6

Extravascular routes of drug administration

Objectives

Upon completion of this chapter, you will have the ability to:

- calculate plasma drug concentration at any given time after the administration of an extravascular dose of a drug, based on known or estimated pharmacokinetic parameters
- interpret the plasma drug concentration versus time curve of a drug administered extravascularly as the sum of an absorption curve and an elimination curve
- employ extrapolation techniques to characterize the absorption phase
- calculate the absorption rate constant and explain factors that influence this constant
- explain possible reasons for the presence of *lag time* in a drug's absorption
- calculate peak plasma drug concentration, $(C_p)_{max}$, and the time, t_{max}, at which this occurs
- explain the factors that influence peak plasma concentration and peak time
- decide when flip-flop kinetics may be a factor in the plasma drug concentration versus time curve of a drug administered extravascularly.

6.1 Introduction

Drugs, through dosage forms, are most frequently administered extravascularly and the majority of them are intended to act systemically; for this reason, absorption is a prerequisite for pharmacological effects. Delays or drug loss during absorption may contribute to variability in drug response and, occasionally, may result in a failure of drug therapy.

The gastrointestinal membrane separates the absorption site from the blood. Therefore, passage of drug across the membrane is a prerequisite for absorption. For this reason, drug must be in a solution form and dissolution becomes very critical for the absorption of a drug. The passage of drug molecules from the gastrointestinal tract to the general circulation and factors affecting this are shown in Figs 6.1 and 6.2. Any factor influencing dissolution of the drug is likely to affect the absorption of a drug. These factors will be discussed, in detail, later in the text.

Drug, once in solution, must pass through membranes before reaching the general circulation. Hence, the physicochemical properties of the drug molecule (pK_a of the drug, partition coefficient of the drug, drug solubility, etc.), pH at the site of drug administration, nature of the membrane, and physiological factors will also influence the absorption of a drug.

The present discussion will deal with general principles that determine the rate and extent of drug absorption and the methods used to assess these and other pharmacokinetic parameters, from plasma concentration versus time data following oral administration of drugs. Emphasis is placed upon absorption of drugs following oral administration because it illustrates all sources of variability encountered during drug absorption.

Note that a similar approach may be applied to determine pharmacokinetic parameters of drugs when any other extravascular route is used.

The following assumptions are made.

- Drug exhibits the characteristics of one-compartment model.
- Absorption and elimination of a drug follow the first-order process and passive diffusion is operative all the time.
- Drug is eliminated in unchanged form (i.e., no metabolism occurs).
- Drug is monitored in the blood.

Useful pharmacokinetic parameters

Figure 6.3 outlines the absorption of a drug that fits a one-compartment model with first-order elimination. The following information is useful:

1. equation for determining the plasma concentration at any time t
2. determination of the elimination half life ($t_{1/2}$) and rate constant (K or K_{el})
3. determination of the absorption half life ($t_{1/2})_{abs}$ and absorption rate constant (K_a)
4. lag time (t_0), if any
5. determination of the apparent volume of distribution (V or V_d) and fraction of drug absorbed (F)
6. determination of the peak time (t_{max})
7. determination of the peak plasma or serum concentration ($C_p)_{max}$.

6.2 Drug remaining to be absorbed, or drug remaining at the site of administration

Equation (6.1) describes the changes in mass of absorbable drug over time at the site of administration.

$$\frac{-dX_a}{dt} = K_a(X_a)_t \tag{6.1}$$

where $-dX/dt$ is the decrease in the amount of absorbable drug present at the site of administration per unit time (e.g., mg h^{-1}); K_a is the first-order absorption rate constant (h^{-1}; min^{-1}); and $(X_a)_t$ is the mass or amount of absorbable drug at the site of administration (e.g., the gastrointestinal tract) at time t.

Upon integration of Eq. (6.1), we obtain the following:

$$(X_a)_t = (X_a)_{t=0}e^{-K_a t} = FX_0 e^{-K_a t} \tag{6.2}$$

where $(X_a)_{t=0}$ is the mass or amount of absorbable drug at the site of administration at time $t = 0$ (for extravascular administration of drug, $(X_a)_{t=0}$ equals FX_0); F is the fraction or percentage of the administered dose that is available to reach the general circulation; and X_0 is the administered dose of drug.

If $F = 1.0$, that is, if the drug is completely (100%) absorbed, then

$$(X_a)_t = X_0 e^{-K_a t}. \tag{6.3}$$
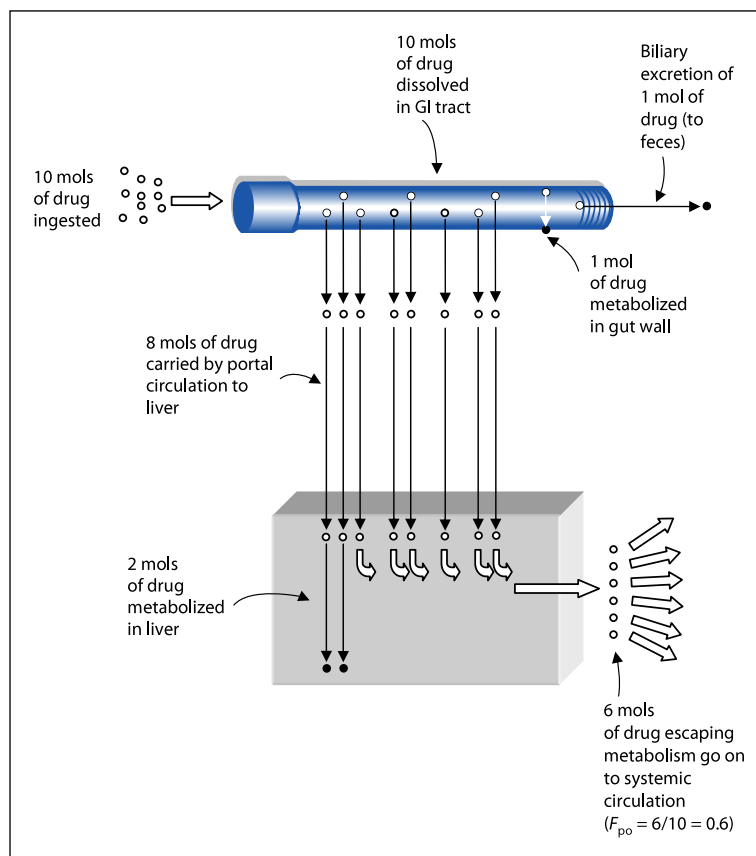
Figure 6.1 Barriers to gastrointestinal absorption.

Both Eqs (6.2) and (6.3) and Fig. 6.4 clearly indicate that the mass, or amount, of drug that remains at the absorption site or site of administration (or remains to be absorbed) declines monoexponentially with time.

However, since we cannot measure the amount of drug remaining to be absorbed (X_a) directly, because of practical difficulty, Eqs (6.2) and (6.3), for the time being, become virtually useless for the purpose of determining the absorption rate constant; and, therefore, we go to other alternatives such as monitoring drug in the blood and/or urine to determine the absorption rate constant and the absorption characteristics.

Monitoring drug in the blood (plasma/serum) or site of measurement

The differential equation that follows relates changes in drug concentration in the blood with time to the absorption and the elimination rates:

$$\frac{dX}{dt} = K_a X_a - KX \tag{6.4}$$

where dX/dt is the rate (mg h^{-1}) of change of amount of drug in the blood; X is the mass or amount of drug in the blood or body at time t; X_a is the mass or amount of absorbable drug at the absorption site at time t; K_a and K are the first-order absorption and elimination rate constants, respectively (e.g., h^{-1}); $K_a X_a$ is the first-order rate of absorption (mg h^{-1}, µg h^{-1}, etc.); and KX is the first-order rate of elimination (e.g., mg h^{-1}).

Equation (6.4) clearly indicates that rate of change in drug in the blood reflects the difference between the absorption and the elimination rates (i.e., $K_a X_a$ and KX, respectively). Following the administration of a dose of drug, the difference between the absorption and elimination rates (i.e., $K_a X_a - KX$) becomes smaller as time increases; at peak time, the difference becomes zero.
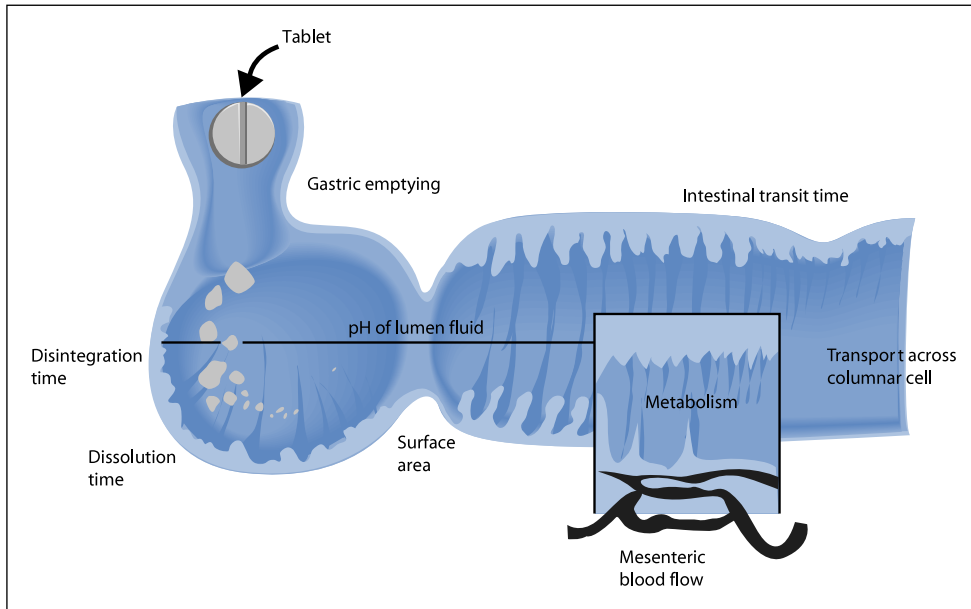
Figure 6.2 Passage of drug in the gastrointestinal tract until transport across the membrane.
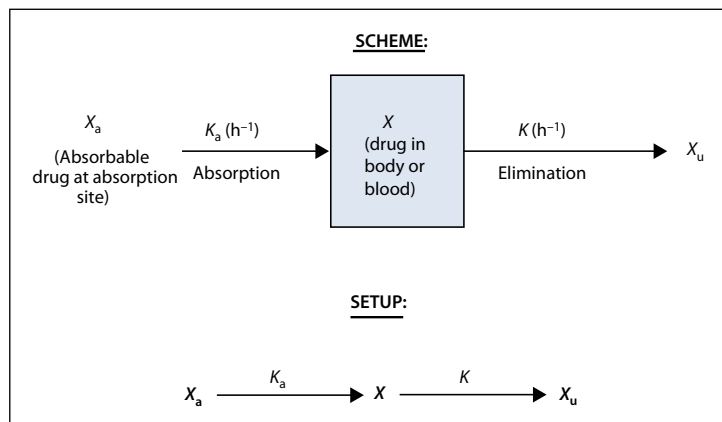
Figure 6.3 Absorption of a one-compartment drug with first-order elimination, where X_a is the mass or amount of absorbable drug remaining in the gut, or at the site of administration, at time t (i.e., drug available for absorption at time t); X is the mass or amount of drug in the blood at time t; X_u is the mass or amount of drug excreted unchanged in the urine at time t; K_a is the first-order absorption rate constant (h^{-1} or min^{-1}); and K (or K_{el}) is the first-order elimination rate constant (h^{-1} or min^{-1}).
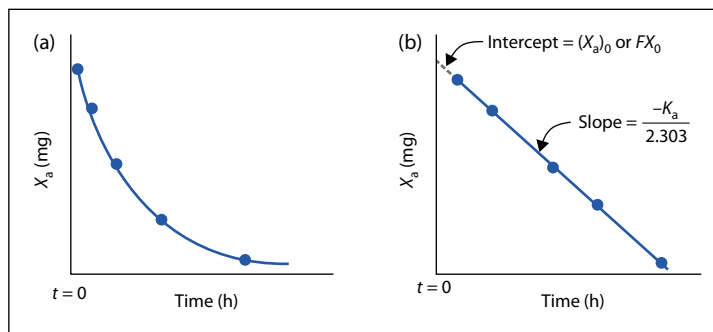
Figure 6.4 Amount of drug remaining at the site of administration against time in a rectilinear plot (a) and a semilogarithmic plot (b). X_a, amount of absorbable drug at the site of administration; $(X_a)_0$, amount of absorbable drug at the site of administration at time $t = 0$; F, fraction of administered dose that is available to reach the general circulation.

Note that, most of the time, the absorption rate constant is greater than the elimination rate constant. (The exceptional situation when $K > K_a$, termed "flip-flop kinetics," will be addressed in Section 6.13.) Furthermore, immediately following the administration of a dose of drug, the amount of (absorbable) drug present at the site of administration will be greater than the amount of drug in the blood. Consequently, the rate of absorption will be greater than the rate of elimination up to a certain time (prior to peak time); then, exactly at peak time, the rate of absorption will become equal to the rate of elimination. Finally, the rate of absorption will become smaller than the rate of elimination (post peak time). This is simply the result of a continuous change in the amount of absorbable drug remaining at the site of administration and the amount of drug in the blood. Note also that rate of absorption and the rate of elimination change with time (consistent with the salient feature of the first-order process), whereas the absorption and the elimination rate constants do not change.

Integration of Eq. (6.4) gives

$$(X)_t = \frac{K_a(X_a)_{t=0}}{K_a - K}(e^{-Kt} - e^{-K_a t})$$

$$= \frac{K_a FX_0}{K_a - K}(e^{-Kt} - e^{-K_a t}) \tag{6.5}$$

where $(X)_t$ is the mass (amount) of drug in the body at time t; X_0 is the mass of drug at the site of administration at $t = 0$ (the administered dose); F is the fraction of drug absorbed; $(X_a)_0 = FX_0$ and is the

mass of administered dose that is available to reach the general circulation, which is the same as the bioavailable fraction times the administered dose.

Equation (6.5) and Fig. 6.5 show that the mass or amount of drug in the body or blood follows a biexponential profile, first rising and then declining.

For orally or extravascularly administered drugs, generally $K_a \gg K$; therefore, the rising portion of the graph denotes the absorption phase.

If $K \gg K_a$ (perhaps indicating a dissolution-rate-limited absorption), the exact opposite will hold true. (See the discussion of the flip-flop model in Section 6.13.)

6.3 Determination of elimination half life ($t_{1/2}$) and elimination rate constant (K or K_{el})

Equation (6.5), when written in concentration (C_p) terms, takes the form

$$(C_p)_t = \frac{K_a FX_0}{V(K_a - K)}(e^{-Kt} - e^{-K_a t}) \tag{6.6}$$

where $K_a FX_0/[V(K_a - K)]$ is the intercept of the plasma drug concentration versus time plot (Fig. 6.6).

When time is large, because of the fact that $K_a \gg K$, $e^{-K_a t}$ approaches zero, and Eq. (6.6) reduces to

$$(C_p)_t = \frac{K_a FX_0}{V(K_a - K)}(e^{-Kt}). \tag{6.7}$$
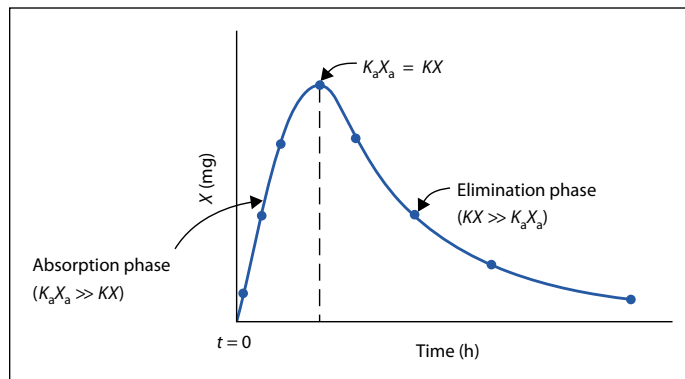
Figure 6.5 A typical rectilinear profile illustrating amount of drug (X) in blood or body against time. X_a, amount of absorbable drug at the absorption site at time t; K_a and K, first-order absorption and elimination rate constants, respectively; K_aX_a and KX, first-order rates of absorption and elimination, respectively.
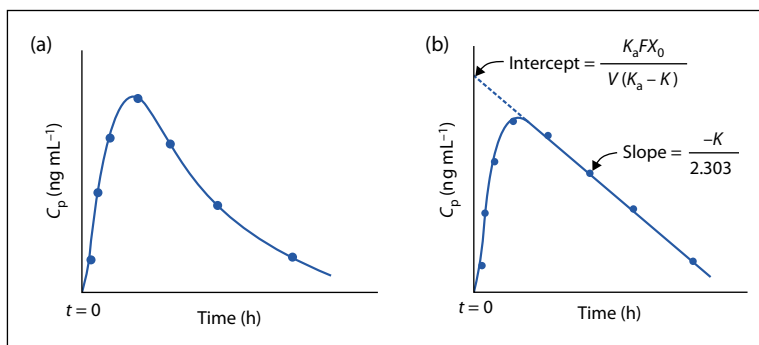
Figure 6.6 A plot of plasma concentration (C_p) against time on rectilinear (a) and semilogarithmic (b) paper. $(X_a)_0$, amount of absorbable drug at the site of administration at time $t = 0$; F, fraction of administered dose that is available to reach the general circulation; K_a and K, first-order absorption and elimination rate constants, respectively; V, apparent volume of distribution.

The elimination half life and elimination rate constant can be obtained by methods described earlier and illustrated in Fig. 6.7.

6.4 Absorption rate constant (K_a)

The absorption rate constant is determined by a method known as "feathering," "method of residuals," or "curve stripping." The method allows the separation of the monoexponential constituents of a biexponential plot of plasma concentration against time. From the plasma concentration versus time data obtained or provided to you and the plot of the data

(as shown in Fig. 6.8) we can construct a table with headings and columns as in Table 6.1 for the purpose of determining the absorption rate constant.

In column 1 of the table, the time values are recorded that correspond to the observed plasma concentrations. This is done only for the absorption phase. In column 2, the observed plasma concentration values provided only from the absorption phase are recorded (i.e., all values prior to reaching maximum or highest plasma concentration value). In column 3, the plasma concentration values obtained only from the extrapolated portion of the plasma concentration versus time plot are recorded (these values are read from the plasma concentration–time

Table 6.1 Illustration of the table created for determination of the first-order absorption rate constant K_a

Time (h)	Observed plasma concentration $(C_p)_{obs}$	Extrapolated plasma concentration $(C_p)_{extrap}$	$(C_p)_{diff} = (C_p)_{extrap} - (C_p)_{obs}$
Time values corresponding to observed plasma concentrations for absorption phase only	Values only from the absorption phase (i.e., all values prior to reaching maximum or highest plasma concentration) (units, e.g., $\mu g\ mL^{-1}$)	Values only from the extrapolated portion of the plot of plasma concentration–time (units, e.g., $\mu g\ mL^{-1}$)	Differences between extrapolated and observed values for each time in the absorption phase (units, e.g., $\mu g\ mL^{-1}$)
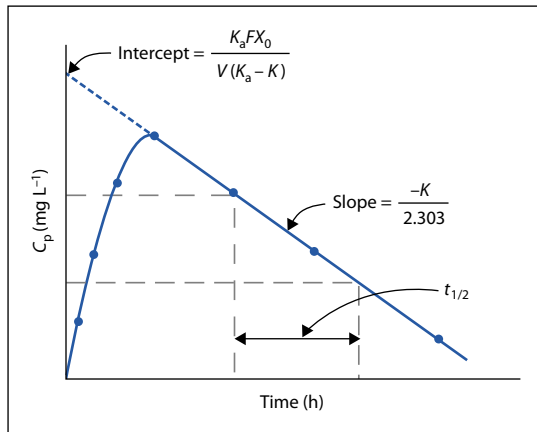
Figure 6.7 Semilogarithmic plot of plasma drug concentration (C_p) versus time of an extravascular dosage form: visualization of elimination half life ($t_{1/2}$). Other abbreviations as in Fig. 6.6.

plot); and, in column 4, the differences in the plasma concentrations $(C_p)_{diff}$ between the extrapolated and observed values for each time in the absorption phase are recorded.

The differences in plasma concentrations between the extrapolated and observed values (in column 4 of Table 6.1) should decline monoexponentially according to the Eq. (6.8):

$$(C_p)_{diff} = \frac{K_a F X_0}{V(K_a - K)}(e^{-K_a t}) \qquad (6.8)$$

where $K_a F X_0/[V(K_a - K)]$ is the intercept of the plasma drug concentration versus time plot. A plot of this difference between extrapolated and observed plasma concentrations against time, on semilogarithmic paper (Fig. 6.9), should yield a straight line, which, in turn, should allow determination of:

- the half life of the feathered or residual line (i.e., the $t_{1/2}$ of the absorption phase)

- the first-order absorption rate constants, using the equation $K_a = 0.693/(t_{1/2})_{abs}$, or $K_a = -(\text{Slope}) \times 2.303$.

6.5 Wagner–Nelson method (one-compartment model) and Loo–Riegelman method (two-compartment model)

1. Wagner–Nelson method from plasma drug level data

Drug that has been absorbed either is still in the body or has been eliminated. Because of the law of mass balance, this statement may be quantified as

$$X_A = X + X_E \qquad (6.9)$$

where X_A is the cumulative amount of absorbed drug at time t; X is the amount of drug present in the body at time t; and X_E is the cumulative amount of drug eliminated at time t.

Differentiating Eq. (6.9) results in

$$\frac{dX_A}{dt} = \frac{dX}{dt} + \frac{dX_E}{dt}. \qquad (6.10)$$
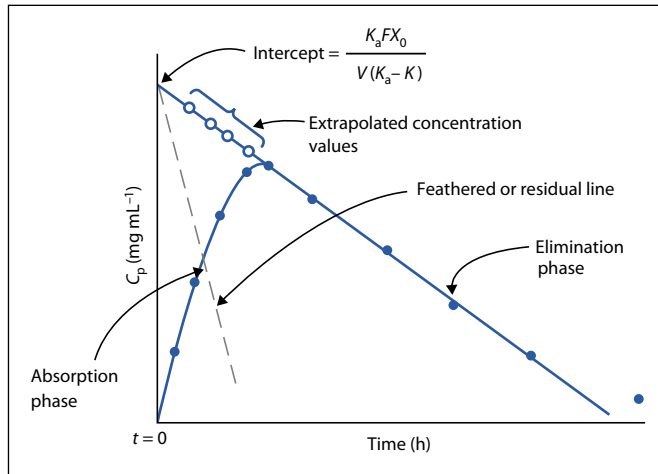
For first-order elimination, this yields

$$\frac{dX_A}{dt} = \frac{dX}{dt} + KX. \qquad (6.11)$$
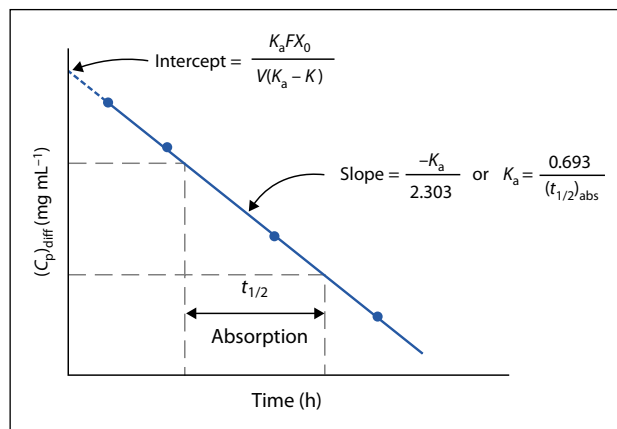
Since $X = VC_p$,

$$\frac{dX_A}{dt} = V\frac{dC_p}{dt} + KVC_p. \qquad (6.12)$$

Integration of Eq. (6.12) from $t = 0$ to t yields

$$(X_A)_t = VC_p + KV \int_0^t (C_p)\,dt$$

$$= VC_p + KV(\text{AUC})_0^t \qquad (6.13)$$

Figure 6.8 Semilogarithmic plot of plasma concentration (C_p) versus time of an extravascular dosage form, showing the method of residuals. Other abbreviations as in Fig. 6.6.

Figure 6.9 Semilogarithmic plot of plasma concentration $(C_p)_{diff}$. between calculated residual concentrations and measured ones versus time, allowing the calculation of the absorption rate constant. $(t_{1/2})_{abs}$, absorption half life; other abbreviations as in Fig. 6.6.

since the integral is simply the area under the plasma drug level versus time curve. It can be shown that this sum represents, respectively, the mass of drug in the body at time t plus the mass of drug that has been eliminated at this same time.

We define $(X_A)_\infty$ as the total amount of drug ultimately absorbed. This is obtained by integrating Eq. (6.12) from $t = 0$ to $t = \infty$, as follows:

$$
\begin{aligned}
(X_A)_\infty &= (VC_p)_0^\infty + KV \int_0^\infty (C_p)\, dt \\
&= V(C_p)_0 - V(C_p)_\infty + KV(AUC)_0^\infty \\
&= KV(AUC)_0^\infty \quad (6.14)
\end{aligned}
$$

since $(C_p)_0$ and $(C_p)_\infty$ both equal zero for an extravascular dose.

In order to obtain the ratio of mass of drug absorbed at a given time t to the maximum amount

of drug that will ultimately be absorbed, we divide Eq. (6.13) by Eq. (6.14):

$$\frac{(X_A)_t}{(X_A)_\infty} = \frac{VC_p + KV(\text{AUC})_0^t}{KV(\text{AUC})_0^\infty}. \tag{6.15}$$

Since the denominator of Eq. (6.15), $KV(\text{AUC})_0^\infty$, is equal to FX_0, i.e., the absorbable dose, it is evident that Eq. (6.15) compares the cumulative amount of drug absorbed at time t to the mass of drug that will ultimately be absorbed (not simply to the administered dose X_0).

Canceling V in numerator and denominator yields

$$\frac{(X_A)_t}{(X_A)_\infty} = \frac{C_p + K(\text{AUC})_0^t}{K(\text{AUC})_0^\infty}. \tag{6.16}$$

Plasma drug samples are assayed at several time points after administration of drug, yielding concentrations $(C_p)_t$. From these data points, one can calculate $(\text{AUC})_0^t$ for the same values of time. These values, along with an estimate of K from the terminal portion of the C_p versus t curve, allow the calculation of several values of $(X_A)_t/(X_A)_\infty$. To obtain good estimates of K and of $(X_A)_\infty$ it is important to collect plasma drug levels for a sufficiently long period of time, preferably at least four elimination half lives.

Next, for each of these time points, one may calculate the drug remaining to be absorbed as a fraction of the absorbable mass of drug:

Percent drug remaining to be absorbed

$$= \left(1 - \frac{(X_A)_t}{(X_A)_\infty}\right)(100). \tag{6.17}$$

The following example may help to clarify the concept of fraction drug remaining to be absorbed. If 90 mg of a 100 mg dose of drug will ultimately be absorbed, and if 30 mg of drug is still at the absorption site (gastrointestinal tract) at 2 h after dosing, then $30/90 = 0.333$ is the fraction of drug remaining to be absorbed, which is equal to 33.3%. At this time exactly 60 mg of drug will have been absorbed; so, by Eq. (6.17), the percentage of drug remaining to be absorbed will equal

$$\left(1 - \frac{60}{90}\right)(100) = 33.3\%$$

which is in agreement with our previous result.

For first-order absorption, drug remaining to be absorbed expressed as a fraction of absorbable drug

is given by the expression

$$\frac{FX_0 e^{-K_a t}}{FX_0} = e^{-K_a t}$$

(see Fig. 6.10). Thus a semilogarithmic plot of unabsorbed drug versus time will yield a straight line with slope of $-K_a/2.303$. K_a can be calculated as $(-2.303)(\text{slope}_{SL})$ (see Fig. 6.11).

Should a *rectilinear* plot of unabsorbed drug versus time yield a straight line, *zero*-order absorption is indicated.

2. Wagner–Nelson method from mass of drug in urine data

We start with Eq. (6.12) from our previous discussion:

$$\frac{dX_A}{dt} = V\frac{dC_p}{dt} + KVC_p. \tag{6.12}$$

For urinary data, we need to modify this equation to substitute for C_p. To do this we realize that parent drug is excreted by the kidney into the urine according to the following first-order process:

$$\frac{dX_u}{dt} = +K_u X \tag{6.18}$$

where dX_u/dt is the rate of increase in the cumulative mass of intact (parent) drug excreted into the urine over time; K_u is the apparent first-order excretion rate constant; and X is the amount of drug in the body at time t.

Substituting $X = VC_p$, yields

$$\frac{dX_u}{dt} = +K_u VC_p. \tag{6.19}$$

Rearranging Eq. (6.19),

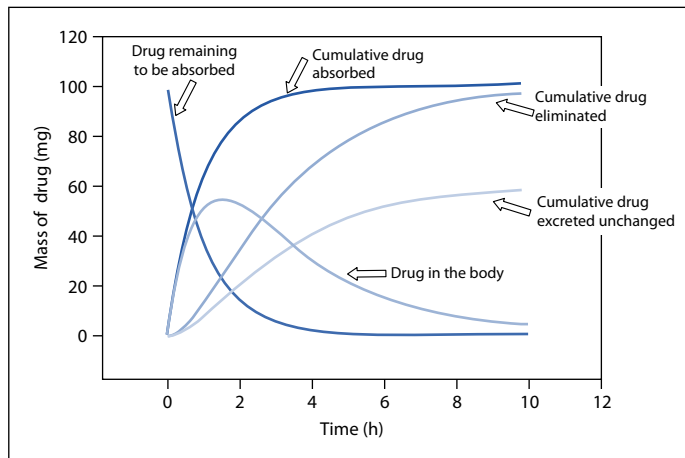$$C_p = \frac{dX_u/dt}{K_u V}. \tag{6.20}$$
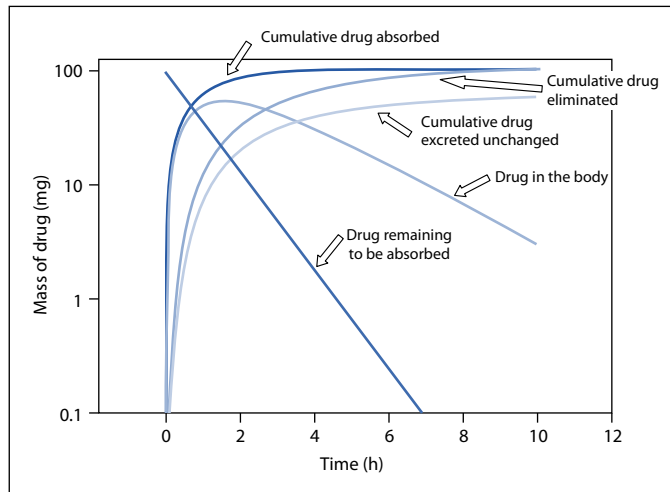
Substituting the above for C_p in Eq. (6.12),

$$\frac{dX_A}{dt} = V\frac{d\frac{dX_u/dt}{K_u V}}{dt} + KV\frac{dX_u/dt}{K_u V}.$$

Canceling V and extracting constants:

$$\frac{dX_A}{dt} = \frac{1}{K_u}\frac{d}{dt}\left(\frac{dX_u}{dt}\right) + \frac{K}{K_u}\frac{dX_u}{dt}. \tag{6.21}$$

Figure 6.10 Rectilinear (RL) plot of disposition of extravascularly administered drug, showing the fraction of drug unabsorbed versus time.

Figure 6.11 Semilogarithmic (SL) plot of disposition of extravascularly administered drug, showing the fraction of drug unabsorbed versus time.

Integration of Eq. (6.21) from $t = 0$ to $t = \infty$ yields

$$(X_A)_t = \frac{1}{K_u}\left(\frac{dX_u}{dt}\right) + \frac{K}{K_u}(X_u)_t. \tag{6.22}$$

From Eq. (6.18), we see that the first term to the right of the equal sign in Eq. (6.22) is equal to $(X)_t$, the amount of drug in the body at time t. In the second term, $(X_u)_t$ is the cumulative amount of drug excreted by the kidney at time t. We may view the ratio K/K_u as a factor that will convert $(X_u)_t$ to the cumulative amount of drug *eliminated* by all pathways, including both renal excretion and metabolism. Thus Eq. (6.22)

shows that cumulative absorbed drug is the sum of drug currently in the body plus the cumulative mass of drug that has already been eliminated at time t.

At $t = \infty$, the rate of urinary excretion of drug is zero; so, the first term of Eq. (6.22) drops out, resulting in

$$(X_A)_\infty = \frac{K}{K_u}(X_u)_\infty \tag{6.23}$$

where $(X_u)_\infty$ is the cumulative amount of excreted drug at time infinity.

The ratio $(X_A)_t/(X_A)_\infty$ is the fraction of absorbable drug that has been absorbed at time t. It is obtained by dividing Eq. (6.22) by Eq. (6.23):

$$\frac{(X_A)_t}{(X_A)_\infty} = \frac{\frac{1}{K_u}\left(\frac{dX_u}{dt}\right) + \frac{K}{K_u}(X_u)_t}{\frac{K}{K_u}(X_u)_\infty}$$

$$= \frac{\left(\frac{dX_u}{dt}\right) + K(X_u)_t}{K(X_u)_\infty}. \tag{6.24}$$

In practice this ratio approaches 1 when the absorption process is virtually complete (i.e., in about 5 *absorption* half lives); so one does not have to collect urine samples until all drug has been eliminated from the body. If absorption is first order, the semilogarithmic plot of $1 - [(X_A)_t/(X_A)_\infty]$, i.e., the fraction of drug remaining to be absorbed, versus time will result in a straight line whose slope is $-K_a/2.303$, as we have seen in the case where plasma drug level data was collected.

3. Loo–Riegelman method (two-compartment model)

This method is relevant for a drug displaying two-compartment pharmacokinetics. We will not describe the entire method. Use of this method requires a separate intravenous administration of drug in each subject who will be tested for absorption of oral drug. In this method the fraction drug absorbed at time t is

$$F_t = \frac{(C_p)_t + K_{10}\int_0^\infty (C_p)\,dt + (X_{peri})_t/V_c}{K_{10}\int_0^\infty (C_p)\,dt} \tag{6.25}$$

where $(X_{peri})_t$ is the amount of drug in the peripheral (tissue) compartment at time t after oral administration and V_c is the apparent volume of distribution of the central compartment. K_{10}, the first-order elimination rate constant of drug from the central compartment, is estimated from an intravenous study in the same subject. The quantity $(X_{peri})_t/V_c$ can be estimated by a rather complicated approximation procedure requiring both oral and intravenous data.

6.6 Lag time (t_0)

Theoretically, intercepts of the terminal linear portion and the feathered line in Fig. 6.8 should be the same; however, sometimes, these two lines do not have the same intercepts, as seen in Fig. 6.12.

A plot showing a lag time (t_0) indicates that absorption did not start immediately following the administration of drug by the oral or other extravascular route. This delay in absorption may be attributed to some formulation-related problems, such as:

- slow tablet disintegration
- slow and/or poor drug dissolution from the dosage form
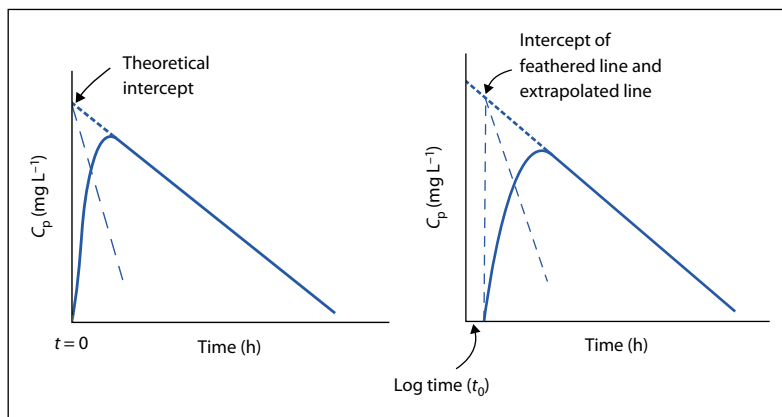
Figure 6.12 Semilogarithmic plots of the extrapolated plasma concentration (C_p) versus time showing the lag time (t_0).

- incomplete wetting of drug particles (large contact angle may result in a smaller effective surface area) owing to the hydrophobic nature of the drug or the agglomeration of smaller insoluble drug particles
- poor formulation, affecting any of the above
- a delayed release formulation.

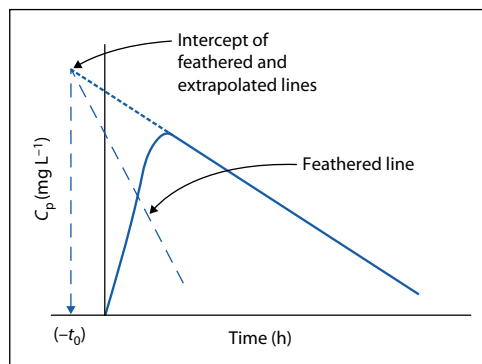## Negative lag time ($-t_0$)

Figure 6.13 shows a plot with an apparent negative lag time.

What does negative lag time mean? Does it mean that absorption has begun prior to the administration of a drug? That cannot be possible unless the body is producing the drug! The presence of a negative lag time may be attributed to a paucity of data points in the absorption as well as in the elimination phase.

The absorption rate constant obtained by the feathering, or residual, method could be erroneous under the conditions stated above. Should that be the case, it is advisable to employ some other methods (Wagner–Nelson method, statistical moment analysis, Loo–Rigelman method for a two-compartment model, to mention just a few) of determining the absorption rate constant. Though these methods tend to be highly mathematical and rather complex, they do provide an accurate estimate of the absorption rate constant, which, in turn, permits accurate estimation of other pharmacokinetic parameters such as peak time and peak plasma concentration, as well as the assessment of bioequivalence and comparative and/or relative bioavailability.

6.7 Some important comments on the absorption rate constant

Figure 6.14 indicates that the greater the difference between the absorption and the elimination rate constants (i.e., $K_a \gg K$), the faster is drug absorption and the quicker is the onset of action (in Fig. 6.14, apply the definition of onset of action). Note the shift in the peak time and peak plasma concentration values as the difference between absorption rate constant (K_a) and elimination rate constant (K) becomes smaller, as you go from left to right of the figure. If the absorption rate constant (K_a) is equal to the elimination rate

Figure 6.13 Semilogarithmic plot of plasma concentration (C_p) versus time showing a negative value for the lag time (t_0).

constant (K), we need to employ a different pharmacokinetic model to fit the data.

Note that the absorption rate constant for a given drug can change as a result of changing the formulation, the dosage form (tablet, suspension, capsule) or the extravascular route of drug administration (oral, intramuscular, subcutaneous, etc.). Administration of a drug with or without food will also influence the absorption rate constant for the same drug administered orally through the same formulation of the same dosage form.

6.8 The apparent volume of distribution (V)

For a drug administered by the oral route, or any other extravascular route of administration, the apparent volume of distribution cannot be calculated from plasma drug concentration data alone. The reason is that the value of F (the fraction of administered dose that reaches the general circulation) is not known. From Eqs. (6.6)–(6.8):

$$\text{Intercept} = \frac{K_a F X_0}{V(K_a - K)}. \tag{6.26}$$

If we can reasonably assume, or if it has been reported in the scientific literature, that $F = 1.0$ (i.e., the entire administered dose has reached the general circulation), only then can we calculate the apparent volume of distribution following the administration of a drug by the oral or any other extravascular route.
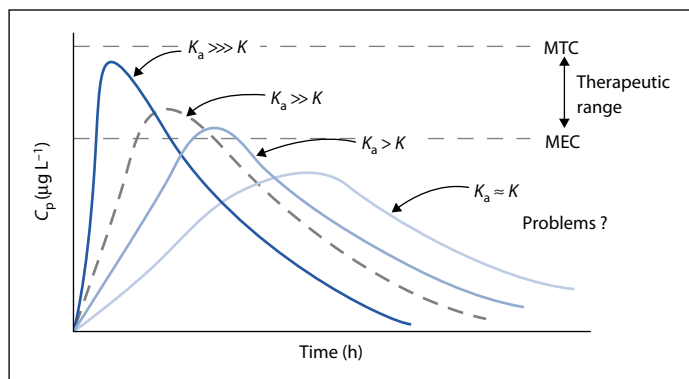
Figure 6.14 Rectilinear plot of plasma concentration (C_p) versus time for various magnitudes of absorption (K_a) and elimination (K) rate constants. MTC, minimum toxic concentration; MEC, minimum effective concentration.

In the absence of data for the fraction of administered dose that reaches the general circulation, the best one can do is to obtain the ratio of V/F:

$$\frac{V}{F} = \frac{K_a X_0}{(K_a - K)}\left(\frac{1}{\text{Intercept}}\right). \qquad (6.27)$$

6.9 Time of maximum drug concentration, peak time (t_{max})

The peak time (t_{max}) is the time at which the body displays the maximum plasma concentration, $(C_p)_{max}$. It occurs when the rate of absorption is equal to the rate of elimination (i.e., when $K_a X_a = KX$). At the peak time, therefore, $K_a(X_a)_{t_{max}} = K(X)_{t_{max}}$.

The success of estimations of the peak time is governed by the number of data points (Fig. 6.15).

Calculating peak time

According to Eq. (6.4), derived above,

$$\frac{dX}{dt} = K_a X_a - KX.$$

When $t = t_{max}$, the rate of absorption ($K_a X_a$) equals the rate of elimination (KX). Hence, Eq. (6.4) becomes

$$\frac{dX}{dt} = K_a(X_a)_{t_{max}} - K(X)_{t_{max}} = 0$$

or

$$K_a(X_a)_{t_{max}} = K(X)_{t_{max}}. \qquad (6.28)$$

We know from earlier equations (Eqs 6.5 and 6.2) that

$$(X)_t = \frac{K_a F X_0}{K_a - K}(e^{-Kt} - e^{-K_a t})$$

and

$$(X_a)_t = F X_0 e^{-K_a t}.$$

When $t = t_{max}$, Eqs (6.5) and (6.2) become Eqs (6.29) and (6.30), respectively:

$$(X)_{t_{max}} = \frac{K_a F X_0}{K_a - K}(e^{-Kt_{max}} - e^{-K_a t_{max}}) \qquad (6.29)$$

$$(X_a)_{t_{max}} = F X_0 e^{-K_a t_{max}}. \qquad (6.30)$$

Equation (6.28) shows that $K_a(X_a)_{t_{max}} = K(X)_{t_{max}}$. Substituting for $(X_a)_{t_{max}}$ (from Eq. 6.30) and $(X)_{t_{max}}$ (from Eq. 6.29) in Eq. (6.28), then rearranging and simplifying, yields

$$K_a e^{-K_a t_{max}} = K e^{-Kt_{max}}. \qquad (6.31)$$

Taking natural logarithms of Eq. (6.31) yields
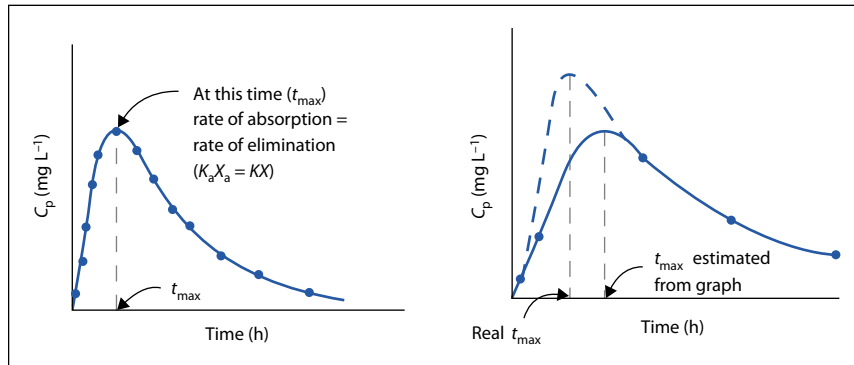
$$\ln K_a - K_a t_{max} = \ln K - Kt_{max}$$
$$\ln K_a - \ln K = K_a t_{max} - Kt_{max}$$
$$\ln(K_a/K) = t_{max}(K_a/K)$$

or

$$t_{max} = \frac{\ln(K_a/K)}{K_a - K}. \qquad (6.32)$$

Equation (6.32) indicates that peak time depends on, or is influenced by, only the absorption and elimination rate constants; therefore, any factor that

Figure 6.15 Dependency of estimate of the peak time (t_{max}) on the numberof data points. K_a, absorption rate constant; K, elimination rate constant; X_a, absorbable mass or amount of drug at the absorption site; X, mass or amount of drug in the blood or body; C_p, plasma concentration.

influences the absorption and the elimination rate constants will influence the peak time value. However, the peak time is always independent of the administered dose of a drug.

What is not immediately apparent from Eq. (6.32) is that a small value for either the absorption rate constant (as may occur in a poor oral formulation) or for the elimination rate constant (as may be the case in a renally impaired patient) will have the effect of lengthening the peak time and slowing the onset of action. This may be proved by changing the value of one parameter at a time in Eq. (6.32).

Significance of peak time

The peak time can be used:

- to determine comparative bioavailability and/or bioequivalence
- to determine the preferred route of drug administration and the desired dosage form for the patient
- to assess the onset of action.

Differences in onset and peak time may be observed as a result of administration of the same drug in different dosage forms (tablet, suspension, capsules, etc.) or the administration of the same drug in same dosage forms but different formulations (Fig. 6.16). Please note that this is due to changes in K_a and not in K (elimination rate constant).

6.10 Maximum (peak) plasma concentration (C_p)$_{max}$

The peak plasma concentration (C_p)$_{max}$ occurs when time is equal to t_{max}.

Significance of the peak plasma concentration

The peak plasma concentration:

- is one of the parameters used to determine the comparative bioavailability and/or the bioequivalence between two products (same and or different dosage forms) but containing the same chemical entity or therapeutic agent
- may be used to determine the superiority between two different dosage forms or two different routes of administration
- may correlate with the pharmacological effect of a drug.

Figure 6.17 shows three different formulations (A, B, and C) containing identical doses of the same drug in an identical dosage form. (Similar plots would arise when giving an identical dose of the same drug via different extravascular routes or when giving identical doses of a drug by means of different dosage forms.)

Note the implicit assumption made in all pharmacokinetic studies that the pharmacological effects
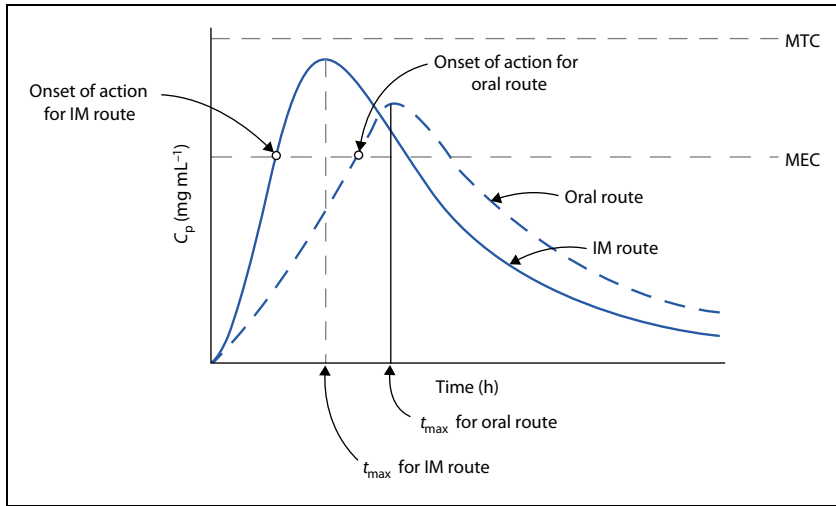
Figure 6.16 Rectilinear plots of plasma concentration (C_p) against time following the administration of an identical dose of a drug via the oral or intramuscular (IM) extravascular routes to show variation in time to peak concentration (t_{max}) and in onset of action. MTC, minimum toxic concentration; MEC, minimum effective concentration.

of drugs depend upon the plasma concentration of that drug in the body. Consequently, the greater the plasma concentration of a drug in the body (within the therapeutic range or the effective concentration range), the better will be the pharmacological effect of the drug.

How to obtain the peak plasma concentration

There are three methods available for determining peak plasma concentration ($C_p)_{max}$. Two are given here.

Method 1. Peak plasma concentration obtained from the graph of plasma concentration versus time (Fig. 6.18).
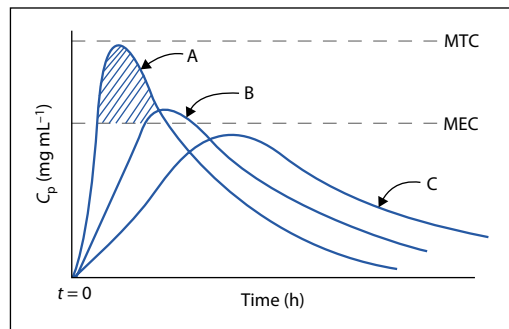
Method 2. Peak plasma concentration obtained using an equation. Equation (6.6) shows that

$$(C_p)_t = \frac{K_a F X_0}{V(K_a - K)} (e^{-Kt} - e^{-K_a t}).$$

If t_{max} is substituted for t in Eq. (6.6),

$$(C_p)_{max} = \frac{K_a F X_0}{V(K_a - K)} (e^{-Kt_{max}} - e^{-K_a t_{max}}).$$
(6.33)

We also know from Eqs (6.6) and (6.7) that the intercept (I) of the plasma concentration–time plot is given

Figure 6.17 Rectilinear plots of plasma concentration (C_p) against time following the administration of an identical dose of a drug via three different formulations (A–C). MTC, minimum toxic concentration; MEC, minimum effective concentration.

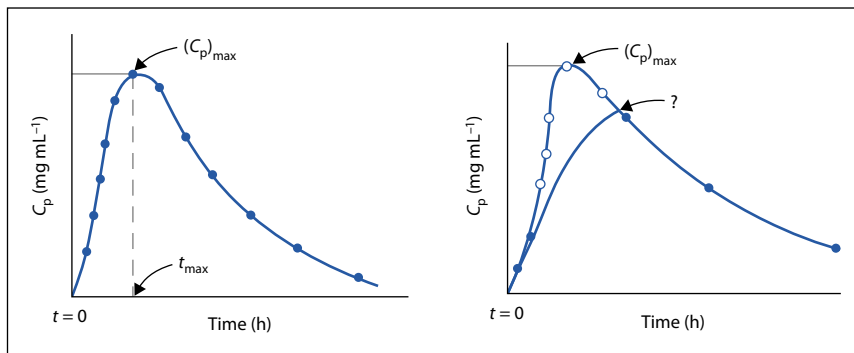by

$$I = \frac{K_a F X_0}{V(K_a - K)}.$$

Hence, substituting for the term $K_a F X_0/[V(K_a - K)]$ in Eq. (6.33) with I will yield Eq. (6.34):

$$(C_p)_{max} = I(e^{-Kt_{max}} - e^{-K_a t_{max}}).$$
(6.34)

Figure 6.19 shows this relationship.

Figure 6.18 Rectilinear plots of plasma concentration (C_p) against time following the administration of a drug via extravascular route. The accuracy of the estimation of the peak plasma concentration (C_p)$_{max}$ depends upon having sufficient data points (full points) to identify the time of peak concentration (t_{max}).
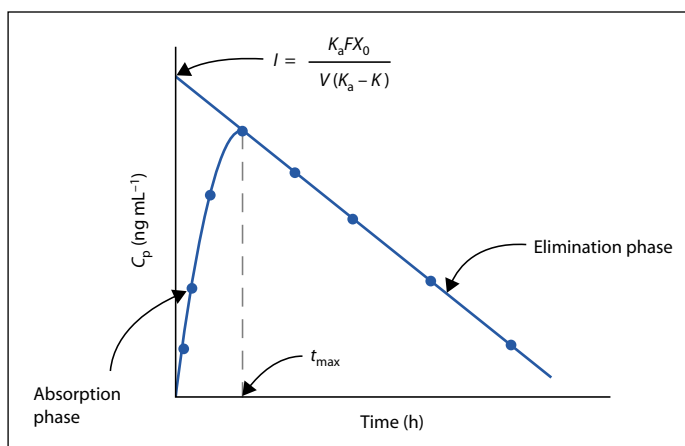
Figure 6.19 Semilogarithmic plot of plasma concentration (C_p) against time following the administration of a drug via the extravascular route, showing the intercept (I) and the time of peak concentration (t_{max}). Other abbreviations as in Fig. 6.6.

We present, without proof, a simpler equation for $(C_p)_{max}$:

$$(C_p)_{max} = \frac{FX_0}{V} e^{-Kt_{max}} \qquad (6.35)$$

where

$$\frac{FX_0}{V} = \left(\frac{K_a - K}{K_a} \right)(I)$$

and I is the intercept of the plasma concentration versus time profile for a single dose.

The peak plasma concentration, like any other concentration parameter, is directly proportional to the mass of drug reaching the general circulation or to the administered dose. This occurs when the first-order process and passive diffusion are operative (another example of linear pharmacokinetics).

6.11 Some general comments

1 The elimination rate constant, the elimination half life, and the apparent volume of distribution are constant for a particular drug administered to a particular patient, regardless of the route of administration and the dose administered.

2 Therefore, it is a common practice to use values of the elimination rate constant, the elimination half life and the apparent volume of

distribution obtained from intravenous bolus or infusion data to compute parameters associated with extravascular administration of a drug.

3 The absorption rate constant is a constant for a given drug formulation, dosage form and route of administration. That is, the same drug is likely to have a different absorption rate constant if it is reformulated, if the dosage form is changed and/or if administered by a different extravascular route.

4 The fraction absorbed, like the absorption rate constant, is a constant for a given drug formulation, a dosage form, and route of administration. The change in any one of these may yield a different fraction absorbed for the same drug.

5 Therefore, if the same dose of the same drug is given to the same subject via different dosage forms, different routes of administration or different formulations, it may yield different peak times, peak plasma concentrations, and area under the plasma concentration–time curve (AUC). Peak time and the area under the plasma concentration–time curve characterize the rate of drug absorption and the extent of drug absorption, respectively. Peak plasma concentration, however, may reflect either or both of these factors.

Tables 6.2–6.4 (Source: *Facts and Comparisons*) and Fig. 6.20 illustrate the differences in the rate and extent of absorption of selected drugs when administered as different salts or via different routes. Note the differences in the fraction absorbed, peak time, and peak plasma concentration but not in the fundamental pharmacokinetic parameters (half life and elimination rate constant) of the drug.

6.12 Example for extravascular route of drug administration

Concentration versus time data for administration of a 500 mg dose of drug are given in Table 6.5 and plotted on rectilinear and semilogarithmic paper in Figs 6.21 and 6.22, respectively. From these data a number of parameters can be derived.

The elimination half life and the elimination rate constant are obtained from the semilogarithmic plot of plasma concentration against time (Fig. 6.22):

- the elimination half life $(t_{1/2}) = 10$ h
- the elimination rate constant $K = 0.693/t_{1/2} = 0.693/10$ h $= 0.0693$ h^{-1}
- the *y*-axis intercept $= \frac{K_a FX_0}{V(K_a - K)} = 67$ µg mL^{-1} for a 500 mg dose.

The absorption rate constant and the absorption phase half life are obtained from the residual or feathering method. From the data in Fig. 6.22, the differences between the observed and the extrapolated plasma concentrations are calculated (Table 6.6, column 4) and are then plotted against time (column 1) on semilogarithmic paper (Fig. 6.23) from which we can calculate:

- the half life of the absorption phase $(t_{1/2})_{abs} = 2.8$ h
- the absorption rate constant $(K_a) = 0.693/2.8$ h $= 0.247$ h^{-1}.

Note that absorption rate constant is greater than the elimination rate constant: $K_a > K$.

The apparent volume of distribution is calculated from the amount (mass) of absorbable drug at the site of administration at time $t = 0$, $(X_a)_{t=0}$. This equals the dose $= X_0 = 500$ mg if it is assumed that the fraction absorbed $(F) = 1.0$. Note that this assumption is made solely for purpose of demonstrating how to use this equation for the determination of the apparent volume of distribution.

$$\text{Intercept} = \frac{K_a FX_0}{V(K_a - K)}$$

where intercept $= 67$ µg mL^{-1}, $K_a = 0.247$ h^{-1}, $F = 1.0$, and $FX_0 = 500$ mg $= 500\,000$ µg. Hence,

$$V = \frac{K_a FX_0}{\text{Intercept}(K_a - K)}$$

$$= \frac{0.247 \text{ h}^{-1} \times 500\,000 \text{ µg}}{67 \text{ µg mL}^{-1}(0.247 - 0.0693) \text{ h}^{-1}}$$

$$= \frac{123\,500 \text{ µg h}^{-1}}{67 \text{ µg mL}^{-1}(0.177 \text{ h}^{-1})}$$

$$= \frac{123\,500}{11.906} = 10\,372.92 \text{ mL or } 10.37 \text{ L}.$$

The peak time can be obtained from the graph (Fig. 6.21): $t_{max} = 8.0$ h. Or it can be calculated using the equation:

$$t_{max} = \frac{\ln(K_a/K)}{K_a - K}.$$

Table 6.2 Lincomycin, an antibiotic used when patient is allergic to penicillin or when penicillin is inappropriate

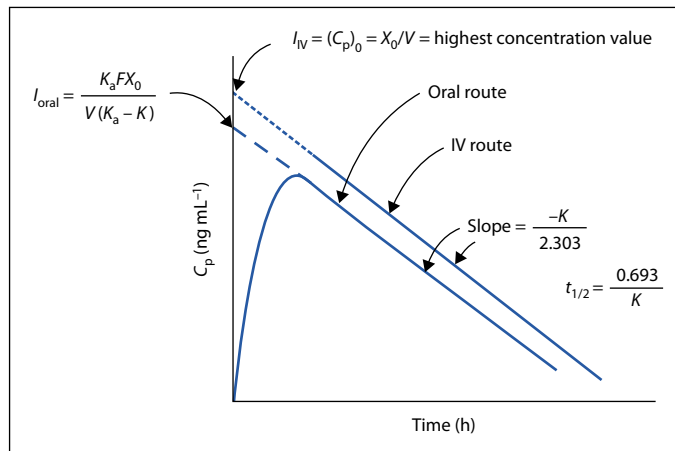| Route of administration	Fraction absorbed	Mean peak serum concentration ($\mu g\ mL^{-1}$)	Peak time (h)
Oral[a]	0.30	2.6	2 to 4
Intramuscular	Not available	9.5	0.5
Intravenous	1.00	19.0	0.0

[a] Not commercially available in the USA.

**Table 6.3** Haloperidol (Haldol), a drug used for psychotic disorder management

Route of administration	Percentage absorbed	Peak time (h)	Half life (h [range])
Oral	60	2 to 6	24 (12–38)
Intramuscular	75	0.33	21 (13–36)
Intravenous	100	Immediate	14 (10–19)

Table 6.4 Ranitidine HCl (Zantac)

Route and dose	Fraction absorbed	Mean peak levels ($ng\ mL^{-1}$)	Peak time (h)
Oral (150 mg)	0.5–0.6	440–545	1–3
Intramuscular or intravenous (50 mg)	0.9–1.0	576	0.25

The figure shows labels:
$I_{IV} = (C_p)_0 = X_0/V$ = highest concentration value

$I_{oral} = \dfrac{K_a F X_0}{V(K_a - K)}$

Oral route

IV route

$\text{Slope} = \dfrac{-K}{2.303}$

$t_{1/2} = \dfrac{0.693}{K}$

C_p (ng mL^{-1})

Time (h)

Figure 6.20 Administration of a drug by intravascular (IV) and extravascular (oral) routes (one-compartment model). Even for administration of the same dose, the value of plasma concentration (C_p) at time zero [$(C_p)_0$] for the intravenous bolus may be higher than the intercept for the extravascular dose. This will be determined by the relative magnitudes of the elimination rate constant (K) and the absorption rate constant (K_a) and by the size of fraction absorbed (F) for the extravascular dosage form. X_0, oral dose of drug; X_0, IV bolus dose of drug.
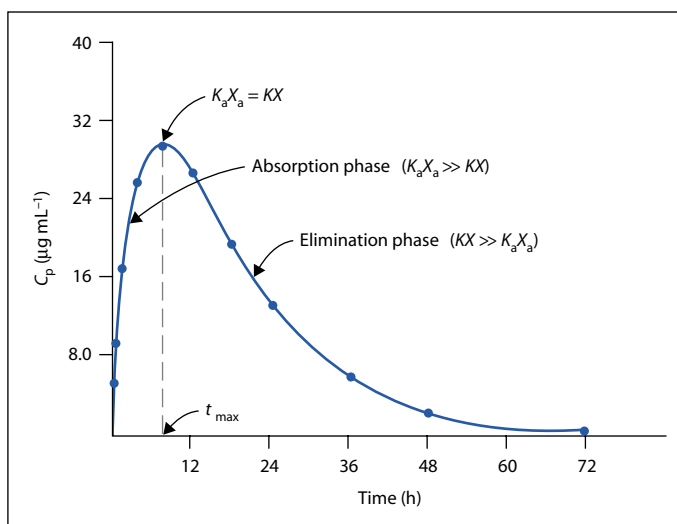
Figure 6.21 Plasma concentration (C_p) versus time on rectilinear paper for administration of 500 mg dose of drug using values in Table 6.5. X_a, amount of absorbable drug at the absorption site at time t; K_a and K, first-order absorption and elimination rate constants, respectively; K_aX_a and KX, first-order rates of absorption and elimination, respectively.

Table 6.5 Plasma concentration–time data following oral administration of 500 mg dose of a drug that is excreted unchanged and completely absorbed ($F = 1.0$); determine all pharmacokinetic parameters

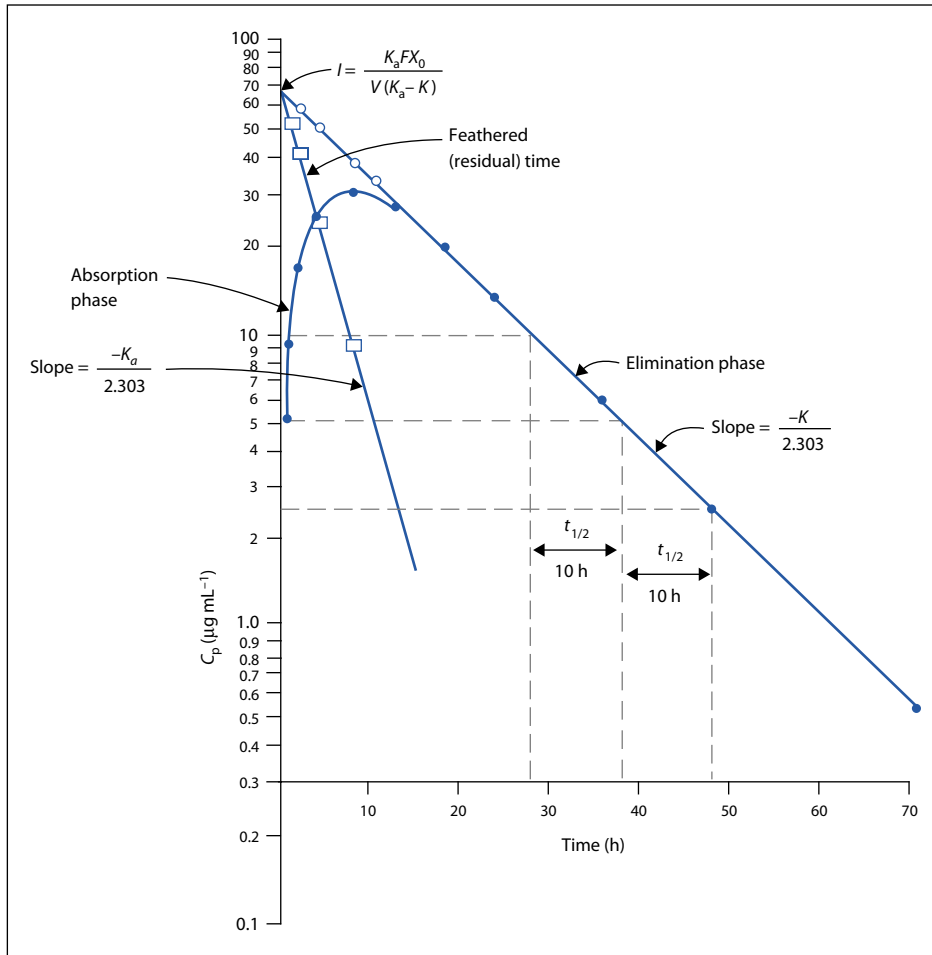| Time (h)	Plasma concentration (μg mL^{-1})
0.5	5.36
1.0	9.35
2.0	17.18
4.0	25.78
8.0	29.78
12.0	26.63
18.0	19.40
24.0	13.26
36.0	5.88
48.0	2.56
72.0	0.49

Table 6.6 Method of residuals to calculate the difference between the extrapolated and observed plasma concentrations values using the data in Table 6.5 plotted as in Fig. 6.20

Time (h)	$(C_p)_{extrap}$ (μg mL^{-1})	$(C_p)_{obs}$ (μg mL^{-1})	$(C_p)_{diff}$ (μg mL^{-1})
0.5	65.0	5.36	59.64
1.0	62.0	9.95	52.05
2.0	58.0	17.18	40.82
4.0	50.0	25.78	24.22
8.0	39.0	29.78	9.22

$(C_p)_{extrap}$, extrapolated plasma concentrations; $(C_p)_{obs}$, observed plasma concentrations; $(C_p)_{diff}$, difference between extrapolated and observed values for each time in the absorption phase.

Note that administration of a different dose (250 or 750 mg) of the same drug via same dosage form, same formulation, and same route of administration will have absolutely no effect on peak time. However, administration of the same drug (either same or different dose) via a different dosage form, different routes of administration, and/or different formulation may result in a different peak time.

If we administer 500 mg of the same drug to the same subject by the intramuscular route and find the absorption rate constant (K_a) to be 0.523 h^{-1}, will

Since $K_a = 0.247$ h^{-1} and $K = 0.0693$ h^{-1},

$$t_{max} = \frac{\ln(0.247/0.0693)}{(0.247 - 0.0693)} = \frac{\ln(3.562)}{(0.1777)}.$$

Since $\ln 3.562 = 1.2703$,

$$t_{max} = 1.2703/0.1777 = 7.148 \text{ h}.$$

Figure 6.22 Plasma concentration (C_p) versus time on semilogarithmic paper for administration of 500 mg dose of drug using values in Table 6.5. The observed plasma concentrations (●) are extrapolated back (○) and then the feathered (residual) method is used to get the residual concentration (□) plot. Other abbreviations as in Fig. 6.6.

the peak time be shorter or longer? Please consider this.

The peak plasma concentration can be obtained from Fig. 6.21: $(C_p)_{max} = 29.78$ µg mL^{-1}. Or it can be calculated using Eq. (6.33):

$$(C_p)_{max} = \frac{K_a F X_0}{V(K_a - K)}(e^{-K t_{max}} - e^{-K_a t_{max}})$$

$$\frac{K_a F X_0}{V(K_a - K)} = \text{Intercept} = 67 \text{ mg mL}^{-1}.$$

We know that $K_a = 0.247$ h^{-1}, $K = 0.0693$ h^{-1} and $t_{max} = 7.148$ h. Substituting these values in the

equation gives:

$$(C_p)_{max} = 67 \text{ µg mL}^{-1}$$
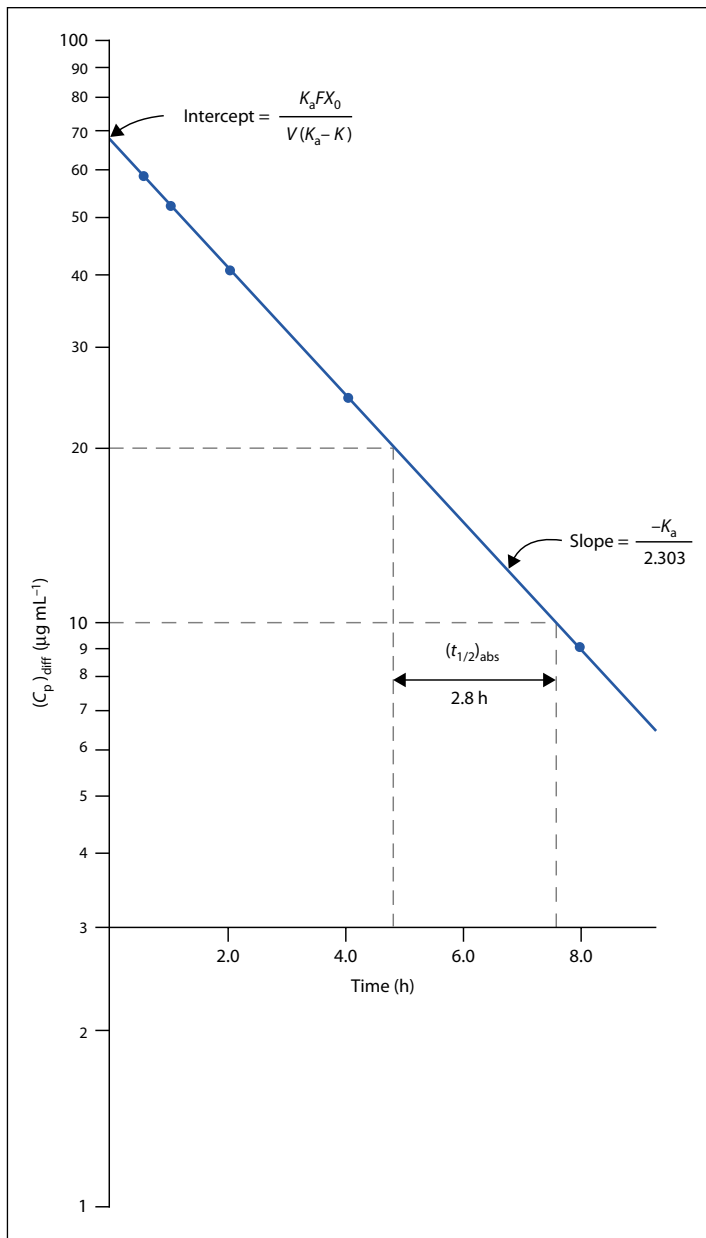$$\times (e^{-0.0693 \times 7.148} - e^{-0.247 \times 7.148})$$
$$(C_p)_{max} = 67 \text{ µg mL}^{-1}(e^{-0.495} - e^{-1.765}).$$

We have

$$e^{-0.495} = 0.6126 \quad \text{and} \quad e^{-1.765} = 0.1720.$$

Hence, $(C_p)_{max} = 67$ µg mL^{-1} (0.6126 − 0.1720) = 67 µg mL^{-1}(0.4406) = 29.52 µg mL^{-1}.

Please note that peak plasma concentration is *always* directly proportional to the administered

Figure 6.23 Feathered (residual) plot of the differences $[(C_p)_{diff}]$ between the observed and the extrapolated plasma concentrations in Fig. 6.20 (as given in Table 6.6, column 4) plotted against time on semilogarithmic paper. $(t_{1/2})_{abs}$, absorption half life; other abbreviations as in Fig. 6.6.

dose of a drug (assuming the first-order process and passive diffusion are operative). Therefore, following the administration of 250 mg and 750 mg doses of the same drug via the same formulation, the same dosage form, and the same route of administration, plasma concentrations of 14.76 µg mL^{-1} and 44.28 µg mL^{-1}, respectively, will result.

It is important to recognize that the intercept of plasma concentration versus time data will have concentration units; therefore, the value of the intercept will also be directly proportional to the administered dose of the drug. In this exercise, therefore, the values of the intercepts of the plasma concentration versus time data for a 250 mg and 750 mg dose will be 33.5 µg mL^{-1} and 100.5 µg mL^{-1}, respectively.

- Is it true that the larger the difference between the intercept of the plasma concentration–time data and the peak plasma concentration, the slower is the rate of absorption and longer is the peak time? (Hint: see Fig. 6.14).
- Is it accurate to state that the larger the difference between the intercept of the plasma concentration time data and the peak plasma concentration, the larger is the difference between the absorption rate constant and the elimination rate constant? Consider why this is *not* true.

6.13 Flip-flop kinetics

Flip-flop kinetics is an exception to the usual case in which the absorption rate constant is greater than the elimination rate constant ($K_a > K$). For a drug absorbed by a slow first-order process, such as certain types of sustained-release formulations, the situation may arise where the elimination rate constant is greater than the absorption rate constant ($K > K_a$). Since the terminal linear slope of plasma drug concentration versus time plotted on semilogarithmic coordinates always represents the slower process, this slope is related to the absorption rate constant; the slope of the feathered line will be related to the elimination rate constant. Figure 6.24 compares a regular and a flip-flop oral absorption model.

In this simulation, the lower graph (solid line) represents the flip-flop situation. Because of a larger value for the elimination rate constant, the flip-flop
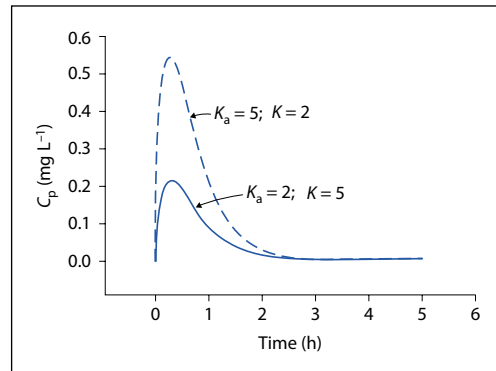
Figure 6.24 Comparison of a regular (– – –) and a flip-flop (—) oral absorption model. In this simulation, the apparent volume of distribution/fraction of administered dose available to reach the general circulation and the dose are the same for both plots; but the values of the elimination rate constant (K) and the absorption rate constant (K_a) are flipped.

graph has both a smaller AUC and a smaller $(C_p)_{max}$ than the normal graph. However, both the regular and flip-flop curves have the same shape and the same t_{max} (0.305 h).

When fitting plasma drug concentration data to the one-compartment extravascular model by nonlinear regression, estimates for the elimination rate constant and absorption rate constant from regular and flip-flop approaches will have exactly the same correlation coefficient, indicating an equally good fit to the model. Whether the computerized fit gives the regular or the flip-flop result is simply a matter of which initial parameter estimates were input into the computer.

So, is there any way to tell which fit represents reality?

One sure way is to have an unambiguous value of the drug's elimination half life (and therefore of the elimination rate constant) determined from a study in which the drug is administered intravenously. Another strong indication that the regular model is the correct model is the situation where the extravascular administration is of a type that should not have any kind of slow, extended absorption. An example of this is an immediate release tablet or a capsule. This type of dosage form should not have an absorption half life that is slower than its elimination half life.