

Effect of Environmental Humidity on the Transformation Pathway of Nitrofurantoin Modifications During Grinding and the Physicochemical Properties of Ground Products

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Abstract—The effect of humidity on the physicochemical properties of nitrofurantoin anhydrate and monohydrate during grinding in a humidity-controlled system was investigated using X-ray diffraction analysis, IR spectroscopy, thermal analysis and scanning electron microscopy. Anhydrate and monohydrate were transformed into a noncrystalline solid and a stable monohydrate, respectively, during grinding in a closed system. During grinding in an open system, in which the humidity level of the air was controlled (5, 50 and 75% r.h.), the anhydrate absorbed moisture from the supplied air and water content was increased at 75% r.h.; thereafter the compound was transformed into monohydrate II. The anhydrate did not absorb at 5 or 50% r.h. and was transformed into a noncrystalline solid. Monohydrate I desorbed crystal water during grinding at 5% r.h. and was transformed into a noncrystalline solid. However, monohydrate I was transformed into monohydrate II at 50 and 75% r.h. without desorption of crystal water. These results suggest that the solid-state transformation of nitrofurantoin during grinding depends upon the environmental humidity.

Since the particle size and crystalline form of a drug affect its bioavailability through its dissolution rate (FDA, guideline paper 1985) which depends on the surface area and solubility of the crystals, mechanical treatment such as grinding and tableting are important processes in the manufacture of high quality pharmaceuticals. However, the physicochemical properties of some drugs are affected by mechanical energy during these processes (Sagawa 1983; Morita et al 1984). We previously investigated the mechanochemical effect on the characteristics of several drugs. Cephalexin (Otsuka & Kaneniwa 1982, 1983) was converted to a noncrystalline solid, and chloramphenicol palmitate (Kaneniwa & Otsuka 1985; Otsuka & Kaneniwa 1985, 1986) was transformed to other polymorphic forms at room temperature (21°C). Indomethacin (Otsuka et al 1986) was transformed into a noncrystalline solid at 5°C, and to other forms at 35°C during grinding.

Nitrofurantoin is widely used as a urinary tract antibacterial drug. It has, however, bioavailability problems; formulation factors, mainly particle size (Paul et al 1967), affect the dissolution rate, bioavailability in man and incidence of side-effects (Cadwallader & Jun 1976). The United States Pharmacopeia XXII monograph for nitrofurantoin tablets requires not less than 25% of a labelled amount of drug to be dissolved within 60 min in phosphate buffer pH 7.2. Gouda et al (1984) and Ebian et al (1985, 1986) reported that the dissolution rate in man and the bioavailability of nitrofurantoin commercial tablets decreased after 1–8 weeks storage at different relative humidities at elevated temperatures. However, they did not clarify the findings based upon the physicochemical properties of the drug. The characterization and compaction behaviour of the anhydrate and monohydrate

of the drug was reported by Marshall & York (1989, 1991) and the stability at high humidity and dissolution behaviour were reported by Otsuka et al (1990, 1991). In this study, we investigated the effect of humidity on the physicochemical properties of nitrofurantoin.

Materials and Methods

Materials

A bulk powder (lot 11085) of nitrofurantoin was obtained from Fukujyu Pharmaceutical Co. Ltd, Japan. The purity of the bulk powder was checked by nuclear magnetic resonance as described in the next section. The anhydrate was obtained by recrystallization from hot saturated ethanol, which was cooled to room temperature after which, the separated crystals were filtered and dried in-vacuo. Monohydrate I was also obtained by recrystallization from a hot saturated aqueous solution of the drug which was processed as described above for the anhydrate. The noncrystalline solid was obtained by grinding the anhydrate for more than 7 h in a closed system as described below. Monohydrate II was obtained by grinding monohydrate I for more than 7 h in a closed system as described below.

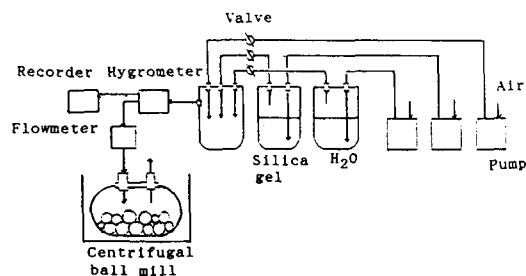


FIG. 1. Grinding instrument.

Table 1. Micromeritic parameters of ground nitrofurantoin.

Sample	Density \pm s.d. ^a (g cm ⁻³)	S _w ^b (m ² g ⁻¹)	D ^c (μ m)
Anhydrate	1.60 \pm 0.01	1.43	2.64
Monohydrate I	1.53 \pm 0.01	1.11	3.54
Noncrystalline solid	—	21.4	—
Monohydrate II	—	5.45	—
Anhydrate ground for 7 h at 5% r.h.	—	19.9	—
Anhydrate ground for 7 h at 75% r.h.	—	7.01	—
Monohydrate I ground for 7 h at 5% r.h.	—	6.02	—
Monohydrate I ground for 7 h at 75% r.h.	—	5.25	—

^a Standard deviation (n=4). ^b Specific surface area. ^c Surface area diameter.

Mechanical processing

Powdered sample (10 g) was ground in a 350 mL agate centrifugal ball mill (Fritsch Co. Ltd, Germany), containing agate balls (the diameter and number of balls were: 10 mm \times 20, 15 mm \times 10, 20 mm \times 4) equipped with an air supply for controlling the relative humidity (r.h.) at $25 \pm 1^\circ\text{C}$ (Fig. 1). The rotating speed of the mill was 225 rev min⁻¹. About 300 mg of ground sample was withdrawn at appropriate intervals, then stored in a closed container at -20°C . There were two methods of grinding; one was a closed system in which the cap of the ball mill remained shut during grinding, and the other was an open system which was supplied with humidity-controlled air (5, 50 and 75 \pm 3% r.h.) at a constant flow rate of 100 mL min⁻¹ during grinding. Both grinding procedures were performed in a constant temperature and humidity room at $25 \pm 1^\circ\text{C}$, 50 \pm 3% r.h.

Micromeritic characterization

The true density of the crystals was determined using an air comparison pycnometer (model 930; Beckman-Toshiba Co.). The specific surface area (S_w) was measured with a gas adsorption apparatus (Flow sorb, model 2300, Shimadzu Co.) using BET gas adsorption. The micromeritic parameters are summarized in Table 1.

X-ray powder diffraction analysis

X-ray powder diffraction profiles were taken at room temperature with an X-ray diffractometer (XD-3A, Shi-

madzu Co.). The operating conditions were as follows: target, Cu; filter, Ni; voltage 20 kV, current, 5 mA; receiving slit, 0.1 mm; time constant, 1 s; counting range, 1000 counter s⁻¹; scanning speed, 1 $^\circ$ 2 θ min⁻¹.

Measurement of the crystal content in anhydrate and monohydrate mixtures

Standard mixtures were obtained by physically mixing noncrystalline solid, anhydrate and monohydrates I and II at various ratios in a mortar. The peak at $2\theta = 21.5^\circ$ of monohydrate I had the same intensity as that of monohydrate II. Therefore, the calibration curves for measuring the crystal content were obtained based upon the characteristic X-ray diffraction intensities at 13.9, 16.5 and 21.5 $^\circ$. The plots gave good linear correlations and were reproducible. The calibration curves for determining the content of crystals were all straight lines, and the following regression equations were obtained:

$$Y_{m1} = 4.40 X_{m1} - 8.33 \quad (r=0.996) \quad (1)$$

$$Y_a = -1.66 X_a + 167 \quad (r=0.988) \quad (2)$$

$$Y_t = -1.64 X_t + 462 \quad (r=0.981) \quad (3)$$

$$X_{m2} = X_t - X_{m1} \quad (4)$$

where Y_{m1}, Y_a and Y_t are intensities of the peaks at $2\theta = 21.5^\circ$ due to monohydrate I, at $2\theta = 16.6^\circ$ due to anhydrate and at

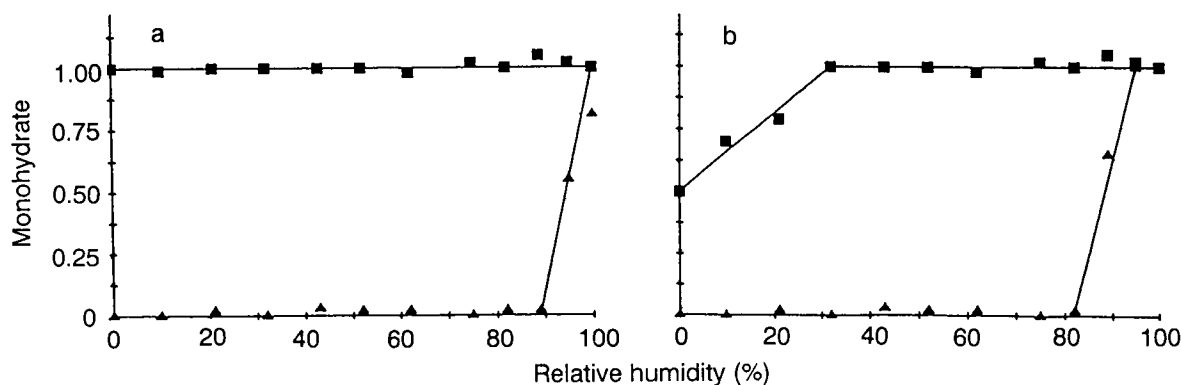


FIG. 2. Effect of relative humidity on the water content of intact anhydrate and monohydrate I at 25 (a) and 40 $^\circ\text{C}$ (b). \blacktriangle Anhydrate, \blacksquare monohydrate I.

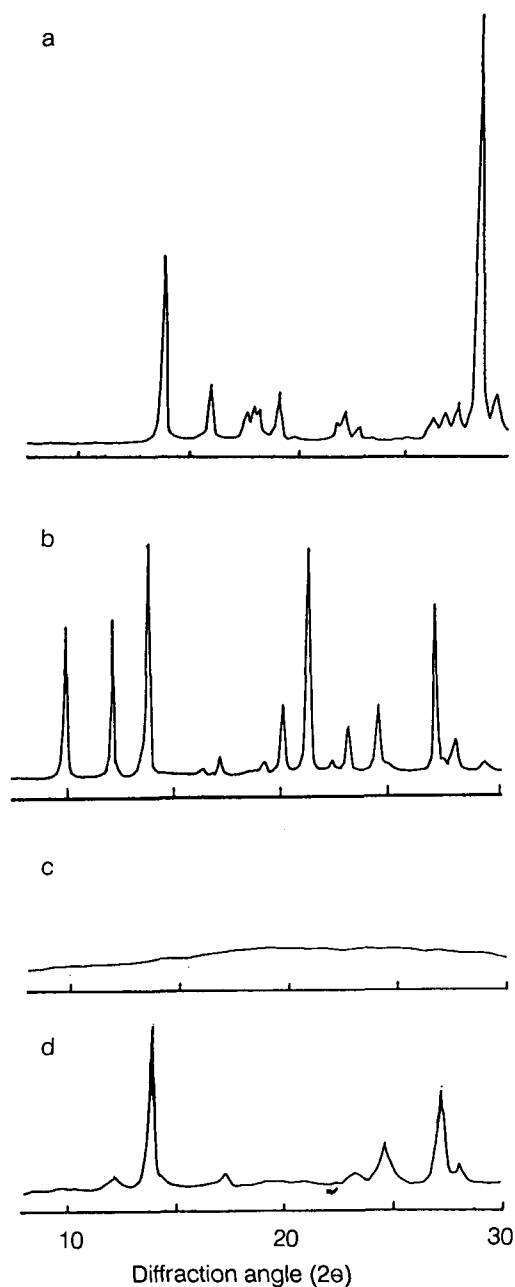


FIG. 3. X-ray powder diffraction profiles of ground anhydrate and monohydrate I. a Anhydrate; b monohydrate I; c noncrystalline solid; d monohydrate II.

$2\theta = 13.9^\circ$ due to monohydrate I or II. X_{m1} , X_{m2} , X_a and X_t are concentrations of monohydrate I, monohydrate II, anhydrate and total of monohydrates I and/or II, respectively, and r is the correlation coefficient.

The contents of all crystal forms were calculated from the straight calibration lines. Hence, these three calibration lines were used to determine the contents of monohydrates and the anhydrate.

Infrared (IR) spectroscopy

IR spectra were taken by the Nujol mull method on an infrared spectrophotometer (type 270-30, Hitachi Co.).

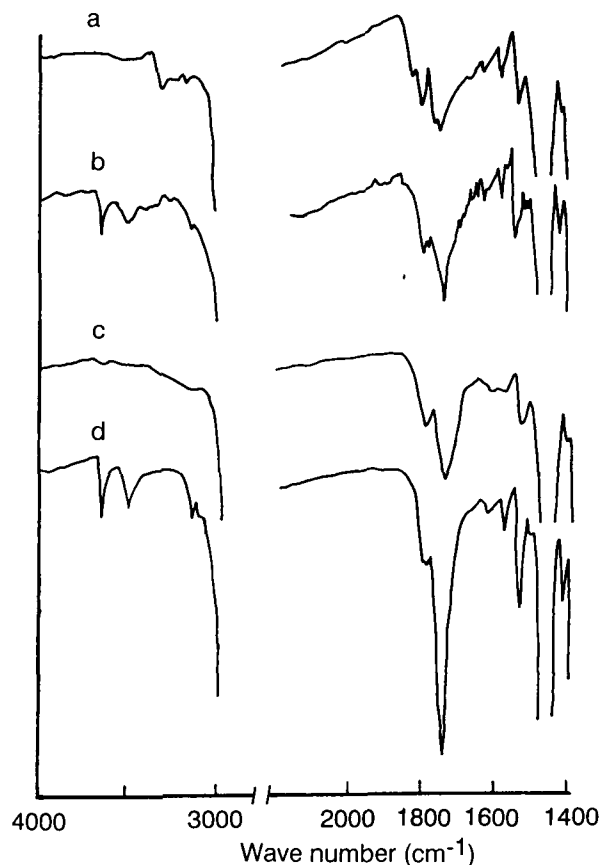


FIG. 4. IR spectra of ground anhydrate and monohydrate I. a Anhydrate; b monohydrate I; c noncrystalline solid; d monohydrate II.

Nuclear magnetic resonance (NMR) spectroscopy

$(CD_3)_2CO$ was used as a solvent with about a 3% concentration of the sample solution. The proton NMR spectra were recorded at 200 MHz (model XL-200; Varian).

Thermal analysis

Differential thermal analysis (DTA) and thermogravimetry (TG) were performed with type DTG-30 and DTA-TG instruments (Shimadzu Co.). Differential scanning calorimetry (DSC) was performed with a type 3100 instrument (Mac Science Co.). The operating conditions in an open-pan system were as follows: sample weight, 5 mg; heating rate, $10^\circ C \text{ min}^{-1}$; N_2 gas flow rate, 50 mL min^{-1} .

Scanning electron microscopy

Scanning electron photomicrographs of samples were taken with a scanning electron microscope (model JSM-T20, Jeol Co.) at a magnification of $\times 1500$.

Results

Stability of intact anhydrate and monohydrate at various relative humidity and temperature levels

Fig. 2 shows the effect of relative humidity on the monohydrate content after storage at 25 and $40^\circ C$ for 4 months. The monohydrate was transformed into the anhydrate at 0-21%

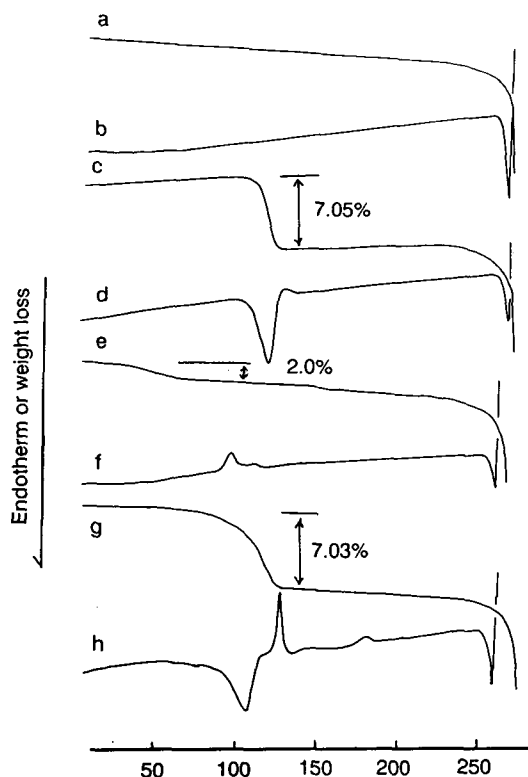


FIG. 5. DTA and TG thermograms of ground anhydrate and monohydrate I. a, c, e, g: TG curves; b, d, f, h: DTA curves; a, b: anhydrate; c, d: monohydrate I; e, f: anhydrate grinding for 7 h (noncrystalline solid); f, h: monohydrate II.

r.h. at 40°C. It was not transformed into the anhydrate at 0–21% r.h. at 25°C. The anhydrate was not transformed into the monohydrate at 89% r.h. but was at 95–100% r.h. at 25°C and at 89–100% r.h. at 40°C. These results suggested that the monohydrate was stable at 32–100% r.h. at 40°C regardless of the humidity levels at 25°C, and that the anhydrate was stable at 0–82% r.h. at 40°C and 0–89% r.h. at 25°C.

Grinding of anhydrate and monohydrate in the closed system

Fig. 3 shows the X-ray diffraction profiles of the ground anhydrate and monohydrate. After grinding the anhydrate and monohydrate for 7 h, the X-ray diffraction profiles of ground anhydrate did not show a characteristic diffraction peak but a halo pattern, suggesting that it was converted to a noncrystalline solid. The diffraction pattern of the ground monohydrate lacked the peaks at 10.1, 20.3 and 21.5° (2θ) compared with that of the intact sample. However, it was not transformed into a noncrystalline solid, suggesting that the diffraction pattern was significantly different from that of the intact sample. Based on the identical proton NMR spectra of both modifications with those previously published (Caddwallader & Jun 1976), we could confirm that no impurities were present in ground anhydrate and monohydrate samples. Therefore, the intact and ground monohydrates were assumed to be monohydrates I and II, respectively.

Fig. 4 shows IR spectra of the ground anhydrate and monohydrate. The absorption peaks of their IR spectra

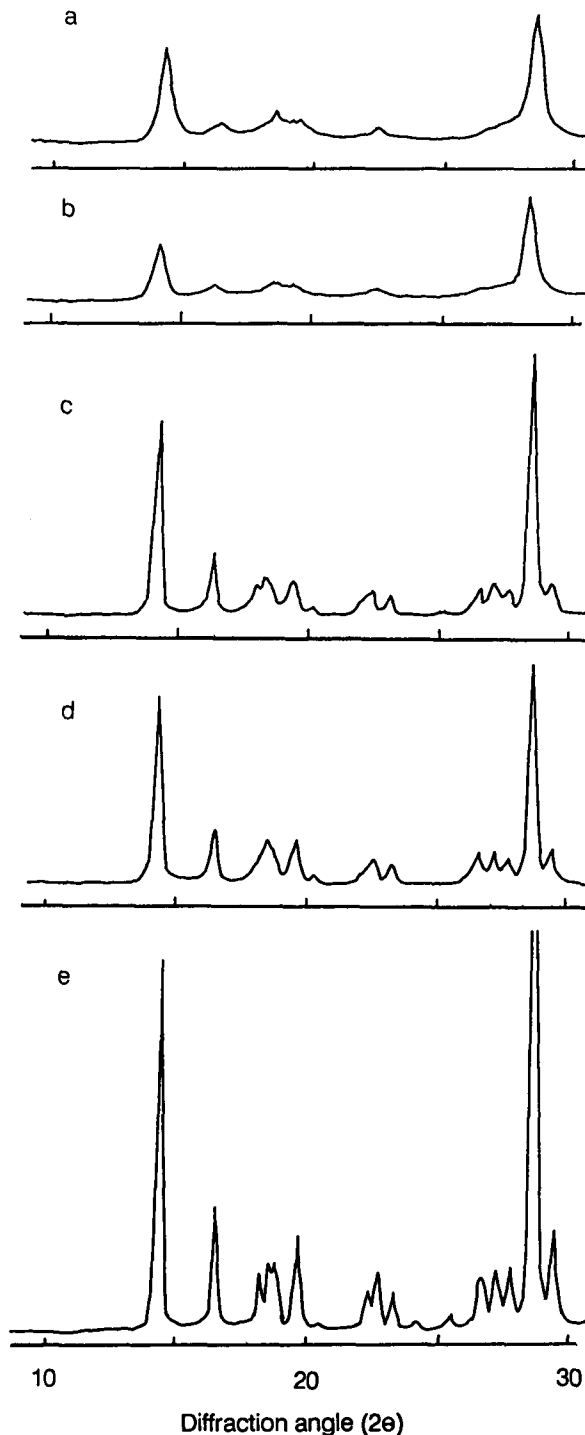


FIG. 6. X-ray powder diffraction profiles of ground anhydrate and monohydrate I after heating. a Anhydrate grinding for 7 h heated at 150°C for 5 min; b monohydrate II heated at 150°C for 5 min; c anhydrate grinding for 7 h heated at 200°C for 5 min; d monohydrate II heated at 200°C for 5 min; e anhydrate.

became broader than those before grinding. However, no changes in the absorption peaks due to the hydrogen group of monohydrate I were observed after grinding.

Fig. 5 shows the DTA and TG curves of the ground anhydrate and monohydrate. The DTA curve of the intact

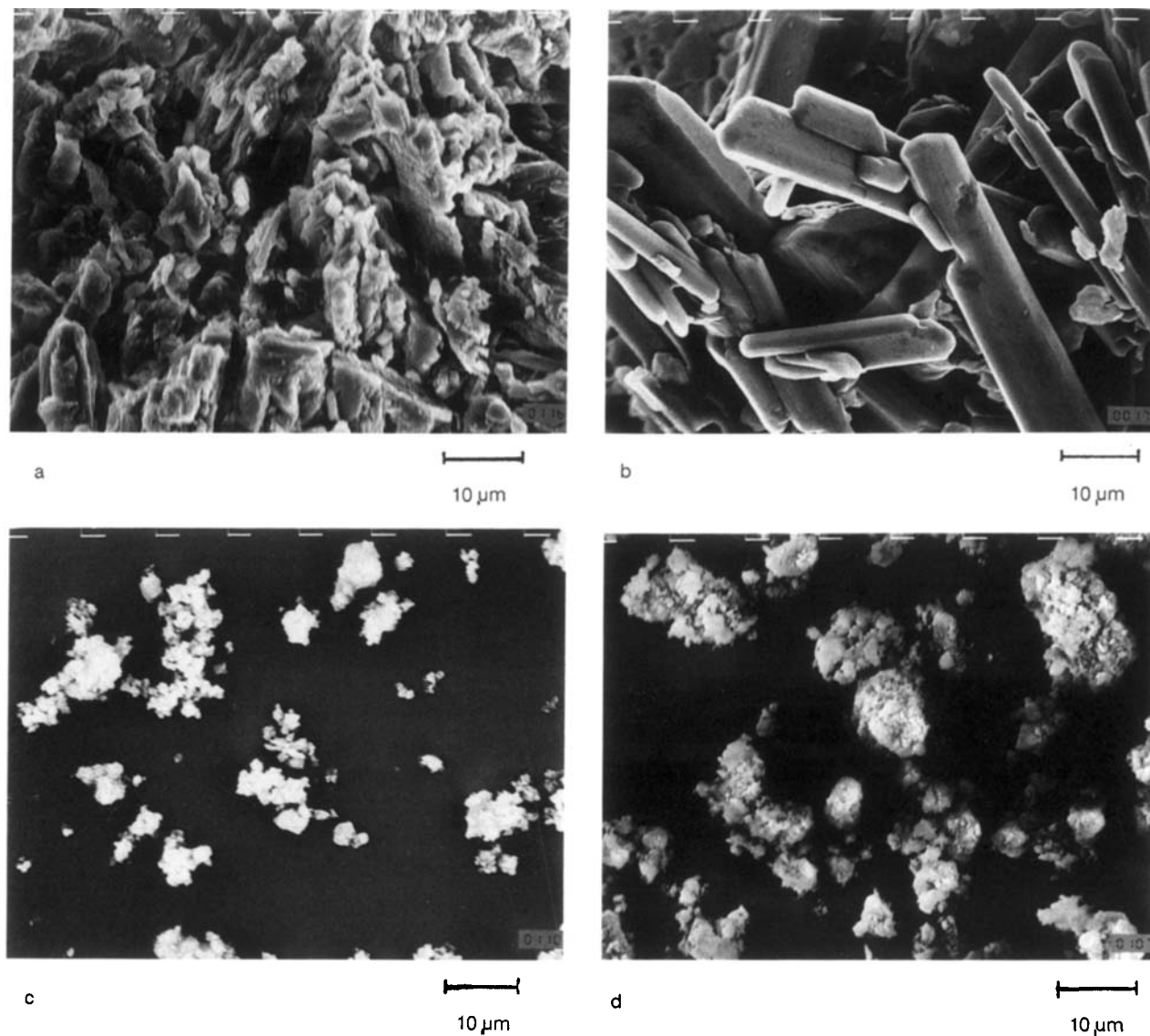


FIG. 7. Scanning electron photomicrographs of ground anhydrate and monohydrate I ($\times 1500$). a Anhydrate; b monohydrate I; c anhydrate ground for 7 h; d monohydrate II.

anhydrate showed an endothermic peak at 272°C , followed by an exothermic peak at 276°C , with a loss of weight on the TG curve due to decomposition after melting. The DTA curve of the intact monohydrate showed an endothermic peak at $120\text{--}128^{\circ}\text{C}$ with a 7.05% loss of weight on the TG curve, a second endothermic peak at 273°C , and a subsequent exothermic peak at 276°C with a loss of weight on the TG curve. These findings suggest that the first endothermic peak was due to dehydration of 1 mol mol^{-1} of crystal water (7.03%), and that the second endo- and exothermic peaks resulted from decomposition after melting. The DTA curve of the ground anhydrate showed an exothermic peak at 90°C due to crystallization and an endothermic peak at 272°C , followed by an exothermic peak at 276°C , with a loss of weight due to decomposition after melting. The DTA curve of the ground monohydrate shows an endothermic peak at $80\text{--}110^{\circ}\text{C}$ with a 7.03% loss of weight due to dehydration, a larger exothermic peak at 125°C due to crystallization, a smaller exothermic peak at 175°C , a second

endothermic peak at 273°C , and an exothermic peak at 276°C due to decomposition.

Fig. 6 shows the X-ray diffraction profiles obtained for the ground anhydrate and monohydrate after heating at 150 and 200°C for 5 min. All diffraction patterns were identical to that of the anhydrate, but all peaks of ground anhydrate and monohydrate after heating at 150°C were much broader than those obtained at 200°C . This suggests that the ground anhydrate and monohydrate were both transformed into the metastable anhydrate which was in low crystallinity after heating at 150°C , and after that, into the anhydrate with higher crystallinity at 200°C .

Fig. 7 shows the scanning electron photomicrographs of the ground anhydrate and monohydrate. Monohydrate I consisted of plate crystals with a smooth surface. After grinding for 7 h it was transformed into monohydrate II, consisting of particles $10\text{--}20\text{ }\mu\text{m}$ in diameter together with fine particles of less than $0.5\text{ }\mu\text{m}$ in diameter, while the intact anhydrate consisted of particles of $20\text{--}30\text{ }\mu\text{m}$ in diameter

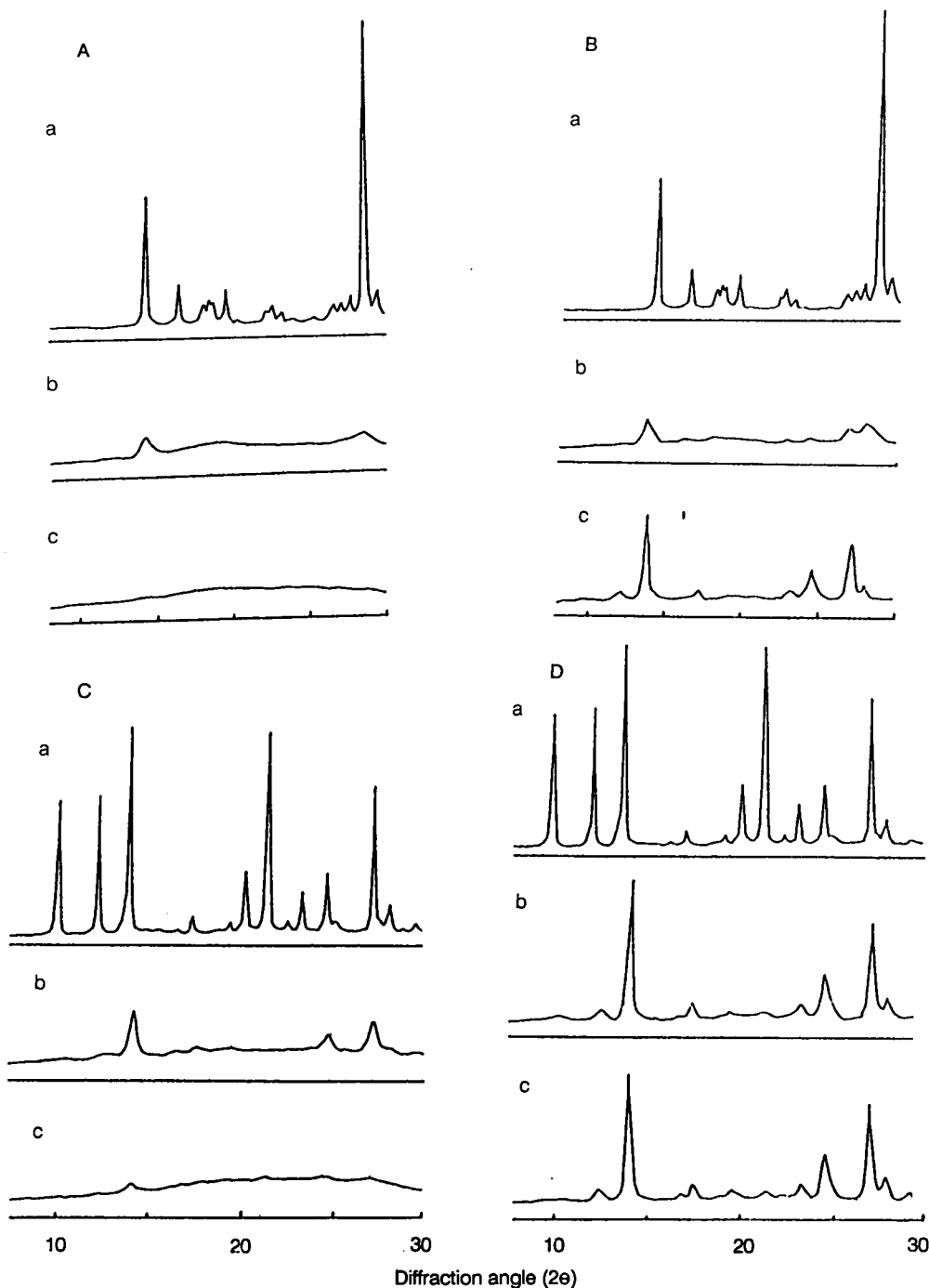


FIG. 8. Change of X-ray powder diffraction profiles of anhydrate and monohydrate I during grinding at various levels of humidity. A Anhydrate at 5% r.h.; B anhydrate at 75% r.h.; C monohydrate I at 5% r.h.; D monohydrate I at 75% r.h.; a ground for 0 h; b ground for 3 h; c ground for 7 h.

with a jagged surface. The anhydrate polycrystals changed to agglomerated particles formed from fine noncrystalline particles of less than $0.5 \mu\text{m}$ in diameter after 7 h grinding.

Grinding the anhydrate and monohydrate in the open system
 Fig. 8 shows the change of the X-ray diffraction profiles in the anhydrate and monohydrate during grinding at 5 and

75% r.h. The X-ray diffraction intensities of the anhydrate decreased with the lapse of grinding time at 5% r.h., the diffraction intensities of sample decreased, and after grinding for 7 h, there was no diffraction peak with a halo. This suggested that the anhydrate converted to noncrystalline solid during grinding at 5% r.h. The diffraction intensities of the anhydrate decreased during grinding at 75% r.h., but

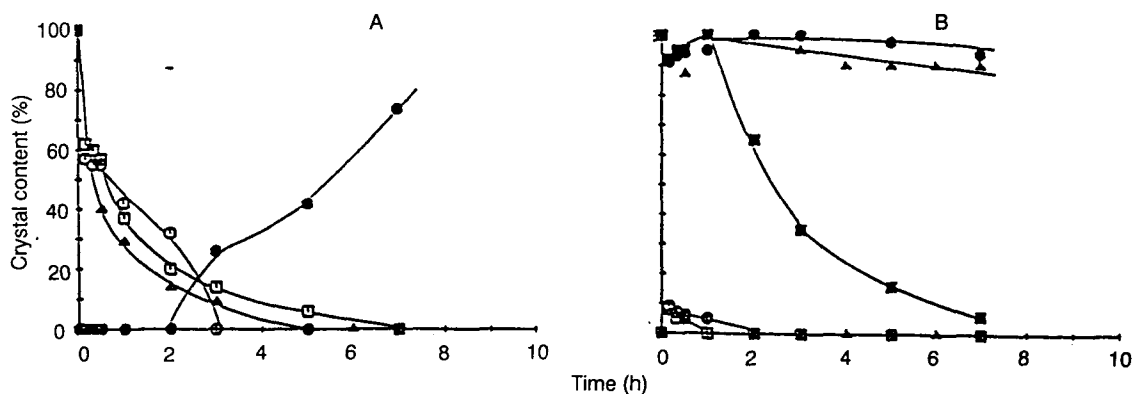


FIG. 9. Effect of relative humidity on the crystal contents of the anhydrate and monohydrate I during grinding. A Anhydrate; B monohydrate I; \square \blacksquare ground at 5% r.h.; \triangle \blacktriangle ground at 50% r.h.; \circ \bullet ground at 75% r.h.. The open and closed symbols represent amounts of anhydrate and monohydrate II, respectively.

even after 7 h grinding it did not transform into a noncrystalline solid, and had the diffraction pattern of monohydrate II. When ground at 5% r.h., the diffraction intensities of monohydrate I decreased with the lapse of grinding time, and was almost entirely converted to the noncrystalline solid after 7 h grinding. However, after grinding for 7 h at 75% r.h., monohydrate I showed the diffraction pattern of monohydrate II. These results suggested that the anhydrate and monohydrate were converted to the noncrystalline solid during grinding at 5% r.h., but that both were transformed to monohydrate II at 75% r.h.

The values of S_w of the ground samples are shown in Table 1; all were increased after grinding. The S_w of anhydrate after grinding for 7 h at 5% r.h. was the largest among all samples, and monohydrate I grinding for 7 h at 75% r.h. was the smallest. The samples after grinding at 5% r.h. had a larger S_w than those at 75% r.h., suggesting that the ground product was transformed into a noncrystalline solid at 5% r.h., but not at 75% r.h.

Fig. 9 shows the change of crystal contents of anhydrate and monohydrate during grinding in the open system at 5, 50 and 75% r.h. After grinding the anhydrate at 5 and 50% r.h., the crystallinity decreased with the lapse of grinding time, and the anhydrate was more easily converted to a noncrystalline solid at 50% r.h. than at 5% r.h. This suggested that the presence of a small amount of adsorbed water was useful for conversion into noncrystalline solid, which contained about 2% of adsorbed water which was lost at the low temperature (Fig. 4). However, after grinding for 2 h at 75% r.h., monohydrate II was formed, after which its level increased with the lapse of grinding time. When monohydrate I was ground at 5% r.h., the crystallinity decreased with the lapse of grinding time, and almost all monohydrate I converted into the noncrystalline solid after grinding for 7 h. Monohydrate I transformed into monohydrate II after grinding for more than 1 h at 50 and 75% r.h., and the crystallinity of monohydrate II did not decrease during grinding, suggesting that monohydrate II was the stable form under grinding conditions of high humidity.

Fig. 10 shows the change of the water content in the

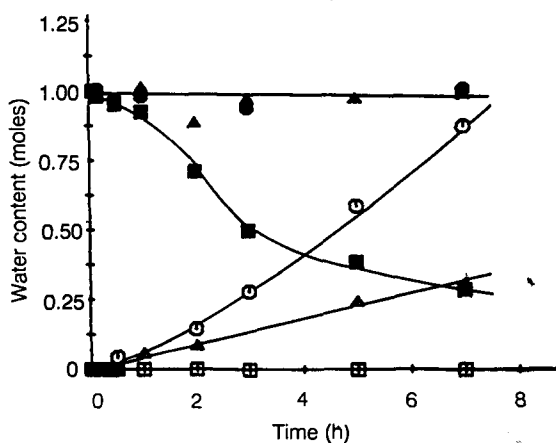


FIG. 10. Effect of relative humidity on the water contents of the anhydrate and monohydrate I during grinding. \square \blacksquare Ground at 5% r.h.; \triangle \blacktriangle ground at 50% r.h.; \circ \bullet ground at 75% r.h.. The open and closed symbols represent the anhydrate and monohydrate I, respectively.

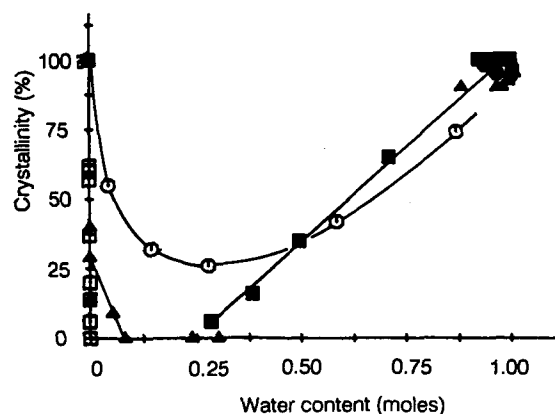


FIG. 11. The relationship between crystallinity and water content of the anhydrate and monohydrate I during grinding. Symbols are the same as those in Fig. 10.

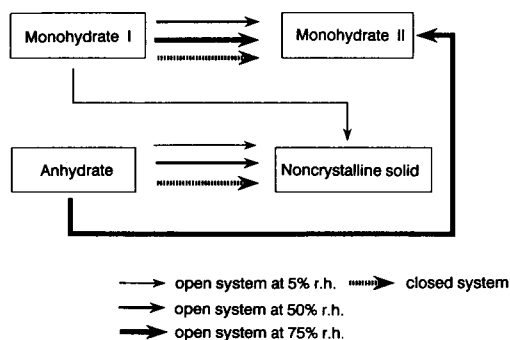


FIG. 12. Transformation pathway during grinding under various levels of humidity at 25°C.

anhydrate and monohydrate during grinding in the open system at 5, 50 and 75% r.h. After grinding the anhydrate at 5% r.h., the water content increased with the lapse of grinding time. After grinding for 7 h, the water content was 62 mg g^{-1} ($0.86 \text{ mol mol}^{-1}$), indicating that the anhydrate was transformed into monohydrate II. During grinding at 50% r.h. the water content gradually increased with increasing grinding time, reaching 22 mg g^{-1} (0.3 mol mol^{-1}) after 7 h and monohydrate II was transformed into a noncrystalline solid. When ground at 5% r.h., the water content was almost zero, after which, the anhydrate was transformed into a noncrystalline solid. When monohydrate I was ground at 50 and 75% r.h., the water content did not decrease, remaining at 1 mol of water, but it decreased with increasing grinding time at 5% r.h., and reached 21 mg g^{-1} after 7 h. Thereafter, monohydrate I was transformed into the noncrystalline solid.

Fig. 11 shows the relationship between crystallinity and the water content of the modifications during grinding. At 5% r.h., the anhydrate transformed into a noncrystalline solid without an increased water content. The relationship between the crystallinity and water content of the anhydrate at 75% r.h. showed a minimum crystallinity of 25% at $0.25 \text{ mol mol}^{-1}$. The crystallinity and water content of monohydrate I at 50 and 75% r.h. did not change, but decreased with the decrease of water content at 5% r.h.

Discussion

The possible transformation pathways of anhydrate and monohydrate I are summarized in Fig. 12. The results from the closed system suggest that the anhydrate and monohydrate I are transformed to the noncrystalline solid and monohydrate II, respectively, assuming that there was no change in the water content during grinding. The results from the open system suggest that the water absorption of the samples stimulated the transformation of noncrystalline solid obtained during grinding to monohydrate II since the noncrystalline solid was unstable at high humidity (the noncrystalline solid transformed to monohydrate II at 25°C at 75% r.h. after one day). These results indicated that the nature of the ground materials affected the crystalline form when ground in the open system, suggesting that the transformation pathway depended on the environmental

humidity. Since the conversion of the anhydrate to the noncrystalline solid during grinding at 50% r.h. was faster than that at 5% r.h., it was also considered that a small amount of adsorbed water accelerated the conversion to the noncrystalline solid. These results suggested that the transformation depended on environmental humidity.

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