Development of Oral Dosage Form for Elderly Patients: Use of Agar as Base of Rapidly Disintegrating Oral Tablets

Akihiko ITO* and Masayasu SUGIHARA

Pharmaceutical Department, Tokyo Women's Medical College, 8–1 Kawada-cho, Shinjuku-ku, Tokyo 162, Japan.
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Rapidly disintegrating tablets as an oral dosage form for elderly patients with impaired swallowing were investigated using agar powders (AG) or treated agar powders (TAG).

When the compression pressure was changed from 0.4 to 2.0 ton/cm^2, the disintegration time of AG tablets increased from about 60 to about 160 s, and the hardness significantly increased from 3 to 13 kgw. The disintegration time and hardness of the TAG tablets were scarcely affected by the compression pressure: the disintegration time was 5—6 s, and the hardness was 2—3 kgw. The rapid disintegration of the TAG tablets seemed due to the rapid water penetration into the tablet resulting from the large pore size and large overall pore volume.

It was found that rapidly disintegrating oral tablets with proper hardness can be prepared using TAG.

Key words rapidly disintegrating tablet; elderly patient; oral dosage form; agar; pore size distribution; hardness

In recent years, the portion of society composed of elderly people has become larger as a result of increased longevity. The elderly have not only a change in pharmacokinetics but also deterioration in their eyesight, hearing, memory and physical abilities and changes in taste and smell. These problems require consideration for proper and rational drug treatment. Elderly individuals having hand tremors have difficulty in taking medicine such as powders and liquid and those with dysphagia have problems in taking medications prescribed in tablet and capsule form. From this perspective, jelly preparations,[1] fast dissolving dosage form in mouth,[2] water absorbing and swelling preparations,[3,4] and fast disintegrating oral tablets[5,6] offer an alternate form of oral medication for the elderly.

Fast disintegrating tablets will be preferred to powders by elderly patients having hand tremors, and those having swallowing disorders were better able to ingest them because of their rapid disintegration in the mouth. Tablets having this property are thus viewed as a valuable dosage form for these patients. Agar powders were selected as rapidly disintegrating substance because they absorb water and swell but do not become gelatinous in water of normal temperature. We investigated using several type of agar powders: Ina Agar; KT, ZR, S-6 and T-1, and found that treated powder of the KT type had the most rapid disintegration ability. In this paper, the disintegration ability of treated powders was compared with that of non treated powder using the KT type of agar powder to develop rapidly disintegrating oral tablets.

Experimental

Materials Agar powders (AG, Ina Agar KT, Ina Food Co., Nagano, Japan) were used.

Preparation of Treated Agar Powders (TAG) TAG were prepared according to the procedure shown Fig. 1.

Agar powders were made with sufficient water absorption and allowed to swell for 1 d. They were then spread out on a tray, dried at room temperature for 3 d and then ground using a grinding apparatus (Konishi Medical Surgical Co., Ltd., Osaka).

Tableting Each material was compressed into flat tablets weighing 150 mg with an 8.0 mm diameter using a compaction instrument for KBr pellets of under 0.4, 2.0, 4.0 or 6.0 ton/cm^2 for 1 min.

Measurement of Particle Size Distribution and Observation of Particles The measurement of particle size distribution was performed by sieving method using a vibration sieve apparatus. Particles of the materials were observed using a CCD camera.

Measurement of Contact Angle The apparent contact angle of each material was measured according to the method of Ishizaka *et al.*,[7] that is, a photograph was taken as soon as 5 μl of distilled water was dropped on the surface of each tablet after compression at 4.0 ton/cm^2 for 1 min. The apparent contact angle (θ) was calculated from Eq. 1. The data are the mean of 6 experiments:

$$\tan(\theta/2) = 2h/d \quad (1)$$

where h is the height of the drop of water and d is the width.

Measurement of Pore Size Distribution The pore size distribution in each powder and tablet was measured using a mercury intrusion porosimeter (Micromeritics Pore Sizer 9320, Shimadzu Co., Ltd., Kyoto, Japan)

Measurement of the Tablet Thickness and Hardness Tablet thickness was measured with calipers, and hardness was measured using a Monsant hardness tester. The data are the mean ± S.D. of 10 tablets.

Disintegration Test The disintegration test was made using a disintegration tester (Toyama Co., Ltd., Tokyo, Japan) without the support disk according to the disintegration method described in JP XII. The test fluid was distilled water at 37 °C. The data are the mean ± S.D. of 6 tablets.

Water Absorption Test The water absorption test was carried out using a water absorption apparatus according to the method of Watanabe and Sugihara[3] for the tablets. The data are the mean of 3 tablets.

Results and Discussion

Physical Properties of Powders Table 1 shows the physical properties of AG and TAG.

For the particle size distributions, the ratio of particles above 100 mesh size was *ca.* 60% in TAG and *ca.* 20% in AG, so that, TAG has larger particles than AG. For

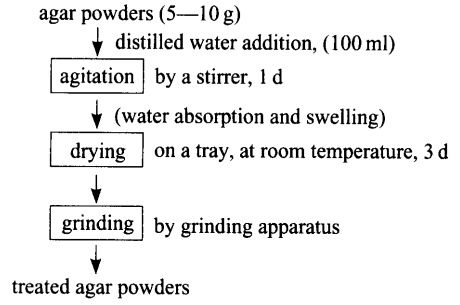

Fig. 1. Preparation Procedure of Treated Agar Powders (TAG)

* To whom correspondence should be addressed.

the bulk density, the TAG showed smaller values than the AG. It was then presumed that the TAG wets more slowly because it has a larger apparent contact angle than the AG.

The large pores of the TAG particles observed in the CCD photograph are shown in Fig. 2. Results of the measurement of pore size distribution by mercury intrusion porosimetry (Fig. 3) showed that the TAG has a larger pore size than the AG: total pore size volume being 1.49 ml/g and 1.04 ml/g respectively. From these results, it was recognized that the treatments of water absorption, swelling, drying at room temperature and grinding of the agar powders form the particle pores. The pores are presumed to be formed when the water absorbed in particles evaporates during drying.

The bacillus number in AG was less than 2000/g. Although that in TAG was higher, it is decreased by the sterilized treatment.

Effect of Compression Pressure on Disintegration Time and Hardness The effect of the compression pressure on disintegration time and hardness of the two types of tablets is shown in Fig. 4.

In AG tablets, when the compression pressure was changed from 0.4 to 2.0 ton/cm^2, the disintegration time increased from *ca.* 60 to *ca.* 160 s, and the hardness increased greatly from 3 to 13 kgw. When the compression pressure was increased from 2.0 to 6.0 ton/cm^2, however, these two factors scarcely changed. On the other hand, in the TAG tablets the disintegration time significantly increased when the compression pressure was changed from 0.4 to 2.0 ton/cm^2 and the hardness increased with increase in pressure. However,the disintegration time was *ca.* 5—6 s and the hardness was *ca.* 2—3 kgw.

Thus the TAG tablets have less hardness than AG tablets but disintegrate very rapidly irrespective of the compression pressure.

The relationship between compression pressure and tablet thickness which implies a change in the volume was investigated (Fig. 5).

The thickness of each tablet decreased as the compression pressure increased from 0.4 to 2.0 ton/cm^2, and the difference was more pronounced in the AG tablets. The effect of compression pressure on tablet thickness was negligible when the pressure was above 2.0 ton/cm^2. No difference of thickness between the two tablet types was observed at 0.4 ton/cm^2, but the AG tablets were thinner than the TAG at pressures above 2.0 ton/cm^2.

From the results of hardness and thickness measurements, it was assumed that the TAG is harder to make tightly compact than the AG.

Pore Size Distribution of Tablets and Water Absorption Test The internal structure of tablets, that is, pore size distribution,[8] water penetration into tablets[9] and swelling of disintegration substance[10] are suggested to be the mechanisim of disintegration. The pore size distribution was then measured and a water absorption test was carried out for each tablet compressed at 0.4 and 4.0 ton/cm^2 (Fig. 6).

Although the difference in pore size between the AG and TAG tablets at 0.4 ton/cm^2 was hardly noticeable, the latter had a larger pore size at 4.0 ton/cm^2. In the AG tablets, the pore size significantly decreased and the total pore volume also significantly decreased from 0.279 to 0.097 ml/g with an increase in the compression pressure. In the TAG tablets, the total pore volume decreased

Table 1. Physical Properties of Agar Powders (AG) and Treated Agar Powders (TAG)

	AG	TAG
Bulk density (g/ml)	0.423	0.330
Tap density (g/ml)	0.588	0.355
Particle size distribution		
Size (mesh)	Weight (%)	
24/ 42	0	8.57
42/ 48	0.30	7.57
48/ 65	0.75	15.00
65/100	20.10	31.58
100/150	19.70	19.14
150/200	35.20	11.43
200/270	13.60	1.14
270 pass	10.35	5.57
Apparent contact angle (°)	42.1	61.6

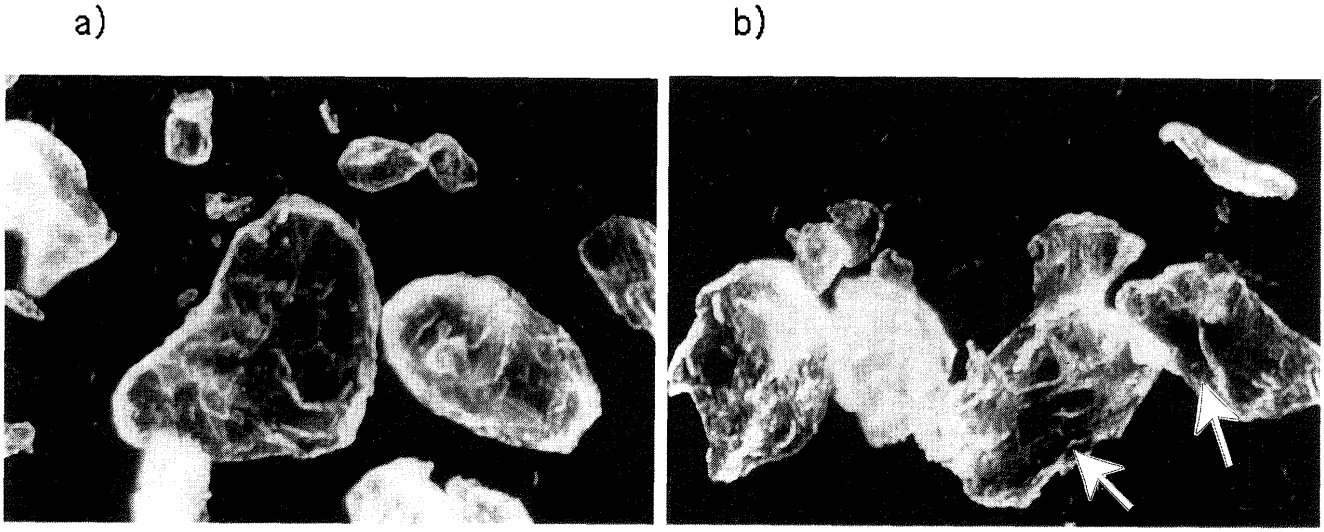

Fig. 2. Photographs of Agar Powders (AG) and Treated Agar Powders (TAG)
a) AG, b) TAG (× 500).

from 0.265 to 0.1611 ml/g with an increase in pressure, but the pore size was hardly changed.

The water absorption test results are shown in Fig. 7.

The water penetration rate into the AG tablets decreased with increase in compression pressure, while that of the TAG tablets changed little. The latter showed rapid water penetration than the former under any pressure. The amount of water absorbed by the TAG tablets after 10 s was 22-fold more than the AG tablets.

It was presumed that the decrease in water penetration rate with increase in compression pressure of the AG tablets is due to the decrease in pore size, and the water penetration rate of the TAG tablets was hardly changed because the pore size was hardly changed. Consequently, it was postulated that the rapid disintegration of the TAG tablets is due to rapid water penetration resulting from large pore size and large overall pore volume. However, although little difference in pore size was observed between the AG and TAG tablets at 0.4 ton/cm^2, the latter showed more rapid disintegration. This phenomenon was believed due to the difference in the kind of pores.

Tablet pores are both intra-particle and inter-particle. The large inter-particle pores allow water to penetrate rapidly into the tablets. In the AG, the difference between bulk density and tap density was significant as noted in Table 1, and tablet thickness was much less and the hardness much more when the compression pressure increased from 0.4 to 2.0 ton/cm^2. Pore size also significantly decreased with an increase in compression pressure as shown in Fig. 6. In the TAG, on the other hand, the difference between the bulk density and tap density was slight, and the change in thickness and hardness of the tablets was minimal compared with that of AG. Tablet pore size changed little with increase in compression pressure. It was therefore presumed that

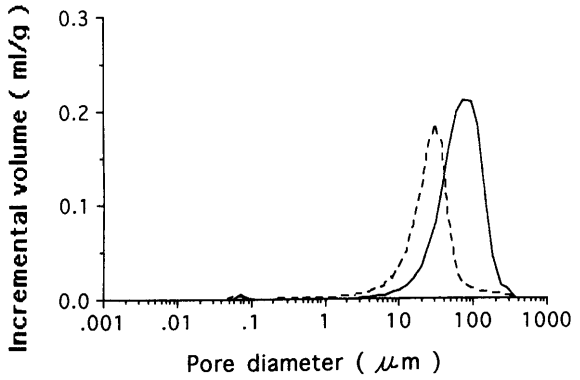

Fig. 3. Pore Size Distributions of Agar Powders (AG) and Treated Agar Powders (TAG)

------, AG; ——, TAG.

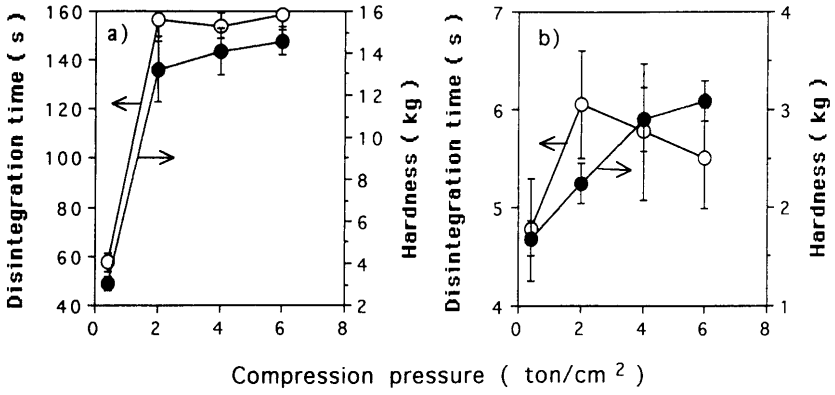

Fig. 4. Effect of Compression Pressure on Disintegration Time and Tablet Hardness

a) AG tablets, b) TAG tablets. ○, disintegration time; ●, hardness.

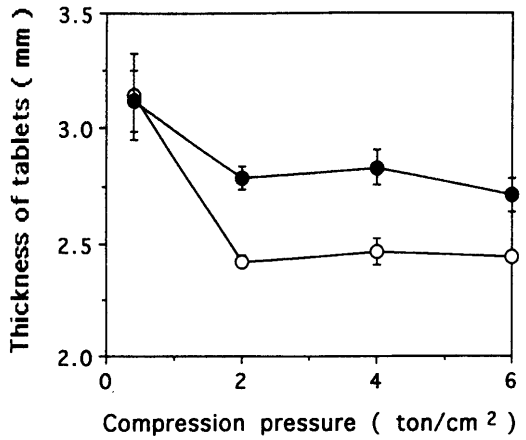

Fig. 5. Relationship between Compression Pressure and Tablet Thickness

○, AG tablets; ●, TAG tablets.

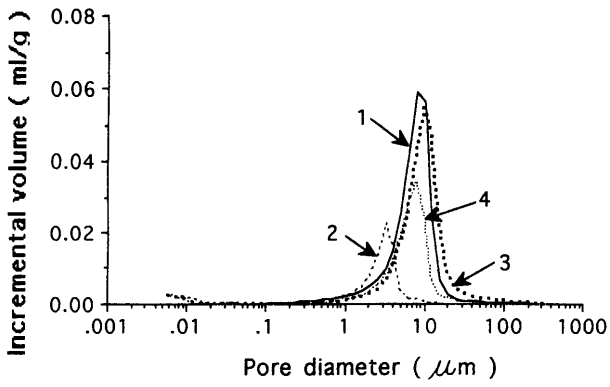

Fig. 6. Pore Size Distribution of Tablets

1. ——, AG tablets (0.4 ton/cm^2); 2. – – –, AG tablets (4.0 ton/cm^2); 3. ·····, TAG tablets (0.4 ton/cm^2); 4. ------, TAG tablets (4.0 ton/cm^2).

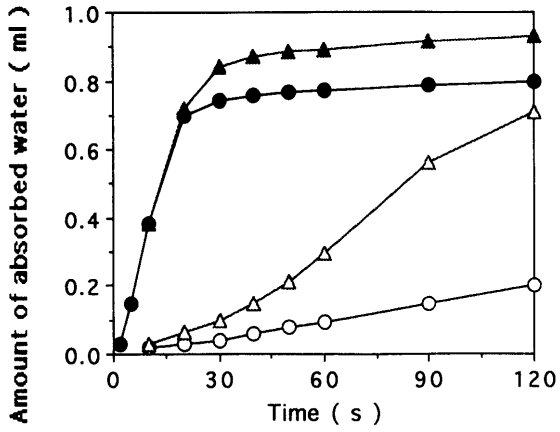

Fig. 7. Water Penetration into Tablets

△, AG tablets (0.4 ton/cm^2); ○, AG tablets (4.0 ton/cm^2); ▲, TAG tablets (0.4 ton/cm^2); ●, TAG tablets (4.0 ton/cm^2).

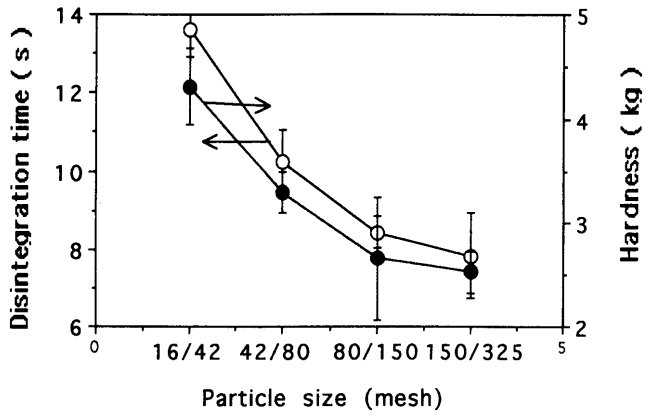

Fig. 8. Effect of Particle Size on Disintegration Time and Hardness of TAG Tablets

Compression pressure: 4.0 ton/cm^2. ○, disintegration time; ●, hardness.

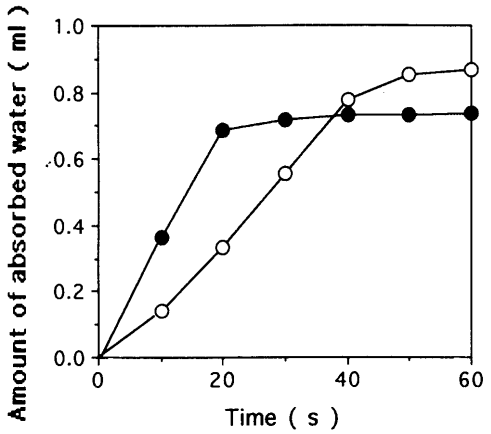

Fig. 9. Effect of Particle Size on Water Penetration into TAG Tablets

Compression pressure: 4.0 ton/cm^2. ○, 16/42 mesh; ●, 150/325 mesh.

the packing is mainly heightened by the decrease in inter-particle pores because the AG easily move in primary compression, and the TAG was primarily compressed by transformation of the porous particles because the TAG is hard to move, that is, the intra-particle pores are decreased, while the inter-particle pores remain. The TAG tablets therefore showed a more rapid water penetration rate than the AG tablets, as well as more rapid disintegration.

Effect of Particle Size in TAG The effect of particle size of the TAG on the disintegration time, tablet hardness and water penetration was investigated for TAG tablets compressed at 4.0 ton/cm^2 because it was suspected that their rapid disintegration is due to the difference in particle size distribution between the AG and the TAG (Fig. 8).

The disintegration time lengthened from *ca.* 8 to *ca.* 14 s and the hardness increased from 2.5 to 4.5 kgw with increase in particle size.

The influence of particle size on thickness of the tablets was found to be negligible.

A water absorption test was carried out for each tablet prepared with 16/42 or 150/325 mesh TAG powders (Fig. 9).

The water penetration rate in the 150/325 mesh was faster than that in the 16/42 mesh, with the amount of absorbed water in the former after 10 s showing about a 3 fold increase over tablets of the 16/42 mesh. The absorbed water saturated at *ca.* 20 s in tablets prepared from the 150/325 mesh, while in those prepared from the 16/42 mesh, the saturation time was *ca.* 50 s. This difference in water penetration reflected the result of the disintegration test, that is, tablets prepared from the 150/325 mesh more rapidly disintegrated because of the more rapid water penetration.

The contact area of the larger particles enlarges and the pore size decreases because the larger particles are more greatly transformed in contact points when the particles are compressed.[11] The disintegration time was therefore believed to be longer because of the lower water penetration in the tablets with increase in particle size, and the hardness increased because the contact force between the particles increased. These results suggested that it may be necessary to select the particle size based on a proper balance between disintegration time and hardness, or to select nonsieved powders based on the results of Fig. 4. Also, the AG tablets prepared from AG containing 60% of powders under 150 mesh size disintegrated at *ca.* 150 s, but the TAG tablets prepared from the 150/325 mesh powders disintegrated at *ca.* 8 s. These findings showed that the rapid disintegration ability of TAG is not due to the difference in particle size distribution, but is the unique nature of TAG.

In conclusion, it is suggested that rapidly disintegrating tablets taken orally and having the proper hardness can be prepared from treated agar powders based on sufficient water absorption and swelling, and proper drying at room temperature followed by grinding treatment.

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