PHARMACOKINETIC MODELS

For Class- B.Pharmacy 6th Semester

Subject- BIOPHARMACEUTICS AND PHARMACOKINETICS (BP604T)

RAMAKANT JOSHI

School of Studies in Pharmaceutical Sciences, Jiwaji University, Gwalior

INTRODUCTION:-

- **Pharmacokinetic modeling** is a mathematical modeling technique for predicting the absorption, distribution, metabolism and excretion (ADME) of synthetic or natural chemical substances in humans and other animal species.

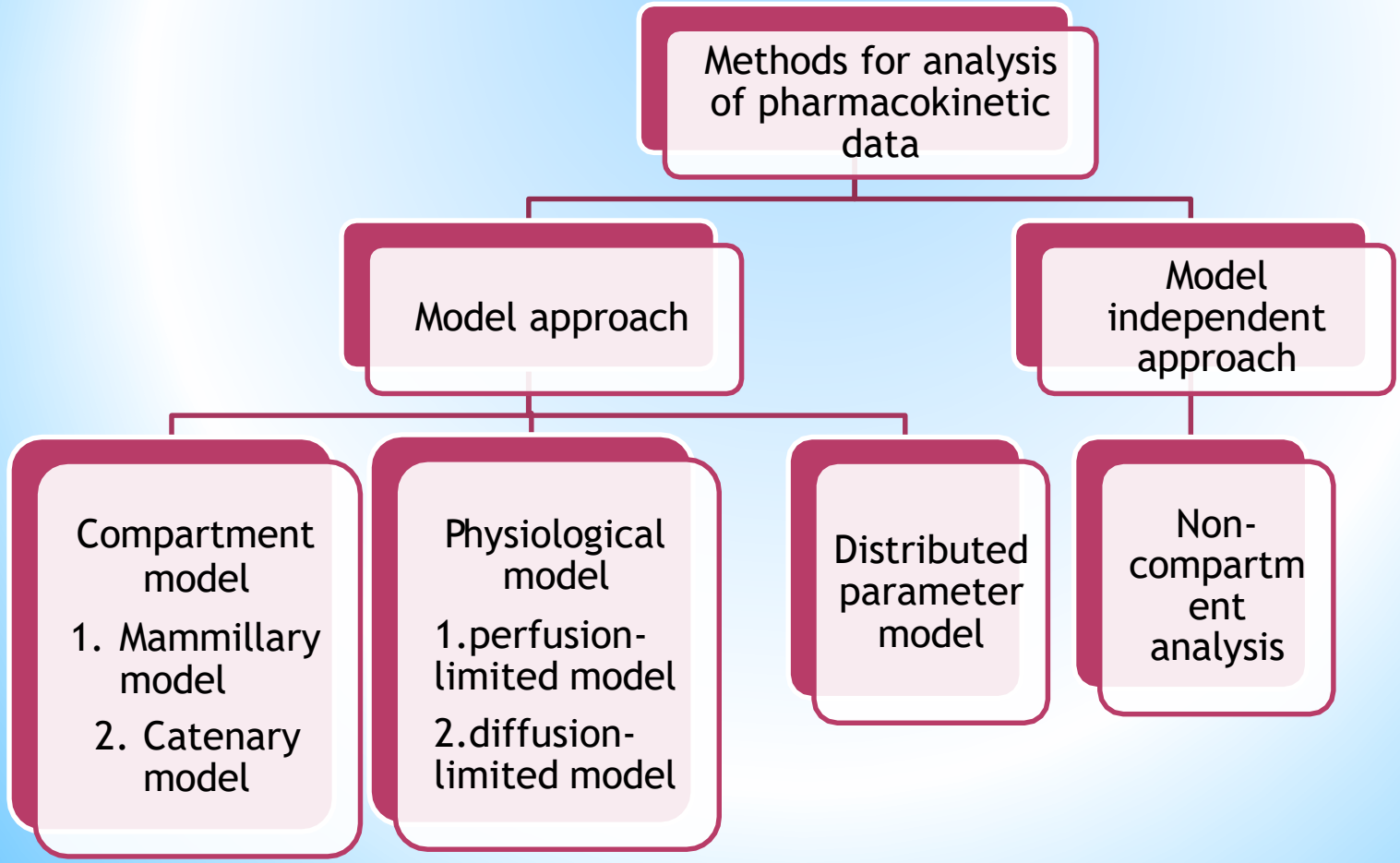
- Drug movement within the body is the complex process to describe and for analysis.

- So 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 (non-compartmental analysis)

METHODS FOR ANALYSIS OF PHARMACOKINETIC DATA:-



PHARMACOKINETIC MODEL APPROACH:-

- In this approach, models are used to describe changes in drug concentration in the body with time.

PHARMACOKINETIC MODEL:

Pharmacokinetic model provides mathematical expression for the time course of drugs throughout the body and compute meaningful pharmacokinetic parameters.

TYPES OF PHARMACOKINETIC MODELS:-

* **Compartment models**
  - Empirical models

Physiological models
- Realistic models

Distributed parameter models
- Realistic models

COMPARTMENT MODELS

- Compartment analysis is the traditional and most commonly used approach to pharmacokinetic characterization of a drugs.
- These models simply interpolate the experimental data and allow an empirical formula to estimate the drugs concentration with time
- Since compartments are hypothetical in nature ,compartments models are based n certain assumptions.

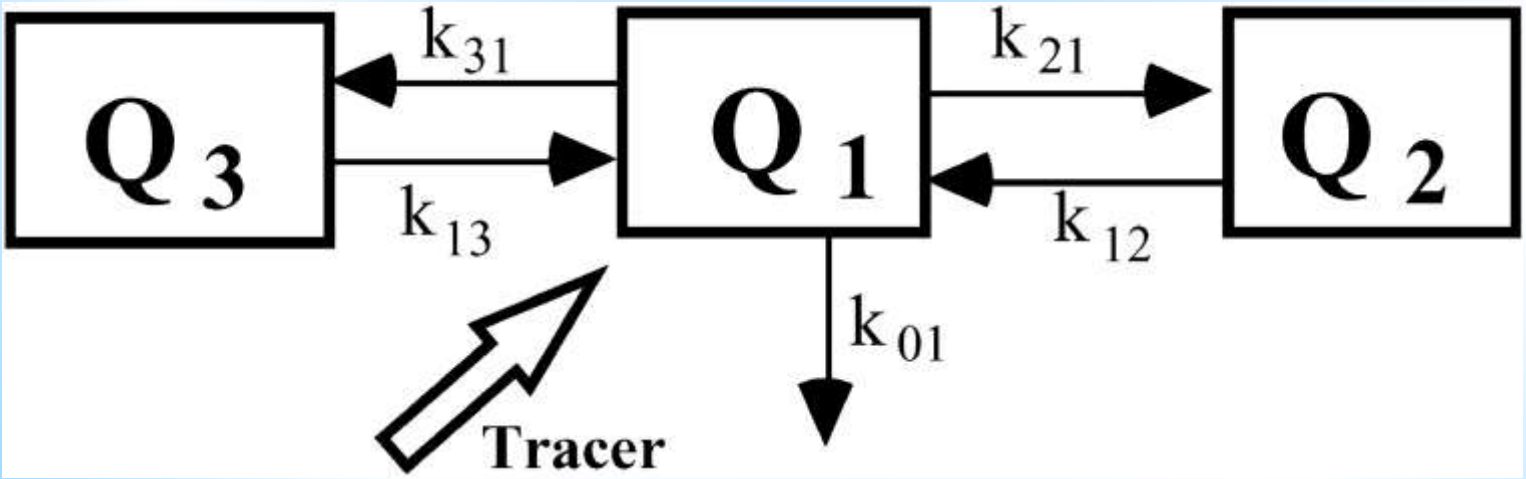
1. The body is represented as a series of compartments arranged either in series or parallel to each other,which communicate reversibly with each other.
2. Each compartment is not a real physiological or anatomical region but fictitious or virtual one and considered as a tissue or group of tissue that have similar drug distribution characteristics
3. Within each compartments the drugs is considered to be rapidly and uniformly distributed
4. The rate of drug movement between compartments described by first order kinetics

- Depending upon whether the compartment are arranged parallel or in series ,compartments models are divided into two categories –
  - Mammillary model
  - Catenary model

MAMMILLARY MODEL-

- It consists of one or more peripheral compartments connected to the central compartment in a manner similar to connection of satellites to a planet
- They are joined parallel to the central compartment
- The central compartment comprises of plasma and highly perfused tissues such as lungs, liver, kidney etc. which rapidly equilibrate with drugs.

MAMMILLARY MODEL-

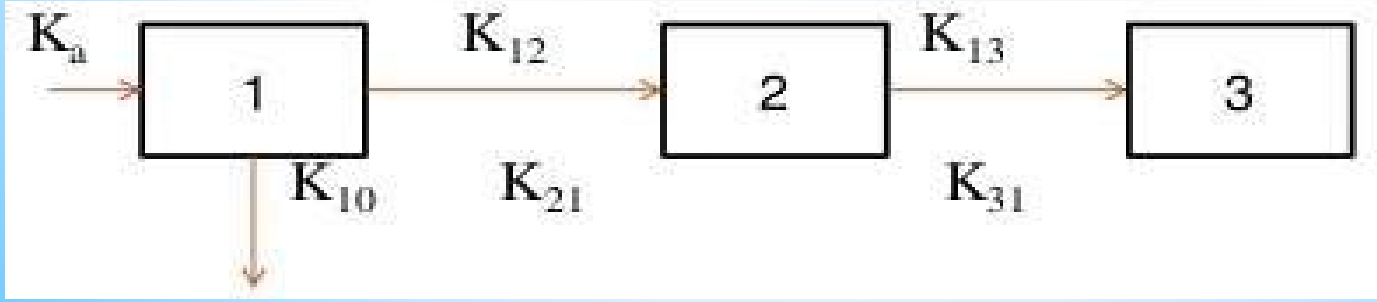


Central compartment

CATENARY MODEL-

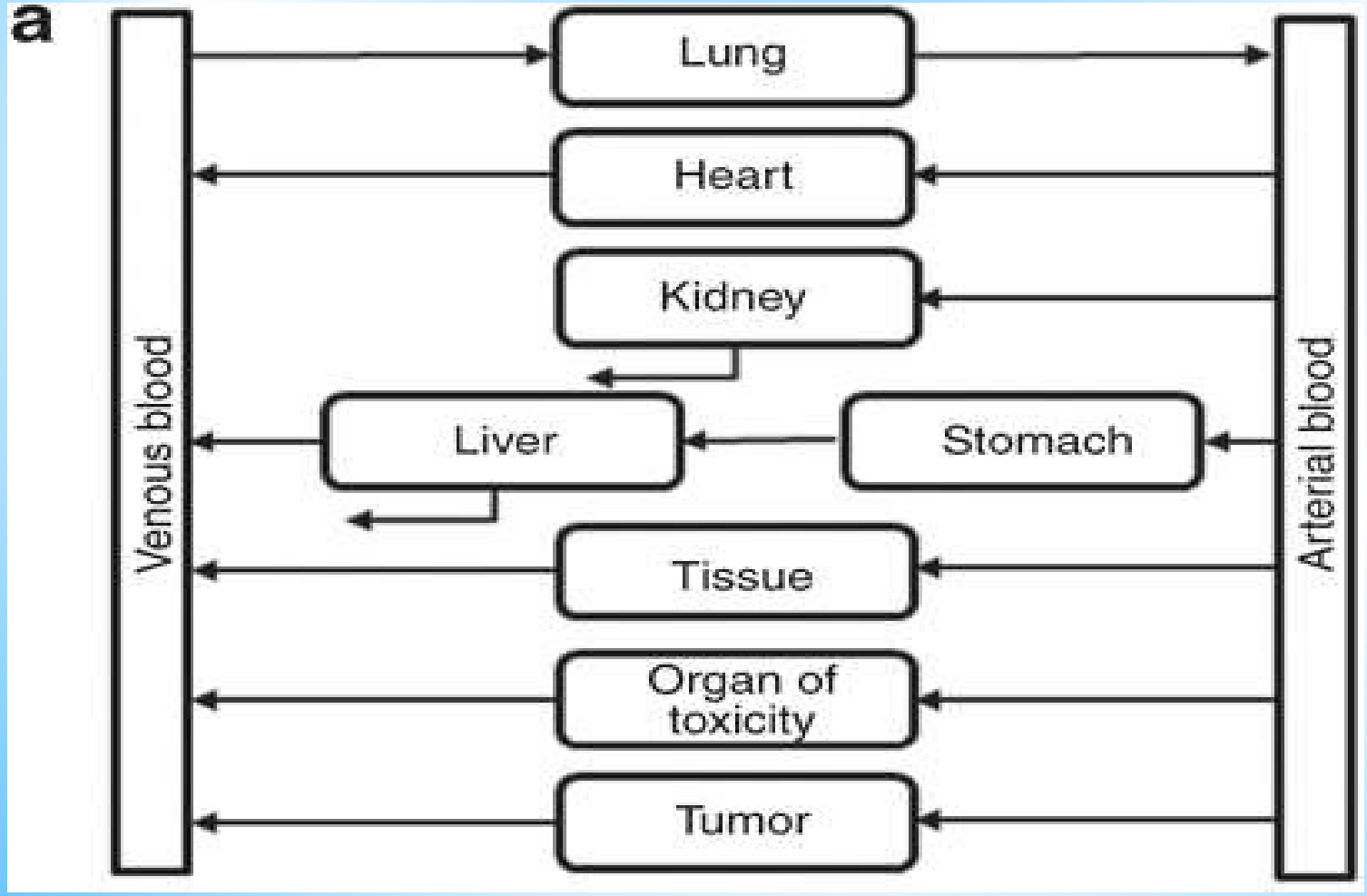
- The compartments are joined to one another in a series like compartments of a train.

- It is rarely used because it is not observed that anatomically or physiologically various organs are directly linked to the blood compartment.



PHYSIOLOGICAL MODELS

- They are drawn on the basis of known anatomical and physiological data
- So it present more realistic picture of drug disposition in various organs and tissues.
- Tissues with similar perfusion properties are grouped into a single compartment
- e.g. lungs, liver, brain and kidney are grouped as rapidly equilibrating tissues
- While muscles and adipose as slowly equilibrating tissues.


a
Venous blood
Lung
Heart
Kidney
Liver
Stomach
Tissue
Organ of toxicity
Tumor
Arterial blood

DISTRIBUTED PARAMETER MODEL

- It is analogous to physiological model but has been designed to take into account
  - Variations in blood flow to an organ
  - Variations in drug diffusion in an organ
- The distributed parameter model differ from physiological model in that the mathematical equation are more complex and collection of drug concentration data is more difficult.

NON-COMPARTMENTAL ANALYSIS

- k/as model independent methods
- Because it does not require the assumption of specific compartment model.
- This method is based on the assumption that the drugs or metabolites follow linear kinetics,
- So this technique can be applied to any compartment model.

- Based on statistical moments theory
- It involves collection of experimental data following a single dose of drug
- If one consider the time course of drug concentration in plasma as a statistical distribution curve, then

$$MRT = AUMC / AUC$$

- Where

  MRT= mean residence time

  AUMC= area under the first moment curve

  AUC= Area under the zero moment curve

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

AUMC and AUC can be calculated from the use of trapezoidal rule.

APPILICATIONS OF PHARMACOKINETIC MODELS:-

- Characterizing the behavior of drugs in patients.
- Correlating plasma drug concentration with pharmacological response.
- Evaluating the bioequivalence\ bioinequivalence between different formulations of the same drugs.
- Determining the influence of altered physiology\disease state on drugs ADME
- Explaining drugs interaction.

ONE-COMPARTMENT OPEN MODEL

(INSTANTANEOUS DISTRIBUTION MODEL)

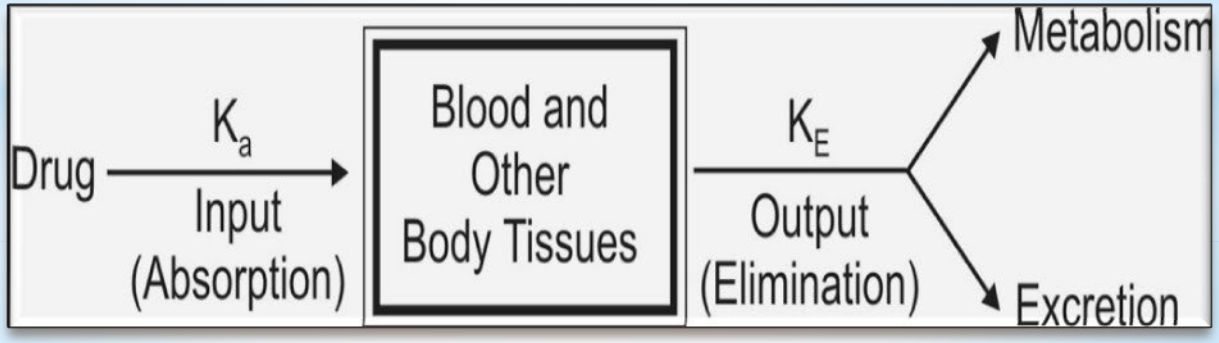
The one-compartment open model is the simplest model.

1. Elimination is a first-order (monoexponential) process with first-order rate constant.

2. Rate of input (absorption) > rate of output (elimination).

3.The anatomical ***reference compartment*** is plasma and concentration of drug in plasma is representative of drug concentration in all body tissues i.e. any change in plasma drug concentration reflects a proportional change in drug concentration throughout the body.

However, the model does not assume that the drug concentration in plasma is equal to that in other body tissues.



One-Compartment Open Model : Intravenous Bolus Administration

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

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

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

Estimation of Pharmacokinetic Parameters

Elimination phase can be characterized by 3 parameters—

1. Elimination rate constant
2. Elimination half-life
3. Clearance.

Elimination Rate Constant:

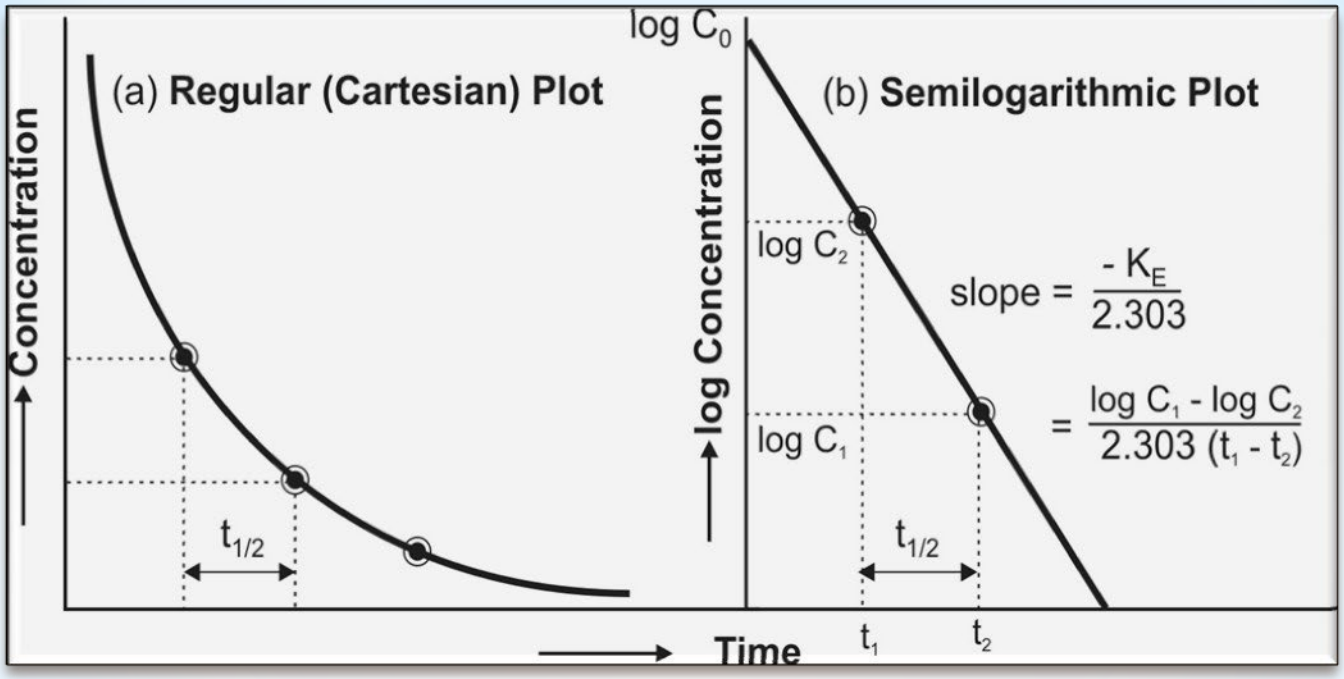
$$\ln X = \ln Xo - KE\ t$$

The above equation shows that *disposition of a drug that follows one-compartment kinetics is* **monoexponential**.

$$X = Xo\ e^{-KEt}$$

$$X = Vd\ C$$

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



$$KE = Ke + Km + Kb + Kl + ...$$

if a drug is eliminated by urinary excretion and metabolism only, then, the fraction of drug

excreted unchanged in urine **Fe** and fraction of drug metabolized **Fm** can be given as:

$$F_e = \frac{K_e}{K_E} \qquad F_m = \frac{K_m}{K_E}$$

Elimination Half-Life:

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

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

- **Apparent volume of distribution, and**
- **Clearance.**

***Since these parameters are closely related with the physiologic mechanisms in the bo they are called as* primary parameters.**

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

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

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.

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

$$Cl_H = \frac{\text{Rate of elimination by liver}}{C}$$

$$Cl_{Others} = \frac{\text{Rate of elimination by other organs}}{C}$$

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

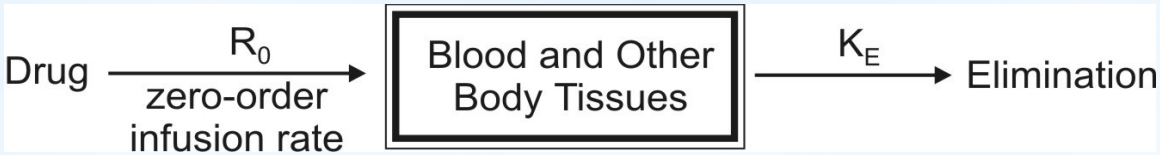
For drugs given as i.v. bolus

$$Cl_T = \frac{X_0}{AUC}$$

For drugs given e.v.

$$Cl_T = \frac{F\, X_0}{AUC}$$

One-Compartment Open Model : Intravenous Infusion



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

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

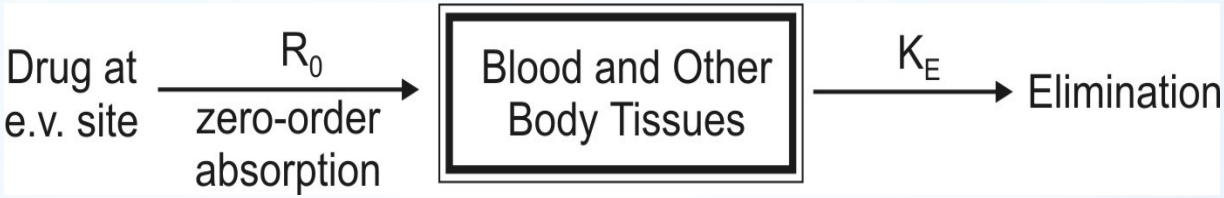
$$C = \frac{R_0}{K_E V_d}(1 - e^{-K_E t}) = \frac{R_0}{Cl_T}(1 - e^{-K_E t})$$

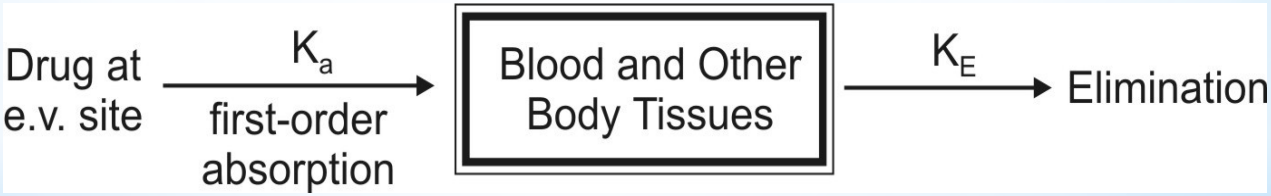
$$C_{ss} = \frac{R_0}{K_E V_d} = \frac{R_0}{Cl_T} \quad \text{i.e.} \quad \frac{\text{Infusion rate}}{\text{Clearance}}$$

One-Compartment Open Model: Extravascular Administration

dX/dt = Rate of absorption – Rate of elimination

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





$$X = \frac{K_a F X_0}{(K_a - K_E)} \left[e^{-K_E t} - e^{-K_a t} \right]$$

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

At peak plasma concentration, the rate of absorption equals rate of elimination i.e. KaXa = $K_E X$

$$\frac{dC}{dt} = \frac{K_a F X_0}{V_d(K_a - K_E)} \left[K_E e^{-K_E t} + K_a e^{-K_a t} \right] = \text{Zero}$$

$$K_E \; e_{-K^{E} t} = K_{a} \; e_{-K^{a} t}$$

$$\log K_E - \frac{K_E t}{2.303} = \log K_a - \frac{K_a t}{2.303}$$

$$t_{max} = \frac{2.303 \log (K_a / K_E)}{K_a - K_E}$$

$$C_{max} = \frac{F \; X_0}{V_d} e^{-K_E t_{max}}$$

Absorption Rate Constant: It can be calculated by the **method of residuals**. The technique is also known as **feathering**, **peeling** and **stripping**. It is commonly used in pharmacokinetics to resolve a multiexponential curve into its individual components. For a drug that follows one-compartment kinetics and administered e.v., the concentration of drug in plasma is expressed by a biexponential equation.

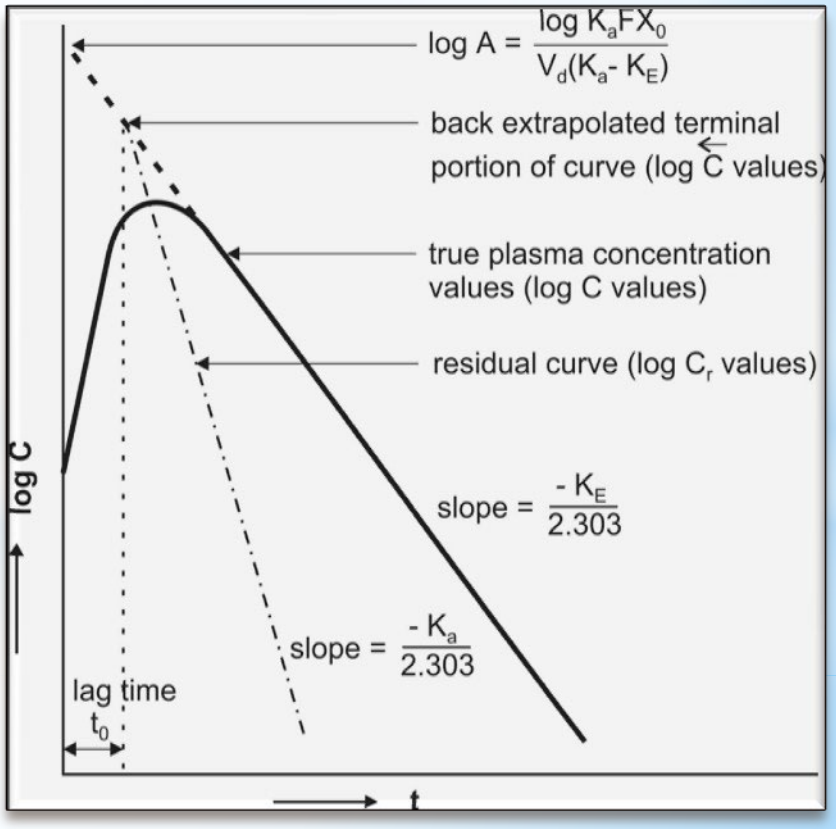
$$C = \frac{K_a F X_0}{V_d (K_a - K_E)} \left[e^{-K_E t} - e^{-K_a t} \right]$$

$$\overleftarrow{C} = A \; e^{-K_E t}$$

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

$$(\overleftarrow{C} - C) = C_\tau = A \; e^{-K_a t}$$

$$\log C_\tau = \log A - \frac{K_a t}{2.303}$$



Wagner-Nelson Method for Estimation of Ka

The method involves determination of Ka from percent unabsorbed-time plots and does not require the assumption of zero- or first-order absorption.

$$X_A = X + X_E$$

$$X_E = K_E V_d [AUC]_0^t$$

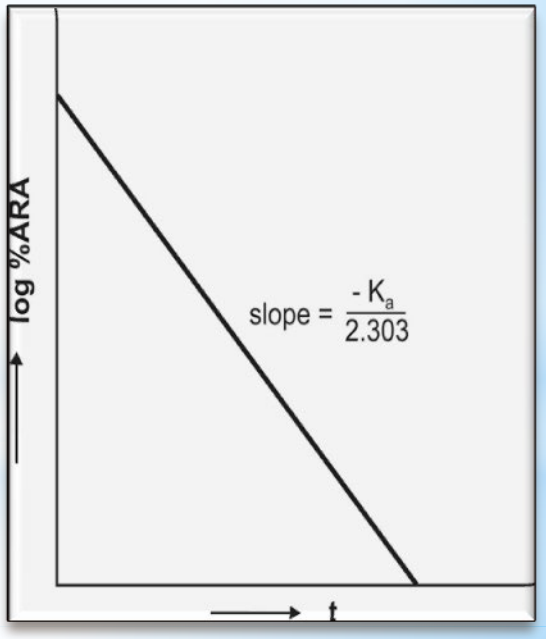
$$X_A = V_d C + K_E V_d [AUC]_0^t$$

$$X_A^\infty = V_d C^\infty + K_E V_d [AUC]_0^\infty$$

$$X_A^\infty = K_E V_d [AUC]_0^\infty$$

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

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



INFLUENCE OF K_A AND K_E ON C_{MAX}, T_{MAX} AND AUC

Parameters affected	*Influence when K_E is constant*		*Influence when K_a is constant*	
	Smaller Ka	*Larger Ka*	*Smaller KE*	*Larger KE*
Cmax	↓	↑	↑	↓
tmax	Long	Short	Long	Short
AUC	No Change	No Change	↑	↓

URINARY EXCRETION DATA

Criteria for Obtaining Valid Urinary Excretion Data

A significant amount of drug must be excreted unchanged in the urine (at least 10%).

1. The analytical method must be specific for the unchanged drug; metabolites should not interfere.

2. *Water-loading* should be done by taking 400 ml of water after fasting overnight, to promote diuresis and enable collection of sufficient urine samples.

3. Before administration of drug, the bladder must be emptied completely after 1 hour from water-loading and the urine sample taken as blank. The drug should then be administered with 200 ml of water and should be followed by 200 ml given at hourly intervals for the next 4 hours.

4. Volunteers must be instructed to completely empty their bladder while collecting urine samples.

5. Frequent sampling should be done in order to obtain a good curve.

6. During sampling, the exact time and volume of urine excreted should be noted.

7. An individual collection period should not exceed one biological half-life of the drug and ideally should be considerably less.

8. Urine samples must be collected for at least 7 biological half-lives in order to ensure collection of more than 99% of excreted drug.

9. Changes in urine pH and urine volume may alter the urinary excretion rate.

* Determination of K_E from Urinary Excretion Data

1. Rate of excretion method, and
2. Sigma-minus method.

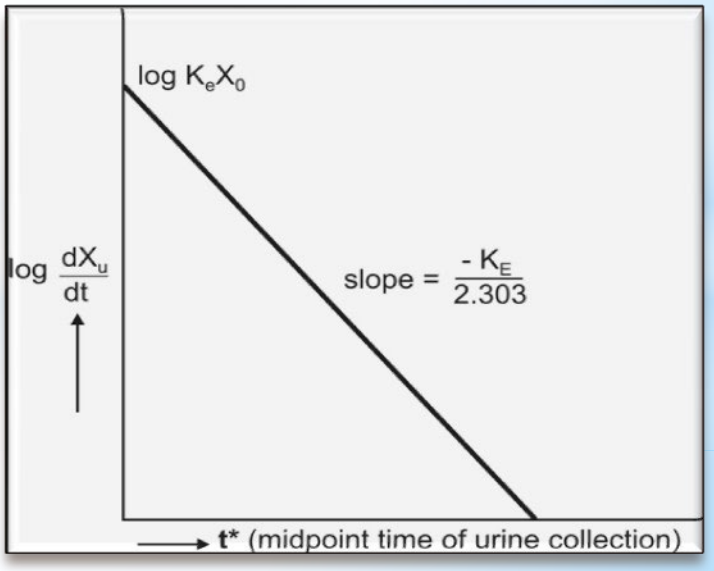
Rate of Excretion Method: The rate of urinary drug excretion dXu/dt is proportional to the amount of drug in the body X and written as:

$$\frac{dX_u}{dt} = K_e X$$

According to first-order disposition kinetics, $X = X_o e^{-K_E t}$

$$\frac{dX_u}{dt} = K_e X_0 e^{-K_E t}$$

$$\log \frac{dX_u}{dt} = \log K_e X_0 - \frac{K_E t}{2.303}$$



Sigma-Minus Method: A *disadvantage of rate of excretion method* in estimating K_E is that fluctuations in the rate of drug elimination are observed to a high degree and in most instances, the data are so scattered that an estimate of half-life is difficult. These problems can be minimized by using the alternative approach called as sigma-minus method.

$$\frac{dX_u}{dt} = K_e X_0 \, e^{-K_E t}$$

$$X_u = \frac{K_E X_0}{K_E}(1 - e^{-K_E t})$$

Xu = cumulative amount of drug excreted unchanged in urine at any time t. As time approaches infinity i.e. after 6 to 7 half-lives, the value e–KE∞ becomes zero and therefore the cumulative amount excreted at infinite time Xu ∞ can be given by equation

$$X_u^{\infty} = \frac{K_e X_0}{K_E}$$

$$X_u^{\infty} - X_u = X_u^{\infty} \, e^{-K_E t}$$

$$\log (X_u^{\infty} - X_u) = \log X_u^{\infty} - \frac{K_E t}{2.303}$$

($Xu_\infty - Xu$) = **amount remaining to be excreted**

i.e. **ARE** at any given time.

A semilog plot of ARE versus t yields a straight line with slope -KE/2.303.

The method is, therefore, also called as **ARE plot method**.

A *disadvantage* of this method is that total urine collection has to be carried out until no unchanged drug can be detected in the urine i.e. upto 7 half-lives, which may be tedious for drugs having long t½.