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Directly Compressed Tablets containing Water-insoluble Glucan and Microcrystalline Cellulose in Addition to Lactose[1)]

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In order to investigate the pharmaceutical availability of the water-insoluble glucan produced by *Streptococcus mutans*, application of the glucan as a filler for directly compressed tablets was studied. The fluidity of combined powder of glucan with lactose was determined and then the hardness and the disintegration properties of directly compressed tablets of these mixtures were studied in comparison with those of tablets containing microcrystalline cellulose (MCC). The fluidity of the powder mixture was not much improved by the addition of glucan to lactose. The hardness of tablets containing glucan was higher than that of tablets containing MCC over the concentration range used in this experiment (4—50%). However, the disintegration properties of tablets containing a large amount of glucan were inferior to those of tablets containing the same amount of MCC, as the disintegration took place immediately when the concentration of glucan was lower than 20% but was retarded gradually at glucan levels higher than 25%. The hardness of tablets containing glucan increased with increase in the compressional pressure, but the disintegration properties were not changed. Further, in the dissolution study of ascorbic acid (V.C.) from the tablets, immediate dissolution of V.C. was obtained and no inhibition of dissolution of V.C. by glucan was observed. Overall, these results suggest that the water-insoluble glucan may be practically useful as a filler for directly compressed tablets.

Keywords——water-insoluble glucan; *Streptococcus mutans*; filler; directly compressed tablet; dissolution study; ascorbic acid

Tablet making by direct compression is a useful method, especially in cases where the ingredient is unstable to water, and has recently been employed in practical processes. Microcrystalline cellulose (MCC) has been widely used in such tablets, and applications of rice starch,[2)] surface-ethylated silica,[3)] hydroxypropyl cellulose,[4)] chitin and chitosan[5)] as fillers for tablets have also been reported. A natural, innocuous substance is desirable as a filler or additive, and a naturally occurring polymer such as glucan is a good candidate.

It has already been recognized that *Streptococcus mutans* produces water-insoluble polysaccharides such as glucan from sucrose,[6)] and many studies on the chemical properties[7,8)] and crystal structure[9)] of glucan have been reported. However, there is no report concerning the utilization of this natural polymer in any field. The present study was designed to investigate the possibility of using glucan as a filler for tablet making by direct compression in comparison with MCC. First, the fluidity of combined powders containing glucan and the hardness and the disintegration properties of directly compressed tablets of these powders were studied. In addition, the dissolution of ascorbic acid (V.C.) from tablets containing the glucan was investigated.

Experimental

Materials——Water-insoluble glucan was obtained by fermentation from sucrose by the action of the extracellular glucosyltransferases present in the culture media of *Streptococcus mutans*. Commercial lactose J.P.X, ascorbic acid J.P.X (V.C.) and micro crystalline cellulose (MCC) marketed as "Avicel PH102" (Asahi Chemical Industry Co., Ltd.) were used. All powders except lactose were used after being sieved at 100—200

mesh (149—77 μm). The arithmetic means of the particle sizes of glucan and MCC determined by using an image analysis system (Hamamatsu TV Co., Ltd. HTV C1285/C995-02) and were 110.5 and 126.2 μm, respectively. The moisture contents of glucan, MCC and lactose determined with a microwave moisture meter (Anritsu Denki K375-A1) were 5.75, 5.62 and 0.06%, respectively.

Measurement of the Angle of Repose of Powder———The angle of repose was measured by dropping an excess amount of powder at about 1 g/min on a stainless steel table of 20 mm diameter from on orifice of 3 mm at 30 mm height.

Tablet making by Direct Compression———Unless otherwise stated, flat-faced tablets (300 mg, 13 mm diameter) were made in an environment with a relative humidity of around 60% at room temperature, by direct static compression for 30 s under 100 kg/cm^2, *i.e.*, 2.0 t/punch using an evacuable die and hydraulic press for preparing KBr tablets for infrared spectroscopy (Shimadzu Corp.). No lubricant was used.

Measurement of the Disintegration Time of Tablets———The method followed the disintegration test in J.P.X using a disintegration tester (Toyama Sangyo T-2HS) except that the disintegration time of each tablet was determined and the auxiliary disk was not used.

Measurement of the Hardness of Tablets———A Monsant hardness tester was used for the measurement.

Dissolutin Study———The dissolution study was carried out according to the dissolution test No. 1 in J.P.X (ratation basket method). Distilled water (500 ml) was used as the dissolution medium and the rotation velocity was 200 rpm. At appropriate time intervals, 1 ml of the solution was taken with a 1 ml transfer pipette equipped with a filter (Ishikawa Manufacturer, Fine Filter-F), then the solution was diluted with distilled water to an appropriate concentration and the concentration of V.C. was measured by the ultraviolet absorption method at 263 nm.

Results and Discussion

Relationship between the Angle of Repose of Powder Mixture and the Concentration of Glucan or MCC

Figure 1 shows the relation between the angle of repose and the concentration of glucan or MCC added to lactose. The fluidity of both powder mixtures improved a little with increase in the concentration of glucan or MCC. The fluidity of MCC or MCC mixtures was a little better than that of glucan or glucan mixtures. However, the effects of glucan and MCC on fluidity were not large, and the use of glidants may be necessary in practical processes.

Relationship between the Hardness of Tablets and the Concentration of Glucan or MCC

The hardness of compressed tablets increased with an increase in concentration of glucan or MCC, as shown in Fig. 2. The hardness of tablets containing glucan was higher than that of

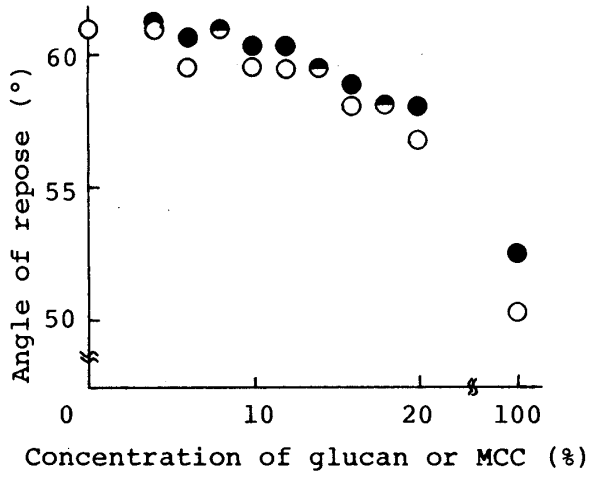

Fig. 1. Relationship between the Angle of Repose and the Concentration of Glucan or MCC

●, lactose/glucan mixture; ○, lactose/MCC mixture. Each point represents the mean of three determinations.

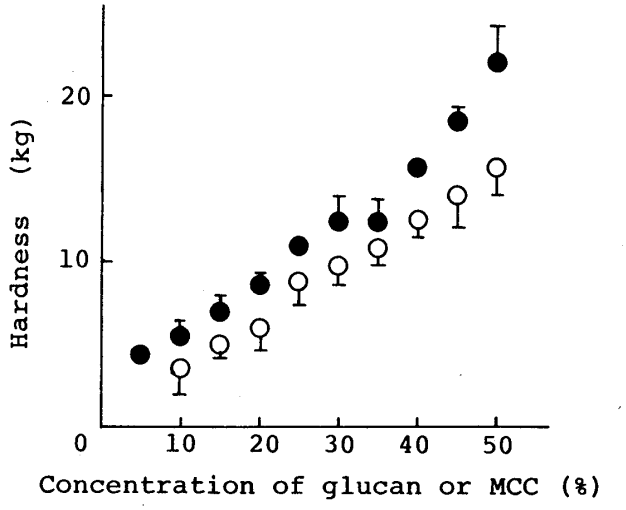

Fig. 2. Relationship between the Hardness of Tablets of Lactose/Glucan Mixture (●) or Lactose/MCC Mixture (○) and the Concentration of Glucan or MCC

Each point represents the mean ± S. D. of six determinations.

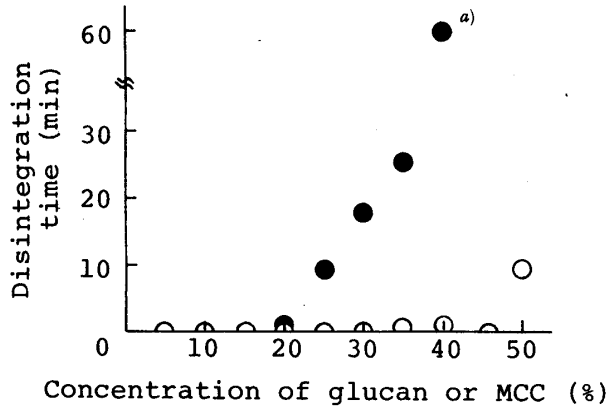

Fig. 3. Relationship between the Disintegration Time of Tablets of Lactose/Glucan Mixture (●) or Lactose/MCC Mixture (○) and the Concentration of Glucan or MCC

a) Disintegration was not completed within 60 min. Each point represents the mean of six determinations.

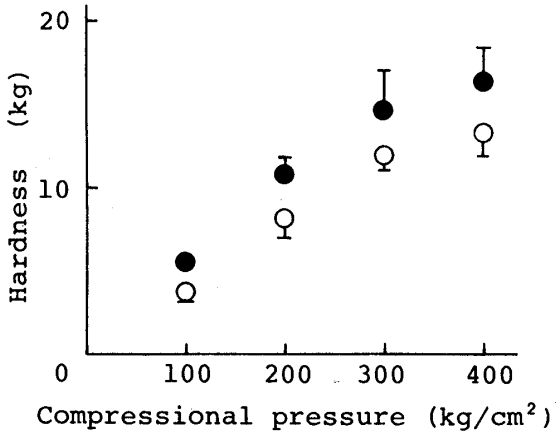

Fig. 4. Relationship between the Compressional Pressure and the Hardness of Tablets of Lactose/Glucan (9 : 1) Mixture (●) or Lactose/MCC (9 : 1) Mixture (○)

Each point represents the mean ± S. D. of six determinations.

tablets containing MCC by 1—6 kg and there were significant differences between glucan and MCC at all concentrations tested, except 35% ($p<0.05$). In addition, it was possible to make tablets with the addition of 5% glucan, but not with the addition of 5% MCC. It is suggested therefore, that glucan could be useful as a binder for tablets at low concentrations. This property of glucan might be due to its ramified chemical structure.[7,8]

Relationship between the Disintegration Time of Tables and the Concentration of Glucan or MCC

The plots of disintegration time against the concentration of glucan or MCC are shown in Fig. 3. The tablets containing MCC disintegrated immediately when the concentration of MCC was below 45%. On the other hand, the tablets containing glucan disintegrated immediately when the concentration of glucan was below 20% but showed longer disintegration times with increase in glucan concentration above 25%. This phenomenon may be due to the characteristic properties of swelling and gelation of glucan differing from those of MCC. The particles of glucan in the tablet might contact and bind to each other at concentrations above 25% and the glucan might form a gelatinous barrier to the further penetration of water into the tablet, thus inhibiting the disintegration of the tablet. This suggested that glucan might be useful in sustained release preparations of drugs at cncentrations above 40%.

Relationship between the Disintegration Time or the Hardness of Tables and the Compressional Pressure

Tablets of 90% lactose and 10% glucan or MCC were made by compression under 100, 200, 300 and 400 kg/cm^2, and the disintegration time or the hardness of these tablets was studied in relation to the compressional pressure. The plots of the hardness of tablets against the compressional pressure are shown in Fig. 4. The hardness of tablets containing glucan or MCC increased with increase in the compressional pressure. The increase in hardness was about 11 and 9 kg in tablets containing glucan and MCC, respectively, when the pressure was increased from 100 to 400 kg/cm^2. However, the tablets containing glucan was generally harder by 2 to 3 kg at any compressional pressure than that containing MCC, and this suggests the superiority of glucan to MCC as a binder.

As shown in Fig. 5, the disintegration time was prolonged with increase in the compressional pressure in tablets containing MCC, while it was not significantly changed in tablets containing glucan. The number of contact points of glucan particles might not increase and

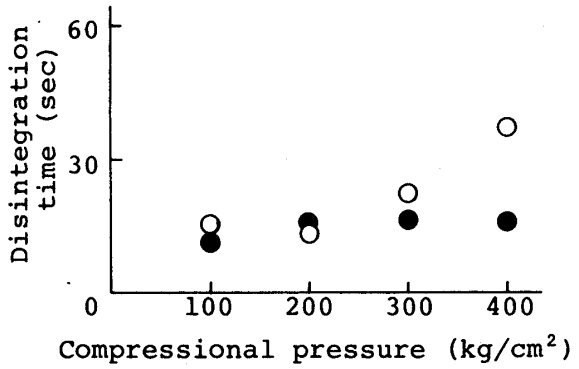

Fig. 5. Relationship between the Compressional Pressure and the Disintegration Time of Tablets of Lactose/Glucan (9 : 1) Mixture (●) or Lactose/MCC (9 : 1) Mixture (○)

Each point represents the mean of six determination.

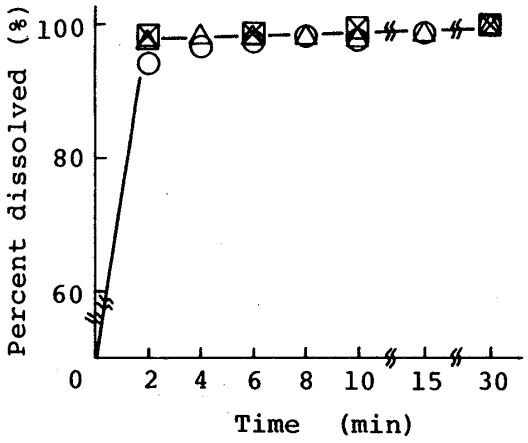

Fig. 6. Dissolution Profiles of Tablets containing Ascorbic Acid (80%) with Glucan or MCC

△, glucan, compressed under 100 kg/cm²; ○, glucan, compressed under 200 kg/cm²; ×, MCC, compressed under 100 kg/cm²; □, MCC, compressed under 200 kg/cm².

Each point represents the mean of three determinations.

TABLE I. Relationship between the Hardness of Ascorbic Acid Tablets compressed under 100 or 200 kg/cm² and the Concentration of Glucan or MCC

Filler	Concentration (%)	Compressional pressure (kg/cm²)	Hardness[a] (kg)
Glucan	10	100	2.33±0.24
		200	4.02±0.43
	20	100	4.90±0.18
		200	9.08±0.77
MCC	10	100	1.47±0.14
		200	2.28±0.24
	20	100	2.83±0.16
		200	4.70±0.15

a) Each value represents the mean ± S.D. of six determinations.

therefore the disintegration time would not be prolonged at this concentration of glucan, 10%. The results obtained above suggest that glucan might be useful as a binder in tablets made by direct compression in combination with appropriate disintegrators.

Relationship between the Hardness or the Disintegration Time of Ascorbic Acid Tablets and the Concentration of Glucan or MCC

Tablets of V.C. (90%)/glucan or MCC (10%) and V.C. (80%)/glucan or MCC (20%) mixtures were made by compression under 100 and 200 kg/cm², and the hardness and disintegration time of these tablets were studied in relation to the concentration of fillers or the compressional pressure.

As shown in Table I, the hardness of tablets containing 10% MCC and compressed under 100 and 200 kg/cm² was about 1.5 and 2.3 kg, respectively, and these tablets were brittle and occasionally showed a tendency to chip. On the other hand, the hardness of tablets containing 10% glucan and compressed under 200 kg/cm² was about 4 kg. This is adequate. In rela-

tion to the disintegration time, all tablets containing MCC made under any conditions disintegrated immediately. However, the disintegration time of tablets containing 20% glucan was significantly prolonged, *i.e.*, about 20 min.

Dissolution of Ascorbic Acid from Tablets containing Glucan or MCC

The relationship between release of V.C. from tablets containing V.C. (80%)/glucan or MCC (20%) and the compressional pressure is shown in Fig. 6. The dissolution of V.C. from tablets containing MCC was completed within two minutes. This results is reasonable in view of the rapid disintegration of tablets containing MCC. A slight delay in the dissolution of V.C. from tablets containing glucan compressed under 200 kg/cm^2 was observed in the initial stage. On the other hand, the disintegration time was about 20 min, and fragments of the tablet were still observed occasionally in the test basket (36 mesh) even after 30 min. However, in view of the complete dissolution of V.C. from the tablet, glucan did not inhibit the dissolution of V.C. A similar phenomenon was reported for tablets containing a high concentration of MCC.[10] The dissolution of V.C. from tablets containing 10% glucan was similar to that from tablets containing 20% glucan except that dissolution was a little more rapid in the initial stage. In conclusion, glucan might be practically useful as a filler for tablets prepared by direct compression and containing a water-soluble drug such as V.C.

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References and Notes

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