



# PHARMACEUTICS

BASIC PRINCIPLES AND APPLICATION  
TO PHARMACY PRACTICE

EDITED BY  
ALEKHA K. DASH | SOMNATH SINGH | JUSTIN TOLMAN



# PHARMACEUTICS

## Basic Principles and Application to Pharmacy Practice

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# PHARMACEUTICS

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*We dedicate this text to our teachers and professors who inculcated in us a love of scientific principles and pharmaceuticals.*

# Preface

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Pharmaceutical education in the United States of America has been undergoing substantial changes over the past several decades to address changes in a pharmacist's role in the provision of pharmaceutical care. Pharmacy education has had a historical perspective that prepared student pharmacists to engage in pharmaceutical dispensing or pursue graduate pharmaceutical education focused on research. Any clinically-focused education was then obtained through post-baccalaureate training and experience. The currently evolving perspective of pharmacy education is focused on preparing student pharmacists as providers of clinical pharmaceutical care and as the medication expert in the healthcare system.

These evolutions have increased the need for pharmacy education to be solidly-grounded in scientific principles. Key domains of pharmaceutical knowledge include: medicinal chemistry and pharmacology for an understanding of drug molecule properties and mechanisms of action; pharmaceutics and biopharmaceutics to utilize physicochemical properties of drugs to develop a safe, effective and reliable drug product and their interactions with human physiology; pharmacokinetics and pharmacodynamics to explain drug movement and pharmacologic effects within systems; pharmacy practice to interpret the role of medications in the diagnosis, treatment, and prevention of disease;

and social and administrative studies to evaluate health services and patient safety. Pharmaceutical education should substantively address all of these domains to provide scientific foundations for rational clinical decision making. Additionally, only pharmacy education can provide the scientific depth and breadth across these various levels of knowledge domains.

This textbook is intended to provide a basic scientific introduction to the fields of pharmaceutics and biopharmaceutics specifically tailored to meet the need of practice of Pharmacy. Current educational resources in these fields are principally focused on a historical perspective of pharmaceutical education. They either provide a mathematically rigorous and theoretical introduction to these fields or are briefly integrated into larger resources focused on other knowledge domains. *Pharmaceutics: Basic Principles and Application to Pharmacy Practice* will help pharmacy students gain the scientific foundation to understand drug physicochemical properties, practical aspects of dosage forms and drug delivery systems, and the biological applications of drug administration.

Alexha H. Dash  
Justin Tolman  
Somnath Singh

*Pharmaceutics: Basic Principles and Application to Pharmacy Practice* includes a companion website with a full color image bank and flip videos featuring difficult processes and procedures, as well as sample questions for students to test their knowledge. To access these resources, please visit [booksite.elsevier.com/9780123868909](http://booksite.elsevier.com/9780123868909).

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P A R T I

# PHYSICAL PRINCIPLES AND PROPERTIES OF PHARMACEUTICS



# Introduction: Terminology, Basic Mathematical Skills, and Calculations

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## CHAPTER OBJECTIVES

- Review the basic mathematics applicable in pharmacy.
- Apply the concept of significant figures in pharmacy.
- Apply basic calculus, logarithms, and antilogarithms to solve pharmaceutical problems.
- Apply basic statistics (mean, mode, median, and standard deviation) to interpret pharmaceutical data.
- Interpret a graph and straight-line trend of data to derive useful information.
- Review frequently used units and dimensions in pharmacy.

drug stable and can be used without compromising its therapeutic efficacy? Why do some drugs expire within 1 month, whereas others expire after a couple of years? How do you interpret data reported in the literature to derive some useful and clinically significant information about the therapeutic outcomes of a drug that can be used to counsel a patient and answer some of the pertinent questions a pharmacist encounters daily? To answer such questions and more, the pharmacist must have adequate mathematical and statistical skills. Therefore, this chapter provides a basic introduction to pharmaceutical calculations, units, and basic statistics terms.

## 1.2. REVIEW OF BASIC MATHEMATICAL SKILLS

### 1.2.1 Integers

The numbers 0, 1, 2, 3, -1, -2, -3, and so on, are called integers or whole numbers, which can be either positive or negative and can be arranged in ascending order, as shown in Figure 1.1, where they increase as you move from left to right on the line. Therefore, a negative integer such as -3 is smaller than -2.

### 1.2.2 Zero and Infinity

Mathematical operations involving zero and infinity do not work in the usual way, which sometimes is the reason for errors in pharmaceutical calculations. The following examples and key concepts illustrate the

## Keywords

- Basic mathematics review
- Basic statistics
- Dimensional analysis
- Graphical representations
- Logarithmic calculations
- Significant figures
- Units and dimensions

## 1.1. INTRODUCTION

How much drug should be prescribed to a newborn baby compared to an adult? How do different pathological conditions affect the prescribed dose? How is the drug therapeutic dose determined? How long is a



FIGURE 1.1 Ascending order of integers from left to right.

special rules governing the role of zero and infinity in mathematical operations:

- Any number multiplied by zero equals zero, e.g.,  $12 \times 0 = 0$ . This result is unusual because generally multiplication of any number  $x$  by  $y$  results in a number that is different from either  $x$  or  $y$ , except when  $y$  is equal to 1, which results in no change in  $x$ . Otherwise,  $x$  increases if  $y$  is a positive integer (i.e., a whole number) greater than 1 and decreases if  $y$  is a fraction or an integer lower than 1. In the following examples,  $x$  is always 12:

$12 \times 1 = 12$  (i.e., no change in the value of  $x$  if  $y = 1$ ).

$12 \times 3 = 36$  (i.e., the value of  $x$  increases from 12 to 36 if  $y = 3$ ).

$12 \times -3 = -36$  (i.e., the value of  $x$  decreases from 12 to -36 if  $y = -3$ ).

$12 \times -\frac{1}{3} = -4$  (i.e., the value of  $x$  decreases from 12 to -4 if  $y = -\frac{1}{3}$  which is a negative fraction).

$12 \times \frac{1}{3} = 4$  (i.e., the value of  $x$  decreases from 12 to 4 if  $y = \frac{1}{3}$  which is a positive fraction).

- Any number multiplied by infinity ( $\infty$ ) equals infinity, e.g.,  $12 \times \infty = \infty$ . This is also unusual following the discussion provided for "multiplication by zero."
- Any number divided by zero is mathematically undefined; e.g.,  $12/0 = \text{Undefined}$ . This result is unusual because generally division of any number  $x$  by  $y$  results in a number  $z$ , which provides  $x$  when multiplied by  $y$ . For example, dividing 12 by 4 results in 3, which is correct because 3 multiplied by 4 provides the original number 12. However, 12 divided by 0 cannot result in a specific number that can provide 12 when multiplied by 0. Therefore, the outcome of 12 divided by 0 is undefined.
- Any number divided by infinity is mathematically undefined; e.g.,  $12/\infty = \text{Undefined}$ . This result is also unusual following the discussion provided for "division by zero" because any number multiplied by  $\infty$  would result in  $\infty$ ; it cannot ever provide the original number, 12.

### 1.2.3 Rule of Indices

A number with a power or exponent such as  $12^7$  is called an indice, where 12 is called the base and 7 is the exponent. Mathematical problems involving indices with a common base are solved easily by applying the following rules:

- Exponents are added when multiplying indices, e.g.,

$$12^7 \times 12^5 = 12^{(7+5)} = 12^{12}$$

$$12^7 \times 12^5 \times 12^{-3} = 12^{(7+5-3)} = 12^9$$

- The exponent of the divisor is subtracted from the exponent of the dividend when dividing one indice by another, e.g.,

$$12^5 \div 12^3 = 12^{(5-3)} = 12^2$$

$$12^3 \div 12^5 = 12^{(3-5)} = 12^{-2}$$

$$(12^9 \times 12^3) \div (12^4 \times 12^2) = 12^{((9+3)-(4+2))} = 12^6$$

- Multiple exponents of a base are multiplied, e.g.,

$$(12^5)^3 = 12^{(5 \times 3)} = 12^{15}$$

$$(12^{-5})^3 = 12^{(-5 \times 3)} = 12^{-15}$$

$$\sqrt{12^6} = 12^{6 \times \frac{1}{2}} = 12^3$$

$$\sqrt[3]{12^6} = 12^{6 \times \frac{1}{3}} = 12^2$$

- An indice having a negative exponent is equal to its inverse with a positive exponent, e.g.,

$$12^{-3} = \frac{1}{12^3}$$

$$\left(\frac{5}{12}\right)^{-3} = \left(\frac{12}{5}\right)^3 = \left(\frac{12 \times 12 \times 12}{5 \times 5 \times 5}\right) = \frac{1728}{125} = 13.82$$

- An indice having a fraction as its exponent is equal to its root with a power equal to the denominator of the fraction followed by an exponent equal to the numerator of the fraction, e.g.,

$$(64)^{\frac{2}{5}} = \left(\sqrt[5]{64}\right)^2 = \left(\sqrt[5]{2 \times 2 \times 2 \times 2 \times 2}\right)^2 = (2)^2 = 4$$

- Any indice having zero as an exponent is equal to 1, e.g.,

$$12^0 = 1$$

$$100^0 = 1$$

- All the rules governing mathematical operations involving indices can be summarized as shown here, assuming  $x$  as a base:

$$x^y \times x^z = x^{y+z}$$

$$\frac{x^y}{x^z} = x^{y-z}$$

$$(x^y)^z = x^{yz}$$

$$x^{-y} = \frac{1}{x^y}$$

$$\frac{y}{x^z} = (\sqrt[z]{x})^y$$

$$x^0 = 1$$

### 1.2.4 Scientific or Exponential Notation

Pharmacists often encounter extremely large or small numbers, which creates a challenge when doing simple mathematical operations involving such numbers. For example, the normal range of testosterone level in men (16–30 years old) is 72–148 pg/mL (i.e., 0.000,000,000,072–0.000,000,000,148 g/mL) [1], and the number of skin cells in humans is 110,000,000,000 [2]. Therefore, scientific notation is used to handle such large or small numbers, using exponential notation or the power of 10. Thus, the testosterone level can be conveniently expressed as  $7.2 \times 10^{-11}$  to  $1.48 \times 10^{-10}$  g/mL. Similarly, the number of skin cells can be represented by  $1.1 \times 10^{11}$ . The number expressed by scientific notation is called the scientific number.

Generally, only one figure appears before the decimal point in the first part of scientific notation; it is called the coefficient. When multiplying or dividing two scientific numbers, the exponents are added or subtracted respectively, as shown below:

#### Multiplication of scientific numbers:

$(1.1 \times 10^{-11}) \times (7.2 \times 10^{10}) = 7.92 \times 10^{-1}$ ; where the exponents,  $-11$  and  $10$ , have been added.

$(1.1 \times 10^{11}) \times (7.2 \times 10^{10}) = 7.92 \times 10^{21}$ ; where the exponents,  $11$  and  $10$ , are added.

#### Division of scientific numbers:

$(1.1 \times 10^{11}) \div (7.2 \times 10^{-11}) = 0.15 \times 10^{22}$  or  $1.5 \times 10^{21}$ ; where exponent  $-11$  is subtracted from exponent  $11$ .

$(1.1 \times 10^{11}) \div (7.2 \times 10^7) = 0.15 \times 10^4$  or  $1.5 \times 10^3$ ; where exponent  $7$  is subtracted from exponent  $11$ .

Addition or subtraction of scientific numbers can be easily carried by following the two steps shown below:

Step 1: The exponent of each number must be same as shown in example below where  $(7.2 \times 10^9)$  has been converted to  $(0.072 \times 10^{11})$ .

Step 2: The coefficients are added or subtracted depending on the problem.

#### Addition of scientific numbers:

$(1.1 \times 10^{11}) + (7.2 \times 10^9) = (1.1 \times 10^{11}) + (0.072 \times 10^{11}) = (1.1 + .072) \times 10^{11}$  or  $1.17 \times 10^{11}$ ; where the decimal point in coefficient  $7.2$  is moved left by two positions to make exponents in both the scientific numbers equal to  $11$ .

Alternatively,  $1.1 \times 10^{11}$  can be converted to  $110.0 \times 10^9$  to make the exponents in both the scientific numbers equal to  $9$  as shown below:

$(1.1 \times 10^{11}) + (7.2 \times 10^9) = (110.0 \times 10^9) + (7.2 \times 10^9) = (110.0 + 7.2) \times 10^9$  or  $117.2 \times 10^9 = 1.17 \times 10^{11}$

#### Subtraction of scientific numbers:

$(1.1 \times 10^{11}) - (7.2 \times 10^9) = (1.1 \times 10^{11}) - (0.072 \times 10^{11}) = (1.1 - .072) \times 10^{11}$  or  $1.028 \times 10^{11} = 1.03 \times 10^{11}$

### 1.2.5 Logarithms and Antilogarithms

Exponential data often are used in pharmacy calculations; e.g., the acidity constant,  $K_a$ , of acetaminophen is  $3.09 \times 10^{-10}$ , [3] which is used for developing its stable formulation. Performing mathematical calculations using such exponentials is not convenient. Furthermore, in many instances such as accelerated stability studies of drugs, it is difficult to find any correlation between exponential data. Another example is of data generated out of first-order rate kinetic studies. In such situations, using logarithms is helpful because it linearizes the data. Using logarithms makes calculations such as multiplication or division involving exponentials easy because it converts them into easy-to-handle simple addition or subtraction problems. A logarithm is the power to which a base must be raised to obtain a number. Therefore, there are two kinds of logarithms on the basis of differences in the base: the *common logarithm* ( $\log$ ), where the base is  $10$ , and *natural logarithm* ( $\ln$ ), where the base is  $e$  (where  $e = 2.7182818...$ ). The following examples clarify this concept:

#### • Using $\log_{10}$ ("log to the base 10"):

$\log_{10} 1000 = 3$  (i.e., log of  $1000$  to the base  $10$  is  $3$ ) is equivalent to  $10^3 = 1000$  where  $10$  is the base,  $3$  is the logarithm (i.e., the exponent or power), and  $1000$  is the number.

#### • Using natural log ( $\log_e$ or $\ln$ ):

$\ln 100 = 4.6052$  (i.e., log of  $100$  to the base  $e$  is  $4.6052$ ) is equivalent to  $e^{4.6052} = 100$  or  $2.7183^{4.6052} = 100$  where  $e$  or  $2.7183$  is the base,  $4.6052$  is the logarithm (i.e., the exponent or power), and  $100$  is the number.

Anytime something,  $c$ , changes at a rate proportional to  $c$ , it is represented by a natural logarithmic equation, e.g., the equation representing the first-order rate kinetics as shown next.

The first-order reaction is represented by  $dc/c = -k_1 dt$ , where  $c$  is the concentration of the reactant at any time,  $t$  and  $k_1$  is the proportionality constant. Integration of this equation between concentration  $C_0$  at time  $t = 0$  and concentration  $C_t$  at time  $t = t$  results in the following equation using natural log:

$$\ln C_t = \ln C_0 - k_1 t$$

Therefore, it is essential to know the interconversion from a common logarithm to a natural logarithm and vice versa, which can be derived as shown next.

TABLE 1.1 Rules for Logarithmic Mathematical Operations

Common Logarithm	Natural Logarithm
$\log xy = \log x + \log y$	$\ln xy = \ln x + \ln y$
$\log \frac{x}{y} = \log x - \log y$	$\ln \frac{x}{y} = \ln x - \ln y$
$\log x^y = y \log x$	$\ln x^y = y \ln x$
$\log \sqrt[y]{x} = \log x^{\frac{1}{y}} = \frac{1}{y} \log x$	$\ln \sqrt[y]{x} = \ln x^{\frac{1}{y}} = \frac{1}{y} \ln x$

Assume that the ratio of a natural and common log of the same number is  $x$ , i.e.

$$\frac{\ln 10}{\log 10} = x$$

Since  $\ln 10 = 2.303$  and  $\log 10 = 1$ , the ratio  $x = 2.303$ .

Therefore, for any number  $y$ ,

$$\ln y = 2.303 \log y$$

Sometimes the logarithm (or  $\ln$ ) of a number is available, but you need to find the number itself, which can be done by finding the antilogarithm of a logarithmic number. Therefore, the antilogarithm is also called the inverse logarithm. The following examples illustrate this concept:

$$\begin{aligned} \log x = 2; x &= \text{antilog of } 2 = 100 \\ &\text{because } 10^2 = 100 \\ \log x = -2; x &= \text{antilog } (-2) = 0.01 \\ &\text{because } 10^{-2} = 0.01 \end{aligned}$$

The natural logarithm also works in the same way:

$$\ln x = 2.303; \text{ so, } x = \text{antiln } (2.303) = 10$$

The rules governing logarithmic calculation are shown in Table 1.1.

## 1.2.6 Accepted Errors and Significant Figures

All numbers can be categorized as either exact or inexact numbers:

- **Exact numbers:** Any numbers that can be determined with complete certainty; e.g., there are 110 students in a class, 12 eggs in one dozen eggs, 7 days in a week, 12 months in a year, etc. All these numbers can be figured out without any doubt.
- **Inexact numbers:** Numbers associated with any measurement are not exact because accuracy depends on the sensitivity of the instrument used in said measurement. You can increase the precision of the measurement by carefully following the standard operating procedure or by selecting a more sensitive instrument.

Let's start by defining and differentiating two terms that often are interchanged mistakenly: accuracy and precision.

*Accuracy* refers to how closely measured values agree with the correct value, whereas *precision* refers to how closely an individual measurement agrees with another. Precision is correlated to reproducibility of a measurement and is indicated by standard deviation of multiple repeated measurements. Obviously, a higher standard deviation indicates a lower precision of measurements. Therefore, a measurement can be of high precision but of low accuracy. For example, 100 grams of a drug are weighed using a balance having +10% errors due to a manufacturing defect. Thus, you can weigh out 100 grams multiple times with 99.99% precision (i.e., each 100 grams weighed out does not differ from another by more than 0.01 gram), but the weight accuracy is 90% due to the systematic error.

In another example, if an assay method reports 495 mg of ampicillin in a 500 mg capsule of ampicillin, the measurement accuracy is 99%  $[(495/500) \times 100]$ , i.e., a 1% error. If the assay is repeated 5 times for the same sample of ampicillin capsule and each time the result is 495 mg of ampicillin, the precision of the experimental method is 100%. Thus, precision indicates the repeatability of an experimental method. If the same error or mistake is repeated during each experiment, the result may be precise but inaccurate.

### 1.2.6.1 Measurement Accuracy

All measurements have a degree of uncertainty because no device can provide absolutely perfect measurement with absolute zero error. The error can be predicted from but not limited to, for example, the process used to prepare the dosage form, the sensitivity of the utilized balance or measuring devices, or the number of significant figures.

#### 1.2.6.1.1 BASED ON THE OFFICIAL COMPENDIA

The U.S. Pharmacopeia [6] states that

Unless otherwise specified, when a substance is weighed for an assay, the uncertainty should not exceed 0.1% of the reading.

Also according to the USP,

Measurement uncertainty is satisfactory if 3 times the standard deviation of not less than 10 replicates weighings divided by the amount weighed, does not exceed 0.001.

Another commonly used parameter is the relative standard deviation (RSD), which equals to *Standard deviation* / *Mean*  $\times 100$ .