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Development of manufacturing method for rapidly disintegrating oral tablets using the crystalline transition of amorphous sucrose

Masaaki Sugimoto [a,*], Shinji Narisawa [a], Koji Matsubara [a], Hiroyuki Yoshino [a], Minoru Nakano [b], Tetsurou Handa [b]

[a] *Pharmaceutical Development Laboratories, Tanabe Seiyaku Co., Ltd., 16-89 Kashima 3-chome, Yodogawa-ku, Osaka 532-8505, Japan*
[b] *Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan*

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Abstract

The industrial manufacturing of rapidly disintegrating oral tablets with a sufficient tensile strength was investigated. The manufacturing method of the tablets involved the crystalline transition of amorphous sucrose that was produced in the process of fluidized bed granulation of mannitol using sucrose solution as a binder. The aim of this article was to clarify the usefulness of amorphous sucrose formed during the granulation for the rapidly disintegrating oral tablets manufacturing, and to investigate the effects of crystalline transition of the amorphous sucrose in granules on the characteristics of the resultant tablets prepared by this crystalline transition (CT) method. The X-ray diffraction measurement and thermal analysis showed that amorphous sucrose was effectively formed in granules consisting of 95% mannitol and 5% sucrose when the granulation was performed on the condition of water content of 4%. The tensile strength of tablets comprised of the granules, which were compressed before the crystallization of amorphous sucrose, increased remarkably after storage, because new internal solid bridges were formed in the tablets as a result of the crystallization. We conclude that rapidly disintegrating oral tablets can effectively be manufactured by the CT method using the granules obtained by the fluidized bed granulation method.

Keywords: Fluidized bed granulation; Amorphous sucrose; Crystallization; Tensile strength; Rapidly disintegrating oral tablet

1. Introduction

Elderly people, children and patients sometimes have difficulties swallowing tablets or hard gelatin capsules. In addition, the difficulties also apply to not only patients but to active working people who have no access to water. These problems can be resolved by means of tablets which disintegrate rapidly in the mouth. Some useful techniques to prepare such tablets have been developed. One is a molding tablet, and others are compressed tablets. A freeze-dried tablet (a molding tablet) made from water-soluble materials disintegrates instantly in the saliva, but the structure is so brittle that it cannot be handled easily (Seager, 1998; Corveleyn and Remon, 1997). In general, compressed tablets can be manufactured at a low price. To give the rapidly disintegrating tablets, low-substituted hydroxypropylcellulose is compressed with microcrystalline cellulose, but the patients often feel a roughness in their mouth due to their incomplete solubility (Bi et al., 1996). Other rapidly disintegrating tablets are the ones with treated agar (Ito and Sugihara, 1996) or camphor as a subliming material (Koizumi et al., 1997). However, the manufacturing methods of these tablets are more or less complicated. Recently, we developed the preparation method for rapidly disintegrating oral tablets, the crystalline transition method (CT method), utilizing the crystalline transition of amorphous sucrose (Sugimoto et al., 2001). The tablets of diluent and amorphous saccharide mixture are produced at low compression pressure and stored for the crystalline transition. The diluents and amorphous saccharides include mannitol, erythritol, xylitol, etc. and sucrose, maltose, lactose, etc., respectively. In our previous study, the factors affecting the characteristics of tablets prepared by CT method were clarified. Especially, the effects of the storage conditions on the characteristics of the tablets were investigated in detail (Sugimoto et al., 2005). Previously, the amorphous sucrose was prepared by freeze–drying aque-

* Corresponding author. Tel.: +81 6 6300 2783; fax: +81 6 6300 2582.
E-mail address: sugimoto@tanabe.co.jp (M. Sugimoto).

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ous sucrose solution. However, the freeze–drying process is not preferable from the viewpoint of productivity in the industrial scale, because the process is very cost consuming. Therefore, we developed a new method of manufacturing amorphous sucrose in the process of granulation using a fluidized bed granulator.

Fluidized bed granulation offers several advantages over other multi-step granulation and drying processes (Gao et al., 2002); mixing of dry powders, granulating, and drying can be successively carried out in the same equipment. In addition, the granulation is widely used to improve flow of materials and enhance the compressibility prior to tabletting. It has been recognized that the crystalline state of either the active drug substance or the excipient changes depending on their processing history such as milling, granulation, and compression processes (Matsumoto et al., 1991; Briggner et al., 1994; Ghorab and Adeyeye, 1996; Wöstheinrich and Schmidt, 2001). The fluidized bed granulation is usually done in the form of liquid bed granulation using a binder solution consisting mostly of water and a binding agent such as sucrose. During the drying phase of the granulation, the binding agent dissolved in the binder solution is solidified, forming solid interparticulate bridges as water is evaporated. It was therefore thought that the solid bridges could be formed from not only the crystalline state but also amorphous state of the saccharide depending on the granulating conditions. The effects of manufacturing conditions such as fluidizing air temperature, spraying rate, and concentration of granulating liquid on the physical properties of granules and the resultant tablets compressed from these granules have been reported (Davies and Gloor, 1973; Wells and Walker, 1983; Ghanta et al., 1986; Wan et al., 1996). However, there are few reports making positive use of the amorphous state of saccharide formed during the granulation, because the amorphous state is usually unstable. We thought to utilize the amorphous saccharide formed during the granulation for the manufacturing of rapidly disintegrating oral tablets.

In this study, the effects of the manufacturing conditions on the formation of amorphous sucrose in granules were investigated. Moreover, the amorphous materials are considered to be metastable relative to the crystalline state and easily change to the crystalline one during storage (Simonelli et al., 1970; Shamblin and Zografi, 1999; Taylor and Zografi, 1997; Yokoi et al., 2004). Therefore, we studied effects of the transition of amorphous sucrose in granules on the characteristics of the resultant tablets. The aim of this study was to clarify the usefulness of amorphous saccharide formed during the fluidized bed granulation for the rapidly disintegrating oral tablets manufacturing, and to investigate the effects of crystalline transition of the amorphous saccharide in granules on the characteristics of the resultant tablets.

2. Materials and methods

2.1. Materials

Sucrose (Taito Co., Ltd., Japan), D-mannitol (Kyowa Hakko Co., Ltd., Japan) and magnesium stearate (NOF Corporation, Japan) used were of Japanese Pharmacopoeia (JP) grade. D-mannitol less than 75 μm in diameter was used (mean particle diameter: D_{50} = approximately 40 μm). All other materials used in this study were of reagent grade.

Table 1
Composition and operating conditions for fluidized bed granulation

Composition	
D-mannitol	380[a]
Sucrose[b]	20[a]
Total	400[a]
Operating conditions	
Fluidizing air temperature (°C)	50, 60
Atomising air pressure (kPa)	80
Spraying rate (g/min)	7
Concentration of binder solution (%)	10
Weight of binder solution (g)	200

[a] Loading weight in grams.
[b] Formulating ratio of sucrose was 5% in the formula.

2.2. Methods

2.2.1. Fluidized bed granulation

Mannitol, sieved through a 710 μm screen in advance, was granulated with sucrose aqueous solution in a fluidized bed granulator equipped with a top spray (MP-01/03, Powrex, Japan). The composition and operating conditions for granulation are presented in Table 1. The different fluidizing air temperatures (50 or 60 °C) were adopted for the operating condition of the granulation. Water contents of the samples during granulation were measured as follows. Each sample of about 1 g was dried at 60 °C for 3 h under reduced pressure in the presence of phosphorus pentoxide. Then, the water content was calculated as the loss on drying.

2.2.2. Manufacturing of granules for compressing

Granules prepared by the fluidized bed granulation and magnesium stearate were mixed by shaking in a plastic bag. The amount of magnesium stearate used was 0.3%, based on the granules.

2.2.3. Compressing

Granules for compressing were compressed into flat tablets of 10 mm diameter using a rotary tabletting machine (VELLA, Kikusui Seisakusho, Japan) at compression forces from approximately 10–100 MPa at a rotation speed of 20 rpm.

2.2.4. Storage of tablets

The tablets were stored at 25 °C and 51% relative humidity for 2 days in a desiccator. The relative humidity of the desiccator was controlled by use of a saturated solution of calcium nitrate tetrahydrate.

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 fol-

lowing equation:

$$T(\mathrm{MPa}) = \frac{2F}{\Pi DH} \times 9.8 \times \frac{1}{1000} \quad (1)$$

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 using the following equation:

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

where M (g) is the tablet weight, V (cm^3) is the tablet volume, and ρ (g/cm^3) is the true density of the powders. The tablet volume was calculated from the diameter and thickness of the tablet measured with a micrometer. The true density of the powder was determined using a pycnometer (autopycnometer type: 1320, Micromeritics, USA).

2.2.7. Measurement of oral disintegration time

The time required for complete oral disintegration was measured using five healthy volunteers. The end point of oral disintegration was when a tablet placed on the tongue had disintegrated until no lumps remained. The volunteers did not move their tongues during the test.

2.2.8. Thermal analysis

Samples weighing about 10 mg were examined using a differential scanning calorimeter (DSC) (DSC-50, Shimazu Seisakusho, Japan). A heating rate of 5 °C/min was employed from room temperature to 250 °C in the atmosphere of nitrogen with the sample kept in an open aluminium pan.

2.2.9. Powder X-ray diffraction measurement

The powder X-ray diffraction patterns were measured at room temperature with an X-ray diffractometer (M03X-HF, MAC Science, Japan). The measurement conditions were as follows: target, Cu; filter, Ni; voltage, 40 kV; current, 35 mA; and scanning speed, 4°/min.

2.2.10. Water activity measurement

The water activity (a_w) of the granules was measured using a water activity meter (Novasina AW SPRINT TH-500, Siber-Hegner K.K., Switzerland). The a_w is defined as the ratio of the water vapor pressure of the sample to that of pure water, which equals to the relative equilibrium humidity (%) of the sample. The a_w value of granules was measured for the sample in the airtight chamber.

3. Results and discussion

3.1. Effect of manufacturing conditions of granules

The manufacturing conditions for fluidized bed granulation to affect the granule properties can be classified as either process or product variables. The process variables are related to the exact procedure used for granulation. One of the most important factors to affect tablet properties as well as granule properties is water content during the granulation (Lipps and Sakrx, 1994). In this study, fluidized bed granulation was therefore performed being controlled to be different water content during the granulation. To achieve the different water content during the granulation, two different fluidizing air temperatures were used (Table 1). The product variables, on the other hand, are related to the amounts and properties of the raw materials. The formulated ratio of sucrose and mannitol in this study was 5 and 95%, respectively (Table 1). Fig. 1 shows the change in water content during granulation. Spraying of 200 g of the binder solution gave the different final water content (FWC) of the granules depending on the fluidizing air temperature when spraying, and then the drying step was run until the water content of the granules reached an equilibrium with the surrounding air. The FWCs of the granules when granulated at the fluidizing air temperature of 60 and 50 °C were 1.8 and 4%, respectively.

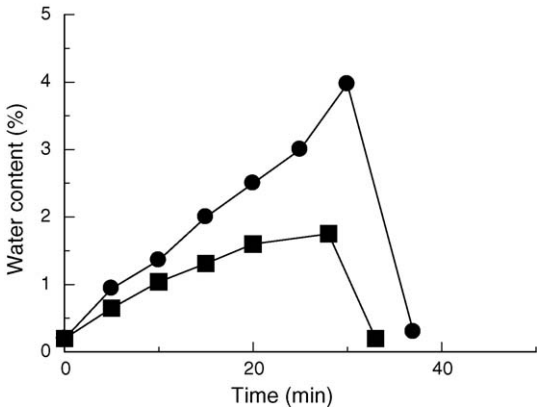

Fig. 1. Change in water content during granulation: (■) 60 °C of fluidizing air temperature; (●) 50 °C of fluidizing air temperature

In order to clarify the physicochemical properties of the granules obtained, powder X-ray diffraction measurements and thermal analyses were conducted. Fig. 2 shows the powder X-ray diffraction patterns of the granules. The powder X-ray diffraction patterns of mannitol, sucrose, and their physical mixture were also included for comparison. The characteristic peaks corresponding to crystalline sucrose indicated by arrows were clearly observed when the FWC during granulation was low (1.8%), whereas these peaks were hardly observed when the FWC was high (4%).

Fig. 3 shows the DSC curves of the granules. The DSC curve of mannitol was also included for comparison. The endothermic peaks of the granules represented two melting points of 150–155 °C and 165–170 °C, which correspond to the eutectic mixture of mannitol and sucrose, and mannitol itself, respectively (Sugimoto et al., 2001). The thermogram of the granules also showed that the exothermic peak of approximately 85 °C preceded the two endothermic peaks, which represents the crystallization of amorphous sucrose. It is however thought that temperature of the exothermic peak is inconstant and different depending on the water content of amorphous sucrose. Because

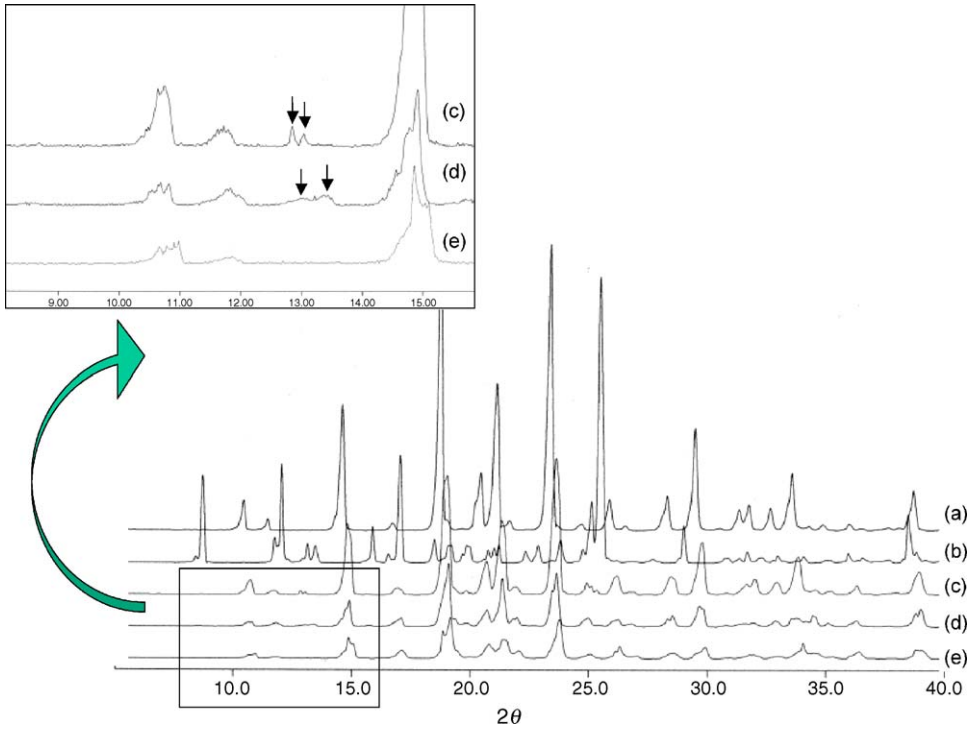

Fig. 2. Powder X-ray diffraction spectra of granules. (a) Intact mannitol powder; (b) intact sucrose powder; (c) physical mixture; (d) granules manufactured at 1.8% of FWC; (e) granules manufactured at 4% of FWC.

the water dissolved in an amorphous material is reported to act as a plasticizer to reduce hydrogen bonding between molecules of the solids, with a corresponding reduction in glass transition temperature, T_g (Ahlneck and Zografi, 1990). The magnitude of the exothermic peak of the granules depended on the FWC during granulation. The higher FWC during granulation provided the larger exothermic peak of the granules: heat of the exothermic peaks for the granules of 1.8 and 4% of the FWC during

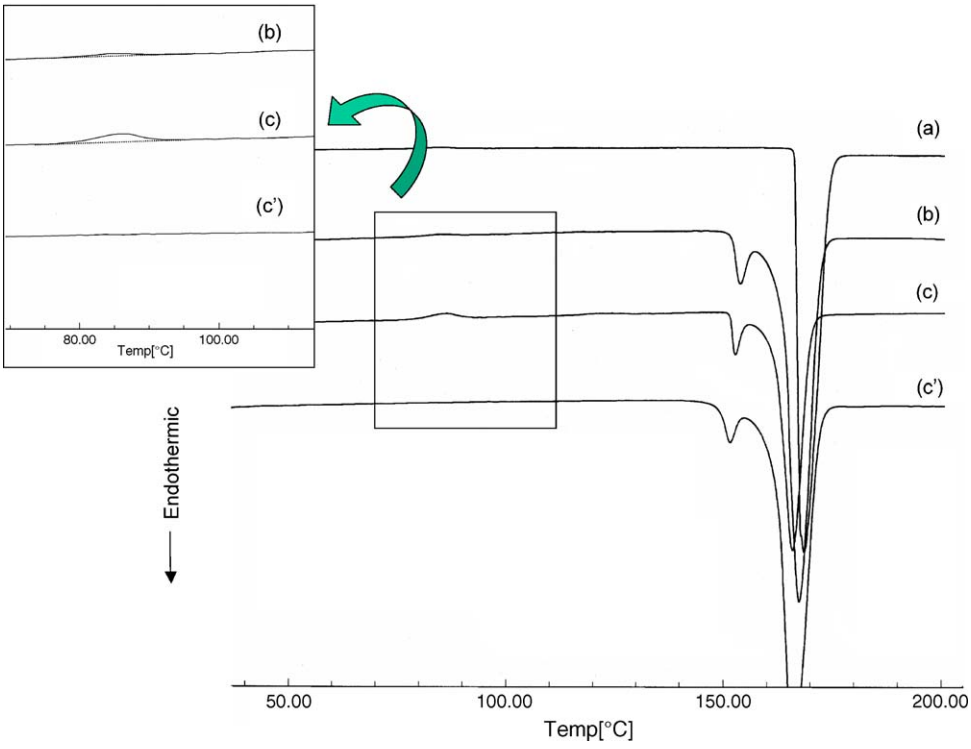

Fig. 3. Differential scanning calorimetry thermograms. (a) Intact mannitol powder; (b) granules manufactured at 1.8% of FWC; (c) granules manufactured at 4% of FWC; (c') tablet after storage at 25 °C under 51% relative humidity comprised of granules manufactured at 4% of FWC.

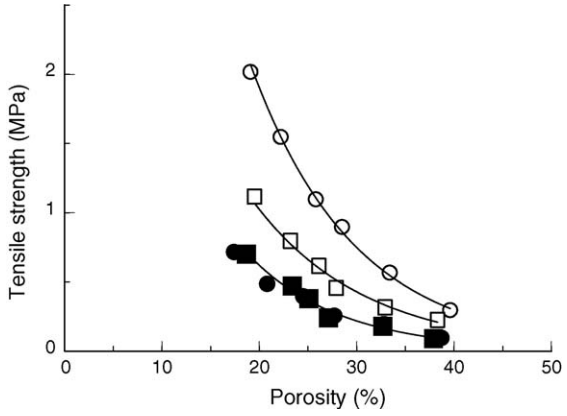

Fig. 4. Change in tensile strength of tablets comprising granules. (■, □) Granules manufactured at 1.8% of FWC; (●, ○) granules manufactured at 4% of FWC. Tensile strength of tablets comprised of granules manufactured by fluidized bed granulation was measured before (■, ●) and after (□, ○) storage at 25 °C under 51% relative humidity.

granulation were 668 and 1560 mJ/g, respectively. These results of powder X-ray diffraction measurement and thermal analysis showed that the amorphous state of sucrose was effectively formed in granules consisting of 95% of mannitol and 5% of sucrose when the granulation was performed on a condition that higher FWC was achieved during granulation.

The granules were compressed after the addition of 0.3% magnesium stearate as a lubricant. The amount of magnesium stearate, which has little effect on the tablet characteristics such as tensile strength and oral disintegration time, was determined prior to compressing (data not shown). The tablets were stored at 25 °C under 51% relative humidity for 2 days. Fig. 4 shows the change in tensile strength of the tablets during storage. The higher FWC during granulation provided the larger increase in tensile strength of the resultant tablets during storage. On the other hand, the porosity of the tablets almost unchanged during storage irrespective of the FWC of granules used. During fluidized bed granulation, it is well known that the existence of granule surface water is important to form a liquid bridge, which produces an adhesive force between the granules (Watano et al., 1996a, 1996b). When the fluidizing air temperature is higher, the rate of water evaporation from the droplet of binder solution is accelerated during granulation. As a result, the sucrose concentration in the droplet becomes higher, and the nucleation energy required for the crystallization of sucrose seems to be lowered (Schmitt et al., 1999; Price and Young, 2004). Thus, it is expected that the crystallization of sucrose was promoted on the granulating condition of low FWC.

Considering the results, it is suggested that the granulating condition of higher FWC is more suitable for the formation of amorphous sucrose during granulation and the increase in tensile strength of the resultant tablet. The increase in tensile strength was occurred due to the crystallization of amorphous sucrose, as the exothermic peak corresponding to the crystallization of amorphous sucrose was not observed in the DSC chart of the tablets after storage (Fig. 3 (c')).

Table 2 lists the characteristics of rapidly disintegrating oral tablets comprised of the granules obtained by the fluidized bed granulation. The tablets after storage showed enough tensile strength of approximately 1 MPa and 10–20 s oral disintegration time, when the FWC during granulation was high (4%).

3.2. Effect of storage of granules

In general, it is well recognized that the amorphous state of materials easily changes to the crystalline state during storage due to the moisture sorption (Larsen et al., 1997; Burnett et al., 2004; Mihranyan et al., 2004). The granules with 5% formulating of sucrose were obtained by the fluidized bed granulation performed on the condition of higher FWC (approximately 4%). The granules obtained were stored at 25 °C under 51% relative humidity for 2 days. The water content due to water sorption during storage was expected to be less than 0.5% from our previous study, because the formulating ratio of sucrose in the granules was only 5% (Sugimoto et al., 2005). The measurement of such a small amount of water in granules seemed to be difficult by either gravimetric measurement or the Karl Fischer method. Thus, the water activity, a_w of the granules was measured to evaluate the relative humidity of the surrounding air of the granules (Ticehurst et al., 2002; Salameh and Taylor, 2005). Fig. 5 shows the change in a_w of the granules as a function of time during storage at 25 °C under 51% relative humidity. The a_w value increased with the time until the maximum value was achieved and then decreased gradually in the amorphous to crystalline transition. This result shows that moisture sorption occurred rapidly followed by slow desorption of water. Buckton et al. investigated the sorption behavior of a small amount of water less than 1% of the total weight, and indicated that the water absorbed in amorphous region has a significant impact on

Table 2
Characteristics of rapidly disintegrating oral tablet comprising the granules manufactured by fluidized bed granulation[a]

FWC (%)[b]	Tablet before storage		Tablet after storage		
	Tensile strength (MPa)	Porosity (%)	Tensile strength (MPa)	Porosity (%)	Oral disintegration time (s)
1.8	0.24 ± 0.00	27.1 ± 0.2	0.45 ± 0.08	28.0 ± 0.2	11 ± 2
	0.38 ± 0.02	25.1 ± 0.5	0.61 ± 0.02	26.2 ± 0.4	18 ± 4
4.0	0.25 ± 0.00	27.8 ± 0.1	0.89 ± 0.05	28.6 ± 0.1	13 ± 3
	0.39 ± 0.02	24.6 ± 0.6	1.09 ± 0.03	25.9 ± 0.6	22 ± 6

[a] All results are represented as mean ± S.D. ($n = 5$).
[b] Final water content (FWC) achieved during granulation is presented. The granules manufactured at different FWC were compressed by varying compression force.

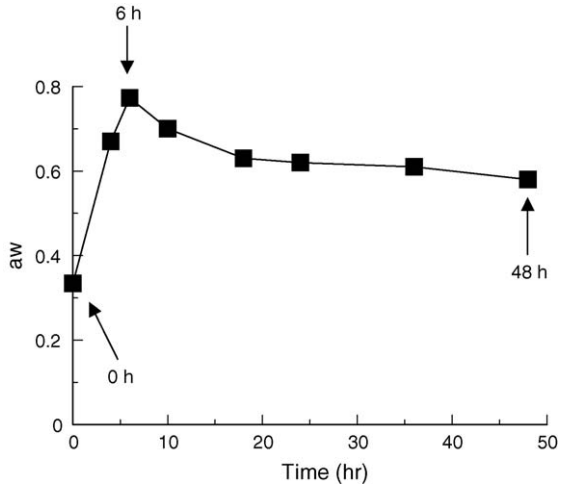

Fig. 5. Change in water activity, a_w, of granules during storage at 25 °C under 51% relative humidity.

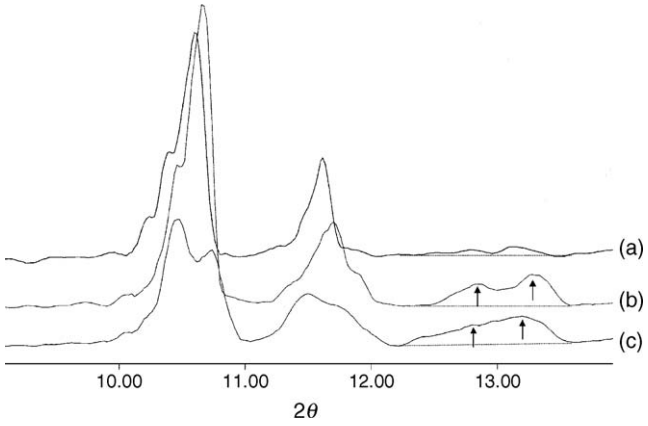

Fig. 6. Powder X-ray diffraction spectra of granules of different storage time at 25 °C under 51% relative humidity. (a) Granules before storage; (b) granules of 6 h storage; (c) granules of 48 h storage.

the physico-chemical nature of the material, which in turn can alter product performance (Buckton and Darcy, 1996; Darcy and Buckton, 1997).

Fig. 6 shows the powder X-ray diffraction pattern of the granules before compression. In the case of the granules immediately after granulation, the characteristic peaks corresponding to crystalline sucrose were little observed. However, the characteristic

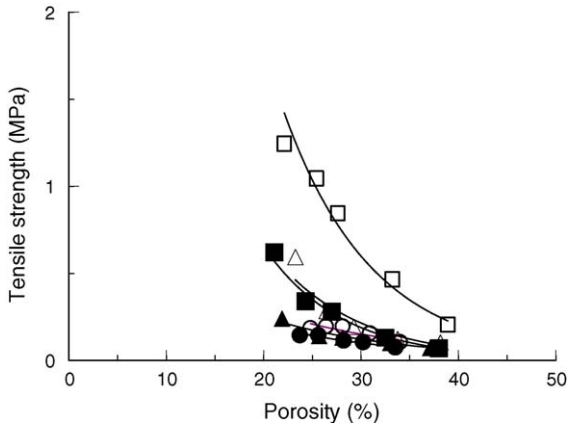

Fig. 7. Change in tensile strength of tablets during storage comprising granules of different pre-storage time. (■, □) Granules without pre-storage; (●, ◯) granules of 6 h pre-storage; (▲, △) granules of 48 h pre-storage. Tensile strength of tablets comprising granules of different pre-storage time at 25 °C under 51% relative humidity was measured before (■, ●, ▲) and after (□, ◯, △) storage on the same conditions.

peaks indicated by arrows were observed clearly with storage of the granules. Moreover, the exothermic peaks representing the crystallization of the amorphous sucrose in the DSC curve decreased with storage of the granules (data not shown). These results suggest that the amorphous sucrose formed in the granules was crystallized during storage.

To clarify the effect of the physical change of the granules on the tablet characteristics, the granules with different a_w value were compressed. Fig. 7 shows the change in tensile strength of the tablets during storage. The tablets were stored at 25 °C under 51% relative humidity. The tensile strength of the tablets comprised of the granules compressed immediately after granulation increased remarkably after storage, while the porosity of the tablets almost unchanged. On the other hand, when the granules of which the a_w had already increased (see in Fig. 5) were compressed, little increase in the tensile strength of the tablets after storage was observed. The results therefore show that the increase in tensile strength of the tablets was attributed to amorphous sucrose formed in the granules.

To improve the stability of the amorphous state of sucrose in the granules, further studies on the stabilization of amorphous form may be required. The method using another amorphous saccharide with a higher T_g, or adding polymer to increase T_g,

Table 3
Characteristics of rapidly disintegrating oral tablet comprised of granules of different storage time[a]

Pre-storage time of granules (h)[b]	Tablet before storage		Tablet after storage		
	Tensile strength (MPa)	Porosity (%)	Tensile strength (MPa)	Porosity (%)	Oral disintegration time (s)
0	0.28 ± 0.04	27.0 ± 0.7	0.84 ± 0.07	27.7 ± 0.8	11 ± 3
	0.34 ± 0.00	24.3 ± 0.1	1.04 ± 0.03	25.5 ± 0.2	18 ± 5
6	0.11 ± 0.00	28.3 ± 0.4	0.19 ± 0.03	28.2 ± 0.1	10 ± 3
	0.14 ± 0.00	25.7 ± 0.6	0.19 ± 0.03	26.5 ± 0.5	15 ± 3
48	0.13 ± 0.00	28.1 ± 0.2	0.19 ± 0.02	29.3 ± 0.3	11 ± 3
	0.14 ± 0.00	25.7 ± 0.1	0.28 ± 0.02	26.5 ± 0.1	21 ± 5

[a] All results are represented as mean ± S.D. ($n = 5$).
[b] The granules of different pre-storage time were compressed by varying compression force.

are considered to be effective for the stabilization of amorphous state (Hancock et al., 1995; Takeuchi et al., 2000a, 2000b).

Table 3 lists the characteristics of rapidly disintegrating oral tablets. When the granules were compressed immediately after granulation, the resultant tablets showed a sufficient tensile strength and rapid oral disintegration time, whereas the resultant tablets comprised of the granules after storage showed insufficient tensile strength to handle easily.

4. Conclusions

The amorphous sucrose was prepared by a fluidized bed granulation method in the process of granulation of mannitol using sucrose solution as a binder. The powder X-ray diffraction measurement and thermal analysis showed that amorphous sucrose was effectively formed in granules consisting of 95% mannitol and 5% sucrose when the granulation was performed on the condition of higher final water content during granulation. The tensile strength of the tablets comprised of the granules, which were compressed immediately after granulation, increased remarkably after storage, whereas little increase in the tensile strength of tablets was observed when the granules were compressed after the amorphous sucrose in the granules had already started to crystallize. We conclude that rapidly disintegrating oral tablets were effectively manufactured by the CT method using the granules containing amorphous sucrose obtained by the fluidized bed granulation method before the crystallization of the amorphous sucrose started.

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