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Effects of spheronization on some properties of uncoated and coated granules containing different kinds of fillers

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Summary

The effects of spheronization on the physico-chemical properties of uncoated and coated granules containing different kinds of fillers were investigated. The fillers used in the granules were water-soluble glucose and lactose, water-insoluble calcium hydrogen phosphate dihydrate, slightly swellable, hydrophilic microcrystalline cellulose and swellable maize starch. The ability of these fillers to spheronize varied depending on the structure of the crystals and the solubility of the material. Of the physical properties of the granules studied, only friability was affected by spheronization. The granules were coated with ethyl cellulose/hydroxypropylmethyl cellulose. Differences were seen in the behaviour of the fillers in the cores during the dissolution test when unspheronized and spheronized granules were compared. The differences were clearest when maize starch or microcrystalline cellulose was used in the cores of film-coated granules. They ruptured the coats of unspheronized and spheronized granules differently.

Introduction

A number of factors contribute to the properties of granules and to the dissolution of drugs from them. The most important factors are usually the drug itself, the filler and the binder solution (Ganderton and Selkirk 1970; Schwartz et al., 1975; Jaiyeoba and Spring, 1980). Drug solubility and filler properties affect drug dissolution from granules, as has been observed in earlier studies (Eerikäinen et al., 1989, 1991; Laakso and Eerikäinen, 1991). In those studies drug solubility and filler properties were found to be the most important factors. The ability of fillers to granulate differs, and their spheronizing abilities also vary. Spheronization affects granule properties such as porosity, density and friability (Sastry and Fuerstenau, 1973). However, the effects of spheronization on these properties depend greatly on the filler properties. Spheronization of granules also affects the procedure of film-coating the granules and how successfully a uniform coat is achieved. If the granules have a rough surface, areas with different permeabilities may arise because the film is not uniform, as has been discovered in the case of tablets (Rowe, 1978). This may also affect the role significance of adjuvants in the cores of granules during drug dissolution tests.

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In the present study granules containing different kinds of filler were made and spheronized with a view to showing whether or not the fillers could be spheronized. The effects of spheronization on the properties of uncoated granules were investigated. The behaviour of fillers in the cores of film-coated unspheronized and spheronized granules during a dissolution test was also studied.

Materials and Methods

The fillers used in unspheronized and spheronized granules were glucose (Ph.Eur.), lactose (Ph.Eur.), microcrystalline cellulose (Avicel PH 102, Serva), calcium hydrogen phosphate dihydrate (Emcompress, Ph.Eur.) and maize starch (Ph.Eur.). The identity and crystal structure of the fillers used in granules were studied using an X-ray powder diffraction method (Siemens D 500, Siemens AG, Karlsruhe, Germany). Samples were mounted for analysis by loosely pressing approx. 500 mg of powder into a cylindrical sample holder, 20 mm in diameter and about 2 mm high. The measurements were made at 25 ± 1°C using a copper anode X-ray tube operating at 1.6 kW (tube powder 40 kV × 40 mA). The X-ray beam was rendered monochromatic using a diffracted beam graphite monochromator (Johann type). The X-ray beam was collimated using an automatic divergence slit (1° maximum of the entrance slit) and a 0.05° receiving slit. The measuring range was 3–53° and the speed 1°/min. The particle size was measured by scanning electron microscope analysis (JEOL JSM-840A, Japan).

Preparation of granules

A batch of filler (250.0 g) was moistened with gelatin (Ph.Eur.) solution. The amount of gelatin added was 4.8% of the weight of each batch of granules. The final mixture was passed through the 2000 μm sieve of an oscillator (Erweka GmbH, Germany). Part of the oscillated mass was spheronized with a Caleva extruder (Caleva 120, G.B. Caleva Ltd, U.K.) at 40 rpm for 3 min. Both unspheronized and spheronized granules were dried overnight at 35°C and screened (0.71–1.68 mm).

Coating

Both unspheronized and spheronized granules (sieve fraction 0.71–1.68 mm) were coated with ethyl cellulose (EC, N-10, Hercules Inc., U.S.A.), the permeability of which was modified by incorporation of hydroxypropylmethyl cellulose (HPMC, Methocel Dow Chemicals, GmbH, U.S.A.). The EC:HPMC ratio in the coats was 65:35 and the coating amounted to about 10% of the total weight of the granules. Granules were coated using the fluid bed technique (Aeromatic Strea 1, Aeromatic AG, Switzerland). Granules were coated in batches of 120 g. The polymer concentration in the coating solution was 5%. Glycerol was used in the film as plasticizer and comprised 20% of the polymer weight. The solvents used were ethanol (Oy Alko Ab, Finland) and dichloromethane (p.a., E. Merck, Germany) in the ratio 1:2. The air flow rate was 100 $m^3\ h^{-1}$ and the drying temperature was adjusted to 32 ± 1°C. The application speed of the coating solution was 8 ml min^{-1} and the pneumatic spraying pressure 1 bar. After coating, the granules were dried, sieved again and the 0.71–1.68 mm sieve fraction was examined further.

Granule characteristics

A dissolution test was performed on 200 mg batches of granules using the USP XXII rotating basket method (Sotax AT 6, Germany). The purpose of the dissolution test was not to examine the dissolution of fillers but to investigate the behaviour of fillers in the core and also the behaviour of film coats during the test. The dissolution medium was 750 ml of phosphate buffer solution at pH 7.2 and 37°C. The rotation speed was adjusted to 60 min^{-1}. Samples of granules were collected over a period of 8 h (1, 2, 4, 6 and 8 h).

A scanning electron microscope (JEOL JSM-820, Japan) was used to study the surface and structure of both uncoated and coated unspheronized and spheronized granules. The granules that had gone through the dissolution test were also studied with a scanning electron micro-

scope. The granules were coated with gold (Jeol Fine coat JFC-1100, Japan) before being photographed at an accelerating voltage of 2.4 kV.

Moisture content of granules

The moisture contents of both unspheronized and spheronized granules were determined immediately after granulation using an Ohaus apparatus (Moisture Determination Balance, Ohaus Scale Corp., U.S.A.). 10.0 g of granules were weighed onto an aluminium plate. The power of the infrared lamp was 10 W (3 W in the case of glucose granules). The end point was seen to be reached when the granules attained constant weight. The loss on drying (LOD) was calculated using the equation:

$$\text{LOD}(\%) = \frac{(\text{weight of moist mass} - \text{weight of dry mass})}{\text{weight of moist mass}} \times 100\%$$

Density of granules

The density of unspheronized and spheronized granules was measured using an air pycnometer (Beckman, Air Comparison Pycnometer model 930, U.S.A.) at a pressure of 133–266 Pa. Each batch was weighed accurately to about 3.0 g. The results were read as volumes (cm^3) of granule batch measured. Three measurements were made on each batch and three batches of granules were taken from each batch used in the granulation and spheronization process.

Friability of granules

The friability of uncoated granules, both unspheronized and spheronized, was examined using a Roche friabilator (Ernst Keller & Co, Switzerland). The speed of the friabilator was 36 rpm. A 5 g sample of granules (sieve fraction 0.71–1.68 mm) was rotated 200 revolutions with 100 glass balls having a diameter of 4 mm. The batch was sieved using a Fritsch shaker (Fritsch 03502, Laborgerätebau, Germany) for 5 min at a frequency of 4. The granules left above the sieve of 710 μm were weighed and the weight loss was calculated. The determination was repeated three times and the average weight loss calculated as a percentage.

Results and Discussion

The fillers differed from each other in terms of their solubility in water. The particle size and crystal structure of the fillers also differed, as can be seen in Table 1. The crystal shape is classified in Table 1 according to B.S. 2955:1958. Lactose and glucose were in the form of their crystalline hydrates and gave sharply defined X-ray diffraction patterns. The rest of the fillers used seemed to be amorphous, as indicated by the broad, diffuse maxima in the diffraction patterns (Fig. 1).

Granulation

The amounts of water needed during the granulation and spheronization processes to obtain granules of the proper size depended on the filler properties (Table 2). Lactose and glucose differed markedly from the other fillers because of their good solubility in water. It has been found that granulated masses containing lactose are difficult to spheronize because of the difficulty of maintaining the proper wet consistency throughout the process (Löfgren, 1983). This can also be the case with glucose granulation. On the other hand, water-soluble fillers will dissolve in the binder solution and increase the liquid volume available for granulation, and this may give mainly large,

TABLE 1

Mean size, size distribution and particle shape of the fillers used

Filler	Mean size (μm)	Size distribution (μm)	Particle shape
Glucose	300	50–1000	plates
Lactose	300	50– 400	angular
Calcium hydrogen phosphate dihydrate	120	25– 300	angular
Maize starch	10	5– 15	globular
Microcrystalline cellulose	100	5– 300	irregular

TABLE 2

Amounts of water (g) added during the granulation process to a batch of filler (250.0 g) ($x \pm$ S.D.) ($n = 3$)

Filler	Amount of water (g)	S.D. (g)
Glucose	60	6
Lactose	60	0
Calcium hydrogen phosphate dihydrate	80	20
Maize starch	170	9
Microcrystalline cellulose	230	40

TABLE 4

Densities of nonspheronized and spheronized granules determined with Beckman air pycnometer (g/cm^3) ($n = 3$)

Filler	Unspheronized granules ($g/cm^3 \pm$ S.D.)	Spheronized granules ($g/cm^3 \pm$ S.D.)
Glucose	1.34 ± 0.00	1.44 ± 0.01
Lactose	1.46 ± 0.02	1.48 ± 0.02
Calcium hydrogen phosphate dihydrate	2.08 ± 0.02	2.14 ± 0.03
Maize starch	1.24 ± 0.02	1.24 ± 0.01
Microcrystalline cellulose	1.41 ± 0.03	1.50 ± 0.02

damp granules. Dissolved fillers form solid strong bridges between particles (Jaiyeoba and Spring, 1980).

Calcium hydrogen phosphate dihydrate needed more water than lactose and glucose to obtain granules of the proper size. One reason for this could be the hydrophilic nature of calcium hydrogen phosphate which increases the amount of water needed in granulation. In addition, the formation of granules also requires water because calcium hydrogen phosphate dihydrate consists not of individual crystals but of aggregates of crystallites (Shangraw et al., 1981). It may be that water is needed to form bridges between the agglomerates.

The effects of hydration and swelling on the amounts of water needed in granulation were observed most clearly when microcrystalline cellulose and maize starch were granulated. Their ability to incorporate water both into and between the particles led to the amounts of water needed in granulation being different from those for other fillers (Nogami et al., 1969). The amounts of water needed were for maize starch nearly 3 times and for microcrystalline cellulose nearly 4 times higher than for lactose granules. Bains and co-workers (1991) have also found it very important to have a proper moisture content when preparing spherical granules from masses containing microcrystalline cellulose.

Moisture content

The differences in the amount of water used in granulation were also clearly seen when the moisture contents of batches made from different fillers were investigated (Table 3). However, there were no differences in the moisture content of batches made from oscillated and spheronized

TABLE 3

Moisture content of 250.0 g batches of filler after the oscillating and spheronization process ($n = 3$)

Filler	Oscillated mass (%)	Spheronized mass (%)
Glucose	14	14
Lactose	18	17
Calcium hydrogen phosphate dihydrate	21	18
Maize starch	33	32
Microcrystalline cellulose	52	50

TABLE 5

Friability of unspheronized and spheronized granules (%), $x \pm$ S.D. ($n = 3$); results tested with Student's t-test

Filler	Unspheronized (% ± S.D.)	Spheronized (% ± S.D.)	Significance
Glucose	17.4 ± 0.7	11.5 ± 1.6	**
Lactose	51.6 ± 5.6	47.9 ± 1.5	n.s.
Calcium hydrogen phosphate dihydrate	49.0 ± 1.6	62.0 ± 1.3	***
Maize starch	12.6 ± 6.3	6.9 ± 1.3	n.s.
Microcrystalline cellulose	38.7 ± 0.1	3.3 ± 1.6	***

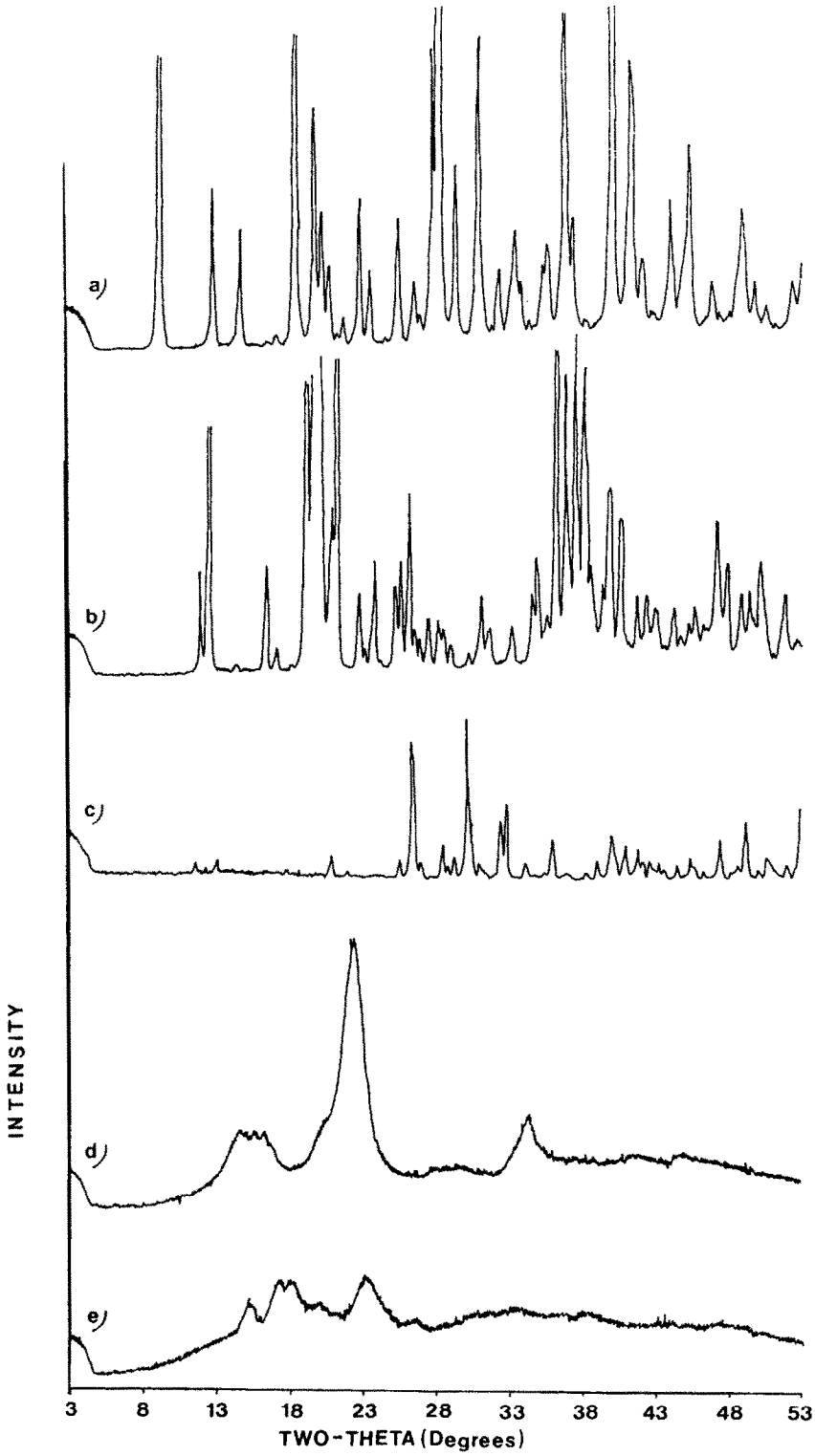

Fig. 1. X-ray diffraction patterns of fillers used in granules: (a) glucose, (b) lactose, (c) calcium hydrogen phosphate dihydrate, (d) microcrystalline cellulose, (e) maize starch.

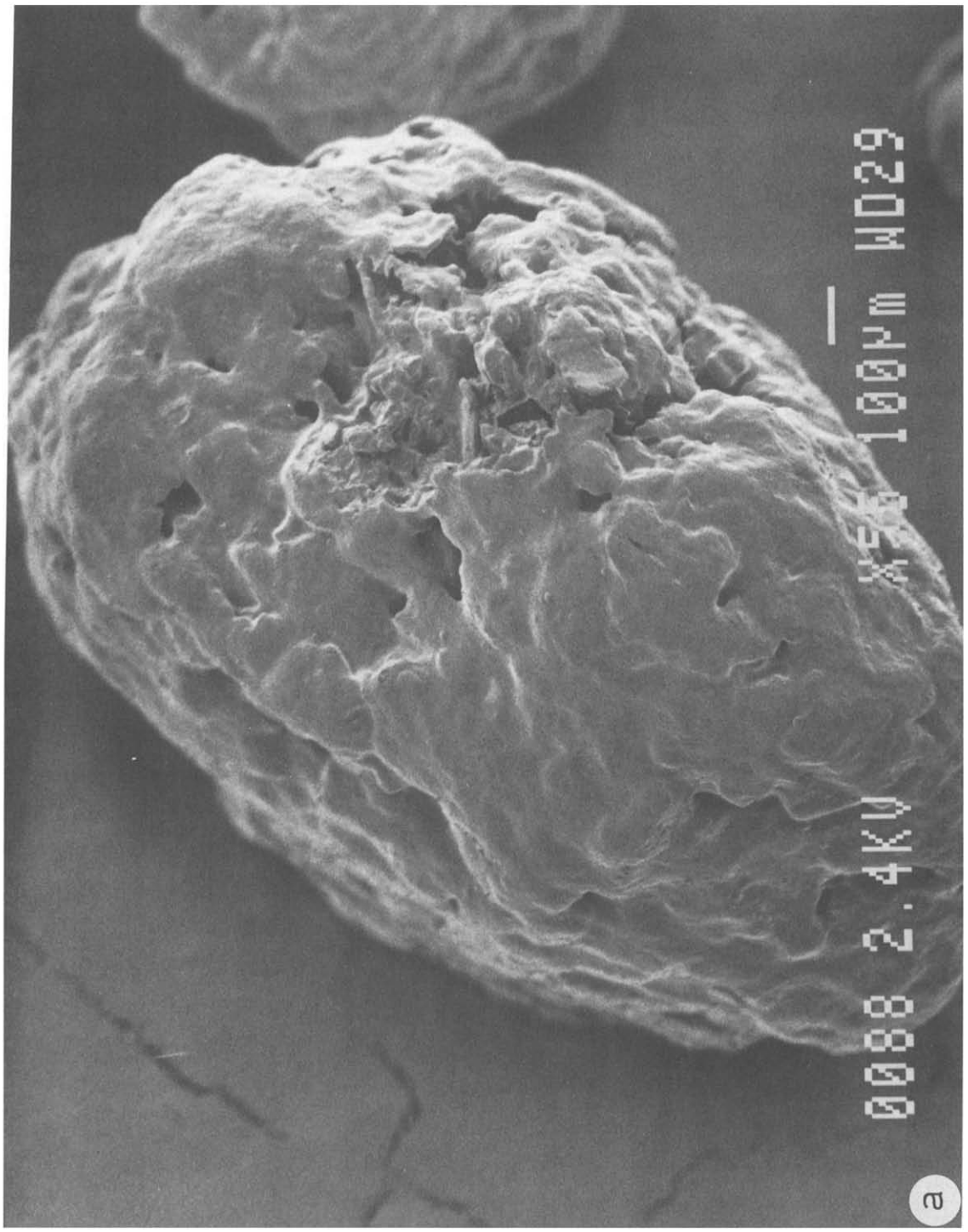

Fig. 2. The coated (EC : HPMC 65 : 35) unspheronized (a) and spheronized (b) glucose granule after the 6 h dissolution test. Bar = 100 μm.

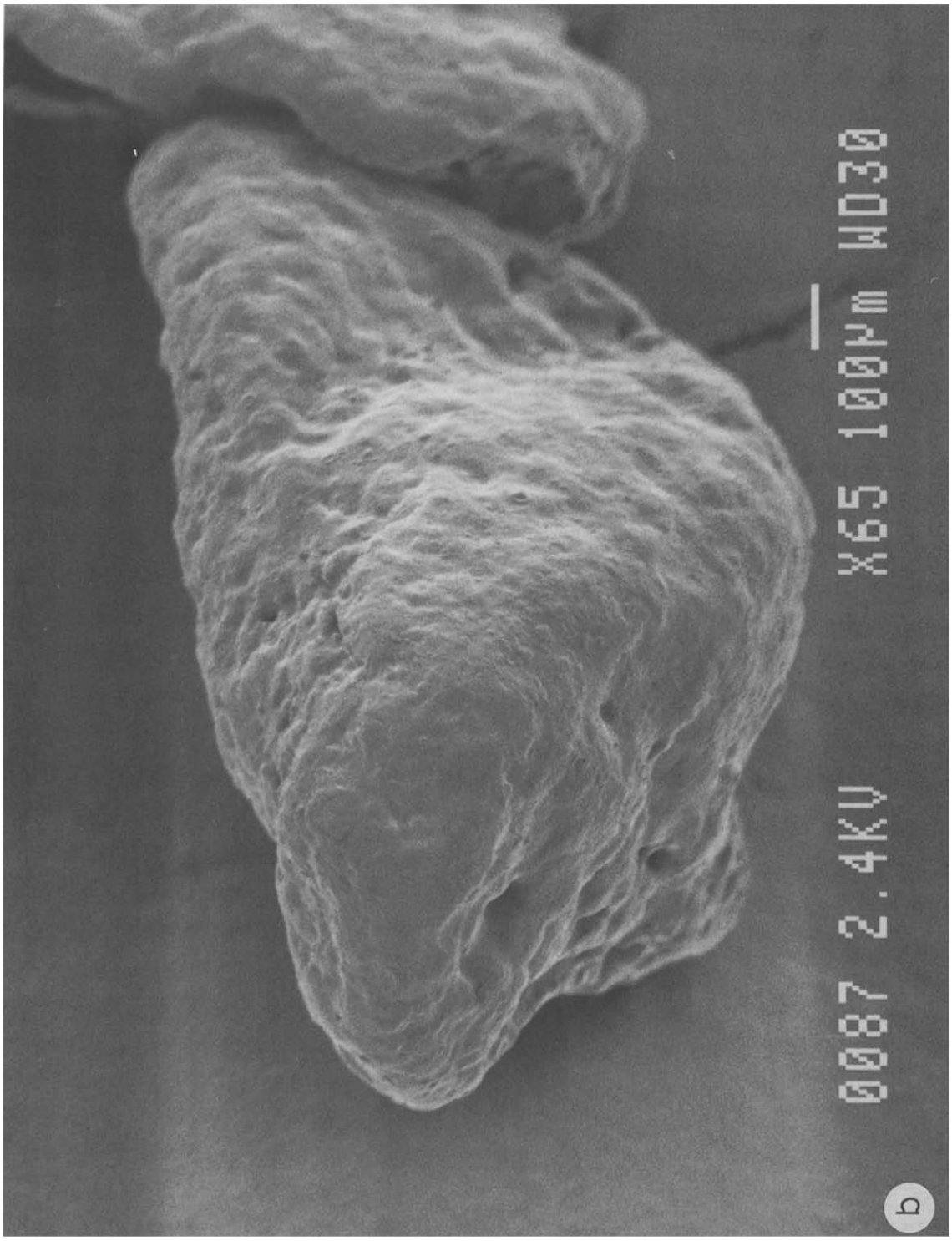

Fig. 2 (b).

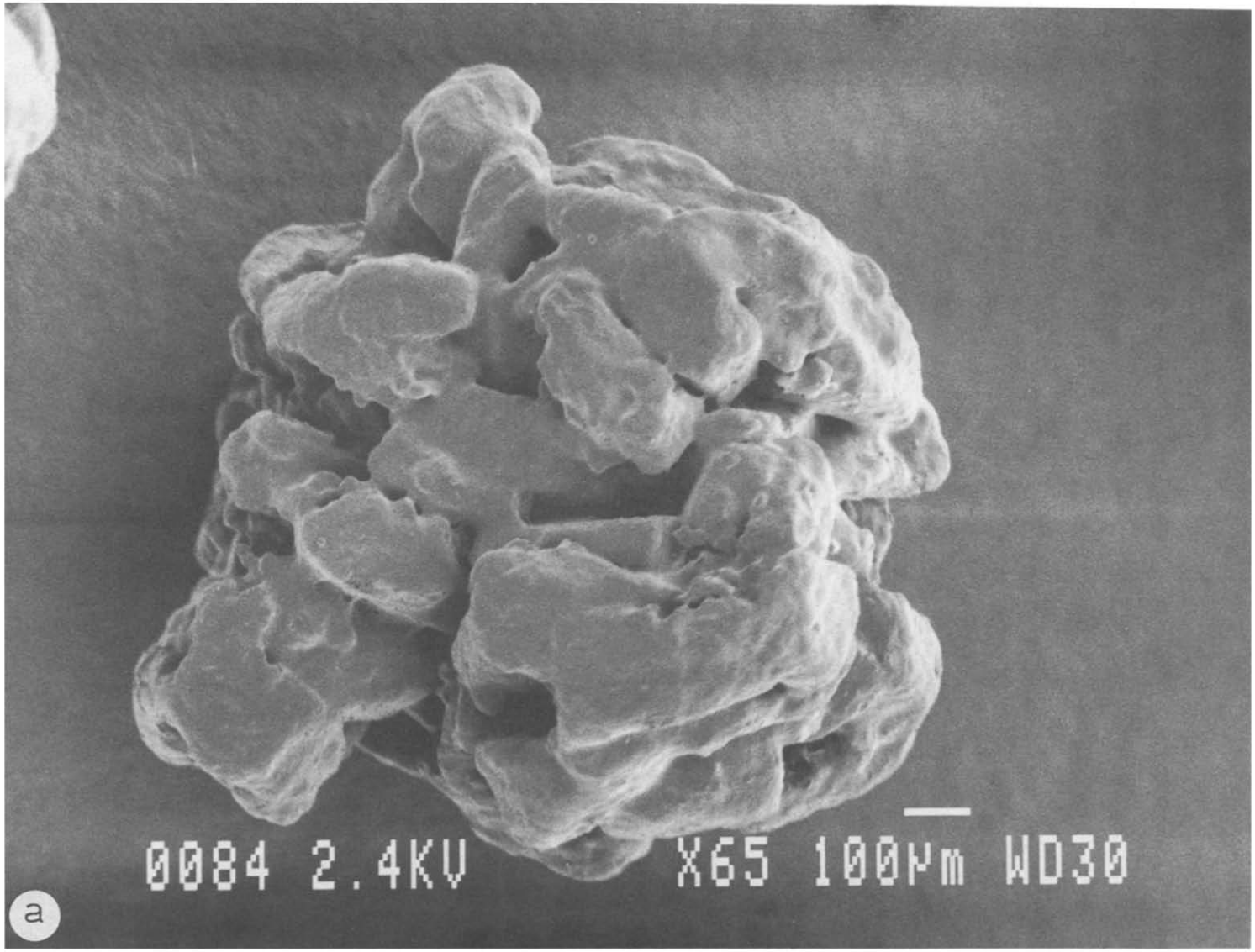

Fig. 3. The coated (EC : HPMC 65 : 35) unspheronized (a) and spheronized (b) lactose granule after the 6 h dissolution test. Bar = 100 μm.

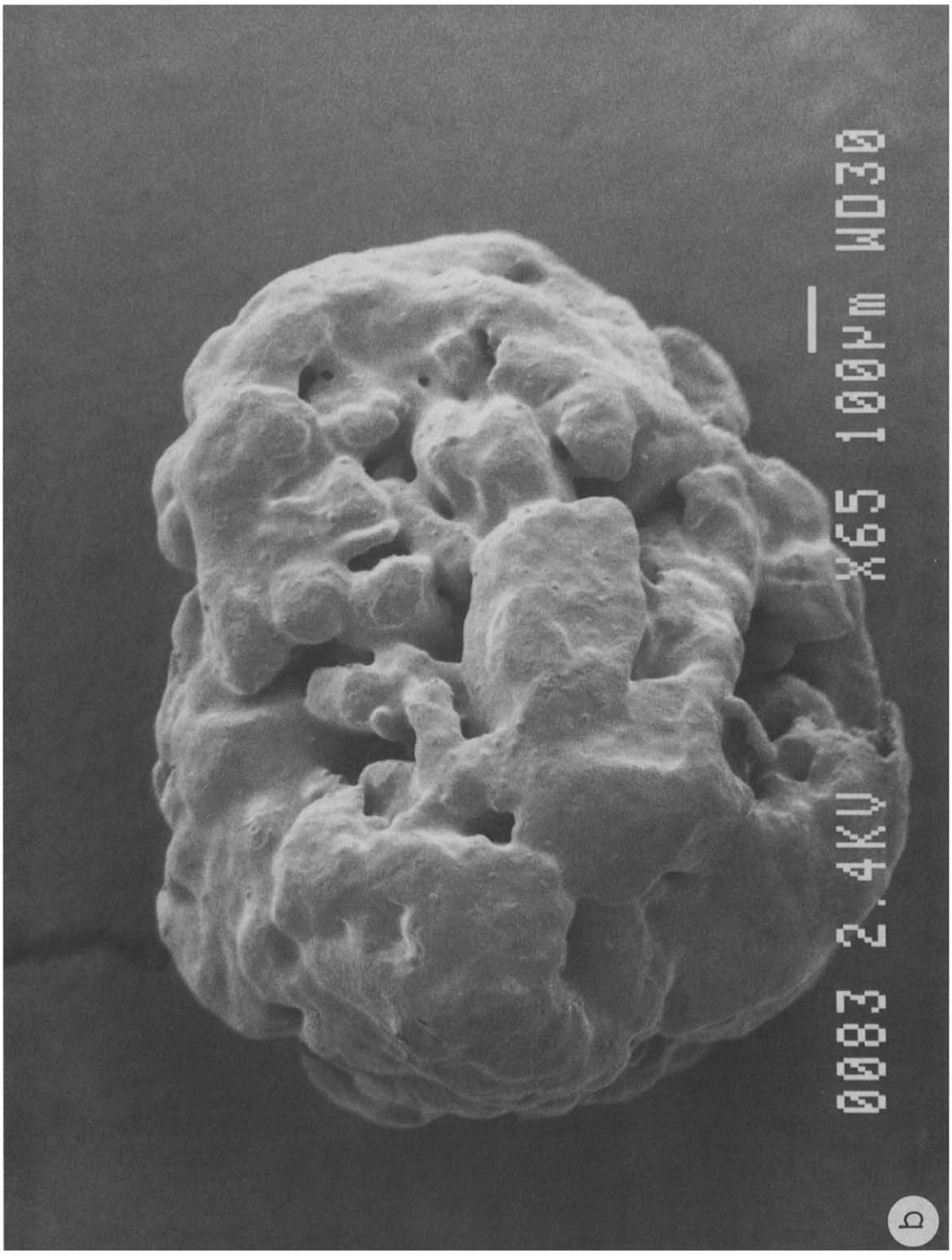

Fig. 3 (b).

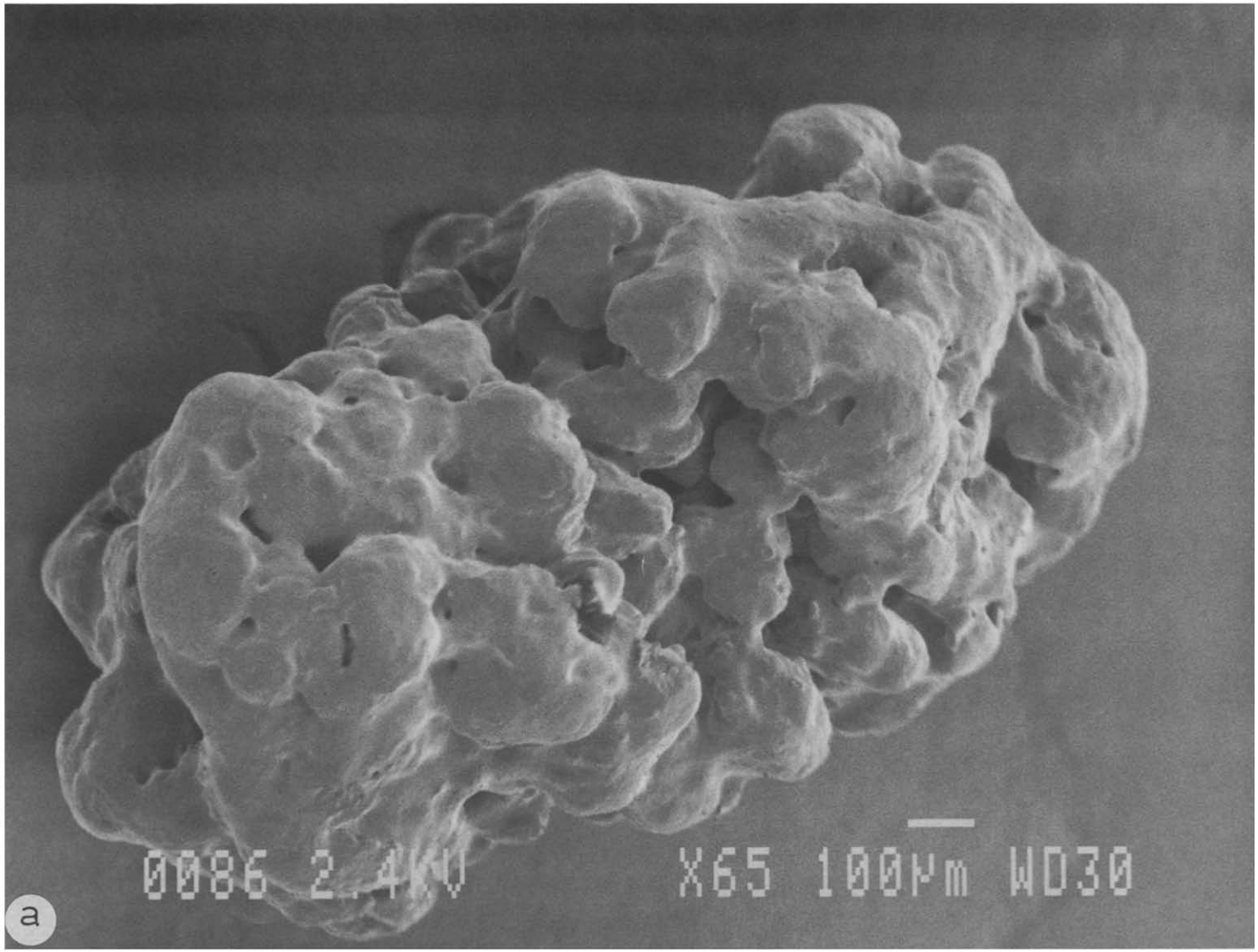

Fig. 4. The coated (EC:HPMC 65:35) unspheronized (a) and spheronized (b) calcium hydrogen phosphate dihydrate granule after the 6 h dissolution test. Bar = 100 μm.

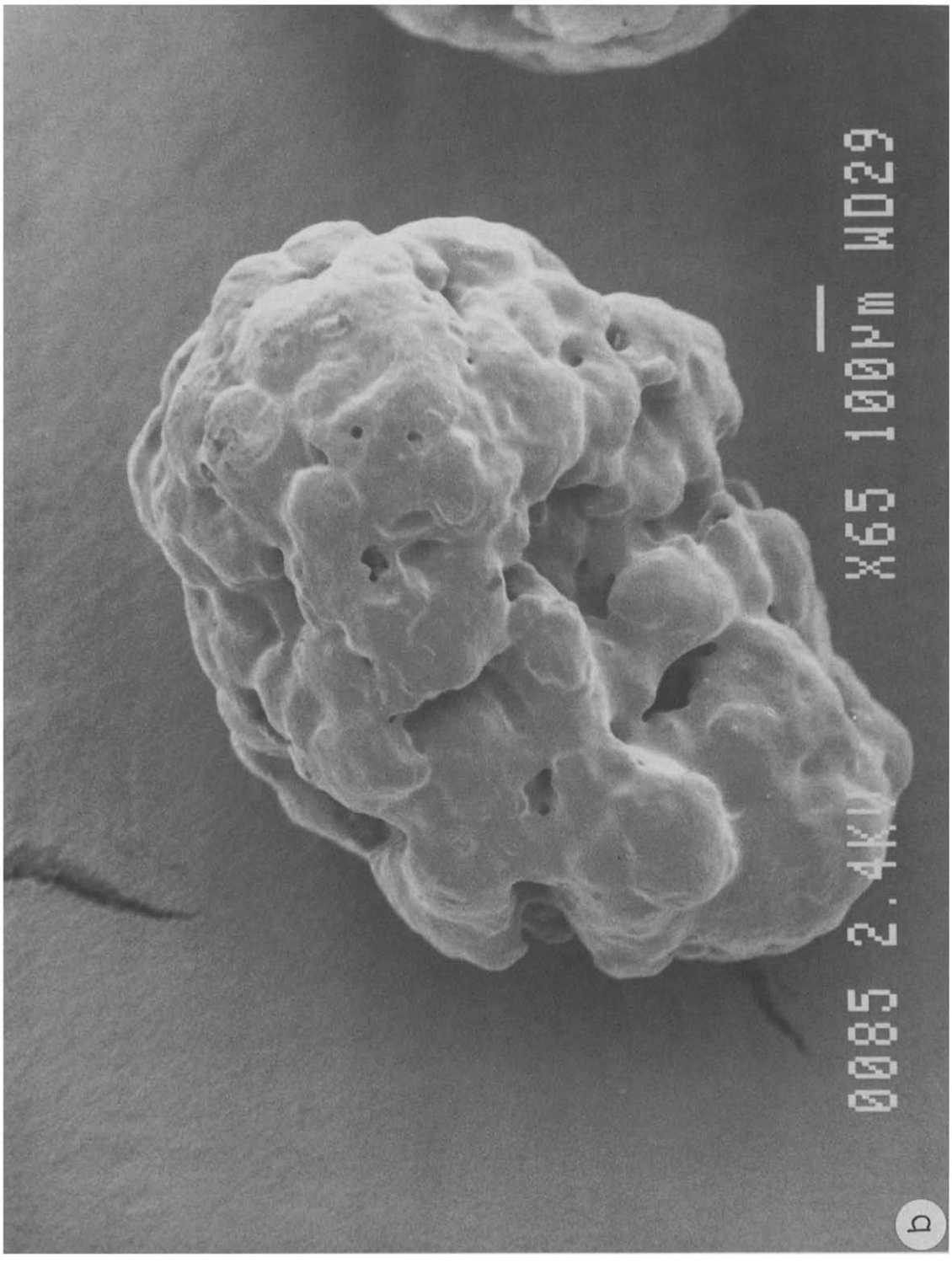

Fig. 4 (b).

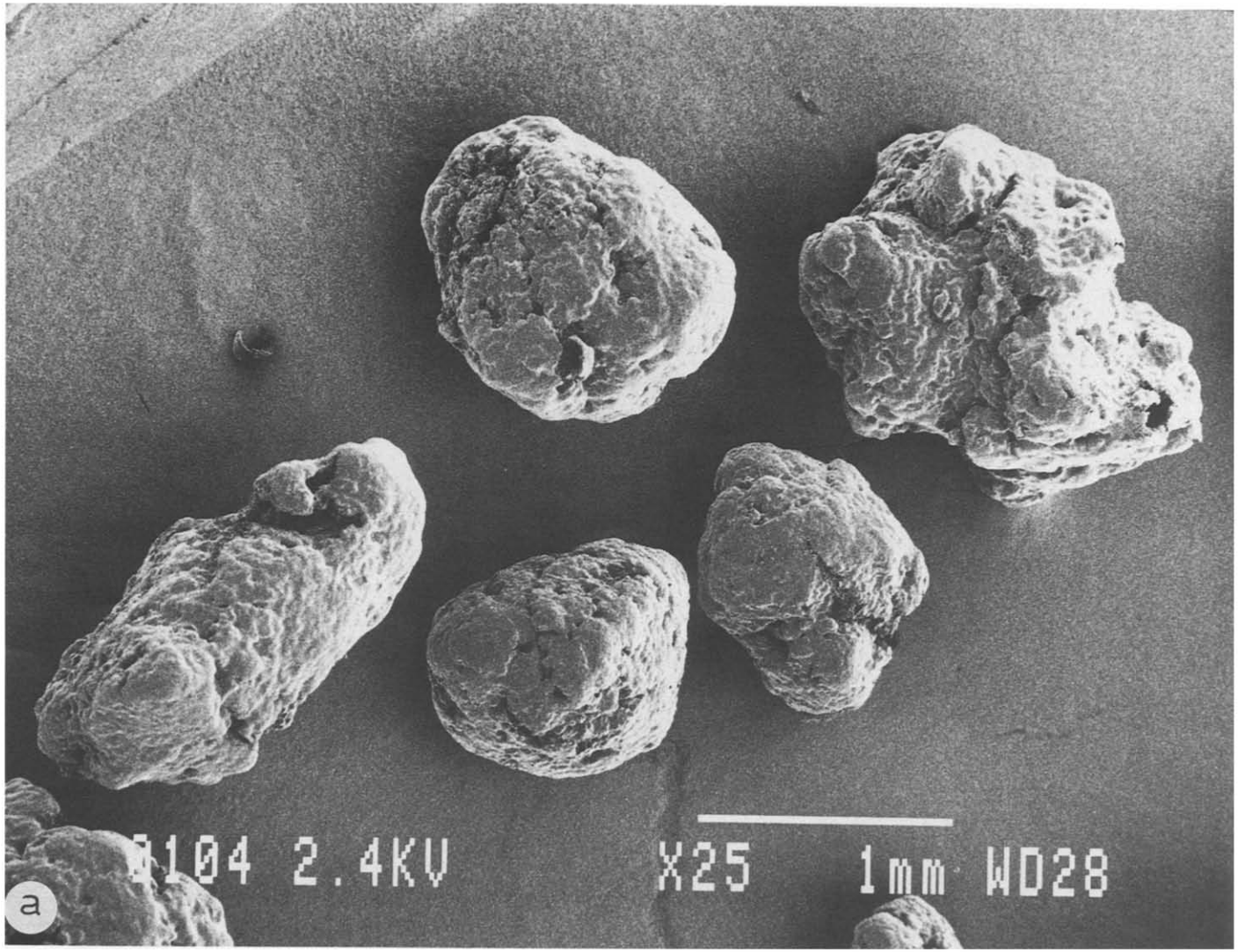

Fig. 5. The coated (EC : HPMC 65 : 35) unspheronized (a) and spheronized (b) maize starch granules after the 6 h dissolution test. Bar = 100 μm.

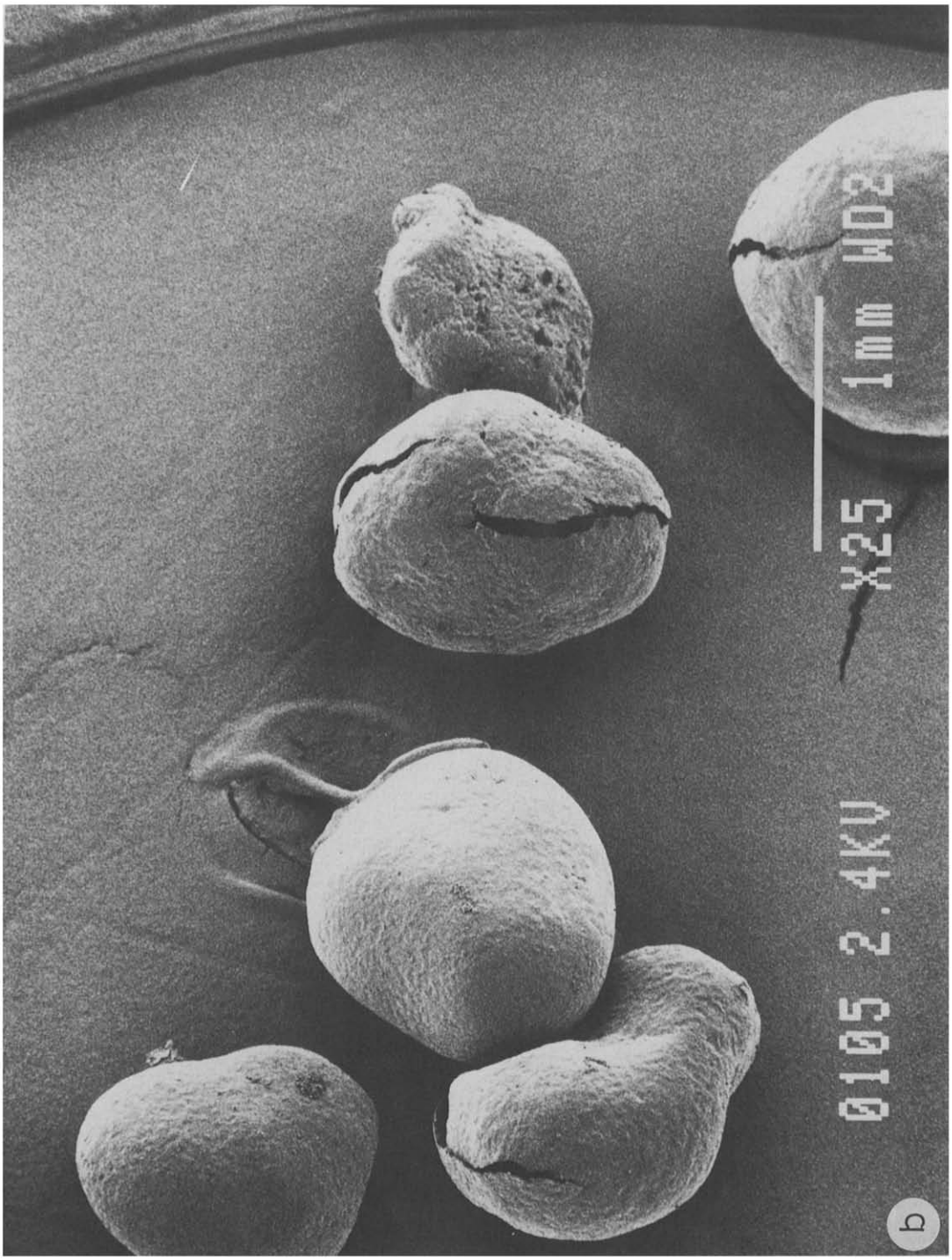

Fig. 5 (b).

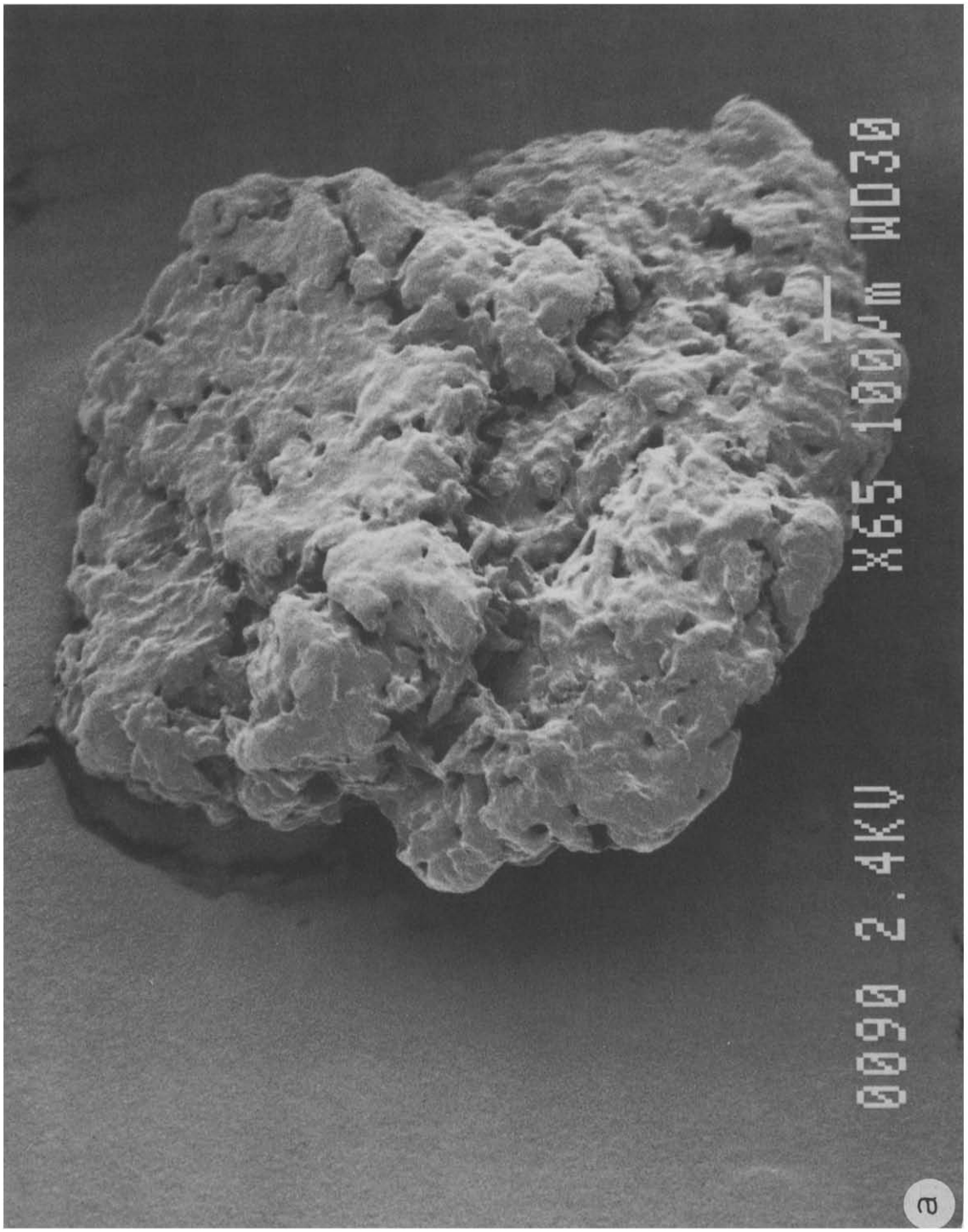

Fig. 6. The coated (EC : HPMC 65 : 35) unspheronized (a) and spheronized (b) microcrystalline cellulose granule after the 6 h dissolution test. Bar = 100 μm.

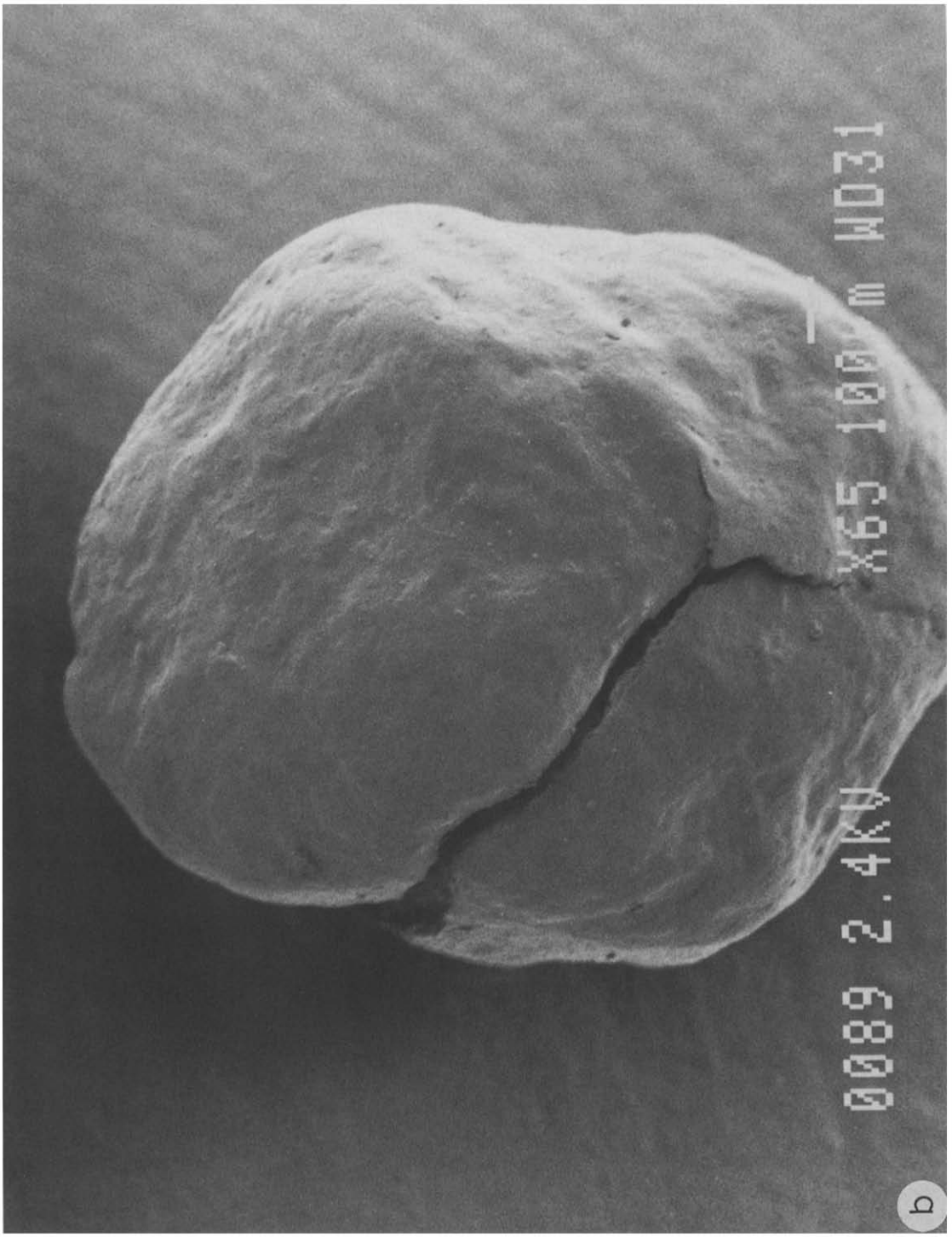

Fig. 6 (b).

masses. Similar results have also been obtained in other studies (Chien and Nuessle, 1985). It appears that in the spheronization process only the particles of fillers are rearranged; however, the whole process is so rapid that no intergranular moisture is lost. There may be a densified, binder-rich layer at the surface, and this may act as a moisture barrier. This moisture barrier is a result of the hardening and densification of the bead and the centrifugal force pulling the liquid from the interstitial spaces to the outer surfaces (Chien and Nuessle, 1985). This barrier may affect drug release from spheronized granules.

Density

Previous studies suggest that the spheronization process affects the density of granules, which in turn may affect dissolution of the drug from the granules (Clarke, 1989; Devereux et al., 1990). Some changes in density were seen in the results (Table 4); as expected, the granules were thicker when spheronized. However, the only major differences were seen in the case of glucose and microcrystalline cellulose granules. The thickening of glucose granules may be partly explained by changes in the granule surface, which were clearly observed in the scanning electron microscope. The plate structured glucose crystals were ground during the spheronization process and the lactose particles were also seen to have undergone some grinding although this did not affect the density of the granules. The results also show that calcium hydrogen phosphate dihydrate granules were somewhat denser than granules containing other fillers. Löfgren (1983) also found that adding calcium hydrogen phosphate dihydrate to the mass to be granulated gave a tough mass and dense extrudates.

Friability

The most marked differences between fillers were seen in terms of the friability of the unspheronized and spheronized granules. Friability is an indication of granule hardness. It has been thought that beads may undergo some hardening and densification during the spheronization process as a result of interparticulate friction and of collisions between beads and the wall of the spheronizer (Chien and Nuessle, 1985). In the present study, maize starch granules seemed to be rather hard; their structure is such that spheronizing has little effect on the granule surface. Glucose granules also appeared to be rather hard, at least in the light of the results of the friability test (Table 5). The difference between unspheronized and spheronized granules can be explained by the fact, as shown in Fig. 2, that glucose particles are ground where the structure has sharp edges. On the other hand, it has been assumed that a very soluble powder will affect the quantity of binder solution available to form liquid bridges between particles (Jaiyeoba and Spring, 1981). These bridges may affect the hardness of the granules. Lactose granules were very weak, their friability being about 50% for both unspheronized and spheronized granules. The forces inside the granules are probably so weak that the crushing forces exerted by the action of the small balls cause the lactose granules to crumble rapidly. The same happens to calcium hydrogen phosphate dihydrate granules, the results indicating that spheronization weakens the intragranular forces. The greatest effect of spheronization was on the friability of microcrystalline cellulose granules. Microcrystalline cellulose has a fibrous structure, and the fibres may rearrange themselves during the spheronization process. This was seen during the process as the oscillated mass first rearranged to a powder form and only then were spheronized granules formed. The spheronized granules were round in shape and their surface smooth just like the surface of spheronized maize starch granules. Maize starch granules were found to be rather hard in this study. However, Bode-Tunji and Jaiyeoba (1984) found that adding 10% starch to lactose or calcium carbonate made the granules more friable.

Granule characteristics

Both unspheronized and spheronized uncoated and coated granules were studied using the scanning electron microscope. The ability of different fillers to spheronize was clearly seen under the microscope. Both unspheronized and spheronized lactose granules were uneven in structure, which may explain the results of the

friability test (Table 5). Spheronization smoothed the surface of the glucose granules, as it did in the case of maize starch and microcrystalline cellulose granules. Changes seen in the calcium hydrogen phosphate dihydrate granules may partly explain the increase in friability after spheronization. Granules of calcium hydrogen phosphate dihydrate agglomerates are formed more irregularly after spheronizing, with the result that the granules are weaker.

After the granules had been coated a dissolution test was performed on each batch of granules in order to ascertain what happens on the surface of the granules, especially in the coat. Previous studies have revealed that in unspheronized granules containing a drug, the dissolution of drug is influenced by effects of the filler on the coat (Eerikäinen et al., 1989, 1991; Laakso and Eerikäinen, 1991). Samples were taken from the granules during the dissolution test over a period of 8 h (1, 2, 4, 6, and 8 h). The figures are for granules after 6 h of dissolution (Figs 2–6). No marked differences were seen between unspheronized and spheronized glucose and lactose granules (Figs 2 and 3). The only visible difference was that glucose granules seemed to be coated more uniformly after being spheronized.

Calcium hydrogen phosphate dihydrate granules appeared to remain unchanged after the 6 h dissolution test (Fig. 4). However, there may still be places in the unspheronized granules where the coat is not uniform, especially where there are holes in the structure of the granules.

In earlier studies, swellable maize starch broke the coat of unspheronized granules and this enhanced the dissolution of drugs from these granules (Eerikäinen et al., 1989, 1991; Laakso and Eerikäinen, 1991). The ruptures seem to be sharper and longer in spheronized granules than unspheronized granules (Fig. 5). This could also affect the release of drugs from the granules because the ruptures seem to be formed more regularly and more slowly than in unspheronized granules. The slow formation of ruptures was observed when the granules were examined using the scanning electron microscope after 1, 2 and 4 h of dissolution.

After the 6 h dissolution test, there were no ruptures in the coat of unspheronized microcrystalline cellulose granules, but the situation was clearly different in the case of spheronized granules (Fig. 6). When coats are attached more tightly and more uniformly onto the smoother surfaces of spheronized granules, the forces arising because of microcrystalline cellulose swelling can be expected to be more powerful inside the coat than in unspheronized granules. On the other hand, the fibrous structure of spheronized microcrystalline cellulose particles may have a retarding effect on drug dissolution if the drug is present in the core.

The results of the present study show that there are differences between unspheronized and spheronized granules. It would therefore be worthwhile carrying out more investigations in order to determine whether these differences are large enough to affect drug release from unspheronized and spheronized granules.

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