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Directly Compressed Tablets containing Chitin or Chitosan in Addition to Lactose or Potato Starch[1]

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As a part of a series of study on pharmaceutical applications of chitin and chitosan, the fluidity and compressibility of combined powders of lactose with chitin and chitosan, and potato starch with chitin and chitosan, as well as the disintegration properties of the tablets made from these powders were investigated in comparison with those of crystalline cellulose with lactose and potato starch. The lubricating properties of combined powders of lactose with chitin and chitosan were also investigated in comparison with those of lactose with crystalline cellulose.

The fluidity of combined powders with chitin and chitosan was greater than that of the powder with crystalline cellulose. The hardest tablet was obtained with chitosan, followed by crystalline cellulose and chitin in that order. Tablets containing less than 70% of chitin or chitosan passed the disintegration test of JP X. The ejection force of the tablets of lactose/chitin and lactose/chitosan was significantly smaller than that of lactose/crystalline cellulose tablets. It is suggested that chitin and chitosan may be suitable for use as diluents with friction-lowering properties in direct compression processes.

Keywords——chitin; chitosan; direct-compression diluent; fluidity; compressibility; lubricating property; ejection force

Chitin [(1→4)-2-acetamido-2-deoxy-β-D-glucan] is a widely occurring, natural structural material. It is a principal constituent of the protective cuticles of crustacea and insects, and also occurs in the cell walls of some fungi and microorganisms. Chitosan [(1→4)-2-amino-2-deoxy-β-D-glucan] can be obtained by alkaline deacetylation of chitin.[2]

Many direct-compression diluents have been reported, but every diluent has some disadvantages.[3] Crystalline cellulose (MCC) has been widely used in Japan. Chitin and chitosan have structural formulae analogous to that of cellulose, and have been reported to be useful for pharmaceutical preparations,[2,4] but no detailed study concerning the application of chitin and chitosan to powdered preparations has yet been reported.

In this study, the fluidity and compressibility of combined powders of lactose with chitin (lactose/chitin) and with chitosan (lactose/chitosan), and potato starch with chitin (potato starch/chitin) and with chitosan (potato starch/chitosan), as well as the disintegration properties of tablets made from these powders, were investigated in comparison with those of combined powders of lactose with MCC (lactose/MCC) and potato starch with MCC (potato starch/MCC) in order to develop new direct-compression diluents as a part of a series of studies on pharmaceutical applications of chitin and chitosan. In a direct-compressed formulation, diluents should have suitable fluidity and compressibility and often act as disintegrating agents.[3] The ejection force of tablets of lactose/chitin, lactose/chitosan and lactose/MCC was also investigated.

Experimental

Materials——Chitin and chitosan, whose degree of deacetylation was caluculated to be 92.7% from the amino group content, for fine chemical use were purchased from Kyowa Oil and Fat Co., Ltd. and were used after passage through a 200-mesh sieve. Commercial lactose JP X, potato starch JP X and MCC JP X marketed as "Avicel PH-101" were used after passage through a 200-mesh sieve. Mixing of powders was carried out in a Tsutsui V-shape blender for 30 min at 50 rpm.

Measurement of Angle of Repose——A Konishi protractor[5] was employed with a table of 10 cm diameter and with 11 cm distance between the autofeeder and the table at a relative humidity between 55 and 65%.

Measurement of Minimum Orifice Diameter for Flow——An apparatus purchased from Konishi Iryoki Co., Ltd. was used at a relative humidity between 55 and 65%;[6] 5 g of powder was applied to orifices of various diameters and the minimum diameter of orifice through which the powder could flow was measured. The orifice diameters were 3.15, 4.0, 5.0, 6.3, 8.0, 10.0, 12.5, 16.0, 20.0, and 25.0 mm.

Tablet-making by Direct Compression——Unless otherwise stated, flat-faced tablets of 300 mg (lactose combination) or 200 mg (potato starch combination, chitin alone, chitosan alone) weight, 13 mm diameter and about 1.7 mm (lactose combination) or 1.1 mm (potato starch combination, chitin alone, chitosan alone) thickness were made by compressing the given amount of powder directly under 100 kg/cm^2 for 30 s using a Shimadzu hydraulic press for KBr tablets for infrared spectroscopy.

Measurement of Hardness of Tablets——A Kiya hardness tester, which can be applied to measure hardness below 20 kg at a relative humidity between 55 and 65%, was used.

Measurement of Disintegration Time of Tablets——A Toyama Sangyo T-2HS type disintegration tester was employed according to the method in JP X, with and without auxiliary disks, using water as the test fluid.

Measurement of Ejection Force——The ejection force required to eject the tablet from the die was measured by an Iwamoto Seisakusho micromeritic tester[7] at the ejection speed of 2 cm/min at a relative humidity between 55 and 65%. In this case, flat-faced tablets of 500 mg, 11.3 mm diameter and about 4.0 mm thickness, were made by compressing the given amount of powder directly under 100 kg/cm^2 for 30 s using a hand-built apparatus.

Results and Discussion

Effect of Addition of Chitin or Chitosan on the Fluidity of Powder Mixtures

The angle of repose and the minimum orifice diameter for flow of lactose/chitin, lactose/chitosan, lactose/MCC, potato starch/chitin, potato starch/chitosan and potato starch/MCC

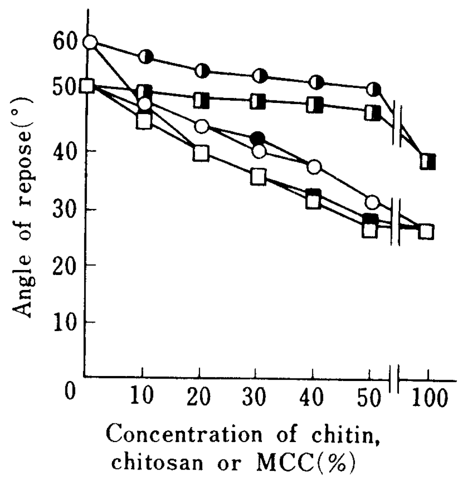

Fig. 1. Relation between Angle of Repose and Concentration of Chitin, Chitosan or MCC added to Lactose and Potato Starch Powders

Lactose combinations, ○: chitin; ●: chitosan; ◑: MCC.
Potato starch combinations, □: chitin; ■: chitosan; ◨: MCC.
Each point represents the mean of 3 determinations.

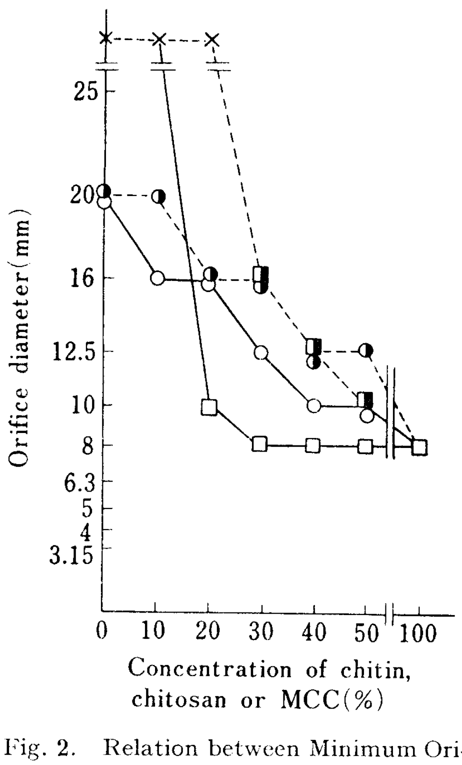

Fig. 2. Relation between Minimum Orifice Diameter and Concentration of Chitin, Chitosan or MCC added to Lactose and Potato Starch Powders

Lactose combinations, —○—: chitin or chitosan; --◑--: MCC.
Potato starch combinations, —□—: chitin or chitosan; --◨--: MCC; ×: above 25 mm.
Each point represents the mean of 3 determinations.

are shown in Figs. 1 and 2. It was found that the decrease of the angle of repose of powders with the addition of chitin or chitosan was larger than that with the addition of MCC, but no clear difference between chitin and chitosan was observed, as shown in Fig. 1. As regards the decrease of the minium orifice diameter for flow with the addition of chitin, chitosan and MCC, the same tendency was observed as in the case of the angle of repose of powders, as shown in Fig. 2. These results indicate that the fluidity of powders was improved by the addition of chitin or chitosan, but not by the addition of MCC.

Relation between the Hardness of Tablets and Compressional Pressure

The effect of compressional pressure on the hardness of tablets of chitin, chitosan and MCC alone is shown in Fig. 3. The higher the compressional pressure was, the larger was the hardness of the tablets. The hardness of the chitin tablets was greater than that of the chitosan tablets. This result might be attributable to the greater stuctural rigidity of chitin due to its acetylamino groups, and further the degree of polymerization of chitin might occur during the deacetylation of chitin with strong alkali to prepare chitosan from chitin.

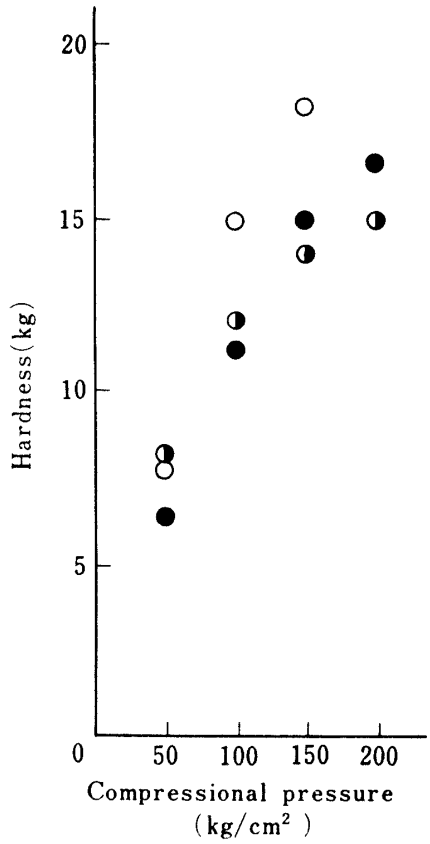

Fig. 3. Relation between Tablet Hardness and Compressional Pressure

○: chitin; ●: chitosan; ◑: MCC.
Each point represents the mean of 5 determinations.

Effect of the Addition of Chitin or Chitosan on the Compressibility of Tablets

The hardness of the tablets of lactose/chitin, lactose/chitosan, and lactose/MCC increased with the addition of chitin, chitosan, and MCC, as shown in Fig. 4 (left). Addition of less than 10% MCC resulted in failure of tablet formation because of crumbling and chiping. Comparing the hardness of the tablets of lactose/chitosan with that of lactose/MCC, there was no statistically significant difference at 20% addition ($p<0.01$), while the hardness of the tablets of lactose/chitosan was significantly greater than that of lactose/MCC at 30, 40, and 70% addition ($p<0.01$). Comparing the hardness of the tablets of lactose/chitin with that of lactose/MCC, there was no statistically significant difference at 20 and 30% addition ($p<0.01$), whereas the hardness of the tablets of lactose/chitin was significantly smaller than that of lactose/MCC at 40 and 50% addition ($p<0.01$).

The hardness of tablets of potato starch/chitin, potato starch/chitosan, and potato starch/MCC increased with the level of addition of chitin, chitosan, and MCC, as shown in Fig. 4 (right). Comparing the hardness of the tablets of potato starch/chitosan with that of potato starch/MCC, that of potato starch/chitosan was significantly larger than that of potato starch/MCC at 10 and 20% addition ($p<0.01$) ,and there was no statistically significant difference at 30, 40 and 50% addition ($p<0.01$). Comparing the hardness of the tablets of potato starch/MCC with that of potato starch/chitin, there was no statistically significant difference at 10 and 30% addition ($p<0.01$), and the hardness of the tablets of potato starch/chitin was significantly smaller than that of potato starch/MCC at 20, 40 and 50% addition ($p<0.01$).

In the combinations with both lactose and potato starch, a greater hardness was obtained

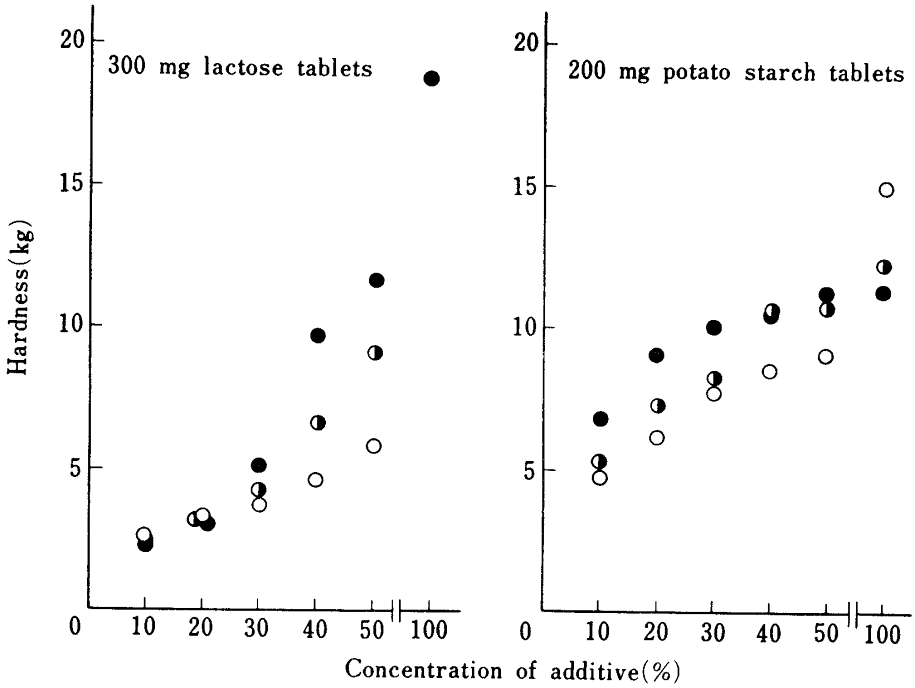

Fig. 4. Relation between Tablet Hardness and Concentration of Additive

○: chitin, ●: chitosan; ◐: MCC.
Each point represents the mean of 5 determinations.

for chitosan tablets at a smaller concentration as compared with MCC. These results suggest that chitin and chitosan are suitable for use as direct-compression diluents, and chitosan especially is superior to MCC, as mentioned above.

Relation between the Disintegration Time of Tablets and the Concentration of Chitin or Chitosan

A very rapid disintegration of compressed tablets of lactose/chitin, lactose/chitosan, lactose/MCC, potato starch/chitin, potato starch/chitosan and potato starch/MCC took place in water below a certain concentration of additives, above which the disintegration time was greatly prolonged, as shown in Figs. 5 and 6. For convenience of discussion, this critical concentration will be described as the "critical disintegration time concentration" (*c.d.t.c.*).[8]

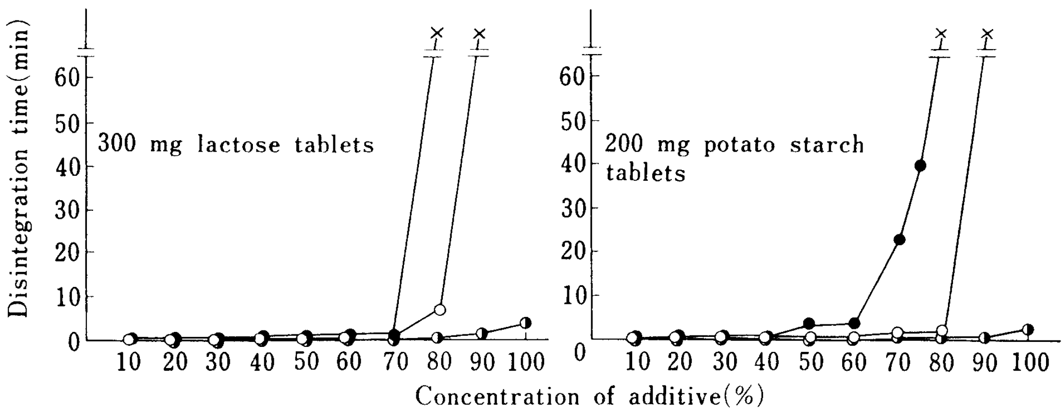

Fig. 5. Relation between Tablet Disintegration Time (with Auxiliary Disk) and Concentration of Additive

○: chitin; ●: chitosan; ◐: MCC; × : disintegration was not completed within 60 min.
Each point represents the mean of 3 determinations.

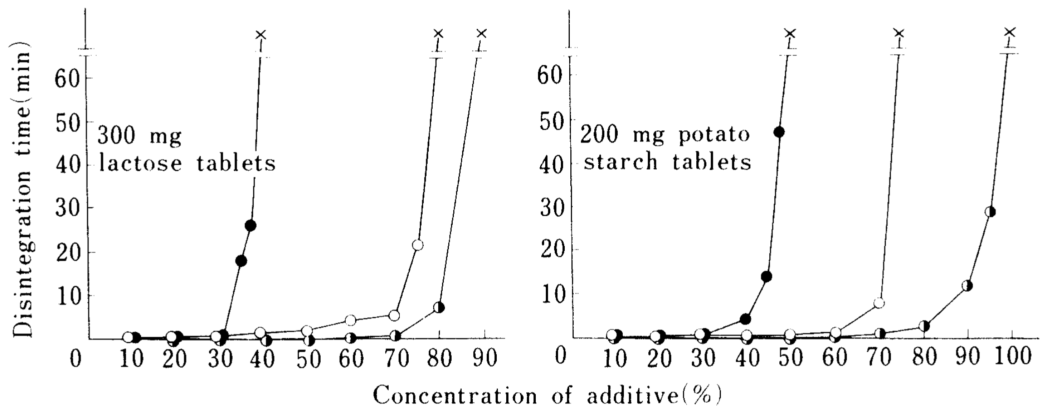

Fig. 6. Relation between Tablet Disintegration Time (without Auxiliary Disk) and Concentration of Additive

○: chitin; ●: chitosan; ◑: MCC; ×: Disintegration was not completed within 60 min. Each point represents the mean of 3 determinations.

The disintegration time of tablets was the shortest for MCC tablets, followed by chitin and chitosan tablets. At the start of disintegration of tablets containing chitin or chitosan above the *c.d.t.c.*, the mode of disintegration was the same as that of tablets containing chitin or chitosan below the *c.d.t.c.*, but disintegration stopped soon and some caky aggregate of parts of the tablet were still present on the mesh of the tester after 60 min. The size of these aggregates increased with the concentration of chitin or chitosan and the surfaces were corvered with a gel-like layer of chitin or chitosan. Tablets of chitin or chitosan alone, except for a 200 mg chitin tablet with an auxiliary disk, kept their original forms on the mesh of the tester even after 60 min, and their surfaces were covered with a gel-like layer. It was considered that the particles of chitin or chitosan above the *c.d.t.c.* might swell and form the gel owing to the penetration of water (necessary for the disintegration of tablets). Comparing the disintegration properties with and without auxiliary disks (Figs. 5 and 6, respectively), the *c.d.t.c.* was higher with auxiliary disks. Tablets were crushed in the glass tubes of the tester by impact of the auxiliary disk before gelation.

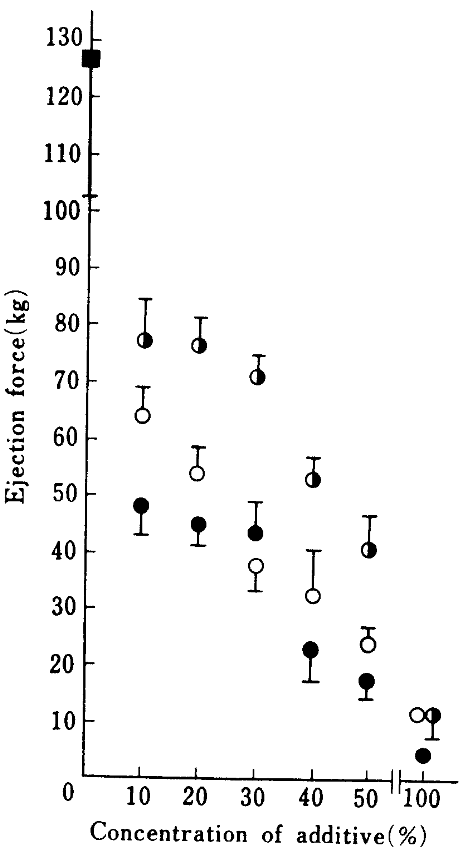

Fig. 7. Relation between Ejection Force and Concentration of Additive in Lactose Tablets

○: chitin; ●: chitosan; ◑: MCC; ■: lactose alone. Each symbol represents the mean of 6 determinations ± S.D.

Effect of Addition of Chitin or Chitosan on the Lubricating Properties of Lactose Tablets

Many studies on the lubricating properties of powders have been reported. Hölzer *et al.*[9] recommended the use of the force required to eject a tablet from a die as a measure for the evaluation of lubricating properties.

Lactose alone and lactose powder containing 10% MCC could not form tablets. A large ejection force was required to eject the lactose tablet from the die because of the large adhesive force of lactose powder to the die wall. The ejection force decreased with the addition of chitin, chitosan or MCC, as shown in Fig. 7, and this result was attributed to the decrease of the area of lactose on the side of a tablet which was in contact with the die. Comparing the ejection force of tablets of lactose/chitin with that of lactose/MCC, the force required was significantly smaller for the former at 10 to 50% addition ($p<0.01$). At more than 10% addition the tablets of lactose/chitosan required significantly smaller ejection force than the tablets of lactose/MCC ($p<0.01$). Thus, it was found that chitin and chitosan had better lubricating properties than MCC.

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References and Notes

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