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X-RAY POWDER DIFFRACTION STUDY ON THE GRINDING EFFECT OF THE POLYMORPHS OF A NOVEL AND ORALLY EFFECTIVE URICOSURIC AGENT: FR76505

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ABSTRACT

The polymorphism of a novel and orally effective uricosuric agent, [3-(4-bromo-2-fluorobenzyl)-7-fluoro-2,4-dioxo-1,2,3,4-tetrahydro-quinazolin-1-yl] acetic acid, designated as FR76505, was characterized by X-ray powder diffractometry and thermal analysis. In the crystalline state, FR76505 exists in at least three polymorphic forms, Forms A, B and C. Among them, Form B is a stable form, and Forms A and C which are transformed to Form B are metastable forms. Form C was not stable enough to keep its state even at room temperature. Therefore, it was not suitable to be used for the pharmaceutical preparation, and further investigation for Form C was not carried out. The mechanochemical effect of grinding makes the crystallite size smaller and the lattice strain larger for both the Forms A and B crystals. After grinding for 60 minutes, both forms changed into noncrystalline powders. Thermal behavior of the ground sample was investigated by the X-ray powder diffractometry under the heating condition, as well as the thermal analysis. It is concluded that the mechanochemical effect of grinding made Form A change into Form B easily, and the increase of a grinding time led the transformation temperature lower.

INTRODUCTION

The compound, [3-(4-bromo-2-fluorobenzyl)-7-fluoro-2,4-dioxo-1,2,3,4-tetrahydro-quinazolin-1-yl] acetic acid, designated as FR76505, is a novel and orally effective uricosuric agent. The chemical structure is shown in Fig.1. It has been developed by Fujisawa Pharmaceutical Company as a potentially useful agent against gout and hyperuricacidemia. In the crystalline state, the drug substance exists in at least three polymorphic forms, Forms A, B and C.

Investigating the polymorphic behavior of drugs is important since physicochemical properties and bioavailabilities of crystalline substances in dosage formulations depend very much on their polymorphic forms.[1-6] Among various treatments for preparing suitable dosage forms, grinding is often carried out as a means to reduce the particle size of powders and to mix drugs in the formulation process. However, it

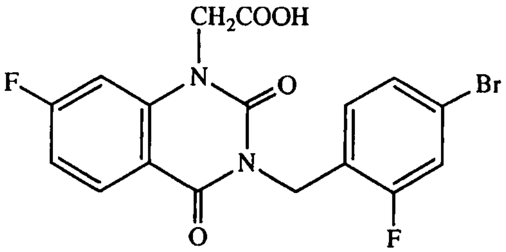

FIGURE 1
Chemical Structure of FR76505

also often induces significant changes in the physicochemical properties of crystalline drugs, such as the conversion to a noncrystalline solid and/or another polymorphic forms.[7-11] Therefore, studying the mechanochemical effect of grinding on the polymorphs is of great value for the proper treatment of drug substances.

This paper deals with the properties of the FR76505 polymorphs by means of X-ray diffractometry and thermal analysis. Thermal behavior, as well as the mechanochemical effects of grinding, on the crystal states of FR76505 polymorphs are studied.

EXPERIMENTAL

Materials

Powdered crystals of Form A of FR76505, which were crystallized from an isopropanol-water(2:1) solution of crude FR76505, were provided from the Technological Development Labs. of Fujisawa Pharmaceutical Company. Another two polymorphic forms, Forms B and C were crystallized from an acetone-water(2:1) and ethanol-water(2:1) solution of Form A, respectively.

X-Ray Powder Diffractometry

X-ray powder diffraction patterns at room temperature were measured with a Philips MPD-1880 X-ray diffraction system with graphite-monochromated Cu-Kα radiation(λ=1.5418Å). The instrument was set as follows: voltage; 40 kV, current; 30 mA, divergence slit; 1°, receiving slit; 0.2 mm, scatter slit; 1°, scanning speed; 0.1°/s, sampling time; 0.2 s, and range of diffraction angle; 2θ=2.5-32.5° with a continuous scan method.

X-ray powder diffraction at high temperature was carried out using the Philips MPD-1880 system with an Anton Paar TTK temperature attachment and controller. The measurement conditions were the same as those at room temperature except for current of 50 mA and range of diffraction angle of 2θ=10-25°.

Determination of Crystallite Size and Lattice Strain

Crystallite size and lattice strain were determined by means of Approximate Size/Strain Analysis Method in the Line Profile Analysis(LPA) program, which is a technique to extract information on the micro-structure (imperfectness of the structure) of crystalline materials from the shape of X-ray diffraction line profiles.[12-14] LPA program was commercially provided as an APD-1700 software package from Philips Analytical(The Netherlands).

X-ray diffraction profile to be analyzed was at 2θ=12.8° of Form A. Those at 2θ=14.8° and 15.4° of Form B were partially overlapping, thus they were separated by means of Profile Fit program in an APD-1700 software package beforehand. A reflection at 2θ=21.4° from (1 0 0) plane of LaB_6 which is a Standard

standard for LPA. The X-ray diffraction system was set so as to obtain more than 10000 counts net on the peak maxima for each peak as follows, Form A: voltage; 40 kV, current; 15 mA, receiving slit; 0.1 mm, step size; 0.005°, sampling time; 1 s and scanning rang of 2θ=11.600°-14.000°. Form B: voltage; 40 kV, current; 50 mA, receiving slit; 0.1 mm, step size; 0.005°, sampling time; 3 s and scanning rang of 2θ=13.800°-16.400°. LaB_6: voltage; 40 kV, current; 50 mA, receiving slit; 0.1 mm, step size; 0.005°, sampling time; 4 s and scanning range of 2θ=20.250°-22.250°. The profiles were measured with a step scan method.

Thermal Analysis

Differential scanning calorimetry(DSC), thermogravimetry(TG) and differential thermal analysis(DTA) were performed by using a Seiko DSC 200 differential scanning calorimeter and TG/DTA 200 thermogravimetric and differential thermal analyzer, respectively, with a SSC 5030 disk station(Seiko Instruments Inc.). Samples of ca. 5 mg were weighted for TG/DTA studies and were analyzed at a heating rate of 10°C/min in opened aluminum pans. The DSC studies were carried out by heating ca. 5 mg of the samples at a heating rate of 10°C/min in closed aluminum pans after calibration with a pure standard sample of indium(99.999%). During the thermal analysis, nitrogen was used as a purge gas at a flow rate of 30 ml/min.

RESULTS AND DISCUSSION

X-Ray Powder Diffractometry

X-ray powder diffraction patterns of Forms A, B and C of FR76505 are shown in Fig.2. The X-ray

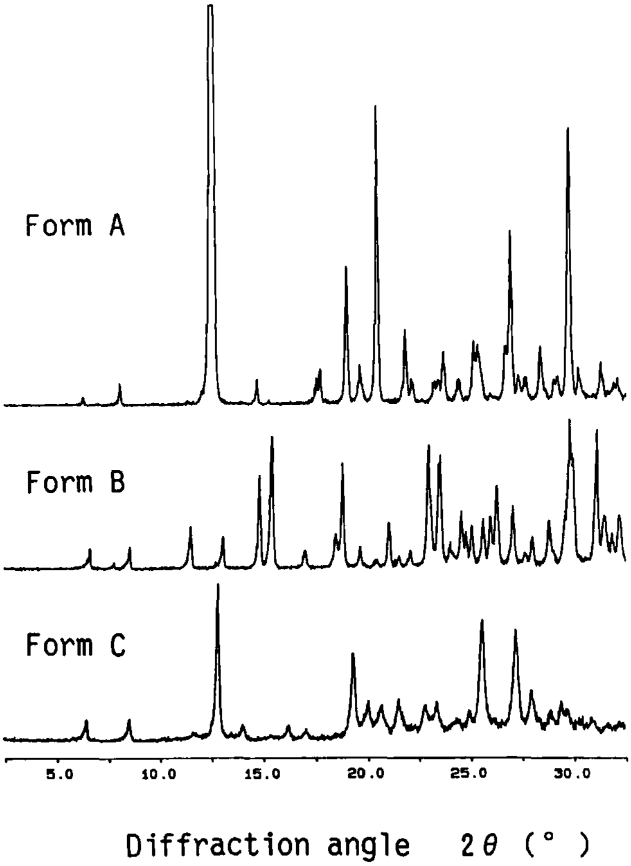

FIGURE 2
X-Ray Powder Diffraction Patterns of the Polymorphs of FR76505

diffraction profiles were sufficiently distinct to characterize each crystal form as Form A shows a specific peak at 2θ=12.8°, Form B at 2θ=14.8° and 15.4° and Form C at 2θ=12.9° and 19.4°.

Thermal Analysis

The TG/DTA curves of Forms A, B and C of FR76505 are shown in Fig.3. Form B showed only an endothermic peak at 214°C due to fusion. Form A showed a small

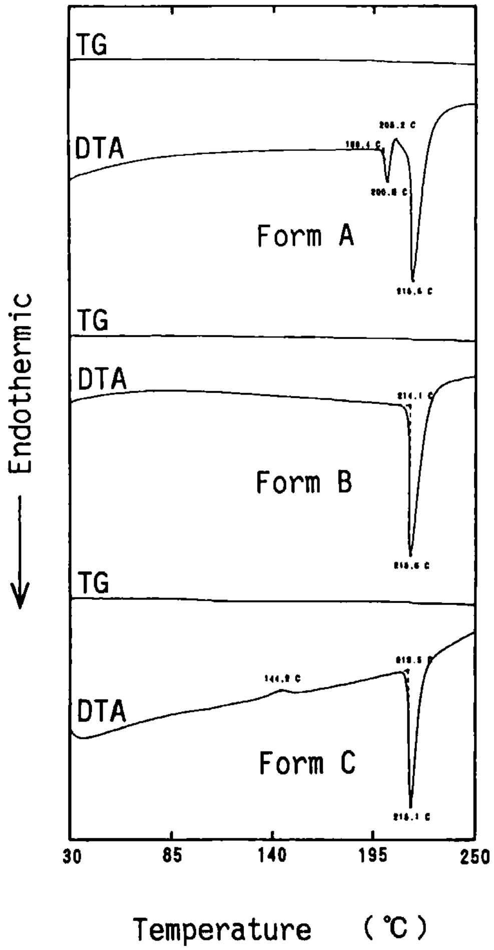

FIGURE 3
TG/DTA Curves of the Polymorphs of FR76505

endothermic peak followed by a small exothermic one between 198°C and 214°C, and then a large endothermic peak was observed at 214°C. The endo- and exothermic peaks between 198°C and 214°C are attributable to a thermal phase transformation from Form A into Form B, which is confirmed by the X-ray powder diffractometry under the heating condition described in the later section (see Fig.6-a). Form C exhibited a small exothermic peak with the peak top of 144°C, which may be ascribed to a transformation from Form C into Form B, following an endothermic peak due to fusion of Form B at 214°C. The result of the thermal analysis suggests that Form B is a stable form, and Forms A and C which are transformed to Form B are metastable forms.

Since the Form B crystal appeared in the Form C sample under ambient storage condition for several days, Form C was not stable enough to keep its state even at room temperature. Therefore, it was considered that Form C was not suitable to be used for the pharmaceutical preparation, and further investigation for Form C was not carried out.

Mechanochemical Effect of Grinding for Forms A and B

The changes in the X-ray powder diffraction patterns of Forms A and B during grinding in a ball mill are shown in Fig.4. The peak intensities of both the forms decreased with increasing a grinding time; the profile broadened after 5 min of grinding and only a halo pattern appeared after 3 hrs of grinding, indicating that both the Forms A and B crystal powders change into noncrystalline ones.

Crystallite Size and Lattice Strain

Line profile Analysis(LPA) was performed in order to estimate a grinding effect on the crystal lattice of FR76505 polymorphs, Forms A and B. X-ray diffraction profiles of test samples and standard materials were measured every three times. Crystallite size and lattice strain were determined for every measurement of test sample against every measurement of standard, and then averaged. The determined crystallite size and lattice strain of the ground samples of Forms A and B are graphed out as Fig.5.

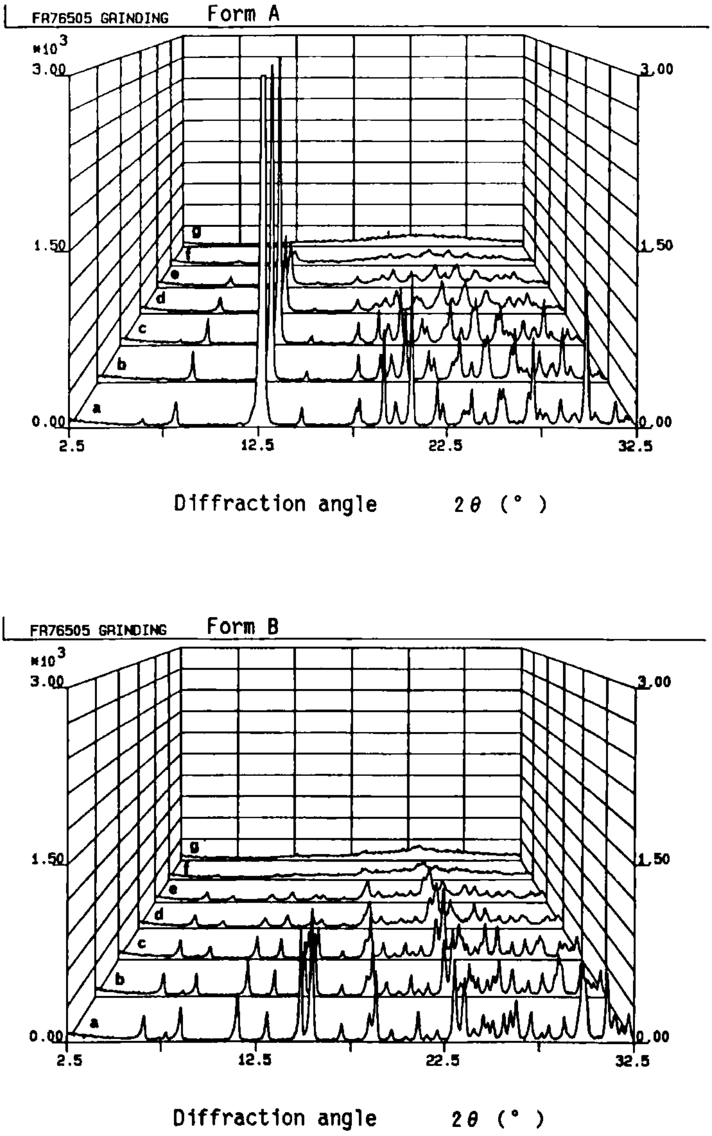

FIGURE 4

Effect of Grinding on X-Ray Powder Diffraction Patterns of Forms A and B: (a)Intact Sample, Grinding with a Ball Mill for (b)0.5 min, (c)1 min, (d)5 min, (e)10 min, (f)1 hr, and (g)3 hrs, respectively

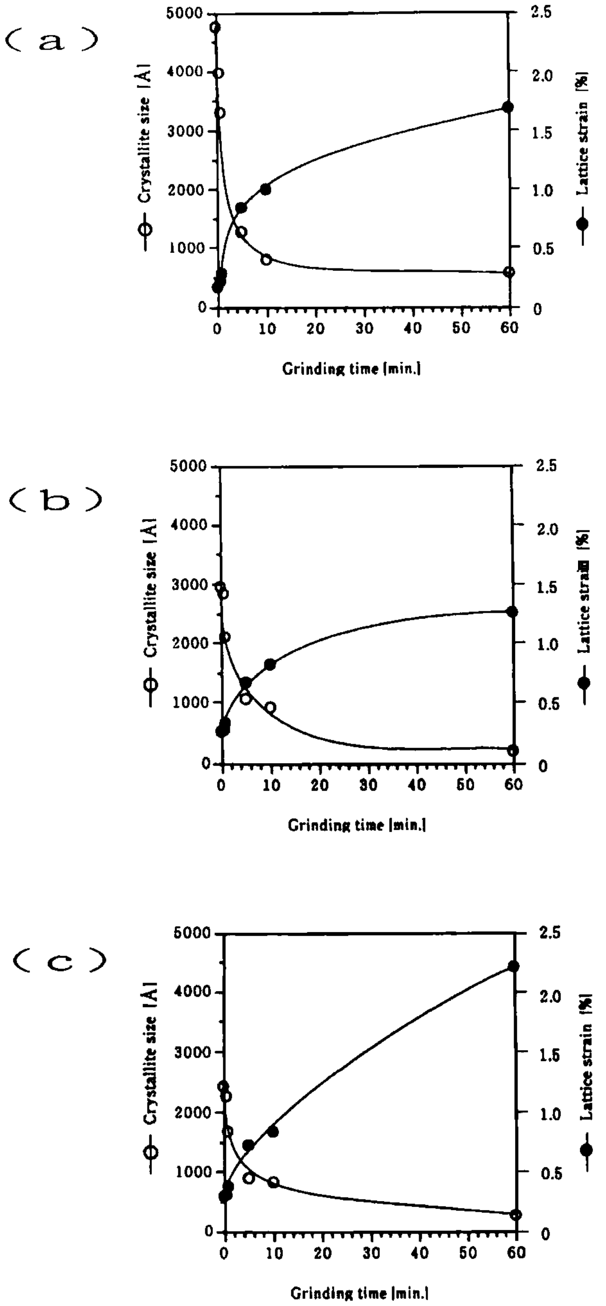

FIGURE 5

Effect of Grinding on the Crystallite Sizes and Lattice Strains Determined with the Profiles at (a) 2θ=12.8° of Form A, (b) 2θ=14.8° and (c) 2θ=15.4° of Form B

The crystallite sizes of both the forms became smaller with the passage of grinding time. Especially, in initial some minutes of grinding, they rapidly decreased. The lattice strains of both the forms increased as grinding time.

Generally a line profile to be analyzed is required not to be overlapping with other peaks. In the case of organic compound like FR76505, only a few peaks in the lower area of Bragg's angle can be used for LPA, because most of peaks of organic compound with larger cell-dimension and lower symmetry are made up of multiple diffractions. A standard material appropriate to LPA should not show finite crystallite size and/or lattice distortion effect, and a standard profile must be set up close to one to be analyzed. LaB_6 provided from NIST is suitable as a standard material of LPA because of the higher physical quality. But it exhibits no peak in the lower area of Bragg's angle. Even the lowest reflection from (1 0 0) plane appears at $2\theta=21.4°$, which is a quite distant to the profiles of FR76505 possible to be used for LPA. Accordingly it is thought that the crystallite sizes and lattice strains determined in this study are not absolute. However, these values may be useful, as far as they are used to be discussed on a series of changes of physical property by grinding effects on the sample. Actually the crystallite sizes and lattice strains within each crystal form indicated the correlation to increasing a grinding time, respectively, as shown in Fig.5. This phenomenon was qualitatively confirmed by the X-ray powder diffractometry for the each crystal form(Fig.4).

Thermal Behavior of the Ground Samples of Form A

X-ray powder diffraction patterns of Form A and its ground samples under the heating condition are

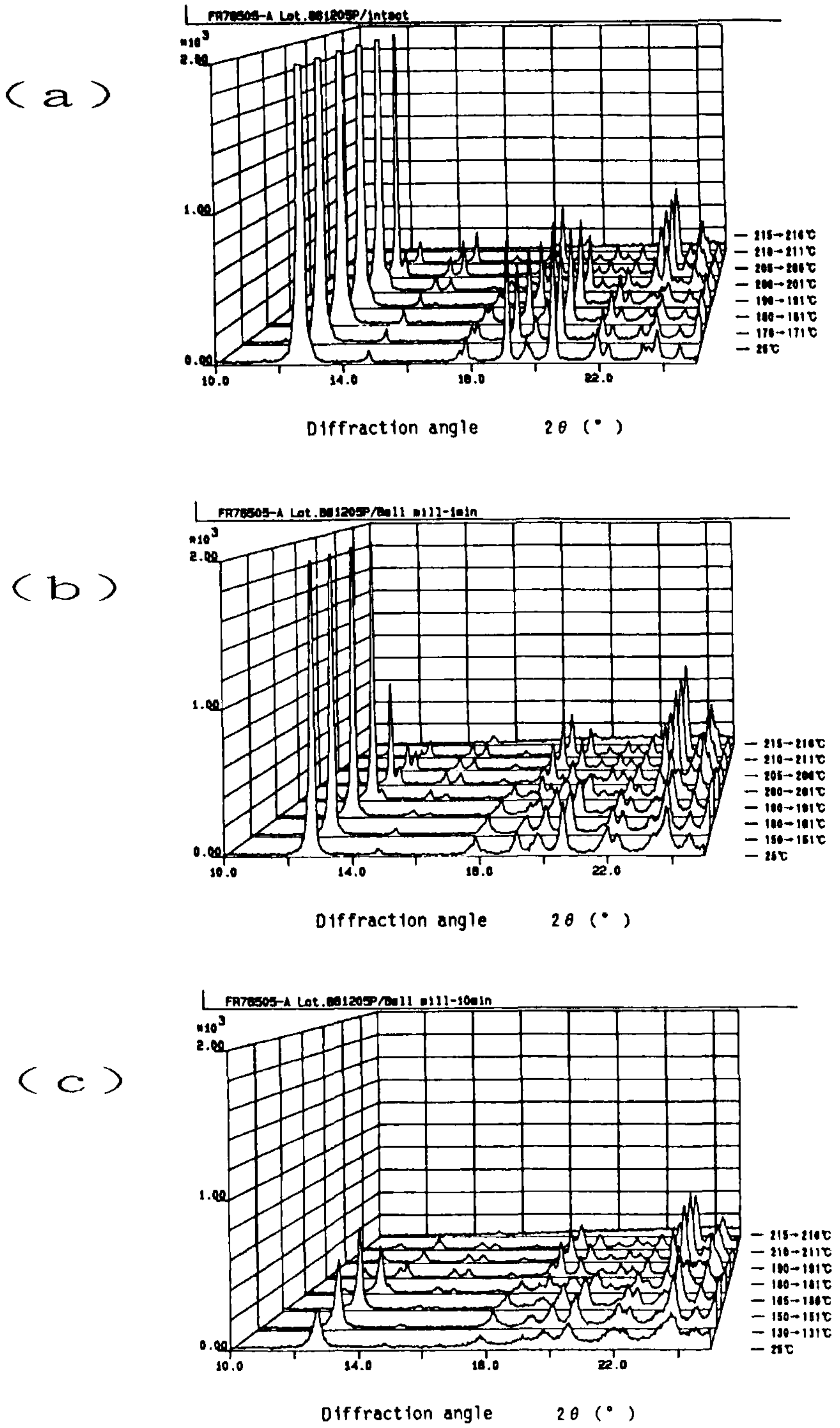

FIGURE 6

The Change of X-Ray Powder Diffraction Patterns when Heating: (a)Intact Sample, Ground Samples of Form A for (b)1 min and (c)10 min

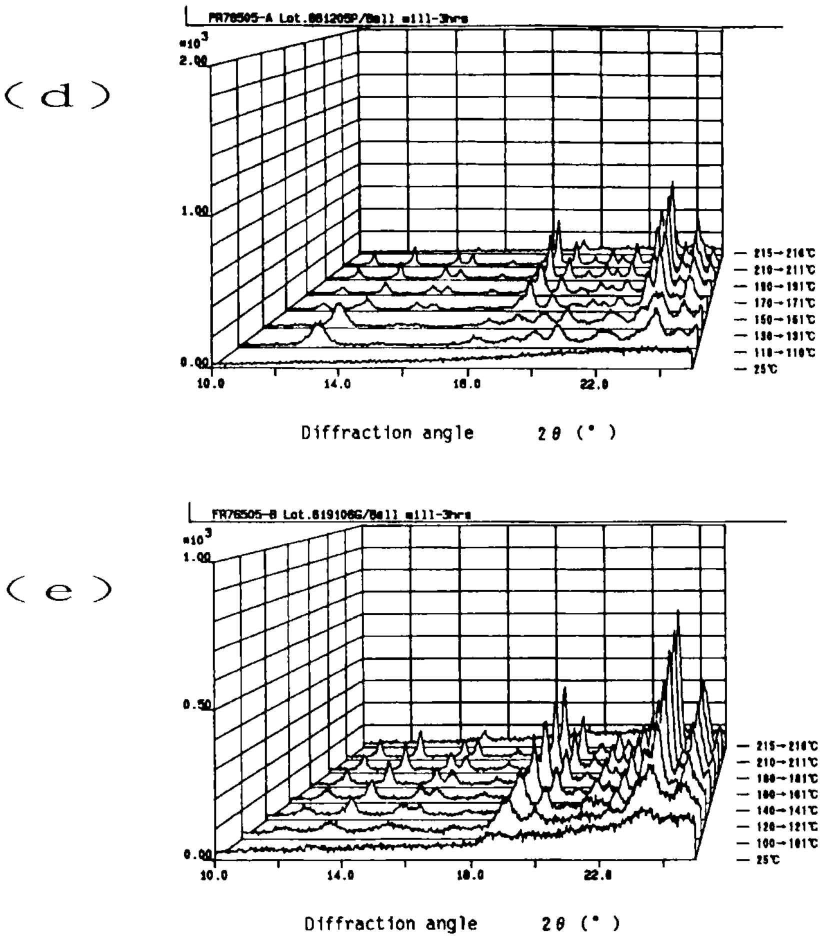

FIGURE 6 (Continued)

The Change of X-Ray Powder Diffraction Patterns when Heating: Ground Samples of (d)Form A and (e)Form B for 3 hrs

shown in Fig.6. That of noncrystalline solid prepared by grinding Form B for 3 hrs is also contained in Fig.6.

The sample for X-ray powder diffraction was heated at a rate of 10°C/min to the temperature at which the transformation is expected to start for each sample, and then, at a heating rate of 0.5°C/min until fusion.

In the heating process, diffraction peaks due to the Form B crystal appeared and successively increased with the raise of temperature, and then the diffraction pattern changed into that of Form B. Lastly, all the diffraction peaks of every sample disappeared at 215°C due to fusion of Form B. For example, for the untreated crystal powder of Form A, an intact one, the characteristic peaks of Form B at $2\theta=14.9°$ and 15.5° appeared at 190°C even though most of the diffraction peaks were due to Form A, and then the diffraction pattern changed into that of Form B at 210°C (Fig.6-a). In the case of the grinding time of 1 min, the transformation into Form B started at ca.180°C and almost ended at ca.205°C (Fig.6-b). In the case of 10 min grinding, the peaks became sharp during the initial heating process up to ca.150°C, indicating a recovery of the crystallinity of Form A. In the following heating process, the peaks of Form B were recognized at ca.150°C and increased, and then the pattern almost changed into that of Form B at 190°C (Fig.6-c). Noncrystalline solid prepared by grinding Form A for 3 hrs also showed the recovery of the crystallinity of Form A up to ca.130°C. The peaks of Form B were appeared at ca.130°C and then the crystal form almost changed into Form B at ca.150°C followed by the betterment of the crystallinity of Form B until its fusion at 215°C (Fig.6-d). The fact that the metastable Form A crystal was formed from the noncrystalline solid in the initial heating process may be interpreted as follows: the noncrystalline solid from Form A contained a very small amount of the seed crystals of Form A, and the seed must play an important part in recovering its crystallinity.

On the other hand, noncrystalline solid prepared by grinding Form B for 3 hrs showed the recovery of the

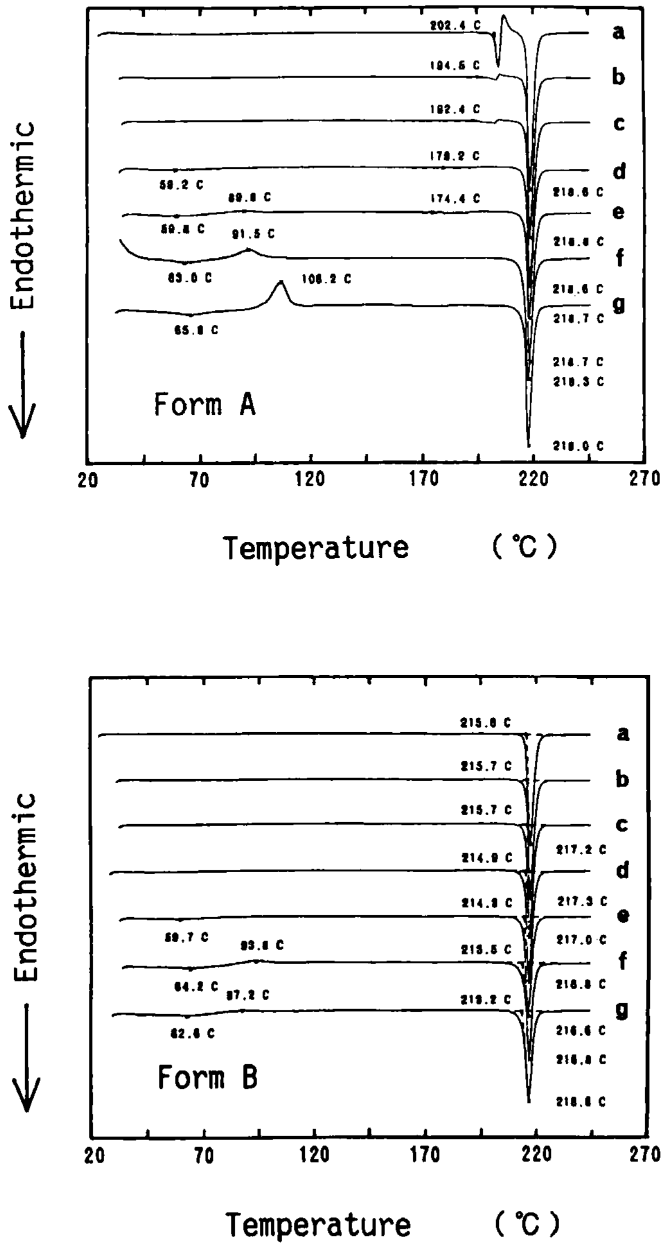

FIGURE 7

Effect of Grinding on DSC Curves of Forms A and B: (a)Intact Sample, Grinding with a Ball Mill for (b)0.5 min, (c)1 min, (d)5 min, (e)10 min, (f)1 hr, and (g)3 hrs, respectively crystallinity of Form B before the melting point (Fig.6-e).

The DSC curves of the ground samples of Form A are shown in Fig.7. The small endo- and exothermic peaks due to the transformation from Form A to Form B between 198°C and 214°C decreased with broadening and shifted to a lower temperature according to a longer grinding time. They disappeared from the DSC curves for more than 1 hr of grinding, because most part of the sample must remain as noncrystalline solid. Moreover, after 10 min of grinding, there appeared a new small-broadened endothermic peak around 60°C followed by a small-broadened exothermic one. They became clearer and shifted to a higher temperature according to a longer grinding time. This thermic phenomenon can be interpreted by comparison with the X-ray diffraction studies under the heating condition(Fig.6); that is, the small-broadened endo- and exothermic peaks are due to a recovery of the crystallinity for Form A suffered the mechanochemical stress of grinding. The sample with a lower crystallinity requires a higher temperature for a recovery of the Form A crystal.

In the case of Form B, the untreated crystal powder, an intact Form B, showed only an endothermic peak due to fusion. This peak became broadening according to the larger mechanochemical stress of grinding. A new small-broadened endo- and exothermic peaks appeared around 60°C-94°C. It is also proved by the X-ray diffraction studies under the heating condition that these peaks are due to a recovery of the crystallinity of Form B received the larger mechanochemical effect of grinding, however, the recovery of the Form B crystal was imperfect within the time scale of the thermal analysis.

Consequently, it is concluded that the mechanochemical effect of grinding made Form A change into Form B easily, and the increase of grinding time led the transformation temperature lower.

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