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Effect of Microcrystalline Cellulose on Liquid Penetration in and Disintegration of Directly Compressed Tablets

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Abstract □ The penetration of isooctane and water into tablets of microcrystalline cellulose, dibasic calcium phosphate dihydrate, spray-crystallized maltose–dextrose, and blends of microcrystalline cellulose with one of the other excipients were studied. The isooctane penetrations occurred according to the Washburn equation and were not affected by the presence of 0.5 or 1.0% magnesium stearate. The inhibition of aqueous penetration into tablets resulting from hydrophobic magnesium stearate was less pronounced for vehicles like dibasic calcium phosphate, which exhibited extensive brittle fracture under compression. Microcrystalline cellulose tablets, both with and without magnesium stearate, exhibited extremely fast aqueous penetration even at low porosities, caused by breaking of the hydrogen bonds and subsequent widening of the pores. Ratios between water uptake and original pore volume up to 20 were obtained for microcrystalline cellulose tablets. This unique property was, however, suppressed by the presence of fast dissolving and highly soluble excipients like dextrose, resulting in an antagonistic disintegration behavior of tablets compressed at pressures over 10,000 N/cm². Improved disintegration properties were obtained by blending microcrystalline cellulose with an insoluble vehicle such as dibasic calcium phosphate dihydrate.

Keyphrases □ Cellulose, microcrystalline—effect on liquid penetration and disintegration of directly compressed tablets □ Penetration, liquid—isooctane and water into directly compressed tablets, effect of microcrystalline cellulose □ Disintegration—directly compressed tablets, effect of microcrystalline cellulose □ Tablets, directly compressed—liquid penetration and disintegration, effect of microcrystalline cellulose □ Excipients, tablet—microcrystalline cellulose, effect on liquid penetration and disintegration of directly compressed tablets

Cellulose was prepared previously in a microcrystalline form having unique properties as a directly compressible tablet vehicle (1). Its disintegration behavior was attributed (2, 3) to the entrance of water into the tablet matrix by capillary forces and subsequent breaking of hydrogen bonds. The hypothesis that hydrogen bonds determine both mechanical strength and disintegration of microcrystalline cellulose tablets was confirmed using a deuterium exchange technique (4).

BACKGROUND

Microcrystalline cellulose was suggested to be useful as a disintegrating agent when used in a proportion of at least 20% (5). One study (6) found that the disintegration properties of microcrystalline cellulose were extremely pressure dependent, and the material was relatively ineffective as a disintegration agent in insoluble, direct compression systems. Microcrystalline cellulose appeared, however, to be a useful complementary disintegrant. The disintegration time of tablets of a cation-exchange resin was reduced significantly in the presence of microcrystalline cellulose (6).

A similar synergistic effect was also reported (7). Tablets containing microcrystalline cellulose and corn starch showed a shorter disintegration time than those containing the disintegrating agent alone. It was suggested that microcrystalline cellulose accelerated water penetration and, thus, swelling of the corn starch.

The penetration rate of a liquid into a porous structure is dependent on the balance between capillary and opposing viscous forces and is given by:

$$L^2 = \frac{2m\,\gamma\cos\theta}{k_0\eta}\,t \qquad \text{(Eq. 1)}$$

where L is the penetrated length at time t, m is the hydraulic pore radius, γ is the surface tension of the liquid, θ is the contact angle between liquid and solid, η is the liquid viscosity, and k_0 is a constant dependent on pore shape. If the total cross-sectional area of the pores does not vary with

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Table I—Compression Force, Tablet Porosity, Calculated Pore Volume, Volumetric Isooctane Uptake, and Ratio of Volumetric Isooctane Uptake and Calculated Pore Volume of the Tablets from Figs. 1 and 2

Formulation	Compression Force, N	Porosity, %	Calculated Pore Volume, cm^3	Volumetric Uptake, cm^3	Ratio of Volumetric Uptake and Calculated Pore Volume
Microcrystalline cellulose	4700	20.3	0.082	0.078	0.95
Dibasic calcium phosphate dihydrate	7900	20.8	0.057	0.053	0.93
Spray-crystallized maltose–dextrose	3400	20.2	0.084	0.068	0.81
Microcrystalline cellulose plus 0.5% magnesium stearate	4700	20.0	0.082	0.078	0.95
Dibasic calcium phosphate dihydrate plus 0.5% magnesium stearate	7900	21.2	0.059	0.055	0.93
Spray-crystallized maltose–dextrose plus 1.0% magnesium stearate	2600	20.4	0.084	0.071	0.85

length, the volume of liquid taken up by a tablet will be proportional to the length of penetration. Therefore, the relationship between the square of volumetric uptake and time is linear (8).

Ganderton and coworkers (9–12) studied liquid penetration of tablets by cyclohexane and water. Highly permeable tablets allowed rapid penetration of the liquid, which isolated a large fraction of the total pore space and resulted in low final degrees of saturation; less permeable tablets became fully saturated. Addition of starch had no significant effect on the pore structure of the tablet but disrupted and altered the structure when penetrated by water (10).

In a study of the effect of magnesium stearate distribution on water penetration, Ganderton (9) reported a large depression of the aqueous penetration rate in the presence of magnesium stearate. The increase in penetration time was roughly proportional to the magnesium stearate concentration and was susceptible to the method of mixing. This finding suggested a proportional increase in the internal surface of the tablet containing magnesium stearate and in the number of capillaries unable to conduct water. The cyclohexane penetration, which freely wets the lubricant, was not inhibited by magnesium stearate.

Previously (13), various excipients were evaluated for tableting by direct compression. The excipients studied could be classified roughly into disintegrating agents with poor flowability (microcrystalline cellulose and directly compressible starch) and into free flowing vehicles exhibiting no disintegration (dibasic calcium phosphate) or disintegration by dissolution (lactose and dextrose). To optimize the characteristics for direct compression, excipients from the group with disintegrant properties were blended with excipients from the group with free flowing properties (14). Blending these excipients resulted, however, in synergism or antagonism in disintegration.

The objectives of the present investigation were to study the effect of microcrystalline cellulose on water penetration into tablets compressed from an insoluble or a soluble directly compressible excipient and to elucidate the difference in disintegration efficiency of this material in different systems.

EXPERIMENTAL

Materials—The directly compressible materials used were microcrystalline cellulose[1], unmilled dibasic calcium phosphate dihydrate[2], and spray-crystallized maltose–dextrose[3]. Dextrose[4] (Ned. Pharm. grade), magnesium stearate[5] (Ph. Ned. grade) (a lubricant), and isooctane[6] (analytical grade) also were used.

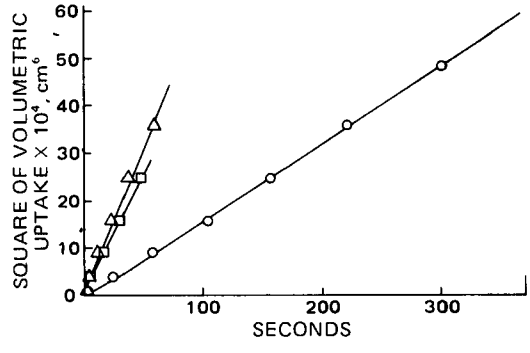

Figure 1—*Isooctane penetration into tablets compressed from dibasic calcium phosphate dihydrate (□), spray-crystallized maltose-dextrose (△), and microcrystalline cellulose (○). Tablet porosity was about 20%.*

Methods—*Mixing*—The excipients were mixed, with (0.5 or 1.0%) or without magnesium stearate, by blending 300 g of material in a 3.4-cubic liter tumbling mixer at 60 rpm for 15 min.

Tablet Compression—Tablets, 9 mm in diameter, were prepared by introducing, manually, 250 or 500 mg of the excipient or blend into the die of a flat-faced punch and die system. The die was prelubricated by careful dusting with magnesium stearate. The punch and die system was mounted between the plattens of an instrumented hydraulic press[7] and loaded at different forces with a compression rate of 2000 N/sec. When the desired force was attained, the crosshead was reversed at the same speed as the compaction process.

The tablets were manually ejected from the die, using a PVC-punch. The porosity and pore volume of a tablet were calculated from its weight and volume and the density of the blend, as measured with an air comparison pycnometer[8].

Crushing Strength—The crushing strength of the tablets was determined immediately after compression by placing the tablets diametrically between the plattens of an instrumented hydraulic press[7] and applying a loading rate of 50 N/sec.

Liquid Penetration—The rate at which liquid penetrated into a tablet was measured by placing the tablet on the glass filter plate of a modified thermostated penetration apparatus, as originally described by Enslin (15). The liquid uptake rate was read from the graduated pipet. Penetrations were carried out with isooctane at 0 ± 0.5° and with water at 37 ± 0.5°. Corrections were made for liquid evaporation. The penetrations and porosity data given are the means of at least five measurements.

Wettability—The wettability of the excipients and blends was characterized by contact angle determinations, as described previously (16).

RESULTS AND DISCUSSION

Figure 1 shows isooctane penetration at 0° into 500-mg tablets of mi-

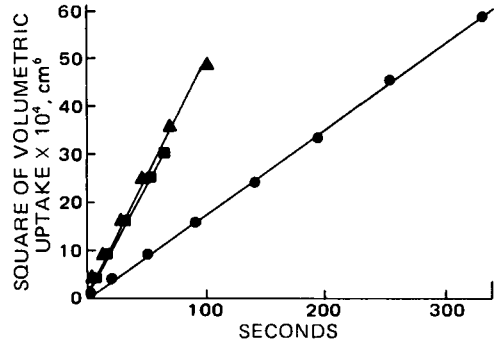

Figure 2—*Isooctane penetration into tablets compressed from dibasic calcium phosphate dihydrate plus 0.5% magnesium stearate (■), spray-crystallized maltose-dextrose plus 1.0% magnesium stearate (▲), and microcrystalline cellulose plus 0.5% magnesium stearate (●). Tablet porosity was about 20%.*

[1] Avicel PH 101, American Viscose Division, FMC Corp., Marcus Hook, Pa.
[2] Emcompress, Edward Mendell Co., New York, N.Y.
[3] Emdex, Edward Mendell Co., New York, N.Y.
[4] Lamers en Indemans, 's-Hertogenbosch, The Netherlands.
[5] Chem. Fabriek Dr. O. Breyer, Venlo, The Netherlands.
[6] E. Merck, Darmstadt, West Germany.
[7] Hydro Mooi, Appingedam, The Netherlands.
[8] Model 930, Beckman Instruments, Fullerton, Calif.

Table II—Compression Force, Tablet Porosity, Calculated Pore Volume, Volumetric Water Uptake, and Ratio of Volumetric Water Uptake and Calculated Pore Volume of the Tablets from Figs. 3–6

Formulation	Compression Force, N	Porosity, %	Calculated Pore Volume, cm^3	Volumetric Uptake, cm^3	Ratio of Volumetric Uptake and Calculated Pore Volume
Microcrystalline cellulose	4,700	20.6	0.042	0.220	5.2
Microcrystalline cellulose plus 0.5% magnesium stearate	4,700	19.7	0.039	0.220	5.6
Microcrystalline cellulose	20,000	5.1	0.009	0.175	19.4
Microcrystalline cellulose plus 0.5% magnesium stearate	20,000	6.1	0.010	0.175	17.5
Microcrystalline cellulose	19,000	5.5	0.010	0.175	17.5
Microcrystalline cellulose plus 0.5% magnesium stearate	30,000	5.5	0.010	0.175	17.5
Dibasic calcium phosphate dihydrate	7,900	20.2	0.056	0.053	0.95
Dibasic calcium phosphate dihydrate plus 0.5% magnesium stearate	7,900	20.9	0.057	0.039	0.68
Dibasic calcium phosphate dihydrate	20,000	15.3	0.039	0.039	1.00
Dibasic calcium phosphate dihydrate plus 0.5% magnesium stearate	20,000	14.9	0.038	0.032	0.84
Spray-crystallized maltose–dextrose	3,400	19.5	0.080	0.140	1.75
Spray-crystallized maltose–dextrose plus 1.0% magnesium stearate	2,600	19.5	0.080	0.030	0.37
Spray-crystallized maltose–dextrose	20,000	2.7	0.005	0	0
Spray-crystallized maltose–dextrose plus 1.0% magnesium stearate	20,000	3.4	0.006	0	0

crocrystalline cellulose, dibasic calcium phosphate dihydrate, or spray-crystallized maltose–dextrose, all having a porosity of about 20%. Table I summarizes compression force, porosity, calculated pore volume, volumetric uptake, and ratio between uptake and pore volume data. A linear relation was obtained between the square of the volumetric uptake and time. This result is in accordance with the Washburn equation, as expected, because isooctane does not loosen bonds between particles, keeping the pore structure constant during penetration.

The dextrose and dibasic calcium phosphate tablets exhibited a higher penetration rate than the microcrystalline cellulose tablets, indicating that the latter had smaller pores. The penetration rate was hardly influenced by magnesium stearate (Fig. 2), because of complete wetting of the excipients and of magnesium stearate by isooctane. Consequently, all tablets became almost saturated (Table I). These results are in agreement with the work of Ganderton (9), who reported that cyclohexane uptake into magnesium carbonate tablets was not affected by magnesium stearate.

Water penetration into tablets containing no lubricant is presented in Fig. 3. A linear relationship existed between the square of volumetric uptake and time only for the dibasic calcium phosphate tablets. The patterns of aqueous penetration into the dextrose and microcrystalline cellulose tablets were quite different. The increased penetration rate of water into dibasic calcium phosphate tablets, compared with the isooctane penetration, was mainly caused by the higher surface tension of water.

The rate at which water entered the dibasic calcium phosphate tablets strongly decreased when the excipient was blended with 0.5% magnesium stearate and compressed to a porosity of about 20% (Fig. 4). Magnesium stearate molecules are sheared off from their crystal surface during a mixing process and are attached to a substrate surface (17, 18). Therefore, a hydrophilic dibasic calcium phosphate surface, exhibiting a contact angle of 0°, can be transformed into a strongly hydrophobic surface, exhibiting a contact angle of about 120°, which corresponds to the contact angle of magnesium stearate (16). This change in surface characteristics can be nullified, however, by fracture of crystalline material during compaction with the creation of clean lubricant-free surfaces. The smaller decrease in the penetration rate found for tablets compressed at a higher compaction force after blending with 0.5% magnesium stearate (Fig. 4) could, therefore, be expected from the compaction behavior of dibasic calcium phosphate, which exhibits an extensive brittle fracture (19).

The ratio between volumetric uptake and calculated pore volume of the tablets is given in Table II. The ratios obtained for the plain dibasic calcium phosphate tablets indicate saturation of the tablets whereas the tablets containing magnesium stearate were less saturated. The observation of an increased saturation with an increase in compaction pressure for the tablets blended prior to compression with magnesium stearate is consistent with the behavior of brittle fracture during compaction.

Spray-crystallized maltose–dextrose tablets showed extremely high penetration rates during the early stages of penetration, but these rates decreased rapidly with time (Fig. 3). The volumetric uptake of the tablets was greater than the calculated pore volume (Table II). The fact that both the initially increased penetration rate and the water uptake were higher than the pore volume was probably caused by the dissolution of the freely soluble dextrose during the penetration process, resulting in wider pores and an increased pore volume. Dissolution, however, sharply increased

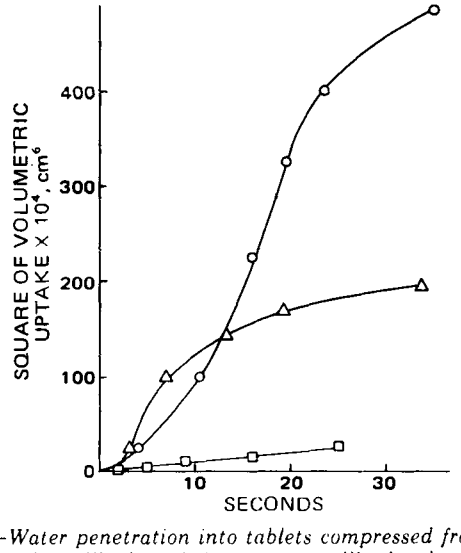

Figure 3—*Water penetration into tablets compressed from dibasic calcium phosphate dihydrate (□), spray-crystallized maltose–dextrose (△), and microcrystalline cellulose (○). Tablet porosity was about 20%.*

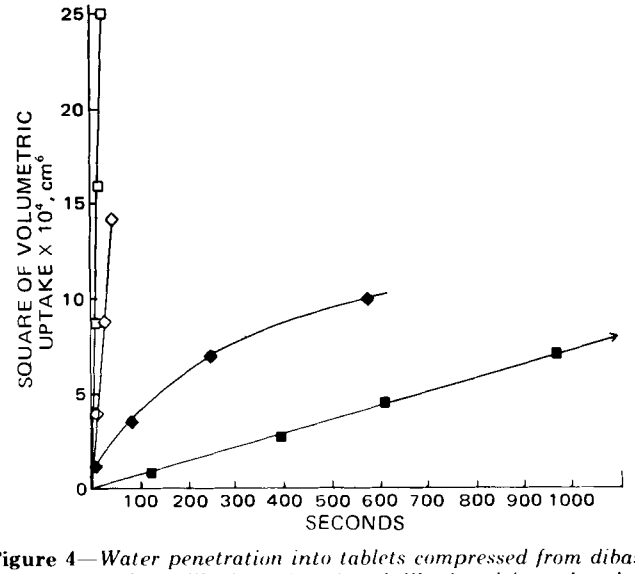

Figure 4—*Water penetration into tablets compressed from dibasic calcium phosphate dihydrate (□, ◇) and dibasic calcium phosphate dihydrate plus 0.5% magnesium stearate (■, ◆). Tablet porosities were about 20% (□, ■) and about 15% (◇, ◆).*

Table III—Compression Force, Tablet Porosity, Calculated Pore Volume, Volumetric Water Uptake, and Ratio of Volumetric Water Uptake and Calculated Pore Volume of the Tablets from Figs. 9 and 10

Formulation[a]	Compression Force, N	Porosity, %	Calculated Pore Volume, cm^3	Volumetric Uptake, cm^3	Ratio of Volumetric Uptake and Calculated Pore Volume
Dibasic calcium phosphate dihydrate (I)	5,000	24.7	0.036	0.015	0.42
I plus 10% microcrystalline cellulose	5,000	23.9	0.036	0.036	1.00
I plus 20% microcrystalline cellulose	5,000	23.7	0.037	0.070	1.90
I plus 40% microcrystalline cellulose	5,000	22.4	0.037	0.120	3.24
Microcrystalline cellulose	5,000	19.7	0.038	0.220	5.3
I	20,000	14.9	0.019	0.018	0.95
I plus 10% microcrystalline cellulose	20,000	12.9	0.017	0.028	1.65
I plus 20% microcrystalline cellulose	20,000	10.5	0.014	0.060	4.28
I plus 40% microcrystalline cellulose	20,000	7.9	0.011	0.100	9.1
Microcrystalline cellulose	20,000	6.1	0.010	0.175	17.5

[a] All formulations contained 0.5% magnesium stearate.

the viscosity of the penetrating liquid, which resulted in a slowdown in the penetration rate.

Water penetration into the dextrose tablets with a porosity of 20% was dramatically inhibited by 1% magnesium stearate and even stopped before saturation of the tablet (Fig. 5 and Table II). Low porosity tablets compressed at 20,000 N, both with and without magnesium stearate, were not penetrated by water at all because of the extremely small pores and dissolution of dextrose.

Microcrystalline cellulose tablets (Fig. 3) showed extremely high penetration rates, which were almost constant (Fig. 6). Furthermore, the tablets, having a porosity of about 20%, exhibited a volumetric uptake about five times higher than the calculated pore volume (Table II); the ratio between uptake and pore volume was about 20 for the tablets with an initial porosity of about 5%. Because of the laminary cracking of 500-mg tablets when penetrated with water, these microcrystalline cellulose tablets were compressed from 250 mg of material, giving lower calculated pore volumes than for the tablets penetrated with isooctane (Table I).

The linearity between the volumetric water uptake and time for the microcrystalline cellulose tablets (Fig. 6) indicates that the capillary force driving the liquid into the tablet is opposed by a constant viscous resistance. A constant viscous resistance can only be realized, however, if the hydraulic radius of the capillaries increases during penetration. Since the binding between microcrystalline cellulose particles is attributed to hydrogen bonds, a fairly constant volumetric penetration rate into these tablets may be explained by the breaking of the hydrogen bonds immediately behind the penetration front and a subsequent increase in the penetrated pore volume. This concept is consistent with the high ratio between water uptake and original pore volume (Table II).

Moreover, observation of the tablet during penetration showed swelling of the penetrated part of the tablet, which was completed when water uptake had finished. In accordance with the findings of Nogami *et al.* (7), swelling of the individual microcrystalline cellulose particles as proposed by Fox *et al.* (2) could not be established. The effect of hydrophobic magnesium stearate on the penetration of water into microcrystalline cellulose tablets is shown in Fig. 6 for different porosities. The 0.5% magnesium stearate decreased the penetration rate into the tablets having a porosity of about 20%. The tablets compressed at a force of 20,000 N exhibited a porosity of 5.1 and 6.1% when compressed without and with 0.5% magnesium stearate, respectively. The increased porosity was caused by an increased relaxation of the tablet when compacted in the presence of magnesium stearate. Because of this relaxation, it was not possible to produce tablets with a porosity of 5.1% from a blend containing 0.5% magnesium stearate. The lowest porosity obtained was 5.5%, and it was reached with a compaction force of 30,000 N or higher. Comparison of lubricated and nonlubricated microcrystalline cellulose tablets with a porosity of 5.5% showed a decreased penetration rate for the lubricated tablets.

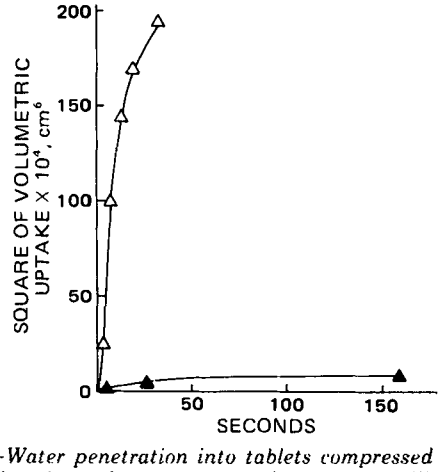

Figure 5—*Water penetration into tablets compressed from spray-crystallized maltose-dextrose (△) and spray-crystallized maltose-dextrose plus 1.0% magnesium stearate (▲). Tablet porosity was about 20%.*

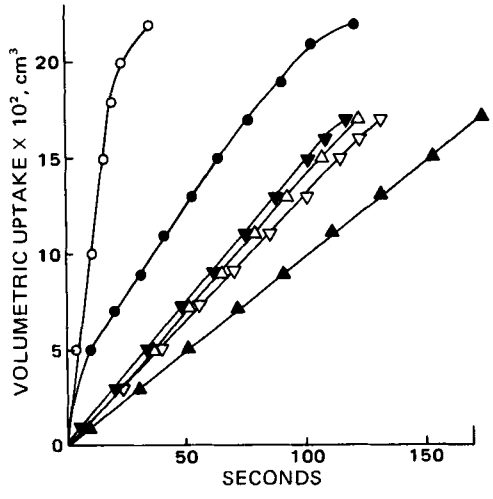

Figure 6—*Water penetration into tablets compressed from microcrystalline cellulose (○,▽,△) and microcrystalline cellulose plus 0.5% magnesium stearate (●,▼,▲). Tablet porosities were about 20% (○,●), 5.5% (△,▲), 5.1% (▽), and 6.1% (▼).*

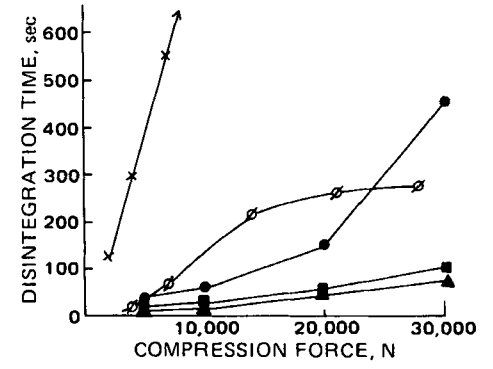

Figure 7—*Disintegration time* versus *applied compression force for tablets compressed from dibasic calcium phosphate dihydrate (×), microcrystalline cellulose (Ø), and blends of dibasic calcium phosphate with 10 (●), 20 (■), and 40% (▲) microcrystalline cellulose. All tablets contained 0.5% magnesium stearate.*

Table IV—Compression Force, Tablet Porosity, Calculated Pore Volume, Volumetric Water Uptake, and Ratio of Volumetric Water Uptake and Calculated Pore Volume of the Tablets from Figs. 11 and 12

Formulation[a]	Compression Force, N	Porosity, %	Calculated Pore Volume, cm^3	Volumetric Uptake, cm^3	Ratio of Volumetric Uptake and Calculated Pore Volume
Spray-crystallized maltose–dextrose (II)	5,000	13.1	0.025	0.014	0.56
II plus 10% microcrystalline cellulose	5,000	13.9	0.026	0.033	1.27
II plus 20% microcrystalline cellulose	5,000	15.9	0.031	0.042	1.35
II plus 40% microcrystalline cellulose	5,000	17.7	0.036	0.163	4.52
Microcrystalline cellulose	5,000	19.7	0.039	0.230	5.9
II	20,000	3.4	0.006	0	0
II plus 10% microcrystalline cellulose	20,000	3.8	0.006	0	0
II plus 20% microcrystalline cellulose	20,000	4.1	0.007	0.005	0.70
II plus 40% microcrystalline cellulose	20,000	5.1	0.009	0.023	2.55
Microcrystalline cellulose	20,000	6.3	0.010	0.190	19.0

[a] All formulations contained 1.0% magnesium stearate.

The penetration measurements presented were performed, as an extension of previous investigations (14), to elucidate the difference in disintegration behavior of the tablets compressed from dibasic calcium phosphate dihydrate–microcrystalline cellulose and from spray-crystallized maltose–dextrose–microcrystalline cellulose blends. Figures 7 and 8 [abstracted from previous work (14)] show a synergistic behavior in disintegration time for the dibasic calcium phosphate–microcrystalline cellulose tablets but an antagonistic behavior for the dextrose–microcrystalline cellulose tablets.

The plain dibasic calcium phosphate tablets, lubricated with 0.5% magnesium stearate, exhibited extremely low penetration rates for compaction forces of 5000 and 20,000 N (Figs. 9 and 10, respectively). When compressed at low compaction forces, the tablets disintegrated because of mechanical damage caused by the disks used for the USP disintegration test. At compaction forces over 10,000 N, the tablets did not disintegrate at all.

Addition of microcrystalline cellulose to the dibasic calcium phosphate strongly increased penetration rates (Figs. 9 and 10). The increased rates were caused by the breaking of the hydrogen bonds between the microcrystalline particles and the subsequent increase in pore volume, expressed by increasing ratios between volumetric water uptake and original pore volume with increasing amounts of microcrystalline cellulose (Table III). This behavior explains the extremely short disintegration time (Fig. 7) for the tablets compressed from dibasic calcium phosphate–microcrystalline cellulose blends. The relatively longer disintegration time for the plain microcrystalline cellulose tablets may be attributed to the maximal number of hydrogen bonds, characterized by a crushing strength of 34 kg for the tablets compacted at a force of 20,000 N in the presence of 0.5% magnesium stearate.

The tablets compressed from dextrose–microcrystalline cellulose blends showed a completely different disintegrating behavior. These tablets were compressed in the presence of 1.0% magnesium stearate to obtain acceptable ejection forces (14). The plain dextrose tablets did not disintegrate but were dissolved by the high solubility of the excipient. The plain tablets compressed at 5000 N exhibited liquid penetration at the early stages of penetration only (Fig. 11). Penetration ceased by fast dissolution of the dextrose, resulting in increasing liquid viscosities in the pores. For these relatively porous tablets, addition of 10% microcrystalline cellulose (w/w) only slightly increased the penetration rate during the early stages. There was, however, a considerable increase in volumetric water uptake (Table IV).

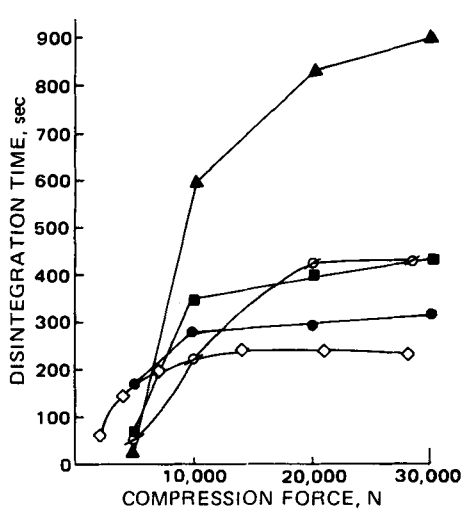

Figure 8—*Disintegration time* versus *applied compression force for tablets compressed from spray-crystallized maltose–dextrose (◇), microcrystalline cellulose (∅), and blends of spray-crystallized maltose–dextrose with 10 (●), 20 (■), and 40% (▲) microcrystalline cellulose. All tablets contained 1.0% magnesium stearate.*

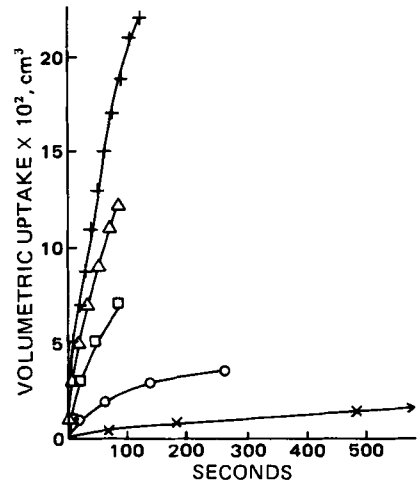

Figure 9—*Water penetration into tablets compressed from dibasic calcium phosphate dihydrate (×), microcrystalline cellulose (+), and blends of dibasic calcium phosphate dihydrate with 10 (○), 20 (□), and 40% (△) microcrystalline cellulose. Compression force was 5000 N. All tablets contained 0.5% magnesium stearate.*

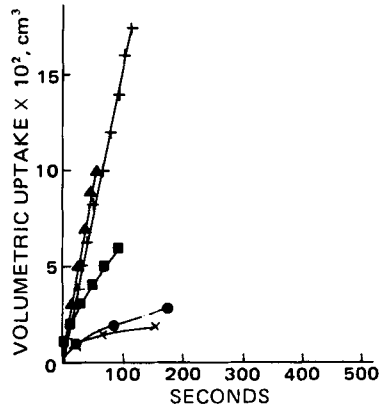

Figure 10—*Water penetration into tablets compressed from dibasic calcium phosphate dihydrate (×), microcrystalline cellulose (+), and blends of dibasic calcium phosphate dihydrate with 10 (●), 20 (■), and 40% (▲) microcrystalline cellulose. Compression force was 20,000 N. All tablets contained 0.5% magnesium stearate.*

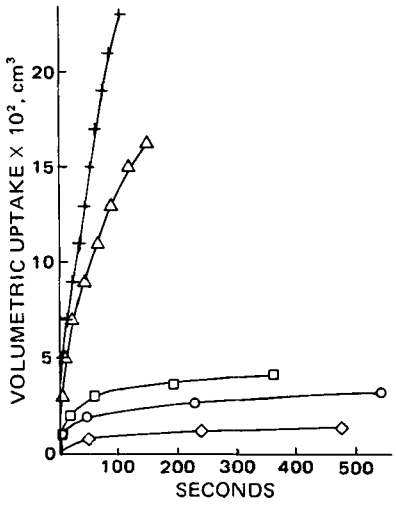

Figure 11—*Water penetration into tablets compressed from spray-crystallized maltose-dextrose (◊), microcrystalline cellulose (+), and from blends of spray-crystallized maltose-dextrose with 10 (○), 20 (□), and 40% (△) microcrystalline cellulose. Compression force was 5000 N. All tablets contained 1.0% magnesium stearate.*

The increase in the ratio between liquid uptake and original pore volume was due to increasing pore volumes during penetration caused by the microcrystalline cellulose. The addition of 40% microcrystalline cellulose resulted in strongly increased penetration rates. These high penetration rates may be attributed to the masking of the dextrose by the microcrystalline cellulose, reducing its dissolution velocity, and the enlargement of the pores. The penetration characteristics obtained were consistent with the disintegration behavior of the tablets compressed at 5000 N. The disintegration time decreased with increasing amounts of microcrystalline cellulose (Fig. 8).

Compaction of the spray-crystallized maltose-dextrose at a force of about 20,000 N gave tablets that exhibited no water penetration at all. Addition of 10% microcrystalline cellulose to the dextrose also resulted in tablets that showed no water penetration. A comparison of the disintegration of plain dextrose tablets with tablets containing 10% microcrystalline cellulose showed slightly longer disintegration times for the latter when compressed at forces over 10,000 N (Fig. 8). Since the dextrose tablets did not really disintegrate but rather dissolved, the increased disintegration time may be ascribed to the masking of the dextrose by the microcrystalline cellulose.

Addition of 20 or even 40% microcrystalline cellulose to the dextrose gave tablets that exhibited only a slight penetration (Fig. 12). The small pores of the tablets, compressed at 20,000 N, indicated low initial penetration rates through which a concentrated dextrose solution was created in the pores by dissolution of the highly soluble excipient. The effect of

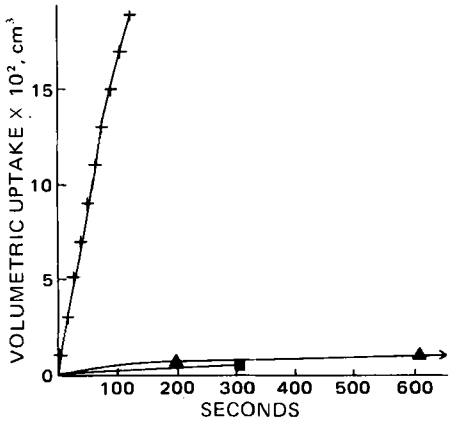

Figure 12—*Water penetration into tablets compressed from microcrystalline cellulose (+) and blends of spray-crystallized maltose-dextrose with 20 (■) and 40% (▲) microcrystalline cellulose. Compression force was 20,000 N. All tablets contained 1.0% magnesium stearate.*

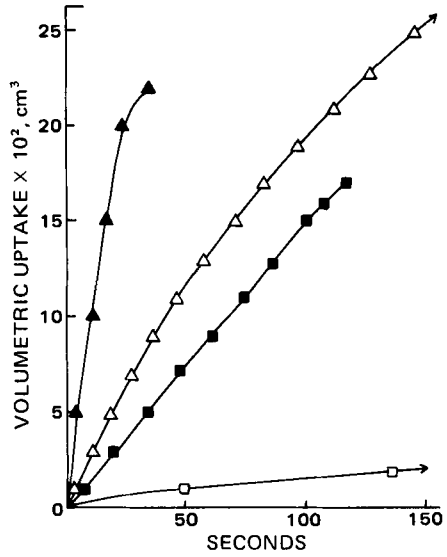

Figure 13—*Penetration into tablets compressed from microcrystalline cellulose using water (▲,■) and a 50% (w/w) dextrose solution (△,□) as the penetrating liquid. Compression forces were 5000 (▲,△) and 20,000 (■,□) N.*

widening of the pores by microcrystalline cellulose during penetration was suppressed, as confirmed by the results shown in Fig. 13. The penetration rate in microcrystalline cellulose tablets was markedly affected by the concentration of the penetrating dextrose solution, especially for the low porosity tablets. Thus, the low porosity dextrose-microcrystalline cellulose tablets exhibited low penetration rates even in the early stages of penetration. The antagonistic behavior of increasing disintegration times (Fig. 8) with increasing amounts of microcrystalline cellulose, when compressed at forces over 10,000 N, can consequently be explained by the masking action of the microcrystalline cellulose on the dissolving dextrose surface and the suppressive action of a dextrose solution on the pore-enlarging effect of the microcrystalline cellulose.

In conclusion, microcrystalline cellulose exhibits, in addition to its high dry binding capacity, extremely fast aqueous penetration into compacts. This behavior is caused by a widening of the pores during penetration. Ratios between water uptake and original pore volume of up to about 20 were obtained for microcrystalline cellulose tablets. This unique property is, however, suppressed by fast dissolving and highly soluble excipients such as dextrose, resulting in an antagonistic disintegration behavior. Improved disintegration properties are obtained by blending microcrystalline cellulose with an insoluble vehicle such as dibasic calcium phosphate dihydrate.

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Preparation and Evaluation of Microencapsulated Ion-Exchange Resin Beads

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Abstract □ Ion-exchange resin beads in the benzoate form were coated by several microencapsulation techniques to alter and improve characteristics, especially the control of drug release, of this type of drug delivery system. The most successful techniques included polymer–polymer interaction, temperature change, and nonsolvent addition. The microencapsulated beads then were studied with respect to the release rate of the organic anion to determine the effects of microencapsulation. The release rate of the organic anion could be controlled over a wide range, depending on the encapsulating material characteristics. Factors affecting the extent and rate of release as a result of microencapsulation are discussed.

Keyphrases □ Microencapsulated ion-exchange resin beads—prepared by various methods, evaluated for release rate □ Ion-exchange microencapsulated resin beads—prepared by various methods, evaluated for release rate □ Delivery systems—microencapsulated ion-exchange resin beads, prepared by various methods, evaluated for release rate □ Dosage forms, potential—microencapsulated ion-exchange resin beads, prepared by various methods, evaluated for release rate

Ion-exchange resins function as effective carriers for prolonging drug release for sustained biological action and for improvement of other pharmacokinetic parameters such as the absorption rate constant (1). In addition, ion-exchange resins are used for binding biological materials such as bile salts and sodium ions within the GI tract (2, 3). While ion-exchange resins form a useful drug delivery system, improvements can be effected in some cases by coating the resin beads with various pharmaceutical adjuvants. Potential improvements are: enhancing the taste of ion-exchange resins (4, 5), decreasing the release rate of drugs from the resins (5, 6), permitting greater saturation of the resin with the drug and a slower elution rate (6), minimizing elution of drug in liquid preparations of ion-exchange resin–drug complexes (6, 7), and minimizing interaction of drugs with resins used as tablet disintegrants (8).

One effective and versatile method of coating small solid particles is microencapsulation, which can be accomplished with various procedures (5, 9, 10). Many researchers discussed the encapsulation of solid particles (11–16), but few applied the process to ion-exchange resins (4, 17). It was deemed appropriate to investigate microencapsulation procedures for the preparation of coated ion-exchange resins to exploit the value of resin beads, such as uniform size and consistent binding of drugs, for improving their pharmaceutical characteristics. Specifically, it was expected that medication with a wide range of prolonged-release characteristics could be prepared. In addition, it was hoped that a uniform coat around the beads could be obtained by various encapsulation methods.

The effect of additives on the characteristics of the film used to coat pharmaceuticals also was investigated. In some cases, additives selected are of such a nature that the rate of transmission or release of drugs is increased (12, 18) or decreased (19). Part of the present research is concerned with employing additives in the preparation of the microencapsulating film to prolong or delay the release so that the coated beads can be considered for other uses in pharmacy besides oral medication.

EXPERIMENTAL

Materials—All experiments were carried out with a 20–50-mesh strongly basic ion-exchange resin[1] in the benzoate form. The resin was screened wet; the beads that passed through a 35-mesh screen but were retained on a 40-mesh screen were used. The resin then was cleaned, conditioned, and converted into the benzoate form by the procedure described previously (20). The average particle size of the resin beads, as determined by microscopic measurement of 30 beads, was 0.366 mm (wet) and 0.325 mm (dry).

Encapsulation Procedures—*Polymer–Polymer Interaction*—The method of Luzzi and Gerraughty (14, 21), adapted from Green and Schleicher (22, 23), was modified for the encapsulation of the resin beads. In this method, the interaction of oppositely charged polyelectrolytes results in the formation of a complex of considerably reduced solubility such that phase separation occurs. The specific procedure used consisted of dissolving 3 g of acacia[2] and 3 g of gelatin[3] separately in 100 ml of distilled water each. The solutions were warmed to 55° and mixed, and the pH was adjusted to 6.5 with 20% NaOH. The resin beads (2 g) then were added, and the pH of the mixture was altered to 4.5 by the dropwise addition of dilute hydrochloric acid with stirring.

The temperature was allowed to drop, and the polymers coalesced around the resin beads. Subsequently, 10 ml of formaldehyde solution USP was added, and the mixture was cooled to 10° by immersion in an ice bath with constant stirring. The pH then was adjusted to 9.0 by the dropwise addition of 20% NaOH. The mixture was diluted to approximately 400 ml with distilled water, left overnight, and then centrifuged for 30 min at 2700 rpm.

The supernate was decanted, and the microencapsulated beads were transferred to a 60-mesh screen and washed with water to remove the empty capsules. The capsules remaining on the screen were poured into a flask along with 100 ml of distilled water. After settling, water was removed by rinsing the capsules with three 50-ml portions of 95% ethanol. The mixture was filtered, washed with ethanol, and dried in a desiccator.

Temperature Change—Five methods of preparation were evaluated.

[1] Dowex 1-X8, Dow Chemical Co., Midland, Mich.
[2] Gum Acacia BP, British Drug Houses (Canada) Ltd., Toronto, Canada.
[3] Gelatin, Pharmagel A., American Agricultural Co., Detroit, Mich.

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