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Phase Transition Method: A Novel Technique for Mouth dissolving tablet

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Abstract: The aim of the present study was to assess the properties of Mouth dissolving (MD) tablets manufactured by the phase transition method. MD tablets were produced by compressing powder containing LMP-SA (Low melting point sugar) and HMP-SA (High melting point sugar), and then heating at about 93^0C for 15 min. The hardness and oral disintegration time of the heated tablets increased with an increase of the LMP-SA content. These results suggested that the heating process and LMP-SA content might influence the properties of MD tablets. Then we evaluated the physicochemical properties of the MD tablets, including the median pore size, crystallinity, hardness, and oral disintegration time of tablets made with and without heating. After heating,the median pore size of the tablets was increased and tablet hardness was also increased. The increase of tablet hardness with heating and storage did not depend on the crystal state of the lower melting point sugar alcohol. It is concluded that a combination of low and high melting point sugar alcohols, as well as a phase transition in the manufacturing process, are important for making MD tablets without any special apparatus.
Keywords: Mouth dissolving tablets; Phase transition; Sugar alcohol.

Introduction[3]

In recent years, in accordance with changes in lifestyle, a demand has arisen for the development of dosage forms that can be readily handled and taken by many patients. In particular, the development of solid dosage forms that can rapidly disintegrate or dissolve even when taken orally without water is necessary to assist in the treatment of elderly people. with respect to various compositions and manufacturing methods of orally disintegrating or dissolving tablets, numerous studies have therefore been reported. For example, a solution or suspension of a drug and excipients was poured into the pockets of a blister pack sheet formed beforehand, and then freeze-dried or vacuum-dried to make an orally disintegrating (OD) product. The oral disintegration time of the product produced by these methods was very short because of its highly porous structure and the high solubility of sugar alcohol (SA) or saccharide used as the diluent in the product. However, the disadvantage of this product was its lack of mechanical strength.In another preparation method, OD tablets have been produced by using wet powder containing a drug and subsequent drying in an oven. Such processes could provide tablets with excellent interoral disintegrating properties and a rather high degree of hardness. However, they require special apparatuses, since it is impossible to compress the wet powder with conventional tabletting machines.

On the other hand, a new method of preparing OD tablets without any special apparatus has been reported. OD tablets can be manufactured using a combination of saccharides with low and high moldability. We focused on the melting points of SA, and proposed a novel method to prepare OD tablets with sufficient

hardness by involving the phase transition of SA. In our preparation method, OD tablets were produced by compressing and subsequently heating tablets that contained two SAs, one with a high and one with a low melting point. Before the heating process, the tablets did not have sufficient hardness because of low compactability. The tablet hardness was increased after the heating process. A combination of two SAs and the heating process was needed to prepare OD tablets with sufficient hardness. It was concluded that tablet hardness was related to the increase in inter-particle bonds or the bonding surface area in tablets induced by the phase transition of the low melting pointSA (LMP-SA).

We hypothesized that inter-particle bonds and the bonding surface mentioned above may be related to the state of LMP-SA distribution in tablets, and thus, in this study, examined the effect of preparation method on characteristics of OD tablets using the direct compression method (DCM) and the wet granulation compression method (WGCM). In the case of DCM, the LMP-SA was distributed as solid particles in the tablets. On the other hand, in the case of WGCM, an aqueous solution of LMP-SA was sprayed onto high melting point SA (HMP-SA) particles during fluid-bed granulation and then compressed. First, the effect of LMP-SA particle size on tablet characteristics was evaluated using tablets made by DCM. Second, the characteristics of tablets prepared by each method were evaluated comparatively to clarify the effect of distributed state of LMP-SA in tablets. Finally, we examined the effect of the amount of LMP-SA on disintegration and hardness stability of OD tablets prepared by WGCM. Based on the results, we discussed the importance of the state of LMP-SA distribution in OD tablet preparation.

Various approaches for formulating mouth dissolving tablets[1]:

Some of the approaches which are employed for the formulation of MDTs are:

1) Disintegrant addition method
2) Freeze drying/Lyophilization
3) Direct compression
4) Sublimation
5) Spray drying
6) Tablet molding
7) Mass extrusion
8) Melt granulation
9) Cotton candy process
10) Phase transition process

Phase transition method (PTM)[4]

Saccharides and sugar alcohols can be categorized not only by compressibility but also by melting point. Basedon the melting point.

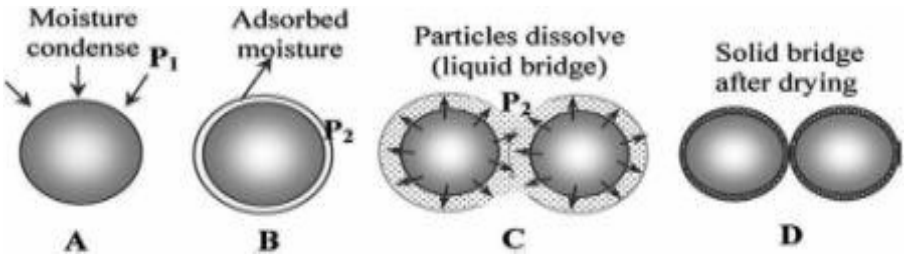

Fig. 1. Schematic view of moisture sorption by water-soluble particles explaining the increase in mechanical strength in FDTs before and after moisture conditioning.

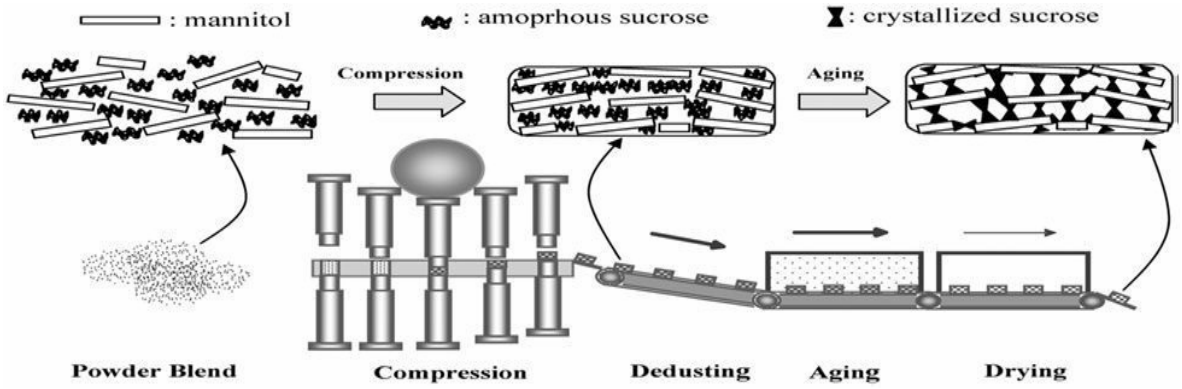

Fig.2 Schematic illustration of the manufacturing process of FDTs prepared by the crystalline transition method usingmannitol and amorphoussucrose.

They were divided into two groups and investigate dusing conventional granulation and compression apparatus.[32]Erythritol is the high melting (122 ^{0}C) and xylitol the low melting (93▪ ~95 ^{0}C) sugar alcohol. Erythritol and xylitol were used as a diluent and a binder, respectively for fluid bed granulation.After compression, the resulting tablets were placed ina drying oven and heated at a temperature close to the melting point of xylitol (approximately 93 ^{0}C). Conditions were maintained for a certain period of time and the tablets then allowed to cool to room temperature. The hardness of the processed tablets was found to increase with increasing xylitol content.Tablet hardness and disintegration time were primarily affected by the heating process, but also by the content of saccharides or sugar alcohols.[32] Heating was found to increase pore size within the tablets. It was suggested that the diffusion of xylitol in the tablets caused increased tablet hardness with increasing pore size. Xylitol melted, diffused, and solidified againsin the heated tablets resulting in a greater bonding surface area between the powder particles and increased hardness. Tablets containing about 5% xylitol showed hardness of 4 kp and an oral disintegration time of < 30 s.[33] It was also suggested that increasing tablet hardness by heating and storage was not dependent on the crystal state of the sugar alcohols, but related to the formation of inter-particle bonds or the increased bonding surface area induced by the melting of xylitol particles and their subsequent solidification upon cooling.[32] Other pharmaceutical materials, such as polyethylene glycol, and wax, have been also applied to the PTM.[34,35]

1. DCM (Direct compression method)

A combination of two SAs was used: either erythritol as the HMP-SA and trehalose as the LMP-SA or erythritol as the HMPSA and xylitol as the LMP-SA. The SAs were mixed in a bottle for 3 min, with the concentration of the LMP-SA in the mixture being set at 5%. The mixture was compressed with an autograph (Shimadzu Corporation), under the following conditions: weight, 300 mg; compression pressure, 500 kgf; punch, 10mm in diameter. The obtained tablets were placed in a drying oven to heat at 93–97 ◦C for 15–60 min and then allowed to cool at room temperature.[3]

2. WGCM (Wet granulation compression method)

Xylitol was dissolved in purified water to make 26.7% (w/w). Erythritol was granulated by using the above solution with a fluidized-bed granulator (Flow coater mini, Fruend.Co.). The granulation conditions were set as follows: inlet temperature, 90 ◦C; outlet temperature, 45 ◦C; spray pressure, 1.5–2.0 kg/cm2; the rate of spray, 0.9 g/min. The granules were compressed with the autograph under the following conditions: weight, 300 mg; compression pressure, 500 kgf; punch, 10mm in diameter. The obtained tablets were placed in a drying oven to heat at 93 ◦C for 5–30 min and then allowed to cool at room temperature.[3]

Recent research endeavours

1. Effect of the phase transition of sugar alcohols on tablet hardness and oral disintegration time.[2]

Tablets were prepared by the granulated powder compression method. Erythritol and xylitol were selected as the high and low melting point sugar alcohols, respectively. The effects of tablet heating conditions and sugar alcohol composition on the hardness and the oral disintegration time of the tablets are seen observed. The heating temperature of the tablets was set at 93 ^{0}C and tablet properties were examined before and after the

heating process. Without heating, no changes in the hardness and oral disintegration time of the tablets were observed with an increase in the content of xylitol. On the other hand, the hardness of heated tablets increased with an increasing xylitol content. The oral disintegration time also became longer with an increase of tablet hardness. It is apparent that both tablet hardness and the disintegration time were mainly affected by the heating process and the sugar alcohol content. The tablet hardness sufficient to withstand actual use would differ depending on its size and shape. However it is generally recognized that the sufficient hardness would be 2 kp or higher.[6,7] In addition, the desirable oral disintegration time would be generally 30 s or shorter in case of RD tablets.[6, 7]

Xylitol in the tablets would melt at 93 ^{0}C, which was set as the heating temperature for this preparation process, since the melting point of xylitol is 93~95 ^{0}C.Accordingly, the melting of xylitol caused by heating probably influenced the increase of tablet hardness. Thesephe-nomena suggested that the heating process and xylitol content might relate to the function of the RD tablet. we have only described the results obtained using erythritol and xylitol as high and low melting point sugar alcohol, respectively, but we have encountered the same phenomena using other sugar alcohols as shown in Table 1. The data indicated that the tablet hardness was increased with heating process. Therefore it would be apparent that this manufacturing technique was also used for other sugar alcohols. In addition, when a drug substance is incorporated in the formulation, it would be important to consider the heating condition to prevent from decomposing of drug substance.

Table 1: Characteristics of rapidly disintegrating tablets prepared with various sugar alcohols

Component	Heating conditions	Before heating		After heating	
(amount mg per tablet)		Hardness	ODT*	Hardness	ODT*
		(Kp)	(S)	(kp)	(S)
Erythritol (285) Xylitol (15)	93^{0}C,15 min	1.0	8	4.7	23
Erythitol, (285) Trehalose (15)	97^{0}C,15 min	1.8	10	6.3	21
Mannitol, (285) Xylitol (15)	93^{0}C,15 min	1.9	10	3.6	17

*Oral disintegration time.

2. Effect of pore size distribution on tablet properties.[2]

The pore size distribution of the erythritol–xylitol tablets was measured in order to clarify factors that affected the hardness and oral disintegration time of the tablets. The pore size of the tablets was enlarged by heating as shown in Fig 3. The median pore size of the tablets before and after heating was 2.37 and5.03 µm, respectively. It is well known that tablet hardness decreases with increasing pore size in the case of common compressed tablets[8, 9]. However, the results shown in Fig.3mean that tablet hardness increased with pore size after the heating process. The bonding surface area between the powder particles also influences tablet hardness[10,11], and hardness increases with more bonding surface area, in general. Our hypothesis is that the increase of tablet hardness with increasing pore size was caused by diffusion of xylitol in the tablets. In other words, xylitol melted, diffused, and solidified again in the heated tablets, so that the hardness increased due to a greater bonding surface area between the powder particles[10,11].With respect to disintegration of the tablets, it is generally recognized that the water penetration rateinto a powder bed is proportional to the pore radius[39]. According to Sunada et al., a increase of pore size is important for tablets to disintegrate rapidly in the oral cavity[37, 38]. Therefore, the increase of pore size caused by heating would contribute to maintaining the RD property of the tablets with the present preparation method, even though tablet hardness was increased.

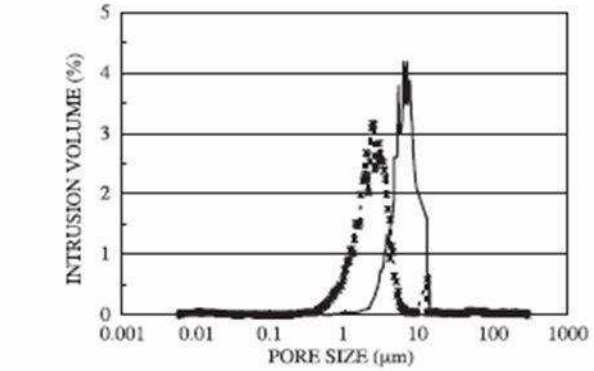

Fig.3. Effect of heating time on distribution of pore size erythritol-xylitol tablets. Dotted line; before heating,thick line:after heating, mixture rate of erytritol-xylitol: 19:1, heating condition: 93 ^{0}C, 15 min

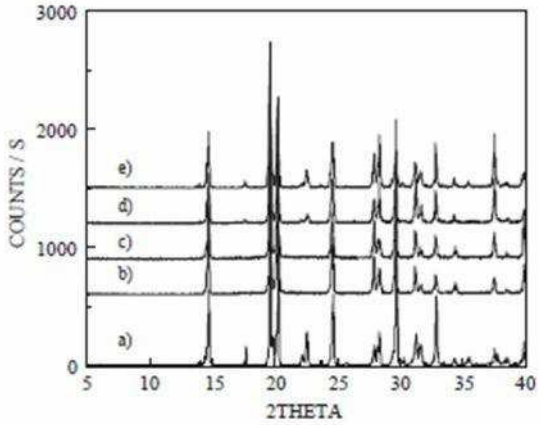

Fig: 4. X-ray pattern of mixture of erythritol and xylitol after heating with storage time a) before heating,b) 0,c) 4, d) 8, e) 12 h after heating.

3. Effect of crystal structure on tablet properties[2]

Besides the pore size distribution, the crystal state of tablets is usually another important factor that affects tablet properties. To evaluate the effect of crystal structure on tablet hardness and the oral disintegration time, the crystal state of the erythritol–xylitol tablets was analyzed. Fig. 3shows changes in the X-ray diffraction pattern of a mixture of erythritol and xylitol before and after the heating process. Before heating, the diffraction peaks of xylitol were observed at 2h =17, 22, and 36. The xylitol peaks disappeared immediately after heating at 93 8C and were absent until 4 h after heating. After 4 h, the intensity of the xylitol peaks increased over time. These results suggest that xylitol was melted by heating and was a non crystalline solid up to 4 h. Thereafter, xylitol returned to the crystalline solid. The X-ray diffraction pattern of xylitol alone showed peaks not only at 178, 228 and 368, but also at 248 and 388. However the intensity of the peaks at 248 and 388 was weaker than those at 178, 228 and 368, so it was not possible to determine if the variation of these peaks was caused by heating or storage.

The oral disintegration time and hardness of the erythritol–xylitol tablets were measured after heating and storage, as shown in Fig. 4. It was found that tablet hardness increased during 4 h of storage at room temperature, and then did not changed thereafter. The data indicated that tablets could be made with hardness above 4 kp and an oral disintegration time of not more than 30 s depending on the xylitol content and the heating process. It was suggested that increasing tablet hardness by heating and storage did not depend on the crystal state of the sugar alcohols. In addition, the increase of tablet hardness was due to the combined effect of melting and subsequent solidification of the sugar alcohols.

The surface structure of the erythritol–xylitol tablet before and after heating was observed with an electron microscope (Fig. 5). The pictures indicated that the surface structure of the tablet was changed by the heating process. A continuous phase of sugar alcohols was formed after heating as the xylitol particles melted and then the expanded solid bridges were formed. Preparation of tablets by this method is illustrated in Fig. 6. Our hypothesis is that the increase of tablet hardness by heating and storage is related to the formation of inter-

particle bonds or an increased bonding surface area induced by the melting of xylitol particles and their subsequent solidification upon cooling.

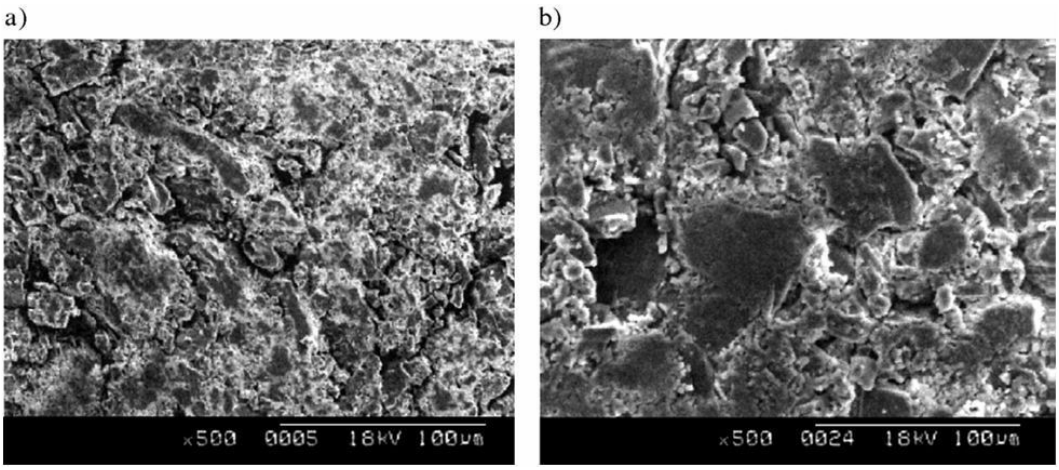

Fig.5. S.E.M. pictures of surface of erythritol–xylitol tablet a) before heating, b) after heating; mixture rate of erythritol–xylitol: 19:1, heatingcondition: 93 ^{0}C, 15 min.

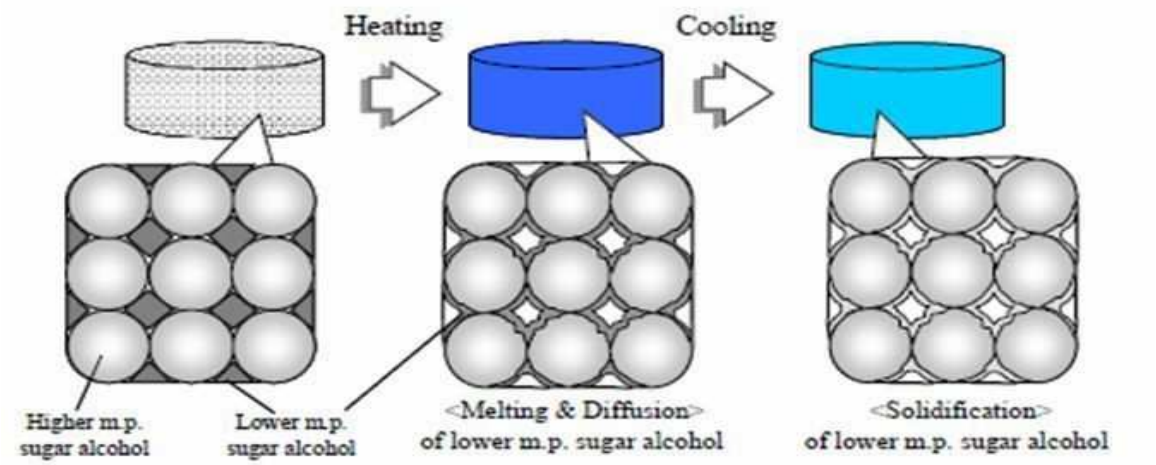

Fig. 6. Schematicdescription of the preparation process of rapidly disintegrating tablets.

4. Effect of particle size of SA on hardness and oral disintegrating time of erythritol–trehalose tablets in DCM.[3]

To evaluate the effect of SA particle size on the hardness and oral disintegration time of the tablets, the properties of tablets containing various particle sizes of LMP-SA were examined using tablets prepared by DCM. Erythritol and trehalose were selected as the HMP-SA and LMP-SA, respectively. Previously it was reported that tablet hardness was increased by heating at about the melting point of the LMP-SA [2]. Therefore, the heating temperature of the tablets was set at 97 ^{0}C, the melting point of trehalose, which was used as the LMP-SA, and the hardness and oral disintegration time were examined before and after the heating process. Trehalose was milled in a mortar for 3 min. The mean particle size of trehalose was measured using a laser light scattering method, and the particle sizes were recorded. The tablet hardness was increased with an increase in heating time, regardless of the particle size of the LMP-SA. The tablets containing non-milled trehalose needed 30 min of heating time to have a hardness greater than 2 kp. However, the tablets containing milled trehalose became harder than the tablets containingnon-milled trehalose after the same amount of heating.With respect to the pore size of the tablets, the median pore sizes of tablets containing non-milled and milled trehalose before heating were 2.3 and 2.1 µm, respectively, as shown inFig. 7a and b). The data also indicated that the pore size of bothtablet was increased by heating. Fig. 7c represents the comparisonof the pore size distribution between the tablet containingnon-milled and milled trehalose after heating. It was evidentthat the pore size of tablets containing milled trehalose becamelarger after heating, compared with that of tablets containing non-milled trehalose. The median pore sizes of tablets containing non-milled and milled trehalose were 3.2 and 3.9 µm, respectively. It is well known that tablet hardness decreases by increasing the pore size in the case of

compressed tablets[12, 13]. The hardness of tablets containing milled trehalose was higher than that of tablets containing non-milled trehalose. It is also well known that tablet hardness increases by increasing the bonding surface area of the inter-particle[14]. The size reduction of trehalose particles should make it easy to diffuse after melting and thus increase the bonding surface area, resulting in an increase in tablet hardness, with respect to disintegration of the tablets, it is generally recognized that the water penetration rate into a powder bed is proportional to the poreradius[16]. On the other hand, it is also known that the disintegration time of the tablets was increased by increasing the tablet hardness[15]. In our preparation method of the OD tablets, the increase of pore size and hardness of tablet was induced by melting, diffusion and solidification of the LMP-SA at the same time. Therefore, the increase in pore size caused by heating must contribute to maintaining the rapid disintegration of the tablets, even though the tablets containing milled trehalose became harder compared to the tablets containing non-milled trehalose.

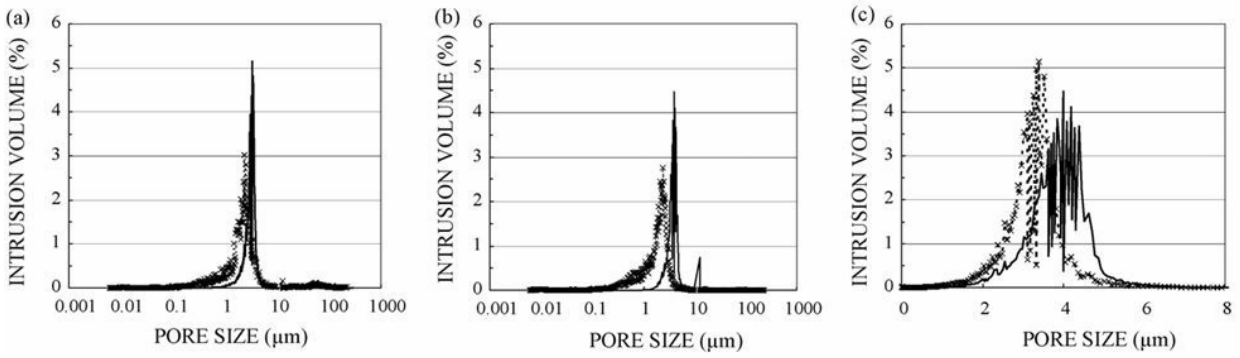

Fig.7. Effect of particle size of SA on distribution of pore size of erythritol–trehalose tablets prepared by DCM. (a) Non-milled trehalose, (b) milled trehalose, dottedsline: before heating, thick line: after heating, and (c) heated tablet, dotted line: non-milled trehalose, thick line: milled trehalose, mixture rate of erythritol–trehalose:19:1, heating condition: 97 ◦C 60 min.

5. Effect of preparation method on hardness and oral disintegrating time of tablets.[3]

In DCM, it was recognized that tablets containing small-sized particles of LMP-SA became harder after a short period of heating compared with tablets containing large-sized particles of LMP-SA. In order to distribute the LMP-SA more uniformly in the tablets, the tablets were produced by WGCM. In WGCM, a LMP-SA solution was sprayed onto erythritol particles to make granulates in a fluidized-bed granulator. Subsequently, the granules obtained were compressed into tablets. Xylitol has a lower m.p. than trehalose, so it was used as the LMP-SA. In DCM, xylitol was milled in a mortar for 3 min. The OD tablets prepared by DCM needed 30 min of heating to have hardness greater than 2 kp. On the other hand, the tablets prepared by WGCM showed hardness over 4 kp after heating for 10 min. These suggested that heating time required for WGCM was much shorter than that for DCM.

To evaluate the effect of preparation method on the crystalline state of the obtained granules, the powder X-ray diffraction pattern of the erythritol–xylitol granules was measured. Fig. 8shows the changes in the X-ray diffraction pattern of erythritol,xylitol, and a mixture of erythritol and xylitol granules manufactured by both methods. The specific peaks of erythritol and xylitol appeared in the X-ray diffraction pattern of the physical mixture of erythritol and xylitol. In addition, the X-ray diffraction pattern of the granules of erythritol and xylitol was the same as that of the physical mixture. These data suggested that spraying a LMP-SA solution onto HMP-SA particles might not affect the crystalline state of erythritol and xylitol.

With respect to the pore size of the tablets, the effect of the heating process on the pore size of the tablets prepared by WGCM was reported previously[2]. It was found that the pore size of tablets prepared by WGCM was enlarged by heating for 15 min. On the other hand, the pore size of tablets prepared by DCM was not changed after15 min of heating in this study. Our hypothesis was that the increase in tablet hardness accompanied by the increase in pore size was caused by the diffusion of LMP-SA in the tablets. In particular, the LMP-SA was uniformly distributed on the surface of HMP-SA particles in WGCM and thus it was assumed that the diffusion of LMP-SA would be made easier.

These results lead to the schematic description of the two preparation processes for OD tablets, as shown in Fig. 9.Our hypothesis is that the WGCM may form more complete inter-particle bonds and pore structures compared with the DCM because of the ease of the diffusion of LMPSA during the heating process. According to the result WGCM enables the OD tablets to maintain rapidly disintegrating properties with greater hardness after a short amount of heating.

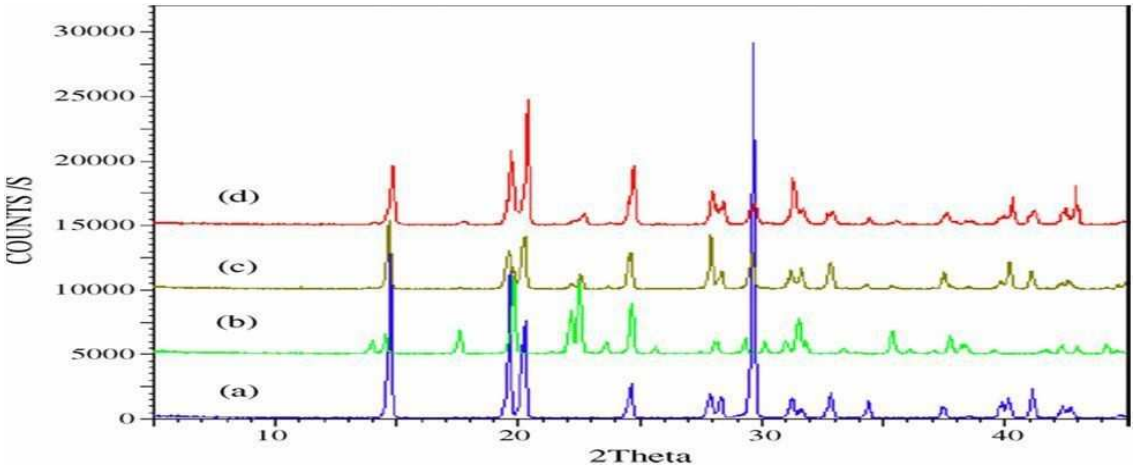

Fig. 8. X-ray pattern of erythritol, xylitol, physical mixture and granule of erythritol–xylitol. (a) Erythritol alone, (b) xylitol alone, (c) physical mixture of erythritol and xylitol, and (d) granule of erythritol and xylitol.

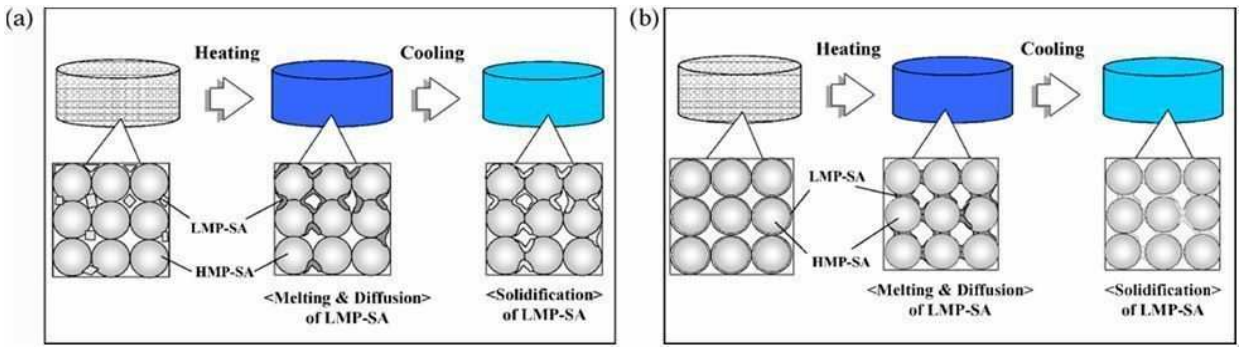

Fig.9. Schematic description of OD tablets prepared by (a) DCM and (b) WGCM.

6. Effect of amount of LMP-SA on disintegrating and hardness stability of tablets prepared by WGCP[3]

A stability test for OD tablets prepared by WGCM was performed to estimate the necessary amount of SA. The storage conditions were set at 25 ◦C/60% R.H. and 50 ◦C for 2 weeks in a glass bottle. Erythritol and xylitol were selected as the high and low melting point SAs, respectively. Without xylitol as the LMP-SA, the hardness and the oral disintegration time of the tablet were not more than 2 kp and 20 s,respectively, and these properties were not changed during storage.On the other hand, tablets containing 1% of xylitol showed a hardness over 4 kp and an oral disintegration time of not morethan 30 s in the initial state of stability test. The tablet hardness increased slightly, and the oral disintegration time as not changed under either stability condition. The tablets containing3% or 5% of xylitol also showed a hardness over 4 kp andan oral disintegration time of not more than 30 s in the initial state. The hardness and oral disintegration time of the tablets, however, increased remarkably with storage time. TheX-ray diffraction pattern in fig.8 data suggested that the peaks of the LMP-SA, xylitol disappeared immediately after heating and were absent for a while. Thereafter, the intensity of the xylitol peaks increased over time. These data suggested that tablets containing 3% or 5% of xylitol required a long time to return to`a crystalline solid. Therefore, it is probable that the hardness of these tablets increased with storage time. On the other hand, the properties of tablets containing 1% of xylitol were not changed after storage time. These phenomena suggested that the content of the LMP-SA is related to the stability properties. Thus, the content of LMP-SA should be regulated to assure the stability of the OD tablet hardness and disintegration properties. In addition, sugar alcohols are very sensitive to humidity, so that it is

important for formulation development to select the moisture proof packaging and container of the OD tablets to prevent from changing of the tablet properties under the humidity condition. It is also necessary to carry out stability studies under humid conditions to clarify stability of the OD tablets after opening.

7. Effect of manufacturing conditions of granules[4]

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 propertiesis water content during the granulation[18]. 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 2). 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 2). 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.

In order to clarify the physicochemical properties of the granules obtained, powder X-ray diffraction measurements and thermal analyses were conducted. Fig. 10shows 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. 11 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 of150–155 ◦C and 165–170 ◦C, which correspond to the eutectic mixture of mannitol and sucrose, and mannitol itself, respectively[20]. 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 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[17]. 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 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. 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.[21]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.[19,36] 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 2lists 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 1MPa and 10–20 s oral disintegration time, when the FWC during granulation was high (4%).

Table 2: Composition and operating conditions for fluidized bed granulation.

Composition	
d-mannitol	380a
Sucrose[b]	20a
Total	400a
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.

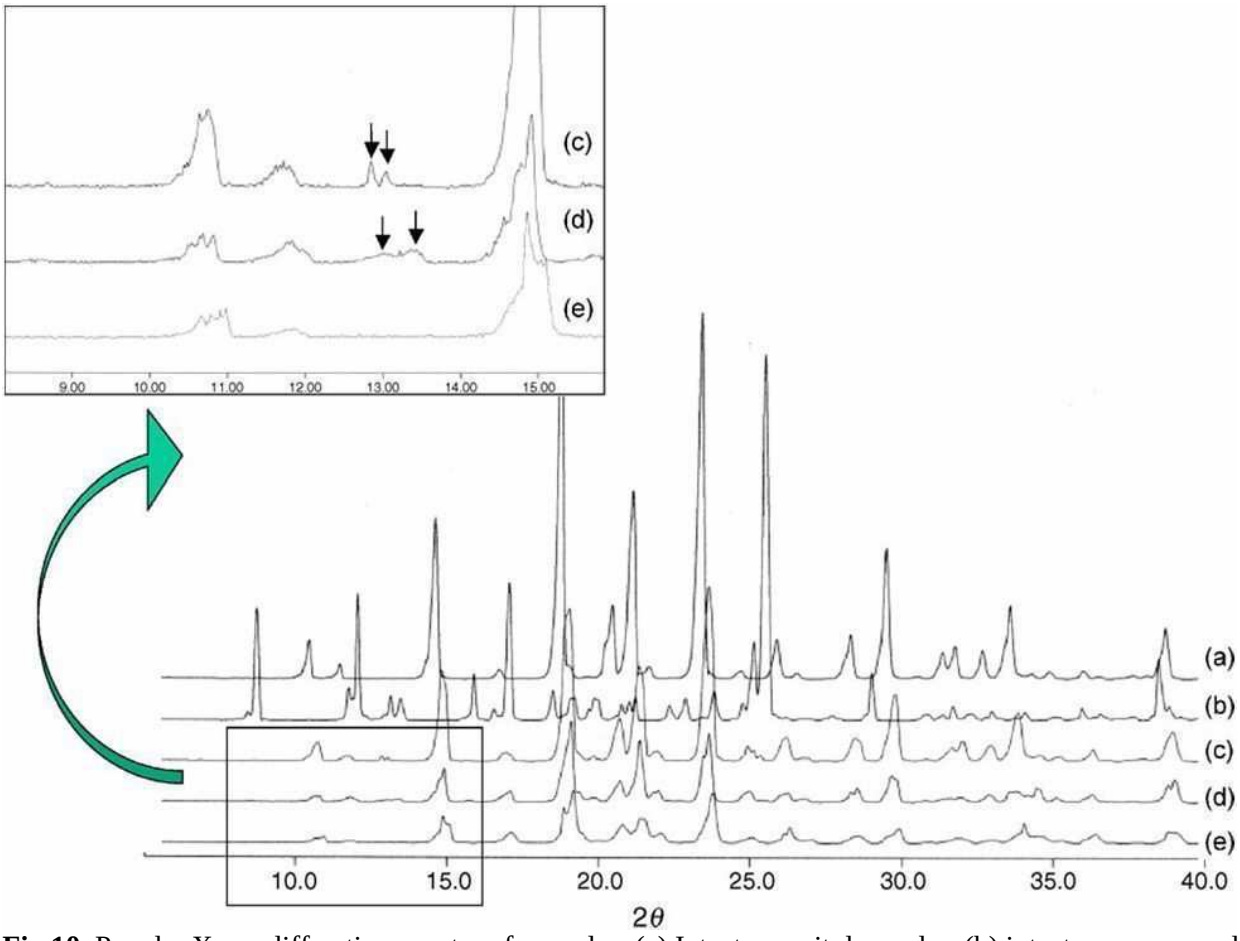

Fig.10. Powder X-ray diffraction spectra of granules. (a) Intact mannitol powder; (b) intact sucrose powder; (c) physical mixture; (d) granules manufactured at 1.8%of FWC; (e) granules manufactured at 4% of FWC.

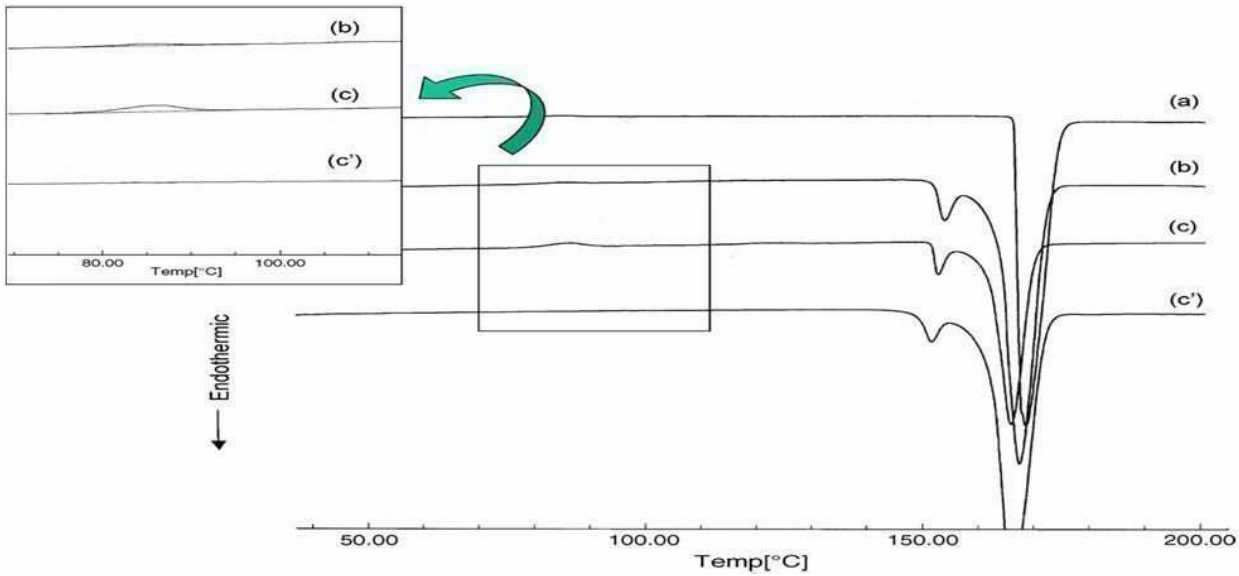

Fig.11. Differential scanningcalorimetrythermograms. (a) Intact mannitol powder; (b) granules manufactured at 1.8% of FWC; (c) granules manufactured at 4% ofFWC; (c') tablet after storage at 25 ◦C under 51% relative humidity comprised of granules manufactured at 4% of FWC.

8. Effect of storage of granules[4]

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.[23, 24, 25] 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%.[27]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.[26, 30, 31]Fig. 12 shows the change in a_w of the granules as a function of time during storage at 25 ◦C under 51% relative humidity. Thea_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. 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 the physico-chemical nature of the material, which in turn can alter product performance[22].

Fig. 13shows 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 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 granuleswas 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.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 thea_W had already increased (see in Fig. 12) 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, are considered to be effective for the stabilization of amorphous state.[28, 29] 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.

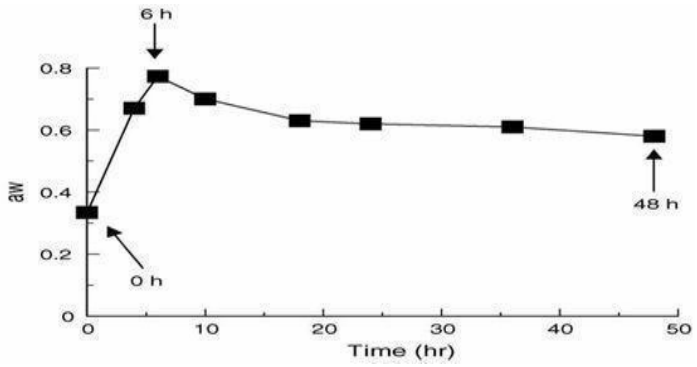

Fig.12. Change in water activity, *a*w, of granules during storage at 25 ◦C under 51% relative humidity.

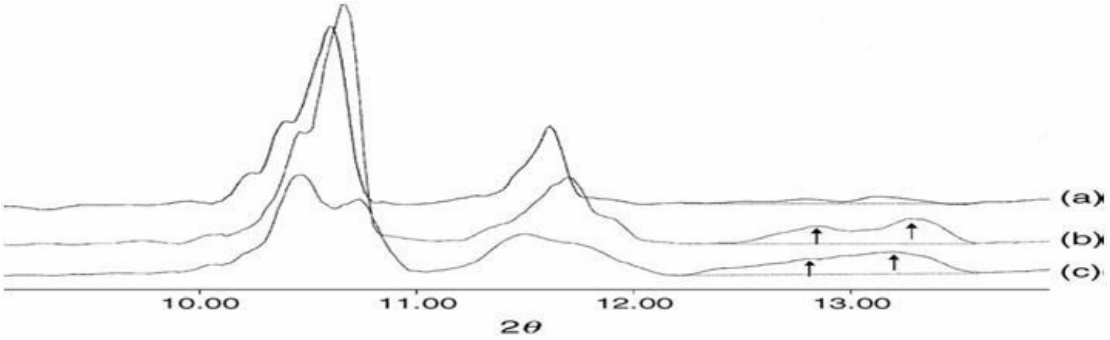

Fig.13. Powder X-ray diffraction spectra of granules of different storage time at25 ◦C under 51% relative humidity. (a) Granules before storage; (b) granules of6 h storage; (c) granules of 48 h storage.

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