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Release of indomethacin from tabletted ethylcellulose microcapsules

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Summary

Indomethacin was microencapsulated in a coacervation process using ethylcellulose as a wall material and polyisobutylene as a coacervation inducing agent. Micronized sodium chloride was added as a pore former into the microcapsule wall. Microcapsules were tabletted with plastically deforming microcrystalline cellulose and fragmenting dicalcium phosphate as well as with their binary mixture. The effect of compression pressure on drug release was evaluated. The release of indomethacin was also studied after effective disintegration of the tablets by crosslinked sodium carboxymethylcellulose. Release of indomethacin from plain microcapsules accelerated markedly when sodium chloride was added in the microcapsule wall. All the tablets without disintegrant stayed nearly intact during the dissolution test. The tablets of microcapsules were composed of a porous ethylcellulose matrix in which the microcapsules were separated from each other by easily wettable tablet adjuvants. The drug release accelerated from the tablets due to the mechanical destruction of microcapsule wall, which was more clearly seen after disintegration of the tablets to the multiple microcapsule units. The rupture of microcapsule films was most extensive with the tablets containing fragmenting dicalcium phosphate as a filler. The addition of sodium chloride in the microcapsule wall seemed to make the polymer film firmer thus reducing the destructive effect of tablet adjuvants.

Introduction

Indomethacin is a commonly used non-steroidal anti-inflammatory drug. Gastrointestinal and CNS side-effects associated with indomethacin have been widely reported (e.g., Boardman and Hart, 1967). The dosage form of indomethacin has been demonstrated to affect the incidence of these side-effects (Carless and Rowe, 1981). Microencapsulation of indomethacin has been stated to reduce the incidence and severity of both gastrointestinal and CNS side-effects compared to conventional oral tablet and capsule formulations of this drug (Rowe and Carless, 1981).

In published studies concerning the applications of microcapsules in tablets, the tablets have been most often compressed without adjuvants (Jalsenjak et al., 1977; Nixon et al., 1978; Agyilirah and Nixon, 1980; Jalsenjak et al., 1980; Nixon and Agyilirah, 1984; Chemtob et al., 1986; Lin and Yang, 1986; Dubernet et al., 1987; Singh and Robinson, 1988). When ethylcellulose was used

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as a wall material of microcapsules a non-disintegrating and insoluble matrix tablet was formed during the compression (Nixon and Agyilirah, 1984; Chemtob et al., 1986; Lin and Yang 1986; Lin, 1988; Singh and Robinson, 1988). The greatly reduced porosity and surface area prolonged the release of the drug from tablets compared to the original microcapsules.

Some recent reports deal with the effects of different tablet adjuvants on the compressional behaviour of microcapsules and on the release of drug from the tablets of microcapsules (Abdel Monem Sayed and Price, 1986; Sakr and Oyola, 1986; Lin 1988; Prapaitrakul and Whitworth, 1989, 1990; Ruiz et al., 1990). Sakr and Oyola (1986) have studied the effects of direct compression adjuvants on the release rate of potassium chloride from the tablets of ethylcellulose microcapsules. They found that dicalcium phosphate enhanced the release of drug from the microcapsules. They also found that microcrystalline cellulose was an ideal adjuvant for the tabletting of microcapsules. Microcrystalline cellulose has also been successfully used in tablets containing cellulose acetate butyrate microcapsules of succinyl sulphathiazole (Abdel Monem Sayed and Price, 1986).

The aim of this study was to evaluate the effects of compression pressure and two differently deforming direct compression adjuvants on the release properties of indomethacin from tablets of ethylcellulose microcapsules. Sodium chloride was tested as a pore former in the microcapsule wall. The release of indomethacin was evaluated both from intact matrix tablets and from multiple microcapsule units after the disintegration of the tablets by crosslinked sodium carboxymethylcellulose.

Materials and Methods

Preparation of microcapsules

Indomethacin (Sigma, St Louis, U.S.A.) with a microscopically measured mean particle diameter and standard error of 18 ± 0.9 μm was microencapsulated, modifying the coacervation technique described by Samejima et al. (1982). Ethylcellulose (Ethocel®, 45 mPa s, Fluka, Buchs, Switzerland) was used as a wall material. With stirring at a rate of 310 rpm ethylcellulose was added to cyclohexane (Merck, Darmstadt, Germany) solution containing 2.3% w/v of polyisobutylene (mol. wt 380000, Aldrich, Steinheim, Germany) as a coacervation inducing agent. The mixture was heated to 78°C and indomethacin was suspended in the solution. The mass ratio of core to wall was 10:1. The system was cooled uniformly to 40°C within 1 h and then quickly to 25°C. The solution was decanted and the microcapsules were washed with cyclohexane and dried at room temperature.

Under similar conditions, corresponding microcapsules with 3.5% w/w of micronized sodium chloride from the amount of ethylcellulose were prepared. According to Tirkkonen and Paronen (1992), 3.5% of sodium chloride in the microcapsule wall clearly enhanced the release of indomethacin from ethylcellulose microcapsules. The microscopically measured mean particle diameter of sodium chloride was 1.6 ± 0.07 μm. Sodium chloride was added to the microencapsulation process after cooling the system to 40°C.

The microcapsules were sieved and the microcapsule fraction of 149–297 μm was used for the further studies. This fraction contained about 55% of the microcapsules of one batch. Indomethacin content of the microcapsules, determined spectrophotometrically (Hitachi 220, Hitachi, Japan) at 318 nm after dissolving the microcapsules in methanol was 91.4% w/w from the total mass of microcapsules. Thus the ethylcellulose added to the manufacturing process was effectively used as the wall material.

Preparation of tablets

Microcapsules 100 mg in weight were mixed manually with 200 mg of either microcrystalline cellulose (Avicel® PH 101, FMC, U.S.A.) or dicalcium phosphate dihydrate (Emcompress®, Mendel, U.S.A.) or their mixture of 1:1. Magnesium stearate (Ph. Eur.) (0.5% w/w) was added to the masses as a lubricant. The weighted quantities of masses were individually poured into the die of 13 mm in diameter and compressed by an instrumented single punch machine (Korsch EK-O, Germany) at accurate compression pressures of 85, 170 or 340 MPa. The tablet formulations

described above were also tabletted after adding 0.75% w/w of crosslinked sodium carboxymethylcellulose (AcDiSol®, FMC, U.S.A.) as a disintegrant. These tablets were compressed at an accurate compressional pressure of 170 MPa. Every tablet composition mentioned above was compressed with microcapsules without and with sodium chloride in the wall.

Evaluation of physical characteristics of tablets

The breaking strength (Schleuniger 2E, Switzerland) was measured as a mean of six tablets. The disintegration of the tablets in 37°C water was studied up to 5 h according to the test for uncoated tablets in Ph. Eur. for six tablets. The effective densities of tablet components were determined with a pycnometric method (Multipycnometer MVP-1, Quanta Chrome, NY, U.S.A.) using helium as an inert gas. Five measurements were taken. The tablet dimensions measured by micrometer screw and the effective densities of tablets, calculated from the density values of plain components considering the component fractions, were used in porosity evaluations.

Evaluation of dissolution of indomethacin

Release of indomethacin from the microcapsules and from the tablets of microcapsules was studied for 7 h with the rotating basket method (Sotax AT6 Dissolution Tester, Sotax AG, Switzerland). The baskets were made of wire netting with quadratic holes of 74 μm. The dissolution medium (750 ml) was previously degassed pH 7.2 phosphate buffer at a temperature of 37 ± 0.5°C. The ionic strength of the dissolution medium was 0.02. The stirring rate of the baskets was 100 rpm. Indomethacin was evaluated spectrophotometrically at 318 nm.

Evaluation of surfaces of microcapsules and tablets

Scanning electron micrographs of microcapsules and tablets were taken before and after the dissolution tests. The samples were dried at room temperature and then coated with gold using a Jeol JFC-1100 sputter coater (Jeol, Japan). Micrographs were taken with a Jeol JSM-35 scanning electron microscope (Jeol, Japan) at an accelerating voltage of 15 kV.

Results and Discussion

Physical characteristics of tablets

The breaking strength of the tablets of microcapsules compressed with dicalcium phosphate was relatively low compared to the corresponding tablets containing microcrystalline cellulose (Table 1). The breaking strength of the mixture tablets was consequently intermediate between those of dicalcium phosphate and microcrystalline cellulose tablets. However, it was possible to compress tablets firm enough for handling, packing, etc., from all the tablet adjuvants tested. The presence of sodium chloride in the microcapsule wall did not affect the mechanical strength of the tablets.

The porosities of tablets with and without sodium chloride in microcapsule wall were equal (Table 1). The porosity values of microcapsule tablets containing different adjuvants were close to each other. Tablets containing dicalcium phosphate or mixture of microcrystalline cellulose and dicalcium phosphate were, however, slightly looser in structure than microcrystalline cellulose tablets.

The microcrystalline cellulose tablets disintegrated relatively fastly while the dicalcium phosphate tablets compressed with moderate or with the highest pressure did not totally disintegrate even during the test period of 5 h (Table 1). Tablets containing dicalcium phosphate underwent, however, softening during the disintegration test. Thus water was able to penetrate inside the tablets. When plain microcrystalline cellulose or both adjuvants were used as a mixture, microcrystalline cellulose seemed to act as a disintegrant making the tablets more hydrophilic and accelerating the disintegration due to the capillary effect (Gissinger and Stamm, 1980). The use of sodium chloride in the microcapsule wall seemed not to have an effect on the disintegration time of the tablets. The increasing compression pressure clearly restrained the disintegration process.

The addition of 'a super disintegrant', crosslinked sodium carboxymethylcellulose, in tablets did not affect their breaking strength or porosity

TABLE 1

Physical properties of tablets containing 33% of indomethacin microcapsules and 66% of adjuvants

Adjuvants	Compression pressure (MPa)	Breaking strength (kp)	Porosity (%)	Disintegration time (s)
E	85	4.1 (0.1)	26.6	9420 (2058)
E	170	6.2 (0.2)	21.2	> 18000
E	340	9.3 (0.2)	16.2	> 18000
E/NaCl	85	4.0 (0.1)	26.4	8196 (1896)
E/NaCl	170	6.3 (0.2)	20.8	> 18000
E/NaCl	340	9.1 (0.3)	15.8	> 18000
A	85	12.6 (0.2)	23.2	22 (1)
A	170	19.2 (0.2)	14.1	53 (2)
A	340	> 20	11.0	120 (7)
A/NaCl	85	12.0 (0.1)	23.4	22 (1)
A/NaCl	170	19.5 (0.3)	14.6	53 (2)
A/NaCl	340	> 20	10.3	111 (4)
E + A	85	8.2 (0.2)	26.2	31 (3)
E + A	170	11.7 (0.1)	19.3	58 (1)
E + A	340	17.7 (0.6)	14.5	55 (4)
E + A/NaCl	85	8.7 (0.1)	26.3	27 (2)
E + A/NaCl	170	12.3 (0.3)	18.5	55 (3)
E + A/NaCl	340	17.9 (0.5)	13.6	129 (6)
E + Ac	170	5.9 (0.1)	20.5	30 (3)
E + Ac/NaCl	170	6.1 (0.3)	20.5	34 (1)
A + Ac	170	19.7 (0.2)	15.9	32 (3)
A + Ac/NaCl	170	19.6 (0.2)	15.5	29 (3)
E + A + Ac	170	12.4 (0.3)	18.5	17 (1)
E + A + Ac/NaCl	170	12.3 (0.2)	19.0	18 (1)

Adjuvants used in the tablets; E, Emcompress, dicalcium phosphate; A, Avicel PH 101, microcrystalline cellulose; Ac, AcDiSol, crosslinked sodium carboxymethylcellulose. Every batch was compressed also using microcapsules with sodium chloride (NaCl) as a pore former in the capsule wall. Formulations of the tablets are described in the text. Values are the means with the standard error of the mean in parentheses ($n = 5–6$).

(Table 1). All the tablets containing this material disintegrated rapidly.

Release of indomethacin from microcapsules and tablets

Indomethacin was released very slowly from the plain microcapsules (Fig. 1). The addition of sodium chloride into the microcapsule wall accelerated dissolution remarkably. According to scanning electron microscopic evaluation, the solid particles of sodium chloride dissolved during the first 10 min after immersing the microcapsules into the dissolution medium. The pores and channels were formed in the microcapsule wall and thus indomethacin was able to diffuse more rapidly out from the microcapsule core. The effect of sodium chloride as a pore formed is discussed in detail in our previous paper (Tirkkonen and Paronen, 1992).

Both microcrystalline cellulose and dicalcium phosphate as well as their binary mixture tabletted with microcapsules formed a tablet matrix. Although these tablets were broken up during the disintegration test, they did not totally disintegrate during the test period of 7 h of the dissolution test. Evidently, the mechanical breaking forces towards the tablets in the dissolution test were much weaker than in the disintegration test. Thus, the solid ethylcellulose bridges probably formed during compression as well as the bonds

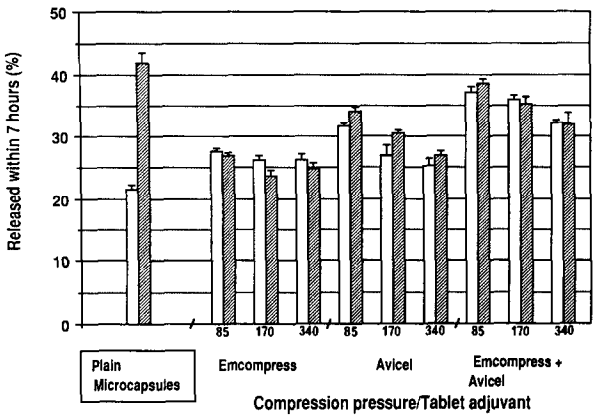

Fig. 1. Amount of indomethacin released (% ± SE, $n = 6$) within 7 h in dissolution test from microcapsules and from microcapsules tabletted with different adjuvants. Unfilled bars represent microcapsules without sodium chloride and hatched bars denote those with sodium chloride in the microcapsule wall. Compression pressures of tablets are expressed in MPa below the columns.

between adjuvant particles were able to maintain the tablet structure intact. However, due to the easily wettable tablet adjuvants, all the tablets clearly wetted and softened during the dissolution test. Thus, dissolution medium was able to penetrate inside the tablet matrix, diffuse into the microcapsules, dissolve indomethacin and diffuse out from the microcapsule wall and tablet matrix.

The effect of compression pressure on the release of indomethacin from tablets was surprisingly small (Fig. 1). Thus, similarly no clear correlation between the porosity of tablets and drug release was observed. Sakr and Oyola (1986) found that in tablets containing smaller amounts than 50% of microcrystalline cellulose with ethylcellulose-walled microcapsules no dependence between the release rate of potassium chloride and compression pressure existed. In this study a larger amount of microcrystalline cellulose (66%) was used in tablet formulation and a slight correlation between increasing compression pressure and decreasing release existed. For the binary mixture of microcrystalline cellulose and dicalcium phosphate this dependence was still smaller and did not exist for dicalcium phosphate tablets. This may be due to the smaller volume fraction of these materials in tablet formulation than using microcrystalline cellulose with very low bulk density. The results of this study indicate that nearly continuous, but due to the tablet adjuvants, rather porous ethylcellulose matrix has been formed during tabletting.

Due to the porous and softened structure of tablet matrices, the structure of microcapsule wall seemed to be very important factor affecting the drug release. Thus the differences in release of tabletted microcapsules would be mainly dependent on the differences in the structure of microcapsule walls.

Effect of tablet adjuvants on the microcapsule wall

During the tabletting process the tablet adjuvants have a direct pushing effect towards the microcapsule wall. Depending on the intensity of pushing forces there might occur mechanical destructions in the polymeric walls of microcapsules. The effect of tablet adjuvants on the microcapsule wall was clearly seen when the tablets were disintegrated by the act of crosslinked sodium carboxymethyl cellulose. All the tablets containing this material disintegrated rapidly in the disintegration test (Table 1) and also in the dissolution test. The tablet adjuvants have an enormous effect on the release of microencapsulated indomethacin (Fig. 2). Indomethacin released from the totally disintegrated tablets of

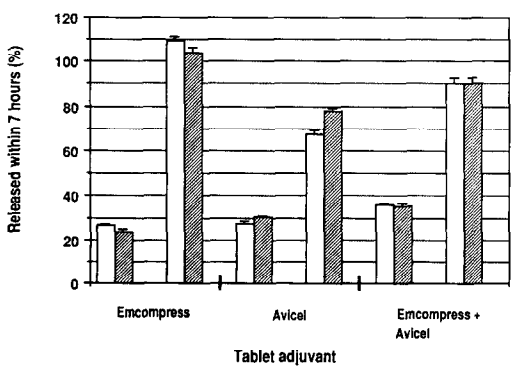

Fig. 2. Amount of indomethacin released (% ± SE, $n = 6$) within 7 h in dissolution test from microcapsules tabletted with different adjuvants and either without (the left two bars per adjuvant) or with (the right two bars per adjuvant) sodium carboxymethylcellulose as a disintegrant. Unfilled bars represent microcapsules without and hatched bars with sodium chloride in the microcapsule wall. Compression pressure was 170 MPa for all tablets.

microcapsules 3–5-times more than from the plain microcapsules and 2–5-times more than from the tablets without disintegrant (Figs. 1 and 2). There was also a clear difference between the adjuvants. Dicalcium phosphate seemed to accelerate drug release much more than microcrystalline cellulose. According to the scanning electron micrographs (Fig. 3) dicalcium phosphate has formed clear ruptures on the microcapsule wall. This effect was less intensive for microcrystalline cellulose. Particles of microcrystalline cellulose deform plastically but dicalcium phosphate undergoes fragmentation during the tabletting process (Rees and Rue, 1978; Paronen, 1986). Thus, small, hard and sharp-edged primary particles of dicalcium phosphate formed during tabletting. These particles had much more intensive mechanical effects on the microcapsule wall than the plastically deforming cellulose particles.

Effect of sodium chloride on the behaviour of microcapsule wall

From all the tablets containing microcapsules without sodium chloride in microcapsule wall, indomethacin released some faster than from corresponding microcapsules (Fig. 1). On the other hand, indomethacin released faster from microcapsules containing sodium chloride than from the corresponding tablets without disintegrant. Tabletting seemed to minimize the enhancing effect of sodium chloride on the release of indomethacin. The difference in release between tabletted microcapsules with or without sodium chloride was in every case relatively small. The use of sodium chloride enhanced the drug release from microcrystalline cellulose tablets, made little difference for the tablets containing both adjuvants and even decreased the release from dicalcium phosphate tablets.

Because the effect of sodium chloride on the release of indomethacin is only slightly enhancing or in the case of dicalcium phosphate even retarding, sodium chloride should modify the microcapsule wall to be better at withstanding the destructive effects of adjuvants. According to the literature results, finely ground solid materials dispersed in polymer films made the elastomer systems harder and thus more resistant towards the mechanical rupturing effects (Pfister et al., 1985). Due to the less extensive destruction of the microcapsule wall in tablets containing plastically deforming microcrystalline cellulose, sodium

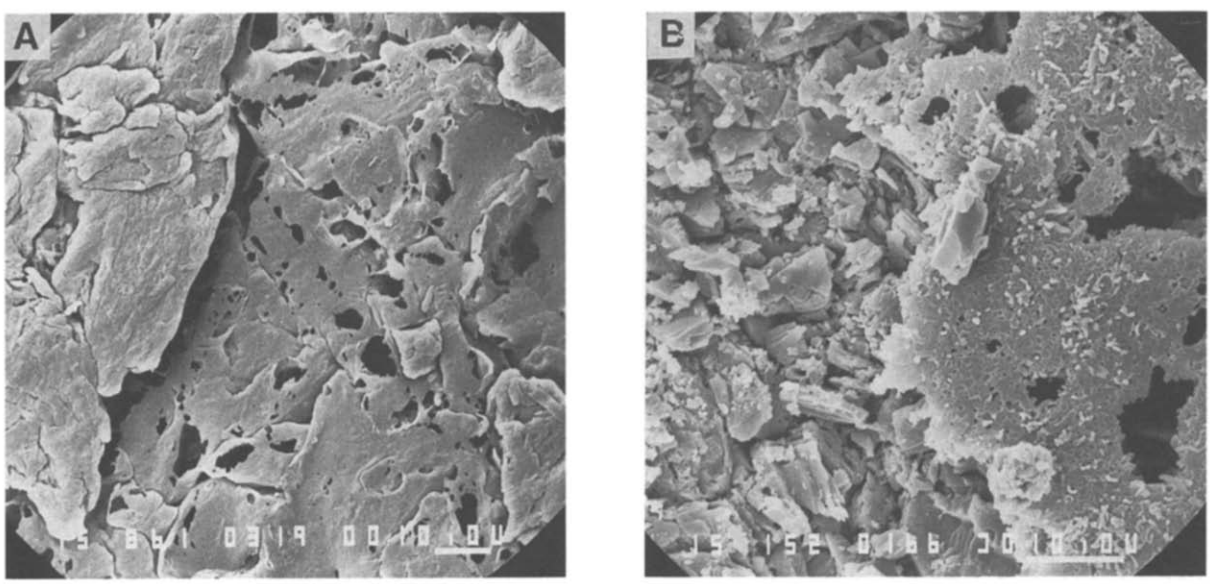

Fig. 3. Scanning electron micrographs from the indomethacin microcapsules after the compression and dissolution test. The adjuvants used in tablets were microcrystalline cellulose, Avicel PH 101 (A) and dicalcium phosphate, Emcompress (B). Bar: 10 μm.

chloride acted in these tablets to some extent as an accelerating agent for drug release (Figs 1 and 2). On the other hand, in dicalcium phosphate tablets, the addition of sodium chloride even retarded the release of indomethacin. This could be due to the firmer microcapsule wall which was less sensitive towards the pushing effect of fragmented particles of dicalcium phosphate. When both adjuvants were used in the mixture, the release behaviour of indomethacin was intermediate between the release from tablets containing plain adjuvants, that is clearly seen from effectively disintegrated tablets (Fig. 2).

In conclusion, tabletting of ethylcellulose walled microcapsules of indomethacin with different adjuvants led to a tablet matrix with solid bridges of ethylcellulose being formed. The effect of compression pressure on the release of indomethacin was noticeable but surprisingly small when microcrystalline cellulose was used as a tablet adjuvant. For dicalcium phosphate there was no correlation between the release of the drug and compression pressure used. The effect of the adjuvant on the microcapsule wall was remarkable. It was clearly evident when sodium carboxymethylcellulose was used to disintegrate the tablets. Dicalcium phosphate appeared to destroy the microcapsule wall during compression, thus accelerating the release of drug. The ethylcellulose wall of microcapsules was more resistant to the mechanical effects of plastically deforming microcrystalline cellulose.

Even though solid sodium chloride in the microcapsule wall increased the release of indomethacin from plain microcapsules, the enhancing effect appeared to disappear when microcapsules were tabletted. In contrast, when dicalcium phosphate was used as a filler the release of the drug even decreased slightly with microcapsules containing sodium chloride in the wall. It is possible that solid particles of sodium chloride made the microcapsule wall firmer against the destructive effect of compression.

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