COMPARTMENT MODELING

A compartment is a group of tissues with similar blood flow and drug affinity. A compartment is physiologic and anatomic region. Compartment is the traditional and most widely used approach to pharmacokinetic characterization of drug.

A model is a mathematical description of biologic system and used to express quantitative relationships.

Compartment models simply interpolate the instrumental data and allow on empirical formula to estimate drug concentration with time.

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

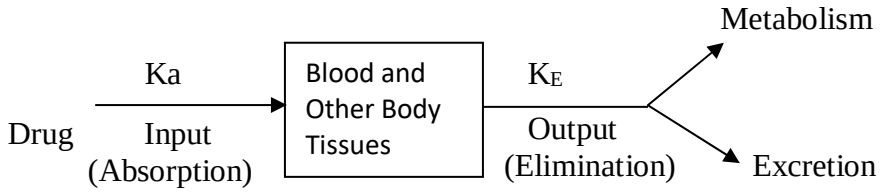


Fig. 1.1 Representation of one-compartment open model showing input and output processes.

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

One – compartment open model, intravenous bolus administration

One –Compartment open model, continuous intravenous infusion

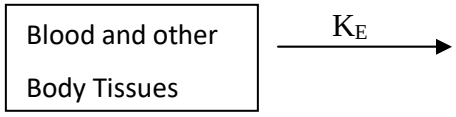
One-compartment open model, extravascular administration, zero-order absorption, and

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), the model can be depicted as follows:



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

$$\frac{dX}{dt} = \text{Rate in (availability)} - \text{Rate out (elimination)} \qquad (1.1)$$

Since **rate in** or absorption is absent, the equation becomes;

$$\frac{dX}{dt} = -\text{Rate out} \qquad (1.2)$$

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

$$\frac{dX}{dt} = -K_E X \qquad (1.3)$$

Where K_E = first-order elimination rate constant, and

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

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

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 1.3 yields:

$$\ln X = \ln X_0 - K_E t \qquad (1.4)$$

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

Equation 1.4 can also be written in the exponential form as :

$$X = X_o e^{-K_E t} \qquad (1.5)$$

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

Transforming equation 1.4 into common logarithms (log base 10), we get:

$$\log X = \log X_0 - \frac{K_E t}{2.303} \qquad (1.6)$$

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

$$X = V_d C \qquad (1.7)$$

Where V_d = proportionality constant popularly known as the apparent volume of distribution. It is a pharmacokinetic parameter that permits the use of drug concentration in place of amount of drug in the body. The equation 1.6 therefore becomes:

$$\log C = \log C_o - \frac{K_E t}{2.303} \qquad (1.8)$$

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

$$t_{1/2} = \frac{0.693}{K_E} \qquad (1.9)$$

Today, increased physiologic understanding of pharmacokinetics shows that *half-life is a secondary parameter that depends upon the primary parameters* clearance and apparent volume of distribution according to following equation :

$$t_{1/2} = \frac{0.693\ Vd}{CL_T}$$

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 mechanisms in the body. *They are called as* **primary parameters.**

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

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

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

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.

Just as V_d 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 drug elimination according to following equation:

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

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

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.

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 as **organ clearance.** It can be estimated by dividing the rate of elimination by each organ with the concentration of drug presented to it. Thus,

$$\text{Renal Clearance } Cl_R = \frac{\text{Rate of elimination by Kidney}}{C}$$

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

Other organ Clearance

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

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

Total Systemic Clearance $Cl_T = Cl_R + Cl_H + Cl_{others}$

Because of the additivity of clearance, the relative contribution by any organ in eliminating a drug can be easily calcualted. Clearance by all organs other than kidney is sometimes known as **non renal clearance** Cl_{NR}. It is the difference between total clearance and renal clearance.

According to an earlier definition ,

$$Cl_T = \frac{dX/dt}{C}$$

Substituting $dX/dt = K_E X$

$$Cl_T = \frac{K_E X}{C}$$

Since $X/C = V_d$, the equation can be written as:

$$Cl_T = K_E V_d$$

Parallel equations can be written for renal and hepatic clearances as :

$$Cl_R = K_E V_d$$
$$Cl_H = K_m V_d$$

Since $K_E = 0.693/ t_{1/2}$, clearance can be related to half-life by the following equation :

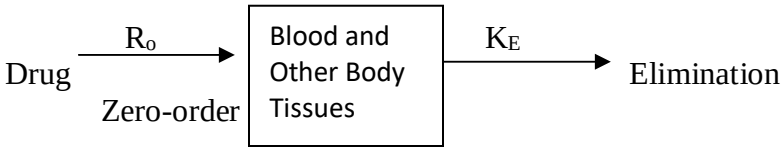
$$Cl_T = \frac{0.693\ V_d}{t_{½}}$$

One-Compartment Open Model -Intravenous Infusion

Rapid i.v. injection is unsuitable when the drug has potential to precipitate toxicity or when maintenance of a stable concentration or amount of drug in the body is desired. In such a situation, the drug (for example, several antibiotics, 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 drugs include –

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

The model can be represented as follows:



Infusion rate

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 rate of elimination, $-K_EX$:

$$\frac{dx}{dt} = R_o - K_E X \qquad (1.36)$$

Integration and rearrangement of above equation yields:

$$X = \frac{R^0}{K_E}(1 - e^{-K_E t}) \qquad (1.37)$$

Since $X = V_d C$, the equation 1.37 can be transformed into concentration terms as follows:

$$C = \frac{R^0}{K_E V_d}(1 - e^{-K_E t}) = \frac{R^0}{Cl_T}(1 - e^{-K_E t}) \qquad (1.38)$$

At the start of constant rate infusion, the amount of drug in the body is zero and hence, there is no elimination. As time passes, the amount of drug in the body 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 equilibrium.

At steady-state, the rate of change of amount of drug in the body is zero, hence the equation 1.36 becomes:

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

or

$$K_E X_{ss} = R_0 \qquad (1.39)$$

Transforming to concentration terms and rearranging the equation:

$$C_{ss} = \frac{R_0}{K_E V_d} = \frac{R_0}{Cl_T} \text{ i.e } \frac{\text{Infusion rate}}{\text{Clearance}} \qquad (1.40)$$

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 semi logarithmic plot (log C versus t) of the plasma concentration-time data generated 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 $R_0/Cl_T = C_{ss}$ from equation 1.40 in equation 1.38 we get:

$$C = C_{ss}(1 - e^{-K_E t}) \qquad (1.41)$$

Rearrangement yields:

$$\frac{C_{ss} - C}{C_{ss}} = e^{-K_E t} \qquad (1.42)$$

Transforming into log form, the equation becomes:

$$\log \frac{C_{ss} - C}{C_{ss}} = \frac{-K_E t}{2.303} \qquad (1.43)$$

A semilog plot of $(C_{ss} - C) / C_{ss}$ versus t results in a straight line with slope $-K_E / 2.303$

The time to reach steady-state concentration is dependent upon the elimination half-life and not infusion rate. An increase rate will merely increase the plasma concentration at steady-state.

Assessment of Pharmacokinetic Parameters

The first-order elimination rate constant and elimination half-life can be computed from a semi log plot of post-infusion concentration-time data. Equation 1.43 can also be used for the same purpose. Apparent volume of distribution and total systemic clearance can be estimated from steady state concentration and infusion rate (equation 1.40). These two parameters can also be computed from the total area under the curve till the end of infusion:

$$AUC = \frac{R_0 T}{K_E V_d} = \frac{R_0 T}{Cl_T} = C_{ss} T \qquad (1.48)$$

Where, T = infusion time.

The above equation is a general expression which can be applied to several pharmacokinetic models.

One-Compartment Open Model –Extra vascular Administration

The rate of absorption may be described mathematically as a zero order or first-order process.

A large number of plasma concentration-time profiles can be described by a one-compartment model with first-order absorption and elimination. However, under certain conditions, the absorption of some drugs may be better described by assuming zero-order (constant rate) kinetics.

Zero-order absorption is characterized by a constant rate of absorption. It is independent of amount remaining to be absorbed (ARA), and its regular ARA versus t plot is linear with slope equal to rate of absorption while the semi log 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 semi log plot a straight line with absorption rate as its slope.

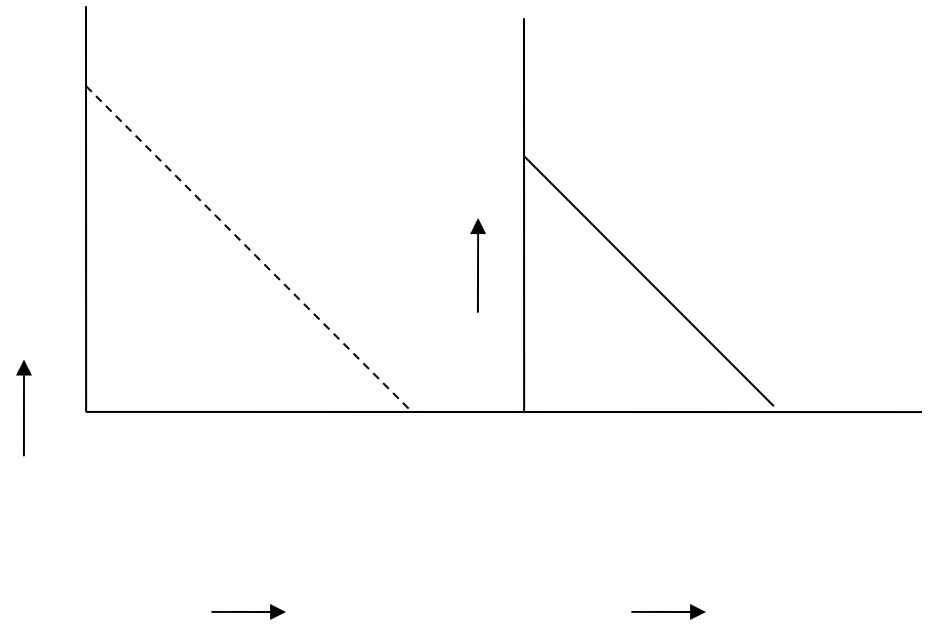


Fig. Distinction between zero-order and first-order absorption processes.
Figure a is regular plot, and Figure b a semi log plot of amount of drug remaining to be Absorbed (ARA) versus time t.

After e.v. administration, the rate of change in the amount of drug in the body dX/dt is the difference between the rate of input (absorption) dX_{ev}/dt and rate of output (elimination).

dX/dt = Rate of absorption – Rate of elimination

$$\frac{dX}{dt} = \frac{dX_{ev}}{dt} - \frac{dX_E}{dt} \qquad (1.49)$$

For a drug that follows one-compartment kinetics, the plasma concentration profile is characterized by absorption phase, post-absorption phase and elimination phase

During the **absorption phase,** the rate of absorption is greater than the rate of elimination

$$\frac{dX_{ev}}{dt} > \frac{dX_E}{dt} \qquad (1.50)$$

At peak plasma concentration, the rate of absorption equals the rate of elimination and the change in amount of drug in the body is zero.

$$\frac{dX_{ev}}{dt} = \frac{dX_E}{dt} \qquad (1.51)$$

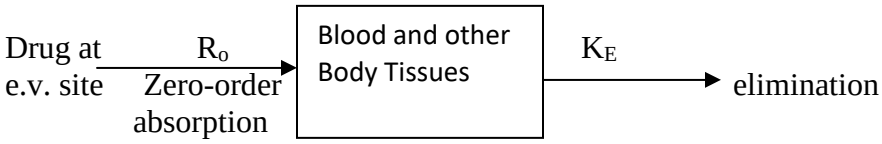
During the post-absorption phase, there is some drug at the extra vascular site still remaining to be absorbed and the rate of elimination at this stage is greater than the absorption rate.

$$\frac{dX_{ev}}{dt} < \frac{dX_E}{dt} \qquad (1.52)$$

After completion of drug absorption, its rate becomes zero and the plasma level time curve is characterized only by the elimination phase.

Zero-order Absorption model

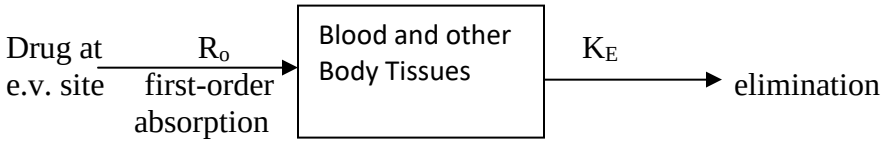
The model is similar to that for constant rate infusion.



The rate of drug absorption, as in the case of several controlled drug delivery systems, is constant and continues until the amount of drug at the absorption site (e.g. GIT) is depleted. All equation that explains the plasma concentration-time profile for constant rate i.v. infusion are also applicable to this model.

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 1.49 is

$$\frac{dx}{dt} = K_a X_a - K_E X \qquad (1.53)$$

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 1.53 yields:

$$X = \frac{K_a F X_0}{(K_a - K_E)} [e^{-K_E t} - e^{-Kat}] \qquad (1.54)$$

Transforming into concentration terms, the equation becomes:

$$C = \frac{K_a F X_0}{V_d(K_a - K_E)} [e^{-K_E t} - e^{-Kat}] \qquad (1.55)$$

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 1.55

$$\frac{dc}{dt} = \frac{K_a F X_0}{(K_a - K_E)} [-K_E e^{-KEt} + K_a e^{-Kat}] = \text{zero} \quad (1.56)$$

On simplifying the above equation becomes:

$$K_E e^{-KEt} = K_a e^{-Kat} \quad (1.57)$$

Converting to logarithmic form,

$$\log K_E - \frac{K_E t}{2.303} = \log K_a - \frac{K^a t}{2.303} \quad (1.58)$$

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

$$t_{max} = \frac{2.303 \log (k_a/K_E)}{K_a - K_E} \quad (1.59)$$

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 1.55. However, a simpler expression for the same is:

$$C_{max} = \frac{F X_0}{V_d} e^{-K_{Et\,max}} \quad (1.60)$$

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:

$$C_{max} = \frac{F X_0}{V_d} e^{-1} = \frac{0.37 F X_o}{V_d} \quad (1.61)$$

Since FX_o/V_d represents C_o following i.v. bolus, the maximum plasma concentration that can be attained after 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 1.55 reduces to:

$$C_{max} = \frac{K_a F X_0}{V_d(K_a - K_E)} e^{-K_{Et}} \qquad (1.62)$$

Transforming into log form, the equation becomes:

$$\log C = \log \frac{K_a F X_0}{V_d (K_a - K_E)} - \frac{K_{Et}}{2.303} \qquad (1.63)$$

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.

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 multi exponential 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 1.55.

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

If $K_aFX_0 / V_d(Ka - K_E) = A$, a hybrid constant, then:

$$C = A e^{-K_{Et}} - Ae^{-Kat} \qquad (1.64)$$

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 1.64 reduces to:

$$\overleftarrow{C} = A e^{-K_E t} \qquad (1.65)$$

In log form, the above equation is:

$$\log \overleftarrow{C} = \log A = \frac{K_E t}{2.303} \qquad (1.66)$$

Where $\overleftarrow{C}$ 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 $-K_E/2.303$. Back extrapolation of this straight line to time zero yields y-intercept equal to log A.

Subtraction of true plasma concentration values i.e. equation 1.64 from the extrapolated plasma concentration values i.e. equation 1.65 yields a series of residual concentration values C_r :

$$(\overleftarrow{C} - C) = C_r = A\, e^{-Kat} \qquad (1.67)$$

Ln log form, the equation is:

$$\log C_r = \log A - \frac{K_a t}{2.303} \qquad (1.68)$$

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.

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:

$$X_A = X + X_E \qquad (1.69)$$

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

$$X_E = K_E V_d [AUC]_0^t \qquad (1.70)$$

Substitution of values of X and X_E in equation yields:

$$X_A = V_d C + K_E V_d [AUC]_0^t \qquad (1.71)$$

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

$$X_A^\infty = V_d C^\infty + K_E V_d [AUC]_0^\infty \qquad (1.72)$$

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

$$X_A^\infty = K_E V_d [AUC]_0^\infty \qquad (1.73)$$

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

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

$$= \frac{C + K_E [AUC]_0^t}{K_E [AUC]_0^\infty} \qquad (1.74)$$

Percent drug unabsorbed at any time is therefore:

$$\%ARA = [1 - \frac{X_A}{X_A^\infty}]100 = [1 - \frac{C + K_E V_d [AUC]_0^t}{K_E [AUC]_0^\infty}] 100 \qquad (1.75)$$

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 $-K_a/2.303$. 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 multi compartment characteristics on i.v. injection.

Effect of K_a and K_E on C_{max}, and t_{max} and AUC

A summary of the influence of change in K_a at constant K_E and of K_E at constant Ka on C_{max}, t_{max} and AUC of a drug administered e.v. is shown in Table

Table
Influence of Ka and K_E on C_{max}, t_{max} and AUC

Parameters Affected	Influence when K_E is Constant		Influence when K_a is Constant	
	Smaller K_a	Large K_a	Smaller K_E	Larger K_E
C_{max}	↓	↑	↑	↓
t_{max}	Long	Short	Long	Short
AUC	No Change	No Change	↑	↓

Where, T = increase and † = decrease

Apparent Volume of Distribution and Clearance : For a drug that follows one-compartment kinetics after e.v. administration. V_d and Cl_T can be computed from equation 1.16 and 1.17 respectively Where F is the fraction absorbed into the systemic circulation.

$$V_d = \frac{F X_0}{K_E \, AUC} \qquad (1.16)$$

$$Cl_T = \frac{F X_0}{AUC} \qquad (1.17)$$

5.7 URINARY EXCRETION DATA

(Disposition Viewed from Urine only)

In the absence of plasma level-time data, useful information can still be obtained from urine data regarding elimination kinetics of a drug. The method has several advantages in the analysis of a pharmacokinetic system:

1. The method is useful when there is lack of sufficiently sensitive analytic techniques to measure concentration of drugs in plasma with accuracy.
2. The method is noninvasive and therefore better subject compliance is assured.
3. Convenience of collecting urine samples in comparison to drawing of blood periodically.
4. Often, a less sensitive analytic method is required for determining urine drug concentration as compared to plasma concentrations; if the urine drug concentration are low, assaying of larger sample volumes is relatively easy.

5. First – order elimination, excretion and absorption rate constants and fraction excreted unchanged can be computed from such data; first order metabolism or extrarenal excretion rate constant can also be calculated subsequently from the difference $(K_E - K_e) = K_m$.
6. Direct measurement of bioavailability, both absolute and relative, is possible without the necessity of fitting the data to a mathematical model.
7. When coupled with plasma level-time data it can also be used to estimate renal clearance of unchanged drug according to following equation:

$$Cl_R = \frac{\text{Total amount of drug excreted unchanged}}{\text{Area under the plasma level-time curve}} \qquad (1.76)$$

If V_d is known, total systemic clearance and nonrenal clearance can also be calculated.

One cannot however compute V_d and Cl_T from urine data alone. One must also remember that urinary excretion data is not an accurate substitute for the plasma level data.

Criteria for Obtaining Valid Urinary Excretion Data

1. A significant amount of drug must be excreted unchanged in the urine (at least 10%).
2. The analytical method must be specific for the unchanged drug; metabolites should not interfere.
3. Water-loading should be done by taking 400 ml of water after fasting overnight, to promote diuresis and enable collection of sufficient urine samples.
4. Before administration of drug, the bladder must be emptied completely after 1 hour from water-loading and the urine sample taken as blank; the drug should then be administered with 200 ml of water and should be followed by 200 ml given at hourly intervals for the next 4 hours.

5. Volunteers must be instructed to completely empty their bladder while collecting urine samples.
6. Frequent sampling should be done in order to obtain a good curve.
7. During sampling, the exact time and volume of urine excreted should be noted.
8. An individual collection period should not exceed one biologic half-life tof the drug and ideally should be considerably less.
9. Urine samples must be collected for at least 7 biological half-lives in order to ensure collection of more than 99% of excreted drug.
10. Changes in urine pH and urine volume may after the urinary excretion rate.

The urine data can be set as shown in the table. Observations include times of urine collection, volumes collected and concentration of unchanged drug in each sample. These data are treated to derive further information.

Determination of K_E from Urinary Excretion Data

The first-order elimination (and excretion) rate constants can be computed from urine data by two methods:

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

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

$$\frac{dX_u}{dt} = K_e X \qquad (1.77)$$

Where K_e = first order urinary excretion rate constant. According to first-order disposition kinetics, $X = X_o\, e^{-K_E t}$ (equation 1.5). Substituting it in above equation yields:

$$\frac{dX_u}{dt} = K_e X_0\, e^{-K_E t} \qquad (1.78)$$

Where X_0 = dose administered (i.v. bolus). Transforming to log form the equation becomes:

$$\log \frac{dX_u}{dt} = \log K_e X_0 - \frac{K_E t}{2.303} \qquad (1.79)$$

The above equation states that a semilog plot of rate of excretion versus time yields a straight line with slope $-K_E/2.303$. It must therefore be remembered that the slope of such an excretion rate versus time plot is related to elimination rate constant K_E and not to excretion rate constant K_e. The excretion rate constant can be obtained from the *Y*-intercept ($\log K_e X_o$). Elimination half-life and non renal elimination rate constant can then the computed from K_E and K_e.

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

From an earlier equation:

$$\frac{dX_u}{dt} = K_e X_0 e^{-K_E t} \qquad (1.80)$$

Integration of equation 1.80 yields:

$$X_u = \frac{K_e X_0}{K_E} = (1 - e^{-K_E t}) \qquad (1.81)$$

Where X_u = cumulative amount of drug excreted unchanged in urine at any time t. As time approaches infinity i.e. after 6 to 7 half-lives, the value $e^{-K_E \infty}$ becomes zero and therefore the cumulative amount excreted at infinite time X_u^{∞} can be given by equation:

$$X_u^{\infty} = \frac{K_e X_0}{K_E} \qquad (1.82)$$

Substitution of equation 1.82 in equation 1.81 and rearrangement yields:

$$X_u^{\infty} - Xu = X_u^{\infty} e^{-K_E t} \qquad (1.83)$$

Converting to logarithms, we get:

$$\text{Log}(X_u^{\infty} - X_u) = \text{Log}X_u^{\infty} - \frac{K^E t}{2.303}$$

Where $(X_u^{\infty} - X_u)$ = amount remaining to be excreted i.e. ARE at any given time. A semilog plot of ARE versus t yields a straight line with slope $-K_E / 2.303$. The method is, therefore, also called as ARE plot method. A disadvantage of this method is that total urine collection has to be carried out until no unchanged drug can be detected in the urine i.e. upon 7 half-lives, which may be tedious for drugs having long $t_{1/2}$.

The equations until now for computing KE from the urinary excretion data apply to a drug that fits one – compartment model and given as i.v. bolus. Similarly, data obtained during constant rate i.v. infusion can be used to evaluate the elimination rate constant. The equation that descrides the urinary excretion rate of unchanged drug when administered as i.v. bolus also applies when it is administered as i.v. infusion. Thus:

$$\frac{dXu}{dt} = K_e X \qquad (1.77)$$

For a drug given as i.v. infusion, the amount of drug in the boby X is given by equation(described earlier)

$$X = \frac{R_0}{K_E}(1 - e^{-K_E t}) \qquad (1.37)$$

Substitution of equation 1.37 in equation 1.77 and integration of the same yields:

$$X_u = \frac{K_e R_0}{K_E} - \frac{K_e R_0}{K_E^2}(1 - e^{-K_E t}) \qquad (1.84)$$

When the drug has been infused for a period long enough to attain steady-state in the plasma, the term e^{-KEt} approaches zero and the above equation reduces to:

$$X_u = \frac{K_e R_0 t}{K_E} - \frac{K_e R_0}{K_E^2} \qquad (1.85)$$

A regular plot of cumulative amount of drug excreted Xu versus t yields a curvilinear plot the linear portion of which has a slope K_eR_o/K_E.

Extrapolation of linear segment to time axis yields x-intercept equal to 1/KE since when Xu = 0, t = 1/KE

Relationships for rate of excretion when the drug is administered e.v. can also be given similarly. Thus:

$$\frac{dXu}{dt} = K_e X \qquad (1.77)$$

For a drug given e.v. and absorbed by a first-order process, X is given as:

$$X = \frac{K_a F X_0}{(K_a - K_E)} e^{-K_E t} - e^{-Kat} \qquad (1.54)$$

Substitution of equation 1.54 in equation 1.77 and integration of the same yields:

$$X_u = \frac{K_e K_a F X_0}{K_E}\left[\frac{1}{Ka} + \frac{e^{-K_E t}}{(K_E - K_a)} - \frac{K_E e^{-K_E t}}{K_a(K_E - K_a)}\right] \qquad (1.86)$$

At time infinity, the equation 1.86 reduces to:

$$ARE = (Xu^{\infty} - X_u) = \frac{Xu^{\infty}}{(K_a - K_E)}(K_a e^{-K_E t} - K_E e^{-K_a t}) \qquad (1.87)$$

Substitution of equation 1.86 in equation 1.87 and subsequent rearrangement yields:

A semilog plot of (Xu - Xu) versus t results in a biexponential curve and if Ka > KE, the slope of the terminal linear portion of the curve will define KE of the drug. The adsorption rate constant Ka can be estimated by the method of residuals using the same data i.e. equation 1.87.

Urinary excretion data after oral administration can also be treated according to Wagner-Nelson method to calculate Ka by construction of % ARA plots. The method requires urine collection for sufficiently long time to ensure accurate estimation of KE but need not be collected to time infinity. The equation derived to relate % ARA with urinary excretion rate is:

$$\%ARA = \left[1 - \frac{XA}{Xu^{\infty}}\right] 100 = \left[1 - \frac{dX_u/dt + K_E X_u}{K_E Xu^{\infty}}\right] 100 \qquad (1.88)$$

A semilog plot of % ARA versus t yields a straight line with slope –Ka/2.303.

Accurate determination of Ka from urinary excretion data is possible only for drugs with slow rate of absorption since for drugs with rapid absorption; collection of urine samples at very short intervals of time is difficult.