# Mathematical Fundamentals in Pharmacokinetics:

Introduction

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# Introduction

- pharmacokinetics and biopharmaceutics have a strong mathematical basis in mathematical principles (algebra, calculus, exponentials, logarithms, and unit analysis).
- Most of the mathematics needed for pharmacokinetics may be performed with pencil, graph paper, and logical thought processes.

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- In pharmacokinetic calculation, the answer is correct only if both the number and the units are correct.
- The units for the answer to a problem should be checked carefully.
- A scientific calculator with logarithmic and exponential functions will make the calculations less tedious.

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# Exponents

- In the expression:

$$N = b^{x}$$

- $x$ 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 above Equation, is 1000

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

1. $m^0 = 1$
2. $m^1 = m$
3. $m^{-1} = 1/m^1$

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# Logarithms

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

$$N = b^{X} \quad \textbf{then} \quad \log_{b} N = X$$

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# Logarithms

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

$$100 = 10^2 \quad \text{then} \quad \log 100 = 2$$

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

$$2.303 \log N = \ln N$$

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

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# Logarithms

- 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.
- The logarithm of a number greater than 1 is a positive number.

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## Laws of Logarithms

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

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

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

Of special interest is the following relationship:

$$\ln e^{-x} = -x$$

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

Ex . . . Log $10^{-2} = -2$

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# Calculus

- **Differential Calculus:**
  - Differential equations are used to relate the concentrations of drugs in various body organs over time.

- **Integrated Calculus:**
  - Integrated equations are frequently used to model the cumulative therapeutic or toxic responses of drugs in the body.

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# Differential Calculus

- It involves finding the rate at which a variable quantity is changing.

- For example, the concentration (c) of a drug changes as a function of time (t).

$$c = f(t)$$

$$\frac{dc}{dt} = f'(t) = rate$$

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# Example

| 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 g/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:

$$\frac{dC}{dt} = 2\mu g/(ml.hr)$$

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# Integral Calculus

- Integration is the reverse of differentiation and is considered the summation of $f(x) \cdot dx$.

- The integral sign $\int$ implies summation.

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# Integral Calculus

- 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 $x = b$.

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# Integral Calculus

- A *definite integral* of a mathematical function is the sum of individual areas under the graph of that function.

- 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).

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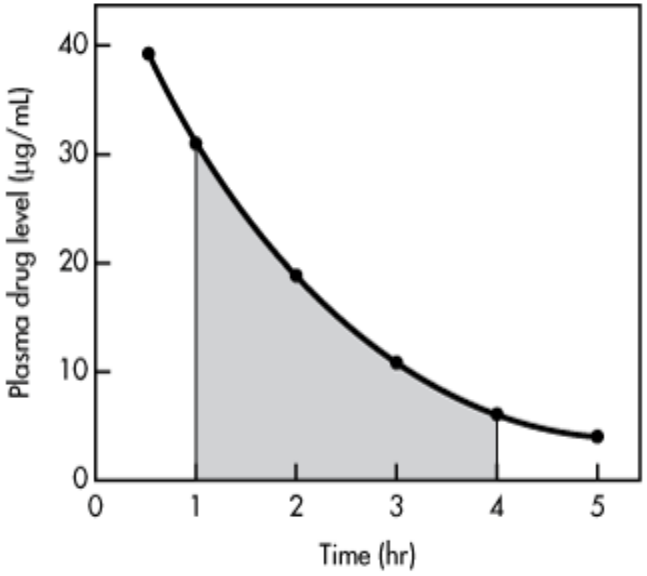
# Trapezoidal Rule

- 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:




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

| 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 |

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# Trapezoidal Rule

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

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

Where:

[AUC] = area under the curve.

$t_n$ = time of observation of drug concentration $C_n$

$t_{n-1}$ = time of prior observation of drug concentration corresponding to $C_{n-1}$.

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- 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:

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

- Similarly, the AUC between 2 and 3, 3 and 4 hours are calculated.
- The total AUC between 1 and 4 hours is obtained by adding the three smaller AUC values together.

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

$$24.35+14.75+8.94 = 48.04\mu g.hr/ml$$

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- 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.

- 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.

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

$$\left[AUC\right]_{t_n}^{t_\infty} = \frac{Cp_n}{k}$$

- Where: $C_{pn}$ = last observed plasma concentration at $t_n$ .
  $k$ = 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:

$$\left[AUC\right]_0^\infty = \sum \left[AUC\right]_{t_{n-1}}^{t_n} + \frac{Cp_n}{k}$$

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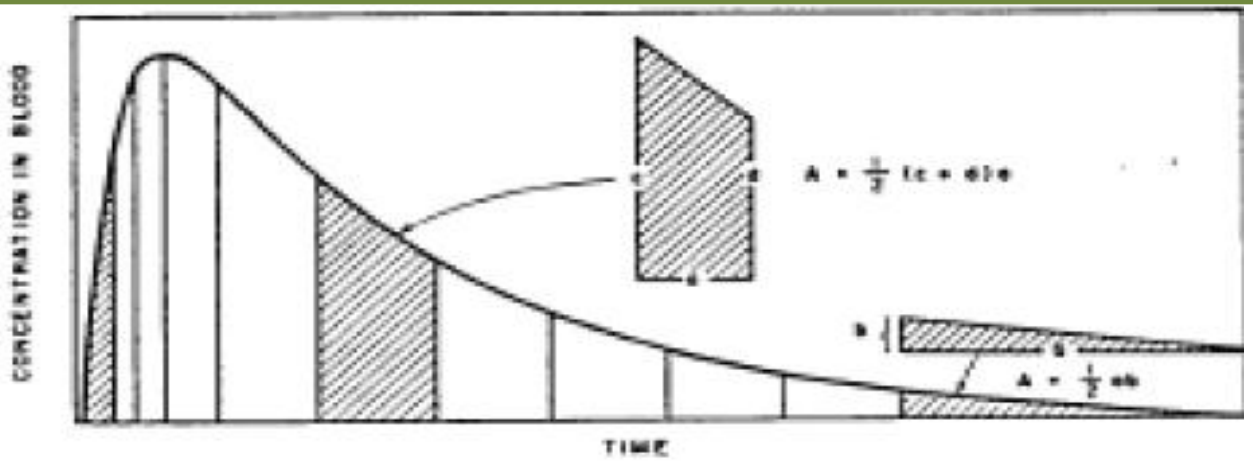
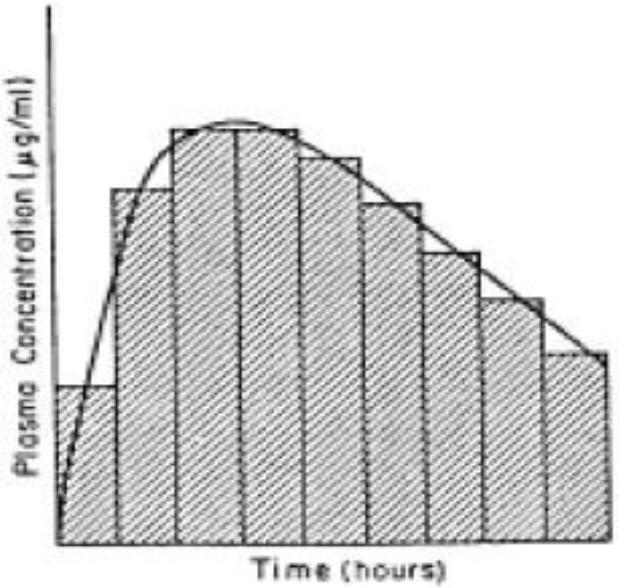
# Trapezoidal AUC

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# GRAPHS

- The construction of a curve 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).
- The values are usually arranged so that they increase from left to right and from bottom to top.

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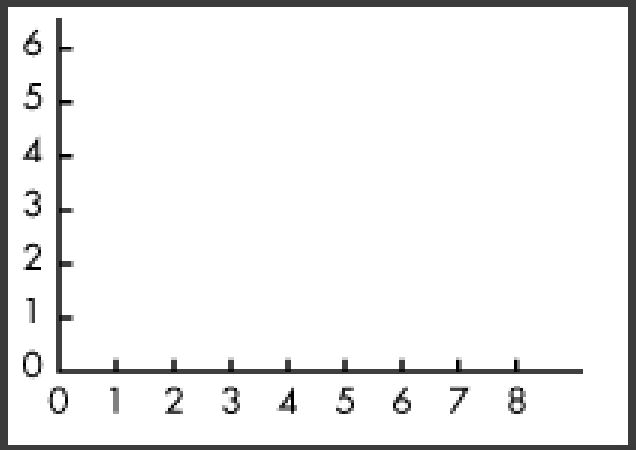
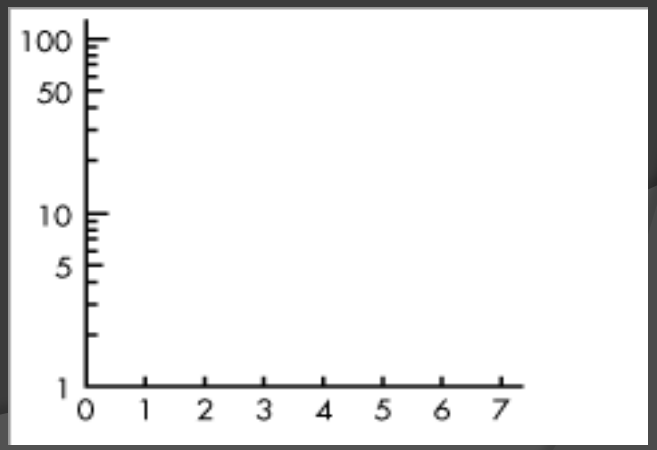
- In pharmacokinetics, time is the independent variable and is plotted on the abscissa (*x* axis), whereas drug concentration is the dependent variable and is plotted on the ordinate (*y* axis).

- Two types of graph paper are usually used in pharmacokinetics:




Rectangular coordinate




Semilog coordinate

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# 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.

- the data may be arranged 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.

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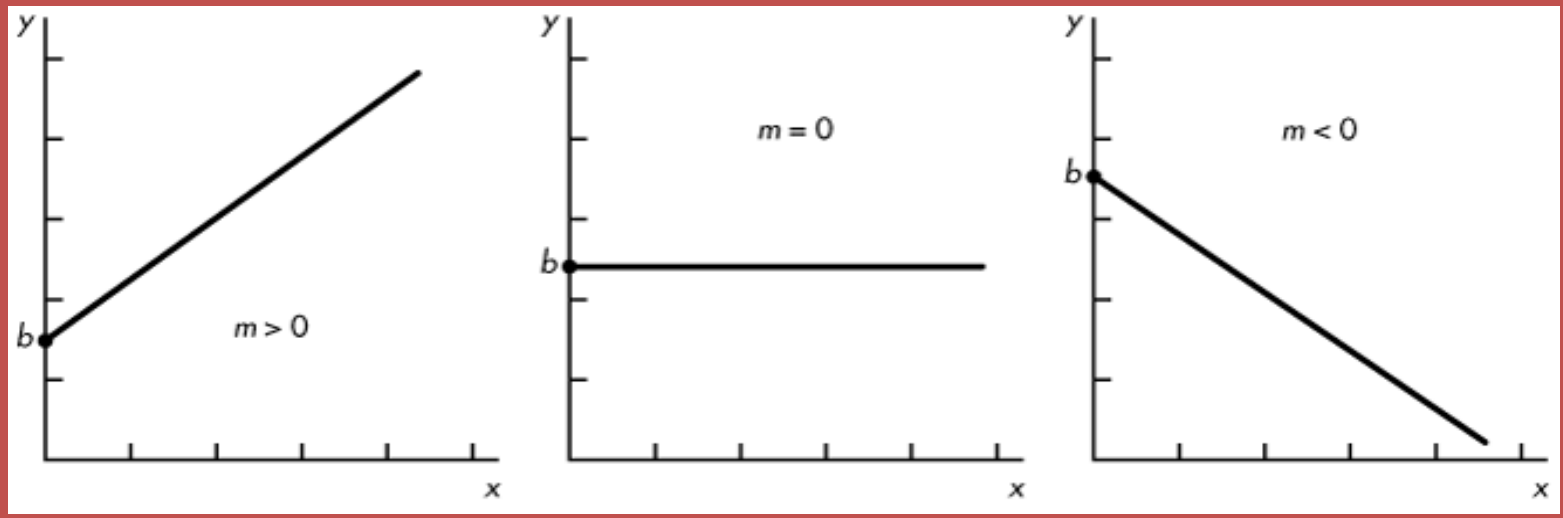
# Curve Fitting

- The general equation of a straight line is

$$Y = mx + b$$

- where ***m*** = slope and ***b*** = *y* intercept

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# Curve Fitting

- 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.

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# 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:

$$Slope = \frac{y_2 - y_1}{x_2 - x_1}$$

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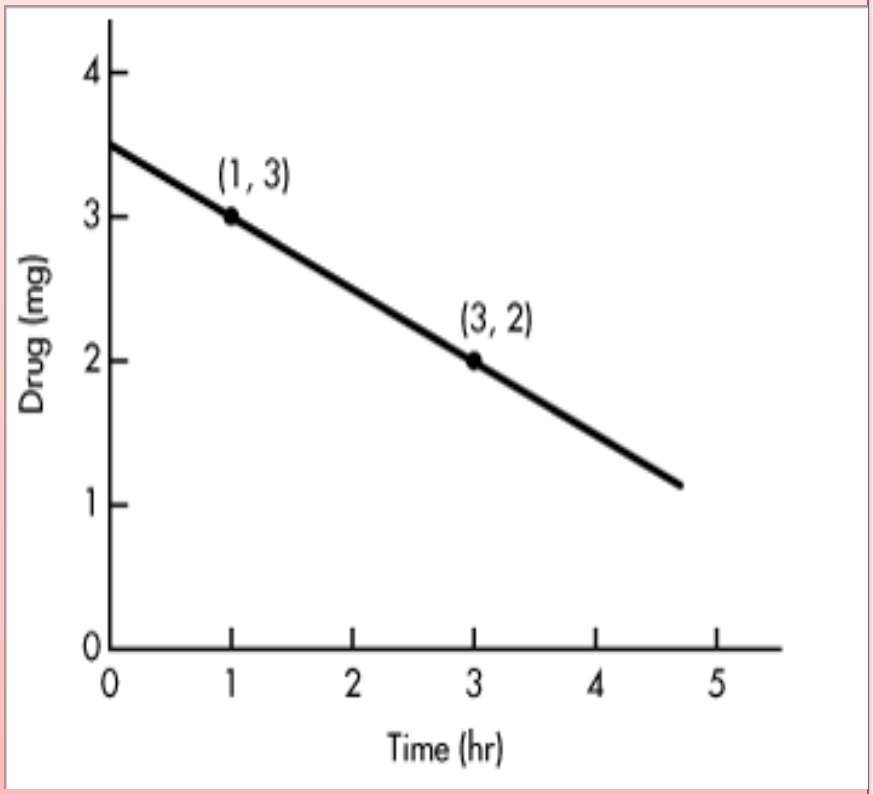
- The slope of the line plotted in is

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




- Because the *y* intercept is equal to 3.5, the equation for the curve is

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

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# Drawing a best-fit line through the Data

- Drawing a line through the data doesn't mean through just two data points but through all the data points.

- The best approach is to put the line through all the data. There should be points above and below the line.

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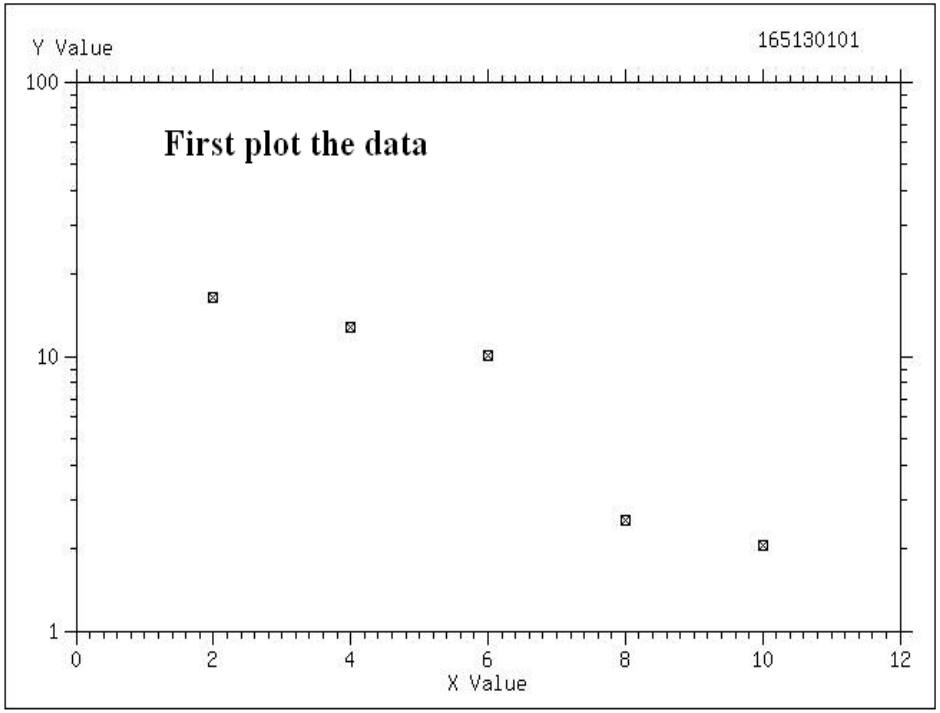


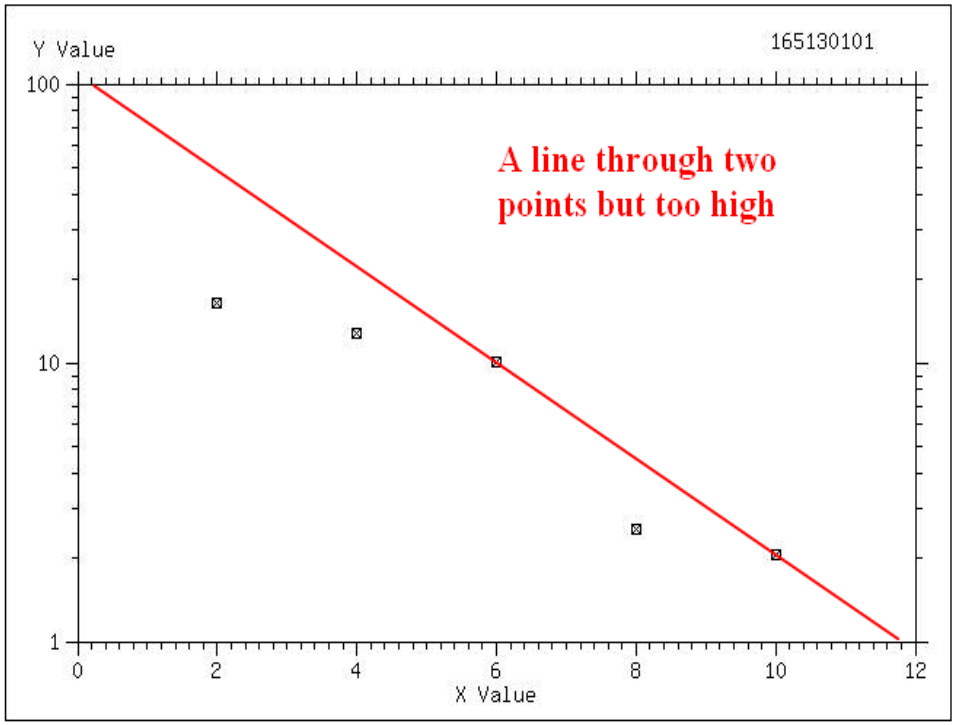


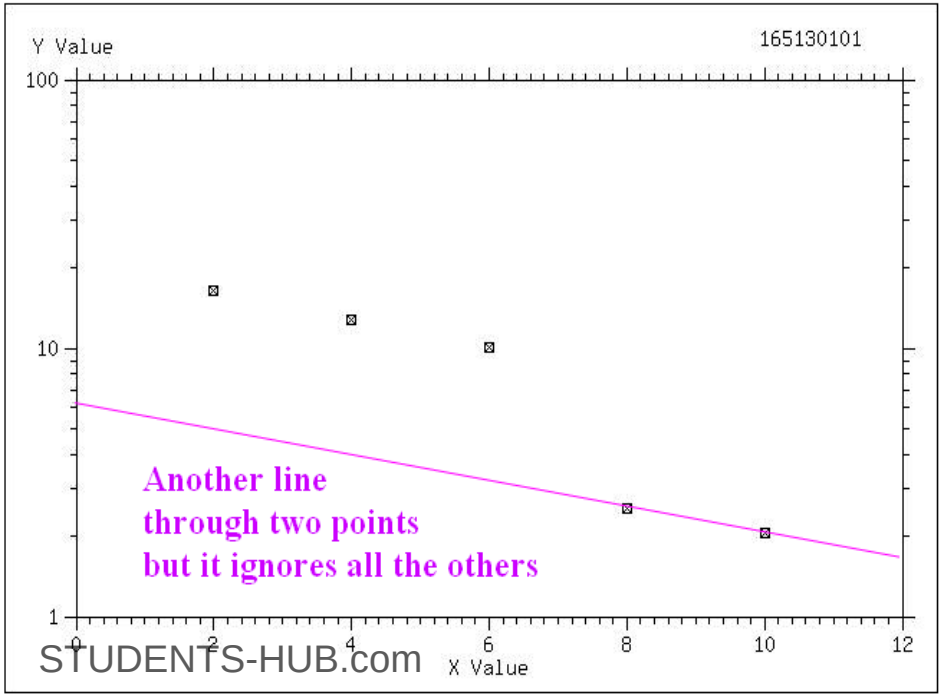


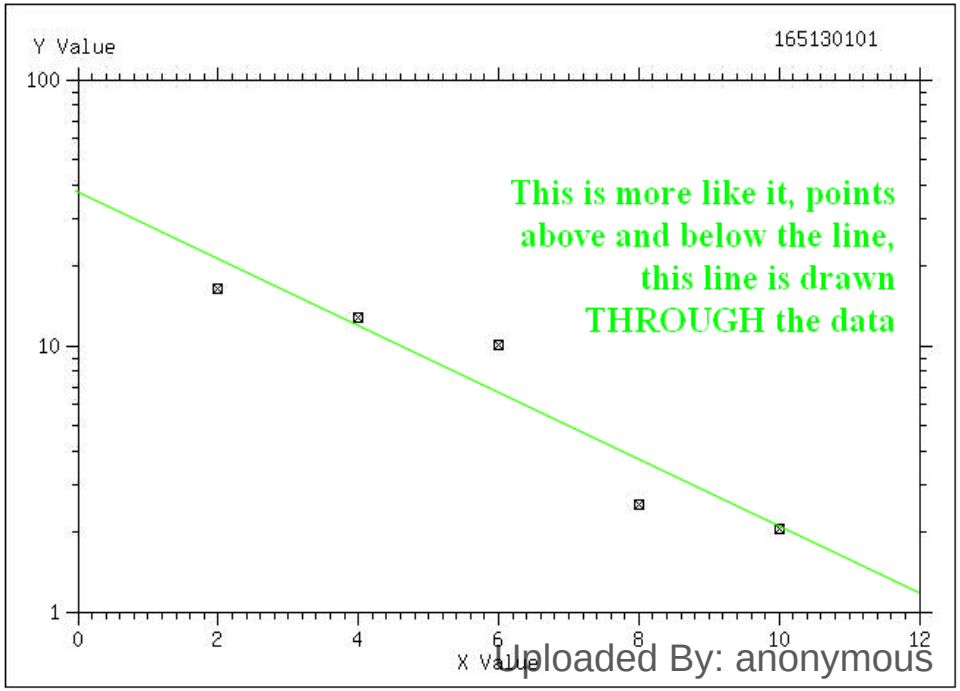


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**TABLE 2-1 Common Units Used in Pharmacokinetics**

| Parameter | Symbol | Unit | Example |
|---|---|---|---|
| Rate | $\frac{dD}{dt}$ | $\frac{\text{Mass}}{\text{Time}}$ | mg/h |
| | $\frac{dC}{dt}$ | $\frac{\text{Concentration}}{\text{Time}}$ | ug/mL/h |
| Zero-order rate constant | $K_0$ | $\frac{\text{Concentration}}{\text{Time}}$ | μg/mL/h |
| | | $\frac{\text{Mass}}{\text{Time}}$ | mg/h |
| First-order rate constant | $k$ | $\frac{1}{\text{Time}}$ | 1/h or $h^{-1}$ |
| Drug dose | $D_0$ | Mass | mg |
| Concentration | $C$ | $\frac{\text{Mass}}{\text{Volume}}$ | μg/mL |
| Plasma drug concentration | Cp | $\frac{\text{Drug}}{\text{Volume}}$ | μg/mL |
| Volume | $V$ | Volume | mL or L |
| Area under the curve | AUC | Constration × time | μg·h/mL |
| Fraction of drug absorbed | $F$ | No units | 0 to 1 |
| Clearance | $Cl$ | $\frac{\text{Volume}}{\text{Time}}$ | mL/h |
| Half-life | $t_{1/2}$ | Time | H |

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# Units for Expressing Blood Concentrations

- Various units used to express drug concentrations in blood, plasma, or serum.
- Drug concentrations or drug levels should be expressed as mass/volume.
- The expressions g/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).

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- 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.

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# Units in Pharmacokinetics

- 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.

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- 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.

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# Statistics

- All measurements have some degree of error.
- 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* is a statistical way of expressing the spread between the individual measurements from the mean.
  - **A small SD** indicates of good consistency and reproducibility of the measurements.
  - **A large SD** indicates poor consistency and data fluctuations.

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# Rates and Orders of Reactions

- The rate of a chemical reaction of process is the velocity with which the reaction occurs.

- Consider the following chemical reaction:

$$DrugA \rightarrow DrugB$$

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

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# Rates and Orders of Reactions

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

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

- The rate of a reaction is determined experimentally by measuring the disappearance of drug A at given time intervals.

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# 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
  – First-Order Reactions

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# 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:

$$-\frac{dA}{dt} = k_0$$

- The term $k_0$ is the zero-order rate constant and is expressed in units of mass/time (eg, mg/min).

- Integration of above Equation, yields the following expression:

$$A = -k_0 t + A_0$$

where $A_0$ is the amount of drug at $t = 0$.

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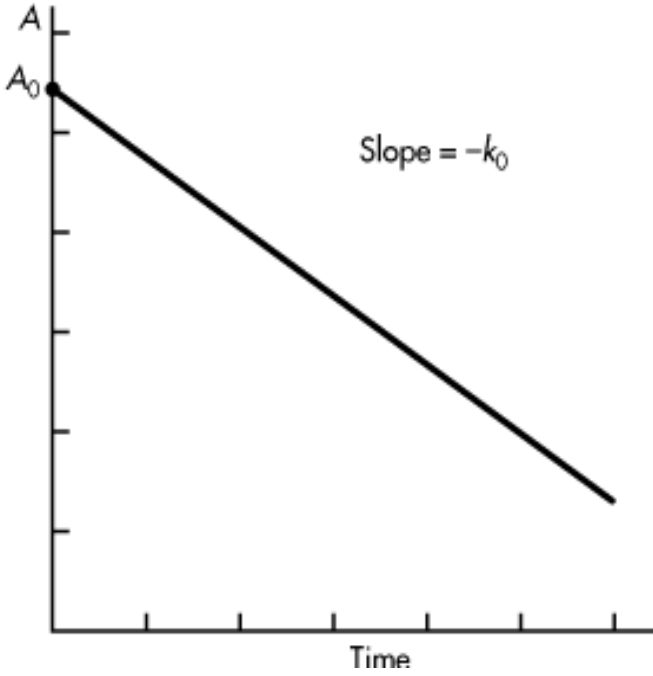
# Zero-Order Reactions

- a graph of *A* versus *t* yields a straight line.
  - The *y* intercept is equal to $A_0$
  - The slope of the line is equal to $k_0$.




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

$$C = -k_0 t + C_0$$

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

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# 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:

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

- where *k* is the first-order rate constant and is expressed in units of time$^{-1}$ (eg, hr$^{-1}$).

- Integration of Equation yields the following expression:

$$\int_{A_0}^{A} \frac{dA}{A} = \int_{0}^{t} -k\,dt$$

$$\ln A = -kt + \ln A_0$$

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# First-Order Reactions

- Equation may also be expressed as:

$$A = A_0 e^{-kt}$$

- Because ln = 2.3 log, Equation becomes:

$$\log A = \frac{-kt}{2.303} + \log A_0$$

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# First-Order Reactions

- 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,

$$\frac{dc}{dt} = -kc$$

$$\ln C = -kt + \ln C_0$$

$$C = C_0 e^{-kt}$$

$$\log C = \frac{-kt}{2.3} + \log C_0$$

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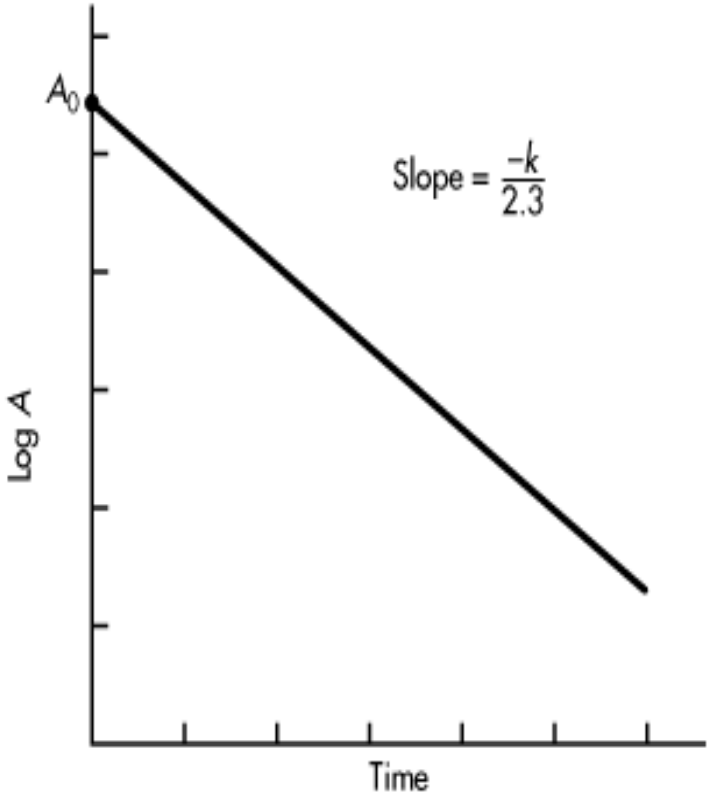
# First-Order Reactions

- a graph of log *A* versus *t* will yield a straight line .
- The *y* intercept will be log $A_0$
- The slope of the line will be $-k/2.3$ .




- Similarly, a graph of log *C* versus *t* will yield a straight line. The *y* intercept will be log $C_0$, and the slope of the line will be $-k/2.3$.

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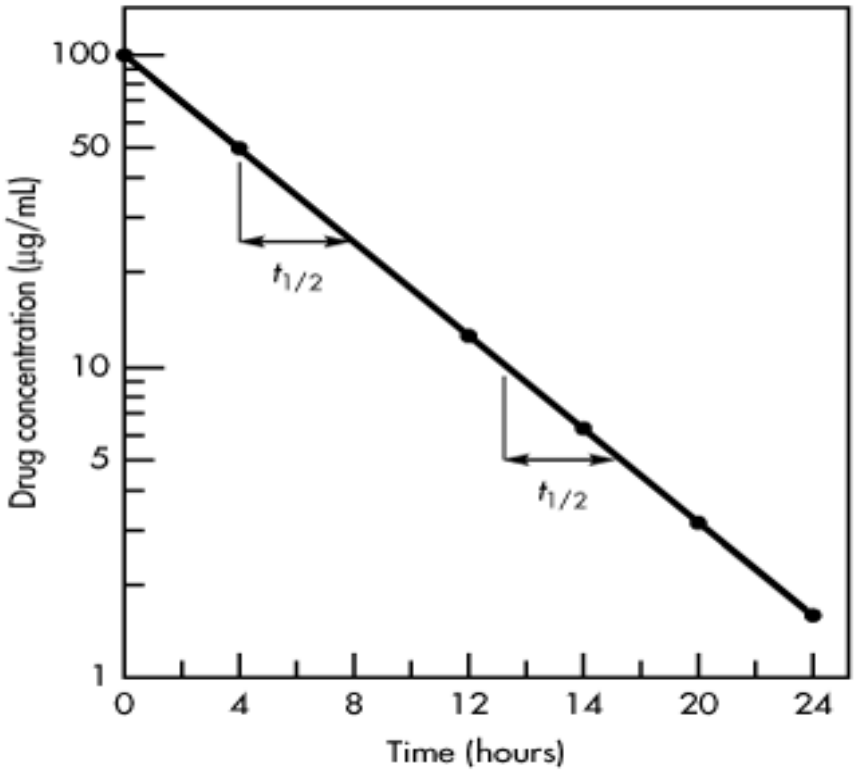
# First-Order Reactions

- *C* versus *t* may be plotted on semilog paper without the need to convert *C* to log *C*. An example is shown:

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# 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.

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# First-Order Half-Life

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

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

- $t_{1/2}$ 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.

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# Zero-Order Half-Life

- 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 $k_0$:

$$t_{1/2} = \frac{0.5A_0}{k_0}$$

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## HALF-LIVES AND PERCENT OF DRUG REMOVED

| NUMBER OF HALF-LIVES | PERCENT OF DRUG REMAINING | PERCENT OF DRUG REMOVED |
|---|---|---|
| 0 | 100 | 0 |
| 1 | 50 | 50 |
| 2 | 25 | 75 |
| 3 | 12.5 | 87.5 |
| 4 | 6.25 | 93.75 |
| 5 | 3.125 | 96.875 |

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# Conc. Vs. time plots

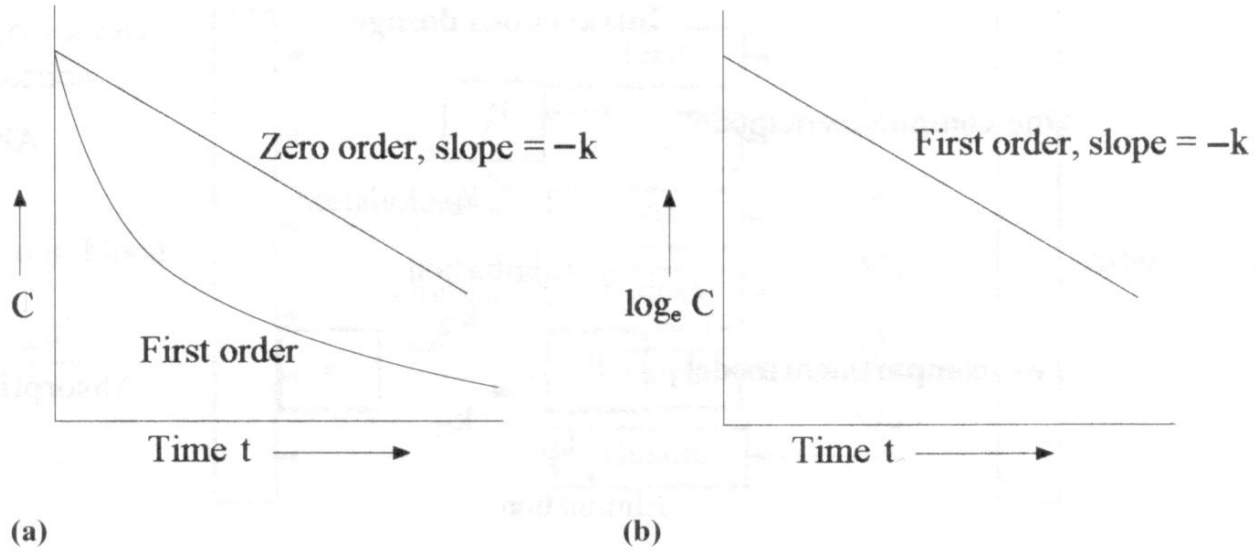


**Figure 5.5.** (a) Zero- and first-order concentration–time plots and (b) first-order log$_e$ concentration–time plots.

$C = C_o - kt$ $\ln C = \ln C_o - kt$

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# Types of Kinetics Commonly Seen

**Zero Order Kinetics**

- Rate = k
- $C = C_o - kt$

- C vs. t graph is LINEAR

**First Order Kinetics**

- Rate = k C
- $C = C_o e^{-kt}$

- C vs. t graph is NOT linear, decaying exponential. Log C vs. t graph is linear.

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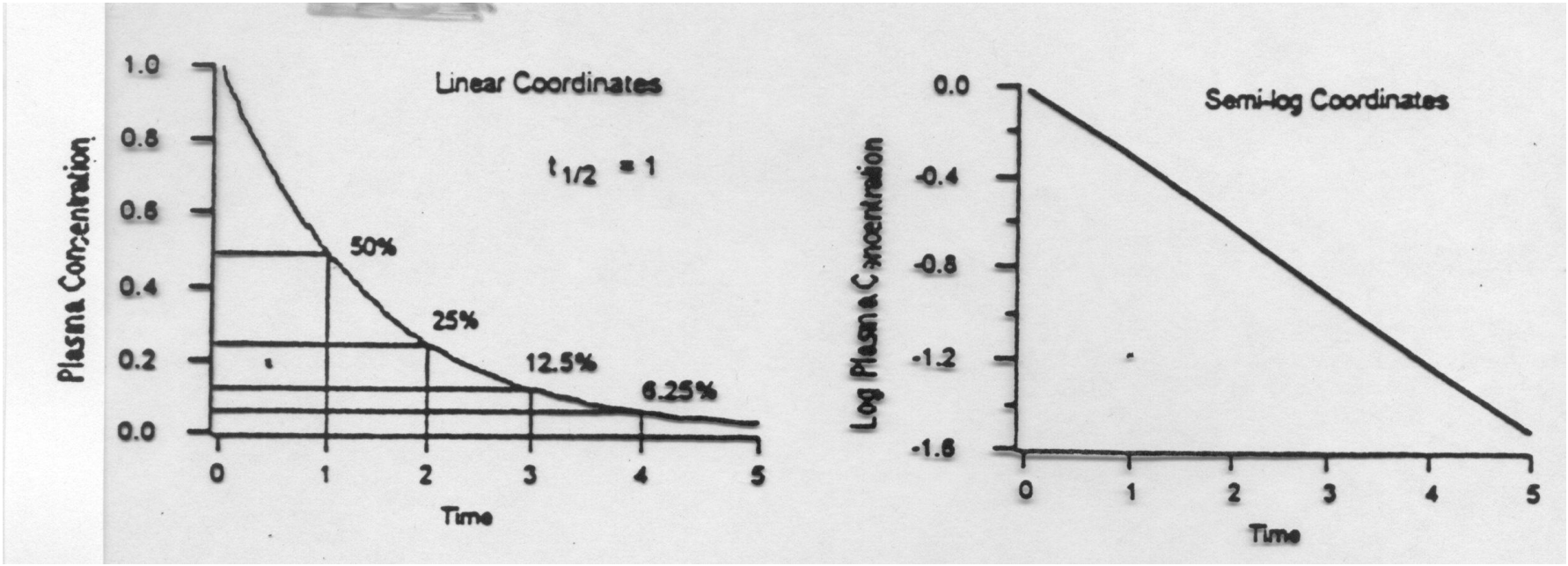
# First-Order Kinetics

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# Comparison

- First Order Elimination
  - [drug] decreases exponentially w/ time
  - Rate of elimination is proportional to [drug]
  - Plot of log [drug] or ln[drug] vs. time are linear
  - $t_{1/2}$ is constant regardless of [drug]

- Zero Order Elimination
  - [drug] decreases linearly with time
  - Rate of elimination is constant
  - Rate of elimination is independent of [drug]
  - No true $t_{1/2}$

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