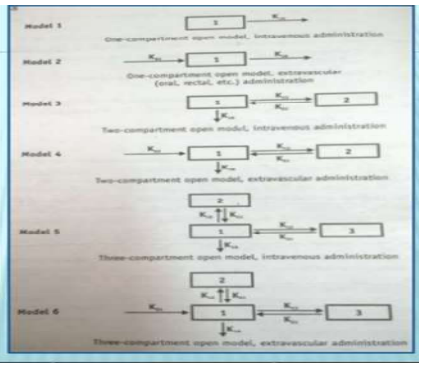
- **Pharmacokinetic Model Approach**
  - **Compartment Models:** The body is divided into hypothetical compartments arranged either in series or parallel to each other, communicating with each other. These compartments are virtual and is considered as tissue or group of tissues that have similar drug distribution characteristics i.e. similar blood flow and affinity. Rate of drug movement between compartments follows first order kinetics.

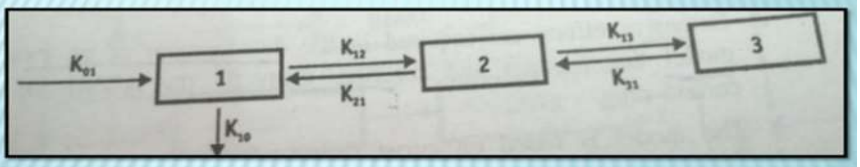
- Depending upon whether the compartments are in series or parallel to each other they are divided in two categories-
  -Mammillary Model
  -Catenary Model

- **Mammillary Model** - It is the most common model. In this model the central compartment or the compartment 1is connected parallel to the peripheral compartment. The central compartment has high vascularity and high perfusion like lungs, liver, kidneys. Elimination also occurs through these compartments in most cases. The peripheral compartments or tissue compartment or compartment denoted by numbers 2,3,4...etc have low vascularity and poor perfusion. Movements of drugs between the compartment follows first order kinetics.
  [Note-K_{12} denotes the drug movement from compartment one to compartment two or from central compartment to one of the peripheral compartment.]

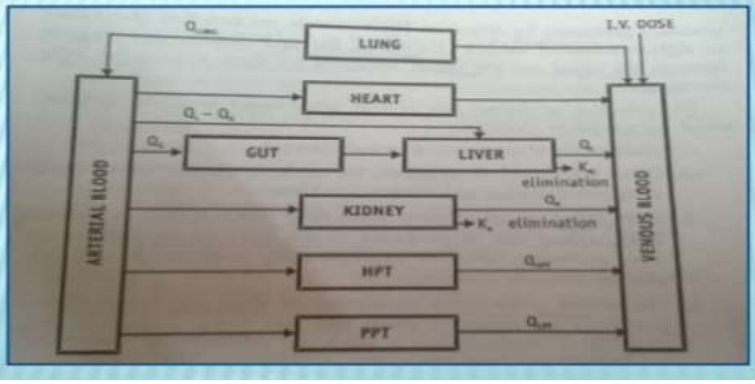
- The number of rate constants can be calculated as,
- For i.v administration, R=2n-1
- For extra-vascular administration, R=2n
  Where,
  R = number of rate constants, and
  n = number of compartments



- **Catenary Model** – In catenary model the compartments are joined in series.
- This model is rarely used.



- **Physiological Models -** They are also called PB-PK models [physiologically based pharmacokinetic models]. They are more realistic as it is based on known anatomic and physiological data.
- Organs with similar perfusion is grouped in a single compartment, like lungs, liver, brain and kidney are grouped as rapidly equilibrating tissues (RET) while muscles and adipose as slowly equilibrating tissues (SET). Organs or tissues such as bones that have no drug penetration is excluded.



- They are of two categories-
  - **Perfusion rate limited/blood flow rate limited** - It is based on the assumption that the drug movement within a body region is much more rapid that its rate of delivery to that region by the perfusing blood. However it is only applicable to the highly membrane permeable drugs i.e. low molecular weight, poorly ionised and highly lipophilic drugs example thiopental, lidocaine etc.
  - **Diffusion rate limited/membrane permeation rate limited models** - It is more complex and is applicable to drugs in which the cell membrane acts as a barrier like for highly polar, ionised and charged drugs.

- **Distributed parameter model -** This model is analogous to physiological model. This model is specifically useful for assessing regional differences in drug concentrations in tumours or necrotic tissues.

- **Applications of pharmacokinetic models**
  - It helps in understanding the behaviour of drugs in patients.
  - It helps in predicting the concentration of drug in various body fluids
  - It helps in optimizing the dosage regimen for individual patients.
  - It helps in evaluating the risk of toxicity.
  - It helps in correlating plasma drug concentration with pharmacological response.
  - It helps in determining the influence of altered physiology on drug ADME.
  - It helps in explaining the drug interactions.

- **Non-compartmental Analysis or Model-Independent method-** It follows linear kinetics so it can be applied to any compartment model. It is based on the statistical moments theory, which involves collection of experimental data following a single dose of drug.

  MRT=AUMC/AUC

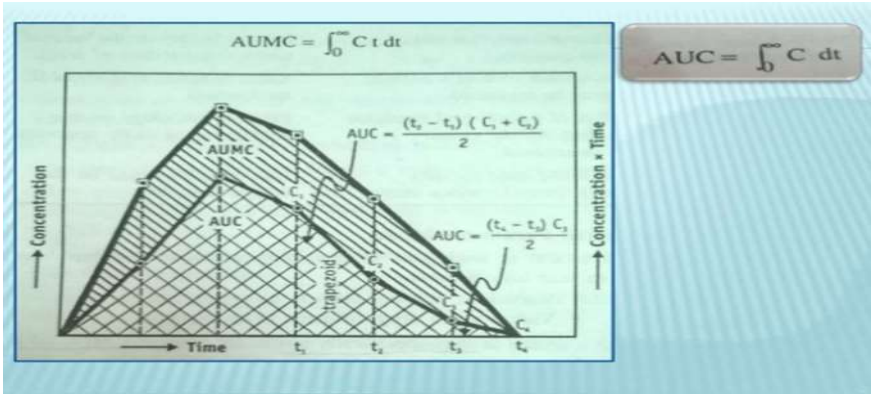
  MRT= mean residence time of drug

  AUMC= area under the first moment curve

  AUC= area under curve/zero moment curve

- AUMC is obtained by the plot of product of plasma drug concentration and time vs time i.e. **C.t vs t**

- AUC is obtained by plotting **C vs t**.



- **Application of Model Independent/Non-compartmental Model-**
  - It is used to estimate the important pharmacokinetic parameters like bioavailability, clearance and apparent volume of distribution.
  - It is used in determining half life, rate of absorption and first order absorption rate constant of the drug.

COMPARTMENTAL MODEL

A compartment is a group of tissues with similar blood flow and drug affinity.

A compartment is physiologic and anatomic region.

Compartment is the traditional and most widely used approach to pharmacokinetic characterization of drug. These models simply interpolate the instrumental data and allow on empirical formula to estimate drug concentration with time.

ASSUMPTIONS OF COMPARTMENTAL MODELS

- The body is represented as a series of compartment arranged in series or parallel to each other.
- The rate of drug movement between compartment is described by first order kinetics.
- Rate constants are used to represent rate of entry into and exit from compartment.
- A statistical analysis of plasma concentration time data is another method used to find out no of compartments.

APPLICATION OF COMPARTMENT MODELLING

i. It is simple and flexible approach and widely used.
ii. It gives a visual representation of various rate process involved in drug disposition.
iii. It is useful in predicting drug concentration time profile in both normal and pathological composition.
iv. It is useful in relating plasma drug levels in therapeutic and toxic levels.

ONE COMPARTMENT MODEL (Instantaneous Distribution Model)

The time course of drug concentration determined after the administration can satisfactorily explained by assuming the body as a single well mixed compartment with first order disposition process.

The body is constituted ***as a single kinetically homogeneous unit with no barriers*** to movement of drug.

Elimination is a first order process with first order rate constant.

Drug moves dynamically in and out of the compartment then rate of input will be greater then the rate of output.

ONE COMPARTMENT "OPEN MODEL"

- *The term open indicates that the input (availability) and output (elimination) are unidirectional and that the drug can be eliminated from the body.*

CLASSIFICATION OF **ONE COMPARTMENT OPEN MODEL**

- Depending upon rate of input ,several one compartment models are defined
- One compartment open model- *intravenous bolus administration*
- One compartment open model- *continuous intravenous infusion*
- One compartment open *model-extra vascular zero – order absorption*
- One compartment open *model- extra vascular first – order absorption*

INTRAVENEOUS BOLUS ADMISINTRATION

- When a drug that distributes in body is given in the form of a lipid intravenous injections , its takes about one or three minutes, for complete circulation.
- The model can be diagrammatically depicted as

It can be mathematically represented as :

- The general expression for **rate of drug presentation to the body is: on**

$$\frac{dX}{dt} = \text{Rate in (availability)} - \text{Rate out (elimination)}$$

Since rate in or absorption is absent, the equation becomes:

$$\frac{dX}{dt} = -\text{Rate out}$$

If the rate out or elimination follows first-order kinetics, then:

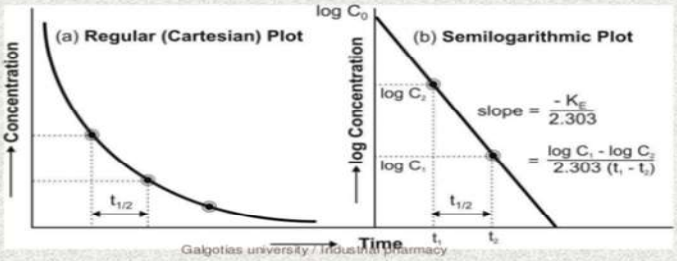
$$\frac{dX}{dt} = -K_E X$$

where, KE = first-order elimination rate constant, and
X = amount of drug in the body at any time t remaining to be eliminated.
Negative sign indicates that the drug is being lost from the body.

Estimation of Pharmacokinetic Parameters

- For a drug that follows one-compartment kinetics and administered as rapid i.v. injection, the decline in plasma drug concentration is only due to elimination of drug from the body (and not due to distribution), the phase being called as elimination phase. **Elimination phase can be characterized by 3 parameters—**
- 1. Elimination rate constant
- 2. Elimination half-life
- 3. Clearance

(a) Cartesian plot of a drug that follows one-compartment kinetics and given by rapid i.v. injection, and (b) Semi logarithmic plot for the rate of elimination in a one-compartment model.



Elimination Half-Life:

- *It is defined as the time taken for the amount of drug in the body as well as plasma concentration to decline by one-half or 50% its initial value.*

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

Clearance

- **Clearance** is defined as the theoretical volume of body fluid containing drug (i.e. that fraction of apparent volume of distribution) from which the drug is completely removed in a given period of time. It is expressed in ml/min or liters/hour.

$$Cl_R = \frac{\text{Rate of elimination by kidney}}{C}$$

- *The total body clearance, ClT, also called as total systemic clearance, is an additive property of individual organ clearances.*

$$Cl_T = Cl_R + Cl_H + Cl_{Others}$$

Apparent Volume of Distribution:

- *These parameters are closely related with the physiologic mechanisms in the body, they are called as **primary parameters.***
- 1. Apparent volume of distribution, and
- 2. Clearance.

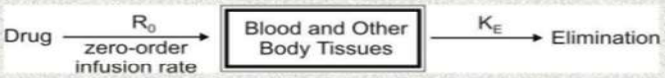
$$V_d = \frac{\text{Amount of drug in the body}}{\text{Plasma drug concentration}} = \frac{X}{C}$$

Intravenous Infusion

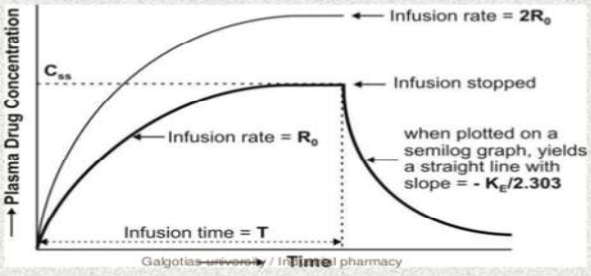
- Rapid i.v. injection is unsuitable when the drug has potential to precipitate toxicity or when maintenance of a stable concentration or amount of drug in the body is desired. In such a situation, the drug (for example, several antibiotics, theophylline, procainamide, etc.) is administered at a constant rate (zero-order) by i.v. infusion.

- In contrast to the short duration of infusion of an i.v. bolus (few seconds), the duration of constant rate infusion is usually much longer than the half-life of the drug.
- ***Advantages of zero-order infusion of drugs include***—
- 1. Ease of control of rate of infusion to fit individual patient needs.
- 2. Prevents fluctuating maxima and minima (peak and valley) plasma level, desired especially when the drug has a narrow therapeutic index.
- 3. Other drugs, electrolytes and nutrients can be conveniently administered simultaneously by the same infusion line in critically ill patients.

The model can be represented as follows:



Plasma concentration-time profile for a drug given by constant rate i.v. infusion (the two curves indicate different infusion rates Ro and 2Ro for the same drug)



Extravascular Administration

- When a drug is administered by extravascular route (e.g. oral, i.m., rectal, etc.), absorption is a prerequisite for its therapeutic activity.
- The rate of absorption may be described mathematically as a zero-order or first-order process. A large number of plasma concentration-time profiles can be described by a one-compartment model with first-order absorption and elimination. However, under certain conditions, the absorption of some drugs may be better described by assuming zero-order (constant rate) kinetics.

Distinction between zero-order and first-order absorption processes. *Figure a is regular plot, and Figure b a semi log plot of amount of drug remaining to be absorbed (ARA) versus time t.*

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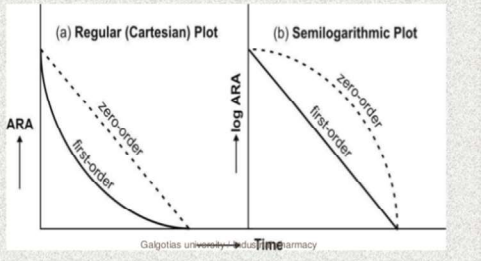

Zero-order absorption is characterized by a constant rate of absorption

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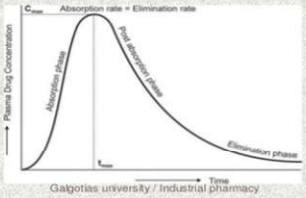
dX/dt = Rate of absorption – Rate of elimination

$$\frac{dX}{dt} = \frac{dX_{ev.}}{dt} - \frac{dX_E}{dt}$$



ZERO ORDER ABSORPTION MODEL

- It is similar to that of constant rate of infusion.

Drug at e.v.site $\xrightarrow[\text{zero order absorption}]{R_o}$ Blood and other body tissues $\xrightarrow{K_E}$ Elimination

- The rate of drug absorption incase of several controlled drug delivery systems.

FIRST ORDER ABSORPTION MODEL

- When ever the drug enters into body it follows first order absorpti according to one compartment kinetics.
- The model can be represented as

Drug at e.v.site → Ka → Blood and other body tissues → K_E → Elimination

first order absorption

The differential form of above equation can be

$$\frac{dx}{dt} = K_a X_a - KeX$$

- Integrating the above equation

$$X = \frac{KaFX_0}{(K_a - KE)}[e^{-KEt} - e^{-Kat}]$$

Transforming into c terms as $X = V_d C$

$$c = \frac{KaFX_0}{(K_a - KE)V_d}[e^{-KEt} - e^{-Kat}]$$

F=Fraction of drug absorbed systematically after e.v.administration

- Here from the EV absorption study the t_{max} and c_{max} can be calculated

$$t_{max} = \frac{2.303\log(\frac{Ka}{Ke})}{Ka - Ke} \quad C_{max} = \frac{FX0}{Vd} e^{-Ketmax}$$

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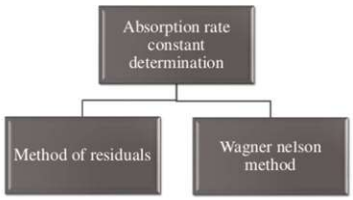
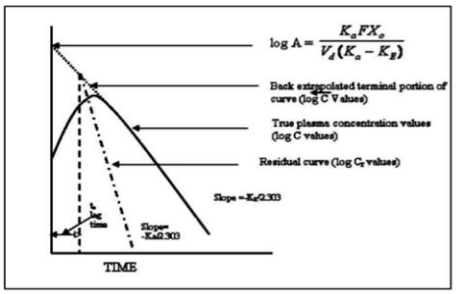
DETERMINATION OF ABSORPTION RATE

- It is the most important pharmacokinetic parameter when a d follows first order absorption. It can be calculated by two meth in one compartment open model they are:



Graphical representation of method of residuals



METHOD OF RESIDUALS

- This method also called as feathering, peeling and stripping. For a drug that follows one compartment and it is a biexponential equation.

$$C = \frac{K_a F X_a}{V_d(Ka - KE)}[e^{-KEt} - e^{-Kat}]$$

$$C = Ae^{-KEt} - Ae^{-Kat}$$

$$\overleftarrow{C} = Ae^{-KEt} \qquad \overleftarrow{logC} = logA - \frac{-KEt}{2.303}$$

- Subtraction of true values to extrapolated concentration that is residual concentration.

$$C_r = Ae^{-Kat}$$

$$logC_r = logA - \frac{-Kat}{2.303}$$

- If $K_E/K_a \geq 3$ the terminal slope eliminates K_a and not K_E. The slope of residual lines gives K_E and not K_a.
- This is also known as flip-flop kineticsas the slopes of two lines exchanged their meanings.

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Lag time:

- It is defined as the time difference between drug administration and start of absorption. It is denoted by t_0.
- This method is best suited for drugs which are rapidly and completely absorbed and follow one compartment kinetics even when given i.v.

WAGNER NELSON METHOD

- One of the best alternatives to curve fitting method in the estimation of K_a is Wagner Nelson method.
- This method involves the determination of K_a from percent unabsorbed time plots and does not require the assumptions of zero or first order absorption.
- According to this the amount of drug in body is depicted as

$$X_A = X + XE$$

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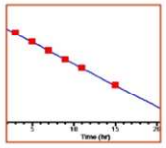
- $X_A{}^t = V_d C + V_d K [AUC]_0^t \longrightarrow (1)$
- $X_A{}^\infty = V_d C^\infty + V_d K [AUC]_0^\infty \longrightarrow (2)$

$$\frac{(1)}{(2)} = \frac{X_A{}^t}{X_A{}^\infty} = \frac{V_d C + V_d K [AUC]_0^t}{V_d K [AUC]_0^\infty}$$

$$= \frac{X_A{}^t}{X_A{}^\infty} = \frac{C + K [AUC]_0^t}{K [AUC]_0^\infty}$$

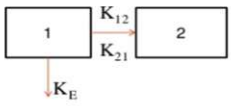
If the fraction of total amount of drug absorbed = 1

- Amount remaining to be absorbed = $1 - \frac{X_A{}^t}{X_A{}^\infty}$.
- Amount remaining to be absorbed = $1 - \frac{C + K [AUC]_0^t}{K [AUC]_0^\infty}$
- % amount remaining to be absorbed= $(1 - \frac{C + K [AUC]_0^t}{K [AUC]_0^\infty})\ 100$
- A graph is plotted by taking log%ARA on Y-axis and time on X-axis a straight line is obtained from that slope K_a is determined.



TWO COMPARTMENT OPEN MODEL

- It is common in all multi compartment models.
- It consists of central compartment i.e., compartment 1 comprising of blood and highly perfused tissues and peripheral compartment i.e., compartment 2 comprising of poorly perfused tissues such as skin and adipose tissues.
- **INTRAVENOUS BOLUS:**



The model can be mathematically represented as

$$\frac{dc_c}{dt} = K_{21} C_p - K_{12} C_c - K E C_c$$

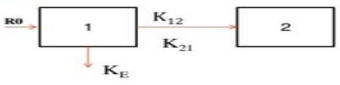
$C_c = Ae^{-\alpha t} - Be^{-\beta t}$

α and β are hybrid constants then

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

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

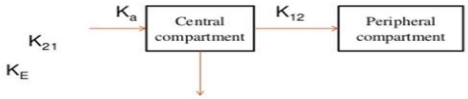
Intravenous infusion



$$c = Ro/VcK_E(1 + (KE - {}^{\beta}/_{\beta-\alpha})e^{-\alpha t} + (K_E - \alpha/\alpha - \beta)e^{-\beta t}).$$

EXTRAVASCULAR ADMINISTRATION

- In two compartment open model for extravascular administration it can be depicted as



$$C = Ne^{-Kat} + Le^{-\alpha t} + Me^{-\beta t}$$

The absorption rate is calculated by Loo-Regeilmann method.

LOO REGEILMANN METHOD

According to mass balance equation

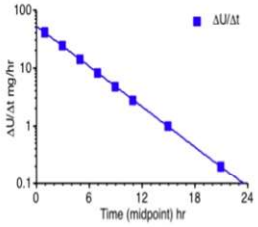
$$X_a = X_c + X_t + X_3$$

from the formula $X = V_d C$

- Fraction remaining to be absorbed= $1 - \frac{X_A{}^t}{X_A{}^\infty}$.
- ARA $= 1 - \frac{C_c + Ct + K [AUC]_0^t}{K [AUC]_0^\infty}$

%ARA $= (1 - \frac{C_c + Ct + K [AUC]_0^t}{K [AUC]_0^\infty}) 100.$

- A graph is plotted by taking log %ARA on y-axis and time on x-axis a straight line is obtained and slope of that gives absorption rate i.e., slope= $\frac{-Ka}{2.303}$.

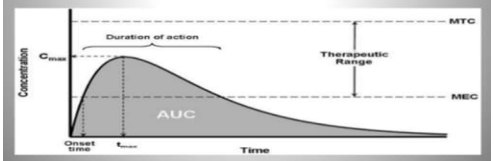


- Compartment model provides a framework for the study of the dynamic flow of chemicals (nutrients, hormones, drugs, radio-isotopes, etc.) between different organs which are assumed as compartments in the human body.

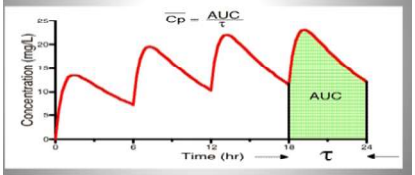
- Multi-compartment models have applications in many fields including pharmacokinetics, epidemiology, biomedicine, systems theory, complexity theory, engineering, physics, information science and social science.

Multiple dosage regimen

- When the duration of treatment of disease is smaller than the therapeutic activity of drug, single dose are given e.g. Aspirin

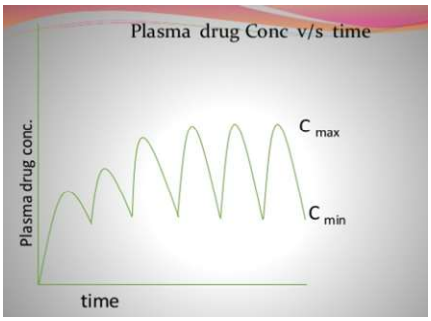


When the duration of treatment of disease is larger than the therapeutic effect of drug, Multiple dosage regimen are given e.g. antibiotics



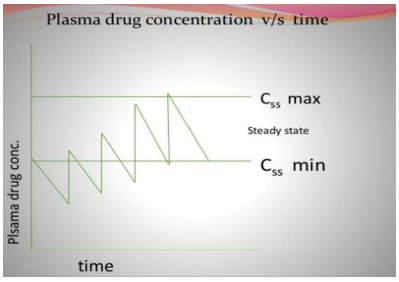
Multiple dosing with respect to oral route

- When an oral multiple dosing regimen is followed, plasma conc. will increase, reach a maximum and begin to decline. A 2nd dose will be administered before all of the absorbed drug from 1st dose is eliminated.
- Consequently plasma conc. resulting from 2nd dose will be higher than from 1st dose. This increase in conc. with dose will continue to occur until a steady state is reach at which rate of drug entry into the body = rate of exit



Multiple dosing with respect to I.V.

- On repeated drug administration, the plasma conc. will be added upon for each dose interval giving a plateau or steady state with the plasma conc. fluctuating between a minimum and maximum



REPETITIVE INTRAVENOUS INJECTION

After single rapid IV injection,

$D_B = D_o e^{-kt}$

If the τ is the dosing interval, then amount of drug remaining in the body after several hr,

$D_B = D_o e^{-k\tau}$

The fraction of the Dose remaining in the body

$f = D_B / D_o = e^{-k\tau}$

INTERMITTENT INTRAVENOUS INFUSION

- The drug may not reach steady state

Short IV infusion → Elimination period → Another short IV infusion

Conc. after one or more short IV infusion

$C_p = D\,(1 - e^{-k\,t}) / t_{inf}\, V_D\, k$

Problem of missed Dose -

Plasma drug conc. at t hr after the nth dose-

$C_p = D_o\, e^{-k\,t}\,(1 - e^{-nk\,\tau}) / V_D\,(1 - e^{-k\tau})$ 1

Conc. contributed by missing dose is

$C_p' = D_o\, e^{-k\,t_{miss}} / V_D$ 2

So missing dose, (eq 1 – eq 2)is

$C_p = D_o(1 - e^{-nk\,\tau})(e^{-k\,t} - e^{-k\,t_{miss}}) / V_D(1 - e^{-k\tau})$

Where, D / t_{inf} = Rate of infusion .i.e. R
D = Size of infusion dose
t_{inf} = infusion period
V_D = volume of distribution
k = elimination rate constant

Drug conc. post IV infusion is

$C_p = C_{stop}\, e^{-kt}$

Where, C_{stop} = Conc. when infusion stop
t = time elapsed since infusion stopped

MULTIPLE – ORAL- DOSE REGIMEN

The plasma conc. at any time during oral multiple dose regimen,

$$C_p = \frac{F.ka.D_o}{V_D(k - ka)}\left[\frac{1 - e^{-nka\,\tau}}{1 - e^{-ka\,\tau}}\, e^{-kat} - \frac{1 - e^{-nk\,\tau}}{1 - e^{-k\,\tau}}\, e^{-k\,t}\right]$$

Where, n= no. of doses
τ = dosing interval
F = fraction of dose absorbed

Max. Conc. & min. Conc. during multiple dosing

$C_{ss,max} = C_o / 1 - e^{-k\tau}$

$C_{ss,min} = C_{ss,max} \cdot e^{-k\tau}$

Ratio of Cmax / Cmin is known as fluctuation, Greater the ratio, greater the fluctuation.

$C_{ss,av} = F\,X_o / Cl_T \cdot \tau$.

FOR MULTIPLE ORAL DOSE

$C_{av}^{\infty} = F\,D_o / Cl_T \cdot \tau$

$C_{max}^{\infty} = F\,D_o\, e^{-k\,tp} / V_D\,(1 - e^{-k\tau})$

$C_{min}^{\infty} = ka\,F\,D_o\, e^{-k\tau} / V_D\,(ka - k)(1 - e^{k\tau})$

LOADING AND MAINTENANCE DOSE

An *initial or first dose* intended to be *therapeutic* is called as priming or ***loading dose***

$D_{o,L} = C_{ss,av} \cdot V_D / F$

For 1 compartment model,

$LD = \frac{V_D \times D_{(P)target}}{F}$

For 2 compartment model,

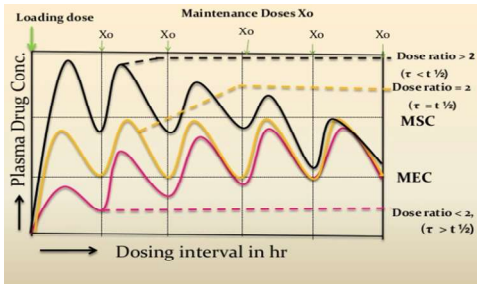
$LD = \frac{V_{D(B)} \times D_{(P)target}}{F}$

OBJECTIVE- to achieve desired plasma conc., $C_{av.}^{ss}$ as quickly as possible.

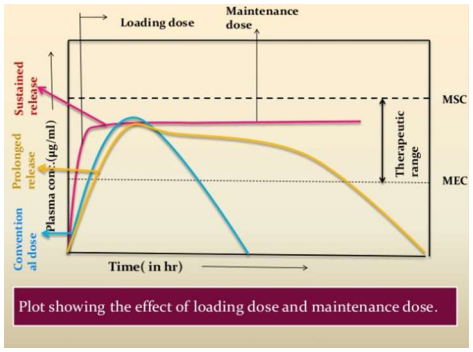
$DI_{max} = 1.44\ t_{½} \times \log TW$

While, $TW = \frac{MSC}{MEC}$

Route of Drug administration (MD /DI)= $\frac{D_{(t)}target \times Cl}{F}$



- A **maintenance dose** is given to maintain C_{av}^{ss} and *steady state* so that the therapeutic effect is also maintained
- The ratio of loading dose to maintenance dose
- *Xo, L / Xo* , is called as ***Dose ratio***
- When, $\tau = t_{½}$, dose ratio should be equal to 2
- $\tau > t_{½}$, dose ratio should be smaller than 2
- $\tau < t_{½}$ dose ratio should be greater than 2



Plot showing the effect of loading dose and maintenance dose.