

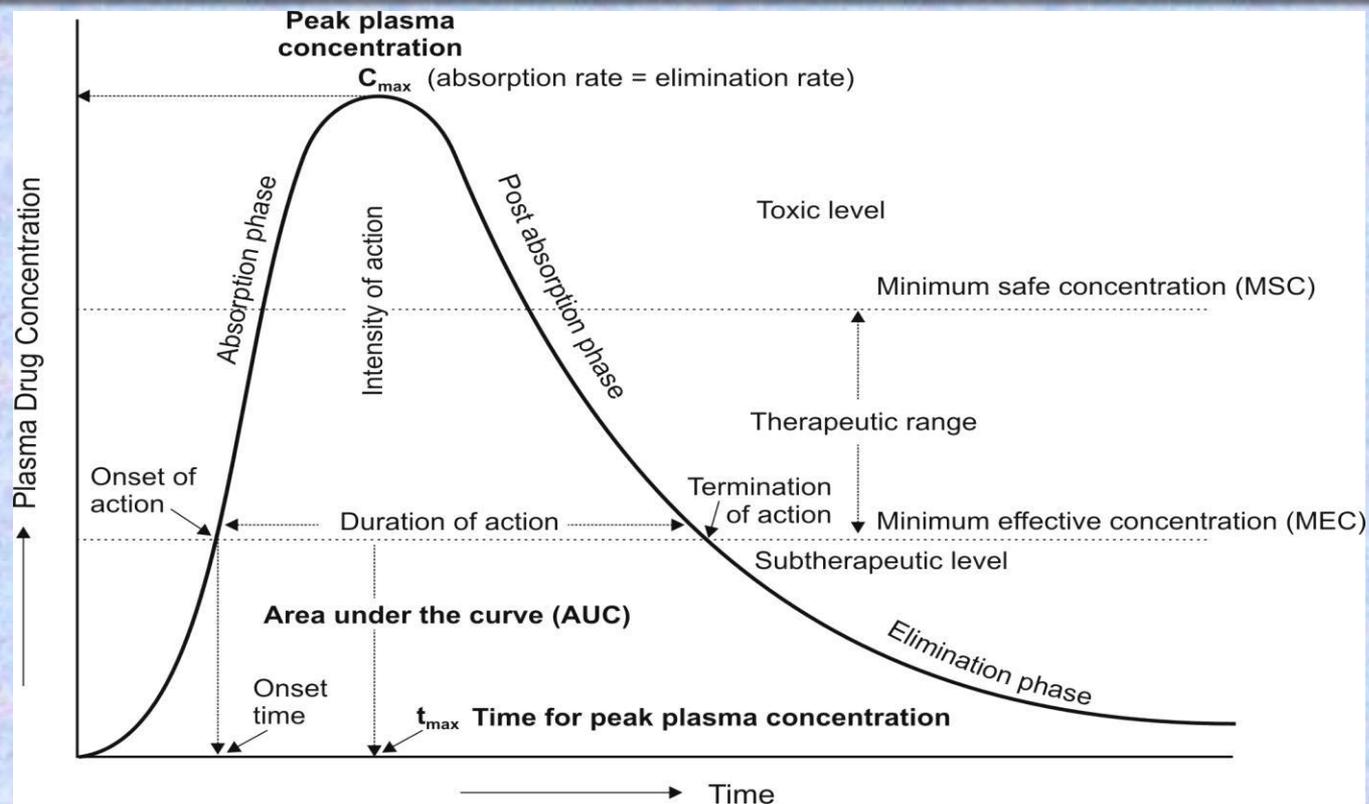
PHARMACOKINETIC MODELS

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Plasma Drug Concentration-Time Profile:-

A direct relationship exists between the concentration of drug at the biophase (site of action) and the concentration of drug in plasma. Two categories of parameters can be evaluated from a plasma concentration time profile –

1. *Pharmacokinetic parameters, and*
2. *Pharmacodynamic parameters.*



Pharmacokinetic Parameters:-

1. Peak Plasma Concentration (C_{max})

The peak plasma level depends upon –

- a) The administered dose
- b) Rate of absorption, and
- c) Rate of elimination.

2. Time of Peak Concentration (t_{max})

3. Area Under the Curve (AUC)

Pharmacodynamic Parameters:-

1. Minimum Effective Concentration (MEC)

2. Maximum Safe Concentration (MSC)

3. Onset of Action

4. Onset Time

5. Duration of Action

6. Intensity of Action

7. Therapeutic Range

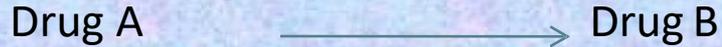
8. Therapeutic Index

Rate, Rate Constants and Orders of Reactions

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

Order of reaction: *The manner in which the concentration of drug (or reactants) influences the rate of reaction or process is called as the **order of reaction** or **order of process**.*

Consider the following chemical reaction:



The rate of forward reaction is expressed as – $-dA/dt$

Negative sign indicates that the concentration of drug A decreases with time t. As the reaction proceeds, the concentration of drug B increases and the rate of reaction can also be expressed as: dB/dt

$$dC/dt = -KC^n$$

K = rate constant

n = order of reaction

Zero-Order Kinetics (Constant Rate Processes)

If $n = 0$, equation becomes:

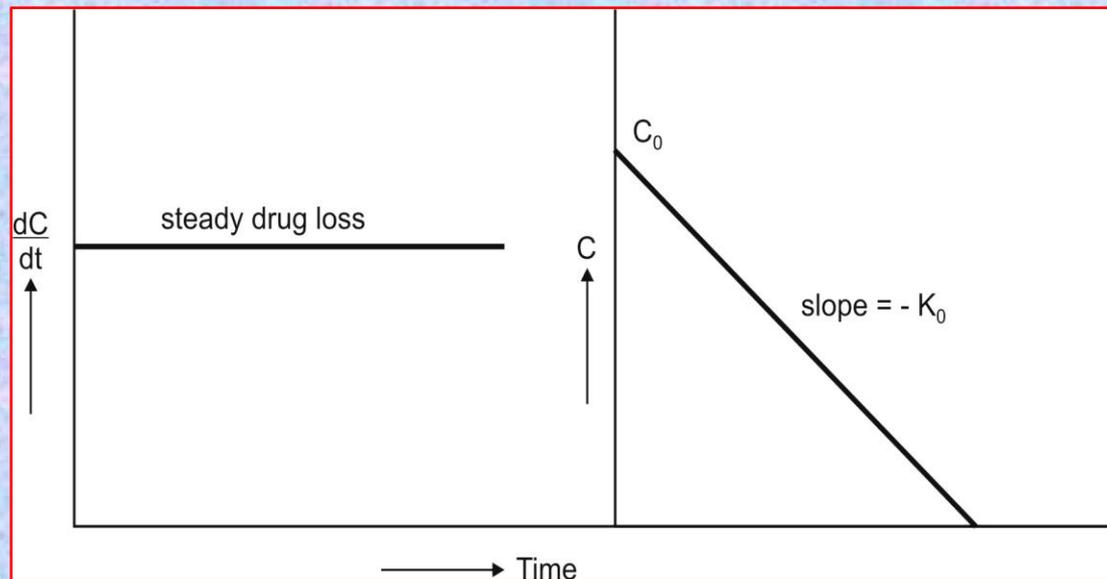
$$dC/dt = -K_0 C^0$$

where K_0 = zero-order rate constant (in mg/min)

Zero-order process can be defined as the one whose rate is independent of the concentration of drug undergoing reaction i.e. the rate of reaction cannot be increased further by increasing the concentration of reactants.

Finally,

$$C = C_0 - K_0 t$$



Zero-Order Half-Life

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

$$t_{1/2} = C_0 / 2 K_0$$

Examples of zero-order processes are –

1. Metabolism/protein-drug binding/enzyme or carrier-mediated transport under saturated conditions. The rate of metabolism, binding or transport of drug remains constant as long as its concentration is in excess of saturating concentration.
2. Administration of a drug as a constant rate i.v. infusion.
3. Controlled drug delivery such as that from i.m. implants or osmotic pumps.

First-Order Kinetics (Linear Kinetics)

If $n = 1$, equation becomes:

$$dC/dt = -K C$$

where K = first-order rate constant (in time⁻¹ or per hour)

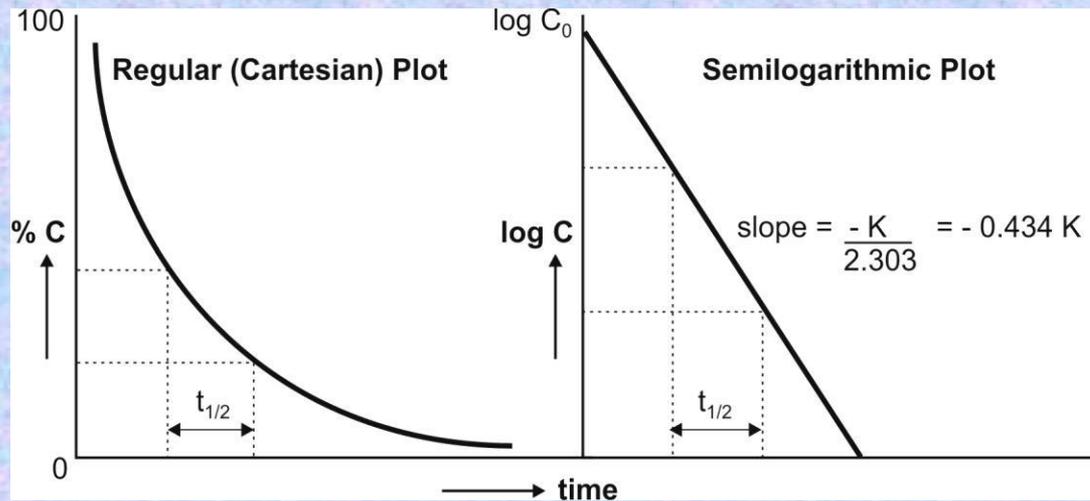
first-order process *is the one whose rate is directly proportional to the concentration of drug undergoing reaction i.e. greater the concentration, faster the reaction.* It is because of such proportionality between rate of reaction and the concentration of drug that a first-order process is said to follow **linear kinetics**.

$$\ln C = \ln C_0 - K t$$

$$C = C_0 - e^{-Kt}$$

$$\log C = \log C_0 - Kt/2.303$$

The first-order process is also called as **monoexponential rate process**. Thus, a first-order process is characterized by **logarithmic** or **exponential kinetics** i.e. *a constant fraction of drug undergoes reaction per unit time.*



$$t_{1/2} = 0.693 / K$$

Equation shows that, in contrast to zero-order process, the half-life of a first-order process is a constant and independent of initial drug concentration i.e. irrespective of what the initial drug concentration is, the time required for the concentration to decrease by one-half remains the same.

Most pharmacokinetic processes *viz.* absorption, distribution and elimination follow first-order kinetics.

PHARMACOKINETIC MODELS

Drug movement within the body is a complex process. The major objective is therefore to develop a generalized and simple approach to describe, analyse and interpret the data obtained during *in vivo* drug disposition studies.

The two major approaches in the quantitative study of various kinetic processes of drug disposition in the body are

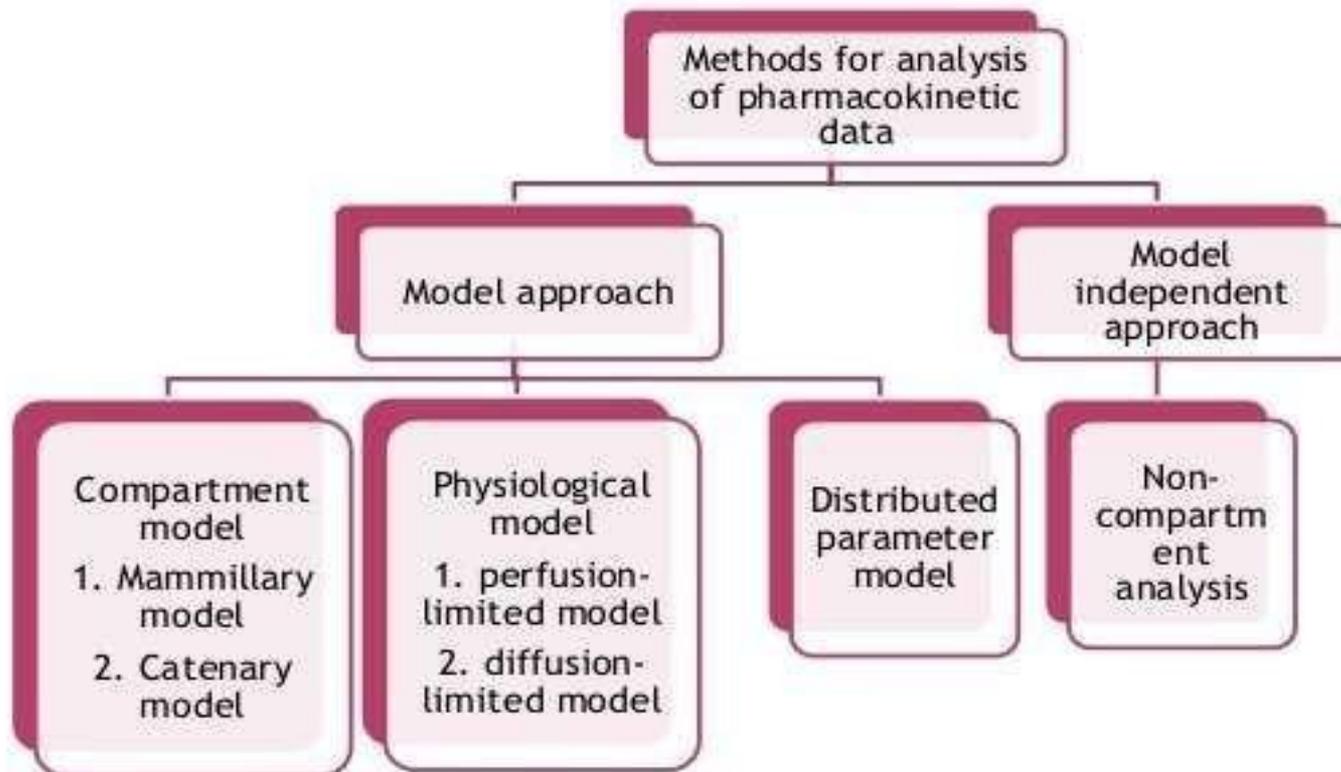
- 1. Model approach, and**
- 2. Model-independent approach (also called as non-compartmental analysis).**

PHARMACOKINETIC MODEL APPROACH

□ **MODEL**:- A model is a hypothesis that employ mathematical terms to concisely describe quantitative relationship.

□ **PHARMACOKINETIC MODEL**:- It provide concise means of expressing mathematically or quantitatively, the time course of drug(s) throughout the body and compute meaningful pharmacokinetic parameters.

METHODS FOR ANALYSIS OF PHARMACOKINETIC DATA:-



Applications of Pharmacokinetic Models –

1. Characterizing the behaviour of drugs in patients.
2. Predicting the concentration of drug in various body fluids with any dosage regimen.
3. Predicting the multiple-dose concentration curves from single dose experiments.
4. Calculating the optimum dosage regimen for individual patients.
5. Evaluating the risk of toxicity with certain dosage regimens.
6. Correlating plasma drug concentration with pharmacological response.
7. Evaluating the bioequivalence/bioinequivalence between different formulations of the same drug.
8. Estimating the possibility of drug and/or metabolite(s) accumulation in the body.
9. Determining the influence of altered physiology/disease state on drug ADME.
10. Explaining drug interactions.

COMPARTMENT MODELS

Compartmental analysis is commonly used to estimate the pharmacokinetic characters of a drug.

The compartments are hypothetical in nature

1. The body is represented as a series of compartments arranged either in series or parallel to each other, that communicate reversibly with each other.
2. Each compartment is not a real physiologic or anatomic region and considered as a tissue or group of tissues that have similar drug distribution characteristics (similar blood flow and affinity).
3. Every organ, tissue or body fluid that can get equilibrated with the drug is considered as a separate compartment.
4. The rate of drug movement between compartments (i.e. entry and exit) is described by first-order kinetics.
5. Rate constants are used to represented to entry and exit from the compartment.

The compartment models are divided into two categories

- A. *Mammillary model*
- B. *Catenary model.*

A. Mammillary model

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

The **central compartment** comprises of plasma and highly perfused tissues such as lungs, liver, kidneys, etc. which rapidly equilibrate with the drug.

The drug is directly absorbed into this compartment (i.e. blood). Elimination too occurs from this compartment since the chief organs involved in drug elimination are liver and kidneys, the highly perfused tissues and therefore presumed to be rapidly accessible to drug in the systemic circulation.

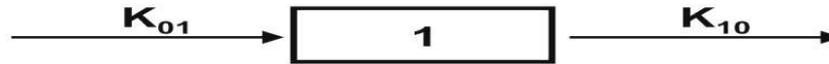
The **peripheral compartments** or **tissue compartments** (denoted by numbers 2, 3, etc.) are those with low vascularity and poor perfusion.

Model 1



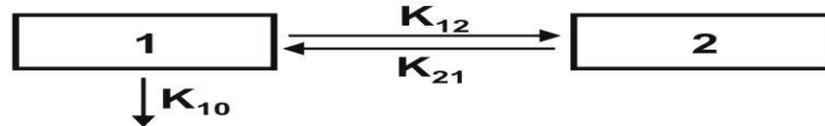
One-compartment open model, intravenous administration

Model 2



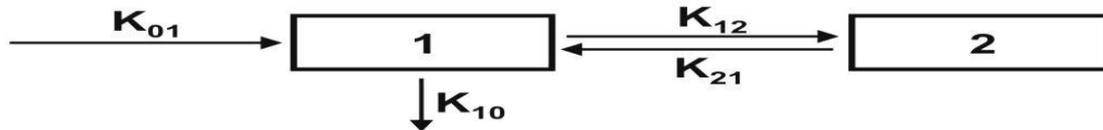
One-compartment open model, extravascular (oral, rectal, etc.) administration

Model 3



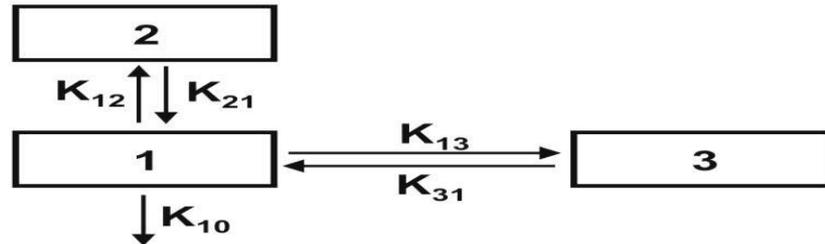
Two-compartment open model, intravenous administration

Model 4



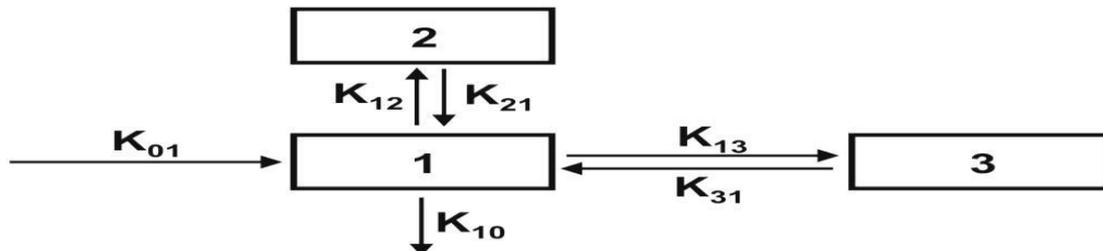
Two-compartment open model, extravascular administration

Model 5



Three-compartment open model, intravenous administration

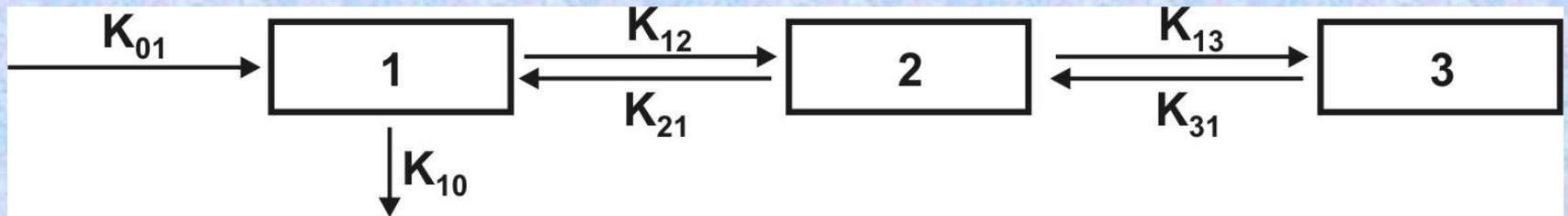
Model 6

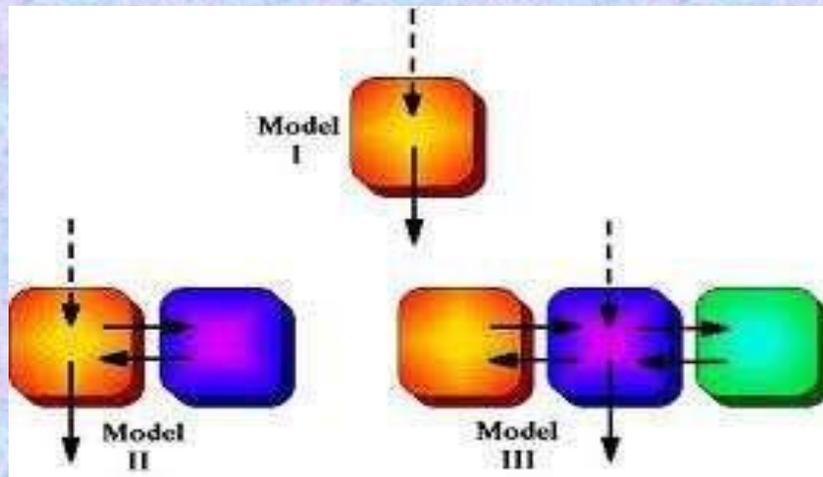


Three-compartment open model, extravascular administration

B. Catenary model

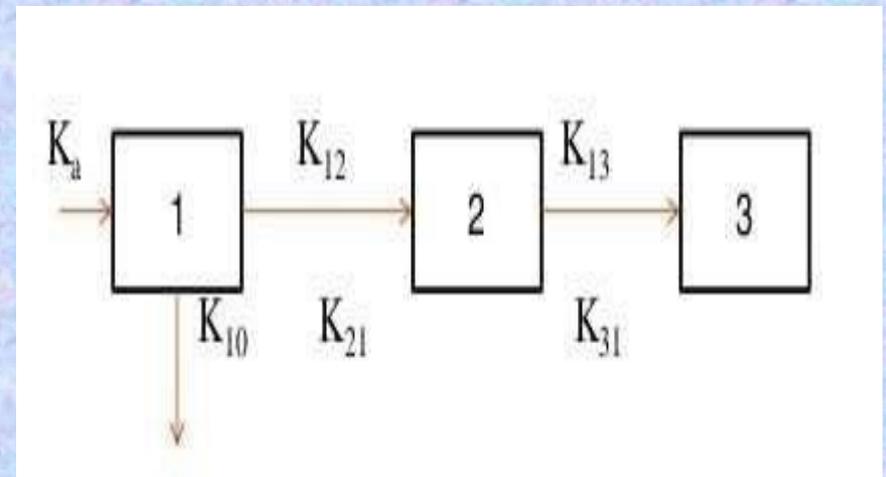
In this model, the compartments are joined to one another in a series like compartments of a train. This is however not observable physiologically/anatomically as the various organs are directly linked to the blood compartment. Hence this model is rarely used.





MAMMILARY MODEL:-

compartment arranged in parallel to central compartment.



CATENARY MODEL:-

Compartment arranged in series with central compartment

ONE-COMPARTMENT OPEN MODEL

(instantaneous distribution model)

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



Depending upon the rate of input, several one-compartment open models can be defined:

1. One-compartment open model, i.v. bolus administration.
2. One-compartment open model, continuous i.v. infusion.
3. One-compartment open model, e.v. administration, zero-order absorption.
4. One-compartment open model, e.v. administration, first-order absorption.

One-Compartment Open Model

Intravenous Bolus Administration

When a drug that distributes rapidly in the body is given in the form of a rapid intravenous injection (i.e. i.v. bolus or slug), it takes about one to three minutes for complete circulation and therefore the rate of absorption is neglected in calculations.

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

Since **rate in** or absorption is absent in IV bolus, 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, K_E = 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.

1. Elimination Rate Constant: Integration of equation

$$\ln X = \ln X_0 - K_E t$$

where, X_0 = amount of drug at time

$t = 0$ i.e. the initial amount of drug injected.

in the exponential form as

$$X = X_0 e^{-K_E t}$$

$$\log X = \log X_0 - \frac{K_E t}{2.303}$$

Since it is difficult to determine directly the amount of drug in the body X , advantage is taken of the fact that a constant relationship exists between drug concentration in plasma C (easily measurable) and X ; thus:

$$X = V_d C$$

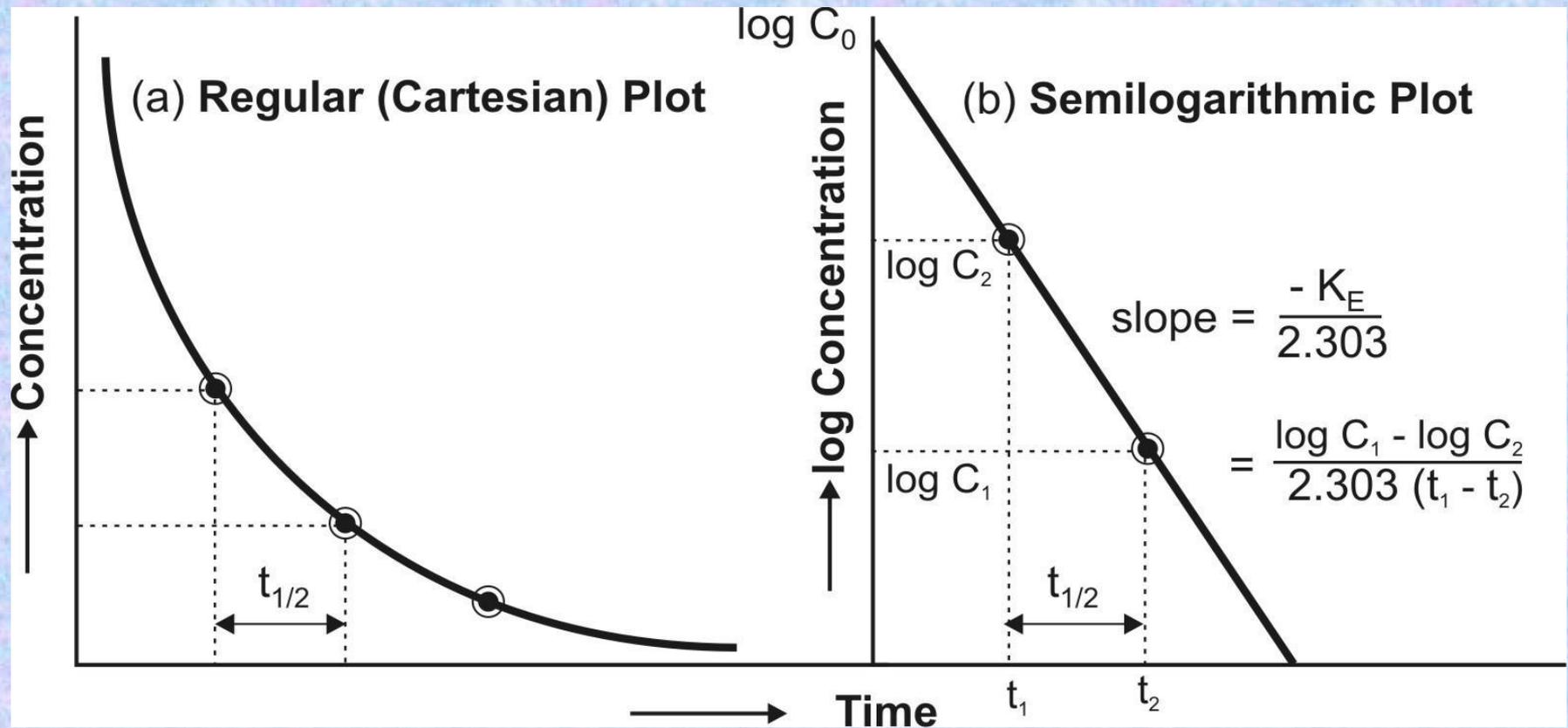
where, $V_d =$ *apparent volume of distribution*.

It is a pharmacokinetic parameter that permits the use of plasma drug concentration in place of amount of drug in the body.

$$\log C = \log C_0 - \frac{K_E t}{2.303}$$

The elimination rate constant is directly obtained from the slope of the line. It has units of min^{-1} .

Thus, a linear plot is easier to handle mathematically than a curve which in this case will be obtained from a plot of Concentration versus time on regular plot.



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

2. Elimination Half-Life:

Also called as **biological half-life**, it is the oldest and the best known of all pharmacokinetic parameters and was once considered as the most important characteristic of a drug.

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.

It is expressed in hours or minutes. Half-life is related to elimination rate constant by the following equation:

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

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

3. Clearance:

Clearance 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 liters/hour.

Clearance is usually further defined as blood clearance (Cl_b), plasma clearance (Cl_p) or clearance based on unbound or free drug concentration (Cl_u) depending upon the concentration measured for the equation

$$\text{Clearance} = \frac{\text{Rate of elimination}}{\text{Plasma drug concentration}}$$

$$\text{or } Cl = \frac{dX/dt}{C}$$

$$Vd = \frac{X_0}{K_E AUC}$$

One-Compartment Open Model

Intravenous Infusion

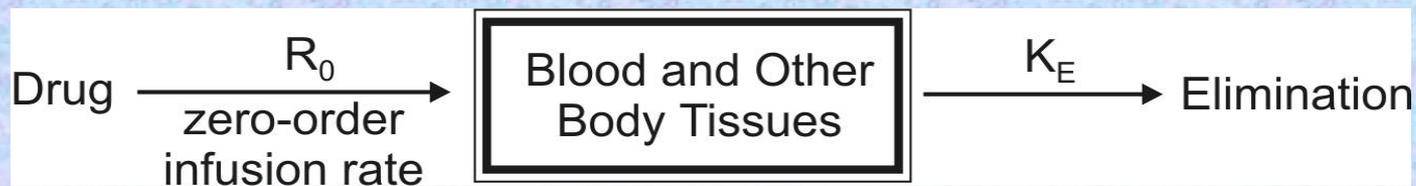
Rapid I.V. injection is unsuitable, when the drug has potential to precipitate toxicity, when a stable concentration of drug in the body is desired.

In such a situation, the drug is administered at a constant rate (zero-order) by i.v. infusion.

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. Electrolytes and nutrients can be conveniently administered simultaneously by the same infusion line in critically ill patients.



At any time during infusion, the rate of change in the amount of drug in the body, dX/dt is the difference between the zero-order rate of drug infusion R_0 and first-order rate of elimination, $-K_E X$:

$$\frac{dX}{dt} = R_0 - K_E X$$

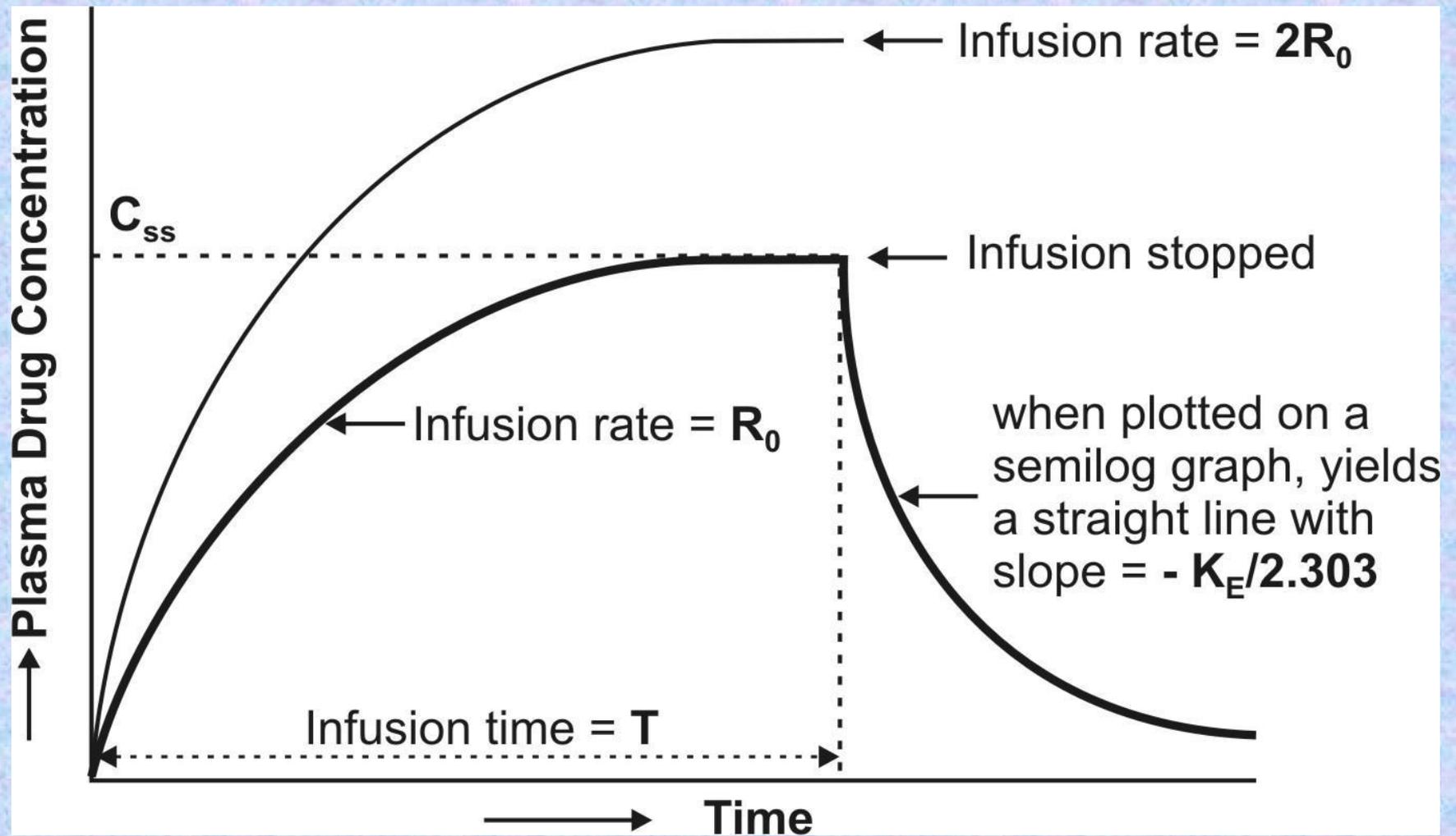
Integration and rearrangement of above equation

$$X = \frac{R_0}{K_E} (1 - e^{-K_E t})$$

Since $X = V_d C$, transformed into concentration terms as follows

$$C = \frac{R_0}{K_E V_d} (1 - e^{-K_E t}) = \frac{R_0}{C l_T} (1 - e^{-K_E t})$$

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



Plasma concentration-time profile for a drug given by constant rate I.V. infusion (the two curves indicate different infusion rates R_0 and $2R_0$ for the same drug)

At steady-state, the rate of change of amount of drug in the body is zero, hence, the equation becomes:

$$\text{Zero} = R_0 - K_E X_{ss}$$

Transforming to concentration terms and rearranging the equation

$$C_{ss} = \frac{R_0}{K_E V_d} = \frac{R_0}{Cl_T} \quad \text{i.e.} \quad \frac{\text{Infusion rate}}{\text{Clearance}}$$

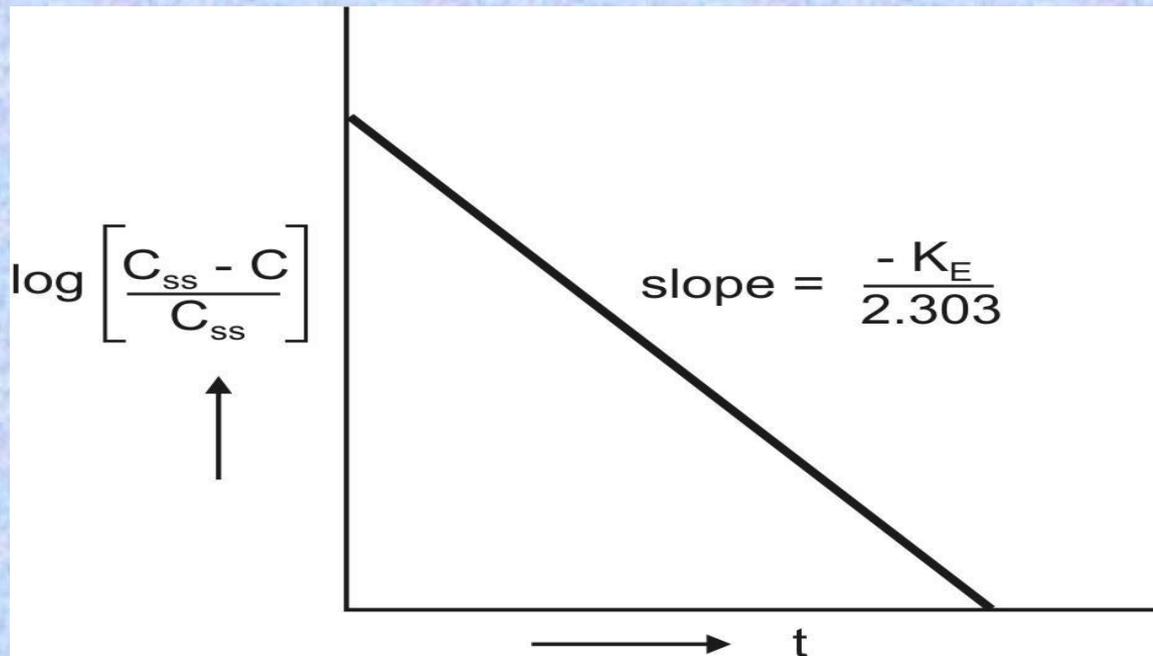
1. where, X_{ss} and C_{ss} are amount of drug in the body and concentration of drug in plasma at steady-state respectively.
2. The value of K_E can be obtained from the slope of straight line obtained after a semilogarithmic plot ($\log C$ versus t)
3. Alternatively, K_E can be calculated from the data collected during infusion to steady-state as follows: Substituting $R_0/Cl_T = C_{ss}$

$$C = C_{ss} (1 - e^{-K_E t})$$

$$\left[\frac{C_{ss} - C}{C_{ss}} \right] = e^{-K_E t}$$

Transforming into log form, the equation becomes

$$\log \left[\frac{C_{ss} - C}{C_{ss}} \right] = \frac{-K_E t}{2.303}$$



Semilog plot to compute K_E from infusion data up to steady-state

One-Compartment Open Model

Extravascular Administration

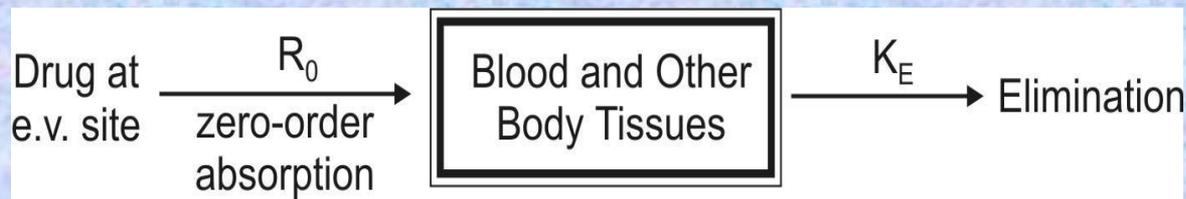
1. When a drug is administered by extravascular route (e.g. oral, i.m., rectal, etc.), absorption is a prerequisite for its therapeutic activity.
2. The rate of absorption may be described mathematically as a zero-order or first-order process.
3. After e.v. administration, the rate of change in the amount of drug in the body dX/dt is the difference between the rate of input (absorption) dX_{ev}/dt and rate of output (elimination) dX_E/dt .

$$dX/dt = \text{Rate of absorption} - \text{Rate of elimination}$$

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

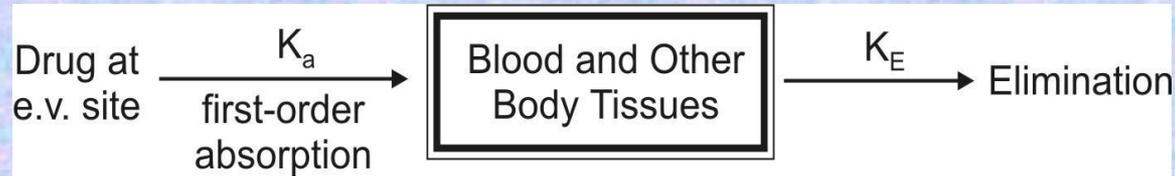
Zero-Order Absorption Model

This model is similar to that for constant rate infusion.



First-Order Absorption Model

For a drug that enters the body by a first-order absorption process, gets distributed in the body according to one-compartment kinetics and is eliminated by a first-order process, the model can be depicted as follows:

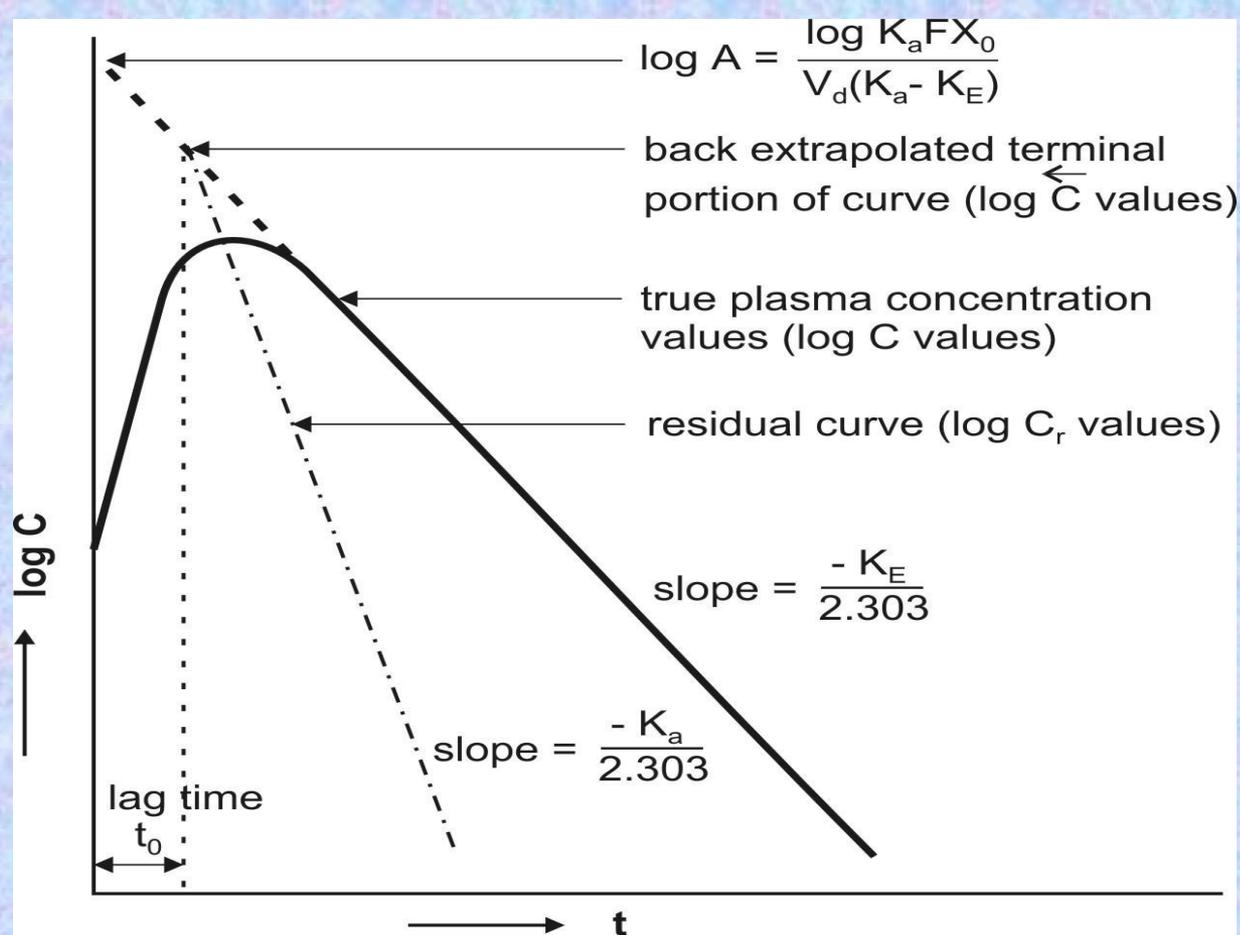


$$\frac{dX}{dt} = K_a X_a - K_E X$$

K_a = first-order absorption rate constant, and X_a = amount of drug at the absorption site remaining to be absorbed i.e. ARA.

Integration of equation $X = \frac{K_a F X_0}{(K_a - K_E)} [e^{-K_E t} - e^{-K_a t}]$

Transforming into concentration terms $C = \frac{K_a F X_0}{V_d (K_a - K_E)} [e^{-K_E t} - e^{-K_a t}]$



Plasma concentration-time profile after oral administration of a single dose of a drug. The biexponential curve has been resolved into its two components—absorption and elimination.

$$\log \bar{C} = \log A - \frac{K_E t}{2.303}$$

Two-Compartment Open Model

Intravenous Bolus Administration

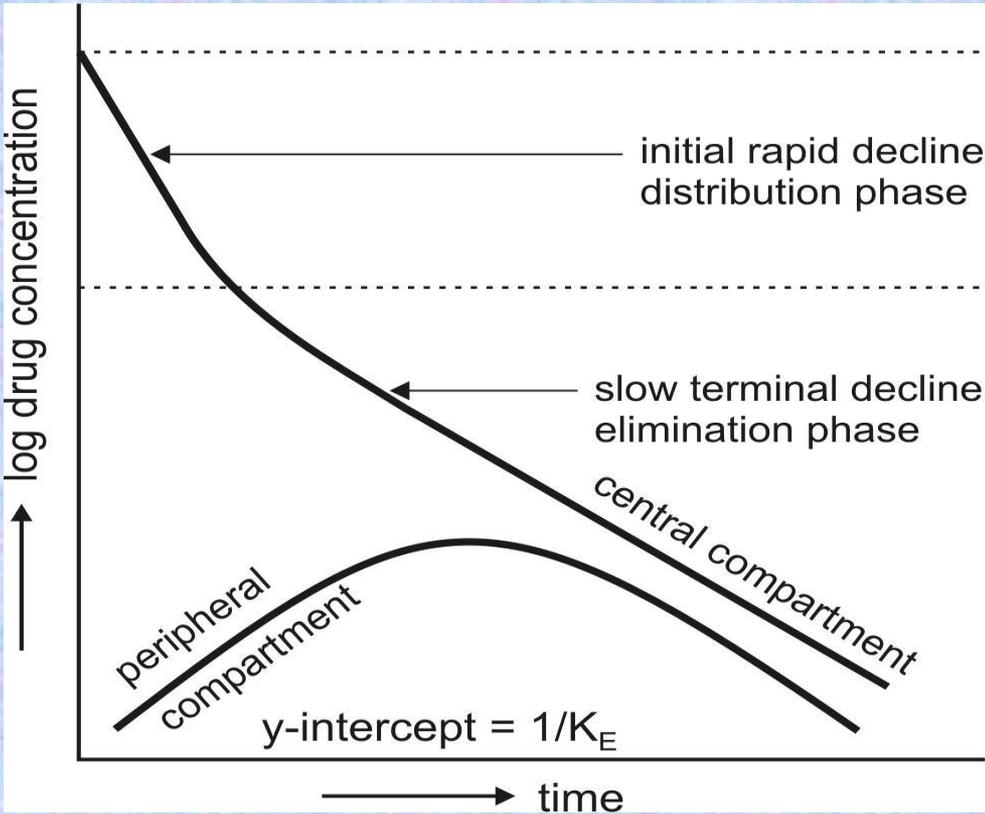
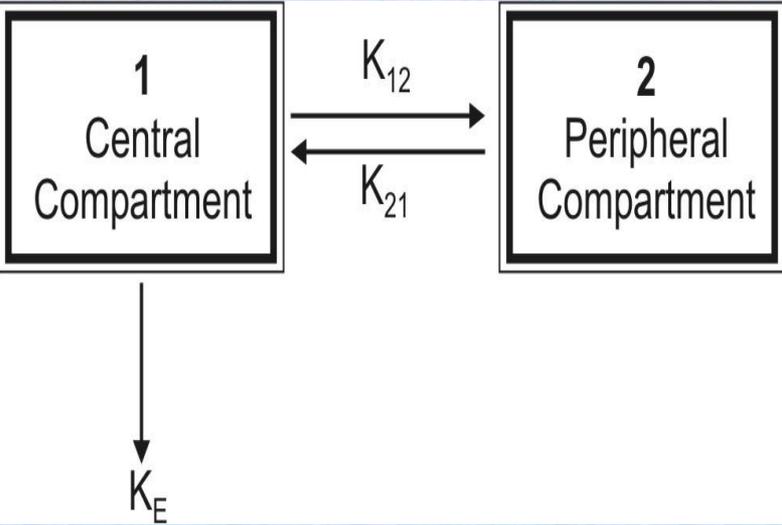
After the I.V. bolus of a drug that follows two-compartment kinetics, the decline in plasma concentration is biexponential indicating the presence of *two disposition processes*

1. *Distribution*
2. *Elimination.*

Initially, the concentration 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 the **distributive phase**.

After sometime, a *pseudo-distribution equilibrium* is achieved between the two compartments following which the subsequent loss of drug from the central compartment is slow and mainly due to elimination.

This *second, slower rate process* is called as the **post-distributive** or **elimination phase**.



Changes in drug concentration in the central and the peripheral compartment after I.V. bolus of a drug that fits two-compartment model

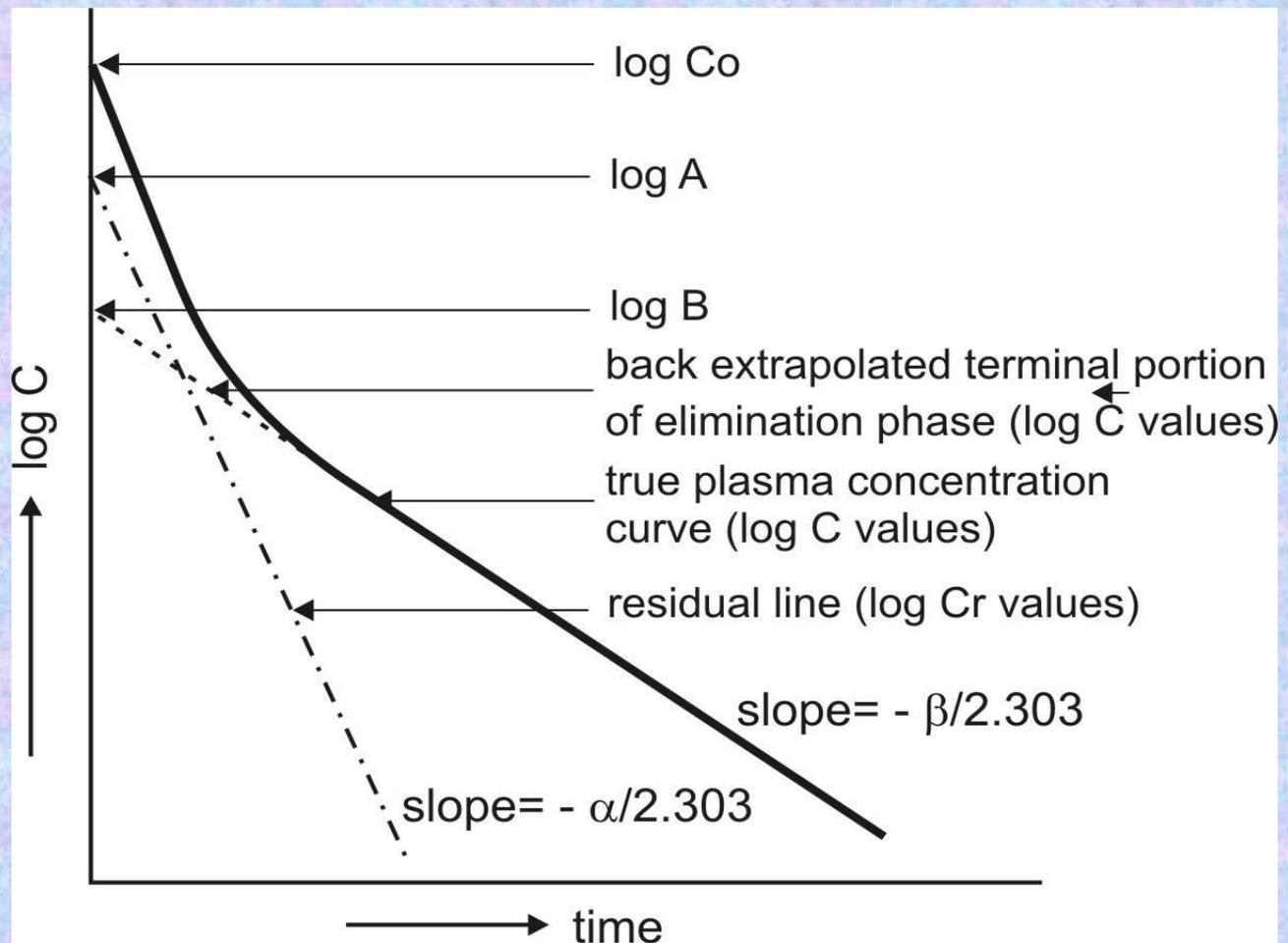
Let K_{12} and K_{21} be the first-order distribution rate constants depicting drug transfer between the central and the peripheral compartments.

The rate of change in drug concentration in the central compartment is given by:

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

Extending the relationship $X = V_d C$ to the above equation

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

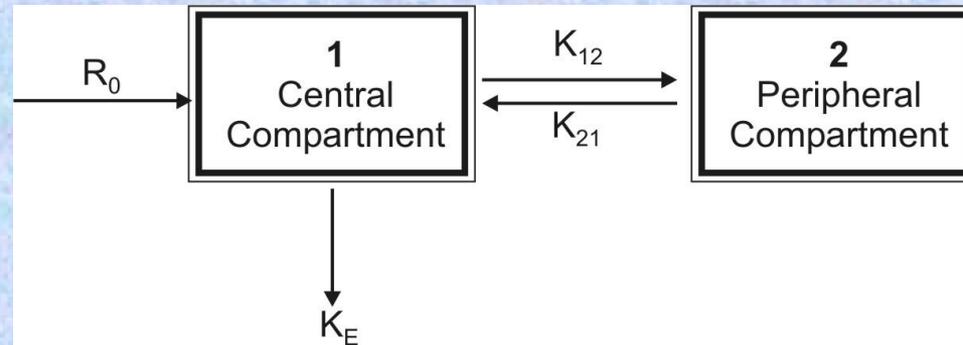


$$\log C_r = \log A - \frac{\alpha t}{2.303}$$

Biexponential plasma concentration-time curve by the method of residuals for a drug that follows two-compartment kinetics on i.v. bolus administration

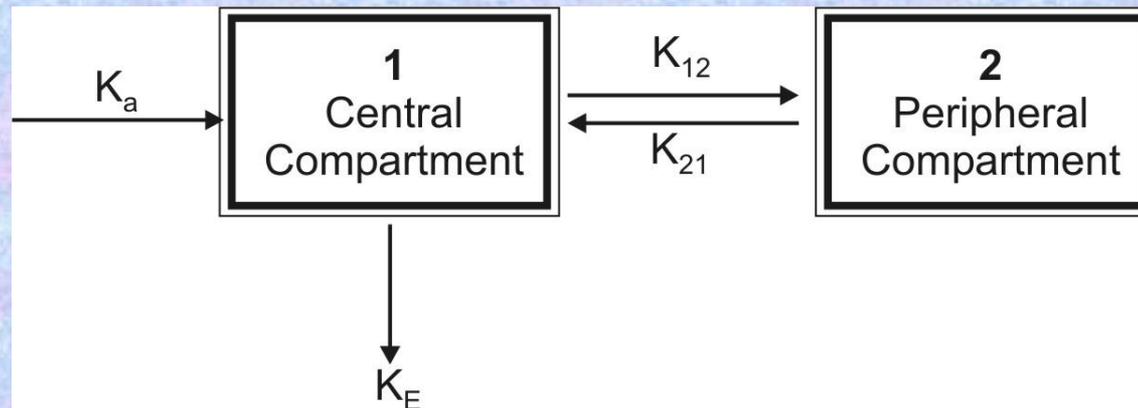
Two-Compartment Open Model

Intravenous Infusion



Two-Compartment Open Model

Extravascular Administration – First-Order Absorption



Noncompartmental Analysis

The *noncompartmental analysis*, also called as the **model-independent method**, does not require the assumption of specific compartment model. This method is, however, *based on the assumption that the drugs or metabolites follow linear kinetics*, and on this basis, this technique can be applied to any compartment model.

The *noncompartmental approach*, based on the **statistical moments theory**, involves collection of experimental data following a single dose of drug. If one considers the time course of drug concentration in plasma as a statistical distribution curve, then:

$$\text{MRT} = \frac{\text{AUMC}}{\text{AUC}} \qquad \text{AUMC} = \int_0^{\infty} C t dt$$

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 concentration and time (i.e. C.t) versus time t from zero to infinity.

AUC is obtained from a plot of plasma drug concentration versus time from zero to infinity. Mathematically, it is expressed by equation

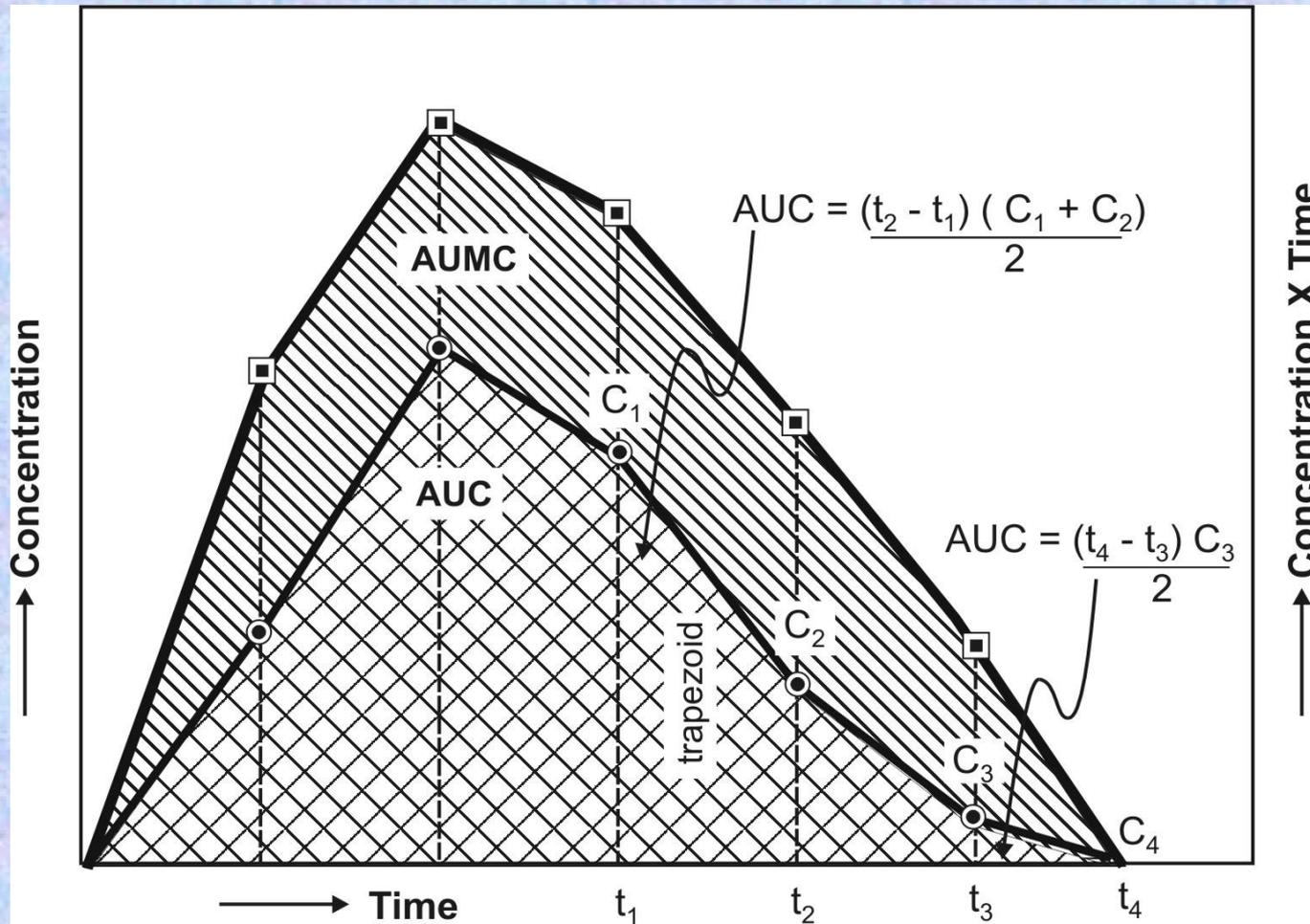
$$AUC = \int_0^{\infty} C \, dt$$

Practically, the AUMC and AUC can be calculated from the respective graphs by the **trapezoidal rule**

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

Applications

- It is widely used to estimate the important pharmacokinetic parameters like bioavailability, clearance and apparent volume of distribution.
- The method is also useful in determining half-life, rate of absorption and first-order absorption rate constant of the drug.



AUC and AUMC plots

NON LINEAR PHARMACOKINETICS

The rate process of a drug's ADME are dependent upon enzymes that are substrate-specific, have definite capacities, and susceptible to saturation at high drug concentration.

In such cases, an essentially first-order kinetics transform into a mixture of first-order and zero-order rate processes and the pharmacokinetic parameters change with the size of the administered dose.

The pharmacokinetics of such drugs are said to be **dose-dependent**. Other terms are **mixed-order**, **nonlinear** and **capacity-limited kinetics**.

CAUSES OF NONLINEARITY

- **Drug Absorption**
- Nonlinearity in drug absorption can arise from 3 important sources –
- *When absorption is solubility or dissolution rate-limited* e.g. griseofulvin. At higher doses, a saturated solution of the drug is formed in the GIT or at any other extravascular site and the rate of absorption attains a constant value.
- *When absorption involves carrier-mediated transport systems* e.g. absorption of riboflavin, ascorbic acid, cyanocobalamin, etc. Saturation of the transport system at higher doses of these vitamins results in nonlinearity.
- *When presystemic gut wall or hepatic metabolism attains saturation* e.g. propranolol, hydralazine and verapamil. Saturation of presystemic metabolism of these drugs at high doses leads to increased bioavailability.

- **Drug Distribution**

- Nonlinearity in distribution of drugs administered at high doses may be due to –
- *Saturation of binding sites on plasma proteins* e.g. phenylbutazone and naproxen. There is a finite number of binding sites for a particular drug on plasma proteins and, theoretically, as the concentration is raised, so too is the fraction unbound.
- *Saturation of tissue binding sites* e.g. thiopental and fentanyl. With large single bolus doses or multiple dosing, saturation of tissue storage sites can occur.

- **Drug Metabolism**

- The nonlinear kinetics of most clinical importance is capacity-limited metabolism since small changes in dose administered can produce large variations in plasma concentration at steady-state. It is a major source of large intersubject variability in pharmacological response.
- Two important causes of nonlinearity in metabolism are –
- *Capacity-limited metabolism due to enzyme and/or cofactor saturation.* Typical examples include phenytoin, alcohol, theophylline, etc.
- *Enzyme induction* e.g. carbamazepine, where a decrease in peak plasma concentration has been observed on repetitive administration over a period of time. Autoinduction characterized in this case is also dose-dependent. Thus, enzyme induction is a common cause of both dose- and time-dependent kinetics.

- **Drug Excretion**

- The two active processes in renal excretion of a drug that are saturable are –
- *Active tubular secretion* e.g. penicillin G. After saturation of the carrier system, a decrease in renal clearance occurs.
- *Active tubular reabsorption* e.g. water soluble vitamins and glucose. After saturation of the carrier system, an increase in renal clearance occurs.

MICHAELIS MENTEN EQUATION

The kinetics of capacity-limited or saturable processes is best described by Michaelis-Menten equation:

$$-\frac{dC}{dt} = \frac{V_{\max} C}{K_m + C}$$

Where,

$-dC/dt$ = rate of decline of drug concentration with time,

V_{\max} = theoretical maximum rate of the process, and

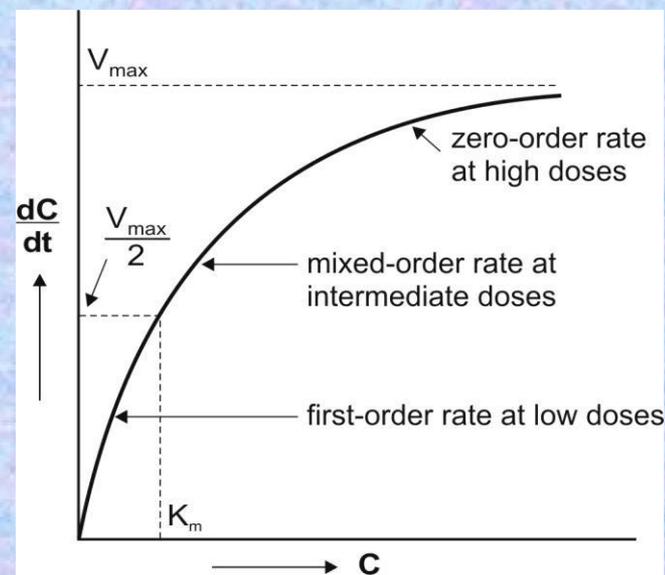
K_m = Michaelis constant.

Three situations can now be considered depending upon the values of K_m and C :

When $K_m = C$

Under this situation, the equation 10.1 reduces to:

$$-\frac{dC}{dt} = \frac{V_{\max}}{2}$$



When $K_m \gg C$

Here, $K_m + C = K_m$ and the equation 10.1 reduces to:

$$-\frac{dC}{dt} = \frac{V_{\max} C}{K_m}$$

When $K_m \ll C$

Under this condition, $K_m + C \approx C$ and the equation 10.1 will become

$$-\frac{dC}{dt} = V_{\max}$$

Estimation of K_m and V_{\max}

$$\log C = \log \bar{C}_0 - \frac{V_{\max}}{2.303 K_m} t$$

