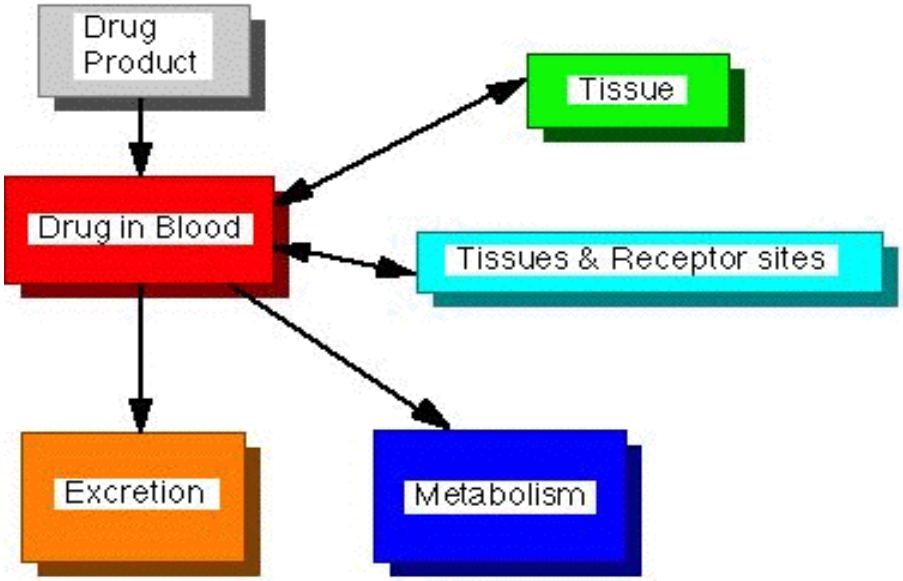
UNIT- III 10 Hours

Pharmacokinetics: Definition and introduction to Pharmacokinetics, Compartment models, Non compartment models, physiological models, One compartment open model. (a). Intravenous Injection (Bolus) (b). Intravenous infusion and (c) Extra vascular administrations. Pharmacokinetics parameters - KE ,t1/2,Vd,AUC,Ka, Clt and CLR- definitions methods of eliminations, understanding of their significance and application.

PHARMACOKINETICS:

- **Pharmacokinetics** is the study of drug and/or metabolite **kinetics** in the body.
- The body is a very complex system and a drug undergoes many steps as it is being **absorbed**, **distributed** through the body, **and metabolized** or **excreted** (**ADME**).



Applications of pharmacokinetics:

- To understand process of absorption, distribution and elimination after administration of drug, Which affects onset and intensity of biological response.
- To access drug moiety in terms of plasma drug conc response which is now considered as more appropriate parameter then intrinsic pharmacological activity .
- In design and utilization of invitro model system that can evaluate dissolution characteristics of new compound formulated as new drug formulations and establish meaningful in vivo-in vitro correlationship.
- In design and development of new drug and their appropriate dosage regimen.
- In safe and effective management of patients by improving drug therapy.

- To understand concept of bioavailability which has been used by regulatory authorities to evaluate and monitor in vivo performance of new dosage forms and generic formulations.

- To carry out bioavailability and bioequivalence studies.

- We can used pharmacokinetic principles in the development of N.D.D.S like micro spheres and Nanoparticles .

e.g. The drug with short half life about 2-6 h can be formulated as controlled release drugs by using polymers .

Pharmacokinetic models:

Means of expressing mathematically or quantitatively, time course of drug throughout the body and compute meaningful pharmacokinetic parameters.

Useful in:

1. Predict plasma, tissue, and urine drug levels with any dosage regimen
2. Calculate the optimum dosage regimen for each patient individually
3. Estimate the possible accumulation of drugs and/or metabolites
4. Correlate drug concentrations with pharmacologic or toxicological activity
5. Evaluate differences in the rate or extent of availability between formulations (bioequivalence)
6. Describe how changes in physiology or disease affect the absorption, distribution, or elimination of the drug
7. Explain drug interactions
8. Characterize the behavior of drug in patient.
9. Predicting conc. of drug in various body fluids with dosage regimen.
10. Calculating optimum dosage regimen for individual patient.
11. Evaluating bioequivalence between different formulations.
12. Explaining drug interaction.

Compartment models:

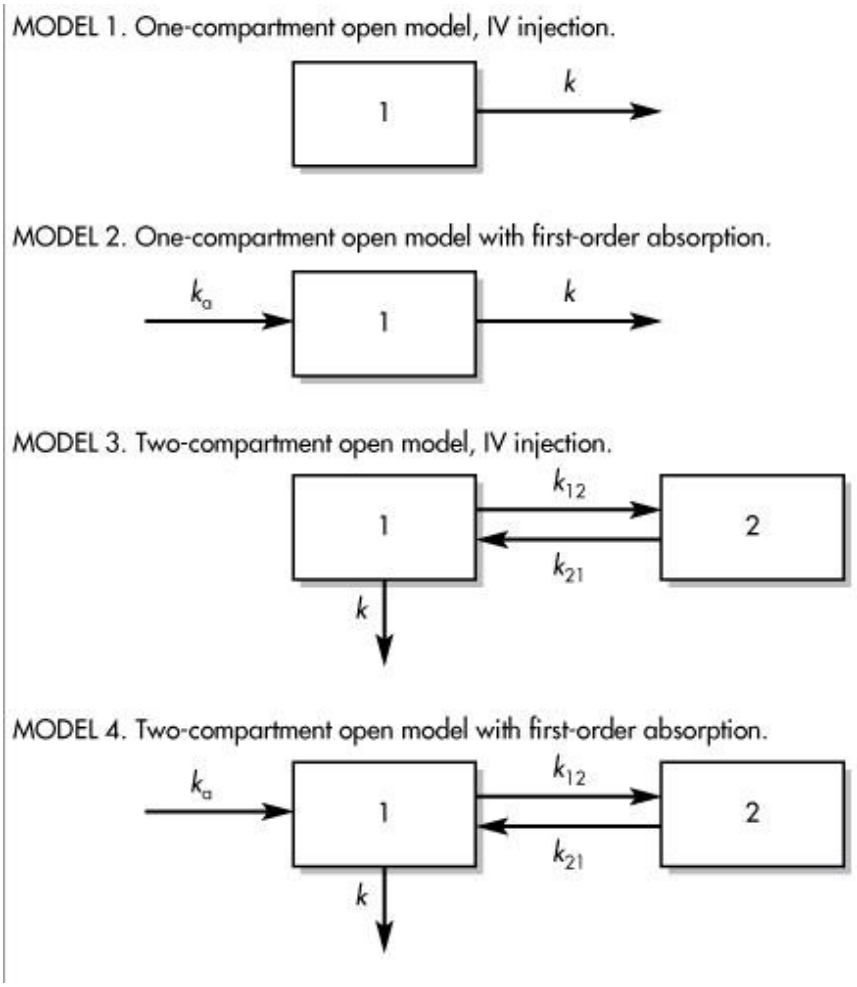
Objective:

1. To understand the assumptions associated with the one compartment model
2. To understand the properties of first order kinetics and linear models
3. To write the differential equations for a simple pharmacokinetic model
4. To derive and use the integrated equations for a one compartment linear model
5. To define, use, and calculate the parameters, Kel (elimination rate constant), t1/2 (half-life), Cl (clearance), V (apparent volume of distribution), and AUC (area under the concentration versus time curve) as they apply to a one compartment linear model

Types of Compartment model:

1. Compartment model
   - **a.** One compartment model
   - **b.** Multi-Compartment model

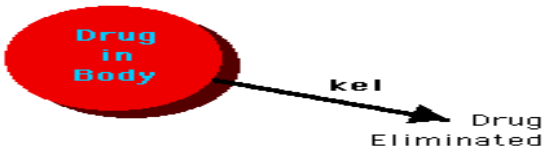
2. Mammillary model
3. Catenary model(Line model)
4. Physiologic model(Flow model)



"OPEN" and "CLOSED" models:

- The term "open" itself mean that, the administered drug dose is removed from body by an excretory mechanism (for most drugs, organs of excretion of drug is kidney)
- If the drug is not removed from the body then model refers as "closed" model.

One Compartment:



Assumptions:

1. One compartment

- The drug in the blood is in rapid equilibrium with drug in the extra vascular tissues.
- This is not an exact representation however it is useful for a number of drugs to a reasonable approximation.

2. Rapid Mixing

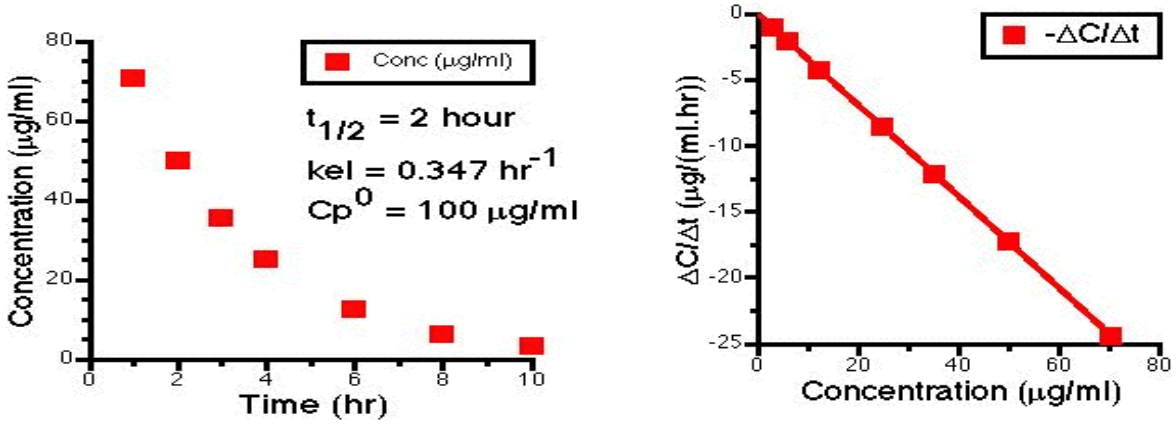
- We also need to assume that the drug is mixed instantaneously in blood or plasma.

3. Linear Model

- We will assume that drug elimination follows first order kinetics.

Linear Model - First Order Kinetics:

- **First-order kinetics**



This behavior can be expressed mathematically as:

$$\text{Rate of Change of Cp versus time} = -\frac{\Delta Cp}{\Delta t} = kel \bullet Cp$$

Change in Cp

Change in time

Proportionality constant called the elimination rate constant, kel

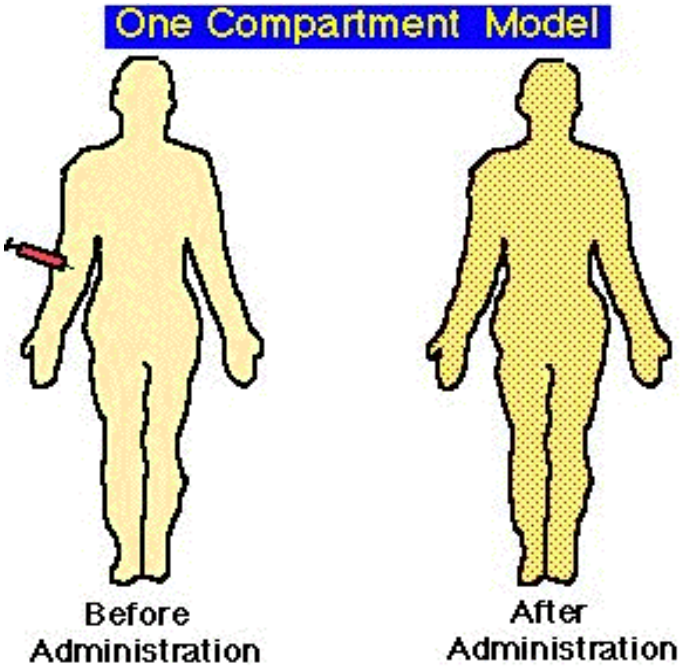
One compartment model:

One compartment model can be defined :

- One com. open model – i.v. bolus.
- One com. open model - cont. intravenous infusion.

- One com. open model - extra vas. administration
  - (zero-order absorption)
- One com. open model - extra vas. Administration
  - (first-order absorption)

One Compartment Model, Intravenous (IV) Bolus Administration:



INTRODUCTION

The time course of drug concentration determined after its administration can be statisfactorily explained by assuming the body as a single, well mixed compartment with first –order desposition processes. In case of other drugs, two or more body compartments may be postulated to decscribe mathematically the data colloected.

ONE-COMPARTMENT OPEN MODEL

(Instantaneous Distribution Model)

The one-compartment open model is the simplest model which depicts the body as a single, kinetically homogenous unit that has no barriers to the movement of drug and final distribution equilibrium between the drug the plasma and other body fluids is attained 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 thorught out the body. However, the model does not assume that the drug concentration in plasma is equal to that in other body tissue. The term openindicates that the input (availability) and output (elimination)

are unidirectional and that the drug can be eliminated from the body. Fig. shows such a one compartment model.

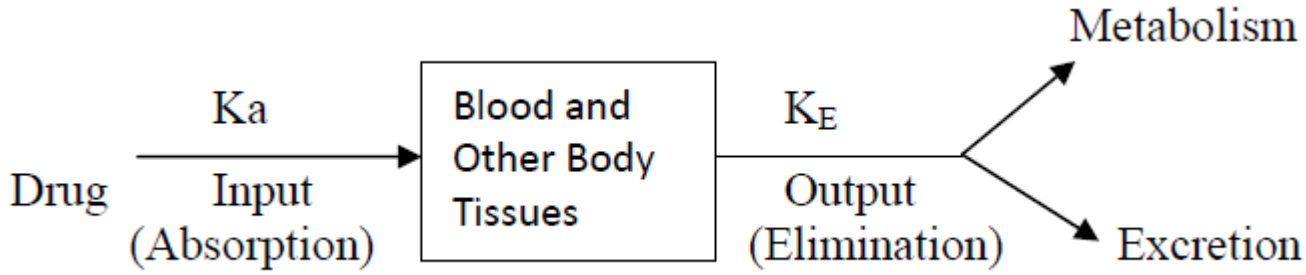


Fig. 1 Representation of one-compartment open model showing input and output

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

One – compartment open model, intravenous bolus administration

One –Compartment open model, continuous intravenous infusion

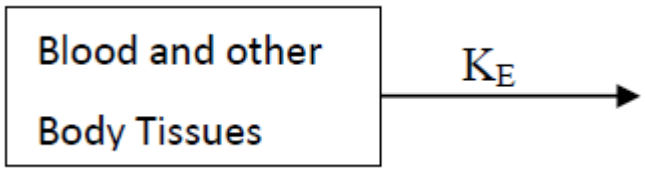
One-compatmtment open model, extravascular administration, zero-order absorption, and

One-Compartment open model, extravascular administration, first-order absorption.

One – Compartment Open Model;

Intravenous Bolus Administration

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



Rate of drug presentation to body is:

$$\frac{dx}{dt} = \text{rate in (availability)} - \text{rate out (elimination)}$$

Since rate in or absorption is absent, equation becomes

$$\frac{dx}{dt} = \text{- rate out}$$

If rate out or elimination follows first order kinetic

$$\frac{dx}{dt} = -K_E X \qquad \text{(eq.1)}$$

Where KE = first-order elimination rate constant, and
X = amount of drug in the body at any time t remaining to be eliminated.
Negative sign indicates that the drug is being lost from the body. The various releted pharmacokinetic parameters can now be estimated.

Elimination phase:

- Elimination phase has three parameters:
- Elimination rate constant
- Elimination half life
- Clearance

ELIMINATION RATE CONSTANT

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

Integration of equation (1)

$$\ln X = \ln Xo - K_E t \qquad \text{(eq.2)}$$

Xo = amt of drug injected at time t = zero i.e. initial amount of drug injected

$$X = Xo\, e^{-KEt} \qquad \text{(eq.3)}$$

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

$$\log X = \log Xo - \frac{K_E}{2.303} t \qquad \text{(eq.4)}$$

Since it is difficult to directly determine amount of drug in body X, we use relationship that exists between drug conc. in plasma C and X; thus

$X = V_dC$ (eq. 5)

So equation-8 becomes

$$\log C = \log Co - \frac{K_E}{2.303} t \quad \text{(eq.6)}$$

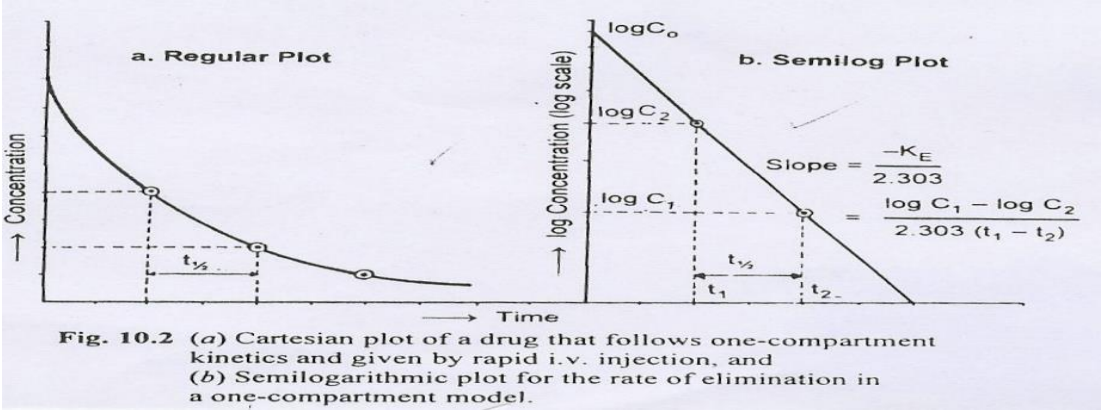


Fig. 10.2 (*a*) Cartesian plot of a drug that follows one-compartment kinetics and given by rapid i.v. injection, and (*b*) Semilogarithmic plot for the rate of elimination in a one-compartment model.

$K_E = Ke + Km + Kb + Kl + \ldots$ (eq.7)

K_E is overall elimination rate constant

BIOLOIGICAL HALF-LIFE

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

ELIMINATION HALF-LIFE:

Elimination Half-Life : Also called as biological half-life. It is the oldest and the best known of all pharmacokinetic parameters and was once considered as the most important characteristic of drug. It is defined as the time taken for the amount of drug in the body as well as plasma concentration to decline by one-half or 50% its initial value. It is expressed in hours or minutes.

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

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

- Elimination half life can be readily obtained from the graph of log C versus t

- Half life is a secondary parameter that depends upon the primary parameters such as clearance and volume of distribution.

$$t_{1/2} = \frac{0.693\, V_d}{cl_T} \qquad \text{(eq.9)}$$

Apparent volume of distribution:

Apparent volume of distribution: Clearance and apparent volume of distribution are two separate and independent pharmacokinetic characteristics of a drug. Since they are closely related with the physiologic mechyanisms in the body. They are called as primary parameters.

Modification of equation defines apparent volume of distribution:

Defined as volume of fluid in which drug appears to be distributed.

$$V_d = \frac{\text{amount of drug in the body}}{\text{Plasma drug concentration}} = \frac{X}{C} \qquad \text{(eq.10)}$$

$V_d = Xo/Co$

$=$i.v.bolus dose/Co (eq.11)

E.g. 30 mg i.v. bolus, plasma conc.= 0.732 mcg/ml.

Vol. of dist. = 30mg/0.732mcg/ml

=30000mcg/0.732mcg/ml

= 41 liter.

For drugs given as i.v.bolus,

V_d (area)$=Xo/K_E.AUC$ …….12.a

For drugs admins. Extra. Vas.

V_d (area)$=F\ Xo/K_E.AUC$ ……..12.b

Significance of V_d

- Drugs can have V_d equal, smaller or greater than the body mass
- Drugs with small V_d are usually confined to the central compartment or highly bound to plasma proteins
- Drugs with large V_d are usually confined in the tissue

- V_d can also be expressed as % of body mass and compared to true anatomic volume
- V_d is constant but can change due to pathological conditions or with age

Clearance:

Difficulties arise when one applies elimination rate constant and half-life as

pharmacokinetic parameters in an anatomical /physiological context and as a measure of drug

elimination mechanisms. A much more valuable alternative appraoch for such applications is use of clearance parameters to characterize drug disposition. 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.

Just as Vd is needed to relate plasma drug concentration with amount of drug in the body, clearance is a parameter to relate plasma drug concentration with the rate of drgu elimination according to following equation:

$$\text{Clearance} = \frac{\text{Rate of eliminatio n}}{\text{Plasma drug concentrat ion}}$$

$$\text{Or, Cl} = \frac{dx/dt}{c} \qquad \text{(eq.13)}$$

Clearance is defined as the theoretical volume of body fluid containing drug. (i.e. that fraction of apparent volume of distribution) from which the drug is completely removed in a given period of time. It is expressed in m1/min or liters/hour. Clearance is usually further defined as blood clearance (Clb), plasma clearance (Clp) or clearance based on unbound or free drug concentration (Clu) depending upon the concentration C measured for the right side of the equation13.

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

Thus

$$\text{Renal clearance} = \frac{\text{Rate pf eliminatio n by kidney}}{C}$$

$$\text{Hepatic clearance} = \frac{\text{Rate pf eliminatio n by liver}}{C}$$

$$\text{Other organ clearance} = \frac{\text{Rate pf eliminatio n by organ}}{C}$$

Total body clearance: $Cl_T = Cl_R + Cl_H + Cl_{other}$ (eq.14)

According to earlier definition

$$\text{Cl} = \frac{dx/dt}{c}$$

Submitting eq.1 $dx/dt = K_E X$, above eq. becomes

$Cl_T = K_E X/ C$ (eq 15)

By incorporating equation 1 and equation for vol. of dist. (Vd= X/C) We can get

$Cl_T = K_E V_d$ (eq.16)

Parallel equations can be written for renal and hepatic clearance.

$Cl_H = K_m V_d$ (eq.17)

$Cl_R = K_e V_d$ (eq.18)

but $K_E = 0.693/t_{1/2}$

$$Cl_T = \frac{0.693 \times V_d}{t_{1/2}} \quad \text{(eq.19)}$$

For non compartmental method which follows one compartmental kinetic is :

For drug given by i.v. bolus

$$Cl_T = \frac{Xo}{AUC} \quad \text{.....20.a}$$

For drug administered by e.v.

$$Cl_T = F \frac{Xo}{AUC} \quad \text{.....20.b}$$

For drug given by i.v. bolus

$$\text{Renal clearance} = \frac{Xu\infty}{AUC} \text{ ---------- eq. 21}$$

Organ clearance:

Rate of elimination by organ= rate of presentation to the organ– rate of exit from the organ

Rate of elimination $=Q. C_{in} - Q.C_{out}$

(Rate of extraction) $=Q (C_{in} - C_{out})$

Cl_{organ} =rate of extraction/C_{in}

$=Q(C_{in}-C_{out})/C_{in}$

$=Q.ER$ …….(eq 22)

Extraction ratio:
$ER= (C_{in} - C_{out})/ C_{in}$

ER is an index of how efficiently the eliminating organs clear the blood flowing through it of drug.

- According to ER, drugs can be classified as-
- Drugs with high ER (above 0.7)
- Drugs with intermediate ER (between 0.7-0.3)
- Drugs with low ER (below 0.3)
- The fraction of drug that escapes removal by organ is expressed as
  - F= 1- ER
- Where F= systemic availability when the eliminating organ is liver.

Hepatic clearance:

$Cl_H = Cl_T - Cl_R$

- Can also be written down from eq 22
- $Cl_H = Q_H\ ER_H$
- Q_H= hepatic blood flow. ER_H = hepatic extraction ratio.
- Hepatic clearance of drug can be divided into two groups :

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

Hepatic blood flow:

- $F=1-ER_H$

$$= \frac{AUC_{oral}}{AUC_{I.V}}$$

Drugs with	Changes in Total Clearance due to			
	↑ Blood Flow	↓ Blood Flow	↑ Binding	↓ Binding
High ER (above 0.7)	↑	↓	No Change	No Change
Low ER (below 0.3)	No Change	No Change	↑	↓

Where,↑ = increase and ↓ = decrease

One-Compartment Open Model

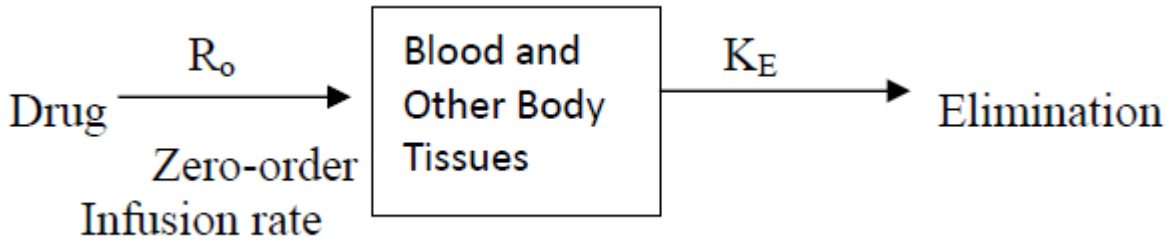
-Intravenous Infusion

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

infusion of an i.v. bolus (few seconds), the duration of constant rate infusion is usually much longer than the half-life of the drug. Advantages of such a zero-order infusion of such a zero order infusion of drugss include –

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

The model can be represented as follows:



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 Ro and first-order rate of elimination, – KEX:

Drug

$dX/dt=R_o-K_EX$ …eq 23

$X=R_o/K_E(1-e^{-KEt})$ …eq 24

Since $X=V_dC$

$C=R_o/K_EVd(1-e^{-KEt})$ …eq 25

$=R_o/Cl_T(1-e^{-KEt})$ …eq 26

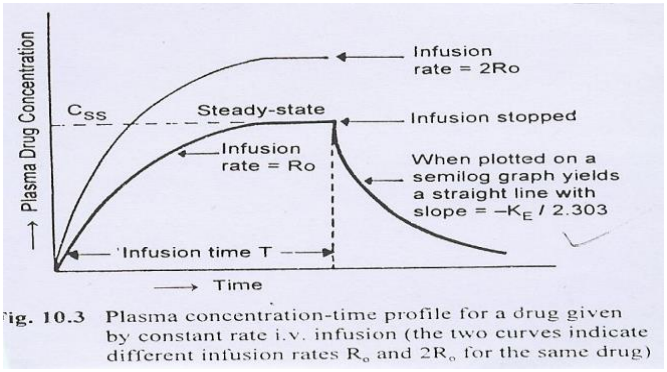


Fig. 10.3 Plasma concentration-time profile for a drug given by constant rate i.v. infusion (the two curves indicate different infusion rates R_o and $2R_o$ for the same drug)

At steady state. The rate of change of amount of drug in the body is zero ,eq 23 becomes

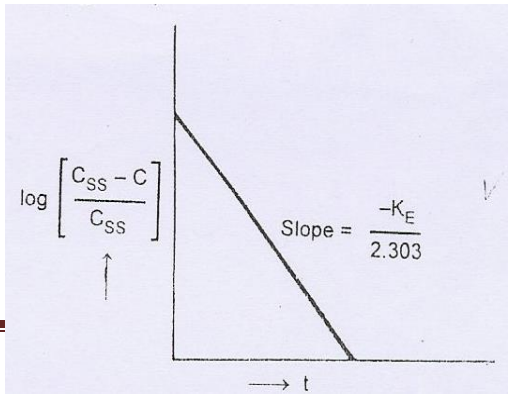
$Zero=R_o-K_EX_{SS}$ …27

$K_EX_{SS}=R_o$ …28

$C_{SS}=R_o/K_EV_d$ …29

$=R_o/Cl_T$ i.e

Substituting eq. 30 in eq. 26



$C=C_{SS}(1-e^{-KEt})$ …31

Rearrangement yields:

$$\frac{[C_{SS}-C]}{C_{SS}} = e^{-KEt} \quad ...32$$

$$\text{Log}\ \frac{[C_{SS}-C]}{C_{SS}} = \frac{K_E}{2.303}\ t \ldots\ldots 33$$

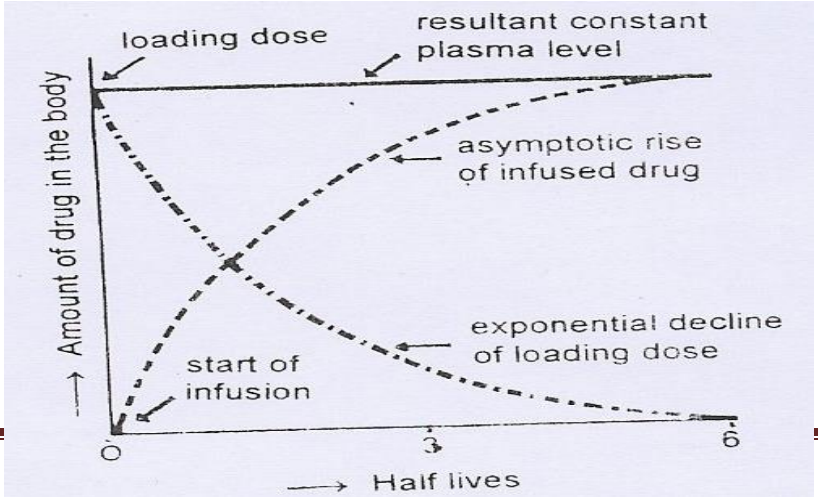
If n is the no. of half lives passed since the start of infusion ($t/t_{1/2}$)

Eq. can be written as

$C=C_{SS}\ [1-(1/2)^n]$ ……34

Half-Life	% Remaining	%	Css	Achieved
1	50	50		
2	25	25	+ 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

Infusion plus loading dose



$Xo,L=C_{SS}V_d$ …35

Substitution of $C_{SS}=R_o/K_EV_d$

$Xo,L=R_o/K_E$ …36

$C=Xo,L/V_d\ e^{-KEt}+ R_o/K_EV_d(1-e^{-KEt})$ …37

Assessment of pharmacokinetic parameter:

$AUC=R_o\ T/K_E\ V_d$

$=R_o\ T/Cl_T$

$=C_{SS}\ T$

Where T=infusion time

One compartment open model: extra vascular administration

When drug administered by extra vascular route (e.g. oral, i.m, rectal), absorption is prerequisite for its therapeutic activity.

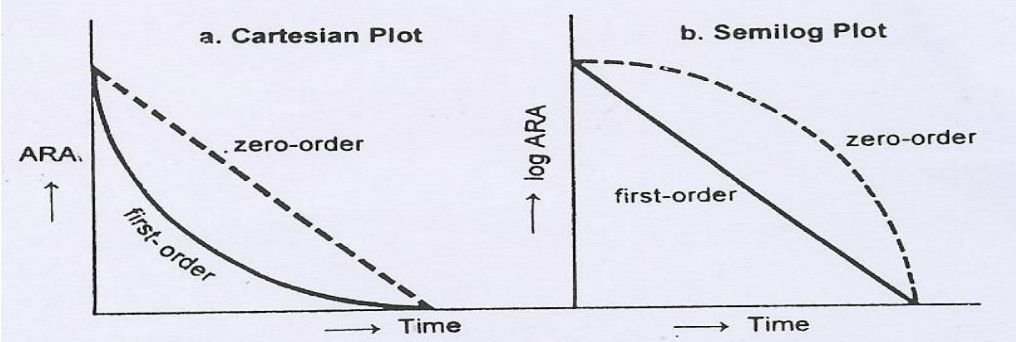


Fig. 10.6 Distinction between zero-order and first-order absorption processes. *Figure a* is regular plot, and *Figure b* a semilog plot of amount of drug remaining to be absorbed (ARA) versus time t.

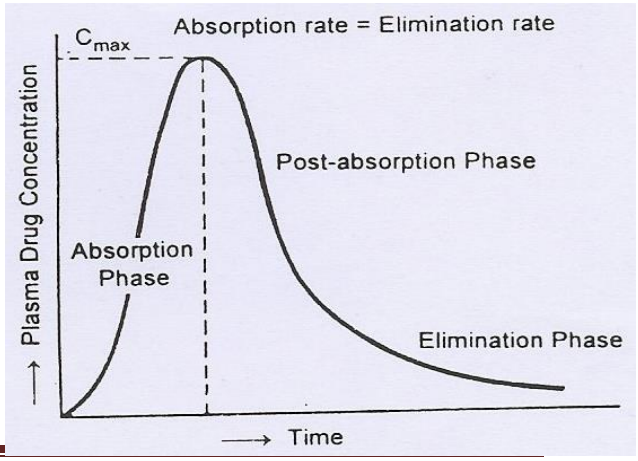
dX/dt=rate of absorption-rate of elimination

$dX /dt = dX_{ev}/dt - dX_E/dt$ …38

$dX_{ev}/dt > dX_E/dt$

$dX_{ev}/dt = dX_E/dt$

$dX_{ev}/dt < dX_E/dt$



One compartment model: extra vascular admin (zero order absorption)

This model is similar to that for constant rate infusion.

- Rate of drug absorption as in case of CDDS, is constant and continues until the amount of drug at the absorption site (e.g. GIT) is depleted.
- All equations for plasma drug conc. profile for constant rate i.v. infusion are also applicable to this model.

One compartment model: extra vascular admin (first order absorption)

Drug that enters the body by first order absorption process gets distributed in the body according to one compartment kinetic and is eliminated by first order process.

The model can be depicted as follows:

The differential form if eq. 38 is

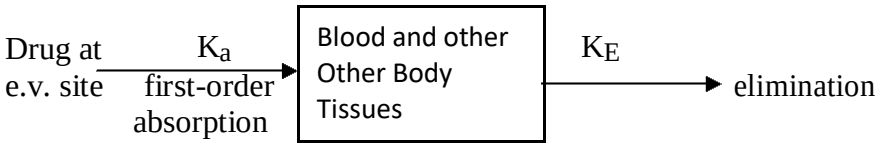
$dX/dt = k_a X_a - K_E X$ …39

$X = K_a F X_o / K_a - K_E [e^{-KEt} - e^{-Kat}]$ …40

$C = K_a F X_o / V_d (K_a - K_E) [e^{-KEt} - e^{-Kat}]$ …41

First –Absorption Model

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



The differential form of the equation 5.49 is

$dx/dt = K_a X_a - K_E X$ —(42)

Where K_a = first-order absorption rate constant, and

X_a = amount of drug at the absorption site remaining to be absorbed i.e.

A.R.A Integration of equation 42 yields:

$$X = \frac{K_a F X_0}{\text{----------}} \quad e^{-K_E t} - e^{-Kat} \qquad (43)$$

$$(K_a - K_E)\left[\quad\right]$$

Transforming into concentration terms, the equation becomes:

$$C = \frac{K_a F X_0}{V_d(K_a - K_E)}\left[e^{-K_E t} - e^{-Kat}\right] \qquad (44)$$

Where F = fraction of drug absorption systemically after e.v. administration.

Assessment of Pharmacokinetic Parameters

C_{max} and t_{max} : At peak plasma concentration, the rate of absorption equals rate of elimination i.e. $K_aX_a = K_EX$ and the rate of change in plasma drug concentration dC/dt = zero. This rate can be obtained by differentiating equation 44

$$\frac{dc}{dt} = \frac{K_a F X_0}{(K_a - K_E)} \left\{ K_E e^{-KEt} + K_a e^{-Kat} \right\} = \text{zero} \quad (45)$$

On simplifying the above equation becomes:

$$K_E e^{-KEt} = K_a e^{-Kat} \quad (46)$$

Converting to logarithmic form,

$$\log K_E - \frac{K_E t}{2.303.} = \log K_a - \frac{K_a t}{2.303.} \quad (47)$$

Where t is t_{max} Rearrangement of above equation yields:

$$t_{max} = \frac{2.303 \log (k_a/K_E)}{K_a - K_E} \quad (48)$$

The above equation shows that 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. C_{max} can be obtained by substituting equation 44. However, a simpler expression for the same is:

$$C_{max} = \frac{F X_0}{V_d} e^{-K_E t_{max}} \quad (49)$$

It has been shown that at C_{max}, when $K_a = K_E$, $t_{max} = 1/ K_E$. Hence, the above equation further reduces to:

$$C_{max} = \frac{F X_0}{V_d} e^{-1} = \frac{0.37 F X_o}{V_d} \quad (50)$$

Since FX_o/V_d represents C_o following i.v. bolus, the maximum plasma concentration that can be attained afetr e.v. administration is just 37% of the maximum level attainable with i.v. 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 e.v., absorption rate is significantly greater than the elimination rate i.e. $K_at > K_Et$. Hence, one can say that e^{-Kat} approaches zero

much faster than does $e^{-K_{Et}}$. At such a stage, when absorption is complete, the change in plasma concentration is dependent only on elimination rate and equation 44 reduces to:

$$C_{max} = \frac{K_a F X_0}{V_d(K_a - K_E)} e^{-K_{Et}} \quad (51)$$

Transforming into log form, the equation becomes:

$$\log C = \log \frac{K_a F X_0}{V_d(K_a - K_E)} - \frac{K_{Et}}{2.303} \quad (52)$$

A plot of log C versus t yields a straight line with slope $-K_E/2.303$ (half-life can then be computed from K_E). K_E can also be estimated from urinary excretion data (see the section on urinary excretion data).

Absorption Rate Constant: it can be calculated by the method of residuals. The technique is also known as feathering peeling and stripping. It is commonly used in pharmacokinetics to resolve a multiexponential curve into its individual components. For a drug that follows one-compartment kinetics and administered e.v. the concentration of drug in plasma is expressed by a biexponential equation 44.

$$C = \frac{K_a F X_0}{V_d(K_a - K_E)} \left(e^{-K_E t} - e^{-Kat} \right) \quad (44)$$

If $KaFX_0 / V_d(Ka - K_E) = A$, a hybrid constant, then:

$$C = A\, e^{-K_{Et}} - e^{-Kat} \quad (53)$$

During the elimination phase, when absorption is almost over, $K_a >> K_E$ and the value of second exponential $e^{-K_E t}$ retains some finite value. At this time, the equation 53 reduces to:

$$\overleftarrow{C} = A\, e^{-K_E t} \quad (54)$$

In log form, the above equation is:

$$\log \overleftarrow{C} = \log A = \frac{K_E t}{2.303} \quad (55)$$

Where represents the back extrapolated plasma concentration values. A plot of log C versus t yields a biexponential curve with a terminal linear phase having slope $-K_E/2.303$ (Fig.). Back extrapolation of this straight line to time zero yields y-intercept equal to log A.

Fig. 5.9 Plasma concentration-time profile after oral administration of single dose of a drug. The biexponential curve has been resolved into its two components-absorption and elimination.

Subtraction of true plasma concentration values i.e. equation 5.64 from the extrapolated plasma concentration values i.e. equation 5.65 yields a series of residual concentration values C_r :

$$(\overleftarrow{C} - C) = C_r = A\, e^{-Kat} \qquad (56)$$

Ln log form, the equation is:

$$\log C_r = \underline{\log}\ A - \frac{K_a t}{2.303} \qquad (57)$$

A plot of log C_r versus t yielys a straight line with slope – K_a/2.303 and y-intercept log A (Fig.). 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 i.v. bolus of the same drug is very large, much larger than the 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 indicates **timelag**. *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 method for the estimation of K_a is a curve-fitting method. The method is best suited for drugs for drugs which are rapidly and completely absorbed and follow one-compartment kinetic even given i.v. However, if the absorption of the drug is affected in some way such as Gl motility or enzymatic degradation and if the drug shows multicompartment characteristics after i.v. administration (which is true for virtually all drugs), then K_a computed by curve-fitting method is incorrect even if the drug were truly absorbed by first-order kinetics. The K_a so obtained is at best, estimate of first-order disappearance of drug from the GIT rather than of first-order appearance in the systemic circulation.

Wagner-Nelson Method for Estimation of K_a

One of the better alternatives to curve-fitting method in the estimation of Ka is Wagner-Nelson method. The method involves determination of Ka from percent unabsorbed-time plots and does not require the 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:

$$X_A = X + X_E \quad (58)$$

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

$$X_E = K_E V_d [AUC]_0^t \quad (59)$$

Substitution of values of X and X_E in equation 10.63 yields:

$$X_A = V_d C + K_E V_d [AUC]_0^t \quad (60)$$

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

$$X_A^\infty = V_d C^\infty + K_E V_d [AUC]_0^\infty \text{ Since at } t = \infty, C^\infty \quad (61)$$

$= 0$, the above equation reduces to:

$$X_A^\infty = K_E V_d [AUC]_0^\infty \quad (62)$$

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

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

$$= \frac{C + K_E [AUC]_0^t}{K_E [AUC]_0^\infty} \quad (63)$$

Percent drug unabsorbed at any time is therefore:

$$\%ARA = \left(1 - \frac{X_A}{X_A^\infty}\right) 100 = \left(1 - \frac{C + K_E V_d [AUC]_0^t}{K_E [AUC]_0^\infty}\right) 100 \quad (5.75)$$

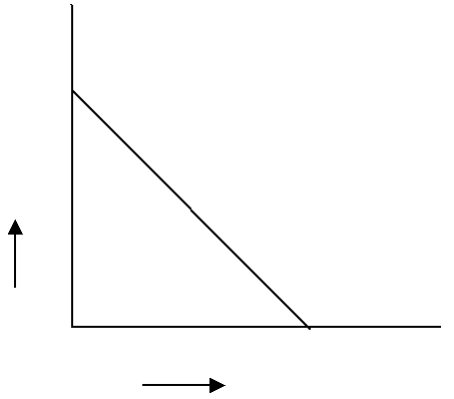


Fig. 5.10 Semilog plot of percent ARA versus t according to Wagner – Nelson method

The method requires collection of blood samples after single oral dose at regular intervals of time till the entire amount of drug is eliminated from the body. K_E is obtained from log C versus t plot and $[AUC]_0^t$ and $[AUC]_0^\infty$ are obtained from plot of C versus t. A semilog plot of percent of unabsorbed (i.e. percent ARA) versus t yields a straight line whose slope is $-K_a/2.303$ (Fig. 5.10). If a regular plot of the same is a straight line, then absorption is zero-order.

K_a can similarly be estimated from urinary excretion data (see the relevant section). 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 e.v. administration shows multicompartment characteristics on i.v. injection.