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Research paper

Effect of the type of lubricant on the characteristics of orally disintegrating tablets manufactured using the phase transition of sugar alcohol

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Abstract

The aim of this study was to evaluate the effect of lubricants on the characteristics of orally disintegrating (OD) tablets manufactured using the phase transition of sugar alcohol. OD tablets were produced by directly compressing a mixture containing lactose–xylitol granules, disintegrant, glidant and lubricant, and subsequent heating. The effect of the type of lubricant on the tablet characteristics was evaluated using magnesium stearate (Mg-St), sodium stearyl fumarate (SSF), and talc as lubricants. The hardness of the tablets increased to ca. 6 kp as a result of heating, regardless of the kind of lubricant. The oral disintegration time of the tablets containing Mg-St or SSF increased with an increase in the hardness. In contrast, the oral disintegration time of the tablets containing talc was not changed despite of an increase in hardness. The water absorption rate of the tablets containing talc was much faster than that of the tablets containing other lubricants. The surface free energy measurement showed that the polarity of the tablet components containing talc was remarkably increased by heating. The water absorption rate of the tablets containing talc was also increased by heating. These results indicate that a more hydrophilic surface might be attained by heating the talc. Consequently, talc was demonstrated to be the most desirable lubricant for the preparation of OD tablets based on the principle of the phase transition of sugar alcohol.

Keywords: Orally disintegrating tablets; Phase transition; Sugar alcohol; Saccharide; Lubricant; Talc

1. Introduction

In accordance with the transition to an aging society and changes in the living environment, a demand has arisen for the development of drug dosage forms that can be readily handled and taken by the elderly, children, or patients whose intake of water is restricted. For example, a dosage form which can be taken without water is useful in the case of the acute onset of a symptom. Thus, attempts have been made to develop an orally disintegrating dosage form which, when taken in the oral cavity, rapidly disintegrates or dissolves merely in the saliva or a small amount of water [1–3]. For example, a solution or suspension containing a drug and excipients is charged into the pockets of a blister pack sheet which has been molded beforehand, and then the sheet is subjected to freeze-drying in order to make the OD product [4]. In another preparation method, OD tablets are produced by using wet powder containing a drug and subsequent drying in an oven [5]. However, these methods require special equipment, since it is impossible to freeze-dry an entire blister pack sheet with ordinary equipment or to compress wet powder using a conventional tabletting machine.

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On the other hand, attempts have been made to develop OD tablets with sufficient hardness by commonly used equipment. Mizumoto et al. reported that OD tablets could be manufactured using a combination of saccharides with low and high moldability [6]. In their method, the OD tablets were manufactured by compressing granules consisting of low and high moldability saccharides, and then conditioning them. The tablet hardness was increased by the crystal change from an amorphous to a crystal state by the conditioning process. Sugimoto et al. also reported preparing OD tablets by storing the tablets compressed with a mixture of mannitol and amorphous sucrose at low compression pressure [7,8]. In this method, the increase in the tablet hardness was due to the transition from amorphous to crystalline sucrose in the tablet.

To obtain OD tablets of sufficient hardness without any special equipment, we focused on the melting points of sugar alcohol (SA) and proposed a novel method to prepare OD tablets of sufficient hardness by utilizing the phase transition of SA [9]. In our preparation method, the tablets are produced by compressing powder or wet granules which are composed of two types of SAs or an SA and a saccharide with high and low melting points, and subsequently heating the obtained tablets. Before the heating process, the tablets do not have sufficient hardness because of low compactability. The tablet hardness is increased by the heating process. The increase in the tablet hardness resulting from heating did not depend on the crystal state of the lower melting point of SA. The tablet hardness was related to the increase of inter-particle bonds or the bonding surface area in tablets induced by the melting, diffusion, and solidification of the lower melting point SA. Therefore, in our preparation method a combination of two SAs or SA and a saccharide and the heating process was needed to prepare OD tablets with sufficient hardness.

We made OD tablets from only two types of SAs or an SA and a saccharide in order to investigate the characteristics and formation mechanism of OD tablets prepared by the phase transition of lower melting point SA. However, lubricants are required for the continuous tabletting of OD tablets because the lubricants prevent the tablets from sticking to the die wall and punch faces. However, it is well known that the lubricant influences the disintegration or dissolution properties of tablets [10,11]. In the case of OD tablets, it is important to maintain the rapid disintegration properties of tablets with a sufficient hardness. Therefore, the purpose of the present study was to evaluate the effect of the type and amount of lubricant on the tablet characteristics of OD tablets prepared based on the principle of the phase transition of SA. We prepared OD tablets containing various types and amounts of lubricants and evaluated the tablet characteristics before and after heating. Additionally, the surface free energy of the tablet components and the water absorption rate of the tablets were measured to evaluate the physicochemical properties related to the disintegration of OD tablets containing various lubricants.

2. Materials and methods

2.1. Materials

Lactose (m.p.: 201.6 °C, Pharmatose 200 M, DMV Japan) was used as the high melting point saccharide. Xylitol (m.p.: 93–95 °C, Towa Chemical Industry Co., Ltd.) was used as the low melting point SA. Crospovidone (Polyplasdone XL, ISP Japan, Ltd.) and light anhydrous silicic acid (Aerosil 200, Nippon Aerosil Co., Ltd.) were used as the disintegrant and glidant, respectively. Magnesium stearate (Nitto Chemical Industry Co., Ltd.), talc (Matsumura sangyo) and sodium stearyl fumarate (Pruv, Mendell) were used as the lubricants.

2.2. Preparation method of tablets

Xylitol was dissolved in purified water to make 26.7 w/w%. Lactose was granulated using the xylitol solution with a fluidized-bed granulator (Flow coater mini, Freund Corporation). The granulation conditions were set as follows: inlet temperature: 90 °C; outlet temperature: 45 °C; spray air pressure: 1.5–2.0 kg/cm^2; rate of spray: 0.9 g/min. According to the composition shown in Table 1, the granules were mixed with crospovidone and light anhydrous silicic acid with a turbula mixer for 10 min, and then mixed with lubricant for 3 min. The mixture was compressed using a single punch tabletting machine (KT-II, Okada-seikou Co., Ltd.) under the following conditions: weight: 300 mg; compression pressure: 500 kgf; punch: 9.5 mm in diameter with a flat surface. The obtained tablets were placed in a drying oven to heat at 95 °C for 15 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 (TBH 21, ERWEKA 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 while moving his tongue ($n = 3$).

2.5. Determination of water absorption rate of tablets

The water absorption rate of the tablets was studied using the apparatus described by Nogami et al. [12]. A tablet containing 10% lubricant was put on the glass filter of the apparatus, as shown in Fig. 1. The water absorption rate of the tablet (mL/s) was calculated from the time until

Table 1
Components and composition of tablets

Components	Amount of lubricant							
	0%		1%		5%		10%	
	mg	%	mg	%	mg	%	mg	%
Lactose	270.2	90.3	267.3	89.1	255.9	85.3	241.7	80.6
Xylitol	14.2	4.7	14.1	4.7	13.5	4.5	12.7	4.2
Crospovidone	15.0	5.0	15.0	5.0	15.0	5.0	15.0	5.0
Light anhydrous silicic acid	0.6	0.2	0.6	0.2	0.6	0.2	0.6	0.2
Lubricant[a]	0.0	0.0	3.0	1.0	15.0	5.0	30.0	10.0
Total	300	100	300	100	300	100	300	100

[a] Lubricant: magnesium stearate (Mg-St), sodium stearyl fumarate (SSF), talc.

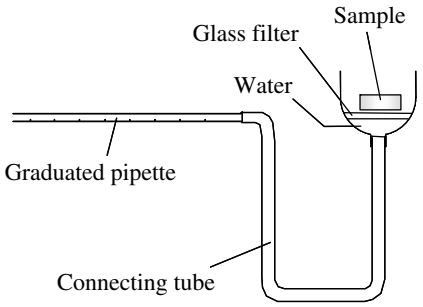

Fig. 1. Instrument for determining water absorption rate of tablets.

the tablet uptake of 0.05 mL of water at room temperature ($n = 3$).

2.6. Determination of compression efficiency

A mixture containing various types and amounts of lubricants, as shown in Table 1, was compressed with an autograph (Shimadzu Corporation) under the following conditions: weight: 300 mg; compression pressure: 500 kgf; punch: 10 mm in diameter. The compression efficiency was calculated using the following equation ($n = 3$):

Compression efficiency
= (Maximum compression force of lower punch/
Maximum compression force of upper punch) × 100.

2.7. Measurement of tablet pore size

The pore size of the tablets was measured using 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:

$$\text{Pore size} = (-4\gamma\cos\theta)/P,$$

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

The distribution of the 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 entered the tablets.

2.8. Measurement of surface free energy of samples

The surface free energy of the samples was studied using the method described by Terada and Yonemochi [13]. The tablets containing 10% of various lubricants before or after the heating process were milled for 3 min in a mortar to make a powdered sample. The liquid penetration rate was measured with a surface tension balance (K21, KRUSS GmbH) at 25 °C. A stainless tube packed with the mixture was lowered into liquid and the recording of the time was started when the liquid had contact with the powder. The weight of the liquid which penetrated into the powder bed was recorded against the time. The penetration rate constant was calculated by the Washburn equation. Benzyl alcohol, *n*-hexane, chloroform, tetrachloro methane, 1-nitro-propane, and toluene were used as probe solvents having different polarities. The surface free energy of the powder was calculated from the Owens, Wendt, Rable, and Kaelble's equation using the contact angle between the liquid and the powder.

$$\frac{1+\cos\theta}{2}\frac{\gamma_L}{\sqrt{\gamma_L^d}} = \sqrt{\gamma_S^p}\cdot\sqrt{\frac{\gamma_L^p}{\gamma_L^d}} + \sqrt{\gamma_S^d},$$

where θ is the contact angle, γ_L and γ_S are the surface free energy of the liquid and solid, respectively, and p and d are the polar and dispersive parts of the surface free energy, respectively. The polarity of the powder was calculated using the following equation:

$$\text{Polarity} = 100\cdot\gamma_S^p/\left(\gamma_S^p+\gamma_S^d\right).$$

3. Results and discussion

3.1. Effect of amount and type of lubricant on tablet hardness and oral disintegration time

The mixture shown in Table 1, containing various types and amounts of lubricants, was compressed. It is known

that magnesium stearate (Mg-St) is hydrophobic and that sodium stearyl fumarate (SSF) is less hydrophobic than Mg-St [14]. Talc has hydrophobic and hydrophilic properties because it can be dispersed into aqueous media and oil [15]. Thus, we selected these three materials as lubricants for this study. The effects of the amount and type of lubricant on the hardness and oral disintegration time of tablets before the heating process were evaluated, as shown in Fig. 2. The hardness of tablets containing Mg-St and SSF was increased to above 2 kp by adding 1% of the lubricant and were slightly increased to 3 kp by the addition of 10% of the lubricant. On the other hand, the hardness of tablets containing talc was slightly increased to 1 kp, despite the addition of 10% of the lubricant. The compression efficiency of the mixture containing various types and amounts of lubricants was measured, as shown in Fig. 3. The results showed that the compression efficiency of the mixture with 1% Mg-St and SSF increased to above 90%. On the other hand, the value of the mixture with 10% talc did not reach above 90%. These data suggested that the hardness of tablets with Mg-St or SSF as a lubricant was higher due to their high compressibility compared to tablets with talc. The oral disintegration time of tablets containing Mg-St were increased to above 40 s by adding 10% lubricant, although the disintegration time of tablets containing SSF or talc remained shorter than 30 s. The differences in the disintegration time of the tablets could be attributable to differences in the hydrophobic properties of the two lubricants. Mg-St is well known as a high hydrophobic lubricant [10,11], so that the oral disintegration time of tablets containing Mg-St is longer than that of others.

The hardness and oral disintegration time of tablets after the heating process was measured, as shown in Fig. 4. After heating, the tablets became harder, as shown in Fig. 2, and the hardness of the tablets containing 10% lubricant was ca 6 kp regardless of the type of lubricant. Fig. 5 shows the pore size of tablets containing 10% Mg-St, SSF, or talc before and after the heating process. The data showed that the pore size of the tablets containing

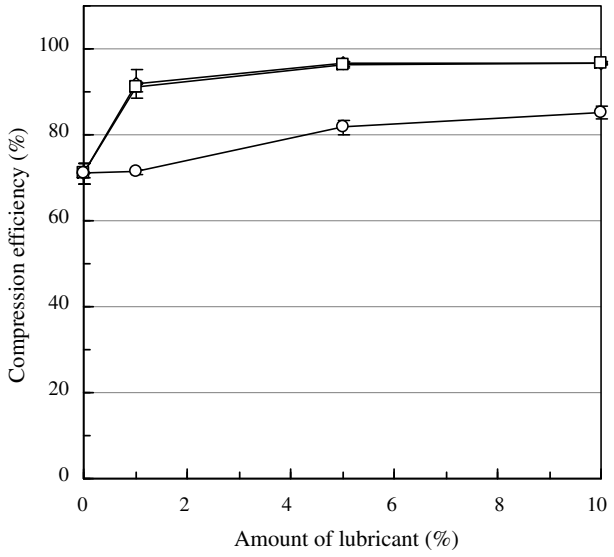

Fig. 3. Effect of amount and type of lubricant on compression efficiency. Type of lubricant: ◇, Mg-St; □, SSF; ○, talc; values are the means ± SD, $n = 3$.

any of the various lubricants was increased by the heating process. It is well known that tablet hardness decreases by increasing the pore size in the case of compressed tablet [16,17]. However, the results shown in Fig. 2, Figs. 4 and 5 showed that the tablet hardness increased with an increase of pore size after heating. On the other hand, it is also well known that tablet hardness increases by increasing the bonding surface area of the inter-particle [18,19]. We previously hypothesized that the increase of tablet hardness was caused by the diffusion of low melting point SA in the tablets during the heating process [9]. Therefore, xylitol having m.p. of 93–95 °C in tablet might diffuse after melting when heating at 95 °C, and thus increase the bonding surface area, resulting in an increase in hardness of the tablets containing any of the various lubricants.

With respect to the oral disintegration time of the tablets, the disintegration time of tablets containing Mg-St

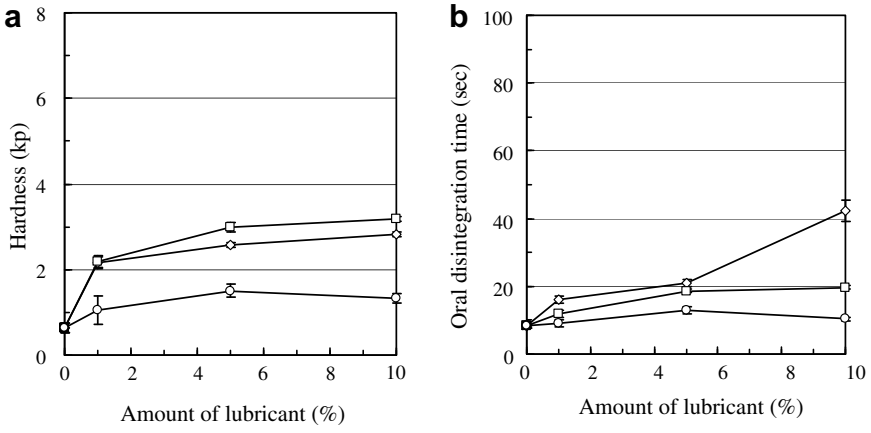

Fig. 2. Effect of amount and type of lubricant on characteristics of tablets before heating. (a) Hardness and (b) oral disintegration time, type of lubricant: ◇, Mg-St; □, SSF; ○, talc; values are the means ± SD, $n = 3$.

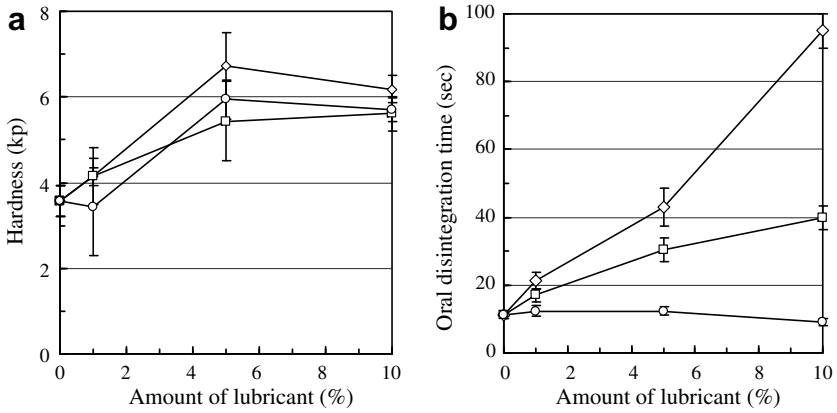

Fig. 4. Effect of amount and type of lubricant on characteristics of tablets after heating. (a) Hardness and (b) oral disintegration time, type of lubricant: ◇, Mg-St; □, SSF; ○, talc; values are the means ± SD, $n = 3$.

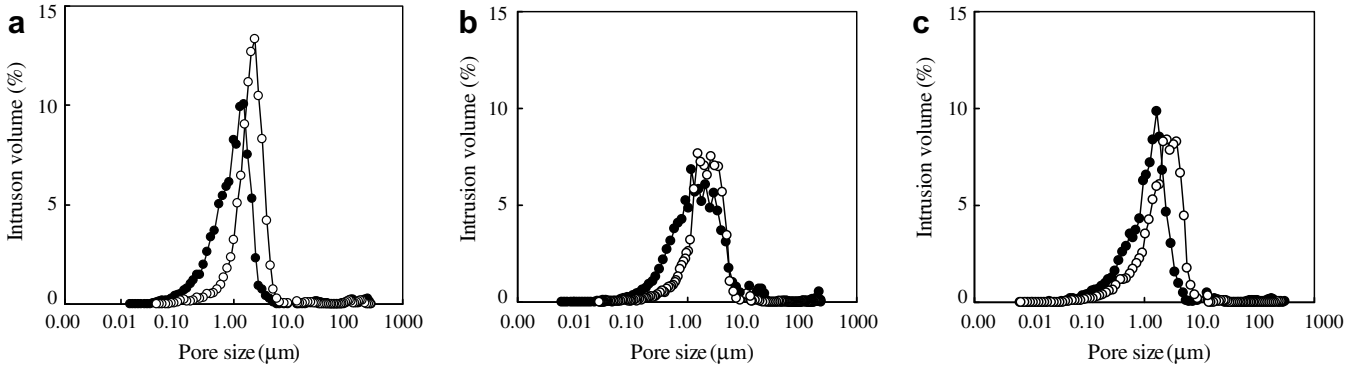

Fig. 5. Effect of heating process on distribution of pore size of orally disintegrating tablets containing 10% of various lubricants. Type of lubricant: (a) Mg-St, (b) SSF, (c) talc, closed symbol: before heating; open symbol: after heating.

or SSF was increased by the heating process. In particular, the oral disintegrating time of tablets containing Mg-St was longer than that of tablets containing other lubricants. Mg-St is well known as a lubricant which affects the dissolution and disintegration properties of tablets during stability testing. The undesirable oral disintegration time of tablets containing Mg-St could be caused by the properties of Mg-St. On the other hand, the oral disintegration time of tablets containing talc was not changed by heating, with the disintegration time remaining below 30 s. These results suggested that talc is an appropriate lubricant in the preparation method of OD tablets using the phase transition of SA. With respect to the compatibility for tabletting, the sticking to the punch face was occurred in the case of 1% and 5% adding of talc, but considerably improved by adding 10% talc. This sticking phenomenon, however, did not affect tablet hardness and disintegration as shown in Fig. 2. On the other hand, the sticking was not observed by adding 1% of Mg-St and SSF. The heated tablets containing 10% lubricant had almost the same hardness, so that the amount of lubricant was set at 10% to clarify the effect of the lubricant on the tablet properties in the following sections.

3.2. Effect of heating process on the water absorption rate of tablets containing various lubricants

The water absorption rate of tablets containing various lubricants was measured to evaluate the effect of the type of lubricant on the water uptake capability of tablets. Fig. 6 shows the water absorption rate of tablets containing 10% lubricant before and after the heating process. The data showed that the water absorption rate of tablets containing talc before heating was faster than that of tablets containing other lubricants. The results also showed that the water absorption rate of the tablets containing Mg-St and SSF was decreased by the heating process. Mg-St with its lower melting point (117–150 °C) may be melted, diffused and solidified in the tablets in a manner similar to xylitol once the heating process was completed. This may cause lower wettability of the tablets. Even though the pore size may increase to some extent, this may result in a severe decrease in the water absorption rate. SSF with hydrophobic properties showed a milder effect than Mg-St, which may have been caused by its high melting point (224–245 °C). On the other hand, the water absorption rate of the tablets containing talc was increased by the heating process. Consequently,

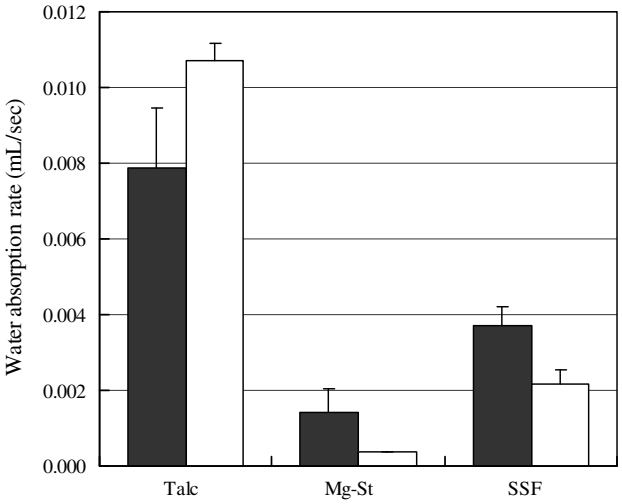

Fig. 6. Effect of heating process on water absorption rate of tablets containing various lubricants. Closed bar: before heating; open bar: after heating, values are the means ± SD, $n = 3$.

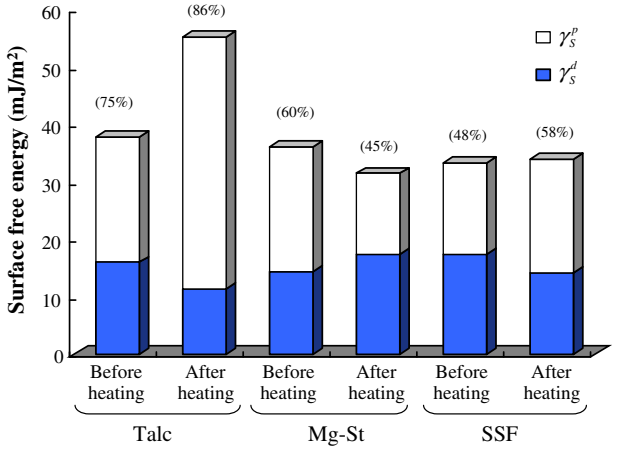

Fig. 7. Effect of heating process on surface free energy of samples containing various lubricants. ( ), polarity of tablets; amount of lubricant: 10%, γ_S^p and γ_S^d are polar and dispersive parts of solid surface free energy, respectively.

although the tablet hardness was increased by the heating process, the oral disintegration time of the heated tablets containing talc was almost unchanged.

3.3. Effect of heating process on surface free energy of samples containing various lubricants

The surface free energy of tablet components containing Mg-St, SSF, or talc was measured by the penetration method. Fig. 7 shows the surface free energy of the samples containing 10% lubricant before and after the heating process. The polarity of the samples containing talc was remarkably increased by heating, although that of the samples containing Mg-St or SSF was hardly changed. Talc is a purified, hydrated, magnesium silicate and may contain small, variable amounts of aluminum silicate. It is also known that talc has layers of silicate whose structure consists of sheets of tetrahedrally coordinated Si. The successive layers are bonded together only by weak van der Waals forces. The softness of talc is also due to the ease of displacement of these layers. Terada et al. reported the polar part of talc was increased by the grinding so that the layer structure of talc might be affected by the grinding process and a more hydrophilic surface might be attained by grinding the talc [13]. On the other hand, Fig. 6 showed that the polar part of the sample containing talc was increased by the heating as in the case of the grinding. It would be suggested that the layer structure of talc might be affected by the energy produced by the heating or the grinding and thus a more hydrophilic surface might be attained by heating. Therefore, the polarity of tablet components containing talc was increased by heating, indicating that tablets containing talc have high water uptake capability compared with tablets containing other lubricants.

4. Conclusions

To obtain OD tablets with sufficient hardness and oral disintegration time, we evaluated the effect of the type of lubricant on the tablet characteristics of OD tablets manufactured by the phase transition of SA. In this study, the tablets were produced by using wet granules that were composed of xylitol as the SA with a low melting point and lactose as the saccharide with a high melting point, and subsequent heating of the obtained tablets. The hardness of the tablets was increased to ca. 6 kp by heating, regardless of the type of lubricant. The data suggested that the phase transition of the low melting point SA would be achieved, no matter which of the lubricants was utilized. On the other hand, the oral disintegration time of the tablets before and after heating depended on the type and amount of the lubricant. The oral disintegration time of tablets containing Mg-St or SSF increased with an increase in the amount of lubricant and the disintegration time was also increased by heating. However, the disintegration time of tablets containing talc was not changed when the amount of lubricant was increased. Furthermore, the disintegration time was hardly changed by heating, although the tablets had sufficient hardness, similar to that of the tablets containing Mg-St or SSF after heating. After heating, the water absorption rate of tablets containing talc increased compared to that of tablets containing other lubricants. As well, the tablet components containing talc remarkably increased the polarity in the surface free energy. These data indicate that a more hydrophilic surface might be attained by heating the talc. Consequently, talc would be a desirable lubricant for OD tablets manufactured using the phase transition of SA.

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