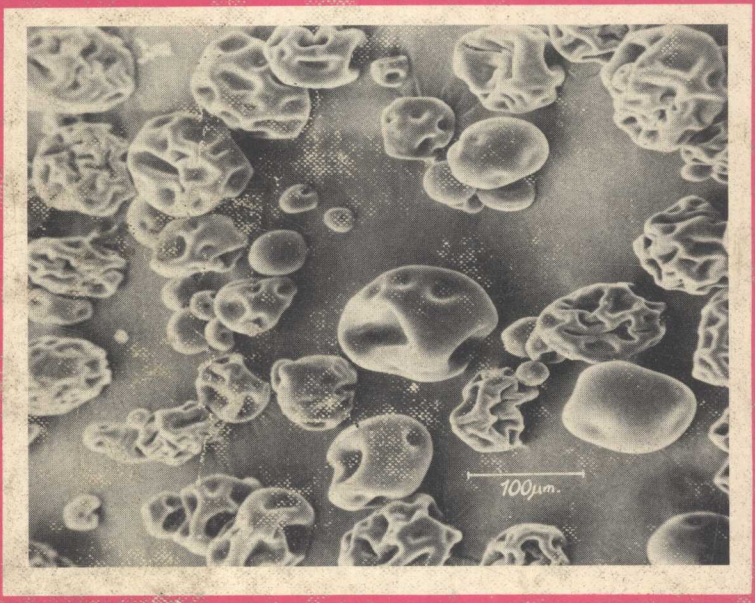
DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 3

Microencapsulation



edited by J. R. Nixon

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Microencapsulation

DRUGS AND THE PHARMACEUTICAL SCIENCES

A Series of Textbooks and Monographs

Editor

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Volume 3. MICROENCAPSULATION, *edited by J. R. Nixon*

Other Volumes in Preparation

PREFACE

The First International Symposium on Microencapsulation was held at the University of Georgia, U.S.A., in January 1973 and in view of its success it was decided to organize a second symposium to be held in Europe. The editor of the present volume was asked to organize the symposium and chose to hold it at Chelsea College, University of London. In the first symposium the papers were almost exclusively of a pharmaceutical nature and consisted mainly of reviews of current knowledge. In the current volume this pharmaceutical bias is still evident, although a veterinary aspect is clearly discernible in chapters dealing with marine filter feeders, prospects for zootechnic use and official U.S. government interest in microencapsulated veterinary products, while clinical interest, particularly in the artificial kidney field, is coming to the fore. The types of paper presented are also more diverse. Thus pure research papers included those by Professor Kondo, Dr. Jenkins, Mr. Luu Si Nang, and Mr. Matthews, while applied research papers, usually in the form of a review, were given by Professors Chang, Maggi and Sparks, and Drs. Jones and de Sabata.

The general review papers contributed have also begun to show a divergence and currently fall into two types: reviews of techniques available for microencapsulation, as given in the papers of Professors Speiser and Luzzi, and reviews of commercial techniques and usages as contributed by the representatives of EURAND, Fuji Photo Film, and 3M (U.K.) Ltd.

In view of the great interest now being shown in microencapsulation and because of its wide-ranging application it is hoped that this will not be the last microencapsulation symposium. There

are currently plans to hold the third such meeting in Tokyo during the fall of 1976 under the guidance of Professor T. Kondo of the Science University of Tokyo.

J. R. Nixon

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CONTENTS

Chapter 1

MICROENCAPSULATION BY COACERVATION, SPRAY ENCAPSULATION, AND NANOENCAPSULATION

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Micronized drug particles or ultrafine drug droplets incorporated in capsules of some few micrometers in size are usually called microcapsules. In pharmacy they are especially important as multi-

compartmental dosage forms to protect against interactions and to ensure the drug's release and its availability. The encapsulation procedure has been used commercially for some years but some progress in the technology of encapsulation is still possible, mainly in the fields of coacervation, film condensation, and microencapsulation by polymerization, especially in the extreme range of several nanometers.

I. MICROENCAPSULATION BY COACERVATION

By coacervation is meant the transfer of macromolecules with film properties from a solvated state (stage 1) via an intermediate phase, the coacervation phase (stage 2), into a phase in which there is a film around each particle (stage 3), and then to a final phase in which this film is solidified or hardened (stage 4)(Fig. 1). Stage 1 is a two-phase system, in which the drug is incorporated in a dissolved or micronized solid form in an outer phase with the solvated film-forming material. In stage 2, a three-phase system is formed. Apart from the external, outer, or coherent phase of the solvated macromolecule a new phase, the so-called coacervation phase

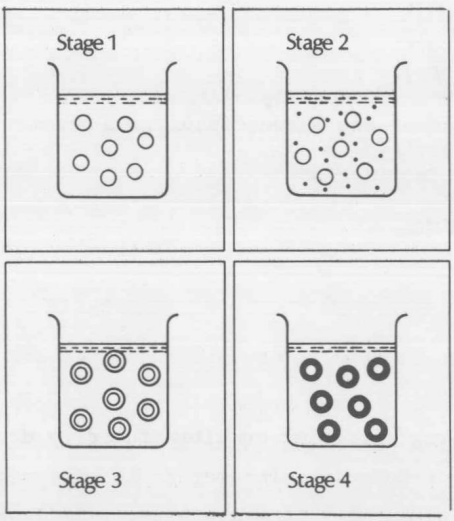

FIG. 1. Schematic diagrams of microencapsulation Stage 1, dispersion; stage 2, coacervation; stage 3, Separation of polymers; stage 4, hardening.

occurs. This is an enrichment of polymer droplets in the solvent. The third phase (the inner, open, or disperse phase) consists of the drug. This three-phase coacervation system can be achieved mostly by physical influences such as changes in pH, changes in temperature, variation of the ionic strength, salting-out effects, osmotic changes, or the addition of an outer phase which reduces the solubility of the solvate.

In stage 3, as a result of further physical influences, a continuous polymer film settles out around each particle. By enriching the coacervate a transition from the sol state into the gel state takes place and the result is again a two-phase system. In stage 4 the wall material is solidified and eventually hardened. Then the microcapsules are isolated and worked up into dosage forms such as capsules, granules, tablets, suspensions, platelets, or strips.

A. Optimization of the Coacervation

The technological optimization of coacervation can be successfully assessed with triangle phase diagrams. If the amount of film-forming macromolecule is plotted against the concentration of coacervating agent one can recognize several areas, namely, area I, in which the macromolecule is only partially dissolved; area II, in which the macromolecule is in the entirely solvated state, due to the addition of electrolytes; area III, in which there is an equilibrium between macromolecules in the sol state and in the gel state; and finally, the small area IV, in which the coacervation is optimal. Therefore, for each microencapsulation problem the coacervation must be optimized.

The microscopic analysis of microcapsules using several drugs as core material, for instance acetylsalicilic or barbituric acids coated with cellulose-acetate-phthalate (CAP) or ethyl cellulose shows that the coat is very regular and that no pores in the coat are visible.

B. Drug Release from Coacervated Microcapsules

Release-rate studies of Acetophenetidine from CAP-microcapsules into artificial intestinal fluid show that the velocity of liberation depends very markedly on the thickness of the pure CAP coat and on the addition of softeners. By increasing the wall thickness of the pure CAP coat without any softener, the release velocity diminishes. Here the rate determining factor is mainly diffusion of the Acetophenetidine molecules through the porous cellulose-acetate-phthalate wall.

The addition of softeners yields a completely different release pattern. Here the velocity of liberation is quick and is found to be identical for three different wall thicknesses. Therefore, the release rate is independent of the capsule wall thickness. The dominant procedure is the dissolution rate of the drug in the capsule itself and not the diffusion of the drug molecules through the CAP coat.

C. Combination of Microcapsule Mixtures for Multicompartmental Dosage Forms

One single microcapsule fraction is pharmaceutically not interesting. Multicompartmental dosage forms with controlled and sustained release can be produced by the combination of various fractions of the microencapsulated drug. These produce harmonized release properties. The aim must be release of an initial dose followed by release of a constant and regular amount of drug as maintenance doses. By stimulating the gastrointestinal passage with a half change test, the release through a coat with softener provides a quick release of the initial dose. The drug diffusion from microcapsules with three different wall thicknesses consisting of pure CAP without any softener is much slower and causes a sustained release. By integration of all four capsule fractions, we get the cumulative release from all compartments containing the initial dose and the maintenance doses. Thus, by combining various microcapsules in one dose (tablet, capsule, or suspension) we can nearly reach the ideal of a biopharmaceutically correct dosage form.

In summary, we may say that coacervation procedures are very

suitable to enclose solid micronized drug particles within a compact layer of macromolecular film. By selecting the correct coacervation procedure, the most suitable film-forming material, the optimal film thickness, the correct amount of drug and the best addition of softener, we can adapt the release properties of a dosage form to any desired availability requirements.

II. MICROENCAPSULATION BY SPRAY PROCEDURES

Microencapsulation by atomization is a relatively recent procedure which is still being developed. Therefore no experimental results can be presented here. The basic principle of spray encapsulation consists of atomizing a micronized drug suspension in an outer aqueous phase or a fine drug emulsion in an aqueous system. As a film-forming material tensioactive reactive monomers or precondensates can be used. Under the influence of heat during spraying these precursors tend to polymerize or polycondense immediately. Because the outer, aqueous phase evaporates quickly after spray heating, an enrichment of the film-forming monomers or polycondensates takes place at the surface of the drug. The precursors polymerize in a few seconds to a network of macromolecular film around each drug particle.

The polycondensation of a reactive tenside is shown here schematically (Fig. 2). A tensioactive hydrophilic precondensate of hexamethylolmelamin type, under the influence of heat, forms a dense network of a hydrophobic macromolecule. By selecting the film-forming material, the ratio between drug and precursor, and the technical spray conditions, we can adapt the film properties and the film thickness to any desired microcapsule or release requirement. Electron stereoscan pictures of micronized phenobarbitone with a hexamethylolmelamin derivative show clearly that the coat is applied homogeneously and without any pores.

In conclusion we may say that microencapsulation by spray coating procedures can be governed in wide ranges. In contrast to coacervation, spray encapsulation is a continuous process which is