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Effect of grinding on the crystallinity and chemical stability in the solid state of cephalothin sodium

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Summary

The effects of grinding on the crystallinity of cephalothin sodium, and on the chemical stability of the ground products were investigated by X-ray diffraction, infrared spectra and differential thermal analysis. The X-ray diffraction peaks of all samples decreased after grinding, but the diffraction profiles had no halo pattern. This suggests that part of the cephalothin sodium was converted into a noncrystalline solid. The crystallinity of cephalothin sodium decreased with increased grinding time during the initial grinding process, and cephalothin sodium ground for 2 h was about 30% crystalline. However, the crystallinity increased after grinding for 3–10 h, reaching equilibrium at about 50%. The decomposition point, measured by differential thermal analysis of the ground products, fell rapidly during early grinding, and then decreased from 202 to 187°C after 2 h. However, it rose to 191°C after 3 h and thereafter stayed at approx. 192°C. The water content of intact cephalothin sodium increased at more than 95% relative humidity (R.H.). The water content after grinding for 2 or 10 h increased at more than 93% R.H. The results suggest that the chemical stability in the solid state and the hygroscopicity of cephalothin sodium are closely related to the crystallinity.

Introduction

Grinding is a means of reducing the particle size of powders, and mixing drugs. The particle size and physicochemical properties of drug powders affect the bioavailability of their preparations through effects on the dissolution rate (FDA, 1985). On the other hand, the surface area and crystallinity of a drug powder affect its chemical stability in the solid-state (Nakagawa et al., 1982). Therefore, basic investigation of the effects of mechanical treatment, such as grinding and tabletting, on the physicochemical properties of drug is important for making high-quality pharmaceutical preparations (Sagawa et al., 1983; Morita et al., 1984).

We have previously reported changes of the physicochemical properties of cephalexin (Otsuka and Kaneniwa, 1982, 1983), chloramphenicol palmitate (Otsuka and Kaneniwa, 1985, 1986), indomethacin (Otsuka et al., 1986) and phenylbutazone (Matsumoto et al., 1988) by mechanochemical energy during compression and grinding.

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Pikal et al. (1978) reported relations between the crystallinities of various kinds of cephalothin sodium obtained by freeze-drying or recrystallization and the decomposition rate in the solid state. They concluded that the chemical stability in the solid state and the crystallinity of cephalothin sodium change, depending on the preparation method. In the present study we investigated the effects of mechanochemical energy on crystallinity and chemical stability in the solid state of cephalothin sodium during grinding.

Materials and Methods

Materials

Bulk powder of crystalline cephalothin sodium (lot. no. ERON-1300; Meiji Seika Ltd) was used.

Mechanical treatment

A sample of cephalothin sodium powder (10 g) was ground in an agate centrifugal ball mill (Fritsch Co.) with a capacity of 350 ml. Ground powder samples of about 300 mg were withdrawn at appropriate grinding time intervals, and then stored in a closed container at $-35\,^{\circ}$C.

The temperature of the ball mill was measured with a thermocouple (C.C. type: JIS) placed on the exterior of the mill, and was recorded continuously. The diameters and numbers of balls were: 10 mm $\times$ 20, 15 mm $\times$ 10, 20 mm $\times$ 4. Speed was 270 rpm at $20 \pm 3\,^{\circ}$C, and $60 \pm 15\%$ relative humidity.

Nuclear magnetic resonance (NMR) spectrum

Deuterium oxide was used as a solvent with about 3% concentration of the sample. The spectrum was recorded at 100 MHz on an NMR instrument (FX-100; Nihon Denshi Co.).

Powder X-ray diffraction analysis

Powder X-ray diffraction was measured at room temperature with a type JDX 7E diffractometer (Nihon Denshi). The measurement conditions were: target, Cu; filter, Ni; voltage, 30 kV; current, 10 mA; time constant, 2 s; measured from $2\theta = 3^{\circ}$ to $40\,^{\circ}$.

Determination of crystallinity

Crystallinity was estimated by the method of Hermans and Weidinger (1948). The degree of crystallinity of an intact sample was regarded as 100%. The crystalline peaks were separated from the diffuse scattering due to noncrystalline material and lattice imperfections. The following separation method is proposed to obtain a standardized noncrystalline scattering line. The minimum diffraction intensity points are determined in X-ray diffraction profiles and a line between two adjacent minimum points is decided, and then the skirts of diffraction peaks due to crystalline solid are separated. The integrated intensities of crystalline and noncrystalline regions were determined by weighing cut-outs of photocopies of the X-ray diffraction profiles as reported previously (Otsuka et al., 1983).

Thermal analysis

Differential thermal analysis (DTA) curves were measured with a type DT-20 DTA instrument (Shimadzu Seisakusho Co.). Measurement conditions were: sample weight, 3 mg for DTA; heating rate, $10\,^{\circ}$C/min; N_2 gas flow, 30 ml/min; sample cell, aluminum crimp cell.

Measurement of water content

After 2 weeks storage at 88% relative humidity (R.H.) at $35\,^{\circ}$C, the water content of the intact cephalothin sodium was 4.2% as measured by the Karl Fisher method, and was almost the same as that evaluated by the weighing method. Therefore, the water content was measured by using the weighing method as follows: 300-mg samples were stored in saturated salt solutions at various R.H. values in desiccators (0–95% R.H.) at $35 \pm 1\,^{\circ}$C, and water content was determined from the weight.

Measurement of specific surface area

The specific surface area of the ground sample powder was measured with a type P-700 BET gas adsorption instrument (Shibata Seisakusho Co.) by using the BET gas adsorption one-point measurement method.

Scanning electron microscopy (SEM)

An SEM (HS-9; Hitachi Seisakusho Co.) was used at an accelerating voltage of 20 kV.

Density determination

True density was determined by using an air comparison pycnometer (model 930; Beckman-Toshiba Ltd). The value for cephalothin sodium was 1.633 ± 0.008.

Results

Change in crystallinity of cephalothin sodium during grinding

Fig. 1 shows the changes in the X-ray diffraction profiles of crystalline cephalothin sodium during grinding. The diffraction peak intensities of all samples decreased with increased grinding time. However, the X-ray diffraction profile of cephalothin sodium ground for 10 h showed several broad diffraction peaks and had no halo pattern. This suggests that part of the cephalothin sodium was converted into a noncrystalline solid. The X-ray diffraction peaks of cephalothin sodium ground for 2 h were broader than those for 10 h.

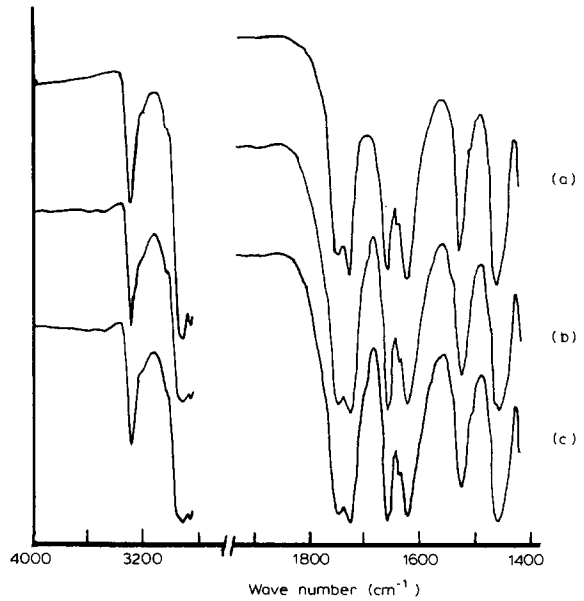

Fig. 2. Change of IR spectra of cephalothin sodium during grinding. (a) Intact, (b) ground for 2 h, (c) ground for 10 h.

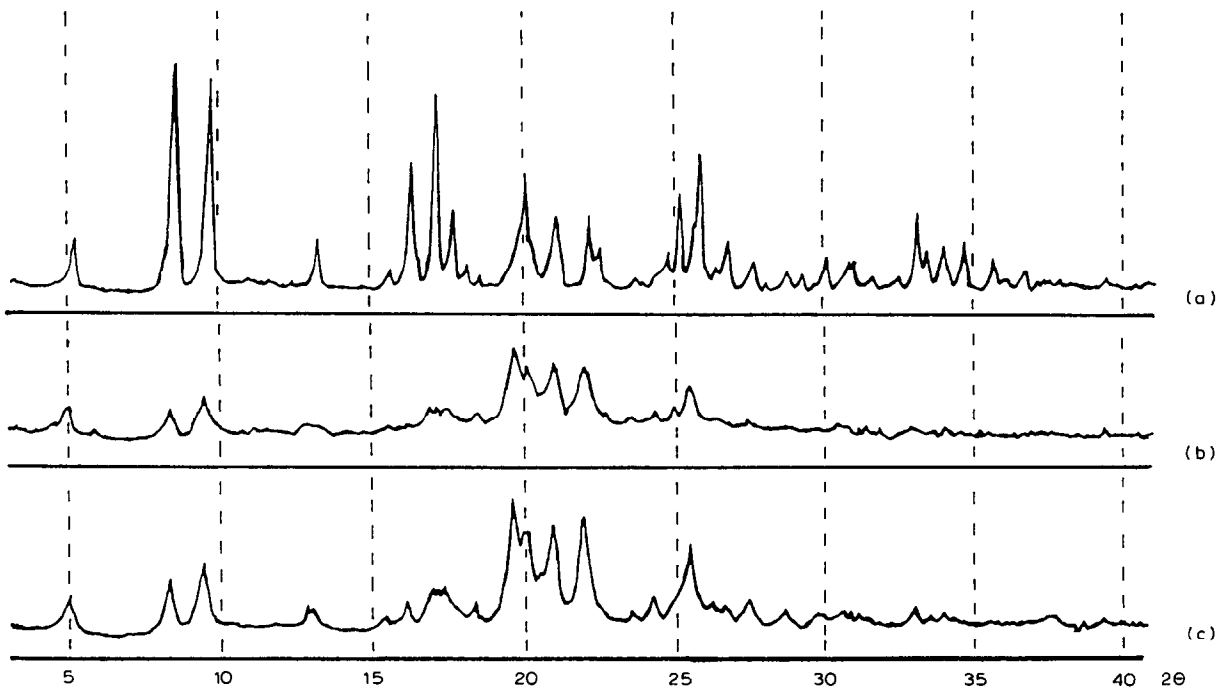

Fig. 1. Change of X-ray diffraction profiles of cephalothin sodium during grinding. (a) Intact, (b) ground for 2 h, (c) ground for 10 h.

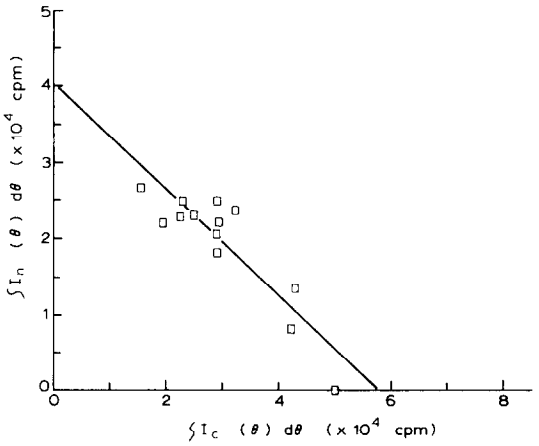

Fig. 3. Hermans' regression line.

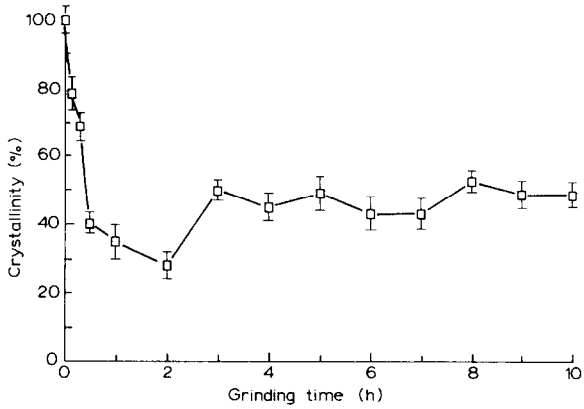

Fig. 4. Effect of mechanochemical stress on the crystallinity of cephalothin sodium during grinding.

Fig. 2 shows the changes in IR spectra of ground cephalothin sodium during grinding. The IR spectrum of ground cephalothin sodium was not significantly different from that of the intact sample.

It appears that no decomposition occurred during grinding for 10 h, since the NMR data for cephalothin sodium ground for 10 h were identical to those of the intact samples.

The temperature of the ball mill rose about 5°C during grinding to about 28° ± 1°C after grinding for 1 h, and stayed at approx. 28°C during prolonged grinding.

Fig. 3 shows Hermans' regression line from the X-ray diffraction profiles of cephalothin sodium. The crystallinities (X_c) of the ground products were estimated from the value (k_c/k_n) of the slope in this plot by using the following equation.

$$X_c = \int I_c(\theta)\,d\theta \Big/ \left(\int I_c(\theta)\,d\theta + k_n/k_c \left(\int I_n(\theta)\,d\theta \right) \right) \quad (1)$$

where $\int I_c(\theta)\,d\theta$ and $\int I_n(\theta)\,d\theta$ denote the integrated intensity from the crystalline and non-crystalline region, respectively.

Fig. 4 shows the change in crystallinity of cephalothin sodium during grinding. The crystallinity of cephalothin decreased with increased grinding time during the initial grinding and had diminished after 2 h to a value of 28%. The crystallinity increased during grinding for 3–10 h and reached equilibrium at about 50%.

Change in DTA curve of cephalothin sodium during grinding

Fig. 5 shows the DTA curves of ground cephalothin sodium samples. The DTA curve of intact cephalothin sodium showed an exothermic peak

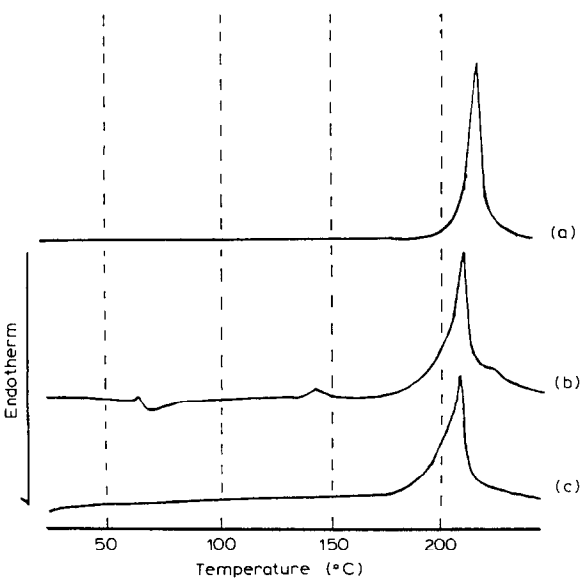

Fig. 5. Change of DTA curves of cephalothin sodium during grinding. (a) Intact, (b) ground for 2 h, (c) ground for 10 h.

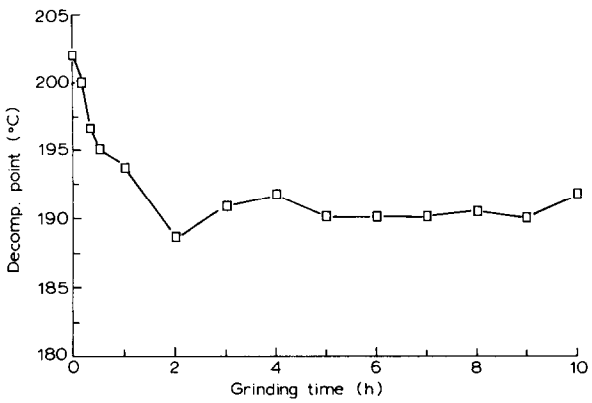

Fig. 6. Effect of mechanochemical stress on the decomposition point of cephalothin sodium during grinding.

due to decomposition at about 215°C. After 2 h grinding, the DTA curve showed new exo- and endothermic peaks due to the glass transition point at about 70°C, a new broad exothermic peak at about 145°C owing to recrystallization of non-crystalline cephalothin sodium, and an exothermic peak shifted to about 208°C, due to decomposition. After decomposition, the sample color had changed to dark brown and smelt gas came from the sample.

Fig. 6 demonstrates the change in decomposition point on the DTA curve of cephalothin sodium during grinding. It was assumed that the decomposition points were extrapolated onset points with the points of intersection between the tangents of the baseline and peaks of the DTA curves.

The decomposition point of the ground products fell rapidly at the beginning, and then decreased gradually to 187°C after 2 h. However, it rose to 191°C after 3 h, and thereafter remained at approx. 192°C.

Change in water content of ground cephalothin sodium

Fig. 7 shows the moisture absorption curves of ground cephalothin sodium at various values of R.H. at 35°C. Intact cephalothin sodium did not absorb water at R.H. < 88%. The moisture adsorption curve of intact cephalothin sodium at 93% R.H. reached a plateau at about 4% water content (1 mol water per mol cephalothin sodium) after 7 days, and at 95% R.H. intact cephalothin sodium absorbed water very rapidly. However, cephalothin sodium ground for 2 and 10 h adsorbed about 3 and 1% water, respectively, at 88% R.H. The cephalothin sodium ground for 3 and 10 h adsorbed water rapidly at 93% R.H. and the water content of the ground product increased with prolonged storage time.

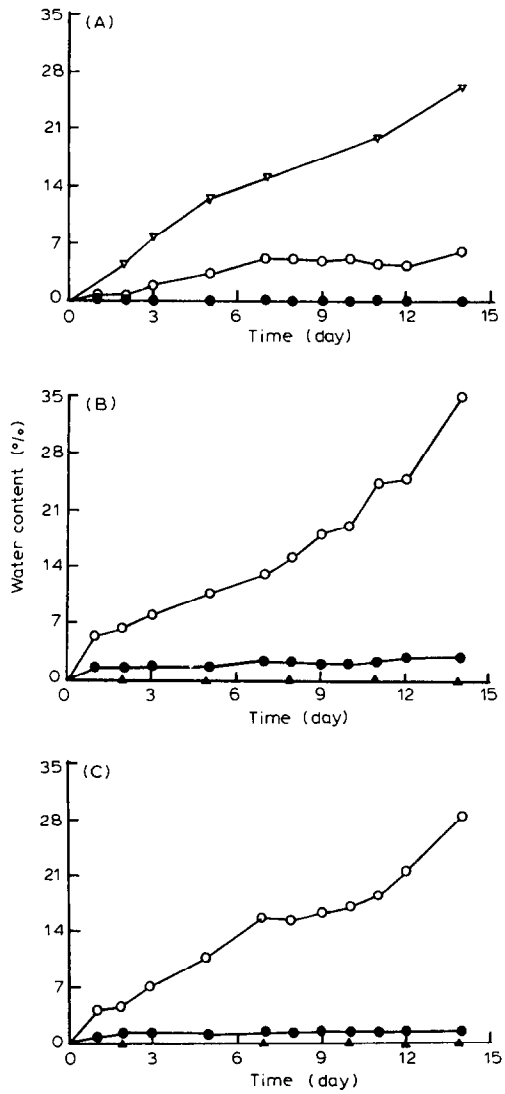

Fig. 7. Change of water content of ground cephalothin sodium at various values of R.H. at 35°C. (A) Intact, (B) ground for 2 h, (C) ground for 10 h. (▽) At 95% R.H., (○) at 93% R.H., (●) at 88% R.H., (▲) at 82% R.H.

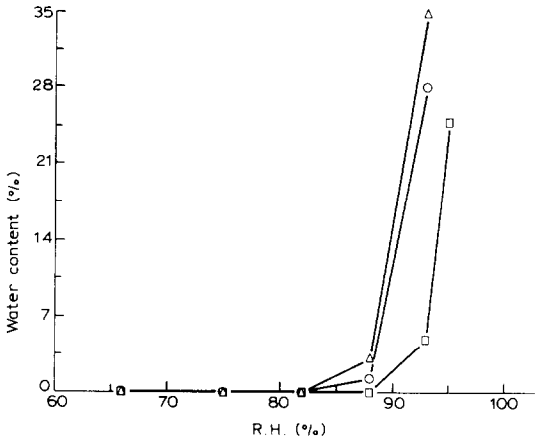

Fig. 8. Relation between water content of ground cephalothin sodium and values of R.H. at 35 °C. The 2-week time points have been plotted. (□) Intact, (△) ground for 2 h, (○) ground for 10 h.

Fig. 8 shows the water content-R.H. diagram after 2 weeks at various R.H. values at 35 °C. The water content of intact cephalothin sodium increased at above 95% R.H. However, those of the products ground for 2 h and 10 h increased at more than 93% R.H.

Change in specific surface area of cephalothin sodium during grinding

Table 1 summarizes the specific surface area (S_w) measured by the BET gas adsorption method and the average particle diameter (d). After 2 h grinding, the S_w value of cephalothin sodium increased 3.3-fold, whereas the S_w values of the products ground for 4 and 10 h were lower than that for 2 h.

TABLE 1

Specific surface area (S_w) and average particle diameter (d) of ground cephalothin sodium

Sample	$S_w \pm$S.D. (m^2/g) ($n = 4$)	d [a] (μm)
Intact powder	2.47 ± 0.02	6.69 [b] (1.49)
Ground for 2 h	8.19 ± 0.03	0.45
Ground for 4 h	6.78 ± 0.01	0.54
Ground for 10 h	5.56 ± 0.02	0.66

d was calculated from the following equation: $d = k/(\text{density} \times S_w)$; k, particle shape constant.

[a] d of the sample powder was calculated from S_w by assuming a spherical shape;

[b] d was calculated by assuming a needle shape (width = length = 10 × height).

SEM photograph of ground cephalothin sodium

Fig. 9 shows SEM photographs of particles of ground cephalothin sodium. The intact crystals were needle-shaped. After 2 h grinding, the ground product contained 3–5 μm secondary particles aggregated with primary particles of less than 1 μm. Product ground for 4 h had some large aggregated particles (about 10 μm). It appeared that the secondary particle size of the product ground for 4 h was greater than that ground for 2 h. After 10 h grinding, there were some large primary particles (5–10 μm) in the powder.

Discussion

Formation of noncrystalline cephalothin sodium during grinding

The degree of crystallinity of cephalothin sodium decreased with increase in grinding time (Fig. 4), and S_w increased during initial grinding, but the mill temperature rose about 5 °C after grinding for 1–10 h. Hence, it seems that the crystallinity of the ground product increased by about 20% after more than 2 h grinding and the S_w decreased to reach a constant level at about 60%. An equation to describe the grinding rate including the processes of grinding and aggregation has been previously reported (Schneider et al., 1967; Kubo, 1978). On the other hand, we reported the effect of environmental temperature on noncrystallization of indomethacin during grinding (Otsuka et al., 1986). Crystalline indomethacin was converted into a noncrystalline solid during grinding at 0 °C, but did not undergo conversion at 30 °C.

These results may be interpreted in accordance with the equation for the apparent grinding kinetics (Eqn 2) which includes grinding and recrystallization processes.

$$-dC/dt = -k_c(C) + k_n(1 - C) \qquad (2)$$

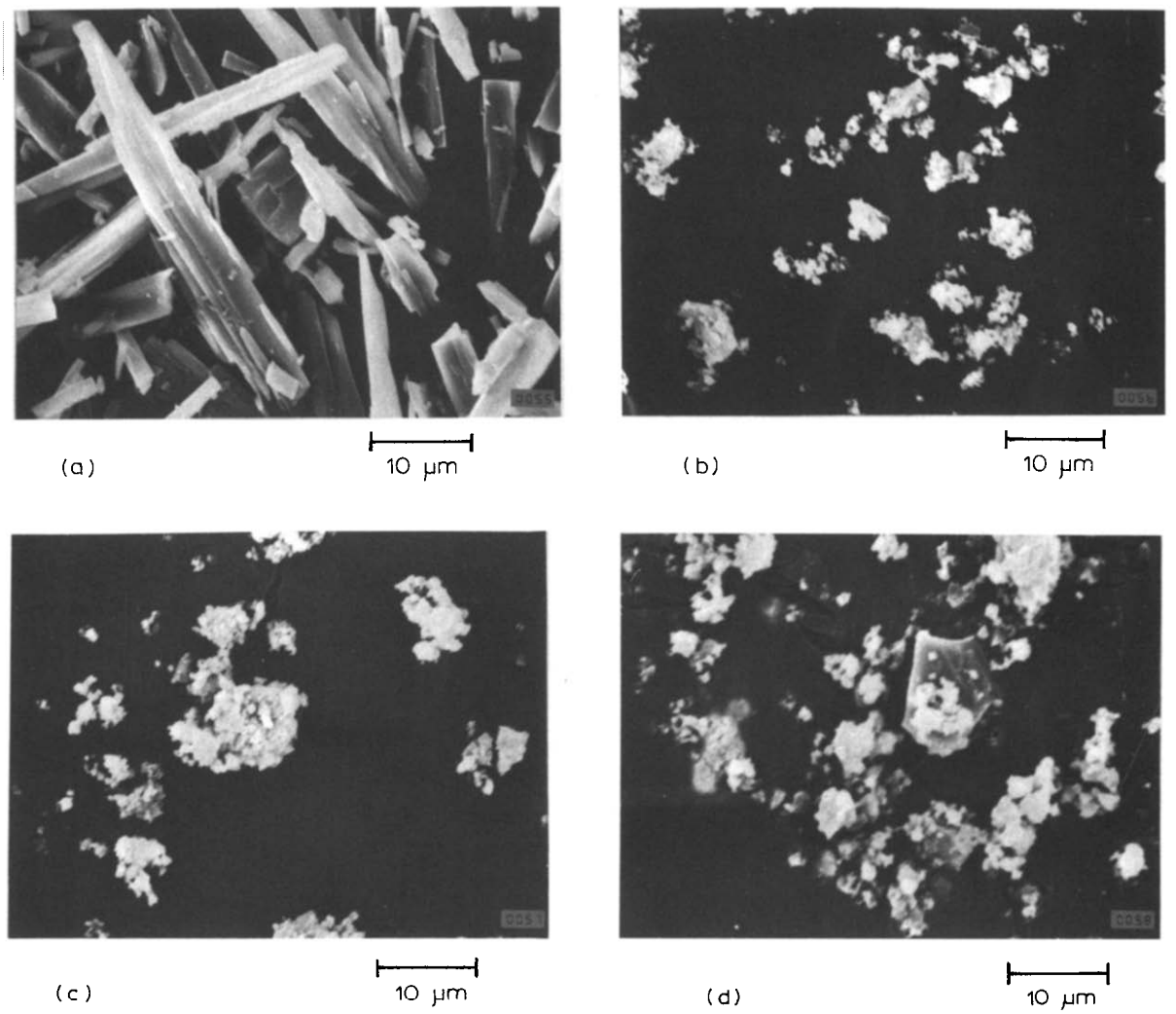

Fig. 9. Change of SEM photographs of the ground cephalothin sodium. (a) Intact, (b) ground for 2 h, (c) ground for 4 h, (d) ground for 10 h.

where C is the degree of crystallinity; k_c is the grinding rate constant of crystalline solid, and k_n is the recrystallization rate constant of noncrystalline solid.

After 1 h grinding, the ball mill temperature rose about 5 °C. It might be assumed that the rate of formation of noncrystalline solid during grinding did not change at the temperature used in the present experiments. However, the recrystallization rate increased with increase in ball mill temperature, since the recrystallization rate constant (k_n) depended on the temperature. Therefore, it appears that the value of the crystallinity at apparent equilibrium increased from 28 to 50% with increase in ambient temperature for the apparent kinetics during grinding, and subsequently, the S_w of cephalothin sodium ground for 2 h was greater than that for 4 and 10 h.

Relation between the degree of crystallinity of cephalothin sodium and chemical stability in the solid state

The decomposition point of cephalothin sodium fell with decrease in the degree of crystallinity

TABLE 2

Relations between degree of crystallinity of cephalothin sodium and chemical stability reported by Pikal et al. (1978)

Sample	Crystallinity [a] (%)	Stability at 50 °C (%)	
		Dryness	At 31% R.H.
Crystallization A	100	100	100
Market product	72	101	100
Freeze-dried A	62	101	100
Freeze-dried B	57	86	–
Freeze-dried C	47	77	85
Spray-dried	37	54	44

[a] External standard X-ray diffraction method.

(Fig. 6). This suggests that the chemical stability of cephalothin sodium in the solid state depends on the crystallinity. Pikal et al. (1978) reported relations between the chemical stability of cephalothin and the degree of crystallinity (Table 2) in an isothermal environment. The chemical stability of cephalexin, an antibiotic with a β-lactam ring structure, decreases with decrease in crystallinity (Otsuka et al., 1984). This suggests that the chemical stability of a drug is affected by the degree of crystallinity, and that the decomposition point of a drug decreases with the degree of crystallinity. Therefore, crystallinity is an important factor in the chemical stability of a drug in the solid state.

Effect of grinding treatment on the hygroscopicity of cephalothin sodium

The equilibrium water content of cephalothin sodium increased after grinding (Fig. 7). The critical relative humidity (C.R.H.) of intact cephalothin sodium was determined at 93%, whereas that of cephalothin sodium ground for 2 or 10 h was below 88% (Fig. 8). The hygroscopicity of cephalothin sodium increased after grinding.

Conclusion

Some crystalline cephalothin sodium was converted into a noncrystalline solid by mechanical stress. The apparent equilibrium value of the crystallinity of cephalothin sodium during grinding was about 60%. The decomposition point of cephalothin sodium fell about 13 °C after 2 h grinding and the crystallinity was reduced to about 30%. The thermal stability of solid-state cephalothin sodium depends on its crystallinity.

Acknowledgments

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