Second Edition

Integrated Pharmaceutics

Applied Preformulation, Product Design, and Regulatory Science

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Mali Ram Gupta
William Craig Stagner

WILEY

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To my wife, Pamela Cardella Al-Achi, and my sons, Elias Gabriel, Anthony William, and John Peter. To my beloved father and mother, Elias and René Nassif Tadros. To my siblings and their families, Peter Al-Achi, Claudette Martone, and Kamil Al Achi.

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

To my wife Nancy, and our children and grandchildren, Ryan, Beth, Ethan; Tripp, Kelly, Amelia; and Justin, Lauren, Henry, Hudson.

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

Contents

Foreword to Second Edition

The breadth and depth of pharmaceutics is expertly covered by this well-written and organized second edition of *Integrated Pharmaceutics: Applied Preformulation, Product Design, and Regulatory Science*. This book should be required reading for educating our next generation of pharmaceutical scientists as it provides up-to-date discussion, explanation, relevant examples, and case studies of a plethora of important topics required for both academic and industrial scientists. Part 1, which covers preformulation aspects that must be considered when developing a drug into a product, includes expanded content of such critical concepts as solubility and dissolution, bioavailability and bioequivalence, interfacial properties, adsorption phenomenon, rheological principles, chemical stability and shelf-life determination, particle science, statistics as related to experimental design, and formulation development concepts. Following in a logical sequence, Part II then provides in-depth instruction directly related to the design and development of specific dosage forms, including tablets, capsules, dispersed systems (e.g. suspensions, emulsions, colloids), aerosol products (including a helpful section on excipients used in aerosol products), sterile injectable products, ophthalmic products, transdermal products, and oral modified-release products (including specific examples of coated and matrix modified-release systems). These chapters will be particularly useful to undergraduate and graduate students in pharmaceutics, pharmacy, and engineering. Lastly, Part III wraps up the book with a comprehensive discussion of the regulatory sciences that every pharmaceutical scientist should have a working knowledge of, including discussion of regulatory practices and guidelines for regulatory agencies around the world, application of regulations for compounding pharmacies, processes involved in IND and NDA drug development studies, regulatory requirements for biological, biosimilar, generic and OTC products, accelerated NDA and expedited access for new therapies, guidance related to drug master files, EU dossiers and API GMP processes, commissioning and qualification, overall quality systems, safety, toxicology and pharmacogenomics studies related to product approval, and discussion of medical devices, combination products, dietary supplements and animal drugs, and devices. It is evident that this second edition provides the reader with important and current aspects of the science involved in successfully developing a pharmaceutical product. As a 35-year veteran industrial and academic pharmaceutical scientist, I commend the authors for having provided this expertly written and updated contribution to the pharmaceutical sciences.

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Foreword to First Edition

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 for 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, covers 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 scientists, and 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.

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Preface to Second Edition

The second edition of *Integrated Pharmaceutics: Applied Preformulation, Product Design, and Regulatory Science* expands on the original edition and emphasizes greater integration among the three main sections of the textbook. It is still our intention for the text to deliver valuable material to practitioners, pharmaceutical scientists, and graduate students engaging in research and learning in pharmaceutical sciences in general and pharmaceutics/industrial pharmacy as a major. To that end, this new edition of the book continues to serve those engaged in designing pharmaceutical drug products. The new material added to the second edition reflects suggestions we heard from colleagues and students and the latest trends in the development of dosage forms. While no text can claim complete inclusion of all material on a given subject, the reader of this second edition can find it more comprehensive in its delivered information. The unique integration of regulatory affairs considerations related to product design discussions continues to be featured. While we added newer material to the text, some of the less helpful content was excluded from this edition. Readers may refer to the first edition if they desire to access these omitted topics.

The reader will find that the new edition still contains the basic information that is necessary to formulate a pharmaceutical dosage form. The second edition expands on these topics by making each chapter more comprehensive. Specifically, some of the modifications made on the first edition that are found in this current edition incorporate the following: methods of API solubility enhancement, nonionic, ionic, and acid–base concepts related to solubility and dissolution; interactions involved the drug's states of matter (solid, liquid, and gas) in a formulation structure and the influence of these interactions on the biological aspects of formulations; liquid–liquid interface, formulation and optimization techniques, and determination of HLB values; data handling in rheometry and the use of rheometry in reverse engineering of a topical dosage form are explored; expanded information on the theoretical aspects of drug stability that include chemical equilibrium theories and applications; particle dimension, types of particle diameter, and the use of particle diameters in formulation development; more examples on statistical analysis, in particular applications related to using JMP® Statistical Discovery Software, Version <14.0>, SAS Institute Inc., Cary, North Carolina in analyzing and interpreting data related to drug development; process analytical technologies (PATs) and scale-up methodologies; vaccines technology; formulation and process designs, container closure characteristics, various attribute tests, and stability assessment of the final ophthalmic product; FDA inspection and CGMP check list; comparison of regional (EMA, China, FDA, Japan, and WHO) GMP chapters; the recent regulations governing compounding (503A and 505B), USP Chapter 797, compounding sterile preparations, self-inspection/audit, and a check list (questionnaire); Part 58 (Good laboratory Practice), CGMP for Phase 1 investigational drugs (Guidance for Industry), sterile drug products produced by aseptic processes (CGMP Guidance for Industry), and ICH E6 (R2) Good Clinical Practice; 21 CFR 320 Bioavailability and Bioequivalence requirements as well as development and approval of biosimilars in the USA and EU; Emergency Use Authorization; Orphan Drugs regulations; risk-based qualifications; Part 820 Quality Systems regulations, Part 820 QSR-Auditor's Check List, and Part 11 Electronic Records/Electronic Signature and Auditor's Check List; GMP guidance (Q7) for APIs. In addition, ICH Q9-Quality Risk Requirement; pharmacovigilance for medical products and the predictive toxicology roadmap; innovation measures for public health adopted by the FDA and critical path initiatives; Part 601 pertaining to licensing biologicals and Part 610 dealing with general biological products standards; Regulations, CGMPs, and guidance covering medical devices, combination products, dietary supplements, and veterinary drugs and devices as enforced by the regulatory authorities in the USA.

Acknowledgments

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Preface to First Edition

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 BS/MS curriculum and cooperative BS/MS 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 post-approval 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

The authors wish to thank Bob Stagner for reviewing Chapters 12 through 20, 23, 25, and 26 and for providing constructive suggestions, and Paul Johnson for reviewing and providing helpful suggestions on chapters 23 and 29. The authors are also indebted to Drs. Keith Johnson and Larry Gatlin for their expert advice on Chapters 16 and 17, respectively. Special thanks go to Scott Staton for his tireless effort in preparing the excellent illustrations.

The authors appreciate the unwavering support of their department chair, Dr. Emanuel Diliberto. We also acknowledge the help of our graduate students in this endeavor.

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About the Companion Website

This book is accompanied by a companion website

www.wiley.com/go/Al-Achi/IntegratedPharmaceutics

The website includes:

- Study guide
- List of equations.

Part I

Applied Preformulation

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, Eq. (1.1) may be used for the determination of $[\mathrm{H_3O^+}]$:

$$10.800 = -\log[\mathrm{H_3O^+}]$$
$$[\mathrm{H_3O^+}] = 1.58 \times 10^{-11}\mathrm{M}$$

Thus, the concentration of hydronium ions in solution was computed from Eq. (1.1) by mathematical manipulation employing the rules of logarithms. The mathematical operator "p" represents the function (−log) in the equation. Thus, (−log $[\mathrm{H^+}]$) becomes pH.

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} is the initial concentration of the drug in the blood immediately following administration, and k is the elimination rate constant. Equation (1.2) can be made linear by converting it to its logarithmic form:

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

The transformation of Eq. (1.2) to Eq. (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 Significant Figures and Rounding off Numbers

The United States Pharmacopeia (USP) emphasizes on the use of significant figures in reporting numerical results. To that end, the reader is encouraged to consult the USP or other resources concerning this topic for more details. The following rules apply to reporting values obtained from mathematical manipulations of data:

1) Intermediate numerical values may be retained to their original decimal figures and the final results are then reported to the significant figures desired.

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2) Zero value may or may not be significant depending on the way it is being reported. A significant zero is emphasized in the number being reported, such as in 109.0 mg. The zero in this number is significant, and thus there are four significant figures in 109.0 mg. However, the zero value appearing immediately after the decimal point in 0.0109 mg is not significant, thus this number has only three significant figures. And the number 0.0009 mg has only one significant figure.
3) In the value such as 1090 mg, the last zero may or may not be considered an approximate digit, depending on the method of analysis being used.
4) When performing mathematical operations, the final number is reported with the least number of significant figures used to generate that number. For example, multiplying 3.40 (three significant figures) by 208.0 (four significant figures) results in the value of 707.2, which should be reported as 707 (the 2 in the final number is not significant). However, if one of the numbers is an absolute value, such as the case with the number of tablets in a bottle, then the final result is reported to the next possible significant figures in the operation. For example, 34 tablets (exact number) of a multivitamin product were reported to have in each tablet 50.00 mg (four significant figures) of vitamin C. Then, $34 \times 50.00 = 1700$ mg (four significant figures).
5) Rounding off the final number to the desired significant figures: If the final number is reported to three significant figures, and the final number was 89.87, then this value would be rounded off to 89.9; likewise if the number is 89.83, it is rounded off to 89.8. Notice that we added (+1) in first case when the last digit was greater than 5 (the same rule applies if the last digit was exactly 5), and we dropped the digit from the answer when the number was less than 5.
6) For logarithms, the number of significant figures in the antilogarithm equals the number of digits in the mantissa. For example, if $\log x = 10.800$ (three significant figures in the mantissa/the part of the number that follows the decimal point), the antilogarithm value would be reported as 6.31×10^{10} (notice that the value 6.31 has three significant figures).

1.3 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 Eq. (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:

$$\text{Absorbance} = -0.0008 + [0.1 \times \text{concentration (mg/mL)}] \tag{1.5}$$

Comparing Eq. (1.4) with Eq. (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 Beer's law (Figure 1.1). It is important always to check whether or not the mathematical relationship adheres to the scientific norms. Using Eq. (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

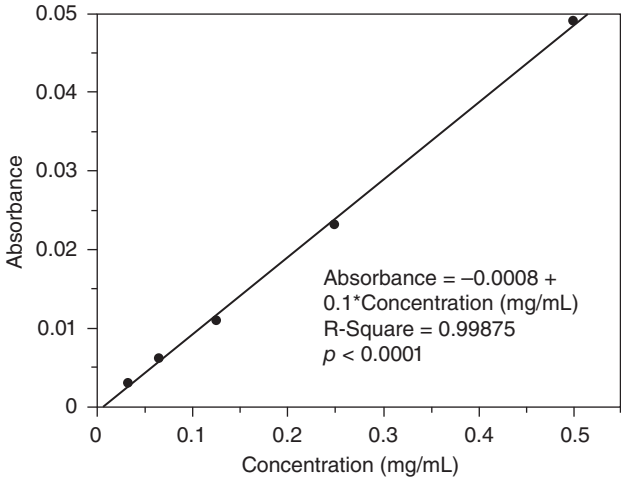

Figure 1.1 Positive linear relationship between the concentration of aspirin in solution and absorbance readings. Data points are experimental values, and the solid line is the best-fit line for the data.

u

v

w

x

y

z