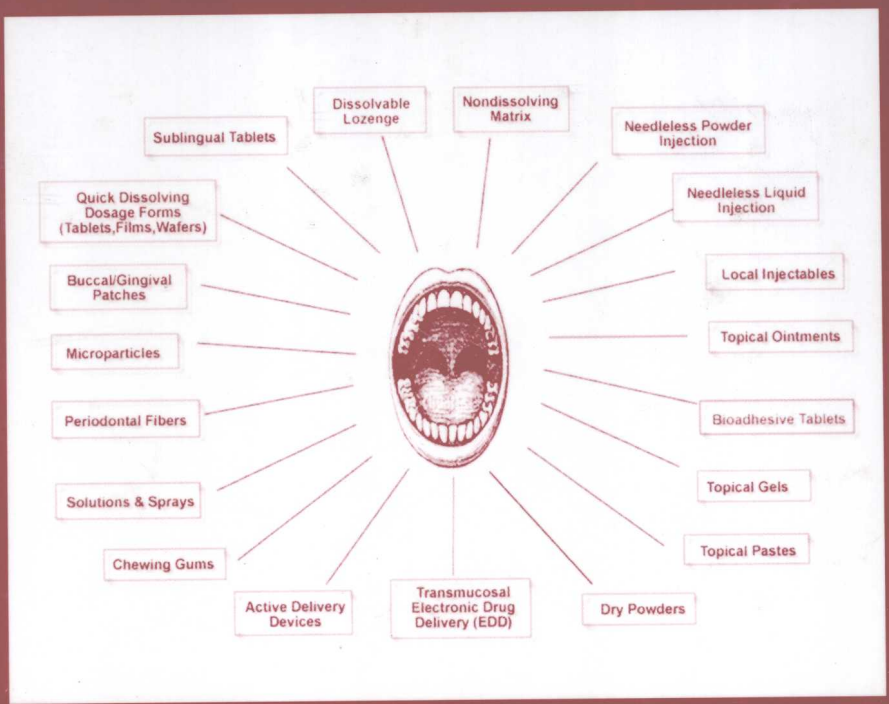
DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 145

Drug Delivery to the Oral Cavity

Molecules to Market



edited by
Tapash K. Ghosh
William R. Pfister

Drug Delivery to the Oral Cavity

Molecules to Market

Tapash K. Ghosh
U.S. Food and Drug Administration
Rockville, Maryland, U.S.A.

William R. Pfister
NexMed, (U.S.A.) Inc.
Robbinsville, New Jersey, U.S.A.

Taylor & Francis
Taylor & Francis Group
Boca Raton London New York Singapore

Published in 2005 by
CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

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: 0-8247-8293-3 (Hardcover)
International Standard Book Number-13: 978-0-8247-8293-1 (Hardcover)
Library of Congress Card Number 2004062072

Library of Congress Cataloging-in-Publication Data

Drug delivery to the oral cavity: molecules to market / Tapash K. Ghosh, William R. Pfister, editors,
p. cm. -- (Drugs and the pharmaceutical sciences)
Includes bibliographical references and index.
ISBN 0-8247-8293-3 (alk. paper)
1. Oral medication. 2. Oral mucosa. I. Ghosh, Tapash K. II. Pfister, William R. III. Series.

RM162.I56 2005
615'.6--dc22 2004062072

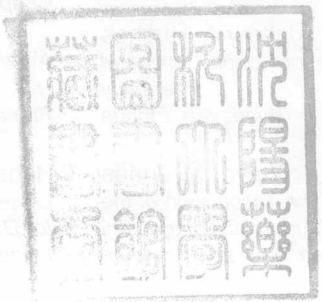
T&F informa
Taylor & Francis Group
is the Academic Division of T&F Informa plc.

Visit the Taylor & Francis Web site at
http://www.taylorandfrancis.com

and the CRC Press Web site at
http://www.crcpress.com

Drug Delivery to the Oral Cavity

Molecules to Market



DRUGS AND THE PHARMACEUTICAL SCIENCES

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 Ghebre-Sellassie*
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 Pharmaceutics: 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 Pharmaceutics and Biopharmaceutics, *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*

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

136. Compliance Handbook for Pharmaceuticals, Medical Devices, and Biologics, *edited by Carmen Medina*

137. Freeze-Drying/Lyophilization of Pharmaceutical and Biological Products: Second Edition, Revised and Expanded, *edited by Louis Rey and Joan C. May*

138. Supercritical Fluid Technology for Drug Product Development, *edited by Peter York, Uday B. Kompella, and Boris Y. Shekunov*

139. New Drug Approval Process: Fourth Edition, Accelerating Global Registrations, *edited by Richard A. Guarino*

140. Microbial Contamination Control in Parenteral Manufacturing, *edited by Kevin L. Williams*

141. New Drug Development: Regulatory Paradigms for Clinical Pharmacology and Biopharmaceutics, *edited by Chandrahas G. Sahajwalla*

142. Microbial Contamination Control in the Pharmaceutical Industry, *edited by Luis Jimenez*

143. Generic Drug Product Development: Solid Oral Dosage Forms, *edited by Leon Shargel and Izzy Kanfer*

144. Introduction to the Pharmaceutical Regulatory Process, *edited by Ira R. Berry*

145. Drug Delivery to the Oral Cavity: Molecules to Market, *edited by Tapash K. Ghosh and William R. Pfister*

Preface

The oral cavity (OC) and its highly permeable mucosal tissues have been taken advantage of for decades as a site of absorption for delivery of drugs to the systemic circulation (oral transmucosal delivery, OTD), and for local delivery to the subjacent tissues (oral mucosal delivery, OMD). Administration of an active agent in a dosage form intended to release the drug in the oral cavity is referred to herein as an intraoral delivery system or intraoral dosage form (IOD). Intraoral delivery may provide for a local effect (i.e., breath freshening), absorption via the oral mucosal tissues for either a local drug effect (i.e., analgesia) or systemic drug effect (i.e., smoking cessation), or, with most drugs, provide for systemic absorption along the segments of the gastrointestinal tract (GIT).

Myriad IODs and drug products are now widely prescribed for systemic diseases, as are OMD products for local treatment of halitosis, bacterial infections, periodontal disease, and other conditions of the mouth. Mouthwash and dentifrice active ingredients are now widely used in a variety of personal care products for local delivery to the oral cavity, periodontal pocket, and the overlying mucosal tissue. The first commercially successful oral transmucosal drug delivery system (OTDS) was a sublingual tablet introduced in the early 1960s containing nitroglycerin for the symptomatic treatment of angina pectoris. Over the past 30 years, many other OTDS have been commercialized for systemic drug delivery and treatment of angina pectoris (i.e., nitroglycerin), moderate to severe pain (i.e., fentanyl), smoking addiction (i.e., nicotine), and so on.

More recently, fast-dissolving or mouth-dissolving tablets and novel film delivery systems have been developed. Dozens of oral mucosal delivery systems (OMDS) targeted at the personal care products market for the local delivery of medicinal agents to the oral cavity have been developed. These IODs include quick-dissolving films, mouthwash, and dentifrice products containing antibacterial agents, fluoride, flavoring agents, and the like. The innovative approaches in OTD and OMD delivery system designs, fundamental understanding of the mechanisms of mucoadhesion, and development of oral transmucosal permeation enhancer technology have paved the way in the development of sophisticated controlled-release delivery strategies for systemic and local therapy, respectively. More recently, interest has focused on the oral transmucosal route for delivery of biotechnology products (i.e., proteins, peptides, antisense compounds, etc.). Due to the high permeability and lower metabolic activity of the oral mucosal tissue compared to skin and the gastrointestinal tract, there are high hopes for the success of the oral transmucosal route for delivery of second-generation biotechnology products, and perhaps for delivery of insulin as well.

The early product successes focused on the "easy-to-deliver" drugs (i.e., nitroglycerin sublingual tablets, nicotine gum, and lozenges) paved the way in the development of new technologies, which may be effective in overcoming the future challenges of controlled delivery of the "difficult-to-deliver" drugs having higher molecular weight (greater than 400 Daltons) such as polypeptides and protein-based therapeutics. These new OTDS arising from our fundamental understanding of transport processes, pharmacology, and biochemistry of the mucosal tissue, and development of predictive modeling, advances in material science, and developments of transmucosal permeation enhancers will allow us to meet the challenges of the future with new and improved IODs for treatment of many other diseases.

The basic science and recent research relating to the oral cavity and oral mucosal drug delivery has been published extensively in the literature, which has emphasized the basic structure, function, biochemistry, and permeability of the oral cavity. Similarly, the scientific foundation is now well established for development of oral mucosal delivery systems, and an understanding of the influence of saliva, mucin, cellular models for predicting mucosal drug transport, and metabolism have also been discussed in numerous review articles and several books, which sets the stage for the topics covered in this book.

The purpose of this book is to bring into perspective the practical and applied aspects of pharmaceutical development of new solid-state dosage forms for OTD and OMD systems, and the strategies that have been employed for effective systemic and local drug delivery to the oral mucosa. The many dental and pharmaceutical prescriptions and OTC products under development and those that have been successfully commercialized are the main focus of this book. It is not the intent to review the numerous nutriceuticals, dietary supplements, vitamins, and consumer products (i.e., gums, breath fresheners, mouthwashes, lozenges, etc.) because these intraoral formulations (i.e., chewable tablets, liquids,

sprays, etc.) are too numerous to adequately address in this volume. Furthermore, the traditional pharmaceutical products marketed as syrups, drops, or suspensions are not reviewed. Rather, the main focus of this book is to provide an overview of the new and emerging IODs and technologies that address the unmet patient and market needs for improved local and systemic drug therapy.

This book consists of 14 chapters that provide the reader with a comprehensive, succinct, state-of-the-art review of the science and innovative technologies currently available for the development of novel delivery systems targeted to the oral cavity for systemic and local delivery. Chapter 1 provides an overview of the fundamentals such as the underlying physiology, biochemistry, and anatomy of the oral mucosa; the various sites of oral mucosal absorption (i.e., gingival, buccal, palatal, sublingual, periodontal, etc.) for local and systemic drug delivery; the local environment of the oral cavity and its impact on drug absorption, distribution, metabolism, and excretion (ADME); and the metabolic barrier to oral mucosal drug absorption. The advantages of systemic drug delivery by the oral transmucosal route and various IODs are discussed. A summary of the IODs in various stages of research as well as those on the market, and a snapshot of the future trends and the next generation products and technologies are also presented, which sets the stage for the chapters to follow. Preformulation considerations are an important first step in the development of IODs.

The key elements in preclinical assessment necessary to predict mucosal permeation, selection of drug candidates and formulation components, as well as delivery system designs are highlighted in Chapter 2. The preclinical assessment of oral mucosal drug delivery and delivery systems is the next important step in the development process. The in vitro and in vivo models used to assess oral transmucosal drug absorption, the fundamental techniques for the in vitro assessment of mucobioadhesive polymers, the ideal characteristics of mucoadhesive pharmaceutical excipients and criteria for their selection, the effects of saliva and mucin on drug permeation, and finally the importance of selection of appropriate animal models for safety assessment of local irritation and sensitization are presented in Chapter 2. The advantages of systemic drug delivery by the oral transmucosal route are discussed and examples of products for the delivery of analgesics, CNS active agents, antiemetics, and so on are also presented in Chapter 2.

The challenges to the formulation scientist in overcoming the barrier properties of the oral mucosa and effective use of various chemical classes of mucosal permeation enhancers (MPE) to upregulate drug absorption are reviewed and summarized in Chapter 3.

A review of recent work in the field of OTM delivery of proteins and peptides and the challenges that need to be overcome to minimize the local enzymatic metabolism of four labile compounds and strategies to maximize their absorption are discussed in Chapter 4.

The next steps in the development cycle consist of the design, clinical development, manufacture, testing, and marketing of oral mucosal delivery systems.

There are now dozens of commercial OTD and OMD products on the market including: quick-dissolving (QD), slow-dissolving (SD), and nondissolving (ND) IODs such as sublingual tablets, quick-dissolving tablets, chewing gums, patches, devices, liposomes, microparticle delivery systems, and so on. Chapters 5 through 10 focus on some of the more recently developed and commercialized SD and ND IODs. Sublingual delivery of nitroglycerin was one of the first life-saving drugs introduced for the prevention of angina pectoris and heart attacks. The products (sublingual tablets) for delivery of organic nitrates including nitroglycerin and isosorbide dinitrate for the treatment of angina pectoris are reviewed in Chapter 5.

Development of a novel oral mucosal technology for delivery of melatonin for normalization of circadian rhythms is discussed in Chapter 6. The many innovative IODs for delivery of nicotine (i.e., gums, lozenges, sublingual tablets, inhalators, sprays, etc.) for smoking cessation therapy, including products on the market and those in development, are reviewed in detail in Chapter 7. The formulation development and preclinical, and clinical assessment of a novel dry powder needleless injection device for the delivery of conventional drugs, polypeptides, and proteins to the mucosal tissue of the oral cavity for local and systemic drug delivery are presented in Chapter 8. Oral TMDS (i.e., liposomes, fibers, microparticles, sustained release depots, etc.) for treatment of periodontal disease are reviewed and contrasted, and the general classes of products for oral hygiene including mouthwash and dentifrice products are reviewed in Chapter 9. The use of local anesthetics in dental and oral surgical applications and the clinical development of a novel mucoadhesive local anesthetic patch are highlighted in Chapter 10.

Novel QD dosage forms that dissolve in the mouth without water, offer patient convenience, and patent life extension for many drugs are reviewed in Chapters 11 through 14. The various QD tablet delivery system designs, considerations in material/excipient selection, manufacturing technologies, testing procedures, and points to consider in scale-up from laboratory to commercial production of quick-dispersing oral drug delivery systems including the chemistry, manufacturing, and controls (CMC) are discussed in Chapter 11. A new innovative QD intraoral drug delivery technology, which does not require water and offers the patient convenience for delivery of a wide variety of drugs, is highlighted in Chapter 12. The considerations in process development and scale-up of QD IOD tablets, and the principals in optimizing process scale-up conditions and product quality issues, are reviewed in Chapter 13. Finally, the scientific and regulatory considerations in developing QD IOD tablets from a clinical pharmacology and biopharmaceutics perspective are critically reviewed in Chapter 14.

In addition, a useful reference guide is provided on worldwide companies developing intraoral drug delivery technologies and products (Appendix 1), as well as selected books and market research reports dealing with intraoral drug delivery (Appendix 2). The reader may find the list of abbreviations at the end

of this book useful to better understanding the unique acronyms used in the IOD literature.

We believe that this book offers a wealth of up-to-date information organized in a logical sequence corresponding to the various stages of research, development, and commercialization of IOD products. Our authors were selected from industry, academia, and government for their expertise and reputation in their selected areas to objectively present a balanced view of the state-of-the-art in IOD product development. Their insights will prove useful to the pharmaceutical scientists in industry and academia who are involved in the development of the next generation of IOD products. This book was written especially for the pharmaceutical development scientists, but should be instructive to R&D managers and those involved in the various stages of laboratory testing, manufacturing, clinical evaluation, marketing, and regulatory affairs. The importance of the book to medical professionals involved in the prescription and use of these emerging dosage forms also should be recognized.

Tapash K. Ghosh

William R. Pfister