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The effect of tableting on the release characteristics of naproxen and ibuprofen microcapsules

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Summary

Tablets were prepared from ethylcellulose walled naproxen and ibuprofen microcapsules. The naproxen and ibuprofen microcapsules were prepared by different methods; the naproxen microcapsules were coated drug crystals whereas ibuprofen microcapsules had a matrix structure. The microcapsules showed good compression behaviour and satisfactory tablets were produced. Release characteristics of the microcapsules changed drastically upon compression and the addition of excipients to the tablets decreased the $t_{50\%}$. The results also indicate that the ibuprofen microcapsules are intact after tableting whereas the coating on the naproxen microcapsules is ruptured to some extent.

Introduction

One of the advantages of the microencapsulation technique is its ability to modify and retard drug release. As a sustained release formulation, the microcapsules can be presented as powder, capsules or as tablets. Microcapsules usually exhibit high mechanical resistance and are therefore able to withstand abrasion and other damage during the manufacturing procedure and subsequent storage. However, there has been some concern that the microcapsules might lose their integrity during tableting, resulting in a subsequent increase in release rate of the active ingredient (Jalsenjak et al., 1977; Abdel Monem Sayed and Price, 1986; Lin, 1988; Prapaitrakul and Whitworth, 1989). In contrast, it has been demonstrated by several researchers (Jalsenjak et al., 1980; Chemtob et al., 1986; Lin, 1988; Pathak and Dorle, 1989), that in many instances compression of microcapsules results in substantial prolongation of the release of the active ingredient.

There are several factors which must be considered in the tableting of microcapsules, as well as for conventional tableting, for example, bulk density, porosity, size distribution, angle of repose and other flow characteristics. These factors and numerous other parameters have been previously studied for microcapsules: for example, compression pressure (Jalsenjak et al., 1976; Prapaitrakul and Withworth, 1989, 1990), core to wall ratio and size distribution (Jalsenjak et al., 1976; Abdel Monem Sayed and Price, 1986), excipients (Nixon and Hassan, 1980; Lin, 1988;

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Pathak and Dorle, 1989; Prapaitrakul and Withworth, 1989), flow characteristics (Nixon and Harris, 1983) and manufacturing conditions and presence of protective colloid (Chemtob et al., 1986).

A prerequisite in tableting is that the tablet should exhibit a sufficient hardness to withstand handling and storage while maintaining wanted release characteristics. When using ethylcellulose as a coating polymer in microencapsulation, previous work (Jalsenjak et al., 1977; Oya Alpar and Walters, 1981) indicates that there is not always an immediate need for fillers, binders, disintegrants or other excipients. Ethylcellulose is frequently used as a binder in conventional tableting and presumably microcapsules prepared from such coating materials should exhibit the same or similar properties. It has also been pointed out (Abdel Monem Sayed and Price, 1986) that one of the determining factors in drug release from tableted microcapsules can be the structure of the microcapsules, with matrix type microcapsules being more resilient than microcapsules consisting of thinly coated drug crystals.

The scope of this work was to prepare tablets from naproxen and ibuprofen microcapsules and investigate how the tableting affected the release properties of the microcapsules. The naproxen and ibuprofen microcapsules were prepared by different methods; naproxen being coated by the coacervation phase separation technique which gives coated drug particles, whereas ibuprofen was was coated by the solvent evaporation method resulting in microcapsules of a matrix structure. This facilitates the comparison of the effect of microcapsule structure on drug release after tableting by direct compression.

Materials and Methods

Materials

Naproxen and ibuprofen conformed to the USP XXII and BP 80 standards respectively. Polyisobutylene (PIB; Mol. Wt 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 and dichloromethane, both spectroscopy grade, were purchased from Merck (Darmstadt, Germany) and Rathburn (Walkerburn, U.K.) respectively. All other materials were analytical grade.

Preparation of microcapsules

The naproxen microcapsules were prepared by the coacervation phase separation technique. Ethylcellulose was used as coating polymer and polyisobutylene as a coacervation inducing agent, according to a method described by Jalsenjak et al., (1976), with modifications (Sveinsson and Kristmundsdóttir, 1992). Naproxen microcapsules were made with 2:1 core (naproxen) to wall (ethylcellulose) ratio

For the microencapsulation of ibuprofen, the solvent evaporation technique was applied. Briefly, both the drug and the coating polymer (ethylcellulose) were codissolved in equal proportions in 100 ml of dichloromethane. When fully dissolved, the solution was poured into an aqueous phase containing 0.27% polyvinyl alcohol and an emulsion was formed while stirring at a rate of 400 rpm. The organic phase was removed at ambient temperature. The microcapsules were collected by filtration and washed with deionized water and dried in a desiccator for 48 h. All batches were made in triplicate.

All microcapsules were sieved into four fractions; 1400–1000, 1000–500, 500–212 and < 212 μm, by using IS standard sieves. The naproxen and ibuprofen content of the microcapsules was determined spectrophotometrically at 271 and 262 nm by dissolving a sample of the microcapsules in methanol and dichloromethane, respectively, using a Perkin Elmer 550 SE UV/Vis spectrophotometer.

Samples of microcapsules and tablets were prepared for examination by scanning electron microscopy (SEM) as described earlier (Sveinsson and Kristmundsdóttir, 1992).

Preparation of tablets from microcapsules

All tablets were prepared using a Carver laboratory press using a 13 mm (diameter) die. For all experiments, 300 mg of microcapsules were compressed applying a pressure of 565 kg/cm^{-2} for 1 min.

Dissolution

All dissolution tests were carried out using a USP XXII dissolution apparatus 2 (paddle method). For each experiment, each tablet was placed in 1000 ml of simulated intestinal fluid, TS, USP XXII (without enzyme). Stirring rate was maintained at 100 rpm and temperature at 37°C. The dissolution test was carried out for 4 and 10 h and each experiment was carried out in triplicate, all results being expressed as mean ± standard deviation (SD). The amount of dissolved naproxen and ibuprofen was determined using a spectrophotometer as described earlier.

Friability, hardness and disintegration

The friability of the tablets was estimated using the Roche Friabilitor, which was operated for 4 min at a rate of 25 rpm. Disintegration test was performed according to USP XXII and the hardness of the tablets was estimated using a Stokes hardness tester.

Statistical analysis

Data sets for each group of measurements were analyzed by ANOVA and two sample t-test to determine whether sample means were statistically different, using pooled standard deviation in Minitab, version 7.1 (Minitab Inc, State College, PA). The difference was found significant if $p < 0.05$, except where otherwise stated.

Results and Discussion

The dissolution behaviour and micrometric properties of the untableted naproxen microcapsules have been previously reported (Sveinsson and Kristmundsdóttir, 1992). Tablets prepared from naproxen microcapsules without any excipients had a low friability index (0.5–0.6% friability, irrespective of the PIB content). The hardness was also found to be unaffected (non-significant differences, $p > 0.05$) by the PIB content and the tablets without any excipients had a mean hardness of 5.8 ± 0.2 kg. None of the tablets made from microencapsulated naproxen disintegrated over the period of 30 min. These results indicate that the coating polymer (ethylcellulose) in the microcapsules acts as a good and efficient binder and the resulting tablets therefore exhibit strong mechanical properties.

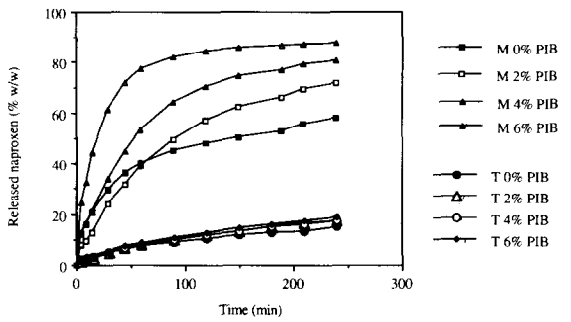

Fig. 1. Comparison of the released amount of naproxen from microcapsules before (M) and after (T) tableting ($n = 3$). Error bars are omitted to avoid overlapping.

Naproxen microcapsules containing 0, 2, 4 and 6% polyisobutylene (PIB) as a coacervation inducing agent released their content proportionally with increasing content of PIB. Fig. 1 shows the comparison of the release behaviour between the tableted microcapsules and the untableted (free) microcapsules. Upon compression, the drug release decreased from 88% (6% PIB) after 4 h for free microcapsules to less than 20% for compressed microcapsules. While the increase ($p < 0.001$) in released naproxen (after 4 h) was more than 30% for free microcapsules when the PIB concentration was increased from 0 to 6%, only a 5% increase ($p > 0.05$) was observed over the same time period when these microcapsules were tableted (Fig. 1). From these results it is apparent that the addition of a disintegrant to these rigid, matrix type tablets, is necessary. Sodium carboxymethylcellulose (Na-CMC) was added in concentrations from 2 to 10% (w/w). The addition of Na-CMC resulted in a rapid increase in the amount of naproxen released from the tablets (Fig. 2). In Fig. 2, it can be seen that Na-CMC increases the release of naproxen from the tablets made from microcapsules containing 6% PIB. The tablets maintained their shape (but had swollen) when 2% Na-CMC concentration was used, but at higher concentrations of Na-CMC (5 and 10%) the tablet disintegrated as soon as it was placed in the dissolution media.

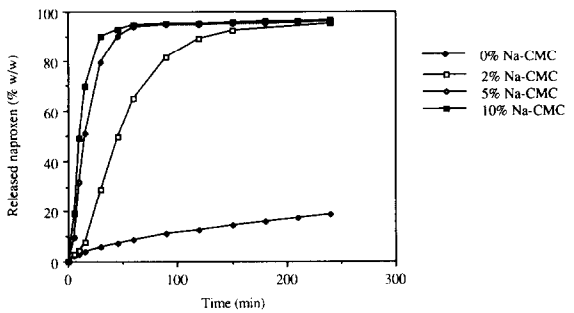

Fig. 2. Effect of sodium carboxymethylcellulose (Na-CMC) on release of naproxen from tableted microcapsules containing 6% PIB ($n = 3$). Error bars are omitted to avoid overlapping.

In Fig. 3, the $t_{50\%}$ (time required to release 50% of the naproxen content) is plotted as a function of Na-CMC content of microcapsules containing 6% PIB. With no disintegrant, $t_{50\%}$ is almost 17 h and decreases rapidly as the Na-CMC concentration increases (Fig. 3). It is worth noting that a tablet made with 10% Na-CMC releases its content more rapidly and to a greater extent than the free untableted microcapsules (Fig. 1). This indicates that upon tableting the ethyl cellulose coating might be ruptured, although that could not be confirmed by scanning electron microscopy (Fig. 4).

Scanning electron microscopic examination revealed that the naproxen microcapsules are irregularly shaped, individually coated naproxen crystals (Sveinsson and Kristmundsdóttir, 1992). The microcapsules can therefore be packed very

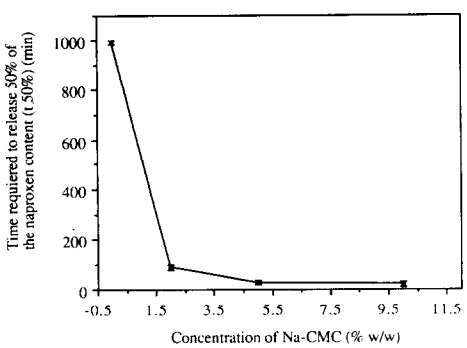

Fig. 3. Effect of sodium carboxymethylcellulose (Na-CMC) on the time required to release 50% of the naproxen content from tableted microcapsules. Error bars represent the standard deviation ($n = 3$).

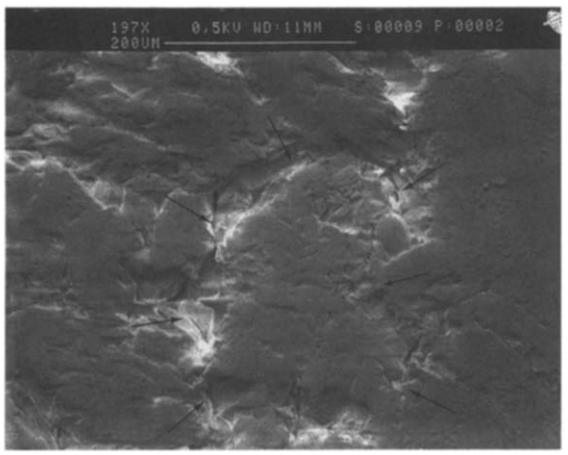

Fig. 4. Scanning electron micrograph of a tablet made from naproxen microcapsules (6% polyisobutylene). The arrows show the position of one microcapsule in the surface of the tablet. Scale bar = 200 μm.

closely together and consequently the dissolution medium is only in contact with the outermost layer of the tablet and diffusion of the drug from deeper layers of the tablet is hindered. Fig. 4 shows the surface of a tablet made from microcapsules containing 6% PIB. It can be seen that the surface appears to be continuous and there are few gaps or pores between the collapsed microcapsules in the surface of the tablet as the microcapsules have undergone plastic deformation during compression (Fig. 4).

Examination of ibuprofen microcapsules by SEM showed that these microcapsules were composed of spherical units with a smooth and continuous surface (Fig. 5). When these microcapsules are tableted it can be seen that the drug release after 4 h decreased from 92% for the free microcapsules to 26% for the tablets (Fig. 6). When the spherical ibuprofen microcapsules are compared with the naproxen microcapsules which are irregularly shaped, it is expected that a lower degree of packing is achieved and consequently less compact tablets are formed from the ibuprofen microcapsules. Tablets were prepared using Na-CMC, microcrystalline cellulose (Avicel®) and magnesium stearate. The effect of all the excipients on the dissolution properties was to decrease the $t_{50\%}$. The addition of 10% Na-CMC decreased the $t_{50\%}$ to 75 min compared to 500 min

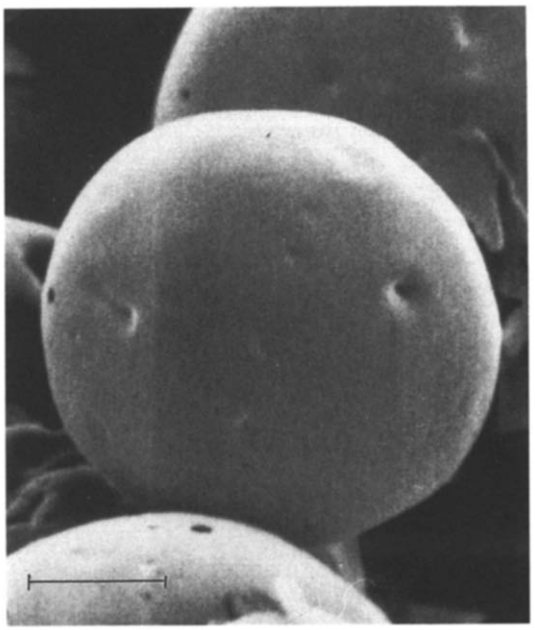

Fig. 5. Scanning electron micrograph of ibuprofen microcapsules. Scale bar = 10 μm.

for tablets without excipients. Also, the addition of 5% Na-CMC, 1% magnesium stearate and 30% Avicel® caused a rapid disintegration of the tablet (Fig. 6). Comparing the release rate of ibuprofen from a tablet prepared with excipients to that from the free microcapsules, no increase in release rate was observed, in contrast to the results obtained for the naproxen microcapsules (Fig. 2). This suggests that the ibuprofen microcapsules are intact after tableting, while the naproxen microcapsules might have lost their integrity.

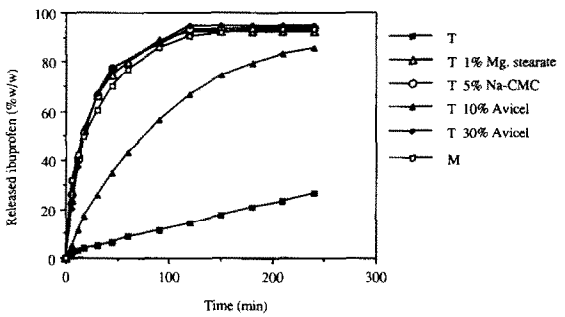

Fig. 6. Comparison of the released amount of ibuprofen from free microcapsules (M) and tableted microcapsules (T); without any excipients, 1% magnesium stearate, 5% Na-CMC, 10% and 30% Avicel ($n = 3$). Error bars are omitted to avoid overlapping.

It can be concluded from this study that the structural characteristics of the microcapsules, i.e., the individually coated naproxen crystals vs the matrix type ibuprofen microcapsules, are a determining factor for the release properties of tablets made from such microcapsules. Also, the choice of excipients must be carefully considered in order to optimize the drug release of the resulting tablets.

Acknowledgement

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