INTEGRATED PHARMACEUTICS

Applied Preformulation, Product Design, and Regulatory Science

Antoine Al-Achi
Mali Ram Gupta
William Craig Stagner

WILEY

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ANTOINE AL-ACHI
MALI RAM GUPTA
WILLIAM CRAIG STAGNER
Campbell University
College of Pharmacy & Health Sciences
Buies Creek, North Carolina

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To my wife, Pamela Al-Achi, and my sons, Elias Gabriel, Anthony William, and John Peter. To my beloved father, Elias, my mother, Renee, and my sister and brothers, Claudette, Peter, and Kamil and their families.

To my wife, Sulochna Gupta, and my children and grandchildren, Michael, Saijal, Nathan, Maya, and Deepak. To my beloved father, Harchand Rai, my mother, Anachhi, and the entire Mittal family.

To my wife, Nancy Stagner, and my children and grandchildren, Ryan, Beth, Ethan, Tripp, Kelly, Amelia, Justin, and Lauren.

To all our students: past, present, and future.

CONTENTS

FOREWORD

The wide variety of topics covered by the authors in this book emphasize both the depth and breadth of knowledge needed for pharmaceutical scientists to bring a drug product to the marketplace successfully. The challenge of designing and developing compounds into pharmaceutical products, which are critical to the survival of both the biotech and pharmaceutical industries, will depend largely on the education and extensive training required of young pharmaceutical scientists. This book gives the reader an understanding of the basic and applied sciences involved in the development and approval of a pharmaceutical product through regulatory authorities. Unfortunately, these topics have slowly lost their emphasis over the past several years in graduate courses taught in our colleges of pharmacy.

The eleven chapters in Part I cover preformulation topics, wherein the physical and chemical properties of a drug substance, along with its stability and interactions with excipients and the biological aspects of the formulations, are discussed in detail. These and other preformulation topics covered in this section outline the basic properties that fingerprint both the characteristics of a drug substance and the properties of ingredients that must be considered when formulating a physically and chemically stable dosage form. Part II, Chapters 12 through 20, cover product design topics. The regulatory science aspects of drug development are covered in Chapters 21 through 31. This is yet another area that has received minimal attention in graduate schools.

For both the academic and industrial scientist, as well as graduate students whose research is focused in this field, the authors have emphasized important aspects of materials science and processing that must be addressed for a successful product introduction following approval through regulatory authorities. The chapters in this book flow extremely well and provide very useful information not only to undergraduate and graduate students in pharmaceutics, pharmacy, materials sciences, and engineering, but also to faculty and industrial scientists in these disciplines.

James W. McGinity, Ph.D.

Professor of Pharmaceutics
The University of Texas at Austin

PREFACE

The idea for this book was born out of the authors' desire to create a textbook to be used for several courses in our pharmaceutical science B.S./M.S. curriculum and cooperative B.S./M.S. engineering/pharmaceutical sciences program approved by North Carolina State University, Raleigh, North Carolina and Campbell University, Buies Creek, North Carolina. The book will also be used as part of the College of Pharmacy & Health Sciences Pharm.D. program. The book's theme and scope focus on the application of the principles of physical pharmacy, product design, and regulatory science and how they relate in an intricate web to produce effective dosage forms that deliver drugs to their site of action. Currently, there is a critical shortage of pharmaceutical scientist specialists in product design and related technologies. Historically, most pharmaceutical scientists were educated in pharmacy schools. These programs integrated biology, pharmacology, chemistry, mathematics, physics, and materials science with one overarching goal: drug delivery to treat the human condition. A majority of the Ph.D. pharmaceutical scientists were educated as B.S. pharmacists. Over the past 30 years, pharmacy education has become more drug therapy focused and less drug delivery oriented. Federal funding has also followed this trend, leaving unprecedented shortages of academic pharmaceutical scientists. In addition, the shift in pharmacy education emphasis has required that the pharmaceutical industry hire chemists, biologists, and engineers who do not have the benefit of the integrated educational program that was once offered by schools of pharmacy. These employees are trained (not educated) on the job, although some schools of engineering are trying to fill some of the educational void.

The novel approach of this book is, as much as possible, to integrate international harmonized pharmaceutical development regulatory guidelines and requirements with the science and technology of pharmaceutical product design. New regulatory guidelines, such as quality by design, design space analysis, process analytical technology, polymorphism characterization, blend sample uniformity, stability protocols, and the biopharmaceutical classification system are integrated throughout the text. In Part I, we present the fundamentals of physical pharmacy and preformulation as they apply to pharmaceutical dosage form design. Topics such as thermodynamics, drug solubility, drug stability, rheological aspects of formulation, interfacial science, bioavailability, and others are covered in this part. Other chapters cover basic mathematical, statistical, and design-of-experiment concepts.

In Part II, we elaborate on the complex multifactorial process that brings together drug delivery to treat a human condition with formulation, manufacturing process, and container closure system design. The inextricable interrelationships among the formulation, the process, and the container closure system

are emphasized by integrating each of these product design features into a single dosage-form chapter. Unification of appropriate preformulation and regulatory science applications is also highlighted. A similar format is incorporated for most chapters: an introduction that discusses the relevant anatomical and bodily function that affect drug delivery, advantages and disadvantages of the product, formulation design that examines dosage-form-specific preformulation, excipient compatibility, formulation development; process design, relevant process analytical technologies, pertinent scale-up models and practices, container closure system design incorporating critical patient and product considerations, risk management, in-process and final product attribute tests, and new drug application stability assessment programs. Most chapters include extensive reference appendixes of functional excipients, their compendial status, and usage levels. Other reference appendixes include surfactant hydrophile-lipophile balance (HLB) values, oil-required HLB values, sequestering agent stability constants, lyophilization bulking agents, and eutectic and collapse temperatures.

Part III covers regulations as specified by the U.S. Food and Drug Administration (FDA), European Medicines Agency, and other international regulatory agencies. This part provides a broad spectrum of topics from compliance requirements (current good manufacturing and good laboratory practices, and others), International Conference on Harmonization and other global harmonization initiatives, the investigational new drug (IND) and new drug application (NDA) phase-appropriate new drug development process, pre- and postapproval processes [INDs, NDAs, abbreviated NDAs, and drug master files], accelerated approval and initiatives for orphan and pediatric drug development, post–drug approval activities, quality system controls, commissioning and qualification (of facilities, equipment, analytical instruments, and test methods, among others), regulatory requirements for all facets of extemporaneous compounding (from handling of prescription for compounding to patient counseling), recommendations for conducting and reporting results of nonclinical and clinical safety and toxicology studies, barriers and benefits of pharmacogenomics studies, to the most recent FDA initiative on regulatory science.

In summary, the book introduces a fresh approach to presenting industrial pharmacy by combining physical pharmacy, product design, and regulatory science issues in a single compendium.The authors hope that the integrated perspective presented will be useful for undergraduate, graduate, and professional pharmacy students and will provide pharmaceutical scientists with a reference resource. The authors will also greatly appreciate feedback and comments that lead to improvements in the book.

Acknowledgments

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alachi@campbell.edu *Antoine Al-Achi*
guptam@campbell.edu *Mali Ram Gupta*
stagnerw@campbell.edu *William Craig Stagner*

PART I

PREFORMULATION

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 *Sörensen's equation*:

$$\mathrm{pH} = -\log[\mathrm{H_3O^+}] \tag{1.1}$$

If the pH meter reads pH 10.8 for the solution, equation (1.1) may be used for the determination of $[\mathrm{H_3O^+}]$:

$$10.8 = -\log[\mathrm{H_3O^+}]$$
$$[\mathrm{H_3O^+}] = 1.58 \times 10^{-11}\ \mathrm{M}$$

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

$$C_{\mathrm{blood}} = C_{\mathrm{initial}} e^{-kt} \tag{1.2}$$

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

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

$$\ln C_{\text{blood}} = \ln C_{\text{initial}} - kt \tag{1.3}$$

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

$$y = a + bx \tag{1.4}$$

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:

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

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

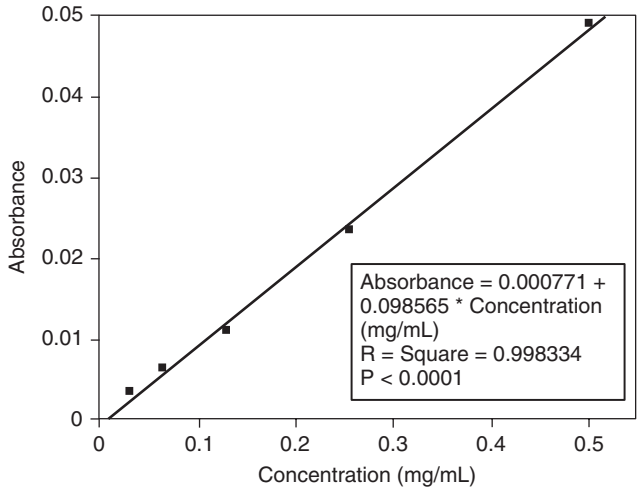

FIGURE 1.1 Positive linear relationship between the concentration of aspirin in solution and absorbance readings. Data points are experimental values, and the solid line is the best-fit line for the data.

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:*

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

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,

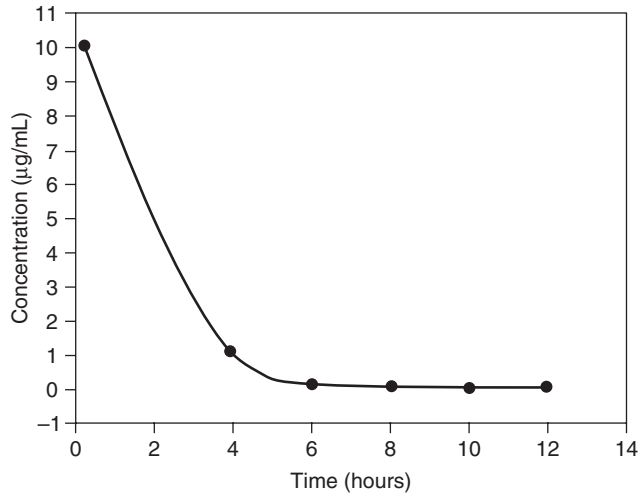

FIGURE 1.2 Exponential decrease in drug blood concentration *vs*. time.

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 (drug blood concentration)] vs. time. The resulting graph is a straight line (Figure 1.3).

Time (h)	Concentration (µg/mL)	ln (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

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

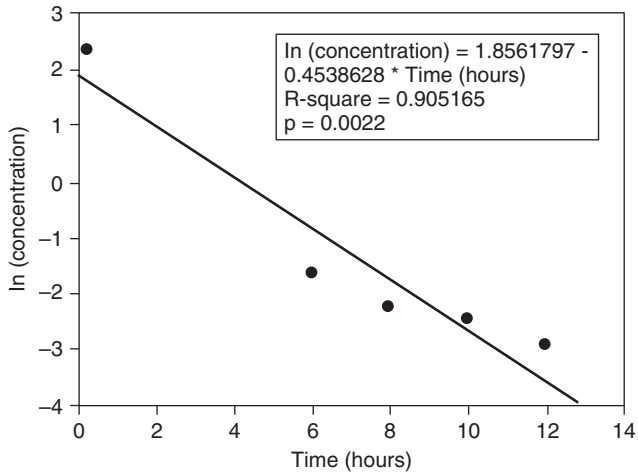

FIGURE 1.3 Linear relationship of the natural logarithm of drug blood concentration *vs*. time.

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

$$\text{slope} = -04538628 = -k_{\text{el}}$$

Therefore,

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

The value of k_{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, $[H_3O^+] = 10^{-4}$ M, and $K_a = 1.47 \times 10^{-4}$, we'llestimate the buffer capacity value. The equation for calculating the buffer capacity is (Martin et al., 1983)

$$\begin{aligned}\text{buffer capacity} &= 2.303C\,\frac{K_a[H_3O^+]}{\{K_a + [H_3O^+]\}^2} \\ &= (2.303)(1)\frac{(1.47\text{x } 10^{-4})(10^{-4})}{[(1.47 \times 10^{-4}) + (10^{-4})]^2} \\ &= 0.56\end{aligned}$$

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 ($e = 2.71828\ldots$). 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. $\ln e = 1$

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

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

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

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

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:

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