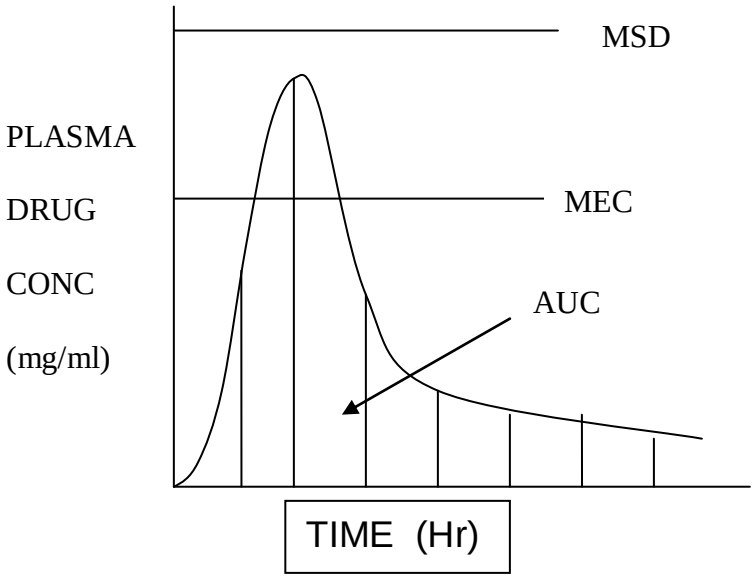
ANALYSIS OF BLOOD & URINE DATA , COMPARTMENT MODELS, KINETICS OF ONE & TWO COMPARTMENT MODELS

We do the analysis of blood & urine data for**:** ---

- experimental determination of bioavailability
- Quantitative evaluation on bioavailability.

[I] ANALYSIS OF BLOOD DATA :-

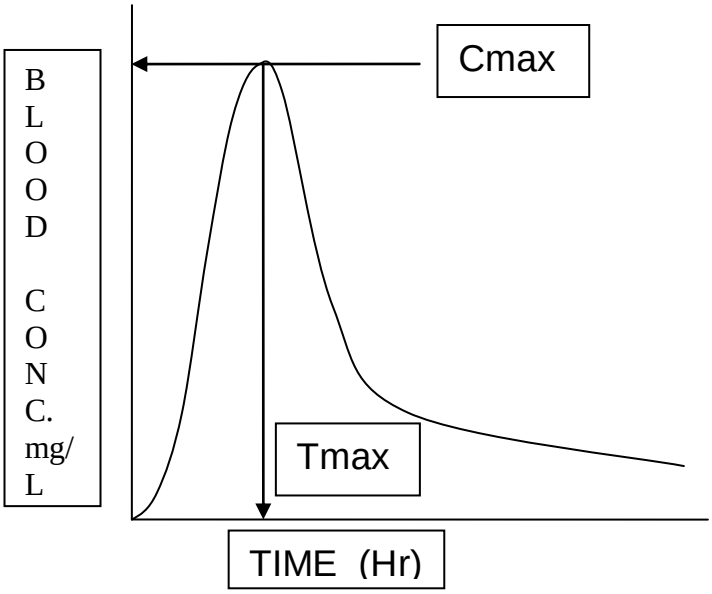
- Blood level studies are the most common type of human bioavailability studies, and are based on the assumption that there is a direct relationship between the concentration of drug in blood or plasma and the concentration of drug at the site of action.
- By monitoring the concentration in the blood, it is thus possible to obtain an indirect measure of drug response.
- The method is based on assumption that two dosage forms that exhibit superimposable plasma level-time profile in a group of subjects should result in identical therapeutic activity.
- The plasma concentration-time curve (blood level curve) is the focal point of bioavailability assessment and is obtain when serial blood samples are taken after drug administration and analyzed for drug concentration
- A typical blood level curve obtained after oral administration of a drug is as follows:-



❖ The key parameters to note from the curve include :-

- MINIMUM EFFECTIVE CONC./ MINIMUM INHIBITORY CONC. (MEC/MIC)-
  - Defined as the minimum dose required achieving the desired therapeutic effect.
- ONSET OF ACTION-
  - It is defined as the time required achieving MEC following administration of dosage form.

- **DURATION OF ACTION-**
  - DEFINED AS length of time for which the drug conc. in the blood remains above the MEC.
- **MAXIMUM SAFE CONCENTRATION/MAXIMUM SAFE DOSE (MSC/MSD)**
  - The maximum amount of drug that can be present in the body above which side effects or toxic effects are seen is called MSD.
- **PEAK PLASMA CONCENTRATION (Cmax)**
  - It is the maximum concentration of the drug that reaches the systemic circulation and expressed as mcg/ml
  - Should be between MEC & MSC
  - Gives an indication that whether the drug is sufficiently absorbed systemically to provide therapeutic response and provides warning of possible toxic levels of drug.
  - It is a function of both the rate of absorption and the extent of absorption & elimination rate.



- **PEAK TIME (Tmax)**
  - Represents the time required to achieve the maximum concentration of drug in the systemic circulation
  - Give indication of rate of absorption and also influenced by the rate of elimination of the drug from the body.
  - However, if one assumes elimination rate does not changes during the period when two or more dosage forms are being tested in a given subject, then observed differences in Tmax will reflect absorption rate differences among the test product.
- **AREA UNDER THE CURVE (AUC)**
  - It represents the total area under the concentration-time curve
  - Expressed as mcg/ml**.**Hr
  - It describes extent of bioavailability and can be used as an estimate of the amount of drug absorbed.
  - The extent of bioavailability can be determined by following equations:--

$$\mathbf{F} = \frac{[AUC]oral}{[AUC]iv} \bullet \frac{Div}{Doral}$$

F is used to characterize a drug's inherent absorption properties from extra vascular site.

$$\mathbf{Fr} = \frac{[AUC]test}{[AUC]std} \bullet \frac{Dstd}{Dtest}$$

Fr is used to characterize absorption of drug from its formulation.

Where,

F = absolute bioavailability
Fr = relative bioavailability
AUC = area under the curve
D = dose administered
IV, oral = route of administration
Test & STD = test and STD doses of the same drug to determine Relative bioavailability.

- Now, a determination of the extent of drug absorption is based on AUC , which is directly proportional to the fraction of the administration dose that reaches the systemic circulation
- AUC can be determined by
    1. using planimeter
    2. cut and weigh method
    3. trapezoidal method
- The AUC is the area under the drug plasma level – time curve from $t = 0$ to $t = \infty$, & is equal to the amount of unchanged drug reaching the general circulation divided by the clearance

$$[AUC]^{\infty}_{0} = \int Cp\, dt$$

- For many drug AUC is directly proportional to dose .For example if a single dose of drug is increased from 250 to 1000 mg, the AUC will also show a four fold increase.
- In some cases the AUC is not directly proportional to the administered dose for all dosage levels .For example, as the dosage of drug is increased one of the pathways of drug metabolism may become saturated. Drug elimination includes the process of metabolism & excretion.

THE SIGNIFICANCE OF MEASURING PLASMA DRUG CONCENTRATIONS:-

- The intensity of pharmacological & toxic effect of a drug is often related to the concentration of the drug at the receptor site usually located in the tissue cells.
- Because most of the tissue cells are richly perfused with tissue fluids or plasma, checking the plasma drug level is a responsive method of monitoring the course of therapy.
- Monitoring of plasma drug concentration s allows for the adjustment of the drug dosage in order to individualize & optimize therapeutic drug regimens.
- It helps in determining therapeutic equivalents & therapeutic substitutions.
- ***THERAPEUTIC EQUIVALENTS***- therapeutic equivalents are the drug products that contain the same therapeutically active drug that should give the same therapeutic effect & have equal potential for adverse effects under the conditions set forth in the labels of these drug products
- ***THERAPEUTIC SUBSITUENTS***- the process of dispensing a therapeutic alternative in place of the prescribed drug product. For example amoxicillin is dispensed for ampicillin etc.

❖ After the serum drug concentrations are measured, the pharmacokineticist must

properly evaluate the data. The pharmacokineticist must be aware of the usual therapeutic range of serum concentration from the literature. The assay results from the laboratory may shows that the patients serum drug levels are higher lower or similar to the expected serum level. Following tables gives as numbers of factors for the pharmacokineticist to consider when the interpreting the drug plasma concentration,

1. Serum concentration lower than anticipated
⇨ Error in dosage regimen ⇨ Wrong drug product(sustained release instead of immediate release) ⇨ Poor bioavaibility ⇨ Rapid elimination ⇨ Reduced plasma protein binding ⇨ Enlarged apparent volume of distribution ⇨ Steady state not reached ⇨ Timing of blood samples ⇨ Drug interaction ⇨ Changing hepatic blood flow
2. Serum concentration higher than anticipated
⇨ Error in dosage regimen ⇨ Wrong drug product(immediate released instead of sustained release) ⇨ Rapid bioavailability ⇨ Smaller apparent volume of distribution ⇨ Slow elimination ⇨ Increased plasma protein binding ⇨ Deteriorating renal/hepatic function ⇨ Drug interaction
3. Serum concentration Correct but patient does not respond to therapy
⇨ Altered receptor sensitivity ⇨ Drug interaction at receptor site ⇨ Changing hepatic blood flow

[II] ANALYSIS OF URINE DATA :-

- Measurement of urinary drug excretion can be used successfully as the method of determination of bioavailability provided that the active ingredient is excreted unchanged in a significant quantity in urine.
- Principle for assessing B.A. is – the urinary excretion of unchanged drug is directly proportional to the plasma concentration of drug.

Objectives

To draw the scheme and differential equations for a one compartment pharmacokinetic model with excretion of drug into urine

- To recognize and use the integrated equations for this pharmacokinetic model
- To construct the plots; cumulative amount excreted versus time, A.R.E. versus time, and rate of excretion versus time (midpoint)
- To calculate excretion and metabolism rate constants for parallel pathway models
- To use fe, the fraction excreted, to calculate overall elimination rate constants in patients with impaired renal function

- To define, use, and calculate the parameter clearance

we can get information from plasma data following a rapid intravenous dose of a drug using a one compartment model. There is another part of the model which can be sampled. Sometimes it is not possible to collect blood or plasma samples but we may be able to measure the amount of drug excreted into urine.

- we may not want to take repeated blood samples from certain patient populations, for example pediatrics
- The apparent volume of distribution maybe so large those plasma concentrations are too small to measure.

If we collect data for amount of drug excreted into urine it may be possible to determine the elimination rate constant or half-life and other pharmacokinetic parameters.

The advantages of using urine for analysis includes

- The method is useful when there is a lack of sufficiently sensitive analytical technique to measure the concentration of drug in plasma with accuracy
- It is more convenient to collect urine samples, than drawing blood out of patient.
- Method is a non invasive type
- 1^{st} order elimination, excretion & absorption rate constants & fractions excreted unchanged can be computed from such data.
- 1^{st} order metabolism or extra renal excretion rate constant can also be calculated subsequently from the difference [KE-Ke] = Km
- Direct measurement of bioavailability can also be done without fitting the data to a mathematical model
- If plasma level time data is also available, coupled with urinary excretion data, it can be used to estimate renal clearance using following equation.

$$CL_R = \frac{\text{Total amount of drug excreted unchanged}}{\text{Area under the plasma level time curve}}$$

Disadvantages of analysis using urinary excretion data

- One cannot however compute Vd & CL_T from the urine data alone
- The urinary data is not considered as an accurate substitution for the plasma level data
- It is taken as rough estimate of pharma-co-kinetic parameter
- If the drug product provides a very slow drug release or if the drug has a very long biological half life the resulting low urinary drug concentration may be too dilute to be assessed with accuracy.
- If this is the case i.e. for drugs with long t ½ urine may have to be collected for several days to account for total drug excreted

Criteria for obtaining valid urinary excretion data –

- A significant amount of drug must be excreted unchanged in the urine (at least 10%).
- The analytical method must be specific for the unchanged drug, the metabolites should not interfere

- Water loading should be done by using 400 ml of water after fasting overnight to promote diuresis & ensure collection of sufficient urine samples.
- Before administration of drug the bladder must be emptied completely after 1 hr from water loading & urine sample is taken as blank the drug should then be administered with 200 ml of water & should be followed by 200 ml given at hourly interval over the next 4 hrs.
- Volunteer must be instructed to completely empty bladder while collecting urine sample
- Frequent sampling should be done in order to get a good curve.
- During sampling the exact time & vol. of urine excreted should be noted
- An individual collection period should not exceed one biological half life of the drug ideally should be considerably less.
- Urine sample must be collected for at least 7 biological t ½ lives in order to ensure collection of more than 99% of excreted drug.
- Change pH & urine volume may alter the urinary excretion rate.

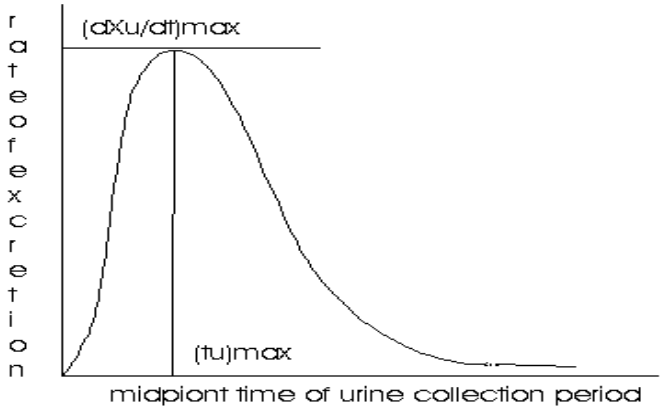
The three parameters examined in urinary excretion data obtained with a single dose study :-

❖ dXu/dt (URINARY EXCRETION RATE) :---

- Directly related to the rate of systemic drug absorption
- As (dXu/dt)max [maximum urinary excretion rate) increases, the rate of and /or extent of absorption increases
- Analogous to Cmax = (dXu/dt)max
- Because most drugs are eliminated by first order rate process, the dXu/dt is dependent on first order rate constant and conc. of drug.

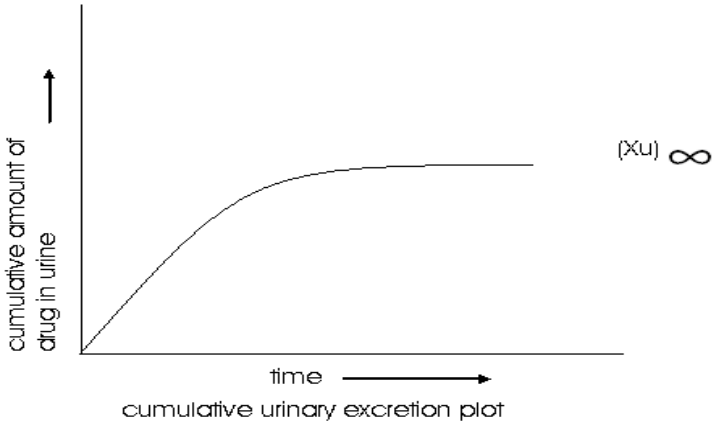
❖ Tu

- Time for the drug to be completely excreted corresponds to the total time for the drug to be systemically absorbed and completely excreted after administration
- (tu)max = time for maximum excretion rate = analogous to tmax of plasma level data.



❖ EXu^{∞}

- It is cumulative amount of drug excreted in urine, related to AUC of the plasma level data and increases as the extent of absorption increases.



cumulative urinary excretion plot

the extent of bioavailability is calculated from equation given below:--

$$F = \frac{(\sum Xu\infty)oral}{(\sum Xu\infty)iv} \bullet \frac{Div}{Doral}$$

$$F = \frac{(\sum Xu\infty)test}{(\sum Xu\infty)std} \bullet \frac{Dstd}{Dtest}$$

with multiple dose study to steady state, the equation for computing bioavailability is

$$Fr = \frac{(\sum Xu.ss)test}{(\sum Xu.ss)std} \bullet \frac{Dstd}{Dtest} \bullet \frac{ttest}{tstd}$$

Where, ($(\sum Xu, ss)$ is the amount of drug excreted unchanged during a single dosing interval at steady state.

Calculation of excretion rate (ER) is based on ---

$$ER = \frac{\sum Xu2 - \sum Xu1}{tu2 - tu1}$$

Where, $\sum Xu2, \sum Xu1$ represents the cumulative amount of drug recovered in the urine samples obtained at sampling times up to tu2 and tu1.

When sufficient urine samples have been collected that no significant amount of drug remains to be excreted, the cumulative urinary recovery is symbolized as $\sum Xu\infty$,

$$\sum Xu\infty = FDKe / K$$

Where, the value of $\sum Xu\infty$ is a function of

F= fraction of administered dose

D = dose absorbed

Ke = renal elimination rate constant

K = overall elimination rate constant

PLOTTING & ANALYZING URINE DATA

A) CUMULATIVE AMOUNT EXCRETED VERSUS TIME

It is related to AUC of the plasma level data and increases as the extent of absorption increases.

The linear plot of cumulative amount excreted into urine as unchanged drug *versus* time is shown below. Notice that the value of U^{∞} is NOT EQUAL to the dose, it is somewhat less than dose, unless the entire dose is excreted into urine as unchanged drug. The remaining portion of the dose should be found as metabolites and from other routes of excretion.

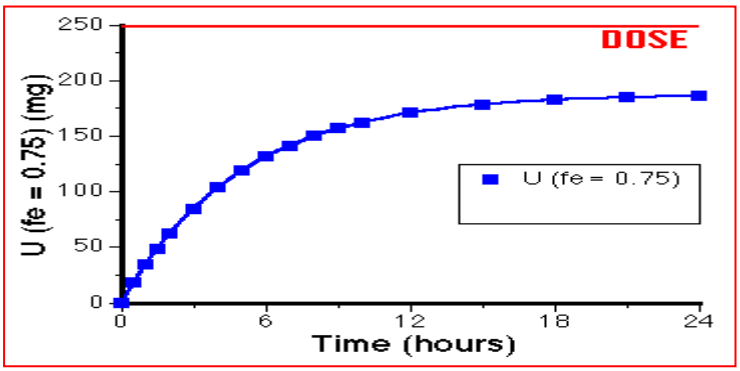


Figure: - Linear Plot of U *versus* Time showing Approach to U∞ not equal to DOSE

B) RATE OF EXCRETION (R/E)

- Directly related to the rate of systemic drug absorption
- As $\mathbf{(dU/dt)_{max}}$ (maximum urinary excretion rate) increases, the rate of and /or extent of absorption increases
- Analogous to Cmax = (dU/dt)max
- Because most drugs are eliminated by first order rate process, the dU/dt is dependent on first order rate constant and conc. of drug.

$$\frac{dU}{dt} = kel \cdot V \cdot Cp = DOSE \cdot kel \cdot e^{-kel \cdot t}$$

Since urine data is collected over an interval of time the data is represented as **ΔU** rather than **dU**. Also, since ΔU is collected over a discrete time interval the time point for this interval should be the midpoint of the interval, $\mathbf{t_{midpoint}}$

$$\frac{\Delta U}{\Delta t} = kel \cdot V \cdot Cp = DOSE \cdot kel \cdot e^{-kel \cdot t_{midpoint}}$$

Equation: - Rate of Excretion of Unchanged Drug *versus* midpoint time

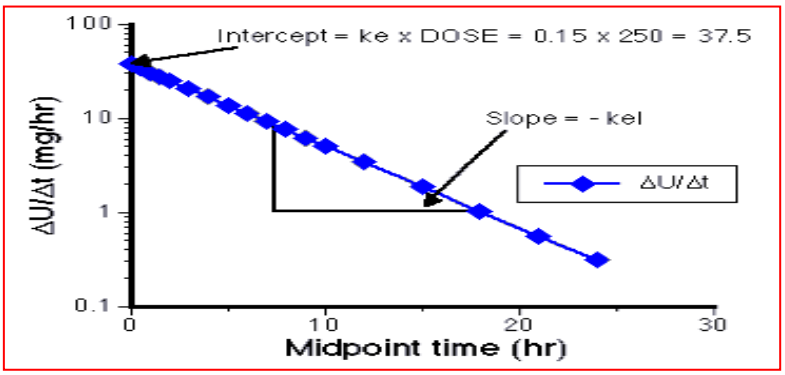


Figure: - Semi-log Plot of ΔU/Δt *versus* $\mathbf{Time_{midpoint}}$

Showing Slope = - $\mathbf{k_{el}}$

with fe = 0.75, kel = 0.2 hr-1; ke = 0.15 hr-1

NOTE: - Rate of excretion plots can be very useful in the determination of the parameters such as kel, ke and fe. Data can be a little more scatter that with the ARE plot, below. Thus, positioning the straight line on a semi-log may be difficult to plot. This means that this method can be difficult to use with drugs which have short half-lives.

However, a significant advantage of the rate of excretion plot is that each data point is essentially independent, especially if the bladder is fully voided for each sample. A missed sample or data points is not critical to the analysis.

C) AMOUNT REMAINING TO BE EXCRETED (ARE)

$$U = \frac{ke \cdot DOSE}{kel} \cdot \left[1 - e^{-kel \cdot t} \right]$$

$$\ln(U^{\infty} - U) = \ln(fe \cdot Dose) - kel \cdot t$$

Equation: - ARE *versus* time

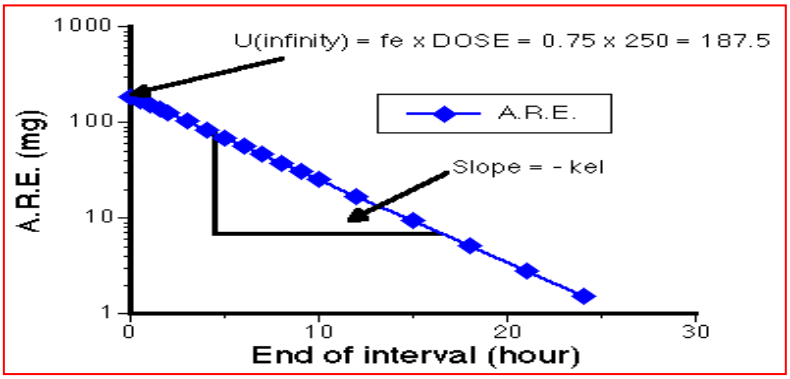


Figure: - Semi-log Plot of ARE *versus* time

Note: - Amount remaining to be excreted (ARE) plots use the **U∞ (**total amount excreted as unchanged in urine) value to estimate each data point.

Sr. no	2) Rate of excretion method	3) ARE method
1.	Does not require knowledge of **U∞**	Require accurate determination of **U∞**
2.	Missed sample is not critical for analysis	Missed sample is critical for analysis
3.	Scattering of data occur	Scattering of data do not occur
4.	Renal drug excretion rate constant may be obtained from this method	Not obtained

- The extent of **bioavailability** is calculated from equation given below:--

$$F = \frac{(\sum Xu\infty)oral}{(\sum Xu\infty)iv} \bullet \frac{Div}{Doral}$$

$$F = \frac{(\sum Xu\infty)test}{(\sum Xu\infty)std} \bullet \frac{Dstd}{Dtest}$$

- With multiple dose study to steady state, the equation for computing bioavailability is

$$Fr = \frac{(\sum Xu.ss)_{test}}{(\sum Xu.ss)_{std}} \bullet \frac{D_{std}}{D_{test}} \bullet \frac{t_{test}}{t_{std}}$$

- Where, $(\sum Xu, ss)$ is the amount of drug excreted unchanged during a single dosing interval at steady state.

D) CLEARENCE

Clearance can be defined as the volume of plasma which is completely cleared of drug per unit time. The symbol is CL and the units are ml/min, L/hr, i.e. volume per time. Another way of looking at Clearance is to consider the drug being eliminated from the body ONLY via the kidneys. [If we were to also assume that the entire drug that reaches the kidneys is removed from the plasma then we have a situation where the clearance of the drug is equal to the plasma flow rate to the kidneys. All of the plasma reaching the kidneys would be cleared of drug.]

The amount cleared by the body per unit time is dU/dt, the rate of elimination (also the rate of excretion in this example). To calculate the volume which contains that amount we can divide by Cp. That is the volume = amount/concentration. Thus:-

$$CL = \frac{dU}{dt} \cdot \frac{1}{Cp}$$

Clearance as the Ratio between Rate of Excretion and Cp

$$\text{Since} \quad \frac{dU}{dt} = kel \cdot V \cdot Cp$$

$$CL = \frac{kel \cdot V \cdot Cp}{Cp} = kel \cdot V$$

As we have defined the term here it is the total body clearance. We have considered that the drug is cleared totally by excretion in urine. Below we will see that the total body clearance can be divided into a clearance due to renal excretion and that due to metabolism.

Clearance is a useful term when talking of drug elimination since it can be related to the efficiency of the organs of elimination and blood flow to the organ of elimination. It is useful in investigating mechanisms of elimination and renal or hepatic function in cases of reduced clearance of test substances. Also the units of clearance, volume/time (e.g. ml/min) are easier to visualize, compared with elimination rate constant (units 1/time, e.g. 1/hr).

Total body clearance, CL, can be separated into clearance due to renal elimination, CLr and clearance due to metabolism, CLm.

CLr = ke * V (renal clearance)

And

CLm = km * V (metabolic clearance)

NOTE

CL = CLr + CLm

ANOTHER METHOD of calculating CL can be derived

Integrating

$$\frac{dU}{dt} = ke \cdot V \cdot Cp = CL_r \cdot Cp$$

Gives

$$U^{\infty} = CL_r \cdot \int_0^{\infty} Cp \cdot dt = CL_r \cdot AUC$$

Thus

$$CL_r = \frac{U^{\infty}}{AUC}$$

Renal Clearance calculated from U^{∞} and AUC also

$$CL_m = \frac{M^{\infty}}{AUC}$$

Metabolic Clearance calculated from M^{∞} and AUC and

$$CL = \frac{DOSE}{AUC}$$

Clearance calculated from Dose and AUC

This equation uses the DATA only (without fitting a line through the data or modeling the data) using the trapezoidal rule. Thus this is a model independent method.

$$\frac{dU}{dt} = CL \cdot Cp$$

Thus a plot of dU/dt versus Cp will give a straight line through the origin with a slope equal to the clearance, CL

CRITERIA FOR OBTAINING VALID URINARY EXCRETION DATA

1. A significant amount of drug must be excreted unchanged in the urine (at least 20%).
2. The analytical method must be specific for the unchanged drug, the metabolites should not interfere
3. Water loading should be done by using 400 ml of water after fasting overnight to promote diuresis & ensure collection of sufficient urine samples.
4. Before administration of drug the bladder must be emptied completely after 1 hr from water loading & urine sample is taken as blank the drug should then be administered with 200 ml of water & should be followed by 200 ml given at hourly interval over the next 4 hrs.
5. Volunteer must be instructed to completely empty bladder while collecting urine sample
6. Frequent sampling should be done in order to get a good curve.
7. During sampling the exact time & volume of urine excreted should be noted.
8. An individual collection period should not exceed one biological half life of the drug ideally should be considerably less.
9. Urine sample must be collected for at least 7 biological $t_{½}$ lifes in order to ensure collection of more than 99% of excreted drug.
10. Change pH & urine volume may alter the urinary excretion rate.

DRUG EXCRETED INTO URINE (U)

The rate of excretion, dU/dt, can be derived from the model, in terms of ke or CL_R,

$$\frac{dU}{dt} = ke \cdot V \cdot Cp$$

$$\frac{dU}{dt} = CL_R \cdot Cp$$

Equation:-Rate of Change of Cumulative Amount Excreted into Urine

After integrating using Laplace transforms we get:

$$U = \frac{ke \bullet Dose}{kel} \bullet \left[1 - e^{-kel \bullet t}\right]$$

$$U = \frac{CL_R \bullet Dose}{CL} \bullet \left[1 - e^{-CL \bullet t/V}\right]$$

$$U^{\infty} = \frac{ke \bullet Dose}{kel} (= fe \bullet Dose)$$

Equation: - Cumulative Amount Excreted as Unchanged Drug *versus* Time

Note: ke or CL_R are in the numerator of Equation 5.2.9. As time approaches infinity the exponential term, $e^{-k \bullet t}$, approaches zero. Setting the $e^{-kel \bullet t}$ term in above Equation to zero gives following Equation for the total amount of unchanged drug excreted in urine, $\mathbf{U^{\infty}}$

SINGLE-DOSE VERSUS MULTIPLE-DOSE

Most bioavailability evaluations are made on the basis of single-dose administration.
The argument has been made that single doses are not representative of the actual clinical situation, since in most instances, patients require repeated administration of a drug.

When a drug is administered repeatedly at fixed intervals, with the dosing frequency less than five half-lives, drug will accumulate in the body and eventually reach a plateau, or a steady-state. At steady-state, the amount of drug eliminated from the body during one dosing interval is equal to the available dose (rate in = rate out); therefore, the area under the curve during a dosing interval at steady-state is equal to the total area under the curve obtained when a single dose is administered. This AUC can therefore be used to assess the extent of absorption of the drug, as well as its absolute and relative bioavailability.

Multiple-dose administration has several advantages over single-dose bioavailability studies, as well as some limitations.

Advantages:

1. Eliminates the need to extrapolate the plasma concentration profiles to obtain the total AUC after a single dose.
2. Eliminates the need for a long wash-out period between doses.
3. More closely reflects the actual clinical use of the drug.
4. Allows blood levels to be measured at the same concentrations encountered therapeutically.
5. Because blood levels tend to be higher than in the single-dose method, quantitative determination is easier and more reliable.
6. Saturable pharmacokinetics, if present, can be more readily detected at steady-state.

Disadvantages:-

1. Requires more time to complete.
2. More difficult and costly to conduct (requiring prolonged monitoring of subjects.
3. Greater problems with compliance control.
4. Greater exposure of subjects to the test drug, increasing the potential for adverse reactions.

PHARMACOKINETIC MODELS

INTRODUCTION :-

- The theoretical aspect of pharmacokinetics involves the development of pharmacokinetic models that predict the drug disposition after drug administration.
- Pharmacokinetics models provide concise means of expressing mathematically or quantitatively, the time course of drug(s) throughout the body and compute meaningful pharmacokinetics parameters.

IMPORTANCE OF PHARMACOKINETIC MODELS

1. Characterizing the behaviour of drugs in patients.
2. Predicting the concentration of the 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 BA/BE between different formulations of same drug.
8. Estimating the possible 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.

Caution must however be exercised in ensuring that the model fits the experimental data, otherwise, a new, more complex and suitable model may be proposed and tested.

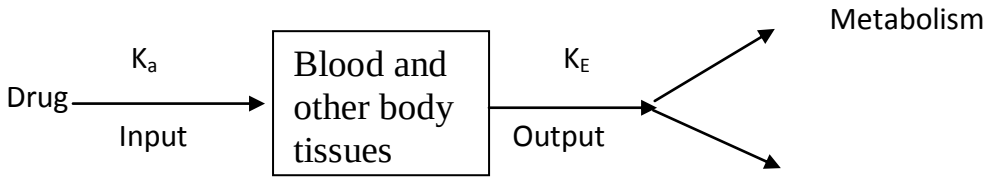
TYPES OF PHARMACOKINETICS MODELS

There are three types of pharmacokinetics models.

1. Compartmental models
   - Mammillary model
   - Caternary model
2. Non-compartmental analysis
3. Physiologic modeling

ONE COMPARTMENT OPEN MODEL
(Instantaneous Distribution Model)

- The one compartment open model is the simplest model which depicts the body as a single, kinetically homogeneous unit having no barriers to the movement of drug and final distribution equilibrium between drug in plasma and other body fluid is obtained instantaneously and maintained at all times.
- This model thus applies only to those drugs that distribute rapidly throughout the body.
- The anatomical reference compartment is the 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.
- The term **open** indicates that the input (availability) and output (elimination) are unidirectional and that the drug can be eliminated from the body.



(Absorption) (Elimination) Excretion

Figure :-One compartment open model showing input and output processes.

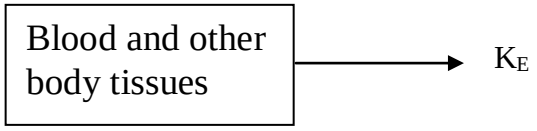
One compartment open model is generally used to describe plasma levels following administration of a single dose of a drug. Depending upon the rate of input, several one compartment open models can be defined:

1. One compartment open model, intravenous bolus administration
2. One compartment open model, continuous intravenous infusion
3. One compartment open model, extravascular administration, zero order absorption and
4. One compartment open model, extravascular administration, 1st order absorption.

[1] 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. IV bolus or slug), it takes about one to three minutes for complete circulation and therefore the rate of absorption is neglected in calculations. The model can be depicted as follows:



$$\frac{dX}{dt} = \text{Rate in (availability) - Rate out (elimination)} \quad \text{------ } \mathbf{1}$$

Since rate in or absorption is absent the equation becomes

$$\frac{dX}{dt} = -\text{ Rate out} \quad \text{------ } \mathbf{2}$$

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

$$\frac{dX}{dt} = -K_E X \quad \textbf{------ 3}$$

Where, K_E = First order elimination rate constant

X = amount of drug in body at any time t remaining to be eliminated.

Negative sign indicates that the drug is being lost form the body.

ELIMINATION RATE CONSTANT:-

- For a drug that follows one compartment kinetics and administered as rapid IV injection, the decline in plasma drug concentration is only due to elimination of drug from the body, the phase being called as elimination phase.

- Elimination phase can be characterized by three parameters
  - Elimination rate constant,
  - Elimination half-life
  - Clearance.

Integration of equation 3 yields

$$\ln X = \ln X_o - K_E t \quad \text{------ } \mathbf{4}$$

Where, X_o = amount of drug at time t = o i.e. the initial amount of drug injected.

Equation 4 can also be written in exponential form as :

$$X = X_o e^{-K_E t} \qquad \text{----- 5}$$

It shows that disposition of drug that follows one compartment kinetics is monoexponential.

Transforming equation 4 into common logarithms (log base 10), we get:

$$\log X = \log X_o - \frac{K_E t}{2.303} \qquad \text{------ 6}$$

- 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 exist between drug concentration in plasma C (easily measurable) and X;
  Thus, $X = V_d C$ **------- 7**
  Where, Vd = proportionality constant popularly known as 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.

The equation 6 therefore becomes:

$$\log C = \log C_o - \frac{K_E t}{2.303} \qquad \text{------ 8}$$

- Equation 8 is that of a straight line and indicates that a semi logarithmic plot of log C versus t will be linear with Y intercept log C_o. The elimination rate constant is directly obtained from slope of the line (figure 5 (b)). 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 C versus t on regular (Cartesian) graph paper Figure 5 (a)
  Thus, C_o, K_E (and $t_{1/2}$) can be readily obtained from log C versus t graph.
- The elimination or removal of the drug from the body is the sum of urinary excretion, metabolism, biliary excretion, pulmonary excretion and other mechanisms involved there in.
- Thus, K_E is an additive property of rate constants for each of these processes and better called as overall elimination rate constant.
  $K_E = K_e + K_m + K_b + K_P + ...$ **------ 9**
- The fraction of drug eliminated by a particular route can be evaluated if the number of rate constants involved and their values are known.
- For example, if a drug is eliminated by urinary excretion and metabolism only, then, the fraction of drug excreted unchanged in urine F_e and fraction of drug metabolized F_m can be given as:

$$F_e = K_e / K_E \qquad \text{------- 10a}$$

$$F_m = K_m / K_E \qquad \text{------ 10b}$$

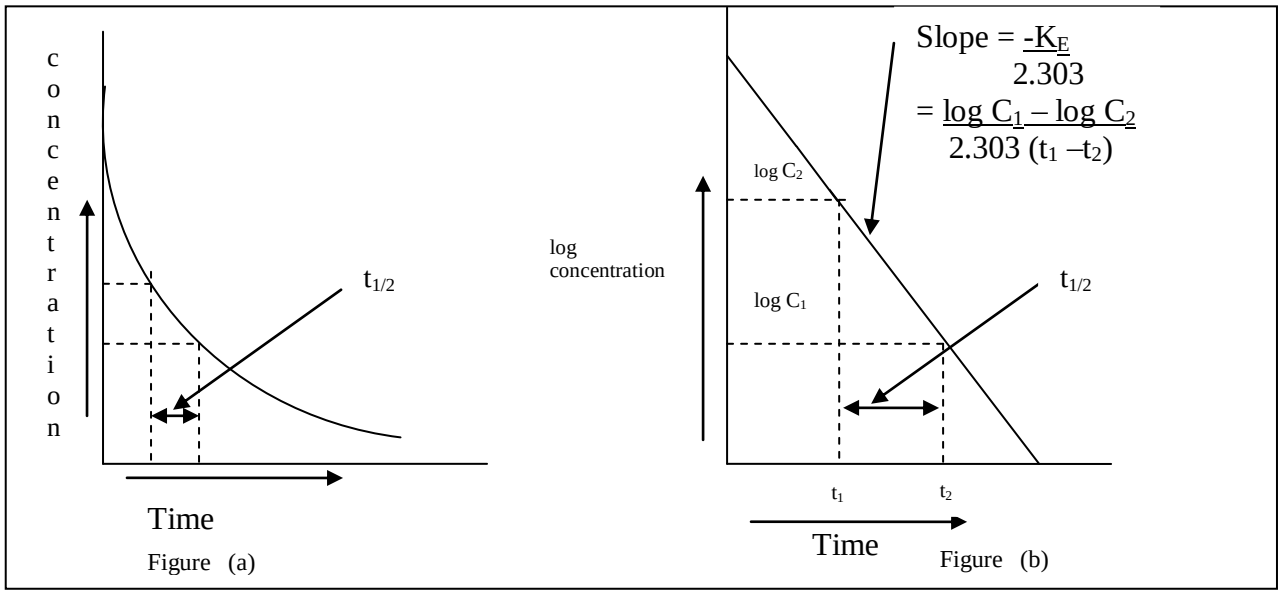


Figure: (a) Cartesian plot of a drug that follows one compartment kinetics and given by rapid IV injection and
Figure: (b) Semi logarithmic plot for the rate of elimination in a one compartment model.

ELIMINATION HALF-LIFE

Half-life is related to elimination rate constant by the following equation:

$$t_{½} = \frac{0.693}{K_E} \qquad \text{------ 11}$$

Most of the drugs are eliminated within 10 half lives.

- Half-life is a secondary parameter that depends upon the primary parameters clearance and apparent volume of distribution as follows:

$$t½ = \frac{0.693}{Cl_T} \qquad \text{…….11(a)}$$

APPARENT VOLUME OF DISTRIBUTION:-

- V_d is a measure of the extent of distribution of drug and is expressed in litres. The best and simplest way of estimating V_d of a drug is administering it by rapid IV injection and using following equation:

$$V_d = \frac{X_o}{C_o} = \frac{\text{i.v. bolus dose}}{C_0} \qquad \text{------13}$$

- Equation 13 can only be used for the drugs that obey one compartment kinetics. This is because the V_d can only be estimated when distribution equilibrium is achieved between drug in plasma and that in tissues and such an equilibrium is instantaneously for a drug that follows one compartment kinetics.
- A more general, more useful non compartmental method that can be applied to many compartment models for estimating the V_d is:

For drug given as IV bolus,

$$V_{d(area)} = \frac{X_o}{K_E.AUC} \qquad \text{-------(14.a)}$$

For drug given as extravascularly

$$V_{d(area)} = \frac{FX_o}{K_E.AUC} \qquad \text{-------(14.b)}$$

Where X_o = dose administered and F= fraction of drug absorbed into systemic circulation.

CLEARANCE :-

- Clearance is the most important parameter in clinical drug applications and is useful in evaluating the mechanism by which a drug is eliminated by the whole organism or by a particular organ.
- Clearance is a parameter that relates plasma drug concentration with rate of drug elimination according to following equation:

$$\text{Clearance} = \frac{\text{Rate of Elimination}}{\text{Plasma drug concentration}} \qquad \text{-------15}$$

Or

$$Cl = \frac{dX/dt}{C} \qquad \text{------16}$$

- Clearance is 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.
- 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 concentration C measured for the right side of equation 16.

TOTAL BODY CLEARANCE

- Elimination of a drug from the body involves processes occurring in kidney, liver, lungs and other eliminating organs. Clearance at an individual organ level is called organ clearance. It can be estimated by dividing the rate of elimination by each organ with the concentration of drug presented to it. Thus,

Renal clearance $Cl_R = \frac{\text{Rate of Elimination by kidney}}{C}$ **------ 17(a)**

Hepatic clearance $Cl_H = \frac{\text{Rate of Elimination by liver}}{C}$ **------ 17(b)**

Other organ clearance

$$Cl_{others} = \frac{\text{Rate of elimination by other organs}}{C} \text{ -- } \mathbf{17(c)}$$

- Total body clearance Cl_T also called as total systemic clearance is an additive property of individual organ clearances. Hence,

Total systemic clearance,

$$Cl_T = Cl_R + Cl_H + Cl_{others} \quad \text{------ 18}$$

- Clearance by all organs other than kidney is sometimes known as nonrenal clearance Cl_{NR}. It is the difference between total clearance and renal clearance.
- Substituting $dx/dt = K_E.X$ in Equation (16), we get

$$Cl_T = \frac{K_E.X}{C} \quad \text{------ 19}$$

Since $X/C = V_d$ (From equation (12)), equation 19 can be written as

$$Cl_T = K_E V_d \quad \text{------ 20}$$

Similar Equation can be written for renal clearance and hepatic clearance

$$Cl_R = K_e V_d \quad \text{------- 20 (a)}$$

$$Cl_H = K_m V_d \quad \text{------ 20 (b)}$$

Since $\mathbf{K_E = 0.693/t_{1/2}}$ from **equation 11**, clearance can be related to half life by the following equation: $Cl_T = \frac{0.693\ V_d}{t_{½}}$ ----------21

- Identical equations can be written for Cl_R and Cl_H in which cases the $t_{1/2}$ will be urinary excretion half-life for unchanged drug and metabolism half-life respectively.
- From equation 21 we can conclude that, increase in $t_{½}$ results in decrease in clearance as in case with renal insufficiency and increase in V_d results in increased Cl_T as in case with obesity and other edematous condition.
- The non compartmental method of computing total clearance of a drug that follows one compartment kinetics is:
  For drugs given as IV bolus,

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

- For drugs administered extravascularly,

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

Where F is the fraction absorbed into systemic circulation.

- For a drug given by IV bolus, the renal clearance Cl_R may be estimated by determining the total amount of unchanged drug excreted in urine, X_u^∞ and AUC.

$$Cl_R = \frac{X_u^\infty}{AUC}$$

ORGAN CLEARANCE

- The best way of understanding clearance is at individual organ level. Such a physiologic approach is advantageous in predicting and evaluating the influence of pathology, blood flow, enzyme activity, etc. on drug elimination. At an organ level, the rate of elimination can be written as:

Rate of Elimination by organ = [Rate of Presentation to organ (input)] – [Rate of exit from organ] ----- 22

- Rate of Presentation (Input) = Organ blood flow **x** Entering concentration
  = Q. C in **------ 23**

- Rate of Exit (output) = Organ blood flow **x** Exiting concentration
  = Q. C out **----- 24**

- Substitution of **equation 23 and 24** in **equation 22** yields:
  Rate of elimination = Q. C_{in} - Q. C_{out}
  (also called as rate of extraction) = Q (C_{in} - C_{out}) **------ 25**

- Division of above equation by concentration of drug that enters the organ of elimination **C_{in}** yields an expression for clearance of drug by the organ under consideration.

$$Cl_{organ} = \frac{Q\,(C_{in} - C_{out})}{C_{in}} = Q.\,ER \qquad \textbf{------ 26}$$

Where ER = (C_{in} - C_{out})/C_{in} which is called extraction ratio.

- It has no units and its value ranges from zero (no elimination) to one (complete elimination). Based on ER values, drugs can be classified into three groups:
- Drugs with high ER (above 0.7)
- Drugs with intermediate ER (between 0.7 to 0.3) and
- Drugs with low ER (below 0.3)
- ER is an index of how efficiently the eliminating organ clears the blood flowing through it of drug.
- For example, ER of 0.6 means 60% of the blood flowing through organ is completely cleared of drug.
- Fraction of drug that escapes removal by organ is expressed as:

$$F = 1 - ER \qquad \textbf{------- 27}$$

Where F= Systemic availability when eliminating organ is liver.

RENAL CLEARANCE

As in Equation (17.a),

Renal Clearance $Cl_R = K_e.V$ **-------- 28**

Or

$CL_R = Q_R.ER_R$ **----- 29**

Where, Q_R = renal blood flow.
ER_R = renal extraction ratio.

- In a certain disease state affecting kidney function, drugs are likely to be retained in body for longer time, this may result in accumulation of drug itself or accumulation of metabolite which may lead toxicity.

HEPATIC CLEARANCE

- For certain drugs, the non renal clearance Cl_{NR} can be assumed as equal to hepatic clearance Cl_H. Modifying **equation 18(a)** gives:

$Cl_H = Cl_T - Cl_R$ **------ 30**

- An equation parallel to 26 can also be written for hepatic clearance:
  $Cl_H = Q_H.\ ER_H$ **------ 31**
  Where Q_H = hepatic blood flow.
  ER_H = hepatic extraction ratio.

- Hepatic clearance of drugs can be divided into two groups

1. Drugs with hepatic blood flow rate limited clearance.
2. Drugs with intrinsic – capacity limited clearance.

1. Hepatic blood flow

- When ER_H is one, Cl_H approaches its maximum value. In such a situation, hepatic clearance is said to be perfusion rate limited or flow dependent.
- Alteration in hepatic blood flow significantly affects the elimination of drugs with high ER_H example propanol, lidocaine,etc.
- First pass hepatic extraction is suspected when there is lack of unchanged drug in systemic circulation after oral administration.
- Maximum oral availability F for such drugs can be computed from equation 27. An extension of the same equation is the non compartmental method of estimating F:

$$F = 1 - ER_H = \frac{AUC_{oral}}{AUC_{I.V.}} \qquad \text{------ 32}$$

2. Intrinsic Capacity Clearance:

- It is defined as the inherent ability of an organ to irreversibly remove a drug in the absence of any flow limitation
- It depends in this case upon the enzyme activity.
- Drugs with low ER_H and drugs with elimination primarily by metabolism are greatly affected by enzyme activity.
- Hepatic clearance of such drugs is said to be capacity limited example theophylline.
- Hepatic clearance of drugs with low ER is independent of blood flow rate but sensitive to changes in protein binding.

[2] ONE COMPARTMENT OPEN MODEL

(Intravenous Infusion)

- Rapid IV 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 is administered at a constant rate (zero order) by IV infusion.

Advantages of such a zero order infusion of drugs include-

- Ease of control of rate of infusion to fit individual patient needs.
- Prevents fluctuating plasma level (maxima and minima), desired especially when the drug has a narrow therapeutic index.
- Other drugs, electrolytes and nutrients can be conveniently administered simultaneously by the same infusion lie in critically ill patients.

The model can be presented as follows:

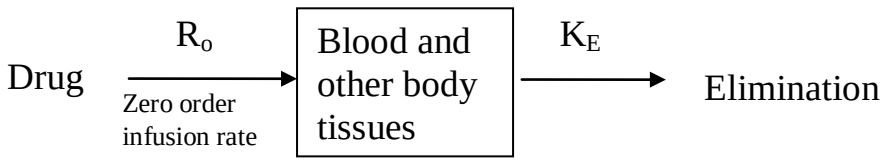


Figure: One compartment open intravenous infusion model.

- 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_o and first order elimination, $-K_E X$:

$$dX/dt = R_o - K_E X \qquad \text{------ 33}$$

Integration and rearrangement of above equation yields

$$X = \frac{R_o}{K_E}(1 - e^{-K_E t}) \qquad \text{-------34}$$

Since $X = V_d C$, **the equation 34** can be transformed into concentration terms as follows:

$$C = \frac{R_o}{K_E V_d}(1 - e^{-K_E t}) = \frac{R_o}{Cl_T}(1 - e^{-K_E t}) \qquad \text{------ 35}$$

- After infusion, as time passes, amount of drug rises gradually (elimination rate less than the rate of infusion) until a point after which the rate of elimination equals the rate of infusion i.e. the concentration of drug in plasma approaches a constant value called as steady state, plateau or infusion equilibrium.

- At steady-state, the rate of change of amount of drug in the body is zero hence the **equation 33** becomes:

$$0 = R_o - K_E X_{SS}$$

Therefore, $K_E X_{SS} = R_o$ ------ **36**

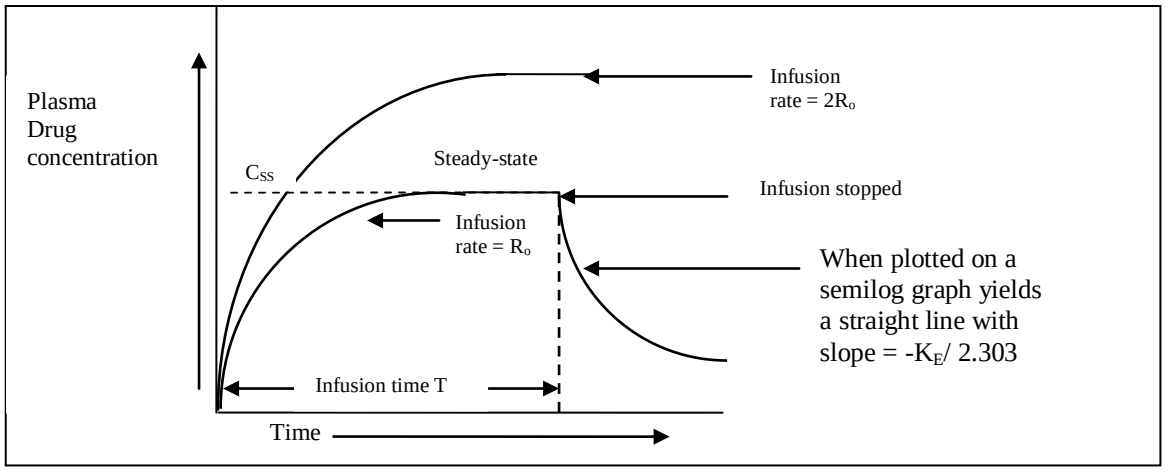


Figure: Plasma concentration time profile for a drug given by constant rate IV infusion (the two curves indicate different infusion rates R_o and $2R_o$ for the same drug).

Transforming to concentration terms ($X_{SS} = V_d C_{SS}$) and rearranging the equation:

$$C_{SS} = \frac{R_o}{K_E V_d} = \frac{R_o}{Cl_T} \text{ i.e. } \frac{\text{Infusion rate}}{\text{Clearance}} \qquad \text{------ 37}$$

Where X_{SS} and C_{SS} are amount of drug in the body and concentration of drug in plasma at steady state respectively.

- The value of K_E (and hence $t_{1/2}$) can be obtained from the slope of straight line obtained after a semilogarithmic plot (log C versus T) of plasma concentration-time data gathered from the time when infusion is stopped.

- Alternatively K_E can be calculated from the data collected during infusion to steady state as follows:

Substituting $R_o/Cl_T = C_{SS}$ from equation 37 in equation 35 we get:

$$C = C_{SS}\,(1 - e^{-K_E t}) \qquad \text{------ 38}$$

- Rearrangement yields:

$$\left[\frac{Css - C}{Css}\right] = e^{-KEt} \qquad \text{------ 39}$$

- Transforming to log form the equation becomes:

$$\log\left[\frac{Css - C}{Css}\right] = \frac{-K_E T}{2.303} \qquad \text{------ 40}$$

- Now, plot of $\log\left[\frac{Css - C}{Css}\right]$ versus **TIME** gives straight line with slope = $\frac{-K_E}{2.303}$

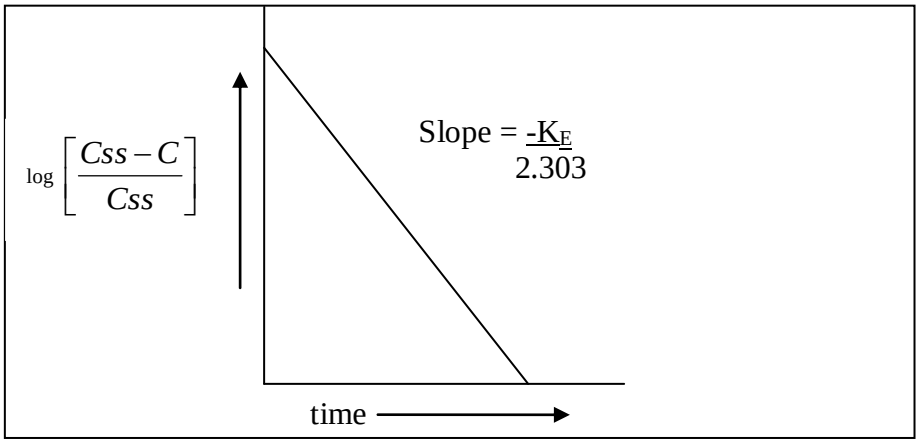


Figure: Plot of $\log\left[\frac{Css - C}{Css}\right]$ versus time

- The time to reach steady state concentration is dependent upon the elimination half life and not infusion rate. An increase in infusion rate will merely increase the plasma concentration attained at steady state (figure 7). If n is the number of half-lives passed since the start of infusion ($t/t_{1/2}$), equation 38 can be written as

$$C = C_{SS}\,[1 - (1/2)^n] \qquad \text{------ 41}$$

- The percent of C_{SS} achieved at the end of each $t_{1/2}$ is the sum of C_{SS} at previous $t_{1/2}$ and the concentration of drug remaining after a given $t_{1/2}$ (Table 1).

TABLE 1.

Half life	% Remaining	% CSS achieved
1	50	50
2	25	50+25=75
3	12.5	75+12.5=87.5
4	6.25	87.5+6.25=93.75
5	3.125	93.75+3.125=96.875
6	1.562	96.875+1.562=98.437
7	0.781	98.437+0.781=99.218

- For therapeutic purpose, more than 90% of the steady state drug concentration in the blood is desired which is reached in 3.3 half lives. It takes 6.6 half lives for the concentration to reach 99% of the steady state. Thus, the shorter the half life (e.g. Penicillin G, 30 minutes), sooner is the steady state reached.

INFUSION PLUS LOADING DOSE

- It takes a very long time for the drugs having longer half-lives before the plateau concentration is reached (e.g. Phenobarbital, 5 days).
- This can be overcome by administering an IV loading dose large enough to yield the desired steady state immediately upon injection prior to starting the infusion. It should then be followed immediately by IV infusion at a rate enough to maintain this concentration.

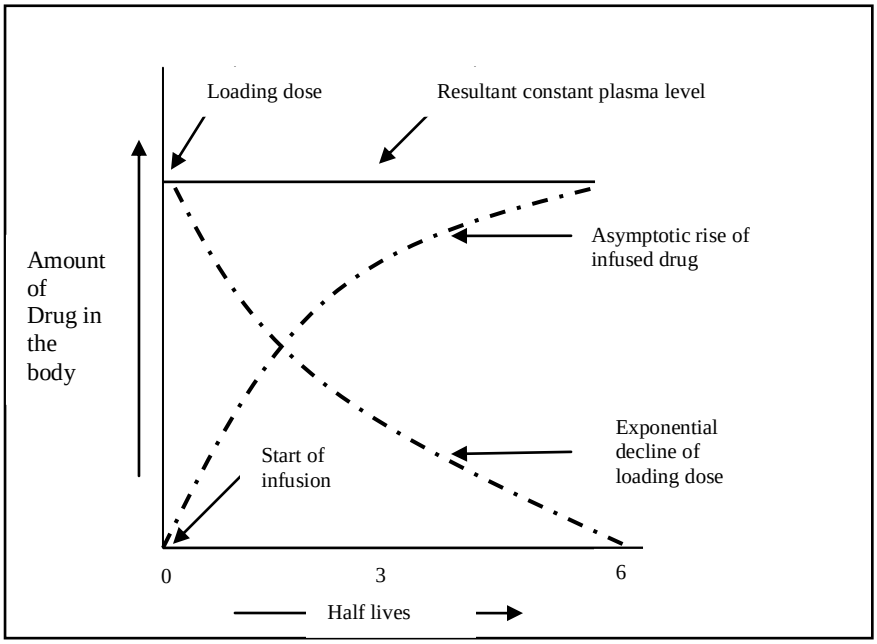


Figure: Intravenous infusion with loading dose. As the amount of bolus dose remaining in the body falls, there is a complementary rise resulting from the infusion.

- Recalling once again the relationship $X = V_d C$, the equation for computing the loading dose $X_{O,L}$ can be given:

$$X_{O,L} = C_{SS} V_d \qquad \text{------ 42}$$

- Substitution of $C_{SS} = R_o/K_E V_d$ from equation 37 in above equation yields another expression for loading dose in terms of infusion rate:

$$X_{O,L} = \frac{R_o}{K_E} \qquad \text{------ 43}$$

- The equation describing the plasma concentration time profile following simultaneous IV loading dose (IV bolus) and constant rate IV infusion is the sum of following two equations (44 and 45) describing each process.

- If we recall **equation 5** for IV bolus

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

- And substituting $X=V_d C$ in above equation we get

$$C = \frac{X_o e^{-K_E t}}{V_d} \qquad \text{------- 44}$$

- And from equation 35 for constant rate IV infusion we know that

$$C = \frac{R_o}{K_E V_d}(1-e^{-K_E t}) \qquad \text{------ 45}$$

$$C = \frac{X_{O,L}}{V_d} e^{-KEt} + \frac{R_O}{K_E V_d}(1-e^{-KE\,t}) \qquad \text{------ 46}$$

- It we substitute C_{SS} V_d **for** $X_{O,L}$ (from equation 42) and $C_{SS}K_EV_d$ **for** R_o (from equation 37) in above equation and simplify it reduces to $C=C_{SS}$ indicating that concentration of drug in plasma remains constant (steady) throughout the infusion time.

[3] ONE COMPARTMENT OPEN MODEL (Extravascular Administration)

- When a drug is administered by extravascular route (e.g. oral,rectal,etc.) absorption is a prerequisite for its therapeutic activity.
- Absorption kinetics of drug may be first order or it may be zero order kinetics in rare cases.
- Zero order absorption is characterized by a constant rate of absorption. It is independent of amount of drug remaining to be absorbed (ARA), and its regular ARA versus t plot is linear with slope equal to rate of absorption while the semilog plot is described by an ever increasing gradient with time. In contrast, the first order absorption process is distinguished by a decline in the rate with ARA i.e. absorption rate is dependent upon ARA; its regular plot is curvilinear and semilog plot of a straight line with absorption rate constant as its slope.

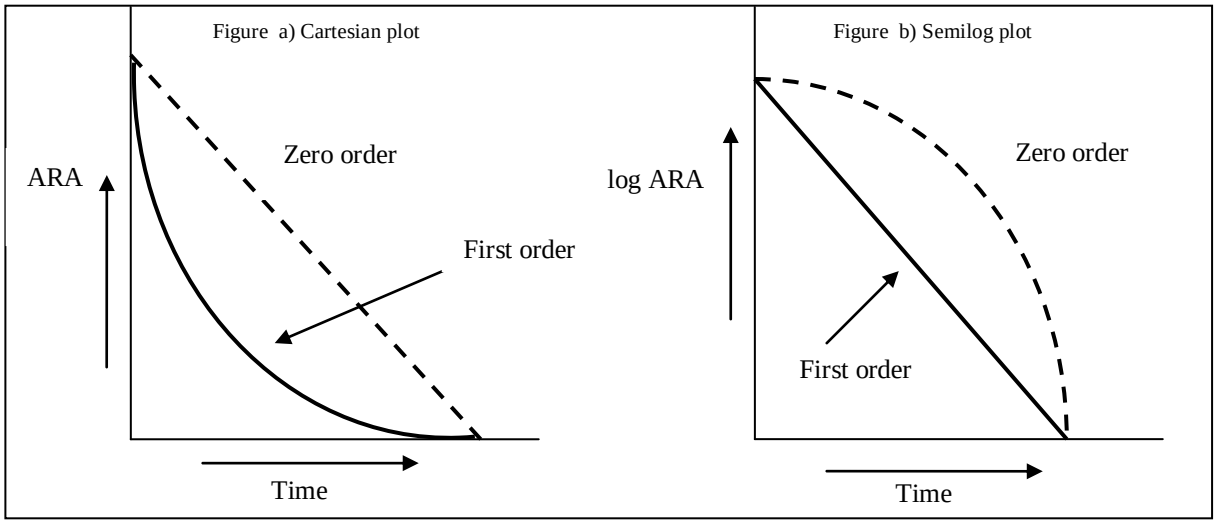


Figure a) and b) Distinction between zero order and first order absorption processes. Figure a) is a regular plot and figure b) is a semilog plot of amount of drug remaining to be absorbed (ARA) versus time.

- After extravascular administration, the rate of change in 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= Rate of absorption – Rate of elimination

$$\frac{dX}{dt} = \frac{dX_{ev}}{dt} - \frac{dX_E}{dt} \qquad \text{------ 48}$$

Various phases of fate of drug in body has been shown in figure

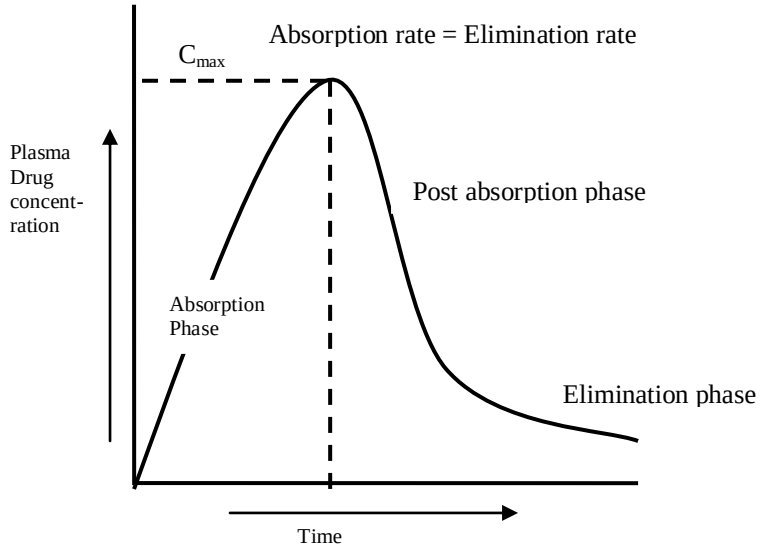


Figure:- The absorption and elimination phase of the plasma concentration time profile obtained after extravascular administration of a single dose of a drug.

ZERO ORDER ABSORPTION MODEL :-

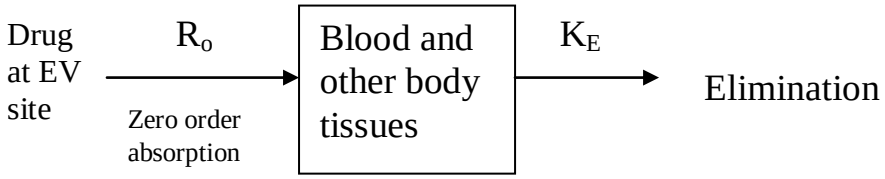


Figure: Zero order absorption model

- This model is similar to that of constant rate IV infusion.
- Example of zero order absorption, rate of drug absorption for controlled drug delivery systems.
- All equations that explain the plasma concentration-time profile for IV infusion are also applicable to this model.

FIRST ORDER ABSORPTION MODEL :-

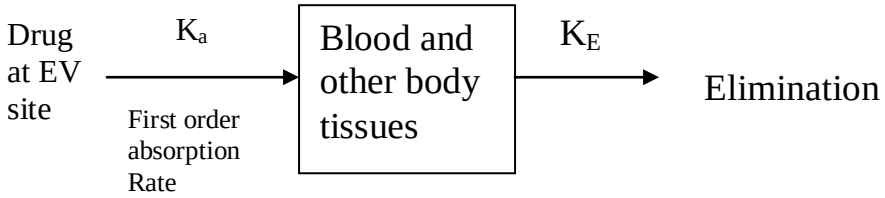


Figure : First order absorption model

Differential form of **equation 48** is

$$\frac{dX}{dt} = K_{\alpha} X_a - K_E X \qquad \text{------ 49}$$

Where, Ka = first order absorption rate constant

Xa = amount of drug at the absorption site remaining to be absorbed

Integration of equation 49 gives

$$X = \frac{K_a F X_o}{(K_a - K_E)}\left[e^{-K_E T} - e^{-K_a t}\right]$$ ------ **50**

Transforming into concentration terms, the equation becomes:

$$C = \frac{K_a F X_o}{V_d (K_a - K_E)}\left[e^{-K_E T} - e^{-K_a t}\right]$$ ------ **51**

Where F= fraction of drug absorbed systemically after extravascular administration.

ASSESSMENT OF PHARMACOKINETIC PARAMETERS C_{max} & t_{max}

- At peak plasma concentration

$K_aX_a = K_EX$ and the rate of change in plasma drug concentration dC/dt = 0.
dC/dt can be obtained by differentiating **equation 51**

$$\frac{dC}{dt} = \frac{K_a F X_o}{V_d (K_a - K_E)}\left[-K_E e^{-K_E t} + K_a e^{-K_a t}\right] = 0$$ ------ **52**

On simplifying the above equation

$$K_E e^{-K_E t} = K_a e^{-K_a t}$$ ------ **53**

Converting to logarithmic form

$$\log K_E - \frac{K_E t}{2.303} = \log K_a - \frac{K_a t}{2.303}$$ ------ **54**

If $t = t_{max}$. Rearrangement of above equation yields:

$$t_{max} = \frac{2.303 \log(K_a/K_E)}{K_a - K_E}$$ ------ **55**

The above equation shows, as K_a becomes larger than K_E, t_{max} becomes smaller since (K_a-K_E) increases much faster than log K_a/K_e.

Substituting equation 55 in equation 51 we get Cmax.
However, a simpler expression for the same is:

$$C_{max} = \frac{F X_o}{V_d} e^{-K_E t_{max}}$$ ------ **56**

At C_{max} ,
When $K_a=K_E$, $t_{max}=1/K_E$
Hence above equation further reduces to

$$C_{max} = \frac{F X_o}{V_d} e^{-1} = \frac{0.37 F X_o}{V_d}$$ ------ **57**

- Since FX_o/V_d represents C_o following IV bolus, the maximum plasma concentration that can be attained after extravascular administration is just 37% of the maximum level attainable with IV bolus in the same dose.
- If bioavailability is less than 100%, still lower concentration will be attained.

ELIMINATION RATE CONSTANT

- This parameter can be computed from the elimination phase of the plasma level time profile.
- For most drugs administered extravascularly, absorption rate is significantly greater than the elimination rate i.e. Kat>>>KEt.
- Hence one can say $e^{-K_a t}$ approaches zero must faster than does $e^{-K_E t}$.
- The stage at which absorption is complete, change in plasma concentration is dependent on elimination rate and equation 51 reduces to:

$$C = \frac{K_a F X_o}{V_d (K_a - K_E)} e^{-K_E t} \qquad \text{------ 58}$$

- Transforming to log form the equation becomes:

$$\log C = \log \frac{K_a F X_o}{V_d (K_a - K_E)} - \frac{K_E t}{2.303} \qquad \text{------ 59}$$

A plot of logC versus t yields a straight line with slope $-K_E/2.303$ (therefore, $t_1/_2 = 0.693/K_E$.

ABSORPTION RATE CONSTANT

- It can be calculated by method of residuals.
- This 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 extravascularly, the concentration of drug in plasma is expressed by a biexponential equation 51:

$$C = \frac{K_a F X_o}{V_d (K_a - K_E)} \left[e^{-K_E T} - e^{-K_a t} \right] \qquad \text{------ 51}$$

If, $\frac{K_a F X_o}{V_d (K_a - K_E)} [\ ]$ = **A**, a hybrid constant then:

$$C = Ae^{-K_E t} - Ae^{-K_a t} \qquad \text{------ 60}$$

- During the elimination phase, when absorption is almost over $K_a >>> K_E$ and the value of second exponential $e^{-K_a t}$ approaches zero whereas the first exponential $e^{-K_E t}$ retains some finite value. At this time equation 60 reduces to:

$$\overleftarrow{C} = Ae^{-K_E t} \qquad \text{------ 61}$$

In log form above equation can be written as:

$$\log \overleftarrow{C} = \log A - \frac{K_E t}{2.303} \qquad \text{------ 62}$$

Where $\log \overleftarrow{C}$ represents the back extrapolate plasma concentration values.

- A plot of log C versus t yields a biexponential curve with a terminal linear phase having slope – K_E/2.303(figure 14). Back extrapolation of this straight line to time zero yields y-intercept equal to log A.

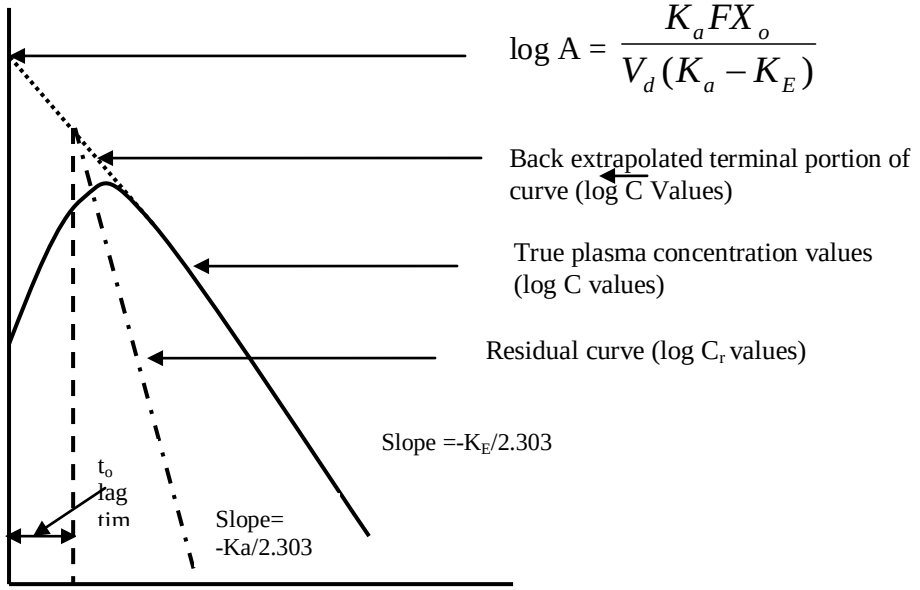


Figure 14 Plasma concentration time profile after oral administration of a single dose of a drug. The biexponential curve has been resolved into its two components- absorption and elimination.

- Substraction of true plasma concentration value i.e. equation 60 from the extrapolated plasma concentration values i.e. equation 61 yields a series of residual concentration values C_r:

$$(\overleftarrow{C} - C) = C_r = A\, e^{-Kat} \qquad \text{------ 63}$$

In log form the equation is:

$$\log C_r = \log A - \frac{K_a t}{2.303} \qquad \text{------ 64}$$

- A plot of log C_r versus t yields a straight line with slope –K_a/2.303 and Y intercept log A. Absorption half life can then be computed from K_a using the relation 0.693/K_a.
- Thus, the method of residuals enables resolution of the biexponential plasma level time curve into its two exponential components.
  The technique works best when the difference between K_a and K_E is large **($K_a/K_e \geq 3$).**
- In some instances, the K_E obtained after IV bolus of the same drug is very large, much larger than K_a obtained by the method of residuals (e.g**. isoprenaline**) and if **$K_E/K_a \geq 3$,** the terminal slope estimates K_a and not K_E whereas the slope of residual line gives K_E and not K_a. This is called as **flip-flop phenomenon** since the slopes of the two lines have exchanged their meanings.
- Ideally, the extrapolated and the residual lines intersect each other on y axis i.e. at time t = zero and there is no lag in absorption. However, if such an intersection occurs at a time greater than zero, it indicate time lag. It is defined as the time difference between drug administration and start of absorption.
- It is denoted by symbol t_o and represents the beginning of absorption process. Lag time should not be confused with onset time.
- The above method for the estimation of K_a is curve fitting method. The method is best suited for drugs which are rapidly and completely absorbed and follow one compartment kinetics.

Wagner-Nelson Method for estimation of K_a

- One of the better alternatives to curve fitting method in the estimation of K_a is Wagner-Nelson method. The method involves the determination of K_a from percent unabsorbed time plots and does not require assumption of zero or first order absorption.
- 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 and the amount of drug eliminated from the body X_E. Thus:

$$X_A = X + X_E \qquad \text{------ 65}$$

- The amount of drug in the body is $X=V_dC$. The amount of drug eliminated at any time t can be calculated as follows:

$$X_E = K_E V_d [AUC]_0^t \qquad \text{------ 66}$$

- Substitution of values of X and X_E in equation 65 yields:

$$X_A = V_d C + K_E V_d [AUC]_0^t \qquad \text{------ 67}$$

- The total amount of drug absorbed into systemic circulation from time zero to infinity X_A^∞ can be given as:

$$X_A^\infty = V_d C^\infty + K_E V_d [AUC]_0^\infty \qquad \text{------ 68}$$

Since at t = ∞, $C^\infty = 0$,the above equation reduces to:

$$X_A^\infty = K_E V_d [AUC]_0^\infty \qquad \text{------ 69}$$

- The fraction of drug absorbed at any time t is given as:

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

$$= \frac{C + K_E [AUC]_0^t}{K_E [AUC]_0^\infty} \qquad \text{------ 70}$$

Percent drug unabsorbed at any time is therefore:

$$\%ARA = \left[1 - \frac{X_A}{X_A^\infty}\right] 100 = \left[1 - \frac{C + K_E [AUC]_0^t}{K_E [AUC]_0^\infty}\right] 100 \qquad \text{------ 71}$$

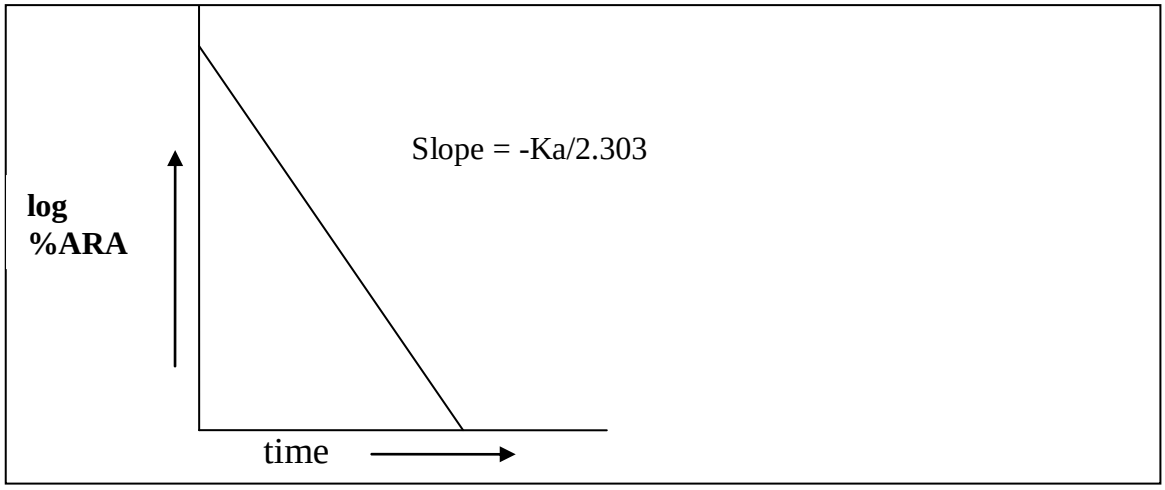


Figure 15 Semilog plot of percent ARA versus t according to Wagner- Nelson method.

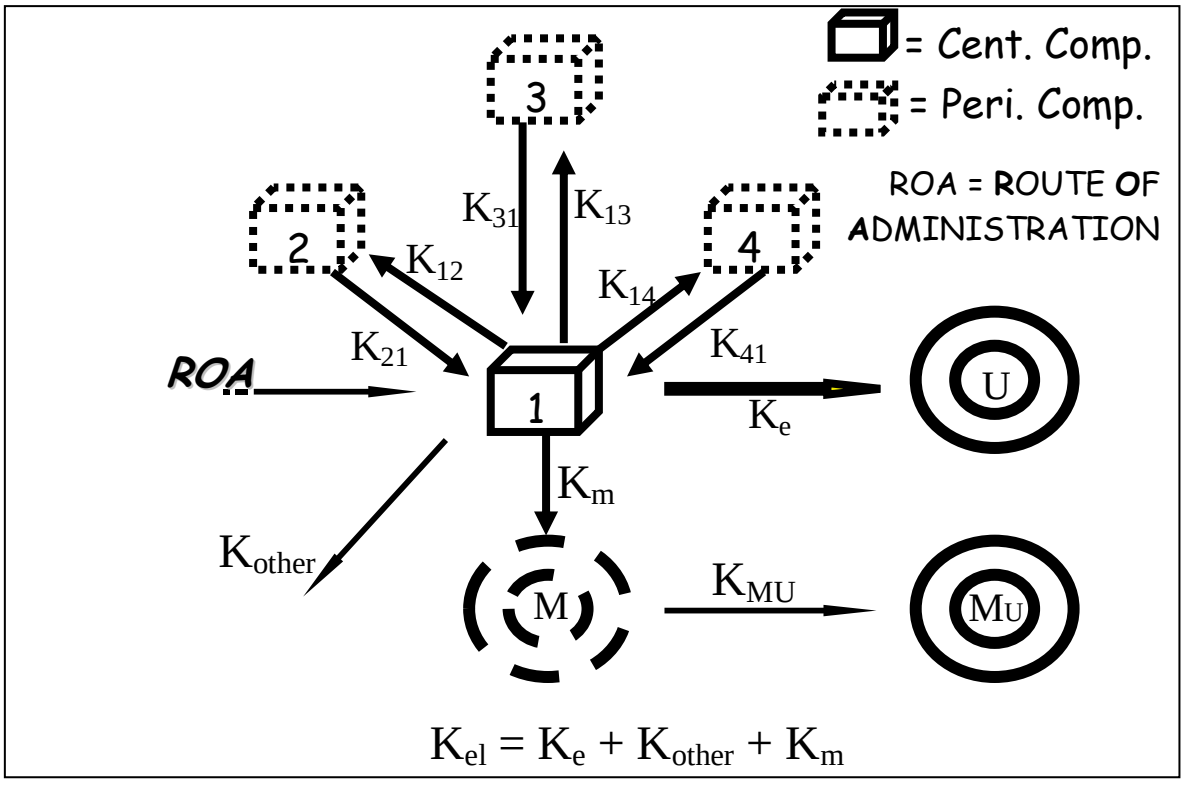
- This method requires collection of blood samples after a single oral dose at regular intervals of time till the entire amount of drug is eliminated from the body.
- K_E is obtained from plot of log C versus t and $[AUC]_0^t$ and $[AUC]_0^\infty$ are obtained from plots of C versus t.

- A semilog plot of percent unabsorbed (i.e. percent ARA) versus t yields a straight line whose slope is $-K_a/2.303$(figure 15). If a regular plot of the same is a straight line, the absorption is zero order.
- K_a can similarly be estimated from urinary excretion data.
- The biggest disadvantage of Wagner-Nelson method is that it applies only to drugs with one compartment characteristics. Problem arises when a drug that obeys one compartment model after extravascular administration shows multicompartment characteristics on IV injection.

MULTICOMPARTMENTAL MODEL

(Delayed distribution models)

- The one compartment model adequately describes pharmacokinetics of many drugs.
- Instantaneous distribution is assumed in such cases and decline in the amount of drug in the body with time is expressed by an equation with mono-exponential term (i.e. elimination).
- However, this is not possible in case of majority of drugs and also drug disposition is not always mono-exponential. It may be bi or multi- exponential.
- This is because the body is composed of a heterogeneous group of tissues each with different degree of blood flow and affinity for drug and therefore different rates of equilibration.
- Ideal a true pharmacokinetic model is one with a rate constant for each tissue undergoing equilibrium. However this approach is difficult mathematically.
- The best approach is therefore to pool together the tissues on the basis of their distribution characteristics and group of tissues thus formed is called a compartment. So for particular drug there could be more than one compartment with difference in their distribution characteristics.
- As in case of one compartment, drug distribution in multi-compartment model is also assumed to be of first order process.
- Multi-compartmental behavior of drug can be well understood by giving drug as i.v. bolus and observing the manner in which its plasma concentration decrease with time.



[Fig.1. General Multi Compartment Pharmacokinetic Model]

⌗ TWO COMPARMENT OPEN MODEL

Definition: The two compartment open model treats the body as two compartments.

1. Central compartment: Comprising of blood and highly perfused tissues like liver, kidney, lungs etc. that equilibrate with the drug rapidly.
   Elimination usually occurs from this compartment.
2. Peripheral or tissue compartment: Comprising of poorly perfused and slow equilibrating tissues such as muscles, skin, adipose etc.

- ✓ Classification of a particular tissue, for example brain into central or peripheral compartment depends upon the physicochemical properties of the drug.
- ✓ A highly lipophilic drug can cross the BBB and Brain would then be included in the central compartment.
- ✓ In contrast, a polar drug can not penetrate the BBB and brain in this case will be a part of peripheral compartment despite the fact that it is a highly perfused organ.

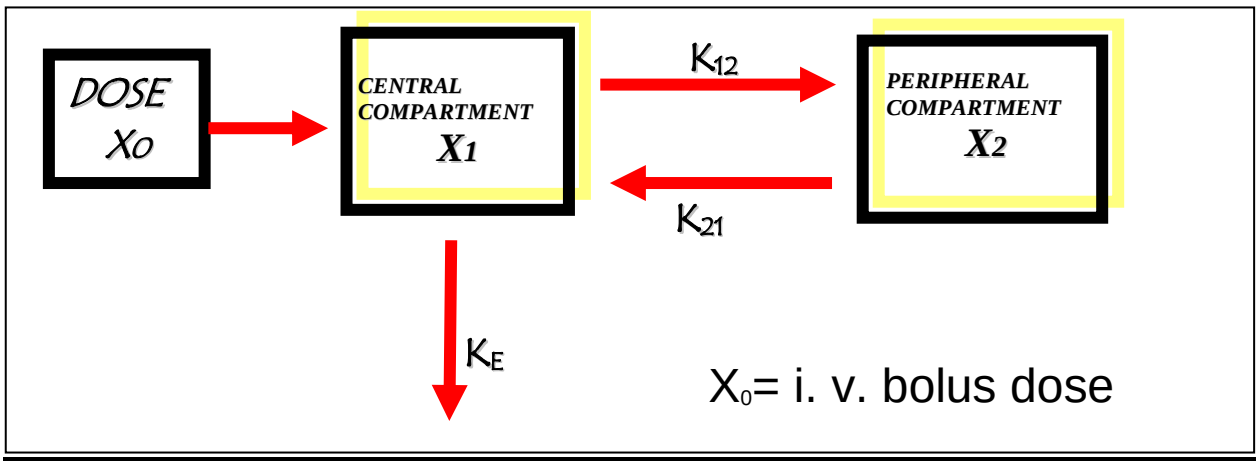
Assumptions:

- All processes are first order.
- Input and output are from the "central" compartment.
- Mixing is instantaneous in within each compartment.
- Mixing between the compartments is slow relative to mixing within the compartments.

- ♦ Three different type of model under this category are:-
  1. Two compartment model with elimination from central compartment.
  2. Two compartment model with elimination from peripheral compartment.
  3. Two compartment model with elimination from both compartment.

  In the absence of information, elimination is assumed to occur exclusively from central compartment.

⌗ IV 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 processes viz. (see fig)

(A) Distribution

(B) Elimination.

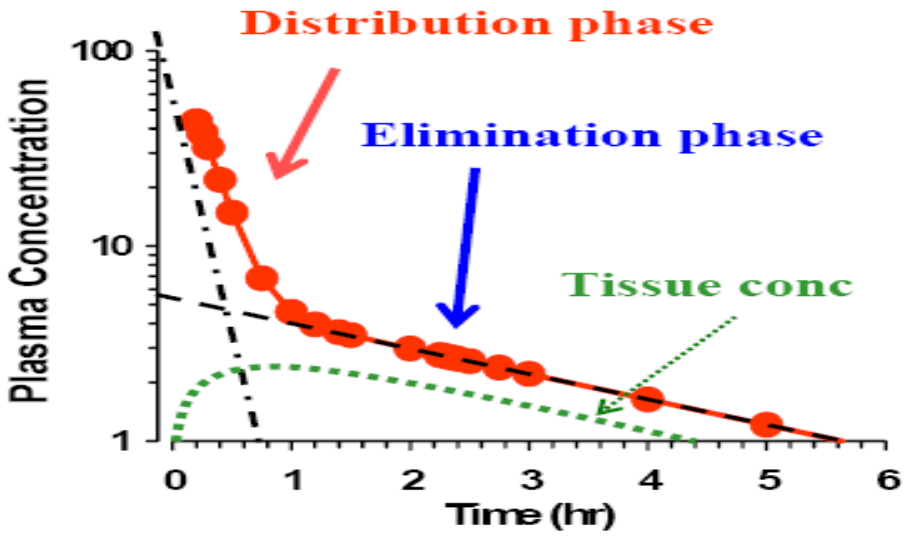


Fig.4

These two processes are not evident to the eyes in a regular arithmetic plot but when a semi log plot of c versus t is made. They can be identified.
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.
The phase during which this occurs is therefore 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 as **elimination phase**.
In contrast to the central compartment, the drug concentration in the peripheral compartment first increase & reaches a maximum, this corresponds with the distribution phase.
Following peak, the drug concentration declines which corresponds to the post distributive phase.

- Let K_{12} and K_{21}, be the first order distribution rate constants depicting drug transfer between the central and the peripheral compartments respectively.
- The rate of change in drug concentration in the central compartment is given by:-

$$\boxed{dC_c/dt = K_{21}\,C_p - K_{12}\,C_c - K_E\,C_c} \qquad \text{....(1)}$$

Extending the relation ship $\mathbf{X = V_d c}$ to the above equation, we have,

$$dC_c/dt = \frac{K_{21}\,X_p}{V_p} - \frac{K_{12}\,X_c}{V_c} - \frac{K_E\,X_c}{V_c} \qquad \text{.....(2)}$$

Where,

X_c = Amount of drug in the central compartment

X_p = Amount drug in the peripheral compartment

V_c = Apparent volumes of the central compartment

V_p = Apparent volumes of the peripheral compartment.

$$dC_p/dt = K_{12}\, C_c - K_{21}\, C_p \qquad \text{.....(3)}$$

$$dC_p/dt = \frac{K_{12}\, X_c}{V_c} - \frac{K_{21}\, X_p}{V_p} \qquad \text{.....(4)}$$

Integration of equations (3) & (4) yields equations that describe the concentration of drug in the central & peripheral compartments at any given time "t".

$$C_c = \left(\frac{X_0}{V_c} \frac{(K_{21} - \alpha)}{(\beta - \alpha)} e^{-\alpha t} + \frac{(K_{21} - \beta)}{(\alpha - \beta)} e^{-\beta t} \right) \qquad \text{.....(5)}$$

$$C_p = \left(\frac{X_0}{V_p} \frac{K_{21}}{\beta - \alpha} e^{-\alpha t} + \frac{K_{21}}{\alpha - \beta} e^{-\beta t} \right) \qquad \text{.....(6)}$$

Where X_0 = i. v. bolus dose , α & β are hybrid first-order constants for the rapid distribution phase and the slow elimination phase respectively which depend entirely upon the first – order constants K_{12}, K_{21} and K_E.

The constants K_{12} and K_{21} that depict reversible transfer of drug between compartments are called as micro constants or transfer constants.

The mathematical relationships between hybrid and micro constants are given as :

$$\alpha + \beta = K_{12} + K_{21} + K_E \qquad \text{.....(7)}$$

$$\alpha\beta = K_{21}\, K_E \qquad \text{.....(8)}$$

Equation (5) can be written in simplified form

$$C_c = A\, e^{-\alpha t} + B\, e^{-\beta t} \qquad \text{.....(9)}$$

C_c = Distribution exponent + Elimination exponent

Where A & B are also hybrid constants for the two exponents and can be resolved graphically by the method of residuals.

$$A = \frac{X_0}{V_c} \left(\frac{K_{21} - \alpha}{\beta - \alpha} \right) = C_0 \left(\frac{K21 - \alpha}{\beta - \alpha} \right) \qquad \text{....(10)}$$

$$B = \frac{X_0}{V_c} \left(\frac{K_{21} - \beta}{\alpha - \beta} \right) = C_0 \left(\frac{K21 - \alpha}{\alpha - \beta} \right) \qquad \text{..(11)}$$

Where,
C_0 = Plasma drug concentration immediately after i.v. injection.

METHOD OF RESIDUAL

(Curve Stripping OR FEATHERING)

The **biexponential disposition curve** obtained after i.v. bolus of a drug that fits two compartment models can be resolved into its individual exponents by the method of residuals.

→ Rewriting the equation (9) $C_c = A\, e^{-\alpha t} + B\, e^{-\beta t}$ ....**(12)**

As per apparent from the biexponential curve given in fig 3, the initial decline due to distribution is more rapid than the terminal decline due to elimination i.e. the rate constant $\alpha >> \beta$ and hence the term $e^{-\alpha t}$ approaches Zero much faster than does $e^{-\beta t}$

→ Thus, equation (9) reduce to

$$C = B e^{-\beta t} \quad \text{.....(13)}$$

→ In log form, the equation becomes :

$$\text{Log } C = \log B - \frac{\beta t}{2.303} \quad \text{.....(14)}$$

Where, C = Back extrapolated plasma concentration values.

A Semi log pot of C versus t yields the terminal linear phase of the curve having slope – β/2.303 and when back extrapolated to time zero, yields y- intercept log B (fig .5).
The $t_{1/2}$ for the elimination equation $\mathbf{t_{1/2} = 0.693/\beta.}$

♦ Subtraction of extrapolated plasma concentration values of the elimination phase (equation 13) from the corresponding true plasma concentration values (equation 9) yields a series of residual concentration values Cr.

$$Cr = C - C = A. e^{-\alpha t} \quad \text{.....(15)}$$

In log form, equation.

$$\text{Log } Cr = \log A - \alpha t/2.303 \quad \text{.....(16)}$$

A semi log plot of Cr versus t yields straight line with slope $-\alpha/2.303$ and y – intercept log A (fig.5).

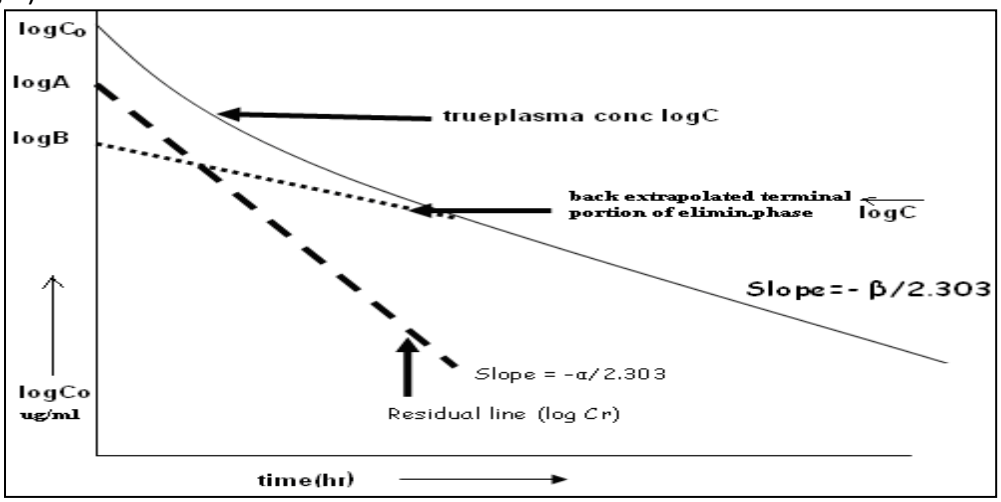


Fig.5. Biexponential plasma concentration curve by method of residues of the drugs

ASSESSMENT OF PHARMACOKINETIC PARAMETERS:

All the parameters of equation (9) can be resolved by the method of residuals as described above.

Other parameters of the model viz K_{12}, K_{21}, K_E etc. can now be derived by proper substitution of these values.

$$C_0 = A + B \quad \text{....(17)}$$

$$K_E = \frac{\alpha\beta C_0}{}$$

$$A\beta + B\alpha \qquad \text{....(18)}$$

$$K_{12} = \frac{AB(\beta - \alpha)^2}{C_0(A\beta + B\alpha)} \qquad \text{.....(19)}$$

OR

$$K_{12} = \alpha + \beta - K_E - K_{21} \qquad \text{...(20)}$$

$$K_{21} = \frac{A\beta + B\alpha}{C_0} \qquad \text{.....(21)}$$

Note: For two compartment model, K_E is the rate constant for elimination of drug from the central compartment and β is the rate constant for elimination from the entire body.

-- Overall elimination $t_{1/2}$ should therefore be calculated from β.

-- Area under the plasma concentration – time curve can be obtained by the following equation:

$$AUC = \frac{A}{\alpha} + \frac{B}{\beta} \qquad \text{....(22)}$$

-- The apparent volume of central compartment Vc is given as

$$V_c = \frac{X_0}{C_0} = \frac{X_0}{K_E\, AUC} \qquad \text{.....(23)}$$

-- Apparent volume of peripheral compartment can be obtained from equation.

$$V_p = \frac{V_c K_{12}}{K_{21}} \qquad \text{.....(24)}$$

- The apparent volume of distribution at steady state or equilibrium can now be defined as:

$$V_{d,ss} = V_c + V_p \qquad \text{....(25)}$$

It is also given as

$$V_{d.area} = \frac{X_0}{\beta\, AUC} \qquad \text{.....(26)}$$

Total systemic clearance is given as

$$CL_T = \beta V_d \qquad \text{.....(27)}$$

The pharmacokinetic parameter can be calculated by using urinary excretion data:

$$dx_u/dt = K_e V_c \qquad \text{.....(28)}$$

An equation identical to equation $\{ Cc = A e^{-\alpha t} + B e^{-\beta t} \}$ can be calculated by using urinary excretion data.

$$dx_u/dt = Ke^{-\alpha t} + K e^{-\beta t} \qquad \text{.....(29)}$$

The above equation can be resolved in to individual exponents by the method of residual s as described for plasma – concentration time data.

Renal clearance is given as,

$$Cl_R = Ke\, Vc \qquad \text{.....(30)}$$

I.V. INFUSION

- The model can be depicted as shown with elimination from the central compartment.

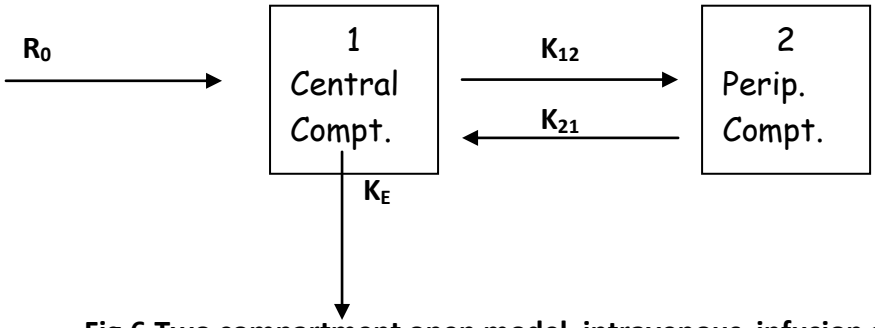


Fig.6.Two compartment open model, intravenous infusion administration

- The plasma or central compartment concentration of a drug that fits two, - compartment model when administered as constant rate (zero-order) i.v. infusion is given by equation.

$$C_c = \frac{X_0}{V_c K_E}\left[1 + \frac{K_E - \beta}{\beta - \alpha} e^{-\alpha t} + \frac{K_E - \alpha}{\alpha - \beta} e^{-\beta t}\right] \quad \text{....(31)}$$

- At steady-state (i.e. at time infinity), the second and the third term in the bracket becomes zero and the equation reduces to:

$$C_{ss} = \frac{R_0}{V_c K_E} = \frac{\text{infusion rate}}{\text{clerance}} \quad \textbf{....(32)}$$

Now, $V_c K_E = V_d \beta$

Substituting this in equation we get:

$$C_{ss} = \frac{R_0}{V_d \beta} = \frac{R_0}{CL_T} \quad \text{.....(33)}$$

The loading dose $X_{0,L}$ to obtain C_{ss} immediately at the start of infusion can be calculated from equation:

$$Xo,L = C_{ss} V_c = \frac{R_0}{K_E} \quad \text{.....(34)}$$

EXTRAVASCULAR ADMINISTRATION

■ First order absorption:-

The model can be depicted as follows.

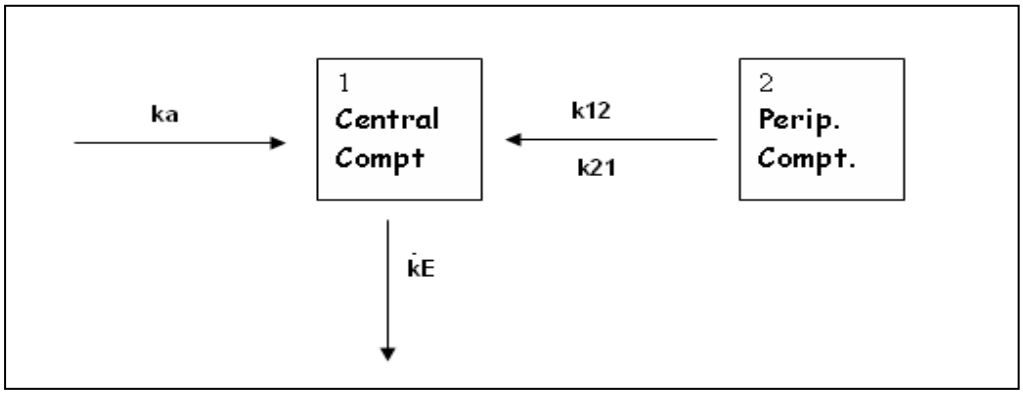
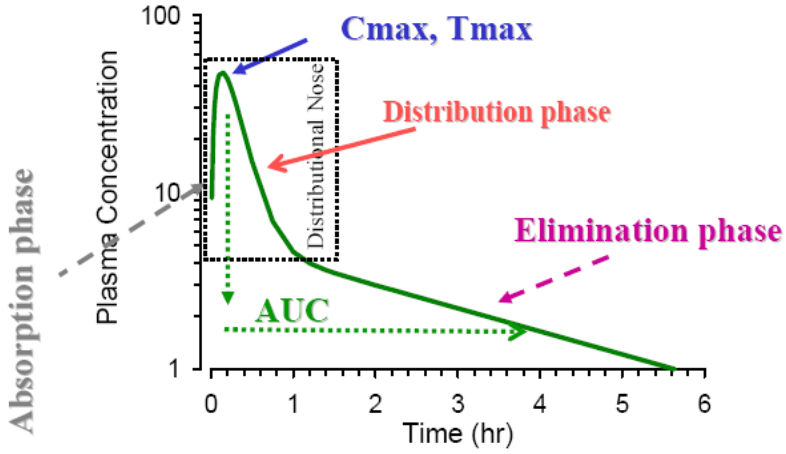


Fig.6. Two compartment open model, extravascular administration



[Fig.2. Typical plasma concentration vs time profile of an orally administered drug that exhibits two compartment model characteristics.]

- For a drug that enters the body by a first – order absorption process and distributed according to two compartment model, the rate of change in drug concentration in the central compartment is described by 3 exponents.

  -An Absorption exponent, and the two usual exponents that describe drug disposition.
  -The plasma concentration at any time t is given by equation:

$$C = N e^{-K_a t} + L e^{-\alpha t} + M e^{-\beta t} \quad \text{.....(35)}$$

C = Absorption exponent + Distribution exponent + Elimination exponent

Where, K_a, α & β have usual meanings L, M and N are coefficients.

The 3 exponents can be resolved by stepwise application of method of residuals assuming $K_a > \alpha > \beta$ as shown in fig.6.

The various pharmacokinetic parameters can then be estimated.

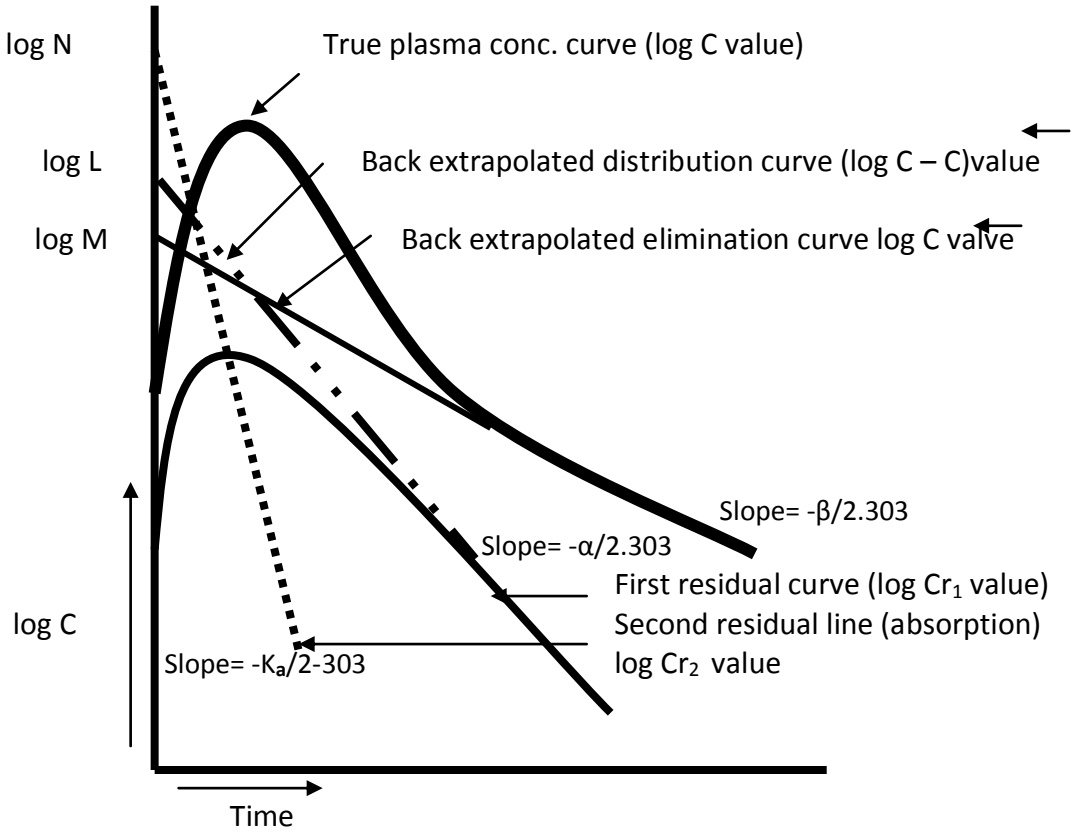


Fig.7.Semilog plot of C versus t of a drug with two compartment characteristics when administrated extravascularly.

- Besides the method of residuals, K_a can also be estimated by Loo – Riegelman method for a drug that follows two – compartment characteristics.

- This method is in contrast to the Wagner Nelson method. For determination of K_a of a drug with one – compartment characteristics.

Loo- Riegelman method:

Besides the method of residual Ka can also be estimated by Loo- Riegelman method.
Wagner-Nelson method can be used only to determine Ka of a drug with one compartment characteristic.

Wagner derived a exact Loo-Riegelman equation:

$$\frac{A_T}{V_p} = C_T + K_{10} \; {}_0\int^T C_P \, dt + K_{12} e^{-K21\,T} \; {}_0\int^T C_P \, e^{+K21\,t} \, dt$$

A_T = Amount of drug absorbed to time T
V_p = Volume of central compartment
C_T = concentration of drug at time T

The Loo- Riegelman method requires plasma drug concentration – time data both after oral and i. v administration of the drug to the same subject at different times in order to obtain all the necessary kinetic constants.
V_P can be obtained by I.V administration of the drug.
Parameters K_{12}, K_{21}, K_{10} can be obtained by plasma concentration- time data after oral administration.
Despite its complexity the method can be applied to drugs that distribute in any number of components.

THREE COMPARTMENT MODEL

- The preferred compartmental model is the one containing the fewest compartments which adequately described the data. While one compartment and two compartment models accommodate a great many drugs, there are a number of cases where these are not sufficient.

- Significant distribution of drug in deep tissues such as bone or fat, or strong binding to any tissues, may results in the appearance of a **TRIEXPONENTAL** blood level curve, indicating the presence of a third compartment.

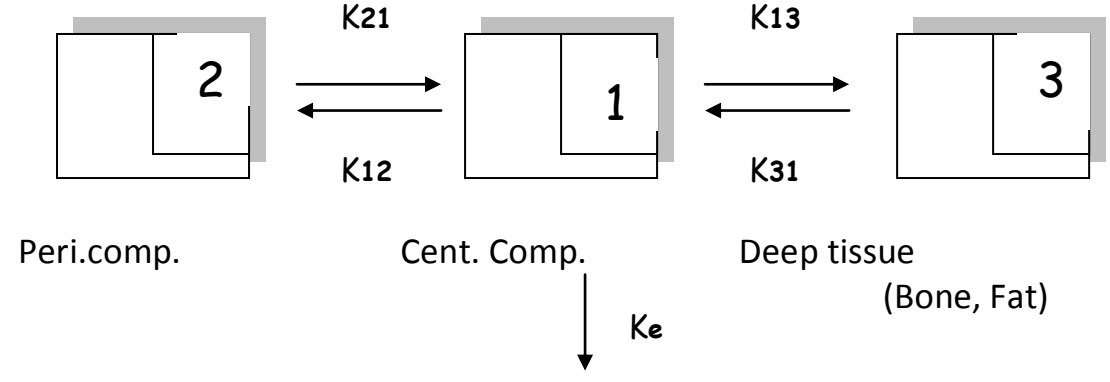


Fig.8.Three compartment open model

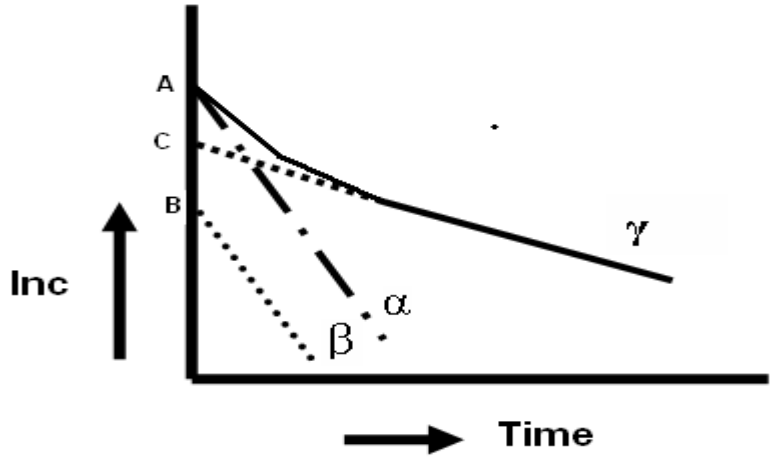


Fig.9.Semilog plot of C versus t of a drug with three compartment characteristics.

$C = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t}$ **……(37)**

A, B, C are the intercept constant (m/L)

α, β, γ are the hybrid constant (T^{-1})

The equation 37 is the same as the equation for two compartment model with an additional term. (term 'C ')

Three compartment model has been proposed for the several drugs like bihydroxycoumarin, turbocurarine etc.

NON-LINEAR PHARMACOKINETIC MODEL:-

❖ DEFINITION:

- ✓ Linear pharmacokinetics is simple first order kinetics where the pharmacokinetic parameters would not change when different doses of multiple doses of drug were given.
- ✓ Non linear pharmacokinetics is observed in some drugs where increase in dosed or chronic medication can cause deviation from the linear pharmacokinetics profile so it is known as dose dependent kinetics.
- ✓ Here rate processes of drug's **ADME** are dependent upon carrier or enzymes that are drug specific, having definite capacities and susceptible to saturation at higher doses, so it is also known as **CAPACITY LIMTED KINETICS.**
- ✓ At lower dose drug shows first order kinetics but at higher dose it shows zero order due to saturation, so it is also known as **mixed order kinetics**.
- ✓ The pharmacokinetic parameter change with size of the administered dose.

❖ TEST TO DETECT NON-LINEARITY:

- ✓ Determine C_{ss} (steady state plasma concentration) at different doses and if C_{ss} is directly proportional to the doses then it is linear else it is non linear.
- ✓ Determine some of important pharmacokinetic parameters such as fraction bioavailable, $t_{1/2,}$ total clearance at different doses. Any change in parameters which are usually constant, means nonlinear.

Drug characteristics that shows non-linearity:

- ✓ Elimination does not follow simple first order kinetics.
- ✓ $t_{1/2}$ changes with increase in dose. Gently $t_{1/2}$ increases with increase dose when saturation of metabolic enzymes occurs which results in more residence time of drug in body and gives more $t_{1/2}$.
- ✓ AUC is not proportional to amount of bioavailable drug.

Example of drugs showing nonlinear pharmacokinetics:

CAUSE	***DRUG***	***EFFECT***
Absorption		
Saturable transport in gut wall	Riboflavin	Decrease F,Ka,Cmax,AUC
Low solubility and high dose	Grisufulvin	
Saturable presystematic metabolism	Propranonol	Increase in F,Ka, Cmax, AUC
Saturable gastric decomposition	Penicillin-G	
Distribution		
Saturable plasma protein binding	Phenyl butazone	Increase in free plasma drug concentration and increase in Vd
Saturable tissue binding sites	Imipramine	
Saturable transport in/out of tissue	Methotrexate	
Metabolism		
Saturable metabolism	Phenytoin	Increase Css, decrease CL
Cofactor or enzyme limitations	Alcohol, PCM	
Enzyme induction	Carbamazepine	Increase CL, decrease Css
Elimination		
Saturable tubular secretion	Mezlocillin	Decrease renal clearance
Saturable tubular reabsorptiion	Vit-C	Increase renal clearance

Cause of nonlinearity

1. Drug absorption

- ✓ When the absorption is solubility or dissolution rate limited example is griseofulvin, at high dose a saturation solution of the drug is formed in the GIT or at any other extra vascular site and the rate of absorption attains a constant value. Decrease F, Ka, Cmax, AUC
- ✓ When absorption involve Carrier mediated transport: saturation at higher dose result in nonlinearity eg. Is riboflavin. Decrease F, Ka, Cmax, AUC
- ✓ When pre systemic gut wall or hepatic metabolism attains saturation eg. In propranol. Increase in F, Ka, Cmax, AUC

2. Drug distribution

- ✓ Saturable plasma protein binding eg. In case of Phenyl-butazone
- ✓ Saturable tissue binding sites eg in case of Imipramine
- ✓ In both the cases Increase in free plasma drug concentration and increase in V_d.
  Clearance of a drug with high ER is greatly increases due to saturation of binding site.

3. Drug metabolism

- ✓ Capacity limited metabolism due to the enzyme or cofactor saturation example include Phenytoin. Increase Css, decrease CL.
- ✓ Enzyme induction example in case of carbamazepine where decrease in plasma concentration is observed on repetitive administration over a period of time. Increase CL, decrease Css
- ✓ Other cause of nonlinearity are hepatotoxicity and change in hepatic blood flow

4. Drug excretion

- ✓ Active tubular secretion as in penicillin. Decrease renal clearance
- ✓ Active tubular reabsorption as in water soluble vitamin. Increase renal clearance
- ✓ Other sources of nonlinearity are forced diuresis change in urine pH.

❖ MICHAELIS MENTEN EQUATION

The kinetic of capacity limited or Saturable process is best described by **michaelis menton equation**. The elimination of drug by a saturable enzymatic process is described by Michaelis menten equation.

$$-\frac{dC}{dt} = \frac{Vmax * C}{Km + C}$$

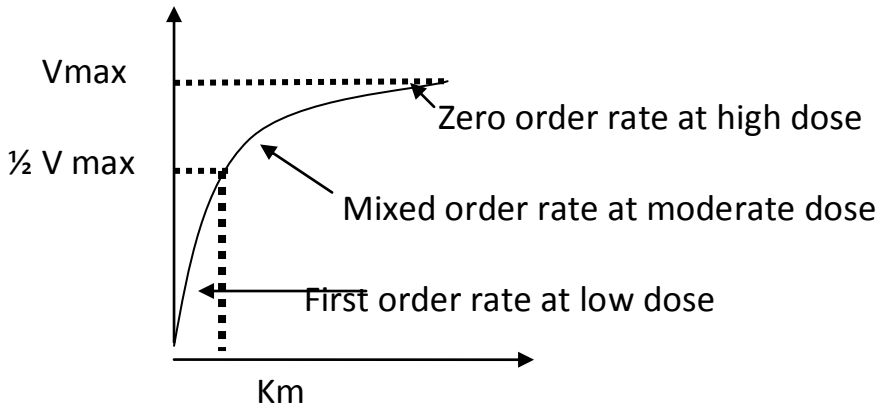
Where C = plasma concentration
-dC/dt = elimination rate = V
Vmax = maximum elimination rate
Km = Michaelis-Menten constant

- ✓ When elimination rate is half of maximum elimination rate….
  V = 0.5 Vmax , then Km = C

So Km is defined as concentration to produce half maximum velocity, means 50% enzymes are bound when Km = C

Km is also known as Brig's Haldone's constant.

Value of Vmax and Km are constant for drug-enzyme system and dependent on nature of drug and enzymatic process involved.

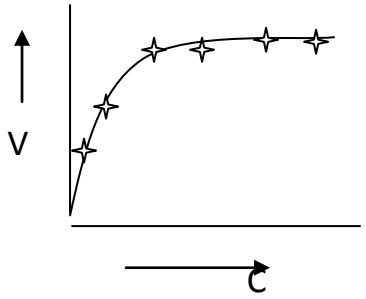


When C << Km	When C = Km	When C >> Km
So Km + C ≈ Km Now from eq. (1) -(dC/dt) = Vmax C /Km Vmax, Km are constant So – dC/dt α C Low dose ⟶ **first order**	So Km + C = 2C Now from eq. (1) -(dC/dt) = Vmax / 2 So rate process is half of maximum elimination rate. Medium dose ⟶ **mixed order**	So Km + C ≈ C Now from eq. (1) -(dC/dt) = Vmax as Vmax is constant so dC/dt is constant High dose ⟶ **Zero order**

❖ DETERMINATION OF THE K_M AND V_{MAX}

For obtaining value of Km and Vmax series of reaction rates (V) for each concentration (C) is measured and graph is plotted. But graph V vs C shows non linear graph…….

V = Vmax C / (Km + C)

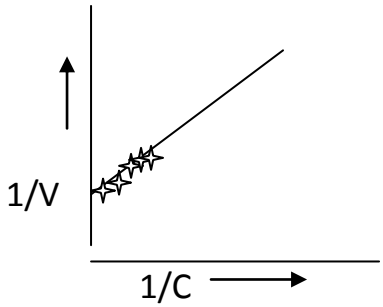


So we can convert **Michaelis Mentens eq.** to following form which is linear equation

[1]Line weaver Burk plot

1/V = {(Km/Vmax) 1/C} + 1/Vmax

Plot of **1/V vs 1/C** is plotted to get a straight line. It is known as **Double reciprocal plot**.



Intercept = 1/ Vmax and slope = Km / Vmax.

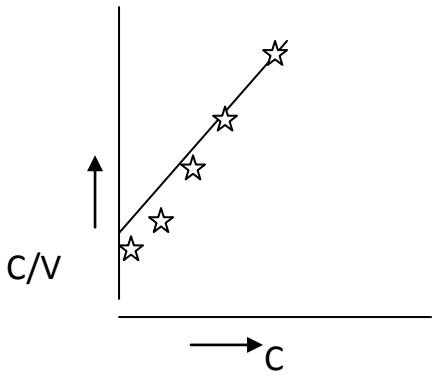
So get Vmax value from intercept and put that value into the slope to get value of Km.

In previous plot points are clustered. So that other method to get spreaded points more evenly is by rearranging Michaelis Menten eq.

[2]Hanes-Woolt plot

C/V = (1/Vmax) C+ (Km/Vmax)

Plot of **C/V vs C** gives straight line

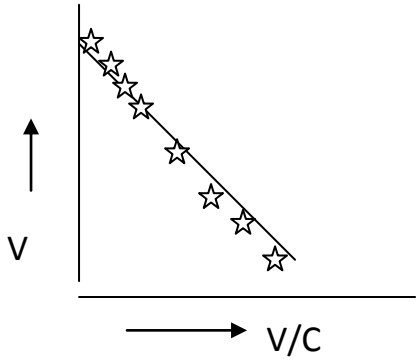


Slope = 1/Vmax and intercept = Km/Vmax

[3]Woolf Augstinsion-Hofstee plot

Similarly other graph is **V vs V/C** which gives some spreaded points and it is known as**.**

V = - Km (V/C) + Vmax



Slope = - Km and intercept = Vmax

Advantage of this plot is we get direct Km and Vmax value

All the above equations and plots are useful for finding Km and Vmax values from the invitro data like rate V at various concentrations C. but we can't find rate V in invivo. So for determination of Km and Vmax in patients following equation is useful.

[4]Finding Km and Vmax values from steady concentration

When a drug is administered as a constant rate i.v. infusion or in a multiple dose regimen the steady state concentration Css is given in terms of dosing rate R as

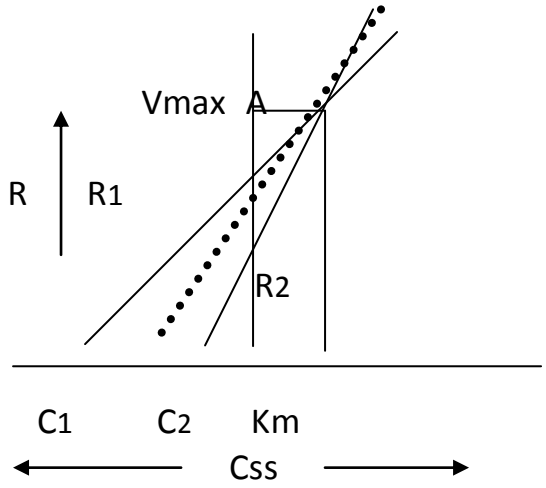
R=Css CL

At steady state the dosing rate equal rate of decline in plasma drug concentration and if the decline is due to single capacity limited process then

$$\mathbf{R = (Vmax\ Css) / (Km + Css)}$$

Where R= dose per day i.e. Dosing rate
Css = steady state plasma concentration

A graph can be plotted of **R vs. Css**



Interpretation from the graph

- ✓ Here when R_1 is dosing rate for getting Css= C_1, similarly for R_2 to get Css = C_2
- ✓ Put the data on graph as soon in graph
- ✓ Draw a line passing through R_1—C_1 and R_2—C_2 then extent both lines to get crossed and crossing point is A.
- ✓ From point A read Vmax on Y axis and read Km on X axis
- ✓ Another direct method is used to get Km and Vmax from only two set of data of R and Css without plotting graph

Two equation are obtain by substituting R and Css with R_1, C_1, R_2, C_2

$$\mathbf{R_1 = (Vmax\ C_1)/ (Km + C_1)}$$
$$\mathbf{R_2 = (Vmax\ C_2)/ (Km + C_2)}$$

By combining the two equations following equation can be yield to get Km

$$\mathbf{Km = (R_1\text{-}R_2) / (R_1/C_1) – (R_2/C_2)}$$

After finding Km put the value of Km in any previous equation to get Vmax

Interpretation of Km and Vmax:

We know that Km indicates the concentration of drug at 50% Vmax. It means at concentration equal to Km, half of the total enzymes are bound with drug and no saturation of enzyme system. So that concentration is generally preferable near which it gives first order.

If Vmax is 600 mg per day i.e. ½ Vmax is 300 mg per day which can be given as daily dose to get steady state concentration similar to Km.

❖ LIMITATION OF Km and Vmax:

We estimate Km and Vmax by assuming one compartment system and single capacity limited process. More complex equation will result and computed Km and Vmax will usually be larger when……..

- The drug eliminated by more than one capacity limited process
- The drug exhibits parallel capacity limited and first order elimination process
- The drug follows multi compartment kinetics.

Elimination rate equation in various conditions:

❖ Elimination by both linear and non-linear process:

$$-dC/dt = \{(Vmax\ C)/(Km+C)\} + KC$$

drug may be metabolized by parallel pathway to different metabolites so sum of both process drug here K = first order elimination rate constant

❖ Linear input and non linear elimination:

$$-dC/dt = \{(Vmax\ C)/(Km + C)\} - KaC_{GI}\, e^{-Kat}$$

Drug absorbed by first order
Ka = absorption rate constant
C_{GI} = Concentration in GI tract

❖ Zero order input and nonlinear elimination:

$$-dC/dt = \{(Vmax\ C) / (Km + C)\} – K_0/Vd$$

where K_0 = infusion rate, and Vd = volume of disreibution

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2. Shargel L., Andrew B.C., Fourth edition “Physiologic factors related to drug absorption” Applied Biopharmaceutics and Pharmacokinetics, Prentice Hall International, INC., Stanford 1999. Page No. 449 - 474 & Chapter no. 3 & 4.
3. Remington ; the science and practice of pharmacy, vol-1 page no : 738—739
4. Gibaldi M., Third edition, “Gastrointestinal absorption-Biologic, Physico-chemical and Role of the dosage form” Biopharmaceutics and Clinical Pharmacokinetics Lea and Febriger, Philadelphia 1984, Page No. 29-64..

FREQUENTLY ASKED QUESTIONS :-

1. Short note on**(2006,LM-06;08)**
1Urine data analysis

2Wagner-Nelson method

2. Classify compartmental model & compare them with non compartmental model & physiological model(2005;LM-05;06;08)
3. Describe method of residual for two compartment I.V model**(2004)**
4. Short note on two compartment models**(LM-08)**
5. What is multi compartment model ?Enlist different type of such model.Note on three compartment open model**(LM-07)**
6. What is pharmacokinetics model ? Why it is required? Enlist different pharmacokinetics models & discuss on physiological model.Note on PBPK**(LM-07)**
7. Discuss delayed distribution model & assessement of pharmacokinetics model**(LM-06)**
8. Explain usefulness of pharmacokinetic models. Classify compartment models, their advantages/disadvantages. Compare it with non-compartment analysis and blood urine data……(2004 internal)
9. Elimination rate differs in various conditions. Justify given statement using Michaelis menten equation. (Uni. Sept. 2006)

STUDY QUESTIONS

1. If a drug is distributed in the one-compartment model, does it mean that there is no drug in the tissue?
2. How analysis of blood data can be done to get bioavailability of drug?
3. Give advantages and disadvantages of urine data analysis over blood data analysis.
4. What is the error if I assume a one-compartment model instead of a two-compartment or multicompartment model?
5. Enlists the criteria for obtaining valid urinary data.
6. What is AUC? And how it can be measured?
7. What is the apparent volume of distribution, and why are there so many different volumes of distribution?
8. Explain One Compartment Open Model – IV administration with equations .
9. Explain One Compartment Open Model – IV infusion with equations and also infusion plus loading dose.
10. Explain One Compartment Open Model – Extravascular administration with equations.
11. What are the assumptions that should be kept in mind while using 2 compartment models?
12. Why we need multi-compatrment model?
13. Describe TWO compartment models with detail.
14. Explain Method of Residual to find distribution exponent and elimination exponent.
15. Two compartmental model for extravascular administration
16. How linear pharmacokinetic differs from nonlinear pharmacokinetics?
17. Write various causes of nonlinearity.
18. Write various methods to establish V_{max} & K_m