

Directly Compressed Tablets Containing Hydroxypropyl Cellulose in Addition to Starch or Lactose^{1,2)}

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Intending to explore useful directly compressible vehicles containing hydroxypropyl cellulose (HPC), investigations were made on the fluidity of the combined powders of HPC with potato starch (PS) and with lactose and then on the hardness and the disintegration property of the directly compressed tablets of these mixtures.

The addition of HPC to PS or lactose gave no remarkable effect on the fluidity of the powder. The plot of the hardness of tablet against the concentration of HPC gave a flexional point in PS/HPC mixture, while not in lactose/HPC mixture. A critical disintegration time concentration (*c.d.t.c.*) of HPC was found for the tablets of both PS/HPC and lactose/HPC mixtures, above which the disintegration time was strikingly prolonged. It was considered from the relationships of tablets between the compressional pressure and such properties as thickness, hardness and disintegration time that a crushing of particles might take place during compression in lactose/HPC mixture, while a rather elastic deformation might take place in PS/HPC mixture. A freeze dried lactose/HPC mixture was considered to be applicable to making troches by direct compression.

As a result, it was shown that HPC would be useful as a binder in a tablet making by direct compression combining properly with such disintegrators as PS and lactose.

A tablet making by direct compression is simple compared with the wet process and is suitable to keeping the active ingredient stable. Therefore, it is desirable that various kinds of good directly compressible vehicles are provided for practical purposes. Microcrystalline cellulose is currently available as a directly compressible diluent. It was reported in a previous paper⁴⁾ that there was an optimum concentration region of microcrystalline cellulose to give a minimum disintegration time of directly compressed tablets containing microcrystalline cellulose and potato starch (PS).

Hydroxypropyl cellulose (HPC) has a good binding property⁵⁾ and thus it is widely used as binders in making granules, pills and tablets and in coating these solid preparations. Moreover, HPC powder has a good plasticity.⁶⁾ Therefore, it may be possible to utilize HPC as a binder in a tablet making by direct compression combining with such disintegrators as starch and lactose. Intending to explore useful directly compressible vehicles containing HPC, the present study was attempted to investigate the fluidity of combined powders PS/HPC and lactose/HPC and then the hardness and the disintegrating property of the directly compressed tablets of these powders.

Additionally, a similar investigation was carried out concerning directly compressed tablets of freeze dried lactose/HPC mixtures in various mixing ratios, as these two components are soluble in water to give a homogeneous mixture.

- 1) Pharmaceutical Interactions in Dosage Form and Processing. Part I.
- 2) A part of this work was presented at the 93rd Annual Meeting of Pharmaceutical Society of Japan, Tokyo, April 1973.
- 3) Location: *Ebara-2-4-41, Shinagawa-ku, Tokyo, 142, Japan.*
- 4) H. Nogami, T. Nagai, E. Fukuoka, and T. Sonobe, *Chem. Pharm. Bull.* (Tokyo), **17**, 1450 (1969).
- 5) N. Ogiwara, Japan Patent Sho-44-298 (1969).
- 6) J. Rossman and J. Desmarais, *Hercules Chemist*, **61**, 9 (1970).

Experimental

Materials—Commercial potato starch J.P. VIII (PS) and lactose J.P. VIII were used. Two kinds of hydroxypropyl cellulose (HPC) supplied by Teijin Co., Ltd., *i.e.*, HPC-M and HPC-L, were sieved, and respective 48—100 mesh (297—149 μ) portions were used as the samples, the viscosities of 2% aqueous solution being 172.4 and 14.7 centi-poise, respectively, by a Tokyo Keiki BL type rotating viscometer. Freeze dried lactose/HPC mixtures passing through a 48 mesh sieve were obtained by freeze drying 100 ml aqueous solutions containing 6 g of lactose/HPC mixtures in various ratios using a Yamato model DC-31 freeze-dryer, pulverizing the products using a Nihon Seiki HB special type universal homogenizer and sieving.

Measurement of the Angle of Repose of Powder—Dropping an excess amount of powder on a stainless steel disk of 40 mm diameter and 5 mm thickness from an oriphis of 4 mm diameter at 40 mm height, the angle of repose was measured by a Konishi protractor.

Tablet Making by Direct Compression—Unless otherwise stated, flat faced tablets of 500 mg, 13 mm diameter and about 3.0 mm thickness were made by compressing the given amount of powder directly under 75 kg/cm² using a Shimadzu evacuable die and hydraulic press for KBr tablet for infrared spectroscopy.

Measurement of the Thickness of Tablet—This was done using a Mitsutoyo micrometer.

Measurement of the Hardness of Tablet—This was done using a Kiya hardness tester, which can be applied to measuring a hardness below 20 kg.

Measurement of the Disintegration Time of Tablet—This was done using a Toyama Sangyo T-2HS type disintegration tester according to the method in J.P. VIII except that the disintegration time of each tablet was determined and the attached disk was not used.

Result and Discussion

Relationship between the Angle of Repose of Powder Mixture and the Concentration of HPC

Generally, the fluidity of the powder mixture increased with the concentration of HPC, as shown in Fig. 1. This tendency was larger in PS/HPC mixture than in lactose/HPC mixture in the practical concentration region of HPC, *i.e.*, below 60%. With the addition of HPC to 50%, the decrease of the angle of repose in comparison with PS or lactose only were as follows: 14% in PS/HPC-M, 25% in PS/HPC-L and 8% in both lactose/HPC-M and lactose/HPC-L. These results may indicate that the addition of HPC to PS or lactose gives no remarkable effect on the fluidity of the powder mixture.

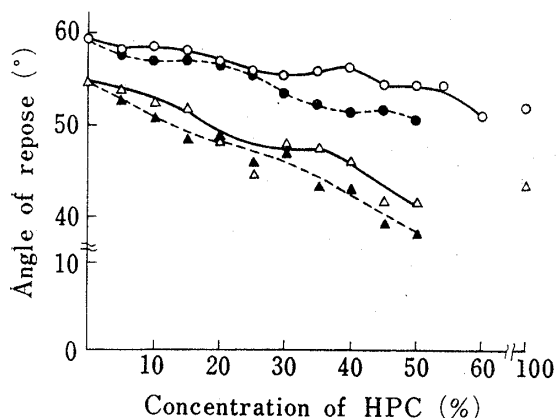


Fig. 1. Relationship between the Angle of Repose and the Concentration of HPC

—○—: lactose/HPC-M mixture
 —●—: lactose/HPC-L mixture
 —△—: PS/HPC-M mixture
 —▲—: PS/HPC-L mixture
 ○ : HPC-M
 △ : HPC-L

Each point represents the mean of 3 determinations.

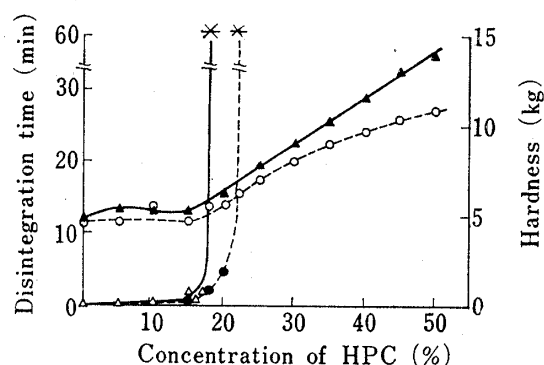


Fig. 2. Relationship between the Disintegration Time or the Hardness of Tablet of PS/HPC Mixture and the Concentration of HPC

—▲—: PS/HPC-M, hardness
 —△—: PS/HPC-M, disintegration time
 —○—: PS/HPC-L, hardness
 —●—: PS/HPC-L, disintegration time
 * : Disintegration was not completed within 60 min.

Each point represents the mean of 3 determinations.

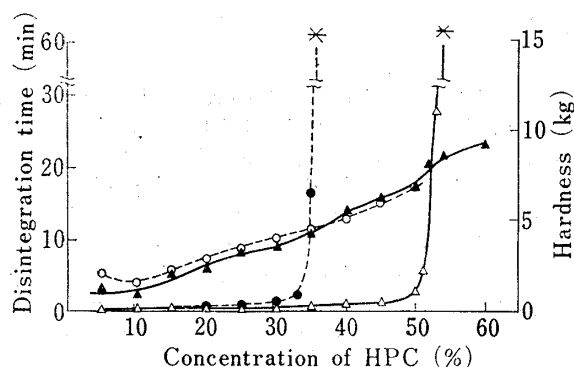


Fig. 3. Relationship between the Disintegration Time or the Hardness of Tablet of Lactose/HPC Mixture and the Concentration of HPC

- ▲—: lactose/HPC-M, hardness
 - △—: lactose/HPC-M, disintegration time
 - : lactose/HPC-L, hardness
 - : lactose/HPC-L, disintegration time
 - * : Disintegration was not completed within 60 min.
- Each point represents the mean of 3 determinations.

ness against the concentration of HPC was considered due to a difference between PS and lactose in a behavior against compression, as will be discussed later in detail.

The results obtained here will be discussed later also in relation to the disintegration time of tablet.

Relationship between the Disintegration Time of Tablet and the Concentration of HPC

A very rapid disintegration of compressed tablet of PS/HPC or lactose/HPC mixture took place below a certain concentration of HPC, above which the disintegration time was strikingly prolonged, as shown in Fig. 2 and 3. For the convenience of discussion, this critical concentration will be described as "critical disintegration time concentration" (*c.d.t.c.*). At the start of disintegration of the tablet containing HPC above *c.d.t.c.*, the phenomenon proceeded in the same way as the one containing HPC below *c.d.t.c.*, but it stopped soon and some caky aggregate parts of tablet left on the mesh of the tester still after 60 min. These aggregate parts of tablet increased in size with the concentration of HPC and each of them was covered with a gel-like layer of HPC on the surface.

In PS/HPC mixture, *c.d.t.c.* was identical with the concentration at the flexional point of hardness, as shown in Fig. 2. It seemed that the particles of HPC in the tablet of PS/HPC mixture might disperse each other below *c.d.t.c.* causing an easy disintegration but might contact and bind each other above *c.d.t.c.* causing an increase in hardness of tablet. Moreover it was considered that the particles of HPC above *c.d.t.c.* might swell and gel owing to penetrating water and then a gel-like layer was formed which might perform a barrier to the further penetration of water necessary for the disintegration of tablet, then the particles dissolving without accompanying a disintegration.

In lactose/HPC mixture, *c.d.t.c.* was higher than in PS/HPC mixture, in addition to the preceding result that there was no flexional point on the hardness-concentration curve as shown in Fig. 3. An explanation for this difference may be given on the consideration that lactose dissolves in water and may retard the formation of a gel-like layer of HPC on the surface of aggregate parts of tablet resulting in a high *c.d.t.c.* compared with that in PS/HPC mixture. Actually, it was observed that the aggregate parts of tablet leaving on the mesh of the disintegration tester dissolved gradually.

Comparing Fig. 2 with Fig. 3 for the plot of disintegration time, it is clear that *c.d.t.c.* was prolonged by HPC-L in PS mixture while was done by HPC-M in lactose mixture. This

Relationship between the Hardness of Tablet and the Concentration of HPC

In PS/HPC mixture, the hardness of compressed tablet was much the same when the concentration of HPC was below 15%, and increased with the concentration of HPC above 15%, the plot of PS/HPC-M mixture increasing more than that of HPC-L mixture, as shown in Fig. 2.

In lactose/HPC mixture, the hardness of compressed tablet increased gradually with the concentration of HPC without giving such a flexional point as in PS/HPC mixture, with no remarkable difference between lactose/HPC-M and lactose/HPC-L mixtures, as shown in Fig. 3.

The difference between PS/HPC and lactose/HPC mixtures in the shape and the increasing tendency of the plot of the hardness against the concentration of HPC was considered due to a difference between PS and

result suggests that there is a difference between PS and lactose in an interaction with HPC, as well as the result described already regarding the plot of hardness.

Relationship between Properties of Tablet and the Compressional Pressure

Tablets of PS (90%)/HPC-M (10%) and lactose (75%)/HPC-M (25%) mixtures were made by compressing under 100, 200, 300 and 400 kg/cm², and the thickness, hardness and disintegration time of these tablets were discussed in relation to the compressional pressure. The concentration of HPC in these mixtures were about a half of the respective values of *c.d.t.c.*.

i) **Thickness of Tablet and the Compressional Pressure**—As shown in Fig. 4, the thickness of tablet of lactose/HPC-M mixture decreased linearly with the increase in compressional pressure, while no remarkable decrease was observed in PS/HPC-M mixture. Considering also that there was found no flexional point on the plot of the hardness of tablet against the concentration of HPC in lactose/HPC mixture as shown in Fig. 3, such a difference between both the mixtures mentioned above seemed due to a difference in a behavior against compression between PS and lactose. In lactose/HPC mixture, a crushing of particles might take place during compression accompanying a decrease of the void spaces between particles, as was considered to be related to the fact that the gloss of tablet surface increased with the compressional pressure. In PS/HPC mixture, an elastic deformation of particles rather than a crushing might take place predominantly during compression without accompanying so great a decrease of void space as in lactose/HPC mixture, as was considered to be related to the fact that no remarkable change in the gloss of tablet surface was observed with the increase in compressional pressure and also some recovery of the thickness was noticed after removing the compressional pressure.

ii) **Hardness of Tablet and the Compressional Pressure**—The hardness of tablet increased with the increase in compressional pressure in PS/HPC mixture, as shown in Fig. 4. Enhancing the pressure from 100 kg/cm² to 400 kg/cm², the increase in hardness was 6.5 kg in

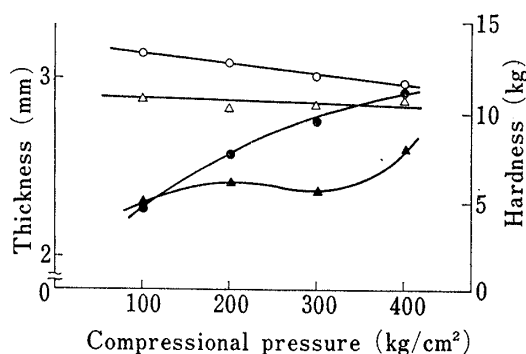


Fig. 4. Plots of the Compressional Pressure against the Thickness and the Hardness of Tablet

—△—: PS (90%)/HPC-M (10%), thickness
 —▲—: PS (90%)/HPC-M (10%), hardness
 —○—: lactose (75%)/HPC-M (25%), thickness
 —●—: lactose (75%)/HPC-M (25%), hardness
 Each point represents the mean of 3 determinations.

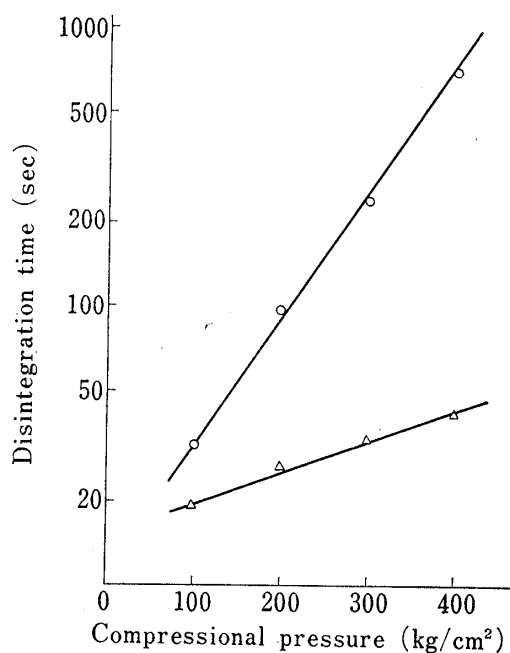


Fig. 5. Relationship between the Disintegration Time of Tablet in Logarithmic Scale and the Compressional Pressure

—△—: PS (90%)/HPC-M (10%)
 —○—: lactose (75%)/HPC-M (25%)
 Each point represents the mean of 3 determinations.

lactose/HPC mixture, while only 3.0 kg in PS/HPC mixture. This result also may be explained on the consideration that a crushing of particles might take place in lactose/HPC mixture while a rather elastic deformation might take place in PS/HPC mixture, as described above.

iii) **Disintegration Time of Tablet and the Compressional Pressure**—The increase in disintegration time with the compressional pressure in lactose/HPC mixture was much larger than in PS/HPC mixture, *i.e.*, 11 min for the former and 22 sec for the latter with the enhancement of pressure from 100 kg/cm² to 400 kg/cm², as shown in Fig. 5. This result also may be explained on the consideration of such a difference in a behavior of particles against compression as described above. Additionally, Fig. 5 shows that a linear relationship was obtained between the disintegration time of tablet in logarithmic scale and the compressional pressure under the present experimental conditions. This relationship is interesting and may give a useful information for practical purposes, and further investigations should be made in order to know the basic mechanism of this phenomenon.

Accordingly, the results of i—iii) mentioned above indicated that the thickness, hardness and disintegration time of tablets were closely related to the compressional pressure.

As a conclusion, it might be possible to utilize HPC as a binder in a tablet making by direct compression combining with such disintegrators as PS and lactose. Here, the concentration of HPC might be desired to be below *c.d.t.c.* with the view of gaining a fluidity of bulk powder suitable to the tablet making process and also gaining a proper hardness and disintegration time of compressed tablet. Lactose/HPC mixture was considered to be applicable for wide purposes because of its high *c.d.t.c.* compared with PS/HPC mixture.

Relationship between Properties of Tablets of Freeze Dried Lactose/HPC Mixture and the Concentration of HPC

A homogeneous lactose/HPC mixture obtained by drying an aqueous solution of these components in the air at a room or high temperature was jellyfied and sticky, but the freeze dried one was obtained in a fine and porous powdered state of a small density by pulverizing the freeze dried product using a homogenizer, being directly compressible. However, the powder thereby obtained was too bulky to make a tablet of the same weight as in the cases

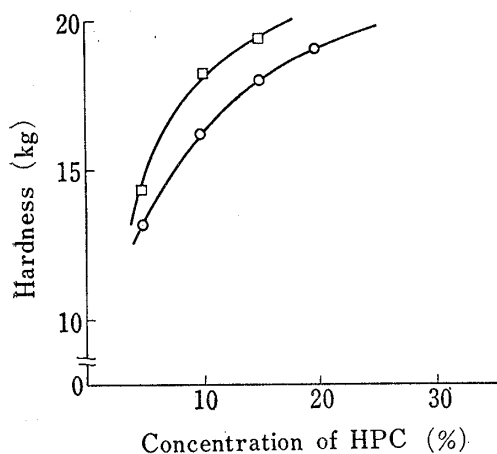


Fig. 6. Relationship between the Hardness of Tablet of Freeze Dried Lactose/HPC Mixture and the Concentration of HPC

—□—: lactose/HPC-M
—○—: lactose/HPC-L
Each point represents the mean of 3 determinations.

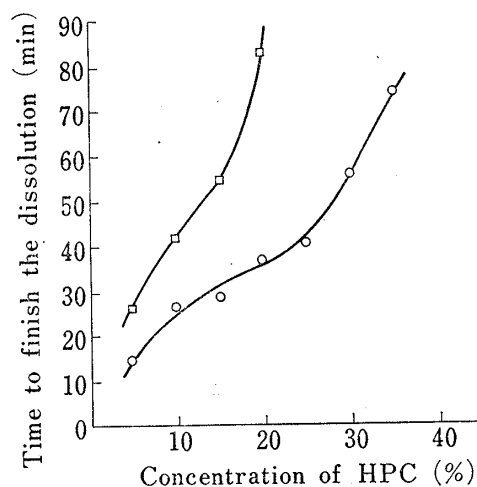


Fig. 7. Relationship between the Time to Finish the Dissolution of Tablet of Freeze Dried Lactose/HPC Mixture and the Concentration of HPC

—□—: lactose/HPC-M
—○—: lactose/HPC-L
Each point represents the mean of 3 determinations.

of the mixtures described already. In this study, therefore, compressing 300 mg of the powder, a tablet of about 1.8 mm thickness was obtained.

The hardness of tablet increased with the concentration of HPC, as shown in Fig. 6. When the concentration of HPC were above 20% for HPC-M and above 25% for HPC-L, the hardness of tablet was over the measurable limit of the tester.

Regarding the disintegration of tablet, the phenomenon was completely different from the cases of the mixtures described already and contained a slow dissolution. A gel-like layer of HPC was not observed on the surface of tablet, which was done in the cases of the mixtures described already. The time required to finish the dissolution was prolonged with the concentration of HPC, as shown in Fig. 7.

The hardness and the disintegration time of tablet of lactose/HPC-M mixture were higher than those of lactose/HPC-L, as was considered due to the difference between HPC-M and HPC-L in degree of polymerization. A freeze dried lactose/HPC mixture made much more possible obtain a very hard and not disintegrating tablet than the simple mixture did. This change in properties of lactose/HPC mixture by freeze drying was considered due to the homogeneous mixing of the two components in molecule level and the general characteristics of freeze dried products.

Practically, it was suggested that a freeze dried lactose/HPC mixture might be applicable to making troches by direct compression.

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