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Directly Compressed Tablets of Acetaminophen using Several Binding Agents[1,2]

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The effects of three binding agents, microcrystalline cellulose (MCC), hydroxypropyl cellulose (HPC) and polyvinylpolypyrrolidone (PVPP), as well as a physical mixture and a freeze-dried mixture of MCC and HPC (4: 1), on the binding and disintegrating properties of acetaminophen (AAP) tablets prepared by direct compression were studied. Several physical properties of the powders and tablets were also studied.

The order of binding ability of the binding agents evaluated from the cohesion was as follows: freeze-dried mixture ≒MCC≒physical mixture>HPC>PVPP. The order of hardness of AAP tablets containing various concentrations of the binding agents was as follows: freeze-dried mixture>physical mixture>MCC>HPC>PVPP.

The disintegration time of AAP tablets containing MCC was very long, while that of tablets containing other binding agents was short. This is probably because crystalline regions of MCC bond strongly to each other in tablets, and this is related to the small amount of water intake and low swelling ratio of MCC. PVPP was shown to have a rather large pore volume and small cohesion, and this is presumably related to the good disintegrating properties of PVPP.

The physical mixture and the freeze-dried mixture of MCC and HPC were excellent binding agents and disintegrators for tablets of drug powders with poor binding properties such as AAP.

Keywords——directly compressed tablet; acetaminophen; microcrystalline cellulose; hydroxypropyl cellulose; polyvinylpolypyrrolidone; physical mixture; freeze-dried mixture; binding property; disintegrating property

It is difficult to prepare tablets of acetaminophen (AAP) by direct compression because of the poor binding properties of the drug. Many workers have reported on the binding properties of microcrystalline cellulose (MCC),[5] and the disintegration mechanism of tablets prepared with MCC and potato starch,[6] and with polyvinylpolypyrrolidone (PVPP).[7] MCC has been widely used as a directly compressible diluent. PVPP was shown to be an excellent disintegrator also having good binding ability.[8] It was reported in a previous paper[9] that hydroxypropyl cellulose (HPC) would be useful as a binding agent in directly compressed tablets containing such disintegrators as potato starch and lactose.

The aim of the present study was therefore to investigate the effects of three binding agents, that is, MCC, HPC and PVPP, on the binding and disintegrating properties of APA tablets prepared by direct compression. The binding agents were examined alone, in a physical mixture or in a freeze-dried mixture. Several physical properties of the powders and tablets of these binding agents were also studied.

Experimental

Materials——Acetaminophen J.P. (AAP) was used after passage through a 200 mesh sieve. Microcrystalline cellulose J.P. (MCC) was purchased from Asahi Kasai Co., Ltd.[10] Hydroxypropyl cellulose (HPC) used was HPC LH-11, purchased from Shinetsu Chemical Co., Ltd., and polyvinylpolypyrrolidone (PVPP) was supplied by GAF Co., Ltd., New York, U.S.A.[11] Physical mixture and freeze-dried mixture of MCC and HPC (4: 1) passing through a 60 mesh sieve were obtained by thoroughly mixing both powders mechanically and by freeze-drying a suspension of MCC and HPC in an adequate amount of distilled water, respectively.

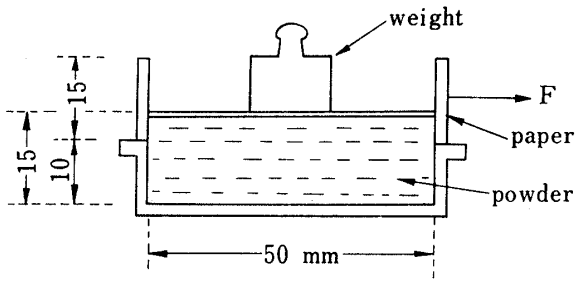

Fig. 1. Ring Shear Apparatus for Measurement of Coefficient of Friction and Cohesion

Tablet Making by Direct Compression——Flat-faced AAP tablets (400 mg, 13 mm in diameter) were made by compressing the given amount of powder directly under 140 kg/cm² (for AAP tablets) or an appropriate compression pressure using a Shimadzu evacuable die and hydraulic press for preparing KBr tablets for infrared spectroscopy.

Measurement of True Density——The true density was measured with a pycnometer with xylene at 37°C as a usual method.

Measurement of Coefficient of Friction and Cohesion——Using the apparatus shown in Fig. 1, the coefficient of friction and cohesion were measured following the method reported by Hayashi.[12]

The weight providing the vertical stress σ was changed from 0 to 65 g. The ring was pulled with a force F which was controlled by dropping water at a constant rate into a beaker from a buret. The force F when a sudden sliding of the ring occurred was taken as the shearing strength τ. The coefficient of friction, tan ϕ, and cohesion c were calculated according to Coulomb's equation: $\tau=\sigma \tan\phi+c$.

Measurement of Hardness of Tablets——A Monsanto hardness tester was used for the measurement and the mean of three tablets was obtained.

Measurement of Disintegration Time of Tablets——A Toyama Sangyo T-2HS type disintegration tester was used according to the method in J.P.IX, except that the attached disk was not used. The mean of six tablets was obtained.

Measurement of Porosity of Tablets——The apparent density of tablets was calculated from the size of tablets measured by means of a micrometer and the true density of the powders. The porosity was calculated as follows: porosity=[(true density)−(apparent density)]/(true density).

Measurement of Amount of Water Intake, Water Intake Rate and Swelling Ratio——Tablets made by compressing 250 mg of powder under 40 kg/cm² and 300 kg/cm² were used, and the amount of water intake and water intake rate were determined in the same way as reported by Nogami *et al.*[6] The swelling ratio is defined as tablet thickness after swelling to the initial tablet thickness.

Measurement of Moisture Content——Moisture content was calculated from weight loss after drying to equilibrium at 105°C.

Results and Discussion

Effects of Binding Agents on Binding Properties

To confirm the accuracy of the apparatus for measuring shearing strength, the relation between vertical stress and shearing strength of MCC, HPC and PVPP was investigated. A good linear plot was obtained for each binding agent and the correlation coefficients were 0.9991, 0.9997 and 0.9997 for MCC, HPC and PVPP, respectively, as shown in Fig. 2. Similar good linear relationships were also observed for the physical mixture and the freeze-dried mixture. The good linearity obtained here indicates that the apparatus used offers high accuracy. From the slope and the intercept of the regression lines of Fig. 2, the coefficient of friction and cohesion were calculated,[12] and the values obtained are listed in Table I. The cohesion of MCC and HPC is significantly larger than that of PVPP, and the order of binding ability of the three binding agents is MCC>HPC≫PVPP. MCC was shown to have the largest cohesion among the three binding agents,

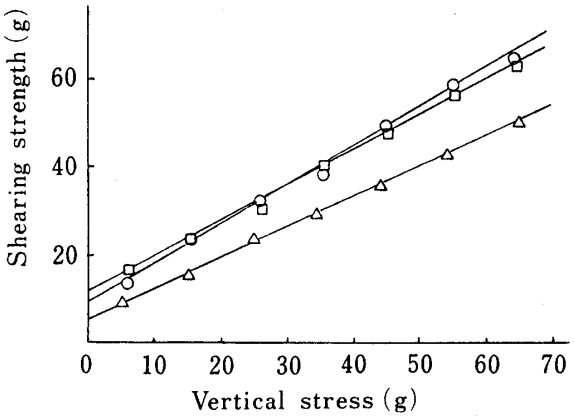

Fig. 2. Relation between Vertical Stress and Shearing Strength

□, MCC; ○, HPC; △, PVPP.

indicating it to be a good binding agent. The cohesion of the physical mixture and freeze-dried mixture was almost the same as that of MCC.

Table I. Coefficient of Friction and Cohesion of Powder Samples

Powder	Coefficient of friction	Cohesion (dyne/cm^2)
MCC	0.804	484
HPC	0.828	447
PVPP	0.686	314
Physical mixture[a)]	0.815	478
Freeze-dried mixture[a)]	0.809	495

a) Mixture of MCC and HPC (MCC: HPC=4: 1).

To investigate the effect of binding agents on the binding properties of AAP tablets, the relation between the porosity of AAP tablets and the concentration of binding agents was studied. As shown in Fig. 3, the porosity decreased with increase in concentration of MCC or HPC, while it increased with increasing concentration of PVPP. This result suggests that particles of MCC and HPC do not deform appreciably during the compression and also that the porosity of PVPP alone is larger than that of AAP alone. The porosity of AAP tablets containing MCC was smaller than that of AAP tablets containing HPC at every concentration. This might be due to the existence of crystalline regions in MCC. Both the physical mixture and the freeze-dried mixture of MCC and HPC had almost the same properties as MCC at every concentration. This indicates that the effect of MCC in both mixtures was predominantly on the compressibility.

The hardness of AAP tablets containing various binding agents is shown in Fig. 4. The hardness of AAP tablets contaning MCC was a little higher than that of tablets containing HPC at high concentration. The higher hardness for HPC might be related to the smaller porosity for HPC shown in Fig. 3. However, the hardness of AAP tablets containing the physical mixture and the freeze-dried mixture was significantly higher than that of tablets containing MCC or HPC alone. The hardness of AAP tablets containing the freeze-dried

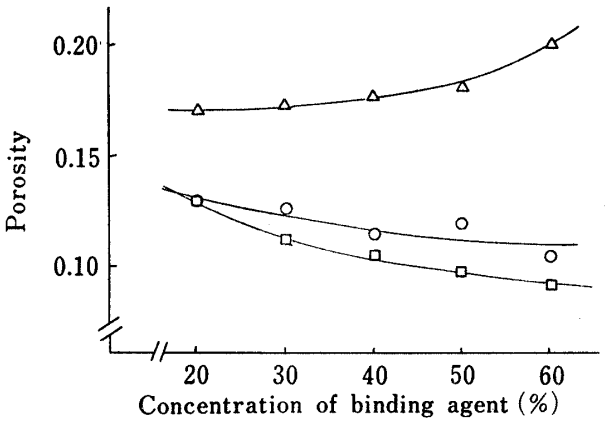

Fig. 3. Relation between Porosity of Acetaminophen Tablets and Concentration of Binding Agents

□, MCC; ○, HPC; △, PVPP.

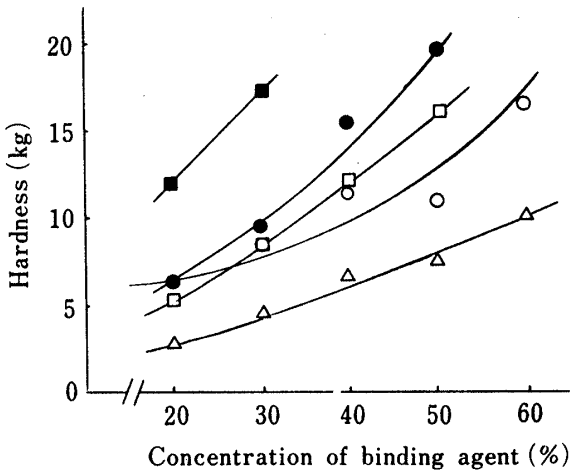

Fig. 4. Relation between Hardness of Acetaminophen Tablets and Concentration of Binding Agents

□, MCC; ○, HPC; △, PVPP; ●, physical mixture (MCC: HPC=4: 1); ■, freeze-dried mixture (MCC: HPC=4: 1).

mixture was especially high. The reason for this result is considered to be that the particle shape of the freeze-dried mixture is irregular and the particle size is small in comparison with that in the physical mixture. These results show that the physical mixture or the freeze-dried mixture of MCC and HPC has good binding properties, while PVPP was the poorest binding agent among the three.

Effects of Binding Agents on Disintegration of Tablets

Several physical properties of tablets of binding agents prepared under 40 and 300 kg/cm^2 are shown in Tables II and III, respectively. The disintegration time of MCC tablets was larger than that of HPC, PVPP and the physical mixture tablets. The disintegration time of the freeze-dried mixture tablet compressed under 300 kg/cm^2 was more than 60 min. This is probably because crystalline regions of MCC bind strongly to each other in the tablets, and this is related to the small amount of water intake and low swelling ratio of MCC. As shown in Fig. 4, the hardness of tablets of the freeze-dried mixture was very high, and thus water might not be able to penetrate easily into the tablet. Usually swelling of additives is very important for the disintegration of tablets, but in this case, the HPC tablet disintegrated slowly in spite of its large swelling ratio. This might be due to the long time required to reach equilibrium of water intake compared with other binding agents, resulting in slow disintegration of the HPC tablet.

Table II. Physical Properties of Tablets compressed at 40 kg/cm^2

	MCC	HPC	PVPP	Physical mixture[c]	Freeze-dried mixture[c]
Disintegration time (min)	12.0	2.4	0.4	0.2	60
Pore volume (mm^3)	45.5	48.0	92.8	51.4	51.6
Amount of water intake (ml)	0.27	2.29	1.12	0.91	0.60
Water intake rate (min)[a]	0.5	12.0	1.0	1.0	2.0
Swelling ratio[b]	1.30	7.36	—[d]	1.93	1.68

a) Time to reach equilibrium water intake.
b) Ratio of tablet thickness after swelling to initial thickness.
c) Mixture of MCC and HPC (MCC: HPC=4: 1).
d) Impossible to measure because of the brittleness of the tablet.

Table III. Physical Properties of Tablets compressed at 300 kg/cm^2

	MCC	HPC	PVPP	Physical mixture[c]	Freeze-dried mixture[c]
Disintegration time (min)	60	8.5	0.8	1.2	60
Pore volume (mm^3)	11.6	23.8	44.0	14.0	15.2
Amount of water intake (ml)	0.20	2.35	1.11	0.96	0.44
Water intake rate (min)[a]	3.0	60	1.5	4.0	4.0
Swelling ratio[b]	1.05	9.40	3.76	4.04	2.01

a) Time to reach equilibrium water intake.
b) Ratio of tablet thickness after swelling to the initial thickness.
c) Mixture of MCC and HPC (MCC: HPC=4: 1)

PVPP was shown to have a large pore volume compared with other binding agents, and this might correlate with the small cohesion of PVPP, as shown in Table I, or with the plastic property of PVPP. The slow disintegration of the PVPP tablet may be due to the high affinity of PVPP for water, as reflected by the large moisture content in Table IV. The true densities of the powders used are also shown in Table IV.

Table IV. True Density and Moisture Content of Powders Used

	AAP	MCC	HPC	PVPP
True density (g/cm³)	1.30	1.45	1.22	1.53
Moisture content (%)	0.2	8.3	11.3	5.2

The disintegration times of tablets of binding agents compressed under 300 kg/cm² were longer than those of tablets compressed under 40 kg/cm². In particular, the disintegration time of MCC tablets was more than 60 min. Both the pore volume and the water intake rate seemed to be decreased by compression of the tablets at high pressure. The water intake rate of HPC was very slow in spite of its large pore volume at high compression pressure, and this might be related to the plastic deformation of HPC under high compression pressure.[8] The water intake was similar for each binding agent at both compression pressures, while the swelling ratio at high compression pressure was generally higher than that at low compression pressure. This is clearly related to the difference of small pore volume at the two compression pressures.

Figure 5 shows the disintegration times of AAP tablets containing various amounts of binding agents from 20 to 60%. The disintegration times were significantly different from those of the binding agents themselves (shown in Tables II and III). The disintegration of AAP tablets containing HPC, PVPP and physical mixture was very fast. The disintegration time of AAP tablets containing the freeze-dried mixture was a little longer, but was still less than about 5 min. Although the disintegration time of the freeze-dried mixture tablet was more than 60 min, the AAP tablet containing the freeze-dried mixture disintegrated fairly rapidly. The reason for this is not clear, but might be related to the small binding ability of AAP tablets.

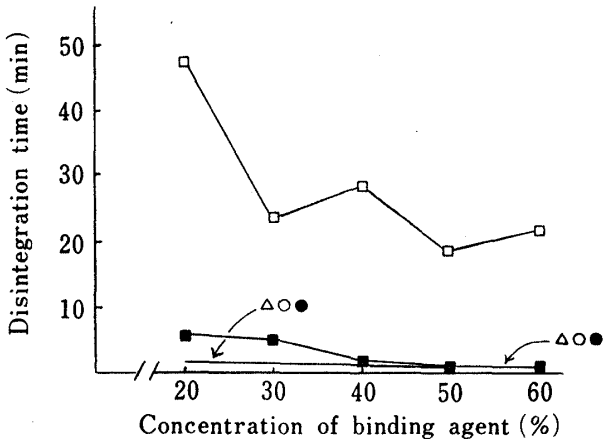

Fig. 5. Relation between Disintegration Time of Acetaminophen Tablets and Concentration of Binding Agents

□, MCC; ○, HPC; △, PVPP; ●, physical mixture (MCC: HPC=4: 1); ■, freeze-dried mixture (MCC: HPC=4: 1).

Tablets containing the physical mixture and the freeze-dried mixture showed stronger binding properties than those containing MCC or HPC alone, and also showed good disintegration behavior. The physical mixture and the freeze-dried mixture of MCC and HPC could be effective binding agents and disintegrators for tablets of powders having poor binding properties such as AAP.

References and Notes

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