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Effects of core components on indomethacin release from film-coated granules

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Summary

The effects of various water-soluble and water-insoluble fillers on the properties of film-coated indomethacin granules were investigated. The fillers used were glucose, lactose, calcium hydrogen phosphate dihydrate, maize starch and microcrystalline cellulose. Swellable maize starch ruptured the film and enhanced indomethacin release. The release profile of indomethacin from granules prepared using glucose and lactose depended on the water solubility of the fillers. The results suggest that indomethacin release from film-coated granules depends on the properties of the fillers used, in particular their solubility in water and swellability.

Introduction

The development of controlled release oral drug delivery systems for drugs poorly soluble in water has been shown to be difficult (Welling, 1983). Controlled release of such drugs is important because instantaneous release of a drug from a dosage form often results in side effects (Boardman and Hart, 1967; Pentikäinen et al., 1982; De Haan and Lerk, 1984). A multiple-unit dosage form offers a potential means of reducing side effects because the units spread over large areas of the gastrointestinal tract and high local concentrations are avoided (Bechgaard et al., 1982).

The release rates of drugs from multiple-unit formulations can be controlled by changing the permeability of the film of granules and by using different excipients in the cores of the granules (Laakso and Paulamäki, 1984; Laakso and Aarinen, 1985; Sarisuta and Sirithunyalug, 1988).

The aim of this study was to investigate the behaviour of various types of fillers in the cores of film-coated granules containing sparingly water-soluble indomethacin. The effects of various fillers on the solubility and release of indomethacin from film-coated granules were also studied.

Materials and Methods

The indomethacin was supplied by Orion Pharmaceuticals Co. Its solubility in water is only 0.014 mg/ml (Krasowska et al., 1972). Its melting point was 157 °C. The particle size was below 5 μm, as determined microscopically. The fillers used in the granules were glucose monohydrate (Ph.Eur.), lactose monohydrate (Ph. Eur.), maize

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starch (Ph. Eur.), microcrystalline cellulose (Avicel PH 102, Serva) and calcium hydrogen phosphate dihydrate (Emcompress, Ph.Eur.).

Solubility of indomethacin

The effects of the fillers on the water solubility of indomethacin were studied using a Souder-Ellenbogen apparatus (1958) for 24 h. Volumes of 25.0 ml of phosphate buffer, pH 7.2, containing different amounts of each filler, were placed in 50.0 ml flasks. The concentrations of the solutions used were 1, 10, 15 and 20%. Indomethacin in an amount greater than the limit of solubility was suspended in the medium. Six determinations were performed at each concentration. The temperature was 37 °C and the stirring speed 60 min^{-1}. The absorptions of filtered and diluted solutions were determined at 320 nm spectrophotometrically (Perkin-Elmer spectrophotometer).

Preparation of granules

The granules consisted of indomethacin (20%) and filler (80%). The indomethacin and the filler were mixed (Turbula Mixer, W.A. Bachofen) for 15 min and moistened with a gelatin solution. The amount of gelatin (Ph.Eur.) added came to 4.8% for each batch of granules. The moistened mixture was granulated in an oscillator (Erweka GmbH) using a mesh size of 2000 μm.

Coating

The granules were coated with ethyl cellulose (EC, N-10 Hercules Inc.). The permeability of the film coating was modified by incorporation of varying amounts of hydroxypropylmethyl cellulose (HPMC, Methocel Dow Chemicals GmbH). The polymer concentration in the coating solution was 5%. Glycerol was used as plasticizer (20% of the polymer weight). The solvents used were alcohol (Oy Alko Ab) and dichloromethane (E. Merck) in the ratio 1 : 2. The EC/HPMC ratios used were 65 : 35, 70 : 30 and 75 : 25. The coating accounted for about 10% of the total weight of the granules.

Granules of sieve fraction 710–1680 μm were coated in 130 g batches, using a fluid bed technique (Aeromatic Strea-1, Aeromatic AG). The flow rate was 100 m^3 h^{-1} and the drying temperature was 32 ± 1 °C. The application speed was 10 ml/min and the pneumatic spraying pressure was 1 bar. The granules were dried overnight and sieved (710–1680 μm).

Granule characteristics

Content uniformity was evaluated for 10 batches (20.0 mg of granules per batch). The indomethacin concentrations in the batches were measured spectrophotometrically at 320 nm (Perkin-Elmer UV-Vis spectrophotometer). The structures of the uncoated and coated granules were studied using a scanning electron microscope (JEOL JSM-820). Before being photographed the granules were coated with gold.

Dissolution test

Dissolution of indomethacin from uncoated and coated granules was studied using the USP XXI rotating basket method (Sotax AT 6). Release was determined from six batches of granules at the same time. The weight of each batch was 200.0 mg. The dissolution medium was 750 ml of phosphate buffer solution, pH 7.2. The temperature was 37 °C and the rotation speed 60 min^{-1}. Samples were taken over periods of 30 min (uncoated granules) and 8 h (coated granules).

The release data were plotted against the square root of time.

Results and Discussion

Solubility of indomethacin

The solubility of indomethacin in the buffer solution of pH 7.2 was 0.960 mg/ml. All of the fillers studied affected indomethacin solubility at the different concentrations (Table 1). Maize starch markedly decreased the solubility of indomethacin at all of the concentrations studied. One explanation for this could be that the drug particles were trapped inside maize starch agglomerates (Nogami et al., 1963; Guyot-Hermann, 1981).

Another swellable filler, microcrystalline cellulose did not have such a noticeable effect on solubility. For example, a concentration of 10% of maize starch decreased the solubility of in-

TABLE 1

Effects of various filler solutions on the solubility of indomethacin (mg/ml) (n = 6)

Filler	Concentration of filler in buffer solution (pH 7.2)				
	0%	1%	10%	15%	20%
Calcium hydrogen phosphate dihydrate	0.960	1.002	0.908	0.946	0.791
Glucose	0.960	0.884	0.816	0.796	0.693
Lactose	0.960	0.925	0.872	0.863	0.781
Maize starch	0.960	0.811	0.512	0.497	0.157
Microcrystalline cellulose	0.960	0.739	0.693	0.662	0.657

domethacin 1.68-times more than the microcrystalline cellulose. The swelling capacity of microcrystalline cellulose is less than that of maize starch.

Glucose and lactose also decreased the solubility of indomethacin but to a lesser degree than the above-mentioned fillers. The effect was greatest with glucose, which is water-soluble. Previous studies have shown that water-soluble sugars and sugar alcohols decrease the solubility of various drugs because they need so much liquid to dissolve that there is not enough liquid to dissolve the drug particles (Braun and Parrott, 1972; Laakso et al., 1982). Calcium hydrogen phosphate dihydrate did not markedly decrease indomethacin solubility until its concentration reached 20%. The decrease of solubility was then 17.6%. As an inert filler, it does not affect solubility. It does not swell, nor does it dissolve.

Uncoated granules

Release of indomethacin from uncoated granules was fastest from granules containing water-soluble glucose, or lactose as filler in 30 min (Fig. 1). The amount released was highest when the granules contained glucose because glucose dissolves faster than lactose. However, the difference was not statistically significant. Duvall et al. (1965) obtained similar results when tablets containing the sparingly water-soluble phenobarbital and glucose or lactose were investigated.

In our study, both glucose and lactose granules seemed crystalline and transparent under the stereomicroscope. The electron micrographs in Fig. 2 show that the granules were irregular. The calcium hydrogen phosphate dihydrate, maize starch and microcrystalline cellulose granules were more uniform in shape.

The release profile of indomethacin from granules containing calcium hydrogen phosphate was fairly similar to that from granules containing glucose or lactose. With maize starch, the release of indomethacin was slower up to 20 min. With microcrystalline cellulose granules, the release was slower over 30 min than the release rates for all the other diluents studied (Fig. 1). Maize starch and microcrystalline cellulose have different swelling mechanisms. Maize starch can absorb water both via a capillary system between particles and into the particles. Microcrystalline cellulose can only absorb water into a capillary system (Nogami et al., 1969). This could explain the delayed release

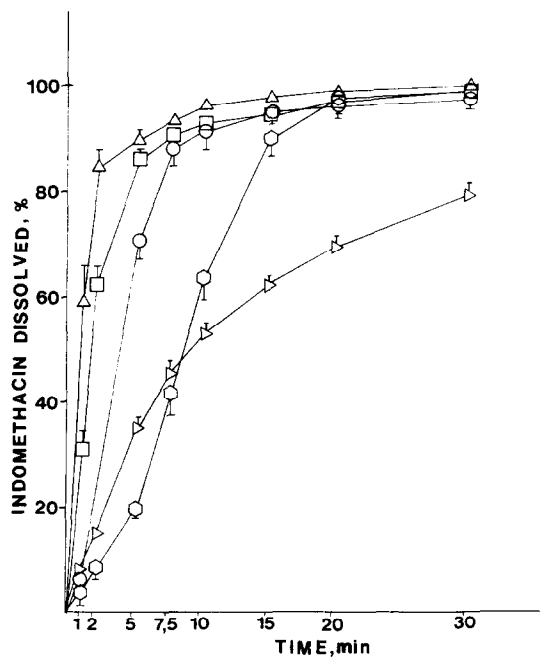

Fig. 1. Cumulative amounts (%) of indomethacin released from uncoated granules ($n = 6$). (○) Calcium hydrogen phosphate dihydrate, (△) glucose, (□) lactose, (○) maize starch, (▷) microcrystalline cellulose.

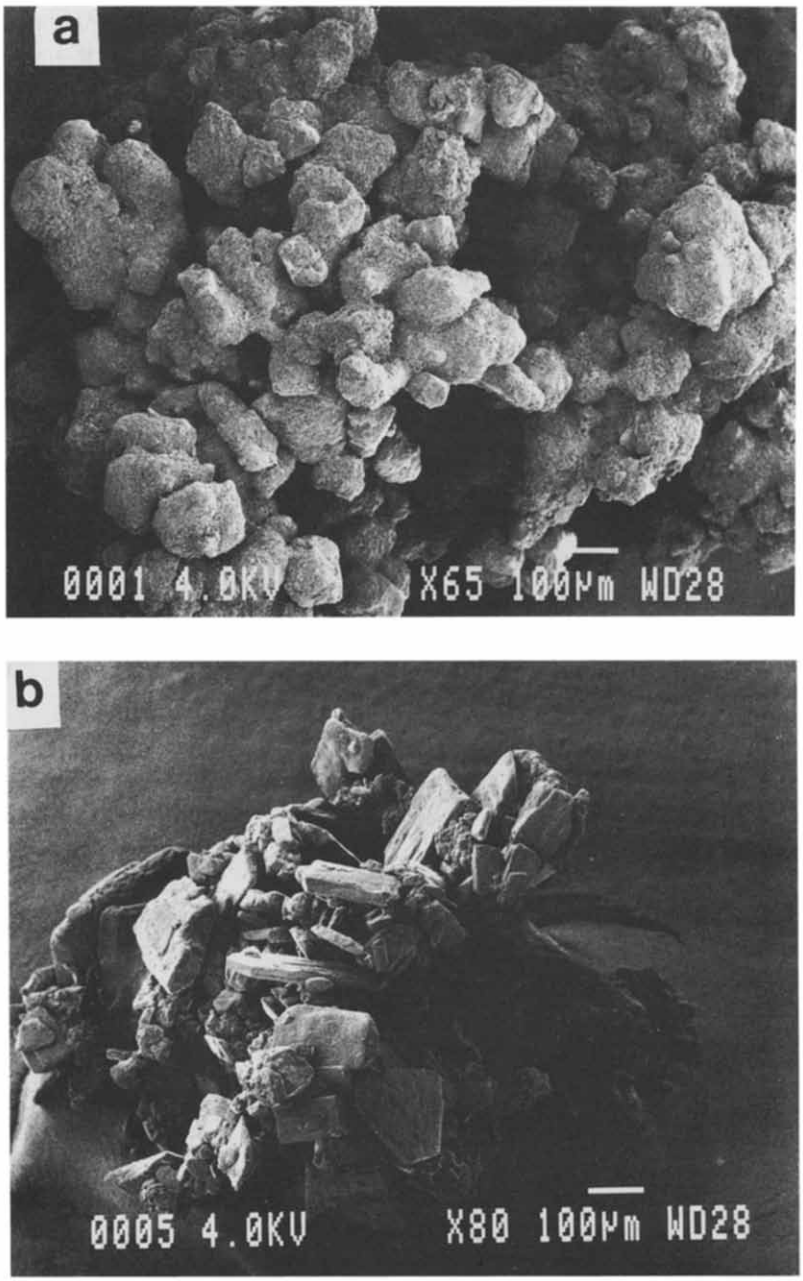

Fig. 2. Scanning electron micrographs of uncoated indomethacin granules containing various fillers; (a) calcium hydrogen phosphate dihydrate, (b) glucose, (c) lactose, (d) maize starch, (e) microcrystalline cellulose. Bar = 100 μm.

of indomethacin from microcrystalline cellulose granules, since wetting of indomethacin is not easy. Maize starch on the other hand could form a gel around the drug particles, through which the drug needs to diffuse. This would explain the differences between amounts released from the maize starch granules and the glucose, lactose and calcium hydrogen phosphate dihydrate granules.

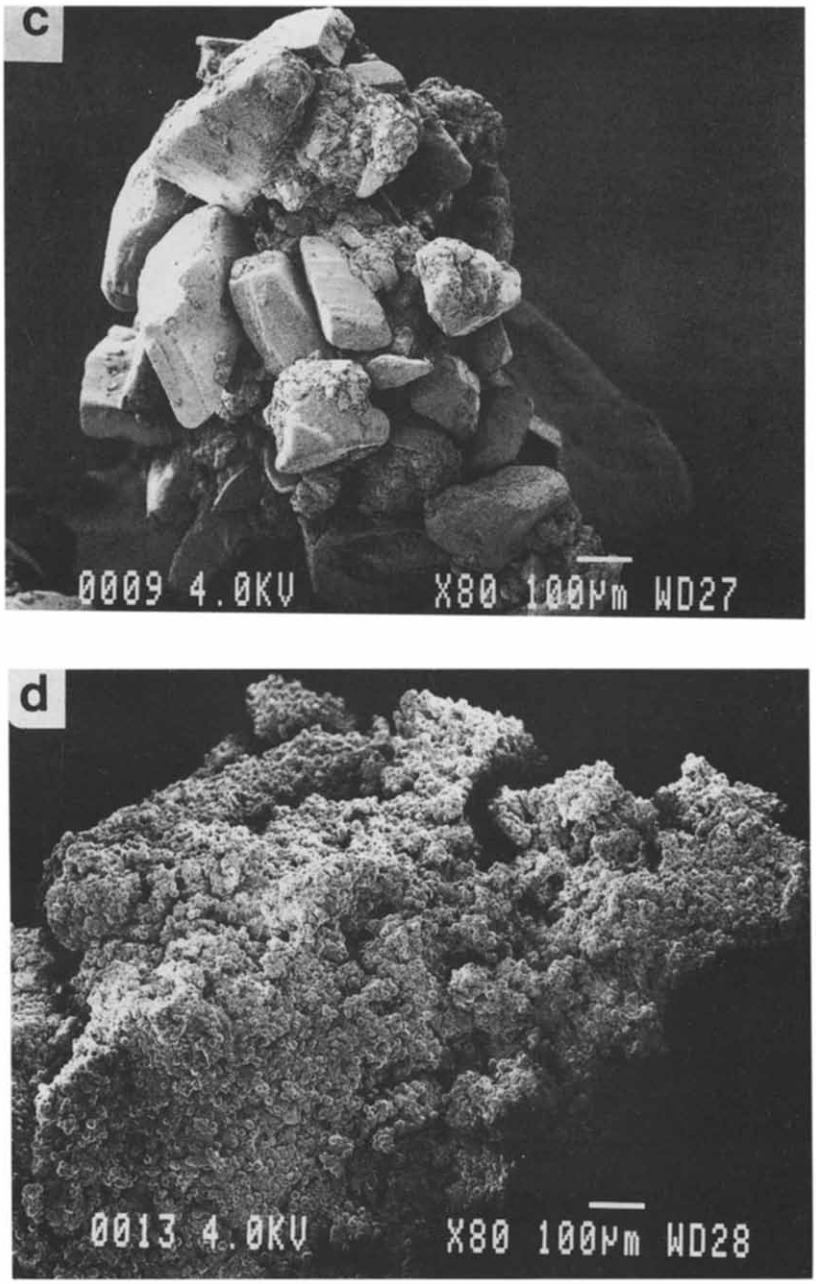

Fig. 2 (c,d).

Coated granules

Scanning electron micrographs of the coated granules showed that the maize starch granules, which were the most uniform in shape also seemed to be covered by the most regular film (Fig. 3). Granules made from the other excipients were all

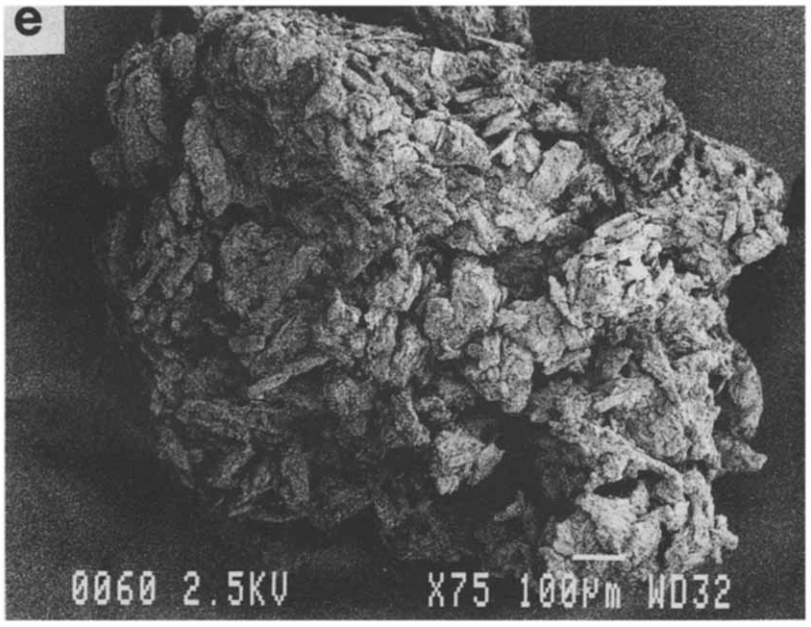

Fig. 2 (e).

fairly similar. An example of these granules is the coated calcium hydrogen phosphate granule shown in Fig. 4.

When the amount of hydroxypropylmethyl cellulose in the film was increased, the release rate also increased for all of the excipients studied

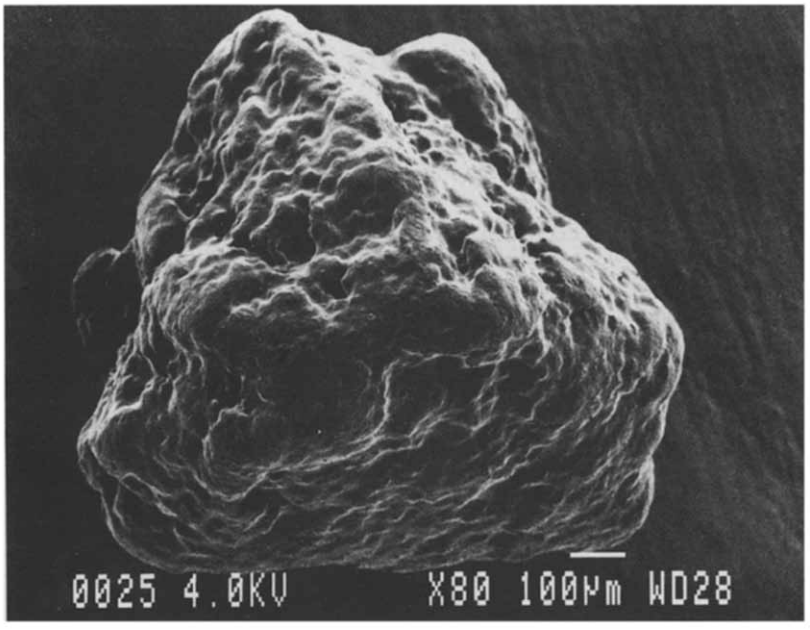

Fig. 3. Scanning electron micrograph of EC/HPMC 65 : 35 coated granule containing maize starch as filler. Bar = 100 μm.

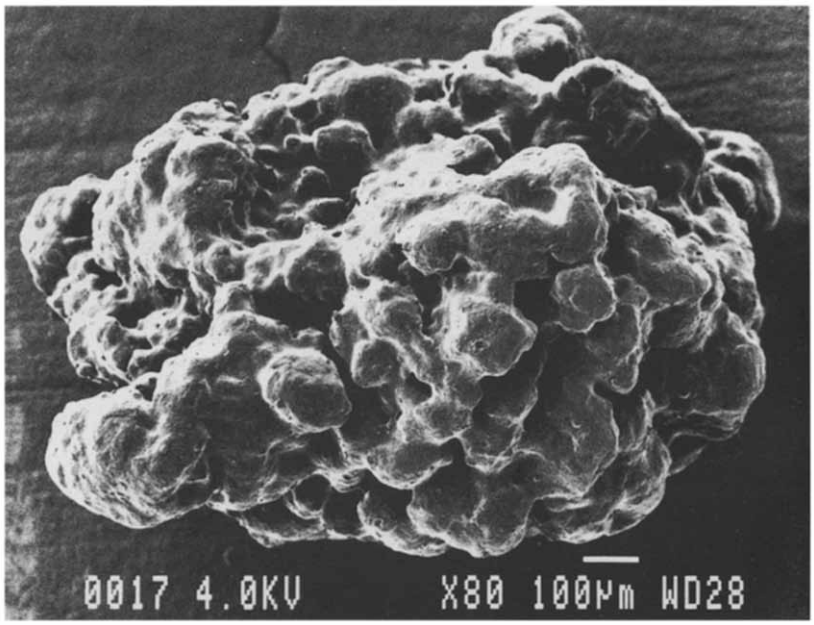

Fig. 4. Scanning electron micrograph of EC/HPMC 65 : 35 coated granule containing calcium hydrogen phosphate dihydrate as filler. Bar = 100 μm.

(Table 2) (Figs 5–7). When the EC : HPMC-ratio in the film was 65 : 35 the indomethacin release rate was fastest from the glucose and maize starch granules (rate constants from square root of time equation 6.255 and 5.875% $min^{-1/2}$, respectively). The mechanisms of indomethacin release from these granules were however different. Because glucose is a water-soluble diluent, it helps in-

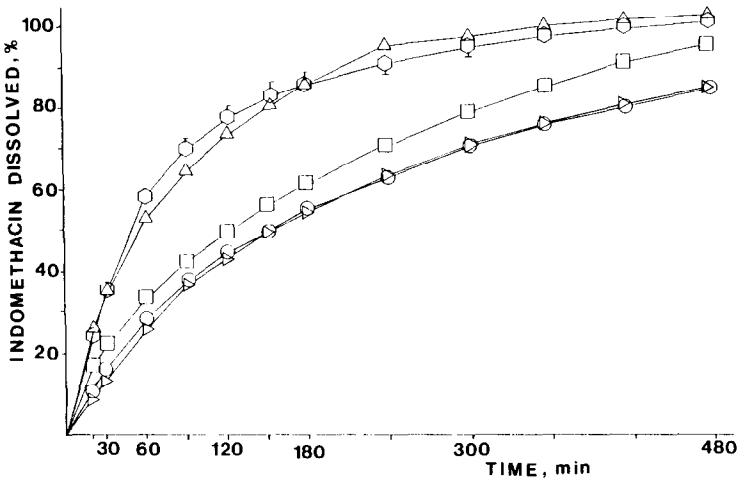

Fig. 5. Cumulative amounts (%) of indomethacin released from EC/HPMC 65 : 35 coated granules ($n = 6$). (○) Calcium hydrogen phosphate dihydrate, (△) glucose, (□) lactose, (⬡) maize starch, (▷) microcrystalline cellulose.

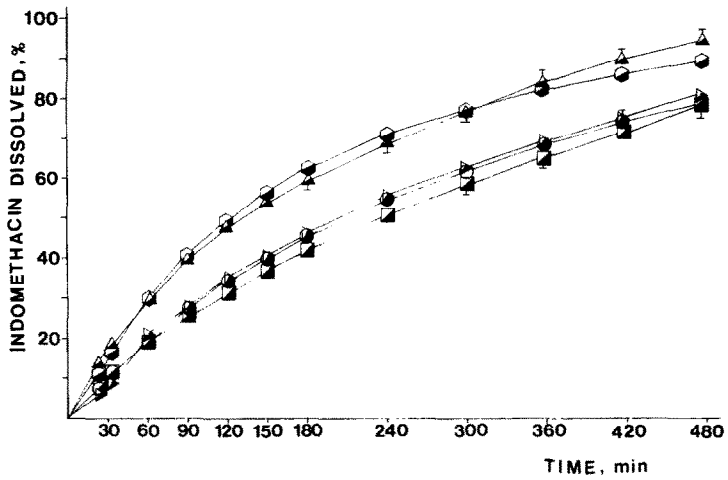

Fig. 6. Cumulative amounts (%) of indomethacin released from EC/HPMC 70 : 30 coated granules ($n = 6$). (◕) Calcium hydrogen phosphate dihydrate, (▲) glucose, (◪) lactose, (◕) maize starch, (▶) microcrystalline cellulose.

domethacin dissolve and be released through the pores in the film. The films of the maize starch granules ruptured during dissolution test because the maize starch swelled in the cores (Fig. 8). Similar behaviour was also seen when tolfenamic acid which is seven times less water-soluble than indomethacin, was used in cores (Eerikäinen et al., 1989).

The other swellable diluent used, microcrystalline cellulose did not have so marked an effect. Microcrystalline cellulose does not swell to such an extent. It has been shown that the swelling

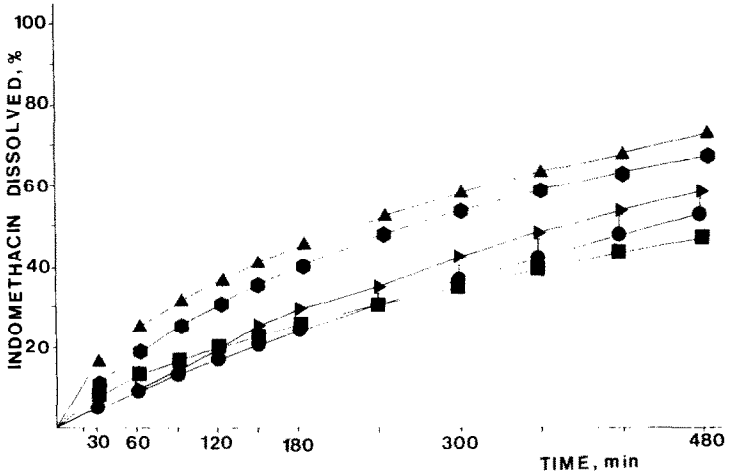

Fig. 7. Cumulative amounts (%) of indomethacin released from EC/HPMC 75 : 25 coated granules ($n = 6$). (●) Calcium hydrogen phosphate dihydrate, (▲) glucose, (■) lactose, (○) maize starch, (▶) microcrystalline cellulose.

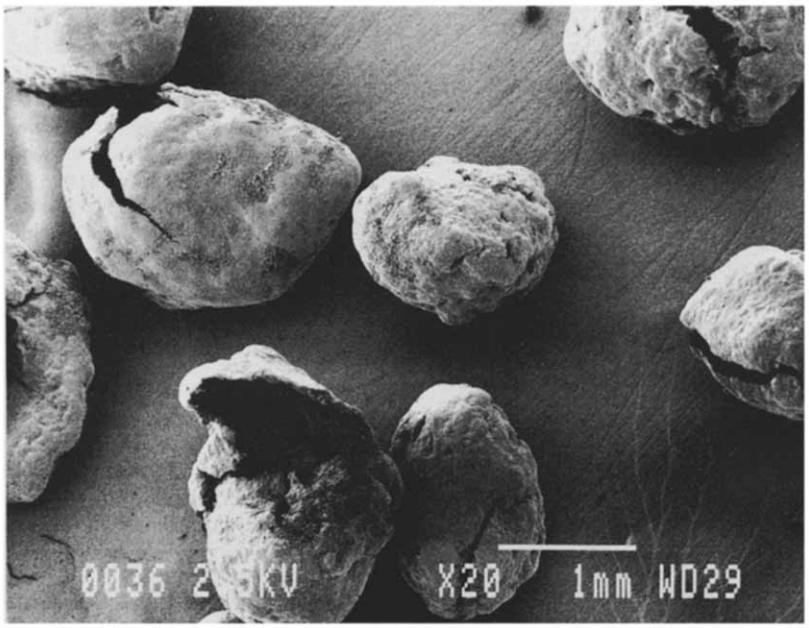

Fig. 8. Scanning electron micrograph of EC/HPMC 65 : 35 coated granule containing maize starch as a filler, after an 8 h dissolution test. Bar = 1 μm.

TABLE 2

Parameters relating to indomethacin release from film-coated granules, assuming the square root of time equation

Formulation	Rate constant (% $min^{-1/2}$)	Correlation coefficient (r)	Lag time (min)
D EC/HPMC 65 : 35	4.403	0.996	2.1
G EC/HPMC 65 : 35	6.255	0.986	0.0
L EC/HPMC 65 : 35	4.715	0.998	0.5
M EC/HPMC 65 : 35	5.875	0.959	0.1
MC EC/HPMC 65 : 35	4.566	0.996	3.3
D EC/HPMC 70 : 30	4.248	0.999	7.8
G EC/HPMC 70 : 30	4.840	0.999	2.2
L EC/HPMC 70 : 30	4.069	0.998	8.1
M EC/HPMC 70 : 30	4.839	0.991	2.6
MC EC/HPMC 70 : 30	4.293	0.999	8.3
D EC/HPMC 75 : 25	2.850	0.993	18.7
G EC/HPMC 75 : 25	3.647	0.999	1.3
L EC/HPMC 75 : 25	2.436	0.999	6.1
M EC/HPMC 75 : 25	3.564	0.999	5.7
MC EC/HPMC 75 : 25	3.207	0.994	14.8

D, calcium hydrogen phosphate dihydrate; G, glucose; L, lactose; M, maize starch; MC, microcrystalline cellulose.

ability of starch is about 1.5 times as great as the swelling ability of microcrystalline cellulose (Gissinger and Stam, 1980; Bolhuis et al., 1982).

When lactose, a disaccharide, was used in cores as a diluent, the indomethacin release rate was slower than that from glucose granules (Table 2). This may partly be explained by the fact that lactose dissolves more slowly than glucose and also retarding the indomethacin dissolution in the core. The osmotic pressure of glucose is about two times the osmotic pressure of lactose. This could also explain the faster release of indomethacin from the glucose granules. The release profile of indomethacin from calcium hydrogen phosphate dihydrate granules was fairly similar to the release profiles of indomethacin from granules containing lactose or microcrystalline cellulose, although calcium hydrogen phosphate dihydrate neither swells nor dissolves in water. This study shows that if the release profile of indomethacin is to be changed markedly, an excipient must be used which is sufficiently water-soluble or swellable.

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