

PART

# *PREFORMULATION*

COPYRIGHTED MATERIAL



# CHAPTER 1

## MATHEMATICAL CONCEPTS

### 1.1 INTRODUCTION

Pharmacy as a profession is art, business, and science. The science of pharmacy, also known as *pharmaceutical science*, requires knowledge of mathematics. Experimentation in pharmaceutical science produces quantitative measures with specific values. Handling these measures mathematically depends on how to apply rules to define them. In turn, these definitions of measures lead to a description of experimental entities. For example, to define a solution's pH, a pH meter is normally used in the measurement. Knowledge of the pH value can define the concentration of hydronium ions present in the solution. The relationship that allows transformation of the pH value to a concentration term is a mathematical expression known as *Sørensen's equation*:

$$\text{pH} = -\log[\text{H}_3\text{O}^+] \quad (1.1)$$

If the pH meter reads pH 10.8 for the solution, equation (1.1) may be used for the determination of  $[\text{H}_3\text{O}^+]$ :

$$\begin{aligned} 10.8 &= -\log[\text{H}_3\text{O}^+] \\ [\text{H}_3\text{O}^+] &= 1.58 \times 10^{-11} \text{ M} \end{aligned}$$

Thus, the concentration of hydronium ions in solution was computed from equation (1.1) by mathematical manipulation employing the rules of logarithms.

Mathematical rules can also aid a pharmaceutical scientist in describing the blood profile following administration of a drug in patients. Following intravenous administration of a drug, the drug is placed in circulation and achieves its highest concentration immediately following injection. The concentration of the drug decreases thereafter through distribution to tissues and via metabolic pathways. The drug disappearance from the circulation over time may be described by an exponential function following the general expression

$$C_{\text{blood}} = C_{\text{initial}}e^{-kt} \quad (1.2)$$

where  $C_{\text{blood}}$  is the drug concentration at time  $t$ ,  $C_{\text{initial}}$  is the initial concentration of the drug in the blood immediately following administration, and  $k$  is the elimination

#### 4 CHAPTER 1 MATHEMATICAL CONCEPTS

rate constant. Equation (1.2) can be made linear by converting it to its logarithmic form:

$$\ln C_{\text{blood}} = \ln C_{\text{initial}} - kt \quad (1.3)$$

The transformation of equation (1.2) to equation (1.3) requires knowledge of the rules of logarithms. *Pharmacokinetics*, which is the study of drug absorption, distribution, and elimination, uses these mathematical manipulations of data to improve patients' therapeutic outcomes. Equation (1.3) describes a linear relationship between the natural logarithm of drug blood concentration and time. This linear relationship is not only important in pharmacokinetics but its applications are well utilized in physical pharmacy applications.

In this chapter we cover the major important mathematical concepts that pharmaceutical scientists utilize in their studies. With the advancement of computer technology, many of these mathematical applications are handled by a computer software program or even by a basic scientific calculator.

## 1.2 THE SIMPLE LINEAR RELATIONSHIP

When two variables  $x$  and  $y$  vary with each other linearly, their function may be written as

$$y = a + bx \quad (1.4)$$

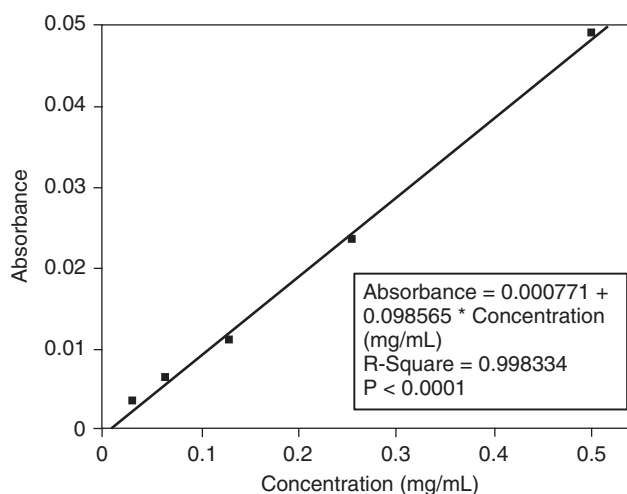
where  $y$  is the dependent variable and  $x$  is the independent variable. The slope of the line is  $b$  and the  $y$ -intercept is  $a$ . The coefficient  $b$  can be positive or negative in value. When  $b$  is positive, an increase in  $x$  results in an increase in  $y$ . Conversely, if  $b$  is negative, an increase in  $x$  produces a decrease in  $y$ . Although equation (1.4) can be found manually, the usual method is to input the  $y$  and  $x$  values into a computer program to generate a linear equation. For example, the following data were obtained from a spectrophotometric experiment measuring the concentration of aspirin in solution:

Concentration (mg/mL)	Absorbance
0.0325	0.003
0.0650	0.006
0.1250	0.011
0.2500	0.023
0.5000	0.049

To obtain the linear relationship between concentration and absorbance, a simple scientific calculator may be used. The following equation is obtained:

$$\text{absorbance} = -0.000771 + 0.098565 \times \text{concentration (mg/mL)} \quad (1.5)$$

Comparing equation (1.4) to equation (1.5), the absorbance value is the dependent variable and the concentration is the independent variable. The  $y$ -intercept is negative in this case, and statistically speaking, is not different from zero. The coefficient  $b$  is positive, which is expected from relationships that represent



**FIGURE 1.1** Positive linear relationship between the concentration of aspirin in solution and absorbance readings. Data points are experimental values, and the solid line is the best-fit line for the data.

Beer's law (Figure 1.1). It is important always to check whether or not the mathematical relationship adheres to the scientific norms. In using equation (1.5), the concentration of aspirin in an unknown solution may be estimated. For example, if the absorbance of an unknown solution of aspirin is 0.015, the estimated concentration of aspirin in solution is

$$0.015 = -0.000771 + 0.098565 \times \text{concentration (mg/mL)}$$

$$\text{concentration (mg/mL)} = 1.6$$

Note that the  $y$ -intercept of  $-0.000771$  was used in estimating the concentration.

Based on Beer's law, the absorbance value is the logarithm of the ratio  $I_0/I$ , where  $I_0$  and  $I$  are the intensities of the incident and emitted light, respectively. The absorbance value is logarithmic; however, the spectrophotometer readily calculates its value and the operator does not need to handle logarithmic calculations. Equation (1.5) follows the general format of *Beer's law*:

$$\text{absorbance} = \text{absorptivity} \times \text{pathlength of light} \times \text{concentration} \quad (1.6)$$

Comparing equation (1.4) to equation (1.6), the theoretical  $y$ -intercept value must be zero, and the coefficient  $b$  is absorptivity  $\times$  pathlength of light. The pathlength of light is predetermined by the instrument's tube holder (normally, 2 cm in length), and thus the slope of line  $b$  allows calculation of the absorptivity value, which is an important physical characteristic of a drug. (The absorptivity value varies with the solvent, the temperature, and the wavelength being used in the experiment.) Under the conditions of this experiment, the absorptivity may be calculated as follows,

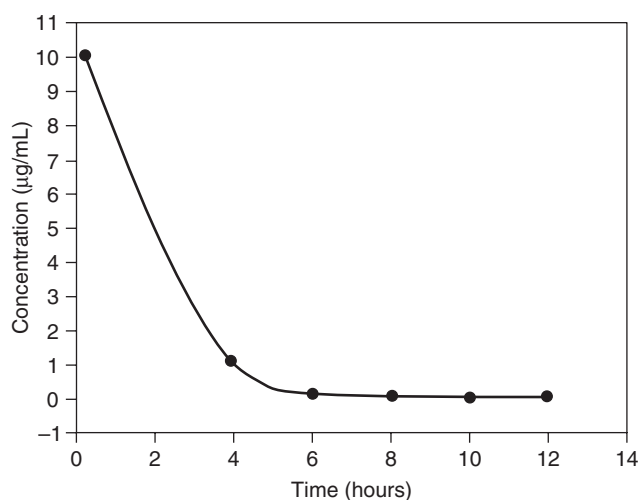


FIGURE 1.2 Exponential decrease in drug blood concentration vs. time.

assuming that the pathlength was 2 cm:

$$b = \text{absorptivity} \times \text{pathlength of light}$$

$$0.098565 = \text{absorptivity} \times 2$$

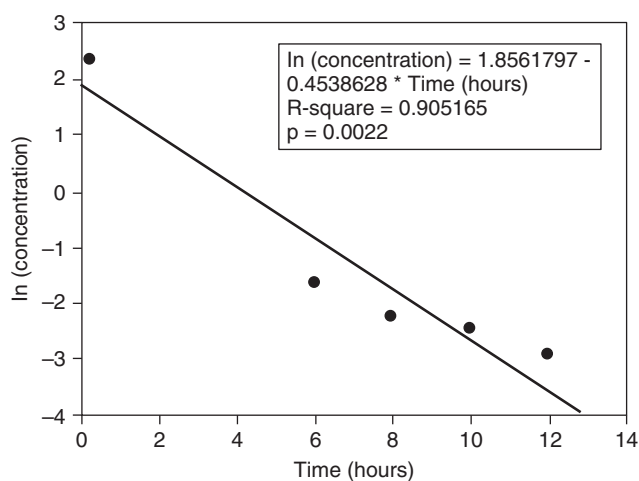
$$\text{absorptivity} = 0.049 \text{ mL}/(\text{mg} \cdot \text{cm})$$

For some linear relationships, the slope of the line is negative. For example, equation (1.3) has a negative slope. The negative slope of equation (1.3) indicates that concentration of the drug in blood decreases with time. It should be emphasized, however, that the linear relationship is between the logarithm of the drug concentration and time, not the concentration of the drug vs. time. Thus, when presented with data such as drug concentration vs. time (Figure 1.2), convert the drug concentration to logarithmic terms (natural or base 10) and then plot  $\ln(\text{drug blood concentration})$  vs. time. The resulting graph is a straight line (Figure 1.3).

Time (h)	Concentration ( $\mu\text{g}/\text{mL}$ )	$\ln(\text{concentration})$
0.25	10	2.30258509
4	1	0
6	0.2	-1.6094379
8	0.1	-2.3025851
10	0.08	-2.5257286
12	0.05	-2.9957323

The equation that relates the drug blood concentration vs. time is presented as

$$\ln(\text{concentration}) = 1.8561797 - 0.4538628 \times \text{time (h)} \quad (1.7)$$



**FIGURE 1.3** Linear relationship of the natural logarithm of drug blood concentration vs. time.

From this equation, the first-order rate constant for elimination may be calculated from the slope:

$$\text{slope} = -0.4538628 = -k_{\text{el}}$$

Therefore,

$$k_{\text{el}} = 0.454 \text{ h}^{-1}$$

The value of  $k_{\text{el}}$  indicates that 45.4% of the drug concentration remaining is eliminated each hour.

### 1.3 EXPONENTIAL RULES

In physical pharmacy expressions, many of the calculations require handling terms with exponents. The rules for handling exponents are (Stein, 1977; Anton, 1980):

1. Any number raised to the power of zero results in a value of 1 :  $x^0 = 1$
2. Any number raised to the power of 1 will equal its value:  $x^1 = x$
3.  $x^n \times x^m = x^{n+m}$
4.  $x^n / x^m = x^{n-m}$
5.  $1/x^n = x^{-n}$
6.  $(x^n)^2 = x^{2n}$

In preparing buffer solutions, the ability of the resulting solution to resist a change in its pH is known as the *buffer capacity*. In calculating the buffer capacity value, the hydronium ion concentration, the acid dissociation constant, and the total buffer concentration must be known. Assuming that the total buffer concentration

was 1 M,  $[\text{H}_3\text{O}^+] = 10^{-4}$  M, and  $K_a = 1.47 \times 10^{-4}$ , the buffer capacity value can be estimated from these values. The equation for calculating the buffer capacity is (Martin et al., 1983)

$$\begin{aligned}\text{buffer capacity} &= 2.303C \frac{K_a[\text{H}_3\text{O}^+]}{\{K_a + [\text{H}_3\text{O}^+]\}^2} \\ &= (2.303)(1) \frac{(1.47 \times 10^{-4})(10^{-4})}{[(1.47 \times 10^{-4}) + (10^{-4})]^2} \\ &= 0.56\end{aligned}$$

The higher the value of the buffer capacity, the higher the resistance of the buffer is to a change in pH.

## 1.4 LOGARITHMIC RULES

For most pharmaceutical applications, the *logarithmic function* serves to convert a nonlinear relationship to a linear one. Linearity allows easier calculations for coefficients from a mathematical model. Logarithmic functions are thought of as exponential equations; thus,  $y = x^z$  translates into  $z = \log_x y$  ( $\log_x =$  logarithm of base  $x$ ). There are two important logarithm symbols:  $\log$  and  $\ln$ ;  $\log$  is the logarithm to the base 10, whereas  $\ln$  denotes a natural logarithmic function to the base  $e$  ( $e = 2.71828\dots$ ). When handling logarithmic terms in an equation, the following mathematical rules apply (Stein, 1977; Anton, 1980):

1.  $\ln x = 2.303 \log x$
2.  $\log(x \times z) = \log x + \log z$
3.  $\log(x/z) = \log x - \log z$
4.  $\log x = z$  or  $x = 10^z$
5.  $\ln x = z$  or  $x = e^z$
6.  $\log x^z = z \log x$
7.  $\ln e = 1$
8.  $\log 10 = 1$

For example, consider equation (1.7) and convert the equation to its log form of base 10:

$$\ln(\text{concentration}) = 1.8561797 - 0.4538628 \times \text{time (h)} \quad (1.7)$$

$$2.303 \log(\text{concentration}) = 1.8561797 - 0.4538628 \times \text{time (h)}$$

$$\log(\text{concentration}) = 0.806 - 0.197 \times \text{time (h)} \quad (1.8)$$

Equations (1.7) and (1.8) are identical mathematically, and they produce the same value for the elimination rate constant. In using equation (1.8) to calculate  $k$ , the slope of the equation is used:

$$\text{slope} = -0.197 = \frac{-k}{2.303}$$



Therefore,  $k = (2.303) \times (0.197) = 0.454 \text{ h}^{-1}$ , which is the same value as that obtained using equation (1.7).

In Chapter 8, concepts related to the shelf-life determination of drug products are introduced. One area of concern is the effect of a change in storage temperature on the stability of a drug. One equation uses the logarithm of the ratio of degradation rate constants at two different temperatures:  $\log(k_2/k_1)$ . The following calculations illustrate the use of logarithmic rules in solving such equations:

$$\begin{aligned}k_1 &= 0.034 \text{ min}^{-1} \\k_2 &= \text{unknown} \\ \log \frac{k_2}{k_1} &= 0.842\end{aligned}$$

To find  $k_2$  we use,

$$\begin{aligned}\log \frac{k_2}{0.034} &= 0.842 \\ \log k_2 - \log(0.034) &= 0.842 \\ \log k_2 &= 0.842 + \log(0.034) = -0.6265 \\ k_2 &= 10^{-0.6265} = 0.236 \text{ min}^{-1}\end{aligned}$$

Since drug degradation occurs with faster rates at higher temperatures than at lower ones,  $k_2$  must occur at a temperature much higher than that observed with  $k_1$ .

Methods for the sterilization of pharmaceutical units may be divided into thermal and nonthermal. Thermal methods utilize heat as a means of achieving the destruction of microorganisms. The rate at which microbes get killed may be described by

$$M = M_0 e^{-kt} \quad (1.9)$$

where  $M_0$  and  $M$  are the initial microbial population and that at time  $t$ , respectively. The rate constant for the process of microorganism killing is  $k$ . Equation (1.9) can be rearranged to read

$$\frac{M}{M_0} = e^{-kt}$$

Taking the natural logarithm of both sides of the equation results in

$$\ln \frac{M}{M_0} = \ln(e^{-kt}) = -kt \quad (1.10)$$

Equation (1.10) allows calculations of the rate constant if  $M_0$  and  $M$  are known. For example, the initial population of spores was  $10^4 \text{ mL}^{-1}$ ; following 60 s of exposure to a temperature of  $120^\circ\text{C}$ , the population was reduced to  $10 \text{ mL}^{-1}$ . Calculate the rate constant:

$$\begin{aligned}\ln \frac{10}{10^4} &= -k(60 \text{ s}) \\ k &= 0.115 \text{ s}^{-1}\end{aligned}$$

This means that 11.5% of the remaining population of microorganisms is destroyed every second at  $120^\circ\text{C}$ .

## 1.5 DIFFERENTIAL EQUATIONS

Differential equations may be employed to solve rate-related problems such as when studying drug degradation at a given rate and order of reaction. *Integration* is viewed as summation and is the opposite of differentiation. In pharmaceutical sciences, the notion of *differentiation* is commonly applied to topics that involve rates, such as drug degradation over time, drug diffusion through a membrane over time, and the rate by which a drug disappears from circulation following administration. The general format for the rate using a differential format is  $dA/dt$ , where  $d$  indicates a small quantity. Thus,  $dA/dt$  indicates that a small change in  $A$  occurs for every small change in  $t$ . When applied to a differential equation, integration (symbol =  $\int$ ) “sums up” all these small changes, thus, integration is considered to be a summation process.

The solutions for some important differential equations in physical pharmacy can be summarized as follows (Stein, 1977; Anton, 1980):

### 1. Zero-order:

$$\begin{aligned}\frac{dA}{dt} &= -k_0 A^0 \\ dA &= -k_0 dt \\ \int_0^A dA &= -k_0 \int_0^t dt & (1.11) \\ A - A_0 &= -k_0(t - t_0) \\ \text{given } t_0 &= 0 \\ A &= A_0 - k_0 t\end{aligned}$$

### 2. First-order:

$$\begin{aligned}\frac{dA}{dt} &= -k_1 A^1 \\ \frac{dA}{A} &= -k_1 dt \\ \int_0^A \frac{dA}{A} &= -k_1 \int_0^t dt & (1.12) \\ \ln A - \ln A_0 &= -k_1(t - t_0) \\ \text{given } t_0 &= 0 \\ \ln A &= \ln A_0 - k_1 t\end{aligned}$$

### 3. Second-order:

$$\begin{aligned}\frac{dA}{dt} &= -k_2 A^2 \\ \frac{dA}{A^2} &= -k_2 dt \\ \int_0^A \frac{dA}{A^2} &= -k_2 \int_0^t dt\end{aligned}$$

$$-\frac{1}{A} - \frac{-1}{A_0} = -k_2(t - t_0)$$

Given  $t_0 = 0$

$$\frac{1}{A} = \frac{1}{A_0} + k_2t \quad (1.13)$$

4. *Partial derivatives* (Adamson, 1969): When a variable such as  $y$  is a function of two or more other variables ( $q, x, w, \dots$ ), the notion of partial derivatives ( $\partial$ ) is applicable. Thus, we express  $y$  with respect to  $q, x$ , as follows (the subscripts indicate that these variables are held constant during the differentiation calculation):

$$\left(\frac{\partial y}{\partial q}\right)_{x,w}$$

$$\left(\frac{\partial y}{\partial x}\right)_{q,w}$$

$$\left(\frac{\partial y}{\partial w}\right)_{q,x}$$

For example, the diffusion coefficient ( $D$ ) is a function of temperature ( $T$ ), viscosity of solution ( $\eta$ ), and radius of particles ( $r$ ).  $A$  is Avogadro's number and  $R$  is the gas constant:

$$D = \frac{RT}{\pi\eta rA} \quad (1.14)$$

Thus, to write  $D$  as a function of  $T, \eta$ , and  $r$ , the following expressions may be used:

$$\left(\frac{\partial D}{\partial T}\right)_{\eta,r}$$

$$\left(\frac{\partial D}{\partial \eta}\right)_{T,r}$$

$$\left(\frac{\partial D}{\partial r}\right)_{T,\eta}$$

When all variables change simultaneously,

$$dD = \left(\frac{\partial D}{\partial T}\right)_{\eta,r} dT + \left(\frac{\partial D}{\partial \eta}\right)_{T,r} d\eta + \left(\frac{\partial D}{\partial r}\right)_{T,\eta} dr$$

Assuming that the temperature is held constant,  $D$  is a function of viscosity, and the radius of particles,  $D = f(\eta, r)$ . From equation (1.14),

$$D = \frac{RT}{\pi A} \eta^{-1} r^{-1}$$

$$= (\text{constant}) \eta^{-1} r^{-1} \quad (1.15)$$

$$D_\eta = -(\text{constant}) \eta^{-2} r^{-1}$$

$$D_r = -(\text{constant}) \eta^{-1} r^{-2}$$

where  $D_\eta$  is the partial derivative of  $D$  with respect to the viscosity of the solution, and  $D_r$  is the partial derivative of  $D$  with respect to the radius of the particles.

5. *Second-order partial derivatives:* With the temperature held constant, equation (1.15) can be written as a function of the viscosity of solution and the particle radius:

$$D = f(\eta, r)$$

$$\frac{\partial(\partial f / \partial \eta)}{\partial r} = \frac{\partial^2 f}{\partial \eta \partial r} \quad (1.16)$$

Equation (1.16) is the form of a second-order partial derivative.

For example, given  $D$  at 25°C, we have

$$D = 31.31 \times 10^{-23} \eta^{-1} r^{-1}$$

To find  $\partial^2 D / (\partial \eta \partial r)$  we write

$$\frac{\partial^2 D}{\partial \eta \partial r} = \frac{\partial(\partial D \partial r)}{\partial \eta} = \frac{\partial(-(\text{constant}) \eta^{-1} r^{-2})}{\partial \eta}$$

$$= (\text{constant}) \eta^{-2} r^{-2} = 31.31 \times 10^{-23} \eta^{-2} r^{-2}$$

In thermodynamics (see Chapter 2), a change of volume of an ideal gas at a constant temperature does not result in a change in the internal energy of the system. Thus,

$$\left( \frac{\partial E}{\partial V} \right)_T = 0 \quad (1.17)$$

In addition, from the *gas law expression*,  $PV = nRT$ , and at a given constant pressure, the following partial differential equation may be written for the change of volume with a change in temperature:

$$\left( \frac{\partial V}{\partial T} \right)_P \quad (1.18)$$

Equation (1.18) and the gas law expression lead to

$$\left( \frac{\partial V}{\partial T} \right)_P = \frac{nR}{P} \quad (1.19)$$

And for 1 mol of an ideal gas ( $n = 1$ ),  $(\partial V / \partial T)_P = R/P = \text{constant}$  (Adamson, 1969).

## 1.6 EXPANDING AND REDUCING FORMULAS

Pharmacists and pharmaceutical scientists are often asked to prepare volumes or quantities different from those given in a prescription or formula. When faced with either expanding or reducing formulas, a simple proportion method is sufficient to

solve the problem. For example, a technician was asked to prepare 200 mL of the following buffer solution:

$K_2HPO_4$	0.50 g
$KH_2PO_4$	0.35 g
Purified water, enough to make	500 mL

Using 200/500 as a proportion, each value in the formula is multiplied by this ratio:

$$\begin{aligned}(0.50 \text{ g})(200/500) &= 0.20 \text{ g} \\ (0.35 \text{ g})(200/500) &= 0.14 \text{ g} \\ (500 \text{ mL})(200/500) &= 200 \text{ mL}\end{aligned}$$

In preparing the buffer solution, the technician mixes 0.20 g of  $K_2HPO_4$  and 0.14 g of  $KH_2PO_4$  and dissolves them in enough purified water to make 200 mL of solution. If the volume of the solution to be prepared were 1 L instead of 200 mL, the calculations above would be repeated using the ratio 1000/500 in the calculations.

Another possible use of formula expansion or reduction is to be asked to calculate the amount of solute needed for a given volume of solution. Assume that a pharmacist was asked to prepare 500 mL of the following solution:

$Na^+$	8 mEq
Purified water, enough to make	100 mL

Following the method described above, multiply the quantities in the formula by the ratio 500/100:

$Na^+$	$(8)(500/100) = 40 \text{ mEq}$
Purified water, enough to make	$(100)(500/100) = 500 \text{ mL}$

If the pharmacist were to use NaCl (molecular mass = 58.44 g/mol) as the salt to provide sodium ions in solution, 40 mEq of NaCl equals  $(40)(0.05844)$  or 2.34 g. Thus, the pharmacist dissolves 2.34 g of NaCl in enough purified water to make 500 mL of solution.

## REFERENCES

- Adamson WA. *Understanding Physical Chemistry*, 2nd ed. Menlo Park, CA: W.A. Benjamin; 1969.
- Anton H. *Calculus*. New York: Wiley; 1980.
- Martin A, Swarbrick J, Cammarata A. Solubility and distribution phenomena. In: *Physical Pharmacy: Physical Chemical Principles in the Pharmaceutical Sciences*, 3rd ed. Philadelphia: Lea & Febiger; 1983. pp. 272–313.
- Stein KS. *Calculus and Analytical Geometry*, 2nd ed. New York: McGraw-Hill; 1977.

## GLOSSARY

<b>Beer's law</b>	States that the absorbance value of a drug solution is directly and linearly proportional to the concentration of the drug in solution. The Beer's law equation is given as $Abs = A_s \times l \times C$ , where $Abs$ is the absorbance, $A_s$ the absorptivity, $l$ the pathlength, and $C$ the concentration of the drug in solution.
<b>Buffer capacity</b>	An indicator of the degree of resistance that a buffer has toward a change in its pH upon challenging it with acids or bases. The higher the value of the buffer capacity, the higher the resistance of the buffer is to a change in pH.
<b>Differential equations</b>	May be employed to solve rate-related problems, such as when studying drug degradation at a given rate and order of reaction. The general format for the rate using a differential format is $dA/dt$ , where $d$ indicates a small quantity. Thus, $dA/dt$ indicates that a small change in $A$ occurs for every small change in $t$ .
<b>Gas law equation for an ideal gas</b>	$PV = nRT$ , where $P$ is the pressure, $V$ is the volume, $n$ the number of moles, $R$ the gas constant, and $T$ the temperature in kelvin.
<b>Integration</b>	Viewed as summation; the opposite of differentiation. When applied in a differential equation, integration ( $\int$ ) "sums up" all these small changes.
<b>Logarithmic functions</b>	Thought of as exponential equations; thus, $y = x^z$ translates into $z = \log_x y$ ( $\log_x =$ logarithm of base $x$ ).
<b>Microbial population estimation for sterilization processes</b>	The rate at which microbes get killed may be described by the equation $M = M_0 e^{-kt}$ , where $M_0$ and $M$ are the initial microbial population and that at time $t$ , respectively. The rate constant for the process of microorganism killing is $k$ .
<b>Partial derivatives</b>	When a variable such as $y$ is a function of two or more other variables ( $q, x, w, \dots$ ), the notion of partial derivatives ( $\partial$ ) is applicable.
<b>pH</b>	The pH scale is used to measure the concentration of hydronium ions $[H_3O^+]$ in solution.