International Journal of Pharmaceutics, 57 (1989) 139–147
Elsevier

IJP 01935

Disintegrant properties of an agglomerated cellulose powder

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(Received 17 April 1989)
(Accepted 20 June 1989)

Key words: Agglomerated cellulose powder; Microcrystalline cellulose; Sodium carboxymethylcellulose; Compressed tablet; Disintegrant efficiency; Disintegrant mechanism

Summary

The disintegrant efficiency and the mechanism of disintegrant action of an agglomerated cellulose powder were evaluated and compared to those of microcrystalline celluloses, Avicel PH 101 and Emcocel, and cross-linked sodium carboxymethylcellulose AcDiSol. Water penetration and tablet expansion rates of dicalcium phosphate tablets containing agglomerated cellulose were similar to those of tablets containing microcrystalline celluloses. The total water uptake and maximum tablet expansion were, however, greater for tablets containing agglomerated cellulose, although not as much as those of tablets containing cross-linked sodium carboxymethylcellulose. Possible explanations for greater expansion of tablets containing agglomerated cellulose compared to tablets containing microcrystalline celluloses are a more pronounced disrupting effect of water on the hydrogen bonds between cellulose particles and an expansion of deformed agglomerated cellulose particles. The maximum expansion of tablets, related to the development of the maximum disintegration force inside a tablet, correlated well with the disintegration time of tablets. The agglomerated cellulose powder was clearly more effective as a disintegrant in an insoluble tablet base than microcrystalline celluloses; however it was not as effective as strongly swelling sodium carboxymethylcellulose.

Introduction

A large number of materials with different chemical and physical properties are used as disintegrants in tablets. A wide range of mechanisms of action for these materials have been suggested. The reviews by Lowenthal (1973), Kanig and Rudnic (1984) and Shangraw et al. (1980) mentioned porosity and capillary action, swelling of disintegrant particles, swelling of deformed disintegrant particles, particle repulsion, heat of wetting and breakage of physico-chemical bonds. It is also possible that several of these mechanisms act simultaneously in disintegration processes.

It has been recognized that, irrespective of the mechanism of action, water uptake must be the first step in any disintegration process (Van Kamp et al., 1986; Caramella et al., 1986). In recent years Colombo, Caramella and coworkers (Caramella et al., 1986, 1988; Colombo et al., 1981, 1988) have related the disintegration process to the development of a disintegrating force inside the tablet. They concluded that water penetration into an insoluble tablet base is accompanied by a proportional force development indicating the relevance of disintegration mechanisms that are ca-

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pable of force development (Caramella et al., 1986).

Cellulose derivates are widely used not only as binding agents but also as disintegrants in tablets (Kanig and Rudnic, 1984; Shangraw et al., 1980; Lerk et al., 1979; Bolhuis et al., 1982). Disintegration of tablets containing microcrystalline cellulose is related to an increased entrance of water by the means of capillaries and the breakage of hydrogen bonds holding cellulose together (Fox et al., 1963; Lerk et al., 1979). Even when present in only small amounts in tablets, cross-linked sodium carboxymethylcellulose is a very effective disintegrant (Gissinger and Stamm, 1980). The disintegrant mechanism of this material is related to an extensive swelling of disintegrant particles (Bolhuis et al., 1982).

Recently, Pesonen et al. (1989) reported the excellent tableting properties of an agglomerated cellulose powder. The binding and deformation properties of this cellulose material were even better than those of microcrystalline celluloses (Pesonen and Paronen, 1989a,b). The aim of this paper was to study the disintegrant efficiency of the agglomerated cellulose powder and to evaluate the mechanism of disintegrant action of this material.

Materials and Methods

The cellulose powders studied were an agglomerated cellulose powder (referred to as ACP), microcrystalline celluloses, Emcocel and Avicel PH 101 and cross-linked sodium carboxymethylcellulose, AcDiSol. The first two materials were supplied by Finnish Sugar (Kantvik, Finland) and the last two were manufactured by FMC Corp. (Philadelphia, PA). Dicalcium phosphate, Emcompress, was manufactured by Edward Mendell Co. (NY, U.S.A.) and the magnesium stearate used was Ph. Eur. grade.

Swelling of cellulose particles in water was studied by comparing the particle size distribution of cellulose powder dispersed in water to that in a less polar solvent, isopropanol. Dispersions were visualized using a video camera connected to a photomicroscope. The picture was projected on a magnetic board plate and the projected area of 300 particles was measured.

Water penetration into cellulose powders was studied using a similar kind of apparatus to that described by Gissinger and Stamm (1980). A pre-weighed powder sample was carefully placed onto a glass sinter of the apparatus and penetration of water into the sample through the sinter was determined using a capillary pipet. The evaporation of water was prevented by closing the small free air space over the sinter with a tight rubber piece. Two samples of each cellulose powder were tested.

The tablets containing dicalcium phosphate, Emcompress, as a base material, mixed with different amounts of celluloses were compressed as described previously (Pesonen et al., 1989) using separately weighed amounts of 500 mg tablet mass. Dicalcium phosphate and cellulose were mixed for 10 min in Turbula 2P mixer (W. Bachofen, Basel) and after the addition of 0.5% magnesium stearate mixing was continued for 5 min.

Porosity of tablets was calculated from the dimensions and weight of the tablets and the apparent particle density of tablet mass (Pesonen et al., 1989). Breaking strength (Schleuniger 2E apparatus, Solothurn, Switzerland) and disintegration time (Ph. Eur. method with discs) were studied as means of six tablets. Cumulative surface area as a function of pore size was determined using mercury penetration as described previously (Pesonen and Paronen, 1989a).

Water penetration into tablets was studied using the same apparatus as in the test of water penetration into cellulose powders. The expansion of tablet, due to the effect of penetrating water, was studied using a similar kind of apparatus to that of Gissinger and Stamm (1980). A tablet was placed onto a glass sinter similar to that in the penetration test. The upper surface of the tablet was in contact with a round flat-faced testing pin connected to an inductive displacement transducer. The expanding tablet pulled the 2.0 g load of the testing pin upward and the movement of the inductive displacement transducer was recorded using a strip chart recorder. Both penetration and tablet expansion tests were carried out using three tablets.

The tablet surface was carefully touched with a moist finger (Hess, 1978) and the changes in structure of the moistened tablet surface were studied visually using scanning electron micrographs taken with a Jeol JSM-35 apparatus.

The distribution of cellulose particles in dicalcium phosphate tablet base was studied by elemental analysis based on the determination of calcium from the tablet surface. Elemental analysis was carried out using a Jeol JSM-840A scanning microscope connected with a Link AN10000 X-ray analyzer.

Results and Discussion

Properties of plain cellulose powders

According to particle size distributions in water and in isopropanol ACP, Avicel and Emcocel were all non-swelling or only slightly swelling materials. The mean particle size of AcDiSol, in contrast, increased 150% in water. Thus, in agreement with earlier studies the swelling of microcrystalline cellulose was negligible and AcDiSol was noted to be a swelling type cellulose derivate (Lerk et al., 1979; Bolhuis et al., 1982; Caramella et al., 1984).

The water penetration rate into cellulose powders was about the same for ACP, Avicel and Emcocel (Fig. 1). The total amount of penetrated water was, however, somewhat greater for ACP than for microcrystalline celluloses. In agreement with the results of Van Kamp et al. (1986) water penetration was clearly slower into AcDiSol powder than into microcrystalline cellulose powders. This was due to the gelling of the particle surfaces due to the partial dissolution of this material in water. Gelling of particle surface was confirmed by visual examination of scanning electron micrographs taken from the sample of dried water suspension of AcDiSol powder. The total amount of penetrated water was due to the swelling ability of individual particles greatest for AcDiSol powder.

Water penetration into tablets

Lerk et al. (1979) showed that addition of microcrystalline cellulose into an insoluble dicalcium phosphate tablet strongly increased water penetration rate into tablets, their results being in agreement with ours. The ability of microcrystalline celluloses, Avicel and Emcocel, to accelerate water penetration was quite similar (Figs. 2 and 3). The instant water penetration rate, up to about 20 s, was nearly equal for ACP tablets and for microcrystalline cellulose tablets. Thereafter, the water

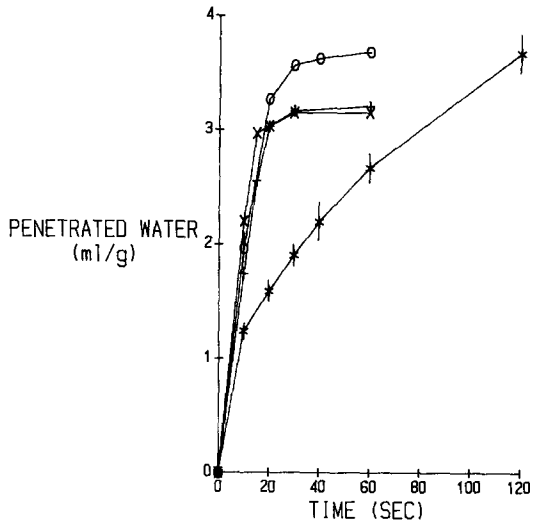

Fig. 1. Water penetration into cellulose powders. Bars indicate standard error of the mean. ACP (○), Avicel PH 101 (×), Emcocel (+) and AcDiSol (*).

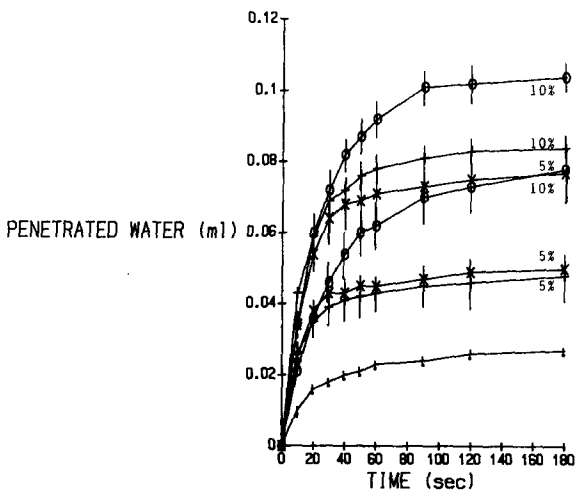

Fig. 2. Water penetration into dicalcium phosphate tablets containing either 5 or 10% of cellulose. Bars indicate standard error of the mean. ACP (○), Avicel PH 101 (×), Emcocel (+) and plain dicalcium phosphate tablets (·).

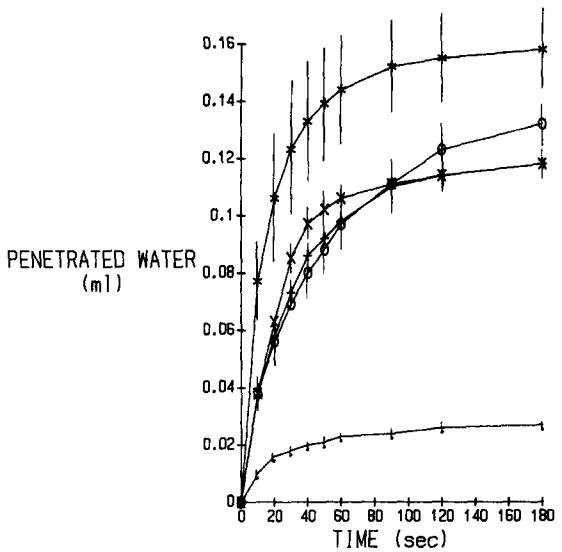

Fig. 3. Water penetration into dicalcium phosphate tablets containing 20% of ACP (○), Avicel PH 101 (×) and Emcocel (+) and 1% of AcDiSol (*) and into plain dicalcium phosphate tablets (·). Bars indicate standard error of the mean.

uptake of tablets containing microcrystalline cellulose was completed rapidly, whereas water penetration into tablets containing ACP continued resulting in a greater total amount of penetrated water. Water penetration was clearly fastest and total water uptake greatest for tablets containing AcDiSol (Fig. 3).

The effect of disruption of hydrogen bonds between cellulose by penetrating water has been shown to increase pore volume of microcrystalline cellulose tablets (Lerk et al., 1979). This concept is consistent with the observed high ratio between water uptake volume and original pore volume of tablets (Table 1). The ratio for tablets containing ACP was greater than for tablets containing Avicel and Emcocel (Table 1). The ratios of tablets containing 20% ACP and tablets containing 1% AcDiSol were the same. It is thus possible that the original pore volume of tablets containing ACP increased more than those of tablets containing microcrystalline celluloses. The greater water uptake volume of tablets containing ACP could, on the other hand, be explained by the greater water sorption capacity of ACP compared to those of microcrystalline celluloses (Fig. 1).

The scanning electron micrographs taken from moistened tablet surface showed clear differences in tablet structure (Fig. 4). The swollen AcDiSol particles were readily observed (Fig. 4E). This is understandable, since AcDiSol is known to cause disintegration by disruption of the tablet matrix due to swelling of disintegrant particles (Bolhuis et al., 1982). A clear difference was also seen between the surfaces of tablets containing ACP and those containing microcrystalline cellulose. The moistened surface of tablets containing ACP in Fig. 4A and B was, in contrast to the cases for microcrystalline celluloses in Fig. 4C and D, covered with clear cracks.

Because of the clearly visible cracks, it was expected that water would penetrate more rapidly into tablets containing ACP as compared to microcrystalline celluloses. Water obviously penetrated at the same time, firstly, towards the tablet center through pores and created cracks and secondly, inside the ACP agglomerates which have been previously noted to be very porous (Pesonen and Paronen, 1989a). The latter process was obviously very slow and thus the total penetration rate into tablets containing ACP was quite similar to those with microcrystalline celluloses. It is also

TABLE 1

Water uptake, pore volume and their ratio for dicalcium phosphate (Emcompress) tablets containing different amounts of cellulose

	Water uptake (ml)	Pore volume (ml)	Water uptake/ pore volume
Emcompress (I)	0.030	0.036	0.8
I+5% ACP	0.080	0.036	2.2
I+10% ACP	0.105	0.034	3.1
I+20% ACP	0.144	0.034	4.2
I+5% Avicel PH 101	0.051	0.034	1.5
I+10% Avicel PH 101	0.079	0.033	2.4
I+20% Avicel PH 101	0.119	0.034	3.5
I+5% Emcocel	0.049	0.034	1.4
I+10% Emcocel	0.087	0.033	2.6
I+20% Emcocel	0.121	0.032	3.8
I+1% AcDiSol	0.155	0.037	4.2

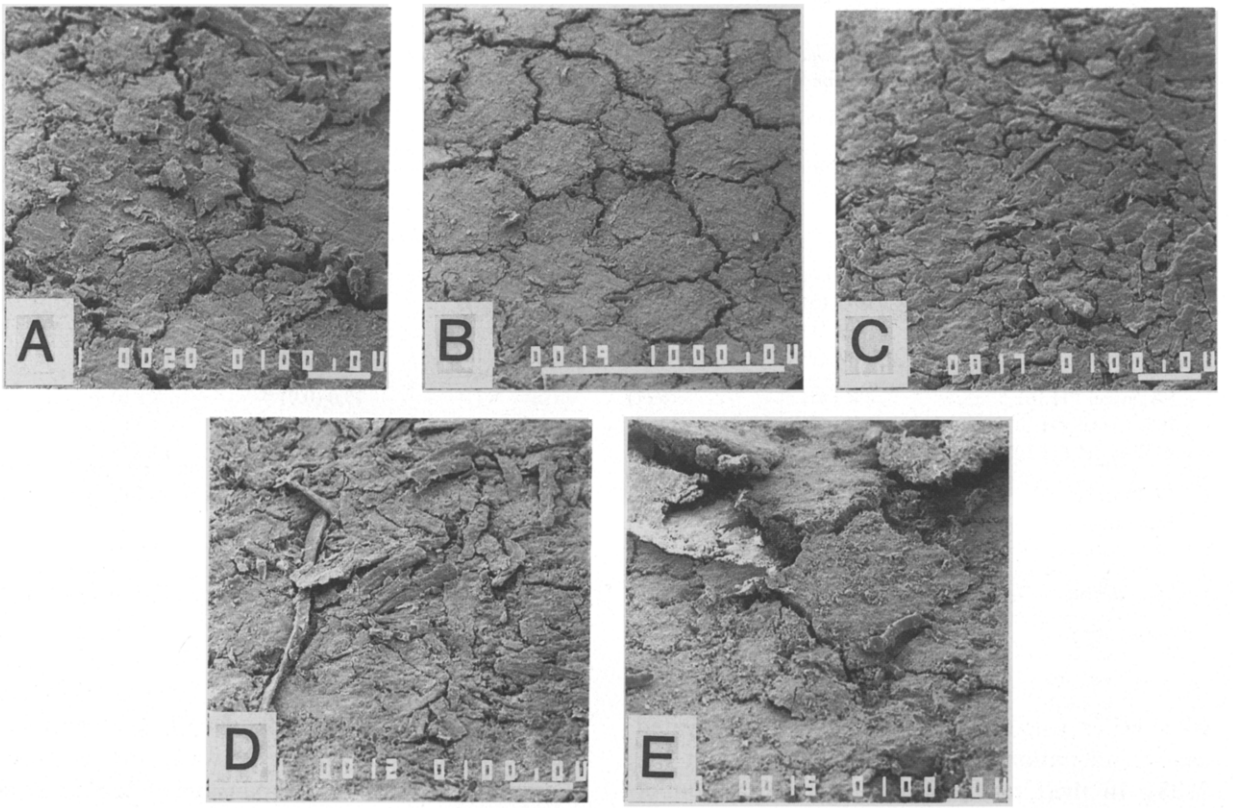

Fig. 4. Scanning electron micrographs taken from the moistened surface of dicalcium phosphate tablets containing 20% of ACP (A, B), Avicel PH 101 (C) and Emcocel (D) and 1% of AcDiSol (E). Bar: 100 μm (1000 μm in panel B).

possible that the mere penetration of water inside the deformed ACP agglomerates actually created the cracks. The difference in water uptake between ACP and microcrystalline cellulose tablets (Table 1) could thus be mainly due to the greater amount of water sorbed by ACP particles.

Because of the effective creation of cracks the initial porosity of ACP tablets had no effect on water penetration. This was confirmed by studying water penetration into dicalcium phosphate tablets containing 10% of ACP and having varying porosity of between 9 and 18%. Water penetration rate as well as total volume of penetrated water showed no distinct trend and were about the same in every case.

The penetration of water is a prerequisite for the disintegration of a tablet because it activates the mechanisms which lead to disintegration (Van Kamp et al., 1986; Caramella et al., 1986). No direct correlation between the instant water penetration rate and disintegration times was observed (Table 2). Both water penetration and tablet disintegration were fastest for AcDiSol tablets. However, despite the clear differences in disintegration times between ACP and microcrystalline cellulose tablets, no great differences in water penetration rates were observed. The total amount of penetrated water correlated rather well with the observed disintegration times.

Expansion of tablet matrix

Caramella and Colombo and co-workers (Colombo et al., 1981, 1988; Caramella et al., 1986, 1988) have developed a model for the development of a disintegrating force inside a tablet due to the penetration of water. They constructed an apparatus with which they were able to measure the force developed by an expanding tablet matrix

TABLE 2

Disintegration time, maximum expansion, half-time of maximum expansion, porosity and breaking strength for dicalcium phosphate (Emcompress) tablets containing different amounts of cellulose

Values expressed as means with the standard error in parentheses.

	Disintegration time (s)	Maximum expansion (%)	Half-time (s)	Porosity (%)	Breaking strength (kp)
Emcompress (I)	> 1 800	< 1		14.0 (0.1)	7.9 (0.3)
I + 5% ACP	107 (3)	18 (2)	10 (1)	13.7 (0.1)	10.4 (0.3)
I + 10% ACP	30 (1)	26 (1)	11 (1)	12.8 (0.1)	11.3 (0.3)
I + 20% ACP	21 (1)	42 (1)	10 (2)	12.5 (0.1)	15.2 (0.3)
I + 5% Avicel PH 101	456 (45)	6 (1)	8 (1)	13.0 (0.0) [a]	8.8 (0.3)
I + 10% Avicel PH 101	111 (3)	14 (2)	11 (1)	12.6 (0.0) [a]	9.5 (0.2)
I + 20% Avicel PH 101	95 (3)	18 (3)	16 (4)	12.3 (0.1)	13.5 (0.2)
I + 5% Emcocel	261 (9)	6 (1)	5 (1)	13.0 (0.1)	8.2 (0.1)
I + 10% Emcocel	135 (6)	9 (1)	15 (3)	12.4 (0.1)	9.7 (0.3)
I + 20% Emcocel	119 (4)	17 (2)	12 (3)	11.7 (0.1)	11.9 (0.3)
I + 1% AcDiSol	8 (1)	47 (2)	13 (3)	14.6 (0.1)	7.2 (0.2)

[a] Below 0.05%.

when water penetrated into the tablet and activated the disintegration mechanisms (Colombo et al., 1988). In their test procedure, the expansion of tablet was prevented by the force measurement load cell and thus a force instead of expansion of a tablet was measured (Colombo et al., 1988). In our measurement system the expanding tablet was able to pull upwards the 2 g load of the measurement pin lying on the upper surface of tablet. Thus an increase in height of an expanding tablet instead of a force was measured.

Colombo et al. (1988) pointed out that two factors were important in the disintegration process: the maximum disintegrating force developed and the rate of development of the disintegrating force, described by the time taken to develop half of the maximum force, i.e. the half-time. Instead of maximum force we measured the maximum expansion of the tablet matrix and the time taken for the expansion corresponding to half of the maximum expansion (Table 2). The scatter in half-times was greater than that in maximum expansion especially for tablets containing greater amounts of microcrystalline cellulose. It could, however, be clearly seen that there were no great differences in half-times.

The maximum expansion of tablets, in contrast, showed clear differences between the cellulose tablets. The maximum expansion of tablets containing ACP was 2–3-times greater than those of tablets containing microcrystalline celluloses (Table 2). The expansion of tablets containing 20% of ACP was almost the same as that of tablets containing 1% of strongly swelling AcDiSol. The measured maximum expansions correlated well with the visual examination of tablet structure after moistening (Fig. 4). It can be concluded, assuming that the expansion of tablet reflects development of disintegrating force, that ACP was able to develop a clearly greater disintegrating force inside an insoluble tablet matrix than microcrystalline celluloses, Avicel and Emcocel.

The values for half-times, maximum expansions and disintegration times (Table 2) agree with the concept of Colombo et al. (1988) that both force development rate and maximum disintegrating force are the important factors in the disintegration of a water-insoluble tablet matrix. No great differences in tablet expansion rates, i.e. in half-times, were observed. Thus the reason for clearly shorter disintegration of AcDiSol and also ACP tablets (Table 2) must be related to the greater

maximum expansion of these tablets. The shortest disintegration of tablets containing AcDiSol resulted obviously from the greatest expansion supported by the fastest water penetration of these tablets. The disintegrant mechanism of AcDiSol is based on an extensive swelling of particles (Bolhuis et al., 1982). The mechanism of disintegrant action of a non-swelling agglomerated cellulose powder must thus be somewhat different from that of AcDiSol.

Breakage of hydrogen bonds

Caramella et al. (1988) have described the concept that the development of disintegrating force is affected by bond separation between particles as a result of water penetration and by the expansion rate of the separated particles or particle layers, which in many cases is related to the swelling of particles themselves. ACP, Avicel and Emcocel all contrasted with AcDiSol, being non-swelling or only slightly swelling materials. Thus, bond separation is obviously an important factor in the development of disintegrating force. This agrees with the study of Lerk et al. (1979), who have related the disintegrant properties of microcrystalline cellulose in dicalcium phosphate tablets to the breakage of hydrogen bonds between microcrystalline cellulose particles due to the penetration of water. The specific surface area of ACP was 50-times greater than those of microcrystalline celluloses (Pesonen et al., 1989), ACP was also slightly more prone to plastic deformation than microcrystalline celluloses and spherical agglomerates of ACP also showed a tendency to undergo fragmentation at low compressional pressures (Pesonen and Paronen, 1989b). It is thus obvious that during compression ACP formed greater contact areas and thus also more hydrogen bonds between cellulose particles than did microcrystalline celluloses. Tablets containing microcrystalline cellulose have been suggested to disintegrate rapidly due to the breakage of hydrogen bonds when placed in water (Lamberson and Raynor, 1976; Lerk et al., 1979). Lerk et al. (1979), on the other hand, related the relatively long disintegration time of plain microcrystalline cellulose tablets to extensive hydrogen bonding characterized by high tablet strength. An optimal number of hydrogen bonds and minimal mechanical interlocking of cellulose particles, compared to that of fibrous microcrystalline cellulose particles (Pesonen and Paronen, 1989a), clearly accounted for the clearly shorter disintegration time of dicalcium phosphate tablets containing ACP.

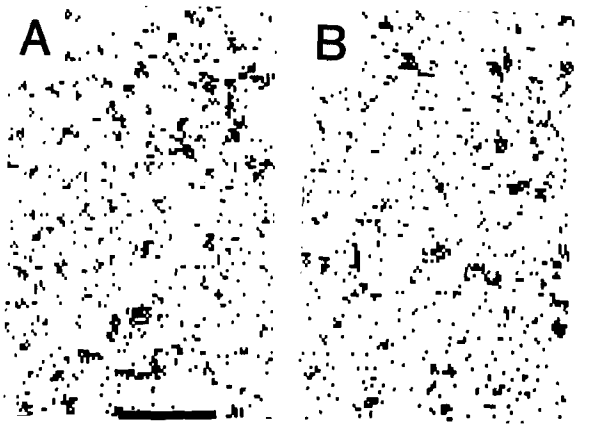

Fig. 5. Distribution of cellulose on the surface of dicalcium phosphate tablet containing 5% of ACP (A) and 5% of Emcocel (B). Bar: 100 μm.

Capillary network

The mean projected particle diameter of ACP, 58 μm, is greater than that of microcrystalline cellulose, viz., 37 μm (Pesonen et al., 1989). A small amount of these materials could therefore be variably distributed in dicalcium phosphate tablets. Fig. 5 shows the distribution of cellulose on the surface of tablets containing 5% of ACP (Fig. 5A) and 5% of Emcocel (Fig. 5B). Elemental analysis, based on determination of calcium from the tablet surface, shows the points without calcium, i.e. cellulose particles, as dark spots in the figure. The distributions of ACP and Emcocel were quite similar, indicating that clearly larger ACP agglomerates had partially fragmented. Fragmentation of ACP should be even more extensive in the interior of tablets. However, possible small differences in the distribution of celluloses studied were obviously not important as a factor accounting for the clearly better disintegrant properties of ACP.

Deformation

A possible explanation for the clearly shorter disintegration time of tablets containing ACP is based on deformation. Kanig and Rudnic (1984) have defined deformation with the concept of tablet disintegrants as being a process in which deformed disintegrant particles swell to precompression size and break up the matrix. Although deformation is considered to be a disintegration mechanism, it has been discussed almost exclusively from a theoretical point of view (Lowenthal, 1973; Shangraw, 1980; Rudnic and Kanig, 1984). This is understandable as direct measurement of deformation is difficult. Possibly the only published experimental approach to the phenomenon is the work by Hess (1978) concerning the deformation of starch grains. In this study, Hess showed with scanning electron micrographs that deformed starch grains regained their original shape when the tablet surface was carefully moistened.

Despite the observation of clear cracks on the surface of ACP tablets, possible differences in deformation behaviour between ACP and microcrystalline cellulose could not be established in scanning electron micrographs (Fig. 4). Only clearly swelling AcDiSol particles were detectable in micrographs. Visual observation of the deformation of ACP agglomerates could be much more difficult than that of starch grains for two reasons. Firstly, the expansion of deformed ACP agglomerates towards the original shape might be more severely restricted than that of starch grains. Secondly, the fragmentation of ACP agglomerates even at small compressional pressures leads to smaller primary particles and the amount and shape of original agglomerates are less readily recognizable than in the case of starch grains, which deform purely by plastic flow and remain at their original boundaries.

An indirect attempt to prove the validity of the deformation theory involved the measurement of cumulative surface areas for ACP samples treated in various ways. The possible differences in the pore size region of intraparticle pores should indicate variations in the structure of ACP agglomerates of the samples. Curves D and E in Fig. 6 represent plain ACP tablets as a dry sample and after immersion in water, respectively. The shape

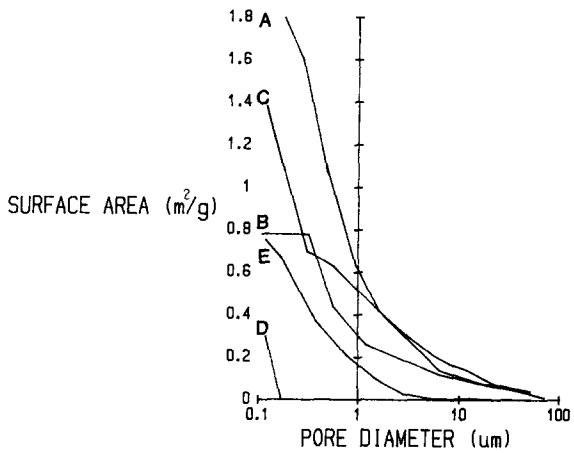

Fig. 6. Cumulative surface area for differently treated ACP samples. (A) Untreated ACP powder, (B) ACP powder compressed in a hydraulic press (3.5 ton load), (C) sample B after immersion in water, (D) plain ACP tablet compressed at 200 MPa, (E) sample D after immersion in water.

of the curves at the intraparticle pore region, i.e. about 1 μm or below, show that the cumulative surface area of the sample immersed in water was much more similar to that of the control sample of untreated ACP powder (curve A) than that of the dry ACP tablet. The effect of cracks formed in the macroscopic structure of tablets did not influence our evaluation regarding the intraparticle pore size region. A similar trend was seen with compressed powder samples (hydraulic press; pressure, 3.5 ton). The sample immersed in water (curve C) clearly bore greater resemblance to the control sample than the dry sample of compressed cellulose powder (curve B).

Expansion of deformed ACP agglomerates, at least to some extent, evidently occurred in water. Even limited expansion of deformed agglomerates towards their original spherical shape might have created stresses and strains inside the tablet resulting in the formation of visual cracks.

Conclusions

The agglomerated cellulose powder was a more effective disintegrant in water-insoluble tablet base than the microcrystalline celluloses, Avicel PH 101 and Emcocel, but not as effective as strongly

swelling sodium carboxymethylcellulose, AcDiSol. Microcrystalline cellulose is known to act as a disintegrant by accelerating water penetration into tablets. The rates of both water penetration and tablet expansion were quite similar for tablets containing agglomerated cellulose powder and those with microcrystalline celluloses. However, total water uptake as well as the maximum expansion of tablets were markedly greater for tablets containing ACP, suggesting a different kind of disintegration mechanism for agglomerated cellulose powder. The possible mechanisms of disintegration in the case of the agglomerated cellulose powder are (i) its ability to accelerate water penetration into tablets, (ii) a pronounced effect of water due to the great amount of hydrogen bonds susceptible to being broken by water and (iii) the expansion of deformed agglomerates. The disintegration mechanism for the agglomerated cellulose powder could thus be described as intermediate between those of strongly swelling crosslinked sodium carboxymethylcellulose and microcrystalline cellulose.

Acknowledgements

The authors express their gratitude to Mr. Esa Muttonen, Orion Pharmaceutica, for assistance in elemental analysis, Mr. Jukka Ilkka for skilful technical assistance and Finnish Sugar Ltd for the supply of cellulose materials. T.P. thanks The Medica Research Foundation for financial support.

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