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Effect of Environmental Temperature on Polymorphic Solid-State Transformation of Indomethacin during Grinding[1)]

MAKOTO OTSUKA, TAKAHIRO MATSUMOTO and NOBUYOSHI KANENIWA*

*School of Pharmaceutical Sciences, Showa University,
Hatanodai 1-5-8, Shinagawa-ku, Tokyo 142, Japan*

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The effect of grinding in an agate centrifugal ball mill at 200 rpm on the physicochemical properties of indomethacin (IMC) polymorphs was studied by means of X-ray diffraction analysis, infrared spectroscopy and differential scanning calorimetry. The α and γ forms (metastable and stable forms) of IMC were ground at 4 °C and at 30 ± 0.5 °C, and the degree of crystallinity (X_c) of the ground products was measured by the X-ray diffractional internal standard method.

The X_c of the γ form ground at 4 °C decreased with increasing grinding time, and was 0% after 4 h, that is, the γ form had been converted to a noncrystalline solid. After grinding for 1 h at 30 °C, about 45% of γ form of IMC was converted to noncrystalline solid, while the product ground for 10 h was transformed to the α form.

The X_c of the α form ground for 2 h at 4 °C was 0%, that is, the α form had been converted to a noncrystalline solid within 2 h at 4 °C. The X_c of the α form ground at 30 °C decreased with increasing grinding time and the value after 10 h was about 60%.

The solubility in distilled water at 35 °C of the γ form ground for 10 h at 4 °C was about 60% larger than that of the intact γ form. The solubilities of the γ form ground for 10 h at 30 °C, the α form ground for 10 h at 4 °C and the α form ground for 10 h at 30 °C were all the same, 0.94 mg/100 ml, which is equal to that of the α form at 35 °C.

Keywords——indomethacin; polymorphism; grinding; X-ray diffraction analysis; thermal behavior; noncrystalline state; transformation; solubility

The particle size and the nature of the polymorphs of a drug affect the bioavailability of preparations through their effects on the dissolution rate. Fine particles of a metastable polymorphic form are suitable for clinical use. We have reported on the effects of grinding on the physicochemical properties of cephalexin[2,3)] and chloramphenicol palmitate.[4,5)] Cephalexin crystals were converted to a noncrystalline solid during grinding and the solubility increased. On the other hand, the metastable forms B and C of chloramphenicol palmitate were transformed to the stable form A during grinding and the solubility of the ground products decreased. In the previous paper,[6)] we established methods for the preparation of pure polymorphs of indomethacin (IMC), α and γ forms. In the present study we investigated the effect of environmental temperature on the physicochemical properties of the polymorphs of IMC as a model drug during grinding.

Experimental

Materials——Highly purified α and γ forms of IMC were obtained as described in the previous paper.[6)] Noncrystalline solid IMC (glassy solid) was obtained by cooling at about −20 °C after fusing the bulk powder of IMC at 165 °C for 5 min.[7)] Standard samples with various degrees of crystallinity were obtained by physically mixing α or γ form and glassy solid IMC, regarding the degrees of crystallinity of α or γ form and glassy solid as 100% and 0%, respectively.

Mechanical Treatment——A sample of α or γ form of IMC (10 g) was ground in an agate centrifugal ball mill (capacity 350 ml: diameter and number of balls, 10 mm × 20, 15 mm × 10, 20 mm × 4) using a grinding apparatus (Fritsch Co., Ltd.) at 200 rpm. The grinding was carried out in a room thermostated at 4 ± 0.5 °C or 30 ± 0.5 °C, and

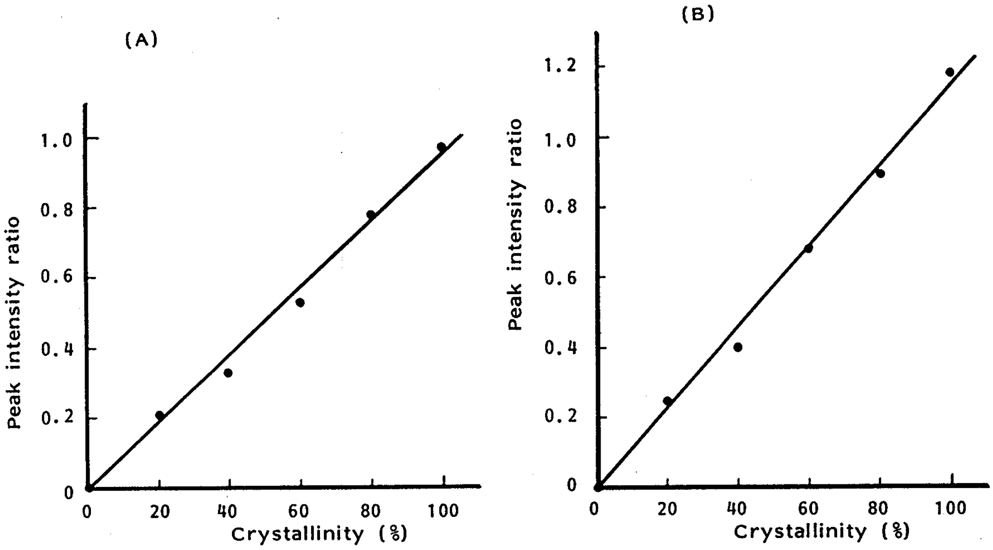

Fig. 1. Degree of Crystallinity of α and γ Forms of IMC *vs.* Peak Intensity Ratios

(A) physical mixture of α form and noncrystalline solid (ratio of $2\theta=8.5°$ *vs.* 38.7°), (B) physical mixture of γ form and noncrystalline solid (ratio of $2\theta=11.6°$ *vs.* 38.7°).

the temperature of the ball mill was measured with a thermocouple (C.C. type: JIS) placed on the exterior of the ball mill, and recorded continuously. The ground samples were stored in closed containers at -20 °C.

X-Ray Diffraction Analysis——The X-ray diffraction profiles of ground samples were measured at room temperature with a type JDX 7E X-ray diffractometer (Nihon Denshi Co., Ltd.). The measurement conditions were as follows; target, Cu; filter, Ni; voltage, 30 kV; current, 6 mA; receiving slit, 0.2 mm; time constant, 2 s; counting range, 6×10^3 cpm; scanning speed; 1 °/min.

Determination of the Crystallinity and the Amounts of Polymorphs of IMC——The X-ray diffraction profiles of mixtures of the standard sample and 20% LiF (internal standard) were measured, and Fig. 1 shows plots of the ratio of the peak areas at $2\theta=8.5°$ due to the α form and at $2\theta=38.7°$ due to LiF *versus* the content of the α form, and that of the peak areas at $2\theta=11.6°$ due to the γ-form and at $2\theta=38.7$ °C due to LiF *versus* the content of the γ form. Each plot gave a straight line, and the degree of crystallinity (X_c) of a sample could be obtained by using these calibration plots. Each value of X_c is the average of 3 measurements.

Nuclear Magnetic Resonance (NMR) Spectra——The NMR spectra were measured with a FX-100 NMR spectrometer (Nihon Denshi Co., Ltd.). Solutions of about 2%—5% of the ground products in deuterated $CDCl_3$ were prepared and the spectra were measured using tetramethylsilane as an internal reference. It was confirmed that no decomposition of the ground products occurred due to mechanical stress during grinding, at least in terms of the NMR spectra.

Infrared (IR) Spectra——The IR spectra were measured as a mull in Nujol on an IR-2 infrared spectrophotometer (Nihon Bunko Co., Ltd.).

Thermal Analysis——The differential scanning calorimetry (DSC) curves were measured with a DSC instrument (Shimadzu Seisakusho Co., Ltd., SC-20B). The measurement conditions were as follows: sample weight, about 5 mg; sample cell, an aluminum crimp cell; N_2 gas flow, 30 ml/min; heating rate, 20 °C/min; measurement temperature range, 10—200 °C, using a cooling instrument containing crushed ice and NaCl freezing mixture. The heats of fusion (H_f) and crystallization (H_c) and the temperatures of fusion and crystallization were corrected based on the measurement of indium as a standard sample. Each value is the average of 3 runs.

Dissolution Curves——A sample (500 mg) of IMC was rapidly placed in 500 ml of distilled water in a 1000 ml round-bottomed flask (JP X; Dissolution test) maintained at 30 ± 0.2 °C. The solution was stirred with paddle at a constant rate of 200 rpm. Samples of the solution were taken by means of a glass syringe at suitable time intervals and filtered immediately through a 0.45 μm membrane filter (Millipore; HAWPO 01300). The filtrate was suitably diluted for spectrophotometric assay (Hitachi Seisakusho Co., Ltd., type 139) at 252 nm.

Results and Discussion

Effect of Environmental Temperature on X-Ray Diffraction Profiles of α and γ Forms of IMC during Grinding

Figures 2 and 3 show the changes of X-ray diffraction profiles of the α and γ forms of

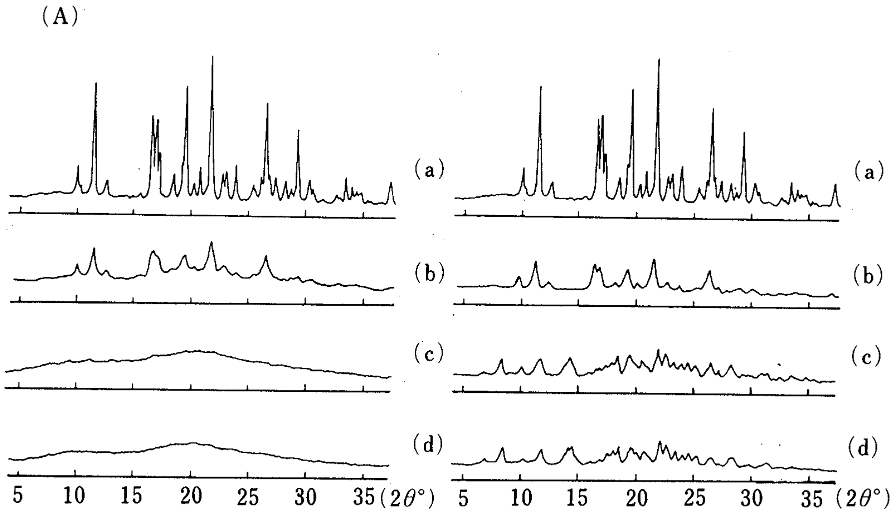

Fig. 2. Change in X-Ray Diffraction Profiles of γ Form of IMC during Grinding at 4 °C (A) and 30 °C (B)

(a) intact γ form, (b) the product ground for 1 h, (c) for 6 h, (d) for 10 h.

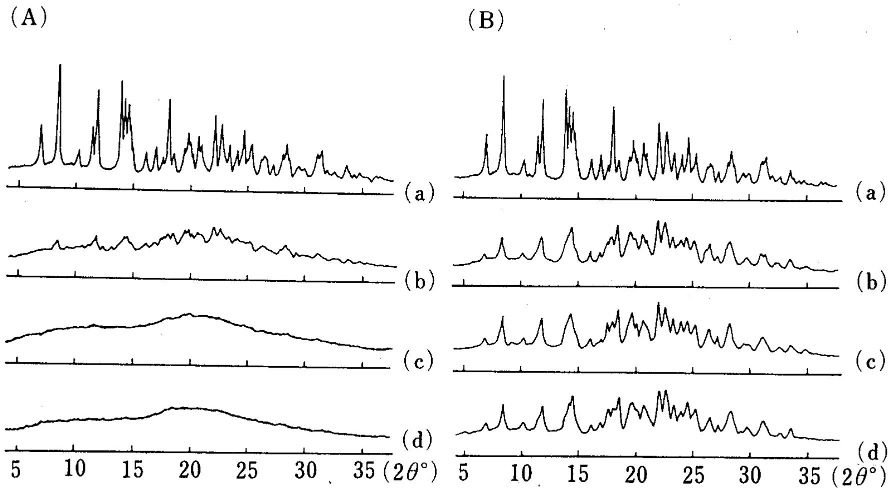

Fig. 3. Change in X-Ray Diffraction Profiles of α Form of IMC during Grinding at 4 °C (A) and 30 °C (B)

(a) intact α form, (b) the product ground for 1 h, (c) for 6 h, (d) for 10 h.

IMC during grinding at 4 and 30 °C. In grinding at 4 °C (Fig. 2A), the peak intensities of the γ form decreased with increasing grinding time; after grinding for 1 h the profile was very broad, and after 4—10 h a halo pattern was seen, that is, the γ form had been converted to noncrystalline solid during grinding.

The peaks of the γ form ground for 1 h at 30 °C (Fig. 2B) were very broad, but the γ form ground for 6 h showed diffraction peaks at $2\theta = 7.2$, 8.5 and 14.0° attributable to α form, and the γ form ground for 10 h showed no diffraction peaks attributable to the γ form.

In grinding at 4 °C (Fig. 3A), the peak intensities of the ground α form decreased with increasing grinding time, and after grinding for 2—10 h a halo pattern was seen, that is, α form had been converted to noncrystalline solid during grinding.

The peaks of the α form ground for 1 h at 30 °C (Fig. 3B) were broad, and the α form ground for 1—10 h showed only diffraction peaks attributable to the α form; the X-ray diffraction profiles were almost unchanged. These results suggested that the α and γ forms of IMC were converted to a noncrystalline solid during grinding at 4 °C by mechanical stress, but

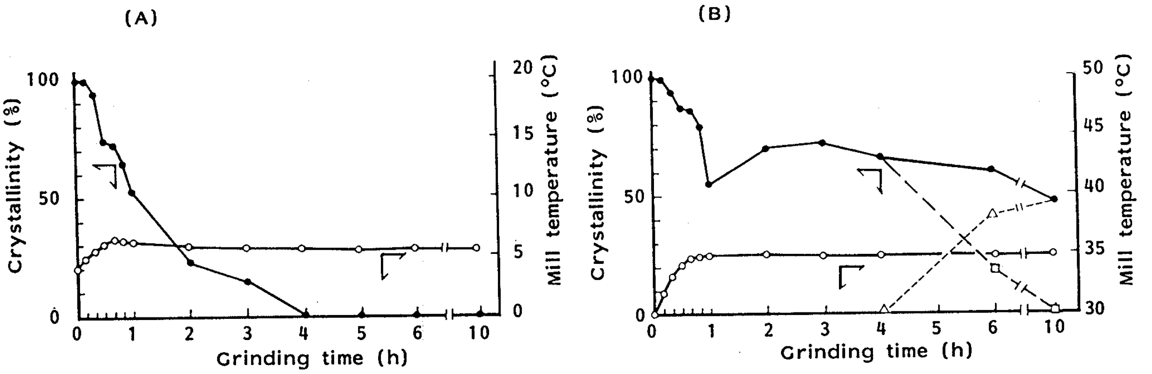

Fig. 4. Effect of Grinding at 4 °C (A) and 30 °C (B) on the Crystallinity of γ Form of IMC

□, the content of γ form; △, the content of α form; ●, the crystallinity; ○, mill temperature.

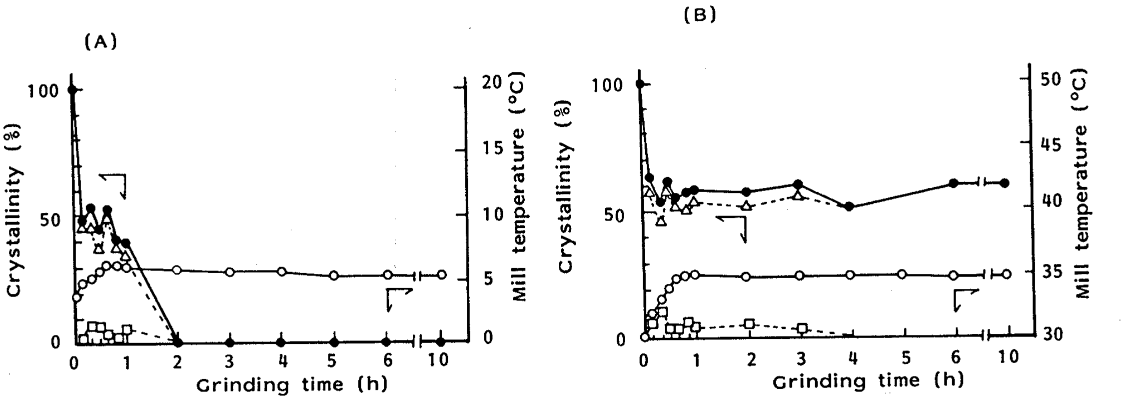

Fig. 5. Effect of Grinding at 4 °C (A) and 30 °C (B) on the Crystallinity of α Form of IMC

□, the content of γ form; △, the content of α form; ●, the crystallinity; ○, mill temperature.

the α form of IMC was more stable than the γ form during grinding at 30 °C since the γ form was transformed to the metastable α form, whereas the α form did not change.

Changes in the Degree of Crystallinity of α and γ Forms of IMC during Grinding at 4 and 30 °C

Figure 4 shows the effect of grinding at 4 and 30 °C on the crystallinity of the γ form. The crystallinity (X_c) of the γ form ground at 4 °C (Fig. 4A) decreased with increasing grinding time; after 1 h, X_c was 53%, and after 4—10 h, X_c was 0%. During grinding, the mill temperature rose slightly; it was 6.5 °C after grinding for 40 min, and 5.5 °C after 1—10 h.

The X_c of the γ form ground for 10 min—1 h at 30 °C (Fig. 4B) decreased with increasing grinding time, and after 1 h, the X_c was 55%. However, the X_c of the γ form ground for 2—4 h increased to about 70%. The γ form ground for 6 h contained 42% of α form and 18% of γ form, and that ground for 10 h contained 37% of α form. The mill temperature rose during grinding; it was 35 °C after grinding for 40 min and stayed at approximately 35 °C, even after prolonged grinding.

Figure 5 shows the effect of grinding at 4 and 30 °C on the crystallinity of the α form of IMC. The X_c of the α form ground at 4 °C for 10 min (Fig. 5A) decreased to 48%, while that after 10—40 min was about 50%, though the product contained about 5% of γ form. After grinding for 2 h, the X_c was 0%, that is, the α form was converted to a noncrystalline solid by grinding for 2 h at 4 °C. The mill temperature was almost constant at 5.5 °C during 1—

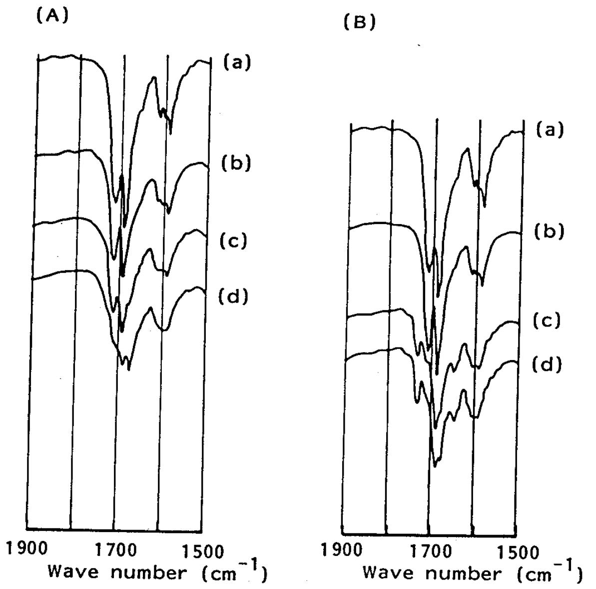

Fig. 6. Changes in IR Spectra of γ Form of IMC during Grinding at 4 °C (A) and 30 °C (B)

(a) intact γ form, (b) the product ground for 1 h, (c) for 6 h, (d) for 10 h

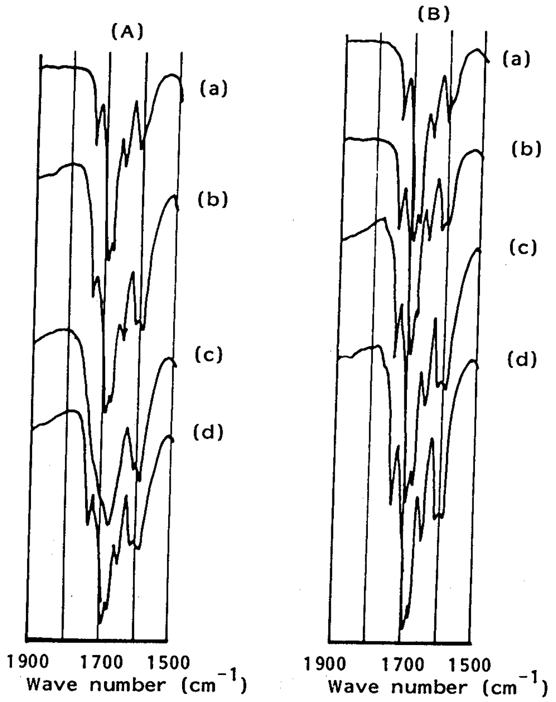

Fig. 7. Changes in IR Spectra of α Form of IMC during Grinding at 4 °C (A) and 30 °C (B)

(a) intact α form, (b) the product ground for 1 h, (c) for 6 h, (d) for 10 h.

10 h of grinding.

The X_{c} of the α form ground for 10 min at 30 °C (Fig. 5B) was 63% and it contained 7% of γ form. After grinding for 10 min—3 h the X_{c} was about 60% and the product contained about 5% of γ form, but the γ form disappeared from the α form ground for 4—10 h and the X_{c} was about 60% (only α form). The mill temperature during grinding for 1—10 h stayed approximately constant at 35 °C.

Since the noncrystalline solid obtained by grinding at 4 °C is stable, the α and γ forms were converted to a noncrystalline solid. However, the noncrystalline solid is unstable at 30 °C, and crystals grew. Therefore the X_{c} of the γ form ground at 30 °C decreased by less than 50%. The crystallization from noncrystalline solid to γ form increased during grinding, until equilibrium with the loss of crystallinity due to grinding was established at $X_{\mathrm{c}}=$ about 70%. Nuclei of the α form appeared after grinding for 6 h, and then the noncrystalline solid was transformed to α form.

In grinding at 30 °C, the α form was transformed to both γ form and noncrystalline solid during grinding for 0—3 h; the ground product contained about 7% of the γ form. After prolonged grinding, the X_{c} of the α form was almost constant at about 60% since the rate of crystallization from noncrystalline solid to α form became equal to the rate of loss of crystallinity due to grinding, and equilibrium was established. It seems that the γ form was more stable than the α form during grinding at 4 °C since the α form was larger enthalpy than the γ form; after grinding for 4 h at 4 °C, the γ form was converted to noncrystalline solid, but the α form was converted in only 2 h.

Changes in IR Spectra of α and γ Forms of IMC during Grinding at 4 and 30 °C

Figure 6 shows IR spectra of the ground γ form. As the γ form was converted to a noncrystalline solid by grinding at 4 °C (Fig. 6A), the peak at 1715 cm^{-1} disappeared and a new peak appeared at 1690 cm^{-1}.

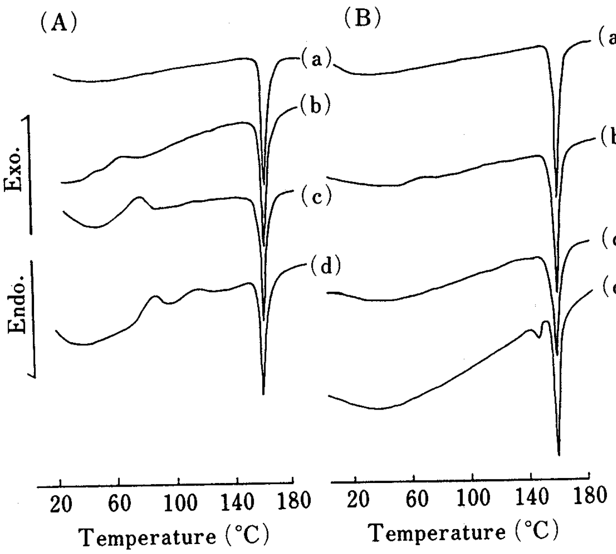

Fig. 8. Changes in DSC Curves of γ Form of IMC during Grinding at 4 °C (A) and 30 °C (B)

(a) intact γ form, (b) the product ground for 1 h, (c) for 6 h, (d) for 10 h.

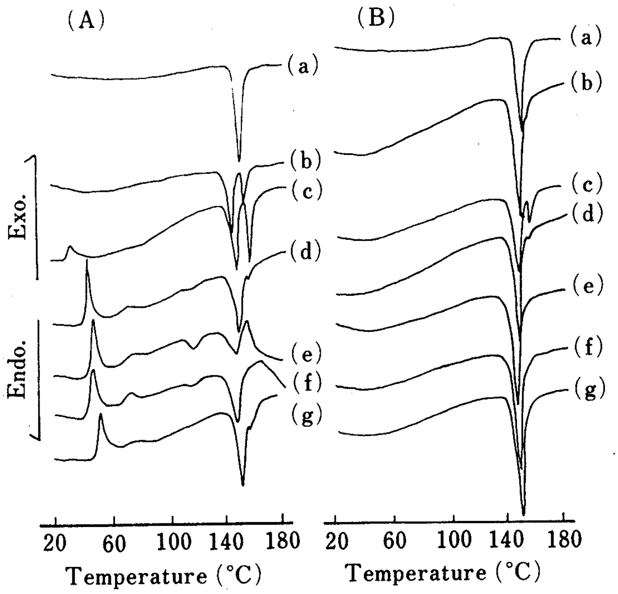

Fig. 9. Changes in DSC Curves of α Form of IMC during Grinding at 4 °C (A) and 30 °C (B)

(a) intact α form, (b) the product ground for 30 min, (c) for 1 h, (d) for 3 h, (e) for 4 h, (f) for 6 h, (g) for 10 h.

The peak at 1715 cm^{-1} due to the γ form disappeared after grinding for 6 h at 30 °C (Fig. 6B), and new two peaks at 1735 and 1650 cm^{-1} attributable to the α form appeared after 10 h.

Figure 7 shows IR spectra of the ground α form. The IR spectra of the α form ground for 10 min—1 h at 4 °C (Fig. 7A) was unchanged except for the peak at 1590 cm^{-1}. The IR spectra after 2—6 h showed a new peak at 1680 cm^{-1} and the peaks at 1715 and 1650 cm^{-1} disappeared, but the IR spectrum at 10 h was again that of the α form.

The IR spectrum of the α form ground at 30 °C did not change except for the peak at 1590 cm^{-1} (Fig. 7B).

Change in Thermal Behavior of Ground α and γ Forms of IMC at 4 and 30 °C

Figure 8 shows the DSC curves of the ground γ form at 4 and 30 °C. The DSC curves of the γ form ground for 1 and 6 h at 4 °C (Fig. 8A) show an exothermic peak at about 60 °C attributable to crystallization and an endothermic peak at about 160 °C due to fusion of the γ form, while that of the product ground for 10 h shows two exothermic peaks at about 95 °C and about 115 °C and an endothermic peak at about 160 °C due to fusion of the γ form. The X-ray diffraction profile of the γ form ground for 6 h after heating at 93 °C for 5 min in a differential thermal analysis instrument was that of the γ form. From the X-ray diffraction profiles, the γ form ground for 10 h was transformed to the α form after heating at 93 °C for 20 s, and to the γ form after heating at 135 °C for 5 min. These results suggested that during DSC curve measurement, noncrystalline solid obtained by grinding for 6 h at 4 °C was transformed to the γ form, whereas noncrystalline solid obtained by grinding for 10 h at 4 °C was transformed to the α form, and then from the α form to the γ form.

The DSC curve of the γ form ground for 1 h at 30 °C (Fig. 8B) showed an exothermic peak at about 60 °C attributable to crystallization and an endothermic peak at about 160 °C due to fusion, and that of the γ form ground for 10 h showed two endothermic peaks at about 150 °C and about 160 °C due to fusion of the α and γ forms, respectively.

Figure 9 shows the DSC curves of the ground α form at 4 and 30 °C. The DSC curve of the α form ground for 30 min at 4 °C (Fig. 9A-b) shows two endothermic peaks at about 150 °C and about 160 °C due to fusion of the α and γ forms. The exothermic peak at about

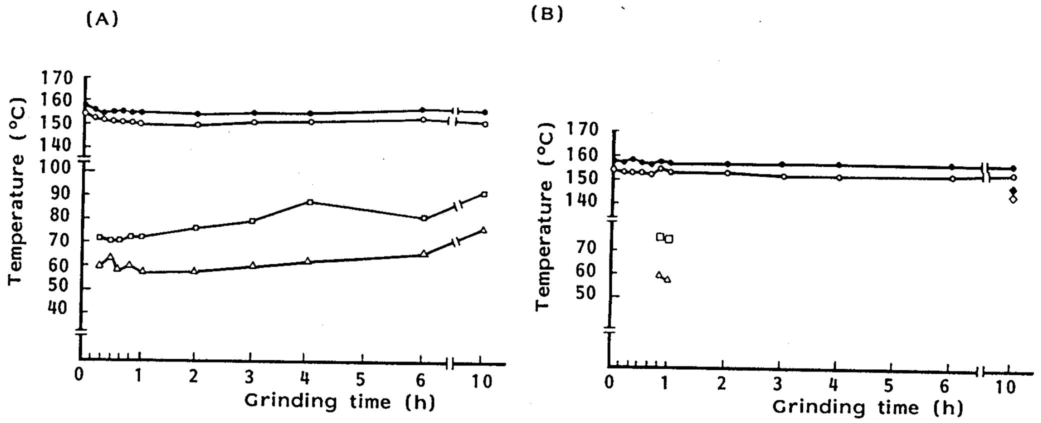

Fig. 10. Changes in Melting and Crystallization Points of γ Form of IMC during Grinding at 4 °C (A) and 30 °C (B)

●, maximum point of fusion due to γ form; ○, extrapolated point of fusion due to γ form; ◆, maximum point of fusion due to α form; ◇, extrapolated point of fusion due to α form; □, maximum point of crystallization; △, extrapolated point of crystallization.

40 °C (Fig. 9A-c) was attributable to the crystallization of the γ form because of the presence of the γ form (content about 5%; see the previous section) as seed crystals. The curves of α form ground for 3 and 10 h show a very sharp exothermic peak at about 50 °C attributable to crystallization and an endothermic peak at 150 °C due to fusion of the α form. The sharp peak was assigned as the exothermic peak of crystallization of the α form by X-ray diffractometry after heating at 70 °C for 5 min. However, the curves of the α form ground for 4 and 6 h show very broad unknown exothermic and endothermic peaks at about 70 °C and at about 120 °C.

The DSC curves of the α form ground for 30 min—3 h at 30 °C (Fig. 9B) show endothermic peaks at 150 and 160 °C due to fusion of the α and γ forms; this finding suggests that the α form was transformed to noncrystalline solid and the γ form simultaneously during grinding for 10 min—3 h at 30 °C.

Figure 10 shows the changes of melting and crystallization points obtained from DSC curves of the ground γ form. The crystallization point (P_{ce}) was obtained by the extrapolation method. The temperature of the maximum point of the exothermic peak attributable to the crystallization is P_{cm}. In grinding from 10 min to 6 h at 4 °C (Fig. 10A), P_{ce} was about 60 °C, but P_{ce} of the product ground for 10 h at 4 °C was 77 °C. The P_{cm} of the γ form ground for 4 h was 87 °C, and the values for the products ground for 6 h and for 10 h were 82 and 92 °C, respectively. The crystallization of the γ form ground for 10 min—6 h was attributable to the γ form, but that of the γ form ground for 10 h was attributable to the α form.

The melting points (P_{me} and P_{mm}) were determined by the extrapolation method and from the maximum point of the endothermic peak, respectively. The P_{me} and the P_{mm} of the γ form ground for 10 min—10 h were about 152 °C and about 157 °C, respectively. The P_{me} of the ground γ form was about 3 °C lower than that of the intact γ form of IMC, presumably because the ground products contained many defects in the crystal lattice.

The γ form ground for 50 min and 1 h at 30 °C (Fig. 10B) showed crystallization points, whereas after prolonged grinding, the crystallization points disappeared. The P_{me} of the ground γ form was about 2 °C lower than that of the intact γ form, and the γ form ground for 10 h showed P_{me} and P_{mm} at 144 and 147 °C, respectively, due to fusion of the α form.

Figure 11 shows the changes of melting and crystallization points of the ground α form of IMC. In grinding at 4 °C (Fig. 11A), the P_{ce} and P_{cm} of the α form ground for 2—6 h were about 44 °C and about 47 °C, while those after 10 h were 50 and 58 °C, respectively. The crystallization of the α form ground for 2—10 h was attributable to the α form, but that at 1 h

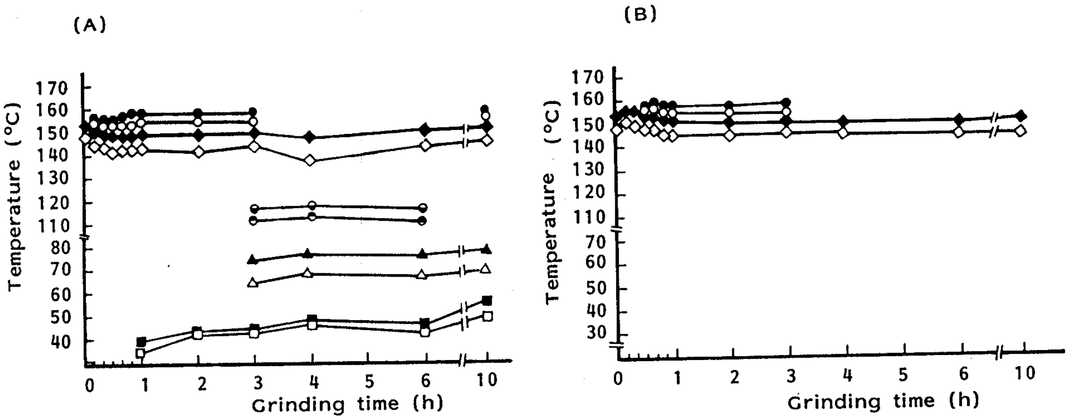

Fig. 11. Changes in Melting and Crystallization Points of α Form of IMC during Grinding at 4 °C (A) and 30 °C (B)

●, maximum point of fusion due to γ form; ○, extrapolated point of fusion due to γ form; ◆, maximum point of fusion due to α form; ◇, extrapolated point of fusion due to α form; ■, maximum point of crystallization; □, extrapolated point of crystallization; ◒, maximum point of unknown endothermic peak; ◓, extrapolated point of endothermic unknown peak; ▲, maximum point of exothermic unknown peak; △, extrapolated point of exothermic unknown peak.

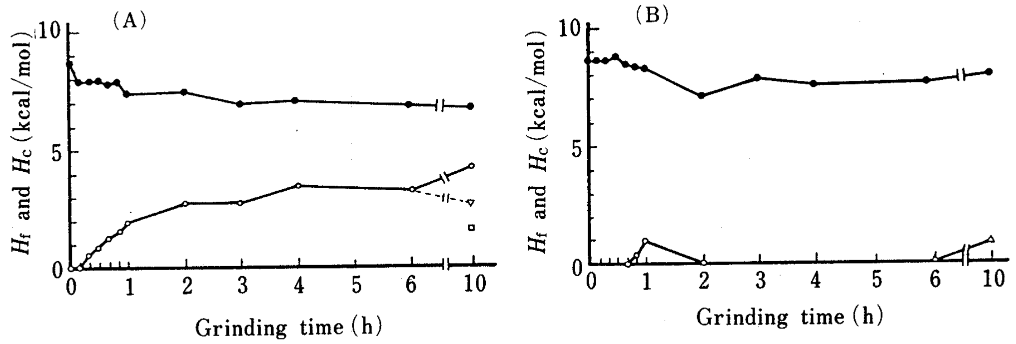

Fig. 12. Changes in Heats of Fusion (H_f) and Crystallization (H_c) of γ Form of IMC during Grinding at 4 °C (A) and 30 °C (B)

●, H_f; △, H_f due to α form; ○, H_c; ▽, H_c of first; □, H_c of second peak.

was attributable to the γ form. An unknown exothermic peak at 60—75 °C appeared in the case of the product ground for 3—10 h, and an unknown endothermic peak at 110—120 °C was seen with the product ground for 3—6 h. The P_{me} and P_{mm} of the α form ground for 10 min—3 h were about 142 °C and about 149 °C due to fusion of the α form. The P_{me} and the P_{mm} of the α form ground for 10 min—10 h were about 152 °C and about 157 °C (except at 4 h), due to fusion of the γ form. At 30 °C (Fig. 11B), the α form ground for 30 min—3 h showed endothermic peaks at about 150 °C due to the α form and at 160 °C due to fusion of the γ form.

The melting points of the ground α and γ forms of IMC were about 4 °C lower than those of the intact α and γ forms, presumably because the ground products contained many crystal lattice defects.

Figure 12 shows the changes of heats of crystallization (H_c) and fusion (H_f) of the γ form of IMC during grinding at 4 °C and 30 °C. The H_c of the ground γ form at 4 °C (Fig. 12A) increased with increasing grinding time; that after 4—6 h was about 3.2 kcal/mol, and that after 10 h was 4.2 kcal/mol (the lower and higher peaks were 2.7 and 1.6 kcal/mol, respectively). From the results obtained by thermal X-ray diffraction analysis (previous section), the noncrystalline solid obtained by grinding for 4—6 h was transformed to the γ form since it

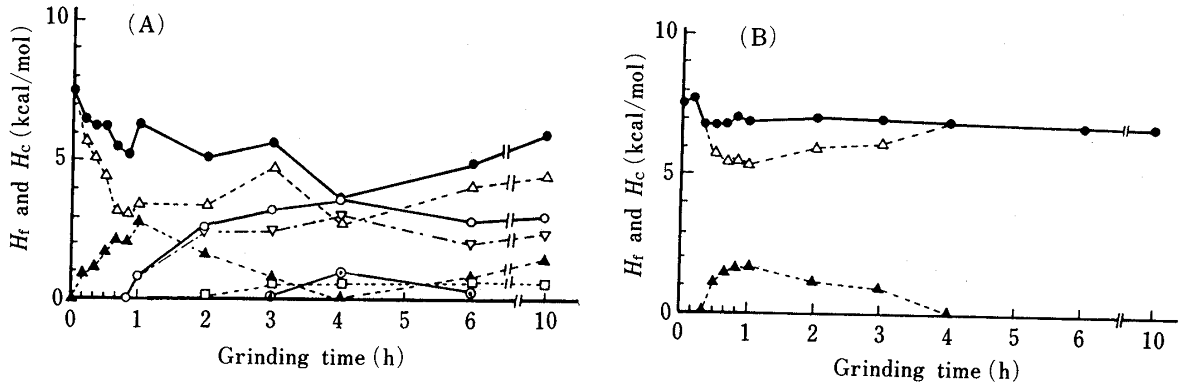

Fig. 13. Changes in Heats of Fusion (H_f) and Crystallization (H_c) of α Form of IMC during Grinding at 4 °C (A) and 30 °C (B)

●, H_f; ▲, H_f due to γ form; △, H_f due to α form; ○, H_c; ▽, H_c of first peak; □, H_c of second peak; ⊙, unknown endothermic peak.

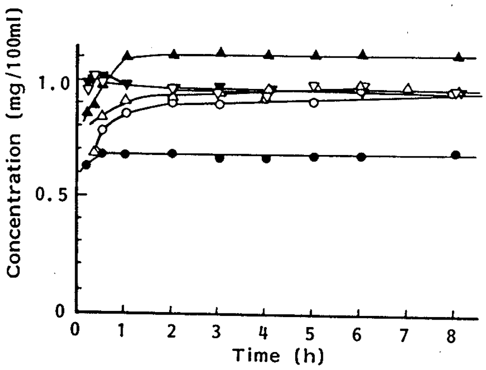

Fig. 14. Dissolution Profiles of Ground Products of IMC in Distilled Water at 35 °C

●, intact γ form; ○, intact α form; ▼, the γ form ground for 10 h at 30 °C; ▲, the γ form ground for 10 h at 4 °C; ▽, the α form ground for 10 h at 30 °C; △, the α form ground for 10 h at 4 °C.

contained fine particles of the γ form which acted as seed crystals; consequently its IR spectrum is similar to that of the intact γ form. On the other hand, since the noncrystalline solid ground for 10 h at 4 °C contained no crystals, its transformation sequence was noncrystalline solid→α form→γ form, following Ostwald's step law.[8)]

The H_f of the ground γ form was about 2 kcal/mol lower than that of the intact γ form, presumably because it contains many crystal lattice defects.

The H_c of the γ form ground for 1 h at 30 °C (Fig. 12B) was about 1 kcal/mol, and the product ground for 2—10 h showed no crystallization peak. This is consistent with the finding of minimum crystallinity at $X_c = 55\%$ in all products ground at 30 °C. The H_c of the γ form ground for 6 or 10 h was not consistent with the content of α form determined by the X-ray diffraction method, because the α form was transformed to the γ form during the DSC measurement.

Figure 13 shows the changes of H_c and H_f of the ground α form during grinding at 4 and 30 °C. The H_c of the ground α form at 4 °C (Fig. 13A) increased with increasing grinding time, being about 3.9 kcal/mol after 4 h, and 3.2 kcal/mol after 10 h. From the results of X-ray diffraction analysis after heating, the noncrystalline solid obtained by grinding for 2—10 h was transformed to the α form after measurement of the DSC curves. Since the α form ground for 10 min—3 h contained a small amount of the γ form which acted as seed crystals during measurement of the DSC curves, H_f due to the γ form was not consistent with the amount of the γ form estimated by the X-ray diffraction method. The H_c and H_f of the α form ground for 4 h were almost the same, suggesting that the energy level of the ground product is equal to that of the fused state of IMC, that is, the ground product is a very active solid state (so-called triboplasma state).[9)] However, on prolonged grinding, it was transformed to a more stable noncrystalline state, because the triboplasma state is very unstable.

The H_f of the α form ground for 10 h at 4 °C was about 1.5 kcal/mol lower than that of the intact γ form, presumably because many crystal lattice defects must be present.

The H_f of the α form ground for 30 min—3 h at 30 °C (Fig. 13B) was about 1 kcal/mol, attributable to the γ form, and the α form ground for 2—10 h lacked the fusion peak due to the γ form. This is consistent with the crystal content of the γ form estimated by the X-ray diffraction method. The H_f of the ground α form was about 1 kcal/mol lower than that of the intact α form, presumably because of the many crystal lattice defects.

The Dissolution Profiles of the Ground Products of IMC

Figure 14 shows the dissolution profiles of the ground α and γ forms and the intact α and γ forms of IMC in distilled water at 35 °C. The concentration of the γ form ground for 10 h at 4 °C reached 1.10 mg/100 ml, 60% larger than that of the intact γ form (0.69 mg/100 ml). The concentration of the α form ground for 10 h at 4 °C reached 0.94 mg/100 ml, equal to that of the intact α form of IMC. In the dissolution profiles of the α and γ forms ground for 10 h at 30 °C, the concentrations at 30 min were 1.01 and 1.01 mg/100 ml, respectively, but the concentrations became constant at 0.94 mg/100 ml, equal to that of the intact α form of IMC. The X-ray diffraction patterns of the α and γ forms ground for 10 h at 4 and 30 °C were those of the α form.

Conclusion

The α and γ forms of IMC were converted to a noncrystalline solid during grinding at 4 °C, but at 30 °C the γ form was converted to metastable α form and the α form remained unchanged. These findings suggest that the γ form of IMC was converted to noncrystalline solid by mechanical stress during grinding. The conversion was irreversible at 4 °C because the noncrystalline solid was stable at 4 °C, but the solid was unstable at 30 °C and crystallized to α form, reaching an equilibrium state where the rate of crystallization is equal to the rate of destruction of crystallinity by grinding. The γ form of IMC was transformed to the α form at 30 °C. These results suggest that the α form of IMC is more stable than the γ form during grinding at 30 °C.

The solubility of the noncrystalline solid obtained from the γ form by grinding at 4 °C was about 60% larger than that of the intact γ form. In general, the temperature of grinding instruments depends on the grinding conditions, and some care seems to be necessary regarding environmental temperature when the polymorphs of drugs are treated mechanically.

References and Notes

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