

# Pharmaceutics

---

The science of dosage form design

Edited by M E Aulton

Churchill Livingstone 

CHURCHILL LIVINGSTONE

Medical Division of Longman Group UK Limited  
Distributed in the United States of America by  
Churchill Livingstone Inc., 650 Avenue of the Americas,  
New York, 10011, and associated companies, branches  
and representatives throughout the world.

© Michael Aulton 1988

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 the prior permission of the publishers  
(Churchill Livingstone, Robert Stevenson House, 1-3  
Baxter's Place, Leith Walk, Edinburgh EH1 3AF), or  
a Licence permitting restricted copying in the United  
Kingdom issued by the Copyright Licensing Agency Ltd,  
90 Tottenham Court Road, London, W1P 9HE.

First published 1988

Reprinted 1989

Reprinted 1990

Reprinted 1991

Reprinted 1992

ISBN 0-443-03643-8

British Library Cataloguing in Publication Data

Pharmaceutics: the science of dosage form  
design.

1. Pharmaceutics

I. Aulton, Michael E.

615'.19 RS403

Library of Congress Cataloging in Publication Data

Pharmaceutics: the science of dosage form design.

Replaces: Cooper and Gunn's tutorial pharmacy.  
6th ed. 1972.

Includes bibliographies and index.

1. Drugs — Design of delivery systems. 2. Drugs  
— Dosage forms. 3. Biopharmaceutics.

4. Pharmaceutical technology. 5. Chemistry,  
Pharmaceutical. 6. Microbiology, Pharmaceutical.

I. Aulton, Michael E.

[DNLM: 1. Biopharmaceutics. 2. Chemistry,  
Pharmaceutical. 3. Dosage Forms. 4. Technology,  
Pharmaceutical. 5. Microbiology, Pharmaceutical.

QV 785 P5366j

RS420.P48 1987 615.5'8 86-25888

Printed in Hong Kong  
CPP/05

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

# Contents

---

Preface	vii	<b>PART FOUR Pharmaceutical</b>	
Contributors	ix	<b>microbiology</b>	<b>423</b>
Acknowledgements	xi	24 Fundamentals of microbiology	425
About this book	xiii	25 The action of physical and chemical agents on micro-organisms	452
1 The design of dosage forms	1	26 Principles of sterilization	472
<b>PART ONE Physicochemical principles of pharmaceutics</b>	<b>15</b>	27 Microbiological contamination and preservation of pharmaceutical preparations	479
2 Rheology and the flow of fluids	17	28 Pharmaceutical applications of microbiological techniques	491
3 Solutions and their properties	38	<b>PART FIVE Pharmaceutical technology</b>	<b>509</b>
4 Surface and interfacial phenomena	50	29 Materials of fabrication and corrosion	511
5 Solubility and dissolution rate	62	30 Heat transfer and the properties of steam	525
6 Disperse systems	81	31 Filtration	538
7 Kinetics and stability testing	119	32 Mixing	550
<b>PART TWO Biopharmaceutics</b>	<b>129</b>	33 Particle size analysis	564
8 Introduction to biopharmaceutics	131	34 Particle size reduction	581
9 Factors influencing bioavailability	135	35 Particle size separation	591
10 Assessment of bioavailability	174	36 Powder flow	600
11 Dosage regimens	191	37 Granulation	616
<b>PART THREE Drug delivery systems</b>	<b>213</b>	38 Drying	629
12 Packs for pharmaceutical products	215	39 Tableting	647
13 Preformulation	223	40 Tablet coating	669
14 Solutions	254	41 Encapsulation	678
15 Suspensions	269	42 Design and operation of clean rooms	686
16 Emulsions	282	43 Sterilization practice	700
17 Powders and granules	300	44 Packaging technology	712
18 Tablets	304	Index	725
19 Capsules	322		
20 Therapeutic aerosols	341		
21 Parenteral products	359		
22 Topical preparations	381		
23 Suppositories and pessaries	412		

# The design of dosage forms

## PRINCIPLES OF DOSAGE FORM DESIGN

### BIOPHARMACEUTICAL CONSIDERATIONS IN

#### DOSAGE FORM DESIGN

#### **Routes of drug administration**

- Oral route*
- Rectal route*
- Parenteral route*
- Topical route*
- Respiratory route*

### DRUG FACTORS IN DOSAGE FORM DESIGN

#### **Organoleptic properties**

#### **Particle size and surface area**

#### **Solubility**

#### **Dissolution**

#### **Partition coefficient and $pK_a$**

#### **Crystal properties; polymorphism**

#### **Stability**

#### **Other drug properties**

### THERAPEUTIC CONSIDERATIONS IN DOSAGE FORM DESIGN

### SUMMARY

## PRINCIPLES OF DOSAGE FORM DESIGN

Drugs are rarely administered solely as pure chemical substances but are almost always given in formulated preparations. These can vary from relatively simple solutions to complex drug delivery systems, through the use of appropriate additives or excipients in the formulations to provide varied and specialized pharmaceutical functions. It is the formulation additives that, amongst other things, solubilize, suspend, thicken, preserve, emulsify, improve the compressibility and flavour drug substances to form various preparations or dosage forms.

The principal objective of dosage form design is to achieve a predictable therapeutic response to a drug included in a formulation which is capable of large scale manufacture with reproducible product quality. To ensure product quality, numerous features are required — chemical and physical stability, with suitable preservation against microbial contamination if appropriate, uniformity of dose of drug, acceptability to users including both prescriber and patient, as well as suitable packaging and labelling. Ideally, dosage forms should also be independent of patient to patient variation although in practice this feature remains difficult to achieve. Future developments in dosage form design may well attempt to accommodate to some extent this requirement.

Reference is made in Part 2 of this book to differences in bioavailability between apparently similar formulations and possible causative reasons. In recent years increasing attention has therefore been directed towards eliminating variation in bioavailability characteristics, particularly for chemically equivalent products since it is

recognized that formulation factors can influence their therapeutic performance. To optimize the bioavailability of drug substances it is often necessary to carefully select the most appropriate chemical derivative of the drug, for example to obtain a specific solubility requirement, as well as its particle size and physical form, to combine it with appropriate additives and manufacturing aids that will not significantly alter the properties of the drug, to select the most appropriate administration route(s) and dosage form(s) and to consider aspects of manufacturing processes and suitable packaging.

There are numerous dosage forms into which a drug substance can be incorporated for the convenient and efficacious treatment of a disease. Dosage forms can be designed for administration by all possible delivery routes to maximize therapeutic response. Preparations can be taken orally or injected, as well as being applied to the skin or inhaled, and Table 1.1 lists the range of dosage forms which can be used to deliver drugs by the various administration routes. However, it is necessary to relate the drug substance and the disease state before the correct combination of drug and dosage form can be made since each disease or illness will require a specific type of drug therapy. In addition factors governing choice of administration route and the specific require-

ments of that route which affect drug absorption need to be taken into account when designing dosage forms.

Versatile drugs are often formulated into several dosage forms of varying strengths, each having particular pharmaceutical characteristics which are suitable for a specific application. One such drug is the glucocorticoid prednisolone. Through the use of different chemical forms and formulation additives a range of effective anti-inflammatory preparations are available including tablet, enteric coated tablet, injections, eye drops and enema. The extremely low aqueous solubility of the base prednisolone and acetate salt makes these forms useful in tablet and slowly absorbed intramuscular suspension injection forms, whilst the soluble sodium phosphate salt enables a soluble tablet form, and solutions for eye drops, enema and intravenous injection to be prepared. The antibacterial drug combination co-trimoxazole, consisting of a mixture of five parts of sulphamethoxazole and one part trimethoprim, is also available in a range of dosage forms and strengths to meet specific needs of the user, including tablets, dispersible tablets, double strength tablets, double strength dispersible tablets, paediatric mixture, intramuscular injection, and a strong sterile solution for the preparation of an intravenous infusion. Because of the low aqueous solubility of both drug substances, specialized solvents are used for the intramuscular injection: 52% glycofurol, and strong sterile solution, 40% propylene glycol.

It is therefore apparent that before a drug substance can be successfully formulated into a dosage form many factors must be considered. These can be broadly grouped into three categories:

- 1 biopharmaceutical considerations, including factors affecting the absorption of the drug substance from different administration routes,
- 2 drug factors, such as the physical and chemical properties of the drug substance, and
- 3 therapeutic considerations including consideration of the disease to be treated and patient factors.

Appropriate and efficacious dosage forms will be prepared only when all these factors are

**Table 1.1** Range of dosage forms available for different administration routes

<i>Administration route</i>	<i>Dosage forms</i>
Oral	Solutions, syrups, elixirs, suspensions, emulsions, gels, powders, granules, capsules, tablets
Rectal	Suppositories, ointments, creams, powders, solutions
Topical	Ointments, creams, pastes, lotions, gels, solutions, topical aerosols
Parenteral	Injections (solution, suspension, emulsion forms), implants, irrigation and dialysis solutions
Lungs	Aerosols (solution, suspension, emulsion, powder forms), inhalations, sprays, gases
Nasal	Solutions, inhalations
Eye	Solutions, ointments
Ear	Solutions, suspensions, ointments

# 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.