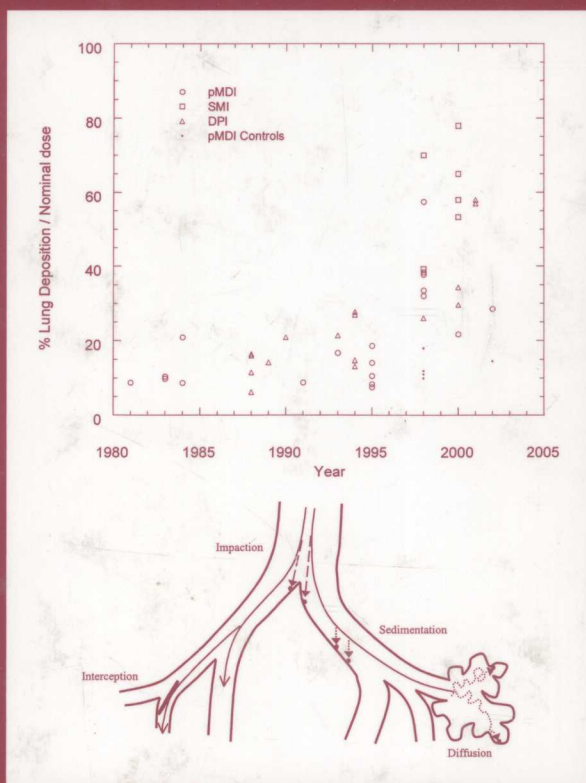


Pharmaceutical Inhalation Aerosol Technology

Second Edition, Revised and Expanded



edited by
Anthony J. Hickey

Pharmaceutical Inhalation Aerosol Technology

Second Edition, Revised and Expanded

edited by

Anthony J. Hickey

University of North Carolina

Chapel Hill, North Carolina, U.S.A.



MARCEL DEKKER, INC.

NEW YORK • BASEL

Although great care has been taken to provide accurate and current information, neither the author(s) nor the publisher, nor anyone else associated with this publication, shall be liable for any loss, damage, or liability directly or indirectly caused or alleged to be caused by this book. The material contained herein is not intended to provide specific advice or recommendations for any specific situation.

Trademark notice: Product or corporate names may be trademarks or registered trademarks and are used only for identification and explanation without intent to infringe.

Library of Congress Cataloging-in-Publication Data

A catalog record for this book is available from the Library of Congress.

ISBN: 0-8247-4253-2

This book is printed on acid-free paper.

Headquarters

Marcel Dekker, Inc., 270 Madison Avenue, New York, NY 10016, U.S.A.
tel: 212-696-9000; fax: 212-685-4540

Distribution and Customer Service

Marcel Dekker, Inc., Cimarron Road, Monticello, New York 12701, U.S.A.
tel: 800-228-1160; fax: 845-796-1772

Eastern Hemisphere Distribution

Marcel Dekker AG, Hutgasse 4, Postfach 812, CH-4001 Basel, Switzerland
tel: 41-61-260-6300; fax: 41-61-260-6333

World Wide Web

<http://www.dekker.com>

The publisher offers discounts on this book when ordered in bulk quantities. For more information, write to Special Sales/Professional Marketing at the headquarters address above.

Copyright © 2004 by Marcel Dekker, Inc. All Rights Reserved.

Neither this book nor any part may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, microfilming, and recording, or by any information storage and retrieval system, without permission in writing from the publisher.

Current printing (last digit):

10 9 8 7 6 5 4 3 2 1

PRINTED IN THE UNITED STATES OF AMERICA

Pharmaceutical Inhalation Aerosol Technology

科技阅览室



Y1902949

DRUGS AND THE PHARMACEUTICAL SCIENCES

Executive Editor

James Swarbrick

*PharmaceuTech, Inc.
Pinehurst, North Carolina*

Advisory Board

Larry L. Augsburger University of Maryland Baltimore, Maryland	David E. Nichols Purdue University West Lafayette, Indiana
--	--

Douwe D. Breimer Gorlaeus Laboratories Leiden, The Netherlands	Stephen G. Schulman University of Florida Gainesville, Florida
--	--

Trevor M. Jones The Association of the British Pharmaceutical Industry London, United Kingdom	Jerome P. Skelly Alexandria, Virginia
--	--

Hans E. Junginger Leiden/Amsterdam Center for Drug Research Leiden, The Netherlands	Felix Theeuwes Alza Corporation Palo Alto, California
--	---

Vincent H. L. Lee University of Southern California Los Angeles, California	Geoffrey T. Tucker University of Sheffield Royal Hallamshire Hospital Sheffield, United Kingdom
---	--

Peter G. Welling
Institut de Recherche Jouveinal
Fresnes, France

DRUGS AND THE PHARMACEUTICAL SCIENCES

A Series of Textbooks and Monographs

1. Pharmacokinetics, *Milo Gibaldi and Donald Perrier*
2. Good Manufacturing Practices for Pharmaceuticals: A Plan for Total Quality Control, *Sidney H. Willig, Murray M. Tuckerman, and William S. Hitchings IV*
3. Microencapsulation, *edited by J. R. Nixon*
4. Drug Metabolism: Chemical and Biochemical Aspects, *Bernard Testa and Peter Jenner*
5. New Drugs: Discovery and Development, *edited by Alan A. Rubin*
6. Sustained and Controlled Release Drug Delivery Systems, *edited by Joseph R. Robinson*
7. Modern Pharmaceutics, *edited by Gilbert S. Banker and Christopher T. Rhodes*
8. Prescription Drugs in Short Supply: Case Histories, *Michael A. Schwartz*
9. Activated Charcoal: Antidotal and Other Medical Uses, *David O. Cooney*
10. Concepts in Drug Metabolism (in two parts), *edited by Peter Jenner and Bernard Testa*
11. Pharmaceutical Analysis: Modern Methods (in two parts), *edited by James W. Munson*
12. Techniques of Solubilization of Drugs, *edited by Samuel H. Yalkowsky*
13. Orphan Drugs, *edited by Fred E. Karch*
14. Novel Drug Delivery Systems: Fundamentals, Developmental Concepts, Biomedical Assessments, *Yie W. Chien*
15. Pharmacokinetics: Second Edition, Revised and Expanded, *Milo Gibaldi and Donald Perrier*
16. Good Manufacturing Practices for Pharmaceuticals: A Plan for Total Quality Control, Second Edition, Revised and Expanded, *Sidney H. Willig, Murray M. Tuckerman, and William S. Hitchings IV*
17. Formulation of Veterinary Dosage Forms, *edited by Jack Blodinger*
18. Dermatological Formulations: Percutaneous Absorption, *Brian W. Barry*
19. The Clinical Research Process in the Pharmaceutical Industry, *edited by Gary M. Matoren*
20. Microencapsulation and Related Drug Processes, *Patrick B. Deasy*
21. Drugs and Nutrients: The Interactive Effects, *edited by Daphne A. Roe and T. Colin Campbell*
22. Biotechnology of Industrial Antibiotics, *Erick J. Vandamme*
23. Pharmaceutical Process Validation, *edited by Bernard T. Loftus and Robert A. Nash*

24. *Anticancer and Interferon Agents: Synthesis and Properties*, edited by Raphael M. Ottenbrite and George B. Butler
25. *Pharmaceutical Statistics: Practical and Clinical Applications*, Sanford Bolton
26. *Drug Dynamics for Analytical, Clinical, and Biological Chemists*, Benjamin J. Gudzinowicz, Burrows T. Younkin, Jr., and Michael J. Gudzinowicz
27. *Modern Analysis of Antibiotics*, edited by Adjoran Aszalos
28. *Solubility and Related Properties*, Kenneth C. James
29. *Controlled Drug Delivery: Fundamentals and Applications*, Second Edition, Revised and Expanded, edited by Joseph R. Robinson and Vincent H. Lee
30. *New Drug Approval Process: Clinical and Regulatory Management*, edited by Richard A. Guarino
31. *Transdermal Controlled Systemic Medications*, edited by Yie W. Chien
32. *Drug Delivery Devices: Fundamentals and Applications*, edited by Praveen Tyle
33. *Pharmacokinetics: Regulatory • Industrial • Academic Perspectives*, edited by Peter G. Welling and Francis L. S. Tse
34. *Clinical Drug Trials and Tribulations*, edited by Allen E. Cato
35. *Transdermal Drug Delivery: Developmental Issues and Research Initiatives*, edited by Jonathan Hadgraft and Richard H. Guy
36. *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms*, edited by James W. McGinity
37. *Pharmaceutical Pelletization Technology*, edited by Isaac Ghebresellassie
38. *Good Laboratory Practice Regulations*, edited by Allen F. Hirsch
39. *Nasal Systemic Drug Delivery*, Yie W. Chien, Kenneth S. E. Su, and Shyi-Feu Chang
40. *Modern Pharmaceuticals: Second Edition, Revised and Expanded*, edited by Gilbert S. Banker and Christopher T. Rhodes
41. *Specialized Drug Delivery Systems: Manufacturing and Production Technology*, edited by Praveen Tyle
42. *Topical Drug Delivery Formulations*, edited by David W. Osborne and Anton H. Amann
43. *Drug Stability: Principles and Practices*, Jens T. Carstensen
44. *Pharmaceutical Statistics: Practical and Clinical Applications*, Second Edition, Revised and Expanded, Sanford Bolton
45. *Biodegradable Polymers as Drug Delivery Systems*, edited by Mark Chasin and Robert Langer
46. *Preclinical Drug Disposition: A Laboratory Handbook*, Francis L. S. Tse and James J. Jaffe
47. *HPLC in the Pharmaceutical Industry*, edited by Godwin W. Fong and Stanley K. Lam
48. *Pharmaceutical Bioequivalence*, edited by Peter G. Welling, Francis L. S. Tse, and Shrikant V. Dinghe
49. *Pharmaceutical Dissolution Testing*, Umesh V. Banakar

50. Novel Drug Delivery Systems: Second Edition, Revised and Expanded, *Yie W. Chien*
51. Managing the Clinical Drug Development Process, *David M. Cocchetto and Ronald V. Nardi*
52. Good Manufacturing Practices for Pharmaceuticals: A Plan for Total Quality Control, Third Edition, *edited by Sidney H. Willig and James R. Stoker*
53. Prodrugs: Topical and Ocular Drug Delivery, *edited by Kenneth B. Sloan*
54. Pharmaceutical Inhalation Aerosol Technology, *edited by Anthony J. Hickey*
55. Radiopharmaceuticals: Chemistry and Pharmacology, *edited by Adrian D. Nunn*
56. New Drug Approval Process: Second Edition, Revised and Expanded, *edited by Richard A. Guarino*
57. Pharmaceutical Process Validation: Second Edition, Revised and Expanded, *edited by Ira R. Berry and Robert A. Nash*
58. Ophthalmic Drug Delivery Systems, *edited by Ashim K. Mitra*
59. Pharmaceutical Skin Penetration Enhancement, *edited by Kenneth A. Walters and Jonathan Hadgraft*
60. Colonic Drug Absorption and Metabolism, *edited by Peter R. Bieck*
61. Pharmaceutical Particulate Carriers: Therapeutic Applications, *edited by Alain Rolland*
62. Drug Permeation Enhancement: Theory and Applications, *edited by Dean S. Hsieh*
63. Glycopeptide Antibiotics, *edited by Ramakrishnan Nagarajan*
64. Achieving Sterility in Medical and Pharmaceutical Products, *Nigel A. Halls*
65. Multiparticulate Oral Drug Delivery, *edited by Isaac Ghebre-Sellassie*
66. Colloidal Drug Delivery Systems, *edited by Jörg Kreuter*
67. Pharmacokinetics: Regulatory • Industrial • Academic Perspectives, Second Edition, *edited by Peter G. Welling and Francis L. S. Tse*
68. Drug Stability: Principles and Practices, Second Edition, Revised and Expanded, *Jens T. Carstensen*
69. Good Laboratory Practice Regulations: Second Edition, Revised and Expanded, *edited by Sandy Weinberg*
70. Physical Characterization of Pharmaceutical Solids, *edited by Harry G. Brittain*
71. Pharmaceutical Powder Compaction Technology, *edited by Göran Alderborn and Christer Nyström*
72. Modern Pharmaceutics: Third Edition, Revised and Expanded, *edited by Gilbert S. Banker and Christopher T. Rhodes*
73. Microencapsulation: Methods and Industrial Applications, *edited by Simon Benita*
74. Oral Mucosal Drug Delivery, *edited by Michael J. Rathbone*
75. Clinical Research in Pharmaceutical Development, *edited by Barry Bleidt and Michael Montagne*

76. **The Drug Development Process: Increasing Efficiency and Cost Effectiveness**, edited by *Peter G. Welling, Louis Lasagna, and Umesh V. Banakar*
77. **Microparticulate Systems for the Delivery of Proteins and Vaccines**, edited by *Smadar Cohen and Howard Bernstein*
78. **Good Manufacturing Practices for Pharmaceuticals: A Plan for Total Quality Control**, Fourth Edition, Revised and Expanded, *Sidney H. Willig and James R. Stoker*
79. **Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms: Second Edition, Revised and Expanded**, edited by *James W. McGinity*
80. **Pharmaceutical Statistics: Practical and Clinical Applications**, Third Edition, *Sanford Bolton*
81. **Handbook of Pharmaceutical Granulation Technology**, edited by *Dilip M. Parikh*
82. **Biotechnology of Antibiotics: Second Edition, Revised and Expanded**, edited by *William R. Strohl*
83. **Mechanisms of Transdermal Drug Delivery**, edited by *Russell O. Potts and Richard H. Guy*
84. **Pharmaceutical Enzymes**, edited by *Albert Lauwers and Simon Scharpé*
85. **Development of Biopharmaceutical Parenteral Dosage Forms**, edited by *John A. Bontempo*
86. **Pharmaceutical Project Management**, edited by *Tony Kennedy*
87. **Drug Products for Clinical Trials: An International Guide to Formulation • Production • Quality Control**, edited by *Donald C. Monkhouse and Christopher T. Rhodes*
88. **Development and Formulation of Veterinary Dosage Forms: Second Edition, Revised and Expanded**, edited by *Gregory E. Hardee and J. Desmond Baggot*
89. **Receptor-Based Drug Design**, edited by *Paul Leff*
90. **Automation and Validation of Information in Pharmaceutical Processing**, edited by *Joseph F. deSpautz*
91. **Dermal Absorption and Toxicity Assessment**, edited by *Michael S. Roberts and Kenneth A. Walters*
92. **Pharmaceutical Experimental Design**, *Gareth A. Lewis, Didier Mathieu, and Roger Phan-Tan-Luu*
93. **Preparing for FDA Pre-Approval Inspections**, edited by *Martin D. Hynes III*
94. **Pharmaceutical Excipients: Characterization by IR, Raman, and NMR Spectroscopy**, *David E. Bugay and W. Paul Findlay*
95. **Polymorphism in Pharmaceutical Solids**, edited by *Harry G. Brittain*
96. **Freeze-Drying/Lyophilization of Pharmaceutical and Biological Products**, edited by *Louis Rey and Joan C. May*
97. **Percutaneous Absorption: Drugs–Cosmetics–Mechanisms–Methodology**, Third Edition, Revised and Expanded, edited by *Robert L. Bronaugh and Howard I. Maibach*

98. **Bioadhesive Drug Delivery Systems: Fundamentals, Novel Approaches, and Development**, edited by *Edith Mathiowitz, Donald E. Chickering III, and Claus-Michael Lehr*
99. **Protein Formulation and Delivery**, edited by *Eugene J. McNally*
100. **New Drug Approval Process: Third Edition, The Global Challenge**, edited by *Richard A. Guarino*
101. **Peptide and Protein Drug Analysis**, edited by *Ronald E. Reid*
102. **Transport Processes in Pharmaceutical Systems**, edited by *Gordon L. Amidon, Ping I. Lee, and Elizabeth M. Topp*
103. **Excipient Toxicity and Safety**, edited by *Myra L. Weiner and Lois A. Kotkoskie*
104. **The Clinical Audit in Pharmaceutical Development**, edited by *Michael R. Hamrell*
105. **Pharmaceutical Emulsions and Suspensions**, edited by *Francoise Nielloud and Gilberte Marti-Mestres*
106. **Oral Drug Absorption: Prediction and Assessment**, edited by *Jennifer B. Dressman and Hans Lennernäs*
107. **Drug Stability: Principles and Practices, Third Edition, Revised and Expanded**, edited by *Jens T. Carstensen and C. T. Rhodes*
108. **Containment in the Pharmaceutical Industry**, edited by *James P. Wood*
109. **Good Manufacturing Practices for Pharmaceuticals: A Plan for Total Quality Control from Manufacturer to Consumer, Fifth Edition, Revised and Expanded**, *Sidney H. Willig*
110. **Advanced Pharmaceutical Solids**, *Jens T. Carstensen*
111. **Endotoxins: Pyrogens, LAL Testing, and Depyrogenation, Second Edition, Revised and Expanded**, *Kevin L. Williams*
112. **Pharmaceutical Process Engineering**, *Anthony J. Hickey and David Ganderton*
113. **Pharmacogenomics**, edited by *Werner Kalow, Urs A. Meyer, and Rachel F. Tyndale*
114. **Handbook of Drug Screening**, edited by *Ramakrishna Seethala and Prabhavathi B. Fernandes*
115. **Drug Targeting Technology: Physical • Chemical • Biological Methods**, edited by *Hans Schreier*
116. **Drug–Drug Interactions**, edited by *A. David Rodrigues*
117. **Handbook of Pharmaceutical Analysis**, edited by *Lena Ohannesian and Anthony J. Streeter*
118. **Pharmaceutical Process Scale-Up**, edited by *Michael Levin*
119. **Dermatological and Transdermal Formulations**, edited by *Kenneth A. Walters*
120. **Clinical Drug Trials and Tribulations: Second Edition, Revised and Expanded**, edited by *Allen Cato, Lynda Sutton, and Allen Cato III*
121. **Modern Pharmaceutics: Fourth Edition, Revised and Expanded**, edited by *Gilbert S. Banker and Christopher T. Rhodes*
122. **Surfactants and Polymers in Drug Delivery**, *Martin Malmsten*
123. **Transdermal Drug Delivery: Second Edition, Revised and Expanded**, edited by *Richard H. Guy and Jonathan Hadgraft*

124. Good Laboratory Practice Regulations: Second Edition, Revised and Expanded, *edited by Sandy Weinberg*
125. Parenteral Quality Control: Sterility, Pyrogen, Particulate, and Package Integrity Testing: Third Edition, Revised and Expanded, *Michael J. Akers, Daniel S. Larrimore, and Dana Morton Guazzo*
126. Modified-Release Drug Delivery Technology, *edited by Michael J. Rathbone, Jonathan Hadgraft, and Michael S. Roberts*
127. Simulation for Designing Clinical Trials: A Pharmacokinetic-Pharmacodynamic Modeling Perspective, *edited by Hui C. Kimko and Stephen B. Duffull*
128. Affinity Capillary Electrophoresis in Pharmaceuticals and Biopharmaceuticals, *edited by Reinhard H. H. Neubert and Hans-Hermann Rüttinger*
129. Pharmaceutical Process Validation: An International Third Edition, Revised and Expanded, *edited by Robert A. Nash and Alfred H. Wachter*
130. Ophthalmic Drug Delivery Systems: Second Edition, Revised and Expanded, *edited by Ashim K. Mitra*
131. Pharmaceutical Gene Delivery Systems, *edited by Alain Rolland and Sean M. Sullivan*
132. Biomarkers in Clinical Drug Development, *edited by John C. Bloom and Robert A. Dean*
133. Pharmaceutical Extrusion Technology, *edited by Isaac Ghebre-Sellassie and Charles Martin*
134. Pharmaceutical Inhalation Aerosol Technology: Second Edition, Revised and Expanded, *edited by Anthony J. Hickey*

ADDITIONAL VOLUMES IN PREPARATION

Pharmaceutical Compliance, *edited by Carmen Medina*

Pharmaceutical Statistics: Practical and Clinical Applications, Fourth Edition, *Sanford Bolton and Charles Bon*

Foreword

It is hard to believe that in ten short years since the publication of *Pharmaceutical Inhalation Aerosol Technology* the number of chapters would be increased two-thirds in order to bring the second edition up to date. But it is true! For one who had the privilege of experiencing the heady days, nearly a half century ago, during the development of early metered-dose inhalers (MDIs), the accelerated pace of development in inhalation technology during the past decade has been truly astonishing.

In the early days, we didn't have the foggiest idea of how much of the drug discharged from our MDIs actually deposited in the lung: we only knew that those patients were getting relief for their asthma. Today, using recently developed mathematical models that are based on lung morphology and aerosol physics, we can estimate with reasonable certainty the amount of drug delivered from an inhaler that is expected to be deposited in the lung. New methods of imaging appropriately labeled drug discharged from inhalers provide exquisite pictures of the distribution and accurate estimate of the quantity of drug deposited in the lung. Greater understanding of the cell biology of the lung and of the pharmacodynamics and pharmacokinetics of drug in the lung helps us understand what happens, and the rate at which it happens, to drug deposited there.

Methods of aerosol generation—ultrasound, electrohydrodynamics, hydrostatic pressure extrusion of liquid through small orifices—that, just ten years ago, might have been considered laboratory curiosities or perhaps only implemented as laboratory prototype generators, are now in late-stage development as handheld inhalers. In addition, precision dry-powder inhalers are in late-stage development. Chlorofluorocarbon (CFC)-free MDIs, often more

efficient than their CFC counterparts, are on the market. The dream of delivering insulin by inhalation to eliminate injection in the treatment of diabetes is coming to fruition. Inhaled insulin, delivered by precision dry-powder inhalers and from metered aqueous-aerosol inhalers, is in late-stage clinical trials with very encouraging results. Ten years ago, gene implantation from inhaled aerosol was only beginning to be talked about. Today it is being explored in clinical trials as treatment for cystic fibrosis. Proteins and peptides comprise a growing number of drugs coming from the biotech industry that are now being developed as aerosol dosage forms.

Keeping pace with this technological development, the science and understanding of formulation factors that govern aerosol generation, of factors governing pulmonary deposition, and of the chemical and biological fate of drug deposited in the respiratory tract are burgeoning. For one experienced in the development of pharmaceutical aerosols, this second addition of *Pharmaceutical Inhalation Aerosol Technology* provides, in a compact way, a useful overview of new developments in the technology. This volume will be particularly useful for the many people entering this increasingly exciting field—pharmaceutical scientists, engineers, and clinicians. It will provide them with a jump start to bring them up to speed in this rapidly expanding field.

Charles G. Thiel
3M Drug Delivery Systems Division, Retired
Maplewood, Minnesota, U.S.A.

Foreword to the First Edition

The metered-dose aerosol inhaler is not only a most convenient system for the delivery of therapeutically active drugs but it has proven to be a life-saving device for many asthmatics. This system has made it possible for millions of asthma sufferers to lead normal lives. The convenience of self-administering a dose of drug accurately and quickly has made the metered-dose aerosol the dosage form of choice for the delivery of drugs to the respiratory system. From epinephrine to albuterol, from triamcinolone to flunisolide, from proteins and peptides to hormones, this dosage form has proven its value.

This volume covers the subject of inhalation technology from start to finish and is a welcome addition to the literature in this area. The reader can quickly become aware of the many ramifications of aerosol inhalation therapy along with the underlying principles for the deposition of particles in the lungs.

Ever since the introduction of the first metered-dose inhaler in the early 1950s, this dosage form has been readily prescribed by the physician and readily accepted by the patient. This text extends our knowledge in this rapidly growing field and will enable the pharmaceutical scientist to develop existing and new drugs in a suitable aerosol system.

*John J. Sciarra
Arnold and Marie Schwartz College of Pharmacy
Long Island University
Brooklyn, New York, U.S.A.*

Preface

When the first edition of *Pharmaceutical Inhalation Aerosol Technology* was published there was a clear need for a concise review of the state-of-the-art technology for those entering the field. During the previous 25 years this had been a relatively dormant field for innovation outside of large corporations, which clearly dominated the market for these products. As the 1990s began, it was clear that interest in the potential of aerosols for the treatment of both local and systemic diseases was increasing. This seemed an ideal time to produce a specialized book in this field. By the end of the 1990s it would not be an overstatement to say that a revolution had occurred. Many new and some existing companies began to focus on aerosols. Hundreds of new openings for personnel were created, and the literature flourished with new and ever more interesting discoveries regarding the administration of drugs as aerosols to the lungs.

In this current climate of discovery and increased commercial activity the time is right for this second edition. In this volume I have tried to incorporate all of the old, yet still relevant topics, and I have included new sections that cover material that was either in the early days of evaluation or unheard of in 1992.

In Part One, chapters have been included covering cell biology and pharmacokinetics. Historically, the pharmacokinetics of locally acting drugs administered in low doses was thought to be an irrelevancy. With the burgeoning interest in the systemic action of drugs intended either for local activity, such as corticosteroids, or for remote activity, such as insulin—the pharmacokinetics of disposition is now key in the development of aerosol products. Needless to say, with this interest in the disposition of drugs from the lungs, the mechanisms of

transport must be elucidated and the tools of cell biology will be necessary to achieve this goal.

Part Two remains largely the same as in the first edition. The fundamentals of aerosol science have changed little in the last decade. However, the original focus was on the pressure-packaged metered-dose inhaler. Environmental concerns over ozone depletion and global warming and the need for alternative formulation strategies for biological molecules have driven the development of new dry-powder inhalers and handheld aqueous aerosol inhalers. These were discussed briefly in the first edition and are now given separate sections.

Part Three is the most extensively modified in the second edition. In the early 1990s asthma was the only disease that was being treated systematically with aerosols. Throughout the decade the concept of treating diabetes with insulin aerosols, cystic fibrosis by gene transfection, and infectious diseases with antimicrobials gained ground. Many of these approaches have yet to be commercial or therapeutic success stories, but by the time this book is in print they may be available to the clinician. Consequently, sections on these topics have been added.

It is worth reiterating a sentiment from the first edition. The literature is replete with publications advancing the frontiers of knowledge. This text is intended to be an overview of the state of the art of the technology. I leave it to others to edit prospective, scientifically detailed books. To remind the readers how far we have come, and how quickly, a concluding chapter is included that reviews the past decade and speculates on the future.

On a personal note, it was most gratifying to see how well the original volume was received. To those of you who read the book, some of whom have thanked me for collating the materials, I owe you a debt of gratitude for applying this knowledge and making it worthwhile. I hope you find this new edition as useful and informative.

Anthony J. Hickey

Contributors

Abeer M. Al-Ghananeem, Ph.D. College of Pharmacy, University of Kentucky, Lexington, Kentucky, U.S.A.

Paul J. Atkins, Ph.D. Oriel Therapeutics, Inc., Research Triangle Park, North Carolina, U.S.A.

Andrew R. Clark, Ph.D. Nektar Therapeutics, Inc., San Carlos, California, U.S.A.

Peter A. Crooks, Ph.D. College of Pharmacy, University of Kentucky, Lexington, Kentucky, U.S.A.

Timothy M. Crowder, Ph.D. Oriel Therapeutics, Inc., Research Triangle Park, North Carolina, U.S.A.

Michelle Dawson Department of Chemical Engineering, Johns Hopkins University, Baltimore, Maryland, U.S.A.

Myrna B. Dolovich, P.Eng. Departments of Medicine and Radiology, McMaster University, Hamilton, Ontario, Canada

David A. Edwards, Ph.D. Department of Engineering and Applied Science, Harvard University, Cambridge, Massachusetts, U.S.A.

Jennifer Fiegel Department of Chemical Engineering, Johns Hopkins University, Baltimore, Maryland, U.S.A.