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# Solid phase transition of CS-891 enantiotropes during grinding

Shuichi Yada [a,b,*], Masaoki Ohya [a], Yuko Ohuchi [a], Takeshi Hamaura [a], Naoki Wakiyama [a], Fusao Usui [a], Akira Kusai [a], Keiji Yamamoto [b]

[a] *Product Development Laboratories, Sankyo Co., Ltd., 1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140-8710, Japan*
[b] *Graduate School of Pharmaceutical Sciences, Chiba University, 1-33 Yayoi-cho Inage-ku, Chiba 263-8522, Japan*

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## Abstract

The physical properties of *N*-[1-(4-methoxyphenyl)-1-methylethyl]-3-oxo-4-aza-5a-androst-1-ene-17β-carboxamide (CS-891), a novel and orally effective testosterone 5-reductase inhibitor, were investigated by differential scanning calorimetry, powder X-ray diffraction at elevated temperature and single crystal X-ray crystallography. CS-891 was revealed to exist as two enantiotropic forms, a low-temperature stable form (Form A) and a high-temperature stable form (Form B) which reversibly transforms to Form A at around 58 °C. The effect of grinding temperature on the transition of CS-891 between the amorphous and the crystalline state during grinding of the eantiotropes was examined. Form A transformed into an amorphous form during the grinding process while the product temperature was kept below the transition temperature. On the other hand, when the product temperature during grinding reached above the transition temperature, Form A transformed into an amorphous form and some of the amorphous form converted back to Form B. Form B crystallized from the amorphous form was physically stable even at below the transition temperature. The amorphous form in equilibrium with Form B exhibited remarkable physical stability in comparison with the amorphous form obtained by continued grinding below the transition temperature.

*Keywords:* Enantiotropic form; Transformation; Grinding; Amorphous; Crystallization

## 1. Introduction

Some drug substances have polymorphs. The transformation process of one polymorph into another is referred to as phase transition, and this occurs during processing or storage. Investigating mechanism of the phase transition of drug substance is important in the manufacturing process of drug product since the dissolution and stability of the drug product depend on the polymorph. When the phase transition is reversible, the two polymorphs are called enantiotropes and the energy of transition by heating is endothermic (Raghavan et al., 1993; Wang et al., 2002; van Hoof et al., 2002). When the phase transition is irreversible, the two polymorphs are called monotropes; only one form is stable irrespective of the temperature, and the transformation of the metastable form to the stable form is exothermic (Koda et al., 2000; Burger and Lettenbichler, 2000).

The dissolution rate of many poorly water-soluble drug limits their bioavailability via absorption into the gastrointestinal tract. The conversion of a poorly water-soluble crystalline drug into an amorphous state by grinding would be one approach for improving the solubility and bioavailability of a solid dosage form (Sugimoto et al., 1998; Yoshihashi et al., 2000).

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[*] Corresponding author. Tel.: +81-3-3492-3131; fax: +81-3-5436-8568.
*E-mail address:* syyada@shina.sankyo.co.jp (S. Yada).

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Regarding the grinding of polymorphs, heat evolved during the grinding process will affect the extent of some polymorphic transitions and the amount of the amorphous form. The milling of polymorphs is referred to as prolonged grinding or ball-milling, whereby unusual thermodynamic stress is imparted on the material (Mura et al., 2002; Miyake et al., 1994; Otsuka et al., 1994; Bartolomei et al., 1999). With respect to the grinding of monotropes, Otsuka et al. (1994) reported that the transformation pathway during grinding and the presence of a metastable crystalline form governed the stability of the noncrystalline form. The metastable α-form and stable γ-form of indomethacine are interconvertible and the amorphous form can be produced during milling at 4 °C. However at 30 °C, the γ-form is irreversibly converted to the α-form. On the other hand, little is known about phase transition of enantiotropes during grinding and the physical stability of the ground sample in the literature. Although Bartolomei et al. (1999) reported that the stability of Form I (a high-temperature stable form) and Form II (a low-temperature stable form) of propranolol hydrochloride significantly depends on the grinding conditions, their experiments were focused on differences between a mild and vigorous grinding force. Little is reported on the grinding temperature that affect the phase transition of enantiotropes during grinding.

CS-891, *N*-[1-(4-methoxyphenyl)-1-methylethyl]-3-oxo-4-aza-5a-androst-1-ene-17β-carboxamide, is a novel and orally effective testosterone 5-reductase inhibitor. The chemical structure, as shown in Fig. 1, is analogous to the aza-steroid finasteride which exists as two enantiotropes (Wenslow et al., 2000). As CS-891 is practically insoluble in water (<1 μ/ml), its bioavailability is very low. The CS-891 amorphous form obtained by grinding using a vibrational mill would be a possible approach to improve the solubility and bioavailability. However, since CS-891 is found to exist as two enantiotropes by powder and single crystal X-ray crystallography as well as thermal analysis, it is necessary to control the grinding conditions, especially grinding temperature.

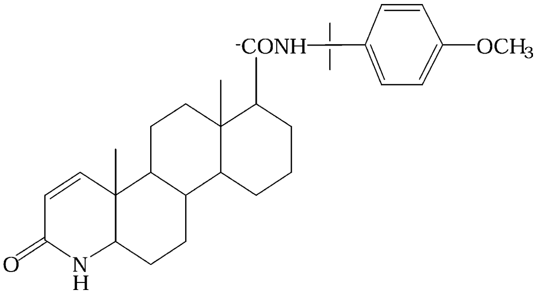

Fig. 1. Chemical structure of CS-891.

In the present study, the effect of grinding temperature on the transformation and crystalline state during the grinding of CS-891 is examined. In addition, various thermal hysteresis and physical stability of a ground sample prepared with a vibrational mill are reported.

## 2. Materials and method

### 2.1. Materials

CS-891 was provided by the Process Development Laboratories, Sankyo Co., Ltd. The assayed purity value of CS-891 (Lot No. KM203) used in this study was 97.8%.

### 2.2. Preparation of ground CS-891

CS-891 of 150 g was ground using a vibrational mill (Fine vibration mill MB-1, Chuokakohki Co., Ltd.) equipped with 11 zirconia rods and a zirconia cell for 15–480 min without temperature control or for 5–240 min with temperature control using a cell-jacket. Water of 10, 50, or 70 °C was circulated through the cell-jacket to maintain a constant grinding temperature. At a specified time, after the product temperature of the CS-891 ground sample was measured with an infrared thermometer (IT2-02, Keyence corporation), the ground sample was withdrawn from the zirconia cell and passed through a 50-mesh screen.

### 2.3. Method

#### 2.3.1. Thermal analysis

Differential scanning calorimetry (DSC) was carried out with a differential scanning calorimeter (Thermo Plus DSC8230L, Rigaku Co.). The samples were placed (5–10 mg) on an open sample pan and scanned at a rate of 2 or 5 °C/min from 30 to 300 °C under a flow of nitrogen gas.

Thermogravimetric (TG) analysis was performed with a TG and differential thermal analyzer (Thermo Plus TG8120, Rigaku Co.). The samples were placed (10 mg) on an open sample pan and scanned at a rate of 5 °C/min from 30 to 300 °C under a flow of nitrogen gas.

### 2.3.2. *Powder X-ray diffraction*

Powder X-ray diffraction patterns were obtained using an X-ray diffractometer (Geiger Flex Rint-2200, Rigaku Co.) with Cu K$\alpha$ radiation at 40 kV/40 mA. The samples were step-scanned with a 0.01° interval from 5.00 to 40.00° ($2\theta$) at a rate of 1°/min.

Powder X-ray diffraction patterns at elevated temperatures were obtained under the same conditions as indicated above but with a temperature control device. During the experiments, samples were heated at a rate of 5 °C/min to a desired temperature which was maintained for a certain period of time. Then, the samples were either heated or cooled to the next temperature for analysis. The samples were step-scanned with a 0.01° interval from 5.00 to 40.00° ($2\theta$) at a rate of 1°/min.

In this study, the powder X-ray diffraction pattern was divided in such a way as to consider the triangular areas formed solely by the peaks (derived from the crystalline phase) from the lower common base area (derived from the amorphous form) to calculate apparent crystallinity. Using a computer program, the respective peak and base areas were calculated for the intact CS-891 form (Form A). The ratio of the peak area over that of the entire area (peaks and base) was to determine the apparent crystallinity and this value for Form A was taken to be 100%. That of the amorphous form prepared from an ethanol solution of CS-891 by spray-drying was taken to represent 0%. Since Form B can only be obtained by heating the Form A, the apparent crystallinity was taken to be 100% as based on the powder X-ray diffraction pattern obtained at 25 and 62 °C. Apparent crystallinity of Form B was determined when the X-ray diffraction peak at $2\theta$ was 16.1°.

### 2.3.3. *Single crystal X-ray diffraction*

A colorless crystal with approximate dimensions of 0.5 mm × 0.3 mm × 0.2 mm obtained by recrystallization from the ethyl acetate solution was used for X-ray analysis. The cell parameters were determined from least-squares refinement where 25 reflections were measured in the range of $58.1^\circ < 2\theta < 59.9^\circ$ at 25 °C, $45.1^\circ < 2\theta < 48.9^\circ$ at 62 °C, and $57.9^\circ < 2\theta < 60.0^\circ$ when cooled back to 25 °C on an automatic diffractometer (AFC-7, Rigaku Corporation) using a graphite monochromated Cu K$\alpha$ radiation ($\lambda = 1.5418$ Å) generated from a rotating anode. The intensity data were collected with a reciprocal lattice of $0 < h < 14$, $0 < k < 23$ and $-14 < l < 0$ up to $2\theta = 120.2^\circ$ at 25 °C; $0 < h < 14$, $0 < k < 24$ and $0 < l < 14$ up to $2\theta = 120.1$ at 62 °C; and $0 < h < 14$, $0 < k < 23$ and $-14 < l < 0$ up to $2\theta = 120.2^\circ$ when cooled back to 25 °C. The $\omega$-$2\theta$ scanning mode was used with a scan speed of 16°/min in $\omega$ and a scan width of $\Delta\omega = (1.84 + 0.30 \tan\theta)^\circ$. The background was measured on each side of the scan for 1.72 s, whereby 1788 reflections at 25 °C, 2224 reflections at 62 °C and 1794 reflections when cooled back to 25 °C were scanned five times depending on the intensity. The structure was solved by a direct method with the program SAPI91 (Fan, 1991) at 25 °C, the program SIR92 (Altmomare et al., 1994) at 62 °C and the program MITHRIL84 (Gilmore, 1984) when cooled back to 25 °C. The nonhydrogen atoms were refined anisotropically. Hydrogen atoms were included isotropically but not refined.

## 2.4. *Stability test*

Samples of CS-891 intact and CS-891 ground were placed on the provided powder X-ray diffraction sample holder and stored under 75% RH at 40 °C. After the storage for definite periods, the samples were subjected for powder X-ray diffraction and DSC measurements.

# 3. Results and discussion

## 3.1. *Characterization of CS-891 enantiotropes*

### 3.1.1. *Thermoanalytical properties of CS-891*

During grinding, as CS-891 was affected by not only the mechanical force but also the temperature, the thermal properties of CS-891 were investigated. As shown in Fig. 2, the DSC curve of CS-891 exhibits a small endothermic peak at 58 °C and a melting endothermic peak at 248 °C. As the TG curve of CS-891

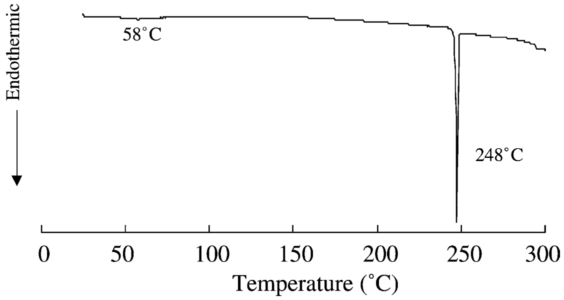

Fig. 2. DSC curve of CS-891 (heating rate 2 °C/min).

did not show any weight loss until melting (data not shown), the small endothermic peak at 58 °C was not attributed to desolvation or degradation. Therefore, the small endotherm on the DSC curve of CS-891 was due to the polymorph transformation from CS-891 to another crystal form. In order to determine the thermal behavior that led to the small endothermic peak at 58 °C, the sample was cooled down (first cooling) to 30 °C after the first heating from room temperature to 100 °C. Then, the second heating to 100 °C was conducted (Fig. 3). An endothermic peak at 58 °C was observed after both the first heating and the second heating, and an exothermic peak at 57 °C was observed after the first cooling. The small endothermic peak at 58 °C was presumed to represent a reversible CS-891 molecular re-arrangement in the crystals. The endotherm with an onset temperature ($T_{\mathrm{ons}}$) of 56.9 °C was observed upon the first heating and the exotherm with $T_{\mathrm{ons}}$ of 57.3 °C was observed upon the first cooling. The difference between the heating and cooling

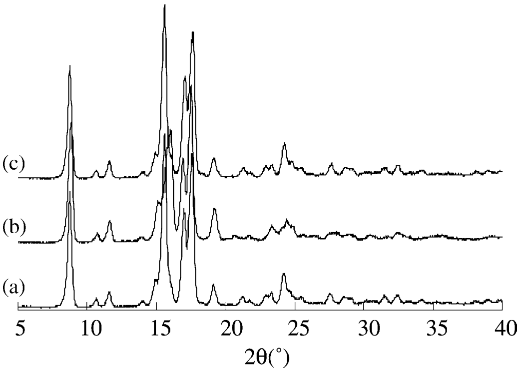

Fig. 4. Change in powder X-ray diffraction patterns of CS-891 at different temperatures: (a) 25 °C, (b) 62 °C, and (c) after cooling back to 25 °C.

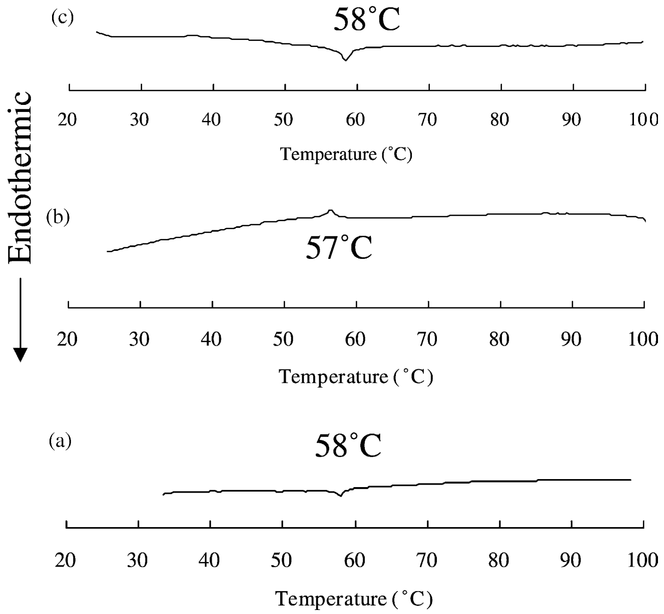

Fig. 3. DSC curves of CS-891: (a) first heating run (heating rate: 2 °C/min), (b) first cooling run (cooling rate: 2 °C/min), (c) second heating run (heating rate: 2 °C/min).

$T_{\mathrm{ons}}$ was attributed to hysteresis, commonly observed in solid phase transformations (Dunitz and Bernstein, 1995). The obtained crystal form was transformed to CS-891 readily upon the first cooling, suggesting a low activation energy barrier between two forms.

#### *3.1.2. Powder X-ray diffraction analysis at different temperature*

The temperature cycling experiment by DSC, as shown in Fig. 3, suggested that CS-891 was reversibly transformed to the other crystal form. In order to confirm the reversible transformation at 58 °C, the powder X-ray diffraction of intact CS-891 at below and above the thermal transition point (around 58 °C) was conducted. The powder X-ray diffraction patterns of CS-891 at 25 and 62 °C, and at 25 °C after the first cooling are shown in Fig. 4. As an endotherm with an offset temperature at 60 °C was observed upon the first heating, we considered that CS-891 transformed to the other form at 62 °C. Characteristic X-ray diffraction peaks were observed at $2\theta = 15.6^{\circ}$ at 25 °C and at $2\theta = 16.1^{\circ}$ at 62 °C. The X-ray diffraction pattern of CS-891 at 25 °C was quite different from that of CS-891 at 62 °C. The sample after cooling gave a similar X-ray diffraction pattern to that at 25 °C before the first heating. From the results of powder X-ray diffraction analysis at different temperatures, the powder X-ray diffraction patterns of CS-891 were clearly distinct from the other crystal form, which could be attributed to either a conformation change or packing difference. The packing difference is the differences in the way relatively rigid molecules are assembled in the crystal lattices.

#### *3.1.3. Single crystal X-ray structure determination*

As the powder X-ray diffraction patterns of the two forms were sufficiently distinct to characterize each crystal form, changes in the crystal structure of CS-891 below and above the thermal transition point were further determined by single crystal X-ray analysis. The single crystal X-ray analysis was carried out using the same crystal at 25 and 62 °C, and at 25 °C after the first cooling. The cell parameters of CS-891 at 25 and 62 °C, and at 25 °C after the first cooling are listed in Table 1. Both the crystals at 25 and 62 °C belonged to the orthorhombic space group of $P2_12_12_1$. The unit cell length, cell volume and calculated density at 62 °C seemed to be different from those at 25 °C. The *a*-axis at 62 °C was shorter by about 0.4 Å, and the *b*- and *c*-axes were longer by about 0.8 and 0.2 Å, respectively. The density at 62 °C was slightly lower than that at 25 °C. The unit cell length at 25 °C after the first cooling returned to original values. Thus, it was considered that the conformations of CS-891 at 25 and 62 °C were similar to each other and it was concluded that CS-891 exists in two enantiotropic polymorphic forms with phase transition occurring at 58 °C, a low-temperature stable form (Form A) and a high-temperature stable form (Form B), of which the melting point of the latter is 248 °C.

### *3.2. Ground CS-891 without temperature control*

In the case of grinding without temperature control, as the product temperature of ground samples increased with increasing grinding time, the phase transition of the ground samples in the long grinding

Table 1
Crystallographic data for CS-891 obtained from single crystal X-ray analysis

| Parameter | 25 °C | 62 °C | 25 °C (after first cooling) |
|---|---|---|---|
| Crystal class | Orthorhombic | Orthorhombic | Orthorhombic |
| Space group | $P2_12_12_1$ | $P2_12_12_1$ | $P2_12_12_1$ |
| Unit cell lengths | | | |
| *a* (Å) | 11.828 | 11.397 | 11.819 |
| *b* (Å) | 19.267 | 20.103 | 19.291 |
| *c* (Å) | 11.541 | 11.726 | 11.564 |
| *V* (cell volume, $Å^3$) | 2630.0 | 2686.5 | 2636.0 |
| *Z* (molecules in unit cell) | 4 | 4 | 4 |
| $D_{\mathrm{calc}}$ (density, $g/cm^3$) | 1.173 | 1.149 | 1.170 |

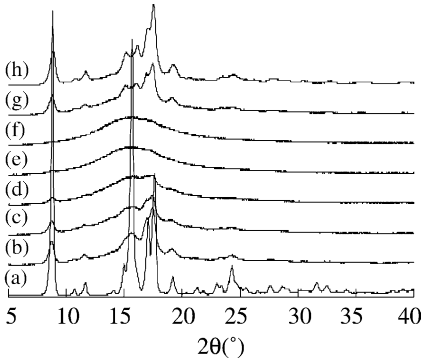

Fig. 5. Time course of powder X-ray diffraction patterns of CS-891 during grinding without temperature control at: (a) 0 min, (b) 15 min, (c) 30 min, (d) 60 min, (e) 120 min, (f) 240 min, (g) 360 min, and (h) 480 min.

process was predicted. The powder X-ray diffraction patterns of ground samples obtained by grinding for 15–480 min without temperature control are shown in Fig. 5. The intensity of the X-ray diffraction peaks and apparent crystallinity decreased with increasing grinding time up to 120 min. Between 120 and 240 min, the powder X-ray diffraction patterns of CS-891 almost displayed halo patterns. After a 360-min grinding, a diffraction pattern respective to Form B was observed even when the measurement was carried out at room temperature. The apparent crystallinity and product temperature of the ground samples are shown in Fig. 6. The apparent crystallinity of the ground samples decreased with grinding, for the first 240 min. Thereafter, a further increase was observed again after 360 min. The product temperature increased with grinding time and surpassed the transition temperature (around 58 °C) after 360 min. It was considered that the transformation of the amorphous form to Form B during grinding is related to the product temperature of the ground samples.

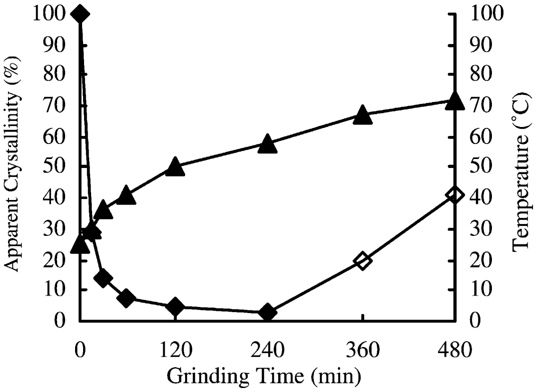

Fig. 6. Time course of apparent crystallinity and product temperature of CS-891 during grinding. The symbols: (◆) apparent crystallinity of Form A, (◇) apparent crystallinity of Form B, and (▲) product temperature of ground samples.

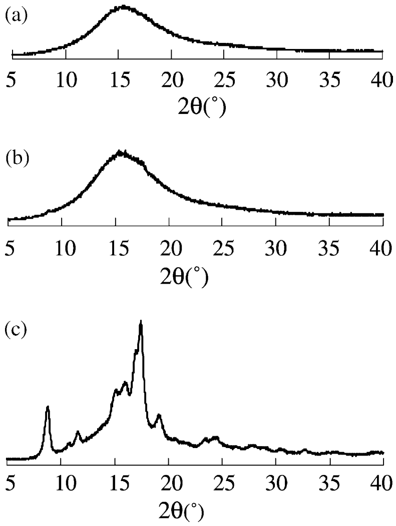

Fig. 7. Powder X-ray diffraction patterns of CS-891 ground for 240 min: (a) at 10 °C, (b) at 50 °C, and (c) at 70 °C.

### 3.3. *Effect of grinding temperature*

The effect of grinding temperature on the apparent crystallinity and crystalline state during the grinding of CS-891 was studied. As the grinding temperature was controlled by maintaining the cell-jacket temperature at 10, 50, or 70 °C, the practical grinding temperature of CS-891 should be higher than the cell-jacket temperature. The grinding temperatures set at below, around and above the transition temperature, were 10, 50, and 70 °C, respectively. The powder X-ray diffraction patterns of samples obtained by grinding for 240 min at 10, 50 and 70 °C are shown in Fig. 7. In the cases of grinding at 10 and 50 °C, the powder X-ray diffraction patterns displayed an almost halo pattern. On the other hand, in the case of grinding at 70 °C, the characteristic diffraction pattern of Form B was observed. The apparent crystallinity and

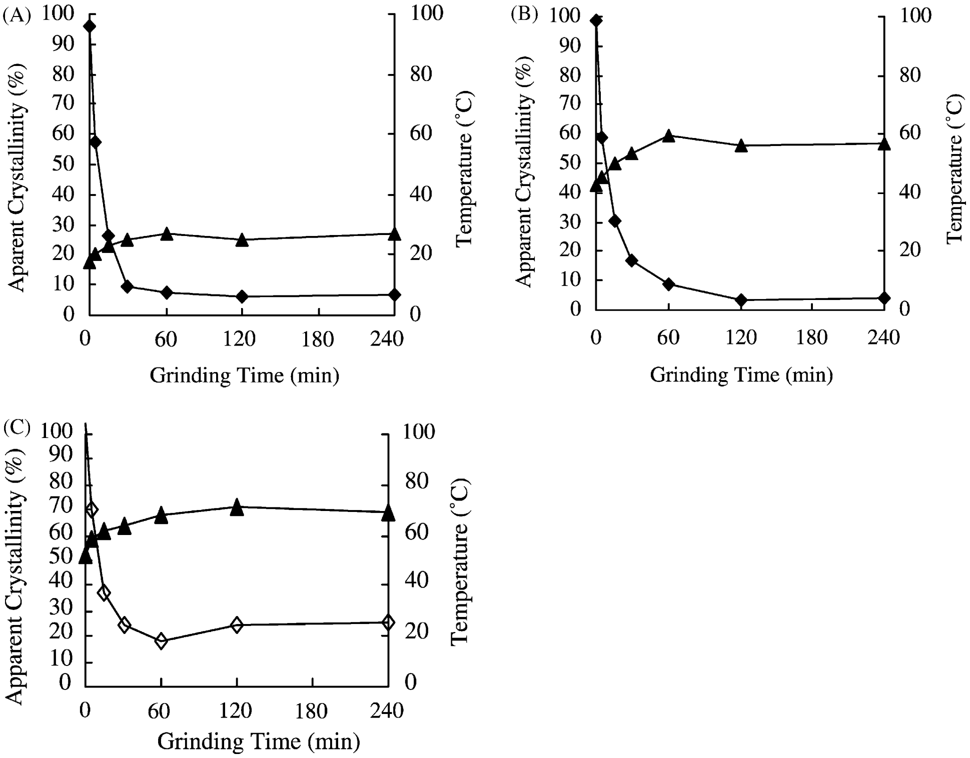

Fig. 8. Time course of apparent crystallinity and product temperature of CS-891 during temperature controlled grinding for: (A) CS-891 ground at 10 °C, (B) CS-891 ground at 50 °C, and (C) CS-891 ground at 70 °C. The symbols: (◆) apparent crystallinity of Form A, (◇) apparent crystallinity of Form B, and (▲) product temperature of ground samples.

product temperature plotted against grinding time are shown in Fig. 8. In the cases of grinding at 10 and 50 °C for 240 min, the apparent crystallinity of CS-891 decreased to about 6 and 4%, respectively, and the product temperatures were 27 and 57 °C, respectively. On the other hand, in the case of grinding at 70 °C, the apparent crystallinity decreased to about 18%, but the apparent crystallinity increased to about 26% after

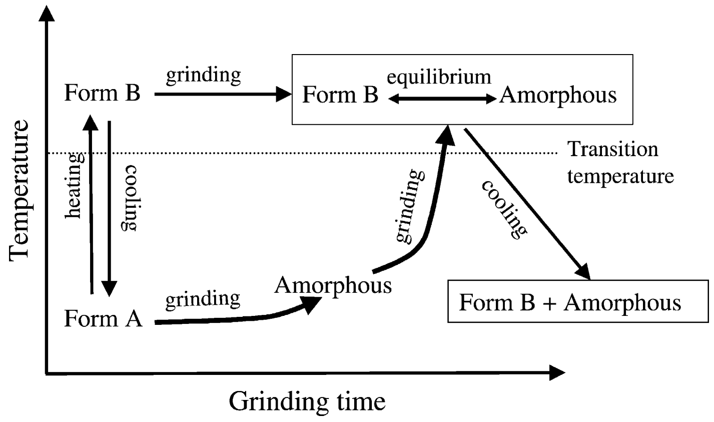

Fig. 9. Schematic representation of CS-891 transformations during grinding.

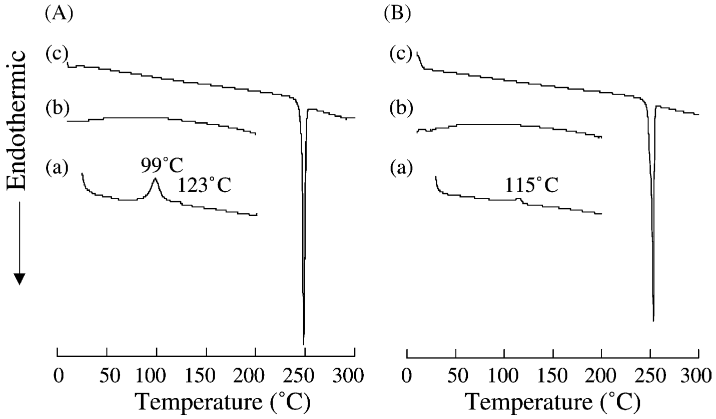

Fig. 10. DSC curves of CS-891 ground for (A) 240 min and (B) 480 min without temperature control. Curve (a): first heating run (heating rate: 5 °C/min), curve (b): first cooling run (cooling rate: 5 °C/min), and curve (c): second heating run (heating rate: 5 °C/min).

grinding for 240 min, when the product temperature reached 69 °C.

The phase transformations of CS-891 during grinding are schematically presented in Fig. 9. When the product temperature during grinding was kept below the transition temperature (around 58 °C), CS-891 remained as Form A, and Form A was transformed into an amorphous form with prolonged grinding. Once the product temperature of the amorphous form during grinding increased to a higher temperature than the transition temperature, some of the amorphous form transformed into Form B, with interconversion of Form B back into the amorphous form. On the other hand, when the product temperature exceeded the transition temperature at the beginning of grinding, Form A was rapidly transformed into Form B, and then Form B was partially transformed into the amorphous form, of which some was transformed back to Form B with further grinding. Form B and the amorphous form were assumed to reach an equilibrium state where the crystallization rate of Form B was equal to the rate of formation of the amorphous form during grinding.

### *3.4. Thermal properties of CS-891 ground samples*

Form B produced from the amorphous form did not transform into Form A, even though the X-ray diffraction pattern of ground CS-891 was measured at room temperature. In contrast, Form A converted to Form B when the product temperature was maintained above the transition temperature and Form B readily converted back to Form A upon cooling (Fig. 3). The thermal behavior of CS-891 ground samples was investigated by thermal analysis, as well as by powder X-ray diffractometry under heating and cooling conditions. The DSC curves of CS-891 ground for 240 and 480 min without temperature control are shown in Fig. 10. The first heating curve of CS-891 ground for 240 min displayed two exothermic peaks, one at 99 °C (large exothermic peak) and the other at 123 °C (small exothermic peak). The first heating curve of CS-891 ground for 480 min showed a broad exothermic peak at 115 °C. The exothermic peak produced due to the transition of Form B to A was not observed in the first cooling curves of CS-891 ground for 240 and 480 min. In the second heating curves, only the melting peaks at around 248 °C were observed. The X-ray diffraction of CS-891 ground for 240 and 480 min without temperature control was measured to evaluate these exothermic peaks (Fig. 11). The powder X-ray diffraction patterns of CS-891 ground for 240 and 480 min were measured at 25, 70, 110, and 140 °C, and at 25 °C after the first cooling. In the case of CS-891 ground for 240 min, the X-ray diffraction pattern at 25 and 70 °C showed a halo pattern, but a diffraction peak at $2\theta = 16.1^\circ$ derived from Form B was observed in the powder X-ray diffraction pattern at 110 and 140 °C, and at 25 °C after the first cooling (Fig. 11A). On the other hand, with respect to CS-891 ground for 480 min (Fig. 11B), every sample exhibited the same X-ray diffraction pattern as that of Form B with an increase in intensity for samples (c) and (d). It was

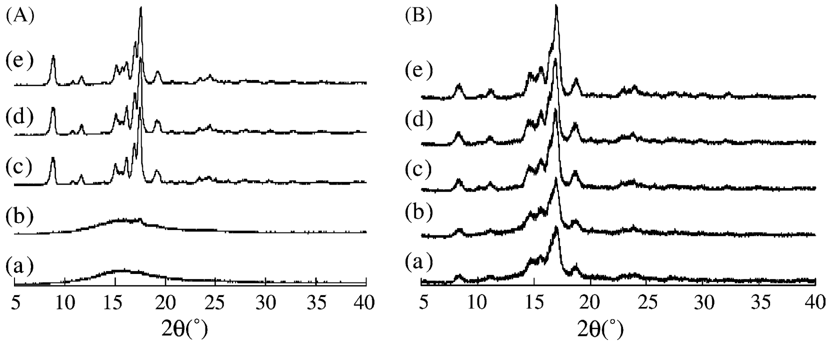

Fig. 11. Change in powder X-ray diffraction patterns of CS-891 ground for (A) 240 min and (B) 480 min without temperature control. (a): at 25 °C, (b): at 70 °C, (c): at 110 °C, (d): at 140 °C, and (e): after cooling back to 25 °C.

apparent that the samples after the first cooling still displayed the diffraction pattern of Form B instead of Form A.

Based on these observations, the thermal behavior of ground CS-891 is schematically presented in Fig. 12. Both exothermic peaks of CS-891 ground for 240 and 480 min without temperature control, i.e. both exothermic peaks of the amorphous form and the amorphous form in equilibrium with Form B, are considered to result from the crystallization of the amorphous form. After cooling from 140 to 25 °C, Form B crystallized by heating remained instead of transforming back to Form A. Although Forms A and B are related enantiotropically and expected to be thermodynamically reversible, Form B which was produced via the amorphous form never reverted to Form A even after cooling. This phenomenon lead to the presumption that Form B crystallized from the amorphous form by heating was more stable than Form B transformed from the intact Form A by heating.

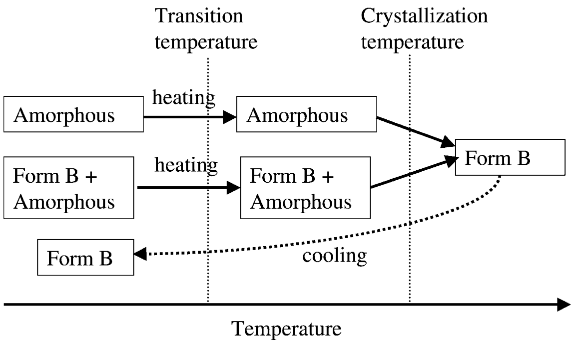

Fig. 12. Schematic representation of thermodynamic behavior of CS-891 ground sample.

### 3.5. Physical stability of CS-891 ground at various temperatures

A stability test at 40 °C and 75% RH was carried out to estimate the physical stability of CS-891 ground at 10, 50, and 70 °C. Fig. 13 shows the relationship between storage time and apparent crystallinity of CS-891 ground at 10, 50, and 70 °C for 240 min. The apparent crystallinity increased with storage time, and the apparent crystallization rate of CS-891 ground

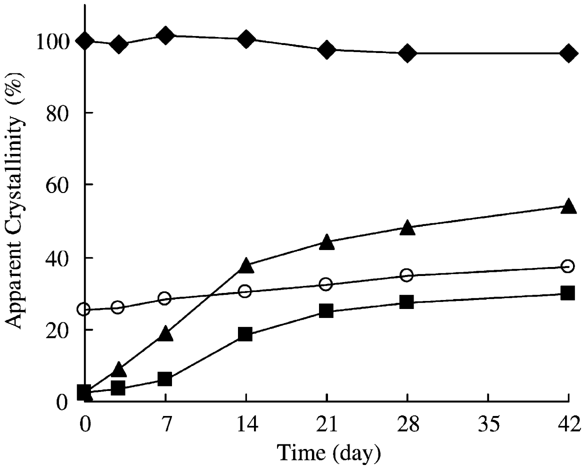

Fig. 13. Change in apparent crystallinity of CS-891 ground for 240 min during storage at 40 °C/75% RH. The symbols: (◆) intact CS-891 (Form A), (■) CS-891 ground at 10 °C, (▲) CS-891 ground at 50 °C, and (○) CS-891 ground at 70 °C.

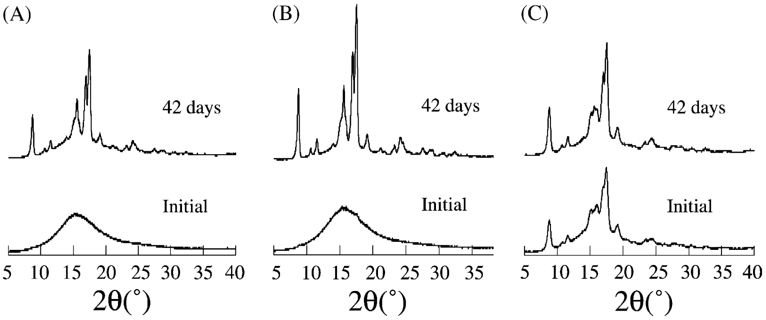

Fig. 14. Change in powder X-ray diffraction patterns of CS-891 ground for 240 min before and after the storage at 40 °C/75% RH for 42 days. (A) CS-891 ground at 10 °C, (B) CS-891 ground at 50 °C, and (C) CS-891 ground at 70 °C.

at 70 °C was obviously lower than that of CS-891 ground at 10 and 50 °C. The powder X-ray diffraction patterns of CS-891 ground at 10, 50, and 70 °C for 240 min after 42 days of storage are shown in Fig. 14. Crystallization of CS-891 from the amorphous form to Form A was found to occur in CS-891 ground at 10 and 50 °C for 240 min. On the other hand, for CS-891 ground at 70 °C for 240 min, there were little changes in the X-ray diffraction patterns after 42 days. The DSC curves of CS-891 ground at 10, 50 and 70 °C and stored for 42 days at 40 °C and 75% RH are shown in Fig. 15. After storage for 42 days, the exothermic peak of CS-891 ground at 10 and 50 °C was clearly decreased, but there was little change in the broad exothermic peak of CS-891 ground at 70 °C.

Thus, the amorphous form ground for 240 min at 70 °C was physically more stable than that ground for 240 min at 10 and 50 °C. As shown in Fig. 15, there were differences in the temperature range and shape of the two exothermic peaks between the amorphous form ground for 240 min at 70 °C and that at 10 and 50 °C. Thus, it was considered that crystallization of the amorphous form to Form A during storage is related to the amorphous state of the ground sample. The heat of crystallization of each CS-891 ground sample calculated from the DSC peak area of CS-891 ground at 10, 50 and 70 °C was 25.5, 23.6 and 13.8 J/g, respectively. According to these data, due to its higher energy state, CS-891 ground at 10 and 50 °C could revert to the thermodynamically stable Form A more rapidly than CS-891 ground at 70 °C.

The powder X-ray diffraction pattern of the amorphous form is typically a halo pattern due to its disordered structure. Yamaguchi et al. (1993) reported that amorphous forms having similar powder X-ray diffraction pattern exhibited different properties depending on the preparation method of the amorphous materials. In fact, the amorphous form prepared from

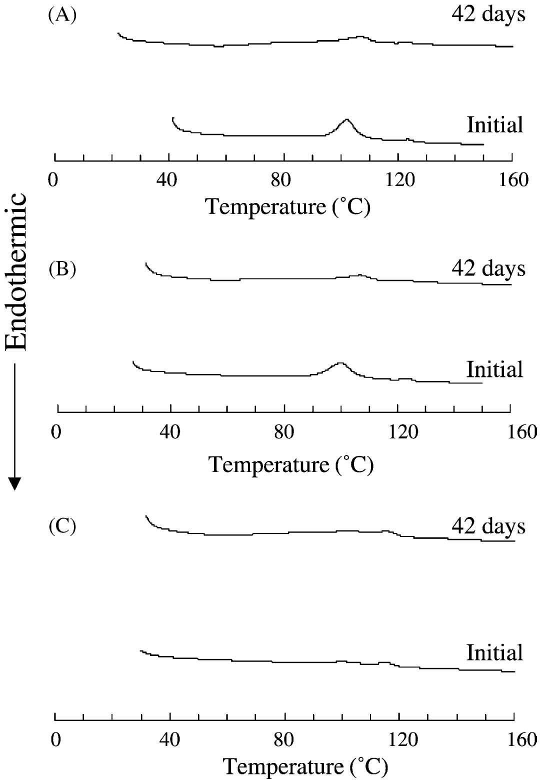

Fig. 15. Change in DSC curves of CS-891 ground for 240 min before and after the storage at 40 °C/75% RH for 42 days. (A) CS-891 ground at 10 °C, (B) CS-891 ground at 50 °C, and (C) CS-891 ground at 70 °C.

an ethanol solution of CS-891 by spray-drying did not crystallize after storage for 42 days at 40 °C and 75% RH (data not shown). The remaining microcrystals dispersed in the amorphous matrix could serve as seeds for crystallization. Yoshioka et al. (1994) reported that the rate of crystallization from the amorphous state increased with a higher number of residual seed crystals. With the amorphous form prepared by grinding at 10 and 50 °C, there will be a very small amount of seeds of Form A, which may accelerate crystallization of the amorphous to Form A, since the nucleation step is usually the slowest step. On the other hand, as the amorphous form obtained by grinding for 240 min at 70 °C was in equilibrium with Form B, which is considered to be stable below the transition temperature, the crystalline growth of Form A was governed by the phase transition from Form B to A, which was extremely slow. Therefore, it was suggested that the stability of the amorphous form depends on the presence of the crystalline form, of Form A or B.

## 4. Conclusion

CS-891 was found to exist as two enantiotropic polymorphic forms, a low-temperature stable form (Form A) and a high-temperature stable form (Form B) with their transition temperature being at 58 °C. When ground below the transition temperature, Form A was transformed into an amorphous form. On the other hand, in the case where the product temperature reached above the transition temperature, the amorphous form was partly transformed into Form B, which is stable below the transition temperature. The amorphous form in equilibrium with Form B was physically more stable than that in the presence of a very small amount of Form A, as a crystallization seed. It was suggested that the stability of the amorphous form is strongly affected by the presence of the crystalline form of Form A or B.

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