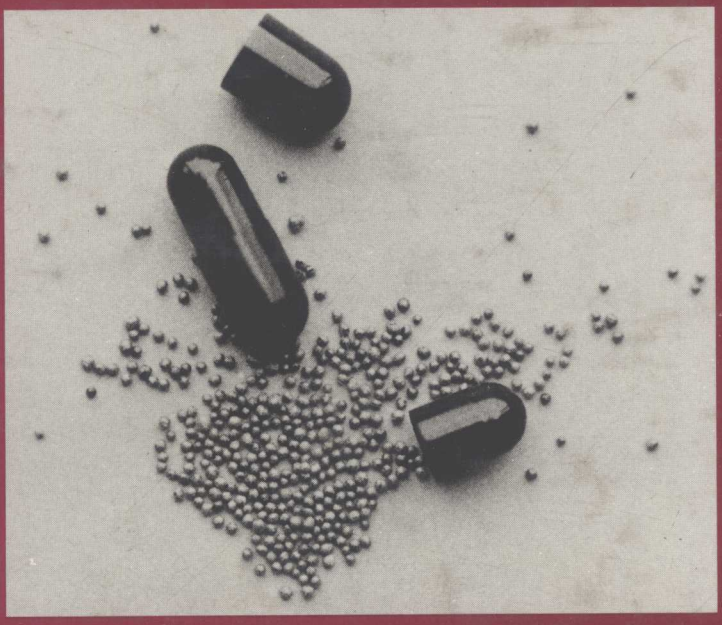
DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 20

Microencapsulation and Related Drug Processes



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Marcel Dekker, Inc. New York and Basel

Library of Congress Cataloging in Publication Data

Deasy, P. B.
Microencapsulation and related drug processes.

(Drugs and pharmaceutical sciences ; v. 20)
Includes bibliographical references and indexes.
1. Microencapsulation. 2. Drugs--Controlled release.
I. Title. II. Series. [DNLM: 1. Capsules. 2. Delayed-action preparations. 3. Technology, Pharmaceutical.
Wl DR893B v. 20 / QV 785 D285m]
RS201.C3D43 1984 615'.191 83-26267
ISBN 0-8247-7162-1

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

Current printing (last digit):
10 9 8 7 6 5 4 3 2 1

PRINTED IN THE UNITED STATES OF AMERICA

Microencapsulation and Related Drug Processes

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To my wife, Philda,
and my children,
Patricia, Deirdre, and Nicola
for their patience and understanding
during the extensive period devoted by
me to the preparation of this text.

Preface

Microencapsulation is now the most frequently employed method of producing controlled-release dosage forms. Over the past two decades enormous progress has been made in developing the technology and in applying it to a diversity of medical and other uses. This book is concerned mainly with defining criteria for drug selection for microencapsulation, with a detailed review of the many techniques used and with a discussion of the mechanism of drug release from such products.

To this end more than 800 references have been cited in the various chapters. This represents a careful selection of the vast amount of published material in this area. In this regard I am most grateful to the many research workers whose findings I have abridged and blended together to present a balanced and comprehensive overview of the subject. I am also grateful to the many publishers and authors for permission to reproduce figures and tables. The extensive references will enable those interested in acquiring greater detail about a particular aspect of the subject to refer easily to primary literature sources.

Many of the references cited are patents. Also, many of the research papers discussed are based on approaches that are the subject of patents. The potential user of the information in this book is hereby advised not to infringe any patent referred to directly or indirectly. However, the reader should be aware that the text contains many useful opportunities for technology transfer between processes without breaching patents. A number of these approaches are discussed in the text.

The physicochemical and pharmacological properties of drugs and the intended use of their products will tend to dictate how they should be microencapsulated. The index will help locate some microencapsulation processes that have been applied to particular drugs. However, more detailed perusal of the text may indicate that a different process, or a modification thereof, may be more suitable. The reader should also be aware that many processes, such as pan coating, are simple to describe, but their practical application requires skills and experience

not easily mastered. Also, scaling-up problems may be encountered. For these reasons it may be necessary to examine a number of microencapsulation processes experimentally before selecting one that readily achieves the specifications required of the end product.

A number of other related processes, such as microparticles, nanocapsules, and nanoparticles, are also referred to in the text. The book should be of primary interest to those in the pharmaceutical industry and schools of pharmacy concerned with the formulation of drugs as microcapsules or related dosage forms. The text should be suitable as a reference for use in conjunction with an undergraduate or postgraduate pharmacy course in this subject area. The book should also be useful to anyone contemplating initiating research in the area so as to avoid the duplication of approach that is often obvious in the existing literature. It should be of interest to those concerned with the development of this type of product in the many other industries, such as foods, cosmetics, photography, and printing, which also use microencapsulation technology.

Research in microencapsulation is being actively pursued by many groups and the next 20 years should continue to yield many useful and innovative ideas. Much work has yet to be done in areas such as the use of novel polymers and other additives for coatings, the construction of laminated films, and the elimination of difficulties such as clumping and lack of coat uniformity associated with existing technologies. Judging by the enormous interest shown in the technology to date, it is likely that many of these problems will be resolved in the future.

I would like to thank Joan Barnes, Joan Byrne, Helen Chambers, Philda Deasy, Dorothy O'Brien, Dolores O'Higgins, and Elizabeth Sherlock for typing the original manuscript. I am grateful to the staff of Marcel Dekker, Inc., for their cooperation in the publication of this book.

Patrick B. Deasy

Contents

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General Introduction

Microcapsules developed for use in medicine consist of a solid or liquid core material containing one or more drugs enclosed in coating as shown in Fig. 1.1. The core may also be referred to as the nucleus or fill and the coating as the wall or shell. Depending on the manufacturing process, various types of microcapsule structure can be obtained as illustrated. The most common type is the mononuclear spherical. Microcapsules usually have a particle size range between 1 and 2000 μm. Products smaller than 1 μm are referred to as nanocapsules, because their dimensions are measured in nanometers. When no distinct coating and core regions are distinguishable, the analogous terms used are microparticles and nanoparticles.

Microcapsules are often described by other terms, such as coated granules, pellets or seeds, microsperules, and spansules. These products differ from larger conventional hard or soft gelatin capsules in a number of important ways apart from size. They differ most notably in the greater variety of coating materials and procedures used, in the comparative thinness of the coating formed, in their unique release properties, and in their greater diversity of application in medicine.

1.1 SOME HISTORICAL AND OTHER CONSIDERATIONS

The first research leading to the development of microencapsulation procedures for pharmaceuticals was published by Bungenburg de Jong and Kaas [1] in 1931 and dealt with the preparation of gelatin spheres and the use of a gelatin coacervation process for coating. In the late 1930s and 1940s, Green and co-workers of The National Cash Register Co., Dayton, Ohio, developed the gelatin coacervation process, which eventually lead to several patents for carbonless carbon paper. This product used a gelatin microencapsulated oil phase usually containing a colorless dye precursor. The microcapsules were afixed to the undersurface of the top page and released the dye precursor upon rupture

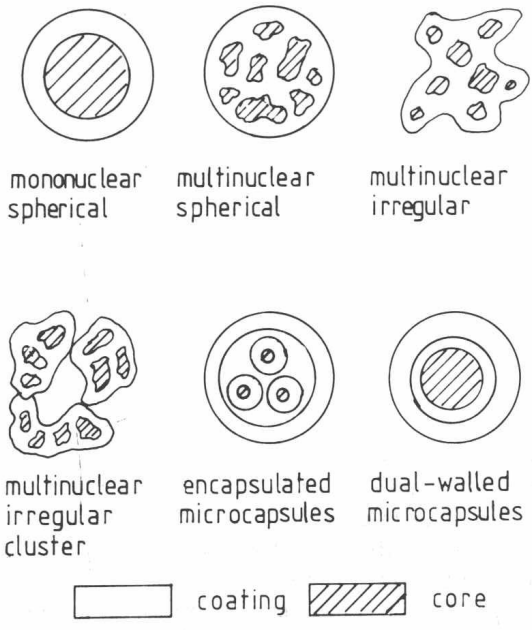

Figure 1.1 Some typical structures of microcapsules.

by pressure from the tip of the writing instrument. The liberated dye precursor then reacted with an acid clay coating on the top surface of the underlying page to form the copy image.

Since then many other coating materials and processes of application have been developed by the pharmaceutical industry for the microencapsulation of medicines. Drug companies have been quick to realize and exploit the enormous potential of the technology for overcoming formulation and delivery problems in many dosage forms such as capsules, tablets, powders, topicals, and injectables. Over the last 25 years numerous patents have been taken out by pharmaceutical companies for microencapsulated drugs. Manufacturers of medical equipment, diagnostic agents, and other health care-related products have also been interested in the commercial possibilities of microencapsulation. Other industries, such as the food, cosmetic, horticultural, paint, print, photographic, computer, fertilizer, adhesives, cleaning, and aerospace industries, have been concerned with microencapsulated products. At the same time the plastics industry has been continually involved in the production and evaluation of new polymers with potential application in microencapsulation. Also during this period research groups in various academic, governmental, and other bodies have become increasingly interested in the technology and have contributed extensively to the published literature.

Despite the intensity of research into the new technology, there are still many difficulties to be resolved. Problems frequently encountered include incomplete or uneven coating deposition, clumping of microcapsules, unsatisfactory or nonreproducible core release, and scale-up difficulties. Every microencapsulated product requires an individual design approach, and there is no one methodology that is suitable in all cases. Any newcomer to the science of microencapsulation will very quickly discover how difficult it is to select and apply the optimum encapsulation procedure for a particular product because of patent restriction and lack of adequate information in the literature.

Another problem hindering the development of microencapsulation procedures for medicines is the reservation of persons in industry and drug regulatory agencies to accept new dosage forms, particularly when they involve the use of novel adjuvants and technologies. Obviously, satisfactory toxicological data on polymers and other materials for use in microencapsulated medicines for use in humans must be available before being authorized for clinical trials and marketing. However, in many potential applications of microencapsulation the coating material is not absorbed, and so long as it is nonreactive with body surfaces, it may be safely used in products whose internal absorption into the body would be contraindicated. It is probable that in the future, as the use of microencapsulated products containing nonbiodegradable coating material increases, greater attention will have to be given to environmental pollution considerations associated with such products.

1.2 REASONS FOR MICROENCAPSULATION

Table 1.1 lists some of the many drugs that have been microencapsulated. Drugs from many different pharmacological classes have been microencapsulated, in particular analgesics, antibiotics, antihistamines, cardiovascular agents, iron salts, tranquilizers, and vitamins. It should be

Table 1.1 Some Examples of Drugs That Have Been Microencapsulated

Drug	Principal reasons for microencapsulation[a]	Primary pharmacological class
Acetazolamide	S.R.	Diuretic
Aminophylline	T.M.	Smooth muscle relaxant
Amitriptyline	S.R.	Antidepressant
Ampicillin (Na and trihydrate)	T.M.	Antibiotic
Aspirin	E.P./S.I./S.R./T.M.	Analgesic

Table 1.1 (Continued)

Drug	Principal reasons for microencapsulation[a]	Primary pharmacological class
Attapulgite	S.I.	Adsorbent
Beclamide	S.I./T.M.	Anticonvulsant
Butobarbitone	T.M.	Hypnotic and sedative
Camphor	S.I.	Counterirritant
Castor oil	L.S.C./O.M./T.M.	Laxative
Chloramphenicol	S.I./S.R.	Antibiotic
Chlorpheniramine maleate	S.R.	Antihistamine
Chlorpromazine HCl	S.R.	Tranquilizer
Citric acid	E.P./S.I./T.M.	Excipient
Clofibrate	L.S.C.	Cholesterol-reducing agent
Cloxacillin	T.M.	Antibiotic
Codeine phosphate	S.R.	Analgesic
Cod liver oil	L.S.C./O.M./T.M.	Vitamin oil
Cyclandelate	T.M.	Peripheral vasodilator
Cysteine	O.M./S.I./T.M.	Amino acid
Diazepam	S.R.	Tranquilizer
Dicloxacillin	T.M.	Antibiotic
Dimethicone fluid	L.S.C.	Silicone
Diphenhydramine HCl	S.R.	Antihistamine
Disulfiram	T.M.	Enzyme inhibitor
Doxycycline HCl	T.M.	Antibiotic
Eprazinone	L.S.C.	Antitussive and expectorant
Fenfluramine	S.R.	Anorectic agent
Ferrous citrate	E.P.	Iron supplement
Ferrous fumarate	S.I./S.R./T.M.	Iron supplement
Ferrous sulfate	E.P./G.I.R./S.I./S.R./T.M.	Iron supplement