

PHARMACEUTICAL MANUFACTURING HANDBOOK

Production and Processes

SHAYNE COX GAD, PH.D., D.A.B.T.

Gad Consulting Services
Cary, North Carolina

 **WILEY-INTERSCIENCE**
A JOHN WILEY & SONS, INC., PUBLICATION

Copyright © 2008 by John Wiley & Sons, Inc. All rights reserved

Published by John Wiley & Sons, Inc., Hoboken, New Jersey
Published simultaneously in Canada

No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, scanning, or otherwise, except as permitted under Section 107 or 108 of the 1976 United States Copyright Act, without either the prior written permission of the Publisher, or authorization through payment of the appropriate per-copy fee to the Copyright Clearance Center, Inc., 222 Rosewood Drive, Danvers, MA 01923, (978) 750-8400, fax (978) 750-4470, or on the web at www.copyright.com. Requests to the Publisher for permission should be addressed to the Permissions Department, John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, (201) 748-6011, fax (201) 748-6008, or online at <http://www.wiley.com/go/permission>.

Limit of Liability/Disclaimer of Warranty: While the publisher and author have used their best efforts in preparing this book, they make no representations or warranties with respect to the accuracy or completeness of contents of this book and specifically disclaim any implied warranties of merchantability or fitness for a particular purpose. No warranty may be created or extended by sales representatives or written sales materials. The advice and strategies contained herein may not be suitable for your situation. You should consult with a professional where appropriate. Neither the publisher nor author shall be liable for any loss of profit or any other commercial damages, including but not limited to special, incidental, consequential, or other damages.

For general information on our other products and services or for technical support, please contact our Customer Care Department within the United States at (800) 762-2974, outside the United States at (317) 572-3993 or fax (317) 572-4002.

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic formats. For more information about Wiley products, visit our web site at www.wiley.com.

Library of Congress Cataloging-in-Publication Data is available.

ISBN: 978-0-470-25958-0

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

CONTENTS

PREFACE	xiii
SECTION 1 MANUFACTURING SPECIALTIES	1
1.1 Biotechnology-Derived Drug Product Development	3
<i>Stephen M. Carl, David J. Lindley, Gregory T. Knipp, Kenneth R. Morris, Erin Oliver, Gerald W. Becker, and Robert D. Arnold</i>	
1.2 Regulatory Considerations in Approval on Follow-On Protein Drug Products	33
<i>Erin Oliver, Stephen M. Carl, Kenneth R. Morris, Gerald W. Becker, and Gregory T. Knipp</i>	
1.3 Radiopharmaceutical Manufacturing	59
<i>Brit S. Farstad and Iván Peñuelas</i>	
SECTION 2 ASEPTIC PROCESSING	97
2.1 Sterile Product Manufacturing	99
<i>James Agalloco and James Akers</i>	
SECTION 3 FACILITY	137
3.1 From Pilot Plant to Manufacturing: Effect of Scale-Up on Operation of Jacketed Reactors	139
<i>B. Wayne Bequette</i>	
	ix

3.2	Packaging and Labeling	159
	<i>Maria Inês Rocha Miritello Santoro and Anil Kumar Singh</i>	
3.3	Clean-Facility Design, Construction, and Maintenance Issues	201
	<i>Raymond K. Schneider</i>	
SECTION 4 NORMAL DOSAGE FORMS		233
4.1	Solid Dosage Forms	235
	<i>Barbara R. Conway</i>	
4.2	Semisolid Dosages: Ointments, Creams, and Gels	267
	<i>Ravichandran Mahalingam, Xiaoling Li, and Bhaskara R. Jasti</i>	
4.3	Liquid Dosage Forms	313
	<i>Maria V. Rubio-Bonilla, Roberto Londono, and Arcesio Rubio</i>	
SECTION 5 NEW DOSAGE FORMS		345
5.1	Controlled-Release Dosage Forms	347
	<i>Anil Kumar Anal</i>	
5.2	Progress in the Design of Biodegradable Polymer-Based Microspheres for Parenteral Controlled Delivery of Therapeutic Peptide/Protein	393
	<i>Shunmugaperumal Tamilvanan</i>	
5.3	Liposomes and Drug Delivery	443
	<i>Sophia G. Antimisiaris, Paraskevi Kallinteri, and Dimitrios G. Fatouros</i>	
5.4	Biodegradable Nanoparticles	535
	<i>Sudhir S. Chakravarthi and Dennis H. Robinson</i>	
5.5	Recombinant <i>Saccharomyces cerevisiae</i> as New Drug Delivery System to Gut: In Vitro Validation and Oral Formulation	565
	<i>Stéphanie Blanquet and Monique Atric</i>	
5.6	Nasal Delivery of Peptide and Nonpeptide Drugs	591
	<i>Chandan Thomas and Fakhrul Ahsan</i>	
5.7	Nasal Powder Drug Delivery	651
	<i>Jelena Filipović-Grčić and Anita Hafner</i>	
5.8	Aerosol Drug Delivery	683
	<i>Michael Hindle</i>	
5.9	Ocular Drug Delivery	729
	<i>Ilva D. Rupenthal and Raid G. Alany</i>	
5.10	Microemulsions as Drug Delivery Systems	769
	<i>Raid G. Alany and Jingyuan Wen</i>	

5.11 Transdermal Drug Delivery	793
<i>C. Scott Asbill and Gary W. Bumgarner</i>	
5.12 Vaginal Drug Delivery	809
<i>José das Neves, Maria Helena Amaral, and Maria Fernanda Bahia</i>	
SECTION 6 TABLET PRODUCTION	879
6.1 Pharmaceutical Preformulation: Physicochemical Properties of Excipients and Powers and Tablet Characterization	881
<i>Beom-Jin Lee</i>	
6.2 Role of Preformulation in Development of Solid Dosage Forms	933
<i>Omathanu P. Perumal and Satheesh K. Podaralla</i>	
6.3 Tablet Design	977
<i>Eddy Castellanos Gil, Isidoro Caraballo, and Bernard Bataille</i>	
6.4 Tablet Production Systems	1053
<i>Katharina M. Picker-Freyer</i>	
6.5 Controlled Release of Drugs from Tablet Coatings	1099
<i>Sacide Alsoy Altinkaya</i>	
6.6 Tablet Compression	1133
<i>Helton M. M. Santos and João J. M. S. Sousa</i>	
6.7 Effects of Grinding in Pharmaceutical Tablet Production	1165
<i>Gavin Andrews, David Jones, Hui Zhai, Osama Abu Diak, and Gavin Walker</i>	
6.8 Oral Extended-Release Formulations	1191
<i>Anette Larsson, Susanna Abrahmsén-Alami, and Anne Juppo</i>	
SECTION 7 ROLE OF NANOTECHNOLOGY	1223
7.1 Cyclodextrin-Based Nanomaterials in Pharmaceutical Field	1225
<i>Erem Bilensoy and A. Attila Hincal</i>	
7.2 Nanotechnology in Pharmaceutical Manufacturing	1249
<i>Yiguang Jin</i>	
7.3 Pharmaceutical Nanosystems: Manufacture, Characterization, and Safety	1289
<i>D. F. Chowdhury</i>	
7.4 Oil-in-Water Nanosized Emulsions: Medical Applications	1327
<i>Shunmugaperumal Tamilvanan</i>	
INDEX	1367

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.