Physical Pharmacy

ALFRED MARTIN

FOURTH EDITION

Physical Pharmacy

PHYSICAL CHEMICAL PRINCIPLES IN THE PHARMACEUTICAL SCIENCES

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Dedicated to my parents
Rachel and Alfred Martin, Sr.,
my wife, Mary, and my sons,
Neil and Douglas.

Preface

The fourth edition of *Physical Pharmacy* is concerned, as were earlier editions, with the use of physical chemical principles as applied to the various branches of pharmacy. Its purpose is to help students, teachers, researchers, and manufacturing pharmacists use the elements of mathematics, chemistry, and physics in their work and study. The new edition has been updated and revised to reflect a decade of current advances, concepts, methods, instrumentation and new dosage forms and delivery systems.

Two chapters in the third edition—Introductory Calculus and Atomic and Molecular Structure—have been removed. The calculus chapter has been replaced by an appendix that provides necessary rules of differentiation and integration. The space made available by these deletions has allowed extensive revision in other chapters: Complexation and Protein Binding, Kinetics, Interfacial Phenomena, Colloids, Rheology, and Coarse Dispersions. The chapter on Drug Product Design has been rewritten and expanded to reflect the many advances in controlled drug delivery systems over the past two decades. The problems at the end of the chapters have been varied and considerably increased in number.* This new and revised edition will bring readers up-to-date with the last 10 years of progress in the physical and chemical foundations of the pharmaceutical sciences.

The author acknowledges the outstanding contributions of Professor Pilar Bustamante to the preparation of this fourth edition with regard to originating new problems and writing a major part of Chapter 19, Drug Product Design. The time and professional devotion she gave to the revision process, in a variety of ways, was exceptional. Dr. A. H. C. Chun prepared most of the illustrations, as he has skillfully done for each of the editions. Dr. Stephen Baron, who checked the problems in the first edition, has again assisted in reviewing the problems and in reading galley proof for the fourth edition.

The author expresses his appreciation for additional contributions to this book by Dr. R. Bodmeier, University of Texas; Dr. Peter R. Byron, Virginia Commonwealth University; Dr. S. Cohen, Tel-Aviv University, Israel; Dr. T. D. J. D'Silva, Rhone-Poulenc; Dr. J. B. Dressman, University of Michigan; Dr. J. Keith Guillory, University of Iowa; Dr. V. D. Gupta, University of Houston; Dr. Bhupendra Hajratwala, Wayne State University; Dr. E. Hamlow, Bristol-Meyers Squibb; Dr. A. J. Hickey, University of Illinois at Chicago; S. Jarmell, Fisher Scientific; Dr. A. E. Klein, Oneida Research Services; Dr. A. P. Kurtz, Rhone-Poulenc; Dr. Z. Liron, Tel-Aviv University, Israel; Dr. T. Ludden, U.S. Federal Food and Drug Administration; Dr. James McGinity, University of Texas; B. Millan-Hernandez, Sterling International, Caracas, Venezuela; Dr. Paul J. Niebergall, Medical University of South Carolina; Dr. Robert Pearlman, University of Texas; Dr. R. J. Prankerd, University of Florida; H. L. Rao, Manipal, India; Dr. E. G. Rippie, University of Minnesota; T. Rossi, Fisher Scientific; Dr. Hans Schott, Temple University; Dr. V. J. Stella, University of Kansas; Dr. Felix Theeuwes, Alza Corporation; Dr. K. Tojo, Kyushu Institute of Technology, Japan; and Dr. J. Zheng, Shanghai Medical University.

Recognition is also given for the use of data and reference material found in the Merck Index, 11th Edition, Merck, 1989; the U.S. Pharmacopeia, XXII-NF XVII, U.S. Pharmacopeial Convention, 1990;

*The percent increase in figures, tables, and so on in the 4th edition of *Physical Pharmacy* as compared with those in the 3rd edition is as follows:

	Figures	Tables	References	Equations	Examples	Problems
% Increase	12	2	45	17	32	107

and the CRC Handbook of Chemistry and Physics, 63rd Edition, CRC Press, 1982. The author acknowledges with thanks the use of problems patterned after some of those in J. William Moncrief and William H. Jones, *Elements of Physical Chemistry*, Addison-Wesley, 1977; Raymond Chang, *Physical Chemistry with Applications to Biological Systems*, 2nd Edition, Macmillan, 1981; and David Eisenberg and Donald Crothers, *Physical Chemistry with Application to the Life Sciences*, Benjamin/Cummings, 1979.

The suggestions and assistance of Dean J. T. Doluisio and colleagues at the University of Texas are acknowledged with thanks. Much of the work by the author was made possible by the professorship provided by Coulter R. Sublett.

Dr. Pilar Bustamante is grateful to Dean Vicente Vilas, to Professor Eugenio Selles, and to her colleagues at the University Alcala de Henares, Madrid, Spain, for their support and encouragement during the many hours of revision work.

George H. Mundorff, Executive Editor; Thomas J. Colaiezzi, Production Manager; and Dorothy A. Di Rienzi, Project Editor of Lea & Febiger have been patient, sympathetic, and helpful during the revision for the fourth edition of *Physical Pharmacy*.

Austin, Texas

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Introduction

The pharmacist today more than ever before is called upon to demonstrate a sound knowledge of pharmacology, organic chemistry, and biochemistry and an intelligent understanding of the physical and chemical properties of the new medicinal products that he or she prepares and dispenses.

Whether engaged in research, teaching, manufacturing, community pharmacy, or any of the allied branches of the profession, the pharmacist must recognize the need to borrow heavily from the basic sciences. This stems from the fact that pharmacy is an applied science, composed of principles and methods that have been culled from other disciplines. The pharmacist engaged in advanced studies must work at the boundary between the various sciences and must keep abreast of advances in the physical, chemical, and biologic fields to understand and contribute to the rapid developments in his own profession.

Pharmacy, like many other applied sciences, has passed through a descriptive and an empiric era and is now entering the quantitative and theoretic stage.

The scientific principles of pharmacy are not as complex as some would believe, and certainly they are not beyond the understanding of the well-educated pharmacist of today. In the following pages, the reader will be directed through fundamental theory and experimental findings to practical conclusions in a manner that should be followed easily by the average pharmacy student.

The name *physical pharmacy* has been associated with the area of pharmacy that deals with the quantitative and theoretic principles of science as they apply to the practice of pharmacy. Physical pharmacy attempts to integrate the factual knowledge of pharmacy through the development of broad principles of its own, and it aids the pharmacist, the pharmacologist, and the pharmaceutical chemist in their attempt to predict the solubility, stability, compatibility, and biologic action of drug products. As a result of this knowledge, the pharmaceutical scientist is in a better position to develop new drugs and dosage forms and to improve upon the various modes of administration.

This course should mark the turning point in the study pattern of the student, for in the latter part of the pharmacy curriculum, emphasis is placed upon the application of scientific principles to practical professional problems. Although facts must be the foundation upon which any body of knowledge is built, the rote memorization of disjointed "particles" of knowledge does not lead to logical and systematic thought. The student should strive in this course to integrate facts and ideas into a meaningful whole. In the pharmacist's career, he or she frequently will call upon these generalizations to solve practical pharmaceutical problems.

The comprehension of course material is primarily the responsibility of the student. The teacher can guide and direct, explain and clarify, but facility in solving problems in the classroom and the laboratory depends largely on the student's understanding of theory, recall of facts, ability to integrate knowledge, and willingness to devote sufficient time and effort to the task. Each assignment should be read and outlined, and assigned problems should be solved outside the classroom. The teacher's comments then will serve to clarify questionable points and aid the student to improve his or her judgment and reasoning abilities.

DIMENSIONS AND UNITS

The properties of matter are usually expressed by the use of three fundamental dimensions: length, mass, and time. Each of these properties is assigned a definite *unit* and a *reference standard.* In the metric system, the units are the centimeter (cm), the gram (g), and the second (sec); accordingly, it is often called the *cgs* system. A reference standard is a fundamental unit

TABLE 1–1. *Fundamental Dimensions and Units*

Dimension (Measurable Quantity)	Dimensional Symbol	CGS Unit	SI Unit	Reference Standard
Length (*l*)	*L*	Centimeter (cm)	Meter (m)	Meter
Mass (*m*)	*M*	Gram (g)	Kilogram (kg)	Kilogram
Time (*t*)	*T*	Second (sec)	Second (s)	Atomic frequency of Cesium 133

relating each measurable quantity to some natural or artificial constant in the universe.

Measurable quantities or dimensions such as area, density, pressure, and energy are compounded from the three fundamental dimensions just referred to. In carrying out the operation of measurement, we assign to each property a dimension that is expressed quantitatively in units. Thus the quantities of length, area, and volume are measured in the dimension of length (L), length squared (L^2), and length cubed (L^3), respectively corresponding to the unit of cm, cm^2, and cm^3 in the cgs system. The fundamental dimensions, units, and reference standards are given in Table 1–1.

The International Union of Pure and Applied Chemistry (IUPAC) has introduced a *Système International* or *SI units* in an attempt to establish an internationally uniform set of units. *Physical Pharmacy* generally uses the cgs or common system of units. However, since SI units appear with increasing frequency in research articles and are found in some textbooks, they are introduced to the student in this chapter. They are also used in Chapter 4 and to some extent elsewhere in the book. SI units are listed in Tables 1–1 and 1–2, and some appear inside the front cover of the book under *Physical Constants*.

Length and Area. The dimension of length serves as a measure of distance and has as its reference standard the *meter*. It is defined as follows:

$$1 \text{ meter} = 1.65076373 \times 10^6 \lambda_{\text{Kr-86}}$$

in which $\lambda_{\text{Kr-86}} = 6.0578021 \times 10^{-7}$ m is the wavelength in vacuo of the transition between two specific energy levels of the krypton-86 atom. Prior to this definition, the meter was arbitrarily defined as the distance between two lines on a platinum–iridium bar preserved at the International Bureau of Weights and Measures in Sèvres, France. The unit of length, the centimeter, is one hundredth of a meter, the common dimensions and multiples of which are found in Table 1–2. In the microscopic range, lengths are expressed as micrometers (μm), nanometers (nm), and angstroms, A, sometimes written Å. Units are often multiplied by positive and negative powers of 10 to indicate their magnitude, the micrometer being 1×10^{-3} millimeters or 10^{-4} cm, the nanometer 0.001 μm, and the angstrom 0.1 nm or 10^{-8} cm. Although the micrometer (μm) is the preferred term for 0.001 mm in modern textbooks on colloid chemistry, the practice is sometimes to use the older and more familiar term, micron (μ). Similarly, the nanometer has replaced the millimicron (mμ). The student should be familiar with the prefixes (see Table 1–2) accompanying units such as mass, volume, and time. For example, a nanosecond, or ns, is 10^{-9} second; a megaton (Mton) is 10^6 tons. Area is the square of a length and has the unit of square centimeters (sq. cm or cm^2).

TABLE 1–2. *Fractions and Multiples of Units*

Multiple	Prefix	Symbol
10^{12}	tera	T
10^{9}	giga	G
10^{6}	mega	M
10^{3}	kilo	k
10^{-3}	milli	m
10^{-6}	micro	μ
10^{-9}	nano	n
10^{-12}	pico	p

Volume. The measurable quantity, volume, is also derived from length. Its reference standard is the *cubic meter;* its cgs unit is one millionth of this value or 1 cubic centimeter (cc or cm^3). Volume was originally defined in terms of the *liter*, the volume of a kilogram of water at 1 atmosphere pressure and 4° C, and was meant to be equivalent to 1000 cm^3. Owing to the failure to correct for the dissolved air in the water, however, the two units do not compare exactly. It has since been established that 1 liter actually equals 1000.027 cm^3. Thus, there is a discrepancy between the milliliter (one thousandth of a liter) and the cubic centimeter, but it is so slight as to be disregarded in general chemical and pharmaceutical practice. Volumes are usually expressed in milliliters in this book, abbreviated ml or mL, in conformity with the U.S. Pharmacopeia and the National Formulary; however, cubic centimeters are used in the book where this notation seems more appropriate.

The pharmacist uses cylindric and conical graduates, droppers, pipettes, and burettes for the measurement of volume; graduates are used more frequently than the other measuring apparatus in the pharmacy laboratory. The flared conical graduate is less accurate than the cylindric type, and the use of the flared graduate should be discouraged except for some liquids that need not be measured accurately. The selection of the correct graduate for the volume of liquid to be measured has been determined by Goldstein et al.[1]