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Size Reducibility of Sulfathiazole by Heat Transition and Subsequent Ball-milling[1]

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In order to examine the feasibility of size reduction by heat transition of polymorphic drugs, crystals of the α-form of sulfathiazole were heated above its transition temperature and the physico-chemical and micromeritical properties of the product were studied by IR spectroscopy, X-ray diffractometry, DSC, BET gas adsorption analysis, and electron microscopy.

The original α-crystals became opaque after transition and the polymorphic form of the product was identified as the β-form of sulfathiazole. Corresponding to the loss of transparency, many cracks and fissures were observed electron-microscopically on the surface. At the same time, a considerable increase of the surface area was found. The convex sections between the cracks and fissures can be ascribed to plastic deformation induced by the stress of transition.

In spite of the remarkable changes in the surface appearance, the β-particles were unexpectedly stable on standing. The extents of the lattice disorder measured by X-ray diffractometry were found to be small. When ball-milling was applied to the β-crystals obtained by heat-induced transition, the particle size was further reduced. However, they became less stable and retransition was induced more easily at room temperature. In addition, lattice disorder attributable to the mechano-chemical effect of grinding was observed in the ground α- and β-powder.

Keywords——sulfathiazole; size reduction; heat transition; change in external appearance; lattice disorder; plastic deformation; ball-milling; increase in surface area; retransition induced by grinding; mechano-chemical effect

The size and size distribution of drug particles in a dosage form are important pharmaceutical factors; in particular, when the drug is poorly soluble, the bioavailability and the therapeutical efficacy are largely dependent upon these factors. In a series of studies, we have developed size reduction methods by the use of solvates and eutectic mixtures. Besides these, Haleblian and McCrone have suggested in their review article[3] the possibility that the size of a polymorphic drug could be effectively reduced by heat transition. Their proposal was based on the observation that a polymorphic substance generally becomes opaque when heated above its transition temperature.

On the other hand, we have observed that loss of transparency does not always occur. For example, crystals of the β-form of sulfanilamide remained almost transparent and retained their original shape even after complete conversion to the γ-form.[4] It also seemed likely that the extent of size reduction would not be large, since the volume change due to polymorphic transition is usually small and the molecules might thus be rather easily rearranged.

We therefore decided to examine the feasibility of size reduction by heat transition experi-

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[1] This paper forms Part X of "Studies of Methods of Particle Size Reduction of Medicinal Compounds." Part IX: Y. Tsuda, M. Kanke, I. Miyachi, K. Maeno, and K. Sekiguchi, *Chem. Pharm. Bull.*, **28**, 947 (1980).

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[3] J. Haleblian and W. McCrone, *J. Pharm. Sci.*, **58**, 911 (1969).

[4] K. Sekiguchi, *Journal of the Society of Materials Science* (Japan), **21**, 502 (1972).

mentally with polymorphic drugs. In the present paper, the α-form of sulfathiazole was converted by heating to its β-form, and the physico-chemical and micromeritical properties before and after the transition were compared. At the same time, the effects of mechanical pulverization upon these properties were investigated.

Experimental

Preparation of Sample Materials——1) α- and β-Crystals by Gradual Recrystallization:[5] The α- and β-form of crystals were isolated gradually from almost saturated solutions of commercial sulfathiazole (J.P. VII grade) in methanol at 60° and in *n*-amylalcohol at 90°, respectively. The α-crystals were screened directly or after triturating lightly in the ranges of 10—16, 60—100, and below 200 mesh.

2) β-Particles by Heat Transition: The graded α-crystals were each converted to the β-form by heating in an oil-bath at 160±1° for 1, 2, and 3 hours.

3) β-Crystals by Rapid Freezing and Freeze-drying: An aqueous solution of commercial sulfathiazole was rapidly frozen in an acetone-dry ice mixture. After complete removal of water by freeze-drying,[6] a crystalline powder of the β-form was obtained.

As shown in Figs. 1—3, the polymorphic forms of the sample materials were identified by IR, X-ray diffractometry, and DSC.

Infrared Spectroscopy (IR)——IR spectra were measured by the Nujol mull method with a Jasco IRA-1 grating infrared spectrophotometer.

X-Ray Powder Diffractometry——A JDX-7F X-ray diffraction analyzer from Japan Electron Optics Lab. Co. was used. Analytical conditions were as follows: scanning speed, 1°/min; receiving slit, 0.2 mm;

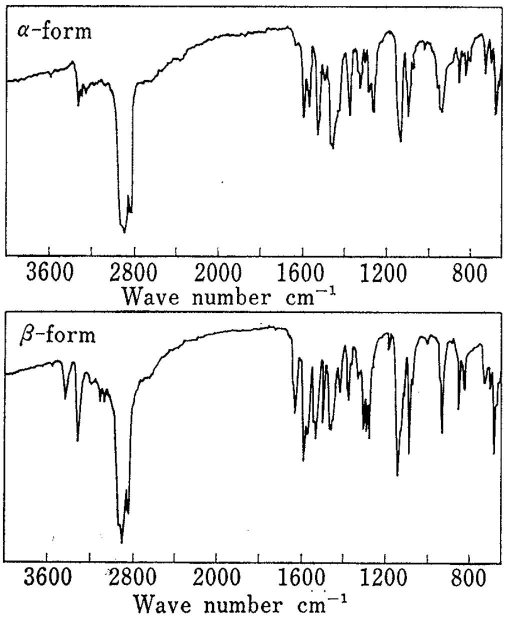

Fig. 1. Infrared Absorption Spectra of Sulfathiazole Polymorphs (Nujol mull)

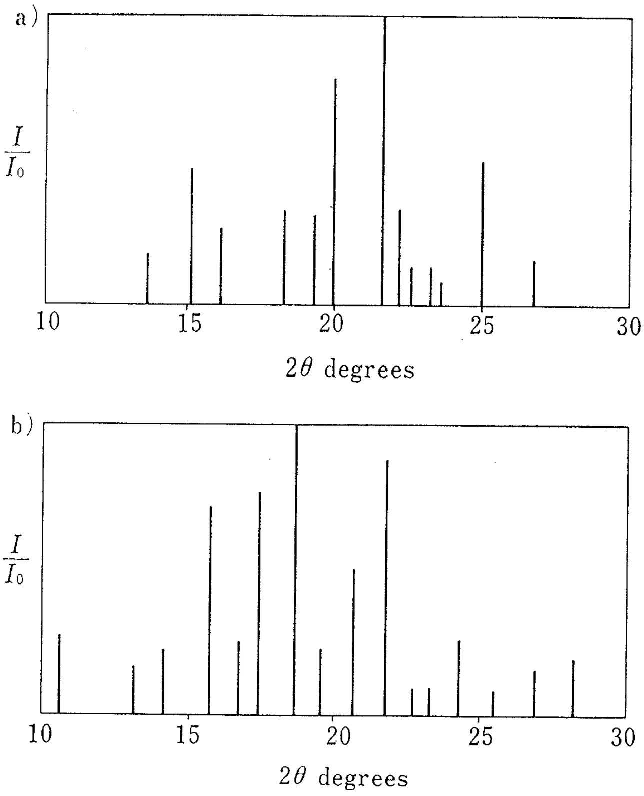

Fig. 2. X-Ray Powder Diffraction Patterns of Sulfathiazole Polymorphs

a) α-form, b) β-form.

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[5] L.S. Shenoda, *J. Pharm. Sci.*, **59**, 785 (1970); M.A. Moustafa and J.E. Carless, *J. Pharm. Pharmacol.*, **21**, 359 (1969); D.C. Grove and G.L. Keenan, *J. Am. Chem. Soc.*, **63**, 97 (1941); M. Kanke and K. Sekiguchi, *Chem. Pharm. Bull.*, **21**, 871 (1973).

[6] The α-crystals are usually obtainable from aqueous solution; however, as expected from Ostwald's law, the β-crystals could be isolated by rapid freezing and freeze-drying.

Ni-filtered CuKα radiation, $\lambda = 1.542$ Å; time constant of rate meter, 4 sec. From the X-ray diagrams, the extents of lattice disorder were estimated by the method of Hall.7) The α- and β-crystals obtained by gradual recrystallization were employed as standards for comparison and their integral breadth values (B_0) and those of other materials (B) were determined at several peak diffraction angles (θ). If the strain were equally produced in all directions inside the crystals, the plots of $(B - B_0) \cdot \cos\theta$ against $\sin\theta$ would be linear theoretically and the slope would provide a measure of lattice disorder in comparison with that of the standard α- or β-crystals.

Differential Scanning Calorimetry (DSC)——The transition and melting temperatures, and the heat of transition were measured with a Perkin-Elmer DSC-1B differential scanning calorimeter.

Density Measurement——The densities of the two formes of sulfathiazole at 25° were determined by the flotation method using comparatively large α- and β-crystals obtained by gradual recrystallization. Benzene–CCl_4 mixtures in various proportions were employed as the floating solvents.

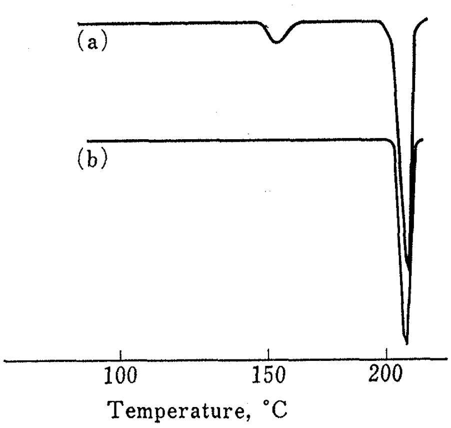

Fig. 3. DSC Curves of Sulfathiazole Polymorphs under Semi-closed Conditions

(a) α-form: 15.577 mg, 16°/min, range 32 mcal/sec,
(b) β-form: 10.941 mg, 16°/min, range 32 mcal/sec.

Pulverization by Ball-milling——The materials for milling were the α-crystals, 10—16 mesh in size, and β-particles obtained from them by heat-induced transition. Portions of 40 g were ground at 180 rpm with a ball mill consisted of a porcelain cylinder of 90 mm diameter containing 20 and 12 porcelain balls of 20 and 12 mm diameter, respectively.

Measurement of Surface Area——A BET gas adsorption apparatus, model p-600, from Shibata Chemical Apparatus Mfg. Co., Ltd. was used. Each measurement was done with a sample of about 5 g. N_2 gas was adopted as the adsorbate and the surface area was calculated by taking the cross-sectional area of an N_2 molecule at $-195.8°$ as 16.2×10^{-16} cm^2.

Observation of Surface Appearance——The surface appearance of the samples before and after heat transition with or without subsequent grinding was observed with a scanning electron microscope (Hitachi-Akashi model MSM-4). The changes in the appearance of α-crystals during heating were also followed closely with a hot-stage microscope (Ernst Leitz model 350).

Results and Discussion

Changes in the External Appearance and the Increase in Surface Area after Heat Transition

The α-crystals of sulfathiazole were clearly outlined, transparent six-sided plates. When they were heated above the transition temperature, they became opaque but retained the external shape of the original α-crystals. The particles obtained in this way showed X-ray and IR patterns8) and a DSC curve characteristic of the β-form. They were stable on prolonged standing at room temperature and maintained the crystal structure of the β-form even after two months.

As can be seen from the electron micrographs in Fig. 4, the α-crystals have smooth surfaces, while many cracks and fissures appeared on the surface of the β-particles obtained by heat-induced transition. Therefore, it is considered that they are secondary agglomerates composed of primary particles of β-crystals.9) In addition, all the sections enclosed by these cracks became clearly convex. These surface changes were caused mainly by the stress due to polymorphic transition. It canbe deduced that the curved surface was formed by volume expansion during transition and plastic deformation induced by the stress of transition, whereas the cracking and fissuring were results of stress-concentration up to the breaking stress.

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7) W.H. Hall, *Proc. Phys. Soc.*, A**62**, 741 (1949).
8) R.J. Mesley, *J. Pharm. Pharmacol.*, **23**, 687 (1971).
9) A primary particle corresponds to a unit region of β-crystals surrounded by cracks and fissures, obtained heat transition of α-crystals.

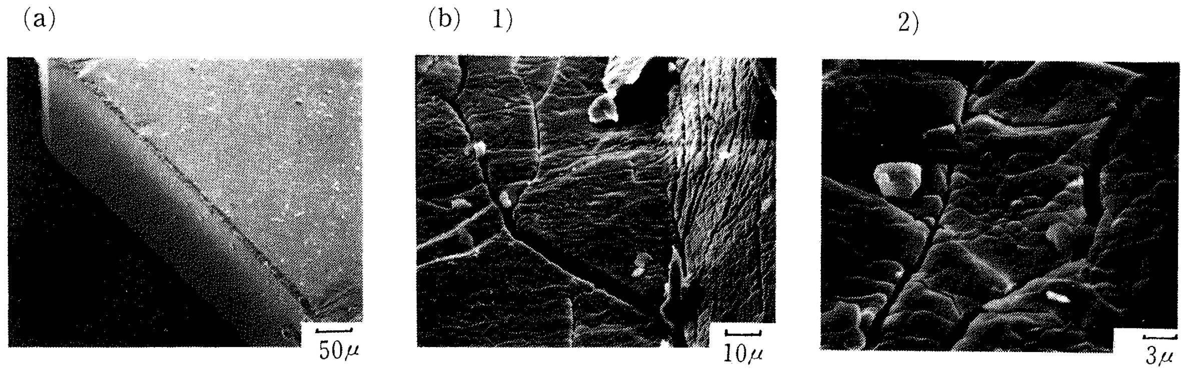

Fig. 4. Scanning Electron Micrographs of Sulfathiazole Polymorphs

(a) α-form (10—16 mesh particle), 200×.
(b) β-form prepared by heat transition of 10—16 mesh particles of α-form, 1) 1000× 2) 3000×.

The specific surface area of the β-particles obtained by heat-induced transition was 0.7±0.1 m^2/g, while that of the original α-crystals (10—16 mesh) was estimated to be 0.1 m^2/g[10] at most by extrapolating the curve in Fig. 6. These results agreed with the microscopic observations. The effect of heating interval upon the surface area was shown in Fig. 5. It appears that the polymorphic transition of α-sulfathiazole was easily induced and proceeded rapidly during heating at 160°, and was accompanied by a considerable increase in surface area. The effect of heating on the size reducibility became less marked as the initial particle size became smaller.

Increase in Surface Area and Induction of Retransition by Grinding

In order to compare the grindability of the β-particles with that of the original α-crystals, each of them was ground by ball-milling, and the increase in the surface area was measured

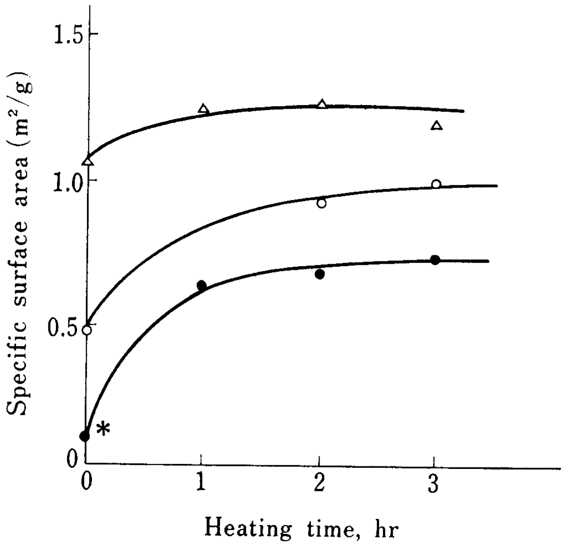

Fig. 5. Effect of Exposure to Heat (160 ±1°) upon the Specific Surface Area of Sulfathiazole

Initial particle size: ●, 10—16 mesh, ○, 60—100 mesh, △, below 200 mesh
* See the text for details.

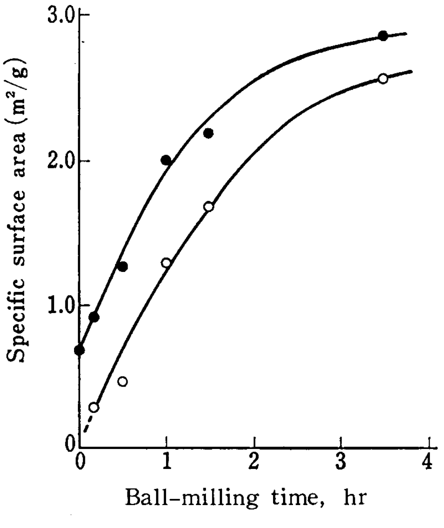

Fig. 6. Increase of Specific Surface Area of Sulfathiazole with Ball-milling Time

○: α-form (10—16 mesh particles).
●: β-form prepared by heat transition of 10—16 mesh particles of α-form.

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[10] The intercept value on the curve in Fig. 6 was used, because it is not possible to measure the surface area of 10—16 mesh powder by the BET gas adsorption method.

at intervals. At the same time, we examined whether or not mechano-chemical retransition occurred in the course of grinding.

As can be seen from the curves in Fig. 6, the specific surface area of the α-crystals and the β-particles increased rapidly and in parallel with each other at the early period of grinding. With increase of the grinding time, the curve for the α-crystals showed a tendency to approach gradually that for the β-particles, but the area of the former was smaller by 0.3 m^2/g even after 3.5 hours. The difference between them can be seen directly by comparing the corresponding electron-micrographs in Fig. 7.

When the ground β-powder was analyzed by X-ray diffractometry, IR spectroscopy, and DSC at every stage of grinding, it was confirmed that complete retransition did not occur. However, the heat of fusion after 3.5 hours of grinding was found to be a little smaller than that of the β-crystals from *n*-amylalcohol (Table I).

When X-ray analysis was done one week after grinding, the diagram showed peaks due to the α-form. It is therefore clear that the retransition of the β-particles is facilitated by the mechano-chemical influences of grinding.

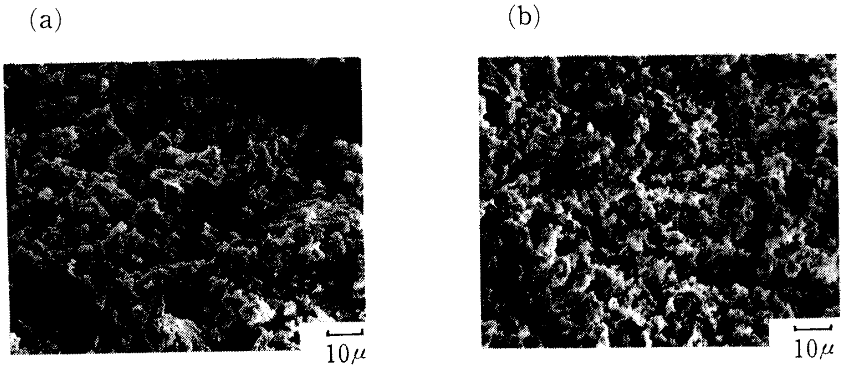

Fig. 7. Scanning Electron Micrographs of Sulfathiazole Particles after 3.5 hr of Ball-milling

(a) α-form, 1000 ×.
(b) β-form prepared by heat transition, 1000 ×.

Table I. Heat of Fusion of Sulfathiazole prepared by Various Methods

Method of preparation	Heat of fusion (kcal/mol)
α-Form recrystallized from methanol	6.96
β-Form recrystallized from *n*-amylalcohol	6.90
α-Form after 3.5 hr of ball-milling	6.49
β-Form after 3.5 hr of ball-milling	6.52
β-Form prepared by freeze-drying	6.14

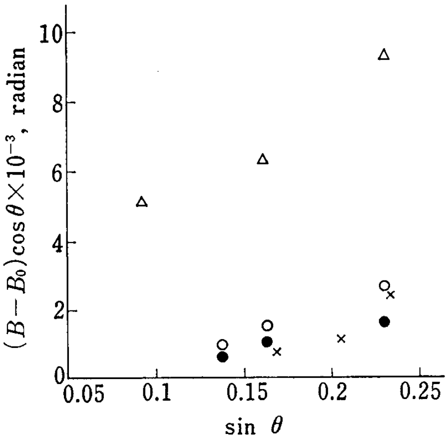

Fig. 8. Lattice Disorder of Sulfathiazole Crystals prepared by Various Methods

●: β-form prepared by heat transition,
×: α-form after 3.5 hr of ball-milling,
○: β-form after 3.5 hr of ball-milling,
△: β-form prepared by freeze-drying.

In the case of α-sulfathiazole, no transition occurred during or after grinding, but the heat of fusion after 3.5 hours of ball-milling was a little smaller than that of the α-crystals from methanol.

Lattice Disorder induced by Heat Transition and by Grinding

In view of the above results, it was supposed that the crystal lattice in each of the sample materials was disordered significantly by heat transition and grinding. Therefore, in order to estimate the extent of the lattice disorder, the method proposed by Hall[7)] was applied. The α- and β-crystals prepared by gradual recrystallization were employed as reference standards, and the extents of lattice disorder of other materials were determined from the broadening of the integral breadths.

As shown in Fig. 8, the values for the β-particles prepared by simple heat transition increased gradually with increasing $\sin\theta$, which suggests that rearrangement of the molecules was somewhat inhibited during transition. On the other hand, the values for the ground α- and β-powders changed considerably; thus, it is clear that the lattice disorder was increased in these cases by mechanical stress. Finally, the largest broadening of X-ray peaks was found for the β-crystals obtained by rapid freezing and freeze-drying, probably due to difficulty in arranging the molecules and in growing crystals regularly under such drastic conditions.

Conclusion

The following conclusions can be derived from the above experimental results.

External and Internal Changes due to Heat Transition

(1) Formation of Cracks, Fissures and Curvatures on the Surface: The loss of transparency of the β-particles obtained by heat-induced transition is directly attributable to optical dispersion by the surface cracks and fissures. Such discontinuities would be formed by cleavage due to stress-concentration caused by the change in molecular volume[11)] during transition. Further, the convex sections on the surface would be formed by plastic deformation below the breaking stress.

(2) Increase in Surface Area upon Heat Transition: As expected from the changes in external appearance, the specific surface area of the β-particles increased considerably as compared with that of the original α-crystals. However, the increase of area was found to be smaller than that obtained by desolvation from solvates. This result suggests that the molecules are more easily rearranged during polymorphic transition, as suggested in the introductory remarks.

(3) Lattice Disorder due to Heat Transition: The lattice disorder of the β-particles obtained by heat-induced transition was found to be somewhat larger than that of the β-crystals obtained by gradual recrystallization. It seems likely that the stress caused during polymorphic transition was relaxed by the formation of the convex portions, fissures and cracks with yielding disorderliness to a certain extent in the crystal lattice.

External and Internal Changes due to Grinding

(1) Effect of Heat Transition on the Grindability: Initially, parallel increases in specific surface area were seen upon ball-milling of the α-crystals and their heat-induced β-product; therefore, both materials have similar grindabilities. The four-fold increase in the area of the β-powder after 3.5 hours of grinding indicates that the β-powder was not only disintegrated into primary particles but also further size-reduced by grinding.

(2) Lattice Disorder due to Grinding: The lattice disorder in the α-crystals and the β-particles was found to be increased considerably by mechanical size reduction with a ball mill.

[11)] densities of sulfathiazole polymorphs: α-form = 1.540; β-form = 1.484.

As a result, the ground β-powder became much less stable than it had been before grinding. Lattice defects formed during grinding may lower the activation energy for the $\beta \rightarrow \alpha$ transition so that the reaction would be more easily induced even by the energy due to thermal motion of the molecules at room temperature.

On the other hand, the ground α-powder showed no transition at room temperature, as might be expected, since the internal energy of the β-powder is greater by the latent heat of transition than that of the α-powder, and the change in free energy of the $\alpha \rightarrow \beta$ reaction is positive.