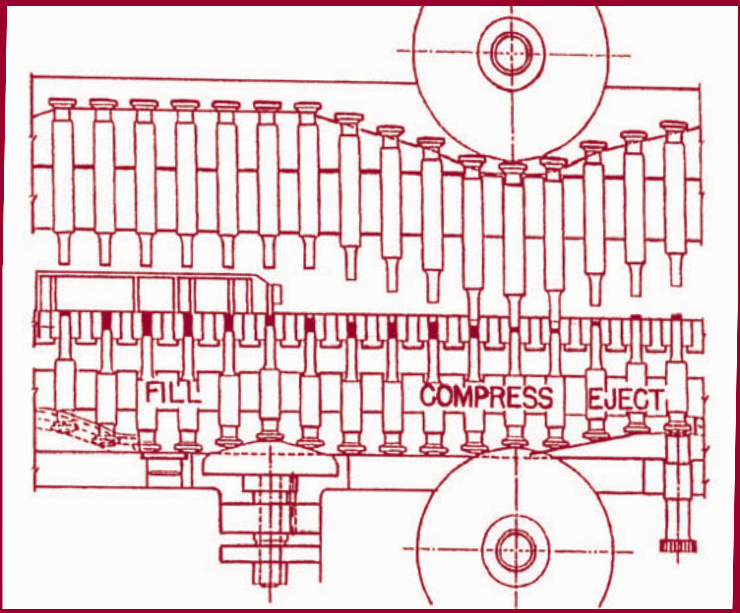
DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 195

SECOND EDITION

Pharmaceutical Process Engineering



Anthony J. Hickey
David Ganderton

informa
healthcare

Pharmaceutical Process Engineering

DRUGS AND THE PHARMACEUTICAL SCIENCES
A Series of Textbooks and Monographs

For information on volumes 1–149 in the *Drugs and Pharmaceutical Science* Series, please visit www.informahealthcare.com

150. Laboratory Auditing for Quality and Regulatory Compliance, *Donald Singer, Raluca-Ioana Stefan, and Jacobus van Staden*
151. Active Pharmaceutical Ingredients: Development, Manufacturing, and Regulation, *edited by Stanley Nusim*
152. Preclinical Drug Development, *edited by Mark C. Rogge and David R. Taft*
153. Pharmaceutical Stress Testing: Predicting Drug Degradation, *edited by Steven W. Baertschi*
154. Handbook of Pharmaceutical Granulation Technology: Second Edition, *edited by Dilip M. Parikh*
155. Percutaneous Absorption: Drugs–Cosmetics–Mechanisms–Methodology, Fourth Edition, *edited by Robert L. Bronaugh and Howard I. Maibach*
156. Pharmacogenomics: Second Edition, *edited by Werner Kalow, Urs A. Meyer and Rachel F. Tyndale*
157. Pharmaceutical Process Scale-Up, Second Edition, *edited by Michael Levin*
158. Microencapsulation: Methods and Industrial Applications, Second Edition, *edited by Simon Benita*
159. Nanoparticle Technology for Drug Delivery, *edited by Ram B. Gupta and Uday B. Kompella*
160. Spectroscopy of Pharmaceutical Solids, *edited by Harry G. Brittain*
161. Dose Optimization in Drug Development, *edited by Rajesh Krishna*
162. Herbal Supplements-Drug Interactions: Scientific and Regulatory Perspectives, *edited by Y. W. Francis Lam, Shiew-Mei Huang, and Stephen D. Hall*
163. Pharmaceutical Photostability and Stabilization Technology, *edited by Joseph T. Piechocki and Karl Thoma*
164. Environmental Monitoring for Cleanrooms and Controlled Environments, *edited by Anne Marie Dixon*
165. Pharmaceutical Product Development: In Vitro-In Vivo Correlation, *edited by Dakshina Murthy Chilukuri, Gangadhar Sunkara, and David Young*
166. Nanoparticulate Drug Delivery Systems, *edited by Deepak Thassu, Michel Deleers, and Yashwant Pathak*
167. Endotoxins: Pyrogens, LAL Testing and Depyrogenation, Third Edition, *edited by Kevin L. Williams*
168. Good Laboratory Practice Regulations, Fourth Edition, *edited by Anne Sandy Weinberg*
169. Good Manufacturing Practices for Pharmaceuticals, Sixth Edition, *edited by Joseph D. Nally*
170. Oral-Lipid Based Formulations: Enhancing the Bioavailability of Poorly Water-soluble Drugs, *edited by David J. Hauss*
171. Handbook of Bioequivalence Testing, *edited by Sarfaraz K. Niazi*
172. Advanced Drug Formulation Design to Optimize Therapeutic Outcomes, *edited by Robert O. Williams III, David R. Taft, and Jason T. McConville*
173. Clean-in-Place for Biopharmaceutical Processes, *edited by Dale A. Seiberling*
174. Filtration and Purification in the Biopharmaceutical Industry, Second Edition, *edited by Maik W. Jornitz and Theodore H. Meltzer*
175. Protein Formulation and Delivery, Second Edition, *edited by Eugene J. McNally and Jayne E. Hastedt*

176. Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms, Third Edition, *edited by James McGinity and Linda A. Felton*
177. Dermal Absorption and Toxicity Assessment, Second Edition, *edited by Michael S. Roberts and Kenneth A. Walters*
178. Preformulation Solid Dosage Form Development, *edited by Moji C. Adeyeye and Harry G. Brittain*
179. Drug-Drug Interactions, Second Edition, *edited by A. David Rodrigues*
180. Generic Drug Product Development: Bioequivalence Issues, *edited by Isadore Kanfer and Leon Shargel*
181. Pharmaceutical Pre-Approval Inspections: A Guide to Regulatory Success, Second Edition, *edited by Martin D. Hynes III*
182. Pharmaceutical Project Management, Second Edition, *edited by Anthony Kennedy*
183. Modified Release Drug Delivery Technology, Second Edition, Volume 1, *edited by Michael J. Rathbone, Jonathan Hadgraft, Michael S. Roberts, and Majella E. Lane*
184. Modified-Release Drug Delivery Technology, Second Edition, Volume 2, *edited by Michael J. Rathbone, Jonathan Hadgraft, Michael S. Roberts, and Majella E. Lane*
185. The Pharmaceutical Regulatory Process, Second Edition, *edited by Ira R. Berry and Robert P. Martin*
186. Handbook of Drug Metabolism, Second Edition, *edited by Paul G. Pearson and Larry C. Wienkers*
187. Preclinical Drug Development, Second Edition, *edited by Mark Rogge and David R. Taft*
188. Modern Pharmaceutics, Fifth Edition, Volume 1: Basic Principles and Systems, *edited by Alexander T. Florence and Juergen Siepmann*
189. Modern Pharmaceutics, Fifth Edition, Volume 2: Applications and Advances, *edited by Alexander T. Florence and Juergen Siepmann*
190. New Drug Approval Process, Fifth Edition, *edited by Richard A.Guarino*
191. Drug Delivery Nanoparticulate Formulation and Characterization, *edited by Yashwant Pathak and Deepak Thassu*
192. Polymorphism of Pharmaceutical Solids, Second Edition, *edited by Harry G. Brittain*
193. Oral Drug Absorption: Prediction and Assessment, Second Edition, *edited by Jennifer J. Dressman, hans Lennernas, and Christos Reppas*
194. Biodrug Delivery Systems: Fundamentals, Applications, and Clinical Development, *edited by Mariko Morishita and Kinam Park*
195. Pharmaceutical Process Engineering, Second Edition, *Anthony J. Hickey and David Ganderton*

SECOND EDITION

Pharmaceutical Process Engineering

Anthony J. Hickey

Cirrus Pharmaceuticals, Inc.
Durham, North Carolina, USA
University of North Carolina
Chapel Hill, North Carolina, USA

David Ganderton

London, UK

informa
healthcare

New York London

Informa Healthcare USA, Inc.
52 Vanderbilt Avenue
New York, NY 10017

Printed in the United States of America on acid-free paper
10 9 8 7 6 5 4 3 2 1

International Standard Book Number-10: 1-4200-8475-5 (Hardcover)
International Standard Book Number-13: 978-1-4200-8475-7 (Hardcover)

Library of Congress Cataloging-in-Publication Data

Hickey, Anthony J., 1955–
Pharmaceutical process engineering / Anthony J. Hickey, David Ganderton. — 2nd ed.
p. ; cm. — (Drugs and the pharmaceutical sciences ; 195)
Includes bibliographical references and index.
ISBN-13: 978-1-4200-8475-7 (hardcover : alk. paper)
ISBN-10: 1-4200-8475-5 (hardcover : alk. paper) 1. Pharmaceutical technology. 2. Production engineering. I. Ganderton, David. II. Title. III. Series: Drugs and the pharmaceutical sciences ; v. 195.
[DNLM: 1. Pharmaceutical Preparations—chemistry. 2. Biomedical Engineering. W1 DR893B v.195 2009 / QV 744 H628p 2009]
RS192.H53 2009
615'.19—dc22

2009025871

For Corporate Sales and Reprint Permissions call 212-520-2700 or write to: Sales Department, 52 Vanderbilt Avenue, 7th floor, New York, NY 10017.

Visit the Informa Web site at
www.informa.com

and the Informa Healthcare Web site at
www.informahealthcare.com

Preface

The motivation for expanding and updating *Unit Processes in Pharmacy* (David Ganderton, 1968) into the first edition of a book titled *Pharmaceutical Process Engineering* was a desire to make this valuable introductory volume available to a new generation of pharmaceutical scientists and technologists. The basic principles have not changed in the intervening years, but the environment in which manufacturing is conducted, both from a practical and a regulatory standpoint, has undergone a substantial evolution. The important principles of Quality by Design and the subtopic of Process Analytical Technology are routinely found on the programs of symposia devoted to pharmaceutical engineering and have a clear impact on the future of pharmaceutical manufacturing.

The present volume covers the basic principles with updated examples of the unit operations in pharmacy and their application. As in the first edition, the many unique drug delivery systems that extend beyond classical oral and parenteral dosage forms are not covered extensively as these are specialized topics covered in other volumes in this series.

A new section has been added on quality principles and the underlying mathematical and statistical methods. Adoption of known input variables that define the relevant process space can bring about consistency of product performance. The current capacity to store and manipulate data could not have been envisaged when the original volume on unit operations was published. The evolving tool of computer-aided design is likely to become a standard procedure in the future and, therefore, deserves to be addressed in the revised edition.

This volume remains an introductory text for pharmaceutical scientists and technologists who require an understanding of engineering principles. We hope that academic, industry, and government scientists and students will find this a useful text that serves the purpose of an easily accessible reference.

Anthony J. Hickey
David Ganderton

Acknowledgments

We are grateful for the support and encouragement of Carolyn Honour and Sandy Beberman, of Informa Healthcare, to prepare a second edition of this book. Kathryn Fiscelli assisted in collating materials used in the manuscript.

The first edition would not have been possible without the contribution of Dr Vasu Sethuraman. His endeavors with respect to integration of chapters, production of figures, and copyediting were the foundation on which the text was built. There is no doubt that his activities contributed to the clarity and continuity of the book. In addition, Dr Paul Pluta was generous in sharing his thoughts on solid dosage forms and allowed their use in the relevant sections of the volume.

The majority of the text continues to be based on a portion of David Ganderton's *Unit Processes in Pharmacy*, a book published in 1968 by Heineman Medical Books, Ltd., and now out of print. It is appropriate to acknowledge the contributions of that original volume.

The original text was the commission of Dr D. M. Moulden. We acknowledge the considerable help given by his ideas, plans, and drafts. In addition, we thank Mr Ian Boyd and Dr John Hersey, who read and evaluated manuscripts.

Contents

Units and Dimensions

The pharmaceutical scientist is familiar with the units (dimensions) of centimeter (length), gram (mass), and second (time) or the conventional Système Internationale (SI) units of meter, kilogram, and second. The engineer, in contrast, will express equations and calculations in units that suit quantities he or she is measuring. To reconcile in part this disparity, a brief account of units and dimensions follows.

Mass (M), length (L), time (T), and temperature (°) are four of six fundamental dimensions, the units of which have been fixed arbitrarily and from which all other units are derived. The fundamental units adopted for this book are the kilogram (kg), meter (m), second (sec), and Kelvin (K). The derived units are frequently self-evident. Examples are area (m^2) and velocity (m/sec). Others are derived from established laws of physics. Thus, a unit of force can be obtained from the law that relates force, F, to mass, m, and acceleration, a:

$$F = kma$$

where k is a constant. If we choose our unit of force to be unity when the mass and acceleration are each unity, the units are consistent. On this basis, the unit of force is Newton (N). This is the force that will accelerate a kilogram mass at 1 m/sec.

Similarly, a consistent expression of pressure [i.e., force per unit area is Newtons per square meter (N/m^2 or Pascal, Pa)]. This expression exemplifies the use of multiples or fractions of the fundamental units to give derived units of practical importance. A second example is dynamic viscosity [M/(L·T)] when the consistent unit kg/(m·sec), which is enormous, is replaced by kg/(m·hr) or even by poise. Basic calculations using these quantities must then include conversion factors.

The relationship between weight and mass causes confusion. A body falling freely due to its weight accelerates at kg·m/sec^2 (g varies with height and latitude). Substituting $k = 1$ in the preceding equation gives $W = mg$, where W is the weight of the body (in Newtons). The weight of a body has dimensions of force, and the mass of the body is given by

$$\text{mass(kg)} = \frac{\text{weight (N)}}{g\,(\text{m/sec}^2)}$$

The weight of a body varies with location; the mass does not. Problems arise when, as in many texts, kilogram is a unit of mass and weight of a kilogram is the unit of force. For example, an equation describing pressure drop in a pipe is

$$\Delta P = \frac{32ul\eta}{d^2}$$

when written in consistent units—ΔP as N/m^2, viscosity (η) as kg/(m·sec), velocity (u) as m/sec, distance (l) as m, and tube diameter (d) as m. However, if the kilogram force is used (i.e., pressure is measured in kg/m^2), the equation must be

$$\Delta P = \frac{32\,ul\eta}{gd^2}$$

where $g = 9.8$ m/sec^2. In tests using this convention, the conversion factor g appears in many equations.

The units of mass, length, and time commonly used in engineering heat transfer are kilogram, meter, and second, respectively. Temperature, which is a fourth fundamental unit, is measured in Kelvin (K). The unit of heat is the Joule (J), which is the quantity of heat required to raise the temperature of 1 g of water by 1 K. Therefore, the rate of heat flow, Q, often referred to as the total heat flux, is measured in J/sec. The units of thermal conductivity are J/(m^2·sec·K/m). This may also be written as J/(m·sec·K), although this form is less expressive of the meaning of thermal conductivity.