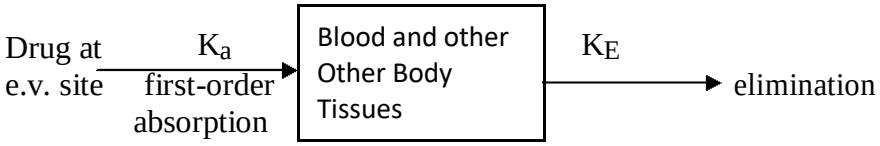
**First –Absorption Model**

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

$$dx/dt = K_a X_a - K_E X \quad \text{—(42)}$$

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:

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

Transforming into concentration terms, the equation becomes:

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

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.

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:

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

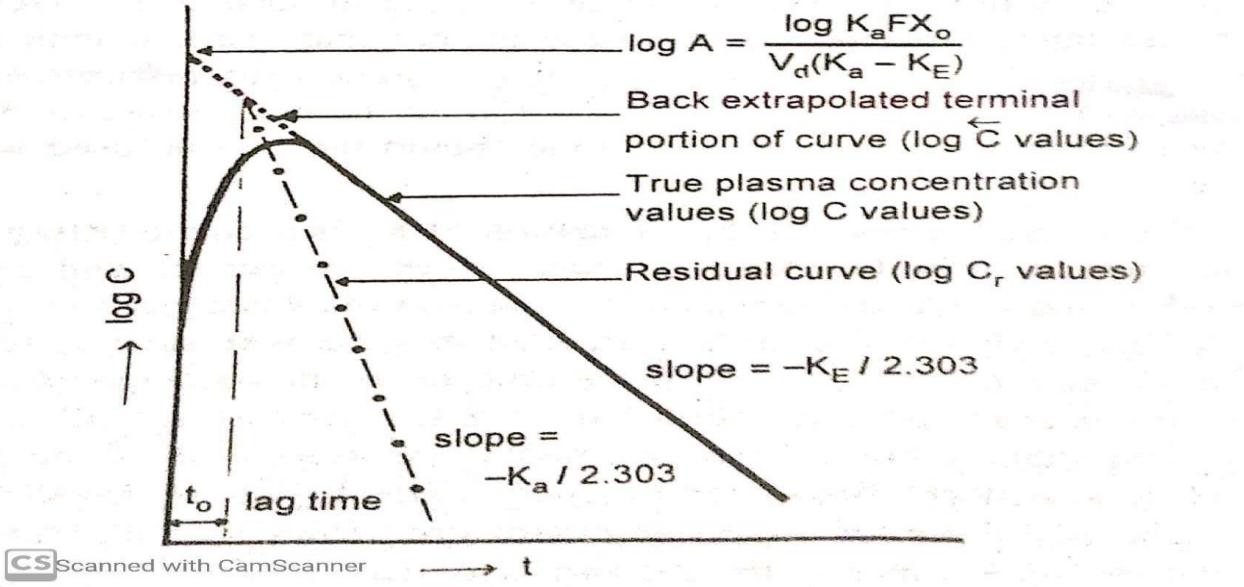



**Fig. 5.9** Plasma concentration-time profile after oral administration of single dose of a drug. The biexponential curve has been resolved into its two components-absorption and elimination

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:

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

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

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

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 $X_A^\infty$ can be given as:

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

$$= 0 \text{ , the above equation reduces to:}$$

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

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:

$$\%ARA = \left(1 - \frac{X_A}{X_A^\infty}\right) 100 = \left(1 - \frac{C + K_E V_d [AUC]_0^t}{K_E [AUC]_0^\infty}\right) 100 \quad (64)$$

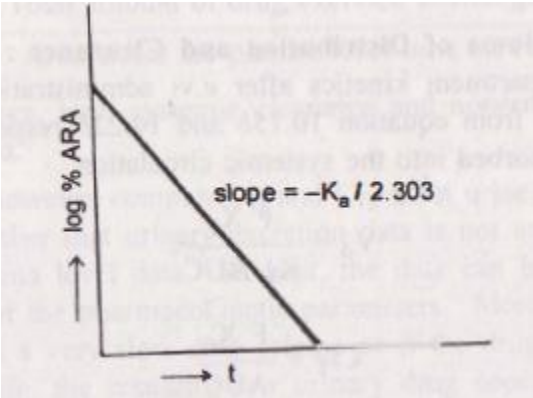


**Fig. 5.10** Semilog plot of percent ARA versus t according to Wagner – Nelson method

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.