

# Pharmaceutics

---

The science of dosage form design

Edited by M E Aulton

Churchill Livingstone 

**DOCKET**  
**A L A R M**

Find authenticated court documents without watermarks at [docketalarm.com](https://docketalarm.com).

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  
CDD/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		

## Capsules

### HISTORICAL DEVELOPMENT OF GELATIN CAPSULES

#### RAW MATERIALS FOR GELATIN CAPSULES

*Gelatin*  
*Plasticizers*  
*Colorants*  
*Preservatives*

#### HARD GELATIN CAPSULES

##### Sizes of hard gelatin capsule shells

*Determination of capsule fill weight*

##### Filling

##### Formulation of powders for filling

##### Formulation of non-powders for filling

*Granules and pellets*  
*Tablets*  
*Semisolids*

##### Bioavailability aspects of hard gelatin capsules

*Disintegration and dissolution*  
*Formulation factors affecting release from hard gelatin capsules*  
**Active ingredient**  
**Diluent**  
**Glidants and lubricants**  
**Wetting: effects of porosity and addition of surfactants**

#### SOFT GELATIN CAPSULES

##### Description

##### Advantages of soft gelatin capsules as a dosage form

*Compression*  
*Mixing and powder flow*  
*Stability*  
*Bioavailability*

##### Formulation of soft gelatin capsules

##### Formulation of the gelatin shell

*Gelatin*  
*Plasticizers*  
*Water*  
*Preservatives*  
*Colours*  
*Opacifiers*  
*Enteric treatment*

##### Formulation of the capsule contents

*Limitations for fill materials*  
*Liquid vehicles*  
**Water-immiscible oils**  
**Water-miscible liquids**  
*Suspensions*

##### Bioavailability aspects of soft gelatin capsules

### HISTORICAL DEVELOPMENT OF GELATIN CAPSULES

The word capsule is derived from the latin 'capsula' meaning a small box. In current English usage it is applied to many different articles ranging from flowers to space craft. In pharmacy the word capsule is used to describe an edible package made from gelatin which is filled with medicines to produce a unit dose, mainly for oral use. There are two types of capsule, differentiated by the adjectives 'hard' and 'soft'. The hard gelatin capsule consists of two pieces, a cap and a body, that fit one inside the other. They are produced empty and are filled in a separate operation. The soft gelatin capsule is a capsule which is manufactured and filled in one operation.

The gelatin capsule originated in the first half of the nineteenth century as a means of masking the flavours of the many obnoxious medicines then

\* Introduction and hard gelatin capsules

in vogue. It was devised by a French pharmacy student, F A B Mothes, who made bubbles of gelatin which could be filled with the drug and sealed with a drop of gelatin solution. These one-piece capsules were prepared by dipping small mercury-filled leather sacs into gelatin solutions, emptying out the mercury to collapse the bag, removing the gelatin films and then air drying them. The first patent was filed in Paris in 1834 by Mothes in association with a registered pharmacist, Dublanc. The capsule became immediately popular because it perfectly fulfilled a need. Within 2 years, capsules were being manufactured as far apart as Berlin and New York. Mothes was an astute businessman in that he allowed the market to develop freely and then in 1836 he used his patent and litigation to restrict the manufacture of capsules to himself. Following on from this there were many attempts to get around the patent by using alternative materials or manufacturing methods. Two products emerged from this work: the gelatin-coated pill and the hard two-piece capsule.

In France the one-piece capsule remained the most popular form. Developments were made in the manufacturing process. The moulds were changed to pear-shaped metal ones mounted on disc which simplified the production process. During the 1840s a completely new process was devised; this used a pair of metal plates which had matching sets of cavities on their surface. Two sheets of gelled gelatin mixture were then laid over each of them. The medicine to be filled was placed in the cavities on one sheet, the matching plate was placed on top and the resulting sandwich passed through a pair of pressure rollers which stamped out the capsules. These capsules were much more regular in size than those made previously and were called 'perles'.

The formulation of these shells was a mixture of gelatin, acacia and honey which produced a hard wall. The next significant change in the process occurred in 1873 when another French pharmacist, Taetz, suggested the inclusion of glycerol into the formulation in order to make them soft and elastic and thus easier to swallow. These capsules were now identical to the modern soft gelatin capsule. Finally in 1932, R P Scherer perfected the rotary die process which was the

first continuous method of encapsulation to be implemented and is still the method of choice.

The hard two-piece capsule was invented by a French pharmacist, J-C Lehuby, who took out a patent in 1846 for 'medicinal envelopes'. These were pairs of open-ended cylinders of gelatin which fitted one inside the other. They were produced by dipping silver plated metal moulds into a gelatin solution, drying the resulting films, cutting them to length and joining the two halves together. The performance of these capsules depends upon the accuracy with which the two pieces were made. The development of these capsules was held up until a cheaper accurate mould system could be developed. The problem was solved by an American pharmacist, Mr Hubel of Detroit. He had the idea of using standard gauged iron rod which was widely used in the engineering industry. He cut this into lengths and mounted them into wooden blocks. In 1874, he commenced the first industrial scale manufacture of hard gelatin capsules. From then until after the second World War, this process was confined to the USA.

After Mr Hubel's success, other companies started their manufacture: Eli Lilly & Company of Indianapolis in 1896 and Parke Davis Company of Detroit in 1901. These two companies remain the leading manufacturers in the world. Currently, hard gelatin capsule manufacturing plants are located in all of the major trading blocs.

## RAW MATERIALS FOR GELATIN CAPSULES

The raw materials used in manufacture are similar for both hard and soft gelatin capsules. The first stage of the process is to prepare a gelatin solution in demineralized water or a mixture of demineralized water and glycerol. To this are added, colorants, preservatives and process aids depending upon the type of capsule required.

### *Gelatin*

Gelatin is the major component of the capsule and has been the only material from which they have been successfully made. The reason for this is that gelatin possesses four essential basic properties:

# 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.