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Effect of Environmental Temperature on the Polymorphic Transformation of Phenylbutazone during Grinding

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The transformation behavior of phenylbutazone polymorphs during grinding at 4 and 35 °C and the solid-state stability and dissolution behavior of the ground crystals were investigated kinetically. The α, β and δ forms were transformed to a new polymorphic ζ form, which in turn was transformed to the ε form, which was stable at 4 °C. On the other hand, during grinding at 35 °C, the δ form was not changed, while the α form was transformed to the δ form by way of the ζ form. The β form was apparently transformed directly to the δ form. The ε form, obtained by grinding, was transformed to the δ form under 0% relative humidity at various storage temperatures after an induction time of a few hours. The mechanism of solid-state transformation of the ε form to the δ form was found to be random nucleation with two-dimensional growth of nuclei (Avrami–Erofeev model) by means of the Hancock and Sharp method, and the activation energy of this transformation was calculated to be 44.5 kcal/mol. The dissolution rate of the ε form was faster than those of other forms in buffer solution, but the ε form was transformed to the δ form during dissolution.

Keywords——phenylbutazone; polymorph; powder X-ray diffraction; thermal analysis; transition; grinding; solid-state stability; dissolution

Introduction

Grinding is often employed as a technique to reduce the particle size of powders or to mix drugs. Frequently, however, not only desired changes in physical properties such as specific area and shape, but also changes in physicochemical properties such as catalytic activity can take place during grinding, that is, polymorphic transformation and conversion to amorphous form may occur. These changes in physicochemical properties during grinding are dependent on the energy supplied to the materials and the environmental temperature during grinding.[1] Previously, we have reported the transformation in suspension of phenylbutazone polymorphs.[2] In this study, we investigated the transformation of phenylbutazone polymorphs during grinding and further, the stability, transition mechanism and dissolution properties of ground crystals.

Experimental

Materials——Phenylbutazone (Lot No. 36607) supplied by Dolder Ltd., Basle, Switzerland, was used.

Preparation and Identification of Polymorphic Forms——The α, β and δ forms of phenylbutazone were prepared and identified as described in a previous paper.[2]

Mechanical Treatment——A sample of each polymorphic form (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 or 35 ± 0.5 °C. The ground samples were stored in a closed container at −20 °C.

X-Ray Diffraction Analysis——The X-ray diffraction profiles of ground samples were measured at room

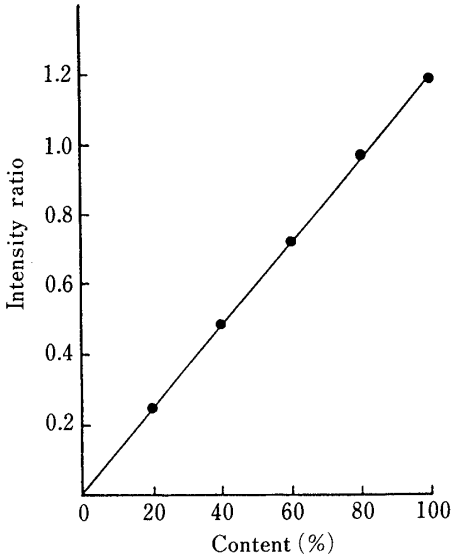


Fig. 1. Relation between Content of the ε Form and the X-Ray Diffraction Intensity Ratio of Phenylbutazone with Respect to the Internal Standard (LiF).

temperature with a type JDX 7E X-ray diffractometer (Nihon Denshi Co., Ltd.) for the δ form and a type 11PA X-ray diffractometer (Nihon Denshi Co., Ltd.) for the α and β forms, as well as for the kinetic study of the isothermal transition of the ε form to the δ form. The measurement conditions were as follows. JDX 7E: target, Cu; filter, Ni; voltage, 30 kV; current, 7.5 mA; receiving slit, 0.2 mm; time constant, 2 s; scanning speed, 1°/min. 11PA: target, Cu; filter, Ni; voltage, 30 kV; current, 7.5 mA; receiving slit, 0.2 mm; step slit, 0.03°; counting time, 0.5 s.

Thermal Analysis——The heat of fusion (ΔH_f) and the melting point were measured with a differential scanning calorimetry instrument (Shimadzu Seisakusho Co., Ltd., SC-20B). The measurement conditions were as follows: sample cell, an aluminum crimp cell; N_2 gas flow, 30 ml/min; heating rate, 20 °C/min. Values were corrected by measurement of indium as a standard sample.

IR Spectroscopy——The infrared (IR) spectra were measured as a mull in Nujol on an IR-810 infrared spectrophotometer (Nihon Bunko Co., Ltd.).

Kinetic Study of Isothermal Transition of the ε Form to the δ Form——A sample (2 g) of the ε form was stored in a P_2O_5 desiccator maintained at 20, 30, 35 or 40±1 °C. About 100 mg of the crystals was withdrawn at appropriate time intervals, and the X-ray diffraction was measured to determine the content of the ε form as described below.

Measurement of the Content of the ε Form——The X-ray diffraction profiles of a physical mixture of the standard sample (the ε form and δ form) and 20% LiF (internal standard) were measured. Figure 1 shows the plot of the ratio of the peak heights at $2\theta = 10.7°$ due to the ε form and at $2\theta = 38.7°$ due to LiF *versus* the content of the ε form. The same sample was replaced in the holder and examined 3 times. The plot gave a good straight line, which was used as a calibration line to determine the content of the ε form.

Scanning Electron Microscopic Study——The scanning electron microscope (S-700; Hitachi Seisakusho Co., Ltd.) was used at an accelerating voltage of 20 kV.

Measurement of Dissolution Curves of ε Form by the Dispersed Amount Method——The dissolution curves were measured by the dispersed amount method, using the apparatus described in a previous paper.[2] A sample (3 g) of the ε form was rapidly placed in 250 ml of buffer solution (JP XI pH 6.8) in a 1000 ml round-bottomed flask maintained at 30, 35, 40 or 45±0.5 °C. A sample of the solution was taken by means of a glass syringe at suitable time intervals and immediately filtered through a 0.45 μm membrane filter. The filtrate was suitably diluted for spectrophotometric assay at 264 nm (Hitachi Seisakusho Co., Ltd., type 139 UV-VIS spectrophotometer).

Determination of the Initial Dissolution Rate of the ε Form——The dissolution rate was determined by a rotating disk method, using the apparatus described in a previous paper.[3] A sample (500 mg) was compressed in a cylindrical die with a Riken oil press for KBr tablets for IR spectroscopy. It was confirmed by X-ray diffraction analysis that no phase transition occurred during the compression. The experimental conditions were as follows: 500 ml of buffer solution (JP XI pH 6.8) as a disintegration dissolution medium; at 35 °C; 400 rpm rotational velocity of the disk; 2.0 cm diameter disk of the drug compressed under 2 t /cm^2. The solution was circulated through a quartz flow cell (layer length 5 mm) by a rotary pump and the concentration was determined by spectrophotometric assay as described above.

Results and Discussion

Mechanochemical Transformation of Phenylbutazone Polymorphs

Previously we have investigated the effect of environmental temperature on the physi-

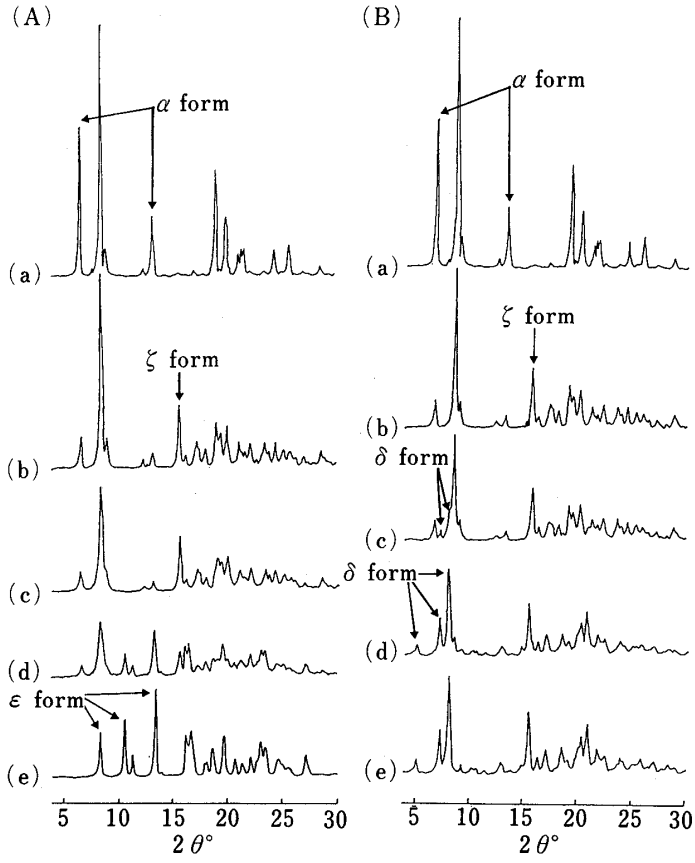


Fig. 2. Changes with Time in the X-Ray Diffraction Pattern of the α Form during Grinding at Each Temperature

(A) 4 °C: (a) 0 h, (b) 10 min, (c) 2 h, (d) 9 h, (e) 11 h. (B) 35 °C: (a) 0 h, (b) 10 min, (c) 3 h, (d) 4 h, (e) 6 h.

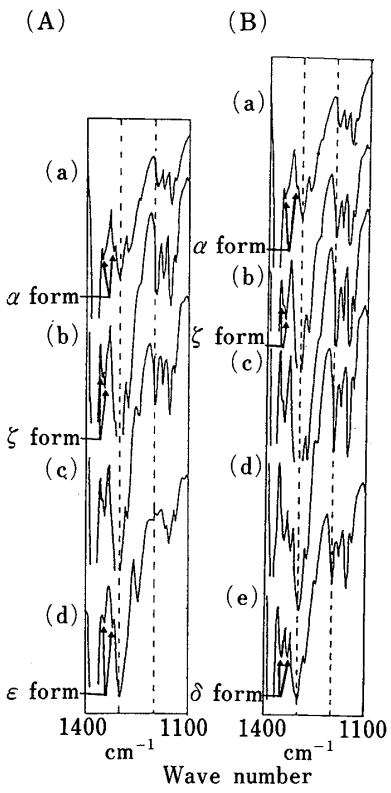


Fig. 3. Changes with Time in the IR Spectrum of the α Form during Grinding at Each Temperature

(A) 4 °C: (a) 0 h, (b) 10 min, (c) 9 h, (d) 11 h. (B) 35 °C: (a) 0 h, (b) 10 min, (c) 1 h, (d) 4 h, (e) 6 h.

cochemical properties of the polymorphs of indomethacin during grinding.[1] In this study, we investigated the mechanochemical solid-state transformation during grinding of phenylbutazone polymorphs.

1) Grinding of the α Form at 4 and 35°C——Figures 2 and 3 show the changes of X-ray diffraction profiles and IR spectra of the α form during grinding at 4 and 35 °C, respectively. In grinding at both 4 and 35°C, the intensity of diffraction peaks at $2\theta=6.7$ and 13.3° decreased and the new peak at $2\theta=15.8°$ appeared, while the IR absorption peak at 1310 cm^{-1} disappeared and the new absorption peak at 1350 cm^{-1} appeared after grinding for 10 min. Then the form remained intact for 1—2 h at both grinding temperature in terms of X-ray diffraction profiles and IR spectra. Therefore, the α form ground for 10 min was named the ζ form as an intermediate product during grinding provisionally, though more extensive research seemed to be necessary to examine the purity of this form. After grinding for 9 h at 4 °C, the diffraction peaks at $2\theta=6.7$ and 15.8° disappeared and new peaks at $2\theta=8.2$, 10.7 and 13.5° appeared in the X-ray diffraction profile. The absorption peaks at 1355 cm^{-1} disappeared and the new absorption peak at 1315 cm^{-1} appeared. It was considered that the ζ form was transformed to the ε form, which has already been reported by Matsuda *et al.*[4] No further changes could be seen in the X-ray diffraction profile and IR spectrum for 13 h. On the other hand, in grinding at 35 °C, the diffraction peaks at $2\theta=5.1$ and 7.3° and the absorption peak at 1320 cm^{-1} attributed to the δ form appeared after grinding for 4 h. That is, the ζ form was transformed to the δ form and remained intact for 18 h. The existence of the common IR

absorption peak at 1350 cm^{-1} among the ζ, ε and δ forms suggested that the ζ form was similar to the ε and δ forms in their molecular structure, that is, this crystalline form was an intermediate product to the ε or δ form during grinding of the α form.

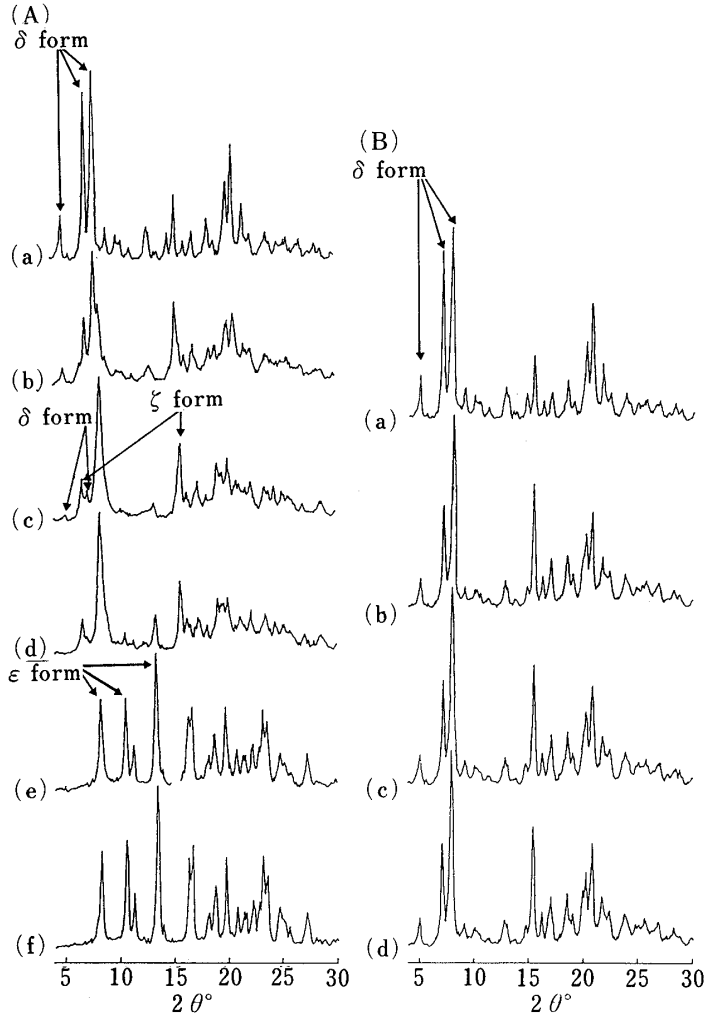


Fig. 4. Changes with Time in the X-Ray Diffraction Pattern of the δ Form during Grinding at Each Temperature

(A) 4 °C: (a) 0 h, (b) 1 h, (c) 2 h, (d) 3 h, (e) 8 h, (f) 24 h. (B) 35 °C: (a) 0 h, (b) 2 h, (c) 8 h, (d) 24 h.

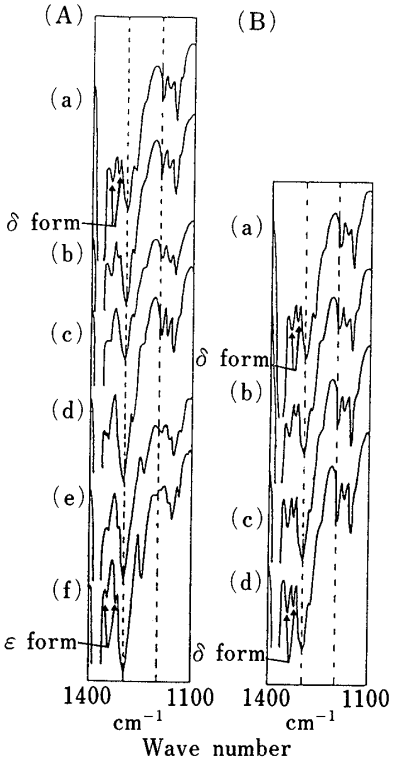


Fig. 5. Changes with Time in the IR Spectrum of the δ Form during Grinding at Each Temperature

(A) 4 °C: (a) 0 h, (b) 1 h, (c) 2 h, (d) 3 h, (e) 4 h, (f) 8 h. (B) 35 °C: (a) 0 h, (b) 2 h, (c) 8 h, (d) 24 h.

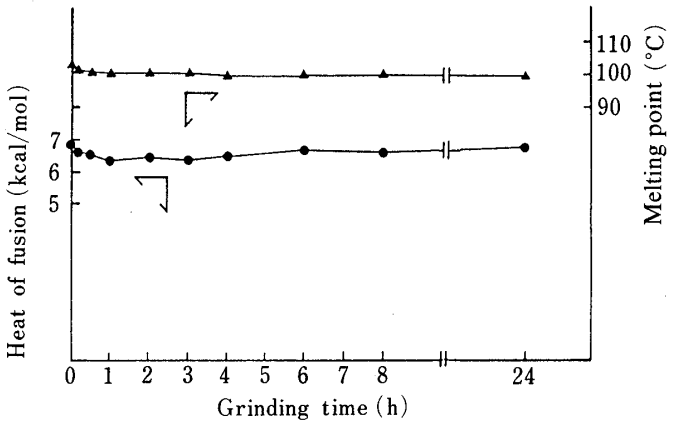


Fig. 6. Changes in Melting Point and Heat of Fusion of the δ Form during Grinding at 35 °C

●, Heat of fusion; ▲, melting point.

2) Grinding of the δ Form at 4 and 35 °C——Figures 4 and 5 show the changes of X-ray diffraction profile and IR spectrum of the δ form during grinding at 4 and 35 °C, respectively. In grinding at 35 °C, the X-ray diffraction profile and IR spectrum were almost unchanged after grinding for 24 h. It was considered that neither polymorphic transformation nor transition to the amorphous form had occurred during grinding at 35 °C. Decrease of the melting point or heat of fusion, attributed to lattice distortion, is sometimes observed during mechanochemical treatments such as grinding and compression.[5,6] Figure 6 shows that no such changes in the heat of fusion and melting point of the δ form could be observed during grinding at 35 °C. These results suggested that the δ form was stable during grinding at 35 °C, presumably because the recrystallization rate of ground crystals was faster than the destruction rate of crystals at 35 °C. In grinding at 4 °C, the intensity of diffraction peaks at $2\theta=6.7°$ increased with time and the peaks at 15.5° attributed to the δ form and at 15.8° attributed to the ζ form were overlapped after grinding for 1 h. The IR spectrum showed absorption peaks at 1350 and 1355 cm^{-1} after grinding for 2 h. Further, the diffraction peak at 13.3° and IR absorption peak at 1310 cm^{-1} attributed to the α form did not show. That is, the δ form seemed to be transformed to a mixture of the ζ form and δ form during grinding. After grinding for 3h, the intensity of diffraction peaks at $2\theta=6.7$ and 15.8° attributed to the ζ form increased and new peaks at $2\theta=13.5°$ attributed to the ε form appeared in the X-ray diffraction profile. On the other hand, the IR spectrum showed an absorption peak at 1350 cm^{-1}. Thus, the ground material was considered to be transformed to a mixture of the ζ form and ε form. After grinding for 4h, the mixture was transformed to the ε form and no further changes could be seen in the X-ray diffraction profile and IR spectrum for 20 h. These results suggested that the ε form is stable during grinding at 4 °C.

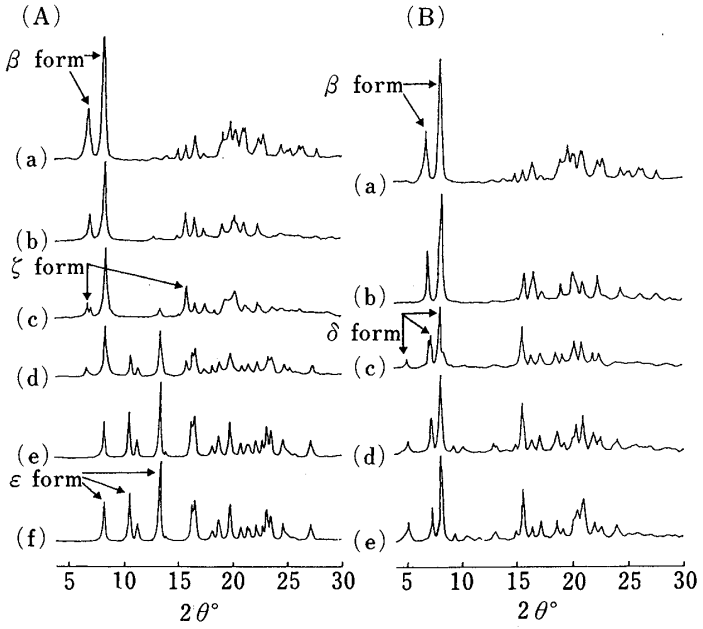


Fig. 7. Changes with Time in the X-Ray Diffraction Pattern of the β Form during Grinding at Each Temperature

(A) 4 °C: (a) 0 h, (b) 2 h, (c) 3 h, (d) 4 h, (e) 6 h, (f) 24 h. (B) 35 °C: (a) 0 h, (b) 30 min, (c) 1 h, (d) 4 h, (e) 6 h.

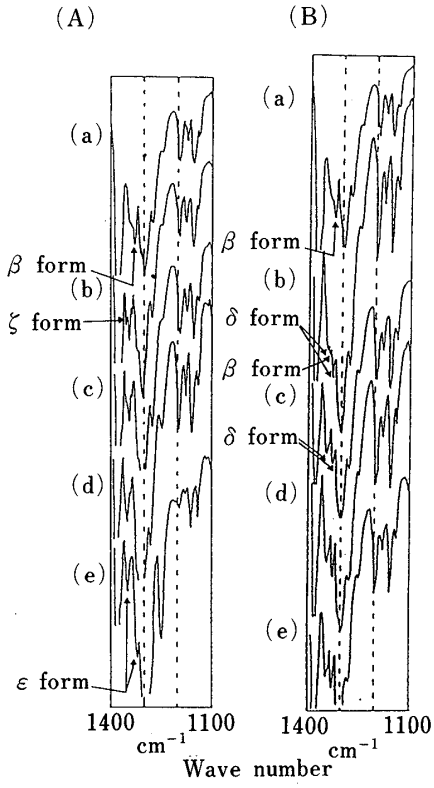


Fig. 8. Changes with Time in the IR Spectrum of the β Form during Grinding at Each Temperature

(A) 4 °C: (a) 0 h, (b) 3 h, (c) 4 h, (d) 6 h, (e) 24 h. (B) 35 °C: (a) 0 h, (b) 30 min, (c) 1 h, (d) 4 h, (e) 6 h.

3) Grinding of the β Form at 4 and 35°C——Figures 7 and 8 show the changes of X-ray diffraction profile and IR spectrum of the β form during grinding at 4 and 35 °C, respectively. In grinding at 4°C, the diffraction peak at $2\theta=6.7°$ appeared and the peak at $2\theta=13.3°$ attributed to the α form did not show. On the other hand, the absorption peak at 1355 cm^{-1} appeared. Therefore, the β form seemd to be transformed to the ε form by way of the ζ form after grinding for 6 h, though differences among the diffraction peaks at $2\theta=8.6°$ attributed to the β form, $2\theta=8.4°$ attributed to the ζ form and $2\theta=8.2°$ attributed to the ε form could not be distinguished clearly. Then, the ε form remained intact for 18 h. In grinding at 35 °C, the diffraction peaks at $2\theta=5.1$, 7.3 and 8.0° in the X-ray diffraction profile and the absorption peaks at 1320 and 1350 cm^{-1} in the IR spectrum attributed to the δ form appeared after grinding for 1 h, that is, it seemed that direct transformation from the β form to the δ form took place.

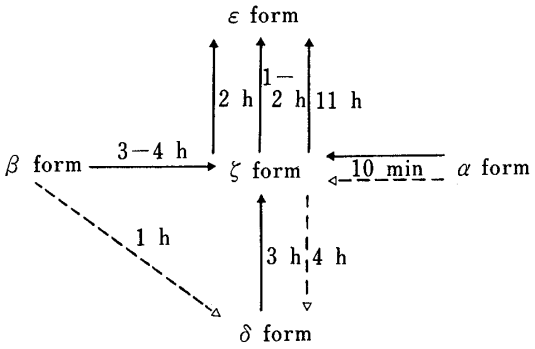


Chart 1. Transformation of Phenylbutazone Polymorphs during Grinding

——, grinding at 4 °C. ◁---, grinding at 35 °C.

Chart 1 shows the transformation of phenylbutazone polymorphs during grinding at 35 and 4 °C. It is difficult to study quantitatively the relationship between the energy required for transformation and the energy supplied to the materials, since polymorphic transformation by mechanochemical treatment is a complex system with regard to the relation between the energy supplied to the materials and the temperature of the materials during treatment. Previously we have reported that a stable form is converted to a noncrystalline solid or transformed to a metastable form by grinding at lower temperature, but at higher temperature, ground noncrystalline material may crystallize.[1] In this study, all polymorphic forms were transformed to the metastable ε form during grinding at 4 °C and to the stable δ form at 35 °C. In addition, the transformation of the ε form could not be observed for several hours during grinding, suggesting that the ε form obtained by grinding is of high purity. Matsuda *et al.*[4] reported that the solubility of the ε form, which was prepared by a spray-drying method, was 1.56 times higher than that of the δ form. The ε form obtained by grinding at 4 °C in this study was also expected to show high solubility. Further research to examine its stability and bioavailability seems to be justified.

Stability of the ε Form and Kinetic Study on Isothermal Transformation of the ε Form to the δ Form

Physicochemical stability of polymorphs is an important factor from a pharmaceutical point of view, *e. g.*, in connection with tableting. However, few kinetic analyses of isothermal transformation in the solid state have been reported.[7,8] We investigated the kinetics and mechanism isothermal transformation of the ε form, which was obtained by grinding the δ form at 4 °C, by means of the X-ray diffraction internal standard method.[1]

Figure 9 shows typical changes with time in the X-ray diffraction profile during the isothermal transformation of the ε form to the δ form at 35 °C. The intensity of the diffraction peak at $2\theta=5.1°$ attributed to the δ form increased and that at $2\theta=10,7°$ attributed to the ε

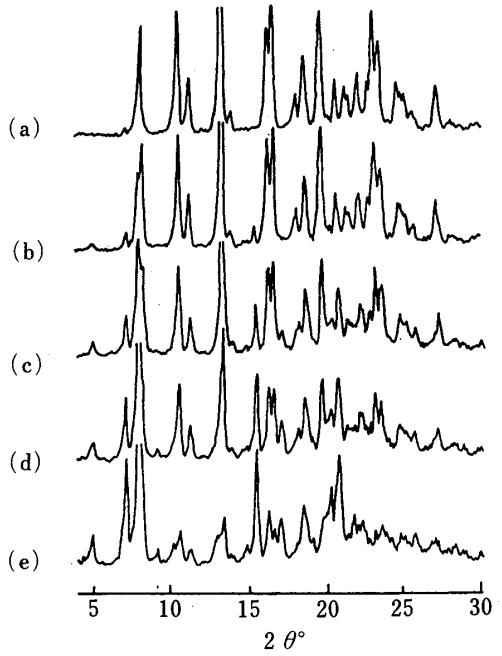


Fig. 9. Changes with Time in the X-Ray Diffraction Pattern for the Isothermal Transformation of the ε Form to the δ Form at 35 °C
(a) 0 h, (b) 12.5 h, (c) 30 h, (d) 42 h, (e) 54 h.

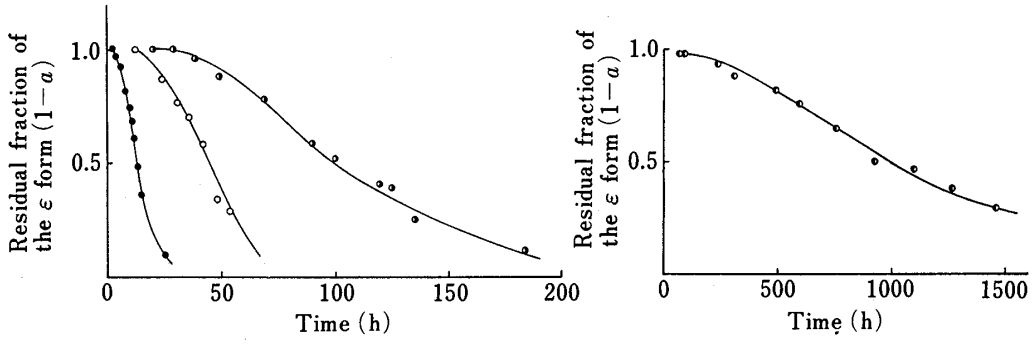


Fig. 10. Residual Fraction of the ε Form during the Isothermal Transformation to the δ Form of Phenylbutazone
●, 40 °C; ○, 35 °C; ◑, 30 °C; ◐, 20 °C.

form decreased with increasing storage time, that is, the ε form was transformed to the δ form on storage at 35 °C, and also at other experimental temperatures. Figure 10 shows the isothermal transformation curves of the ε form to the δ form during storage at 20, 30, 35 and 40 °C. After an induction time of a few hours, the ε form was transformed to the δ form at any storage temperature examined, and the transformation rate was temperature-dependent.

Kinetic analysis of the isothermal transformation of the ε form to the δ form was carried out according to the method of Hancock and Sharp.[9] In this method, the slope (m) based on Eq. 1 is used in order to distinguish the reaction mechanisms.

$$\ln(-\ln(1-a)) = m\ln(t-t_i) + \ln B \quad (a=0.15-0.5) \tag{1}$$

where a is the fraction of transformation, B is a constant and t_i is the induction time. The parameter m can be assigned specific values for various theoretical models of solid-state decomposition. The relationship between the theoretical equations and the value of m has been reported by Hancock and Sharp.[9] Figure 11 shows the plots of $\ln(-\ln(1-a))$ against $\ln(t-t_i)$ at each temperature; the value of m for isothermal transformation of the ε form to the δ form was 1.84 ± 0.26 (mean ± S.D., $n=4$). Therefore the transformation seemed to follow the mechanism of random nucleation and two-dimensional growth of nuclei (Avrami–Erofeev

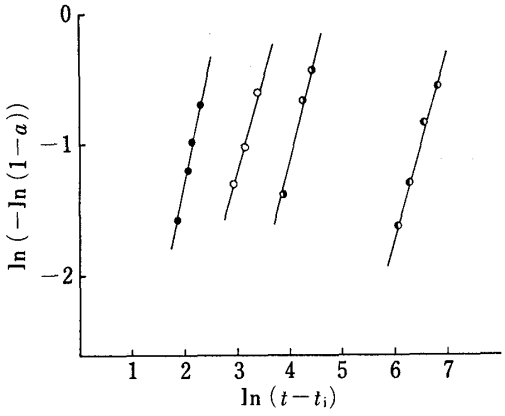


Fig. 11. Plots of $\ln(-\ln(1-a))$ *versus* $\ln(t-t_i)$ for the Isothermal Transformation of the ε Form to the δ Form of Phenylbutazone ($a=0.15$—0.5)

●, 40 °C ($m=2.08$, $r=0.996$); ○, 35 °C ($m=1.50$, $r=0.989$); ◑, 30 °C ($m=2.00$, $r=0.997$); ◐, 20 °C ($m=1.77$, $r=0.997$).

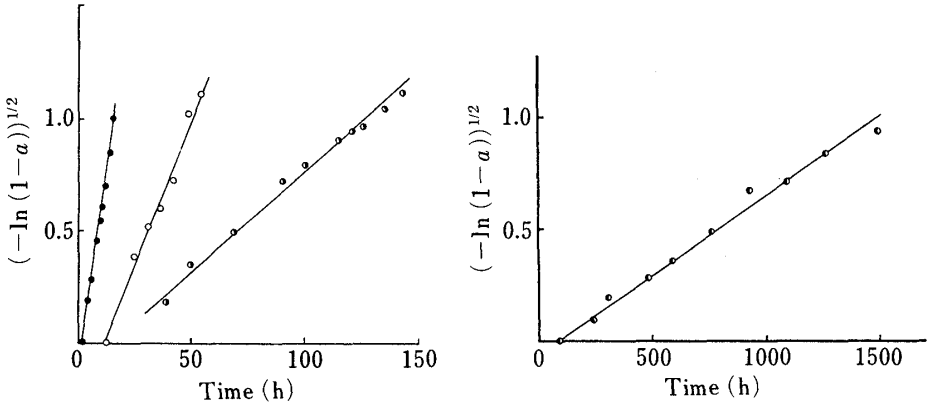


Fig. 12. Plots of $(-\ln(1-a))^{1/2}$ *versus* Time for the Isothermal Transformation of the ε Form to the δ Form of Phenylbutazone

●, 40 °C ($r=0.995$); ○, 35 °C ($r=0.991$); ◑, 30 °C ($r=0.996$); ◐, 20 °C ($r=0.995$).

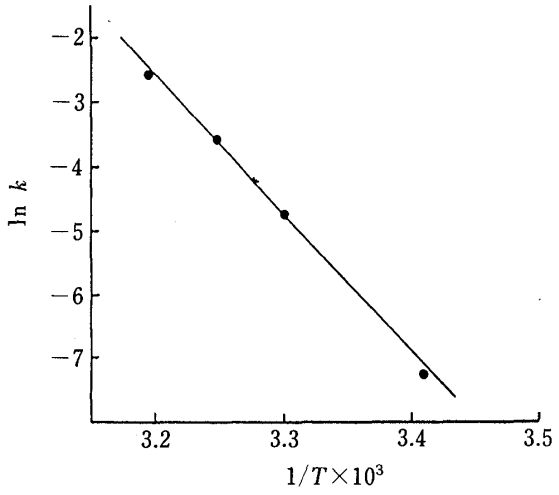
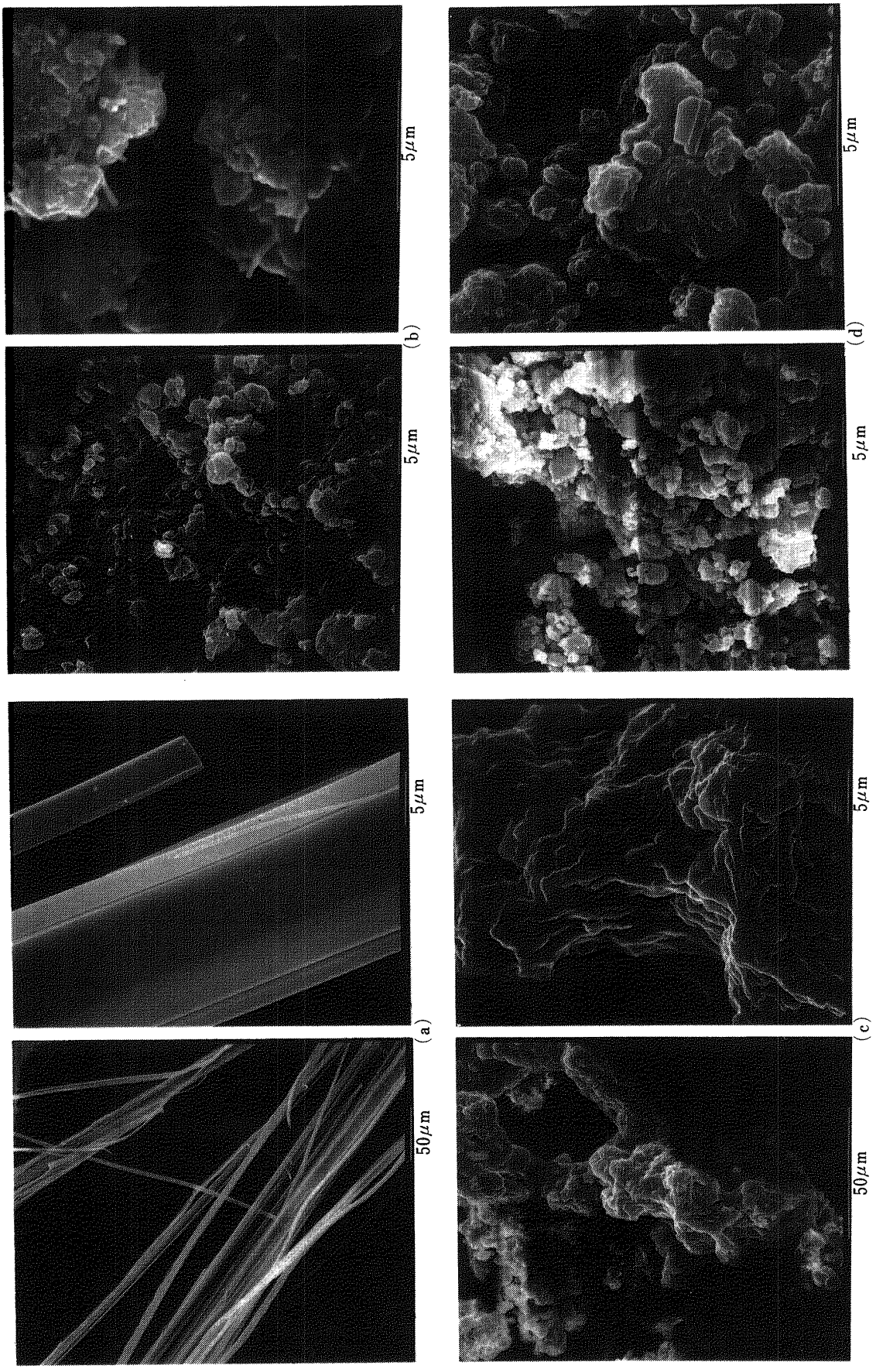


Fig. 13. Arrhenius Plot for the Isothermal Transformation of the ε Form to the δ Form of Phenylbutazone

equation). Furthermore, the plots of $(-\ln(1-a))^{1/2}$ against time at each temperature gave straight lines, as shown in Fig. 12. The apparent transformation rate constants were obtained from the slopes of the straight lines in Fig. 12, and the activation energy for the isothermal transformation of the ε form to the δ form was calculated to be 44.5 kcal/mol from the slope of the Arrhenius plot shown in Fig. 13.

Scanning Electron Microscopic Study

Figure 14 shows scanning electron microphotographs of the δ form during grinding at



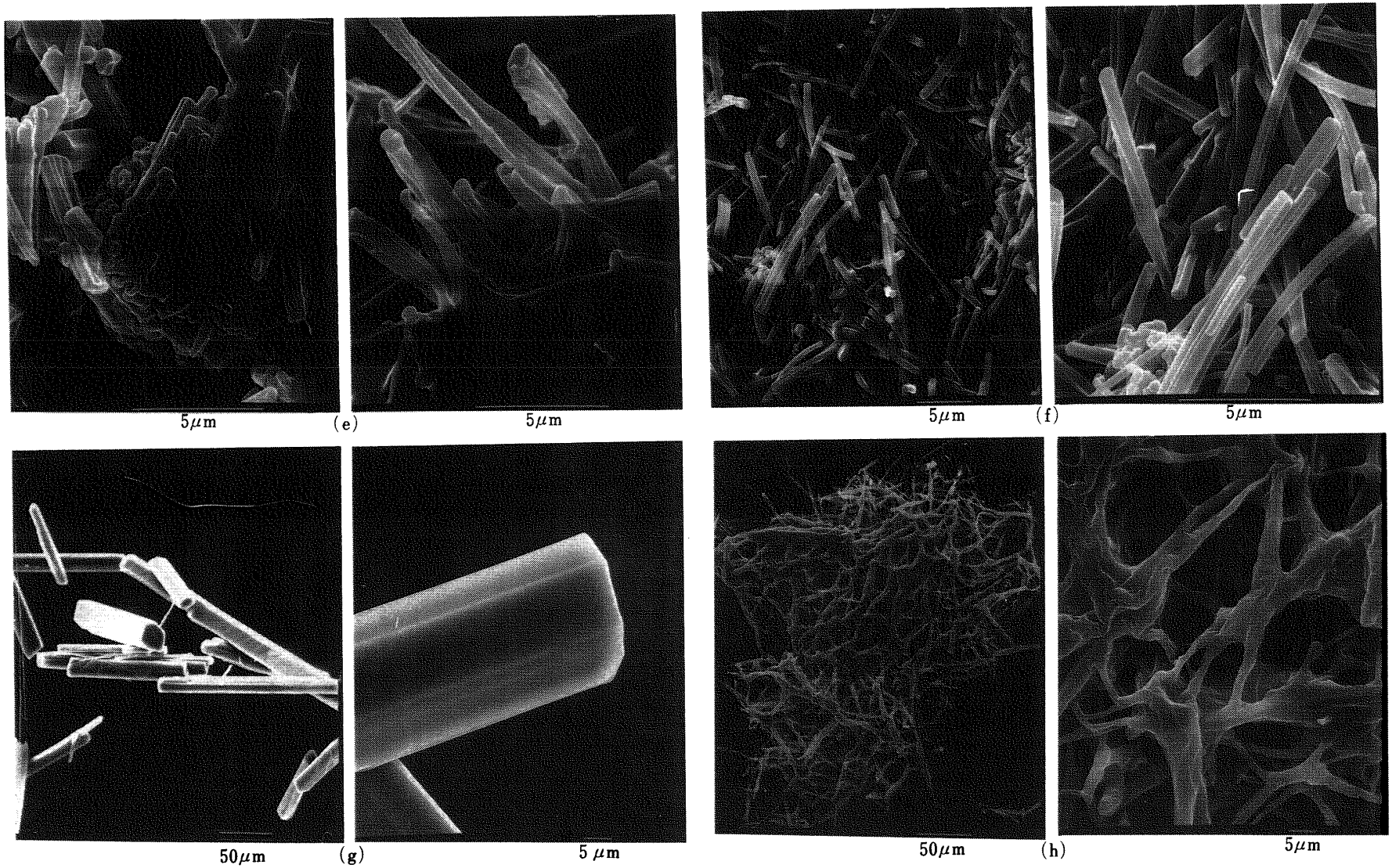


Fig. 14. Scanning Electron Microphotographs of the Change in Crystal Shape of the δ Form during Grinding and Isothermal Transformation of the ε Form to the δ Form on Storage at 35 °C

(a) δ form, (b) δ form after grinding for 2 h at 4 °C, (c) δ form after grinding for 3 h at 4 °C, (d) δ form after grinding for 24 h at 4 °C, (e) ε form under storage for 30 h at 35 °C, (f) ε form under storage for 54 h at 35 °C, (g) α form, (h) β form.

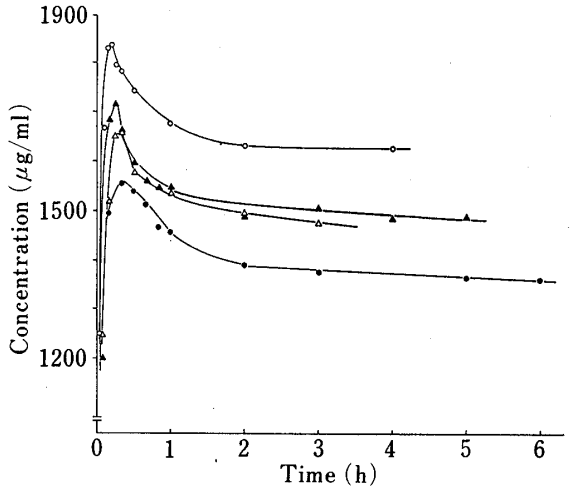


Fig. 15. Dissolution Curves for the ε Form of Phenylbutazone in Buffer Solution at pH 6.8 at Various Temperature

○, 45 °C; ▲, 40 °C; △, 35 °C; ●, 30 °C.

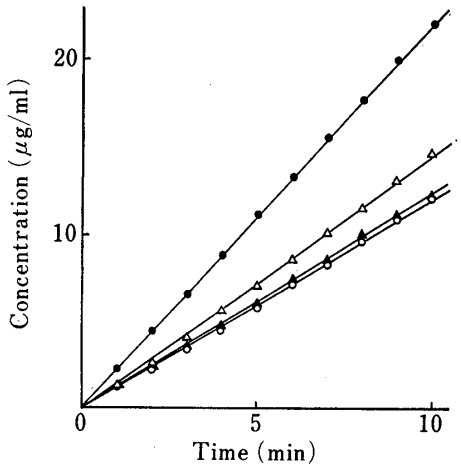


Fig. 16. Initial Dissolution Curves for Phenylbutazone Polymorphs in Buffer Solution at pH 6.8 at 35 °C

○, α form; △, β form; ▲, δ form; ●, ε form.

4 °C and the change in crystal shape during isothermal transformation of the ε form to the δ form on storage at 35 °C. Needle-like crystals of the δ form cohered with the reduction of particle size at the early period during grinding at 4 °C, then changed to imbricate particles which were identified as being of the ζ form from the peaks in the X-ray diffraction pattern and IR spectrum. The particle size of the ε form obtained by grinding the δ form for 24 h at 4 °C was smaller than that of the ζ form.

Figure 14e suggested that nuclei of the δ form randomly developed within ground fine particles, and then grew during storage. On the other hand, the crystal shapes of the α and β forms were columns and networks, as shown in Fig. 14g and 14h, respectively.

Dissolution Properties of the ε Form

Figure 15 shows the dissolution curves of the ε form determined by the dispersed amount method. The concentration of the ε form reached a maximum more quickly than that of the β form, as reported previously,[2] and then decreased gradually at any temperature. It was confirmed by X-ray diffraction analysis that the ε form was transformed to the δ form to a greater or lesser degree after the dissolution experiment. There results indicate that the dissolution rate of the ε form is much larger than those of other polymorphic forms.

Figure 16 shows the initial dissolution curves of the ε form compared with those of other polymorphic forms reported previously,[3] determined by the rotating disk method. A good straight line was obtained in each case, and it was confirmed by X-ray diffraction analysis that transformation of the ε form did not take place during the dissolution experiment. The apparent dissolution rate of the ε form which was calculated from the slope of the line was 1.5 times higher than that of the β form.

Conclusion

In this study, a new polymorphic ζ form was identified as an intermediate product leading to the ε form, the formation of which was dependent on the temperature during grinding. The ε form has superior dissolution properties, but is less stable in the solid state, and further development may be necessary before it can be applied for pharmaceutical purposes.

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