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.

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

Contents

*B E Jones**, *H Seager***, *M E Aulton*** *and F S S Morton***

Capsules

* Introduction and hard 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

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 pharmicist, 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:

DOCKET ALARM

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.