[Chem. Pharm. Bull.
31(6)2085—2093(1983)]

Solvate Formation of Sulfathiazole with Acetone, 2-Butanone, 2-Pentanone and Dioxane, and Its Application to Particle Size Reduction[1]

KEN-ICHI SHIROTANI,* ETSUKO SUZUKI, and KEIJI SEKIGUCHI

*School of Pharmaceutical Sciences, Kitasato University, 9-1,
Shirokane 5-chome, Minato-ku, Tokyo 108, Japan*

(Received November 22, 1982)

Solvates of sulfathiazole with acetone, 2-butanone, 2-pentanone and dioxane were isolated, and their physico-chemical properties were investigated by infrared spectroscopy, X-ray powder diffractometry, differential scanning calorimetry (DSC), thermogravimetry and scanning electron microscopy. The process of desolvation was observed thermomicroscopically and the specific surface areas of the desolvated products were measured by the BET method.

The combining ratios of all the solvates were determined to be 1: 1 from the weight descrease in the thermogravimetric curves. The DSC measurements and the visual observations revealed that these solvates belong to the class of compounds with incongruent melting points. The kinetic analysis of the isothermal desolvation showed that the desolvation proceeded in accordance with the mechanism of random nucleation and two-dimensional crystal growth as represented by the Avrami–Erofeev equation. The effects of desolvating conditions and the molecular volume of the solvent on the particle size and the surface appearance of recovered sulfathiazole were examined in detail.

Keywords——solvate formation of sulfathiazole; kinetic analysis of desolvation; size reduction; thermal analysis as a condensed system; specific surface area; scanning electron microscopy

Previously, the ethanol, *n*-propanol and isopropanol solvates of cortisone acetate were identified and their physico-chemical and micromeritical properties as well as those of their desolvated products were investigated.[2]

In the present paper, as a continuation of our series of studies on solvate formation and its application to particle size reduction, the solvate formation of sulfathiazole with acetone, 2-butanone, 2-pentanone and dioxane was investigated. The desolvation mechanisms and the factors favoring effective size reduction *via* these solvates were also fully investigated.

Experimental

Materials——Sulfathiazole of J.P. VII grade was recrystallized from methanol solution. Acetone, 2-butanone (methyl ethyl ketone), 2-pentanone (methyl *n*-propyl ketone) and dioxane were reagent-grade products, and were used after dehydration and subsequent distillation.

Preparation and Identification of Solvates——Sulfathiazole was dissolved in hot solvent and the solution was allowed to stand at 20°C until the corresponding solvate crystallized out. Identification of each solvate was done by means of infrared spectroscopy (IR), X-ray powder diffractometry, differential scanning calorimetry (DSC) and thermogravimetry (TG).

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

X-Ray Powder Diffractometry——A JDX 7F X-ray diffraction analyzer made by Japan Electron Optics Laboratory Co., Ltd. was used (Ni filter, Cu-$K\alpha$ radiation, $\lambda = 1.542$ Å).

Simultaneous DSC and TG——Simultaneous measurements were carried out with a Thermoflex TG-DSC machine (Rigaku Denki Co., Ltd.) using about 10 mg of a sample (heating rate, 5°C/min; nitrogen gas flow, 50 ml/min). Under open conditions, a solid sample pan was employed without a pan cover, while under closed conditions, the sample solvate was sealed hermetically in a high pressure pan capable of withstanding a pressure of about 50 kg/cm^2.

Analysis of Desolvation Mechanisms and Estimation of Activation Energies——In the TG furnace, fairly large crystals of the solvate (about 1.5 mm in length) were desolvated at several constant temperatures. As described in a previous paper,[2] the fractions desolvated in the course of desolvation were introduced into various kinetic equations based on different mechanisms. The desolvation rate constants were determined with the equation showing the best linear fit; thus the activation energy for each solvate was calculated from the slope of the Arrhenius plots.

Measurements of Specific Surface Areas of Sulfathiazole Particles prepared under Various Conditions——Specific surface areas were measured by the BET method using a model p-600 apparatus (Shibata Chemical Apparatus Co., Ltd.). The samples were particles of sulfathiazole recovered by the following procedures:

1) Desolvation below the peritectic temperatures in an open system: For the ketone solvates, a temperature of 25°C was adopted, while the dioxane solvate was desolvated at 60° or 95°C. In each case, the pressure was maintained at 1 atm or lowered to 2 mmHg.

2) Desolvation beyond the peritectic temperature in an open system: Under a pressure of 1 atm or 2 mmHg, the ketone solvates were heated to and kept at 95°C, but in the case of the dioxane solvate, the maintenance temperature was 145°C. Under such conditions, solid phase desolvation occurred in a part of each solvate, while the rest was desolvated by way of peritectic liquefaction.

3) Desolvation beyond the peritectic temperature in a closed system (separation of sulfathiazole crystals from the peritectic liquid): In a sealed tube, the acetone, 2-butanone or 2-pentanone solvate was heated at 120°C for half an hour. Then, the tube was cooled rapidly and the newly deposited crystals were separated from the liquid by pressing them between filter papers. The crystals were mainly those of sulfathiazole formed by the peritectic reaction, since resolvation was strongly retarded by the above procedure.

Observation of Desolvation Process——One crystal of the acetone solvate was heated on a hot plate at 50°C and the surface changes due to desolvation were followed photomicrographically.

Surface Appearance of the Desolvated Particles by Scanning Electron Microscopy——The influence of

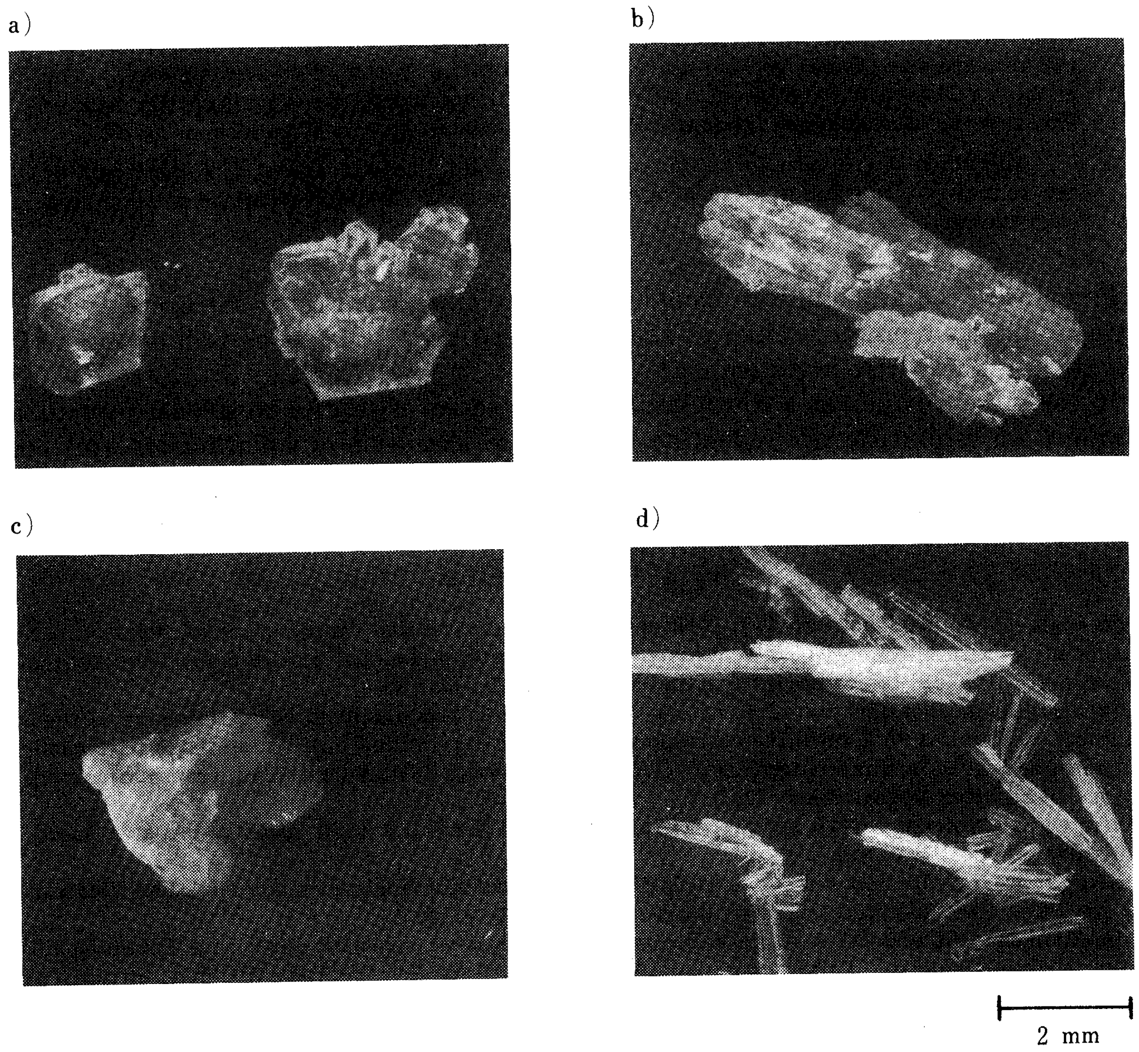

Fig. 1. Shapes of the Crystals

a) The acetone solvate. b) The 2-butanone solvate.
c) The 2-pentanone solvate. d) The dioxane solvate.

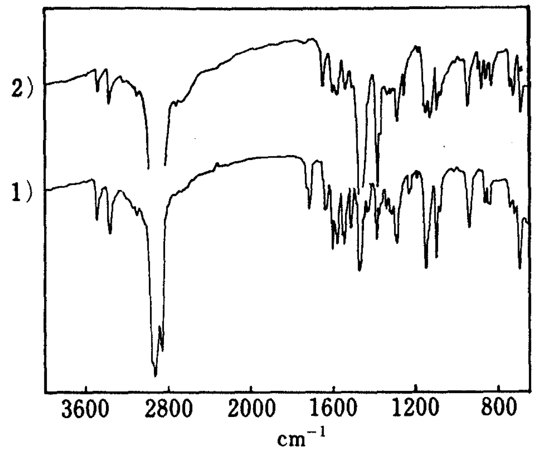

Fig. 2. IR Spectra of the Acetone and Dioxane Solvates (Nujol Mull)

1) The acetone solvate.
2) The dioxane solvate.

desolvation conditions on the surface appearance of the recovered sulfathiazole was examined with a Hitachi-Akashi MINI-SEM scanning electron microscope.

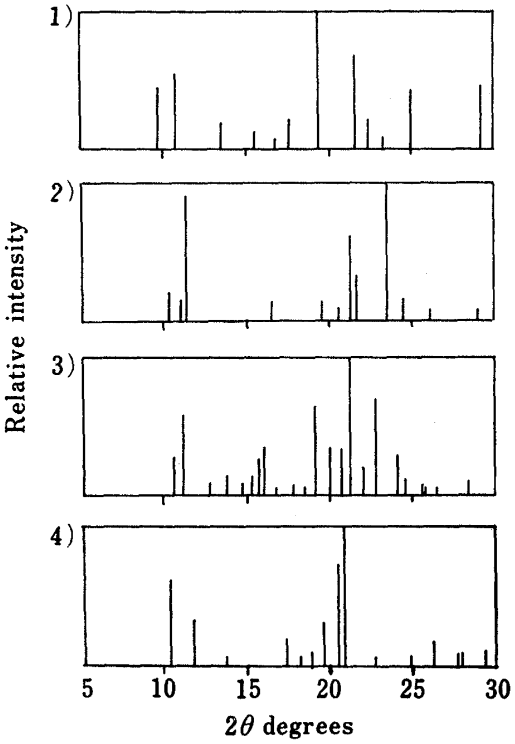

Fig. 3. X-Ray Powder Diffraction Patterns

1) The acetone solvate.
2) The 2-butanone solvate.
3) The 2-pentanone solvate.
4) The dioxane solvate.

Results and Discussion

IR Spectra and X-Ray Powder Diffraction

Crystals of the four solvates are shown in Fig. 1. The IR spectra of the ketone solvates showed the -C=O stretching bands at about 1720 cm^{-1}, while in the dioxane solvate, the C–O–C stretching band due to the solvent component appeared at 1125 cm^{-1}. (Fig. 2) Each of the solvates gave an individual X-ray diffraction pattern which is different from that of any known polymorph of sulfathiazole$^{3)}$ (Fig. 3).

When crystals of these solvates were exposed to air, they became opaque even at room temperature and ultimately changed into agglomerates of primary particles of sulfathiazole by releasing all their solvent components. In this connection, it was confirmed by IR that under such conditions, the recovered particles from the three ketone solvates belonged to the α-form (form III) of sulfathiazole; however, in the case of the dioxane solvate, the α'-form (form II) was produced with or without a small amount of the β-form (form I).

Simultaneous DSC and TG

Measurements were carried out under two types of conditions as follows:

1) **Open Conditions**——Two endothermic peaks were found in the DSC curve of each ketone solvate (Fig. 4 (1)—(3)). The first one is due to desolvation of the solvent component, while the second peak at about 202°C is assigned to melting of sulfathiazole. Since the transition peak (α→β) was absent, it is certain that the recovered sulfathiazole belongs to the β-form, not to the α-form obtained at room temperature. This was also confirmed by IR and X-ray diffraction measurements.

In the DSC curve of the dioxane solvate (Fig. 4 (4)), there appeared three endothermic peaks and one exothermic peak, for which the following assignments seem reasonable: (i) the first endothermic peak at 80—100°C---desolvation of dioxane, (ii) the second endothermic one at about 195°C---partial melting of the α'-form, (iii) the successive exothermic one---

solidification of the β-form from the metastable melt, and (iv) the third endothermic one---melting of the β-form. Thus, the same product was formed as the one at room temperature.

In each of the simultaneous TG curves, a single step appeard at the first endothermic DSC peak. From the decrease in weight, it is indicated that all the solvates have the same combining ratio of 1: 1.

2) **Closed Conditions**——In the DSC curve of each solvate, there appeared two endothermic peaks; however, the corresponding TG curve showed no decrease in weight (Fig. 4 (5)—(8)). This means that each solvate can be treated as a condensed system by the use of a high-pressure pan.[4] Accordingly, the first peak represents the peritectic fusion and the second one can be ascribed to melting of sulfathiazole in the peritectic liquid.

By taking the onset of fall and by measuring the areas of the first DSC peaks, the peritectic points as well as the enthalpies of the peritectic reactions were determined, and the results are shown in Table I.

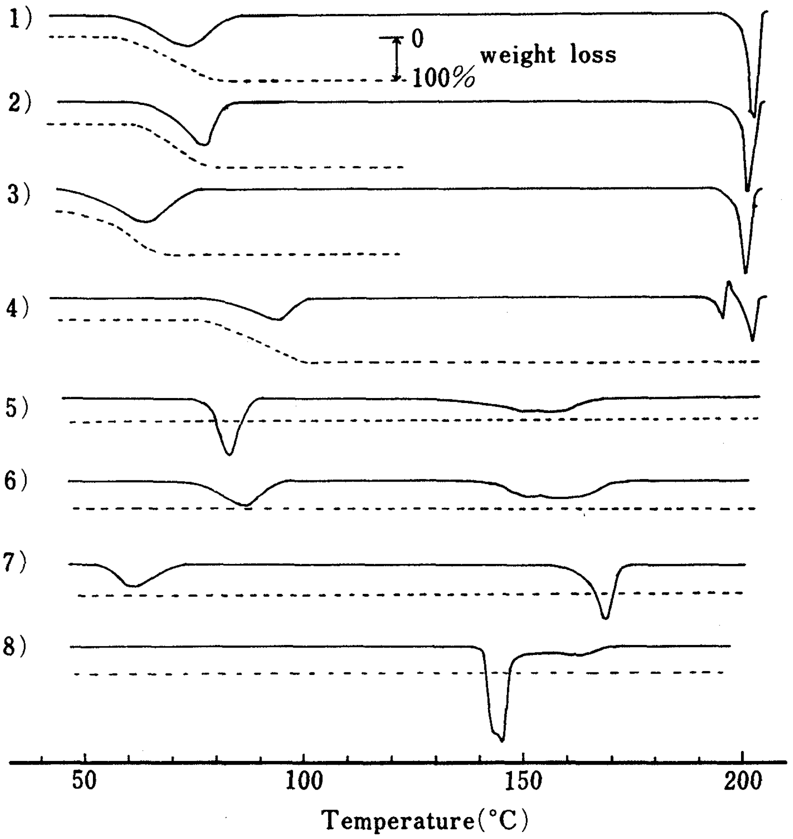

Fig. 4. Simultaneous DSC-TG Curves

—— DSC Curve, ---- TG Curve

Open conditions (1—4)
1) The acetone solvate: DSC range, ±8 mcal/s; heating rate, 5°C/min; sample weight, 13.303 mg; weight loss, 13.303 → 10.859 mg.
2) The 2-butanone solvate: DSC range, ±8 mcal/s; heating rate, 5°C/min; sample weight, 16.00 mg; weight loss, 16.00 → 12.57 mg.
3) The 2-pentanone solvate: DSC range, ±8 mcal/s; heating rate, 5°C/min; sample weight; 16.424 mg; weight loss, 16.424 → 12.294 mg.
4) The dioxane solvate: DSC range, ±8 mcal/s; heating rate, 5°C/min; sample weight, 9.222 mg; weight loss, 9.222 → 6.929 mg.

Closed conditions (5—8)
5) The acetone solvate: DSC range, ±4mcal/s; heating rate, 5°C/min; sample weight, 14.110 mg.
6) The 2-butanone solvate: DSC range, ±4 mcal/s; heating rate, 5°C/min; sample weight, 12.091 mg.
7) The 2-pentanone solvate: DSC range, ±4 mcal/s; heating rate, 5°/min; sample weight, 11.303 mg.
8) The dioxane solvate: DSC range, ±4 mcal/s; heating rate, 5°C/min; sample weight, 11.145 mg.

TABLE I. Enthalpies of Peritectic Reactions and Activation Energies of Desolvation of Sulfathiazole Ketone and Dioxane Solvates

	Acetone	2-Butanone	2-Pentanone	Dioxane
Peritectic temperature (°C)	78.5	76.0	56.5	141.0
ΔH (kcal/mol)	3.7	3.2	3.2	—
Activation energy (kcal/mol)	25.2	25.5	28.9	29.0

Visual Observation of Peritectic Fusion

When crystals of each solvate were heated in a sealed glass tube, partial liquefaction was observed in all cases at almost the same temperature as the first DSC peak under closed conditions. Thus, it was confirmed visually that all the solvates belong to the class of compounds with incongruent melting points.

Kinetic Analysis of Desolvation Mechanisms and Estimation of Activation Energies

TG measurements were conducted at several constant temperature below the peritectic

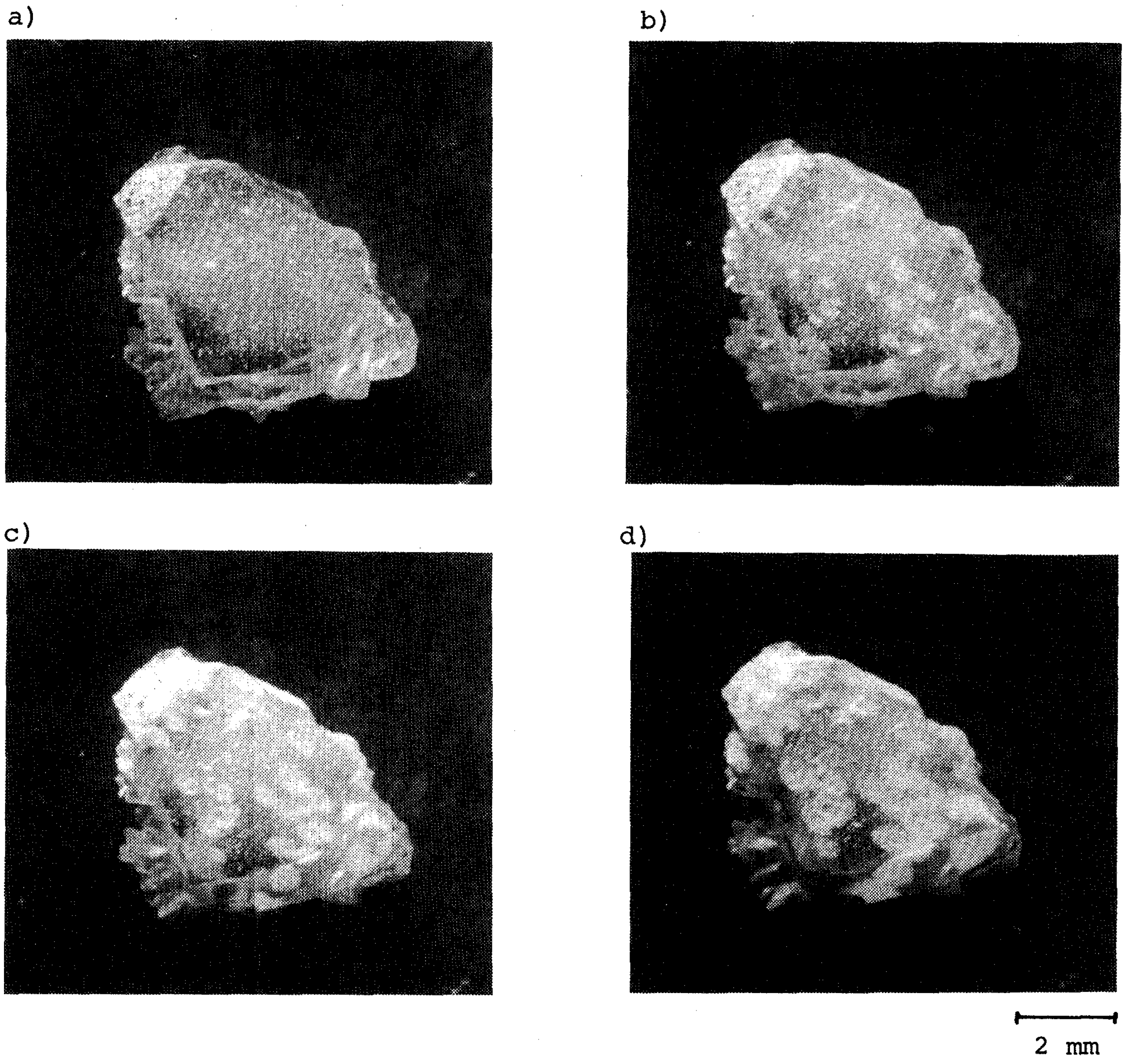

Fig. 5. Desolvation Process of the Acetone Solvate Crystal at 50°C

After heating for, a) 19.6 min, b) 26.0 min, c) 29.0 min, d) 32.0 min.

point of each solvate and the fractions desolvated were substituted into kinetic equations derived from different mechanisms of solid state decomposition. Among the isothermal desolvation curves thus obtained, the best linearity was found in every case with the A_2-type of Avrami–Erofeev equations based on random nucleation and two-dimensional crystal growth.[5]

The above desolvation mechanism is also supported by the photographs in Fig. 5 which show qualitatively that the nuclei were formed randomly and grew on the crystal surface.

From the slopes of the above linear desolvation curves, the most reliable rate constants were obtained. Thus, the activation energies for desolvation were estimated (Table I) from the slopes of the Arrhenius plots (Fig. 6).

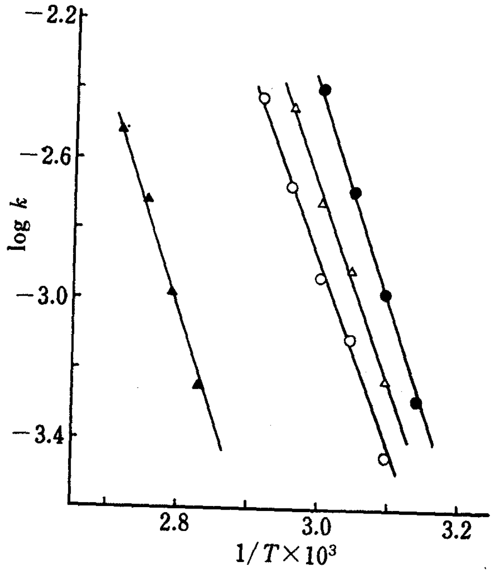

Fig. 6. Plots of log $k^{a)}$ against $1/T$ for the Desolvation of Sulfathiazole Ketone and Dioxane Solvates

○; the acetone solvate;
△; the 2-butanone solvate;
●; the 2-pentanone solvate;
▲; the dioxane solvate.
a) k is the rate constant of the Avrami–Erofeev equation.

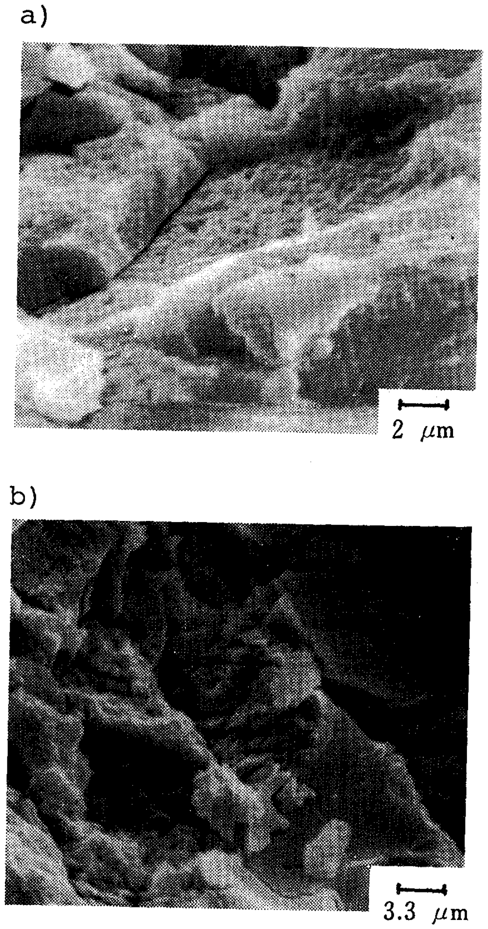

Fig. 7. Scanning Electron Microphotographs of Sulfathiazole recovered from Its Acetone Solvate

a) After desolvation at 25°C under 1 atm; ×5000.
b) After desolvation at 95°C under 1 atm; ×3000.

Effect of Desolvating Conditions on Size Reduction of the Recovered Sulfathiazole

As mentioned in the experimental section, specific surface areas of the desolvated particles were measured under various conditions. The results shown in Table II can be summarized as follows.

1) Significant differences in specific surface areas were obtained with all four solvates between desolvation below and above the peritectic temperatures.

2) Even in solid phase decomposition, the lower the temperature, the larger the specific surface area attained, as can be seen in the desolvations of the dioxane solvate at 60°C and at 95°C.

3) Although in some cases, the effect of pressure was negligible, desolvation under reduced pressure seemed to be preferable, if the temperature was kept below the peritectic point.

4) When the solvates have the same combining ratio, the greater the molecular weight or the molecular volume of the solvent component, the more effectively the size was reduced. This is particularly evident with the ketone solvates, since the combining forces in them

might be similar.

5) After complete peritectic decomposition where liquid phase crystallization of the solid component is possible, the specific surface areas were found to be much less than those obtained by solid phase desolvation.

TABLE II. Specific Surface Areas of the Powders recovered after Desolvation of the Ketones and Dioxane Solvates

		Acetone	2-Butanone	2-Pentanone	Dioxane
25°C	1 atm	2.4 m^2/g	7.3 m^2/g	18.7 m^2/g	—
	2 mmHg	2.8	7.4	23.1	
60°C	1 atm				13.5 m^2/g
	2 mmHg				16.7
95°C	1 atm	1.8	4.1	11.4	9.0
	2 mmHg	1.7	3.9	15.5	8.4
145°C	1 atm	—	—	—	2.8
	2 mmHg				3.8
After peritectic reaction in sealed glass tube		0.47	0.40	0.48	—

Surface Appearance of the Recovered Sulfathiazole Particles

Based on the differences in specific surface area, it was considered that the conditions during desolvation significantly influence the surface state of the recovered sulfathiazole. For this reason, particles desolvated from the four solvates were examined by scanning electron microscopy (Figs. 7—10). The following characteristic changes were noticed in the surface appearance under various conditions.

1) After desolvation below the peritectic temperature, ecah solvate turned to loose aggregates composed of tiny particles of sulfathiazole. However, the aggregates retained the extenal form of the original solvate.

2) The primary particles took a long or short rod shape with rounded corners. This can be attributed to disappearance of crystal apexes and edges because of the tendency for a decrease of the surface energy with small particles.

3) Under the same conditions below the peritectic temperature, the size of the primary particles from the three ketone solvates became smaller in order of the molecular weight of the solvent component.

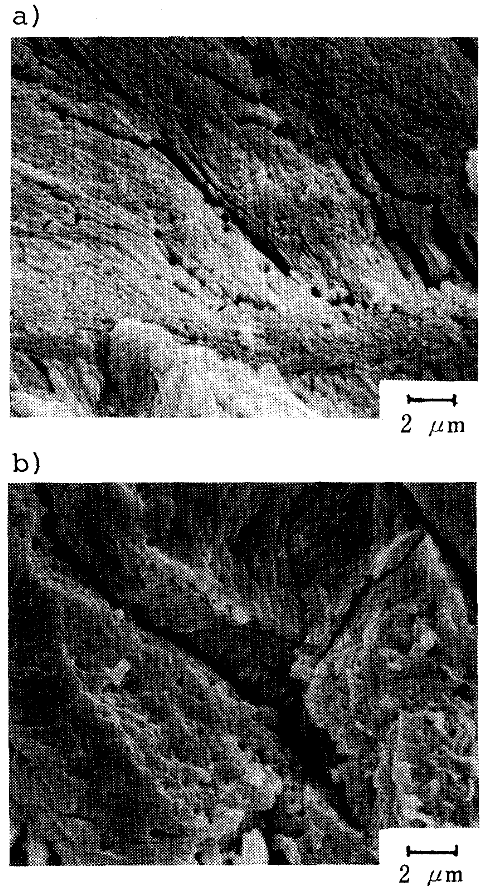

Fig. 8. Scanning Electron Microphotographs of Sulfathiazole recovered from Its 2-Butanone Solvate

a) After desolvation at 25°C under 1 atm; ×5000.
b) After desolvation at 95°C under 2 mmHg; ×5000.

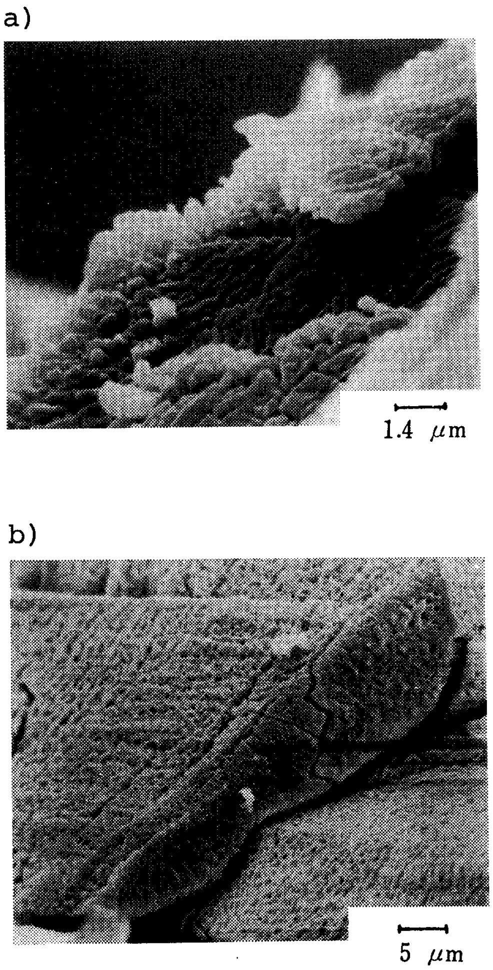

Fig. 9. Scanning Electron Microphotographs of Sulfathiazole recovered from Its 2-Pentanone Solvate

a) After desolvation at 25°C under 1 atm; ×7000.
b) After desolvation at 95°C under 2 mmHg; ×2000.

4) When the solvate was heated over the peritectic temperature, it was observed that many pores of submicron size were distributed on the surface. Also, masses with flat surfaces and sharp edges were often found in other parts. The former is a result of bumping of the peritectic liquid through the already desolvated portions, while the latter is a result of crystallization in the peritectic liquid.

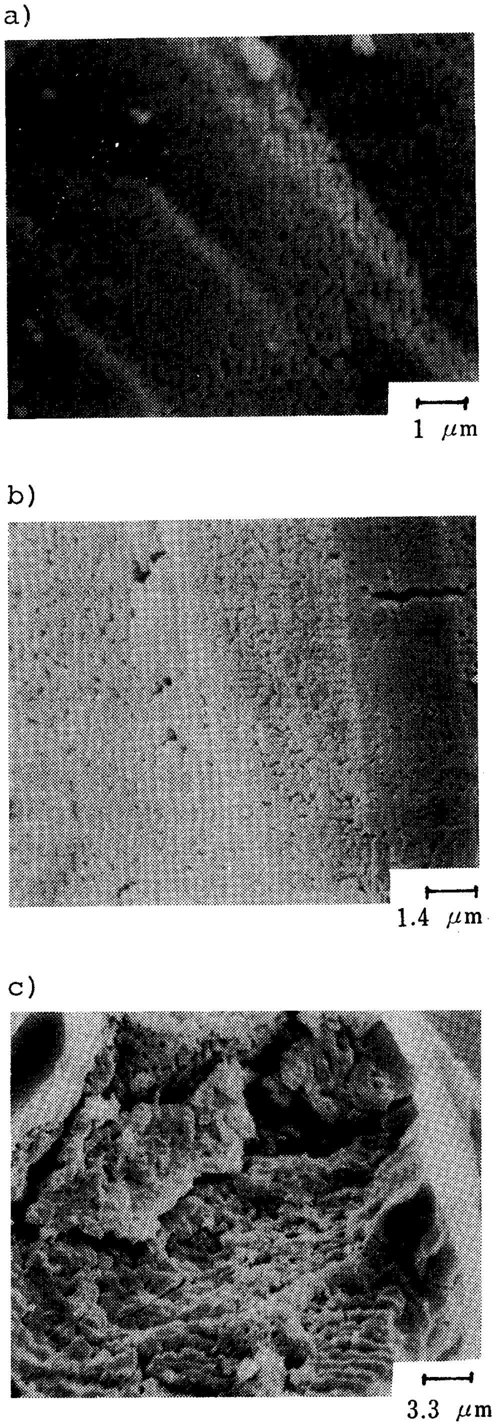

Fig. 10. Scanning Electron Microphotographs of Sulfathiazole recovered from Its Dioxane Solvate

a) After desolvation at 60° under 1 atm; ×10000.
b) After desolvation at 95° under 1 atm; ×7000.
c) After desolvation at 145° under 2 mmHg; ×3000.

These findings again confirm that for effective size reduction *via* a solvate, solid phase desolvation is necessary; if even partial liquefaction occurs, the surface area of the product will be reduced significantly.

References and Notes

1) This forms Part XIX of the series entitled "Studies on Methods of Particle Size Reduction of Medicinal Compounds" Part XVIII: K. Sekiguchi, Y. Tsuda, K. Chihara, and E. Suzuki, *Yakugaku Zasshi*, **103**, 213 (1983).
2) K. Shirotani and K. Sekiguchi, *Chem. Pharm. Bull.*, **29**, 2983 (1981).
3) M. Kanke and K. Sekiguchi, *Chem. Pharm. Bull.*, **21**, 871 (1973); G.J. Kruger and G. Gafner, *Acta Cryst.*, **B28**, 272 (1972); G.J. Kruger and G. Gafner, *Acta Cryst.*, **B27**, 326 (1971); M. Lagas and G.F. Lerk, *International Journal of Pharmaceutics*, **8**, 11 (1981).
4) H. W. Hoyer, "Thermal Analysis Comparative Studies on Materials," ed. by H. Kambe and P.D. Garn, John Wiley and Sons, Inc., New York, 1974, pp. 65—78.
5) V. Satava, *Thermochim. Acta*, **2**, 423 (1971); J.M. Criado, J. Morales, and V. Rives, *Journal of Thermal Analysis*, **14**, 221 (1978); W.E. Garner, "Chemistry of the Solid States," Academic Press, Inc., New York, 1955; M. Avrami, *J. Chem. Phys.*, **7**, 1103 (1939); *idem, ibid.*, **8**, 212 (1940); *idem, ibid.*, **9**, 177 (1941).