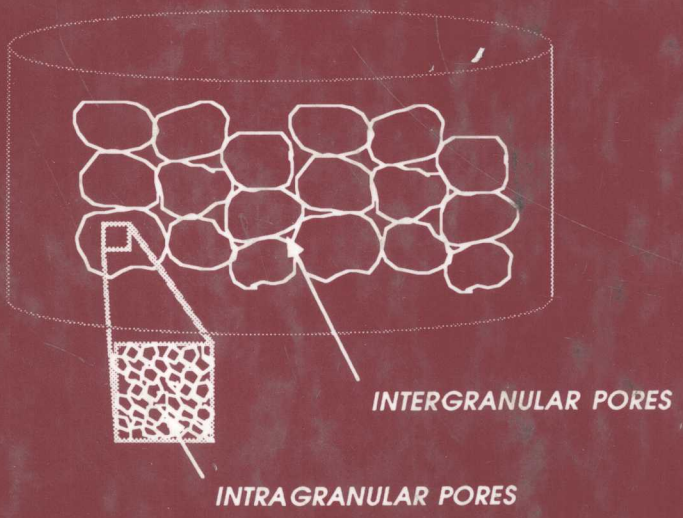
DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 71

Pharmaceutical Powder Compaction Technology



edited by
Göran Alderborn
Christer Nyström

Pharmaceutical Powder Compaction Technology

edited by
Göran Alderborn
Christer Nyström
Uppsala University
Uppsala, Sweden

Marcel Dekker, Inc. New York • Basel • Hong Kong

Library of Congress Cataloging-in-Publication Data

Pharmaceutical powder compaction technology / edited by Göran Alderborn, Christer Nyström.
p. cm. -- (Drugs and the pharmaceutical sciences ; v. 71)
Includes bibliographical references and index.
ISBN 0-8247-9376-5
1. Tablets (Medicine) I. Alderborn, Göran.
II. Nyström, Christer. III. Series.
RS201.T2P465 1995
615'.19--dc20 96-24571
CIP

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

This book is printed on acid-free paper.

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

Current printing (last digit):
10 9 8 7 6 5 4 3 2 1

PRINTED IN THE UNITED STATES OF AMERICA

Pharmaceutical Powder Compaction Technology

DRUGS AND THE PHARMACEUTICAL SCIENCES

A Series of Textbooks and Monographs

edited by

James Swarbrick
AAI, Inc.
Wilmington, North Carolina

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*

ADDITIONAL VOLUMES IN PREPARATION

Preface

Oral administration is the dominant method of delivering drugs to the human systemic blood circulation because of its safety and simplicity. Thus, great interest has been focused within pharmaceutical science on the design of oral dosage forms with optimal therapeutic properties. The prevailing oral dosage form today is the tablet due to its elegance. Tablets of various types and biopharmaceutical properties—from conventional, disintegrating tablets, to advanced modified release systems—exist, but their common denominator is the way in which they are formed, i.e., powder compaction. Physical and technological aspects of this process, from a pharmaceutical point of view, are the theme of this book.

The complexity of the compaction process—what at first sight seems to be a simple mechanical operation—was recognized early. Problems still exist in large-scale production of tablets, such as low tablet strength, capping, limited use of direct compression, and sensitivity to batch variability of starting materials. Moreover, the use of basic physical data in formulation work in order to predict tableting behavior of particles such as compressibility (ability to reduce in volume) and compactibility (ability to cohere into compacts) is limited. Thus, tablet formulation must still be based to a large extent on empirical knowledge rather than on scientific theory.

An improved theoretical understanding of the compaction process will enable a more rational approach to the formulation of tablets. However, the investments in research on the physics of the compaction process

have, in relative terms, been limited in universities and the pharmaceutical industry. In spite of this, a large number of publications on the theme of the formation of tablets by compaction exist today in the pharmaceutical literature. This literature can be broadly classified into three categories: (1) reports on specific formulations and their compactibility and on formulation solutions to compaction-related problems, (2) studies on mechanisms of and theories for the compression and the compaction of pharmaceutical powders (such studies also include articles dealing with the development and evaluation of methods for theoretical studies), and (3) evaluation, with recognized methods and theories, of the compression and compaction behavior of pharmaceutical tableting excipients.

In the older literature, publications were focused mainly on the practical aspects of the preparation of tablets. However, since the late 1940s, articles focused on the theoretical aspects of the compaction process have been presented in the pharmaceutical scientific literature. As a consequence of the growing interest in directly compactable formulations, new excipients with improved tableting performance have been developed and the compaction characteristics of these have been the object of scientific studies. Despite this growing literature on the physics and technology of powder compaction, the interest in bringing together the accumulated knowledge in the form of comprehensive reference works has hitherto been limited. It is thus a great pleasure for the editors of this volume to present a book on theoretical and practical aspects of the process of forming compacts by powder compression. This is, to our knowledge, the first book devoted entirely to this theme. It has been made possible by the contribution of chapters from researchers throughout Europe and North America. To achieve the high level needed, only recognized scientists, representing academia or the pharmaceutical industry, have been involved, and each contributor has been encouraged to focus on his or her field of expertise. The role of the editors has been to primarily select topics and authors for the contributions and to find a suitable structure for the book. The consequence of this is that different concepts and beliefs in the field of powder compaction are presented and discussed in the book, and we have not attempted to hide this diversity. This diversity reflects the complexity of studying and establishing theories for the handling and processing of "real" materials. Moreover, there are also different traditions with respect to the nomenclature used in the discussion on powder compaction, and this inconsistency among researchers in this respect is also reflected in this book. The editors allowed each author to use terms in accordance with his or her tradition. However, to improve the stringency in the use of the nomenclature for the future, a short list of definitions follows this preface.

During the preparation of this book, some topics within the area of

pharmaceutical powder compaction have not been dealt with as separate chapters, as they are not covered extensively in the literature. Examples of such topics are energy aspects of the formation of tablets, physical instability in compacts during storage, and mathematical expressions for the tensile strength of compacts. However, these topics are discussed and references are given in some of the chapters of this book.

Although great progress in the theoretical understanding of the compaction process has been made since the late 1940s, the need for further research is obvious. It is our hope that this volume can contribute to and stimulate such intellectually challenging research.

We are very grateful to Marcel Dekker, Inc., for taking the initiative to prepare a book on pharmaceutical powder compaction technology. We express our sincere appreciation especially to Sandra Beberman and Ted Allen, for pleasant cooperation during the preparation of this book, for their qualified contributions, and for their support and patience with us in our role as editors.

We are also very grateful to all contributors to this volume, for their positive attitude to share their expertise in the field of powder compaction and for the time and effort taken to write articles of high quality. Without their collaboration and contributions, the writing of this book would never have been accomplished.

Finally, we would like to thank Mrs. Eva Nises-Ahlgren for qualified administrative work in connection with the preparation of this book.

Göran Alderborn
Christer Nyström

Nomenclature

Below are the definitions of some terms commonly used in relation to powder compaction. It should be noted that within this book the terms are not used strictly in accordance with these definitions, as some authors have used the terms differently. The list is narrow in that it presents only the terms that seem to cause the most confusion in discussions of powder compaction. Less ambiguous terms, describing mechanical properties of and bonding mechanisms between particles, are defined within the individual chapters and in other books on material science and chemical engineering.

Compactibility The ability of a powder bed to cohere into or to form a compact. Usually described in terms of tablet strength as a function of applied compaction stress.

Compaction The transformation of a powder into a coherent specimen of defined shape by powder compression.

Compressibility The ability of a powder bed to be compressed (be reduced in volume) due to the application of a given stress.

Compression The reduction in volume of a powder bed due to the application of a stress, e.g., loading or vibration.

Consolidation Mostly used synonymously with compaction. The term has also been used to describe compression of powders.

Elastic deformation of particles Time-independent, recoverable deformation of a particle. Deformation occurs parallel to a contraction of the particle.

Hardness The resistance of a specimen against penetration into the surface of the specimen.

Particle deformation The change in shape of a particle during compression. Can be quantified with some shape factor for the particle as a function of applied stress during compression.

Plastic deformation of particles Time-independent, permanent deformation of a particle. Degree of deformation is thus controlled by the applied stress and independent of the time of loading. Deformation occurs without a change in particle volume.

Particle fragmentation The fracturing of a particle into a number of smaller, discrete fragments during compression. Can be quantified as the change in particle size or particle surface area with applied stress during compression.

Time-dependent deformation of particles Degree of deformation of a particle is controlled by the applied stress and the time of loading.

Viscoelastic deformation of particles Time-dependent recoverable deformation of a particle.

Viscous deformation of particles Time-dependent permanent deformation of a particle.

Contributors

Göran Alderborn, Ph.D. Division of Pharmaceutics, Uppsala University, Uppsala, Sweden

N. Anthony Armstrong, Ph.D. Welsh School of Pharmacy, University of Wales, Cardiff, United Kingdom

Gerad K. Bolhuis, Ph.D. Department of Pharmaceutical Technology and Biopharmacy, University of Groningen, Groningen, The Netherlands

Jean-Daniel Bonny, Ph.D. School of Pharmacy, University of Basel, Basel, Switzerland

Zak T. Chowhan, Ph.D. Department of Formulation Development, Syntex Research Institute of Pharmaceutical Sciences, Palo Alto, California

Peter N. Davies, Ph.D.* School of Pharmacy, University of London, London, United Kingdom

---

**Current affiliation:* Roche Products, Welwyn Garden City, Hertfordshire, United Kingdom

Wendy C. Duncan-Hewitt, Ph.D. Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada

John T. Fell, Ph.D. Department of Pharmacy, University of Manchester, Manchester, United Kingdom

Claus Führer, Ph.D. Institut für Pharmazeutische Technologie der Technischen Universität Braunschweig, Braunschweig, Germany

Everett N. Hiestand, Ph.D.* Upjohn Company, Kalamazoo, Michigan

Arne W. Hölzer, Ph.D. Astra Hässle AB, Mölndal, Sweden

Jukka Ilkka, M.Sc. Department of Pharmaceutical Technology, University of Kuopio, Kuopio, Finland

Per-Gunnar Karehill, Ph.D. Astra Hässle AB, Mölndal, Sweden

Ruth Leu, Ph.D. School of Pharmacy, University of Basel, Basel, Switzerland

Hans Leuenberger, Ph.D. School of Pharmacy, University of Basel, Basel, Switzerland

Fritz Müller, Ph.D. Pharmazeutisches Institut der Universität Bonn, Bonn, Germany

J. Michael Newton, Ph.D. School of Pharmacy, University of London, London, United Kingdom

Christer Nyström, Ph.D. Division of Pharmaceutics, Uppsala University, Uppsala, Sweden

Petteri Paronen, Ph.D. Department of Pharmaceutical Technology, University of Kuopio, Kuopio, Finland

Fridrun Podczeck, Ph.D. School of Pharmacy, University of London, London, United Kingdom

*Retired. Residing in Galesburg, Michigan

Gert Ragnarsson, Ph.D.* Pharmacia Biopharmaceuticals, Stockholm, Sweden

Ron J. Roberts, Ph.D. Zeneca Pharmaceuticals, Macclesfield, Cheshire, United Kingdom

Ray C. Rowe, Ph.D. Zeneca Pharmaceuticals, Macclesfield, Cheshire, United Kingdom

Martin Wikberg, Ph.D. Kabi Pharmacia Therapeutics Uppsala, Uppsala, Sweden

Current affiliation: Astra Draco AB, Lund, Sweden

Contents