Note: Large images and tables on this page may necessitate printing in landscape mode.

Applied Biopharmaceutics & Pharmacokinetics > Chapter 7. Pharmacokinetics of Oral Absorption >

PHARMACOKINETICS OF DRUG ABSORPTION

The pharmacokinetics of drugs following intravenous drug administration are more simple to model compared to extravascular delivery (see , , , , , and). Extravascular delivery routes, particularly oral dosing, are important and popular means of drug administration. Unlike intravenous administration, in which the drug is injected directly into the plasma, pharmacokinetic models after extravascular drug administration must consider systemic drug absorption from the site of administration, eg, the lung, the gut, etc., into the plasma. Extravascular drug delivery is further complicated by variables at the absorption site, including possible drug degradation and significant inter- and intrapatient differences in the rate and extent of absorption. Absorption and metabolic variables are characterized using pharmacokinetic methods. The variability in systemic drug absorption can be minimized to some extent by proper biopharmaceutical design of the dosage form to provide predictable and reliable drug therapy (, , and). The major advantage of intravenous administration is that the rate and extent of systemic drug input is carefully controlled.

The systemic drug absorption from the gastrointestinal (GI) tract or from any other extravascular site is dependent on (1) the physicochemical properties of the drug, (2) the dosage form used, and (3) the anatomy and physiology of the absorption site. Although this chapter will focus primarily on oral dosing, the concepts discussed here may be easily extrapolated to other extravascular routes. For oral dosing, such factors as surface area of the GI tract, stomach-emptying rate, GI mobility, and blood flow to the absorption site all affect the rate and the extent of drug absorption. In pharmacokinetics, the overall rate of drug absorption may be described as either a first-order or zero-order input process. Most pharmacokinetic models assume first-order absorption unless an assumption of zero-order absorption improves the model significantly or has been verified experimentally.

The rate of change in the amount of drug in the body, dD_B/dt, is dependent on the relative rates of drug absorption and elimination (). The net rate of drug accumulation in the body at any time is equal to the rate of drug absorption less the rate of drug elimination, regardless of whether absorption is zero-order or first-order.
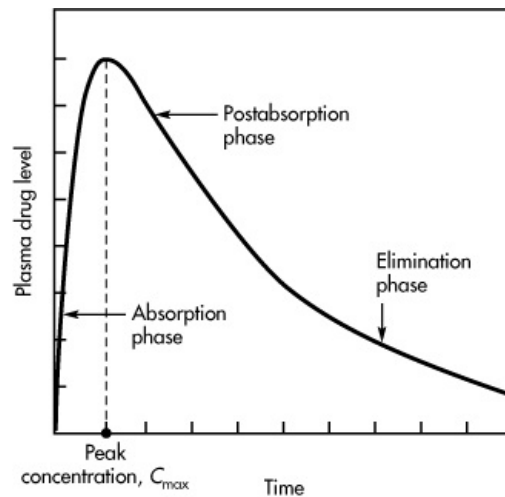
Figure 7-1.

Source: Shargel S, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 5th Edition: http://www.accesspharmacy.com
Copyright © The McGraw-Hill Companies, Inc. All rights reserved.
Model of drug absorption and elimination.

$$\frac{dD_B}{dt} = \frac{dD_{GI}}{dt} - \frac{dD_E}{dt} \qquad (7.1)$$

Where D_{GI} is amount of drug in the gastrointestinal tract and D_E is amount of drug eliminated. A plasma level–time curve showing drug adsorption and elimination rate processes is given in . During the *absorption phase* of a plasma level–time curve (), the rate of drug absorption is greater than the rate of drug elimination. Note that during the absorption phase, elimination occurs *whenever* drug is present in the plasma, even though absorption predominates.

Figure 7-2.

Plasma level–time curve for a drug given in a single oral dose. The drug absorption and elimination phases of the curve are shown.

$$\frac{dD_{GI}}{dt} > \frac{dD_E}{dt} \qquad (7.2)$$

At the *peak drug concentration* in the plasma () the rate of drug absorption just equals the rate of drug elimination, and there is no net change in the amount of drug in the body.

$$\frac{dD_{GI}}{dt} = \frac{dD_E}{dt} \qquad (7.3)$$

Immediately after the time of peak drug absorption, some drug may still be at the absorption site (ie, in the GI tract or other site of administration). However, the rate of drug elimination at this time is faster than the rate of absorption, as represented by the *postabsorption phase* in .

$$\frac{dD_{GI}}{dt} < \frac{dD_E}{dt} \qquad (7.4)$$

When the drug at the absorption site becomes depleted, the rate of drug absorption approaches zero, or $dD_{GI}/dt = 0$. The plasma level–time curve (now the *elimination phase*) then represents only the elimination of drug from the body, usually a first-order process. Therefore, during the elimination phase the rate of change in the amount of drug in the body is described as a first-order process,
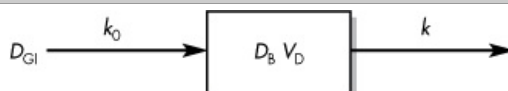
$$\frac{dD_B}{dt} = -kD_B \qquad (7.5)$$

where k is the first-order elimination rate constant.

ZERO-ORDER ABSORPTION MODEL

Zero-order drug absorption from the dosing site into the plasma usually occurs when either the drug is absorbed by a saturable process or a zero-order controlled-release delivery system is used (see). The pharmacokinetic model assuming zero-order absorption is described in . In this model, drug in the gastrointestinal tract, D_{GI}, is absorbed systemically at a constant rate, k_0.

Drug is simultaneously and immediately eliminated from the body by a first-order rate process defined by a first-order rate constant, k. This model is analogous to that of the administration of a drug by intravenous infusion ().

Figure 7-3.

One-compartment pharmacokinetic model for zero-order drug absorption and first-order drug elimination.

The rate of first-order elimination at any time is equal to $D_B k$. The rate of input is simply k_0. Therefore, the net change per unit time in the body can be expressed as

$$\frac{dD_B}{dt} = k_0 - kD_B \qquad (7.6)$$

Integration of this equation with substitution of $V_D C_p$ for D_B produces

$$C_P = \frac{k_0}{V_D k}\left(1 - e^{-kt}\right) \qquad (7.7)$$

The rate of drug absorption is constant until the amount of drug in the gut, D_{GI}, is depleted. The time for complete drug absorption to occur is equal to D_{GI}/k_0. After this time, the drug is no longer available for absorption from the gut, and Equation 7.7 no longer holds. The drug concentration in the plasma subsequently declines in accordance with a first-order elimination rate process.

FIRST-ORDER ABSORPTION MODEL

Although zero-order absorption can occur, absorption is usually assumed to be a first-order process. This model assumes a first-order input across the gut wall and first-order elimination from the body (). This model applies mostly to the oral absorption of drugs in solution or rapidly dissolving dosage (immediate release) forms such as tablets, capsules, and suppositories. In addition, drugs given by intramuscular or subcutaneous aqueous injections may also be described using a first-order process.

Figure 7-4.

Source: Shargel S, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 5th Edition: http://www.accesspharmacy.com
Copyright © The McGraw-Hill Companies, Inc. All rights reserved.

One-compartment pharmacokinetic model for first-order drug absorption and first-order elimination.

In the case of a drug given orally, the dosage form first disintegrates if it is given as a solid, then the drug dissolves into the fluids of the GI tract. Only drug in solution is absorbed into the body. The rate of disappearance of drug from the gastrointestinal tract is described by

$$\frac{dD_{GI}}{dt} = -k_a D_{GI} F \qquad (7.8)$$

where k_a is the first-order absorption rate constant from the GI tract, F is the fraction absorbed, and D_{GI} is the amount of drug in solution in the GI tract at any time t. Integration of the differential equation (7.8) gives

$$\frac{dD_{GI}}{dt} = D_0 e^{-k_a t} \qquad (7.9)$$

where D_0 is the dose of the drug.

The rate of drug elimination is described by a first-order rate process for most drugs and is equal to $-kD_B$. The rate of drug change in the body, dD_B/dt, is therefore the rate of drug in, minus the rate of drug out—as given by the differential equation, Equation 7.10:

$$\frac{dD_B}{dt} = \text{rate in} - \text{rate out}$$

$$\qquad (7.10)$$

$$\frac{dD_B}{dt} = Fk_a D_{GI} - kD_B$$

where F is the fraction of drug absorbed systemically. Since the drug in the gastrointestinal tract also follows a first-order decline (ie, the drug is absorbed across the gastrointestinal wall), the amount of drug in the gastrointestinal tract at any time t is equal to $D_0 e^{-k_a t}$.

$$\frac{dD_B}{dt} = Fk_a D_0 e^{-k_a t} - kD_B$$

The value of F may vary from 1 for a fully absorbed drug to 0 for a drug that is completely unabsorbed. This equation can be integrated to give the general oral absorption equation for calculation of the drug concentration (C_p) in the plasma at any time t, as shown below.

$$C_P = \frac{Fk_a D_0}{V_D(k_a - k)}\left(e^{-kt} - e^{-k_a t}\right) \qquad (7.11)$$

A typical plot of the concentration of drug in the body after a single oral dose is presented in .

Figure 7-5.
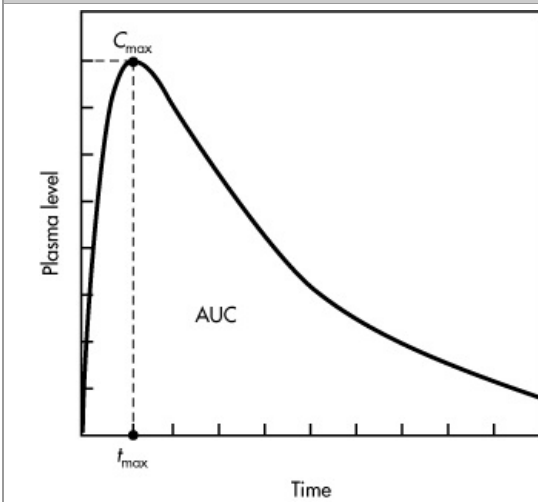
Typical plasma level–time curve for a drug given in a single oral close.

The maximum plasma concentration after oral dosing is C_{max}, and the time needed to reach maximum concentration is t_{max}. The t_{max} is independent of dose and is dependent on the rate constants for absorption (k_a) and elimination (k) (Eq. 7.13a). At C_{max}, sometimes called *peak concentration*, the rate of drug absorbed is equal to the rate of drug eliminated. Therefore, the net rate of concentration change is equal to zero. At C_{max}, the rate of concentration change can be obtained by differentiating Equation 7.12, as follows:

$$dC_p/dt = \frac{k_a D_0 F}{V_D(k_a - k)}\left(-ke^{-kt} + k_a e^{-k_a t}\right) = 0 \qquad (7.12)$$

This can be simplified as follows:

$$-ke^{-kt} + k_a e^{-k_a t} = 0 \qquad \text{or} \qquad ke^{-kt} = k_a e^{-k_a t} \qquad (7.13)$$

$$\ln k - kt = \ln k_a - k_a t$$

$$t_{max} = \frac{\ln k_a - \ln k}{k_a - k} = \frac{\ln(k_a/k)}{k_a - k}$$

$$t_{max} = \frac{2.3 \log(k_a/k)}{k_a - k} \qquad (7.13a)$$

As shown in Equation 7.13a, the time for maximum drug concentration, t_{max}, is dependent only on the rate constants k_a and k. In order to calculate C_{max}, the value for t_{max} is determined via Equation 7.13a and then substituted into Equation 7.11, solving for C_{max}. Equation 7.11 shows that C_{max} is directly proportional to the dose of drug given (D_0) and the fraction of drug absorbed (F). Calculation of t_{max} and C_{max} is usually necessary, since direct measurement of the maximum drug concentration may not be possible due to improper timing of the serum samples.

The first-order elimination rate constant may be determined from the elimination phase of the plasma level–time curve (). At later time intervals, when drug absorption has been completed, ie, $e^{-k_a t} \approx 0$, Equation 7.11 reduces to

$$C_p = \frac{F k_a D_0}{V_D(k_a - k)} e^{-kt} \qquad (7.14)$$

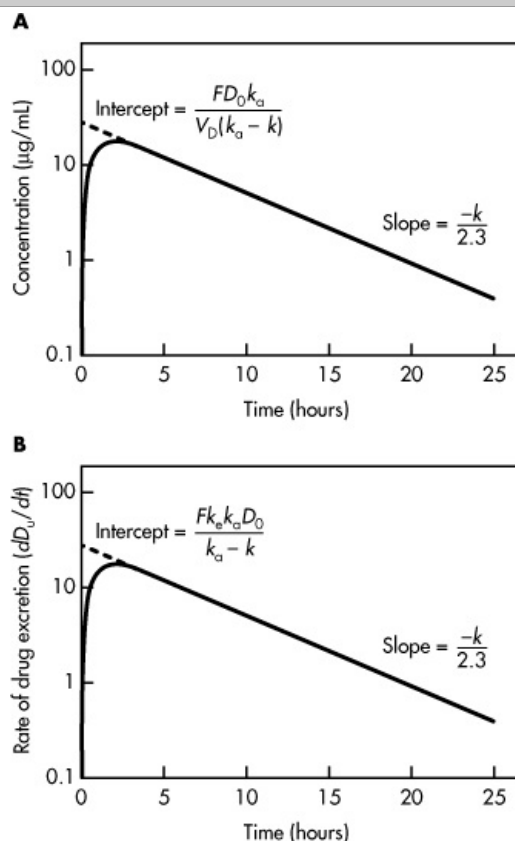Taking the natural logarithm of this expression,

$$\ln C_p = \ln \frac{F k_a D_0}{V_D(k_a - k)} - kt \qquad (7.15)$$

Substitution of common logarithms gives

$$\log C_{\mathrm{p}} = \log \frac{Fk_a D_0}{V_D(k_a - k)} - \frac{kt}{2.3} \qquad (7.16)$$

With this equation, a graph constructed by plotting log C_{p} versus time will yield a straight line with a slope of $-k/2.3$ ().

Figure 7-6.

Source: Shargel S, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 5th Edition: http://www.accesspharmacy.com

A. Plasma drug concentration versus time, single oral dose. **B.** Rate of urinary drug excretion versus time, single oral dose.

With a similar approach, urinary drug excretion data may also be used for calculation of the first-order elimination rate constant. The rate of drug excretion after a single oral dose of drug is given by

$$\frac{dD_u}{dt} = \frac{Fk_a k_e D_0}{k_a - k} - \left(e^{-kt} - e^{-k_a t}\right) \qquad (7.17)$$

where dD_u/dt = rate of urinary drug excretion, k_e = first-order renal excretion constant, and F = fraction of dose absorbed.

A graph constructed by plotting dD_u/dt versus time will yield a curve identical in appearance to the plasma level–time curve for the drug (). After drug absorption is virtually complete, $-e^{-k_a t}$ approaches zero, and Equation 7.17 reduces to

$$\frac{dD_u}{dt} = \frac{Fk_a k_e D_0}{k_a - k} e^{-kt} \qquad (7.18)$$

Figure 7-7.
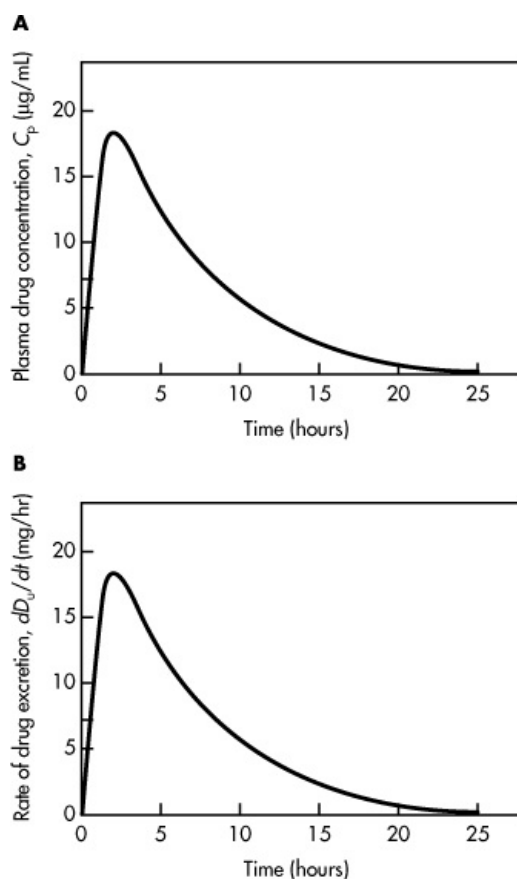
A

B

A. Plasma drug concentration versus time, single oral dose. **B.** Rate of urinary drug excretion versus time, single oral dose.

Taking the natural logarithm of both sides of this expression and substituting for common logarithms, Equation 7.18 becomes

$$\log \frac{dD_u}{dt} = \log \frac{F k_a k_e D_0}{k_a - k} - \frac{kt}{2.3} \qquad (7.19)$$

When log (dD_u/dt) is plotted against time, a graph of a straight line is obtained with a slope of $-k/2.3$ (). Because the rate of urinary drug excretion, dD_u/dt, cannot be determined directly for any given time point, an average rate of urinary drug excretion is obtained (see also), and this value is plotted against the midpoint of the collection period for each urine sample.

To obtain the cumulative drug excretion in the urine, Equation 7.17 must be integrated, as shown below.
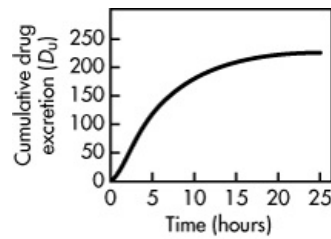
$$D_u = \frac{F k_a k_e D_0}{k_a - k} \left(\frac{e^{-k_a t}}{k_a} - \frac{e^{-kt}}{k} \right) + \frac{F k_e D_0}{k} \qquad (7.20)$$

A plot of D_u versus time will give the urinary drug excretion curve described in . When all of the drug has been excreted, at $t = \infty$. Equation 7.20 reduces to

$$D_u^\infty = \frac{F k_e D_0}{k} \qquad (7.21)$$

where D_u^∞ is the maximum amount of active or parent drug excreted.

Figure 7-8.

Cumulative urinary drug excretion versus time, single oral dose. Urine samples are collected at various time periods after the dose. The amount of drug excreted in each sample is added to the amount of drug recovered in the previous urine sample (cumulative addition). The total amount of drug recovered after all the drug is excreted is D^{∞}_u.

Determination of Absorption Rate Constants from Oral Absorption Data
METHOD OF RESIDUALS

Assuming $k_a \gg k$ in Equation 7.11, the value for the second exponential will become insignificantly small with time (ie, $e^{-k_a t} \approx 0$) and can therefore be omitted. When this is the case, drug absorption is virtually complete. Equation 7.11 then reduces to Equation 7.22.

$$C_P = \frac{F k_a D_0}{V_D (k_a - k)} e^{-kt} \qquad (7.22)$$

From this, one may also obtain the intercept of the y axis ().

$$\frac{F k_a D_0}{V_D (k_a - k)} = A$$

where A is a constant. Thus, Equation 7.22 becomes

$$C_P = A e^{-kt} \qquad (7.23)$$

This equation, which represents first-order drug elimination, will yield a linear plot on semilog paper. The slope is equal to $-k/2.3$. The value for k_a can be obtained by using the method of residuals or a feathering technique, as described in . The value of k_a is obtained by the following procedure:

1. Plot the drug concentration versus time on semilog paper with the concentration values on the logarithmic axis ().

2. Obtain the slope of the terminal phase (line BC,) by extrapolation.

3. Take any points on the upper part of line BC (eg, $x'_1, x'_2, x'_3, \ldots$) and drop vertically to obtain corresponding points on the curve (eg, $x_1, x_2, x_3, \ldots$).

4. Read the concentration values at x_1 and x'_1, x_2 and x'_2, x_3 and x'_3, and so on. Plot the values of the differences at the corresponding time points $\Delta_1, \Delta_2, \Delta_3, \ldots$. A straight line will be obtained with a slope of $-k_a/2.3$ ().

Figure 7-9.
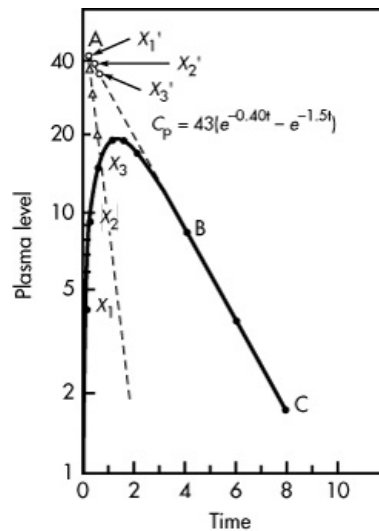
Plasma level–time curve for a drug demonstrating first-order absorption and elimination kinetics. The equation of the curve is obtained by the method of residuals.

When using the method of residuals, a minimum of three points should be used to define the straight line. Data points occurring shortly after t_{max} may not be accurate, because drug absorption is still continuing at that time. Because this portion of the curve represents the postabsorption phase, only data points from the elimination phase should be used to define the rate of drug absorption as a first-order process.

If drug absorption begins immediately after oral administration, the residual lines obtained by feathering the plasma level–time curve (as shown in) will intersect on the y axis at point A. The value of this y intercept, A, represents a hybrid constant composed of k_a, k, V_D, and FD_0. The value of A has no direct physiologic meaning (see Eq. 7.23).

$$A = \frac{Fk_aD_0}{V_D(k_a - k)}$$

The value for A, as well as the values for k and k_a, may be substituted back into Equation 7.11 to obtain a general theoretical equation that will describe the plasma level–time curve.

LAG TIME

In some individuals, absorption of drug after a single oral dose does not start immediately, due to such physiologic factors as stomach-emptying time and intestinal motility. The time delay prior to the commencement of first-order drug absorption is known as *lag time*.

The lag time for a drug may be observed if the two residual lines obtained by feathering the oral absorption plasma level–time curve intersect at a point greater than $t = 0$ on the x axis. The time at the point of intersection on the x axis is the lag time ().
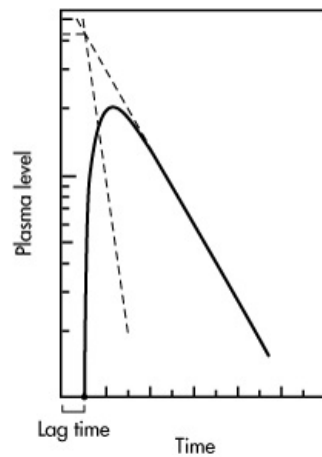
Figure 7-10.

The lag time can be determined graphically if the two residual lines obtained by feathering the plasma level–time curve intersect at a point where $t > 0$.

The lag time, t_0, represents the beginning of drug absorption and should not be confused with the pharmacologic term *onset time*, which represents latency, eg, the time required for the drug to reach minimum effective concentration.

Two equations can adequately describe the curve in . In one, the lag time t_0 is subtracted from each time point, as shown in Equation 7.24.

$$C_P = \frac{Fk_aD_0}{V_D(k_a - k)}\left(e^{-k(t-t_0)} - e^{-k_a(t-t_0)}\right) \qquad (7.24)$$

where $Fk_aD_0/V_D(k_a-k)$ is the y value at the point of intersection of the residual lines in .

The second expression that describes the curve in omits the lag time, as follows:

$$C_P = Be^{-kt} - Ae^{-k_at} \qquad (7.25)$$

where A and B represents the intercepts on the y axis after extrapolation of the residual lines for absorption and elimination, respectively.

FLIP-FLOP OF K_A AND K

In using the method of residuals to obtain estimates of k_a and k, the terminal phase of an oral absorption curve is usually represented by k whereas the steeper slope is represented by k_a (). In a few cases, the elimination rate constant k obtained from oral absorption data does not agree with that obtained after intravenous bolus injection. For example, the k obtained after an intravenous bolus injection of a bronchodilator was 1.72 hr^{-1}, whereas the k calculated after oral administration was 0.7 hr^{-1} (). When k_a was obtained by the method of residuals, the rather surprising result was that the k_a was 1.72 hr^{-1}.

Figure 7-11.
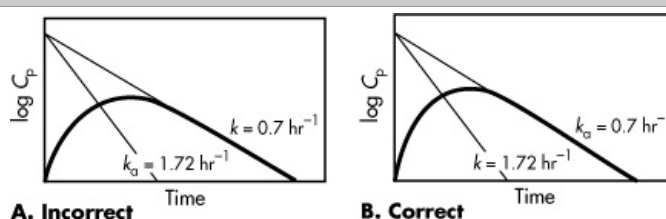
Flip-flop of k_a and k. Because $k > k_a$, the right-hand figure and slopes represent the correct values for k_a and k.

Apparently, the k_a and k obtained by the method of residuals has been interchanged. This phenomenon is called *flip-flop* of the absorption and elimination rate constants. Flip-flop, or the reversal of the rate constants, may occur whenever k_a and k are estimated from oral drug absorption data. Use of computer methods does not ensure against flip-flop of the two constants estimated.

In order to demonstrate unambiguously that the steeper curve represents the elimination rate for a drug given extravascularly,

125 / 599

the drug must be given by intravenous injection into the same patient. After intravenous injection, the decline in plasma drug levels over time represents the true elimination rate. The relationship between k_a and k on the shape of the plasma drug concentration–time curve for a constant dose of drug given orally is shown in .

Most of the drugs observed to have flip-flop characteristics are drugs with fast elimination (ie, $k > k_a$). Drug absorption of most drug solutions or fast-dissolving products are essentially complete or at least half-complete within an hour (ie, absorption half-life of 0.5 or 1 hr, corresponding to a k_a of 1.38 hr^{-1} or 0.69 hr^{-1}). Because most of the drugs used orally have longer elimination half-lives compared to absorption half-lives, the assumption that the smaller slope or smaller rate constant (ie, the terminal phase of the curve in) should be used as the elimination constant is generally correct.

For drugs that have a large elimination rate constant ($k > 0.69$ hr^{-1}), the chance for flip-flop of k_a and k is much greater. The drug isoproterenol, for example, has an oral elimination half-life of only a few minutes, and flip-flop of k_a and k has been noted (). Similarly, salicyluric acid was flip-flopped when oral data were plotted. The k for salicyluric acid was much larger than its k_a (). Many experimental drugs show flip-flop of k and k_a, whereas few marketed oral drugs do. Drugs with a large k are usually considered to be unsuitable for an oral drug product due to their large elimination rate constant, corresponding to a very short elimination half-life. An extended-release drug product may slow the absorption of a drug, such that the k_a is smaller than the k and producing a flip-flop situation.

DETERMINATION OF K$_A$ BY PLOTTING PERCENT OF DRUG UNABSORBED VERSUS TIME (WAGNER–NELSON METHOD)

After a single oral dose of a drug, the total dose should be completely accounted for in the amount present in the body, the amount present in the urine, and the amount present in the GI tract. Therefore, dose (D_0) is expressed as follows:

$$D_0 = D_{GI} + D_B + D_u \qquad (7.26)$$

Let Ab = D_B + D_u = amount of drug absorbed and let Ab$^\infty$ = amount of drug absorbed at $t = \infty$. At any given time the fraction of drug absorbed is Ab/Ab$^\infty$, and the fraction of drug unabsorbed is 1 – (Ab/Ab$^\infty$). The amount of drug excreted at any time t can be calculated as

$$D_u = kV_D[\text{AUC}]_0^t \qquad (7.27)$$

The amount of drug in the body (D_B), at any time, = $C_p V_D$. At any time t, the amount of drug absorbed (Ab) is

$$\text{Ab} = C_p V_D + kV_D[\text{AUC}]_0^t \qquad (7.28)$$

At $t = \infty$, $C^\infty_p = 0$ (ie, plasma concentration is negligible), and the total amount of drug absorbed is

$$\text{Ab}^\infty = 0 + kV_D[\text{AUC}]_0^\infty \qquad (7.29)$$

The fraction of drug absorbed at any time is

$$\frac{\text{Ab}}{\text{Ab}^\infty} = \frac{C_p V_D + kV_D[\text{AUC}]_0^t}{kV_D[\text{AUC}]_0^\infty} \qquad (7.30)$$

$$\frac{\text{Ab}}{\text{Ab}^\infty} = \frac{C_p + k[\text{AUC}]_0^t}{k[\text{AUC}]_0^\infty} \qquad (7.31)$$

The fraction unabsorbed at any time t is

$$1 - \frac{\text{Ab}}{\text{Ab}^\infty} = 1 - \frac{C_p + k[\text{AUC}]_0^t}{k[\text{AUC}]_0^\infty} \qquad (7.32)$$

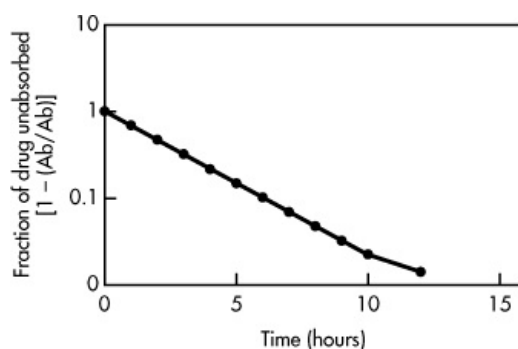The drug remaining in the GI tract at any time t is

$$D_{GI} = D_0 e^{-k_a t} \qquad (7.33)$$

Therefore, the fraction of drug remaining is

$$\frac{D_{GI}}{D_0} = e^{-k_a t} \qquad \log \frac{D_{GI}}{D_0} = \frac{-k_a t}{2.3} \qquad (7.34)$$

Because D_{GI}/D_0 is actually the fraction of drug *unabsorbed*—that is, 1 – (Ab/Ab$^\infty$)—a plot of 1 – (Ab/Ab$^\infty$) versus time gives $-k_a/2.3$ as the slope ().

Figure 7-12.

Semilog graph of data in , depicting the fraction of drug unabsorbed versus time using the Wagner–Nelson method.

The following steps should be useful in determination of k_a:

1. Plot log concentration of drug versus time.

2. Find k from the terminal part of the slope when the slope = $-k/2.3$.

3. Find $[AUC]_0^t$ by plotting C_p versus t.

4. Find $k[AUC]_0^t$ by multiplying each $[AUC]_0^t$ by k.

5. Find $[AUC]_0^\infty$ by adding up all the [AUC] pieces, from $t = 0$ to $t = \infty$

6. Determine the $1 - (Ab/Ab^\infty)$ value corresponding to each time point t by using .

7. Plot $1 - (Ab/Ab^\infty)$ versus time on semilog paper, with $1 - (Ab/Ab^\infty)$ on the logarithmic axis.

Table 7.1 Blood Concentrations and Associated Data for a Hypothetical Drug

Time t_n (hr)	Concentration C_P (μg/mL)	$[AUC]_{t_{n-1}}^{t_n}$	$[AUC]_0^t$	$k[AUC]_0^t$	$C_p + k[AUC]_0^t$	$\dfrac{Ab}{Ab^\infty}$	$\left(1 - \dfrac{Ab}{Ab^\infty}\right)$
0	0.	0.	0.				1.000
1	3.13	1.57	1.57	0.157	3.287	0.328	0.672
2	4.93	4.03	5.60	0.560	5.490	0.548	0.452
3	5.86	5.40	10.99	1.099	6.959	0.695	0.305
4	6.25	6.06	17.05	1.705	7.955	0.794	0.205
5	6.28	6.26	23.31	2.331	8.610	0.856	0.140
6	6.11	6.20	29.51	2.951	9.061	0.905	0.095
7	5.81	5.96	35.47	3.547	9.357	0.934	0.066
8	5.45	5.63	41.10	4.110	9.560	0.955	0.045
9	5.06	5.26	46.35	4.635	9.695	0.968	0.032
10	4.66	4.86	51.21	5.121			
12	3.90	8.56	59.77	5.977			
14	3.24	7.14	66.91	6.691			
16	2.67	5.92	72.83	7.283			
18	2.19	4.86	77.69	7.769			
24	1.20	10.17	87.85	8.785			
28	0.81	4.02	91.87	9.187			
32	0.54	2.70	94.57	9.457			
36	0.36	1.80	96.37	9.637			
48	0.10	2.76	99.13	9.913			

$k = 0.1$ hr^{-1}

If the fraction of drug unabsorbed, $1 - Ab/Ab^\infty$, gives a linear regression line on a semilog graph, then the rate of drug absorption, dD_{GI}/dt, is a first-order process. Recall that $1 - Ab/Ab^\infty$ is equal to dD_{GI}/dt ().

As the drug approaches 100% absorption, C_p becomes very small and difficult to assay accurately. Consequently, the terminal part of the line described by $1 - Ab/Ab^\infty$ versus time tends to become scattered or nonlinear. This terminal part of the curve is excluded, and only the initial linear segment of the curve is used for the estimate of the slope.

PRACTICE PROBLEM

Drug concentrations in the blood at various times are listed in . Assuming the drug follows a one-compartment model, find the k_a, and compare it with the k_a value obtained by the method of residuals.

Solution

The AUC is approximated by the trapezoidal rule. This method is fairly accurate when there are sufficient data points. The area between each time point is calculated as

$$[\text{AUC}]_{t_{n-1}}^{t_n} = \frac{C_{n-1} + C_n}{2}(t_n - t_{n-1}) \qquad (7.35)$$

where C_n and C_{n-1} are concentrations. For example, at $n = 6$, the [AUC] is

$$\frac{6.28 + 6.11}{2}(6 - 5) = 6.20$$

To obtain $[\text{AUC}]_0^\infty$, add all the area portions under the curve from zero to infinity. In this case, 48 hours is long enough to be considered as infinity, because the blood concentration at that point already has fallen to an insignificant drug concentration, 0.1 μg/mL. The rest of the needed information is given in . Notice that k is obtained from the plot of log C_p versus t; k was found to be 0.1 hr^{-1}. The plot of $1-(Ab/Ab^\infty)$ versus t on semilog paper is shown in .

A more complete method of obtaining the is to estimate the residual area from the last observed plasma concentration, C_{p_n} at t_n to time equal to infinity. This equation is

$$[\text{AUC}]_t^\infty = \frac{C_{p_n}}{k} \qquad (7.36)$$

The total $[\text{AUC}]_0^\infty$ is the sum of the areas obtained by the trapezoidal rule, $[\text{AUC}]_0^\infty$, and the residual area $[\text{AUC}]_t^\infty$, as described in the following expression:

$$[\text{AUC}]_0^\infty = [\text{AUC}]_0^t + [\text{AUC}]_t^\infty \qquad (7.37)$$

ESTIMATION OF K_A FROM URINARY DATA

The absorption rate constant may also be estimated from urinary excretion data, using a plot of percent of drug unabsorbed versus time. For a one-compartment model:

Ab = total amount of drug absorbed—
    that is, the amount of drug in the body
    plus the amount of drug excreted
D_B = amount of drug in the body
D_u = amount of unchanged drug excreted in the urine
C_P = plasma drug concentration
D_E = total amount of drug eliminated (drug and metabolites)
$Ab = D_B + D_E$

$$\qquad (7.38)$$

The differential of Equation 7.38 with respect to time gives

$$\frac{dAb}{dt} = \frac{dD_B}{dt} + \frac{dD_E}{dt} \qquad (7.39)$$

Assuming first-order elimination kinetics with renal elimination constant k_e,

$$\frac{dD_u}{dt} = k_e D_B = k_e V_D C_p \qquad (7.40)$$

Assuming a one-compartment model,

$$V_D C_P = D_B$$

Substituting $V_D C_p$ into Equation 7.39,

$$\frac{dAb}{dt} = V_D \frac{dC_P}{dt} + \frac{dD_E}{dt} \qquad (7.41)$$

And rearranging Equation 7.40,

$$C_P = \frac{1}{k_e V_D}\left(\frac{dD_u}{dt}\right) \qquad (7.42)$$

$$\frac{dC_P}{dt} = \frac{d\left(dD_u/dt\right)}{dt\, k_e V_D} \qquad (7.43)$$

Substituting for dC_p/dt into Equation 7.41 and kD_u/k_e for D_E,

$$\frac{dAb}{dt} = \frac{d\left(D_u/dt\right)}{k_e\, dt} + \frac{k}{k_e}\left(\frac{dD_u}{dt}\right) \qquad (7.44)$$

When the above expression is integrated from zero to time t,

$$Ab_t = \frac{1}{k_e}\left(\frac{dD_u}{dt}\right)t + \frac{k}{k_e}(D_u)t \qquad (7.45)$$

At $t = \infty$ all the drug that is ultimately absorbed is expressed as Ab^∞ and $dD_u/dt = 0$. The total amount of drug absorbed is

$$Ab^\infty = \frac{k}{k_e}D_u^\infty$$

where D^∞_u is the total amount of unchanged drug excreted in the urine.

The fraction of drug absorbed at any time t is equal to the amount of drug absorbed at this time, Ab_t, divided by the total amount of drug absorbed, Ab^∞.

$$\frac{Ab_t}{Ab^\infty} = \frac{(dD_u/dt)_t + k(D_u)_t}{kD_u^\infty} \qquad (7.46)$$

A plot of the fraction of drug unabsorbed, $1 - Ab/Ab^\infty$, versus time gives $-k_a/2.3$ as the slope from which the absorption rate constant is obtained (; refer to Eq. 7-34).

When collecting urinary drug samples for the determination of pharmacokinetic parameters, one should obtain a valid urine collection as discussed in . If the drug is rapidly absorbed, it may be difficult to obtain multiple early urine samples to describe the absorption phase accurately. Moreover, drugs with very slow absorption will have low concentrations, which may present analytical problems.

## EFFECT OF K_A AND K ON C_{MAX}, T_{MAX}, AND AUC

Changes in k_a and k may affect t_{max}, C_{max}, and AUC as shown in . If the values for k_a and k are reversed, then the same t_{max} is obtained, but the C_{max} and AUC are different. If the elimination rate constant is kept at 0.1 hr^{-1} and the k_a changes from 0.2 to 0.6 hr^{-1} (absorption rate increases), then the t_{max} becomes shorter (from 6.93 to 3.58 hr), the C_{max} increases (from 5.00 to 6.99 μg/mL), but the AUC remains constant (100 μg hr/mL). In contrast, when the absorption rate constant is kept at 0.3 hr^{-1} and k changes from 0.1 to 0.5 hr^{-1} (elimination rate increases), then the t_{max} decreases (from 5.49 to 2.55 hr), the C_{max} decreases (from 5.77 to 2.79 μg/mL), and the AUC decreases (from 100 to 20 μg hr/mL). Graphical representations for the relationships of k_a and k on the time for peak absorption and the peak drug concentrations are shown in and .

Table 7.2 Effects of the Absorption Rate Constant and Elimination Rate[a]				
Absorption Rate Constant k_a (hr^{-1})	Elimination Rate Constant k (hr^{-1})	t_{max} (hr)	C_{max} (μg/mL)	AUC (μg hr/mL)
0.1	0.2	6.93	2.50	50
0.2	0.1	6.93	5.00	100
0.3	0.1	5.49	5.77	100
0.4	0.1	4.62	6.29	100
0.5	0.1	4.02	6.69	100
0.6	0.1	3.58	6.99	100
0.3	0.1	5.49	5.77	100
0.3	0.2	4.05	4.44	50
0.3	0.3	3.33	3.68	33.3
0.3	0.4	2.88	3.16	25
0.3	0.5	2.55	2.79	20

t_{max} = peak plasma concentration, C_{max} = peak drug concentration, AUC = area under the curve. Values are based on a single oral dose (100 mg) that is 100% bioavailable (F = 1) and has an apparent V_D of 10 L. The drug follows a one-compartment open model. t_{max} is calculated by Eq. 7.13 and C_{max} is calculated by Eq. 7.11. The AUC is calculated by the trapezoidal rule from 0 to 24 hours.
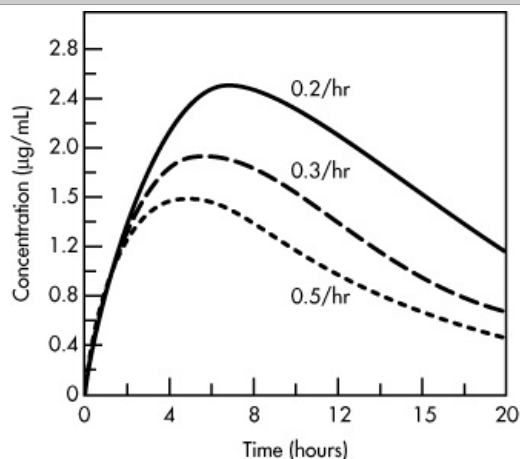
Figure 7-13.
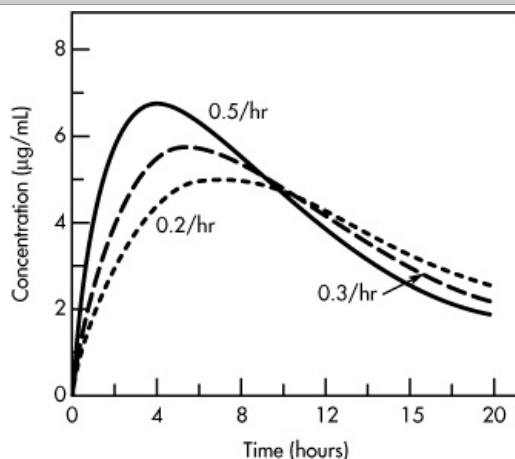
Source: Shargel S, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 5th Edition: http://www.accesspharmacy.com

Effect of a change in the absorption rate constant, k_a, on the plasma drug concentration-versus-time curve. Dose of drug is 100 mg, V_D is 10 L, and k is 0.1 hr^{-1}.

Figure 7-14.

Source: Shargel S, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 5th Edition: http://www.accesspharmacy.com

Effect of a change in the elimination rate constant, k, on the plasma drug concentration-versus-time curve. Dose of drug is 100 mg, V_D is 10 L, and k_a is 0.1 hr^{-1}.

## DETERMINATION OF K_A FROM TWO-COMPARTMENT ORAL ABSORPTION DATA (LOO–RIEGELMAN METHOD)

Plotting the percent of drug unabsorbed versus time to determine the k_a may be calculated for a drug exhibiting a two-compartment kinetic model. As in the method used previously to obtain an estimate of the k_a, no limitation is placed on the order of the absorption process. However, this method does require that the drug be given intravenously as well as orally to obtain all the necessary kinetic constants.

After oral administration of a dose of a drug that exhibits two-compartment model kinetics, the amount of drug absorbed is calculated as the sum of the amounts of drug in the central compartment (D_p) and in the tissue compartment (D_t) and the

amount of drug eliminated by all routes (D_u) ().

$$Ab = D_p + D_t + D_u \qquad (7.47)$$
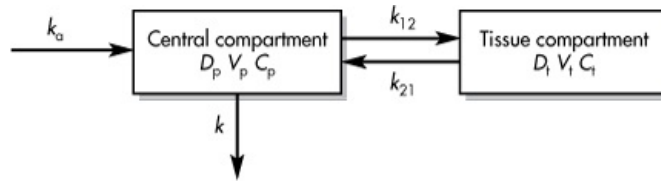
Two-compartment pharmacokinetic mode. Drug absorption and elimination occur from the central compartment.

Each of these terms may be expressed in terms of kinetics constants and plasma drug concentrations, as follows:

$$D_p = V_p C_p \qquad (7.48)$$

$$D_t = V_t C_t \qquad (7.49)$$

$$\frac{dD_u}{dt} = k V_p C_p \qquad (7.50)$$

$$D_u = k V_p [AUC]_0^t$$

Substituting the above expression for D_p and D_u into Equation 7.46,

$$Ab = V_p C_p + D_t + k V_p [AUC]_0^t \qquad (7.51)$$

By dividing this equation by V_p to express the equation on drug concentrations, we obtain

$$\frac{Ab}{V_p} = C_p + \frac{D_t}{V_p} + k[AUC]_0^t \qquad (7.52)$$

At $t = \infty$ this equation becomes

$$\frac{Ab}{V_p} = k[AUC]_0^\infty \qquad (7.53)$$

Equation 7.53 divided by Equation 7.54 gives the fraction of drug absorbed at any time.

$$\frac{Ab}{Ab^\infty} = \frac{C_p + \left(\dfrac{D_t}{V_p}\right) + k[AUC]_0^t}{k[AUC]_0^\infty} \qquad (7.54)$$

A plot of the fraction of drug unabsorbed, $1 - Ab/Ab^\infty$, versus time gives $-k_a/2.3$ as the slope from which the value for the absorption rate constant is obtained (refer to Eq. 7-34).

C_p and $k[AUC]^t_0$ are calculated from a plot of C_p versus time. Values for (D_t/V_p) can be approximated by the Loo–Riegelman method, as follows:

$$(C_t)_{t_n} = \frac{k_{12} \Delta C_p \Delta t}{2} + \frac{k_{12}}{k_{21}}(C_p)_{t_{n-1}}(1 - e^{-k_{21}\Delta t}) + (C_t)_{t_{n-1}} e^{-k_{21}\Delta t} \qquad (7.55)$$

where C_t is D_t/V_p, or apparent tissue concentration; t = time of sampling for sample n; t_{n-1} = time of sampling for the sampling point preceding sample n; and $(C_p)_{t_{n-1}}$ = concentration of drug at central compartment for sample $n - 1$.

Calculation of C_t values is shown in , using a typical set of oral absorption data. After calculation of C_t values, the percent of drug unabsorbed is calculated with Equation 7.54, as shown in . A plot of percent of drug unabsorbed versus time on semilog graph paper gives a k_a of approximately 0.5 hr^{-1}.

Table 7.3 Calculation of C_t Values[a]

$(C_t)_{t_n}$	$(t)_{t_n}$	ΔC_p	Δt	$\dfrac{(k_{12}\Delta C_p \Delta t)}{2}$	$(C_p)_t$	$(k_{12}/k_{21}) \times (1 - e^{-k})$	$(C_p)_{t_{n-1}} k_{12}/k_{21} \times (1 - e^{-k})$	$(C_t)_{t_{n-1}} e^{-k}$	$(C_t)_{t_n}$

| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
3.00	0.5	3.0	0.5	0.218	0	0.134	0	0	0.218
5.20	1.0	2.2	0.5	0.160	3.00	0.134	0.402	0.187	0.749
6.50	1.5	1.3	0.5	0.094	5.20	0.134	0.697	0.642	1.433
7.30	2.0	0.8	0.5	0.058	6.50	0.134	0.871	1.228	2.157
7.60	2.5	0.3	0.5	0.022	7.30	0.134	0.978	1.849	2.849
7.75	3.0	0.15	0.5	0.011	7.60	0.134	1.018	2.442	3.471
7.70	3.5	−0.05	0.5	−0.004	7.75	0.134	1.039	2.976	4.019
7.60	4.0	−0.10	0.5	−0.007	7.70	0.134	1.032	3.444	4.469
7.10	5.0	−0.50	1.0	−0.073	7.60	0.250	1.900	3.276	5.103
6.60	6.0	−0.50	1.0	−0.073	7.10	0.250	1.775	3.740	5.442
6.00	7.0	−0.60	1.0	−0.087	6.60	0.250	1.650	3.989	5.552
5.10	9.0	−0.90	2.0	−2.261	6.00	0.432	2.592	2.987	5.318
4.40	11.0	−0.70	2.0	−0.203	5.10	0.432	2.203	2.861	4.861
3.30	15.0	−1.10	4.0	−0.638	4.40	0.720	3.168	1.361	3.891

[a]Calculated with the following rate constants: $k_{12} = 0.29$ hr^{-1}, $k_{21} = 0.31^{-1}$.

Adapted with permission from .

Table 7.4 Calculation of Percentage Unabsorbed[a]

Time (hr)	$(C_p)t_n$	$[AUC]^{t_n}_{t_{n-1}}$	$[AUC]^{t_n}_{t_0}$	$k[AUC]^{t_n}_{t_0}$	$(C_t)t_n$	Ab/V_p	%Ab/V_p	$100\% - Ab/V_p\%$
0.5	3.00	0.750	0.750	0.120	0.218	3.338	16.6	83.4
1.0	5.20	2.050	2.800	0.448	0.749	6.397	31.8	68.2
1.5	6.50	2.925	5.725	0.916	1.433	8.849	44.0	56.0
2.0	7.30	3.450	9.175	1.468	2.157	10.925	54.3	45.7
2.5	7.60	3.725	12.900	2.064	2.849	12.513	62.2	37.8
3.0	7.75	3.838	16.738	2.678	3.471	13.889	69.1	30.9
3.5	7.70	3.863	20.601	3.296	4.019	15.015	74.6	25.4
4.0	7.60	3.825	24.426	3.908	4.469	15.977	79.4	20.6
5.0	7.10	7.350	31.726	5.084	5.103	17.287	85.9	14.1
6.0	6.60	6.850	38.626	6.180	5.442	18.222	90.6	9.4
7.0	6.00	6.300	44.926	7.188	5.552	18.740	93.1	6.9
9.0	5.10	11.100	56.026	8.964	5.318	19.382	96.3	3.7
11.0	4.40	9.500	65.526	10.484	4.861	19.745	98.1	1.9
15.0	3.30	15.400	80.926	12.948	3.891	20.139	100.0	0

$$^a Ab/V_p = (C_p) + k[AUC]_0^{t_n} + (C_t)_{t_n}$$

$$(C_t)_{t_n} = k_{12}\Delta C_p \Delta t/2 + k_{12}/k_{21} \; (C_p)_{t_{n-1}}(1 - e^{-k_{21}\Delta t}) + (C_t)_{t_{n-1}} e^{-k_{21}\Delta t}$$

$$k = 0.16; k_{12} = 0.29; k_{21} = 0.31$$

For calculation of the k_a by this method, the drug must be given intravenously to allow evaluation of the distribution and elimination rate constants. For drugs that cannot be given by the IV route, the k_a cannot be calculated by the Loo–Riegelman method. For these drugs, given by the oral route only, the Wagner–Nelson method, which assumes a one-compartment model, may be used to provide an initial estimate of k_a. If the drug is given intravenously, there is no way of knowing whether there is any variation in the values for the elimination rate constant k and the distributive rate constants k_{12} and k_{21}. Such variations alter the rate constants. Therefore, a one-compartment model is frequently used to fit the plasma curves after an oral or intramuscular dose. The plasma level predicted from the k_a obtained by this method does deviate from the actual plasma level. However, in many instances, this deviation is not significant.

CUMULATIVE RELATIVE FRACTION ABSORBED

The fraction of drug absorbed at any time t (Eq. 7.31) may be summed or cumulated for each time period for which a plasma drug sample was obtained. From Equation 7.31, the term Ab/Ab$^\infty$ becomes the *cumulative relative fraction absorbed* (CRFA).

$$\text{CRFA} = \frac{C_{\mathrm{p}_t} + k[\text{AUC}]_0^t}{k[\text{AUC}]_0^\infty} \qquad (7.56)$$

where C_{p_t} is the plasma concentration at time t.

In the Wagner–Nelson equation, Ab/Ab$^\infty$ or CRFA will eventually equal unity, or 100%, even though the drug may not be 100% systemically bioavailable. The percent of drug absorbed is based on the total amount of drug absorbed (Ab$^\infty$) rather than the dose D_0. Because the amount of the drug ultimately absorbed, Ab$^\infty$, is equal to $k[\text{AUC}]^\infty_0$, the numerator will always equal the denominator, whether the drug is 10, 20, or 100% bioavailable. The percent of drug absorbed based on Ab/Ab$^\infty$ is therefore different from the real percent of drug absorbed unless $F = 1$. However, for the calculation of k_a, the method is acceptable.

To determine the real percent of drug absorbed, a modification of the Wagner–Nelson equation was suggested by . A reference drug product was administered and plasma drug concentrations were determined over time. CRFA was then estimated by dividing Ab/Ab$^\infty$ $_\text{ref}$, where Ab is the cumulative amount of drug absorbed from the drug product and Ab$^\infty$ $_\text{ref}$ is the cumulative final amount of drug absorbed from a reference dosage form. In this case, the denominator of Equation 7.56 is modified as follows:

$$\text{CRFA} = \frac{C_{\mathrm{p}} + k[\text{AUC}]_0^\infty}{k_{\text{ref}}[\text{AUC}]_{\text{ref}}^\infty} \qquad (7.57)$$

where k_ref and $[\text{AUC}]^\infty_\text{ref}$ are the elimination constant and the area under the curve determined from the reference product. The terms in the numerator of Equation 7.57 refer to the product, as in Equation 7.56.

Each fraction of drug absorbed is cumulated and plotted against the time interval in which the plasma drug sample was obtained (). An example of the relationship of CRFA versus time for the absorption of tolazamide from four different drug products is shown in . The data for were obtained from the serum tolazamide levels–time curves in . The CRFA–time graph provides a visual image of the relative rates of drug absorption from various drug products. If the CRFA–time curve is a straight line, then the drug was absorbed from the drug product at an apparent zero-order absorption rate.
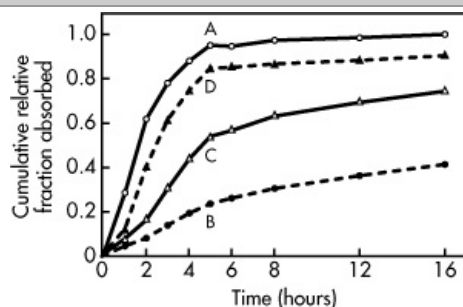
Figure 7-16.
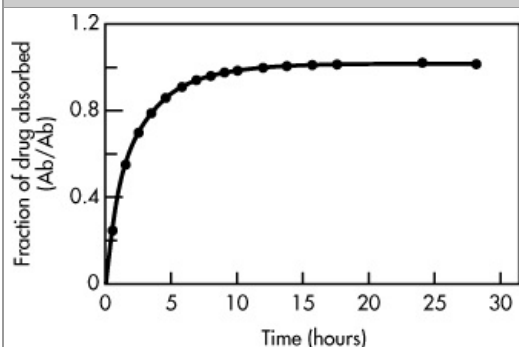
Fraction of drug absorbed. (Wagner–Nelson method).

Figure 7-17.

Mean cumulative relative fractions of tolazamide absorbed as a function of time.

()

Figure 7-18.
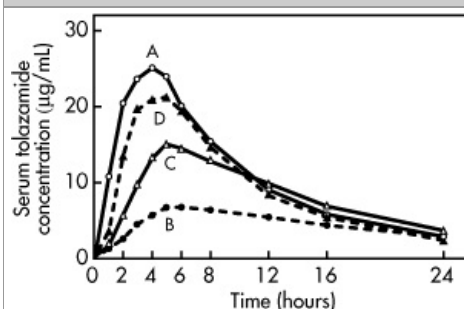
Source: Shargel S, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 5th Edition: http://www.accesspharmacy.com
Copyright © The McGraw-Hill Companies, Inc. All rights reserved.

Mean serum tolazamide levels as a function of time.

()

SIGNIFICANCE OF ABSORPTION RATE CONSTANTS

The overall rate of systemic drug absorption from an orally administered solid dosage form encompasses many individual rate processes, including dissolution of the drug, GI motility, blood flow, and transport of the drug across the capillary membranes and into the systemic circulation. The rate of drug absorption represents the net result of all these processes. The selection of a model with either first-order or zero-order absorption is generally empirical.

The actual drug absorption process may be zero-order, first-order, or a combination of rate processes that is not easily quantitated. For many immediate-release dosage forms, the absorption process is first-order due to the physical nature of drug diffusion. For certain controlled-release drug products, the rate of drug absorption may be more appropriately described by a zero-order rate constant.

The calculation of k_a is useful in designing a multiple-dosage regimen. Knowledge of the k_a and k allows for the prediction of peak and trough plasma drug concentrations following multiple dosing. In bioequivalence studies, drug products are given in chemically equivalent (ie, pharmaceutical equivalents) doses, and the respective rates of systemic absorption may not differ markedly. Therefore, for these studies, t_{max}, or time of peak drug concentration, can be very useful in comparing the respective rates of absorption of a drug from chemically equivalent drug products.

FREQUENTLY ASKED QUESTIONS

1. What is the absorption half-life of a drug and how is it determined?

2. When one simulates drug absorption with the oral one-compartment model, would a greater absorption rate constant result in a greater amount of drug absorbed?

3. How do you explain that k_a is often greater than k with most drugs?

4. Drug clearance is dependent on dose and area under the time–drug concentration curve. Would drug clearance be affected by the rate of absorption?

5. In switching a drug from IV to oral dosing, what is the most important consideration?

LEARNING QUESTIONS

1. Plasma samples from a patient were collected after an oral bolus dose of 10 mg of a new benzodiazepine solution as follows:

Time (hr)	Concentration (ng/mL)
0.25	2.85
0.50	5.43
0.75	7.75
1.00	9.84
2.00	16.20
4.00	22.15
6.00	23.01
10.00	19.09
14.00	13.90
20.00	7.97

From the data above:

a. Determine the elimination constant of the drug.

b. Determine k_a by feathering.

c. Determine the equation that describes the plasma drug concentration of the new benzodiazepine.

2. Assuming that the drug in Question 1 is 80% absorbed, find **(a)** the absorption constant, k_a; **(b)** the elimination half-life, $t_{1/2}$; **(c)** the t_{max}, or time of peak drug concentration; and **(d)** the volume of distribution of the patient.

3. Contrast the percent of drug-unabsorbed methods for the determination of rate constant for absorption, k_a, in terms of **(a)** pharmacokinetic model, **(b)** route of drug administration, and **(c)** possible sources of error.

4. What is the error inherent in the measurement of k_a for an orally administered drug that follows a two-compartment model when a one-compartment model is assumed in the calculation?

5. What are the main pharmacokinetic parameters that influence **(a)** time for peak drug concentration and **(b)** peak drug concentration?

6. Name a method of drug administration that will provide a zero-order input.

7. A single oral dose (100 mg) of an antibiotic was given to an adult male patient (43 years, 72 kg). From the literature, the pharmacokinetics of this drug fit a one-compartment open model. The equation that best fits the pharmacokinetics of the drug is

$$C_p = 45(e^{-0.17t} - e^{-1.5t})$$

From the equation above, calculate **(a)** t_{max}, **(b)** C_{max}, and **(c)** $t_{1/2}$ for the drug in this patient. Assume C_p is in µg/mL and the first-order rate constants are in hours^{-1}.

8. Two drugs, A and B, have the following pharmacokinetic parameters after a single oral dose of 500 mg:

Drug	k_a (hr^{-1})	k (hr^{-1})	V_D (mL)
A	1.0	0.2	10,000
B	0.2	1.0	20,000

Both drugs follow a one-compartment pharmacokinetic model and are 100% bioavailable.

a. Calculate the t_{max} for each drug.

b. Calculate the C_{max} for each drug.

9. The bioavailability of phenylpropanolamine hydrochloride was studied in 24 adult male subjects. The following data represent the mean blood phenylpropanolamine hydrochloride concentrations (ng/mL) after the oral administration of a single 25-mg dose of phenylpropanolamine hydrochloride solution.

Time (hr)	Concentration (ng/mL)	Time (hr)	Concentration (ng/mL)
0	0	3	62.98
0.25	51.33	4	52.32
0.5	74.05	6	36.08
0.75	82.91	8	24.88
1.0	85.11	12	11.83
1.5	81.76	18	3.88
2	75.51	24	1.27

a. From the data, obtain the rate constant for absorption, k_a, and the rate constant for elimination, k, by the method of residuals.

b. Is it reasonable to assume that $k_a > k$ for a drug in a solution? How would you determine unequivocally which rate constant represents the elimination constant k?

c. From the data, which method, Wagner–Nelson or Loo–Riegelman, would be more appropriate to determine the order of the rate constant for absorption?

d. From your values, calculate the theoretical t_{max}. How does your value relate to the observed t_{max} obtained from the subjects?

e. Would you consider the pharmacokinetics of phenylpropanolamine HCl to follow a one-compartment model? Why?

REFERENCES

Levy G, Amsel LP, Elliot HC: Kinetics of salicyluric acid elimination in man. *J Pharm Sci* **58:**827–829, 1969 [PMID: 5810199]

Loo JCK, Riegelman S: New method for calculating the intrinsic absorption rate of drugs. *J Pharm Sci* **57:**918–928, 1968 [PMID: 5671338]

Portmann G: Pharmacokinetics. In Swarbrick J (ed), *Current Concepts in the Pharmaceutical Sciences*, vol 1. Philadelphia, Lea & Febiger, 1970, Chap 1

Welling PG: *Pharmacokinetics: Processes and Mathematics*. ACS monograph 185. Washington, DC, American Chemical Society, 1986, pp 174–175

Welling PG, Patel RB, Patel UR, et al: Bioavailability of tolazamide from tablets: Comparison of in vitro and in vivo results. *J Pharm Sci* **71:**1259, 1982 [PMID: 7175719]

Wagner JG: Use of computers in pharmacokinetics. *Clin Pharmacol Ther* **8:**201–218, 1967 [PMID: 6015601]

BIBLIOGRAPHY

Boxenbaum HG, Kaplan SA: Potential source of error in absorption rate calculations. *J Pharmacokinet Biopharm* **3:**257–264, 1975 [PMID: 1185523]

Boyes R, Adams H, Duce B: Oral absorption and disposition kinetics of lidocaine hydrochloride in dogs. *J Pharmacol Exp Ther* **174:**1–8, 1970 [PMID: 5424701]

Dvorchik BH, Vesell ES: Significance of error associated with use of the one-compartment formula to calculate clearance of 38 drugs. *Clin Pharmacol Ther* **23:**617–623, 1978 [PMID: 648075]

Wagner JG, Nelson E: Kinetic analysis of blood levels and urinary excretion in the absorptive phase after single doses of drug. *J Pharm Sci* **53:**1392, 1964 [PMID: 14253604]

Medical

a **silverchair** information system

The McGraw·Hill Companies