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Factors affecting the characteristics of rapidly disintegrating tablets in the mouth prepared by the crystalline transition of amorphous sucrose

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Abstract

The aim of this study is to investigate the factors affecting the characteristics of rapidly disintegrating tablets containing an amorphous ingredient prepared by crystalline transition method (CTM) under various storage conditions. Effect of storage conditions and formulating ratio of amorphous sucrose on the characteristic changes (tensile strength, porosity, and disintegration time) of the rapidly disintegrating tablets was studied. The storage conditions of different temperature and humidity affected the rate of crystalline transition and the increase in the tablet tensile strength. The faster crystalline transition resulted in a faster rate of increase in the tablet tensile strength. Regarding the effect of the formulating ratio of amorphous sucrose, in the case of 20–100%, the tensile strength after storage as a function of the porosity could be plotted on the same curve. For tablets containing 100% amorphous sucrose, the tablets with different porosity changed to almost the same structure due to the crystalline transition. Hence, the higher formulating ratio of amorphous sucrose provided the longer disintegration time in the mouth. Therefore, we concluded that the formulating ratio of 10–20% of the amorphous sucrose in the tablet is suitable for the rapidly disintegrating tablet in the mouth when prepared by CTM.

Keywords: Tensile strength; Porosity; Amorphous sucrose; Crystalline transition; Rapidly disintegrating tablet

1. Introduction

In recent years, various pharmaceutical dosage forms which can improve patient compliance have been actively developed. Among them, a rapidly disintegrating tablet in the mouth after oral administration is one of the most promising dosage forms.

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In our previous study, we reported that the rapidly disintegrating tablet was prepared by storing the tablet compressed with a mixture of mannitol and amorphous sucrose at low compression pressure under certain conditions (e.g. 25 °C and 34% relative humidity) (Sugimoto et al., 2001). The tensile strength of the tablet remarkably increased during storage, although the porosity of the tablet seemed hardly changed. It was determined that the increase in the tensile strength of the tablet was due to the transition from amorphous to crystalline sucrose, and the crystalline sucrose forms new internal contact points in the tablet (crystalline transition method (CTM)).

It has been suggested that the change in the water contents of the tablets during storage is greatly related to the tablet characteristics such as hardness, surface area, and disintegration time (Nyqvist and Nicklasson, 1981; Nyqvist and Lundgren, 1982; Vromans et al., 1987; Alderborn and Ahlneck, 1991). In the case of tablets containing an amorphous ingredient, one of the most important properties is its physical instability when exposed to moisture. It is well recognized that the moisture sorption of an amorphous ingredient results in crystallization, depending on the amount of sorbed moisture, temperature, and time (Roos and Karel, 1992; Sebhatu et al., 1994). Therefore, it is very important to investigate the relationship between changes in water content and tensile strength of the tablets during storage. Furthermore, the amount of amorphous ingredient in the tablet is also considered to be an important factor affecting the change of tablet characteristics.

The change in tensile strength of the tablet during storage has been the subject of numerous studies (Lordi and Shiromani, 1983, 1984; Elamin et al., 1994). However, very little fundamental study has been conducted regarding porosity change of the tablet accompanied with the crystallization, although a relatively large amount of articles reported the crystallization of the amorphous ingredient in the tablet (Rees and Shotton, 1970; Down and Mcmullen, 1985; Stubberud et al., 1996).

In the present study, using sucrose as the amorphous ingredient, the factors affecting the characteristics of rapidly disintegrating tablets in the mouth prepared by CTM is investigated. The aim of the study is to determine the factors affecting the change of tensile strength, porosity, and disintegration time of the rapidly disintegrating tablet during storage due to the crystalline transition of amorphous sucrose.

2. Materials and methods

2.1. Materials

Sucrose (Taito Co., Ltd., Japan) and D-mannitol (Kyowa Hakko Co., Ltd., Japan) used were of JP grade. D-mannitol less than 75 μm in diameter was used (mean particle diameter: D50 = approximately 40 μm). All of other materials used in this study were of reagent grade.

2.2. Methods

2.2.1. Preparation of amorphous sucrose by freeze drying

A 5% (w/v) solution was prepared by dissolving sucrose in water. The solution was placed on the shelf in a vacuum freeze-dryer (RL-100BS, Kyowa, Japan) and frozen at −50 °C for 5 h. Primary drying was performed at 0 °C (shelf temp.) for 40 h, accompanied by secondary drying at 40 °C (shelf temp.) for 20 h.

2.2.2. Mixing

Tablets containing different levels of amorphous sucrose were prepared. The mixtures of amorphous sucrose and D-mannitol in various weight ratios were mixed in a plastic bag. The mixture was sieved using a 500 μm opening screen to enhance homogeneity. Amorphous sucrose alone was also treated as well for preparing a tablet containing 100% amorphous sucrose.

2.2.3. Compressing

Each of the samples equivalent to 200 mg was compressed into flat tablets with a diameter of 10 mm using a rotary tabletting machine (F-9, Kikusui Seisakusho, Japan) at compression forces from 10 to 150 MPa. The rotating speed of the tabletting machine was set at 20 rpm. The punches and die were lubricated with a small amount of magnesium stearate using a cotton swab preceding compression.

2.2.4. Storage of tablets

The tablets were stored in desiccators over saturated salt solutions to provide constant relative humidity conditions. The relative humidity conditions

of approximately 34, 51, and 75% were controlled by using saturated solutions of magnesium chloride hexahydrate, calcium nitrate tetrahydrate, and sodium chloride, respectively. Experiments were carried out at several temperatures (25, 30, 35, and 40 °C).

2.2.5. Measurement of tablet tensile strength

The tablet crushing load (F), which is the force required to break a tablet by diametral compression, was measured using a tablet hardness tester (Tablet Tester 6D, SCHLEUNIGER, Germany). The tensile strength (T) was calculated using the following equation:

$$T(\mathrm{MPa}) = \frac{2F}{\pi DH} \times \frac{1}{1000} \quad (1)$$

Where F (N) is the crushing load, and D (cm) and H (cm) are the diameter and thickness of the tablet, respectively. The data given are the means of at least five measurements.

2.2.6. Measurement of tablet porosity

The porosity of the tablet (ε) was calculated from the tablet weight (M (g)), tablet volume (V (cm^3)), and thickness and true density of powders (ρ (g/cm^3)) using the following equation:

$$\varepsilon(\%) = \left(1 - \frac{M}{V\rho}\right) \times 100 \quad (2)$$

The diameter and thickness of tablet for calculation of tablet volume were measured with a micrometer. The tablet volume was calculated from the diameter and thickness. The true density of powder was determined by a pycnometer (autopycnometer type: 1320, Micromeritics, USA).

2.2.7. Measurement of disintegration time in the mouth

The time required for complete disintegration in the mouth was measured in five healthy volunteers. The end point for the disintegration in the mouth is the time when the tablet placed on the tongue disintegrates until no lumps remain. The volunteers kept their tongues motionless during the test.

2.2.8. Scanning electron microscopy (SEM)

The morphology of a cross section of a tablet consisting of 100% amorphous sucrose or the crystallized sucrose was investigated by SEM (S-2250N, HITACHI, Japan) at an accelerating voltage of 15 kV.

2.2.9. Measurement of water content

Water content was determined gravimetrically by the decrease in weight to constant value while increasing in temperature from room temperature to 200 °C. Samples weighing about 5 mg were examined using a thermogravimetric analyzer (TGA-50, Shimazu Seisakusho, Japan). A heating rate of 5 °C/min was employed in the atmosphere of nitrogen with the sample kept in an aluminum pan.

3. Results and discussion

3.1. Effect of storage conditions on the characteristics of rapidly disintegrating tablets

Fig. 1 shows the moisture sorption profiles of tablets containing mannitol and amorphous sucrose (8:2) stored under different relative humidity conditions at 25 °C. Under any relative humidity condition, the water content increased to about 1.5%, followed by a decrease to almost zero. This moisture sorption behavior of tablets should almost correspond to that of the amorphous sucrose (Palmer et al., 1956; Saleki-Gerhardt and Zografi, 1994), since the critical relative humidity of mannitol is over 90%.

It is generally recognized that moisture sorption is accompanied by the crystallization of amorphous sucrose (Makower and Dye, 1956). At the first stage of the moisture sorption profile, moisture is absorbed into the amorphous sucrose, leading to the formation of hydrate amorphous. The absorbed water can act as a plasticiser and greatly influence the free volume, due to breakage or a rupture of hydrogen bonds between the solid molecules. This leads to a decrease in the solid glass transition temperature (T_g) to or below the operation temperature, with a change from a glassy state to a rubbery state. At the second stage (lag time and loss of water), the hydrate amorphous with an increased physical reactivity can not retain the relatively large amount of moisture and the loss of moisture is initiated, i.e., crystallization of the amorphous sucrose occurs with consequent release of the sorbed water.

Therefore, these results indicate that the hydrated amorphous in the tablet was converted into the

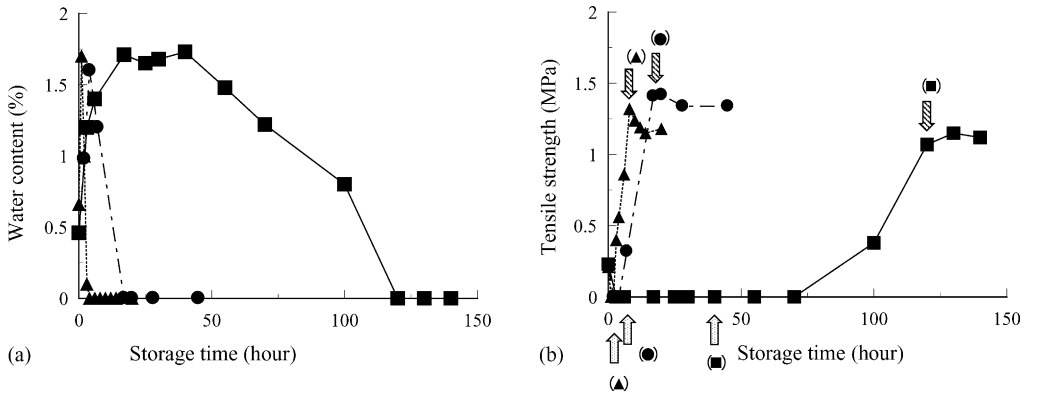

Fig. 1. Moisture sorption profiles (a) and change in tensile strength (b) of tablets containing mannitol and amorphous sucrose (8:2), stored under different relative humidity conditions at 25 °C. The arrows in (b) represent the starting points of moisture desorption (⇧) or the ending points of moisture desorption (⇩). (■), 34% RH; (●), 51% RH and (▲), 75% RH.

crystalline form. Furthermore, storage under higher relative humidity conditions led to a faster moisture uptake in a shorter time period before the crystallization took place. When stored under 51 or 75% relative humidity, therefore, the obvious time lag before leading to the loss of water was not observed because of a too high rate of crystallization, though the time lag was observed under the storage condition of 34% relative humidity.

As shown in Fig. 1(b), the tensile strength changes were observed in the tablets stored under different relative humidity conditions at 25 °C. The tensile strength increased with the storage time under every humidity condition investigated, and the plateau levels of tensile strength were almost same regardless of the storage humidity. Furthermore, the higher storage humidity resulted in a faster rate of increase in the tensile strength.

Next, a closer observation revealed that the tensile strength decreased to zero at an extremely early stage of storage. The observed decrease in tensile strength should be caused by a moisture sorption at this stage. The amorphous sucrose absorbed the moisture, and a glass-to-rubber transition took place along with an increased molecular mobility. This result confirms that the absorbed moisture plasticizes the amorphous sucrose regions and ruptures hydrogen bonds (Ahlneck and Zografi, 1990). Consequently, the moisture could soften the solidified amorphous bridges between mannitol particles, and the tablet tensile strength could be decreased. To clarify the relationship between the crystallization of the amorphous sucrose and the change in tensile strength, the starting points of moisture sorption and the ending points of loss of moisture absorbed are also shown in Fig. 1(b), by arrows. The starting points of the loss of moisture corresponds to an initiation of crystallization of the amorphous sucrose, and the points where no further loss of moisture was observed correspond to the end of crystallization (Scoik and Carstensen, 1990). Therefore, it seems reasonable to conclude that the tensile strength reached the plateau level when the crystallization of the amorphous sucrose was completed.

Furthermore, the effect of storage temperature on the moisture uptake of amorphous sucrose was studied. The tablets were stored at different temperatures (25, 30, 35, and 40 °C) under 34% relative humidity. As shown in Fig. 2(a), at any temperature, the moisture uptake reached the peak level of about 1.5%, followed by a sharp decrease almost to zero, which is consistent with the findings stored at different humidity conditions shown in Fig. 1(a). The higher storage temperature resulted in the higher rate of the moisture uptake and loss, and the lag time for moisture uptake was not observed since the rate of the crystallization was too high.

The tensile strength increased and reached plateau level with the storage time at any given temperature, as shown in Fig. 2(b). The plateau level was almost independent of the storage temperature. The rate of change in the tensile strength, however, increased with increasing the storage temperature. It is reported that the rate of crystallization increased with the difference between storage temperature and glass transition temperature (Hancock et al., 1995). Therefore, the

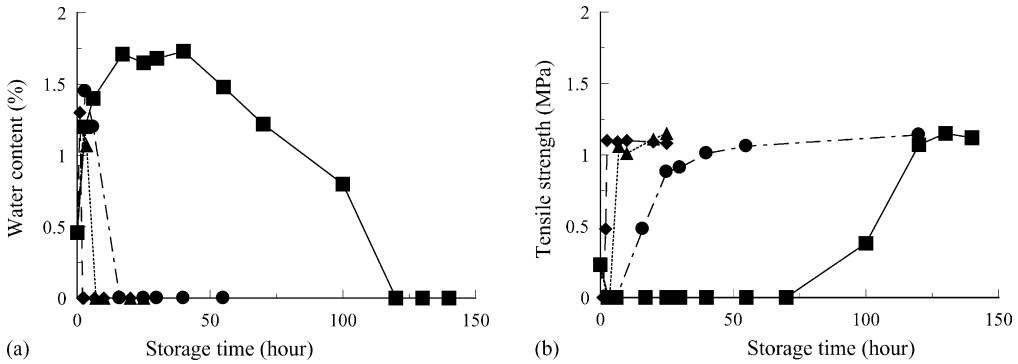

Fig. 2. Moisture sorption profiles (a) and change in tensile strength (b) of tablets containing mannitol and amorphous sucrose (8:2), stored at different temperatures under 34% RH. (■), 25 °C; (●), 30 °C; (▲), 35 °C and (♦), 40 °C.

higher storage temperature provides a higher rate of crystallization of the amorphous part, and hence it is faster to reach plateau level of tensile strength of the tablet.

The rate constants of crystallization versus temperature are plotted in Fig. 3 according to the Arrhenius equation. Carstensen and Scoik studied the moisture uptake profile for amorphous sucrose in details. In the study, it was revealed that hydrated amorphous sucrose converted into anhydrous crystalline sucrose at the point where water loss has completed (Carstensen and Scoik, 1990). Therefore, the rate constants were determined by the reciprocal of time when the moisture loss was completed, i.e., the amorphous sucrose was completely crystallized. The Arrhenius type plot shown in Fig. 3 is quite linear (correlation coefficient: 0.957), and this result indicates that the rate of crystallization is only dependent on the storage temperature when the relative humidity is constant.

3.2. *Effect of the formulating ratio of amorphous sucrose on the characteristics of rapidly disintegrating tablets*

Fig. 4 shows tensile strength–compression pressure profiles for tablets containing various ratios of mannitol and amorphous sucrose. The tensile strength increased with an increase in compression pressure over the entire range of pressure investigated, and also increased with the higher formulating ratios of amorphous sucrose. This result is attributed to the good compactability of amorphous sucrose.

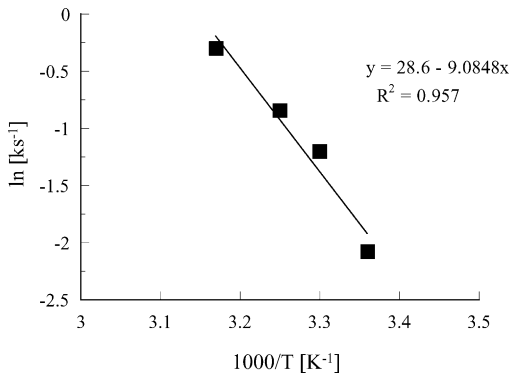

Fig. 3. Arrhenius plot of crystallization rate of amorphous sucrose. Intrinsic rate constant, *k*, represents the crystallization rate of amorphous sucrose determined by the reciprocal of time when the moisture loss was completed.

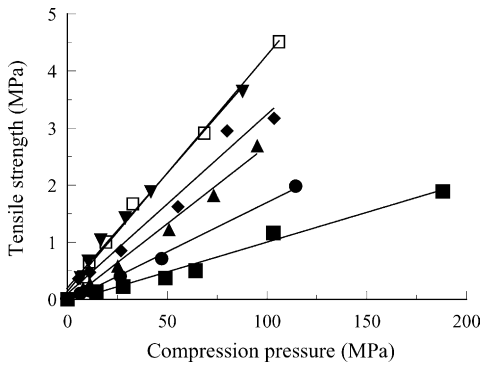

Fig. 4. Tensile strength-compression pressure profiles for tablets containing various ratios of mannitol and amorphous sucrose before storage. Formulating ratio of sucrose: (■), 10%; (●), 20%; (▲), 40%; (♦), 60%; (▼), 80% and (□), 100%.

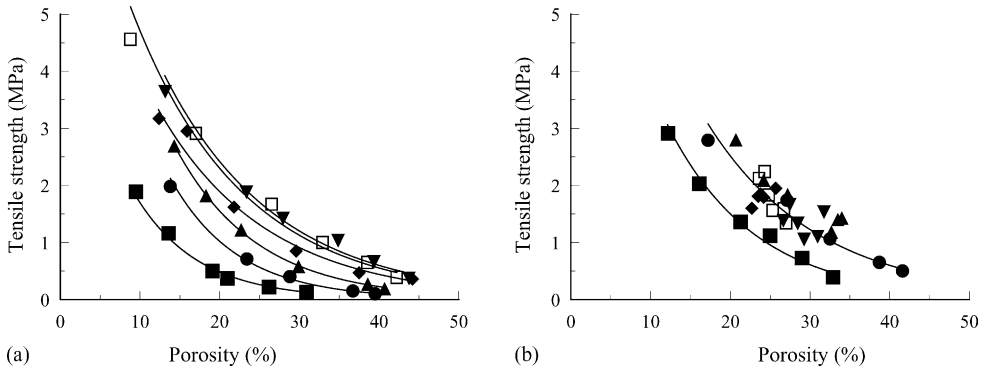

Fig. 5. Relationship between tensile strength and porosity of tablets containing various ratios of mannitol and amorphous sucrose before (a) and after (b) storage under conditions of 25 °C and 34% relative humidity for five days. Formulating ratio of sucrose: (■), 10%; (●), 20%; (▲), 40%; (♦), 60%; (▼), 80% and (□), 100%.

These tablets were stored at 25 °C under 34% relative humidity for five days, and comparison of the tensile strength of the tablets with different porosities prepared by the changing compression force was made between before and after storage.

With regard to the tablets before storage (Fig. 5 (a)), the higher formulating ratio of amorphous sucrose provided higher tensile strength. On the other hand, tensile strength and porosity of the tablets had remarkably changed after storage (Fig. 5 (b)). The result of powder X-ray diffraction measurement showed that this change was caused by the crystallization of amorphous sucrose in the tablets (Sugimoto et al., 2001). In the case of 10% sucrose, although the increased tensile strength of tablets after storage was a little less than 1 MPa at suitable porosity for the rapidly disintegrating tablets (25–30%), it seemed to be possible for patients to take the tablets out of the blister. In the case of 20–100% of sucrose, the tensile strength was sufficiently high to use and was surprisingly plotted on the same curve.

Relationship between changes in tensile strength and changes in porosity during storage is shown in Fig. 6. In the case of 60–100% of the formulating ratio, the larger change in porosity provided the larger change in tensile strength. In this figure, the positive change in porosity indicates the expansion of the tablets. On the other hand, the negative change in porosity indicates the shrink of the tablets. This result shows that the tensile strength increased in accordance with the shrink of the tablets, whereas the tensile strength decreased in accordance with expansion of the tablets. In the case of 10 and 20% of the formulating ratio, however, the tensile strength increased with a little increase in porosity. Therefore, from the result, this range of formulating ratio (10–20%) of sucrose was considered to be suitable for the rapidly disintegrating tablets in the mouth, because the disintegration time in the mouth will not be delayed. In addition, in the case of 40% of the formulating ratio, the intermediate change between 10–20% and 60–100% of the formulating ratio was observed.

To clarify the morphological change in the internal structure, the scanning electron micrographs of the 100% amorphous sucrose tablet before and after crystallization are shown in Fig. 7. In the tablets before crystallization, a different internal structure was observed according to the compression pressure. On the other hand, in the crystallized tablets, almost the

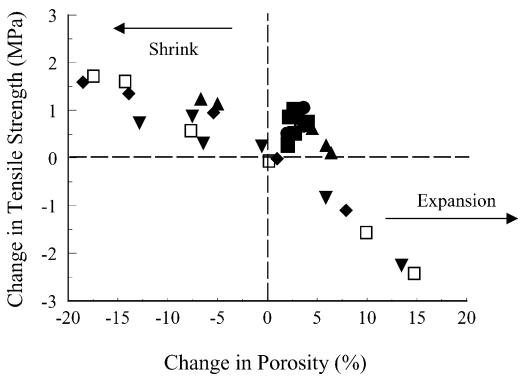

Fig. 6. Relationship between change in tensile strength and porosity of tablets containing mannitol and amorphous sucrose during storage. Formulating ratio of sucrose: (■), 10%; (●), 20%; (▲), 40%; (♦), 60%; (▼), 80% and (□), 100%.

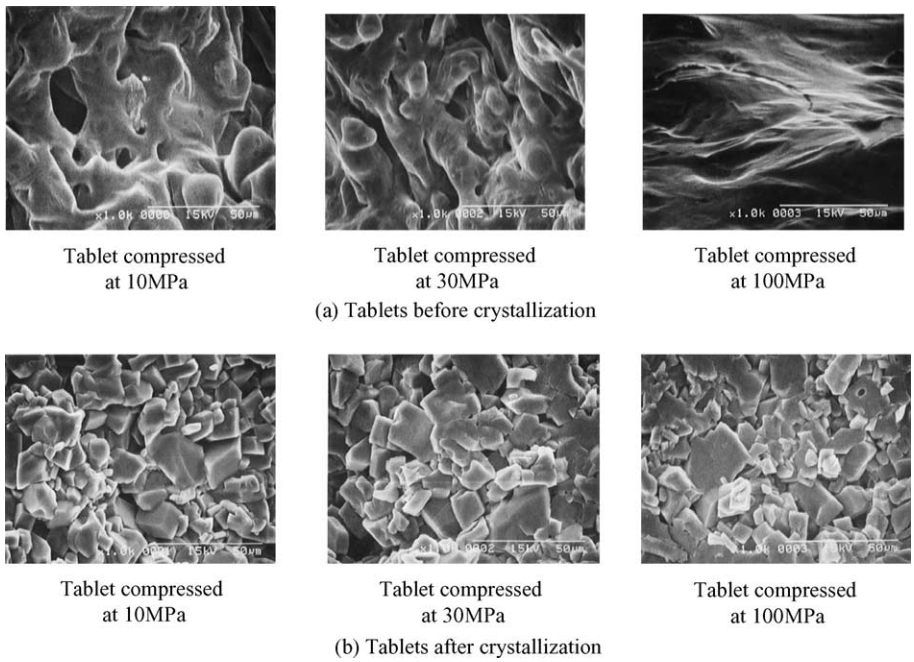

Fig. 7. Scanning electron micrographs of tablets containing 100% amorphous sucrose before and after crystallization.

same structure where the crystallized particles were arranged regularly was observed. Therefore, it is considered that, as a result of the crystallization, the same packing structure where the spherical particles are most closely packed (porosity: 25–30%) was produced, i.e., the tablets with higher initial porosity shrank, whereas the tablets with lower porosity expanded due to the crystallization of amorphous sucrose.

For the rapidly disintegrating tablets, it is required to maintain high porosity during the manufacturing process, to have a good disintegrating property in the mouth. In the case of 40–100% of the formulating ratio of sucrose, however, the above results indicate that there is a tendency toward decrease in the tablet porosity in the range of more than approximately 25–30%. Therefore, the effect of the formulating ratio on the characteristics of the rapidly disintegrating tablet was investigated.

Table 1 lists the effect of the formulating ratio of sucrose on the characteristics of rapidly disintegrating tablets. In the previous paper (Sugimoto et al., 2001), we reported that the tablets containing mannitol and sucrose (20%) with approximately 30% porosity are desirable for rapidly disintegrating tablets in the mouth. In this study, the characteristics of tablets with different ratio of sucrose were compared. In the case of 10% of the formulating ratio, the disintegrating time in the mouth was within 10 s, whereas the tensile strength was a little less than the desirable value (1 MPa). It is reported that a tablet with a diameter of 8 mm and a hardness of 5 kg is satisfactorily applicable to the manufacture of rapidly disintegrating tablets (Shu et al., 2002). The hardness corresponds to approximately 1 MPa of tensile strength. In the case of 20% of the formulating ratio, the higher tensile strength resulted in the longer disintegration time in the mouth. Among them, a tablet with 33% porosity was the most suitable for rapidly disintegrating tablets in the mouth (tensile strength: 1.05 MPa; disintegration time in the mouth: 16 s). This result indicates that the characteristics of tablets with the same formulation are mainly influenced by the porosity of tablets. However, the disintegration time in the mouth of tablets with more than 40% of the formulating ratio was remarkably prolonged to be more than 80 s. Furthermore, for the tablets with 20% of the formulating ratio, the disintegration time in the mouth of the tablets with 1.73 MPa of tensile strength was 50 s, and was obviously shorter than that

Table 1
Effect of formulating ratio of sucrose on the characteristics of rapidly disintegrating tablets in the mouth[a]

Formulating ratio of sucrose (%)	Tablet properties after storage		
	Tensile strength (MPa)	Porosity (%)	Disintegration time in the mouth (s)
0	0.11 ± 0.01	27.0 ± 1.0	6 ± 1
10	0.73 ± 0.05	29.0 ± 0.3	12 ± 3
20	0.64 ± 0.02	38.8 ± 0.7	10 ± 2
	1.05 ± 0.08	33.0 ± 2.1	16 ± 4
	1.73 ± 0.11	27.2 ± 0.6	50 ± 7
40	1.18 ± 0.16	32.7 ± 0.8	80 ±13
80	1.33 ± 0.10	28.5 ± 1.2	120 ± 19
100	1.55 ± 0.58	25.8 ± 2.2	>120

[a] All results are represented as mean ± S.D. ($n = 5$).

of the tablets with 80–100% of the formulating ratio having a little lower tensile strength. Therefore, it is obvious that, in the case of tablets except for 10% of the formulating ratio, regardless of having similar tensile strength, the higher formulating ratio of the amorphous sucrose provided the longer disintegration time in the mouth. Consequently, it is concluded that the tablets with the formulating ratio of 10–20% are suitable for rapidly disintegrating tablets with respect to tablet characteristics, tensile strength, and disintegration time in the mouth.

4. Conclusions

We investigated the factors affecting the characteristics of rapidly disintegrating tablets in the mouth prepared by CTM, using sucrose as the amorphous ingredient. The rate of increase in the tensile strength of tablets containing mannitol and amorphous sucrose was found to be dependent on the relative humidity or temperature during storage. The storage at higher relative humidity or higher temperature resulted in the faster increase in the tablet tensile strength caused by the faster moisture uptake and crystallization of the amorphous sucrose.

Regarding the effect of the formulating ratio of amorphous sucrose on the tablet characteristics, remarkable change in tensile strength and porosity of the tablets were observed during storage. In the case of 20–100% of amorphous sucrose, the tensile strength as a function of the porosity was plotted on the same curve, due to the crystallization of amorphous sucrose. For tablets containing 100% amorphous sucrose, the porosity and tensile strength of tablets compressed at different pressures changed to almost the same level due to the crystallization of amorphous sucrose. That value of porosity (approximately 25–30%) corresponded to the packing characteristics where the spherical particles are most closely packed. For a rapidly disintegrating tablet in the mouth prepared by using CTM, we concluded that the formulating ratio of 10–20% of amorphous sucrose in the tablet is optimal.

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