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IBUPROFEN MICROCAPSULES: THE EFFECT OF PRODUCTION VARIABLES ON MICROCAPSULE PROPERTIES

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ABSTRACT

Ibuprofen was microencapsulated with ethylcellulose using the solvent evaporation method. The effect of production variables on the properties of the microcapsules and drug release from them is described. Results show that size distribution, drug loading and the amount of free drug on the surface of the microcapsules is affected by production variables. The release of drug from the microcapsules was observed to be strongly influenced by parameters affecting the presence of uncoated drug on the microcapsule surface.

INTRODUCTION

Ibuprofen is a non-steroidal anti-inflammatory drug which is widely used. Maximum plasma concentration is achieved 1-2 hours after ingestion but the elimination of ibuprofen is rapid, with a half-life

of elimination of around two hours[1]. The short half-life makes it necessary to administer the drug frequently (3 or 4 times daily) in order to maintain therapeutic concentration, but by slowing down the release of the drug from the dosage form it would be possible to achieve a once daily dosage regimen. The slow release of the drug could also decrease the occurrence of gastro-intestinal side effects.

Microencapsulation has proved to be a useful method for prolonging drug release from dosage forms and reducing adverse action. A well known method of microencapsulation is the solvent evaporation method which gives microcapsules with the encapsulated drug dispersed throughout a polymeric matrix. The amount of drug in the microcapsule depends upon the ratio of drug to coating material but is also dependent upon the solubility of the drug in the processing medium i.e. unless the drug is relatively insoluble in the processing medium, a proportion of the drug will be lost from the microcapsules during preparation.

Several process parameters can be adjusted to control the characteristics of the microencapsulated product. The solvent evaporation method of microencapsulation has been used extensively for the preparation of polylactic acid microspheres[2, 3, 4] but has only recently been used for other coating materials[5, 6].

The aim of this study was to investigate the effect of production variables on ibuprofen microcapsule characteristics and drug release from them. The production variables examined are evaporation procedure; the amount of organic phase used and drying conditions.

MATERIALS AND METHODS

Materials

Ibuprofen confirmed to the USP standard. Ethylcellulose (48 % ethoxy content, viscosity of a 5 % solution 100 cp) from Aldrich Chemical Company (Milwaukee, WI, U.S.A.), polyvinyl alcohol (molecular weight 72.000) from Merck. All other chemicals used were commercially available products of special reagent grade.

Preparation of microcapsules

The microcapsules were prepared by the solvent evaporation method. The drug and coating material were dissolved in 40 mls of methylene chloride. The aqueous phase was prepared by dissolving 0.27 % polyvinyl alcohol in 500 ml of water. The organic phase was then emulsified into the aqueous phase by stirring at 800rpm and the mixture was stirred continuously until the methylene chloride had evaporated. The microcapsules were collected by filtration, washed with deionized water and dried at 55°C in a vacuum oven. Microcapsules were prepared with core to wall ratios 1:2.

The microcapsules were sieved into five fractions; > 1400, 1400-1000, 1000-500, 500-212 and <212 μm, by using IS standard sieves. The ibuprofen content of the microcapsules was determined spectrophotometrically at 262 nm by dissolving a sample of the microcapsules in methylene chloride, using Perkin Elmer 550 SE UV/VIS spectrophotometer.

For surface characterisation, samples of the microcapsules were mounted on aluminium stubs and coated with a gold palladium mixture in an Edward's S150B sputter-coating apparatus and the surface topography was examined using a Cambridge Instruments Stereoscan 240 scanning electron microscope.

Production variables:

Interrupted evaporation method: Stirring was stopped after 2 hours, the microcapsules allowed to settle and the aqueous phase decanted. After washing the microcapsules three times with distilled water they were resuspended in distilled water and stirring continued until all the methylene chloride had evaporated.

Amount of organic phase: The microencapsulation was carried out using 20, 30, 40, 50 and 60 mls of methylene chloride.

Drying of the microcapsules: Instead of drying the microcapsules in a vacuum oven at 55°C for 1 hour they were dried in air overnight and then in a dessicator for 24 hours.

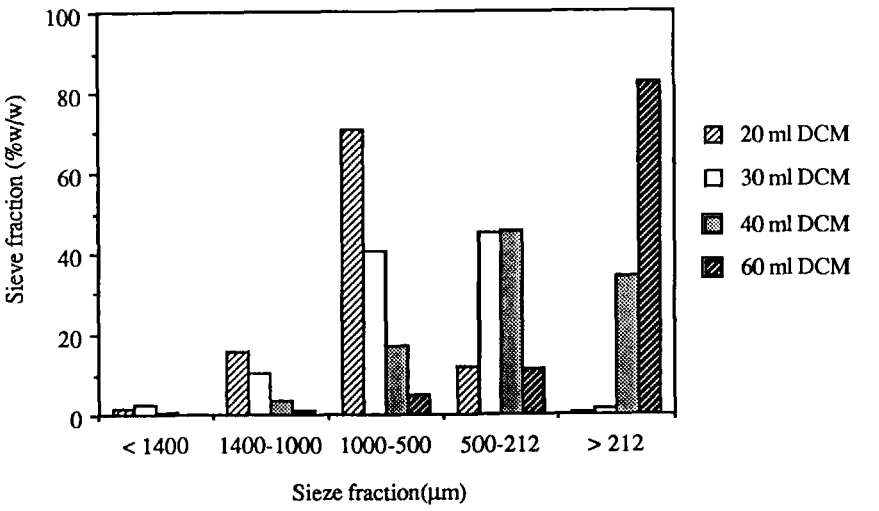

FIGURE 1

The effect of volume of methylene chloride (DCM) used in the micro-encapsulation process on the size distribution of the microspheres.

Release studies

The release studies were carried out using the USPXXII described paddle apparatus (Prolabo from Groupe Rhone-Poluenc, France) for dissolution rate determination. For each experiment, a sample of the microcapsules was dispersed onto the surface of 1000 ml of simulated intestinal fluid, TS, USP XXII (without enzyme, pH 7.5). Stirring rate was maintained at 100 rpm and temperature at 37°C. Samples (6.0 ml) were withdrawn at various time intervals, filtrated through 0.45 μm membrane filters (Millex-HV; Millipore, U.S.A.) and analysed by UV. Each experiment was carried out in triplicate.

RESULTS AND DISCUSSION

Effect of volume of organic phase

The amount of methylene chloride used in the production process had a considerable effect upon the size distribution of the

TABLE 1

The effect of organic phase volume on microcapsule drug loading, slope and correleation coefficients of a plot of drug release vs the square root of time

Amount of methylene chloride, ml	drug loading %	slope	correlation coefficient
20	29.07	2.2795	0.991
30	29.85	2.6614	0.990
40	28.31	2.7565	0.976
60	27.41	1.7342	0.971

microcapsules. Figure 1 shows that an increase in volume of the organic phase resulted in smaller microcapsules but microscopic examination revealed that the larger size fractions were to some degree composed of clusters of smaller microcapsules. An increase in volume of methylene chloride improved the yield but caused a slight lowering in the drug loading of the microspheres (Table 1). This is in agreement with results obtained by Bodmeier and McGinity[4] in their work on polylactic acid microspheres. Dissolution testing revealed that initial release of drug increases in proportion to the amount of methylene chloride used in the preparation of microcapsules (Figure 2). This can be explained by the fact that when a low volume of organic phase is used its evaporation and subsequent precipitation of drug and polymer is rapid thereby minimising the amount of drug gathering at the droplet boundary. With an increased volume of organic phase evaporation is slower and the microcapsules take longer to form which leads to more drug at or near the interface. This is confirmed by the dissolution results, which show that with increasing volume of organic phase the burst effect becomes larger. Once the drug on the surface of the

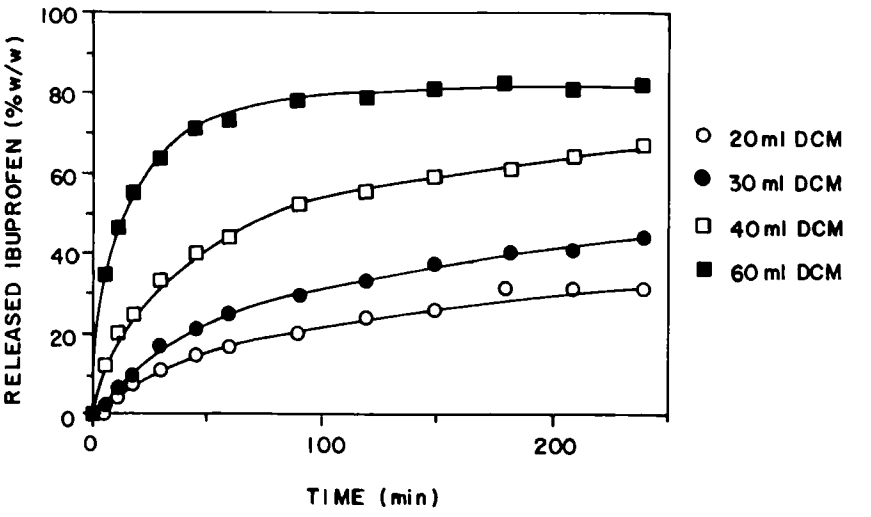

FIGURE 2

The release of ibuprofen from microcapsules prepared with different amounts of methylene chloride (DCM).

microcapsules has dissolved, drug release obeys the Higuchi membrane diffusion controlled model[7]. The drug release rate is not significantly different except when the largest amount of solvent (60 ml) is used, when it decreases. This could be caused by a large proportion of the drug being on or near the surface as indicated by the large burst effect. The release rate of the remaining drug, embedded in the matrix is governed by the channels formed by the dissolving drug. It is therefore logical that drug release from a matrix containing less drug would be slower.

Microscopic examination (Figure 3) revealed that the microcapsules are spherical with a smooth surface and some uncoated drug adhering to the surface.

Comparison of drying procedures

In comparing the drying procedures it was found that when drying in air overnight and then in a dessicator, the larger part of the

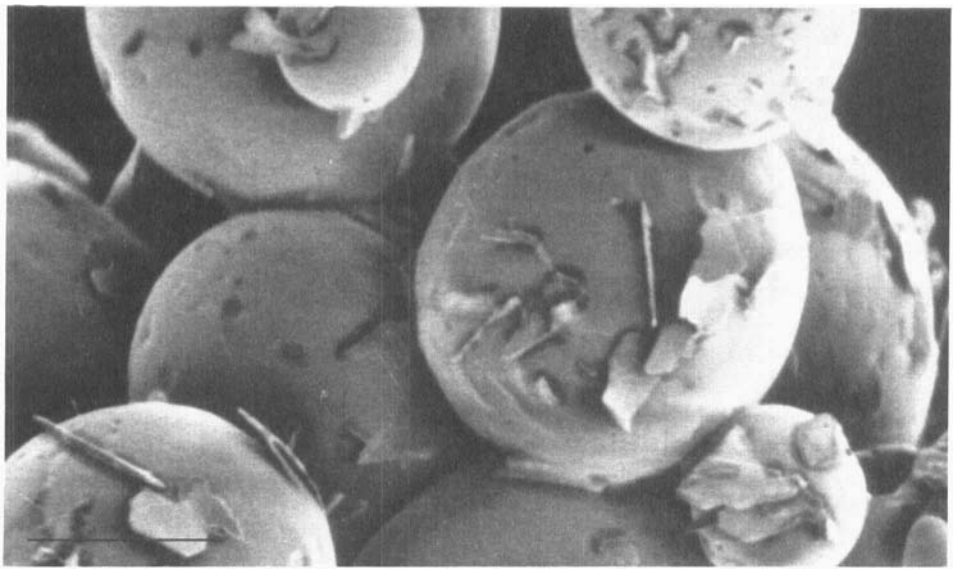

FIGURE 3

Scannig electron micrograph of ibuprofen microcapsules prepared with 60 mls of methylene chloride. Scale bar 50 μm.

microcapsules fell into the size fraction smaller than 212 μm (Figure 4). Drying the microcapsules in a vacuum oven caused the size distribution to shift towards the larger sizes, with 60 % falling into the size fraction 500-212 μm. Presumably vacuum oven drying increases the tendency of the moist microcapsule surfaces to adhere together and form hard lumps composed of many small microcapsules upon drying completely. This was confirmed by microscopic examination. Method of drying affects the size distribution but other parameters such as drug release or drug loading are unaffected.

Comparison of the continuous evaporation process and the interrupted evaporation process.

Other workers[8] have shown that it is possible to decrease the amount of uncoated drug in the continuous phase and on the surface of

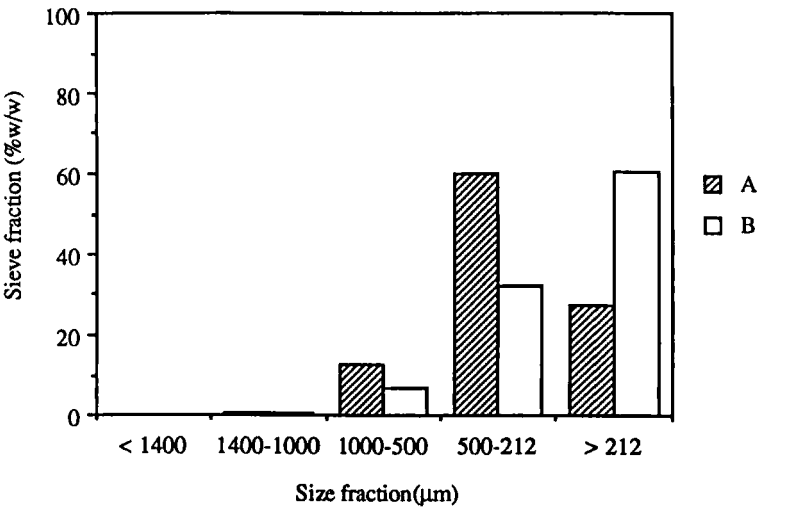

FIGURE 4

The effect of drying procedure on the size distribution of ibuprofen microcapsules. A - dried in a vacuum oven, B - dried in a dessicator.

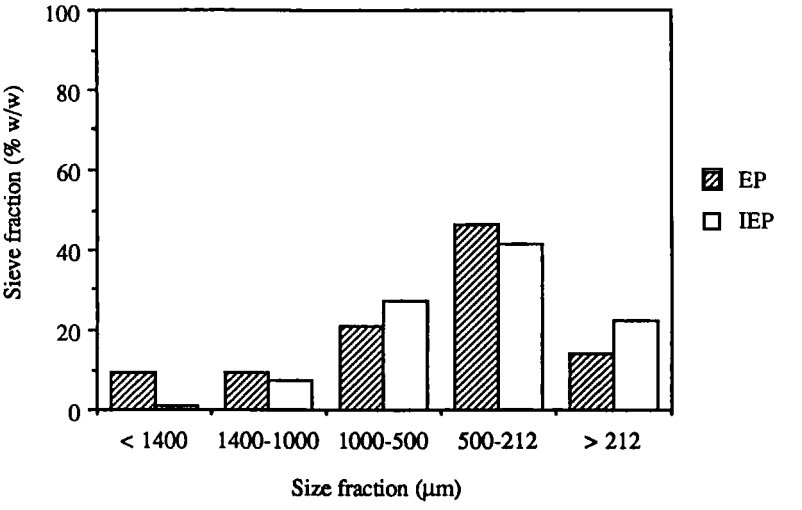

FIGURE 5

Comparison of the size distribution of microcapsules prepared by the continuous evaporation method (EP) and the interrupted evaporation method (IEP).

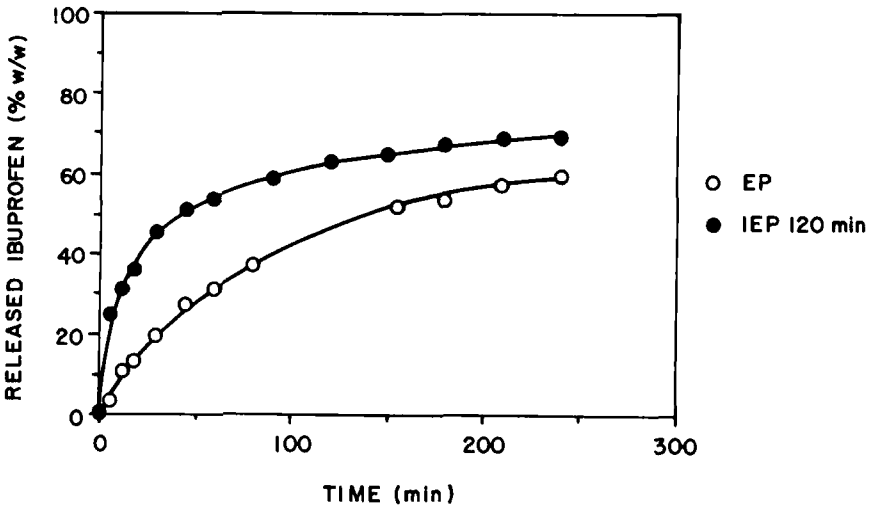

FIGURE 6

The release of ibuprofen from microcapsules prepared by the continuous evaporation method (EP) and the interrupted evaporation method (IEP).

microcapsules by removing the surfactant before all the methylene chloride has evaporated. In the interrupted evaporation process agitation is stopped before methylene chloride evaporation is complete, the partially dried microcapsules allowed to settle, and the aqueous phase that contains the surfactant replaced with water by three washing and decantation steps. The interrupted process caused microcapsule size distribution to be shifted slightly to the smaller size (Figure 5). There was only a small difference found in the drug loading of microcapsules manufactured by both processes. This is not in accordance with previously reported results but the emulsifier used in this work, polyvinylalcohol, is mostly effective as an emulsion stabiliser but is not very effective as a surfactant[9].

Figure 6 shows drug release from the microcapsules. The initial burst release of drug from microcapsules made according to the interrupted evaporation process, indicates the presence of drug on or

near the surface which would have been solubilized to a larger extent if the emulsifier had remained in the aqueous phase.

CONCLUSIONS

It can be concluded from this study that the size distribution and the drug loading of the microcapsules is influenced by several production parameters. The release of drug from the microcapsules was observed to be strongly influenced by parameters affecting the presence of uncoated drug on the microcapsule surface.

ACKNOWLEDGEMENT

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