

## Transformation of Lactitol Crystals and Dehydration with Grinding

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The transformation of monohydrate, dihydrate, two polymorphic forms (A and B) of anhydrate and the amorphous form of lactitol [(+)-4-*O*- $\beta$ -D-galactopyranosyl-D-glucitol] were investigated by infrared spectrum, differential scanning calorimetry and X-ray powder diffraction. Monohydrate and dihydrate were transformed to anhydrate A and anhydrate B after storage at 80 °C for 24 h under reduced pressure, respectively, but both hydrates changed to anhydrate A after being at 105 °C for 3 d. Five solid forms were stored under the relative humidity (RH) range from 12 to 93% at 25 °C for 14 d. Monohydrate was transformed into dihydrate at RH more than 90%, but no change was observed in the range from 12 to 84% RH. Dihydrate did not show any transformation in the experimental RH range, though weight increase and decrease were observed at 12 and 93% RH, respectively. Both anhydrate A and B, however, were changed to monohydrate but this transformation occurred under different RH conditions (anhydrate A: 22% RH, anhydrate B: 75% RH). The amorphous form was transformed into monohydrate and dihydrate in the RH range from 53 to 84% and at 90% RH, respectively. The effect of grinding on the thermal behavior of the two hydrates was investigated, dehydration temperatures of monohydrate, which was determined by controlled rate thermogravimetry, was about 15 °C lower than the intact monohydrate. However, no change in dehydration temperature was observed for dihydrate. These results suggest that the influence of grinding on thermal behavior was different for the two hydrates.

**Key words** lactitol; transformation; dehydration

Lactitol [(+)-4-*O*- $\beta$ -D-galactopyranosyl-D-glucitol] is generally obtained by hydrogenation of lactose and is used as a sweetener in confectionery.<sup>1)</sup> It is also viewed as a drug for the treatment of ammoniemia and hepatic encephalopathy.<sup>2)</sup> Three hydrate forms (monohydrate,<sup>3-8)</sup> dihydrate,<sup>8-10)</sup> and trihydrate<sup>11,12)</sup>, two anhydrate forms<sup>13-15)</sup> and one amorphous form<sup>9)</sup> of lactitol are reported to exist in solid form. Although physical characterization by single crystal X-ray diffraction analysis and IR-spectra was carried out individually on each solid form, the transformations of these solid forms under specific environmental conditions and the comparison of their physicochemical properties were not described in detail.

Polymorphism and solvate of a compound often have a significant influence on various properties of dosage form, e.g., stability,<sup>16)</sup> bioavailability<sup>17)</sup> and release rate of the drug.<sup>18)</sup> The solid state of a drug may also be changed by various storage conditions and processes employed in the manufacturing of pharmaceuticals, such as grinding, drying and compressing. Therefore, the characterization of these physicochemical properties in drugs is of importance in the design of their dosage form.

The purpose of the present work was to study the transformations and thermal behaviors of five solid forms (except for trihydrate) of lactitol under various storage conditions using X-ray powder diffraction (XRPD), infrared (IR) spectra, differential scanning calorimetry (DSC) and thermogravimetry (TG). The influence of the grinding process, which is commonly employed in the size reduction of particles or granules, on the transformation of lactitol was also investigated.

### Experimental

**Materials** Monohydrate, dihydrate and anhydrate B of lactitol were obtained from Towa Chemical Industry, Tokyo, Japan and used as supplied. Crystal potassium bromide (KBr) for IR spectra was purchased

from Shimadzu, Kyoto, Japan. All other chemicals were of analytical grade.

**Preparation of Anhydrates and Amorphous** Two anhydrates having different melting points are reported to exist in lactitol and are called anhydrate A (mp about 121 °C)<sup>13)</sup> and anhydrate B (mp about 151 °C).<sup>14)</sup> Anhydrate A was prepared by heating monohydrate at 80 °C for 24 h under reduced pressure. In preparing amorphous lactitol, 10 ml of 50% aqueous solution of lactitol monohydrate was frozen with liquid nitrogen and dried for 24 h using a freeze dryer (FD-80, Tokyorika Co., Ltd.).

**Preparation of Ground Samples** Monohydrate and dihydrate were ground by agate mortar and pestle and passed through a 100 mesh screen. The samples obtained were ground monohydrate and ground dihydrate.

**X-Ray Powder Diffraction (XRPD)** In the measurement of the XRPD, all of the samples were ground by agate mortar and pestle. Diffractograms were taken with two types of X-ray diffractometers: the MXP3VA-HF-22 and MXP18VA-HF-22, both from MAC Science Co., Ltd. The former was operated under the following conditions: CuK $\alpha$  radiation, voltage 50 kV, current 40 mA, scan speed 3°/min and the range  $2\theta = 5-40^\circ$ . The behavior of the hydrate with heating was studied using MXP18VA-HF-22 under operating conditions of: CuK $\alpha$  radiation, voltage 45 kV, current 30 mA, scan speed 5°/min and the range  $2\theta = 5-40^\circ$ .

**IR Spectroscopy** The IR spectra were recorded on KBr disks using an IR-700 system (Jasco Co., Ltd.).

**DSC and TG Analysis** Differential scanning calorimetry (DSC) and thermogravimetry (TG) were carried out using DSC-3100 and TG-DTA 2000 systems (MAC Science Co., Ltd.), respectively. The operating conditions were: sample weight about 5 mg, heating rate 5 °C/min, open pan and N<sub>2</sub> gas flow rate 50 ml/min.

**Hot Stage Microscopy** A polarized light microscope BH-2, (Olympus Co., Ltd.) connected to a temperature controller (Lynkam Co., Ltd.) was used. The samples were heated at a rate of 10 °C/min.

**Controlled Rate Thermogravimetry (CRTG)** CRTG was carried out using a TAS 300 (Rigaku Co., Ltd.) with a dynamic rate controlled (DRC) method and a dry air flow rate of 200 ml/min.

**Hydration and Dehydration Study of Each Form at Various Relative Humidities** Samples (about 0.4 g) were placed in glass containers, then stored at 12, 22, 31, 43, 53, 63, 75, 84, 90 and 93% (in various saturated salt solutions) relative humidity (RH) at 25 °C in a desiccator for 14 d.

### Results and Discussion

**XRPD Profiles and IR Spectra of Modifications** The XRPD profiles of these five solid forms of lactitol are significantly different from each other, as shown in Fig.

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1. The forms showed the following specific X-ray diffraction peaks: monohydrate: 8.9, 17.3 and 17.8°; dihydrate: 7.7, 15.5 and 16.2°; anhydrate A: 9.1, 9.2, 12.0, 18.7 and 22.5°; and anhydrate B: 12.9° ( $2\theta$ ). These peaks are indicated by arrows in Fig. 1. The freeze-dried sample showed a halo pattern and was confirmed to be an amorphous state. Single crystal X-ray diffractions of monohydrate and dihydrate were reported by Kanters and Schouten<sup>8)</sup> and Kivikoski *et al.*<sup>10)</sup> Based on their results, the XRPD profiles simulated using the RITAN94<sup>19)</sup> program agreed with those obtained in the present study.

The IR spectra of the five solid forms are presented in Fig. 2, showing distinct spectra, particularly in the wave number range from 700 to 1500  $\text{cm}^{-1}$  and from 3300 to 3500  $\text{cm}^{-1}$ , depending upon solid form. The absorptions centered at 3500 and 1450  $\text{cm}^{-1}$  are assigned to OH

stretching and CH bending, respectively. The absorptions from 1350 to 1260  $\text{cm}^{-1}$  and from 1150 to 1000  $\text{cm}^{-1}$  are referred to as the OH bending and the OH and CO stretching vibrations, respectively.

Based on these results, we thought it possible to identify these five solid forms of lactitol from their X-ray diffraction patterns and IR spectra.

**Thermal Properties of Modifications** DSC and TG curves of the five solid forms are shown in Fig. 3. Monohydrate has an endothermic peak at 98.9°C on DSC curve and weight losses in the temperature ranges from 60 to 110°C and from 120 to 200°C were obtained on the TG curve. The first and second weight losses correspond to 2.7% and 1.9%, respectively. When all water contained

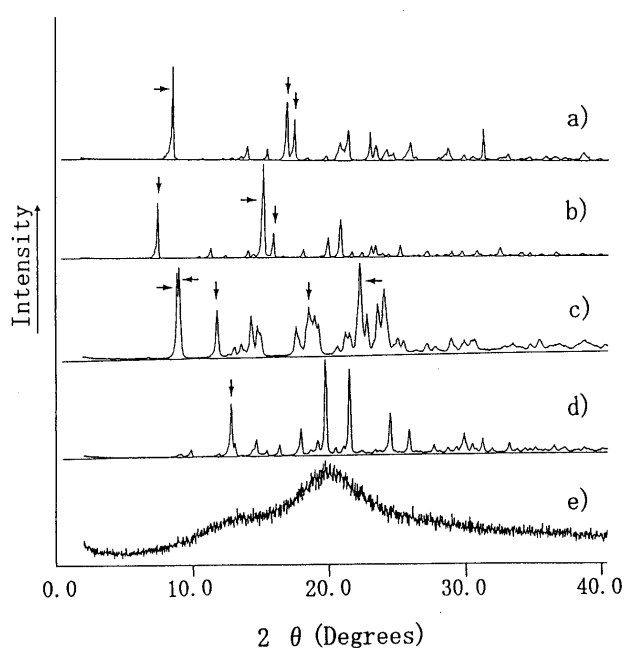


Fig. 1. X-Ray Powder Diffraction Patterns of the Five Solid Forms of Lactitol

a) monohydrate, b) dihydrate, c) anhydrate A, d) anhydrate B, e) amorphous form.

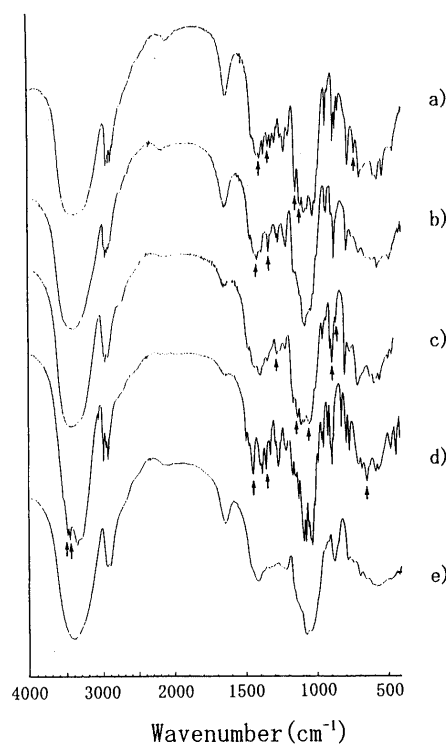


Fig. 2. IR Spectra of the Five Solid Forms of Lactitol

a) monohydrate, b) dihydrate, c) anhydrate A, d) anhydrate B, e) amorphous form.

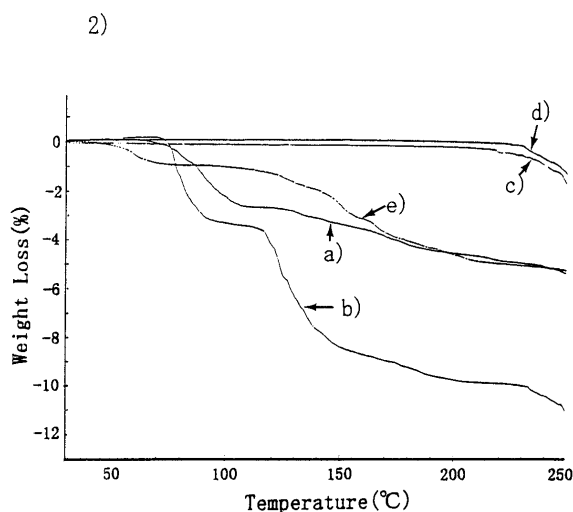
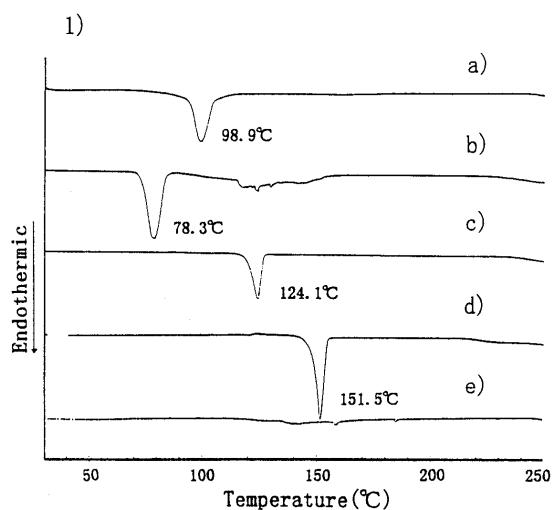


Fig. 3. DSC and TG Curves of the Five Solid Forms of Lactitol (Heating Rate, 5°C/min)

1) DSC curves, 2) TG curves. a) monohydrate, b) dihydrate, c) anhydrate A, d) anhydrate B, e) amorphous form.

in monohydrate is released, the weight loss observed is 5.0% of the TG measurement. These results indicate that all of the water in monohydrate was released in two steps within the experimental temperature range. The release of water from monohydrate, however, did not occur all at once, but gradually with an increase in temperature, especially with regard to the second weight loss. Furthermore, the fact that the monohydrate melting point was around 100 °C suggested that one endothermic peak observed on the DSC curve was due to dehydration and melting.

Two types of endothermic peaks, a sharp one at 78.3 °C and a broad one in the temperature range from 120 to 160 °C, were observed on the dihydrate DSC curve. A significant weight loss (about 3.6%) was obtained around 80 °C on the dihydrate TG curve. In addition to this change, an observation by the hot stage microscope indicated that a transformation accompanied by melting occurred around 80 °C. These results suggest that the endothermic peak at 78.3 °C was due to simultaneous dehydration and transformation of dihydrate. In order to identify the new state formed by the transformation, IR spectra of the sample after heating to 100 °C were obtained and showed a typical anhydrate B pattern not shown in this report. This result suggests that dihydrate was transformed to anhydrate form not *via* monohydrate in the heating process. About 10% weight loss is expected if all water in the dihydrate is released. However, the fact that only a 3.6% weight loss was observed up to 100 °C indicates that residual water may not exist in hydrate form, but as trapped water in the formed anhydrate B. The weight loss (about 6.5%) observed in the temperature range from 100 to 200 °C may result from the release of this trapped water. Further, the trapped water is thought to play an important role for the reason why no endothermic peak due to melting of anhydrate B was observed on the dihydrate DSC curve.

As mentioned above, part of the water contained in both monohydrate and dihydrate was not released after they melted. This trapped water is assumed to be due to the strong interaction between the hydroxyl group in lactitol and water molecules.

With regard to thermal properties of anhydrates A and B, no weight loss on their TG curves was observed at temperatures at which endothermic peaks were seen on their DSC curves; nor was any transformation of the two anhydrates found in observations by hot stage microscope. These results suggest that the endothermic peaks, 124.1 °C for anhydrate A and 151.5 °C for anhydrate B, were due to their melting. Only a few small endothermic peaks were observed on the DSC curve of the amorphous form in the temperature range from 130 to 160 °C, though about a 5.1% weight loss was observed in the temperature range from 30 to 200 °C on the TG curve. Observation by hot stage microscope confirmed that no transformation had occurred. It also showed that glass transition occurred at around 50 °C, and thereafter the crystalline form appeared. From these results we believe that the small endothermic peaks were due to dehydration and melting of the crystalline form appearing after glass transition.

**Change in Hydrates with Heating** Nguyen *et al.*<sup>20)</sup>

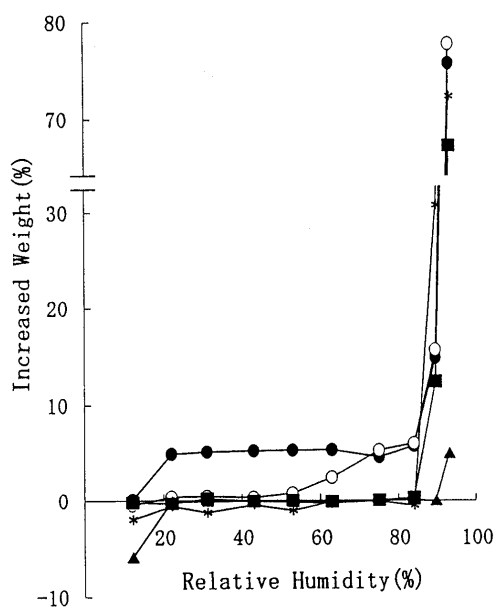


Fig. 4. Moisture Sorption Curves of the Five Solid Forms of Lactitol at 25 °C

■, monohydrate; ▲, dihydrate; ●, anhydrate A; ○, anhydrate B; \*, amorphous form.

reported that cabovir hydrate changed to a different anhydrate depending on heating temperature. Two types of hydrates of lactitol may also transform into different types of anhydrate, so this transformation was evaluated after storage for 24 h at 80 °C under reduced pressure (condition 1) and for 3 d at 105 °C (condition 2). Identification by XRPD revealed that dihydrate altered to anhydrate B under both conditions, but monohydrate yielded different types of anhydrate (anhydrate A at condition 1 and anhydrate B at condition 2). As shown by DSC measurement, monohydrate does not melt at 80 °C, but at a higher temperature of 98.9 °C. Dihydrate, on the other hand, is assumed to melt under both conditions. This suggests that hydrate will transform into anhydrate B after melting, but if dehydration occurs before melting, monohydrate yields hydrate A. The reason for this difference is probably anhydrate B's greater physicochemical stability.

**Differing Changes at Various Relative Humidities** To investigate the transformation of lactitol under various conditions, five solid forms were stored in the RH range from 12 to 93% at 25 °C for 14 d and their weight changes were calculated. Solid states after storage were identified by XRPD and IR spectra. The weight changes of the five forms are plotted as a function of RH in Fig. 4 and representative XRPD patterns of the five forms, which showed a large weight change, are shown in Fig. 5.

Monohydrate showed no transformation or weight change in the RH range from 12 to 84% but was found to transform into dihydrate at 90% RH (as shown in Fig. 5a), at which the weight of the sample increased about 13%. Dihydrate did not show any transformation in the RH range of 22 to 93% after a 6.0% weight loss was observed at 12% RH, and an increase (4.9%) in weight occurred at 93% RH. Although weight changes were observed at 12% RH and 93% RH, typical XRPD peaks of dihydrate (shown by arrows in Fig. 1) existed in all

stored dihydrate samples. As an example, the XRPD pattern at 12% RH is shown in Fig. 5b. This suggests that no transformation occurred, presumably due to the low temperature (25 °C) compared with melting point.

The weight of anhydrate A increased first at 22% RH and then at 90 and 93% (deliquescence). In the RH range from 22 to 90%, the formation of monohydrate was suggested from the XRPD pattern shown in Fig. 5c. Anhydrate B was also found to transform into monohydrate after significant weight increase at 75% RH (Fig. 5d). The XRPD pattern of amorphous form stored at RH above 12% showed several small peaks (Fig. 5e). These

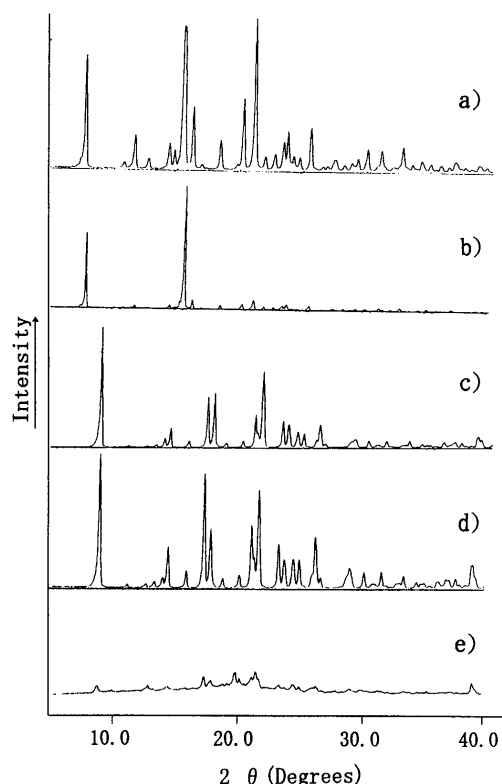


Fig. 5. X-Ray Powder Diffraction Patterns of Each Form of Lactitol after Storage under Various Relative Humidity at 25 °C for 14 Days

a) monohydrate (90% RH), b) dihydrate (12% RH), c) anhydrate A (90% RH), d) anhydrate B (90% RH), e) amorphous (12% RH).

peaks are similar to those of monohydrate and become more evident with increase in RH. In addition, IR spectra at 53% RH showed a typical monohydrate pattern; accordingly, the amorphous form transformed into monohydrate form in the RH range from 53 to 84%. Two states (solid and liquid) co-existed at 90% RH and were fully deliquescent at 93% RH. The form of the solid state at 90% RH was found to be dihydrate from IR spectra. The present observation suggested that free water in amorphous form would be changed to hydrate water under these humidity conditions. All of the solid forms except dihydrate were deliquescent at 93% RH. The schematic figure of the transformation behaviors of the five solid forms is presented in Fig. 6.

#### Changes in Thermal Behavior Caused by Grinding

Grinding is often employed to reduce the size of particles and granules in the manufacture of pharmaceuticals. Therefore, changes in solid form during processing should be carefully evaluated to avoid a significant influence on various properties of a dosage form. Lactitol is commercially available in hydrate form, so the effect of grinding on thermal behavior of monohydrate and dihydrate were investigated in the present study.

Ground monohydrate, as shown in Fig. 7a, has three endothermic peaks at 87.2, 97.3 and 123.0 °C after grinding. The first two peaks are believed to be due to dehydration and transformation of monohydrate because a 4.6% weight loss was observed in the temperature range from 60 to 110 °C on the TG curve and observation by hot stage microscope did not indicate melting in this temperature range, whereas the last peak did show melting. Further, the XRPD patterns of monohydrate after grinding did not change at 80 °C (Fig. 8a) but showed that of anhydrate A at 110 °C (Fig. 8b), indicating that anhydrate A was formed after dehydration. As described before, intact monohydrate showed a two step weight loss, and an endothermic peak due to dehydration and melting was observed at 98.9 °C. This result indicates that grinding causes a lowering of the dehydration temperature of monohydrate. Controlled rate thermogravimetry (CRTG) was employed to investigate the result in detail. In this method of measurement, the heating rate of the sample is

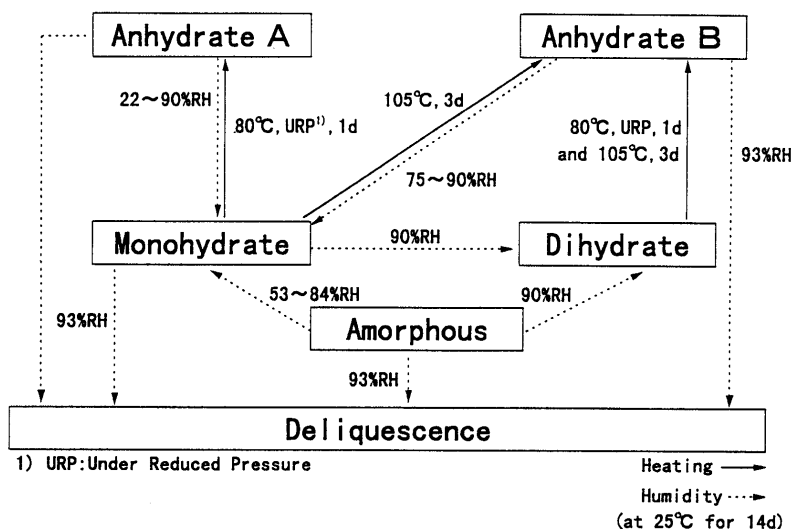


Fig. 6. Interconversion of the Five Solid Forms of Lactitol

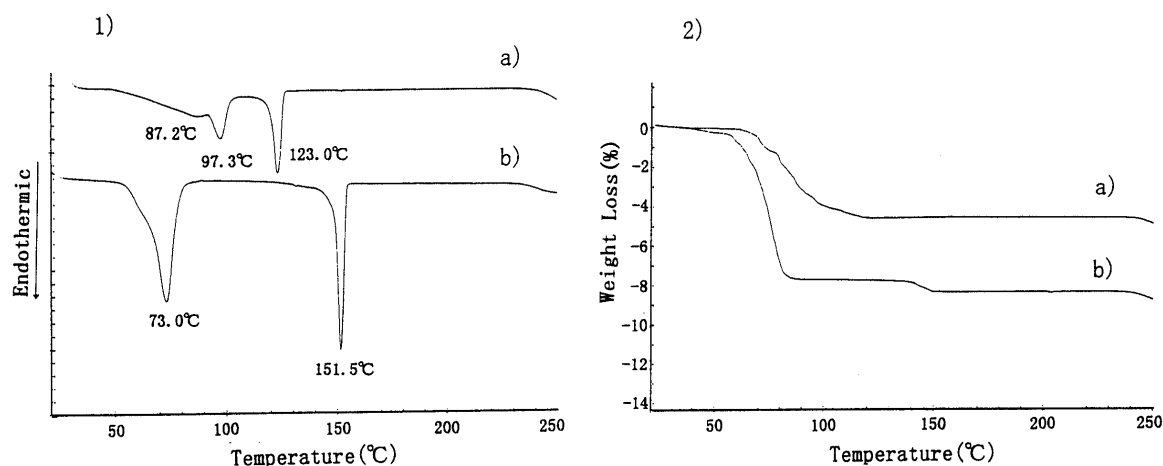


Fig. 7. DSC and TG Curves of Ground Lactitol Hydrates (Heating Rate, 5 °C/min)  
 1) DSC curves, 2) TG curvsa. a) ground monohydrate, b) ground dihydrate.

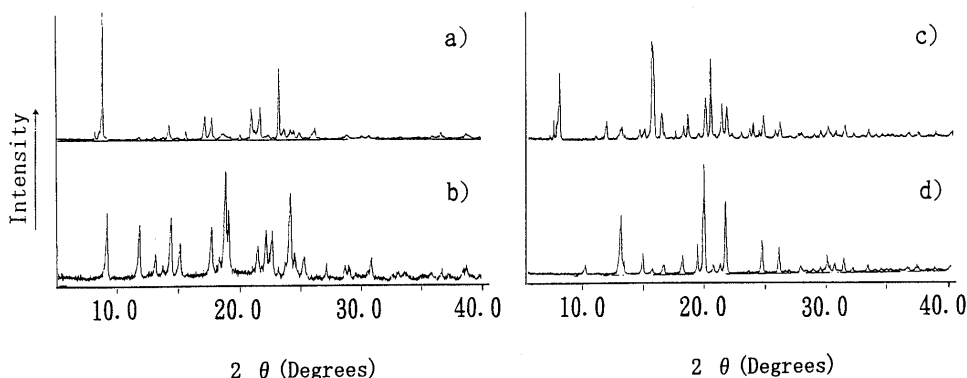


Fig. 8. X-Ray Powder Diffraction Patterns of Lactitol Hydrates with Heating  
 a) monohydrate (80 °C), b) monohydrate (110 °C), c) dihydrate (70 °C), d) dihydrate (90 °C).

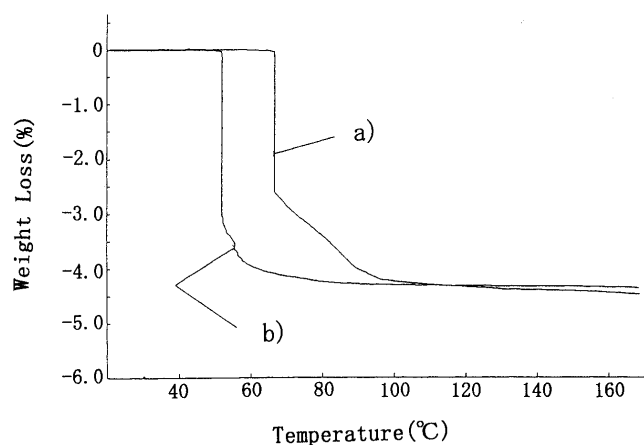


Fig. 9. CRTG Curves of Lactitol Monohydrate  
 a) intact monohydrate, b) ground monohydrate.

dynamically and continuously adjusted to the change in sample dehydration rate. Ariei *et al.*,<sup>21,22</sup>) reported that free water and hydrate water can be distinguished clearly using CRTG. According to their results, dehydration of free water is observed as gradual weight loss at a relatively low temperature on the CRTG curve while dehydration of hydrate water shows abrupt weight loss at a relatively high temperature. The CRTG curves of monohydrate before and after grinding are shown in Fig. 9, indicating

that hydration of monohydrate after grinding occurs in one step and about 15 °C lower than before grinding. What change there is in monohydrate caused by grinding is not understood yet, but the effect of particle size may be involved.

As shown in Fig. 7, ground dihydrate had two endothermic peaks at 73.0 and 151.5 °C and a two-step weight loss was noted on the TG curve. The first endothermic peak was explained by dehydration and transformation of dihydrate from the TG curve and observation through a hot stage microscope. The other endothermic peak was believed due to melting of anhydrate B, which was formed after the first endothermic peak and identified by the XRPD measurement (Fig. 8d). Total weight loss observed on the TG curve is 8.4% (7.6% at the first step and 0.8% at the second step) and this value is lower than the theoretical one (10%). This result suggests that part of the water in dihydrate may be released during grinding. As shown in Fig. 10, the CRTG curve of dihydrate indicates that dehydration of both samples (before and after grinding) occurred at 60 °C and the difference of dehydration temperature obtained in monohydrate was not seen. Weight loss of intact dihydrate observed at temperatures higher than 90 °C was also not seen after grinding. This result suggests that grinding may cause water to release more easily from dihydrate. Dihydrate is believed not to be transformed *via* mono-

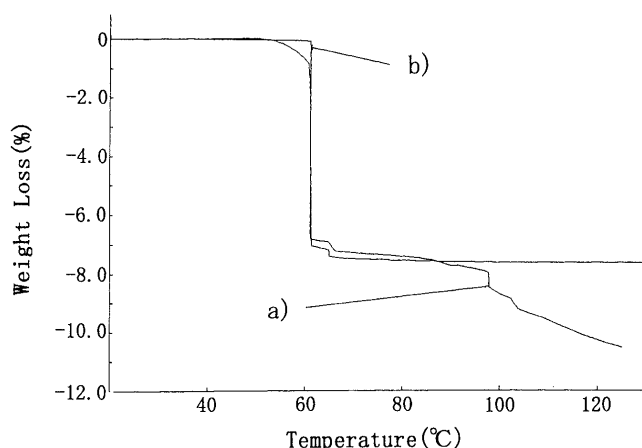


Fig. 10. CRTG Curves of Lactitol Dihydrate  
a) intact dihydrate, b) ground dihydrate.

hydrate into anhydrate B after grinding based on XRPD measurement. The difference in thermal behavior of the two hydrates after grinding could not be clearly explained.

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