

# 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](mailto: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 Congress

**Note**

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.

**ELSEVIER  
SCIENCE** your source for books,  
journals and multimedia  
in the health sciences

[www.elsevierhealth.com](http://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  
*Josef 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
39. **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

### CHAPTER CONTENTS

**The concept of preformulation 114**

**Spectroscopy 114**

**Solubility 115**

- Aqueous solubility 115
  - Intrinsic solubility ( $C_0$ ) 115
  - $pK_a$  from solubility data 116
  - Salts 116
  - Solvents 118
- Partition coefficient ( $K_w$ ) 119
  - Solvent solubility 119
  - Methodology and structure activity prediction 119
    - Choice of non-aqueous solvent (oil) 119
    - Structure–activity relationships 120
- Dissolution 122
  - Intrinsic dissolution rate 122
    - Measurement of intrinsic dissolution rate 123
  - Common ion effect 123

**Melting point 124**

- Techniques 124
  - Capillary melting 124
  - Hot-stage microscopy 124
  - Differential scanning calorimetry and thermal analysis 124
- Polymorphism 124
  - Pseudopolymorphism (solvates) 125
  - True polymorphism 126
- Crystal purity 126
- Solubility 126

**Assay development 127**

- UV spectroscopy 128
  - Molecular weight 128
  - $pK_a$  128
- Thin-layer chromatography 128
- High-performance liquid chromatography (HPLC) 128

- Normal-phase HPLC 129
- Reverse-phase HPLC 129

**Drug and product stability 129**

- Temperature 130
- Order of reaction 130
- Hydrolysis 130
- The influence of pH 130
- Solvolytic 131
- Oxidation 131
- Chelating agents 131
- Photolysis 131
- Solid-state stability 132
- Hygroscopicity 132
- Stability assessment 132

**Microscopy 132**

- Crystal morphology 133
- Particle size analysis 133

**Powder flow properties 133**

- Bulk density 133
- Angle of repose 134

**Compression properties 134**

- Plastic material 134
- Fragmentation 135
- Elastic material 135
- Punch filming (sticking) 136

**Excipient compatibility 136**

- Method 136
- Interpretation 136

**Conclusions 138**

**References 138**

**Bibliography 138**

113

**PFIZER, INC. v. NOVO NORDISK A/S - IPR2020-01252, Ex. 1061, p. 5 of 66**



# 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.