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Naproxen microcapsules: preparation and in vitro characterization

S.J. Sveinsson and T. Kristmundsdóttir

Department of Pharmacy, University of Iceland, 101 Reykjavik (Iceland)

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Summary

Microcapsules were prepared from naproxen and ethylcellulose by coacervation phase separation, using polyisobutylene as a coacervation-inducing agent. The micrometric properties of the microcapsules and dissolution behaviour were examined. Using polyisobutylene at different concentrations, it was possible to regulate the release of naproxen during an in vitro dissolution test from 60 to 90%. Scanning electron micrographs revealed that the microcapsules were aggregates of individually coated naproxen crystals clustered together.

Introduction

In recent years, considerable effort has been put into the development of new and improved dosage forms where release of the active ingredient can be controlled and/or modified. One of the techniques used to achieve this goal is that of microencapsulation. By definition, microencapsulation is a process where thin film coatings are deposited onto small individual particles or groups of particles. Microencapsulation can be applied in many fields of pharmaceutical formulations, but is most frequently employed to modify and to retard drug release. Coacervation from aqueous solution and organic solvents is probably the most common method of microencapsulation.

It has been well documented that the modification of preparations influences the characteristics of the microcapsules. For example, Chemtob et al. (1986) studied the effect of stirring rate and other parameters on the properties of the microcapsules and several published reports describe the effects of coacervation-inducing agents on the procedure of microencapsulation (Benita and Donbrow, 1980, 1982; Nixon and Agyilirah, 1982; Samejima et al., 1982; Lin, 1985; Chemtob et al., 1986, 1989).

This work was undertaken in order to prepare naproxen microcapsules from ethylcellulose and polyisobutylene, and to investigate how different parameters in the manufacturing process can be used to modify the drug release.

Correspondence: T. Kristmundsdóttir, Dept of Pharmacy, University of Iceland, 101 Reykjavik, Iceland.

Materials and Methods

Materials

Naproxen conformed to the USP XXI standard. Polyisobutylene (molecular weight 380000) and ethylcellulose (ethoxy content 48%, viscosity 100 cp, 5% solution in toluene-ethanol 80:20 w/w) were purchased from Aldrich Chemical Co. (Dorset, U.K.). Cyclohexane, spectroscopy grade, was purchased from Merck (Darmstadt, Germany). All other materials were analytical grade.

Preparation of microcapsules

Microcapsules were prepared by coacervation phase separation according to a method described by Jalsenjak et al. (1976) and Chemtob et al. (1986) with modifications. In preparing a batch, polyisobutylene (PIB) was dissolved in 300 ml of cyclohexane by heating. Ethylcellulose was added to the warm solution (50°C) while stirring and the rate of stirring was maintained at 400 or 700 rpm. The naproxen (core material) was dispersed in a solution of the coating polymer (wall material) and the temperature was held at 80°C for 1 h. Phase separation and subsequent coacervation was induced by lowering the temperature to 45°C over a period of 1 h. The microcapsule wall was rigidified by rapid cooling to 20°C. Microcapsules were allowed to sediment and were separated by decantation. Each batch was washed three times with 200 ml of cold cyclohexane, vacuum filtered and dried at 50°C for 30 min.

Microcapsules were prepared with core-to-wall ratios 1:1 and 1:2 and the PIB concentration ranged from 0 to 8% (w/w). Each batch was made in triplicate except for microcapsules without PIB where only one batch was prepared.

The microcapsules were sieved into four fractions (1400–1000, 1000–500, 500–212 and < 212 μm) by using IS standard sieves. The naproxen content of microcapsules was determined spectrophotometrically at 271 nm by dissolving a sample of the microcapsules in methanol, using a Perkin Elmer 550 SE UV/Vis spectrophotometer.

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

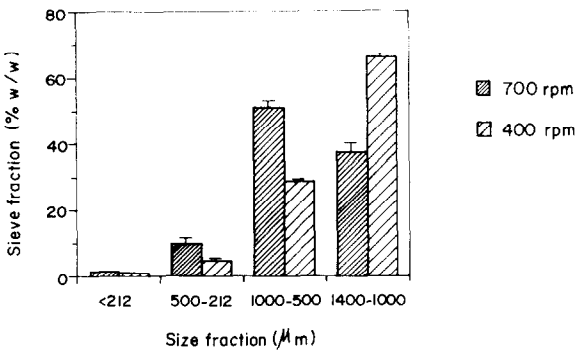

Fig. 1. Effect of stirring rate on size distribution of microcapsules. Core-to-wall ratio 1:1. Error bars represent the standard deviation of the mean ($n = 3$).

All dissolution tests were carried out using the USP XXI dissolution apparatus 2 (paddle method). For each experiment, a sample of microcapsules was dispersed onto the surface of 1000 ml of simulated intestinal fluid, TS, USP XXI (without enzyme, pH 7.5). Stirring rate was maintained at 100 rpm and temperature at 37°C. The dissolution test was conducted for 4 h and each experiment was carried out in triplicate. The amount of dissolved naproxen was determined spectrophotometrically.

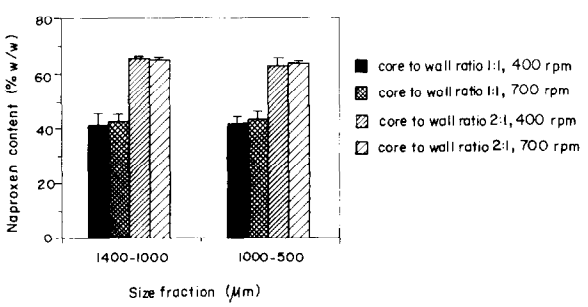

Fig. 2. Naproxen content of microcapsules prepared at two stirring rates (400 and 700 rpm). Error bars represent the standard deviation of the mean ($n = 3$).

Results and Discussion

The influence of the different parameters in the manufacturing of microcapsules on the size distribution and drug content is demonstrated in Figs 1 and 2. For microcapsules with a core-to-wall ratio of 1 : 1, it can be seen that in the case where the stirring rate was maintained at 400 rpm, almost 70% of the microcapsules had a mean diameter of 1400–1000 μm. By increasing the rate of stirring to 700 rpm, the deposition of coacervated ethyl cellulose onto the naproxen crystals was improved and consequently a greater proportion of smaller microcapsules were formed. However, no significant ($p > 0.05$) differences were found in the naproxen content of the microcapsules manufactured at the two stirring rates (Fig. 2). Fig. 2 also demonstrates that no significant difference ($p > 0.05$) was observed in the drug content of microcapsules of different size fractions. According to dissolution tests, the speed of stirring (400 vs 700 rpm) during the preparation of the microcapsules did not affect the amount or rate of the released drug (results not shown). From these data, it is evident that the speed of stirring only changes the particle size distribution, whilst other parameters such as the dissolution characteristics and drug loading remained unaffected.

The coacervation-inducing agent used in these experiments, PIB, is a linear molecule of high molecular weight and therefore due to its high viscosity, microcapsules were prepared using a maximum concentration of 8% PIB (w/w). Earlier reports (e.g. Nixon and Agyilirah, 1982; Chemtob et al., 1989) indicate that PIB reduces aggregation of the microcapsules. The results from the sieving analysis indicated that the presence of PIB resulted in an overall decrease in size of the microcapsules. The effect of 1 and 6% PIB on microcapsules with both core-to-wall ratios is illustrated in Figs 3 and 4. The effect of size reduction is more pronounced for microcapsules with the core-to-wall ratio of 1 : 1, where larger microcapsules were predominantly formed at low PIB concentration, whilst the size distribution was completely shifted to the smaller size range at higher PIB concentration (6%).

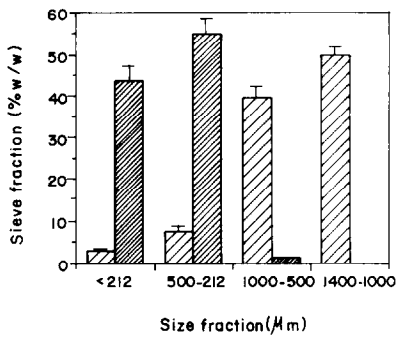

Fig. 3. Effect of the coacervation-inducing agent on the size distribution of microcapsules with a core-to-wall ratio of 1 : 1. Error bars represent the standard deviation of the mean ($n = 3$).

Microscopic examination revealed that the microcapsules were irregularly shaped and that the surface of the microcapsules prepared without a protective colloid had a multiple-pore structure. The microcapsules had a loose internal structure and individual ethylcellulose-coated crystals of naproxen could be observed. On increasing the concentration of PIB, the surface of the microcapsules became smoother and compact although their shape remained irregular (Fig. 5). Fig. 5 also demonstrates that the microcapsules are present as aggregates composed of individually coated naproxen crystals.

The release of the active ingredient was determined by dissolution tests. Over a period of 4 h,

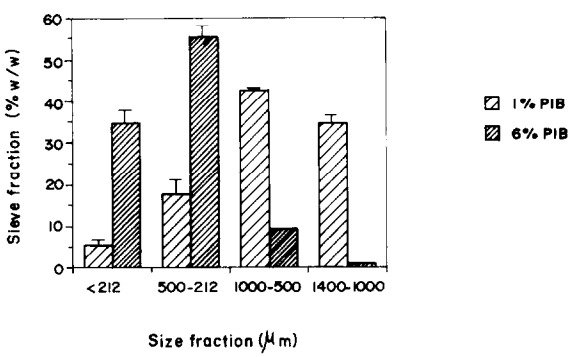

Fig. 4. Effect of the coacervation-inducing agent on the size distribution of microcapsules with a core-to-wall ratio of 2 : 1. Error bars represent the standard deviation of the mean ($n = 3$).

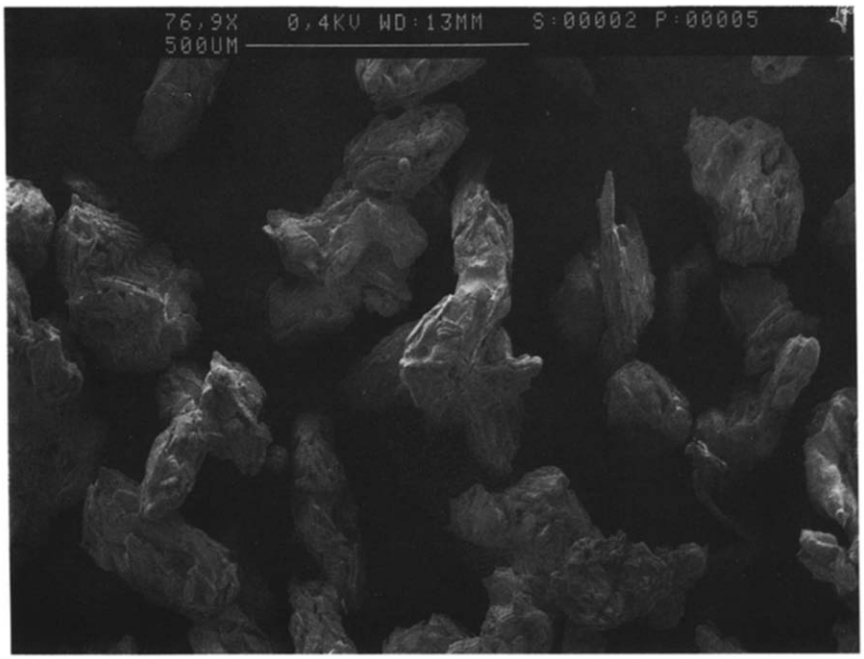

Fig. 5. Scanning electron micrograph of naproxen microcapsules prepared with a core-to-wall ratio of 2:1 and 6% PIB. Scale bar: 50 μm.

approx. 60–90% of the total amount of encapsulated drug was released depending on the concentration of PIB. Table 1 summarizes the values of $t_{50\%}$ for microcapsules with the core-to-wall ratio of 2:1. Microcapsules prepared without PIB released approx. 50% of their content while 90% was released by microcapsules containing 6% PIB (Fig. 6). These observations are consistent with the findings of Benita and Donbrow (1982) who reported a similar trend for salicylamide and theophylline microcapsules.

From the results of the present work, it can be concluded that it is possible to control the amount and rate of release of naproxen from ethylcellulose wall microcapsules using PIB as a coacervation-inducing agent.

TABLE 1

$t_{50\%}$ for microcapsules with a core-to-wall ratio of 2:1

Polyisobutylene concentration (% w/w)	$t_{50\%}$ (min)
0	140 ± 3
2	90 ± 2
4	52 ± 4
6	20 ± 3

Data are means of three determinations ± SD.

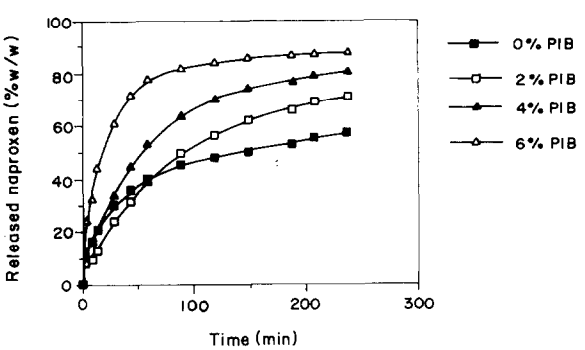

Fig. 6. Dissolution profiles ($n = 3$) of microcapsules with a core-to-wall ratio of 2:1.

Acknowledgements

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