MATHEMATICAL FUNDAMENTALS IN PHARMACOKINETICS: INTRODUCTION

Because pharmacokinetics and biopharmaceutics have a strong mathematical basis, a solid foundation in mathematical principles in algebra, calculus, exponentials, logarithms, and unit analysis are critical for students in these disciples. A self-exam is included in this chapter to provide a self-assessment of possible weaknesses in one's basic math skills. Difficulties with questions in the self-exam indicate that a review of mathematical essentials is necessary. Mathematical fundamentals are summarized here for review purposes only. For a more complete discussion of fundamental principles, a suitable textbook in mathematics should be consulted.

MATH SELF-EXAM

1. What are the units for concentration?

2. A drug solution has a concentration of 50 mg/mL. What amount of drug is contained within 20.5 mL of the solution? In 0.4 L? What volume of the solution will contain 30 mg of drug?

3. Convert the units in the above solution from mg/mL to g/L and µg/uL. If the molecular weight of the drug is 325 Da, what are the units in M?

4. If 20 mg of drug are added to a container of water and result in a concentration of 0.55 mg/L, what volume of water was in the container?

5. For the following equation:

$$y = 0.5x + 2$$

a. Sketch a plot of the equation.

b. Describe the relevance of each part of this equation.

c. If x = 0.6, what is y?

d. If y = 4.1, what is x?

6. Solve the following equations for x:

a. log x = 0.95

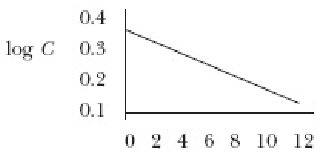
b. e^{x} = 0.44

c. ln x = 1.22

7. What is the slope of the line that connects the following two points?

$$y = 0.5x + 2$$

8. For the following graph, determine C if x = 2. If x = 12.



ESTIMATION AND THE USE OF CALCULATORS AND COMPUTERS

Most of the mathematics needed for pharmacokinetics and other calculations presented in this book may be performed with pencil, graph paper, and logical thought processes. A scientific calculator with logarithmic and exponential functions will make the calculations less tedious. Special computer software (see) are available for disease state calculations in clinical pharmacokinetics.

Whenever a calculation affecting drug dose is made, one should mentally approximate whether the answer is correct given the set of information. For example, for a given problem, consider whether the number in the answer has the correct magnitude and units; eg, if the correct answer should be between 100 and 200 mg, then answers such as 12.5 mg or 1250 mg have to be wrong.

The units for the answer to a problem should be checked carefully; eg, if the expected answer is a concentration unit, then mg/L or µg/mL are acceptable; and units such as L or mg/hr are definitely wrong. Wrong units may be caused by an incorrect substitution or by the selection of an incorrect formula. In pharmacokinetic calculation, the answer is correct only if both the number and the units are correct.

Approximation

Approximation is a useful process for checking whether the answer to a given set of calculations is probably correct. Approximation can be performed with pencil and paper and sometimes with a pencil, graph paper, and ruler. The procedure is especially useful in a busy environment when answers must be checked quickly.

To estimate a series of computations, round the numbers and write the numbers using scientific notation. Then perform the series of calculations, remembering the laws of exponents. For example, estimate the answer to the following problem:

$$\frac{58 \times 489}{2114 \times 0.04} \approx \frac{6 \times 10 \times 5 \times 10^2}{2 \times 10^3 \times 4 \times 10^{-2}} \approx \frac{30 \times 10^3}{8 \times 10} \approx 400$$

The precise answer to the above calculation is 335.4. Notice, the approximated answer should be somewhat less than 400, since 30 ÷ 8 is between 3 and 4.

For some pharmacokinetic problems, data, such as time versus drug concentration, may be placed on either regular or semilog graph paper. The approximated answer to the problem may be obtained by inspection of the line that is fitted to all the data points. Graphical methods for solving pharmacokinetic problems are given later in this chapter.

Calculators

A scientific handheld calculator is essential for calculations. Most scientific calculators include exponential and logarithmic functions, which are frequently used in pharmacokinetics. Additional functions such as mean, standard deviation, and linear regression analysis are used to determine the half-life of drugs. Statistical parameters, such as correlation coefficient, are used to determine how well the model agrees with the observed data.

Exponents and Logarithms

EXPONENTS

In the expression

$$N = b^x \qquad \textbf{(2.1)}$$

x is the exponent, *b* is the base, and *N* represents the number when *b* is raised to the *x*th power, ie, b^x. For example,

$$1000 = 10^3$$

where 3 is the exponent, 10 is the base, and 10^3 is the third power of the base, 10. The numeric value, *N* in Equation 2.1, is 1000. In this example, it can be reversely stated that the log of *N* to the base 10 is 3. Thus, taking the log of the number *N* has the effect of "compressing" the number; some numbers are easier to handle when "compressed" or transformed to base 10. Transformation simplifies many mathematical operations.

Laws of Exponents	Example
$a^x \cdot a^y = a^{x+y}$	$10^2 \cdot 10^3 = 10^5$
$(a^x)^y = a^{xy}$	$(10^2)^3 = 10^6$
$\frac{a^x}{a^y} = a^{x-y}$	$\frac{10^2}{10^4} = 10^{-2}$
$\frac{1}{a^x} = a^{-x}$	$\frac{1}{10^2} = 10^{-2}$
$\sqrt[y]{a} = a^{1/y}$	$\sqrt[3]{a} = a^{1/3}$

LOGARITHMS

The logarithm of a positive number *N* to a given base *b* is the exponent (or the power) *x* to which the base must be raised to equal the number *N*. Therefore, if

$$N = b^x \qquad \textbf{(2.2)}$$

then

$$\log_b N = x \qquad \textbf{(2.3)}$$

For example, with common logarithms (log), or logarithms using base 10,

$$100 = 10^2$$

$$\log 100 = 2$$

The number 100 is considered the *antilogarithm* of 2.

Natural logarithms (ln) use the base *e*, whose value is 2.718282. To relate natural logarithms to common logarithms, the following equation is used:

$$2.303 \log N = \ln N \qquad \textbf{(2.4)}$$

Exponential Expression	Logarithmic Statement
$10^3 = 1000$	$\log 1000 = 3$
$10^2 = 100$	$\log 100 = 2$
$10^1 = 10$	$\log 10 = 1$
$10^0 = 1$	$\log 1 = 0$
$10^{-1} = 0.1$	$\log 0.1 = -1$
$10^{-2} = 0.01$	$\log 0.01 = -2$
$10^{-3} = 0.001$	$\log 0.001 = -3$

Laws of Logarithms

$$\log ab = \log a + \log b$$

$$\log \frac{a}{b} = \log a - \log b$$

$$\log a^x = x \log a$$

$$-\log \frac{a}{b} = + \log \frac{a}{b}$$

Of special interest is the following relationship:

$$\ln e^{-x} = -x \qquad (2.5)$$

Equation 2.5 can be compared with the following example:

$$\log 10^{-2} = -2$$

A logarithm does not have units. A logarithm is dimensionless and is considered a real number. The logarithm of 1 is zero; the logarithm of a number less than 1 is a negative number, and the logarithm of a number greater than 1 is a positive number.

PRACTICE PROBLEMS

Many calculators and computers have logarithmic and exponential functions. The following problems review methods for calculations involving logarithmic or exponential functions using a calculator. Earlier editions of this text demonstrate the use of logarithmic and exponential tables to perform these problems. Before starting any new calculations, be sure to clear the calculator of any previous numbers.

1. Find the log of 35.

Solution

Enter the number 35 into your calculator.

Press the LOG function key.

Answer = 1.5441

(For some calculators, the LOG function key is pressed first, followed by the number; the answer is obtained by pressing the = key).

Notice that the correct answer for log 35 is the same as calculating the exponent of 10, which will equal 35 as shown below.

$$35 = 10^{1.5441}$$

Estimation—Since the number 35 is between 10 and 100 (ie, 10^1 and 10^2), then the log of 35 must be between 1.0 and 2.0.

2. Find the log of 0.028.

Estimation—Since the number 0.028 is between 10^{-1} and 10^{-2}, then the log of 0.028 must be between –1.0 and –2.0.

Solution

Use the same procedure above.

Enter the number 0.028 into your calculator.

Press the LOG function key.

Answer = –1.553

3. Find the antilog of 0.028.

The process for finding an antilog is the reverse of finding a log. The antilog is the number that corresponds to the logarithm, such that the antilog for 3 (in base 10) is 1000 (or 10^3). This problem is the inverse of Practice Problem 2, above. In this case, the calculation determines what the number is when 10 is raised to 0.028 (ie, $10^{0.028}$).

Solution

The following methods may be used, depending on the type of calculator being used.

Method 1

If your calculator has a function key marked 10^x, then do the following:

Enter 0.028.

Press 10^x.

Answer = 1.0666

Method 2

Some calculators assume that the user knows that 10^x is the inverse of log x. For this calculation:

Enter 0.028.

Press the key marked INV.

Then press the key marked LOG.

Answer = 1.0666

4. Evaluate $e^{-1.3}$

Solution

The following methods may be used, depending on the type of calculator being used.

Method 1

If your calculator has a function key marked e^x, then do the following:

Enter 1.3.

Change the sign to minus by pressing the key marked ±.

Press e^x.

Answer = 0.2725

Method 2

Some calculators assume that the user knows that e^x is the inverse of ln x. For this calculation:

Enter 1.3.

Change the sign to minus by pressing the key marked ±.

Press the key marked INV.

Then press the key marked LN.

Answer = 0.2725

Thus, $e^{-1.3} = 0.2725$

5. Find the value of k in the following expression:

$25 = 50e^{-4k}$

Solution

$$e^{-4k} = \frac{25}{50} = 0.50$$

Take the natural logarithm, ln, for both sides of the equation:

$$\ln e^{-4k} = \ln 0.50$$

From Equation 2.5, $\ln e^{-x} = -x$. Therefore, $\ln e^{-4k} = -4k$ and $\ln 0.50 = -0.693$.

(Calculator: Enter 0.5, then press LN function key.)

$$-4k = -0.693$$
$$k = \frac{-0.693}{-4} = 0.173$$

6. A very common problem in pharmacokinetics is to evaluate an expression such as

$$C_p = C_p^0 e^{-kt}$$

For example, find the value of C_p in the following equation when $t = 2$:

$$C_p = 35e^{-0.15t}$$

Solution

Using a calculator:

Enter 0.15.

Press ± key	= −0.15
Multiply by 2	= −0.30
Press e^x function key	= 0.7408
Multiply by 35	= 25.93

$$C_p = 35e^{-0.15t} = 35(0.7408) = 25.93$$

Because $e^{-x} = 1/e^{x}$, as the value for x becomes larger, the value for e^{-x} becomes smaller.

Spreadsheets for Performing Calculations

Spreadsheet software, such as LOTUS 123, QUATRO PRO, and EXCEL, is available on many personal computers, including both the MAC and IBM-compatible PCs. These spreadsheets are composed of a grid as shown in . Detailed spreadsheet operation examples are found in .

CALCULUS

Since pharmacokinetics considers drugs in the body to be in a dynamic state, calculus is an important mathematic tool for analyzing drug movement quantitatively. Differential equations are used to relate the concentrations of drugs in various body organs over time. Integrated equations are frequently used to model the cumulative therapeutic or toxic responses of drugs in the body.

Differential Calculus

Differential calculus is a branch of calculus that involves finding the rate at which a variable quantity is changing. For example, a specific amount of drug X is placed in a beaker of water to dissolve. The rate at which the drug dissolves is determined by the rate of drug diffusing away from the surface of the solid drug and is expressed by the *Noyes-Whitney equation*:

$$\text{Dissolution rate} = \frac{dX}{dt} = \frac{DA}{l}(C_1 - C_2)$$

where d = denotes a very small change; X = drug X; t = time; D = diffusion coefficient; A = effective surface area of drug; l = length of diffusion layer; C_1 = surface concentration of drug in the diffusion layer; and C_2 = concentration of drug in the bulk solution.

The derivative dX/dt may be interpreted as a change in X (or a derivative of X) with respect to a change in t.

In pharmacokinetics, the amount of drug in the body is a variable quantity (dependent variable), and time is considered to be an independent variable. Thus, we consider the amount of drug to vary with respect to time.

EXAMPLE

The concentration C of a drug changes as a function of time t:

$$C = f(t) \qquad \textbf{(2.6)}$$

Consider the following data:

Time (hr)	Plasma Concentration of Drug C (μg/mL)
0	12
1	10
2	8
3	6
4	4
5	2

The concentration of drug C in the plasma is declining by 2 μg/mL for each hour of time. The rate of change in the concentration of the drug with respect to time (ie, the derivative of C) may be expressed as

$$\frac{dC}{dt} = 2\ \mu\text{g/mL/hr}$$

Here, $f(t)$ is a mathematical equation that describes how C changes, expressed as

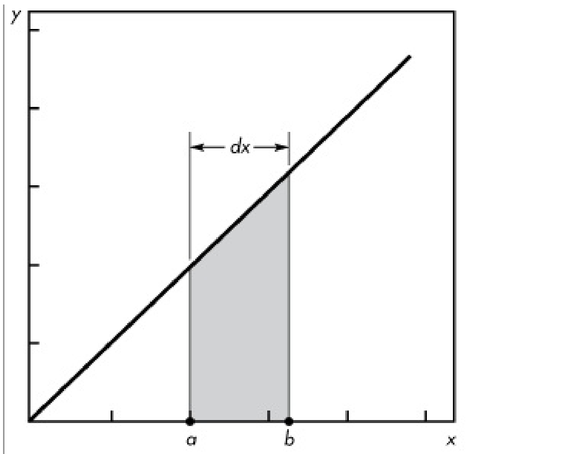
$$C = 12 - 2t \qquad \textbf{(2.7)}$$

Integral Calculus

Integration is the reverse of differentiation and is considered the summation of $f(x) \cdot dx$; the integral sign ∫ implies summation.

For example, given the function $y = ax$, plotted in , the integration is $\int ax \cdot dx$. is a graph of the function $y = Ae^{-x}$, commonly observed after an intravenous bolus drug injection. The integration process is actually a summing up of the small individual pieces under the graph. When x is specified and is given boundaries from a to b, then the expression becomes a definite integral, ie, the summing up of the area from $x = a$ to $x = b$.

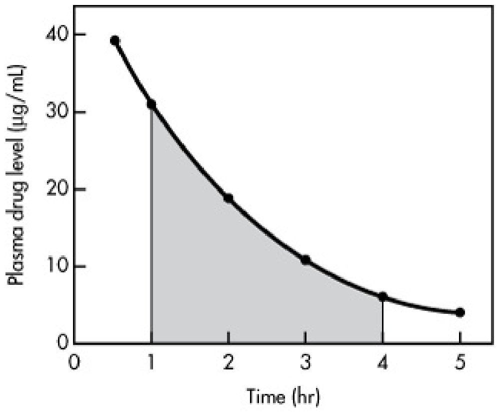
Figure 2-1.



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

Integration of $y = ax$ or $\int ax \cdot dx$.

Figure 2-2.



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Graph of the elimination of drug from the plasma after a single IV injection.

A *definite integral* of a mathematical function is the sum of individual areas under the graph of that function. There are several reasonably accurate numerical methods for approximating an area. These methods can be programmed into a computer for rapid calculation. The *trapezoidal rule* is a numerical method frequently used in pharmacokinetics to calculate the area under the plasma drug concentration-versus-time curve, called the area under the curve (AUC). For example, shows a curve depicting the elimination of a drug from the plasma after a single intravenous injection. The drug plasma levels and the corresponding time intervals plotted in are as follows:

Time (hr)	Plasma Drug Level (µg/mL)
0.5	38.9
1.0	30.3
2.0	18.4
3.0	11.1
4.0	6.77
5.0	4.10

The area between time intervals is the area of a trapezoid and can be calculated with the following formula:

$$[\mathrm{AUC}]_{t_{n-1}}^{t_n} = \frac{C_{n-1} + C_n}{2}(t_n - t_{n-1}) \qquad (2.8)$$

where [AUC] = area under the curve, t_n = time of observation of drug concentration C_n, and t_{n-1} = time of prior observation of drug concentration corresponding to C_{n-1}.

To obtain the AUC from 1 to 4 hours in , each portion of this area must be summed. The AUC between 1 and 2 hours is calculated by proper substitution into Equation 2.8:

$$[\mathrm{AUC}]_{t1}^{t2} = \frac{30.3 + 18.4}{2}(2-1) = 24.35\ \mu\mathrm{g\ hr/mL}$$

Similarly, the AUC between 2 and 3 hours is calculated as 14.75 µg hr/mL, and the AUC between 3 and 4 hours is calculated as 8.94 µg hr/mL. The total AUC between 1 and 4 hours is obtained by adding the three smaller AUC values together.

$$[\mathrm{AUC}]_{t1}^{t4} = [\mathrm{AUC}]_{t1}^{t2} + [\mathrm{AUC}]_{t2}^{t3} + [\mathrm{AUC}]_{t3}^{t4}$$

$$= 24.35 + 14.75 + 8.94$$

$$= 48.04\ \mu\mathrm{g\ hr/mL}$$

The total area under the plasma drug level-versus-time curve () is obtained by summation of each individual area between two consecutive time intervals using the trapezoidal rule. The value on the *y* axis when time equals zero is estimated by back extrapolation of the data points using a log linear plot (ie, log *y* versus *x*).

This numerical method of obtaining the AUC is fairly accurate if sufficient data points are available. As the number of data points increases, the trapezoidal method of approximating the area becomes more accurate.

The trapezoidal rule assumes a linear or straight-line function between data points. If the data points are spaced widely, then the normal curvature of the line will cause a greater error in the area estimate.

At times, the area under the plasma level time curve is extrapolated to $t = \infty$. In this case the residual area $[\mathrm{AUC}]^{t\infty}_{tn}$ is calculated as follows:

$$[\mathrm{AUC}]_{tn}^{t\infty} = \frac{C_{\mathrm{p}n}}{k} \qquad (2.9)$$

where $C_{\mathrm{p}n}$ = last observed plasma concentration at t_n and k = slope obtained from the terminal portion of the curve.

The trapezoidal rule written in its full form to calculate the AUC from $t = 0$ to $t = \infty$ is as follows:

$$[\mathrm{AUC}]_0^\infty = \Sigma[\mathrm{AUC}]_{tn-1}^{tn} + \frac{C_{\mathrm{p}n}}{k}$$

GRAPHS

The construction of a curve or straight line by plotting observed or experimental data on a graph is an important method of visualizing relationships between variables. By general custom, the values of the independent variable (*x*) are placed on the horizontal line in a plane, or on the abscissa (*x* axis), whereas the values of the dependent variable are placed on the vertical line in the plane, or on the ordinate (*y* axis), as demonstrated in . The values are usually arranged so that they increase from left to right and from bottom to top. The values may be spaced arbitrarily along each axis to optimize any observable relationships between the two variables.

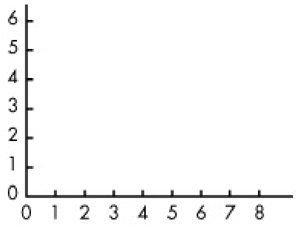
Figure 2-3.

Standard arrangement of independent (*x*) and dependent (*y*) variables on a graph.

In pharmacokinetics, time is the independent variable and is plotted on the abscissa (*x* axis), whereas drug concentration is the dependent variable and is plotted on the ordinate (*y* axis).

Two types of graph paper are usually used in pharmacokinetics. These are Cartesian or rectangular coordinate graph paper () and semilog graph paper ().

Figure 2-4.



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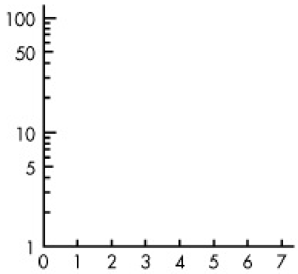
Rectangular coordinates.

Figure 2-5.



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Semilog coordinates.

Semilog paper is available with one, two, three, or more cycles per sheet, each cycle representing a 10-fold increase in the numbers, or a single log10 unit. This paper allows placement of the data at logarithmic intervals so that the numbers need not be converted to their corresponding log values prior to plotting on the graph.

Curve Fitting

Fitting a curve to the points on a graph implies that there is some sort of relationship between the variables *x* and *y*, such as dose of drug versus pharmacologic effect (eg, lowering of blood pressure). Moreover, the relationship is not confined to isolated points but is a continuous function of *x* and *y*. In many cases, a hypothesis is made concerning the relationship between the variables *x* and *y*. Then, an empirical equation is formed that best describes the hypothesis. This empirical equation must satisfactorily fit the experimental or observed data.

Physiological variables are not always linearly related. However, the data may be arranged or transformed to express the relationship between the variables as a straight line. Straight lines are very useful for accurately predicting values for which there are no experimental observations. The general equation of a straight line is

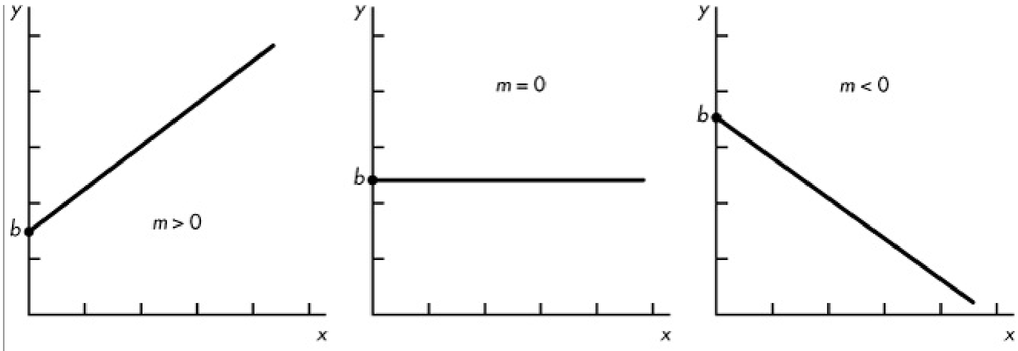
$$y = mx + b \qquad (2.10)$$

where *m* = slope and *b* = *y* intercept. Equation 2.10 could yield any one of the graphs shown in , depending on the value of *m*. The absolute magnitude of *m* gives some idea of the steepness of the curve. For example, as the value of *m* approaches 0, the line becomes more horizontal. As the absolute value of *m* becomes larger, the line slopes farther upward or downward, depending on whether *m* is positive or negative, respectively. For example, the equation

$$y = -15x + 7$$

indicates a slope of –15 and a *y* intercept at +7. The negative sign indicates that the curve is sloping downward from left to right.

Figure 2-6.



Graphic demonstration of variations in slope (*m*).

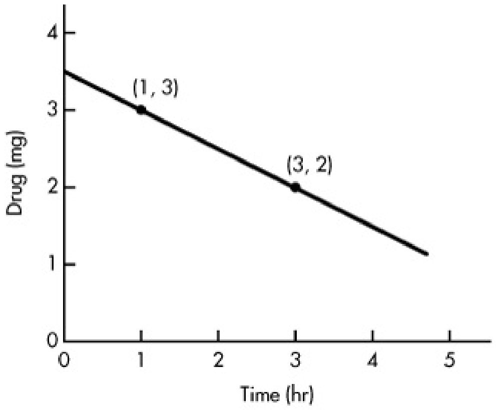
Determination of the Slope

SLOPE OF A STRAIGHT LINE ON A RECTANGULAR COORDINATE GRAPH

The value of the slope may be determined from any two points on the curve (). The slope of the curve is equal to $\Delta y/\Delta x$, as shown in the following equation:

$$\text{Slope} = \frac{y_2 - y_1}{x_2 - x_1} \qquad (2.11)$$

Figure 2-7.



Graphic representation of a line with a slope value of $m = -1/2$.

The slope of the line plotted in is

$$m = \frac{2 - 3}{3 - 1} = \frac{-1}{2}$$

Because the *y* intercept is equal to 3.5, the equation for the curve by substitution into Equation 2.10 is

$$y = -\frac{1}{2}x + 3.5$$

SLOPE OF A STRAIGHT LINE ON A SEMILOG GRAPH

When using semilog paper, the *y* values are plotted on a logarithmic scale without performing actual logarithmic conversions, whereas the corresponding *x* values are plotted on a linear scale. Therefore, to determine the slope of a straight line on semilog paper graph, the *y* values must be converted to logarithms, as shown in the following equation:

$$\text{Slope} = 2.3\frac{(\log y_2 - \log y_1)}{x_2 - x_1} = \frac{\ln y_2 - \ln y_1}{x_2 - x_1} \qquad (2.12)$$

The slope value is often used to calculate *k*, a constant that determines the rate of drug decline:

$$k = 2.3 \text{ slope}$$

LEAST-SQUARES METHOD

Very often an empirical equation is calculated to show the relationship between two variables. Experimentally, data may be obtained that suggest a linear relationship between an independent variable *x* and a dependent variable *y*. The straight line that characterizes the relationship between the two variables is called a *regression line*. In many cases, the experimental data may have some error and therefore show a certain amount of scatter or deviations from linearity. The *least-squares method* is a useful procedure for obtaining the line of best fit through a set of data points by minimizing the deviation between the experimental and the theoretical line. In using this method, it is often assumed, for simplicity, that there is a linear relationship between the variables. If a linear line deviates substantially from the data, it may suggest the need for a nonlinear regression model, although several variables (multiple linear regression) may be involved. Nonlinear regression models are complex mathematical procedures that are best performed with a computer program (see).

When the equation of a linear model is examined, the dependent variables can be expressed as the sum of products of the independent variables and parameters. In nonlinear models, at least one of the parameters appears as other than a coefficient. For example,

Linear model: $y = ax$, $y = ax + bx + cx^2$, $y = ax + bx_1 + cx^2$
Nonlinear model: $y = ax/(b + cx)$, $y = 10e^{-3x}$
(a, b, and c are parameters and x and x_1 are variables)

The second nonlinear example as written is nonlinear, but may be transformed to a linear equation by taking the natural log on both sides:

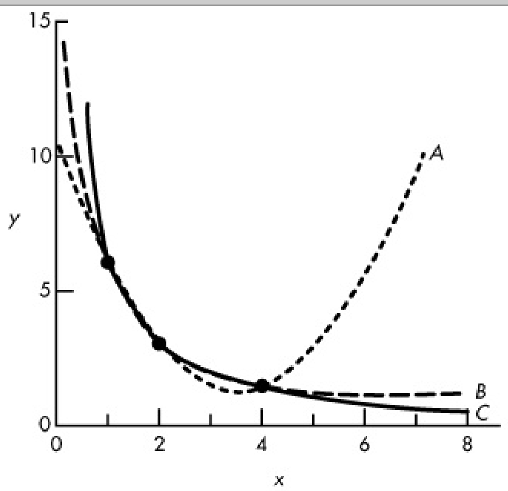
$$\ln y = -3x$$

PROBLEMS OF FITTING POINTS TO A GRAPH

When *x* and *y* data points are plotted on a graph, a relationship between the *x* and *y* variables is sought. Linear relationships are useful for predicting values for the dependent variable *y*, given values for the independent variable *x*.

The *linear regression* calculation using the least-squares method is used for calculation of a straight line through a given set of points. However, it is important to realize that, when using this method, one has already assumed that the data points are related linearly. Indeed, for three points, this linear relationship may not always be true. As shown in , calculated three different curves that fit the data accurately. Generally, one should consider the *law of parsimony*, which broadly means "keep it simple"; that is, if a choice between two hypotheses is available, choose the more simple relationship.

Figure 2-8.



Three points equally well fitted by different curves. The parabola, $y = 10.5 - 5.25x + 0.75x^2$ (*curve A*); the exponential, $y = 12.93e^{-1.005x} + 1.27$ (*curve B*); and the rectangular hyperbola, $y = 6/x$ (*curve C*) all fit the three points (1, 6), (2, 3), and (4, 1.5) perfectly, as would an infinite number of other curves.

()

If a linear relationship exists between the *x* and *y* variables, one must be careful as to the estimated value for the dependent variable *y*, assuming a value for the independent variable *x*. *Interpolation*, which means filling the gap between the observed data on a graph, is usually safe and assumes that the trend between the observed data points is consistent and predictable. In contrast, the process of *extrapolation* means predicting new data beyond the observed data, and assumes that the same trend obtained between two data points will extend in either direction beyond the last observed data points. The use of extrapolation may be erroneous if the regression line no longer follows the same trend beyond the measured points.

Practice Problems

1. Plot the following data and obtain the equation for the line that best fits the data by (a) using a ruler and (b) using the method of least squares.

x (mg)	*y* (hr)	*x* (mg)	*y* (hr)
1	3.1	5	15.3
2	6.0	6	17.9
3	8.7	7	22.0
4	12.9	8	23.0

Solution

a. *Ruler*

Place a ruler on a straight edge over the data points and draw the best line that can be observed. Take any two points and determine the slope by the slope formula given in Equation 2.11 and the *y* intercept. This method can give a reasonably quick approximation if there is very little scatter in the data.

b. *Least-Squares Method*

In the least-squares method the slope *m* and the *y* intercept *b* (Eq. 2.13) are calculated so that the average sum of the deviations squared is minimized. The deviation, *d*, is defined by

$$b + mx - y = d \qquad \textbf{(2.13)}$$

If there are no deviations from linearity, then $d = 0$ and the exact form of Equation 2.13 is as follows:

$$b + mx - y = 0$$

To find the slope, *m*, and the intercept, *b*, the following equations are used:

$$m = \frac{\Sigma(x)\,\Sigma(y) - n\Sigma(xy)}{[\Sigma(x)]^2 - n\Sigma(x^2)} \qquad \textbf{(2.14)}$$

where *n* = number of data points.

$$b = \frac{\Sigma(x)\,\Sigma(xy) - \Sigma(x^2)\,\Sigma y}{[\Sigma(x)]^2 - n\Sigma(x^2)} \qquad \textbf{(2.15)}$$

where Σ is the sum of *n* data points.

Using the data above, tabulate values for *x, y,* x^2, and *xy* as shown below:

x	y	x^2	xy
1	3.1	1	3.1
2	6.0	4	12.0
3	8.7	9	26.1
4	12.9	16	51.6
5	15.3	25	76.5
6	17.9	36	107.4
7	22.0	49	154.0
8	23.0	64	184.0
$\Sigma x = 36$	$\Sigma y = 108.9$	$\Sigma x^2 = 204$	$\Sigma xy = 614.7$

Now substitute the values into Equations 2.14 and 2.15.

$$b = \frac{(36)(614.7) - (204)(108.9)}{(36)^2 - (8)(204)} = 0.257\ \text{mg}$$

$$m = \frac{(36)(108.9) - (8)(614.7)}{(36)^2 - (8)(204)} = 2.97\ \text{mg/hr}$$

Therefore, the linear equation that best fits the data is

$$y = 2.97x + 0.257$$

Although an equation for a straight line is obtained by the least-squares procedure, the reliability of the values should be ascertained. A correlation coefficient, *r,* is a useful statistical term that indicates the relationship of the *x, y* data to a straight line. For a perfect linear relationship between *x* and *y*, $r = +1$ if the slope is ascending and −1 if the slope is descending. If $r = 0$, then no linear relationship exists between *x* and *y*. Usually, $r \geq 0.95$ demonstrates good evidence or a strong correlation that there is a linear relationship between *x* and *y*.

2. *Determination of slope can be carried out using a calculator*. Many calculators have a statistical linear regression program to determine the slope of the regression line and the coefficient of correlation. The calculator must be cleared and the statistical routine initiated. For regular linear regression, the data may be entered directly in pairs as follows:

a. *Linear Regression*

Enter Time	Enter Concentration
0	0
2	20
4	40

In this case, the slope should be 10 if linear regression is performed correctly, and the process is zero order. This slope value should be close to the slope determined by graphic method on regular graph paper.

b. *Log Linear Regression*

In this case, the data below is not a linear relationship but can be transformed (take the log of concentration) to make the data linear. Use the same linear regression program above, except, each time after concentration is entered, press LOG as shown below:

Enter Time	Enter Concentration	Key Stroke
0	10	LOG
2	5	LOG
4	2.5	LOG

The slope obtained should approximate the value determined by graphic method on the semilog paper. The slope value is −0.151.

If the LN key is pressed each time instead of LOG in all the steps above, the slope will be −0.346, or equal to $-k$, the elimination constant. This is a shortcut method sometimes used to determine k of a first-order process. The regression involves regressing ln concentration versus time directly, ie, ln C versus t, because ln $C = -kt$ + intercept, the slope m is $-k$ (see later section of this chapter).

UNITS IN PHARMACOKINETICS

For an equation to be valid, the units or dimensions must be constant on both sides of the equation. Many different units are used in pharmacokinetics, as listed in . For an accurate equation, both the integers and the units must balance. For example, a common expression for total body clearance is

$$Cl_T = kV_d \qquad (2.16)$$

Table 2.1 Common Units Used in Pharmacokinetics

PARAMETER	SYMBOL	UNIT	EXAMPLE
Rate	$\frac{dD}{dt}$	$\frac{\text{Mass}}{\text{Time}}$	mg/hr
	$\frac{dc}{dt}$	$\frac{\text{Concentration}}{\text{Time}}$	μg/mL hr
Zero-order rate constant	k_0	$\frac{\text{Concentration}}{\text{Time}}$	μg/mL hr
		$\frac{\text{Mass}}{\text{Time}}$	mg/hr
First-order rate constant	k	$\frac{1}{\text{Time}}$	1/hr or hr^{-1}
Drug dose	D_0	Mass	mg
Concentration	C	$\frac{\text{Mass}}{\text{Volume}}$	μg/mL
Plasma drug concentration	C_p	$\frac{\text{Drug}}{\text{Volume}}$	μg/mL
Volume	V	Volume	mL or L
Area under the curve	AUC	Concentration × time	μg hr/mL
Fraction of drug absorbed	F	No units	0 to 1
Clearance	Cl	$\frac{\text{Volume}}{\text{Time}}$	mL/hr
Half-life	$t_{1/2}$	Time	hr

After insertion of the proper units for each term in the above equation from ,

$$\frac{\text{mL}}{\text{hr}} = \frac{1}{\text{hr}}\,\text{mL}$$

Thus, the above equation is valid, as shown by the equality mL/hr = mL/hr.

An important rule in using equations with different units is that the units may be added, subtracted, divided, or multiplied as long as the final units are consistent and valid. When in doubt, check the equation by inserting the proper units. For example,

$$\text{AUC} = \frac{FD_0}{kV_D} = \text{concentration} \times \text{time} \qquad \textbf{(2.17)}$$

$$\frac{\mu\text{g}}{\text{mL}}\,\text{hr} = \frac{1\ \text{mg}}{\text{hr}^{-1}\,\text{liter}} = \frac{\mu\text{g hr}}{\text{mL}}$$

Certain terms have no units. These terms include logarithms and ratios. Percent may have no units and is expressed mathematically as a decimal between 0 and 1 or as 0 to 100%, respectively. On occasion, percent may indicate mass/volume, volume/volume, or mass/mass. lists common pharmacokinetic parameters with their symbols and units.

A constant is often inserted in an equation to quantitate the relationship of the dependent variable to the independent variable. For example, *Fick's law of diffusion* relates the rate of drug diffusion, dQ/dt, to the change in drug concentration, C, the surface area of the membrane, A, and the thickness of the membrane h. In order to make this relationship an equation, a diffusion constant D is inserted:

$$\frac{dQ}{dt} = \frac{DA}{h} \times \triangle C \qquad \textbf{(2.18)}$$

To obtain the proper units for D, the units for each of the other terms must be inserted:

$$\frac{\text{mg}}{\text{hr}} = \frac{D\,(\text{cm}^2)}{\text{cm}} \times \frac{\text{mg}}{\text{cm}^3}$$

$$D = \text{cm}^2/\text{hr}$$

The diffusion constant D must have the units of area/time or cm^2/hr if the rate of diffusion is in mg/hr.

Graphs should always have the axes (abscissa and ordinate) properly labeled with units. For example, in the amount of drug on the ordinate (y axis) is given in milligrams and the time on the abscissa (x axis) is given in hours. The equation that best fits the points on this curve is the equation for a straight line, or $y = mx + b$. Because the slope $m = \Delta y/\Delta x$, the units for the slope should be milligrams per hour (mg/hr). Similarly, the units for the y intercept b should be the same units as those for y, namely, milligrams (mg).

MEASUREMENT AND USE OF SIGNIFICANT FIGURES

Every measurement is performed within a certain degree of accuracy, which is limited by the instrument used for the measurement. For example, the weight of freight on a truck may be measured accurately to the nearest 0.5 kg, whereas the mass of drug in a tablet may be measured to 0.001 g (1 mg). Measuring the weight of freight on a truck to the nearest milligram is not necessary and would require a very costly balance or scale to detect a change in a milligram quantity.

Significant figures are the number of accurate digits in a measurement. If a balance measures the mass of a drug to the nearest milligram, measurements containing digits representing less than 1 mg are inaccurate. For example, in reading the weight or mass of a drug of 123.8 mg from this balance, the 0.8 mg is only approximate; the number is therefore rounded to 124 mg and reported as the observed mass.

For practical calculation purposes, all figures may be used until the final number (answer) is obtained. However, the answer should retain only the number of significant figures in the least accurate initial measurement.

UNITS FOR EXPRESSING BLOOD CONCENTRATIONS

Various units have been used in pharmacology, toxicology, and the clinical laboratory to express drug concentrations in blood, plasma, or serum. Drug concentrations or drug levels should be expressed as mass/volume. The expressions mcg/mL, µg/mL, and mg/L are equivalent and are commonly reported in the literature. Drug concentrations may also be reported as mg% or mg/dL, both of which indicate milligrams of drug per 100 mL (deciliter). Two older expressions for drug concentration occasionally used in veterinary medicine are the terms ppm and ppb, which indicate the number of parts of drug per million parts of blood (ppm) or per billion parts of blood (ppb). One ppm is equivalent to 1.0 µg/mL. The accurate interconversion of units is often necessary to prevent confusion and misinterpretation.

STATISTICS

All measurements have some degree of error. An *error* is the difference between the true or absolute value and the observed value. Errors in measurement may be *determinate* (constant) or *indeterminate* (random, accidental). Determinate errors may be minimized in analytical procedures by using properly calibrated instrumentation, standardized chemicals, and appropriate blanks and control samples. Indeterminate errors are random and occur due to chance. For practical purposes, several measurements of a given sample are usually performed, and the result averaged. The mean ± SD is often reported. SD or *standard deviation* (see) is a statistical way of expressing the spread between the individual measurements from the mean. A small SD relative to the mean value is indicative of good consistency and reproducibility of the measurements. A large SD indicates poor consistency and data fluctuations. Frequently, the variability of the measurements may be expressed as RSD or *relative standard deviation*, which is calculated as the SD divided as the mean of the data. RSD allows variability to be expressed on a percent basis and is useful in comparing the variability of two sets of measurements when the means are different.

In measurements involving a single subject or sample, only measuring error is involved. On the other hand, when two or more samples or subjects in a group are measured, there is usually variation due to individual differences. For example, the weight of each student in a class is likely different from that of the others because of individual physical differences such as height and sex. Therefore, in determining the weight of a group of students, we deal with variations due to biologic differences as well as weighing errors. A major error in group measurement is *sampling error*, an error due to nonuniform sampling. Sampling is essential because the measurement of all members in the group is not practical.

We use statistics to obtain a valid interpretation of the experimental data. *Statistics* is the logical use of mathematics, which includes (1) experimental design, (2) collection of data, (3) analysis of data, (4) interpretation of data, and (5) hypothesis testing. A more complete discussion of statistics is found in .

Practical Focus

In pharmacokinetics and therapeutics, plasma or tissue samples are often monitored to determine if a prescribed dose needs to be adjusted. Comparisons of literature data from several medical centers are often made. The pharmacist should to be familiar with all units involving dosing and be able to make conversions. Some physicians prescribe a drug dose based on body weight, whereas others prefer the body surface area method. Significant differences in plasma drug concentrations may result if the dose is based on a different method. Drug concentrations may also be different if a dose is injected rapidly versus infused over a period of time. lists some of the common methods of dosing.

Table 2.2 Dosing Unit Based on Body Weight or Body Surface Area[a]

Method	Oral Drug Unit	Infusion Unit	Remarks
General	mg	mg/hr	BW not used
BW	mg/kg	mg/kg/hr	Known BW
BSA	mg/1.73 m^2	mg/1.73 m^2/hr	Estimated BSA

[a]BW, body weight; BSA, body surface area.

Most potent drugs are dosed precisely for the individual patient, and the body weight of the patient should be known. For example, theophylline is dosed at 5 mg/kg. Since the body weight (BW) of individuals may vary with age, sex, disease, and nutritional state, an individualized dose based on body weight will more accurately reflect the appropriate therapy needed for the patient. For drugs with a narrow therapeutic index and potential for side effects, dosing based on body surface is common. During chemotherapy with antitumor drugs, many drugs are dosed according to the body surface area (BSA) of the patient. The body surface area may be determined from the weight of the patient using the empirical equation

$$\text{BSA} = \left(\frac{\text{BW}}{70\ \text{kg}}\right)^{0.73} \times 1.73\ \text{m}^2$$

where BSA = body surface area in m^2, and BW = body weight in kg. Some common units and conversions used in pharmacokinetics and toxicology are listed in .

Table 2.3 Pharmacokinetic Units and Conversions

Units in Volume	Volume (Based on Body Weight)
mL	mL/kg
dL	dL/kg
L	L/kg

Concentration	Weight Conversion
gm/L	1 kg = 1000 g
mg/L	1 g = 1000 mg
mg/dL	1 mg = 1000 µg
mg/mL	1 µg = 1000 ng
ng/mL	1 ng = 1000 pg
pg/mL	

Examples of Concentration Conversion Used in Toxicology and Therapeutics
1 mg% = 1 mg/dL
1 mg/L = 1 µg/mL

1 µg/L = 1 ng/mL	
1 ng/L = 1 pg/mL	

Example

The rate of ethanol elimination in four alcoholics undergoing detoxification was reported to be 17 to 33 mg/dL/hr (). (1) What is the rate of elimination in µg/mL/hr? (2) The peak blood concentration in one subject (SP) is 90 µg/dL. What is his peak blood concentration in µg/mL? (3) To which category would SP belong according to the following classification for blood alcohol (where values are in mg%)?

a. >0.55 mg%—fatal

b. 0.50–0.55 mg%—dead drunk

c. 0.10–0.50 mg%—illegal

d. 0.05–0.10 mg%—questionable

e. <0.05 mg%—safe

Solution

1. 17 µg/dL/hr = 17,000 µg/100 mL/hr = 170 µg/mL/hr

33 µg/dL/hr = 33,000 µg/100 mL/hr = 330 µg/mL/hr

2. 90 mg/dL = 90 µg/100 mL = 0.9 µg/mL

3. 90 mg/dL = 0.090 mg/100 dL = 0.090 mg%

Subject SP is questionable.

Practice Problem

The volume of distribution of theophylline is 0.7 L/kg. In most patients, the optimal benefits of theophylline therapy are seen at serum concentration of >10 mg/L; setting a plasma drug concentration of 5 mg/L lower therapeutic limit may result in reduced clinical efficacy (). (1) What is the volume of distribution in a 20-year-old male patient weighing 70 kg? (2) What is the total dose for the patient if he is dosed at 5 mg/kg?

Solution

(1) (5 mg/L is an alternative way to express 5 µg/mL)

Volume of patient = 0.7 L/kg x 70 kg = 49 L

(2) Dose for patient = 5 mg/kg x 70 kg = 350 mg

RATES AND ORDERS OF REACTIONS

Rate

The rate of a chemical reaction of process is the velocity with which the reaction occurs. Consider the following chemical reaction:

$$\text{drug A} \rightarrow \text{drug B}$$

If the amount of drug A is decreasing with respect to time (that is, the reaction is going in a forward direction), then the rate of this reaction can be expressed as

$$-\frac{dA}{dt}$$

Since the amount of drug B is increasing with respect to time, the rate of the reaction can also be expressed as

$$+\frac{dB}{dt}$$

Usually only the parent (or pharmacologically active) drug is measured experimentally. The metabolites of the drug or the products of the decomposition of the drug may not be known or may be very difficult to quantitate. The rate of a reaction is determined experimentally by measuring the disappearance of drug A at given time intervals.

Rate Constant

The order of a reaction refers to the way in which the concentration of drug or reactants influences the rate of a chemical reaction or process.

Zero-Order Reactions

If the amount of drug A is decreasing at a constant time interval *t*, then the rate of disappearance of drug A is expressed as

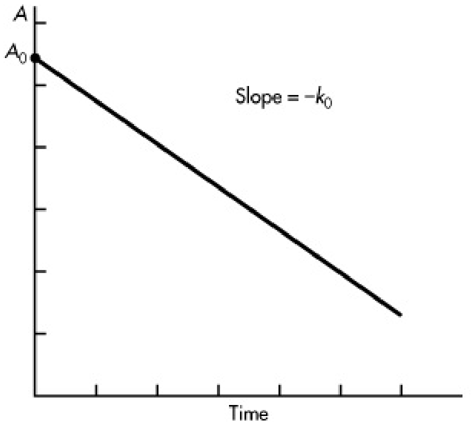
$$\frac{dA}{dt} = -k_0 \qquad \textbf{(2.19)}$$

The term k_0 is the zero-order rate constant and is expressed in units of mass/time (eg, mg/min). Integration of Equation 2.19 yields the following expression:

$$A = -k_0 t + A_0 \qquad (2.20)$$

where A_0 is the amount of drug at t = 0. Based on this expression (Eq. 2.20), a graph of A versus t yields a straight line (). The y intercept is equal to A_0, and the slope of the line is equal to k_0.

Figure 2-9.



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

Graph of Equation 2.20.

Equation 2.20 may be expressed in terms of drug concentration, which can be measured directly.

$$C = -k_0 t + C_0 \qquad (2.21)$$

C_0 is the drug concentration at time 0, C is the drug concentration at time t, and k_0 is the zero-order decomposition constant.

EXAMPLE

A pharmacist weighs exactly 10 g of a drug and dissolves it in 100 mL of water. The solution is kept at room temperature, and samples are removed periodically and assayed for the drug. The pharmacist obtains the following data:

Drug Concentration (mg/mL)	Time (hr)
100	0
95	2
90	4
85	6
80	8
75	10
70	12

From these data, a graph constructed by plotting the concentration of drug versus time will yield a straight line. Therefore, the rate of decline in drug concentration is of zero order.

The zero-order rate constant k_0 may be obtained from the slope of the line or by proper substitution into Equation 2.21.

If

$$C_0 = \text{concentration of 100 mg/mL at } t = 0$$

and

$$C = \text{concentration of 90 mg/mL at } t = 4 \text{ hr}$$

then

$$90 = -k_0(4) + 100$$

and

$$k_0 = 2.5 \text{ mg/mL hr}$$

Careful examination of the data will also show that the concentration of drug declines 5 mg/mL for each 2-hour interval. Therefore, the zero-order rate constant may be obtained by dividing 5 mg/mL by 2 hours:

$$k_0 = \frac{5 \text{ mg/ml}}{2 \text{ hr}} = 2.5 \text{ mg/mL hr}$$

First-Order Reactions

If the amount of drug A is decreasing at a rate that is proportional to the amount of drug A remaining, then the rate of disappearance of drug A is expressed as

$$\frac{dA}{dt} = -kA \qquad (2.22)$$

where k is the first-order rate constant and is expressed in units of time^{-1} (eg, hr^{-1}). Integration of Equation 2.22 yields the following expression:

$$\ln A = -kt + \ln A_0 \qquad (2.23)$$

Equation 2.23 may also be expressed as

$$A = A_0 e^{-kt} \qquad (2.24)$$

Because ln = 2.3 log, Equation 2.23 becomes

$$\log A = \frac{-kt}{2.3} + \log A_0 \qquad (2.25)$$

When drug decomposition involves a solution, starting with initial concentration C_0, it is often convenient to express the rate of change in drug decomposition, dC/dt, in terms of drug concentration, C, rather than amount because drug concentration is assayed. Hence,

$$\frac{dC}{dt} = -kC \qquad (2.26)$$

$$\ln C = -kt + \ln C_0 \qquad (2.27)$$

Equation 2.27 may be expressed as

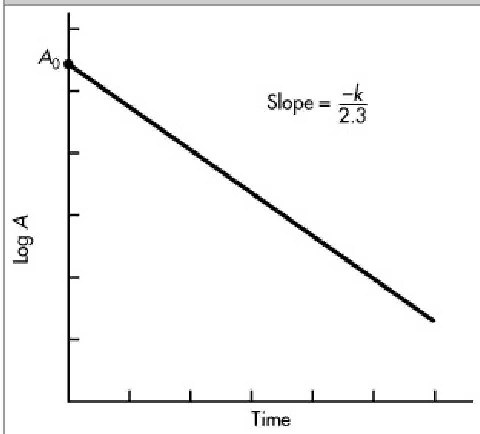
$$C = C_0 e^{-kt} \qquad (2.28)$$

Because ln = 2.3 log, Equation 2.27 becomes

$$\log C = \frac{-kt}{2.3} + \log C_0 \qquad (2.29)$$

According to Equation 2.25, a graph of log A versus t will yield a straight line (), the y intercept will be log A_0, and the slope of the line will be $-k/2.3$ (). Similarly, a graph of log C versus t will yield a straight line according to Equation 2.29. The y intercept will be log C_0, and the slope of the line will be $-k/2.3$. For convenience, C versus t may be plotted on semilog paper without the need to convert C to log C. An example is shown in .

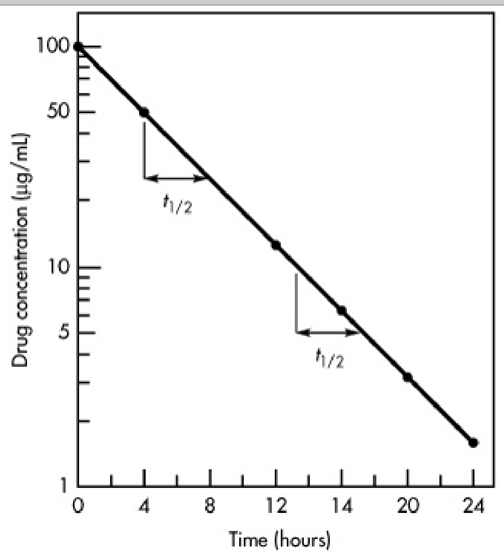
Figure 2-10.



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

Graph of Equation 2.25.

Figure 2-11.



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

This graph demonstrates the constancy of the $t_{1/2}$ in a first-order reaction.

Half-Life

Half-life ($t_{1/2}$) expresses the period of time required for the amount or concentration of a drug to decrease by one-half.

FIRST-ORDER HALF-LIFE

The $t_{1/2}$ for a first-order reaction may be found by means of the following equation:

$$t_{1/2} = \frac{0.693}{k} \qquad (2.30)$$

It is apparent from this equation that, for a first-order reaction, $t_{1/2}$ is a constant. No matter what the initial amount or concentration of drug is, the time required for the amount to decrease by one-half is a constant ().

ZERO-ORDER HALF-LIFE

In contrast to the first-order $t_{1/2}$, the $t_{1/2}$ for a zero-order process is not constant. The zero-order $t_{1/2}$ is proportional to the initial amount or concentration of the drug and is inversely proportional to the zero-order rate constant k_0:

$$t_{1/2} = \frac{0.5A_0}{k_0} \qquad (2.31)$$

Because the $t_{1/2}$ changes as drug concentrations decline, the zero-order $t_{1/2}$ has little practical value.

EXAMPLE

A pharmacist dissolves exactly 10 g of a drug into 100 mL of water. The solution is kept at room temperature, and samples are removed periodically and assayed for the drug. The pharmacist obtains the following data:

Drug Concentration (mg/mL)	Time (hr)	Log Drug Concentration
100.00	0	2.00
50.00	4	1.70
25.00	8	1.40
12.50	12	1.10
6.25	16	0.80
3.13	20	0.50
1.56	24	0.20

With these data, a graph constructed by plotting the logarithm of the drug concentrations versus time will yield a straight line on rectangular coordinates. More conveniently, the drug concentration values can be plotted directly at a logarithmic axis on semilog paper against time, and a straight line will be obtained (). The relationship of time versus drug concentration in indicates a first-order reaction.

The $t_{1/2}$ for a first-order process is constant and may be obtained from any two points on the graph that show a 50% decline in drug concentration. In this example, the $t_{1/2}$ is 4 hours. The first-order rate constant may be found by (1) obtaining the product of 2.3 times the slope or (2) by dividing 0.693 by the $t_{1/2}$, as follows:

$$\text{Slope} = -\frac{k}{2.3} = \frac{\log y_2 - \log y_1}{x_2 - x_1}$$

$$-k = \frac{2.3\ (\log 50 - \log 100)}{4 - 0} \qquad k = 0.173\ \text{hr}^{-1}$$

$$k = \frac{0.693}{t_{1/2}}$$

$$k = \frac{0.693}{4} = 0.173\ \text{hr}^{-1}$$

FREQUENTLY ASKED QUESTIONS

1. How do I know my graph is first order when plotted on semilog paper?

2. I plotted the plasma drug concentration versus time data on semilog paper, and got a slope with an incorrect *k*. Why?

3. I performed linear regression on *t* versus ln C_p. How do I determine the C^0_p from the intercept?

LEARNING QUESTIONS

1. Plot the following data on both semilog graph paper and standard rectangular coordinates.

Time (min)	Drug A (mg)
10	96.0
20	89.0
40	73.0
60	57.0
90	34.0
120	10.0
130	2.5

a. Does the decrease in the amount of drug A appear to be a zero-order or a first-order process?

b. What is the rate constant *k*?

c. What is the half-life $t_{1/2}$?

d. Does the amount of drug A extrapolate to zero on the *x* axis?

e. What is the equation for the line produced on the graph?

2. Plot the following data on both semilog graph paper and standard rectangular coordinates.

Time (min)	Drug A (mg)
4	70.0
10	58.0
20	42.0
30	31.0
60	12.0
90	4.5
120	1.7

Answer questions **a, b, c, d,** and **e** as stated in Question 1.

3. A pharmacist dissolved a few milligrams of a new antibiotic drug into exactly 100 mL of distilled water and placed the solution in a refrigerator (5°C). At various time intervals, the pharmacist removed a 10-mL aliquot from the solution and measured the amount of drug contained in each aliquot. The following data were obtained.

Time (hr)	Antibiotic (μg/mL)
0.5	84.5
1.0	81.2
2.0	74.5
4.0	61.0
6.0	48.0

8.0	35.0
12.0	8.7

a. Is the decomposition of this antibiotic a first-order or a zero-order process?

b. What is the rate of decomposition of this antibiotic?

c. How many milligrams of antibiotics were in the original solution prepared by the pharmacist?

d. Give the equation for the line that best fits the experimental data.

4. A solution of a drug was freshly prepared at a concentration of 300 mg/mL. After 30 days at 25°C, the drug concentration in the solution was 75 mg/mL.

a. Assuming first-order kinetics, when will the drug decline to one-half of the original concentration?

b. Assuming zero-order kinetics, when will the drug decline to one-half of the original concentration?

5. How many half-lives ($t_{1/2}$) would it take for 99.9% of any initial concentration of a drug to decompose? Assume first-order kinetics.

6. If the half-life for decomposition of a drug is 12 hours, how long will it take for 125 mg of the drug to decompose by 30%? Assume first-order kinetics and constant temperature.

7. Exactly 300 mg of a drug are dissolved into an unknown volume of distilled water. After complete dissolution of the drug, 1.0-mL samples were removed and assayed for the drug. The following results were obtained:

Time (hr)	Concentration (mg/mL)
0.5	0.45
2.0	0.3

Assuming zero-order decomposition of the drug, what was the original volume of water in which the drug was dissolved?

8. For most drugs, the overall rate of drug elimination is proportional to the amount of drug remaining in the body. What does this imply about the kinetic order of drug elimination?

9. A single cell is placed into a culture tube containing nutrient agar. If the number of cells doubles every 2 minutes and the culture tube is completely filled in 8 hours, how long does it take for the culture tube to be only half full of cells?

10. The volume of distribution of warfarin is 9.8 ± 4.2 L. Assuming normal distribution, this would mean that 95% of the subjects would have a volume of distribution ranging from _____ L to _____ L.

11. Which of the following functions has the steepest declining slope? (*t* is the independent variable and *y* is the dependent variable.)

a. $y = 2e^{-3t}$

b. $y = 3e^{-2t}$

c. $y = 2e^{t}$

12. Which of the following equations predicts *y* increasing as *t* increases? (*t* is a positive number.)

a. $y = 2e^{-3t}$

b. $y = 3e^{-2t}$

c. $y = 2e^{t}$

13. Which of the following would result in an error message if you took the log of *x* using a calculator?

a. $x = 2.5$

b. $x = 0.024$

c. $x = 10^{-2}$

d. $x = -0.2$

14. Which of the following equation(s) would have the greatest value at *t* equal to zero assuming that *t* is not negative.

a. e^{-3t}

b. $3e^{-2t}$

c. $2/e^{t}$

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