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Disintegration of the Aspirin Tablets containing Potato Starch and Microcrystalline Cellulose in Various Concentrations[1,2]

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Aspirin (ASP) tablet containing potato starch (PS) (ASP+PS) generally took a short disintegration time. ASP tablet containing microcrystalline cellulose (MCC) (ASP+MCC) showed an optimum concentration region of MCC to give a minimum disintegration time, while (ASP+PS) did not. From the data of water intake and swelling of the powder beds of PS and MCC, PS was more affinitive to water than MCC, and from the data of capillarity, hardness and disintegration of (ASP+PS) and (ASP+MCC), it was concluded that both the mean capillary diameter and the hardness were not always correlated with the disintegration time.

Taking these results into consideration, the mechanism of tablet disintegration was discussed on the basis of cohesive and adhesive properties of particles. Finally, it might be concluded that the penetration of water into a tablet was necessary for the disintegration as the first step without being sufficient and that the work of dispersion of particles caused through the penetration of water had to overcome the binding work of particles caused through cohesion and adhesion, accordingly giving an optimum mixing ratio of drug and additive, as was shown by (ASP+MCC).

It has been reported that there is an optimum concentration of disintegrating agent for the disintegration of the tablet containing wood products, corn starch, or cellulose,[4] and that the disintegration time is lengthened with the concentration of cellulose disintegrating agents.[5,6]

On the other hand, various discussions have been given of the tablet disintegration phenomena based on such mechanisms as the water absorption of a tablet,[7] the swelling action of disintegrating agents,[8,9] and the penetration of water into the porous structure of a tablet.[10] However, any generalized mechanism has never been known.

The present work was attempted to investigate the difference in the mechanism of disintegration between the tablet containing potato starch (PS) and that containing microcrystalline cellulose (MCC), discussing the cohesive and adhesive properties of the component particles based on the water intake and swelling of powder beds of PS and MCC and on the capillarity and hardness of aspirin (ASP) tablet containing PS or MCC.

1) This paper formes Part XXVIII of "Studies on Powdered Preparations." Preceding paper, Part XXVII: H. Nogami, T. Nagai, and T. Yotsuyanagi, *Chem. Pharm. Bull.* (Tokyo), **17**, 499 (1969).
2) This work was presented at the 88th Annual Meeting of Pharmaceutical Society of Japan, Tokyo, April 1968.
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4) T.A. Fakough, N.F. Billups, and R.W. Sager, *J. Pharm. Sci.*, **52**, 700 (1963).
5) N.F. Billups and B.F. Cooper, *Forest Prod. J.*, **2**, 630 (1962).
6) W. Feinstein and A.J. Bartilucci, *J. Pharm. Sci.*, **55**, 332 (1966).
7) N.F. Billups and B.F. Cooper, *Am. J. Pharm.*, **136**, 25 (1964).
8) N.R. Patel and R.E. Hopponen, *J. Pharm. Sci.*, **55**, 1065 (1966).
9) J.T. Ingram and W. Lowenthal, *J. Pharm. Sci.*, **55**, 614 (1966).
10) H. Nogami, J. Hasegawa, and M. Miyamoto, *Chem. Pharm. Bull.* (Tokyo), **15**, 279 (1967).

Experimental

Materials——Aspirin J.P. VII (ASP) was ground in a mortar with a pestle and sieved, the two parts ASPL and ASPS shown in Table I being used as the samples. Potato starch J.P. VII (PS) and microcrystalline cellulose (MCC) marketed as "Avicel" for medical use by Asahi Kasei Co., Ltd. were used after sieving. Physical properties of the samples are shown in Table I.

Table I. Properties of Powder Samples

	ASPL	ASPS	MCC	PS
Particle size (μ)[a]	840/297	77/44	77/44	77/44
Specific gravity[b]	1.37	1.37	1.56	1.46
Moisture content (%)[c]	0.187	0.187	5.58	16.6
Sedimentation volume (ml/g)[d]	—	—	3.73	1.70
Heat of immersion (cal/g)[e]	—	—	12.1	24.8

a) sieved by the sieves of Japan Industrial Standard
b) measured with a Weld pycnometer replaced with xylene at 37°
c) weight loss after degassing-drying at a room temperature to attain to equilibrium
d) after 24 hr dispersion in 20 ml of distilled water at 37°
e) by an adiabatic bomb calorimeter with a thermister

Measurement of Penetration of Water into Powder Bed——A given amount of powder was packed in a graduated glass tube with a fine silk cloth at the bottom by tapping mechanically to get an equilibrium depth of bed and the measurement was carried out in the same way as described in the previous paper.[11]

Measurement of Water Intake and Swelling of Powder Bed——The apparatus of Baver[12] was modified as shown in Fig. 1. A given amount of powder was packed in a graduated glass tube with a fine silk cloth at the bottom in the same way as described above. The tube and powder were then placed upon the moist glass filter plate, and the intake of water and the swelling of powder bed were measured at a room temperature.

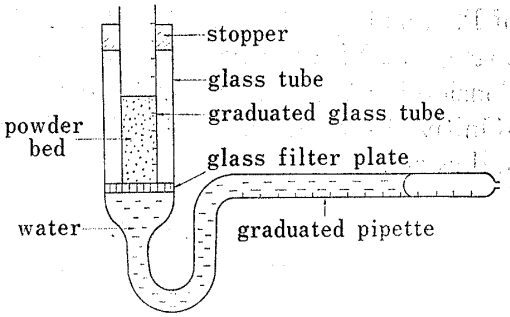

Fig. 1. Apparatus for Measurement of Water Intake and Swelling of Powder Bed

Making of Tablets——1 g of powder was compressed directly by the same operation as described in the previous paper,[10] with a single punch tableting machine Kimura MC-2, equipped with a set of 20 mm flat-faced punch and die. Neither of binder nor lubricant was incorported. The amount of PS or MCC added was changed from 0 to 50%.

Measurement of Disintegration Time of Tablet——The method and apparatus were according to the disintegration test in J.P. VII (or U.S.P. XVII) except that the disintegration time of each tablet was determined.

Measurement of Mean Capillary Diameter of Tablet——According to the air-permeametry method, the measurement was carried out in the same way as described in the previous paper.[13]

Measurement of Hardness of Tablet——A Stokes hardness tester was used for the measurement.

Results and Discussion

Water Intake of Powder Beds of Potato Starch (PS) and Microcrystalline (MCC)

As shown in Table I, the moisture content of MCC was about 1/3 of that of PS, but the sedimentation volume of MCC was twice larger than that of PS. This might indicate that PS was more dispersible in water and more affinitive to water than MCC. Considering that

11) H. Nogami, T. Nagai, and H. Uchida, *Chem. Pharm. Bull.* (Tokyo), **14**, 152 (1966).
12) L.D. Baver, "Soil Physics," 3rd ed., John Wiley & Sons, Inc., New York, 1956, p. 89.
13) H. Nogami, H. Fukuzawa, and Y. Nakai, *Chem. Pharm. Bull.* (Tokyo), **11**. 1389 (1963).

the work of adhesion to water corresponds to the free energy decrease of dispersion of powder, the result of heat of immersion shown in Table I is quite reasonable.

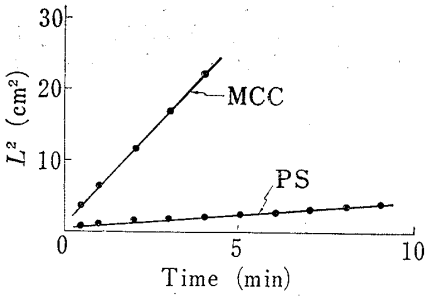

Fig. 2. Penetration of Water into Powder Bed Plotted according to Washburn's Equation

For the rate study of the water intake by powder, the penetration of water into powder bed is shown in Fig. 2, being plotted according to Washburn's equation, *i.e.*,

$$L^2=\frac{r\gamma\cos\theta}{2\eta}t \qquad (1)$$

where L is the penetrating length at time t, r the average radius of void space, θ the contact angle between liquid and powder surface, and γ and η are the surface tension and the viscosity of liquid, respectively. Since the slope of plot for MCC was about 14 times larger than that for PS, it was shown that water penetrated faster into MCC bed than into PS bed, even if the change of r during the penetration was taken into consideration. However, this result seemed to be contradictory to the above result that PS was more affinitive to water than MCC. This problem will be discussed in the following section regarding the swelling of powder bed.

Swelling of Powder Bed by Penetration of Water

The data obtained by the apparatus shown in Fig. 1 are listed in Table II. The equilibrium amount of water intake by MCC apparently was larger than by PS, while the swelling of PS was larger than that of MCC. The water intake by MCC was almost equal to the void space, but PS absorbed water more than its void space and swelled much more than MCC. Considering the fact that water penetrated faster into MCC than into PS though PS was more affinitive to water than MCC, the following mechanism might be proposed for the water intake and swelling.

Table II. Water Intake and Swelling of Powder Beds

	MCC	PS
Water intake (ml/g)[a]	1.39	0.964
Swelling (ml/g)[b]	0.186	0.536
Void space (ml/g)[c]	1.32	0.344

a) equilibrium amount of water intake of the bed
b) volume change of the bed after water intake
c) before water intake

MCC is a crystalline material and thus it may hardly absorb water into its particles, while PS is amorphous in a great part and thus it may absorb water into its particles to cause a very large swelling compared with the void space. Therefore, as shown in Fig. 3, water may penetrate into the powder bed of MCC as a simple capillary phenomenon, while it may be absorbed into the particles of PS during its penetration into the powder bed, resulting in a apparently small penetration rate as shown in Fig. 2.

Relationship between Disintegration Time of Aspirin Tablet and Concentration of Additive

The plots of disintegration time against the concentration of additive are shown in Fig. 4. Generally, the tablet containing MCC took a longer disintegration time than that containing PS. Especially, the tablet of aspirin of small particle size (ASPS) containing MCC (ASPS +MCC) did not disintegrate in the experimental period (60 min). The disintegration time of ASPS tablet containing PS (ASPS+PS) decreased with the concentration of PS, while

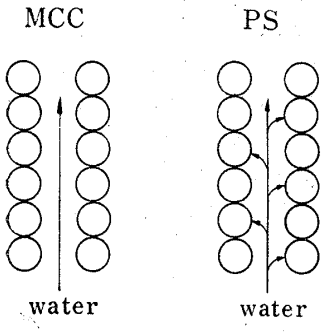

Fig. 3. Schematic Illustration of Water Penetration into Powder Beds of PS and MCC

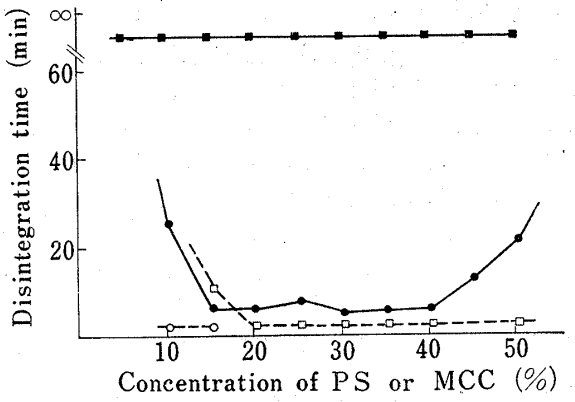

Fig. 4. Relationship between Disintegration Time of Tablet and Concentration of PS or MCC

Each point represents the mean of 6 determinations.
—●—: ASPL+MCC —■—: ASPS+MCC
···○···: ASPL+PS ···□···: ASPS+PS

the tablet of aspirin of larger particle size (ASPL) containing MCC (ASPL+MCC) showed an optimum concentration region of MCC to give a minimum disintegration time.

Effect of Capillarity on Disintegration Time of Aspirin Tablet

The plots of mean capillary diameter against the concentration of additive are shown in Fig. 5. Besides ASPL tablet containing PS (ASPL+PS), the mean capillary diameter was almost constant regardless of the concentration of additive. In the case of ASPL, it was unable to make a tablet containing more than 20% of PS, but the mean capillary diameter was recognized to increase with the concentration of PS in the tabletable region. This corresponded to the result reported in the previous paper[10] that starch could develop the capillary structure in aspirin tablet.

Although (ASPL+MCC) gave the largest mean capillary diameter, it did not always give the shortest disintegration time, as shown in Fig. 4. Moreover, although (ASPS+PS) and (ASPS+MCC) gave about the same mean capillary diameter, they gave remarkably different disintegration times. Therefore, the size of mean capillary diameter was not considered to be important for the disintegration in these cases. In other words, considering the contact angles between water are 84.5° and 68.5° for starch and MCC, respectively,[14] the penetration of water may not always be rate-determinant for the disintegration of tablet.

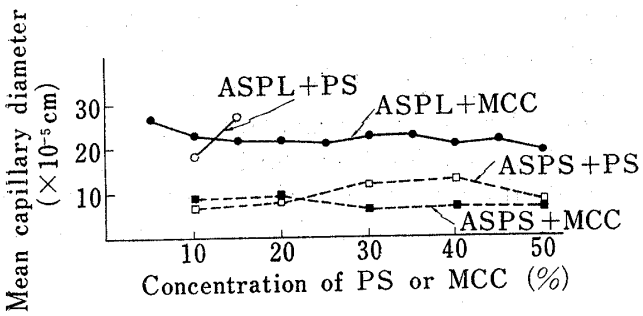

Fig. 5. Relationship between Mean Capillary Diameter of Tablet and Concentration of PS or MCC

Each point represents the mean of 3 determinations.

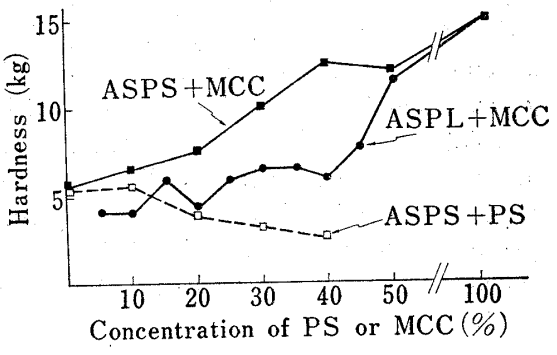

Fig. 6. Relationship between Hardness of Tablet and Concentration of PS or MCC

Each point represents the mean of 3 determinations.

Relationship between Hardness of Tablet and Concentration of Additive

As shown in Fig. 6, PS and MCC had different types of hardening effect on aspirin tablet. The hardness of tablet decreased with the concentration of PS.[15] On the contrary, the hardness increased with the concentration of MCC. Comparing the results shown in Fig. 4 and 6, there was not found any correlation between the hardness and the disintegration time in the case of MCC. Considering that MCC particles have larger cohesive force and inner frictional coefficient than PS or lactose[14] and thus MCC may be more adhesive than PS, it seems reasonable that the hardness of tablet increased with the concentration of MCC. In this connection, it is considered that MCC might take a plastic deformation while PS might take an elastic deformation during the compression.

General Discussion on the Possible Mechanism of Disintegration of ASP Tablet containing PS and MCC

The results obtained will be summarized as follows: for the powder beds, (1) dispersability in water: PS>MCC; (2) amount of water intake per void space: PS>MCC; (3) rate of water penetration: PS<MCC; (4) swelling: PS>MCC; (5) an explanation for the results (1) to (4) was given by Fig. 3; for the tablets, (6) (ASP+PS) generally took a shorter disintegration time than (ASP+MCC); (7) (ASPL+MCC) showed an optimum concentration region of MCC to give a minimum disintegration time, while (ASP+PS) did not; (8) size of mean capillary diameter showed very little effect on the disintegration and then the penetration of water was not considered to be rate-determinant for the disintegration; (9) (ASP+MCC) showed no correlation between the hardness and the disintegration time.

From the results (1) to (4), it was concluded that PS was more affinitive to water than MCC. Therefore, the result (6) corresponded to the report that the disintegration time of a tablet containing powdered corn cob, corn starch, lactose, or starch mixed with MCC decreased with the increase of water absorbability of such disintegrating agents.[1]

It has been reported that the tablet containing a mixture of cellulose and corn starch shows a shorter disintegration time than that containing the respective disintegrating agent only.[1] This may be explained on the consideration that cellulose accelerates the water penetration as is expected from the result shown in Fig. 2 and thus the swelling of corn starch by the water absorbed is also accelerated to cause the tablet disintegration under a suitable mixing ratio of both materials. However, if the concentration of cellulose increases, the cohesive and adhesive work of cellulose may overcome the dispersing work of powder particles, resulting in the difficulty in disintegration. Therefore, the work of cohesion and adhesion of particles should be important to discuss the tablet disintegration.

The result (7) may be explained on the basis of cohesive and adhesive properties of particles as follows. Since MCC is considered to be much more cohesive and adhesive than PS, as the contact area between ASP and MCC increases with the addition of MCC, the binding work between particles may increase, and after a certain concentration of MCC such work may overcome the dispersing work of particles caused by the penetration of water. In other words, when the concentration of MCC is low, water can hardly penetrate into the interior of tablet because of the large contact angle of ASP and thus the tablet can not be disintegrated. As the concentration of MCC increases before the optimum concentration, the resultant increase of penetrability of water may make the disintegration time shorter. Then, over the optimum concentration of MCC, the cohesive and adhesive force of MCC may give effect as a negative force though much water penetrate into the tablet, resulting in a long disintegration time.

14) K. Omura, "Abiseru-Jiho," No. 7, Asahi Kasei Co., Ltd., Tokyo, 1965, p. 2.
15) ASPL tablets containing PS were broken too easily to measure the hardness.
16) C.D. Fox, M.D. Richman, G.E. Reier, and R. Shangraw, *Drug Cosmetic Ind.*, **92**, 161 (1963).
17) G.E. Reier and R.F. Shangraw, *J. Pharm. Sci.*, **55**, 510 (1966).

The cohesive properties of MCC have been investigated from the standpoint of hydrogen bonding.[16,17] Milosovich suggested that a "cold bonding" between crystal lattices might be formed in a tablet containing crystalline materials.[18] During the compression process of a tablet containing a high concentration of MCC, MCC may take a plastic deformation rather than an elastic one through shearing, resulting in the increase of contact area between crystalline particles and in the formation of such a bonding as described above to make a compactly packed state. In a tablet containing a low concentration of MCC, the cold bonding of MCC may not be formed because of the difference in crystal structure between ASP and MCC, and the mutual frictional force may play a role as the binding force. As the concentration of MCC decreases further, the cold bonding of ASP may be formed.

On the other hand, after the penetration of water, the work of dispersion of particles may be made of the expanding force of air in the tablet caused by the heat of immersion,[19] the surface tension of water,[20] or swelling of particles.[8] Accordingly, such work of dispersion must overcome the binding work of particles for the disintegration of tablet.

Finally, it may be concluded that the penetration of water into a tablet is necessary for the disintegration as the first step without being sufficient and that the work of dispersion of particles caused through the penetration of water must overcome the binding work of particles for the disintegration, accordingly giving an optimum mixing ratio of drug and additive, as was shown by (ASPL+MCC). In this connection, the following explanation seems possible for the fact that ASP tablet containing PS generally shows a good disintegration without giving a minimum disintegration time as shown in Fig. 4. PS may always make a good lot of dispersing work after water penetrates into the tablet because it has the very good affinity to water and the good swelling property, while it may make a small amount of binding work because it has weak cohesive and adhesive properties and moreover because it consists of spherical particles which take an elastic deformation during compression, resulting in a small contact area between PS–PS or ASP–PS interface. Therefore, the dispersing work may always overcome the binding one.

Additionally, it seems necessary to take the mixing ratio and the particle sizes of drug and additive into consideration in making the tablet containing MCC, though MCC has various advantages such as the good binding property to be used for the direct compression.

18) G. Milosovich, *Drug Cosmetic Ind.* **92**, 557 (1963).
19) H. Matsumaru, *Yakugaku Zasshi*, **79**, 63 (1959).
20) H. Matsumaru, *Yakugaku Zasshi*, **79**, 854 (1959).