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ScienceDirect
International Journal of Pharmaceutics 355 (2008) 87–92
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Effect of preparation method on properties of orally disintegrating tablets made by phase transition

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Received 29 August 2007; received in revised form 6 November 2007; accepted 27 November 2007
Available online 4 December 2007

Abstract

In order to evaluate the effect of preparation method on the properties of orally disintegrating (OD) tablets, OD tablets were prepared by compressing a mixture of high melting point sugar alcohol (HMP-SA) and low melting point sugar alcohol (LMP-SA) and subsequent heating. In the direct compression method (DCM) where the LMP-SA was added as a powder, both hardness and disintegration time were increased by decreasing the particle size of the LMP-SA. In the wet granule compression method (WGCM), where the LMP-SA was added as an aqueous binder solution, the tablets became harder with less heating compared to tablets prepared by DCM. Using 1% xylitol as the LMP-SA provided tablets with sufficient hardness when prepared by WGCM, as opposed to DCM where 5% xylitol was necessary to prepare tablets with similar hardness. These results suggest that uniformly distributed LMP-SA on the surface of HMP-SA particles in WGCM might diffuse more easily during the heating process compared to mechanically mixed LMP-SA in DCM, resulting in an increase in tablet hardness even with a short heating time and low content of LMP-SA. In addition, disintegration and hardness stability of the tablets were affected by the LMP-SA content when prepared by WGCM, suggesting that the LMP-SA content should be regulated to assure the stability of OD tablet characteristics.

Keywords: Orally disintegrating tablets; Phase transition; Sugar alcohol

1. Introduction

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 (Watanabe et al., 1998; Sunada and Bi, 2002; Fukami et al., 2006). 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 (Masaki, 1997; Katou et al., 1993). 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 (Tsushima, 1997). 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. Mizumoto et al. (2005) reported that 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 (Kuno et al., 2005). 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

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doi:10.1016/j.ijpharm.2007.11.046

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 point SA (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.

2. Experimental

2.1. Materials

Erythritol (M.P.: 126 °C, Nikken Chemical Co. Ltd.), xylitol (M.P.: 93–95 °C, Towa Chemical Industry Co. Ltd.), and trehalose (M.P.: 97 °C, Asahi Kasei Co. Ltd.) were used as the SA.

2.2. Preparation method of tablets

2.2.1. DCM

A combination of two SAs was used: either erythritol as the HMP-SA and trehalose as the LMP-SA or erythritol as the HMP-SA 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, 10 mm 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.

2.2.2. WGCM

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/cm^2; 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, 10 mm 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.

2.3. Measurement of tablet hardness

Tablet hardness, which is defined as the force required to break a tablet by radial compression, was measured with a tablet hardness tester (Elbaker GmbH) ($n = 3$).

2.4. Determination of disintegration time

A tablet was put into the mouth of a healthy male adult volunteer without water and the oral disintegration time was recorded as the time until the volunteer felt that the tablet had disappeared in his mouth ($n = 3$).

2.5. Evaluation of crystalline state

The crystalline state of the tablet powder was characterized by using a powder X-ray diffraction system (X'Pert PRO, Philips). The measurement conditions were as follows: target: Cu Kα; generator voltage: 45 kV; tube current: 40 mA; and data angle range: $2\theta = 5$–$45°$. The samples were erythritol, xylitol, and a mixture of erythritol and xylitol granule manufactured by DCM or WGCM, with the concentration of xylitol in the mixture being set at 12.5%.

2.6. Measurement of tablet pore size

The pore size of the tablets was measured with a mercury porosimeter (Pore Sizer 9320, Micromeritics). The contact angle between the mercury and the sample was set at 130° and the surface tension was set at 485 dynes/cm. The pore size was calculated using the following equation:

$$\text{Pore size} = \frac{-4\gamma\cos\theta}{P}$$

where P is the pressure (psia), θ the contact angle, and γ is the surface tension of the mercury.

The distribution of pore size in the tablets was calculated from the ratio of the volume of mercury entering the tablets at a particular pressure relative to the total volume of mercury. The median pore size by volume was defined as that at which 50% of the total volume of the mercury had entered the tablets.

3. Results and discussion

3.1. Effect of particle size of SA on hardness and oral disintegrating time of erythritol–trehalose tablets in DCM

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

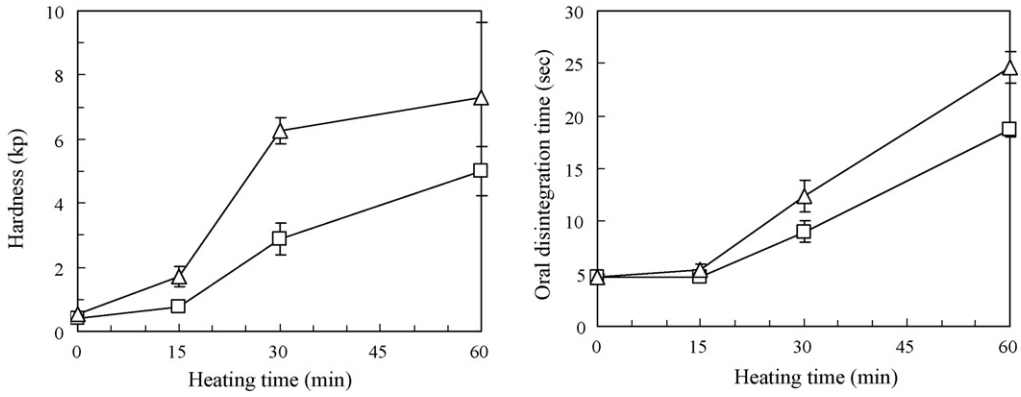

Fig. 1. Effect of particle size of LMP-SA on hardness and disintegration time of erythritol–trehalose tablets prepared by DCM. Trehalose; (△): millded, (□): non-milled, mean particle size of non-milled trehalose: 63.5 μm, milled trehalose: 24.2 μm, mixture rate of erythritol–trehalose: 19:1, heating temperature: 97 °C, values are the means ± S.D., $n = 3$.

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 (Kuno et al., 2005). Therefore, the heating temperature of the tablets was set at 97 °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 as follows: non-milled trehalose, 63.5 μm; milled trehalose, 24.2 μm. As shown in Fig. 1, 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 containing non-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 in Fig. 2a and b). The data also indicated that the pore size of both tablet was increased by heating. Fig. 2c represents the comparison of the pore size distribution between the tablet containing non-milled and milled trehalose after heating. It was evident that the pore size of tablets containing milled trehalose became larger 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 (Anne, 1996; Mattsson and Nyström, 2001). However, the results shown in Fig. 1 showed that 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 (Nyström and Karehill, 1986; Nyström et al., 1993). 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 pore radius (Washburn, 1921). On the other hand, it is also known that the disintegration time of the tablets was increased by increasing the tablet hardness (Sunada and Bi, 2002). 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

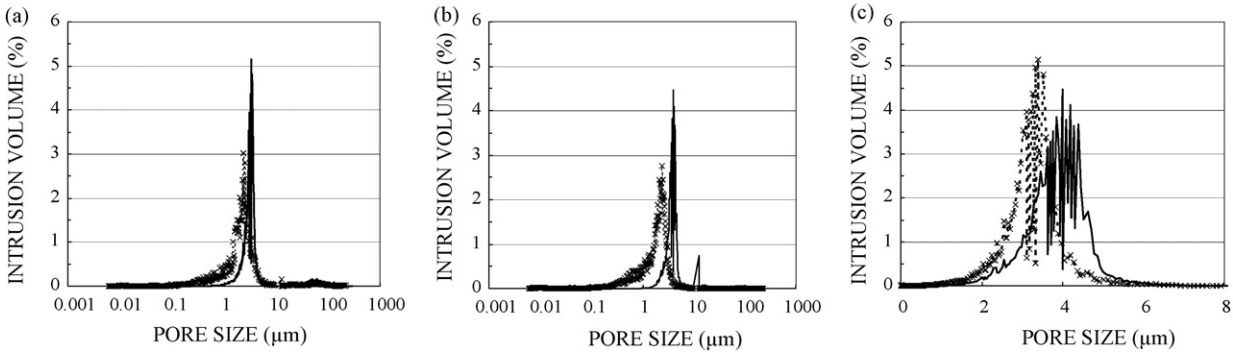

Fig. 2. Effect of particle size of SA on distribution of pore size of erythritol–trehalose tablets prepared by DCM. (a) Non-milled trehalose, (b) milled trehalose, dotted line: before heating, thick line: after heating, and (c) heated tablet, dotted line: non-milled trehalose, thick line: milled trehalose, mixture rate of erythritol–trehalose: 19:1, heating condition: 97 °C 60 min.

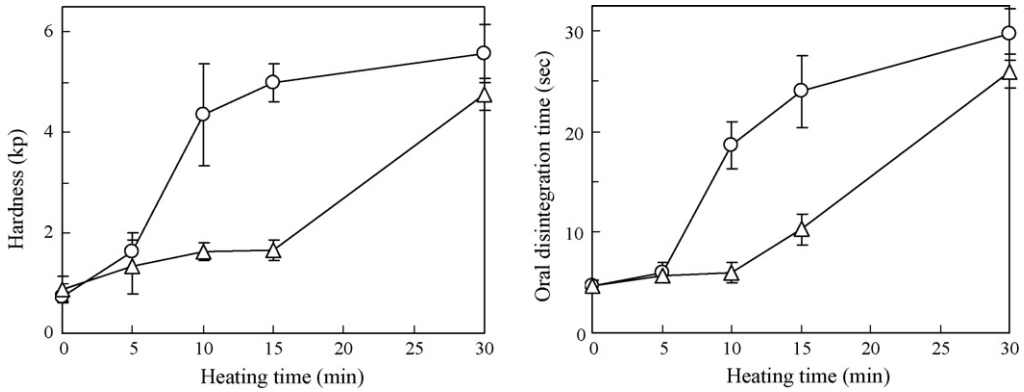

Fig. 3. Effect of preparation method on hardness and oral disintegration time of erythritol–xylitol tablets. Preparation method; (◯): WGCM, (△): DCM, mixture rate of erythritol–xylitol: 19:1, heating condition: 93 °C, values are the means ± S.D., $n = 3$.

rapid disintegration of the tablets, even though the tablets containing milled trehalose became harder compared to the tablets containing non-milled trehalose.

3.2. Effect of preparation method on hardness and oral disintegrating time of tablets

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. The characteristics of the tablets obtained by DCM and WGCM are shown in Fig. 3. 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 data showed that the OD tablets prepared by DCM needed 30 min of heating to have a hardness greater than 2 kp. On the other hand, the tablets prepared by WGCM showed a hardness over 4 kp after heating for 10 min. These data 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. 4 shows 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 (Kuno et al., 2005). 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 after 15 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. 5. 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 LMP-SA during the heating process. According to the results, WGCM enables the OD tablets to maintain rapidly disintegrating properties with greater hardness after a short amount of heating.

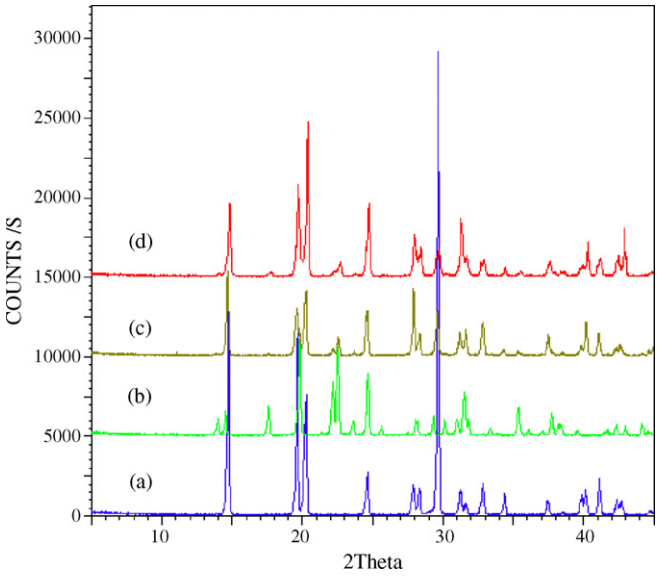

Fig. 4. X-ray pattern of erythritol, xylitol, physical mixture and granule of erythritol–xylitol. (a) Erythritol alone, (b) xylitol alone, (c) physical mixture of erythritol and xylitol, and (d) granule of erythritol and xylitol.

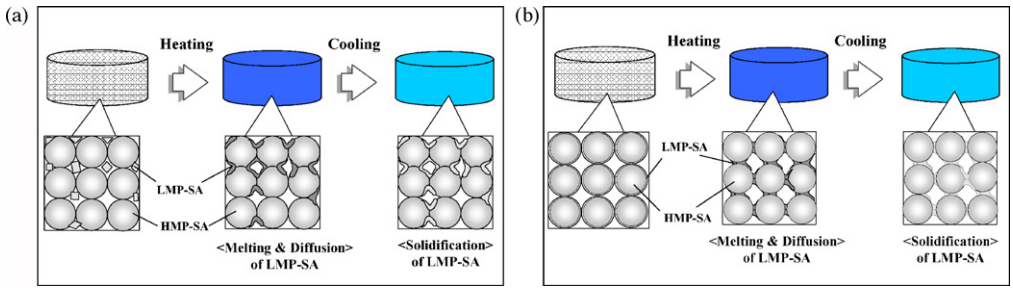

Fig. 5. Schematic description of OD tablets prepared by (a) DCM and (b) WGCM.

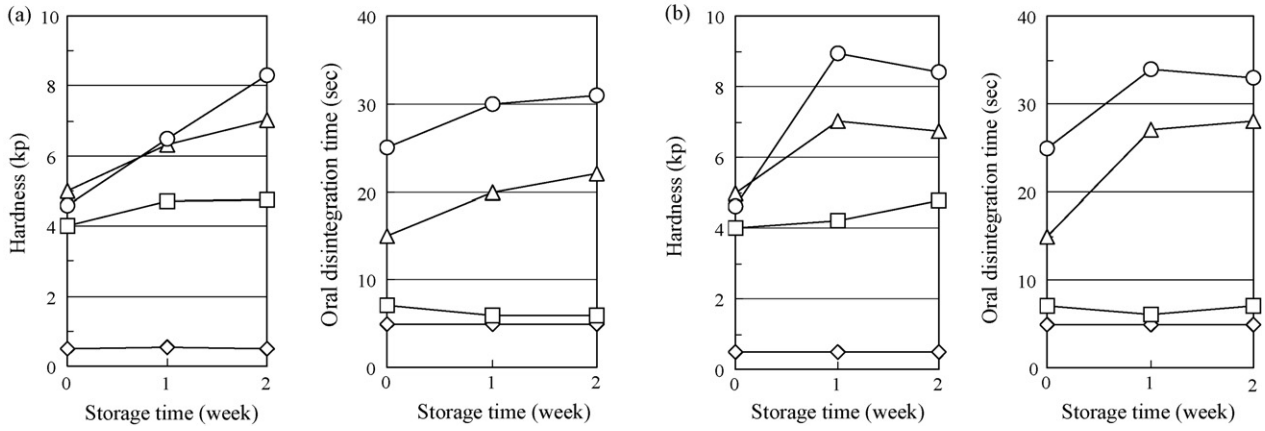

Fig. 6. Effect of amount of LMP-SA on hardness and oral disintegration stability of tablets prepared by WGCM. Storage conditions: (a) 25 °C/60% R.H. in glass bottle and (b) 50 °C in glass bottle, amount of xylitol in tablet; (◇): 0%, (□): 1%, (△): 3%, (◯): 5%.

3.3. Effect of amount of LMP-SA on disintegrating and hardness stability of tablets prepared by WGCP

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, as shown in Fig. 6. 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 more than 30 s in the initial state of stability test. The tablet hardness increased slightly, and the oral disintegration time was not changed under either stability condition. The tablets containing 3% or 5% of xylitol also showed a hardness over 4 kp and an 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. Previously, we evaluated the effect of the crystalline state on the hardness and the oral disintegration time of erythritol–xylitol tablets. The X-ray diffraction pattern 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.

4. Conclusions

In our preparation methods, the tablets were produced by compressing powder or wet granules which were composed of two types of SA having high and low melting points and subsequently heating the tablets obtained. To clarify the effect of the distributed state of LMP-SA on the tablet properties, tablets containing various states of LMP-SA were prepared by DCM and WGCM and the OD tablet properties were evaluated. In DCM, the tablets containing small-sized particles of LMP-SA became harder after a short period of heating compared with the tablets containing large-sized particles of LMP-SA. It could be suggested that the reduction in size of the LMP-SA particles

made it easier to diffuse after melting and increased the bonding surface area in the tablet, so that the tablet hardness was increased with a short heating time. On the other hand, the heating time required for the OD tablets prepared by WGCM was much shorter than that for tablets prepared by DCM. This was likely due to the spraying of the LMP-SA solution onto the HMP-SA and thus the diffusion of LMP-SA was probably accelerated during the heating process of tablets. In addition, disintegration and hardness stability of the tablets were affected by the LMP-SA content in WGCM. The LMP-SA content, therefore, should be regulated to assure the stability of OD tablet characteristics.

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