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The behaviour of various fillers in spheronized uncoated and film-coated granules containing slightly water-soluble indomethacin

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Summary

The release of indomethacin from uncoated and film-coated spheronized granules was investigated. Granules containing indomethacin and various fillers were spheronized using a Calevaspheronizer. The characteristics of the granules and the release of indomethacin from them were examined. The fillers used in the granules were microcrystalline cellulose, lactose, glucose, calcium hydrogen phosphate dihydrate and maize starch. Marked differences were observed in spheronizing ability between the various fillers. It was most difficult to obtain perfect spheres with the crystalline fillers glucose and lactose. Spheronizing was best for granules containing maize starch or microcrystalline cellulose. Release from uncoated granules was very fast. In 10 min nearly 100% of the drug was released, whatever filler was used. The spheronization process only affected drug release from granules containing microcrystalline cellulose as filler. It changed the apparent densities of granules only in the case of those containing glucose. The ethyl cellulose : hydroxypropylmethyl cellulose ratio affected the release rate of indomethacin from all granules film-coated using a fluidized-bed technique irrespective of the filler. As the permeabilities of the film fell the release rates also decreased. Spheronization of the core resulted in release rates of indomethacin differing from those in earlier studies on the release of indomethacin from unspheronized granules. Release of the drug was slowest from granules containing microcrystalline cellulose (some 30% in 8 h).

Introduction

Fillers in granules, tablets and capsules significantly affect drug release behaviour. It has been shown that particular attention must be paid to the characteristics of fillers in coated granules when the drug in the core is poorly water-soluble (Laakso and Eerikäinen, 1991). When a drug is almost insoluble in water, e.g. tolfenamic acid, or very water-soluble, such as the sodium salt of indomethacin, solubility is the most important factor governing release (Eerikäinen et al., 1989, 1991).

It might be assumed that in addition to its composition, the shape of a core would affect the release of a poorly water-soluble drug. Spheronization of granules affects their hardnesses and

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densities and, in turn, should affect drug release. The aim of this study was to investigate the effects of spheronization on the release of indomethacin, which is poorly water-soluble, from uncoated and ethyl cellulose/hydroxypropylmethyl cellulose-coated granules. The effects of spheronization on properties such as granule density and shape were also examined.

Materials and Methods

The indomethacin used was supplied by Orion Pharmaceutica R & D. Glucose monohydrate (Ph.Eur.), lactose monohydrate (Ph.Eur.), maize starch (Ph.Eur.), microcrystalline cellulose (Avicel PH 102, Serva, U.S.A.) and calcium hydrogen phosphate dihydrate (Emcompress, Ph.Eur.) were used as fillers.

Preparation of granules

Granules were prepared from 250.0 g batches of powders containing 20% of indomethacin and 80% of filler. The blends were mixed (Turbula Mixer, W.A. Bachofen, Switzerland) for 15 min and moistened with gelatin solution. The amount of gelatin (Ph.Eur.) added was 4.8% (calculated as dry powder) for each batch of granules. The moist mass was passed through the 2.0 mm sieve of an oscillator (Erweka GmbH, Germany) and some of the granules were spheronized (Caleva 120, G.B. Caleva Ltd, U.K.). Spheronization was conducted using batches of 50 g of oscillated mass for 3 min at speeds of 20 or 40 rpm. The spheronized granules were dried overnight at 35 °C and screened (710–1680 μm).

Coating

Screened granules spheronized at 40 rpm for 3 min were coated with ethyl cellulose (EC, N-10 Hercules Inc., U.S.A.). Permeability of the film was modified by incorporating varying amounts of hydroxypropylmethyl cellulose (HPMC, Methocel E 5, Methocel Dow Chemicals GmbH, U.S.A.). The total polymer concentration in the coating solution was 5%. The polymers were dissolved in ethanol (Oy Alko Ab, Finland)/dichloromethane (for analysis, E. Merck) 1:2. Glycerol was used as plasticizer (20% of the polymer weight). The EC/HPMC ratios used were 65:35, 70:30 and 75:25. The coating accounted for about 10% of the total weight of granules.

The 710–1680 μm fraction of the granules was coated using a fluidized bed technique (Aeromatic Strea 1, Aeromatic AG, Switzerland). The air flow rate was 100 $m^3\ h^{-1}$ and the drying temperature 32 ± 1 °C. Coating solutions were pumped at a flow rate of 10 ml/min. The spraying pressure was 1 bar. After coating granules were dried overnight at 35 °C and sieved. The 710–1680 μm fraction was examined further.

Content uniformity and surface morphology of granules

Content unformity was evaluated for 10 batches of 20.0 mg of granules each. The indomethacin contents of the batches were measured spectrophotometrically at 320 nm (Perkin-Elmer UV-Vis Spectrophotometer, Japan). 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.

Granule densities

The densities of the 710–1680 μm fraction of uncoated granules were determined using a pycnometer. Petroleum ether (for analysis, May & Baker, U.K.) was used as intrusion fluid. Determinations were repeated three times on batches of granules weighing between 1.5 and 2.0 g.

Dissolution test

Release of indomethacin from 200.0 mg batches of granules was determined using the USP XXI rotating-basket method (Sotax AT 6, Switzerland). The granules examined were uncoated, unspheronized granules and spheronized granules (spheronized at 20 or 40 rpm) and spheronized, coated granules (spheronized at 40 rpm). Release rates were determined for six batches of granules simultaneously. The dissolution medium was 750 ml of phosphate buffer solution (pH 7.2), the temperature being 37 °C. The speed of rotation was 60 min^{-1}. Samples

were taken over periods of 30 min (uncoated granules) and 8 h (coated granules).

Kinetic models and statistical calculations

Release data relating to granules containing microcrystalline cellulose, maize starch or calcium hydrogen phosphate dihydrate were analyzed with the equation $Q(t) = K\sqrt{t}$, where Q is the amount of drug dissolved at time t and K is the corresponding release rate constant. Lag time was defined as the value of t corresponding to $Q = 0$.

Student's t-test was used to assess the significances of differences in granule densities.

Results and Discussion

Effects of spheronization on uncoated granules

The spheronization conditions were established empirically. Fairly rounded granules were obtained with all fillers and indomethacin spheronized for 3 min at a speed of 40 rpm. These conditions were chosen as final spheronization conditions. Scanning electron micrographs showed that there were differences between the fillers. The crystalline fillers, glucose and lactose, turned out to be insufficiently plastic to allow granules to approach the ideal of perfect spheres adequately (Figs 1 and 2). Both fillers, because of their crystalline nature, do not rearrange during spheronization but are ground away. The sharp corners of the crystals become more rounded. In previous studies, lactose was found to be associated with greater difficulty in spheronization because it fragmented and was unstable during spheronization (Harrison et al., 1985; Vromans et al., 1986). Glucose spheronizes better than lactose due to its solubility. It may partly dissolve in granulation solutions, and melt during spheronization as a result of a temperature increase, with some recrystallization possibly occurring during drying as a consequence.

Granules containing calcium hydrogen phosphate dihydrate appear to consist of small aggregates. The spheronization process had a less marked effect on them than on lactose or glucose (Fig. 3). It has been shown that calcium hydrogen phosphate dihydrate fragments when compressed, and that very dense, hard extrudates are formed (Lövgren, 1983; Garr and Rubinstein, 1990).

Granules containing microcrystalline cellulose and maize starch seemed to be the most readily spheronized (Figs 4 and 5). Microcrystalline cellulose, in particular, is used with other fillers in order to improve the spheronization properties of granules (Jalal et al., 1972; Chien and Nuessle, 1985). Microcrystalline cellulose is easily deformed. During spheronization the small particles become rearranged and the ideal of perfect spheres is closely approached. Masses containing maize starch moistened irregularly but spheronized well. However, in studies using starches it has been shown that spheronization does not result in a close approach to perfect spheres (O'Connor et al., 1984).

Spheronization was expected to affect the release of indomethacin from uncoated granules, since it is known that spheronization exerts an influence on various properties of granules, e.g., density, disintegration and friability. In addition to examining the effect of spheronization on drug release, the effect of rotation speed was also monitored. Two speeds, 20 and 40 rpm, were used. The duration of spheronization was 3 min. Drug release from unspheronized granules was also investigated. Neither spheronization nor spheronization speed affected the release of indomethacin from granules containing glucose, lactose, calcium hydrogen phosphate dihydrate or maize starch (Table 1). Release was very rapid (almost 100% in 5 min) when glucose or lactose, which are water-soluble, was used. Release was almost 100% in 10 min from granules containing maize starch or calcium hydrogen phosphate dihydrate. Spheronization and the speed of spheronization only affected drug release from granules containing microcrystalline cellulose as filler. Release from unspheronized granules was fastest, such granules disintegrating during the dissolution test. Granules of microcrystalline cellulose were clearly hardened by being subjected to spheronization. The speed of rotation affected granule characteristics and indomethacin release.

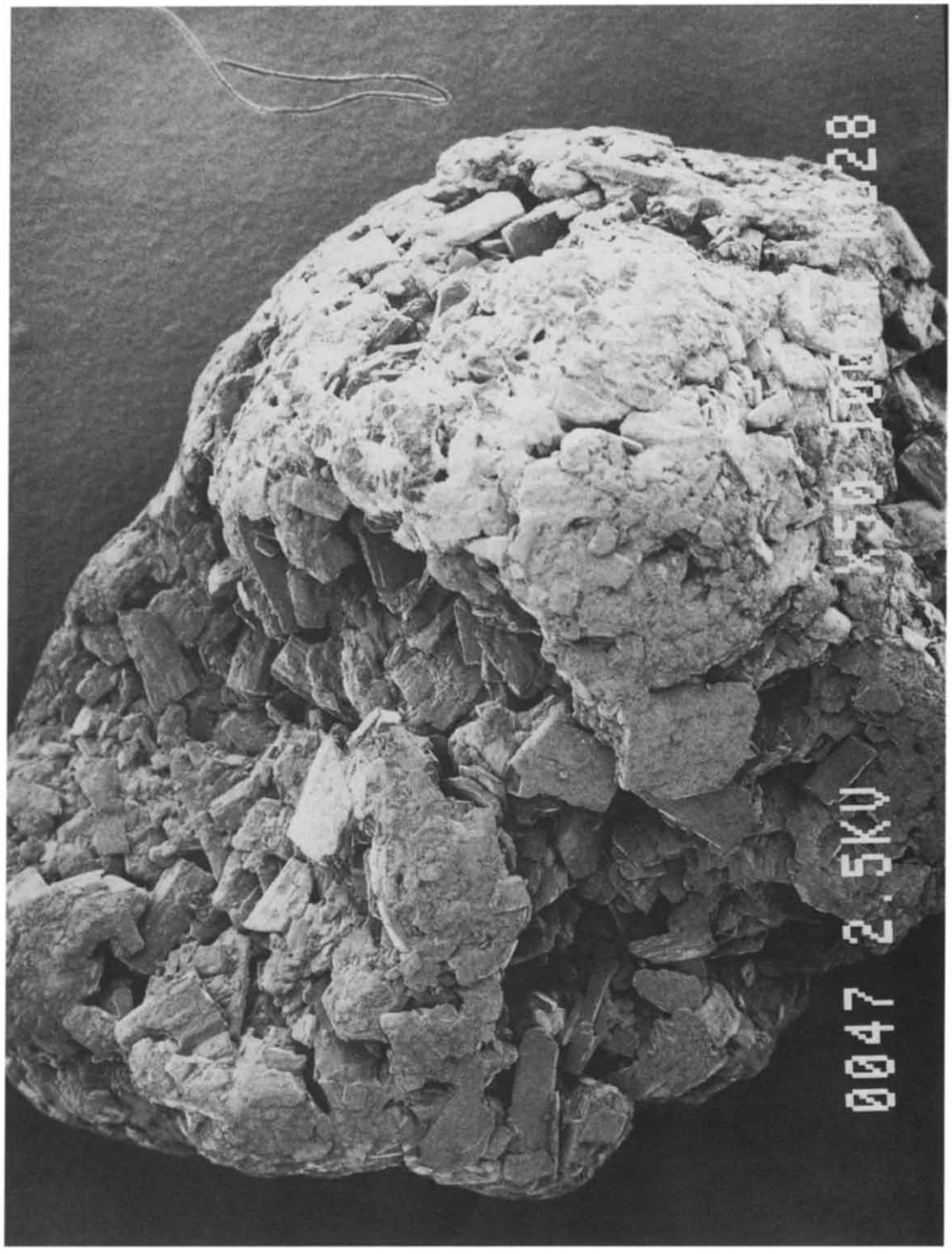

Fig. 1. Scanning electron micrograph of uncoated spheronized granule containing glucose. Bar = 100 μm.

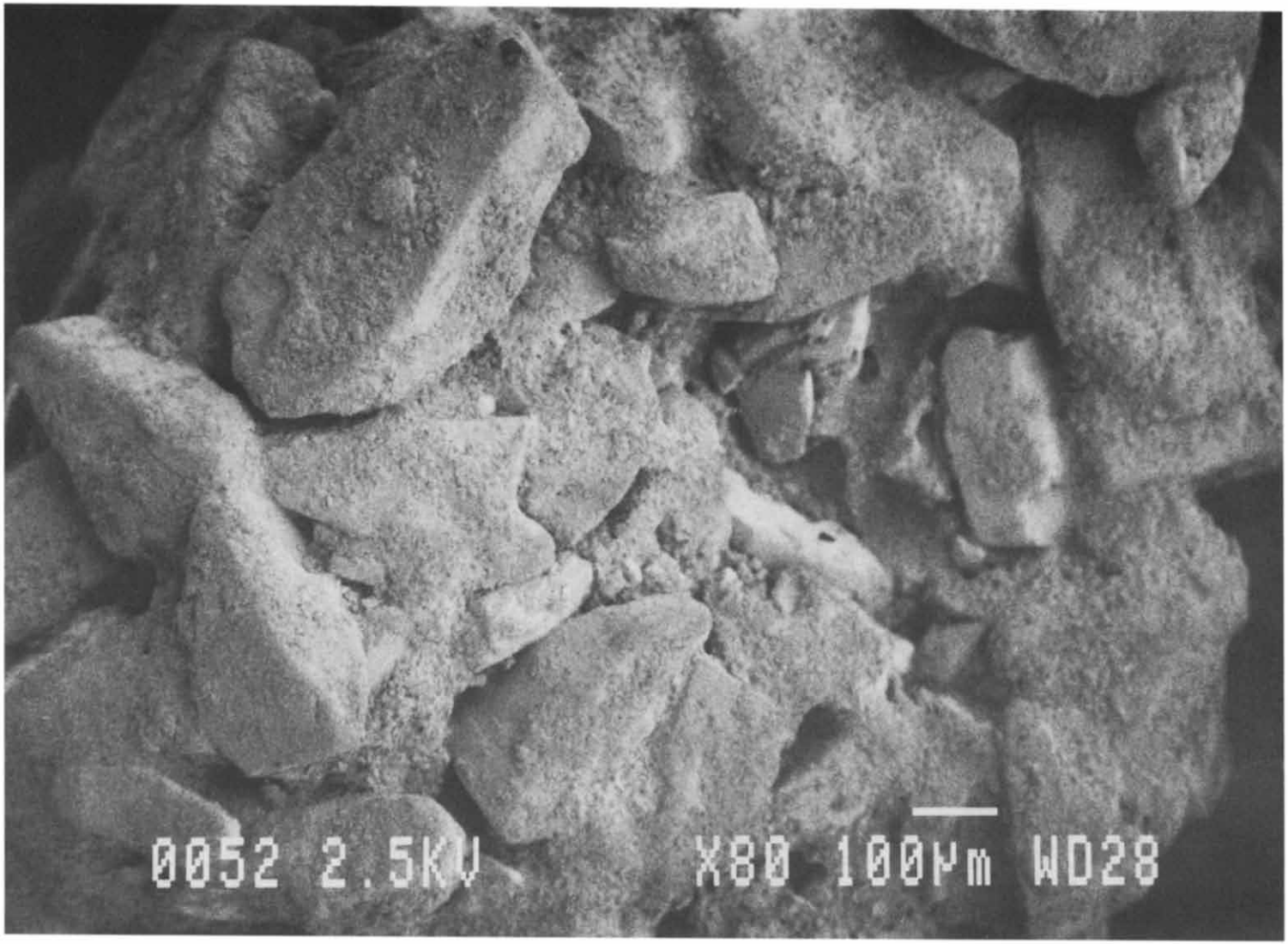

Fig. 2. Scanning electron micrograph of uncoated spheronized granule containing lactose. Bar = 100 μm.

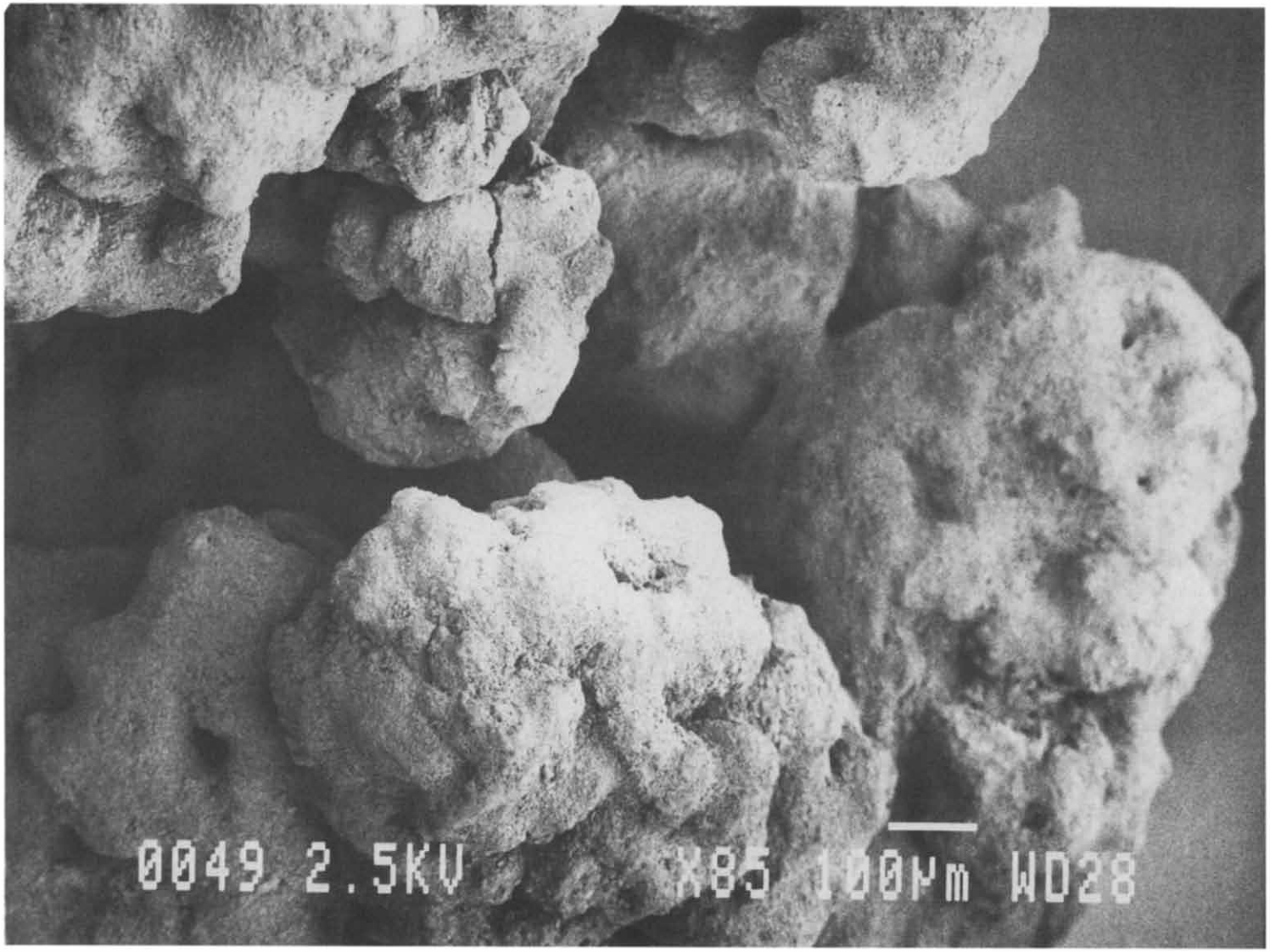

Fig. 3. Scanning electron micrograph of uncoated spheronized granule containing calcium hydrogen phosphate dihydrate. Bar = 100 μm.

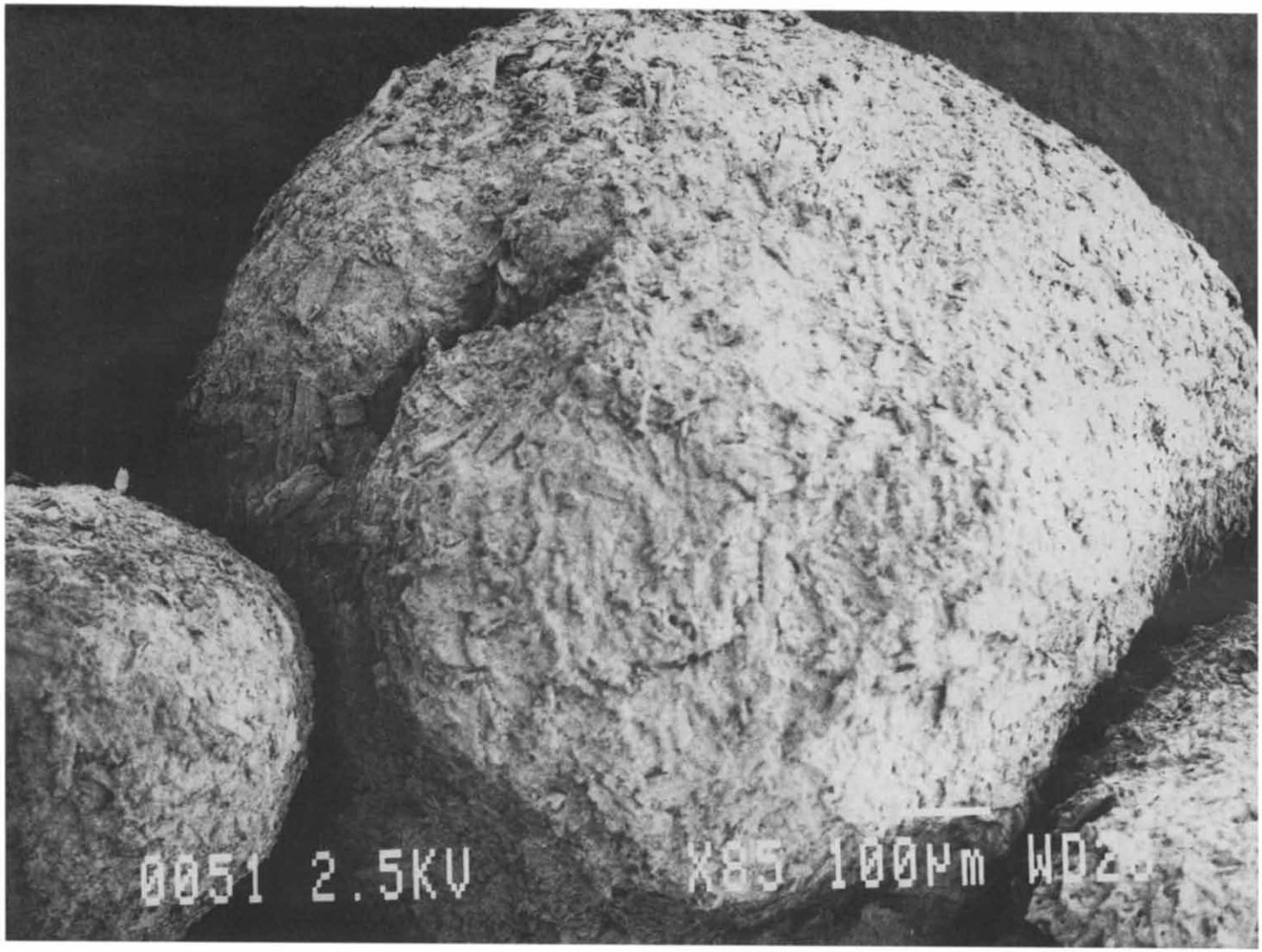

Fig. 4. Scanning electron micrograph of uncoated spheronized granule containing microcrystalline cellulose. Bar = 100 μm.

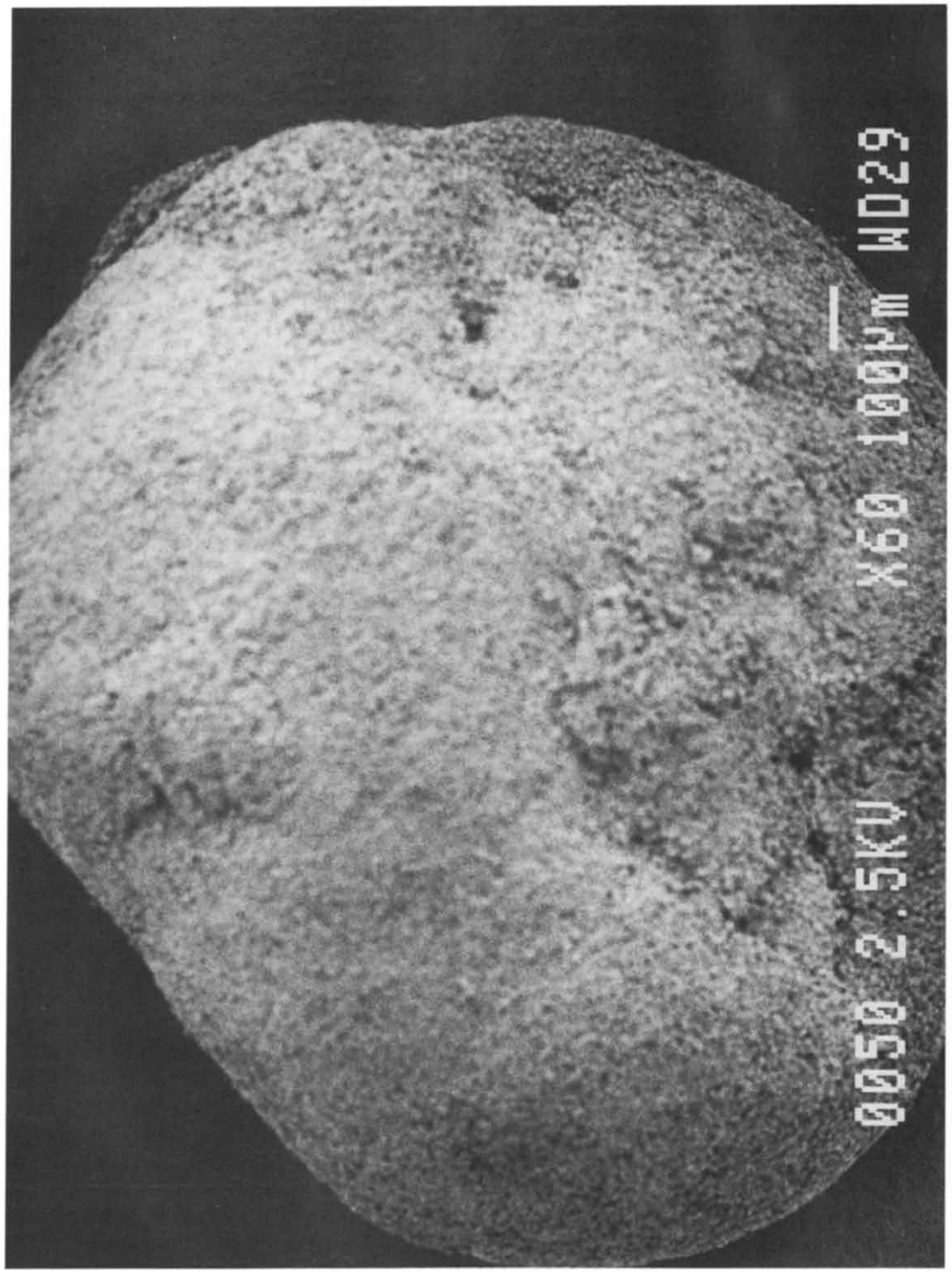

Fig. 5. Scanning electron micrograph of uncoated spheronized granule containing maize starch. Bar = 100 μm.

TABLE 1

Cumulative percentages of indomethacin released in 30 min from uncoated unspheronized granules (I), from granules spheronized at 20 rpm for 3 min (II) and from granules spheronized at 40 rpm for 3 min (III) (n = 6)

Filler		Release time (min)					
		1	3	5	10	20	30
Glucose	I	53.9	95.3	95.8	96.6	97.1	97.8
	II	48.5	97.1	97.1	98.0	98.9	99.5
	III	48.8	95.0	96.0	96.9	97.5	98.1
Lactose	I	57.2	91.1	94.6	95.6	96.3	96.5
	II	38.3	90.1	95.1	96.3	97.1	97.3
	III	29.5	87.4	94.1	95.4	96.0	96.0
Calcium hydrogen phosphate dihydrate	I	17.8	69.7	85.1	91.1	93.3	94.1
	II	19.3	74.7	89.3	92.8	94.9	95.5
	III	11.2	59.2	85.3	91.6	94.2	94.8
Maize starch	I	29.6	75.2	89.2	95.9	96.8	97.0
	II	30.9	64.8	86.2	99.0	99.9	100.0
	III	25.7	58.8	78.0	98.0	99.5	99.5
Microcrystalline cellulose	I	6.9	20.9	34.2	51.6	68.1	78.7
	II	2.4	7.9	14.3	24.2	36.5	45.7
	III	1.0	2.4	3.9	6.6	10.9	14.3

Granules spheronized at a speed of 20 rpm disintegrated but more slowly than did unspheronized granules. Spheronization probably results in granules becoming harder, thereby decreasing disintegration and drug release. Granules made using a rotation speed of 40 rpm behaved as nondisintegrating matrices. Release took place in accordance with a square root of time equation. Such release kinetics may be a consequence of thickening of the granules during spheronization and increases in forces between particles (Zhang et al., 1990). On swelling, microcrystalline cellulose may not have exerted enough force to break the matrix and the indomethacin may therefore have diffused rather slowly from the granules.

Apparent densities of uncoated granules

The apparent densities of uncoated granules are listed in Table 2. Significances of differences were tested using Student's *t*-test. Spheronization markedly affected granule density only when glucose was used as a filler ($p < 0.001$). Densities of granules containing indomethacin and various

TABLE 2

Apparent densities (g / ml) of granules containing 20% indomethacin produced using an oscillator and granules spheronized for 3 min at 40 rpm (means ± standard deviations, n = 3)

Filler	Not spheronized	Spheronized	Significance
Lactose	1.48 ± 0.01	1.46 ± 0.02	not significant
Maize starch	1.47 ± 0.06	1.46 ± 0.05	not significant
Microcrystalline cellulose	1.43 ± 0.05	1.43 ± 0.04	not significant
Calcium hydrogen phosphate dihydrate	2.16 ± 0.07	2.09 ± 0.05	not significant
Glucose	1.37 ± 0.03	1.33 ± 0.00	highly significant ($p < 0.001$)

fillers did not differ markedly, except for those containing calcium hydrogen phosphate dihydrate, possibly because of the property of the latter of forming granules from small aggregates which stick tightly together. Densities of spheronized and unspheronized microcrystalline cellulose granules were similar. The slower rate of release of indomethacin from spheronized granules containing microcrystalline cellulose cannot be explained by their having different densities.

Release of indomethacin from uncoated spheronized granules

Release curves alter with filler in cores spheronized at 40 rpm for 3 min (Table 1). Release was most rapid from granules containing the water-soluble fillers glucose and lactose. Indomethacin was released from granules containing maize starch or calcium hydrogen phosphate dihydrate at similar rates. Microcrystalline cellulose in granules markedly decreased the rate of release of indomethacin. During a period of 30 min only some 15% was released.

The results relating to glucose, lactose, calcium hydrogen phosphate dihydrate and maize starch granules compare well with previous results with unspheronized granules (Laakso and Eerikäinen, 1991). Spheronization does not appear to affect the release behaviour of indomethacin, which is slightly water-soluble, when these fillers are used. Spheronization does not retard the dissolution of glucose or lactose, or the swelling of maize starch, or the disintegration of calcium hydrogen phosphate dihydrate granules. However, in the case of granules containing microcrystalline cellulose, the release of indomethacin was markedly slower over a period of 30 min than in earlier studies of unspheronized granules. Spheronization may harden microcrystalline cellulose granules due to the rearrangement of microcrystalline cellulose particles during spheronization.

Coated granules

It was expected that granules spheronized would be coated more uniformly than granules straight from the oscillator. The surface of spheronized granules is smoother and the film should fit more homogeneously over the surface of granules. The coated surfaces of the granules appeared uniform on examination using a scanning electron microscope, as expected. However, no differences were evident when spheronized and unspheronized granules were compared. Since the rough edges of glucose and lactose granules were partly smoothed out, the coatings seemed to be fairly uniform. Nevertheless, scanning electron microscopy revealed that some rough edges persisted beneath the coating in lactose granules. The EC/HPMC ratio in the cores influenced the rate of release of indomethacin from all granules, regardless of filler. These findings were in accordance with those in previous studies of indomethacin release from unspheronized granules (Laakso and Eerikäinen, 1991). The effect of the EC/HPMC ratio on the rate of release was most apparent when the water-soluble fillers glucose and lactose were used. Table 3 lists the release parameters calculated on the basis of a square root of time equation. Spheronization retarded the rate of release of indomethacin from granules containing maize starch, microcrystalline cellulose and calcium hydrogen phosphate dihydrate (Figs 6–8) as compared with that from unspheronized granules (Laakso and Eerikäinen, 1991). It is obvious that

TABLE 3

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

Formulation	Rate constant ($\%min^{-\frac{1}{2}}$)	Correlation coefficient (r)	Lag time (min)
C EC/HPMC 65:35	3.660	1.000	4.6
M EC/HPMC 65:35	3.240	0.984	−0.5
MC EC/HPMC 65:35	2.073	0.997	9.9
C EC/HPMC 70:30	2.863	0.998	7.5
M EC/HPMC 70:30	2.320	0.999	3.3
MC EC/HPMC 70:30	1.430	0.985	18.9
C EC/HPMC 75:25	0.826	0.981	19.2
M EC/HPMC 75:25	0.552	0.983	18.3
MC EC/HPMC 75:25	0.632	0.946	31.2

C, calcium hydrogen phosphate dihydrate; M, maize starch; MC, microcrystalline cellulose.

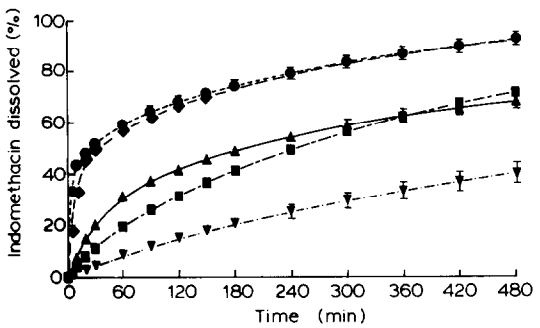

Fig. 6. Cumulative percentages of indomethacin released from spheronized granules (40 rpm, 3 min) containing various fillers and coated with a coating with an EC/HPMC ratio of 65:35 ($n = 6$). (●) Glucose; (◆) lactose; (▲) maize starch; (■) calcium hydrogen phosphate dihydrate; (▼) microcrystalline cellulose.

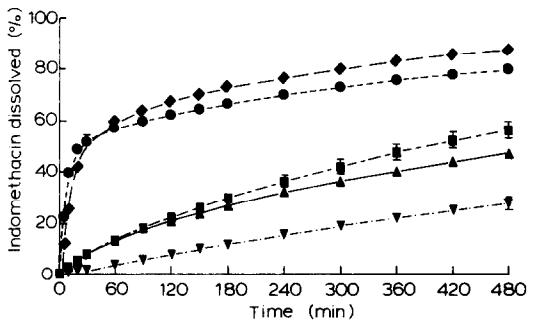

Fig. 7. Cumulative percentages of indomethacin released (%) from spheronized granules (40 rpm, 3 min) containing various fillers and coated with a coating with an EC/HPMC ratio of 70:30 ($n = 6$). Symbols as in Fig. 6.

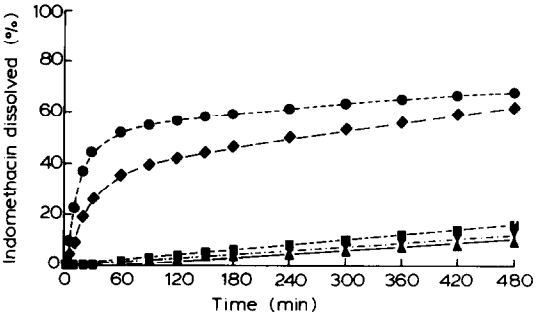

Fig. 8. Cumulative amounts of indomethacin released (%) from spheronized granules (40 rpm, 3 min) containing various fillers and coated with a coating with an EC/HPMC ratio of 75:25 ($n = 6$). Symbols as in Fig. 6.

some compaction and rearrangement of particles occur during spheronization. This particularly affects dissolution from cores when granules are coated. The dissolution medium penetrates into the cores more slowly than it does in the case of uncoated granules.

The coats of maize starch granules ruptured during dissolution tests as they did when unspheronized granules were studied. However, rupture was less marked and dramatic. The breaks were smaller and fewer, perhaps because of the coating being distributed more uniformly over the granules, with no thin areas where rupture would be more obvious. Previous studies have shown that there may be some gel formation beneath the coat during core dissolution. The gel formed may retard the release of indomethacin from spheronized granules.

Rates of release of indomethacin from granules containing microcrystalline cellulose or calcium hydrogen phosphate dihydrate were fairly slow. The amounts released over 8 h were small. The capacity of microcrystalline cellulose to swell was not powerful enough to rupture the coat. The granules were intact after dissolution testing.

The effect of spheronization on indomethacin release was most apparent when glucose and lactose, which are water-soluble, were used. Some 30–60% of indomethacin was released from granules containing lactose, and 50–60% from granules containing glucose, during the first hour of dissolution testing. The amount of indomethacin released depended on the EC/HPMC ratio of the coat. After the first hour, the rate of release decreased markedly. The explanation could be that, in such granules, a certain degree of movement of indomethacin particles took place during spheronization. When samples of uncoated granules taken at different times ($\frac{1}{2}$, $1\frac{1}{2}$, $2\frac{1}{2}$ and 3 min) during spheronization were examined under a scanning electron microscope with the help of an atomic analyser it was noted that the indomethacin particles showed an increasing extent of coverage of the surfaces of the glucose and lactose particles as spheronization time increased. These indomethacin particles obviously dissolve first when pores are formed in a coating, and the drug initially diffuses fairly rapidly from

the core. After this initial dissolution, the water-soluble fillers themselves dissolve and may, at the same time, increase liquid viscosity inside the core. This in turn would retard dissolution of indomethacin within the granules. This effect has also been observed in other studies (Lerk et al., 1979). The granules seemed to remain intact, with uniform coatings after dissolution testing when examined using a scanning electron microscope. It would therefore seem that the filler was the most important factor governing drug release.

When release rates of indomethacin from granules containing different fillers were compared, release was found to be fastest from granules containing glucose or lactose which are water-soluble, irrespective of the EC/HPMC ratio in the coating used (Figs 6–8). Release rates of drug from granules containing maize starch or calcium hydrogen phosphate dihydrate were about the same. They were, however, slower than from the granules mentioned earlier. As the permeability of the coat decreased, the release rates approached those in the case of indomethacin from granules containing microcrystalline cellulose, from which release was slowest. The internal structure of microcrystalline cellulose granules was very fibrous as assessed by scanning electron microscopy. When this fibrous structure swells as dissolution medium diffuses into cores it may hinder efficient dissolution of the drug and diffusion of liquid in and out of the core.

Acknowledgements

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