_e t} - e^{-K_a t}\right] - ③$$

Transforming into conc^n form ($C = V_d \cdot X$)

$$C = \frac{K_a f X_0}{V_d (K_a - K_e)} \left[e^{-K_e t} - e^{-K_a t}\right] - ④$$

where, f = fraction of drug absorbed systemically after e.v. administration. The eq^n ④ is bieksponential form.

Wagner - Nelson Method for Estimation of Ka : (Ka = absorption rate constant)

This method involves determination of Ka from percentage unabsorbed - time plots

After oral administration of a single dose of a drug, at any given time, the amount of drug absorbed into the systemic circulation 'X_a', is the sum of amount of drug in the body 'X' & the amount of drug eliminated from the body 'X_e'.

Then,

$$X_A = X + X_e \quad -①$$

where, $X = Vd \cdot C$

$$X_e = K_e \cdot Va \, [AUC]_0^t$$

put the value X, X_e in eq^n ①

$$X_A = Vd \cdot C + K_e \cdot Vd \, [AUC]_0^t \quad -②$$

The total amount of drug absorbed in the systemic circulation from tym zero to infinity, the eq^n becomes:

$$X_A^{\infty} = Vd\, C^{\infty} + K_e Vd \, [AUC]_0^{\infty} \quad -③$$

Since at $t = \infty$ then $C = 0$, the eq^n ③ reduce to:

$$X_A^{\infty} = K_e \, Vd \, [AUC]_0^{\infty} \quad -④$$

The fraction of drug absorbed at any time 't' is given as -

$$\frac{X_A}{X_a^{\infty}} = \frac{Vd \cdot C + K_e Vd \, [AUC]_0^t}{K_e Vd \, [AUC]_0^{\infty}}$$

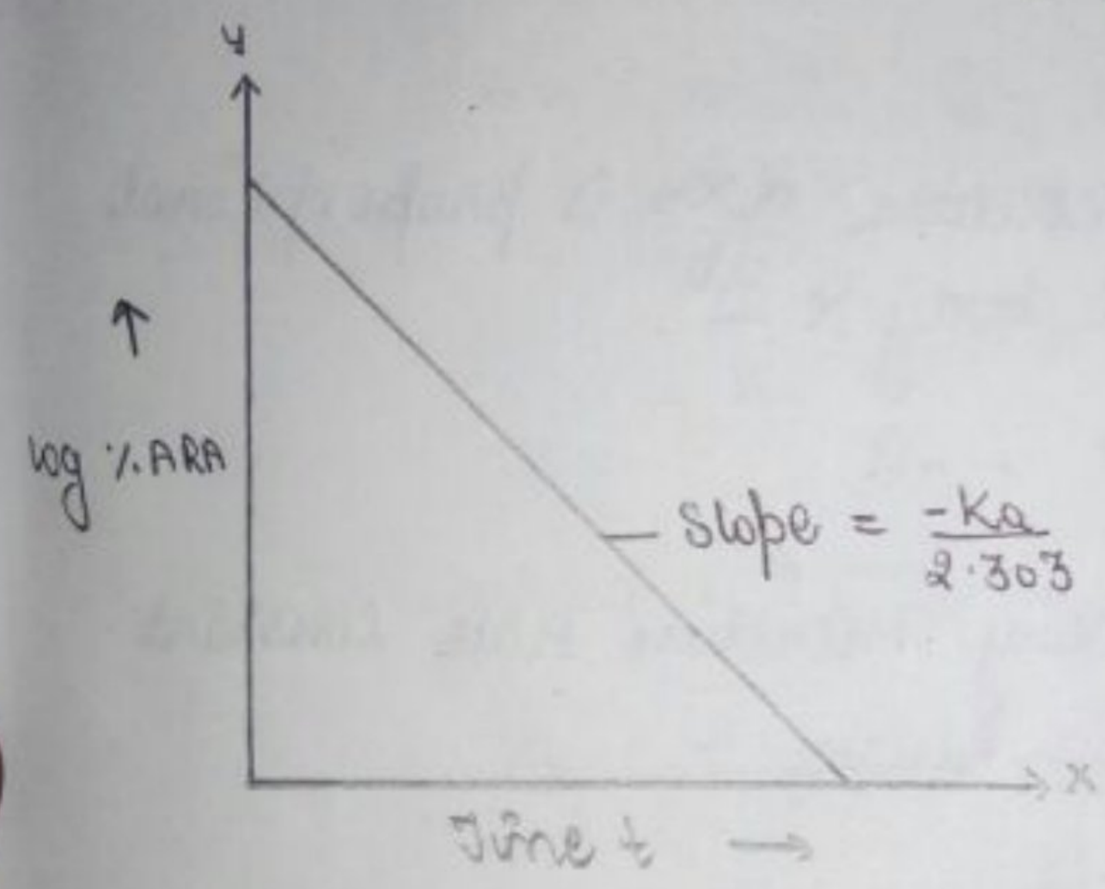
$$= \frac{Vd \, (C + K_e \, (AUC)_0^t}{K_e \, Vd \, [AUC)_0^{\infty}}$$

$$\frac{X_A}{X_A^\infty} = \frac{C + K_6 (AUC)_0^t}{K_6 (AUC)_0^\infty} \quad \text{---} (7)$$

Percentage drug unabsorbed at any time 't' is -

$$\% \text{ ARA} = \left[1 - \frac{X_A}{X_A^\infty}\right] \times 100$$

$$\% \text{ ARA} = \left[1 - \frac{C + K_E [AUC]_0^t}{K_E [AUC]_0^\infty}\right] \times 100$$



Semilog plot of % ARA versus t according to Wagner-Nelson method

From the graph, Slope is obtained than 'Ka' is calculated by :

$$\text{Slope} = \frac{y_2 - y_1}{x_2 - x_1}$$

V.V. Imp

Determination of K_E from Urinary Excretion data :

The first-order elimination rate constants can be determined from urinary data by two methods :

(a) Rate of excretion method.

(b) Sigma-minus method.

V.V. Imp

→ Rate of Excretion Method –

The rate of urinary drug excretion $\frac{dX_u}{dt}$ is proportional to the amount of drug in the body X –

$$\frac{dX_u}{dt} = K_e X \quad \text{—①}$$

where K_e = first order urinary excretion rate constant.

Acc. to the first order disposition kinetics –

$$X = X_0 e^{-K_E t} \quad \text{—②}$$

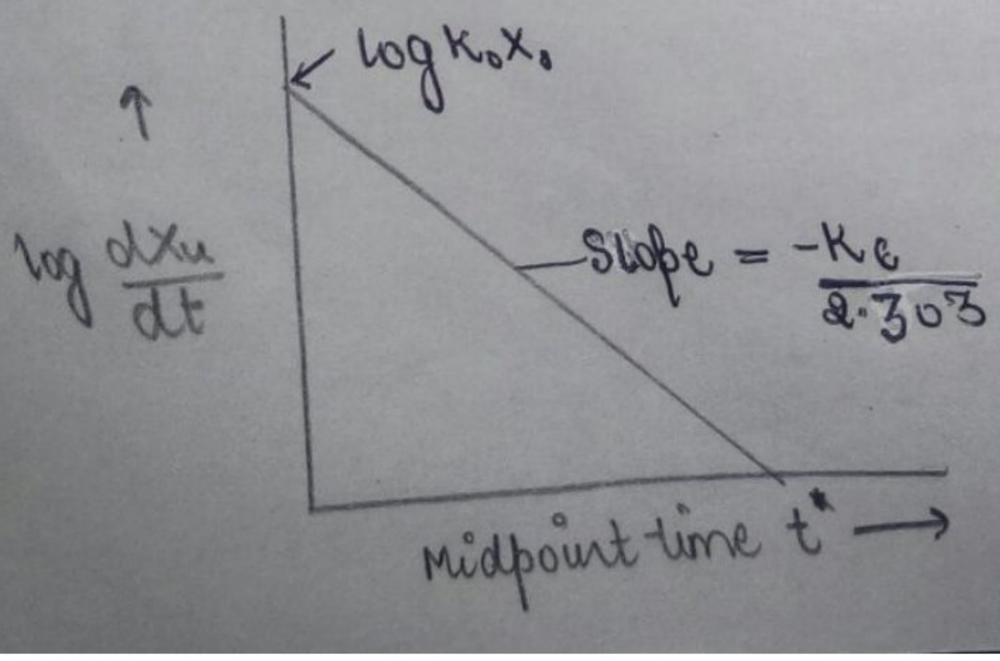
eq^n ② put in eq^n ①

$$\frac{dX_u}{dt} = K_e X_0 e^{-K_E t} \quad \text{—③}$$

where X_0 = dose administered (i.v. bolus)

eq^n ③ transformed into log form –

$$\log \frac{dX_u}{dt} = \log K_e X_0 - \frac{K_E t}{2.303} \quad \text{—④}$$



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V.V.Imp

Sigma-Minus Method -

The rate of urinary drug excretion $\frac{dXu}{dt}$ is proportional to the amount of drug in the body X -

$$\frac{dXu}{dt} = Ke\,X \quad -①$$

where, Ke = first order urinary excretion rate constant.

According to disposition kinetics -

$$X = X_0 e^{-K_6 t} \quad -②$$

put eq^n ② in eq^n ① -

$$\frac{dX_u}{dt} = K_e\,X_0 e^{-K_6 t} \quad -③$$

on integrating of eq^n ③ & simplify -

$$X_u = \frac{K_e X_0}{K_6}\left(1 - e^{-K_6 t}\right) \quad -④$$

where X_u = cumulative amount of drug excreted unchanged in urine at any time 't'.

The cumulative amount excreted at infinity time X_u^∞ -

$$X_u^\infty = \frac{K_e X_0}{K_\epsilon} \quad -⑤$$

eq^n ⑤ substitution in eq^n ④

$$X_u = X_u^\infty\left(1 - e^{-K_\epsilon t}\right)$$

$$X_u = X_u^\infty - X_u^\infty e^{-K_\epsilon t}$$

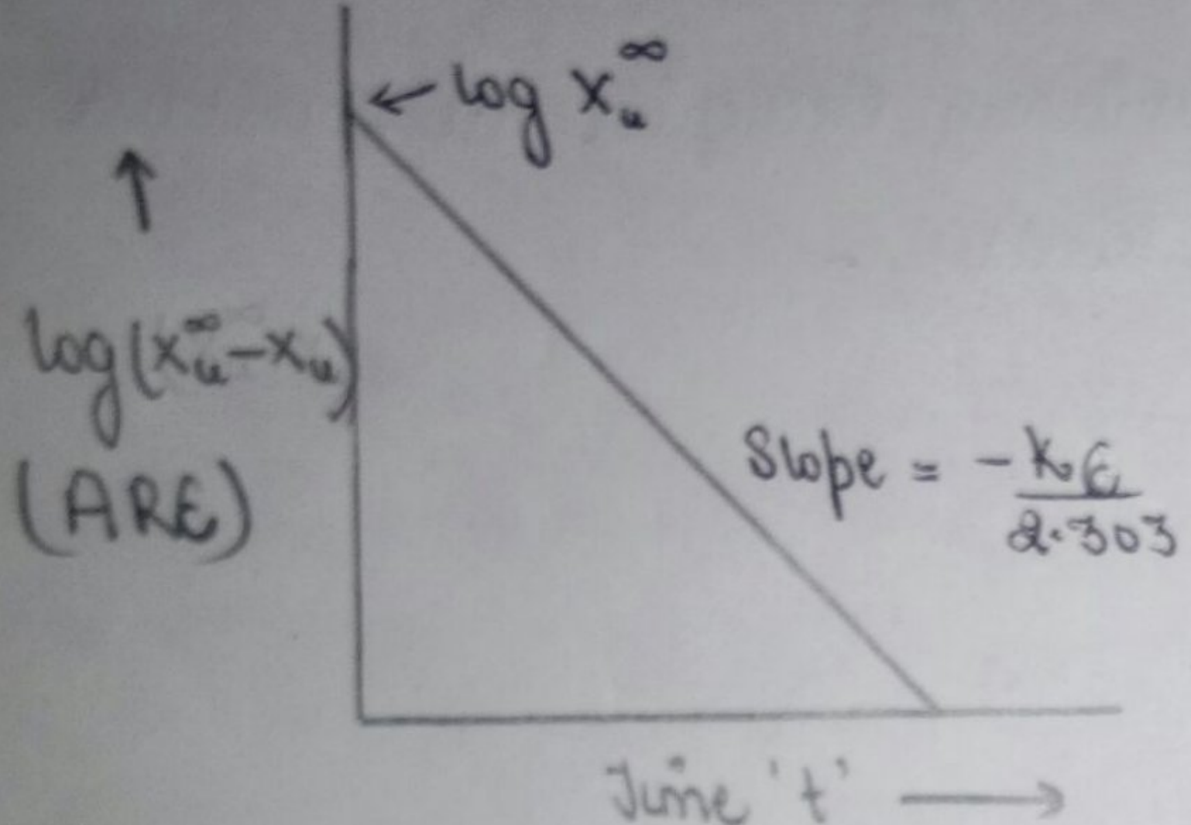
On simplify, $X_u^\infty - X_u = X_u^\infty e^{-K_\epsilon t} \quad -⑥$

eq^n ⑥ converting into log form -

$$\log\left(X_u^\infty - X_u\right) = \log X_u^\infty - \frac{K_\epsilon t}{2.303} \quad -⑦$$

where, $(X_u^\infty - X_u)$ = amount remaining to be excreted (ARE).

A semilog plot of 'ARE' versus 't' yields a straight line with slope $-K_e/2.303$.



- It is also called ARE plot Method.
- From the graph, slope can be determine & put the value & K_e can be formed.

$$\text{Slope} = \frac{Y_2 - Y_1}{X_2 - X_1}$$