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Effect of Humidity on Solid-state Isomerization of Various Kinds of Lactose During Grinding

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Abstract—The effect of humidity on isomerization during grinding of α-monohydrate, α-anhydrate and β-anhydrate of lactose was investigated. Samples were ground in an agate centrifugal ball mill at 270 rev min^{-1} at room temperature (21°C) and at 5 and 60% relative humidity. Crystallinity of the ground lactose was measured by Hermans' method from the powder X-ray diffraction profiles. The α- and β-lactose content of the ground lactose was measured by using angular rotation spectrophotometry. The crystalline lactose samples were transformed into noncrystalline solids by mechanical stress during grinding. After grinding, the adsorbed water content of all ground lactose samples increased, and the isomerized amount increased with increase of the water content during grinding at 5 and 60% relative humidity. The results suggest that the isomerization rate of α-monohydrate during grinding may depend on the crystallinity, but those of α- and β-anhydrate depend on the content of adsorbed water.

Four kinds of crystallographic forms, α-monohydrate, α-anhydrate, β-anhydrate and amorphous forms have been reported by Norris & Greenstreet (1958), Goulden (1958) and Itoh et al (1977, 1978), so that many grades of lactose are commercially available, such as crystalline, anhydrate, spray-dried, or granulated. Lerk et al (1983) reported that the binding properties of α-lactose monohydrate increased with increasing dehydration of the solid. Crystalline α-lactose monohydrate has been transformed into a noncrystalline lactose during grinding (Morita et al 1984), and the hardness of tablets made from the ground lactose increases with increase of grinding time (Sagawa 1983). We have investigated the physicochemical stability of various kinds of crystalline lactose during manufacture of pharmaceutical preparations, as a basis of information for formulation scientists, and found isomerization of lactose in the solid-state during grinding (Otsuka et al 1991). In the present study we investigated the effects of humidity on isomerization of various kinds of crystalline lactose during grinding.

Materials and Methods

Materials

Crystalline α-lactose monohydrate (Wako Pure Chemical Industries Ltd) was of Pharmacopoeia Japonica XI grade. α-Anhydrate was prepared by recrystallization from methanol (Lerk et al 1983) and β-anhydrate was prepared by recrystallization from distilled water at 100°C (Itoh et al 1978).

Mechanical treatment

A 10 g sample of lactose powder was ground in an agate centrifugal ball mill (Fritsch Co. Ltd) with a capacity of 250 mL at 20°C. The diameters and numbers of balls were: 10 mm × 20, 15 mm × 10, and 20 mm × 4. Speed was 270 rev min^{-1}.

Grinding was performed at 60 ± 10% relative humidity (r.h.) measured by a psychrometer, and two holes of 8 mm diameter on the cover of the mill pot were open during grinding. The mill was opened and 500 mg ground samples were removed at 1, 2, 4, 7 and 10 h at 60% r.h.

Grinding at the lower r.h. was performed by supplying silica gel-dried air (less than 5% r.h.) at a rate of 20 mL min^{-1}, and samples were removed under the same condi-

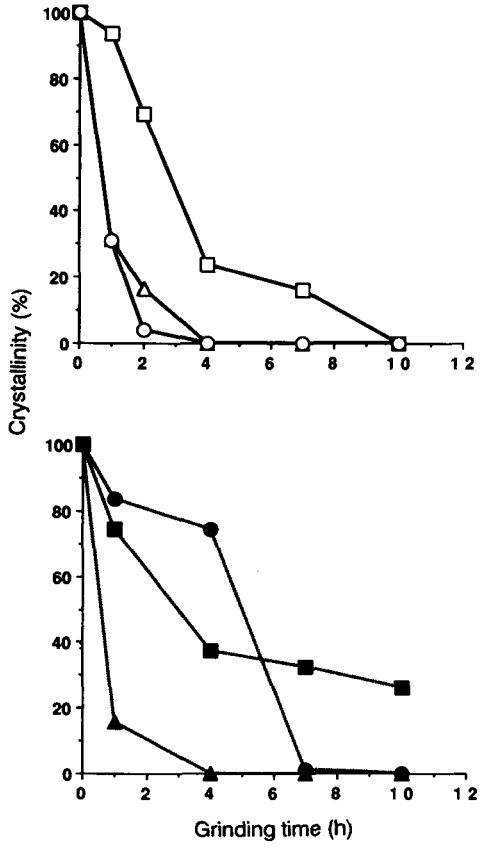

FIG. 1. Change of crystallinity of various kinds of crystalline lactose during grinding at 5 (open symbols) and 60% r.h. (closed symbols). □ ■ α-Monohydrate, △ ▲ α-anhydrate, ○ ● β-anhydrate.

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tions. These samples were stored in closed containers at −35°C.

Powder X-ray diffraction analysis

Powder X-ray diffraction was measured at room temperature (21°C) with a type 11 PA diffractometer (Nihon Denshi Co., Ltd). The measurement conditions were: target, Cu; filter, Ni; voltage, 30 kV; current. 7·5 mA; time constant, 1 s; step slit, 0·03°; counting time, 0·5 s; measured from $2\theta = 5°$ to $2\theta = 40°$.

Measurement of infrared (IR) spectra

The IR spectra were measured as mulls in Nujol on an IR-2 infrared spectrophotometer (Nihon Bunko Co. Ltd).

Determination of crystallinity

Crystallinity was estimated by Hermans' method (Hermans & Weidinger 1948) as described previously (Otsuka et al 1991).

Thermal analysis

Differential thermal analysis (DTA) curves and thermogravimetry (TG) curves were measured with a type DT-20 DTA instrument and a type TG-30 instrument (Shimadzu Seisakusho Co. Ltd), respectively, as described previously (Otsuka et al 1991).

Determination of water content of lactose

The water content of lactose was measured by the TG method; it was assumed that the weight loss below 100°C was adsorbed water and the weight loss above 100°C was crystalline water (Otsuka et al 1991).

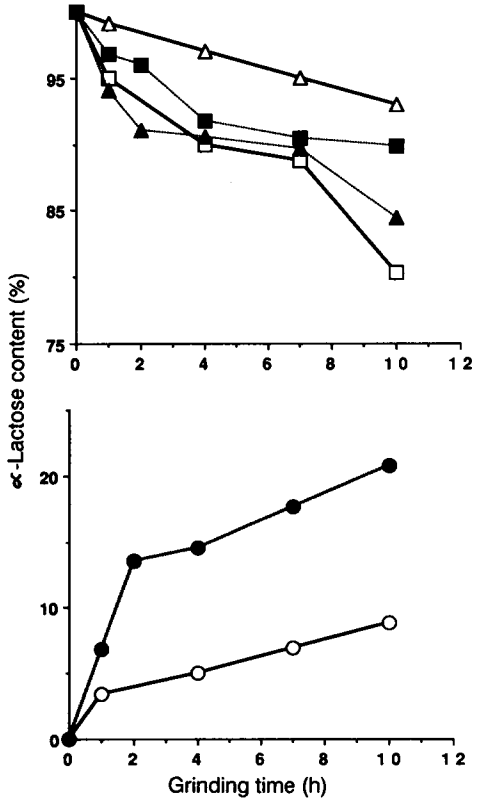

FIG. 2. Change of α-lactose content of various kinds of crystalline lactose during grinding at 5 (open symbols) and 60% r.h. (closed symbols). □ ■ α-Monohydrate, △ ▲ α-anhydrate, ○ ● β-anhydrate.

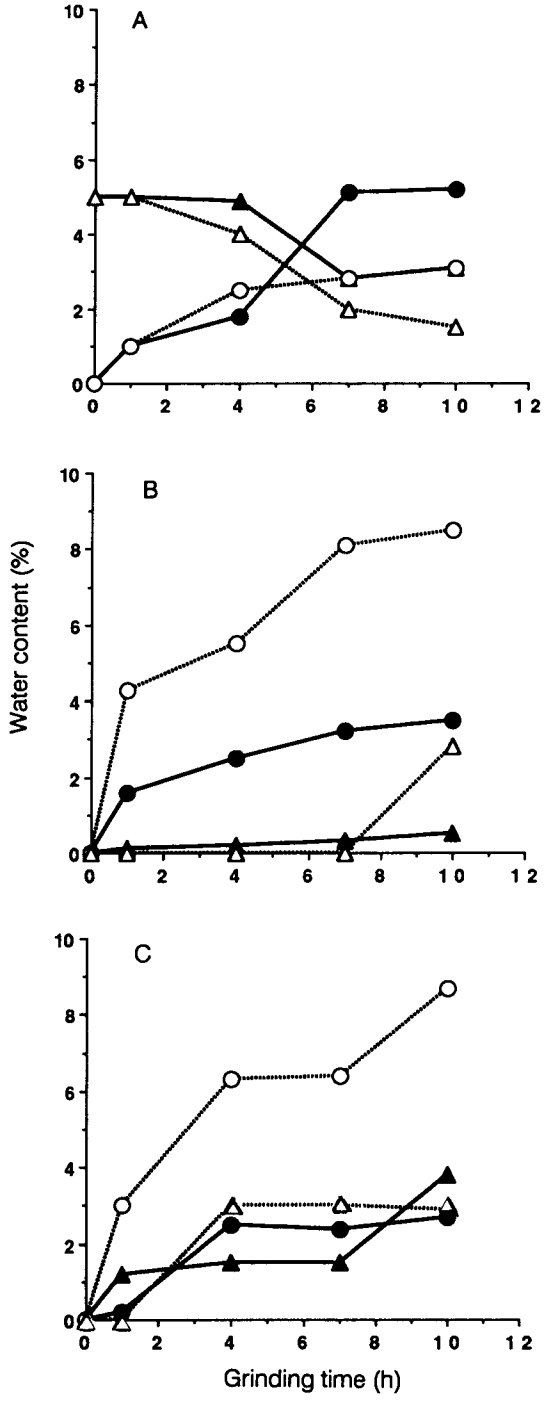

FIG. 3. Change of adsorbed and crystal water content of: A, α-monohydrate; B, α-anhydrate; C, β-anhydrate during grinding at 5 (open symbols) and 60% r.h. (closed symbols). ○ ● Adsorbed water content, △ ▲ crystal water content.

Determination of the α-lactose content

The content of α-lactose was estimated from the specific rotation (Otsuka et al 1991).

Results and Discussion

The results are summarized in Figs 1–6.

Effect of humidity on the transformation to noncrystallized lactose

Various kinds of crystalline lactose were transformed into noncrystalline lactose by mechanical stress during grinding at 5 and 60% r.h. (Fig. 1). The water content of the ground products of all kinds of lactose increased as a consequence of decreased crystallinity of the samples. This suggests that noncrystalline lactose was hygroscopic, so that the adsorbed water increased with increase of noncrystalline lactose (Fig. 3). Lactose molecules are packed in the crystal by hydroxyl group hydrogen bonds (Noordik et al 1984). It is considered that the hydrogen binding network of lactose was destroyed by mechanical force, and water was adsorbed on the active hydrogen binding site on the new surface of the ground lactose, which contained disordered crystals or noncrystalline parts. Therefore, it seems that the amount of adsorbed water of crystalline lactose increased as a consequence of decreased crystallinity of ground lactose.

The profile of relation between the adsorbed water content and crystallinity of α-monohydrate at 5% r.h. was similar to those at 60% during grinding (Fig. 5), but that of crystal water at 5% r.h. was different from that 60% r.h. indicating that the crystallinity depended on decrease of the crystal water content, but the transformation to the noncrystallized form was affected by environmental humidity (Fig. 1). On the other hand, the relation between the adsorbed water content and the crystallinity of α-anhydrate and β-anhydrate ground at 5% r.h. depended on the environmental humidity (Fig. 5), indicating that the adsorbed water content during grinding was not affected by the conversion of α-anhydrate or β-anhydrate to the non crystalline form.

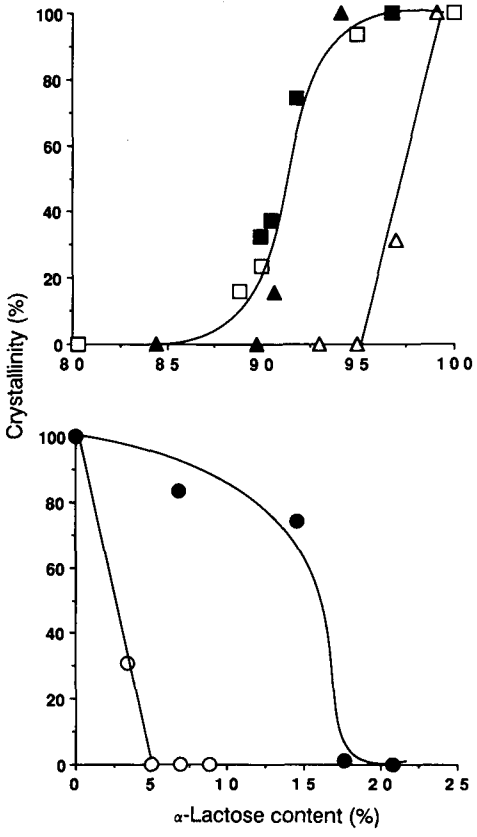

FIG. 4. Effects of humidity on the relation between α-lactose content and the crystallinity of various kinds of crystalline lactose after grinding at 5 (open symbols) and 60% r.h. (closed symbols). □ ■ α-Monohydrate, △ ▲ α-anhydrate, ○ ● β-anhydrate.

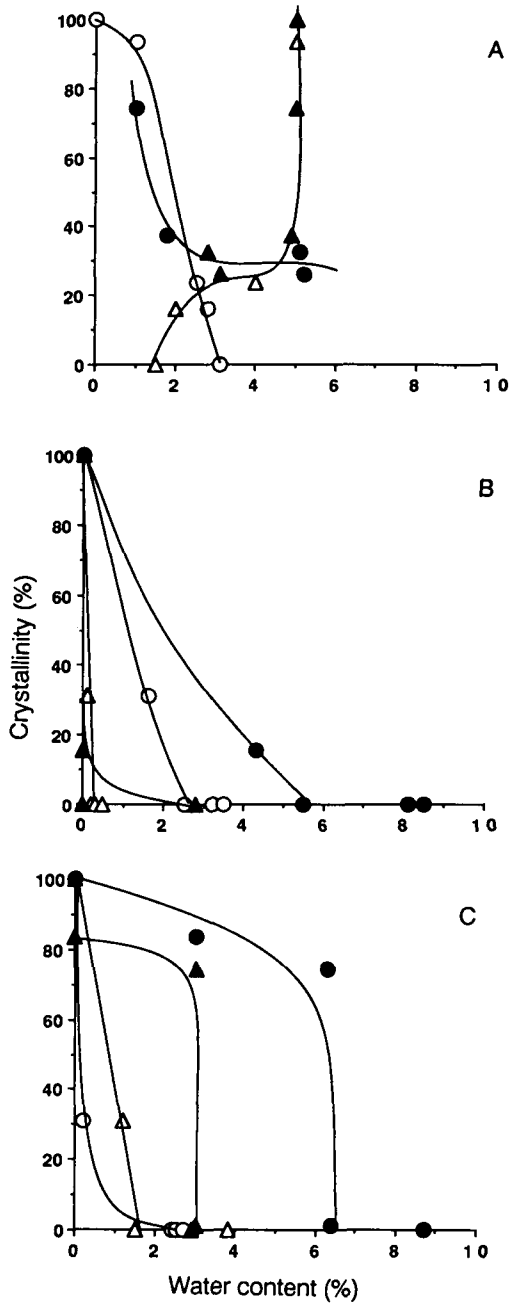

FIG. 5. Effects of humidity on the relation between water content and crystallinity of: A, α-monohydrate; B, α-anhydrate; C, β-anhydrate ground at 5 (open symbols) and 60% r.h. (closed symbols). △ ▲ Crystal water content, ○ ● adsorbed water content.

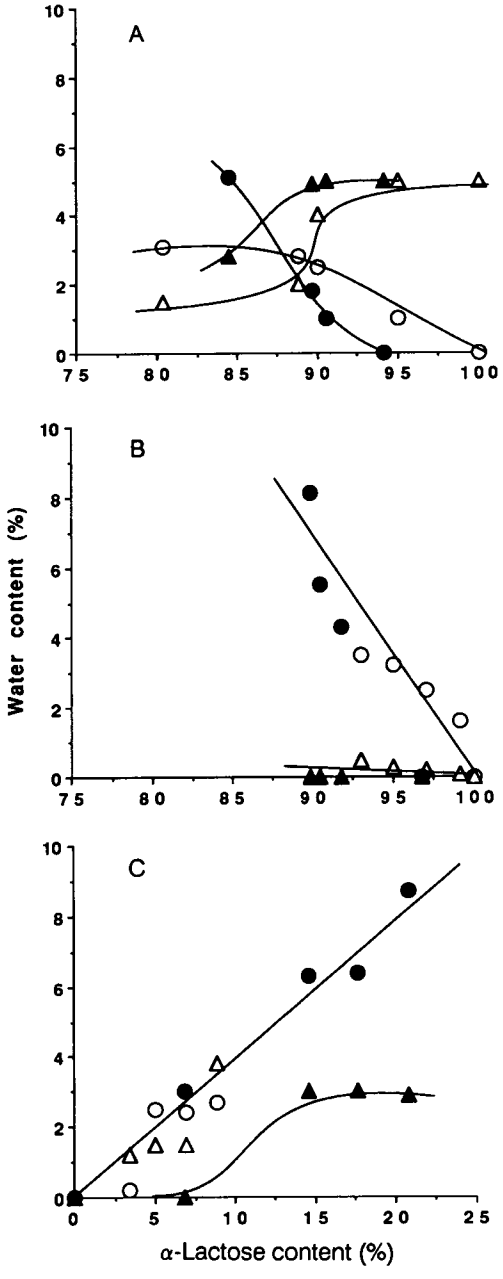

FIG. 6. Effect of humidity on the relation between α-lactose content and water content of: A, α-monohydrate; B, α-anhydrate; C, β-anhydrate ground at 5 (open symbols) and 60% r.h. (closed symbols). △ ▲ Crystal water content, ○ ● adsorbed water content.

Effect of humidity on the isomerization of lactose by mechanochemical activation during grinding

The effect of humidity on the change of α-lactose content of various kinds of lactose during grinding suggested that isomerization of α-anhydrate and β-anhydrate was affected by environmental humidity, but the dependence of α-monohydrate was not significant (Fig. 2). The isomerization of lactose did not proceed in the solid-state under normal storage conditions (0–40°C, 75% r.h.), but isomerization of lactose in the solid state occurred during grinding, the triboplasma state (Senna 1985). The isomerized amount of α-monohydrate ground for 0–7 h at 5% r.h. was not significantly different from that at 60% r.h., since the α-monohydrate ground for 0–7 h at 5 and 60% r.h. retained 40–50% of the crystal water. After grinding for 10 h the sample ground at 60% r.h. had about 30% crystalline α-monohydrate and 0·62 mol mol^{-1} of crystal water, but α-monohydrate ground at 5% r.h. was almost transformed into a noncrystalline solid. Thus, about 30% of the total water is crystal water which is inactive in the isomerization of lactose, and the crystal water (indicating crystalline lactose) is more stable when ground at high humidity. The isomerization rate of α-monohydrate did not show significant dependence on the adsorbed water content (Fig. 6). However, the isomerization rate of α-monohydrate depended on the crystallinity (Fig. 4). On the other hand, the isomerization rates of α-anhydrate and β-anhydrate did not depend on the crystallinity (Fig. 5) since they were easily transformed to noncrystalline solids and the isomerization rate depended on the adsorbed water content (Fig. 6). The results suggest the following mechanism of crystalline lactose isomerization:

$$\text{Crystalline lactose} \xrightarrow{{}^{*}E_c} \text{Noncrystalline lactose, } X_n \xrightarrow{{}^{*}H_2O} \text{Isomer lactose}$$

where $^{*}E_c$ is mechanical energy, X_n is noncrystalline content and $^{*}H_2O$ is adsorbed water content.

We conclude that crystalline lactoses were transformed into noncrystalline solids at 5 and 60% r.h., and α- and β-lactose were transformed into their solid-state counterparts by the mechanical and chemical effects of grinding. The isomerization rate of α-monohydrate depended on the noncrystalline lactose content, but those of α-anhydrate and β-anhydrate depended on the adsorbed water content.

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