Pharmaceutics

The Science of Dosage Form Design

Edited by

Michael E. Aulton BPharm PhD FAAPS MRPharmS Professor of Pharmaceutical Technology, School of Pharmacy, De Montfort University, Leicester, UK

SECOND EDITION



EDINBURGH LONDON NEW YORK OXFORD PHILADELPHIA ST LOUIS SYDNEY TORONTO 2002



CHURCHILL LIVINGSTONE An imprint of Elsevier Science Limited

- © Harcourt Publishers Limited 2002
- © Elsevier Science Limited 2002. All rights reserved.

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 or otherwise, without either the prior permission of the publishers or a licence permitting restricted copying in the United Kingdom issued by the Copyright Licensing Agency, 90 Tottenham Court Road, London W1T 4LP. Permissions may be sought directly from Elsevier's Health Sciences Rights Department in Philadelphia, USA: phone: (+1) 215 238 7869, fax: (+1) 215 238 2239, e-mail: healthpermissions@elsevier.com. You may also complete your request on-line via the Elsevier Science homepage (http://www.elsevier.com), by selecting 'Customer Support' and then 'Obtaining Permissions'.

First published 1988 Second Edition 2002 Reprinted 2002 twice

Standard edition ISBN 0 443 05517 3

International Student Edition ISBN 0 443 05550 5 Reprinted 2002 twice

British Library Cataloguing in Publication Data A catalogue record for this book is available from the British Library

Library of Congress Cataloging in Publication Data
A catalog record for this book is available from the Library of

Note

Congress

Medical knowledge is constantly changing. As new information becomes available, changes in treatment, procedures, equipment and the use of drugs become necessary. The editor, contributors and the publishers have taken care to ensure that the information given in this text is accurate and up to date. However, readers are strongly advised to confirm that the information, especially with regard to drug usage, complies with the latest legislation and standards of practice.



www.elsevierhealth.com

The publisher's policy is to use paper manufactured from sustainable forests

Printed in Spain



Contents

What is 'Pharmaceutics'? xiii

1. The design of dosage forms 1 Peter York

PART ONE Scientific principles of dosage form design 13

- 2. Dissolution and solubility 15 Michael Aulton
- 3. Properties of solutions 33 Michael Aulton
- 4. Rheology 41 Chris Marriott
- 5. Surface and interfacial phenomena 59 John Fell
- 6. Disperse systems 70 David Attwood
- 7. Kinetics and product stability 101 John Pugh
- 8. Pharmaceutical preformulation 113 James Wells

PART TWO

Particle science and powder technology 139

- 9. Solid-state properties 141 Graham Buckton
- 10. Particle-size analysis 152 John Staniforth
- 11. Particle-size reduction 166 John Staniforth
- 12. Particle-size separation 174 John Staniforth

13. Mixing 181

Andrew Twitchell

14. Powder flow 197 John Staniforth

PART THREE Biopharmaceutical principles of drug delivery 211

- 15. Introduction to biopharmaceutics 213 Marianne Ashford
- 16. The gastrointestinal tract physiology and drug absorption 217 Marianne Ashford
- 17. Bioavailability physicochemical and dosage form factors 234 Marianne Ashford
- 18. Assessment of biopharmaceutical properties 253 Marianne Ashford
- 19. Dosage regimens 275 Stuart Proudfoot, (updated by John Collett)
- 20. Modified-release peroral dosage form 289 John Collett, Chris Moreton

PART FOUR Dosage form design and manufacture 307

- 21. Solutions 309 Michael Billany
- 22. Clarification 323 Andrew Twitchell
- 23. Suspensions and emulsions 334 Michael Billany



CONTENTS

- 24. Powders and granules 360
 Malcolm Summers
- 25. **Granulation** 364
 Malcolm Summers, Michael Aulton
- 26. Drying 379
 Michael Aulton
- 27. Tablets and compaction 397
 Göran Alderborn
- 28. Coating of tablets and multiparticulates 441 John Hogan
- 29. Hard gelatin capsules 449
 Brian Jones
- 30. **Soft gelatin capsules** 461 *Keith Hutchison, Josephine Ferdinando*
- 31. Pulmonary drug delivery 473 Kevin Taylor
- 32. Nasal drug delivery 489
 Peter Taylor
- 33. Transdermal drug delivery 499 Brian Barry
- 34. Rectal and vaginal drug delivery 534 fosef Tukker

- 35. Delivery of pharmaceutical proteins 544
 Daan Crommelin, Ewoud van Winden
 Albert Mekking
- 36. Packs and packaging 554
 Dixie Dean
- 37. Pharmaceutical plant design 571
 Michael Aulton, Andrew Twitchell
- 38. Heat transfer and the properties and use of steam 586

 Andrew Twitchell

PART FIVE Pharmaceutical microbiology 597

- Fundamentals of microbiology 599
 Geoff Hanlon
- 40. Pharmaceutical applications of microbiological techniques 623

 Norman Hodges
- 41. The action of physical and chemical agents on microorganisms 643

 Geoff Hanlon, Norman Hodges
- 42. Microbiological contamination and preservation of pharmaceutical products 658

 Malcolm Parker, Norman Hodges

Index 669



8

Pharmaceutical preformulation: the physicochemical properties of drug substances

James Wells

	Normal-phase HPLC 129 Reverse-phase HPLC 129
Spectroscopy 114	neverse-phase neto 129
	Drug and product stability 129
Solubility 115	Temperature 130
Aqueous solubility 115	Order of reaction 130
Intrinsic solubility (C ₀) 115	Hydrolysis 130
pK _a from solubility data 116	The influence of pH 130
Salts 116	Solvolysis 131
Solvents 118	Oxidation 131
Partition coefficient (K° _w) 119	Chelating agents 131
Solvent solubility 119	Photolysis 131
Methodology and structure activity	Solid-state stability 132
prediction 119	Hygroscopicity 132
Choice of non-aqueous solvent (oil) 119	Stability assessment 132
Structure-activity relationships 120	100 Mario 1 Mario 2 Mario 10 M
Dissolution 122	Microscopy 132
Intrinsic dissolution rate 122	Crystal morphology 133
Measurement of intrinsic dissolution rate 123 Common ion effect 123	Particle size analysis 133
	Powder flow properties 133
Melting point 124	Bulk density 133
Techniques 124	Angle of repose 134
Capillary melting 124	
Hot-stage microscopy 124	Compression properties 134
Differential scanning calorimetry and thermal	Plastic material 134
analysis 124	Fragmentation 135
Polymorphism 124	Elastic material 135
Pseudopolymorphism (solvates) 125	Punch filming (sticking) 136
True polymorphism 126	3/
Crystal purity 126	Excipient compatibility 136
Solubility 126	Method 136
	Interpretation 136
Assay development 127	
UV spectroscopy 128	Conclusions 138
Molecular weight 128	
p <i>K</i> _a 128	References 138
Thin-layer chromatography 128	
High-performance liquid chromatography	Bibliography 138

113





DOCKET

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.

