

# 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 P5366]

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 pharmaceuticals</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		

## Parenteral products

### THE BIOPHARMACY OF INJECTIONS

#### Routes of administration

*Intracutaneous or intradermal route*

*Subcutaneous or hypodermic route*

*Intramuscular route*

*Intravascular routes*

*Intracardiac route*

*Intraspinal routes*

*Intra-articular and intrabursal routes*

*Ophthalmic routes*

#### Bioavailability of drugs from injections

### FORMULATION OF INJECTIONS

#### Volume of the injection

##### The vehicle

*Water and pyrogens*

*Water-miscible vehicles*

*Water-immiscible vehicles*

##### Osmotic pressure

*Intravascular injections*

*Intrathecal injections*

*Intramuscular injections*

*Intracutaneous injections*

*Subcutaneous injections*

##### Hydrogen ion concentration (pH)

*To increase the stability of the injection*

*To minimize pain, irritation and necrosis on injection*

*To provide unsatisfactory conditions for growth of micro-organisms*

*To enhance physiological activity*

*Buffers*

##### Specific gravity of injections

##### Suspensions for injection

*Wettability*

*Sedimentation rate*

*Claying*

*Size and shape of particles*

*Thixotropy*

*Preparation of aqueous suspension injections*

*Suspensions in oily vehicles*

**Addition of a gelling agent**

**Particle size**

##### Emulsions for injection

*Intravenous therapy and emulsions*

##### Colloidal dispersions and solubilized products

### QUALITY ASSURANCE OF INJECTIONS

#### Microbiological preservation

*The use of bactericides in single-dose injections*

*The use of bactericides in multiple-dose injections*

*Bactericides suitable for aqueous injections*

*Bactericides suitable for oily injections*

*Limitations in the use of bactericides*

*Incompatibilities of common bactericides*

#### Chemical stability of the medicament

*Adjustment of pH*

*Addition of a reducing agent or antioxidant*

*Replacement of air by an inert gas*

*Use of a sequestering agents*

*Inclusion of specific stabilizers*

**Calcium Gluconate Injection BP**

**Sodium Bicarbonate Injection BP**

**Mersalyl Injection BP**

*Limitations in the use of additives*

#### Particulate contamination

### PACKAGING OF INJECTIONS

#### Containers for injections

*Ideal properties*

*Types of container*

*Single-dose versus multiple-dose containers*

#### Materials for injection containers

*Glass*

**Types of glass**

**Associated problems for parenterals***Plastics***Types of plastics****Associated problems for parenterals***Closures***Types and properties of closure materials****Associated problems for parenterals**

## STERILIZATION OF INJECTIONS

Injections are sterile products intended for administration into the bodily tissues. Their formulation involves careful consideration of all the following inter-relating factors:

- 1 the proposed route of administration,
- 2 the volume of the injection,
- 3 the vehicle in which the medicament is to be dissolved or suspended,
- 4 the osmotic pressure of the solution,
- 5 the use of preservative,
- 6 the pH of the solution,
- 7 the stability of the medicament and methods of sterilization,
- 8 the specific gravity of the injection,
- 9 the properties of suspensions for injection,
- 10 the properties of emulsions for injection,
- 11 containers or closures for injections,
- 12 particulate contamination,
- 13 biopharmacy of injections.

## THE BIOPHARMACY OF INJECTIONS

Injections are administered into the body by many routes. The route of administration affects the formulation and biopharmaceutics of the preparation. There now follows a description of routes of administration to clarify nomenclature used throughout the rest of the chapter. Fig. 21.1 shows the sites of injection.

**Routes of administration**

The most important routes are as follows.

*Intracutaneous or intradermal route*

Injections are made into the skin between the

inner layer (dermis) and the outer layer (epidermis). The volume that can be injected intradermally is small, usually 0.1–0.2 ml, due to the poor vascularity of the site which gives poor dispersion of the drug, and leaves blisters or weals at the site of the injection. The route is used mainly for diagnostic tests.

*Subcutaneous or hypodermic route*

Injections are made under the skin into the subcutaneous tissue. The volume injected is usually 1 ml or less. This route is not used for aqueous suspensions or oily suspensions and fluids since these would cause pain and irritation at the injection site.

*Intramuscular route*

Injections are made by passing the needle into the muscle tissue via the skin, subcutaneous tissue and membrane enclosing the muscle. The volume is usually no greater than 2 ml and should not exceed 4 ml. This route is used for aqueous and oily suspensions and oily solutions, since if they were injected intravenously blockage of small blood vessels might occur leading to poor vascular supply of local tissues possibly resulting in gangrene.

*Intravascular routes*

These are either intra-arterial (into arteries) or intravenous (into veins). The intra-arterial route is used for an immediate effect in a peripheral organ, e.g. to improve circulation to the extremities when arterial flow is restricted by arterial spasm or early gangrene. Tolazoline hydrochloride, a peripheral vasodilator, is sometimes administered by this route.

Substances are introduced directly into the blood stream by the intravenous route. The most common site is the median basilic vein at the anterior surface of the elbow. The volume can vary from less than 1 ml to in excess of 500 ml. Small volumes may be administered for a rapid effect (e.g. anaesthetics) and large volumes (perfusion or infusion fluids) to replace body fluid loss in shock, severe burns, vomiting and diar-

# 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.