

VOLUME 1

Encyclopedia of PHARMACEUTICAL TECHNOLOGY

Third Edition



edited by
James Swarbrick

Volume 1

21 CFR Part 11 Revisited / 1
Absorption Enhancers / 13
Absorption of Drugs / 19
Adsorption at Solid Surfaces: Pharmaceutical Applications / 34
Adverse Drug Reactions / 46
Advertising and Promotion of Prescription and Over-the-Counter
Drug Products / 57
Alternative Medicines / 66
Amorphous Pharmaceutical Systems / 83
Analytical Procedures: Validation / 92
Animals in Drug Development / 114
Aseptic Processing: Validation / 127
Autoxidation and Antioxidants / 139
Bioabsorbable Polymers / 155
Bioavailability of Drugs and Bioequivalence / 164
Biodegradable Polymers as Drug Carriers / 176
Biologic Fluids: Analysis / 194
Biopharmaceutics / 208
Biosynthesis of Drugs / 228
Biotechnology and Biological Preparations / 258
Biotechnology-Derived Drug Products: Formulation Development / 281
Biotechnology-Derived Drug Products: Stability Testing,
Filling, and Packaging / 302
Biotransformation of Drugs / 310
Bio-Validation of Steam Sterilization / 325
Blood Substitutes: Fluorocarbon Approach / 335
Blood Substitutes: Hemoglobin-Based Oxygen Carriers / 353
Blow-Fill-Seal: Advanced Aseptic Processing / 378
Buffers, Buffering Agents, and Ionic Equilibria / 385
Calorimetry in Pharmaceutical Research and Development / 393
Capsules, Hard / 406
Capsules, Soft / 419
Carcinogenicity Testing: Past, Present, and Future / 431
Chiroptical Analytical Methods / 445
Chromatographic Methods of Analysis: Gas Chromatography / 463
Chromatographic Methods of Analysis: High Performance Liquid
Chromatography / 526
Chromatographic Methods of Analysis: Thin Layer Chromatography / 538
Clinical Data Management Systems / 551
Clinical Evaluation of Drugs / 560
Clinical Pharmacokinetics and Pharmacodynamics / 572
Clinical Supplies Manufacture: GMP Considerations / 591
Coacervation and Phase Separation / 600
Cocrystals: Design, Properties and Formation Mechanisms / 615
Colloids and Colloid Drug Delivery System / 636
Coloring Agents for Use in Pharmaceuticals / 648

Volume 2

Complexation: Cyclodextrins / 671
Complexation: Non-Cyclodextrins / 697
Computer Systems Validation / 707
Computer-Assisted Drug Design / 714
Computers in Pharmaceutical Technology / 732
Continuous Processing of Pharmaceuticals / 743
Contract Manufacturing / 750
Cooling Processes and Congealing / 761
Copolymerization and Melts / 774
Corrosion of Pharmaceutical Equipment / 782
Cosmetics and Their Relation to Drugs / 798
Cosolvents and Cosolvency / 806
Crystal Habit Changes and Dosage Form Performance / 820
Crystallization: General Principles and Significance on Product
Development / 834
Crystallization: Particle Size Control / 858
Dendrimers / 872
Dental Products / 891
Dissolution and Dissolution Testing / 908
DNA Probes for the Identification of Microbes / 929
Dosage Form Design: A Physicochemical Approach / 939
Dosage Forms and Basic Preparations: History / 948
Dosage Forms: Lipid Excipients / 975
Dosage Forms: Non-Parenterals / 988
Dosage Forms: Parenterals / 1001
Dosage Regimens and Dose-Response / 1012
Dressings in Wound Management / 1023
Drug Abuse / 1038
Drug Delivery Systems: Neutron Scattering Studies / 1049
Drug Delivery: Buccal Route / 1071
Drug Delivery: Controlled Release / 1082
Drug Delivery: Fast-Dissolve Systems / 1104

Volume 2 (Continued)

Drug Delivery: Liquid Crystals in / 1115
Drug Delivery: Monoclonal Antibodies / 1132
Drug Delivery: Monoclonal Antibodies in Imaging and Therapy / 1149
Drug Delivery: Mucoadhesive Hydrogels / 1169
Drug Delivery: Nanoparticles / 1183
Drug Delivery: Nasal Route / 1201
Drug Delivery: Needle-Free Systems / 1209
Drug Delivery: Ophthalmic Route / 1220
Drug Delivery: Oral Colon-Specific / 1228
Drug Delivery: Oral Route / 1242
Drug Delivery: Parenteral Route / 1266
Drug Delivery: Pulmonary Delivery / 1279
Drug Delivery: Pulsatile Systems / 1287
Drug Delivery: Rectal Route / 1298
Drug Delivery: Topical and Transdermal Routes / 1311
Drug Delivery: Tumor-Targeted Systems / 1326
Drug Delivery: Vaginal Route / 1339
Drug Design: Basic Principles and Applications / 1362
Drug Development Management / 1370
Drug Information Systems / 1385
Drug Interactions / 1392
Drug Master Files / 1401
Drug Safety Evaluation / 1406
Dry Powder Aerosols: Emerging Technologies / 1428

Volume 3

Drying and Dryers / 1435
Economic Characteristics of the R&D Intensive Pharmaceutical
Industry / 1450
Effervescent Pharmaceuticals / 1454
Elastomeric Components for the Pharmaceutical Industry / 1466
Electrical Power Systems for Pharmaceutical Equipment / 1482
Electroanalytical Methods of Analysis: Polarography and Voltammetry / 1490
Electroanalytical Methods of Analysis: Potentiometry / 1502
Electrochemical Detection for Pharmaceutical Analysis / 1516
Electrostatic Charge in Pharmaceutical Systems / 1535
Emulsions and Microemulsions / 1548
Enzyme Immunoassay and Related Bioanalytical Methods / 1566
Equipment Cleaning / 1580
European Agency for the Evaluation of Medicinal Products (EMA) / 1593
Evaporation and Evaporators / 1600
Excipients for Pharmaceutical Dosage Forms / 1609
Excipients: Parenteral Dosage Forms and Their Role / 1622
Excipients: Powders and Solid Dosage Forms / 1646
Excipients: Safety Testing / 1656
Expert Systems in Pharmaceutical Product Development / 1663
Expiration Dating / 1685
Extractables and Leachables in Drugs and Packaging / 1693
Extrusion and Extruders / 1712
Film Coating of Oral Solid Dosage Forms / 1729
Filters and Filtration / 1748
Flame Photometry / 1759
Flavors and Flavor Modifiers / 1763
Fluid Bed Processes for Forming Functional Particles / 1773
Food and Drug Administration: Role in Drug Regulation / 1779
Fractal Geometry in Pharmaceutical and Biological Applications / 1791
Freeze Drying / 1807
Freeze Drying, Scale-Up Considerations / 1834
Gastro-Retentive Systems / 1850
Gelatin-Containing Formulations: Changes in Dissolution
Characteristics / 1861
Gels and Jellies / 1875
Generic Drugs and Generic Equivalency / 1891
Genetic Aspects of Drug Development / 1897
Geriatric Dosing and Dosage Forms / 1905
Good Clinical Practices (GCPs): An Overview / 1925
Good Laboratory Practices (GLPs): An Overview / 1931
Good Manufacturing Practices (GMPs): An Overview / 1941
Handling Hazardous Chemicals and Pharmaceuticals / 1948
Harmonization of Pharmacopeial Standards / 1955
Headspace Oxygen Analysis in Pharmaceutical Products / 1967
Health Care Systems: Outside the United States / 1977
Health Care Systems: Within the United States / 1985
Homogenization and Homogenizers / 1996
Hot-Melt Extrusion Technology / 2004
Hydrogels / 2021
Hydrolysis of Drugs / 2040
Immunoassay / 2048
In Vitro-In Vivo Correlation / 2062
Inhalation: Dry Powder / 2077
Inhalation: Liquids / 2092

Encyclopedia of
PHARMACEUTICAL
TECHNOLOGY
Third Edition
VOLUME 1

Drugs and the Pharmaceutical Sciences

A comprehensive series of more than 160 volumes on all aspects of pharmaceutical science

Series Executive Editor: James Swarbrick

Herbal Supplements-Drug Interactions: Scientific and Regulatory Perspectives

Edited by: Y.W. Francis Lam, Shiew-Mei Huang and Stephen D. Hall
ISBN: 0-8247-2538-7

Dose Optimization In Drug Development

Edited by: Rajesh Krishna
ISBN: 1-5744-4808-0

Spectroscopy of Pharmaceutical Solids

Edited by: Harry G. Brittain
ISBN: 1-5744-4893-5

Nanoparticle Technology for Drug Delivery

Edited by: Ram B. Gupta and Uday B. Kompella
ISBN: 1-5744-4857-9

Microencapsulation: Methods and Industrial Applications, Second Edition

Edited by: Simon Benita
ISBN: 0-8247-2317-1

Pharmaceutical Process Scale-Up, Second Edition

Edited by: Michael Levin
ISBN: 1-5744-4876-5

Pharmacogenomics, Second Edition

Edited by: Werner Kalow, Urs B. Meyer, and Rachel F. Tyndale
ISBN: 1-5744-4878-1

Handbook of Pharmaceutical Granulation Technology, Second Edition

Edited by: Dilip M. Parikh
ISBN: 0-8247-2647-2

Preclinical Drug Development

Edited by: Mark C. Rogge
ISBN: 1-5744-4882-X

Percutaneous Absorption: Drugs, Cosmetics, Mechanisms, Methods, Fourth Edition

Edited by: Robert L. Bronaugh and Howard I. Maibach
ISBN: 1-5744-4869-2

Pharmaceutical Stress Testing: Predicting Drug Degradation

Edited by: Steven W. Baertschi
ISBN: 0-8247-4021-1

Active Pharmaceutical Ingredients: Development, Manufacturing, and Regulation

Edited by: Stanley Nusim
ISBN: 0-8247-0293-X

Injectable Dispersed Systems: Formulation, Processing and Performance

Edited by: Diane J. Burgess
ISBN: 0-8493-3699-6

Polymeric Drug Delivery Systems

Edited by: Glen S. Kwon
ISBN: 0-8247-2532-8

Drug Delivery to the Oral Cavity

Edited by: Tapash K. Ghosh and William Pfister
ISBN: 0-8247-8293-3

Generic Drug Development: Solid Oral Dosage Forms

Edited by: Leon Shargel
ISBN: 0-8247-5460-3

Introduction to the Pharmaceutical Regulatory Process

Edited by: Ira R. Berry
ISBN: 0-8247-5464-6

New Drug Development: Regulatory Paradigms for Clinical Pharmacology and Biopharmaceutics

Edited by: Chandrah Sahajwalla
ISBN: 0-8247-5465-4

Freeze-Drying/Lyophilization of Pharmaceutical and Biological Products, Second Edition

Edited by: Louis Rey and Joan C. May
ISBN: 0-8247-4868-9

Pharmaceutical Statistics, Fourth Edition

Sanford Bolton and Charles Bon
ISBN: 0-8247-4695-3

Pharmaceutical Inhalation Aerosol Technology, Second Edition

Edited by: Anthony J. Hickey
ISBN: 0-8247-4253-2

Biomarkers in Clinical Drug Development

Edited by: John C. Bloom and Richard A. Dean
ISBN: 0-8247-4026-2

Pharmaceutical Extrusion Technology

Edited by: Isa Ghebre-Selassie and Charles Martin
ISBN: 0-8247-4050-5

Pharmaceutical Gene Delivery Systems

Edited by: Alain Rolland and Sean M. Sullivan
ISBN: 0-8247-4235-4

Pharmaceutical Process Validation: An International Third Edition

Edited by: Robert A. Nash and Alfred H. Wachter
ISBN: 0-8247-0838-5

Ophthalmic Drug Delivery Systems, Second Edition

Edited by: Ashim K. Mitra
ISBN: 0-8247-4124-2

Affinity Capillary Electrophoresis in Pharmaceutics and Biopharmaceutics

Edited by: Reinhard Neubert
ISBN: 0-8247-0951-9

Parenteral Quality Control: Sterility, Pyrogen, Particulate, and Package Integrity Testing: Third Edition

Michael K. Akers, Daniel S. Larrimore, and Dana Morton Guazzo
ISBN: 0-8247-0885-7

Modified-Release Drug Delivery Technology

Edited by: Michael J. Rathbone
ISBN: 0-8247-0869-5

Simulation for Designing Clinical Trials: A Pharmacokinetic-Pharmacodynamic Modeling Perspective

Edited by: Hui Kimko
ISBN: 0-8247-0862-8

Transdermal Drug Delivery Second Edition

Edited by: Jonathan Hadgraft
ISBN: 0-8247-0861-X

Surfactants and Polymers in Drug Delivery

Martin Malmsten
ISBN: 0-8247-0804-0

Modern Pharmaceutics, Fourth Edition

Edited by: Gilbert S. Banker and Christopher T. Rhodes
ISBN: 0-8247-0674-9

Handbook of Pharmaceutical Analysis

Edited by: Lena Ohannesian
ISBN: 0-8247-0462-2

Drug-Drug Interactions

Edited by: A. David Rodrigues
ISBN: 0-8247-0283-2

Handbook of Drug Screening

Edited by: Ramakrishn Seethala
ISBN: 0-8247-0562-9

Pharmaceutical Process Engineering

Edited by: Anthony J. Hickey
ISBN: 0-8247-0298-0

Drug Stability, Third Edition, Revised, and Expanded: Principles and Practices

Edited by: Jens T. Carstensen
ISBN: 0-8247-0376-6

Coming Soon!

November 2006

Environmental Monitoring for Cleanrooms and Controlled Environments

Edited by: Anne Marie Dixon
ISBN: 0-8247-2359-7

Pharmaceutical Photostability and Stabilization Technology

Edited by: Joseph T. Piechocki
ISBN: 0-8247-5924-9

December 2006

Good Manufacturing Practices for Pharmaceuticals: A Plan for Total Quality Control from Manufacturer to Consumer, Sixth Edition

Edited by: Joseph Nally
ISBN: 0-8493-3972-3

February 2007

Pharmaceutical Product Development: In Vitro-In Vivo Correlation

Edited by: Dakshina Chilukuri
ISBN: 0-8493-3827-1

Endotoxins: Pyrogens, LAL Testing and Depyrogenation, Third Edition

Kevin L. Williams
ISBN: 0-8493-9372-8

April 2007

Good Laboratory Practice Regulations, Fourth Edition

Edited by: Sandy Weinberg
ISBN: 0-8493-7583-5

June 2007

Filtration and Purification in the Biopharmaceutical Industry, Second Edition

Edited by: Theodore H. Meltzer and Maik Jorntz
ISBN: 0-8493-7953-9

To order, call 1-800-634-7064 (North America) or +44 (0) 1264 343071 (Intl.)

E-Mail books@informausa.com

Encyclopedia of
PHARMACEUTICAL
TECHNOLOGY
Third Edition
VOLUME 1

edited by
James Swarbrick
PharmaceuTech, Inc.
Pinehurst, North Carolina, USA

informa
healthcare

New York London

Informa Healthcare USA, Inc.
270 Madison Avenue
New York, NY 10016

© 2007 by Informa Healthcare USA, Inc.
Informa Healthcare is an Informa business

No claim to original U.S. Government works
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: 0-8493-9399-X (Hardcover: Set)
International Standard Book Number-10: 0-8493-9396-5 (Hardcover: Volume 1)
International Standard Book Number-10: 0-8493-9395-7 (Hardcover: Volume 2)
International Standard Book Number-10: 0-8493-9394-9 (Hardcover: Volume 3)
International Standard Book Number-10: 0-8493-9393-0 (Hardcover: Volume 4)
International Standard Book Number-10: 0-8493-9392-2 (Hardcover: Volume 5)
International Standard Book Number-10: 0-8493-9391-4 (Hardcover: Volume 6)
International Standard Book Number-13: 978-0-8493-9399-0 (Hardcover: Set)
International Standard Book Number-13: 978-0-8493-9396-9 (Hardcover: Volume 1)
International Standard Book Number-13: 978-0-8493-9395-2 (Hardcover: Volume 2)
International Standard Book Number-13: 978-0-8493-9394-5 (Hardcover: Volume 3)
International Standard Book Number-13: 978-0-8493-9393-8 (Hardcover: Volume 4)
International Standard Book Number-13: 978-0-8493-9392-1 (Hardcover: Volume 5)
International Standard Book Number-13: 978-0-8493-9391-4 (Hardcover: Volume 6)

This book contains information obtained from authentic and highly regarded sources. Reprinted material is quoted with permission, and sources are indicated. A wide variety of references are listed. Reasonable efforts have been made to publish reliable data and information, but the author and the publisher cannot assume responsibility for the validity of all materials or for the consequences of their use.

No part of this book may be reprinted, reproduced, transmitted, or utilized in any form by any electronic, mechanical, or other means, now known or hereafter invented, including photocopying, microfilming, and recording, or in any information storage or retrieval system, without written permission from the publishers.

For permission to photocopy or use material electronically from this work, please access www.copyright.com (<http://www.copyright.com/>) or contact the Copyright Clearance Center, Inc. (CCC) 222 Rosewood Drive, Danvers, MA 01923, 978-750-8400. CCC is a not-for-profit organization that provides licenses and registration for a variety of users. For organizations that have been granted a photocopy license by the CCC, a separate system of payment has been arranged.

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

Visit the Informa Web site at
www.informa.com

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

To James C. Boylan
Co-Editor of the First and Second Editions
A great colleague and friend.

Editorial Advisory Board

Jean-Marc Aiache

*Biopharmaceutics Department, University of Clermont
Ferrand, Clermont Ferrand, France*

David Attwood

*School of Pharmacy & Pharmaceutical Sciences,
University of Manchester, Manchester, U.K.*

Larry L. Augsburger

*Department of Pharmaceutics, University of Maryland
at Baltimore, Baltimore, Maryland, U.S.A.*

Roland A. Bodmeier

*College of Pharmacy, Freie Universität Berlin,
Berlin, Germany*

J. Phillip Bowen

*Center for Biomolecular Structure and Dynamics,
Department of Chemistry, University of Georgia,
Athens, Georgia, U.S.A.*

Gayle A. Brazeau

*School of Pharmacy, State University of New York at
Buffalo, Amherst, New York, U.S.A.*

Harry G. Brittain

*Center for Pharmaceutical Physics, Milford,
New Jersey, U.S.A.*

Les F. Chasseaud

*Drug Metabolism and Pharmacokinetics (DMPK),
Cambridge, U.K.*

Yie W. Chien

*Research and Development, Kaohsiung Medical
University, Kaohsiung, Taiwan*

Bradley A. Clark

Solvay Pharmaceuticals, Marietta, Georgia, U.S.A.

Owen I. Corrigan

*Department of Pharmaceutics, School of Pharmacy,
University of Dublin, Trinity College, Dublin, Ireland*

Gillian M. Eccleston

*Department of Pharmaceutical Sciences, University of
Strathclyde, Glasgow, Scotland, U.K.*

James L. Ford

*School of Pharmacy and Chemistry, Liverpool John
Moores University, Liverpool, U.K.*

Igor Gonda

*Acrux Limited, West Melbourne,
Victoria, Australia*

Anthony J. Hickey

*Department of Pharmaceutics, School of Pharmacy,
University of North Carolina at Chapel Hill,
Chapel Hill, North Carolina, U.S.A.*

Hideki Ichikawa

*Faculty of Pharmaceutical Sciences,
Kobe Gakuin University, Kobe, Japan*

Brian E. Jones

Qualicaps, S.A., Penarth, U.K.

James C. McElnay

*Faculty of Science and Agriculture, Queen's University
Belfast, Belfast, U.K.*

Iain J. McGilveray

*McGilveray Pharmacon Inc., Nepean,
Ontario, Canada*

Kinam Park

*School of Pharmacy and Pharmacal Sciences, Purdue
University, West Lafayette, Indiana, U.S.A.*

Michael J. Pikal

*School of Pharmacy, University of Connecticut, Storrs,
Connecticut, U.S.A.*

Naír Rodríguez-Hornedo

*Department of Pharmaceutical Sciences, College of
Pharmacy, University of Michigan, Ann Arbor,
Michigan, U.S.A.*

Stephen G. Schulman

*Department of Medicinal Chemistry, College of
Pharmacy, University of Florida, Gainesville,
Florida, U.S.A.*

Jerome P. Skelly

*Pharmaceutical Consultant, Alexandria,
Virginia, U.S.A.*

Clive G. Wilson

*Department of Pharmaceutical Sciences,
Strathclyde Institute for Biomedical Sciences (SIBS),
University of Strathclyde,
Glasgow, U.K.*

Contributors

- Ragheb Abu-Rmaileh** / *School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Manchester, U.K.*
- Phillip M. Achey** / *Department of Microbiology and Cell Science, Institute of Food and Agricultural Sciences, University of Florida, Gainesville, Florida, U.S.A.*
- James P. Agalloco** / *Agalloco and Associates Inc., Belle Mead, New Jersey, U.S.A.*
- Vikas Agarwal** / *CIMA Labs, Inc., Brooklyn Park, Minnesota, U.S.A.*
- Alaa M. Ahmad** / *Department of Clinical Pharmacology, Vertex Pharmaceuticals, Inc., Cambridge, Massachusetts, U.S.A.*
- Jean-Marc Aiache** / *Biopharmaceutics Department, University of Clermont-Ferrand, Clermont Ferrand, France*
- James E. Akers** / *Akers Kennedy and Associates, Kansas City, Missouri, U.S.A.*
- Michael J. Akers** / *Martinsville, Indiana, U.S.A.*
- Hemant H. Alur** / *Division of Pharmaceutical Sciences, School of Pharmacy, University of Missouri-Kansas City, Kansas City, Missouri, U.S.A.*
- David G. Allison** / *School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Manchester, U.K.*
- Norman Anthony Armstrong** / *Welsh School of Pharmacy, Cardiff University, Cardiff, U.K.*
- Agnès Artiges** / *European Directorate for the Quality of Medicines (EDQM), Strasbourg Cedex, France*
- Carolyn H. Asbury** / *Department of Medicine, University of Pennsylvania Health System, Philadelphia, Pennsylvania, U.S.A.*
- C. K. Atterwill** / *Biosciences Division, Huntingdon Life Sciences, Cambridgeshire, U.K.*
- David Attwood** / *School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Manchester, U.K.*
- Larry L. Augsburger** / *Department of Pharmaceutics, University of Maryland at Baltimore, Baltimore, Maryland, U.S.A.*
- J. Desmond Baggot** / *School of Veterinary Medicine, St. George's University, Grenada, West Indies*
- Mark L. Balboni** / *KMI, A Division of PAREXEL International, LLC, Waltham, Massachusetts, U.S.A.*
- Paul Baldrick** / *Covance Laboratories, Ltd., North Yorkshire, U.K.*
- Samuel B. Balik** / *GlaxoSmithKline, Research Triangle Park, North Carolina, U.S.A.*
- David J. Barlow** / *Molecular Biophysics Group, Pharmaceutical Science Research Division, King's College London, College London, London, U.K.*
- Debra Barnes** / *Roche Global Development, Palo Alto, California, U.S.A.*
- Onkaram Basavapathruni** / *Pharmacia, Skokie, Illinois, U.S.A.*
- Annette Bauer-Brandl** / *Institute of Pharmacy, Department of Pharmaceutics and Biopharmaceutics, The University of Tromsø, Tromsø, Norway*
- G.J.P.J. Beernink** / *Amsterdam, The Netherlands*
- Leslie Z. Benet** / *Department of Biopharmaceutical Sciences, University of California San Francisco, San Francisco, California, U.S.A.*
- David H. Bergstrom** / *Cardinal Health Pharmaceutical Development, Somerset, New Jersey, U.S.A.*
- Ira R. Berry** / *International Regulatory Business Consultants, LLC, Maplewood, New Jersey, U.S.A.*

- Guru Betageri** / *College of Pharmacy, Western University of Health Sciences, Pomona, California, U.S.A.*
- Erick Beyssac** / *Biopharmaceutical Department, Faculty of Pharmacy, University of Auvergne, Clermont-Ferrand, France*
- Haresh Bhagat** / *Alcon Research, Ltd., Fort Worth, Texas, U.S.A.*
- Hridaya Bhargava** / *Massachusetts College of Pharmacy and Health Sciences, Boston, Massachusetts, U.S.A.*
- María Dolores Blanco** / *Departamento de Bioquímica y Biología Molecular, Universidad Complutense de Madrid, Madrid, Spain*
- Maria Jose Blanco-Príeto** / *University of Navarra, Pamplona, Spain*
- E. Daniel Blankschtein** / *Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts, U.S.A.*
- Roland A. Bodmeier** / *College of Pharmacy, Freie Universität Berlin, Berlin, Germany*
- Michael J. Bogda** / *Barr Laboratories, Inc., Woodcliff Lake, New Jersey, U.S.A.*
- René Bommer** / *Ing. Erich Pfeiffer GmbH, Radolfzell, Germany*
- Charles Bon** / *AAI Pharma, Inc., Wilmington, North Carolina, U.S.A.*
- Carol A. Borynec** / *Capital Health, Edmonton, Alberta, Canada*
- David W.A. Bourne** / *College of Pharmacy, Health Sciences Center, The University of Oklahoma, Oklahoma City, Oklahoma, U.S.A.*
- J. Phillip Bowen** / *Center for Biomolecular Structure and Dynamics, University of Georgia, Athens, Georgia, U.S.A.*
- Richard D. Braatz** / *Department of Chemical and Biomolecular Engineering, University of Illinois at Urbana-Champaign, Urbana, Illinois, U.S.A.*
- Daniel A. Brazeau** / *Department of Pharmaceutical Sciences, The State University of New York at Buffalo, Buffalo, New York, U.S.A.*
- Gayle A. Brazeau** / *School of Pharmacy, The State University of New York at Buffalo, Buffalo, New York, U.S.A.*
- Ron J. Brendel** / *Mallinckrodt, Inc., St. Louis, Missouri, U.S.A.*
- Harry G. Brittain** / *Center for Pharmaceutical Physics, Milford, New Jersey, U.S.A.*
- Albert W. Brzeczko** / *APC/Niro Inc., Columbia, Maryland, U.S.A.*
- Robert A. Buerki** / *College of Pharmacy, The Ohio State University, Columbus, Ohio, U.S.A.*
- Diane J. Burgess** / *Department of Pharmaceutical Sciences, University of Connecticut, Storrs, Connecticut, U.S.A.*
- Till Bussemer** / *Aventis Pharma Deutschland GmbH, Frankfurt am Main, Germany*
- John B. Cannon** / *Abbott Laboratories, North Chicago, Illinois, U.S.A.*
- J.-M. Cardot** / *Biopharmaceutical Department, Faculty of Pharmacy, University of Auvergne, Clermont-Ferrand, France*
- Ralph B. Caricofe** / *GlaxoSmithKline, Research Triangle Park, North Carolina, U.S.A.*
- Eugene Carstea** / *Invitrogen Corporation, Carlsbad, California, U.S.A.*
- Allen Cato** / *Cato Research Ltd., Durham, North Carolina, U.S.A.*
- Allen Cato III** / *Cato Research Ltd., San Diego, California, U.S.A.*
- Hak-Kim Chan** / *University of Sydney, Sydney, New South Wales, Australia*
- Les F. Chasseaud** / *Drug Metabolism and Pharmacokinetics (DMPK), Cambridge, U.K.*
- Xiu Xiu Cheng** / *Andrx Pharmaceuticals, Inc., Fort Lauderdale, Florida, U.S.A.*
- David L. Chesney** / *KMI, A Division of PAREXEL International, LLC, Waltham, Massachusetts, U.S.A.*
- Nora Y.K. Chew** / *Acrux DDS Pty Ltd., West Melbourne, Victoria, Australia*
- Yie W. Chien** / *Research and Development, Kaohsiung Medical University, Kaohsiung, Taiwan*
- Andrea Chieppo** / *Analytical Research Laboratories, Oklahoma City, Oklahoma, U.S.A.*

- Sally Y. Choe** / *Pfizer Global Research and Development, Ann Arbor, Michigan, U.S.A.*
- Masood Chowhan** / *Alcon Laboratories, Fort Worth, Texas, U.S.A.*
- Sebastian G. Ciancio** / *Department of Periodontics and Endodontics, The New York State University at Buffalo, Buffalo, New York, U.S.A.*
- Emil W. Ciurczak** / *Integrated Technical Solutions, Goldens Bridge, New York, U.S.A.*
- Bradley A. Clark** / *Solvay Pharmaceuticals, Inc., Marietta, Georgia, U.S.A.*
- C. Randall Clark** / *School of Pharmacy, Auburn University, Auburn, Alabama, U.S.A.*
- Nigel Clarke** / *Schering-Plough Research Institute, Kenilworth, New Jersey, U.S.A.*
- Sophie-Dorothée Clas** / *Merck Frosst Canada and Company, Pointe Claire-Dorval, Quebec, Canada*
- Sarah M.E. Cockbill** / *University of Wales Cardiff, Cardiff, U.K.*
- Douglas L. Cocks** / *Eli Lilly and Company, Indianapolis, Indiana, U.S.A.*
- Elizabeth Colbourn** / *Intelligensys Ltd., Billingham, Teesside, U.K.*
- James J. Conners** / *Sepracor, Marlborough, Massachusetts, U.S.A.*
- Kenneth A. Connors** / *Center for Health Sciences, University of Wisconsin at Madison, Madison, Wisconsin, U.S.A.*
- Antonio Conto** / *ChemSafe S.a.s., Colletterto Giacosa (TO), Italy*
- Chyung S. Cook** / *Pharmacia Corporation, Skokie, Illinois, U.S.A.*
- James F. Cooper** / *Charles River Endosafe, Charleston, South Carolina, U.S.A.*
- Geoffrey A. Cordell** / *College of Pharmacy, University of Illinois at Chicago, Chicago, Illinois, U.S.A.*
- Owen I. Corrigan** / *Trinity College, University of Dublin, Dublin, Ireland*
- Michael Cory** / *GlaxoSmithKline, Research Triangle Park, North Carolina, U.S.A.*
- Diane D. Cousins** / *U.S. Pharmacopeial Convention, Inc., Rockville, Maryland, U.S.A.*
- Kathleen A. Cox** / *Schering-Plough Research Institute, Kenilworth, New Jersey, U.S.A.*
- Charles W. Crew** / *GlaxoSmithKline, Research Triangle Park, North Carolina, U.S.A.*
- Alan L. Cripps** / *GlaxoSmithKline, Hertfordshire, U.K.*
- Mary E.M. Cromwell** / *Genentech, Inc., South San Francisco, California, U.S.A.*
- Patrick J. Crowley** / *GlaxoSmithKline, Essex, U.K.*
- Anthony M. Cundell** / *Microbiological Development and Statistics, Wyeth-Ayerst Pharmaceuticals, Pearl River, New York, U.S.A.*
- Chad R. Dalton** / *Merck Frosst Canada and Company, Pointe Claire-Dorval, Quebec, Canada*
- James T. Dalton** / *Division of Pharmaceutics, College of Pharmacy, The Ohio State University, Columbus, Ohio, U.S.A.*
- Wenbin Dang** / *Cardinal Health Pharmaceutical Development, Somerset, New Jersey, U.S.A.*
- Ira Das** / *St. Louis, Missouri, U.S.A.*
- Judith A. Davis** / *Department of Pharmacy Health Care Administration, College of Pharmacy, University of Florida, Gainesville, Florida, U.S.A.*
- Michael R. DeFelippis** / *Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana, U.S.A.*
- M. Begoña Delgado-Charro** / *Centre Interuniversitaire de Recherche et d'Enseignement, Universities of Geneva and Lyon, Archamps, Switzerland*
- Antony D'Emanuele** / *School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Manchester, U.K.*
- Nigel J. Dent** / *Country Consultancy Ltd., Milton Malsor, U.K.*
- Jack DeRuiter** / *School of Pharmacy, Auburn University, Auburn, Alabama, U.S.A.*
- Jeffrey Ding** / *Battelle Pulmonary Therapeutics, Inc., Columbus, Ohio, U.S.A.*
- Marilyn D. Duerst** / *Department of Chemistry, University of Wisconsin-River Falls, River Falls, Wisconsin, U.S.A.*

- A. Mark Dyas** / *School of Pharmacy and Chemistry, Liverpool John Moores University, Liverpool, U.K.*
- Stefan Eberl** / *Department of PET and Nuclear Medicine, Royal Prince Alfred Hospital, Sydney, New South Wales, Australia*
- Gillian M. Eccleston** / *Department of Pharmaceutical Sciences, Strathclyde Institute for Biomedical Sciences, Glasgow, Scotland, U.K.*
- Joachim Ermer** / *Aventis Pharma AG, Frankfurt am Main, Germany*
- Ene I. Ette** / *Department of Clinical Pharmacology, Vertex Pharmaceuticals, Inc., Cambridge, Massachusetts, U.S.A.*
- Ronald P. Evens** / *MAPS 4 Biotech, Inc., Jacksonville, Florida, U.S.A.*
- Kevin L. Facchine** / *GlaxoSmithKline, Research Triangle Park, North Carolina, U.S.A.*
- Gordon J. Farquharson** / *Bovis Tanvec, Ltd., Tanshire House, Surrey, U.K.*
- Elias Fattal** / *School of Pharmacy, University of Paris XI, Châtenay-Malabry, France*
- Linda A. Felton** / *College of Pharmacy, University of New Mexico, Albuquerque, New Mexico, U.S.A.*
- Charles W. Fetrow** / *St. Francis Medical Center, Pittsburgh, Pennsylvania, U.S.A.*
- John W.A. Findlay** / *Pfizer Global Research and Development, Groton, Connecticut, U.S.A.*
- Barrie C. Finnin** / *Monash University, Parkville, Victoria, Australia*
- Elizabeth S. Fisher** / *Merck and Co., Inc., Rahway, New Jersey, U.S.A.*
- Joseph A. Fix** / *Yamanouchi Pharma Technologies, Inc., Palo Alto, California, U.S.A.*
- Farrel L. Fort** / *TAP Pharmaceutical Products, Inc., Lake Forest, Illinois, U.S.A.*
- Miriam K. Franchini** / *Bristol-Myers Squibb, New Brunswick, New Jersey, U.S.A.*
- Cara R. Frosch** / *Covance Central Laboratory Services Inc., Indianapolis, Indiana, U.S.A.*
- Mitsuko Fujiwara** / *Department of Chemical and Biomolecular Engineering, University of Illinois at Urbana-Champaign, Urbana, Illinois, U.S.A.*
- Yoshinobu Fukumori** / *Kobe Gakuin University, Kobe, Hyogo, Japan*
- Kumar G. Gadamasetti** / *ChemRx Advanced Technologies, South San Francisco, California, U.S.A.*
- Bruno Gander** / *Institute of Pharmaceutical Sciences, ETH Zürich, Zürich, Switzerland*
- David Ganderton** / *Devon, U.K.*
- Isaac Ghebre-Sellassie** / *Pharmaceutical Technology Solutions, Morris Plains, New Jersey, U.S.A.*
- Peter J. Giddings** / *SmithKline Beecham, Brentford, U.K.*
- Peter Gilbert** / *University of Manchester, Manchester, U.K.*
- Daniëlle Giron** / *Analytical Research and Development, Sandoz Pharma, Basel, Switzerland*
- Samuel V. Givens** / *Hoffmann-La Roche, Inc., Nutley, New Jersey, U.S.A.*
- William Glover** / *University of Sydney, Sydney, New South Wales, Australia*
- Igor Gonda** / *Acrux Limited, West Melbourne, Australia*
- Michelle M. Gonzalez** / *Amgen Inc., Thousand Oaks, California, U.S.A.*
- Lee T. Grady** / *McLean, Virginia, U.S.A.*
- Alice T. Granger** / *Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Connecticut, U.S.A.*
- Jerome J. Groen** / *Abbott Laboratories, Abbott Park, Illinois, U.S.A.*
- Richard A. Guarino** / *Oxford Pharmaceutical Resources, Inc., Totowa, New Jersey, U.S.A.*
- Pramod K. Gupta** / *Baxter Healthcare Corporation, Round Lake, Illinois, U.S.A.*
- Richard H. Guy** / *Centre Interuniversitaire de Recherche et d'Enseignement, Universities of Geneva and Lyon, Archamps, Switzerland*
- J. Richard Gyory** / *ALZA Corporation, Spring Lake Park, Minnesota, U.S.A.*
- Huijeong Ashley Hahm** / *Office of Generic Drugs, U.S. Food and Drug Administration, Rockville, Maryland, U.S.A.*
- Nigel A. Halls** / *NHC-Nigel Halls Consulting, Herts, U.K.*
- Jerome A. Halperin** / *Silver Spring, Maryland, U.S.A.*
- Bruno C. Hancock** / *Pfizer Inc., Groton, Connecticut, U.S.A.*

- Henri Hansson** / *Galenica AB, Medeon, Malmo, Sweden*
- Gary C. Harbour** / *Pharmacia Enterprises S.A., Luxembourg, G. D. Luxembourg*
- Adam Harris** / *Invitrogen Corporation, Carlsbad, California, U.S.A.*
- D. R. Hawkins** / *Huntingdon Life Sciences, Cambridgeshire, U.K.*
- Leslie C. Hawley** / *Pharmacia Corporation, Kalamazoo, Michigan, U.S.A.*
- Anne Marie Healy** / *Department of Pharmaceutics, School of Pharmacy, University of Dublin, Dublin, Ireland*
- Herbert Michael Heise** / *University of Dortmund, Dortmund, Germany*
- Paul W.S. Heng** / *Department of Pharmacy, National University of Singapore, Singapore*
- Jeffrey M. Herz** / *Omeros Medical Systems, Inc., Seattle, Washington, U.S.A.*
- Anthony J. Hickey** / *Department of Pharmaceutics, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, U.S.A.*
- Gregory J. Higby** / *American Institute of the History of Pharmacy, Madison, Wisconsin, U.S.A.*
- Anthony J. Hlinak** / *Searle Research and Development, Skokie, Illinois, U.S.A.*
- Amnon Hoffman** / *Department of Pharmaceutics, Pharmacy School, The Hebrew University of Jerusalem, Jerusalem, Israel*
- Harm HogenEsch** / *Department of Veterinary Pathobiology, Purdue University, West Lafayette, Indiana, U.S.A.*
- R. Gary Hollenbeck** / *Department of Pharmaceutics, University of Maryland at Baltimore, Baltimore, Maryland, U.S.A.*
- J. Hotta** / *Bayer Corporation, Research Triangle Park, North Carolina, U.S.A.*
- Shelley Hough** / *Invitrogen Corporation, Carlsbad, California, U.S.A.*
- Stephen A. Howard** / *Purdue Pharma L.P., Ardsley, New York, U.S.A.*
- Carmel M. Hughes** / *School of Pharmacy, Medical Biology Centre, The Queen's University of Belfast, Belfast, U.K.*
- Jeffrey A. Hughes** / *College of Pharmacy, University of Florida, Gainesville, Florida, U.S.A.*
- Kang Moo Huh** / *Departments of Pharmaceutics and Biomedical Engineering, Purdue University, West Lafayette, Indiana, U.S.A.*
- Ho-Wah Hui** / *Abbott Laboratories, North Chicago, Illinois, U.S.A.*
- Laura Hungerford** / *U.S. Food and Drug Administration, Rockville, Maryland, U.S.A.*
- D. Hunkeler** / *Laboratoire des Polyélectrolytes et BioMacromolécules, EPFL, Lausanne, Switzerland*
- Desmond G. Hunt** / *Department of Standards Development, United States Pharmacopeia, Rockville, Maryland, U.S.A.*
- Anwar A. Hussain** / *Department of Pharmaceutics, University of Kentucky, Lexington, Kentucky, U.S.A.*
- Daniel A. Hussar** / *University of the Sciences in Philadelphia, Philadelphia, Pennsylvania, U.S.A.*
- Hideki Ichikawa** / *Kobe Gakuin University, Kobe, Hyogo, Japan*
- Juhana E. Idanpaan-Heikkilä** / *World Health Organization, Geneva, Switzerland*
- Victoria Imber** / *Evergreen, Colorado, U.S.A.*
- Barbara Immel** / *Immel Resources, Petaluma, California, U.S.A.*
- David M. Jacobs** / *European Agency for the Evaluation of Medicinal Products, Basel, Switzerland*
- Adivaraha Jayasankar** / *Department of Pharmaceutical Sciences, University of Michigan, Ann Arbor, Michigan, U.S.A.*
- Bradford K. Jensen** / *Aventis Pharmaceuticals, Inc., Bridgewater, New Jersey, U.S.A.*
- Thomas P. Johnston** / *Division of Pharmaceutical Sciences, School of Pharmacy, University of Missouri-Kansas City, Kansas City, Missouri, U.S.A.*
- Brian E. Jones** / *Qualicaps Europe, S.A., Alcobendas, Madrid, Spain*
- Deborah J. Jones** / *Steripak Limited, Cheshire, U.K.*
- Maik W. Jornitz** / *Sartorius Group, Goettingen, Germany*

- Jose C. Joseph** / *Abbott Laboratories, Abbott Park, Illinois, U.S.A.*
- Hans E. Junginger** / *Division of Pharmaceutical Technology, Leiden/Amsterdam Center for Drug Research, Leiden, The Netherlands*
- Galina N. Kalinkova** / *Department of Pharmaceutical Chemistry, Medical University, Sofia, Bulgaria*
- Werner Kalow** / *Department of Pharmacology, University of Toronto, Toronto, Ontario, Canada*
- Fumio Kamiyama** / *Department of Biopharmaceutics, Kyoto Pharmaceutical University, Kyoto, Japan*
- Isadore Kanfer** / *Rhodes University, Grahamstown, South Africa*
- Aziz Karim** / *Pharmacia Corporation, Skokie, Illinois, U.S.A.*
- Brian H. Kaye** / *Department of Physics and Astronomy, Laurentian University, Sudbury, Ontario, Canada*
- Ron C. Kelly** / *SSCI, Inc., West Lafayette, Indiana, U.S.A.*
- György M. Keserü** / *Computer Assisted Drug Discovery and HTS Unit, Gedeon Richter Ltd., Budapest, Pest, Hungary*
- David P. Kessler** / *Department of Chemical Engineering, Purdue University, West Lafayette, Indiana, U.S.A.*
- Rajendra K. Khankari** / *CIMA Labs, Inc., Brooklyn Park, Minnesota, U.S.A.*
- Ban-An Khaw** / *Center for Cardiovascular Targeting, School of Pharmacy, Northeastern University, Boston, Massachusetts, U.S.A.*
- Arthur H. Kibbe** / *Department of Pharmaceutical Sciences, Wilkes University, Wilkes-Barre, Pennsylvania, U.S.A.*
- Robert G. Kieffer** / *RGK Consulting, Palm Desert, California, U.S.A.*
- Chris C. Kiesnowski** / *Bristol-Myers Squibb Pharmaceutical Research Institute, New Brunswick, New Jersey, U.S.A.*
- Kwon H. Kim** / *Department of Pharmacy and Administrative Sciences, College of Pharmacy and Allied Health Professions, St. John's University, Jamaica, New York, U.S.A.*
- Toby King** / *Aradigm Corporation, Hayward, California, U.S.A.*
- Florence K. Kinoshita** / *Hercules Incorporated, Wilmington, Delaware, U.S.A.*
- Cathy M. Klech-Gelotte** / *McNeil Consumer Healthcare, Fort Washington, Pennsylvania, U.S.A.*
- A. Klos** / *Bayer Corporation, Research Triangle Park, North Carolina, U.S.A.*
- Axel Knoch** / *Pfizer Global Research and Development, Freiburg, Germany*
- John J. Koleng, Jr.** / *College of Pharmacy, University of Texas at Austin, Austin, Texas, U.S.A.*
- Uday B. Kompella** / *Department of Pharmaceutical Sciences, University of Nebraska Medical Center, Omaha, Nebraska, U.S.A.*
- Sheldon X. Kong** / *Merck and Co., Inc., Whitehouse Station, New Jersey, U.S.A.*
- Mark J. Kontny** / *Pharmacia, Skokie, Illinois, U.S.A.*
- Bhavesh H. Kothari** / *CIMA Labs, Inc., Brooklyn Park, Minnesota, U.S.A.*
- Rajesh Krishna** / *Aventis Pharmaceuticals, Inc., Bridgewater, New Jersey, U.S.A.*
- Amit Kulkarni** / *Department of Clinical Sciences and Administration, College of Pharmacy, University of Houston, Houston, Texas, U.S.A.*
- Thomas Kupiec** / *Analytical Research Laboratories, Oklahoma City, Oklahoma, U.S.A.*
- Philip Chi Lip Kwok** / *University of Sydney, Sydney, New South Wales, Australia*
- Sylvie Laganière** / *Integrated Research, Inc., Montreal, Quebec, Canada*
- Duane B. Lakings** / *DSE Consulting, Birmingham, Alabama, U.S.A.*
- John S. Landy** / *Aventis Pharmaceuticals, Bridgewater, New Jersey, U.S.A.*
- Robert Langer** / *Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts, U.S.A.*
- M. Jayne Lawrence** / *Molecular Biophysics Group, Pharmaceutical Science Research Division, King's College London, College London, London, U.K.*
- Destin A. LeBlanc** / *Cleaning Validation Technologies, San Antonio, Texas, U.S.A.*

- Chao-Pin Lee** / *GlaxoSmithKline Pharmaceuticals, Collegeville, Pennsylvania, U.S.A.*
- Chi H. Lee** / *School of Pharmacy, Division of Pharmaceutical Sciences, University of Missouri, Kansas City, Kansas City, Missouri, U.S.A.*
- Kyung Hee Lee** / *College of Pharmacy, University of Illinois at Chicago, Chicago, Illinois, U.S.A.*
- Mike S. Lee** / *Milestone Development Services, Newtown, Pennsylvania, U.S.A.*
- Sang Cheon Lee** / *Korea Institute of Ceramic Engineering and Technology, Seoul, South Korea*
- Vincent H.L. Lee** / *Department of Pharmaceutical Sciences, University of Southern California, Los Angeles, California, U.S.A.*
- Kristi L. Lenz** / *Department of Pharmacy Practice, Medical University of South Carolina, Charleston, South Carolina, U.S.A.*
- Jason M. LePree** / *Roche Pharmaceuticals, Inc., Nutley, New Jersey, U.S.A.*
- Michael Levin** / *Metropolitan Computing Corporation, East Hanover, New Jersey, U.S.A.*
- Gareth A. Lewis** / *Sanofi-Synthelabo Research, Chilly Mazarin, France*
- Luk Chiu Li** / *HPD Advanced Drug Delivery, Abbott Park, Illinois, U.S.A.*
- S. Kevin Li** / *Department of Pharmaceutics and Pharmaceutical Chemistry, College of Pharmacy, University of Utah, Salt Lake City, Utah, U.S.A.*
- Yu Li** / *GlaxoSmithKline Pharmaceuticals, Collegeville, Pennsylvania, U.S.A.*
- Eric J. Lien** / *Biomedical Chemistry and Pharmaceutics, University of Southern California, Los Angeles, California, U.S.A.*
- Senshang Lin** / *College of Pharmacy and Allied Health Professions, St. John's University, Jamaica, New York, U.S.A.*
- Nils-Olof Lindberg** / *Pharmacia and Upjohn AB, Helsingborg, Sweden*
- Blythe Lindsay** / *Department of Pharmaceutical Sciences, University of Strathclyde, Glasgow, U.K.*
- Thomas Linz** / *Schering AG, Berlin, Germany*
- John M. Lipari** / *Abbott Laboratories, North Chicago, Illinois, U.S.A.*
- Linda Lisgarten** / *Library and Information Services, School of Pharmacy, University of London, London, U.K.*
- G. Brian Lockwood** / *University of Manchester, Manchester, U.K.*
- Orlando Lopez** / *Johnson & Johnson, Raritan, New Jersey, U.S.A.*
- Joseph W. Lubach** / *Department of Pharmaceutical Chemistry, University of Kansas, Lawrence, Kansas, U.S.A.*
- Craig E. Lunte** / *Department of Chemistry, University of Kansas, Lawrence, Kansas, U.S.A.*
- Robert L. Maher, Jr.** / *Duquesne University, Pittsburgh, Pennsylvania, U.S.A.*
- Joseph Maida** / *Maida Engineering, Inc., Fort Washington, Pennsylvania, U.S.A.*
- Henri R. Manasse, Jr.** / *American Society of Health-System Pharmacists, Bethesda, Maryland, U.S.A.*
- Laviero Mancinelli** / *Daly City, California, U.S.A.*
- Peter Markland** / *Southern Research Institute, Birmingham, Alabama, U.S.A.*
- Diego Marro** / *Centre Interuniversitaire de Recherche et d'Enseignement, Universities of Geneva and Lyon, Archamps, Switzerland*
- Marilyn N. Martinez** / *U.S. Food and Drug Administration, Rockville, Maryland, U.S.A.*
- Luigi G. Martini** / *GlaxoSmithKline, Essex, U.K.*
- Michael B. Maurin** / *QS Pharma, Boothwyn, Pennsylvania, U.S.A.*
- Joachim Mayer** / *Institute of Medicinal Chemistry, University of Lausanne, Lausanne, Switzerland*
- Aaron S. Mayo** / *Department of Pharmaceutical Sciences, University of Nebraska Medical Center, Omaha, Nebraska, U.S.A.*
- Orla McCallion** / *Vandsons Research, London, U.K.*
- James C. McElnay** / *Queen's University Belfast, Belfast, U.K.*

- Iain J. McGilveray** / *McGilveray Pharmacon, Inc., Nepean, Ontario, Canada*
- Jim W. McGinity** / *College of Pharmacy, University of Texas at Austin, Austin, Texas, U.S.A.*
- Michael McKenna** / *Pfizer Pharmaceuticals Group, New York, New York, U.S.A.*
- Marghi R. McKeon** / *Lab Safety Corporation, Des Plaines, Illinois, U.S.A.*
- Eugene J. McNally** / *Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Connecticut, U.S.A.*
- Duncan E. McVean** / *Ben Venue Laboratories, Solon, Ohio, U.S.A.*
- Mark R. Mecedon** / *Novartis Pharmaceuticals, East Hanover, New Jersey, U.S.A.*
- Thomas Medwick** / *Department of Pharmaceutical Chemistry, Rutgers University, New Brunswick, New Jersey, U.S.A.*
- Robert W. Mendes** / *Dedham, Massachusetts, U.S.A.*
- Jonathan M. Miller** / *Department of Pharmaceutical Sciences, University of Michigan, Ann Arbor, Michigan, U.S.A.*
- Ronald W. Miller** / *Bristol-Myers Squibb, New Brunswick, New Jersey, U.S.A.*
- Ashim K. Mitra** / *Division of Pharmaceutical Sciences, School of Pharmacy, University of Missouri-Kansas City, Kansas City, Missouri, U.S.A.*
- Samir S. Mitragotri** / *Department of Chemical Engineering, University of California, Santa Barbara, Santa Barbara, California, U.S.A.*
- Suresh K. Mittal** / *Department of Veterinary Pathobiology, Purdue University, West Lafayette, Indiana, U.S.A.*
- Derek V. Moe** / *CIMA Labs, Inc., Brooklyn Park, Minnesota, U.S.A.*
- Nicholas Mohr** / *Department of Emergency Medicine, Indiana University School of Medicine, Indianapolis, Indiana, U.S.A.*
- Matthew J. Mollan, Jr.** / *Pfizer Global Research and Development, Ann Arbor, Michigan, U.S.A.*
- Lorie Ann Morgan** / *GlaxoSmithKline, Research Triangle Park, North Carolina, U.S.A.*
- Karen Morisseau** / *College of Pharmacy, University of Rhode Island, Kingston, Rhode Island, U.S.A.*
- Takahiro Morita** / *Tanabe Pharmaceuticals Co., Ltd., Osaka, Japan*
- Gerold Mosher** / *CyDex, Inc., Overland Park, Kansas, U.S.A.*
- Ronald L. Mueller** / *GlaxoSmithKline, King of Prussia, Pennsylvania, U.S.A.*
- Christel C. Mueller-Goymann** / *Institut für Pharmazeutische Technologie, Technischen Universität Braunschweig, Braunschweig, Germany*
- Suman K. Mukherjee** / *Department of Pharmaceutical Sciences, South Dakota State University, Brookings, South Dakota, U.S.A.*
- James O. Mullis** / *Department of Analytical Sciences, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Connecticut, U.S.A.*
- Sandy J.M. Munro** / *GlaxoSmithKline, Hertfordshire, U.K.*
- Eric J. Munson** / *Department of Pharmaceutical Chemistry, University of Kansas, Lawrence, Kansas, U.S.A.*
- Thomas D. Murphy** / *Morristown, New Jersey, U.S.A.*
- Fernando J. Muzzio** / *Department of Chemical and Biochemical Engineering, Rutgers University, Piscataway, New Jersey, U.S.A.*
- Paul B. Myrdal** / *Department of Pharmacy Practice and Science, College of Pharmacy, The University of Arizona, Tucson, Arizona, U.S.A.*
- Venkatesh Naini** / *Barr Laboratories, Inc., Pomona, New York, U.S.A.*
- Jintana Napaporn** / *Department of Pharmaceutics, College of Pharmacy, University of Florida, Gainesville, Florida, U.S.A.*
- Robert A. Nash** / *Consultant, Mahwah, New Jersey, U.S.A.*
- Sarah J. Nehm** / *Department of Pharmaceutical Sciences, University of Michigan, Ann Arbor, Michigan, U.S.A.*
- Deanna J. Nelson** / *BioLink Life Sciences, Inc., Cary, North Carolina, U.S.A.*

- Sandeep Nema** / *Pharmacia Corp., Skokie, Illinois, U.S.A.*
- Michael T. Newhouse** / *Inhale Therapeutic Systems, Inc., San Carlos, California, U.S.A.*
- Ann W. Newman** / *SSCI, Inc., West Lafayette, Indiana, U.S.A.*
- J. M. Newton** / *Department of Pharmaceutics, University of London, London, U.K.*
- Daniel L. Norwood** / *Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Connecticut, U.S.A.*
- Thomas M. Nowak** / *Abbott Laboratories, Abbott Park, Illinois, U.S.A.*
- John P. Oberdier** / *Abbott Laboratories, Abbott Park, Illinois, U.S.A.*
- Thomas M. O'Connell** / *GlaxoSmithKline, Research Triangle Park, North Carolina, U.S.A.*
- Claudia C. Okeke** / *Department of Patient Safety, United States Pharmacopeia, Rockville, Maryland, U.S.A.*
- Clyde M. Ofner III** / *University of the Sciences in Philadelphia, Philadelphia, Pennsylvania, U.S.A.*
- Rosa Maria Olmo** / *Departamento de Bioquímica y Biología Molecular, Universidad Complutense de Madrid, Madrid, Spain*
- Wayne P. Olson** / *Beecher, Illinois, U.S.A.*
- Bridget O'Mahony** / *Department of Pharmaceutical Sciences, University of Strathclyde, Glasgow, U.K.*
- Christine K. O'Neil** / *School of Pharmacy, Duquesne University, Pittsburgh, Pennsylvania, U.S.A.*
- Tooru Ooya** / *Japan Advanced Institute of Science and Technology, Ishikawa, Japan*
- Damon Osbourn** / *Department of Chemistry, University of Kansas, Lawrence, Kansas, U.S.A.*
- Rama V. Padmanabhan** / *ALZA Corporation, Spring Lake Park, Minnesota, U.S.A.*
- Sariputta P. Pakhale** / *National Institute of Pharmaceutical Education and Research, Punjab, India*
- Mark G. Papich** / *Department of Anatomy, Physiological Sciences and Radiology, North Carolina State University, Raleigh, North Carolina, U.S.A.*
- Jagdish Parasrampur** / *Johnson & Johnson, Skillman, New Jersey, U.S.A.*
- Eun Jung Park** / *Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Illinois at Chicago, Chicago, Illinois, U.S.A.*
- Jung Y. Park** / *Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Connecticut, U.S.A.*
- Kinam Park** / *Departments of Pharmaceutics and Biomedical Engineering, Purdue University, West Lafayette, Indiana, U.S.A.*
- Diane M. Paskiet** / *West Monarch Analytical Laboratories, Maumee, Ohio, U.S.A.*
- Barbara Perry** / *Hoffmann-La Roche, Welwyn, U.K.*
- Adam Persky** / *Department of Pharmaceutics, College of Pharmacy, University of Florida, Gainesville, Florida, U.S.A.*
- Gregory F. Peters** / *Lab Safety Corporation, Des Plaines, Illinois, U.S.A.*
- S. Petteway, Jr.** / *Bayer Corporation, Research Triangle Park, North Carolina, U.S.A.*
- John M. Pezzuto** / *School of Pharmacy and Pharmaceutical Sciences, Purdue University, West Lafayette, Indiana, U.S.A.*
- J. Bradley Phipps** / *ALZA Corporation, Mountain View, California, U.S.A.*
- D. Pifat** / *Bayer Corporation, Research Triangle Park, North Carolina, U.S.A.*
- Michael J. Pikal** / *School of Pharmacy, University of Connecticut, Storrs, Connecticut, U.S.A.*
- Wayne L. Pines** / *Pharmaceutical Consultant, Washington, D.C., U.S.A.*
- Terezinha de Jesus Andreo Pinto** / *Department of Pharmacy, University of Sao Paulo, Sao Paulo, Brazil*
- Dario Pistolesi** / *Fedegari Autoclavi SpA, Albuzzano, Italy*
- Stephen William Pitt** / *Johnson & Johnson, Skillman, New Jersey, U.S.A.*
- Michael E. Placke** / *Battelle Pulmonary Therapeutics, Inc., Columbus, Ohio, U.S.A.*
- Fridrun Podczeck** / *Institute of Pharmacy, University of Sunderland, Sunderland, U.K.*
- Therese I. Poirier** / *Department of Clinical Pharmacy, Duquesne University, Pittsburgh, Pennsylvania, U.S.A.*

- Tímea Polgár** / *Gedeon Richter Ltd., Budapest, Pest, Hungary*
- Jacques H. Poupaert** / *Department of Medicinal Chemistry, Catholic University of Louvain, Brussels, Belgium*
- Sunil Prabhu** / *College of Pharmacy, Western University of Health Sciences, Pomona, California, U.S.A.*
- Neil Purdie** / *Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma, U.S.A.*
- Bashir A. Qadri** / *Department of Pharmaceutics, Pharmacy School, The Hebrew University of Jerusalem, Jerusalem, Israel*
- Fenghe Qiu** / *Department of Analytical Sciences, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Connecticut, U.S.A.*
- Ying-shu Quan** / *Department of Biopharmaceutics, Kyoto Pharmaceutical University, Kyoto, Japan*
- Saeed A. Qureshi** / *Health Products and Food Branch, Health Canada, Sir F.G. Banting Research Centre, Ottawa, Ontario, Canada*
- R. Raghavan** / *Abbott Laboratories, Abbott Park, Illinois, U.S.A.*
- Natarajan Rajagopalan** / *Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana, U.S.A.*
- Judy A. Raper** / *Department of Chemical Engineering, University of Missouri-Rolla, Rolla, Missouri, U.S.A.*
- Suneel Rastogi** / *Forest Laboratories, Inc., Inwood, New York, U.S.A.*
- William R. Ravis** / *School of Pharmacy, Auburn University, Auburn, Alabama, U.S.A.*
- Brian James Reamer** / *SciRegs Consulting, Columbia, Maryland, U.S.A.*
- Robert A. Reed** / *Merck Research Laboratories, Merck & Co., Inc., West Point, Pennsylvania, U.S.A.*
- Thomas L. Reiland** / *Abbott Laboratories, North Chicago, Illinois, U.S.A.*
- J. P. Remon** / *Laboratory of Pharmaceutical Technology, Ghent University, Ghent, Belgium*
- Steven Shijun Ren** / *Maxim Pharmaceuticals, Inc., San Diego, California, U.S.A.*
- Michael A. Repka** / *School of Pharmacy, The University of Mississippi, University, Mississippi, U.S.A.*
- Christopher T. Rhodes** / *College of Pharmacy, University of Rhode Island, Kingston, Rhode Island, U.S.A.*
- Martin M. Rieger** / *Morris Plains, New Jersey, U.S.A.*
- Jean G. Riess** / *Les Giaines, Falicon, France*
- Thomas N. Riley** / *Department of Pharmaceutical Sciences, Auburn University, Auburn, Alabama, U.S.A.*
- Diane Rindgen** / *Schering-Plough Research Institute, Kenilworth, New Jersey, U.S.A.*
- Ronald J. Roberts** / *AstraZeneca, Cheshire, U.K.*
- Naír Rodríguez-Hornedo** / *Department of Pharmaceutical Sciences, University of Michigan, Ann Arbor, Michigan, U.S.A.*
- Raymond C. Rowe** / *University of Bradford, Cheshire, U.K.*
- Alan E. Royce** / *Novartis Pharmaceuticals, East Hanover, New Jersey, U.S.A.*
- Joseph T. Rubino** / *Wyeth-Ayerst Research, Pearl River, New York, U.S.A.*
- Colleen E. Ruegger** / *Novartis Pharmaceuticals, East Hanover, New Jersey, U.S.A.*
- Effendi Rusli** / *Department of Chemical and Biomolecular Engineering, University of Illinois at Urbana-Champaign, Urbana, Illinois, U.S.A.*
- J. Howard Rytting** / *Department of Pharmaceutical Chemistry, The University of Kansas, Lawrence, Kansas, U.S.A.*
- Rosalie Sagraves** / *University of Illinois, Chicago, Illinois, U.S.A.*
- Dmitry Samarsky** / *Invitrogen Corporation, Carlsbad, California, U.S.A.*
- Ronald A. Sanftleben** / *GlaxoSmithKline, Research Triangle Park, North Carolina, U.S.A.*
- Sujit S. Sansgiry** / *Department of Clinical Sciences and Administration, College of Pharmacy, University of Houston, Houston, Texas, U.S.A.*

- Peter C. Schmidt** / *Nuernberg, Germany*
- David R. Schoneker** / *Colorcon, Inc., West Point, Pennsylvania, U.S.A.*
- Stephen G. Schulman** / *Department of Medicinal Chemistry, University of Florida, Gainesville, Florida, U.S.A.*
- Erik R. Scott** / *Medtronic, Inc., Brooklyn Center, Minnesota, U.S.A.*
- Sigrun Seeger** / *Schering AG, Berlin, Germany*
- Siri H. Segalstad** / *Segalstad Consulting AS, Oslo, Norway*
- Richard B. Seymour** / *Haight Ashbury Free Clinics, San Francisco, California, U.S.A.*
- Jaymin C. Shah** / *Pfizer Global Research and Development, Groton, Connecticut, U.S.A.*
- Umang Shah** / *Pfizer Global Research and Development, Morris Plains, New Jersey, U.S.A.*
- Utpal U. Shah** / *School of Pharmacy and Chemistry, Liverpool John Moores University, Liverpool, U.K.*
- Shalaby W. Shalaby** / *Poly-Med, Inc., Anderson, South Carolina, U.S.A.*
- Leon Shargel** / *Eon Labs Manufacturing, Inc., Laurelton, New York, U.S.A.*
- Eric B. Sheinin** / *Pharmaceutical Ingredient Verification Program, United States Pharmacopeia, Rockville, Maryland, U.S.A.*
- Joseph Sherma** / *Department of Chemistry, Lafayette College, Easton, Pennsylvania, U.S.A.*
- Paul J. Sheskey** / *The Dow Chemical Company, Midland, Michigan, U.S.A.*
- Troy Shinbrot** / *Department of Chemical and Biochemical Engineering, Rutgers University, Piscataway, New Jersey, U.S.A.*
- Leonid Shnayder** / *Aker Kvaerner Pharmaceuticals, Bridgewater, New Jersey, U.S.A.*
- Gauri Shringarpure** / *Department of Clinical Sciences and Administration, College of Pharmacy, University of Houston, Houston, Texas, U.S.A.*
- Lynn Simpson** / *Department of Clinical Sciences and Administration, College of Pharmacy, University of Houston, Houston, Texas, U.S.A.*
- Brent D. Sinclair** / *Abbott Laboratories, Abbott Park, Illinois, U.S.A.*
- Ambarish K. Singh** / *Bristol-Myers Squibb Pharmaceutical Research Institute, New Brunswick, New Jersey, U.S.A.*
- Brahma N. Singh** / *Forest Laboratories, Inc., Commack, New York, U.S.A.*
- Saranjit Singh** / *National Institute of Pharmaceutical Education and Research, Punjab, India*
- Shailesh K. Singh** / *Wyeth Research, Pearl River, New York, U.S.A.*
- Jerome P. Skelly** / *Pharmaceutical Consultant, Alexandria, Virginia, U.S.A.*
- Michael F. Skinner** / *Rhodes University, Grahamstown, South Africa*
- William H. Slattey III** / *House Ear Clinic, Los Angeles, California, U.S.A.*
- A. Ian Smith** / *Baker Heart Research Institute, Melbourne, Victoria, Australia*
- David E. Smith** / *Haight Ashbury Free Clinics, San Francisco, California, U.S.A.*
- Edward J. Smith** / *Wyeth Pharmaceuticals, Collegeville, Pennsylvania, U.S.A.*
- Marshall Steinberg** / *International Pharmaceuticals Council, Kennett Square, Pennsylvania, U.S.A.*
- Ralph Stone** / *Alcon Laboratories, Fort Worth, Texas, U.S.A.*
- Robert G. Strickley** / *Gilead Sciences Inc., Foster City, California, U.S.A.*
- Muppalla Sukumar** / *Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana, U.S.A.*
- Raj Suryanarayanan** / *College of Pharmacy, University of Minnesota, Minneapolis, Minnesota, U.S.A.*
- Stuart R. Suter** / *Patent Attorney and Consultant, Glenside, Pennsylvania, U.S.A.*
- Lynda Sutton** / *Cato Research Ltd., Durham, North Carolina, U.S.A.*
- C. Jeanne Taborsky** / *SciRegs Consulting, Columbia, Maryland, U.S.A.*
- Hua Tang** / *TransForm Pharmaceuticals, Inc., Lexington, Massachusetts, U.S.A.*
- P. Tang** / *University of Sydney, Sydney, New South Wales, Australia*
- Kevin M.G. Taylor** / *School of Pharmacy, University of London, London, U.K.*

- José María Teijón** / *Departamento de Bioquímica y Biología Molecular, Universidad Complutense de Madrid, Madrid, Spain*
- Allen C. Templeton** / *Merck Research Laboratories, Merck & Co., Inc., West Point, Pennsylvania, U.S.A.*
- Bernard Testa** / *Institute of Medicinal Chemistry, University of Lausanne, Lausanne, Switzerland*
- Maya Thanou** / *Centre for Polymer Therapeutics, Welsh School of Pharmacy, Cardiff University, Cardiff, U.K.*
- C. Thomasin** / *The R.W. Johnson Pharmaceutical Research Institute, Schaffhausen, Switzerland*
- Diane O. Thompson** / *CyDex, Inc., Overland Park, Kansas, U.S.A.*
- William J. Thomsen** / *Arena Pharmaceuticals, San Diego, California, U.S.A.*
- Youqin Tian** / *Alcon Laboratories, Fort Worth, Texas, U.S.A.*
- Jeffrey Tidwell** / *GlaxoSmithKline, Research Triangle Park, North Carolina, U.S.A.*
- Stephen Tindal** / *Cardinal Health Pharmaceutical Development, Somerset, New Jersey, U.S.A.*
- James E. Tingstad** / *Tingstad Associates, Green Valley, Arizona, U.S.A.*
- A. K. Tiwary** / *Department of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala, India*
- Hanne Hjorth Tonnesen** / *School of Pharmacy, University of Oslo, Oslo, Norway*
- Edward H. Trappier** / *Lyophilization Technology, Inc., Ivyland, Pennsylvania, U.S.A.*
- Richard Turton** / *Department of Chemical Engineering, College of Engineering and Mineral Resources, West Virginia University, Morgantown, West Virginia, U.S.A.*
- Mitsuru Uchiyama** / *Society of Japanese Pharmacopeia, Tokyo, Japan*
- Merlin L. Utter** / *Wyeth Research, Pearl River, New York, U.S.A.*
- Madhu K. Vadnere** / *Schein Pharmaceutical, Inc., Florham Park, New Jersey, U.S.A.*
- Stephen J. Valazza** / *Novartis Pharmaceuticals, East Hanover, New Jersey, U.S.A.*
- Lynn Van Campen** / *Nektar Therapeutics, San Carlos, California, U.S.A.*
- Koen Van Deun** / *Janssen Pharmaceutica N.V., Beerse, Belgium*
- Mark D. VanArendonk** / *Pharmacia Corporation, Kalamazoo, Michigan, U.S.A.*
- Jason M. Vaughn** / *College of Pharmacy, The University of Texas at Austin, Austin, Texas, U.S.A.*
- Christine Vauthier** / *School of Pharmacy, University of Paris XI, Châtenay-Malabry, France*
- Helena J. Venables** / *School of Pharmacy and Chemistry, Liverpool John Moores University, Liverpool, U.K.*
- Geraldine Venthoye** / *Inhale Therapeutic Systems, Inc., San Carlos, California, U.S.A.*
- J. Coos Verhoef** / *Division of Pharmaceutical Technology, Leiden/Amsterdam Center for Drug Research, Leiden, The Netherlands*
- C. Vervaet** / *Laboratory of Pharmaceutical Technology, Ghent University, Ghent, Belgium*
- Vesa Virtanen** / *Department of Pharmaceutical Product Development, Orion Pharma, Kuopio, Finland*
- Imre M. Vitez** / *Bristol-Myers Squibb Pharmaceutical Research Institute, New Brunswick, New Jersey, U.S.A.*
- Karel Vytras** / *Department of Analytical Chemistry, University of Pardubice, Pardubice, Czech Republic*
- Robert F. Wagner** / *Novartis Pharmaceuticals, East Hanover, New Jersey, U.S.A.*
- Michelle Wake** / *Library and Information Services, School of Pharmacy, University of London, London, U.K.*
- Roderick B. Walker** / *Rhodes University, Grahamstown, South Africa*
- Kenneth A. Walters** / *An-eX Analytical Services, Ltd., Cardiff, U.K.*
- Ch. Wandrey** / *Laboratoire des Polyélectrolytes et BioMacromolécules, EPFL, Lausanne, Switzerland*
- Richard Washkuhn** / *Consultant, Lexington, Kentucky, U.S.A.*
- Alan L. Weiner** / *Alcon Research, Ltd., Fort Worth, Texas, U.S.A.*

- Peter Welch** / *Invitrogen Corporation, Carlsbad, California, U.S.A.*
- Peter G. Welling** / *Kent, U.K.*
- Mickey L. Wells** / *GlaxoSmithKline, Research Triangle Park, North Carolina, U.S.A.*
- Hong Wen** / *Wyeth Research, Pearl River, New York, U.S.A.*
- Albert I. Wertheimer** / *School of Pharmacy, Temple University, Philadelphia, Pennsylvania, U.S.A.*
- Paul K. Whitcraft** / *Rolled Alloys, Temperance, Michigan, U.S.A.*
- Cheryl A. Wiens** / *University of Alberta, Edmonton, Alberta, Canada*
- Nina F. Wilkins** / *Acrux DDS Pty Ltd., West Melbourne, Victoria, Australia*
- Ellen M. Williams** / *Pfizer, Inc., New York, New York, U.S.A.*
- Paul J. Williams** / *Department of Pharmacy Practice, School of Pharmacy, University of the Pacific, Stockton, California, U.S.A.*
- Robert O. Williams III** / *College of Pharmacy, The University of Texas at Austin, Austin, Texas, U.S.A.*
- Roger L. Williams** / *United States Pharmacopeia, Rockville, Maryland, U.S.A.*
- Clive G. Wilson** / *Department of Pharmaceutical Sciences, University of Strathclyde, Glasgow, U.K.*
- M. G. Wing** / *Biosciences Division, Huntingdon Life Sciences, Cambridgeshire, U.K.*
- Tin Wui Wong** / *University Technology MARA, Selangor, Malaysia*
- A. Wayne Wood** / *GlaxoSmithKline, Research Triangle Park, North Carolina, U.S.A.*
- A. David Woolfson** / *School of Pharmacy, The Queen's University of Belfast, Belfast, U.K.*
- Thomas J. Wubben** / *Department of Chemical and Biomolecular Engineering, University of Illinois at Urbana-Champaign, Urbana, Illinois, U.S.A.*
- Dawei Xuan** / *Pfizer Global Research and Development, Ann Arbor, Michigan, U.S.A.*
- Samuel H. Yalkowsky** / *Department of Pharmacy Practice and Science, College of Pharmacy, The University of Arizona, Tucson, Arizona, U.S.A.*
- Hiroshi Yamahara** / *Tanabe Seiyaku Co., Ltd., Osaka, Japan*
- Victor C. Yang** / *Department of Pharmaceutical Sciences, The University of Michigan, Ann Arbor, Michigan, U.S.A.*
- Charles R. Yates** / *Department of Pharmaceutical Sciences, College of Pharmacy, University of Tennessee, Memphis, Tennessee, U.S.A.*
- Yoon Yeo** / *Department of Industrial and Physical Pharmacy, Purdue University, West Lafayette, Indiana, U.S.A.*
- Andrew B.C. Yu** / *Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Rockville, Maryland, U.S.A.*
- Mark J. Zellhofer** / *Guilford Pharmaceuticals, Inc., Baltimore, Maryland, U.S.A.*
- Feng Zhang** / *College of Pharmacy, University of Texas at Austin, Austin, Texas, U.S.A.*
- William C. Zimlich, Jr.** / *Battelle Pulmonary Therapeutics, Inc., Columbus, Ohio, U.S.A.*

Contents

<i>Contributors</i>	ix
<i>Topical Table of Contents</i>	xxxi
<i>Preface</i>	liii

Volume 1

21 CFR Part 11 Revisited / <i>Thomas Linz and Sigrun Seeger</i>	1
Absorption Enhancers / <i>J. P. Remon</i>	13
Absorption of Drugs / <i>Peter G. Welling</i>	19
Adsorption at Solid Surfaces: Pharmaceutical Applications / <i>Hong Wen</i>	34
Adverse Drug Reactions / <i>Therese I. Poirier and Robert L. Maher, Jr.</i>	46
Advertising and Promotion of Prescription and Over-the-Counter Drug Products / <i>Wayne L. Pines</i>	57
Alternative Medicines / <i>Kristi L. Lenz</i>	66
Amorphous Pharmaceutical Systems / <i>Bruno C. Hancock</i>	83
Analytical Procedures: Validation / <i>Joachim Ermer and John S. Landy</i>	92
Animals in Drug Development / <i>Farrel L. Fort</i>	114
Aseptic Processing: Validation / <i>James P. Agalloco and James E. Akers</i>	127
Autoxidation and Antioxidants / <i>John M. Pezzuto and Eun Jung Park</i>	139
Bioabsorbable Polymers / <i>Shalaby W. Shalaby</i>	155
Bioavailability of Drugs and Bioequivalence / <i>James T. Dalton and Charles R. Yates</i>	164
Biodegradable Polymers as Drug Carriers / <i>Peter Markland and Victor C. Yang</i>	176
Biologic Fluids: Analysis / <i>Stephen G. Schulman, Judith A. Davis, and Gayle A. Brazeau</i>	194
Biopharmaceutics / <i>Leon Shargel and Andrew B.C. Yu</i>	208
Biosynthesis of Drugs / <i>Geoffrey A. Cordell and Kyung Hee Lee</i>	228
Biotechnology and Biological Preparations / <i>Ronald P. Evens</i>	258
Biotechnology-Derived Drug Products: Formulation Development / <i>Mary E.M. Cromwell</i>	281
Biotechnology-Derived Drug Products: Stability Testing, Filling, and Packaging / <i>Mary E.M. Cromwell</i>	302
Biotransformation of Drugs / <i>Les F. Chasseaud and D. R. Hawkins</i>	310
Bio-Validation of Steam Sterilization / <i>Nigel A. Halls</i>	325
Blood Substitutes: Fluorocarbon Approach / <i>Jean G. Riess</i>	335
Blood Substitutes: Hemoglobin-Based Oxygen Carriers / <i>Deanna J. Nelson</i>	353
Blow-Fill-Seal: Advanced Aseptic Processing / <i>Deborah J. Jones</i>	378
Buffers, Buffering Agents, and Ionic Equilibria / <i>Harry G. Brittain</i>	385
Calorimetry in Pharmaceutical Research and Development / <i>Sophie-Dorothée Clas,</i> <i>Chad R. Dalton, and Bruno C. Hancock</i>	393
Capsules, Hard / <i>Brian E. Jones</i>	406
Capsules, Soft / <i>David H. Bergstrom, Stephen Tindal, and Wenbin Dang</i>	419
Carcinogenicity Testing: Past, Present, and Future / <i>Koen Van Deun</i>	431

Chiroptical Analytical Methods / Neil Purdie	445
Chromatographic Methods of Analysis: Gas Chromatography / Isadore Kanfer, Roderick B. Walker, and Michael F. Skinner	463
Chromatographic Methods of Analysis: High Performance Liquid Chromatography / R. Raghavan and Jose C. Joseph	526
Chromatographic Methods of Analysis: Thin Layer Chromatography / Joseph Sherma	538
Clinical Data Management Systems / Samuel V. Givens, Debra Barnes, Victoria Imber, and Barbara Perry	551
Clinical Evaluation of Drugs / Lynda Sutton, Allen Cato, and Allen Cato III	560
Clinical Pharmacokinetics and Pharmacodynamics / Leslie Z. Benet and Laviero Mancinelli	572
Clinical Supplies Manufacture: GMP Considerations / David L. Chesney and Mark L. Balboni	591
Coacervation and Phase Separation / Bruno Gander, Maria Jose Blanco-Prieto, C. Thomasin, Ch. Wandrey, and D. Hunkeler	600
Cocrystals: Design, Properties and Formation Mechanisms / Naír Rodríguez-Hornedo, Sarah J. Nehm, and Adivaraha Jayasankar	615
Colloids and Colloid Drug Delivery System / Diane J. Burgess	636
Coloring Agents for Use in Pharmaceuticals / David R. Schoneker	648
Index	II

Volume 2

Complexation: Cyclodextrins / Gerold Mosher and Diane O. Thompson	671
Complexation: Non-Cyclodextrins / Galina N. Kalinkova	697
Computer Systems Validation / Orlando Lopez	707
Computer-Assisted Drug Design / J. Phillip Bowen and Michael Cory	714
Computers in Pharmaceutical Technology / Onkaram Basavapathruni	732
Continuous Processing of Pharmaceuticals / J. P. Remon and C. Vervaet	743
Contract Manufacturing / Duncan E. McVean	750
Cooling Processes and Congealing / Richard Turton and Xiu Xiu Cheng	761
Coprecipitates and Melts / Madhu K. Vadnere	774
Corrosion of Pharmaceutical Equipment / Paul K. Whitcraft	782
Cosmetics and Their Relation to Drugs / Martin M. Rieger	798
Cosolvents and Cosolvency / Joseph T. Rubino	806
Crystal Habit Changes and Dosage Form Performance / A. K. Tiwary	820
Crystallization: General Principles and Significance on Product Development / Naír Rodríguez-Hornedo, Ron C. Kelly, Brent D. Sinclair, and Jonathan M. Miller	834
Crystallization: Particle Size Control / Richard D. Braatz, Mitsuko Fujiwara, Thomas J. Wubben, and Effendi Rusli	858
Dendrimers / Antony D'Emanuele, David Attwood, and Ragheb Abu-Rmaileh	872
Dental Products / Sebastian G. Ciancio	891
Dissolution and Dissolution Testing / A. Mark Dyas and Utpal U. Shah	908
DNA Probes for the Identification of Microbes / Wayne P. Olson	929
Dosage Form Design: A Physicochemical Approach / Michael B. Maurin and Anwar A. Hussain	939
Dosage Forms and Basic Preparations: History / Robert A. Buerki and Gregory J. Higby	948
Dosage Forms: Lipid Excipients / Alan L. Weiner	975
Dosage Forms: Non-Parenterals / Shailesh K. Singh and Venkatesh Naini	988
Dosage Forms: Parenterals / Gayle A. Brazeau, Adam Persky, and Jintana Napaporn	1001

Dosage Regimens and Dose-Response / Chyung S. Cook and Aziz Karim	1012
Dressings in Wound Management / Sarah M.E. Cockbill	1023
Drug Abuse / Richard B. Seymour and David E. Smith	1038
Drug Delivery Systems: Neutron Scattering Studies / M. Jayne Lawrence and David J. Barlow	1049
Drug Delivery: Buccal Route / James C. McElnay and Carmel M. Hughes	1071
Drug Delivery: Controlled Release / Yie W. Chien and Senshang Lin	1082
Drug Delivery: Fast-Dissolve Systems / Vikas Agarwal, Bhavesh H. Kothari, Derek V. Moe, and Rajendra K. Khankari	1104
Drug Delivery: Liquid Crystals in / Christel C. Mueller-Goymann	1115
Drug Delivery: Monoclonal Antibodies / John B. Cannon, Ho-Wah Hui, and Pramod K. Gupta	1132
Drug Delivery: Monoclonal Antibodies in Imaging and Therapy / Ban-An Khaw	1149
Drug Delivery: Mucoadhesive Hydrogels / Hans E. Junginger, J. Coos Verhoef, and Maya Thanou	1169
Drug Delivery: Nanoparticles / Elias Fattal and Christine Vauthier	1183
Drug Delivery: Nasal Route / René Bommer	1201
Drug Delivery: Needle-Free Systems / Toby King	1209
Drug Delivery: Ophthalmic Route / Masood Chowhan, Alan L. Weiner, and Haresh Bhagat	1220
Drug Delivery: Oral Colon-Specific / Vincent H.L. Lee and Suman K. Mukherjee	1228
Drug Delivery: Oral Route / Brahma N. Singh and Kwon H. Kim	1242
Drug Delivery: Parenteral Route / Michael J. Akers	1266
Drug Delivery: Pulmonary Delivery / Michael T. Newhouse	1279
Drug Delivery: Pulsatile Systems / Till Bussemer and Roland A. Bodmeier	1287
Drug Delivery: Rectal Route / J. Howard Rytting and Joseph A. Fix	1298
Drug Delivery: Topical and Transdermal Routes / Kenneth A. Walters	1311
Drug Delivery: Tumor-Targeted Systems / Yu Li and Chao-Pin Lee	1326
Drug Delivery: Vaginal Route / Yie W. Chien and Chi H. Lee	1339
Drug Design: Basic Principles and Applications / Jacques H. Poupaert	1362
Drug Development Management / James E. Tingstad	1370
Drug Information Systems / Linda Lisgarten and Michelle Wake	1385
Drug Interactions / Daniel A. Hussar	1392
Drug Master Files / C. Jeanne Taborsky and Brian James Reamer	1401
Drug Safety Evaluation / Farrel L. Fort	1406
Dry Powder Aerosols: Emerging Technologies / Hak-Kim Chan and Nora Y.K. Chew	1428
Index	II

Volume 3

Drying and Dryers / Anthony J. Hlinak and Bradley A. Clark	1435
Economic Characteristics of the R&D Intensive Pharmaceutical Industry / Douglas L. Cocks	1450
Effervescent Pharmaceuticals / Nils-Olof Lindberg and Henri Hansson	1454
Elastomeric Components for the Pharmaceutical Industry / Edward J. Smith	1466
Electrical Power Systems for Pharmaceutical Equipment / Joseph Maida	1482
Electroanalytical Methods of Analysis: Polarography and Voltammetry / A. David Woolfson	1490
Electroanalytical Methods of Analysis: Potentiometry / Karel Vytras	1502
Electrochemical Detection for Pharmaceutical Analysis / Craig E. Lunte and Damon Osbourn	1516

Electrostatic Charge in Pharmaceutical Systems / Philip Chi Lip Kwok and Hak-Kim Chan	1535
Emulsions and Microemulsions / Gillian M. Eccleston	1548
Enzyme Immunoassay and Related Bioanalytical Methods / John W.A. Findlay and Ira Das	1566
Equipment Cleaning / Destin A. LeBlanc	1580
European Agency for the Evaluation of Medicinal Products (EMA) / David M. Jacobs	1593
Evaporation and Evaporators / David P. Kessler	1600
Excipients for Pharmaceutical Dosage Forms / Patrick J. Crowley and Luigi G. Martini	1609
Excipients: Parenteral Dosage Forms and Their Role / Sandeep Nema, Ron J. Brendel, and Richard Washkuhn	1622
Excipients: Powders and Solid Dosage Forms / Hak-Kim Chan and Nora Y.K. Chew	1646
Excipients: Safety Testing / Marshall Steinberg and Florence K. Kinoshita	1656
Expert Systems in Pharmaceutical Product Development / Raymond C. Rowe and Ronald J. Roberts	1663
Expiration Dating / Leslie C. Hawley and Mark D. VanArendonk	1685
Extractables and Leachables in Drugs and Packaging / Daniel L. Norwood, Alice T. Granger, and Diane M. Paskiet	1693
Extrusion and Extruders / J. M. Newton	1712
Film Coating of Oral Solid Dosage Forms / Linda A. Felton	1729
Filters and Filtration / Maik W. Jornitz	1748
Flame Photometry / Thomas M. Nowak	1759
Flavors and Flavor Modifiers / Thomas L. Reiland and John M. Lipari	1763
Fluid Bed Processes for Forming Functional Particles / Yoshinobu Fukumori and Hideki Ichikawa	1773
Food and Drug Administration: Role in Drug Regulation / Roger L. Williams	1779
Fractal Geometry in Pharmaceutical and Biological Applications / P. Tang, Hak-Kim Chan, and Judy A. Raper	1791
Freeze Drying / Michael J. Pikal	1807
Freeze Drying, Scale-Up Considerations / Edward H. Trappler	1834
Gastro-Retentive Systems / Amnon Hoffman and Bashir A. Qadri	1850
Gelatin-Containing Formulations: Changes in Dissolution Characteristics / Saranjit Singh and Sariputta P. Pakhale	1861
Gels and Jellies / Clyde M. Ofner III and Cathy M. Klech-Gelotte	1875
Generic Drugs and Generic Equivalency / Arthur H. Kibbe	1891
Genetic Aspects of Drug Development / Werner Kalow	1897
Geriatric Dosing and Dosage Forms / Cheryl A. Wiens and Carol A. Borynec	1905
Good Clinical Practices (GCPs): An Overview / Richard A. Guarino	1925
Good Laboratory Practices (GLPs): An Overview / Nigel J. Dent	1931
Good Manufacturing Practices (GMPs): An Overview / Ira R. Berry	1941
Handling Hazardous Chemicals and Pharmaceuticals / Antonio Conto	1948
Harmonization of Pharmacopeial Standards / Lee T. Grady and Jerome A. Halperin	1955
Headspace Oxygen Analysis in Pharmaceutical Products / Allen C. Templeton and Robert A. Reed	1967
Health Care Systems: Outside the United States / Albert I. Wertheimer and Sheldon X. Kong	1977
Health Care Systems: Within the United States / Henri R. Manasse, Jr.	1985
Homogenization and Homogenizers / Shailesh K. Singh and Venkatesh Naini	1996
Hot-Melt Extrusion Technology / Jim W. McGinity, Michael A. Repka, John J. Koleng, Jr., and Feng Zhang	2004

Hydrogels / <i>Mariá Dolores Blanco, Rosa Maria Olmo, and José Mariá Teijón</i>	2021
Hydrolysis of Drugs / <i>Jason M. LePree and Kenneth A. Connors</i>	2040
Immunoassay / <i>Stephen G. Schulman and G.J.P.J. Beernink</i>	2048
In Vitro–In Vivo Correlation / <i>J.-M. Cardot and Erick Beyssac</i>	2062
Inhalation: Dry Powder / <i>Lynn Van Campen and Geraldine Venthoye</i>	2077
Inhalation: Liquids / <i>Michael E. Placke, Jeffrey Ding, and William C. Zimlich, Jr.</i>	2092
Index	II

Volume 4

Iontophoresis / <i>J. Bradley Phipps, Erik R. Scott, J. Richard Gyory, and Rama V. Padmanabhan</i>	2119
Isolators for Pharmaceutical Application / <i>Gordon J. Farquharson</i>	2133
Isomerism / <i>Thomas N. Riley, Jack DeRuiter, William R. Ravis, and C. Randall Clark</i>	2142
Laboratory Information Management System (LIMS) / <i>Siri H. Segalstad</i>	2164
Laminar Airflow Equipment: Applications and Operation / <i>Gregory F. Peters</i>	2171
Lead Optimization in Pharmaceutical Development: Molecular and Cellular Approaches / <i>C. K. Atterwill and M. G. Wing</i>	2192
Lens Care Products / <i>Masood Chowhan and Ralph Stone</i>	2202
Liquid Oral Preparations / <i>Jagdish Parasrampur and Stephen William Pitt</i>	2216
Lozenges / <i>Robert W. Mendes and Hridaya Bhargava</i>	2231
Materials of Construction for Pharmaceutical Equipment / <i>Michelle M. Gonzalez</i>	2237
Medication Errors / <i>Diane D. Cousins</i>	2243
Melt Processes for Oral Solid Dosage Forms / <i>Paul W.S. Heng and Tin Wui Wong</i>	2257
Metabolite Identification in Drug Discovery / <i>Kathleen A. Cox, Nigel Clarke, and Diane Rindgen</i>	2262
Metered Dose Inhalers / <i>Sandy J.M. Munro and Alan L. Cripps</i>	2269
Microbial Control of Pharmaceuticals / <i>Nigel A. Halls</i>	2286
Microbiologic Monitoring of Controlled Processes / <i>Gregory F. Peters and Marghi R. McKeon</i>	2298
Microencapsulation Technology / <i>Kinam Park and Yoon Yeo</i>	2315
Microsphere Technology and Applications / <i>Diane J. Burgess and Anthony J. Hickey</i>	2328
Milling of Active Pharmaceutical Ingredients / <i>Elizabeth S. Fisher</i>	2339
Mixing and Segregation in Tumbling Blenders / <i>Troy Shinbrot and Fernando J. Muzzio</i>	2352
Moisture in Pharmaceutical Products / <i>R. Gary Hollenbeck</i>	2368
Nanoparticle Engineering / <i>Robert O. Williams III and Jason M. Vaughn</i>	2384
Neural Computing and Formulation Optimization / <i>Elizabeth Colbourn and Raymond C. Rowe</i>	2399
Non-Prescription Drugs / <i>Sujit S. Sangsiry, Lynn Simpson, Gauri Shringarpure, and Amit Kulkarni</i>	2413
Nutraceutical Supplements / <i>G. Brian Lockwood</i>	2431
Optimization Methods / <i>Gareth A. Lewis</i>	2452
Orphan Drugs / <i>Carolyn H. Asbury</i>	2468
Otic Preparations / <i>William H. Slattery III</i>	2475
Outsourcing / <i>Duane B. Lakings</i>	2486
Packaging Materials: Glass / <i>Claudia C. Okeke and Desmond G. Hunt</i>	2508
Packaging Systems: Compendial Requirements / <i>Claudia C. Okeke, Desmond G. Hunt, Nicholas Mohr, Thomas Medwick, Eric B. Sheinin, and Roger L. Williams</i>	2526

Paperless Documentation Systems / <i>Ellen M. Williams and Michael McKenna</i>	2551
Particle Engineering / <i>Miriam K. Franchini</i>	2567
Particle-Size Characterization / <i>Brian H. Kaye</i>	2582
Partition Coefficients / <i>Eric J. Lien and Steven Shijun Ren</i>	2595
Patents: International Perspective / <i>Stuart R. Suter and Peter J. Giddings</i>	2604
Patents: United States Perspective / <i>Lorie Ann Morgan and Jeffrey Tidwell</i>	2616
Pediatric Dosing and Dosage Forms / <i>Rosalie Sagraves</i>	2629
Pelletization Techniques / <i>Isaac Ghebre-Sellassie and Axel Knoch</i>	2651
Peptides and Proteins: Buccal Absorption / <i>Ashim K. Mitra, Hemant H. Alur, and Thomas P. Johnston</i>	2664
Peptides and Proteins: Nasal Absorption / <i>Takahiro Morita and Hiroshi Yamahara</i>	2678
Peptides and Proteins: Non-Invasive Delivery / <i>Michael R. DeFelippis, Muppalla Sukumar, and Natarajan Rajagopalan</i>	2692
Peptides and Proteins: Oral Absorption / <i>Eugene J. McNally and Jung Y. Park</i>	2713
Peptides and Proteins: Pulmonary Absorption / <i>Igor Gonda</i>	2731
Peptides and Proteins: Transdermal Absorption / <i>Richard H. Guy, M. Begoña Delgado-Charro, and Diego Marro</i>	2741
Pharmaceutical Data: Mathematical Modeling / <i>David W.A. Bourne</i>	2757
Pharmaceutical Excipient Testing: Regulatory and Preclinical Perspective / <i>Paul Baldrick</i>	2771
Pharmaceutical Quality Assurance Microbiology Laboratories / <i>Anthony M. Cundell</i>	2783
Pharmacogenomics and Genomic Technologies / <i>Daniel A. Brazeau</i>	2794
Pharmacokinetic/Pharmacodynamic Modeling and Simulations in Drug Development / <i>Dawei Xuan and Sally Y. Choe</i>	2802
Pharmacokinetics: Effects of Food and Fasting / <i>Rajesh Krishna and Bradford K. Jensen</i>	2816
Index	II

Volume 5

Pharmacopeial Standards: European Pharmacopeia / <i>Agnès Artiges</i>	2829
Pharmacopeial Standards: Japanese Pharmacopeia / <i>Mitsuru Uchiyama</i>	2836
Pharmacopeial Standards: United States Pharmacopeia and National Formulary / <i>Lee T. Grady</i>	2841
Photodecomposition of Drugs / <i>Hanne Hjorth Tonnesen</i>	2859
Physiological Factors Affecting Oral Drug Delivery / <i>Clive G. Wilson, Bridget O'Mahony, and Blythe Lindsay</i>	2866
Pilot Plant Design / <i>Mickey L. Wells, Samuel B. Balik, Ralph B. Caricofe, Charles W. Crew, Ronald A. Sanftleben, and A. Wayne Wood</i>	2875
Pilot Plant Operation / <i>Mickey L. Wells, A. Wayne Wood, Samuel B. Balik, Ralph B. Caricofe, Ronald A. Sanftleben, and Charles W. Crew</i>	2886
Plants as Drugs / <i>Christine K. O'Neil and Charles W. Fetrow</i>	2901
Polymeric Delivery Systems for Poorly Soluble Drugs / <i>Kang Moo Huh, Sang Cheon Lee, Tooru Ooya, and Kinam Park</i>	2913
Polymers in Transdermal Delivery Systems / <i>Fumio Kamiyama and Ying-shu Quan</i>	2925
Polymorphism: Pharmaceutical Aspects / <i>Harry G. Brittain</i>	2935
Population Pharmacokinetics / <i>Ene I. Ette, Alaa M. Ahmad, and Paul J. Williams</i>	2946
Powder Sampling / <i>Helena J. Venables</i>	2959
Powders as Dosage Forms / <i>Jean-Marc Aiache and Erick Beyssac</i>	2971
Preservation of Pharmaceutical Products / <i>Peter Gilbert and David G. Allison</i>	2983
Process Chemistry in the Pharmaceutical Industry / <i>Kumar G. Gadamasetti and Ambarish K. Singh</i>	2993
Prodrug Design / <i>Bernard Testa and Joachim Mayer</i>	3008

Project Management / Jerome J. Groen and Cara R. Frosch	3015
Protein Binding of Drugs / Sylvie Laganière and Iain J. McGilveray	3027
Proteomics: Pharmaceutical Applications / A. Ian Smith	3041
Pyrogens and Endotoxin Detection / James F. Cooper	3052
Quality Assurance of Pharmaceuticals / Barbara Immel	3064
Quality Systems Management / Gary C. Harbour and Robert G. Kieffer	3075
Radiochemical Methods of Analysis / R. Raghavan and Jose C. Joseph	3082
Radiolabeling of Pharmaceutical Aerosols and Gamma Scintigraphic Imaging for Lung Deposition / Hak-Kim Chan, Stefan Eberl, and William Glover	3094
Receptors for Drugs: Discovery in the Post-Genomic Era / Jeffrey M. Herz and William J. Thomsen	3108
Rheology of Pharmaceutical Systems / Fridrun Podczek	3128
RNAi in Drug Development / Dmitry Samarsky, Shelley Hough, Adam Harris, Eugene Carstea, and Peter Welch	3147
Roller Compaction Technology for the Pharmaceutical Industry / Ronald W. Miller and Paul J. Sheskey	3159
Salt Forms: Pharmaceutical Aspects / Owen I. Corrigan	3177
Scale-Up and Post Approval Changes (SUPAC) / Jerome P. Skelly	3188
Scale-Up of Solid Dosage Forms / Colleen E. Ruegger, Alan E. Royce, Matthew J. Mollan, Jr., Robert F. Wagner, Stephen J. Valazza, and Mark R. Mecadon	3193
Secondary Electron Microscopy in Pharmaceutical Technology / Peter C. Schmidt	3217
Semisolid Preparations / Guru Betageri and Sunil Prabhu	3257
Solids: Flow Properties / Stephen A. Howard	3275
Solid-State NMR in the Characterization of Pharmaceutical Formulations / Eric J. Munson and Joseph W. Lubach	3297
Solubilization of Drugs in Aqueous Media / Paul B. Myrdal and Samuel H. Yalkowsky	3311
Solubilizing Excipients in Pharmaceutical Formulations / Robert G. Strickley	3334
Spectroscopic Methods of Analysis: Atomic Absorption and Emission Spectrophotometry / John P. Oberdier	3367
Spectroscopic Methods of Analysis: Diffuse Reflectance Spectroscopy / Herbert Michael Heise	3375
Spectroscopic Methods of Analysis: Fluorescence Spectroscopy / Stephen G. Schulman and Jeffrey A. Hughes	3387
Spectroscopic Methods of Analysis: Infrared Spectroscopy / Marilyn D. Duerst	3405
Spectroscopic Methods of Analysis: Mass Spectrometry / Mike S. Lee	3419
Spectroscopic Methods of Analysis: Near-Infrared Spectrometry / Emil W. Ciurczak	3434
Spectroscopic Methods of Analysis: Nuclear Magnetic Resonance Spectroscopy / Thomas M. O'Connell and Kevin L. Facchine	3440
Spectroscopic Methods of Analysis: Ultraviolet and Visible Spectrophotometry / R. Raghavan and Jose C. Joseph	3460
Starches and Starch Derivatives / Ann W. Newman, Ronald L. Mueller, Imre M. Vitez, and Chris C. Kiesnowski	3476
Index	II

Volume 6

Statistical Methods / Charles Bon	3483
Statistical Process Control and Process Capability / Thomas D. Murphy, Shailesh K. Singh, and Merlin L. Utter	3499
Sterilization: Dry Heat / Andrea Chieppo and Thomas Kupiec	3512
Sterilization: Ethylene Oxide / Terezinha de Jesus Andreo Pinto	3519

Sterilization: Moist Heat / <i>Dario Pistolesi</i>	3529
Sterilization: Radiation / <i>Stephen G. Schulman and Phillip M. Achey</i>	3540
Super Disintegrants: Characterization and Function / <i>Larry L. Augsburger,</i> <i>Albert W. Brzezczko, Umang Shah, and Huijeong Ashley Hahm</i>	3553
Supercritical Fluid Technology in Pharmaceutical Research / <i>Aaron S. Mayo and</i> <i>Uday B. Kompella</i>	3568
Surfactants in Pharmaceutical Products and Systems / <i>Owen I. Corrigan and</i> <i>Anne Marie Healy</i>	3583
Suspensions / <i>Robert A. Nash</i>	3597
Tablet Compression: Machine Theory, Design, and Process Troubleshooting / <i>Michael J. Bogda</i>	3611
Tablet Evaluation Using Near-Infrared Spectroscopy / <i>Christopher T. Rhodes and</i> <i>Karen Morisseau</i>	3630
Tablet Formulation / <i>Larry L. Augsburger and Mark J. Zellhofer</i>	3641
Tablet Manufacture / <i>Norman Anthony Armstrong</i>	3653
Tablet Manufacture by Direct Compression / <i>Norman Anthony Armstrong</i>	3673
Tablet Press Instrumentation / <i>Michael Levin</i>	3684
Tablet Testing / <i>Saeed A. Qureshi</i>	3707
Technology Transfer Considerations for Pharmaceuticals / <i>Ira R. Berry</i>	3717
Thermal Analysis of Drugs and Drug Products / <i>Daniëlle Giron</i>	3726
Titrimetry / <i>Vesa Virtanen</i>	3752
Tonicity / <i>Jaymin C. Shah</i>	3768
Tooling for Tableting / <i>Annette Bauer-Brandl</i>	3782
Trace Level Impurity Analysis / <i>Daniel L. Norwood, Fenghe Qiu, and James O. Mullis</i>	3797
Transdermal Delivery: Anatomical Site Influence / <i>Nora Y.K. Chew,</i> <i>Nina F. Wilkins, and Barrie C. Finnin</i>	3814
Transdermal Delivery: Sonophoresis / <i>Samir S. Mitragotri, Hua Tang,</i> <i>E. Daniel Blankschtein, and Robert Langer</i>	3828
Transdermal Delivery: Technologies / <i>S. Kevin Li</i>	3843
Ultrasonic Nebulizers / <i>Kevin M.G. Taylor and Orla McCallion</i>	3854
Unit Processes in Pharmacy: Fundamentals / <i>Anthony J. Hickey and David Ganderton</i>	3862
Unit Processes in Pharmacy: Operations / <i>Anthony J. Hickey and David Ganderton</i>	3879
Vaccines and Other Immunological Products / <i>Suresh K. Mittal, Harm HogenEsch, and</i> <i>Kinam Park</i>	3908
Validation of Pharmaceutical Processes / <i>Robert A. Nash</i>	3928
Veterinary Dosage Forms / <i>J. Desmond Baggot</i>	3941
Veterinary Pharmaceuticals: Factors Influencing Their Development and Use / <i>Marilyn N. Martinez, Laura Hungerford, and Mark G. Papich</i>	3978
Viral Inactivation Issues in Aseptically Processed Parenterals / <i>J. Hotta, A. Klos,</i> <i>S. Petteway, Jr., and D. Pifat</i>	3997
Virtual Screening / <i>Tímea Polgár and György M. Keserü</i>	4013
Water for Pharmaceuticals / <i>Leonid Shnayder</i>	4039
Water Sorption of Drugs and Dosage Forms / <i>Mark J. Kontny and James J. Connors</i>	4049
Waxes / <i>Roland A. Bodmeier</i>	4066
Wet Granulation: End-Point Determination and Scale-Up / <i>Michael Levin</i>	4078
World Health Organization (WHO): Global Harmonization of Requirements for Medicinal Products / <i>Juhana E. Idanpaan-Heikkilä</i>	4099
X-Ray Powder Diffractometry / <i>Raj Suryanarayanan and Suneel Rastogi</i>	4103
Zeta Potential / <i>Luk Chiu Li and Youqin Tian</i>	4117
Index	II

Topical Table of Contents

Analytical Methods

Chromatographic Methods

Chromatographic Methods of Analysis: Gas Chromatography / Isadore Kanfer, Roderick B. Walker, and Michael F. Skinner	463
Chromatographic Methods of Analysis: High Performance Liquid Chromatography / R. Raghavan and Jose C. Joseph	526
Chromatographic Methods of Analysis: Thin Layer Chromatography / Joseph Sherma	538

Electroanalytical Methods

Electroanalytical Methods of Analysis: Polarography and Voltammetry / A. David Woolfson	1490
Electroanalytical Methods of Analysis: Potentiometry / Karel Vytras	1502
Electrochemical Detection for Pharmaceutical Analysis / Craig E. Lunte and Damon Osbourn	1516

Miscellaneous Methods

Analytical Procedures: Validation / Joachim Ermer and John S. Landy	92
Biologic Fluids: Analysis / Stephen G. Schulman, Judith A. Davis, and Gayle A. Brazeau	194
Chiroptical Analytical Methods / Neil Purdie	445
Good Laboratory Practices (GLPs): An Overview / Nigel J. Dent	1931
Headspace Oxygen Analysis in Pharmaceutical Products / Allen C. Templeton and Robert A. Reed	1967
Drug Delivery Systems: Neutron Scattering Studies / M. Jayne Lawrence and David J. Barlow	1049
Laboratory Information Management System (LIMS) / Siri H. Segalstad	2164
Metabolite Identification in Drug Discovery / Kathleen A. Cox, Nigel Clarke, and Diane Rindgen	2262
Titrimetry / Vesa Virtanen	3752
Trace Level Impurity Analysis / Daniel L. Norwood, Fenghe Qiu, and James O. Mullis	3797

Radiochemical Methods

Enzyme Immunoassay and Related Bioanalytical Methods / John W.A. Findlay and Ira Das	1566
Immunoassay / Stephen G. Schulman and G.J.P.J. Beernink	2048
Radiochemical Methods of Analysis / R. Raghavan and Jose C. Joseph	3082
Radiolabeling of Pharmaceutical Aerosols and Gamma Scintigraphic Imaging for Lung Deposition / Hak-Kim Chan, Stefan Eberl, and William Glover	3094

Analytical Methods (*cont'd.*)

Spectroscopic Methods

Flame Photometry / Thomas M. Nowak	1759
Solid-State NMR in the Characterization of Pharmaceutical Formulations / Eric J. Munson and Joseph W. Lubach	3297
Spectroscopic Methods of Analysis: Atomic Absorption and Emission Spectrophotometry / John P. Oberdier	3367
Spectroscopic Methods of Analysis: Diffuse Reflectance Spectroscopy / Herbert Michael Heise	3375
Spectroscopic Methods of Analysis: Fluorescence Spectroscopy / Stephen G. Schulman and Jeffrey A. Hughes	3387
Spectroscopic Methods of Analysis: Infrared Spectroscopy / Marilyn D. Duerst	3405
Spectroscopic Methods of Analysis: Mass Spectrometry / Mike S. Lee	3419
Spectroscopic Methods of Analysis: Near-Infrared Spectrometry / Emil W. Ciurczak	3434
Spectroscopic Methods of Analysis: Nuclear Magnetic Resonance Spectroscopy / Thomas M. O'Connell and Kevin L. Facchine	3440
Spectroscopic Methods of Analysis: Ultraviolet and Visible Spectrophotometry / R. Raghavan and Jose C. Joseph	3460
Tablet Evaluation Using Near-Infrared Spectroscopy / Christopher T. Rhodes and Karen Morisseau	3630

Thermal Methods

Calorimetry in Pharmaceutical Research and Development / Sophie-Dorothée Clas, Chad R. Dalton, and Bruno C. Hancock	393
Thermal Analysis of Drugs and Drug Products / Daniëlle Giron	3726

Bioavailability and Bioequivalence

Absorption Enhancers / J. P. Remon	13
Absorption of Drugs / Peter G. Welling	19
Bioavailability of Drugs and Bioequivalence / James T. Dalton and Charles R. Yates	164
Biopharmaceutics / Leon Shargel and Andrew B.C. Yu	208
Biotransformation of Drugs / Les F. Chasseaud and D. R. Hawkins	310
Generic Drugs and Generic Equivalency / Arthur H. Kibbe	1891
Salt Forms: Pharmaceutical Aspects / Owen I. Corrigan	3177

Biotechnology, Biological Products, and Biological Applications

Biologic Fluids: Analysis / Stephen G. Schulman, Judith A. Davis, and Gayle A. Brazeau	194
Biosynthesis of Drugs / Geoffrey A. Cordell and Kyung Hee Lee	228
Biotechnology and Biological Preparations / Ronald P. Evens	258
Biotechnology-Derived Drug Products: Formulation Development / Mary E.M. Cromwell	281
Biotechnology-Derived Drug Products: Stability Testing, Filling, and Packaging / Mary E.M. Cromwell	302
Blood Substitutes: Fluorocarbon Approach / Jean G. Riess	335

Blood Substitutes: Hemoglobin-Based Oxygen Carriers / Deanna J. Nelson	353
Colloids and Colloid Drug Delivery System / Diane J. Burgess	636
DNA Probes for the Identification of Microbes / Wayne P. Olson	929
Drug Delivery: Monoclonal Antibodies / John B. Cannon, Ho-Wah Hui, and Pramod K. Gupta	1132
Drug Delivery: Monoclonal Antibodies in Imaging and Therapy / Ban-An Khaw	1149
Enzyme Immunoassay and Related Bioanalytical Methods / John W.A. Findlay and Ira Das	1566
Fractal Geometry in Pharmaceutical and Biological Applications / P. Tang, Hak-Kim Chan, and Judy A. Raper	1791
Genetic Aspects of Drug Development / Werner Kalow	1897
Immunoassay / Stephen G. Schulman and G.J.P.J. Beernink	2048
Lead Optimization in Pharmaceutical Development: Molecular and Cellular Approaches / C. K. Atterwill and M. G. Wing	2192
Peptides and Proteins: Buccal Absorption / Ashim K. Mitra, Hemant H. Alur, and Thomas P. Johnston	2664
Peptides and Proteins: Nasal Absorption / Takahiro Morita and Hiroshi Yamahara	2678
Peptides and Proteins: Non-Invasive Delivery / Michael R. DeFelippis, Muppalla Sukumar, and Natarajan Rajagopalan	2692
Peptides and Proteins: Oral Absorption / Eugene J. McNally and Jung Y. Park	2713
Peptides and Proteins: Pulmonary Absorption / Igor Gonda	2731
Peptides and Proteins: Transdermal Absorption / Richard H. Guy, M. Begoña Delgado-Charro, and Diego Marro	2741
Pharmacogenomics and Genomic Technologies / Daniel A. Brazeau	2794
Plants as Drugs / Christine K. O'Neil and Charles W. Fetrow	2901
Proteomics: Pharmaceutical Applications / A. Ian Smith	3041
Vaccines and Other Immunological Products / Suresh K. Mittal, Harm HogenEsch, and Kinam Park	3908

Chemical Properties Associated with Pharmaceutical Systems

Autoxidation and Antioxidants / John M. Pezzuto and Eun Jung Park	139
Biosynthesis of Drugs / Geoffrey A. Cordell and Kyung Hee Lee	228
Biotechnology and Biological Preparations / Ronald P. Evens	258
Corrosion of Pharmaceutical Equipment / Paul K. Whitcraft	782
Dendrimers / Antony D'Emanuele, David Attwood, and Ragheb Abu-Rmaileh	872
Drug Design: Basic Principles and Applications / Jacques H. Poupaert	1362
Drug Master Files / C. Jeanne Taborsky and Brian James Reamer	1401
Gelatin-Containing Formulations: Changes in Dissolution Characteristics / Saranjit Singh and Sariputta P. Pakhale	1861
Hydrolysis of Drugs / Jason M. LePree and Kenneth A. Connors	2040
Isomerism / Thomas N. Riley, Jack DeRuiter, William R. Ravis, and C. Randall Clark	2142
Lead Optimization in Pharmaceutical Development: Molecular and Cellular Approaches / C. K. Atterwill and M. G. Wing	2192
Photodecomposition of Drugs / Hanne Hjorth Tonnesen	2859
Process Chemistry in the Pharmaceutical Industry / Kumar G. Gadamasetti and Ambarish K. Singh	2993
Salt Forms: Pharmaceutical Aspects / Owen I. Corrigan	3177

Clinical Aspects of Drug Development and Use

Adverse Drug Reactions / <i>Therese I. Poirier and Robert L. Maher, Jr.</i>	46
Advertising and Promotion of Prescription and Over-the-Counter Drug Products / <i>Wayne L. Pines</i>	57
Alternative Medicines / <i>Kristi L. Lenz</i>	66
Clinical Data Management Systems / <i>Samuel V. Givens, Debra Barnes, Victoria Imber, and Barbara Perry</i>	551
Clinical Evaluation of Drugs / <i>Lynda Sutton, Allen Cato, and Allen Cato III</i>	560
Clinical Pharmacokinetics and Pharmacodynamics / <i>Leslie Z. Benet and Laviero Mancinelli</i>	572
Clinical Supplies Manufacture: GMP Considerations / <i>David L. Chesney and Mark L. Balboni</i>	591
Dosage Regimens and Dose-Response / <i>Chyung S. Cook and Aziz Karim</i>	1012
Drug Abuse / <i>Richard B. Seymour and David E. Smith</i>	1038
Drug Delivery: Monoclonal Antibodies in Imaging and Therapy / <i>Ban-An Khaw</i>	1149
Drug Delivery: Tumor-Targeted Systems / <i>Yu Li and Chao-Pin Lee</i>	1326
Good Clinical Practices (GCPs): An Overview / <i>Richard A. Guarino</i>	1925
Medication Errors / <i>Diane D. Cousins</i>	2243
Orphan Drugs / <i>Carolyn H. Asbury</i>	2468
Vaccines and Other Immunological Products / <i>Suresh K. Mittal, Harm HogenEsch, and Kinam Park</i>	3908

Computer Use in Pharmaceutical Technology

Computer Systems Validation / <i>Orlando Lopez</i>	707
Computer-Assisted Drug Design / <i>J. Phillip Bowen and Michael Cory</i>	714
Computers in Pharmaceutical Technology / <i>Onkaram Basavapathruni</i>	732
Neural Computing and Formulation Optimization / <i>Elizabeth Colbourn and Raymond C. Rowe</i>	2399
Paperless Documentation Systems / <i>Ellen M. Williams and Michael McKenna</i>	2551
Virtual Screening / <i>Tímea Polgár and György M. Keserü</i>	4013

Dispersed Systems

Emulsions and Microemulsions / <i>Gillian M. Eccleston</i>	1548
Gels and Jellies / <i>Clyde M. Ofner III and Cathy M. Klech-Gelotte</i>	1875
Surfactants in Pharmaceutical Products and Systems / <i>Owen I. Corrigan and Anne Marie Healy</i>	3583
Suspensions / <i>Robert A. Nash</i>	3597
Zeta Potential / <i>Luk Chiu Li and Youqin Tian</i>	4117

Drug Delivery

Absorption of Drugs / <i>Peter G. Welling</i>	19
Amorphous Pharmaceutical Systems / <i>Bruno C. Hancock</i>	83
Bioavailability of Drugs and Bioequivalence / <i>James T. Dalton and Charles R. Yates</i>	164

Biodegradable Polymers as Drug Carriers / <i>Peter Markland and Victor C. Yang</i>	176
Biopharmaceutics / <i>Leon Shargel and Andrew B.C. Yu</i>	208
Dendrimers / <i>Antony D'Emanuele, David Attwood, and Ragheb Abu-Rmaileh</i>	872
Dosage Regimens and Dose-Response / <i>Chyung S. Cook and Aziz Karim</i>	1012
Drug Delivery Systems: Neutron Scattering Studies / <i>M. Jayne Lawrence and David J. Barlow</i>	1049
Drug Delivery: Buccal Route / <i>James C. McElnay and Carmel M. Hughes</i>	1071
Drug Delivery: Controlled Release / <i>Yie W. Chien and Senshang Lin</i>	1082
Drug Delivery: Fast-Dissolve Systems / <i>Vikas Agarwal, Bhavesh H. Kothari, Derek V. Moe, and Rajendra K. Khankari</i>	1104
Drug Delivery: Liquid Crystals in / <i>Christel C. Mueller-Goymann</i>	1115
Drug Delivery: Monoclonal Antibodies / <i>John B. Cannon, Ho-Wah Hui, and Pramod K. Gupta</i>	1132
Drug Delivery: Monoclonal Antibodies in Imaging and Therapy / <i>Ban-An Khaw</i>	1149
Drug Delivery: Mucoadhesive Hydrogels / <i>Hans E. Junginger, J. Coos Verhoef, and Maya Thanou</i>	1169
Drug Delivery: Nanoparticles / <i>Elias Fattal and Christine Vauthier</i>	1183
Drug Delivery: Nasal Route / <i>René Bommer</i>	1201
Drug Delivery: Needle-Free Systems / <i>Toby King</i>	1209
Drug Delivery: Ophthalmic Route / <i>Masood Chowhan, Alan L. Weiner, and Haresh Bhagat</i>	1220
Drug Delivery: Oral Colon-Specific / <i>Vincent H.L. Lee and Suman K. Mukherjee</i>	1228
Drug Delivery: Oral Route / <i>Brahma N. Singh and Kwon H. Kim</i>	1242
Drug Delivery: Parenteral Route / <i>Michael J. Akers</i>	1266
Drug Delivery: Pulmonary Delivery / <i>Michael T. Newhouse</i>	1279
Drug Delivery: Pulsatile Systems / <i>Till Bussemer and Roland A. Bodmeier</i>	1287
Drug Delivery: Rectal Route / <i>J. Howard Rytting and Joseph A. Fix</i>	1298
Drug Delivery: Topical and Transdermal Routes / <i>Kenneth A. Walters</i>	1311
Drug Delivery: Tumor-Targeted Systems / <i>Yu Li and Chao-Pin Lee</i>	1326
Drug Delivery: Vaginal Route / <i>Yie W. Chien and Chi H. Lee</i>	1339
Polymeric Delivery Systems for Poorly Soluble Drugs / <i>Kang Moo Huh, Sang Cheon Lee, Tooru Ooya, and Kinam Park</i>	2913

Dosage Forms

Capsules, Hard / <i>Brian E. Jones</i>	406
Capsules, Soft / <i>David H. Bergstrom, Stephen Tindal, and Wenbin Dang</i>	419
Colloids and Colloid Drug Delivery System / <i>Diane J. Burgess</i>	636
Coprecipitates and Melts / <i>Madhu K. Vadnere</i>	774
Dosage Form Design: A Physicochemical Approach / <i>Michael B. Maurin and Anwar A. Hussain</i>	939
Dosage Forms and Basic Preparations: History / <i>Robert A. Buerki and Gregory J. Higby</i>	948
Dosage Forms: Lipid Excipients / <i>Alan L. Weiner</i>	975
Dosage Forms: Non-Parenterals / <i>Shailesh K. Singh and Venkatesh Naini</i>	988
Dosage Forms: Parenterals / <i>Gayle A. Brazeau, Adam Persky, and Jintana Napaporn</i>	1001
Drug Delivery: Needle-Free Systems / <i>Toby King</i>	1209
Drug Delivery: Pulsatile Systems / <i>Till Bussemer and Roland A. Bodmeier</i>	1287

Drug Delivery (*cont'd.*)

Dosage Forms (*cont'd.*)

Drug Delivery: Tumor-Targeted Systems / Yu Li and Chao-Pin Lee	1326
Effervescent Pharmaceuticals / Nils-Olof Lindberg and Henri Hansson	1454
Emulsions and Microemulsions / Gillian M. Eccleston	1548
Gastro-Retentive Systems / Amnon Hoffman and Bashir A. Qadri	1850
Geriatric Dosing and Dosage Forms / Cheryl A. Wiens and Carol A. Borynec	1905
Hydrogels / María Dolores Blanco, Rosa Maria Olmo, and José María Teijón	2021
Liquid Oral Preparations / Jagdish Parasrampur and Stephen William Pitt	2216
Lozenges / Robert W. Mendes and Hridaya Bhargava	2231
Metered Dose Inhalers / Sandy J.M. Munro and Alan L. Cripps	2269
Pediatric Dosing and Dosage Forms / Rosalie Segraves	2629
Powders as Dosage Forms / Jean-Marc Aiache and Erick Beyssac	2971
Suspensions / Robert A. Nash	3597
Ultrasonic Nebulizers / Kevin M.G. Taylor and Orla McCallion	3854
Veterinary Dosage Forms / J. Desmond Baggot	3941

Dosage Forms, Miscellaneous

Alternative Medicines / Kristi L. Lenz	66
Cosmetics and Their Relation to Drugs / Martin M. Rieger	798
Non-Prescription Drugs / Sujit S. Sansgiry, Lynn Simpson, Gauri Shringarpure, and Amit Kulkarni	2413
Nutraceutical Supplements / G. Brian Lockwood	2431

Drug Absorption, Distribution, Metabolism, and Elimination

Bioavailability of Drugs and Bioequivalence / James T. Dalton and Charles R. Yates	164
Biotransformation of Drugs / Les F. Chasseaud and D. R. Hawkins	310
Clinical Pharmacokinetics and Pharmacodynamics / Leslie Z. Benet and Laviero Mancinelli	572
Drug Interactions / Daniel A. Hussar	1392
Metabolite Identification in Drug Discovery / Kathleen A. Cox, Nigel Clarke, and Diane Rindgen	2262
Prodrug Design / Bernard Testa and Joachim Mayer	3008

Routes of Administration and Physiological Factors

Drug Delivery: Buccal Route / James C. McElnay and Carmel M. Hughes	1071
Drug Delivery: Mucoadhesive Hydrogels / Hans E. Junginger, J. Coos Verhoef, and Maya Thanou	1169
Drug Delivery: Nasal Route / René Bommer	1201
Drug Delivery: Ophthalmic Route / Masood Chowhan, Alan L. Weiner, and Haresh Bhagat	1220
Drug Delivery: Oral Colon-Specific / Vincent H.L. Lee and Suman K. Mukherjee	1228
Drug Delivery: Oral Route / Brahma N. Singh and Kwon H. Kim	1242

Drug Delivery: Parenteral Route / Michael J. Akers	1266
Drug Delivery: Pulmonary Delivery / Michael T. Newhouse	1279
Drug Delivery: Rectal Route / J. Howard Rytting and Joseph A. Fix	1298
Drug Delivery: Topical and Transdermal Routes / Kenneth A. Walters	1311
Drug Delivery: Vaginal Route / Yie W. Chien and Chi H. Lee	1339
Otic Preparations / William H. Slattery III	2475
Peptides and Proteins: Buccal Absorption / Ashim K. Mitra, Hemant H. Alur, and Thomas P. Johnston	2664
Peptides and Proteins: Nasal Absorption / Takahiro Morita and Hiroshi Yamahara	2678
Peptides and Proteins: Non-Invasive Delivery / Michael R. DeFelippis, Muppalla Sukumar, and Natarajan Rajagopalan	2692
Peptides and Proteins: Oral Absorption / Eugene J. McNally and Jung Y. Park	2713
Peptides and Proteins: Pulmonary Absorption / Igor Gonda	2731
Peptides and Proteins: Transdermal Absorption / Richard H. Guy, M. Begoña Delgado-Charro, and Diego Marro	2741
Physiological Factors Affecting Oral Drug Delivery / Clive G. Wilson, Bridget O'Mahony, and Blythe Lindsay	2866
Transdermal Delivery: Anatomical Site Influence / Nora Y.K. Chew, Nina F. Wilkins, and Barrie C. Finnin	3814
Transdermal Delivery: Technologies / S. Kevin Li	3843
Transdermal Delivery: Sonophoresis / Samir S. Mitragotri, Hua Tang, E. Daniel Blankschtein, and Robert Langer	3828

Drug Development

Animals in Drug Development / Farrel L. Fort	114
Calorimetry in Pharmaceutical Research and Development / Sophie-Dorothée Clas, Chad R. Dalton, and Bruno C. Hancock	393
Clinical Evaluation of Drugs / Lynda Sutton, Allen Cato, and Allen Cato III	560
Drug Development Management / James E. Tingstad	1370
Expert Systems in Pharmaceutical Product Development / Raymond C. Rowe and Ronald J. Roberts	1663
Genetic Aspects of Drug Development / Werner Kalow	1897
In Vitro–In Vivo Correlation / J.-M. Cardot and Erick Beyssac	2062
Lead Optimization in Pharmaceutical Development: Molecular and Cellular Approaches / C. K. Atterwill and M. G. Wing	2192
Outsourcing / Duane B. Lakings	2486
Patents: International Perspective / Stuart R. Suter and Peter J. Giddings	2604
Patents: United States Perspective / Lorie Ann Morgan and Jeffrey Tidwell	2616
Pharmacokinetic/Pharmacodynamic Modeling and Simulations in Drug Development / Dawei Xuan and Sally Y. Choe	2802
Pharmacokinetics: Effects of Food and Fasting / Rajesh Krishna and Bradford K. Jensen	2816
Prodrug Design / Bernard Testa and Joachim Mayer	3008
RNAi in Drug Development / Dmitry Samarsky, Shelley Hough, Adam Harris, Eugene Carstea, and Peter Welch	3147
Veterinary Pharmaceuticals: Factors Influencing Their Development and Use / Marilyn N. Martinez, Laura Hungerford, and Mark G. Papich	3978

Drug Discovery

Computer-Assisted Drug Design / <i>J. Phillip Bowen and Michael Cory</i>	714
Drug Design: Basic Principles and Applications / <i>Jacques H. Poupaert</i>	1362
Economic Characteristics of the R&D Intensive Pharmaceutical Industry / <i>Douglas L. Cocks</i>	1450
Metabolite Identification in Drug Discovery / <i>Kathleen A. Cox, Nigel Clarke, and Diane Rindgen</i>	2262
Patents: International Perspective / <i>Stuart R. Suter and Peter J. Giddings</i>	2604
Patents: United States Perspective / <i>Lorie Ann Morgan and Jeffrey Tidwell</i>	2616
Receptors for Drugs: Discovery in the Post-Genomic Era / <i>Jeffrey M. Herz and William J. Thomsen</i>	3108
Virtual Screening / <i>Tímea Polgár and György M. Keserü</i>	4013

Drug Dissolution and In Vivo/In Vitro Correlations

Dissolution and Dissolution Testing / <i>A. Mark Dyas and Utpal U. Shah</i>	908
Gelatin-Containing Formulations: Changes in Dissolution Characteristics / <i>Saranjit Singh and Sariputta P. Pakhale</i>	1861
In Vitro–In Vivo Correlation / <i>J.-M. Cardot and Erick Beyssac</i>	2062

Equipment Used in Pharmaceutical Development and Manufacturing

Continuous Processing of Pharmaceuticals / <i>J. P. Remon and C. Vervaet</i>	743
Corrosion of Pharmaceutical Equipment / <i>Paul K. Whitcraft</i>	782
Electrical Power Systems for Pharmaceutical Equipment / <i>Joseph Maida</i>	1482
Equipment Cleaning / <i>Destin A. LeBlanc</i>	1580
Extrusion and Extruders / <i>J. M. Newton</i>	1712
Fluid Bed Processes for Forming Functional Particles / <i>Yoshinobu Fukumori and Hideki Ichikawa</i>	1773
Homogenization and Homogenizers / <i>Shailesh K. Singh and Venkatesh Naini</i>	1996
Isolators for Pharmaceutical Application / <i>Gordon J. Farquharson</i>	2133
Laminar Airflow Equipment: Applications and Operation / <i>Gregory F. Peters</i>	2171
Materials of Construction for Pharmaceutical Equipment / <i>Michelle M. Gonzalez</i>	2237
Roller Compaction Technology for the Pharmaceutical Industry / <i>Ronald W. Miller and Paul J. Sheskey</i>	3159
Tablet Compression: Machine Theory, Design, and Process Troubleshooting / <i>Michael J. Bogda</i>	3611
Tablet Press Instrumentation / <i>Michael Levin</i>	3684
Tooling for Tableting / <i>Annette Bauer-Brandl</i>	3782

Excipient Use and Testing in Drug Development

Dosage Forms: Lipid Excipients / <i>Alan L. Weiner</i>	975
Excipients for Pharmaceutical Dosage Forms / <i>Patrick J. Crowley and Luigi G. Martini</i>	1609
Excipients: Parenteral Dosage Forms and Their Role / <i>Sandeep Nema, Ron J. Brendel, and Richard Washkuhn</i>	1622

Excipients: Powders and Solid Dosage Forms / Hak-Kim Chan and Nora Y.K. Chew	1646
Excipients: Safety Testing / Marshall Steinberg and Florence K. Kinoshita	1656
Pharmaceutical Excipient Testing: Regulatory and Preclinical Perspective / Paul Baldrick	2771
Solubilizing Excipients in Pharmaceutical Formulations / Robert G. Strickley	3334
Starches and Starch Derivatives / Ann W. Newman, Ronald L. Mueller, Imre M. Vitez, and Chris C. Kiesnowski	3476
Super Disintegrants: Characterization and Function / Larry L. Augsburger, Albert W. Brzezczko, Umang Shah, and Huijeong Ashley Hahm	3553
Waxes / Roland A. Bodmeier	4066

Formulation Aspects of Pharmaceutical Technology

General Formulation Aspects

Biopharmaceutics / Leon Shargel and Andrew B.C. Yu	208
Biotechnology-Derived Drug Products: Formulation Development / Mary E.M. Cromwell	281
Coloring Agents for Use in Pharmaceuticals / David R. Schoneker	648
Dental Products / Sebastian G. Ciancio	891
Dosage Form Design: A Physicochemical Approach / Michael B. Maurin and Anwar A. Hussain	939
Excipients for Pharmaceutical Dosage Forms / Patrick J. Crowley and Luigi G. Martini	1609
Expert Systems in Pharmaceutical Product Development / Raymond C. Rowe and Ronald J. Roberts	1663
Flavors and Flavor Modifiers / Thomas L. Reiland and John M. Lipari	1763
Fractal Geometry in Pharmaceutical and Biological Applications / P. Tang, Hak-Kim Chan, and Judy A. Raper	1791
Neural Computing and Formulation Optimization / Elizabeth Colbourn and Raymond C. Rowe	2399
Optimization Methods / Gareth A. Lewis	2452
Packaging Materials: Glass / Claudia C. Okeke and Desmond G. Hunt	2508
Salt Forms: Pharmaceutical Aspects / Owen I. Corrigan	3177
Solid-State NMR in the Characterization of Pharmaceutical Formulations / Eric J. Munson and Joseph W. Lubach	3297
Supercritical Fluid Technology in Pharmaceutical Research / Aaron S. Mayo and Uday B. Kompella	3568
Surfactants in Pharmaceutical Products and Systems / Owen I. Corrigan and Anne Marie Healy	3583
Tonicity / Jaymin C. Shah	3768
Veterinary Pharmaceuticals: Factors Influencing Their Development and Use / Marilyn N. Martinez, Laura Hungerford, and Mark G. Papich	3978
Waxes / Roland A. Bodmeier	4066

Formulation Aspects Relevant to Liquids and Semi-Solids

Buffers, Buffering Agents, and Ionic Equilibria / Harry G. Brittain	385
Coacervation and Phase Separation / Bruno Gander, Maria Jose Blanco-Prieto, C. Thomasin, Ch. Wandrey, and D. Hunkeler	600
Complexation: Cyclodextrins / Gerold Mosher and Diane O. Thompson	671
Complexation: Non-Cyclodextrins / Galina N. Kalinkova	697

Formulation Aspects of Pharmaceutical Technology (*cont'd.*)

Formulation Aspects Relevant to Liquids and Semi-Solids (cont'd.)

Cosolvents and Cosolvency / Joseph T. Rubino	806
Dosage Forms: Lipid Excipients / Alan L. Weiner	975
Drug Delivery: Liquid Crystals in / Christel C. Mueller-Goymann	1115
Excipients: Parenteral Dosage Forms and Their Role / Sandeep Nema, Ron J. Brendel, and Richard Washkuhn	1622
Gels and Jellies / Clyde M. Ofner III and Cathy M. Klech-Gelotte	1875
Inhalation: Liquids / Michael E. Placke, Jeffrey Ding, and William C. Zimlich, Jr.	2092
Iontophoresis / J. Bradley Phipps, Erik R. Scott, J. Richard Gyory, and Rama V. Padmanabhan	2119
Rheology of Pharmaceutical Systems / Fridrun Podczek	3128
Solubilization of Drugs in Aqueous Media / Paul B. Myrdal and Samuel H. Yalkowsky	3311
Solubilizing Excipients in Pharmaceutical Formulations / Robert G. Strickley	3334

Formulation Aspects Relevant to Particles and Solids

Adsorption at Solid Surfaces: Pharmaceutical Applications / Hong Wen	34
Amorphous Pharmaceutical Systems / Bruno C. Hancock	83
Cocrystals: Design, Properties and Formation Mechanisms / Naír Rodríguez-Hornedo, Sarah J. Nehm, and Adivaraha Jayasankar	615
Cooling Processes and Congealing / Richard Turton and Xiu Xiu Cheng	761
Coprecipitates and Melts / Madhu K. Vadnere	774
Crystal Habit Changes and Dosage Form Performance / A. K. Tiwary	820
Crystallization: General Principles and Significance on Product Development / Naír Rodríguez-Hornedo, Ron C. Kelly, Brent D. Sinclair, and Jonathan M. Miller	834
Dissolution and Dissolution Testing / A. Mark Dyas and Utpal U. Shah	908
Drug Delivery: Controlled Release / Yie W. Chien and Senshang Lin	1082
Drug Delivery: Fast-Dissolve Systems / Vikas Agarwal, Bhavesh H. Kothari, Derek V. Moe, and Rajendra K. Khankari	1104
Dry Powder Aerosols: Emerging Technologies / Hak-Kim Chan and Nora Y.K. Chew	1428
Excipients: Powders and Solid Dosage Forms / Hak-Kim Chan and Nora Y.K. Chew	1646
Film Coating of Oral Solid Dosage Forms / Linda A. Felton	1729
Gelatin-Containing Formulations: Changes in Dissolution Characteristics / Saranjit Singh and Sariputta P. Pakhale	1861
Hot-Melt Extrusion Technology / Jim W. McGinity, Michael A. Repka, John J. Koleng, Jr., and Feng Zhang	2004
Inhalation: Dry Powder / Lynn Van Campen and Geraldine Venthoye	2077
Melt Processes for Oral Solid Dosage Forms / Paul W.S. Heng and Tin Wui Wong	2257
Microencapsulation Technology / Kinam Park and Yoon Yeo	2315
Microsphere Technology and Applications / Diane J. Burgess and Anthony J. Hickey	2328
Polymorphism: Pharmaceutical Aspects / Harry G. Brittain	2935
Solids: Flow Properties / Stephen A. Howard	3275
Starches and Starch Derivatives / Ann W. Newman, Ronald L. Mueller, Imre M. Vitez, and Chris C. Kiesnowski	3476

Super Disintegrants: Characterization and Function / Larry L. Augsburger, Albert W. Brzezczko, Umang Shah, and Huijeong Ashley Hahm	3553
Tablet Formulation / Larry L. Augsburger and Mark J. Zellhofer	3641
Tablet Testing / Saeed A. Qureshi	3707
X-Ray Powder Diffractometry / Raj Suryanarayanan and Suneel Rastogi	4103
Zeta Potential / Luk Chiu Li and Youqin Tian	4117

Genomics and Drug Discovery and Development

Genetic Aspects of Drug Development / Werner Kalow	1897
Pharmacogenomics and Genomic Technologies / Daniel A. Brazeau	2794
Proteomics: Pharmaceutical Applications / A. Ian Smith	3041
Receptors for Drugs: Discovery in the Post-Genomic Era / Jeffrey M. Herz and William J. Thomsen	3108
RNAi in Drug Development / Dmitry Samarsky, Shelley Hough, Adam Harris, Eugene Carstea, and Peter Welch	3147

Good Clinical, Laboratory, and Manufacturing Practices

Clinical Supplies Manufacture: GMP Considerations / David L. Chesney and Mark L. Balboni	591
Food and Drug Administration: Role in Drug Regulation / Roger L. Williams	1779
Good Clinical Practices (GCPs): An Overview / Richard A. Guarino	1925
Good Laboratory Practices (GLPs): An Overview / Nigel J. Dent	1931
Good Manufacturing Practices (GMPs): An Overview / Ira R. Berry	1941

Management of Pharmaceutical Systems and Procedures

Clinical Data Management Systems / Samuel V. Givens, Debra Barnes, Victoria Imber, and Barbara Perry	551
Drug Development Management / James E. Tingstad	1370
Expert Systems in Pharmaceutical Product Development / Raymond C. Rowe and Ronald J. Roberts	1663
Laboratory Information Management System (LIMS) / Siri H. Segalstad	2164
Outsourcing / Duane B. Lakings	2486
Paperless Documentation Systems / Ellen M. Williams and Michael McKenna	2551
Project Management / Jerome J. Groen and Cara R. Frosch	3015
Quality Systems Management / Gary C. Harbour and Robert G. Kieffer	3075

Manufacture of Pharmaceutical Products

Capsules, Hard / Brian E. Jones	406
Capsules, Soft / David H. Bergstrom, Stephen Tindal, and Wenbin Dang	419
Clinical Supplies Manufacture: GMP Considerations / David L. Chesney and Mark L. Balboni	591
Continuous Processing of Pharmaceuticals / J. P. Remon and C. Vervaet	743

Manufacture of Pharmaceutical Products (*cont'd.*)

Contract Manufacturing / <i>Duncan E. McVean</i>	750
Drug Master Files / <i>C. Jeanne Taborsky and Brian James Reamer</i>	1401
Drying and Dryers / <i>Anthony J. Hlinak and Bradley A. Clark</i>	1435
Elastomeric Components for the Pharmaceutical Industry / <i>Edward J. Smith</i>	1466
Electrical Power Systems for Pharmaceutical Equipment / <i>Joseph Maida</i>	1482
Evaporation and Evaporators / <i>David P. Kessler</i>	1600
Extrusion and Extruders / <i>J. M. Newton</i>	1712
Film Coating of Oral Solid Dosage Forms / <i>Linda A. Felton</i>	1729
Fluid Bed Processes for Forming Functional Particles / <i>Yoshinobu Fukumori and Hideki Ichikawa</i>	1773
Freeze Drying, Scale-Up Considerations / <i>Edward H. Trappler</i>	1834
Good Manufacturing Practices (GMPs): An Overview / <i>Ira R. Berry</i>	1941
Handling Hazardous Chemicals and Pharmaceuticals / <i>Antonio Conto</i>	1948
Homogenization and Homogenizers / <i>Shailesh K. Singh and Venkatesh Naini</i>	1996
Mixing and Segregation in Tumbling Blenders / <i>Troy Shinbrot and Fernando J. Muzzio</i>	2352
Packaging Materials: Glass / <i>Claudia C. Okeke and Desmond G. Hunt</i>	2508
Pilot Plant Design / <i>Mickey L. Wells, Samuel B. Balik, Ralph B. Caricofe, Charles W. Crew, Ronald A. Sanfileben, and A. Wayne Wood</i>	2875
Pilot Plant Operation / <i>Mickey L. Wells, A. Wayne Wood, Samuel B. Balik, Ralph B. Caricofe, Ronald A. Sanfileben, and Charles W. Crew</i>	2886
Process Chemistry in the Pharmaceutical Industry / <i>Kumar G. Gadamasetti and Ambarish K. Singh</i>	2993
Roller Compaction Technology for the Pharmaceutical Industry / <i>Ronald W. Miller and Paul J. Sheskey</i>	3159
Scale-Up and Post Approval Changes (SUPAC) / <i>Jerome P. Skelly</i>	3188
Scale-Up of Solid Dosage Forms / <i>Colleen E. Ruegger, Alan Royce, Matthew J. Mollan, Jr., Robert Wagner, Stephen Valazza, and Mark Mecadon</i>	3193
Tablet Manufacture / <i>Norman Anthony Armstrong</i>	3653
Tablet Manufacture by Direct Compression / <i>Norman Anthony Armstrong</i>	3673
Tablet Press Instrumentation / <i>Michael Levin</i>	3684
Technology Transfer Considerations for Pharmaceuticals / <i>Ira R. Berry</i>	3717
Unit Processes in Pharmacy: Fundamentals / <i>Anthony J. Hickey and David Ganderton</i>	3862
Unit Processes in Pharmacy: Operations / <i>Anthony J. Hickey and David Ganderton</i>	3879

Oral Delivery of Drugs

Drug Delivery: Buccal Route / <i>James C. McElnay and Carmel M. Hughes</i>	1071
Drug Delivery: Oral Colon-Specific / <i>Vincent H.L. Lee and Suman K. Mukherjee</i>	1228
Drug Delivery: Oral Route / <i>Brahma N. Singh and Kwon H. Kim</i>	1242
Film Coating of Oral Solid Dosage Forms / <i>Linda A. Felton</i>	1729
Gastro-Retentive Systems / <i>Amnon Hoffman and Bashir A. Qadri</i>	1850
Liquid Oral Preparations / <i>Jagdish Parasrampur and Stephen William Pitt</i>	2216
Lozenges / <i>Robert W. Mendes and Hridaya Bhargava</i>	2231

Peptides and Proteins: Oral Absorption / Eugene J. McNally and Jung Y. Park	2713
Physiological Factors Affecting Oral Drug Delivery / Clive G. Wilson, Bridget O'Mahony, and Blythe Lindsay	2866

Organizations Involved in Pharmaceuticals

European Agency for the Evaluation of Medicinal Products (EMA) / David M. Jacobs	1593
Food and Drug Administration: Role in Drug Regulation / Roger L. Williams	1779
Harmonization of Pharmacopeial Standards / Lee T. Grady and Jerome A. Halperin	1955
Health Care Systems: Outside the United States / Albert I. Wertheimer and Sheldon X. Kong	1977
Health Care Systems: Within the United States / Henri R. Manasse, Jr.	1985
Pharmacopeial Standards: European Pharmacopeia / Agnès Artiges	2829
Pharmacopeial Standards: Japanese Pharmacopeia / Mitsuru Uchiyama	2836
Pharmacopeial Standards: United States Pharmacopeia and National Formulary / Lee T. Grady	2841
World Health Organization (WHO): Global Harmonization of Requirements for Medicinal Products / Juhana E. Idanpaan-Heikkilä	4099

Packaging of Pharmaceuticals

Blow-Fill-Seal: Advanced Aseptic Processing / Deborah J. Jones	378
Elastomeric Components for the Pharmaceutical Industry / Edward J. Smith	1466
Extractables and Leachables in Drugs and Packaging / Daniel L. Norwood, Alice T. Granger, and Diane M. Paskiet	1693
Packaging Materials: Glass / Claudia C. Okeke and Desmond G. Hunt	2508
Packaging Systems: Compendial Requirements / Claudia C. Okeke, Desmond G. Hunt, Nicholas Mohr, Thomas Medwick, Eric B. Sheinin, and Roger L. Williams	2526
Water Sorption of Drugs and Dosage Forms / Mark J. Kontny and James J. Connors	4049

Parenteral Delivery of Drugs

Dosage Forms: Parenterals / Gayle A. Brazeau, Adam Persky, and Jintana Napaporn	1001
Drug Delivery: Needle-Free Systems / Toby King	1209
Drug Delivery: Parenteral Route / Michael J. Akers	1266
Pyrogens and Endotoxin Detection / James F. Cooper	3052
Sterilization: Dry Heat / Andrea Chieppo and Thomas Kupiec	3512
Sterilization: Ethylene Oxide / Terezinha de Jesus Andreo Pinto	3519
Sterilization: Moist Heat / Dario Pistolesi	3529
Sterilization: Radiation / Stephen G. Schulman and Phillip M. Achey	3540
Viral Inactivation Issues in Aseptically Processed Parenterals / J. Hotta, A. Klos, S. Petteway, Jr., and D. Pifat	3997

Particle Size Characterization, Modification and Significance

Colloids and Colloid Drug Delivery System / Diane J. Burgess	636
Crystal Habit Changes and Dosage Form Performance / A. K. Tiwary	820

Particle Size Characterization, Modification and Significance (*cont'd.*)

Crystallization: General Principles and Significance on Product Development / <i>Nair Rodríguez-Hornedo, Ron C. Kelly, Brent D. Sinclair, and Jonathan M. Miller</i>	834
Crystallization: Particle Size Control / <i>Richard D. Braatz, Mitsuko Fujiwara, Thomas J. Wubben, and Effendi Rusli</i>	858
Drug Delivery: Nanoparticles / <i>Elias Fattal and Christine Vauthier</i>	1183
Dry Powder Aerosols: Emerging Technologies / <i>Hak-Kim Chan and Nora Y.K. Chew</i>	1428
Microsphere Technology and Applications / <i>Diane J. Burgess and Anthony J. Hickey</i>	2328
Milling of Active Pharmaceutical Ingredients / <i>Elizabeth S. Fisher</i>	2339
Nanoparticle Engineering / <i>Robert O. Williams III and Jason M. Vaughn</i>	2384
Particle Engineering / <i>Miriam K. Franchini</i>	2567
Particle-Size Characterization / <i>Brian H. Kaye</i>	2582
Pelletization Techniques / <i>Isaac Ghebre-Sellassie and Axel Knoch</i>	2651
Secondary Electron Microscopy in Pharmaceutical Technology / <i>Peter C. Schmidt</i>	3217
Supercritical Fluid Technology in Pharmaceutical Research / <i>Aaron S. Mayo and Uday B. Kompella</i>	3568
X-Ray Powder Diffractometry / <i>Raj Suryanarayanan and Suneel Rastogi</i>	4103

Peptides and Proteins in Pharmaceuticals

Genetic Aspects of Drug Development / <i>Werner Kalow</i>	1897
Peptides and Proteins: Buccal Absorption / <i>Ashim K. Mitra, Hemant H. Alur, and Thomas P. Johnston</i>	2664
Peptides and Proteins: Nasal Absorption / <i>Takahiro Morita and Hiroshi Yamahara</i>	2678
Peptides and Proteins: Non-Invasive Delivery / <i>Michael R. DeFelippis, Muppalla Sukumar, and Natarajan Rajagopalan</i>	2692
Peptides and Proteins: Oral Absorption / <i>Eugene J. McNally and Jung Y. Park</i>	2713
Peptides and Proteins: Pulmonary Absorption / <i>Igor Gonda</i>	2731
Peptides and Proteins: Transdermal Absorption / <i>Richard H. Guy, M. Begoña Delgado-Charro, and Diego Marro</i>	2741
Pharmacogenomics and Genomic Technologies / <i>Daniel A. Brazeau</i>	2794
Protein Binding of Drugs / <i>Sylvie Laganière and Iain J. McGilveray</i>	3027
Proteomics: Pharmaceutical Applications / <i>A. Ian Smith</i>	3041
Receptors for Drugs: Discovery in the Post-Genomic Era / <i>Jeffrey M. Herz and William J. Thomsen</i>	3108
RNAi in Drug Development / <i>Dmitry Samarsky, Shelley Hough, Adam Harris, Eugene Carstea, and Peter Welch</i>	3147

Pharmacokinetics and Pharmacodynamics

Biotransformation of Drugs / <i>Les F. Chasseaud and D. R. Hawkins</i>	310
Clinical Pharmacokinetics and Pharmacodynamics / <i>Leslie Z. Benet and Laviero Mancinelli</i>	572
Geriatric Dosing and Dosage Forms / <i>Cheryl A. Wiens and Carol A. Borynec</i>	1905
Pediatric Dosing and Dosage Forms / <i>Rosalie Sagraves</i>	2629

Pharmacokinetic/Pharmacodynamic Modeling and Simulations in Drug Development / <i>Dawei Xuan and Sally Y. Choe</i>	2802
Pharmacokinetics: Effects of Food and Fasting / <i>Rajesh Krishna and Bradford K. Jensen</i>	2816
Population Pharmacokinetics / <i>Ene I. Ette, Alaa M. Ahmad, and Paul J. Williams</i>	2946
Protein Binding of Drugs / <i>Sylvie Laganière and Iain J. McGilveray</i>	3027

Physical Properties Associated with Pharmaceutical Systems

Buffers, Buffering Agents, and Ionic Equilibria / <i>Harry G. Brittain</i>	385
Coacervation and Phase Separation / <i>Bruno Gander, Maria Jose Blanco-Prieto,</i> <i>C. Thomasin, Ch. Wandrey, and D. Hunkeler</i>	600
Cocrystals: Design, Properties and Formation Mechanisms / <i>Nair Rodríguez-Hornedo,</i> <i>Sarah J. Nehm, and Adivaraha Jayasankar</i>	615
Complexation: Cyclodextrins / <i>Gerold Mosher and Diane O. Thompson</i>	671
Complexation: Non-Cyclodextrins / <i>Galina N. Kalinkova</i>	697
Cooling Processes and Congealing / <i>Richard Turton and Xiu Xiu Cheng</i>	761
Coprecipitates and Melts / <i>Madhu K. Vadnere</i>	774
Cosolvents and Cosolvency / <i>Joseph T. Rubino</i>	806
Crystal Habit Changes and Dosage Form Performance / <i>A. K. Tiwary</i>	820
Crystallization: General Principles and Significance on Product Development / <i>Nair Rodríguez-Hornedo, Ron C. Kelly, Brent D. Sinclair, and Jonathan M. Miller</i>	834
Crystallization: Particle Size Control / <i>Richard D. Braatz, Mitsuko Fujiwara,</i> <i>Thomas J. Wubben, and Effendi Rusli</i>	858
Dissolution and Dissolution Testing / <i>A. Mark Dyas and Utpal U. Shah</i>	908
Dosage Form Design: A Physicochemical Approach / <i>Michael B. Maurin and</i> <i>Anwar A. Hussain</i>	939
Drug Delivery: Controlled Release / <i>Yie W. Chien and Senshang Lin</i>	1082
Drug Delivery: Fast-Dissolve Systems / <i>Vikas Agarwal, Bhavesh H. Kothari,</i> <i>Derek V. Moe, and Rajendra K. Khankari</i>	1104
Drug Delivery: Liquid Crystals in / <i>Christel C. Mueller-Goymann</i>	1115
Effervescent Pharmaceuticals / <i>Nils-Olof Lindberg and Henri Hansson</i>	1454
Electrostatic Charge in Pharmaceutical Systems / <i>Philip Chi Lip Kwok and</i> <i>Hak-Kim Chan</i>	1535
Fractal Geometry in Pharmaceutical and Biological Applications / <i>P. Tang,</i> <i>Hak-Kim Chan, and Judy A. Raper</i>	1791
Freeze Drying / <i>Michael J. Pikal</i>	1807
Gastro-Retentive Systems / <i>Amnon Hoffman and Bashir A. Qadri</i>	1850
Particle-Size Characterization / <i>Brian H. Kaye</i>	2582
Partition Coefficients / <i>Eric J. Lien and Steven Shijun Ren</i>	2595
Polymorphism: Pharmaceutical Aspects / <i>Harry G. Brittain</i>	2935
Rheology of Pharmaceutical Systems / <i>Fridrun Podczek</i>	3128
Solids: Flow Properties / <i>Stephen A. Howard</i>	3275
Supercritical Fluid Technology in Pharmaceutical Research / <i>Aaron S. Mayo and</i> <i>Uday B. Kompella</i>	3568
Tonicity / <i>Jaymin C. Shah</i>	3768
X-Ray Powder Diffractometry / <i>Raj Suryanarayanan and Suneel Rastogi</i>	4103
Zeta Potential / <i>Luk Chiu Li and Youqin Tian</i>	4117

Polymers used in Pharmaceutical Systems and Technology

Bioabsorbable Polymers / <i>Shalaby W. Shalaby</i>	155
Biodegradable Polymers as Drug Carriers / <i>Peter Markland and Victor C. Yang</i>	176
Dendrimers / <i>Antony D'Emanuele, David Attwood, and Ragheb Abu-Rmaileh</i>	872
Drug Delivery: Mucoadhesive Hydrogels / <i>Hans E. Junginger, J. Coos Verhoef, and Maya Thanou</i>	1169
Elastomeric Components for the Pharmaceutical Industry / <i>Edward J. Smith</i>	1466
Gels and Jellies / <i>Clyde M. Ofner III and Cathy M. Klech-Gelotte</i>	1875
Hydrogels / <i>Mari�a Dolores Blanco, Rosa Maria Olmo, and Jos�� Mari�a Teij��n</i>	2021
Polymeric Delivery Systems for Poorly Soluble Drugs / <i>Kang Moo Huh, Sang Cheon Lee, Tooru Ooya, and Kinam Park</i>	2913
Polymers in Transdermal Delivery Systems / <i>Fumio Kamiyama and Ying-shu Quan</i>	2925

Pulmonary Delivery of Pharmaceuticals

Drug Delivery: Pulmonary Delivery / <i>Michael T. Newhouse</i>	1279
Dry Powder Aerosols: Emerging Technologies / <i>Hak-Kim Chan and Nora Y. K. Chew</i>	1428
Inhalation: Dry Powder / <i>Lynn Van Campen and Geraldine Venthoye</i>	2077
Inhalation: Liquids / <i>Michael E. Placke, Jeffrey Ding, and William C. Zimlich, Jr.</i>	2092
Metered Dose Inhalers / <i>Sandy J.M. Munro and Alan L. Cripps</i>	2269
Peptides and Proteins: Pulmonary Absorption / <i>Igor Gonda</i>	2731
Radiolabeling of Pharmaceutical Aerosols and Gamma Scintigraphic Imaging for Lung Deposition / <i>Hak-Kim Chan, Stefan Eberl, and William Glover</i>	3094
Ultrasonic Nebulizers / <i>Kevin M.G. Taylor and Orla McCallion</i>	3854

Quality Assurance and Control

Pharmaceutical Quality Assurance Microbiology Laboratories / <i>Anthony M. Cundell</i>	2783
Quality Assurance of Pharmaceuticals / <i>Barbara Immel</i>	3064
Quality Systems Management / <i>Gary C. Harbour and Robert G. Kieffer</i>	3075

Regulatory, Legal, and Compendial Aspects and Requirements

21 CFR Part 11 Revisited / <i>Thomas Linz and Sigrun Seeger</i>	1
Adverse Drug Reactions / <i>Therese I. Poirier and Robert L. Maher, Jr.</i>	46
Advertising and Promotion of Prescription and Over-the-Counter Drug Products / <i>Wayne L. Pines</i>	57
Alternative Medicines / <i>Kristi L. Lenz</i>	66
Carcinogenicity Testing: Past, Present, and Future / <i>Koen Van Deun</i>	431
Clinical Data Management Systems / <i>Samuel V. Givens, Debra Barnes, Victoria Imber, and Barbara Perry</i>	551
Clinical Evaluation of Drugs / <i>Lynda Sutton, Allen Cato, and Allen Cato III</i>	560
Coloring Agents for Use in Pharmaceuticals / <i>David R. Schoneker</i>	648
Contract Manufacturing / <i>Duncan E. McVean</i>	750
Cosmetics and Their Relation to Drugs / <i>Martin M. Rieger</i>	798
Drug Information Systems / <i>Linda Lisgarten and Michelle Wake</i>	1385

Drug Master Files / <i>C. Jeanne Taborsky and Brian James Reamer</i>	1401
Drug Safety Evaluation / <i>Farrel L. Fort</i>	1406
Equipment Cleaning / <i>Destin A. LeBlanc</i>	1580
European Agency for the Evaluation of Medicinal Products (EMA) / <i>David M. Jacobs</i>	1593
Excipients: Safety Testing / <i>Marshall Steinberg and Florence K. Kinoshita</i>	1656
Expiration Dating / <i>Leslie C. Hawley and Mark D. VanArendonk</i>	1685
Food and Drug Administration: Role in Drug Regulation / <i>Roger L. Williams</i>	1779
Generic Drugs and Generic Equivalency / <i>Arthur H. Kibbe</i>	1891
Harmonization of Pharmacopeial Standards / <i>Lee T. Grady and Jerome A. Halperin</i>	1955
Non-Prescription Drugs / <i>Sujit S. Sansgiry, Lynn Simpson, Gauri Shringarpure, and Amit Kulkarni</i>	2413
Nutraceutical Supplements / <i>G. Brian Lockwood</i>	2431
Orphan Drugs / <i>Carolyn H. Asbury</i>	2468
Packaging Systems: Compendial Requirements / <i>Claudia C. Okeke, Desmond G. Hunt, Nicholas Mohr, Thomas Medwick, Eric B. Sheinin, and Roger L. Williams</i>	2526
Paperless Documentation Systems / <i>Ellen M. Williams and Michael McKenna</i>	2551
Pharmaceutical Excipient Testing: Regulatory and Preclinical Perspective / <i>Paul Baldrick</i>	2771
Pharmacopeial Standards: European Pharmacopeia / <i>Agnès Artiges</i>	2829
Pharmacopeial Standards: Japanese Pharmacopeia / <i>Mitsuru Uchiyama</i>	2836
Pharmacopeial Standards: United States Pharmacopeia and National Formulary / <i>Lee T. Grady</i>	2841
Scale-Up and Post Approval Changes (SUPAC) / <i>Jerome P. Skelly</i>	3188

Safety Considerations of Drugs and Pharmaceutical Products

Absorption Enhancers / <i>J. P. Remon</i>	13
Adsorption at Solid Surfaces: Pharmaceutical Applications / <i>Hong Wen</i>	34
Animals in Drug Development / <i>Farrel L. Fort</i>	114
Autoxidation and Antioxidants / <i>John M. Pezzuto and Eun Jung Park</i>	139
Carcinogenicity Testing: Past, Present, and Future / <i>Koen Van Deun</i>	431
Coloring Agents for Use in Pharmaceuticals / <i>David R. Schoneker</i>	648
Drug Abuse / <i>Richard B. Seymour and David E. Smith</i>	1038
Drug Design: Basic Principles and Applications / <i>Jacques H. Poupaert</i>	1362
Drug Information Systems / <i>Linda Lisgarten and Michelle Wake</i>	1385
Drug Interactions / <i>Daniel A. Hussar</i>	1392
Drug Safety Evaluation / <i>Farrel L. Fort</i>	1406
Excipients: Safety Testing / <i>Marshall Steinberg and Florence K. Kinoshita</i>	1656
Expiration Dating / <i>Leslie C. Hawley and Mark D. VanArendonk</i>	1685
Extractables and Leachables in Drugs and Packaging / <i>Daniel L. Norwood, Alice T. Granger, and Diane M. Paskiet</i>	1693
Handling Hazardous Chemicals and Pharmaceuticals / <i>Antonio Conto</i>	1948
Isolators for Pharmaceutical Application / <i>Gordon J. Farquharson</i>	2133
Medication Errors / <i>Diane D. Cousins</i>	2243
Microbial Control of Pharmaceuticals / <i>Nigel A. Halls</i>	2286
Non-Prescription Drugs / <i>Sujit S. Sansgiry, Lynn Simpson, Gauri Shringarpure, and Amit Kulkarni</i>	2413

Safety Considerations of Drugs and Pharmaceutical Products (*cont'd.*)

Pharmaceutical Excipient Testing: Regulatory and Preclinical Perspective / <i>Paul Baldrick</i>	2771
Plants as Drugs / <i>Christine K. O'Neil and Charles W. Fetrow</i>	2901
Pyrogens and Endotoxin Detection / <i>James F. Cooper</i>	3052
Trace Level Impurity Analysis / <i>Daniel L. Norwood, Fenghe Qiu, and James O. Mullis</i>	3797

Scale-Up and Pilot Plant Design and Operation

Freeze Drying, Scale-Up Considerations / <i>Edward H. Trappler</i>	1834
Pilot Plant Design / <i>Mickey L. Wells, Samuel B. Balik, Ralph B. Caricofe,</i> <i>Charles W. Crew, Ronald A. Sanftleben, and A. Wayne Wood</i>	2875
Pilot Plant Operation / <i>Mickey L. Wells, A. Wayne Wood, Samuel B. Balik,</i> <i>Ralph B. Caricofe, Ronald A. Sanftleben, and Charles W. Crew</i>	2886
Scale-Up and Post Approval Changes (SUPAC) / <i>Jerome P. Skelly</i>	3188
Scale-Up of Solid Dosage Forms / <i>Colleen E. Ruegger, Alan Royce, Matthew J. Mollan, Jr.,</i> <i>Robert Wagner, Stephen Valazza, and Mark Mecadon</i>	3193
Technology Transfer Considerations for Pharmaceuticals / <i>Ira R. Berry</i>	3717
Wet Granulation: End-Point Determination and Scale-Up / <i>Michael Levin</i>	4078

Semi-Solids as Pharmaceuticals

Capsules, Soft / <i>David H. Bergstrom, Stephen Tindal, and Wenbin Dang</i>	419
Rheology of Pharmaceutical Systems / <i>Fridrun Podczek</i>	3128
Semisolid Preparations / <i>Guru Betageri and Sunil Prabhu</i>	3257
Waxes / <i>Roland A. Bodmeier</i>	4066

Solids and Powders as Pharmaceuticals

Adsorption at Solid Surfaces: Pharmaceutical Applications / <i>Hong Wen</i>	34
Amorphous Pharmaceutical Systems / <i>Bruno C. Hancock</i>	83
Capsules, Hard / <i>Brian E. Jones</i>	406
Cocrystals: Design, Properties and Formation Mechanisms / <i>Nair Rodríguez-Hornedo,</i> <i>Sarah J. Nehm, and Adivaraha Jayasankar</i>	615
Crystal Habit Changes and Dosage Form Performance / <i>A. K. Tiwary</i>	820
Effervescent Pharmaceuticals / <i>Nils-Olof Lindberg and Henri Hansson</i>	1454
Powder Sampling / <i>Helena J. Venables</i>	2959
Powders as Dosage Forms / <i>Jean-Marc Aiache and Erick Beyssac</i>	2971
Scale-Up of Solid Dosage Forms / <i>Colleen E. Ruegger, Alan Royce, Matthew J. Mollan, Jr.,</i> <i>Robert Wagner, Stephen Valazza, and Mark Mecadon</i>	3193
Solids: Flow Properties / <i>Stephen A. Howard</i>	3275
Tablet Formulation / <i>Larry L. Augsburger and Mark J. Zellhofer</i>	3641
Tablet Manufacture / <i>Norman Anthony Armstrong</i>	3653

Solubilization and Solubilized Systems

Cosolvents and Cosolvency / <i>Joseph T. Rubino</i>	806
Polymeric Delivery Systems for Poorly Soluble Drugs / <i>Kang Moo Huh, Sang Cheon Lee, Tooru Ooya, and Kinam Park</i>	2913
Solubilization of Drugs in Aqueous Media / <i>Paul B. Myrdal and Samuel H. Yalkowsky</i>	3311
Solubilizing Excipients in Pharmaceutical Formulations / <i>Robert G. Strickley</i>	3334
Surfactants in Pharmaceutical Products and Systems / <i>Owen I. Corrigan and Anne Marie Healy</i>	3583

Stability and Preservation of Drugs and Drug Products

Autoxidation and Antioxidants / <i>John M. Pezzuto and Eun Jung Park</i>	139
Biotechnology-Derived Drug Products: Stability Testing, Filling, and Packaging / <i>Mary E.M. Cromwell</i>	302
Expiration Dating / <i>Leslie C. Hawley and Mark D. VanArendonk</i>	1685
Headspace Oxygen Analysis in Pharmaceutical Products / <i>Allen C. Templeton and Robert A. Reed</i>	1967
Hydrolysis of Drugs / <i>Jason M. LePree and Kenneth A. Connors</i>	2040
Microbial Control of Pharmaceuticals / <i>Nigel A. Halls</i>	2286
Moisture in Pharmaceutical Products / <i>R. Gary Hollenbeck</i>	2368
Photodecomposition of Drugs / <i>Hanne Hjorth Tonnesen</i>	2859
Preservation of Pharmaceutical Products / <i>Peter Gilbert and David G. Allison</i>	2983
Water Sorption of Drugs and Dosage Forms / <i>Mark J. Kontny and James J. Connors</i>	4049

Statistics

Statistical Methods / <i>Charles Bon</i>	3483
Statistical Process Control and Process Capability / <i>Thomas D. Murphy, Shailesh K. Singh, and Merlin L. Utter</i>	3499

Sterile Products and Microbiological Monitoring and Control

Aseptic Processing: Validation / <i>James P. Agalloco and James E. Akers</i>	127
Bio-Validation of Steam Sterilization / <i>Nigel A. Halls</i>	325
Blow-Fill-Seal: Advanced Aseptic Processing / <i>Deborah J. Jones</i>	378
DNA Probes for the Identification of Microbes / <i>Wayne P. Olson</i>	929
Dressings in Wound Management / <i>Sarah M.E. Cockbill</i>	1023
Filters and Filtration / <i>Maik W. Jornitz</i>	1748
Isolators for Pharmaceutical Application / <i>Gordon J. Farquharson</i>	2133
Laminar Airflow Equipment: Applications and Operation / <i>Gregory F. Peters</i>	2171
Microbiologic Monitoring of Controlled Processes / <i>Gregory F. Peters and Marghi R. McKeon</i>	2298
Pharmaceutical Quality Assurance Microbiology Laboratories / <i>Anthony M. Cundell</i>	2783
Pyrogens and Endotoxin Detection / <i>James F. Cooper</i>	3052
Sterilization: Dry Heat / <i>Andrea Chieppo and Thomas Kupiec</i>	3512
Sterilization: Ethylene Oxide / <i>Terezinha de Jesus Andreo Pinto</i>	3519

Sterile Products and Microbiological Monitoring and Control (*cont'd.*)

Sterilization: Moist Heat / <i>Dario Pistolesi</i>	3529
Sterilization: Radiation / <i>Stephen G. Schulman and Phillip M. Achey</i>	3540
Viral Inactivation Issues in Aseptically Processed Parenterals / <i>J. Hotta, A. Klos, S. Petteway, Jr., and D. Pifat</i>	3997

Tableting of Pharmaceuticals

Starches and Starch Derivatives / <i>Ann W. Newman, Ronald L. Mueller, Imre M. Vitez, and Chris C. Kiesnowski</i>	3476
Super Disintegrants: Characterization and Function / <i>Larry L. Augsburger, Albert W. Brzezcko, Umang Shah, and Huijeong Ashley Hahm</i>	3553
Tablet Compression: Machine Theory, Design, and Process Troubleshooting / <i>Michael J. Bogda</i>	3611
Tablet Evaluation Using Near-Infrared Spectroscopy / <i>Christopher T. Rhodes and Karen Morisseau</i>	3630
Tablet Formulation / <i>Larry L. Augsburger and Mark J. Zellhofer</i>	3641
Tablet Manufacture / <i>Norman Anthony Armstrong</i>	3653
Tablet Manufacture by Direct Compression / <i>Norman Anthony Armstrong</i>	3673
Tablet Testing / <i>Saeed A. Qureshi</i>	3707
Tooling for Tableting / <i>Annette Bauer-Brandl</i>	3782
Wet Granulation: End-Point Determination and Scale-Up / <i>Michael Levin</i>	4078

Topical and Transdermal Delivery and Application

Cosmetics and Their Relation to Drugs / <i>Martin M. Rieger</i>	798
Dressings in Wound Management / <i>Sarah M.E. Cockbill</i>	1023
Drug Delivery: Topical and Transdermal Routes / <i>Kenneth A. Walters</i>	1311
Iontophoresis / <i>J. Bradley Phipps, Erik R. Scott, J. Richard Gyory, and Rama V. Padmanabhan</i>	2119
Peptides and Proteins: Transdermal Absorption / <i>Richard H. Guy, M. Begoña Delgado-Charro, and Diego Marro</i>	2741
Polymers in Transdermal Delivery Systems / <i>Fumio Kamiyama and Ying-shu Quan</i>	2925
Transdermal Delivery: Anatomical Site Influence / <i>Nora Y.K. Chew, Nina F. Wilkins, and Barrie C. Finnin</i>	3814
Transdermal Delivery: Technologies / <i>S. Kevin Li</i>	3843
Transdermal Delivery: Sonophoresis / <i>Samir S. Mitragotri, Hua Tang, E. Daniel Blankschtein, and Robert Langer</i>	3828

Unit Operations and Processing Techniques Employed in Pharmaceutical Development and Manufacturing

Continuous Processing of Pharmaceuticals / <i>J. P. Remon and C. Vervaet</i>	743
Cooling Processes and Congealing / <i>Richard Turton and Xiu Xiu Cheng</i>	761
Drying and Dryers / <i>Anthony J. Hlinak and Bradley A. Clark</i>	1435
Evaporation and Evaporators / <i>David P. Kessler</i>	1600
Extrusion and Extruders / <i>J. M. Newton</i>	1712

Filters and Filtration / Maik W. Jornitz	1748
Fluid Bed Processes for Forming Functional Particles / Yoshinobu Fukumori and Hideki Ichikawa	1773
Freeze Drying / Michael J. Pikal	1807
Freeze Drying, Scale-Up Considerations / Edward H. Trappler	1834
Homogenization and Homogenizers / Shailesh K. Singh and Venkatesh Naini	1996
Hot-Melt Extrusion Technology / Jim W. McGinity, Michael A. Repka, John J. Koleng, Jr., and Feng Zhang	2004
Melt Processes for Oral Solid Dosage Forms / Paul W.S. Heng and Tin Wui Wong	2257
Microencapsulation Technology / Kinam Park and Yoon Yeo	2315
Microsphere Technology and Applications / Diane J. Burgess and Anthony J. Hickey	2328
Milling of Active Pharmaceutical Ingredients / Elizabeth S. Fisher	2339
Mixing and Segregation in Tumbling Blenders / Troy Shinbrot and Fernando J. Muzzio	2352
Nanoparticle Engineering / Robert O. Williams III and Jason M. Vaughn	2384
Optimization Methods / Gareth A. Lewis	2452
Particle Engineering / Miriam K. Franchini	2567
Pelletization Techniques / Isaac Ghebre-Sellassie and Axel Knoch	2651
Roller Compaction Technology for the Pharmaceutical Industry / Ronald W. Miller and Paul J. Sheskey	3159
Unit Processes in Pharmacy: Fundamentals / Anthony J. Hickey and David Ganderton	3862
Unit Processes in Pharmacy: Operations / Anthony J. Hickey and David Ganderton	3879

Validation of Pharmaceutical Processes and Techniques

Analytical Procedures: Validation / Joachim Ermer and John S. Landy	92
Aseptic Processing: Validation / James P. Agalloco and James E. Akers	127
Bio-Validation of Steam Sterilization / Nigel A. Halls	325
Computer Systems Validation / Orlando Lopez	707
Equipment Cleaning / Destin A. LeBlanc	1580
Filters and Filtration / Maik W. Jornitz	1748
Validation of Pharmaceutical Processes / Robert A. Nash	3928

Water in Pharmaceutical Manufacturing and Products

Moisture in Pharmaceutical Products / R. Gary Hollenbeck	2368
Water for Pharmaceuticals / Leonid Shnayder	4039
Water Sorption of Drugs and Dosage Forms / Mark J. Kontny and James J. Connors	4049
Wet Granulation: End-Point Determination and Scale-Up / Michael Levin	4078

Freeze Drying

Michael J. Pikal

School of Pharmacy, University of Connecticut, Storrs, Connecticut, U.S.A.

INTRODUCTION

Freeze drying, also termed “lyophilization,” is a drying process employed to convert solutions of labile materials into solids of sufficient stability for distribution and storage. A typical production scale freeze dryer consists of a drying “chamber” containing temperature-controlled shelves, which is connected to a “condenser” chamber via a large valve. The condenser chamber houses a series of plates or coils capable of being maintained at very low temperature (i.e., less than -50°C). One or more vacuum pumps in series are connected to the condenser chamber to achieve pressures in the range of 0.03–0.3 Torr in the entire system during operation. A commercial freeze dryer may have 10–20 shelves with a total load of the order of 50,000 vials. The objective in a freeze-drying process is to convert most of the water into ice in the *freezing stage*, remove the ice by direct sublimation in the *primary drying stage*, and finally remove most of the unfrozen water in the *secondary drying stage* by desorption. The water removed from the product is reconverted into ice by the condenser.

In a typical freeze-drying process, an aqueous solution containing the drug and various formulation aids, or “excipients,” is filled into glass vials, and the vials are loaded onto the temperature-controlled shelves. The shelf temperature is reduced, typically in several stages, to a temperature in the vicinity of -40°C , thereby converting nearly all the water into ice. Some excipients, such as buffer salts and mannitol, may partially crystallize during freezing, but most “drugs,” particularly proteins, remain amorphous. The drug and excipients are typically converted into an amorphous glass also containing large amounts of unfrozen water (15–30%) dissolved in the solid (i.e., glassy) amorphous phase. Thus, most of the desiccation actually occurs during the freezing stage of the freeze-drying process. After all water and solutes have been converted into solids, the entire system is evacuated by the vacuum pumps to the desired control pressure, the shelf temperature is increased to supply energy for sublimation, and primary drying begins. Due to the large heat flow required during primary drying, the product temperature runs much lower than the shelf temperature. The removal of ice crystals by sublimation creates an open network of “pores,” which

allows pathways for escape of water vapor from the product. The ice–vapor boundary (i.e., the boundary between frozen and “dried” regions) generally moves from the top of the product toward the bottom of the vial as primary drying proceeds. Primary drying is normally the longest part of the freeze-drying process. Primary drying times of the order of days are not uncommon, and in rare cases, weeks may be required for a combination of poor formulation and suboptimal process design. Although some secondary drying does occur during primary drying (i.e., desorption of water from the amorphous phase occurs to a limited extent once the ice is removed from that region), the start of secondary drying is normally defined, in an operational sense, as the end of primary drying (i.e., when all ice is removed). Of course, because not all vials behave identically, some vials enter secondary drying whereas other vials are in the last stages of primary drying. When the judgment is made that all vials are devoid of ice, the shelf temperature is typically increased to provide the higher product temperature required for efficient removal of the unfrozen water. The final stages of secondary drying are normally carried out at shelf temperatures in the range of 25 – 50°C for several hours. Here, because the demand for heat is low, the shelf temperature and the product temperature are nearly identical.

As freeze-drying plants are very expensive and process times are often long, a freeze-dried dosage form is relatively expensive to produce. Indeed, because of both cost and ease of use, a ready-to-use solution is the preferred option for a parenteral dosage form, particularly if the solution can withstand terminal heat sterilization. When an aqueous solution does not have sufficient stability, the product must be produced in solid form. At least for small molecules, stability normally increases in the following order: solution < glassy solid < crystalline solid,^[1–3] this is likely a result of restricted motion in solids with the high degree of order in the crystalline solid limiting reactivity even further. As many pharmaceuticals cannot be produced on a commercial scale by crystallization, a glassy solid may be the only solid-state option.

Freeze drying^[4–7] and spray drying^[8–10] are drying methodologies in common use in the pharmaceutical industry, and are suitable for the production of

glassy solids. Freeze drying is a low-temperature process. In general, a formulation can be dried to 1% water or less, without any of the product exceeding 30°C. Thus, conventional wisdom states that freeze-drying is less likely to cause thermal degradation than a high-temperature process such as spray drying. Historically, freeze-drying is the method of choice for products intended for parenteral administration. Sterility and relative freedom from particulates are critical quality attributes for parenterals. Largely because the solution is sterile filtered immediately before filling into the final container, and further processing is relatively free of exposure to humans, a freeze-drying process maintains sterility and particle-free characteristics of the product much more easily than do processes that must deal with dry powder handling issues, such as dry powder filling of a spray-dried or bulk-crystallized powder. Indeed, with modern robotics automatic loading systems,^[11] humans can be removed from the sterile processing area entirely, at least in principle. Furthermore, as the vials are sealed in the freeze dryer, moisture control and control of headspace gas can easily be controlled, an important advantage for products whose storage stability is adversely affected by residual moisture and/or oxygen. As the critical heat and mass transfer characteristics for freeze-drying are nearly the same at the laboratory scale as in full production, resolution of scale-up problems tends to be easier for a freeze-drying process than for spray drying, at least in our experience. Also, development of a freeze-dried product requires less material for formulation and process development, a particularly important factor early in a project.

While freeze-drying has a long history in the pharmaceutical industry as a technique for stabilization of labile drugs, including proteins, many proteins suffer irreversible change, or degradation, during the freeze-drying process.^[12-16] Even when the labile drug survives the freeze-drying process without degradation, the resulting product is rarely found perfectly stable during long-term storage, particularly when analytical techniques with a sensitivity to detect low levels of degradation ($\approx 0.1\%$) are employed. Both small molecules^[1-3,17] and proteins^[18-21] show degradation during storage of the freeze-dried glass. In some cases, instability is serious enough to require refrigerated storage.^[18,19,22]

Stability problems are most often addressed by a combination of formulation optimization and attention to process control. Lyoprotectants are added for stability during the freeze-drying process as well as to provide storage stability, and the level and type of buffer is optimized. Optimization of the freezing process may be critical; control of product temperature during drying is critical for products that tend to suffer cake collapse during primary drying, and control of residual moisture is nearly always critical for storage stability.

Formulation and process are interrelated: A bad formulation can be nearly impossible to freeze dry, and even with a well designed formulation, a poorly designed process may require more than a week to produce material of suboptimal quality. Although blind empiricism may, in time, yield an acceptable formulation and process, an appreciation for the materials science of amorphous systems and some understanding of heat and mass transfer relevant to freeze-drying are needed for efficient development of freeze-dried products. Obviously, one also requires at least a phenomenological understanding of the major degradation pathways specific to the drug under consideration.

The objective of this article is to present the scientific and engineering fundamentals most useful in the development of formulations and processes for the manufacture of freeze-dried pharmaceuticals. Generalizations are illustrated with specific examples from the literature, but no attempt is made to survey all published works. Most of the section on the freeze-drying process applies equally well to small molecules and proteins, whereas most of the section on formulation and stability is specific to proteins.

THE FREEZE-DRYING PROCESS

Freezing

Freeze concentration

The objective of freezing is to remove most of the water from the system by formation of ice and to convert all solutes into solids, either crystalline solids or a glass. Once the sample is a solid, primary drying may begin. As a sample is cooled, the system remains liquid well below the equilibrium freezing point, but with sufficient supercooling, nucleation of ice proceeds rapidly and growth of ice crystals begins. As liquid water converts to ice, all solutes are concentrated in the regions between ice crystals, ultimately concentrating until they crystallize or until the system increases in viscosity sufficiently to transform into a solid amorphous system, or glass. The example shown in Fig. 1 is representative of a solute that does not crystallize during freeze-drying. The system supercools about 10°C to a temperature of -15°C before ice nucleation becomes rapid enough to generate crystals of ice. The evolution of heat caused by the sudden crystallization of ice increases the sample temperature to roughly the equilibrium freezing point (-5°C). The sudden ice crystallization also results in a small but sharp decrease in the percentage of water in the solute phase (given on the right vertical axis). After the initial ice nucleation and crystallization at 10 min, the product cools with continuous conversion of water to ice, thereby

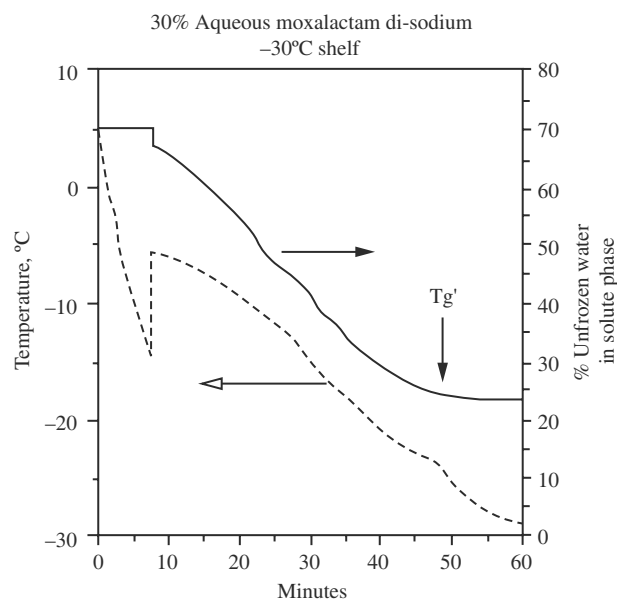


Fig. 1 Freeze concentration in an amorphous system. The product temperature is shown as a broken line whereas the percentage of unfrozen water is shown as a solid line. (From Ref.^[6].)

decreasing the amount of water in the solute phase and increasing the concentration of solute in the remaining solution. When the product temperature reaches about -24°C , denoted as T_g' , the concentration of water in the solute phase has been reduced to about 24%, and further reduction in water concentration is curtailed on the time scale of freezing, even though the sample temperature decreases further to about -30°C at the end of the freezing process at 60 min. Here, the solute phase has been concentrated from about 30% solute to about 76% solute, and most of the water has been separated from the solute phase as ice. Had the initial concentration been much lower, say 1%, the final concentration would still be 76%, although the freezing profile would differ quantitatively from that shown in Fig. 1. Clearly, most of the desiccation in a freeze-drying process occurs during the freezing process. While desiccation is indeed the objective, it must be recognized that concentration of all solutes during freezing will dramatically increase the probability of bimolecular collisions, which could produce unexpected instability in the partly frozen system. If a system, initially at 1% solute, is susceptible to a second-order degradation reaction with an activation energy of 25 kcal/mol, a reduction in temperature from 5°C to -24°C would reduce the rate constant by a factor of 200, but an increase in concentration from 1% to 76% would increase the concentration factor in the rate equation by a factor of 5800, yielding a factor of 29 net increase in reaction rate. Although this example is an oversimplification, it is significant to

note that increases in second-order degradation rates have been observed in model systems during freeze concentration.^[23]

T_g' is the temperature at which a sharp increase in baseline occurs during a differential scanning calorimeter (DSC) scan of a frozen solution, suggesting a sharp increase in heat capacity, and has been referred to as the glass transition temperature of the maximally concentrated freeze concentrate.^[24] A sharp decrease in electrical resistance of the frozen system is noted at the same temperature.^[25] Structural collapse of a cake structure in the dried region, indicating viscous flow, occurs during primary drying at the collapse temperature, denoted by T_c' , which is only slightly higher than T_g' .^[25] It is clear that T_g' corresponds to the temperature at which mobility in the system is manifested on an experimental timescale. Effectively, the system behaves as a solid below T_g' .

Various electrolytes, such as buffer salts and NaCl, if present in the formulation, will also concentrate during the freezing process. Such exposure to high concentrations of electrolytes (i.e., about 6 molal NaCl during freezing a 0.15 M NaCl solution) might contribute to the destabilization of the native conformation, thereby leading to degradation during freezing.

Crystallization of excipients and consequences

In the case of protein drugs, the drug does not crystallize, but other solute components may (or may not) crystallize, depending on their nature and concentration, other formulation components, and the details of the freezing process. High initial concentrations and slow freezing tend to favor crystallization. Depending on the intended role of the excipient, crystallization may be desirable or undesirable, and it may be important just when in the process crystallization does occur. For example, if mannitol is intended only as a bulking agent, and is not expected to play a role in stabilization of the drug, crystallization is desirable as crystalline mannitol can easily be freeze dried at high temperatures to give an elegant product, meaning a short freeze-drying cycle and freedom from product defects such as collapse. Here, the drug form is that of an amorphous coating on the crystalline mannitol, with stability properties normally close to that of a system freeze dried without the mannitol. If mannitol remains amorphous during freezing and crystallizes as the product temperature is increased in early primary drying, extensive vial breakage can occur.^[26] Conversely, if mannitol is intended to serve as a stabilizer during drying and/or storage, crystallization is undesirable. Complete crystallization yields a system equivalent to a physical mixture of glassy drug particles and crystalline mannitol, with no opportunity for a stabilizing interaction except at the phase boundary between the

particles, no dilution of drug molecules, and no separation of “reactants” in the protein phase from the protein molecules. In short, any plausible stabilization mechanism requires that at least some of the mannitol remain molecularly dispersed in the amorphous drug phase. Of course, just as crystalline mannitol has some solubility in any liquid, mannitol will have a nonzero thermodynamic solubility in the drug phase. Thus, even if mannitol crystallization proceeds to thermodynamic equilibrium, a small amount of mannitol will remain in the drug phase. However, most of the stabilization potential of the mannitol will be lost upon crystallization. As mannitol does tend to crystallize nearly completely when present as the major formulation component, mannitol is generally a poor choice as a stabilizer for freeze drying.

Although buffers are included in a formulation to maintain constant pH, selective crystallization of the less soluble buffer component during freezing can result in massive pH shifts in the freeze concentrate. Fig. 2 shows the pH changes observed during equilibrium freezing of several pure buffer systems.^[27] Freezing was carried out while seeding with ice and crystalline buffer salts, so the data represent near-equilibrium behavior. Over the temperature range studied, the citrate buffer system showed no significant pH shift. The sodium phosphate buffer system shows a dramatic decrease in pH of about 4 pH units due to crystallization of the basic buffer component, $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$. Conversely, the potassium phosphate system shows only a modest increase in pH of about 0.8 pH unit. Under non-equilibrium conditions (i.e., no seeding) and with lower buffer concentrations, the degree of crystallization is less, and the resulting pH shifts are moderated.^[28] Table 1

Table 1 Shifts in pH during non-equilibrium freezing with phosphate buffer systems

Concentration (mM)	Initial pH	Frozen pH	Δ pH
Sodium phosphate buffer			
100	7.5	4.1	−3.4
8	7.5	5.1	−2.4
Potassium phosphate buffer			
100	7.0	8.7	+1.7
100	5.5	8.6	+3.1
10	5.5	6.6	+1.1

(From Refs.^[29,30].)

shows data accumulated^[29,30] during freezing of phosphate buffer solutions in large volumes at cooling rates intended to mimic freezing in vials. For the concentrated buffer solutions (100 mM), the frozen pH values are close to the equilibrium values given in Fig. 2. However, lowering the buffer concentration by an order of magnitude considerably reduces the pH shift observed during freezing. It should also be noted that the small pH shift for potassium phosphate buffer noted in Fig. 2 is a result of the starting pH being 7.5. As shown in Table 1, if the initial pH is 5.5, the 100 mM potassium phosphate buffer increases by 3.1 pH units during freezing. In short, the frozen system pH is near 8.7, regardless of whether the initial pH is 7.0 or 5.5. Clearly, if drug stability is sensitive to pH shifts, buffer crystallization must be avoided. In our experience, the best solution is to formulate such that the weight ratio of buffer to other solutes is very low.^[18,22] However, the precise meaning of “very low” varies with the nature and amount of the other solutes as well as with the nature of the buffer.

Instability during freezing and T_g'

Most small molecules are stable during the freezing process, even though storage stability may be marginal. Proteins show a wide range of formulation-sensitive instability. Some proteins survive freezing with little or no measurable loss in activity, whereas others are irreversibly deactivated by the freezing process.^[12–21,31–33] An environment quite different from a dilute aqueous solution is created during freezing. All solute species are dramatically concentrated, ionic strength increases, the pH may shift, and above all, hydrophobic interactions that stabilize the native conformation in water are reduced or eliminated as bulk water is removed from the protein phase. In addition, just as proteins undergo thermal denaturation at elevated temperature, proteins also undergo spontaneous unfolding at very low temperature, called “cold denaturation”.^[34,35] Estimated cold denaturation temperatures are often below the T_g' of a protein formulation and therefore of questionable relevance

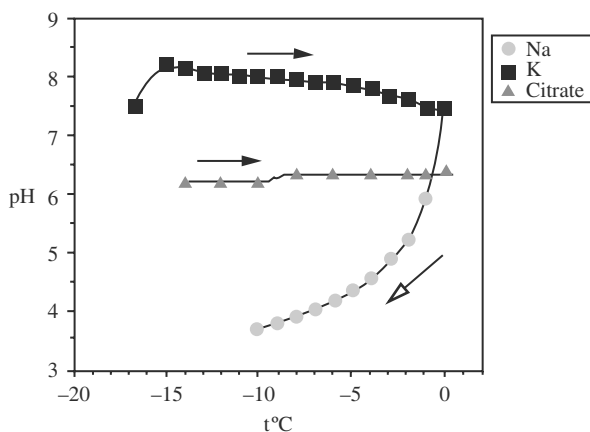


Fig. 2 Shifts in pH during freezing arising from buffer salt crystallization. Near-equilibrium conditions were achieved by seeding with ice and salt. circles: sodium phosphate; squares: potassium phosphate; triangles: citrate. (Data from Ref.^[27].)

to freeze-drying. However, these estimates are based upon thermodynamic parameters measured in dilute aqueous solutions. The impact of perturbations caused by freeze concentration is largely unknown.

Because of these many freezing stresses that may decrease the free energy of denaturation, thermodynamic destabilization of the native conformation during freezing is not surprising. Indeed, it appears surprising that all proteins do not spontaneously unfold and degrade during freezing. However, for a destabilized protein to unfold and engage in subsequent irreversible reactions, the rate of unfolding must be fast relative to the timescale of freezing. Even in dilute aqueous solution at room temperature, protein unfolding may involve time constants of the order of hours.^[36,37] In the freeze concentrate approaching T_g' , at temperatures $\approx 30^\circ\text{C}$ lower than room temperature and viscosities about 10 orders of magnitude greater than in a dilute aqueous solution, one would expect greatly reduced unfolding rates, perhaps sufficiently reduced to prevent degradation during freezing. Kinetic studies of unfolding near T_g' would resolve this question. Unfortunately, such data are not available. However, it has been argued on theoretical grounds that rate processes, in general, should be slowed greatly as the system temperature approaches a glass transition temperature.^[33] Experimental studies of three different reactions in frozen maltodextrin systems lend support to this view, although not all reactions show the same strong temperature dependence near a glass transition.^[38] As a general rule, it would seem prudent to minimize the time a protein spends in a freeze concentrate above T_g' (i.e., minimize freezing time), and primary drying should be carried out near or below T_g' . However, these precautions do not always guarantee stability.

Optimum freezing rate

Frequently, the freezing process is characterized by specification of freezing rate, where in most cases it is really the temperature change of the heat sink that is specified, or at best, the cooling rate of the solution is given. However, there are at least two freezing parameters that are needed to define the freezing process—the degree of supercooling and the rate of ice crystallization. The degree of supercooling is the difference between the equilibrium freezing point and the temperature at which ice crystals first form in the sample. The degree of supercooling determines the number of nuclei and, therefore, determines the number of ice crystals formed in the sample. A high degree of supercooling produces a large number of ice crystals, and as the total amount of water that freezes is fixed, the ice crystals produced after completion of freezing are small in size. Size of ice crystals impacts on process design and may also affect product quality, as will be

discussed later. The rate of ice crystal growth determines the residence time of the product in a freeze-concentrated fluid state. A rapid growth rate minimizes the residence time, normally allowing less degradation during the freezing process. In practical freeze-drying applications, heat transfer limits the rate of ice growth. Therefore, in vials and pans where heat removal is through the container bottom, rapid ice growth is facilitated by a small fill volume to container area ratio (i.e., small fill depth) and good contact between the container bottom and the freeze dryer shelf. In general, rapid ice growth is also promoted by a low shelf temperature. However, if a warm vial with a large fill depth is placed directly on a very cold shelf, a very high degree of supercooling may be produced near the vial bottom before convective mixing cools the upper portion of the solution. Ice then forms near the vial bottom whereas the remainder of the solution remains completely liquid. Freezing then continues slowly from bottom to top as a freezing front. Such a freezing pattern normally produces a dried cake with two distinct structures: a region of very fine pores near the bottom, with most of the cake having very large pores due to the very large ice crystals that formed during advance of the freezing front. The product may be perceived as “lacking in elegance.” At the least, a process designed to produce a fast freeze gives instead a slow freeze.

A high degree of supercooling produces small ice crystals and small pore size in the dried layer, which results in a high resistance to water vapor transport during primary drying.^[39] Consequently, long primary drying times result. Small ice crystals also mean a high specific surface area in the dried product, which decreases secondary drying time.^[40] These trends suggest that a moderate degree of supercooling is optimal. While the size of ice crystals would not normally be expected to impact on product quality, it is clear that if a protein were to denature at the aqueous ice interface, small ice crystals would mean a large interfacial area and more denaturation, perhaps leading to increased aggregation during freezing. There is now clear evidence that, at least in some cases, proteins may indeed denature at the aqueous–ice interface.^[41,42]

In general, the optimum freezing process produces moderate and uniform supercooling and fast ice growth. Uniformity within a given vial avoids heterogeneous cake structure, and uniformity between vials minimizes variation in drying rates and sample temperatures. The combination of moderate supercooling and fast ice growth is difficult to achieve as, in usual practice, the cooling rate of the heat sink (i.e., the shelf) is the only controllable factor in freezing. A general procedure that normally gives satisfactory results may be summarized as follows. First, the product load is cooled to a temperature below the equilibrium

freezing point but above the temperature where experience has demonstrated that ice nucleation does not occur (i.e., typically $\approx -5^\circ\text{C}$), and the load is equilibrated at this temperature for a short time (i.e., 15–30 min). Next, the shelf temperature is decreased quickly toward the final temperature (i.e., to -40°C at $\approx 1^\circ\text{C}/\text{min}$). At least with a small fill depth ($\approx 1\text{ cm}$), ice nucleation usually occurs uniformly with moderate supercooling, yet ice growth proceeds relatively rapidly. When product temperature is monitored with temperature sensors in selected vials, the time at which all measured product temperatures are below a given temperature (i.e., time when the product is several degrees above the final shelf temperature) is recorded. Since vials containing temperature sensors often freeze sooner than the batch as a whole,^[43] the product load is allowed to soak for a fixed time (about an hour) to allow all vials to “catch up” and reach the desired temperature at which all product is in the solid state.

Primary Drying

Mass transfer resistance, product temperature, and drying rate

The effect of product temperature and mass transfer resistance on sublimation rate may be mathematically illustrated^[39,44] by expressing the sublimation rate per vial, dm/dt , in terms of the driving force for transport of water vapor from the ice–vapor interface to the chamber, $P_0 - P_c$.

$$\frac{dm}{dt} = \frac{P_0 - P_c}{R_p + R_s} \quad (1)$$

where P_0 is the equilibrium vapor pressure of ice at the temperature of the frozen product, P_c is the pressure in the drying chamber, R_p is the resistance of the dried product layer, and R_s is the stopper resistance. As P_0 increases exponentially with temperature, it is obvious that the driving force for sublimation, and, therefore, also the sublimation rate, increases dramatically as the product temperature increases (about a factor of two per 5°C increase in temperature). The decrease in primary drying time with increasing product temperature is illustrated by Fig. 3. These data represent calculations based upon integration of Eq. (1) for a hypothetical (but typical) product at both a small (0.5 cm) and large (2.0 cm) fill depths. The value of chamber pressure used varies due to an attempt to maintain the condition $P_0 \approx P_c$, but yet employ chamber pressures near the optimum range for uniform heat transfer (≈ 0.1 – 0.2 Torr) when possible.^[44] At the lowest product temperatures, the chamber pressures selected are well below the optimum for uniform heat

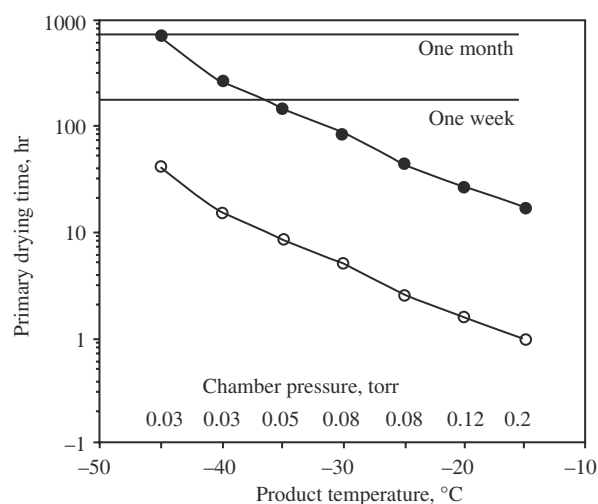


Fig. 3 Calculated primary drying times for a typical product as a function of product temperature. Open circles = 0.5-cm fill depth; filled circles = 2.0-cm fill depth.

transfer, but much higher pressures would give very long drying times. At each temperature, drying time is roughly proportional to the square of the fill depth, and target temperatures below -40°C become impractical for 2-cm fill depths.

It should be noted that Eq. (1) assumes that the gas in the vial is essentially 100% water vapor. Both theoretical and experimental evidence indicate that, during most primary drying conditions of practical interest, the gas in the vial and the gas in the drying chamber is nearly all water vapor, even when the chamber pressure is being controlled by an inert gas leak.^[44] The molar flow rate of inert gas (i.e., N_2) leaked into the drying chamber is generally much smaller than the molar flow rate of water vapor during primary drying, so the composition of gas in the drying chamber remains mostly water vapor. The inert gas “overwhelms” the vacuum pumps and, therefore, increases the total pressure in pumping system, which then causes a “back-up” of water vapor into the drying chamber.

Clearly, fast freeze-drying demands both high target product temperature and a small fill depth, which unfortunately is not always possible. To maintain product elegance, and in some cases to minimize degradation, primary drying must be carried out at product temperatures below the collapse temperature. As noted earlier, the collapse temperature and T_g' are closely related, with the collapse temperature normally being several degrees higher than T_g' . In practice, recognizing that not all vials freeze dry at exactly the same temperature, the target product temperature is chosen several degrees below the collapse temperature to provide a safety margin. A collapse temperature is a property of all components in the amorphous phase,

and consequently the collapse temperature is highly formulation dependent.^[45,46]

Although the product temperature is generally the most important factor in determining the rate of primary drying, product resistance is also an important parameter. The dried product resistance, R_p , depends on the cross-sectional area of the product, A_p , by the relation $R_p = \hat{R}_p/A_p$, where $\hat{R}_p$ is the area normalized product resistance, which is independent of the sample area but depends on both the nature of the product and the thickness of the dried product. Thus, R_p depends on the container used in that A_p is fixed by the internal diameter of the vial. The units used for $\hat{R}_p$ ^[39,44] are $\text{cm}^2 \text{ Torr hr g}^{-1}$. With this choice of units, the numerical value of $\hat{R}_p$ represents the approximate time (in hours) to freeze dry a 1–2 cm thick sample at a temperature of -20°C , if the resistance would remain constant over the duration of primary drying. As one might expect, the resistance increases as the dry layer increases in thickness, and therefore, resistance increases as primary drying proceeds. However, the relationship between resistance and thickness is not usually a direct proportion, although the resistance is often roughly linear in dry layer thickness.^[39,44]

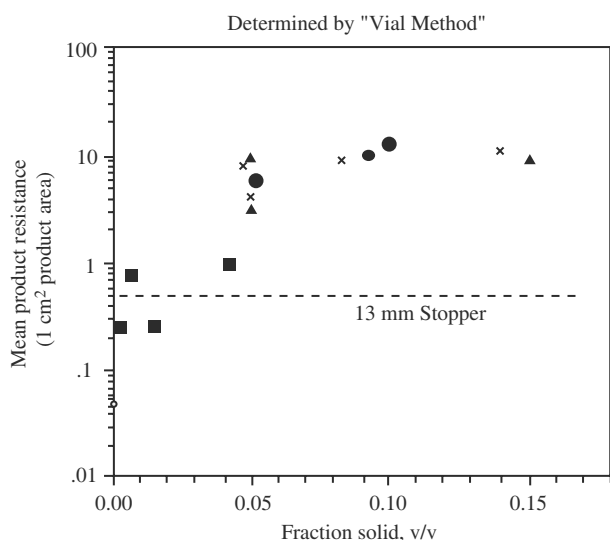
Variation of product resistance with concentration is illustrated by the data in Fig. 4, where values of the mean product resistance, $\langle R_p \rangle$, are given for various product types at different total solute concentrations. The mean product resistance is the mean resistance over a dry layer thickness interval of 0–1 cm. The scatter reflects formulation-specific effects whereas the

general trend with increasing concentration illustrates the tendency of higher concentrations to produce higher resistance and therefore, longer drying times. A typical value for the resistance of a small 13-mm finish stopper is shown as a straight line. Note that except for very dilute solutions, $R_p \gg R_s$.

Process control: product temperature measurement

In most commercial freeze drying processes, chamber pressure, shelf temperature, and time are the only controllable process parameters. Product temperature is not directly controlled. It is the balance between heat and mass transfer that determines the product temperature.^[47] Obviously, shelf temperature is important in determining the heat transfer and product temperature. However, because much of the heat is transferred through the gas phase (i.e., collisions of gas molecules with the hot shelf surface and the cold vial bottom), heat transfer as well as mass transfer Eq. (1) is determined, in part, by the chamber pressure. Therefore, product temperature is determined by shelf temperature, chamber pressure, the heat transfer characteristics of the vials, and the mass transfer characteristics of the product and semistoppered vials.

Conventionally, product temperature is monitored in a small number of vials by placing temperature sensors at the bottom center of the vials. It is assumed that at least the average of the measured temperatures is representative of the rest of the vials. The trend in product temperature with time is often used to determine the end of primary drying. That is, when the measured product temperature shows a sharp increase near the anticipated end of primary drying, and begins to approach the shelf temperature, it is assumed that all ice in that vial has been removed. Generally, for that vial, this assumption is correct. When all vials containing temperature sensors are judged dry by this criterion, one might be tempted to assume that all vials in the batch are dry. This assumption is not generally correct. Vials containing temperature sensors are not representative of the batch as a whole. There exists a temperature and drying rate bias between the monitored vials and the rest of the batch. Monitored vials usually freeze sooner with less supercooling than does the batch as a whole.^[43] This effect is particularly significant in production where due to the particle-free environment, the introduction of a temperature sensor introduces a significantly higher level of heterogeneous nucleation sites, thereby causing nucleation of ice at a lower temperature than in vials without temperature sensors. Observations made during a production run on moxalactam are illustrated in Fig. 5.^[43] Monitored vials supercool to around -15°C and then begin freezing. The vials not monitored do not begin freezing until



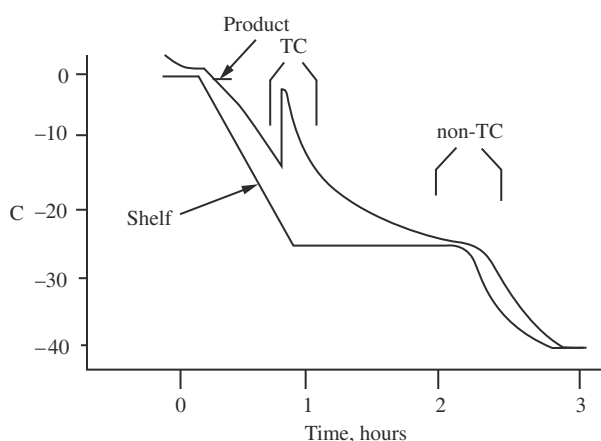


Fig. 5 Experimental observation of freezing bias: a production run of moxalactam di-sodium (from Ref.^[42].)

much later, at which time the product temperature must be close to the shelf temperature of -25°C . Thus, non-monitored vials undergo a much greater degree of supercooling, have smaller ice crystals, smaller pores, more resistance to mass transfer, freeze dry at higher temperature, and require more time to dry than the rest of the vials. The temperature bias during primary drying is usually small, $\approx 1^{\circ}\text{C}$, but the drying time bias is 10% of the primary drying time, which can be quite significant for long primary drying times.^[43] To compensate for this bias in drying time, a soak period of 10–15% of the primary drying time is imposed following the time when all monitored vials are judged dry. Only after this soak period is the shelf temperature increased for secondary drying. Premature increase of the shelf temperature carries a high risk of collapse. Thus, although monitoring the temperature of the product in vials does provide some information on the progress of primary drying, the information provided is far from perfect!

Location of the monitored vials in the vial array on the shelf is also an important factor in recording representative data. Vials on the edge of an array (i.e., facing the dryer door or walls) normally are not representative of the vials in the interior of an array, which are surrounded by other vials.^[44] Due to differences in radiative heat transfer, such vials normally dry faster at a higher temperature. With a shelf temperature around 5°C , temperature bias is about 1°C , with drying time bias about 10%,^[44] and the effect increases in magnitude as the difference between shelf temperature and ambient temperature increases and chamber pressure decreases. However, to minimize the risk of loss of sterility in surrounding vials, the temperature sensors are frequently placed in vials on the edge of the vial array facing the door. Again, the monitored vials are not representative of the batch as a whole.

Clearly, minimizing the risk of product contamination with microorganisms is extremely important. From a sterility assurance viewpoint, the ultimate low-risk process is achieved with fully automatic loading systems, which, in principle, can eliminate the need for human presence in the sterile block except in emergency situations. However, it is difficult—perhaps impossible—to place temperature sensors in product vials when using an automatic loading system. Given the problems noted above with the routine use of product temperature sensors, it would seem reasonable to employ product temperature sensors only in development and validation, where vials near the center of an array could be monitored. With a robust process and suitable validation data, it may be assumed that production batches would run with the same product temperature history as the development and validation batches. Thus, product temperature would not be monitored during routine manufacturing. The simplest process design involves using a fixed shelf temperature : chamber pressure : time program.

Designing an *efficient* and *robust* process based upon a fixed shelf temperature : chamber pressure : time program is not a difficult assignment when the primary drying time is short. For example, if the primary drying time of an average batch is 6 h, designing for worst case of perhaps twice the primary drying time of an average batch would extend the average process time by only 6 h; however, if the primary drying time of an average batch is 4 days, designing for worst case will result in a significant reduction of production capacity. By using methodology for remote sensing of the end point of primary drying,^[43] which will be discussed later, this process inefficiency can be virtually eliminated. Moreover, it is both possible and practical to monitor product temperature without placing temperature sensors in the product vials.^[48] This methodology, called manometric temperature measurement, is based on an analysis of the rate of pressure increase in the chamber when the valve separating the drying chamber from the condenser chamber is periodically quickly closed (and the pressure control system is deactivated) for a brief period of time ($\approx 15\text{ s}$). When the drying chamber is thus isolated from the condenser chamber, the chamber pressure increases due to four effects (Fig. 6): (1) sublimation at the ice–vapor interface at constant product temperature and transfer of water vapor through the dried cake; (2) dissipation of the temperature gradient in the frozen layer, thereby increasing the temperature at the ice–vapor interface; (3) heat flow from the shelf to the product, thereby increasing the temperature at the ice–vapor interface; and (4) natural air leaks from the surroundings into the chamber. The pressure rise data is fitted to a theoretical function to obtain the average product temperature at the ice–vapor interface. Effects (3) and (4)

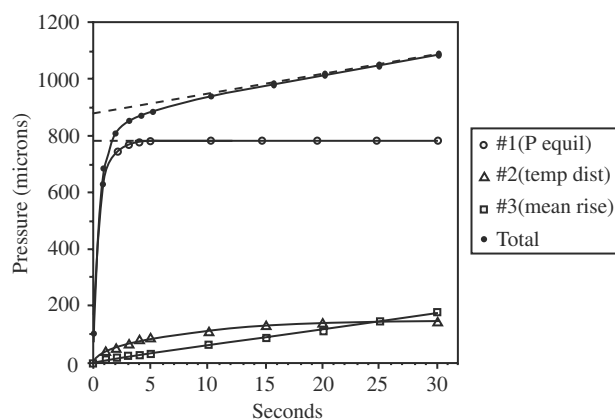


Fig. 6 Calculated contributions to the pressure rise in a manometric temperature measurement experiment. Calculations were made for a typical product with an initial ice temperature of -20°C , corresponding to an initial vapor pressure of 775 m Torr. Open circles = effect 1, sublimation; open triangles = effect 2, dissipation of temperature gradient; open squares = effect 3, heat flow from shelf to product; filled circles = sum of all effects. (Adapted from Ref.^[48].)

both produce a linear increase in pressure with time whereas the other two effects are non-linear. Effect (1) is dominant (Fig. 6), but a consideration of the other effects is necessary to obtain accurate product temperatures.^[48] Manometric temperature measurement gives the temperature at the ice-vapor interface, which is the temperature relevant to collapse, and most important, gives a representative temperature of the product vials without risk of sterility compromise. The freeze dryer, however, must be computer-controlled so that product temperature data can be obtained in real time via mathematical analysis of the pressure rise data. Manometric temperature measurement can also be used to sense the end point of primary drying as well as providing accurate dried layer resistance data.^[48]

Process control and chamber pressure

Pressure control may be accomplished by one of three methods: controlled nitrogen leak, conductance control, or condenser temperature control. Pressure control by "controlled nitrogen leak" is accomplished by opening/closing a needle valve connected to a nitrogen source at atmospheric pressure in response to the deviation of the measured chamber pressure from the set point. Very fine pressure control, within ± 5 m Torr, can be achieved. Typically, sterile nitrogen is leaked into the drying chamber, but equally fine pressure control is achieved by leaking nitrogen into the vacuum line near the vacuum pumps. Although, to my knowledge, no relevant data exists, current dogma suggests that leaking into the drying chamber is preferred because the risk of

sterility compromise is less. Conductance control is based upon modulating the resistance of the chamber to condenser pathway by partially closing/opening the valve separating the drying chamber from the condenser chamber.^[49] One disadvantage of this technique is the inability to control pressure during secondary drying. Once evolution of water vapor slows to very low rates (during secondary drying), the chamber pressure will reduce to whatever ultimate vacuum the system will produce that day. Although control of chamber pressure to regulate heat input is only necessary in primary drying, one could argue that a process that does not control pressure throughout the process is not fully reproducible. In general, this argument is without scientific foundation, but there are special circumstances where product contamination by adsorption of volatile stopper impurities (or other foreign vapors in the freeze dryer) may occur, and such contamination is more serious at very low chamber pressures.^[50] Here, one would want to control chamber pressure in secondary drying at a somewhat elevated level (≈ 200 m Torr). Chamber pressure can also be controlled by control of condenser temperature, provided the freeze dryer design provides for fine control of condenser temperature.^[49] Control of condenser temperature controls the vapor pressure of ice on the condenser, thereby controlling the partial pressure of water in the drying chamber. Due to natural air leaks and the finite pressure difference between condenser and chamber required for mass transfer, the controlled chamber pressure will be somewhat higher than the vapor pressure of ice on the condenser, perhaps 20–50 m Torr higher. Thus, to control chamber pressure at 200 m Torr, the condenser temperature would be controlled at a temperature around -35°C . With this mode of pressure control, the vapor in the drying chamber remains essentially 100% water vapor throughout the process, including secondary drying. Conversely, with pressure control by a nitrogen leak, the vapor changes from essentially 100% water vapor in primary drying to mostly nitrogen during secondary drying (Fig. 7). Thus, a process run with a nitrogen leak to provide pressure control is not necessarily the same as the corresponding process run with pressure control via control of condenser temperature. In general, the difference is not expected to be of practical significance. With a final product temperature of 25°C or greater in secondary drying, a chamber pressure of 200 m Torr pure water vapor produces a relative humidity of less than 0.8%, which is not high enough to impede secondary drying of most materials. However, chamber pressure control via condenser temperature control will not produce the change in gas composition noted in Fig. 7, as the system passes from primary drying to secondary drying, which does limit the process control options for determining the end point of primary drying.

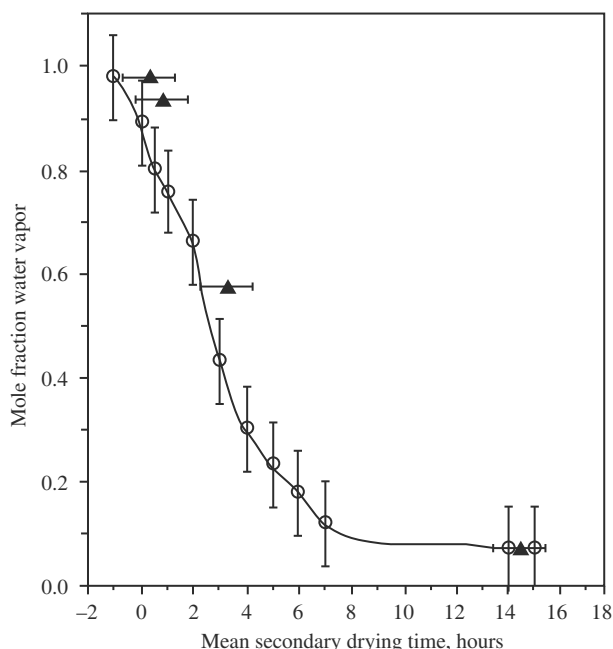


Fig. 7 Typical variation in gas composition in the drying chamber during secondary drying. Open circles: experimental values determined in a laboratory freeze dryer; filled triangles: theoretical values calculated from mass transfer theory and freeze dryer characteristics. (M.J. Pikal, Eli Lilly & Co., unpublished results.)

Process control: effect of condenser performance

Depending upon dryer design and operating conditions, the condenser temperature may vary over a wide range. As long as the condenser temperature remains sufficiently low to allow control of the chamber pressure at the desired set point, the temperature of the condenser has no impact on the freeze drying process [i.e., no change in any of the variables in Eq. (1)]. For example, if the chamber pressure is being controlled (via a nitrogen leak) at the target pressure of 0.10 Torr with a condenser temperature of -50°C , reduction of the condenser temperature to -70°C will have no effect on the process. Here, the reduced partial pressure of water at the condenser will be compensated by an increased partial pressure of nitrogen arising from an (automatic) increase in nitrogen leak rate. Although a detailed analysis of condenser performance is complex^[49] and beyond the scope of this chapter, it should be noted that under conditions of very high sublimation rate, the condenser system may be overloaded, resulting in loss of pressure control (i.e., the chamber pressure increases beyond control). Unless the shelf temperature is sharply decreased, a “run-away” condition may develop with loss of product temperature control and ultimately, loss of the batch due to product collapse or ice melt. An overloaded

condenser may reflect uneven ice build-up at the condenser plates caused by suboptimal design or operation, but may also arise from operation beyond the design capability of the refrigeration system.^[49] That is, the refrigeration system may not be able to remove heat from rapidly condensing water vapor (i.e., from very high sublimation rate) and yet maintain the condenser plate temperature low.

Process control: determination of the end point of primary drying

Typically the shelf temperature setting used in primary drying is much lower than the shelf temperature required for efficient removal of residual water during secondary drying. Because an increase in shelf temperature before all vials have completed primary drying carries a high risk of product collapse, some indicator of the end of primary drying is needed for optimum process control. Of course, one can increase the temperature for secondary drying at a fixed time, but as discussed earlier, such a process is not an optimum one (i.e., the process is normally longer than necessary). Product temperature response is the most common indicator of the end of primary drying. Here, the time is noted when all product temperature sensors approach the shelf temperature being used in primary drying. Next, a delay time or soak period is introduced to compensate for the fact that the vials containing temperature sensors are not typical of the batch as a whole. After this delay time, the shelf temperature is increased from the primary drying setting to the setting used for secondary drying. As determination of the appropriate delay time is difficult, the delay times used are often quite arbitrary. The principle problem is that freezing bias normally differs considerably between development and manufacturing. Thus, the optimum delay time for manufacturing cannot be determined in most development laboratories. It is obvious that use of product temperature sensors to determine the end point of primary drying is not entirely satisfactory. As suggested earlier, manometric temperature measurement may be used to determine the end point of primary drying. A far simpler method is to base the determination of the end point upon a real time measurement of the vapor composition in the freeze dryer chamber. As primary drying ends, and the process passes into secondary drying, the composition of the vapor in the drying chamber shifts from nearly pure water vapor to nearly pure nitrogen (Fig. 7), assuming chamber pressure is being controlled via a nitrogen gas leak. A sensitive and inexpensive measurement of vapor composition is provided by an electronic moisture sensor with output in dew point or partial pressure of water.^[43,51] An electronic moisture sensor has the sensitivity to determine presence of residual

ice in less than 1% of the vials,^[43] and under some conditions can also be employed to determine the end point of secondary drying (i.e., when the residual moisture has been reduced to below the target level).^[51]

Secondary Drying: Desorption of Water from the Freeze Concentrate

Product temperature control and glass transitions

The concept that one must maintain the product temperature below the collapse temperature during primary drying is now well accepted. Exceeding the collapse temperature will cause loss of product elegance, which will vary from moderate deformation and shrinkage to a complete melt and deposition along the walls and bottom of the vial. Structural collapse also may occur during secondary drying or during storage of the dried product, particularly if the dried product contains high levels of residual moisture, and the storage temperature is high. If the product temperature exceeds its glass transition temperature, cake shrinkage and deformation will occur. Such an event is a less common problem during secondary drying than is collapse during primary drying, largely because most secondary drying processes are extremely conservative during the early stage where a glass transition is most likely. As the water content of the amorphous phase decreases during drying, the glass transition temperature increases very sharply. Some representative data are shown in Fig. 8. If the shelf temperature remains at the setting used in primary drying for the first few hours of secondary drying, as is common

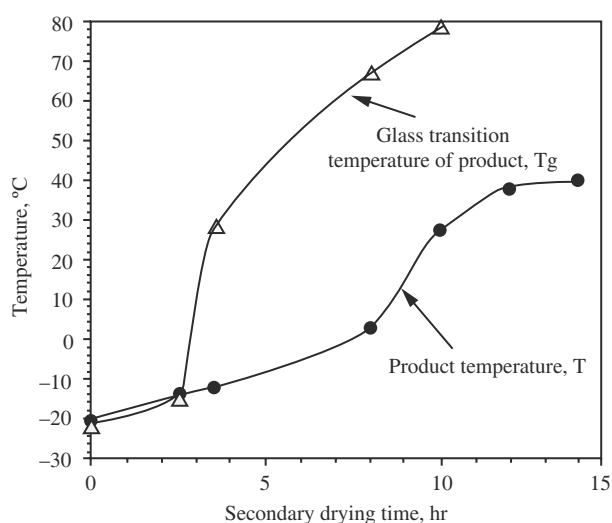


Fig. 8 Variation of glass transition temperature and product temperature for moxalactam di-sodium during secondary drying. (Calculated from data in Refs.^[25,40].)

practice, the glass transition temperature will nearly always rise much faster than will the product temperature. However, if one were to optimize secondary drying, and therefore, eliminate most of the dead time in early secondary drying, the potential for a glass transition would increase dramatically. Here, a knowledge of the glass transition temperature as a function of water content would be required for process optimization.

Optimum residual moisture

The optimum residual moisture for a given product must be established by empirical studies. Certainly, to eliminate the possibility of a structural collapse during storage, the water content needs to be low enough so that the glass transition temperature is well above the highest temperature relevant to product distribution and storage. Moreover, in our experience with both small molecules and proteins, in-process degradation is generally relatively insensitive to the final moisture content, and storage stability normally improves as residual moisture decreases, although the relationship between stability and residual water is not necessarily linear. Data for human growth hormone (hGH) formulated with glycine and mannitol,^[19] human serum albumin,^[52] and hemoglobin formulated with sucrose^[53] illustrate the range of behavior normally encountered (Fig. 9). The rate of chemical degradation of hGH at 25°C (methionine oxidation and asparagine deamidation) increases in highly non-linear

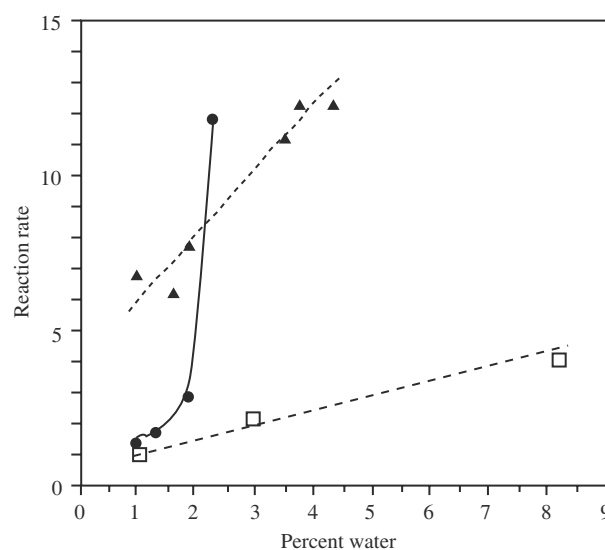


Fig. 9 The effect of residual water on the stability of freeze-dried proteins. Circles = human growth hormone deamidation and oxidation at 25°C, %/month; squares = aggregation of human serum albumin at 50°C, %/day; triangles = hemoglobin oxidation at 23°C in a sucrose formulation, %/year (From Ref.^[19,52,53].)

fashion by nearly an order of magnitude as the moisture content varies from 1% to 2.5%;^[19] the rate of aggregation of human serum albumin increases linearly with increasing moisture content,^[52] and the rate of hemoglobin oxidation at room temperature doubles as the residual water content increases from 1% to 4%.^[53] Although the optimum moisture content for storage stability may be zero, the gain in stability between about 1% water and zero water content is often not sufficient to justify the additional processing complications in achieving and maintaining extremely low water contents. An exception is storage stability of a monoclonal antibody–vinca alkaloid conjugate formulation where stability is sensitive to very low levels of residual moisture.^[22]

The decrease in storage stability accompanied by an increase in residual moisture is often interpreted in terms of molecular mobility in the solid. That is, higher water content facilitates the mobility needed to support reactivity of the protein. One interpretation states that above monolayer levels of water, the protein has increased conformational flexibility, and the additional water has the ability to mobilize water and other potential reactants in the amorphous protein phase.^[54] Both effects are expected to increase the rate of protein degradation. Alternatively, water plasticizes the amorphous phase, thereby lowering the glass transition temperature, T_g . Indeed, if sufficient water is present to lower T_g below the storage temperature, the amorphous phase would be in a fluid state, with greater mobility and greater reactivity than when stored below T_g in a glassy solid state. A system stored above its T_g would also suffer cake collapse and loss of pharmaceutical elegance. Although the monolayer and the glass transition interpretations are similar in that they both attribute the increased reactivity to water induced mobility in the amorphous phase, they differ in that a system above the monolayer level of water is not necessarily above the glass transition temperature. Furthermore, as the level of water equivalent to monolayer coverage is essentially independent of temperature, the monolayer concept predicts that the trend in stability with water content is independent of temperature. For example, if monolayer coverage is equivalent to 10% water, protein reactivity would increase sharply above 10% water at all temperatures. Conversely, the glass transition interpretation states that the key stability variable is the difference between the glass transition temperature and the storage temperature, $T - T_g$. Here, reactivity increases sharply when $T > T_g$, so the sudden onset of reactivity depends on both T and the water content through the effect of water content on T_g .

Although most empirical and theoretical evidence suggest that storage stability improves monotonically as the water content decreases, we must also acknowledge

the common assumption that there is a critical nonzero level of water that a protein requires for conformational stability in the freeze dried solid, and therefore, some intermediate level of residual water would be optimum for stability. Although direct experimental evidence for this assumption is meager, some systems do have inferior stability when highly desiccated. Influenza virus is clearly less stable when the residual moisture deviates from the optimum 1.7%,^[55] but the direct relevance of this observation to protein formulations is uncertain. Aggregation of excipient-free tissue plasminogen activator at high temperature is faster at low water content,^[56] and aggregation of excipient-free hGH during storage at 25°C is faster in samples that, at some time in their history, have been highly desiccated.^[19]

Factors impacting drying rate

Water removal during secondary drying involves diffusion of water in the glassy solid, evaporation at the solid–vapor boundary, and flow through the pore structure of the dried cake. During the early portion of secondary drying, water content is high, and the drying rate is high in spite of the relatively low temperature of the solid.^[40] An illustration of secondary drying kinetics under isothermal conditions is given in Fig. 10^[40] for samples initially about 7% water. Mannitol is crystalline whereas povidone and

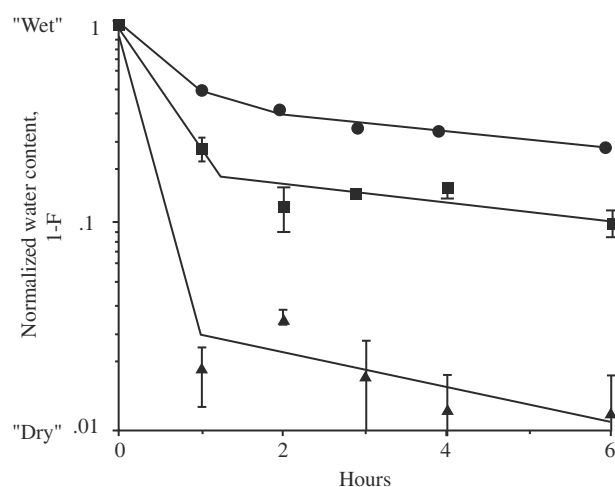


Fig. 10 Examples of the kinetics of secondary drying. Triangles = mannitol (crystalline); squares = poly(vinylpyrrolidone); circles = moxalactam di-sodium (amorphous). All solids were prepared by freeze-drying a 5% aqueous solution from a 1-cm fill depth, followed by hydration to a uniform moisture level of $\approx 7\%$. The quantity, F , is the fractional attainment of equilibrium, which corresponds to near zero water content. The secondary drying conditions were: product temperature = 18°C; chamber pressure = 200 m Torr. (From Ref.^[40].)

moxalactam are 100% amorphous. Even at the start of the experiment, the glass transition temperatures of povidone and moxalactam are well above the sample temperature of 18°C. Thus, water is being removed from either an essentially crystalline solid (mannitol) or glassy amorphous solids (povidone and moxalactam). The symbol F represents the fractional attainment of equilibrium, which in these experiments is near zero water content. Thus, $1-F$ represents a normalized water content with a value of unity representing no progress in drying. Although the quantitative aspects of drying behavior are obviously specific to the product, in each case, the water content is reduced sharply during the first 1–2 h, followed by a period of much lower drying rate. If the drying rate were directly proportional to the residual water content, drying kinetics would be first order, and the curves in Fig. 10 would be straight lines. A simple diffusion model based upon constant diffusion constant and constant area for diffusion would also predict linear semilog drying curves.^[40] Obviously, the curves are not straight lines. The residual water content appears to approach a plateau level, which is specific to the product. For the mannitol data, the plateau level of residual water is very low (≈ 0.1 – 0.2%) and probably represents occluded water in the crystalline mannitol. For the amorphous samples, povidone and moxalactam, the plateau levels are quite high, $\approx 1\%$ for povidone and $\approx 3\%$ for moxalactam (i.e., a significant fraction of the water appears to be bound). However, calculations based upon equilibrium water desorption isotherms and the measured partial pressures of water in the drying chamber demonstrate that the residual water present at the end of 6 h is far above the equilibrium water content.^[40] Thus, the residual water is *not* bound in a thermodynamic sense, but rather is kinetically trapped, a result, at least in part, of decreasing effective surface area for desorption of water as the smaller more rapidly drying solid particles are dried.^[40] For a given product, the plateau level of water decreases as the drying temperature is increased, decreases as the specific surface area of the solid increases, but is relatively insensitive to the thickness of the dried cake.^[40]

Traditional freeze drying practice has often used very low chamber pressures during secondary drying, presumably in the belief that the rate of secondary drying would be accelerated by the use of the low pressures. However, it is found^[40] that the rate of secondary drying is insensitive to chamber pressure, at least with pressures in the range of 0–0.2 Torr.^[40] This empirical observation is consistent with the conclusion that the rate-limiting mass transfer process for drying an amorphous solid is either diffusion in the solid or evaporation at the solid–vapor boundary, probably the latter.^[40] As the use of very low pressures in

secondary drying may facilitate contamination of the product by adsorption of impurity gases from the stopper or other sources,^[50] it is clear that relatively high chamber pressures (≈ 0.1 – 0.2 Torr) should generally be used for secondary drying. Of course, extremely high chamber pressures (≈ 1 Torr) should perhaps be avoided. With very high chamber pressures, flow of water vapor through the pore structure would become rate limiting, and the very high pressure would then decrease the rate of drying.

Changes in moisture content during storage

Often one employs a heroic secondary drying process to reduce the residual water content to very low levels only to find that the moisture content increases during storage. Although moisture transfer from ambient through the stopper is possible, the increase in moisture content is most often related to moisture release by the stopper.^[57] This phenomenon is illustrated in Fig. 11, where the time dependence of moisture content in 25 mg of freeze-dried lactose is given. Here, the stoppers were gray butyl stoppers that had been previously steam sterilized, followed by 1 h of vacuum drying to remove excess water. The symbols represent experimental data for 40°C, 25°C, and 5°C storage, and the smooth curves represent the best fit to a theoretical model.^[57] It should be noted that at least at 40°C and 25°C storage, the moisture content increases sharply from 1%, but then reaches a plateau value of about

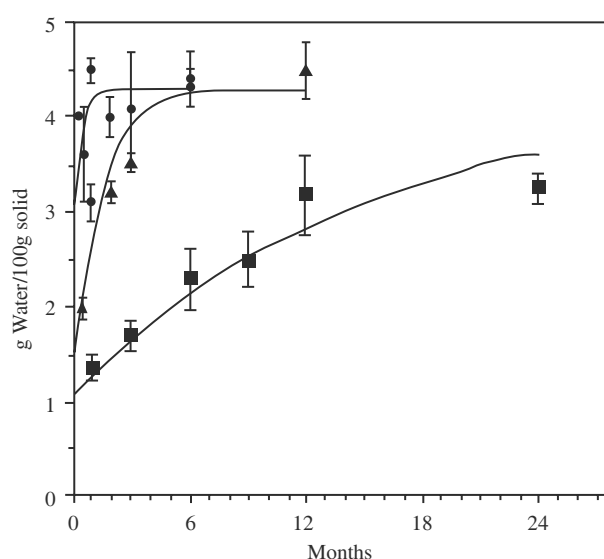


Fig. 11 Kinetics of water transfer from stoppers to 25 mg freeze dried lactose. The stoppers were 13 mm finish West 1816 gray butyl stoppers that were steam sterilized and vacuum dried for 1 hour. Circles = 40°C; triangles = 25°C; squares = 5°C. (From Ref.^[57].)

4.3%, suggesting that equilibrium has been reached. That is, at the plateau value of 4.3% water, the activity of the water in the stopper is equal to the activity of water in the lactose and mass transfer ceases. In other studies, we have noted samples deliberately prepared to be initially of high water content have lost water during storage. In short, there is moisture equilibration between moisture in the stopper and moisture in the product that may either increase the moisture content of a dry product or decrease the moisture content of a wet product. The plateau or equilibrium level of water appears to be independent of temperature. The equilibrium values for 40°C storage and 25°C storage are identical, and the moisture content values for 5°C storage appear to be approaching the same equilibrium value of 4.3%. The rates of approach to equilibrium, however, is strongly temperature dependent. The equilibrium level of water is strongly dependent upon the stopper treatment history. Stoppers vacuum dried for 8 h after steam sterilization allowed only a small increase in moisture content during storage. The equilibrium water content is lower for a higher mass of solid, and is slightly higher for a more hygroscopic product.^[57]

The moisture exchange between stopper and product may have important stability consequences. Absorption of moisture from the stopper may result in a product which has, after time, a moisture content high enough so that the glass transition temperature is below the storage temperature. Structural collapse will result, and stability of the product may well be compromised. Moreover, because the glass transition temperature often changes dramatically in a narrow range of water content, the onset of instability could be quite sudden. Moisture exchange may be moderated by extensive high temperature vacuum drying of the stoppers after steam sterilization. A better solution is to employ alternate rubber formulations that are less prone to release water to the product. Such stopper formulations are now available from several vendors.

FORMULATION AND STABILITY

Function of Excipients

Most freeze-dried products contain several components in addition to the drug or active component. These additional components, called excipients, are intended to serve a specific function, normally related to stability or process, and may constitute the major fraction of the freeze-dried solid.

With some products, the quantity of drug per vial is extremely small. Here, bulking agents such as mannitol or glycine are used to provide product elegance (i.e., satisfactory appearance) as well as to provide sufficient

cake mechanical strength to avoid product blow-out. When a very dilute solution is freeze dried, the flow of water vapor during primary drying may generate sufficient force on the fragile cake to break the cake structure and carry some of the product out of the vial with the water vapor stream. Product blow-out normally occurs only when the solution to be freeze dried is very low in total solids (1% or less). Thus, with low dose drugs, a bulking agent may be a critical formulation component.

Collapse temperature modifiers are excipients that will increase the collapse temperature to allow more efficient freeze drying without collapse. Such materials may also function as bulking agents and/or stabilizers. Dextran ($T_c = -10^\circ\text{C}$), hydroxyethyl starch ($T_c = -10^\circ\text{C}$), ficoll ($T_c = -20^\circ\text{C}$), gelatin ($T_c = -8^\circ\text{C}$) are examples. Although none of these materials are commonly used in parenteral formulations, dextran and hydroxyethyl starch are used in large quantities as IV therapeutic agents, and therefore, would presumably be acceptable as excipients. Usually, the collapse temperature of a mixture is intermediate between the collapse temperatures of the individual components,^[58] but collapse temperatures of candidate formulations cannot be predicted with high accuracy.

Macroscopic collapse may often be avoided by use of a crystalline matrix component. Here a readily crystallizable component is added at a relatively high level (i.e., more than 50% of total solids and ideally much more) such that a crystalline matrix is formed. Freeze drying such a formulation amounts to freeze drying with microscopic or partial collapse (i.e., complete collapse of the amorphous phase), but cake structure is maintained by the crystalline component. Thus, both elegance and good reconstitution time will be maintained, and the samples will normally dry to low residual water with ease. However, if collapse of the amorphous phase containing the protein leads to degradation, this method for circumventing collapse is not viable. Glycine and mannitol are commonly used as crystalline matrix components. This excipient function is, in reality, a special case of the use of a bulking agent.

Particularly with proteins, excipients are often added to prevent degradation, as for example, lyoprotectants, antioxidants, non-ionic surfactants, metal ion chelators, and other proteins such as BSA in diagnostic products. In many cases, the stabilizer may also serve as a bulking agent. Glycine, mannitol, sucrose, and lactose are perhaps the most commonly used stabilizers. However, as lactose is a reducing sugar and commonly reacts with proteins, its use must be questioned. Mannitol tends to crystallize, and is, therefore, generally a poor choice as a stabilizer. Sugars, in particular sucrose, are often effective lyoprotectants, as well as enhancers of storage stability.

Buffers are often added to control pH, but caution must be exercised when buffers are used in a formulation to be freeze dried. As discussed earlier, crystallization of either buffer component (acid or base) during freezing may cause a significant pH shift during freezing, thereby causing greater pH variation than would have been obtained in an unbuffered system.

Products intended for human use are occasionally formulated with NaCl or glycerol to make the reconstituted product isotonic. This practice is normally not a requirement for IV drugs, but can be quite important in minimizing pain on injection of subcutaneous and IM doses. In general, and in particular with proteins, isotonic adjustment is best accomplished by including the tonicity modifier in the diluent rather than in the freeze-dried product. Sodium chloride and glycerol can lower the collapse temperature significantly, and sodium chloride may cause aggregation of the protein during freeze drying.

With multidose products, there is a need for use of a preservative to prevent microbial growth during the period of product use. Mixtures of ethyl- and methyl-parabens are a common choice as are phenol and *m*-cresol. As preservatives are used at extremely low levels (i.e., $\leq 0.1\%$ w/w in solution), they normally would not alter the collapse characteristics of the formulation. However, since the preservative is not needed during the freeze drying process, to keep the formulation for freeze drying as simple as possible, preservatives are best introduced via the diluent intended for reconstitution.

Surfactants may be added at low levels (i.e., $\approx 0.05\%$ w/w in solution) for several purposes. Surfactants may aid reconstitution if the drug does wet well, and surfactants are often added to low dose products to minimize losses due to surface adsorption. Surfactants may also be effective as stabilizers in low dose protein systems.

Relationships between Formulation and Process

Particularly for freeze-dried products, formulation and process are interrelated. Properties of the formulation, in particular the collapse temperature, will have a significant impact on the ease of processing. An efficient process is one that runs at a high product temperature. However, the temperature cannot be too high or product quality will be compromised. As the glass transition temperature depends on chemical composition of the amorphous phase, T'_g and collapse temperature are strongly formulation dependent. Collapse temperatures for common excipient systems vary from less than -50°C to around -10°C (Table 2).

The collapse temperature depends upon the composition of the amorphous phase, and crystallization of

one or more components may significantly alter the collapse temperature. In this way, process variations that induce crystallization may alter the physical state of the formulation. For example, human growth hormone (hGH) formulated with glycine and mannitol in a hGH:glycine:mannitol weight ratio of 1:1:5 may form a completely amorphous system if frozen very quickly. Here, the collapse temperature is -24°C . However, a slower freeze allows crystallization of most of the mannitol, resulting in a collapse temperature greater than -5°C .^[18] Another example is provided by the glycine:sucrose system^[64-68] where glycine is present in excess of the sucrose. If frozen quickly, glycine remains amorphous, and the glycine:sucrose freeze concentrate has a very low collapse temperature (i.e., roughly -45°C , depending upon the exact composition). However, if glycine is allowed to crystallize, the glass transition temperature is essentially that of a sucrose freeze concentrate (i.e., about -34°C). Further, as the structure is maintained by the crystalline glycine, exceeding T'_g does not result in macroscopic collapse, and the system may be freeze dried without apparent collapse even at temperatures exceeding -15°C . Thus, crystallization can transform a formulation from one that is nearly impossible to freeze dry in a commercial operation to one where freeze drying is relatively easy. Clearly, if both glycine and sucrose are included in the formulation, the level of glycine must be either very low or very high relative to sucrose. If the level of glycine in the sucrose phase is very low, glycine will not crystallize but the impact on T'_g will be minimal. If the level of glycine is high, glycine can be induced to crystallize nearly completely,^[66,68] thereby minimizing the level of glycine in the amorphous phase and maximizing the T'_g of the formulation.

The glass-transition temperature of a multicomponent amorphous system may be estimated from glass transition temperatures of the individual amorphous components.^[69] The simplest expression, commonly referred to as the Fox equation, is

$$\frac{1}{T_g} = \frac{w_1}{T_{gi}} + \frac{w_2}{T_{g2}} \quad (2)$$

where w_i is the weight fraction of component i and T_{gi} is the glass transition temperature of pure component i . Generalization of Eq. (2) to systems of more than two components is obvious. The effect of a second solute component on a formulation may be roughly calculated from Eq. (1) if T_{gi} in Eq. (2) is identified with T'_g of aqueous component i , and w_i are weight fractions of solute relative to the total mass of solute. Although Eq. (2) does not strictly apply to a freeze concentrate containing two (or more) solute components and

Table 2 Collapse temperature T_c (°C), and glass transition, T_g' (°C) data for selected excipients^a

Material	T_g' (°C)	References	T_c (°C)	References
Polymers				
BSA	−11	[46]		
Dextran	−10	[46,59]	−10	[60,61]
Ficoll	−19	[59]	−20	[45]
Gelatin	−9	[59]	−8	[45]
PVP (40k)	−20	[59]	−23	[45]
Saccharides and polyols				
Dextrose	−44	[59]		
Hydroxypropyl β -cyclodextrin			−18	[60]
Lactose	−28	[46,59]	−31	[60,61]
Mannitol	−35, −28	[46,59]		
Raffinose	−27	[62]	−26	[45]
Sorbitol	−46	[59]	−45	[45]
Sucrose	−32, −35	[46,63]	−34, −32	[60,61]
Trehalose	−27, −29	[46,59]	−34	[60]
Amino acids				
β -Alanine	−65	[46]		
Glycine	(−62)	[64]		
Histidine	−33	[46]		
Salts and buffer components				
Acetate, potassium	−76	[46]		
Acetate, sodium	−64	[46]		
CaCl ₂	−95	[46]		
Citric acid	−54	[46]		
Citrate, potassium	−62	[46]		
Citrate, sodium	−41	[46]		
HEPES	−63	[46]		
NaHCO ₃	−52	[46]		
Phosphate, KH ₂ PO ₄	−55	[46]		
Phosphate, K ₂ HPO ₄	−65	[46]		
Phosphate, NaH ₂ PO ₄	−45	[46]		
Tris base	−51	[46]		
Tris HCl	−65	[46]		
Tris acetate	−54	[46]		
ZnCl ₂	−88	[46]		

^aCollapse temperature data were obtained with freeze drying microscopy and T_g' data were obtained by DSC at roughly 10°C/min heating rates and represent mid-points of the glass transition region. Molecular weight is given for polymers when the data are sensitive to molecular weight. When significant differences exist between laboratories, both values are given. Values in parentheses were estimated by extrapolation from non-crystallizing mixtures to the pure compound.

water, such calculations from T_g' data are sufficiently accurate to be of practical use. For example, the effect of glycine on T_g' of aqueous sucrose systems^[65] is fully consistent with Eq. (2).

Bulking Agents

General considerations

Bulking agents are intended to be inert and simply function as fillers to increase the density of the product cake. Product elegance is improved and product blow-out is prevented, but the bulking agent is not

intended to provide enhanced chemical or physical stability of the drug substance. Amorphous excipients can function as bulking agents, but most amorphous excipients have relatively low collapse temperatures and therefore require low drying temperatures and long processing times. For example, although lactose has been used as a bulking agent, the relatively low collapse temperature (−31°C) requires long processing times. In addition, lactose is a reducing sugar and will chemically react with amine functionality, and therefore, cannot be used with many drugs. Although not in common use as a freeze-drying excipient, hydroxyethylstarch is an example of an inert amorphous additive with a high collapse temperature and

therefore, could function as a bulking agent without requiring long processing times. However, hydroxyethylstarch tends to undergo some cake shrinkage and cracking during drying and therefore, provides a less elegant product than do the common crystalline bulking agents, glycine and mannitol. Since sorbitol is simply an isomer of mannitol, one might expect sorbitol could serve as a bulking agent. However, sorbitol does not easily crystallize during freeze-drying, and amorphous sorbitol has a collapse temperature around -45°C (Table 2), thereby preventing its use at high levels in formulations for freeze-drying. Human serum albumin (HSA) or in diagnostic products, bovine serum albumin (BSA), have seen use as bulking agents and/or stabilizers. However, given current concerns regarding excipients isolated from human sources, use of HSA in new pharmaceutical products should be questioned. Mannitol is by far the most commonly used bulking agent. A mannitol-based formulation is elegant, reconstitutes quickly, and except for the potential of vial breakage^[26,70,71] is generally easy to freeze dry without risk of product defects. Vial breakage is minimized by small fill depths, lower mannitol concentration, slow freezing, and avoiding freezing temperatures less than about -25°C until crystallization is complete. Glycine functions well as a bulking agent. Glycine crystallizes easily to form an elegant product that reconstitutes quickly and does not induce vial breakage. However, a glycine cake is more fragile than a mannitol cake, and is generally perceived as being somewhat less elegant than a mannitol cake.

Polymorphism in crystalline bulking agents

In general, the polymorphism issue of greatest significance in freeze-drying is whether or not a given component is crystalline or amorphous. Which crystalline polymorph forms is usually of secondary importance. However, it should be noted that both mannitol and glycine do exhibit crystalline polymorphism in freeze-dried systems.^[72–75] The only crystal polymorphism issue of known significance is the formation of a hydrate of mannitol.^[73,75] Under some conditions, not fully understood, mannitol forms a hydrate that does not easily desolvate to an anhydrate during secondary drying. Secondary drying at temperatures in excess of 50°C appear to be necessary to desolvate the hydrate. Thus, samples of freeze-dried mannitol may have high residual water content if secondary drying temperatures were moderate. If this residual water were to remain bound in the hydrate crystal lattice, the high residual water content would simply be a curiosity. However, during storage, particularly at elevated temperature, the hydrate slowly desolvates, thereby releasing water to the amorphous drug phase. Such a

scenario may compromise storage stability, particularly during accelerated stability tests.

Conditions for crystallization of bulking agents

A number of factors are critical for crystallization of the bulking agent. First, the nature of the bulking agent is of obvious importance. Unless the bulking agent will readily crystallize from an aqueous system at ambient temperatures, crystallization during freezing is unlikely. Although both mannitol and glycine do readily crystallize during freezing, there are many other solutes that readily crystallize and are at least potentially acceptable as excipients for parenteral drugs. Mannitol and glycine are simply the most commonly used bulking agents. Crystallization is favored by higher concentrations of crystallizable solute, and perhaps most important, the bulking agent must be the major solute component to obtain reliable crystallization. The presence of high levels of other solutes, particularly those that remain amorphous, will generally impede or prevent crystallization of the bulking agent. As a general formulation rule, one should employ the crystallizable bulking agent at a concentration (weight percent) that is at least a factor of three greater than the sum of the concentrations of all other solute components. In addition, because resistance of the dry layer to flux of water vapor increases as the concentration of total solids increases, thereby prolonging primary drying, one should avoid total solids concentrations much above 100 mg/ml when possible. A rigid adherence to both of these rules would suggest that one would not employ a bulking agent if the drug concentration were much in excess of 25 mg/ml. Indeed, because a bulking agent is normally not needed to avoid product blow-out at drug concentrations above 25 mg/ml, one should question the use of bulking agents in such applications.

Surfactants

Generally, surfactants are employed to reduce surface adsorption losses of low-dose drugs, to improve wetting and reconstitution behavior, and to stabilize proteins during freezing. In nearly all applications, it is a nonionic surfactant that is used, and by far the most commonly used surfactant is polysorbate 80. However, it should be noted that the popularity of polysorbate 80 is due more to its extensive history of use and presumed greater acceptance by regulatory agencies than to its demonstrated superior performance in a given application. In practice, the surfactant level is very low, typically 0.01–0.1% w/v.

Proteins and surface active drugs often adsorb on filters, solution-processing equipment, and container

surfaces, thereby producing loss of drug. Such losses are normally only of practical significance if the drug concentration is very low (i.e., when the total amount of drug loss is a significant percentage of the drug in solution). Addition of a low concentration of surfactant will frequently reduce the level of drug adsorption simply because the surfactant is preferentially adsorbed at the surfaces. With proteins, surface-adsorption effects may be considerably more complex and damaging. Many proteins adsorb at interfaces, particularly the air–water interface, suffer a conformational change, desorb from the interface, and either refold or combine with other conformationally altered molecules, thereby leading to irreversible aggregation.

Human growth hormone aggregates extensively during shaking an aqueous solution, but this aggregation can be nearly eliminated by adding Polysorbate 20 to the formulation.^[76] It should be noted that although other surfactants (including polysorbate 80) were studied, Polysorbate 20 was the most effective stabilizer. In this study, all surfactant levels studied were above the surfactant critical micelle concentration (CMC), but the rate of aggregation decreases linearly as a function of increasing polysorbate 20 : hGH mole ratio until it exceeds 2.0. This linearity provides a clue to the stabilization mechanism. As surfactant adsorption to the air–water interface would be expected to depend on the surfactant monomer concentration, and the monomer concentration is constant above the CMC, a stabilization mechanism involving adsorption of surfactant to the air–water interface would be expected to produce a roughly constant stabilization effect at all surfactant concentrations above the CMC. The data are not consistent with this prediction. However, it is known that polysorbate 20 binds to hGH with a stoichiometry of about 2.5 to 4.^[77] Thus, it seems plausible that stabilization during shaking involves binding of surfactant to the surface of the protein.^[77]

Aggregation of hemoglobin during freeze–thaw is essentially eliminated by addition of polysorbate 80 at concentrations from 0.0125% to 0.1%.^[78] Without polysorbate 80, particle formation after five freeze–thaw cycles increased by more than an order of magnitude when freezing to -20°C and by about a factor of five when freezing to -80°C . However, use of polysorbate 80 reduced particulate generation at both freezing temperatures to a level where particulate levels after freeze–thaw were not significantly different than before freezing. Attempts to demonstrate binding of the surfactant to hemoglobin were unsuccessful, suggesting that the stabilization mechanism does not involve binding to the protein. Rather, it was proposed that stabilization involves surfactant adsorption at the interface, thereby preventing the protein from adsorbing at interfaces.

Although one cannot always expect protein aggregation to be eliminated as effectively by addition of surfactant as demonstrated in the above examples, it is certainly prudent to test the effect of surfactants in situations where protein aggregation is a problem during freeze–thaw or during solution handling.

Stabilizers

Types of stabilizers

A stabilizer is simply a formulation component without physiological effect that is added to the formulation to maintain the physical or chemical stability of the drug substance. As discussed in the previous section, the function of a surfactant may be to stabilize, and as control of pH is often critical to stability, one might consider buffers to be stabilizers. However, in this section we will address stabilizers other than surfactants or buffers. Further, as most of the stabilization literature deals with proteins, our discussion will focus on proteins, although in principle many stabilization principles apply to small molecules as well.

Minimizing oxidation

Although oxidation is a very common degradation pathway in pharmaceutical systems, one might expect that oxidation problems in freeze-dried products would be easily solved by elimination of oxygen from the system during processing; that is, because the product is dried in a vacuum environment and the vials either sealed in vacuum or in an atmosphere of an inert gas (i.e., nitrogen), no oxygen will be present to support an oxidation reaction. Indeed, storage stability of human growth hormone is greatly improved in vials back-filled with nitrogen compared to vials back-filled with oxygen.^[19] However, significant oxidation was also observed in samples back-filled with nitrogen. In practice, complete elimination of oxygen from the solution being processed is unlikely, and some oxygen may well be trapped in the amorphous solute phase after freezing and not be completely removed during drying. Further, due to a variety of causes including diffusion from the atmosphere over time, oxygen content in the vial headspace may easily reach levels of about 1%. Even 1% oxygen in the vial headspace is sufficient, from a stoichiometric viewpoint, to produce substantial decomposition, particularly with high-molecular-weight drugs. For example, with a 5-mg dose of human growth hormone ($M = 22.5\text{ kD}$) in a 5-cc vial, 1% oxygen in the headspace represents a factor of ten excess of the oxygen required for complete oxidation of the protein.

As ground-state molecular oxygen is not particularly reactive, presence of oxygen is not the only requirement for a rapid oxidation reaction. Activation of molecular oxygen to more reactive species requires light (i.e., photoactivation to singlet oxygen, $^1\text{O}_2$), or presence of a reducing agent and trace levels of transition metal ions (i.e., iron and/or copper), which can then convert molecular oxygen into more reactive oxidizing agents such as superoxide radical ($\text{O}_2^{\cdot-}$), hydroxyl radical ($\cdot\text{OH}$), or hydrogen peroxide (H_2O_2).^[79] Transition metal ions are often present in excipients, and processing in stainless steel equipment can lead to significant iron contamination. As the role of the transition metal ion is catalytic, only trace levels are required. The reducing agent is consumed in the conversion of molecular oxygen into reactive oxygen species, so higher levels of reducing agent are required for significant degradation of a drug. However, higher levels could still represent contamination from impurities in the drug and/or excipients. In the example of 5 mg hGH, a low-molecular-weight reducing agent ($M \approx 100$) present at a level of 0.1% w/w of the amount of hGH could lead to oxidation of more than 10% of the protein. The reducing agent could also originate from a misguided attempt to suppress oxidation by addition of an antioxidant such as ascorbate. Ascorbate may function as an antioxidant in some circumstances but will also function as an effective prooxidant and reduce molecular oxygen to reactive oxygen species in the presence of transition metal ions such as iron or copper.^[79,80] Finally, peroxides are common contaminants in polyethylene glycols and nonionic surfactants and can serve as the oxidant. Thus, an attempt to stabilize protein conformation by addition of these materials may well chemically destabilize if oxidation is a possible degradation pathway.

A number of amino acid residues are subject to oxidation. Metal-catalyzed oxidation of methionine to methionine sulfoxide and other products is perhaps the most common pathway. Oxidation of cysteine to form either nonnative intra- or intermolecular disulfide bonds is also common, and histidine residues are also easily oxidized in metal-catalyzed pathways, with tryptophan and tyrosine being degraded by light-catalyzed oxidations.^[79] Mechanisms are complex, and even with a given reaction such as methionine oxidation, the active oxygen species and reaction product(s) varies with the experimental conditions;^[79,80] thus, stabilization is difficult. Certainly, oxygen content in the solution being processed should be minimized, and the product should be sealed in the freeze dryer with either vacuum or nitrogen in the headspace. Due to the negative impact of even small amounts of transition metal ions, prooxidants, and peroxides, the bulk drug substance and excipients need to have rigid

specifications. Formulation pH and the type of buffer salt may also be important.^[80] The optimum conditions vary with the application, and some empirical screening experiments are necessary to optimize a given formulation.

Specific chemical components may also be added in an attempt to retard oxidation. The classical solution, addition of an antioxidant, must be approached with caution as the antioxidant may function as a prooxidant in a metal-catalyzed conversion of molecular oxygen into reactive oxygen species. Likewise, addition of a metal-complexing agent such as EDTA does not always retard oxidation. In fact, oxidation may be accelerated by complexing the transition metal.^[80] With most metal-catalyzed oxidations, the oxidation mechanism is a site-specific one, where the reduced form of the metal binds to a residue such as histidine on the protein and converts oxygen to reactive oxygen species at that site, which in turn oxidizes another residue nearby.^[81] In cases where complexation with EDTA facilitates oxidation, it is assumed that the EDTA-metal complex binds more strongly to the protein and is therefore more effective in generation of reactive oxygen species near a reactive residue.^[81] However, addition of EDTA does retard oxidation in some cases,^[82] and it would seem prudent to screen several complexing agents for impact on oxidation. Scavengers for reactive oxygen species, hydroxyl radical, $\cdot\text{OH}$, and singlet oxygen, $^1\text{O}_2$, may also retard oxidation,^[79,83] but the results are highly specific to the system. For example, for iron-catalyzed oxidation of a methionine-containing peptide, thiourea was found effective for both ascorbate and dithiothreitol prooxidant systems but mannitol was effective only for the dithiothreitol prooxidant system.^[83]

Stabilization during freezing

In the context of proteins, stability has two distinct meanings. The term pharmaceutical stability refers to the ability of a protein to be processed, distributed, and used without irreversible change in primary structure, conformation, or state of aggregation. We refer to pharmaceutical instability as degradation. However, the phrase protein stability is also commonly used to describe the position of the equilibrium between native and unfolded conformations. If a protein formulation requires a high level of chemical denaturant, or a high temperature, to shift the equilibrium between native and unfolded in favor of the unfolded state, the protein is said to be stable. This meaning of stability I call "thermodynamic stability." Thermodynamic instability involves physical changes, somewhat analogous to a thermodynamic change of state. Pharmaceutical instability may be purely a result of a physical change (i.e., non-covalent aggregation), but may also involve

changes in primary structure or, in other words, chemical degradation. Certainly, chemical transformations such as oxidation and deamidation are degradations as is aggregation to form insoluble precipitates.

Pharmaceutical stability and thermodynamic stability are not necessarily directly related. For example, a protein may exhibit thermodynamic instability during freeze-drying and unfold, but if no irreversible reactions occur during storage or during reconstitution, the reconstituted protein may refold completely within seconds and, therefore, display perfect pharmaceutical stability. A protein that remains in the native state and is thermodynamically stable may still degrade via chemical reactions such as deamidation and oxidation over storage times of years, particularly if the reactive moiety is located on the protein surface. Conversely, thermodynamic instability may well be a prelude to degradation. Certainly, an unfolded protein could expose normally buried and protected methionine and asparagine residues to the solution environment and render these residues more reactive. Also, degradation via irreversible aggregation is believed to often proceed through unfolded or partially unfolded conformations as intermediates.^[84]

Many proteins survive the freeze-drying process with little or no degradation, whereas other proteins exhibit significant degradation and loss of activity during processing. Degradation during the freeze-drying process may arise during freezing and/or during drying, and it is useful to establish when in the process degradation occurs. As a measure of the degradation during freezing, freeze-thaw stability studies are carried out, and to estimate (roughly) the degradation during drying, stability during freeze-drying is compared to stability during freeze-thaw. The basic assumption is that degradation during thawing is comparable to degradation during reconstitution; therefore, the difference in activity between a freeze-dried-reconstituted sample and a freeze-thawed sample is a measure of the loss in activity during drying. This assumption is likely a reasonable approximation for a fast thawing process. One observation of particular significance is that some excipients stabilize during both freezing and drying (called lyoprotectants), whereas others stabilize only during freezing (called cryoprotectants).^[41,85,86]

If degradation occurs only during freezing and practical variations in the freezing process do not eliminate the problem, it is obvious that a cryoprotectant system is required. However, as a number of distinct stresses may develop during freezing, the proper choice of cryoprotectant is not always obvious. Provided some information regarding the degradation pathway is available, the stabilization strategy could be quite specific. For example, if oxidation is suspected to be a major pathway, the recommendations regarding

minimization of oxidation should be followed. If aggregation is a major problem, the use of nonionic surfactants should be considered, or if it is known that a change in pH caused by buffer crystallization is a problem, steps to minimize pH change during freezing need to be taken. Use of an alternative buffer system or simply use of very low levels of the buffer might well eliminate the pH change and solve the stability problem. Alternatively, addition of an excipient (i.e., sucrose or trehalose) that will interfere with buffer crystallization will also prevent excessive pH shift during freezing.^[41,85,86]

In addition to the specific stabilization strategies noted, one may also employ a general stabilization strategy that is based upon addition of components that normally increase the thermodynamic stability of the protein. That is, addition of a component that will increase the free energy of denaturation will moderate the effect of various freezing stresses that cause a decrease in the free energy of denaturation, with the net result that even during freezing, the native conformation will remain the dominant conformation and degradation will be reduced. The assumption is that increasing thermodynamic stability will also increase pharmaceutical stability. A number of solute types (i.e., amino acids, saccharides, polyols, polyethylene glycols, and some other classes) have been found effective both in increasing thermodynamic stability and in increasing pharmaceutical stability during freezing.^[85,86] These solutes are referred to as excluded solutes because such solutes are present in lower concentration near the surface of a protein. The thermodynamic consequence of such exclusion is that the protein is preferentially hydrated, and the chemical potential of the protein is increased. It may be argued that the increase in the chemical potential will be much greater for the unfolded state than for the native state, thereby increasing the free energy of denaturation and stabilizing the native conformation.^[85,86] Although the increase in protein chemical potential due to solute exclusion does not always correlate quantitatively with the effectiveness of that solute as a cryoprotectant, it would be prudent to test several pharmaceutically acceptable excluded solutes (i.e., glycine, mannitol, disaccharides, polyethylene glycols) as potential cryoprotectants in cases where freezing instability might involve conformational destabilization. Obviously, polyethylene glycols would not be a good choice if oxidation were an issue. For cryoprotection, it is the concentration of the cryoprotectant in solution that is the key concentration variable, regardless of the concentration of protein in the formulation. With non-polymer excluded solutes, relatively high concentrations (i.e., 0.2–0.5 M) are normally required for effective cryoprotection.^[85]

Stabilization during drying

In addition to the stresses that develop during freezing, drying imposes an additional stress associated with essentially complete removal of water. Indeed, the water substitute hypothesis^[41,85–87] is based upon the proposition that a significant thermodynamic destabilization occurs when the hydrogen bonding between protein and water is lost during the last stages of drying. The use of a water substitute as a lyoprotectant allows a hydrogen-bonding interaction between protein and the water substitute, which thermodynamically stabilizes the native conformation and preserves activity. A water substitute is a moiety that is capable of hydrogen bonding to the protein surface much as water and stabilizes via a thermodynamic mechanism; that is, stabilization is achieved by maintaining the free energy of unfolding very high such that essentially all of the protein is maintained in the native conformation. However, it must be recognized that most observations can also be rationalized in terms of a purely kinetic stabilization mechanism. In general, drying is conducted at temperatures sufficiently low that the protein exists in a glassy solid state where molecular mobility is greatly restricted. It may be argued^[41] that a good stabilizer is a component that effectively couples protein dynamics to the dynamics of the glass such that even if the protein is destabilized thermodynamically, motion in the protein is too slow to allow significant unfolding during the drying operation. Thus, the protein conformation is stabilized regardless of the free energy of unfolding.

Non-reducing di- and tri-saccharides such as sucrose, trehalose, or raffinose are normally good drying stabilizers.^[41,85,86] They qualify as good water substitutes and also form glasses which, via hydrogen bonding, can couple protein dynamics to matrix dynamics. Under conditions of acid pH, particularly below pH 5, trehalose is a much more effective stabilizer than are sucrose or raffinose. Sucrose and raffinose hydrolyze to their reducing sugar components much more rapidly in the solid state than does trehalose, thereby leading to degradations initiated by reducing sugars.^[88] The key concentration variable in drying stabilization is the weight ratio (or mole ratio) of saccharide to protein, with the weight ratio of stabilizer to protein normally being between 1:1 and 10:1. The principle here is to insure that the protein is in a matrix of the stabilizer. Thus, with dilute protein systems, good stabilization can often be obtained at rather low concentrations of stabilizer. Here, it may be desirable to employ both a bulking agent such as glycine or mannitol, as well as a stabilizer. This strategy can yield both an elegant cake structure as well as optimal stability without the high solute concentrations than can slow primary drying.

Stabilization during storage

Although the destabilization stresses during storage remain much the same as the drying stresses, the time scale of storage is obviously much longer than the timescale of freeze-drying. In addition, the freeze-dried product is normally being stored well below its glass transition temperature, meaning molecular mobility is greatly restricted.^[41,85,86] Because of these differences, the dominant degradation pathway during storage may differ from the degradation pathway during freeze-drying. For example, deamidation of asparagine residues is a very common degradation pathway during storage but rarely is a problem during processing. This observation does not imply that deamidation is faster in the dry glassy solid than in solution, but rather is simply the result of the much longer time scale of storage. Indeed, because of the need to insure stability over the shelf life of about 2 years, storage stability normally presents a more serious problem than does stability during processing. Degradation during storage may arise from chemical degradation, such as oxidation and asparagine deamidation, and/or aggregation to non-covalent or covalent aggregates.^[41,85,86] Aggregation often means formation of a population of very large insoluble aggregates that precipitate from solution. It must be admitted, however, that the observation that the level of aggregation increases during storage does not necessarily mean that the bimolecular process of aggregation occurs in the solid state. It is also possible that only conformational changes occur during storage. Aggregation of a fraction of the conformationally modified protein could then occur instantaneously during reconstitution. The remaining fraction would then refold to the native conformation. As aggregation is normally measured in solution, it is not possible to determine just when the aggregation step actually does occur. When the amount of aggregation measured depends on the reconstitution procedure and/or the composition of the diluent (i.e., presence of surfactant) used to reconstitute,^[32] one would conclude that, at least in part, aggregation of (partially) unfolded protein occurs during reconstitution.

Stabilization strategies focus on three general factors: (1) specific chemical requirements; (2) physical state of the solid; and (3) structure of the protein. Depending on the degradation pathway(s) and mechanisms, any one or all of these factors could be critical. Certainly, if oxidation is a major degradation pathway, stabilization requires attention to the chemical composition of the system, including both the effects of impurities and addition of stabilizers as discussed earlier. Although pH has no real meaning in the solid state, the degree of ionization in the solid does reflect the pH of the solution from which the solid was

prepared, and pH of the solution can be a major variable. Because differences in polarity of the environment between a dry solid and an aqueous solution may mean that the optimum pH for solid stability is somewhat different than the optimal pH for a solution, some solid-state screening experiments are necessary to define the precise optimum pH for stability of the freeze-dried solid.

The physical state of the system is of obvious importance. We freeze dry to increase storage stability relative to the solution state, assuming that the restricted molecular mobility of the solid state will lead to stabilization. In general, an amorphous solid (i.e., glass) is several orders of magnitude more stable than the corresponding aqueous solution, and at least with small molecules, crystalline drugs are much more stable than glasses.^[89] However, proteins cannot be crystallized during freeze-drying, so the only solid-state option is a glass. Forming a glass does not insure adequate stability. Pure dried proteins are glasses and often do not have sufficient stability for long-term storage at the temperatures of interest, and excipients are added to the formulation to stabilize. Because a physical mixture of protein and excipient will not provide additional stabilization, it is necessary that the proposed stabilizer system remain at least partially amorphous and in the same phase as the protein.^[41,85,86] Further, to avoid chemical reactions between the excipient and protein, the excipient system must be inert. The most common violation of inertness is the use of reducing sugars such as lactose in an attempt to stabilize the protein. For example, while lactose will stabilize hGH against aggregation, an adduct of lactose and hGH quickly forms during storage of the freeze-dried solid.^[18]

Drying also removes water, a reactant in a hydrolysis reaction, and stability is normally best at very low water content.^[41,85,86] However, the effect of residual moisture on stability is far more complex than its possible role as a reactant. Residual water has a major effect on the physical state of the system in that increasing levels of residual moisture decreases the glass transition temperature of the amorphous system, thereby making the system less solid-like at a given temperature, and eventually causing the glass to transform into a fluid at the storage temperature. Fig. 12 illustrates the effect of residual moisture on the glass transition temperature of two common stabilizers, sucrose and trehalose.^[90] For both examples, small amounts of residual water greatly depress the glass transition temperature, but since dry sucrose has a much lower glass transition temperature than does dry trehalose, the water content that gives a glass transition temperature at room temperature, T_g (25°C), is much lower for sucrose. Thus, in applications where maintaining very low water content is difficult, trehalose is a better choice for a stabilizer than is sucrose.

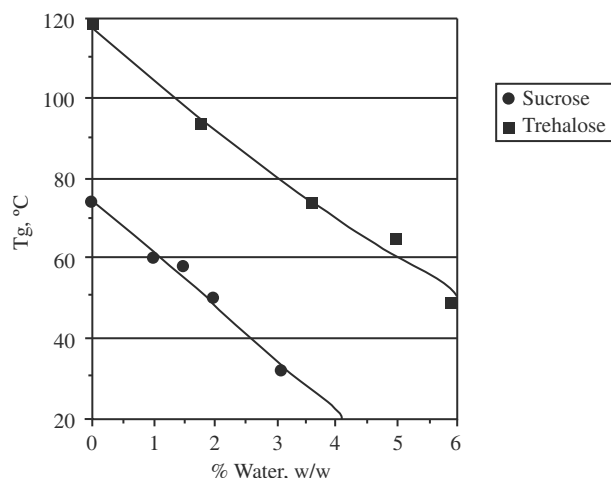


Fig. 12 The effect of residual water on the glass transition temperatures of sucrose and trehalose. (From Ref.^[90].)

Generally, chemical and physical stability decrease sharply as the system enters the fluid state.^[41,86,91,92] Chemical degradation of hGH in a trehalose formulation illustrates this behavior.^[92] The trehalose formulation shows a well-defined glass transition temperature with DSC, with the expected decrease in T_g as the water content is increased. The rate constant for chemical degradation is essentially independent of water content while the system remains glassy, but at least for the 50°C data, degradation increases sharply as increasing water content depresses the system glass transition temperature significantly below the storage temperature (Fig. 13). Rates of aggregation show essentially the same behavior.^[92] However, as stability is not sensitive to water content in the glassy state, stability is not correlated with $T - T_g$ below the glass transition temperature. The study of formulation effects on hGH stability suggests the same conclusion. Chemical and aggregation stability of hGH in several formulations is compared in Fig. 14.^[92] The glycine:mannitol formulation is a 1:1:5 weight ratio of hGH:glycine:mannitol, where only the mannitol is crystalline. The other formulations are 100% amorphous. Hydroxyethyl starch (HES), stachyose, and trehalose are formulated in a 1:1 weight ratio of excipient:hGH, whereas the dextran formulation is 6:1 dextran:hGH. While the concept that an excipient system must remain at least partially amorphous to improve protein stability is not in question, it is clear that remaining amorphous is not a sufficient condition for stability. Apparent aggregation in the dextran formulation is greater than in the pure protein. Hydroxyethyl starch shows a slight improvement in stability over the pure protein, but is not nearly as effective as the glycine:mannitol formulation, and increasing the level of HES to 3:1 HES:hGH does not improve stability.^[92] Conversely, both stachyose

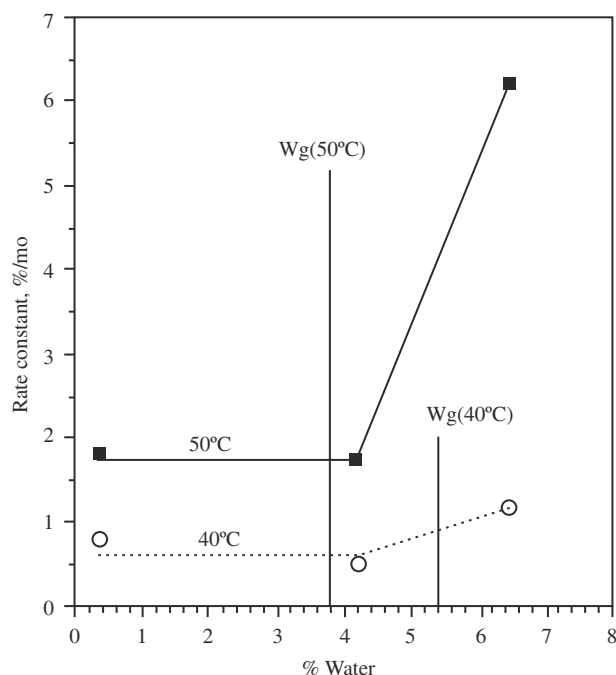


Fig. 13 Chemical degradation in freeze dried hGH formulated with trehalose as a function of water content at 40°C and 50°C. The pseudo first-order rate constant for degradation (%/month) is given for the combination of asparagine deamidation and methionine oxidation. The formulation is hGH:trehalose in a 1:6 weight ratio with sodium phosphate buffer (pH 7.4) at 15% of the hGH content. The highest moisture content samples were collapsed after storage at both 40°C (moderate collapse) and 50°C (severe collapse). The water content that reduces the glass transition temperature of the formulation to the storage temperature is denoted “Wg.” ○ = 40°C storage; ■ = 50°C storage. (From Ref.^[86].)

and trehalose provide better stability than the glycine:mannitol system does, with trehalose superior to stachyose. All systems are glasses at the storage temperature of 40°C, and for those formulations where glass transition temperatures are available, it is clear that storage is well below the T_g , and there is no simple relationship between T_g and stability. Although one might speculate that a glass is more solid, and therefore more stable, the larger the difference between T_g and the storage temperature, the data are not consistent with this speculation. Comparing the stachyose and trehalose formulations, which are both 1:1 formulations with hGH, the T_g of the stachyose formulation is nearly 20°C higher than that of the trehalose formulation, but trehalose offers slightly better stability than does stachyose. These observations and other similar results^[92] suggest that while it is necessary for the formulation to have a T_g well above the highest anticipated storage temperature for both elegance and stability reasons, stability well below T_g is not

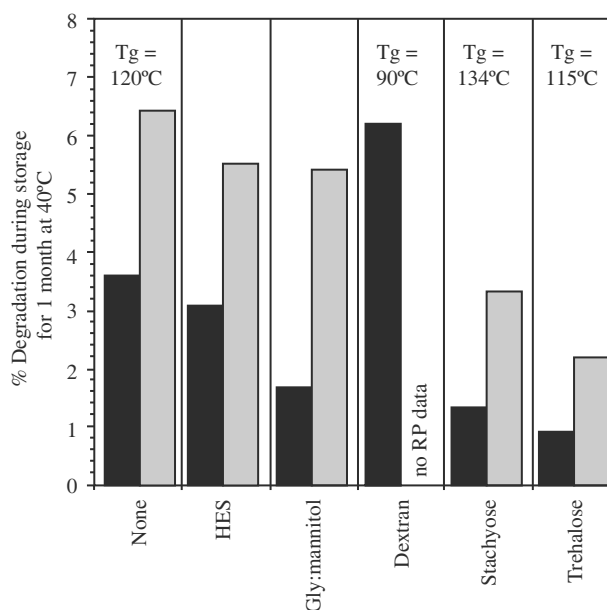


Fig. 14 The effect of excipients on the storage stability of freeze-dried human growth hormone (hGH). Samples were stored for 1 month at 40°C. Solid bars: aggregation (primarily dimer), shaded bar = chemical degradation via methionine oxidation and asparagine deamidation. The glass transition temperatures of the initial freeze-dried formulations are given above the bars when a glass transition temperature could be measured by DSC. The glycine:mannitol formulation is a weight ratio of hGH:glycine:mannitol of 1:1:5, the dextran formulation is 1:6 hGH:dextran 40, none means no stabilizer, and the others are 1:1 hGH:stabilizer. All formulations contain sodium phosphate buffer (pH 7.4) at 15% of the hGH content. Initial moisture contents are all ≈1%. (From Ref.^[86].)

directly related to the precise difference between storage temperature and T_g .

The lack of a clear correlation between stability and T_g for systems well below T_g is not entirely unexpected. Molecular mobility slows greatly below T_g , but does not approach zero until some temperature much lower than T_g .^[41,86] Thus, dynamics in the glass depend not only on the value of T_g but are also extremely sensitive to other characteristics of the glass as well as the thermal history of the glass.^[41,93] Even if the major component of the glassy matrix (i.e., the sucrose) were to have essentially zero mobility (i.e., negligible translational and rotational motion), mobility of small molecules (i.e., diffusion of water) could still be significant, and mobility of potentially reactive groups on the protein (i.e., asparagine side chain) could be sufficient to reorient into the transition state and react.^[41] Thus, it is not only necessary that the matrix itself be solid-like, but effective coupling between matrix mobility and the mobility critical for degradation is needed for solid-like stability behavior.^[41] Although the molecular

characteristics required for effective coupling are not fully understood, it does seem that hydrogen bonding between protein and stabilizer provides one coupling mechanism.^[41,86] Thus, disaccharides and trisaccharides are effective stabilizers.

With proteins, structure is also a critical stability variable. It is now common knowledge that proteins often suffer significant conformational changes on freeze-drying that may be moderated by addition of stabilizers to the formulation.^[41,85,86] In principle, different conformations may have different stability characteristics with the native conformation normally believed to represent the most stable conformation.^[41,85,86] Indeed data for rIL-2 show a strong correlation between storage stability and structure as measured by Fourier transform infrared spectroscopy (FTIR),^[21] with a more native conformation associated with greater storage stability. Likewise, formulations of freeze-dried hGH having more native-like conformations are more stable to both aggregation and chemical degradation during storage.^[92] Thus, degradation of a protein in any given formulation is a function of the distribution and reactivities of the protein substates created during the freeze-drying process, with greater stability being associated with the more native-like substates. From this viewpoint, a good stabilizer is one that maximizes the population of native-like substates. Empirical evidence suggests that disaccharides perform this function quite well, regardless of what mechanism might be postulated to explain the observation.^[41,85,86]

In summary, guidelines for stabilization during storage involve the following principles: 1) optimize pH and address specific chemical effects such as oxidation; 2) disperse the protein in an inert glassy matrix with strong coupling between protein dynamics and matrix dynamics to form an amorphous phase such that at all residual water contents and storage temperatures of interest the protein phase will be well below its glass-transition temperature (note that this requires both protein and stabilizer exist in the same glassy phase); 3) employ a formulation (and process) such that the dried protein will retain the native conformation.

Retention of native conformation, coupling of protein mobility with matrix mobility, and formation of a single phase with the stabilizer all require an excipient that interacts, probably via hydrogen bonding, with the surface of the protein. Little or no interaction would likely lead to phase separation, poor coupling of protein mobility with matrix mobility, and no opportunity for the excipient to stabilize the native conformation by either water substitution or immobilization of the protein. Disaccharides (i.e., sucrose and trehalose) and trisaccharides (i.e., raffinose) seem to satisfy these criteria and are generally good stabilizers. Polymers are generally much less effective.

A product glass-transition temperature well above all anticipated storage conditions is an important product quality attribute. Glass transition temperatures of selected amorphous excipients are given in Table 3. Both trehalose and raffinose have much higher glass transition temperatures than does sucrose, and in this sense, would be better choices for stabilizers. However, as long as the residual water content is maintained low and the product is not plasticized by other low-molecular-weight formulation components, a sucrose formulation will be well below its glass-transition temperature at all practical storage temperatures. Due to a very low T_g , sorbitol should not be used as a major formulation component. Incomplete crystallization of glycine or mannitol may also lead to low product glass-transition temperatures. Lactose and maltose have high glass transition temperatures but are reducing sugars and, therefore, are poor stabilizer candidates. As noted earlier, applications at low pH pose problems for both sucrose and raffinose due to rapid hydrolysis to the reducing sugar components. Trehalose is a better choice for low pH applications.

As with drying stabilization, stabilization of a protein for storage with saccharides generally requires a weight ratio of stabilizer to protein between 1:1 and 10:1, with better stabilization at the higher excipient levels. At least for hGH, the rate constants for degradation (chemical degradation and aggregation) decrease linearly on a plot of the logarithm of rate constant as a function of stabilizer:hGH weight ratio.^[92] With high dose products where the protein concentration in the fill solution is high, use of high ratios of stabilizer to protein may not be feasible due to the extremely high concentration of stabilizer that would be required.

Table 3 Glass transition temperatures, (T_g), of selected excipients measured by differential scanning calorimetry^a

Compound	T_g (°C)	References
Citric acid	11	[94]
Glycine	(≈ 30) ^b	[66]
Lactose	114	[95]
Maltose	100	[95]
Mannitol	13	[74,96]
Raffinose	114	[95]
Sorbitol	-1.6	[96]
Sucrose	75	[95]
Trehalose	118	[95]
Maltodextrin 860	169	[95]
PVP K90	176	[95]

^aConsult the references for details of the techniques.

^bValue in parentheses is extrapolated from mixtures using the Fox equation and is highly approximate.

REFERENCES

- Pikal, M.J.; Lukes, A.L.; Lang, J.E. Thermal decomposition of amorphous beta-lactam antibacterials. *J. Pharm. Sci.* **1977**, *66*, 1312–1316.
- Pikal, M.J.; Lukes, A.L.; Lang, J.E.; Gaines, K. Quantitative crystallinity determinations of beta-lactam antibiotics by solution calorimetry: correlations with stability. *J. Pharm. Sci.* **1978**, *67*, 767–773.
- Pikal, M.J.; Dellerman, K.M. Stability testing of pharmaceuticals by high-sensitivity isothermal calorimetry at 25°C: cephalosporins in the solid and aqueous solution states. *Int. J. Pharm.* **1989**, *50*, 233–252.
- Pikal, M.J. Freeze drying of proteins, part I: process design. *Biopharm.* **1990**, *3* (8), 18–27.
- Pikal, M.J. Freeze drying of proteins: part II. formulation selection. *Biopharm.* **1990**, *3* (9), 26–30.
- Pikal, M.J. Freeze drying of proteins: process, formulation, and stability. In *Formulation and Delivery of Proteins and Peptides*; Cleland, J.L., Langer, R., Eds.; ACS Symposium Series 567; ACS: Washington, DC, 1994; 120–133.
- MacKenzie, A.P. Factors affecting the mechanism of transformation of ice into water vapor in the freeze drying process. *Ann. N. Y. Acad. Sci.* **1965**, *125*, 522–547.
- Broadhead, J.; Rouan, S.K.E.; Rhodes, C.T. The spray drying of pharmaceuticals. *Drug Dev. Ind. Pharm.* **1992**, *18*, 1169–1206.
- Mumenthaler, M.; Hsu, C.C.; Pearlman, R. Feasibility study on spray-drying protein pharmaceuticals: recombinant human growth hormone and tissue-type plasminogen activator. *Pharm. Res.* **1994**, *11*, 12–20.
- Masters, K. Applications of spray-drying in the food industry, in the pharmaceutical-biochemical industry. In *Spray-Drying Handbook*, 5th Ed.; Longman Scientific and Technical: Essex, UK, 1991; 491–676.
- Parenteral lyophilization facilities: an innovative approach to loading and unloading operations. Proceedings of the International Congress, on Advanced Technologies for Manufacturing of Aseptic and Terminally Sterilized Pharmaceuticals and Biopharmaceuticals Basel Switzerland Feb. 17–19, 1992; 4–30.
- Carpenter, J.; Crowe, J.; Arakawa, T. Comparison of solute-induced protein stabilization in aqueous solution and in the frozen and dried states. *J. Dairy Sci.* **1990**, *73*, 3627–3636.
- Tanaka, R.; Takeda, T.; Miyajima, K. Cryoprotective effect of saccharides on denaturation of catalase by freeze drying. *Chem. Pharm. Bull.* **1991**, 1091–1094.
- Hellman, K.; Miller, D.; Cammack, K. The effect of freeze drying on the quaternary structure of L-asparaginase from *erwinia carotovora*. *Biochim. Biophys. Acta* **1983**, *749*, 133–142.
- Ressing, M.E.; Jiskoot, W.; Talsma, H.; van Ingen, C.W.; Beuvery, E.C.; Crommelin, D.J.A. The influence of sucrose, dextran, and hydroxypropyl- β -cyclodextrin as lyoprotectants for a freeze dried mouse IgG_{2a} monoclonal antibody (MN12). *Pharm. Res.* **1992**, *9*, 266–270.
- Izutsu, K.; Yoshioka, S. Stabilization of protein pharmaceuticals in freeze dried formulations. *Drug Stabil.* **1995**, *1*, 11–21.
- Bell, L.N.; Hageman, M.J. Differentiating between the effects of water activity and glass transition dependent mobility on a solid state chemical reaction: aspartame degradation. *J. Agric. Food Chem.* **1994**, *42*, 2398–2401.
- Pikal, M.J.; Dellerman, K.M.; Roy, M.L.; Riggan, R.M. The effects of formulation variables on the stability of freeze dried human growth hormone. *Pharm. Res.* **1991**, *8*, 427–436.
- Pikal, M.J.; Dellerman, K.M.; Roy, M.L. Formulation and stability of freeze dried proteins: effects of moisture and oxygen on the stability of freeze dried formulations of human growth hormone. *Develop. Biol. Standard* **1991**, *74*, 323–340.
- Townsend, M.W.; DeLuca, P.P. Use of lyoprotectants in the freeze drying of a model protein. Ribonuclease A. *J. Parenter. Sci., Technol.* **1988**, *42*, 190–199.
- Prestrelski, S.J.; Pikal, K.A.; Arakawa, T. Optimization of lyophilization conditions for recombinant interleukin-2 by dried-state conformational analysis using fourier-transform infrared spectroscopy. *Pharm. Res.* **1995**, *12*, 1250–1259.
- Roy, M.L.; Pikal, M.J.; Rickard, E.C.; Maloney, A.M. The effects of formulation and moisture on the stability of a freeze dried monoclonal antibody-vinca conjugate: a test of the wlf glass transition theory. *Develop. Biol. Standard* **1991**, *74*, 323–340.
- Kiovsky, T.E.; Pincock, R.E. Kinetics of reactions in frozen solutions. *J. Am. Chem. Soc.* **1966**, *88*, 7704–7710.
- Franks, F. Freeze drying: from empiricism to predictability. *Cryo-Letters* **1990**, *11*, 93–110.
- Pikal, M.J.; Shah, S. The collapse temperature in freeze drying: dependence on measurement methodology and rate of water removal from the glassy phase. *Int. J. Pharm.* **1990**, *62*, 165–186.
- Williams, N.A.; Dean, T. Vial breakage by frozen mannitol solutions: correlation with thermal characteristics and effect of stereoisomerism, additives, and vial configuration. *J. Parenter. Sci. Technol.* **1991**, *45*, 94–100.
- Larsen, S.S. Studies on stability of drugs in frozen systems. *Arch. Pharm. Chem. Sci. Ed.* **1973**, *1*, 41–53.
- Murase, N.; Franks, F. Salt precipitation during the freeze-concentration of phosphate buffer solutions. *Biophys. Chem.* **1989**, *34*, 293–300.
- Gomez, G.; Rodriguez-Hornedo, N.; Pikal, M.J. Effect of freezing on the pH of sodium phosphate buffer solutions. *Pharm. Res.* **1994**, *11*, S-265, PPD 7364.
- Szkudlarek, B.A.; Rodriguez-Hornedo, N.; Pikal, M.J. Analysis of pH changes of potassium phosphate buffer salt solutions during freezing. *Pharm. Res.* **1994**, *11*, S-228, PPD 7215.
- Arakawa, T.; Prestrelski, S.; Kinney, W.; Carpenter, J.F. Factors affecting short-term and long-term stabilities of proteins. *Adv. Drug Delivery Rev.* **1993**, *10*, 1–28.
- Carpenter, J.F.; Prestrelski, S.; Arakawa, T. Separation of freezing- and drying-induced denaturation of lyophilized proteins by stress-specific stabilization: I. Enzyme activity and calorimetric studies. *Arch. Biochem. Biophys.* **1993**, *303*, 456–464.
- Franks, F.F. Product stability during drying. *BioPharm Conference, Proceedings 1993, Advanstar Communications: Eugene, Oregon, 1993; 78–87.*
- Franks, F. *Biophysics and Biochemistry at Low Temperature*; Cambridge University Press: London, 1985.
- Privalov, P. Cold denaturation of proteins. *Biochem. and Mol. Biol.* **1990**, *25*, 281–305.
- Tsong, T.Y.; Baldwin, R.L. Effects of solvent viscosity and different guanidine salts on the kinetics of ribonuclease a chain folding. *Biopolymers* **1978**, *17*, 1669–1678.
- Kiefhaber, T.; Quaas, R.; Hahn, U.; Schmid, F.X. Folding of ribonuclease T₁. 1. Existence of multiple unfolded states created by proline isomerization. *Biochemistry* **1990**, *29*, 3053–3061.
- Lim, M.; Reid, D. Studies of reaction kinetics in relation to the T_g' of polymers in frozen model systems. In *Water Relationships in Food*; Levine, H., Slade, L., Eds.; Plenum Press: New York, 1991; 103–122.
- Pikal, M.J.; Shah, S.; Senior, D.; Lang, J.E. Physical chemistry of freeze drying: measurement of sublimation rates for frozen aqueous solutions by a micro balance technique. *J. Pharm. Sci.* **1983**, *72*, 635–650.
- Pikal, M.J.; Shah, S.; Roy, M.L.; Putman, R. The secondary drying stage of freeze drying: drying kinetics as a function of temperature and chamber pressure. *Int. J. Pharm.* **1990**, *60*, 203–217.
- Pikal, M.J. Mechanisms of protein stabilization during freeze drying and storage: the relative importance of thermodynamic stabilization and glassy state relaxation dynamics. In *Freeze Drying/Lyophilization of Pharmaceutical*

- and Biological Products; Rey, L., May, J., Eds.; Marcel Dekker, Inc., 1999.
42. Chang, B.S.; Kendrick, B.S.; Carpenter, J.F. Surface-induced denaturation of proteins during freezing and its inhibition by surfactants. *J. Pharm. Sci.* **1996**, *85*, 1325–1330.
 43. Roy, M.L.; Pikal, M.J. Process control in freeze drying: determination of the end point of sublimation drying by an electronic moisture sensor. *J. Parenter. Sci. Technol.* **1989**, *60*, 60–66.
 44. Pikal, M.J.; Roy, M.L.; Shah, S. Mass and heat transfer in vial freeze drying of pharmaceuticals: role of the vial. *J. Pharm. Sci.* **1984**, *73*, 1224–1237.
 45. MacKenzie, A.P. Basic principles of freeze drying for pharmaceuticals. *Bull. Par. Drug Assoc.* **1966**, *20*, 101–129.
 46. Chang, B.S.; Randall, C.S. Use of subambient thermal analysis to optimize protein lyophilization. *Cryobiology* **1992**, *29*, 632–656.
 47. Pikal, M.J. Use of laboratory data in freeze drying process design: heat and mass transfer coefficients and the computer simulation of freeze drying. *J. Parenter. Sci., Technol.* **1985**, *39*, 115–138.
 48. Milton, N.; Nail, S.L.; Roy, M.L.; Pikal, M.J. Evaluation of manometric temperature measurement as a method of monitoring product temperature during lyophilization. *PDA J. Pharm. Sci. Technol.* **1997**, *51*, 7–16.
 49. Kobayashi, M. Development of new refrigeration system and optimum geometry of the vapor condenser for pharmaceutical freeze dryers proceedings of the 4th International drying symposium, Kyoto, Japan, July 9–12, 1984; Toei, R.R., Mujumdar, A., Eds.; *2*, 464–471.
 50. Pikal, M.J.; Lang, J.E. Rubber closures as a source of haze in freeze dried parenterals: test methodology for closure evaluation. *J. Parenter Drug Assoc.* **1978**, *32*, 162.
 51. Bardat, A.; Biguet, J.; Chatenet, J.; Courteille, F. Moisture measurement: a new method for monitoring freeze drying cycles. *J. Parenter Sci. Technol.* **1993**, *47*, 293–299.
 52. Moreira, T.; Cabrera, L.; Gutierrez, A.; Cadiz, A.; Castellano, M. Role of temperature and moisture on monomer content of freeze dried human albumin. *Acta Pharm. Nord.* **1992**, *4*, 59–60.
 53. Pristoupil, T.; Kramlova, M.; Fortova, H.; Ulrych, S. Haemoglobin lyophilized with sucrose: the effect of residual moisture on storage. *Haematologia* **1985**, *18*, 45–52.
 54. Hageman, M.J. The role of moisture in protein stability. *Drug Dev. Ind. Pharm.* **1988**, *14*, 2047–2070.
 55. Greiff, D. Protein structure and freeze drying: the effects of residual moisture and gases. *Cryobiology* **1971**, *8*, 145–152.
 56. Hsu, C.; Ward, C.; Pearlman, R.; Nguyen, H.; Yeung, D.; Curley, J. Determining the optimum residual moisture in lyophilized protein pharmaceuticals. *Develop. Biol. Standard* **1991**, *74*, 255–271.
 57. Pikal, M.J.; Shah, S. Moisture transfer from stopper to product and resulting stability implications. *Develop. Biol. Standard* **1991**, *74*, 165–179.
 58. MacKenzie, A.P. Collapse during freeze drying qualitative and quantitative aspects. In *Freeze Drying and Advanced Food Technology*; Goldblith, S.A., Rey, L., Rothmayr, W.W., Eds.; Academic Press: London, 1975; 277–307.
 59. Her, L.M.; Nail, S.L. Measurement of glass transition temperatures of freeze-concentrated solutes by differential scanning calorimetry. *Pharm. Res.* **1994**, *11*, 54–59.
 60. Pikal, M.J.; Shah, S. Unpublished Data Eli Lilly & Co.
 61. MacKenzie, A.P.; as Cited in Ref.^[4].
 62. Slade, L.; Levine, H. Beyond water activity: recent advances based on an alternative approach to the assessment of food quality and safety. *Crit. Rev. Food Sci. Nutr.* **1991**, *30*, 115–360.
 63. Pikal, M.J.; Chang, L.Q.; Unpublished Data University of Connecticut.
 64. Shalae, E.Y.; Kanev, A.N. Study of the solid-liquid state diagram of the water–glycine–sucrose system. *Cryobiology* **1994**, *31*, 374–382.
 65. Shalae, E.; Malakhov, D.V.; Kanev, A.N.; Tuzikov, F.V.; Varaskin, N.D.; Vavilin, V.I. Study of the phase diagram water fraction of the system water–glycine–sucrose by DTA and X-ray diffraction methods. *Thermochim. Acta* **1992**, *196*, 213–220.
 66. Lueckel, B.; Bodmer, D.; Helk, B.; Leuenberger, H. Formulations of sugars with amino acids or mannitol-influence of concentration ratio on the properties of the freeze-concentrate and the lyophilizate. *Pharm. Develop. and Technol.* **1998**, *3*, 325–336.
 67. Suzuki, T.; Franks, F. Solid–liquid phase transitions and amorphous states in ternary sucrose–glycine–water systems. *J. Chem. Soc., Faraday Trans.* **1993**, *89*, 3283–3288.
 68. Kassraian, K.; Spitznagel, T.; Juneau, J.; Yim, K. Characterization of the sucrose/glycine/water system by differential scanning calorimetry and freeze drying microscopy. *Pharm. Develop. and Technol.* **1998**, *3*, 233–239.
 69. Hancock, B.C.; Zografi, G. The relationship between the glass transition temperature and the water content of amorphous pharmaceutical solids. *Pharm. Res.* **1994**, *11*, 471–477.
 70. Williams, N.A.; Lee, Y.; Polli, G.P.; Jennings, T.A. The effects of cooling rate on solid phase transitions and associated vial breakage occurring in frozen mannitol solutions. *J. Parentes. Sci. and Tech.* **1986**, *40*, 135.
 71. Williams, N.A.; Guglielmo, J. Thermal mechanical analysis of frozen solutions of mannitol and some related stereoisomers: evidence of expansion during warming and correlation with vial breakage during lyophilization. *J. Parenter Sci., and Technol.* **1993**, *47*, 119–123.
 72. Akers, M.J.; Milton, N.; Byrn, S.R.; Nail, S.L. Glycine crystallization during freezing: the effects of salt form, pH, and ionic strength. *Pharm. Res.* **1995**, *12*, 1457–1461.
 73. Yu, L.; Milton, N.; Groleau, E.; Mishra, D.; Vansickle, R. Existence of a mannitol hydrate during freeze drying and practical implications. *J. Pharm. Sci.* **1999**, *88*, 196–199.
 74. Kim, A.I.; Akers, M.J.; Nail, S.L. The physical state of mannitol after freeze drying: effects of mannitol concentration, freezing rate, and a noncrystallizing cosolute. *J. Pharm. Sci.* **1998**, *87*, 931–935.
 75. Cavatur, R.K.; Suryanarayanan, R. Characterization of phase transitions during freeze drying by in situ X-ray powder diffractometry. *Pharm. Develop. and Technol.* **1998**, *3*, 579–586.
 76. Bam, N.B.; Cleland, J.L.; Yang, J.; Manning, M.C.; Carpenter, J.F.; Kelley, R.F.; Randolph, T.W. Tween protects recombinant human growth hormone against agitation-induced damage via hydrophobic interactions. *J. Pharm. Sci.* **1998**, *87*, 1554–1559.
 77. Bam, N.B.; Randolph, T.W.; Cleland, J.L. Stability of protein formulations: investigation of surfactant effects by a novel EPR spectroscopic technique. *Pharm. Res.* **1995**, *12*, 2–11.
 78. Kerwin, B.A.; Heller, M.C.; Levin, S.H.; Randolph, T.W. Effects of tween 80 and sucrose on acute short-term stability and long-term storage at -20°C of a recombinant hemoglobin. *J. Pharm. Sci.* **1998**, *87*, 1062–1068.
 79. Li, S.; Schoneich, C.; Borchard, R. Chemical instability of protein pharmaceuticals: mechanisms of oxidation and strategies for stabilization. *Biotech. Bioeng.* **1995**, *48*, 490–500.
 80. Li, S.; Schoneich, C.; Wilson, G.; Borchardt, R. Chemical pathways of peptide degradation. V. Ascorbic acid promotes rather than inhibits the oxidation of methionine to methionine sulfoxide in small model peptides. *Pharm. Res.* **1993**, *10*, 1572–1579.
 81. Stadman, E.R. Metal ion-catalyzed oxidation of proteins: biochemical mechanism and biological consequences. *Free Radical Biol. Med.* **1990**, *9*, 315–325.
 82. Hall, P.; Roberts, R. Methionine oxidation and inactivation of α_1 -proteinase inhibitor by Cu^{2+} and glucose. *Biochim. Biophys. Acta* **1992**, *1121*, 325–330.
 83. Li, S.; Schoneich, C.; Borchardt, R. Chemical pathways of peptide degradation. VIII. Oxidation of methionine in small model peptides by prooxidant/transition metal ion systems: influence of selective scavengers for reactive oxygen intermediates. *Pharm. Res.* **1995**, *12*, 348–355.

84. Brems, D.N. Solubility of different folding conformers of bovine growth hormone. *Biochemistry* **1988**, *27*, 4541–4546.
85. Carpenter, J.R.; Pikal, M.J.; Chang, B.S.; Randolph, T.W. Rational design of stable lyophilized protein formulations: some practical advice. *Pharm. Res.* **1997**, *14*, 969–975.
86. Pikal, M.J. Freeze drying of proteins. In *Peptide and Protein Delivery*; Lee, V.H.L., Ed.; Marcel Dekker, Inc.: New York. *In press*.
87. Arakawa, T.; Kita, Y.; Carpenter, J.F. Protein–solvent interactions in pharmaceutical formulations. *Pharm. Res.* **1991**, *8*, 285–291.
88. Pikal, M.; Busse, J.; Kovach, P. Unpublished Results Eli Lilly & Co.
89. Pikal, M.J. Impact of polymorphism on the quality of lyophilized products. In *Polymorphism in Pharmaceutical Solids*; Brittain, H.G., Ed.; Marcel Dekker, Inc.: New York, 1999.
90. Saleki-Gerhardt, A. Ph.D. thesis, university of Wisconsin-Madison, 1993.
91. Duddu, S.; Zhang, G.; Dal Monte, P. The relationship between protein aggregation and molecular mobility below the glass transition temperature of lyophilized formulations containing a monoclonal antibody. *Pharm. Res.* **1997**, *14*, 596–600.
92. Pikal, M.J.; Roy, M.L.; Rigsbee, D.R. Unpublished Data Eli Lilly & Co.
93. Shamblin, S.L.; Tang, X.; Chang, L.; Hancock, B.C.; Pikal, M.J. Characterization of the time scales of molecular motion in pharmaceutically important glasses. *J. Phys. Chem. B.* **1999**, *103*, 4113–4121.
94. Lu, Q.; Zografi, G. Properties of citric acid at the glass transition. *J. Pharm. Sci.* **1997**, *86*, 1374–1378.
95. Taylor, L.; Zografi, G. Sugar–polymer hydrogen bond interactions in lyophilized amorphous mixtures. *J. Pharm. Sci.* **1998**, *87*, 1615–1620.
96. Yu, L.; Mishra, D.; Rigsbee, D. Determination of the glass properties of D-mannitol using sorbitol as an impurity. *J. Pharm. Sci.* **1998**, *87*, 774–777.