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Studies on the Ethanol, *n*-Propanol and Isopropanol Solvates of Cortisone Acetate[1)]

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Solvates of cortisone acetate with ethanol, *n*-propanol and isopropanol were isolated, and their physico-chemical properties were investigated by X-ray powder diffractometry, infrared spectroscopy, differential scanning calorimetry, thermogravimetry, and scanning electron microscopy. Also, the specific surface areas and pore volumes of the desolvated products were measured by the BET method.

The combining ratios of the solvates were all determined to be 1 : 1 from the weight change in thermogravimetric curves. From the kinetic analysis of the thermal desolvation, it appeared that the desolvation proceeded in accordance with the mechanism of the two-dimensional growth of nuclei as represented by the Avrami–Erofeev equation. In addition, it was found that the powders recovered by desolvation had fairly large specific surface areas and pore volumes, and were easily divided into fine powders by only slight trituration.

Keywords——cortisone acetate; solvate; physico-chemical properties of solvates; kinetic analysis of desolvation, Avrami–Erofeev equation; specific surface area; pore volume; size reduction

Organic solid drugs often form solvates with a variety of solvents as a result of secondary forces such as hydrogen bonding and dipole interactions. These solvates are usually unstable on standing; therefore, it is possible to obtain the original drugs as aggregates of very fine powder by releasing the solvent components in the gaseous state.

In the present paper, isolation of the ethanol, *n*-propanol and isopropanol solvates of cortisone acetate was attempted and their identities were confirmed by several instrumental methods. Also, desorption mechanisms from these solvates as well as size reducibility *via* these solvates were examined by isothermal kinetic analysis and by surface area measurement.

Experimental

Materials——1) Cortisone Acetate: In most cases, cortisone acetate of J.P. IX was used. However, for identifying the polymorphic form of the desolvated products, forms II and I of the steroid were prepared by recrystallization from benzene and by heat transition at about 200°C, respectively.[2–4)]

2) Ethanol, *n*-Propanol and Isopropanol: Reagent-grade products were used after dehydration and subsequent distillation.

Preparation of Solvates——Each solvate was prepared by recrystallization from the corresponding alcohol solution at room temperature or by sorbing the alcohol vapour. For isothermal kinetic experiments, the recrystallized solvates were used after being crushed lightly and graded between 0.25 and 0.5 mm in size.

Identification of the Solvates and Their Desolvated Products——The identity of each solvate was confirmed by differential scanning calorimetry (DSC), thermogravimetry (TG), infrared spectrophotometry (IR) and X-ray powder diffractometry. The apparatus and the procedures were the same as described in the previous paper.[5–7)] In addition, the presence of ethanol, *n*-propanol or isopropanol and the absence of water in the solvates were confirmed by nuclear magnetic resonance spectroscopy (NMR). For this purpose, about 2.0—5.0% solutions of these solvates in deuterated $CHCl_3$ were prepared and their spectra were measured with a JNM PS-100 NMR spectrometer (Japan Electron Optics Laboratories Co., Ltd.) using tetramethylsilane as an internal reference.

IR Spectral Change during Heat Desolvation——Crystals of the ethanol solvate were triturated in Nujol and put in an IR heating cell. The temperature of the cell was maintained at 100 ± 1°C and the spectral changes in the –OH stretching region were examined intermittently until the solvate was completely desolvated.

Estimation of Activation Energies for Desolvation——The rate of decomposition of a solvate is expressed generally as

$$d\alpha/dt = k \cdot f(\alpha) \quad (1)$$

at constant temperature, where α is the fraction desolvated and k is the rate constant. Integrating equation (1) yields

$$\int_0^\alpha \frac{d\alpha}{f(\alpha)} = g(\alpha) = kt \quad (2)$$

As listed in Table I, a number of functions $g(\alpha)$ have been proposed by several authors on the basis of various assumed mechanisms for solid decomposition.[8,9] If a straight line is obtained by plotting the values of a certain $g(\alpha)$ calculated from the isothermal desolvation data against time t, the kinetic equation is considered to be valid. Also, from the rate constants k at different temperatures, the activation energy E can be estimated by means of the Arrhenius equation

$$k = A \exp(-E/RT)$$

where A is the frequency factor and T is the absolute temperature.

Table I. Kinetic Equations for the Most Common Mechanisms believed to operate in Solid-state Decomposition

Symbol	$g(\alpha)$	Mechanism
R_1	α	Zero-order mechanism (Polany–Wigner equation)
R_2	$1-(1-\alpha)^{1/2}$	Phase boundary reaction; cylindrical symmetry
R_3	$1-(1-\alpha)^{1/3}$	Phase boundary reaction; spherical symmetry
F_1	$-\ln(1-\alpha)$	Random nucleation; one nucleus on each particle
A_2	$[-\ln(1-\alpha)]^{1/2}$	Random nucleation; two-dimensional growth of nuclei (Avrami–Erofeev equation)
A_3	$[-\ln(1-\alpha)]^{1/3}$	Random nucleation; three-dimensional growth of nuclei (Avrami–Erofeev equation)
D_1	α^2	One-dimensional diffusion
D_2	$(1-\alpha)\ln(1-\alpha)+\alpha$	Two-dimensional diffusion
D_3	$[1-(1-\alpha)^{1/3}]^2$	Three-dimensional diffusion (Jander equation)
D_4	$(1-2\alpha/3)-(1-\alpha)^{2/3}$	Three-dimensional diffusion (Grinstring–Brounshtein equation)

Surface Appearance of the Desolvated Particles by Scanning Electron Microscopy——The effects of desolvating conditions on the surface appearance of the recovered steroid were examined with a Hitachi-Akashi MINI-SEM scanning electron microscope.

Measurement of Specific Surface Area and Total Pore Volume[10]——Adsorption isotherms for N_2 on the cortisone acetate recovered after desorption from the solvate crystals were constructed by using a BET apparatus (Model p-600, Shibata Chemical Apparatus Mfg. Co., Ltd.). The total pore volume of the pores having diameter less than 600 Å and their mean sizes were calculated from the following equations (3) and (4).

$$V_p = V \times 1.555 \times 10^{-3} \quad (3)$$

V_p: total pore volume (ml/g)
V: amount of N_2 adsorbed at a relative pressure of 0.967 at S.T.P. (ml/g)

$$d = 4V_p/S_w \quad (4)$$

d: mean pore diameter
S_w: specific surface area

Results and Discussion

Solvate Formation of Cortisone Acetate with Ethanol, *n*-Propanol and Isopropanol

Cortisone acetate was easily crystallized out from ethanol, *n*-propanol and isopropanol. As shown in Fig. 1, these crystals were all long rods with sharp ends, very similar in shape, and remained transparent for over one month at room temperature; however, on heating they quickly became opaque. Judging from these observations, it is quite probable that solvates

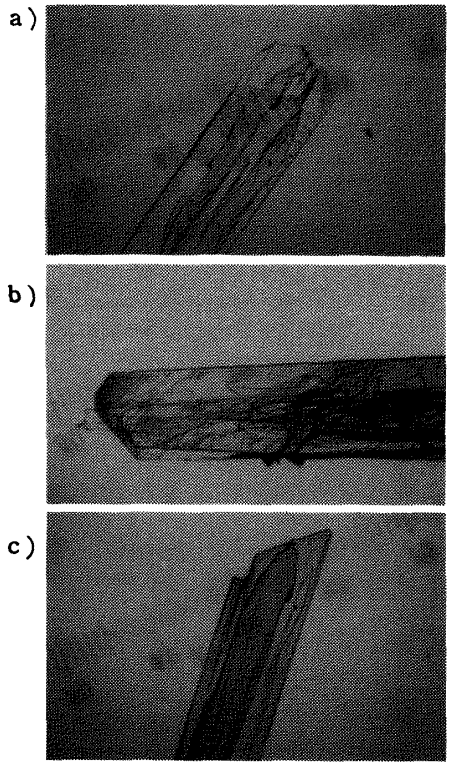

Fig. 1. Optical Microphotographs of Cortisone Acetate Alcohol Solvates

a) the ethanol solvate prepared by recrystallization; ×40,
b) the *n*-propanol solvate prepared by recrystallization; ×40,
c) the isopropanol solvate prepared by recrystallization; ×40.

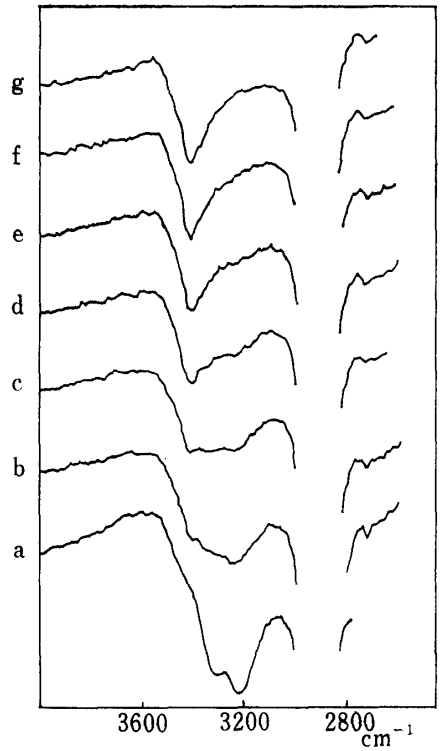

Fig. 3. IR Spectral Change of the Cortisone Acetate Ethanol Solvate in a Heating Cell maintained at 100°C

a) before heating, and after heating for, b) 1 min, c) 3 min, d) 5 min, e) 7 min, f) 10 min, g) 15 min.

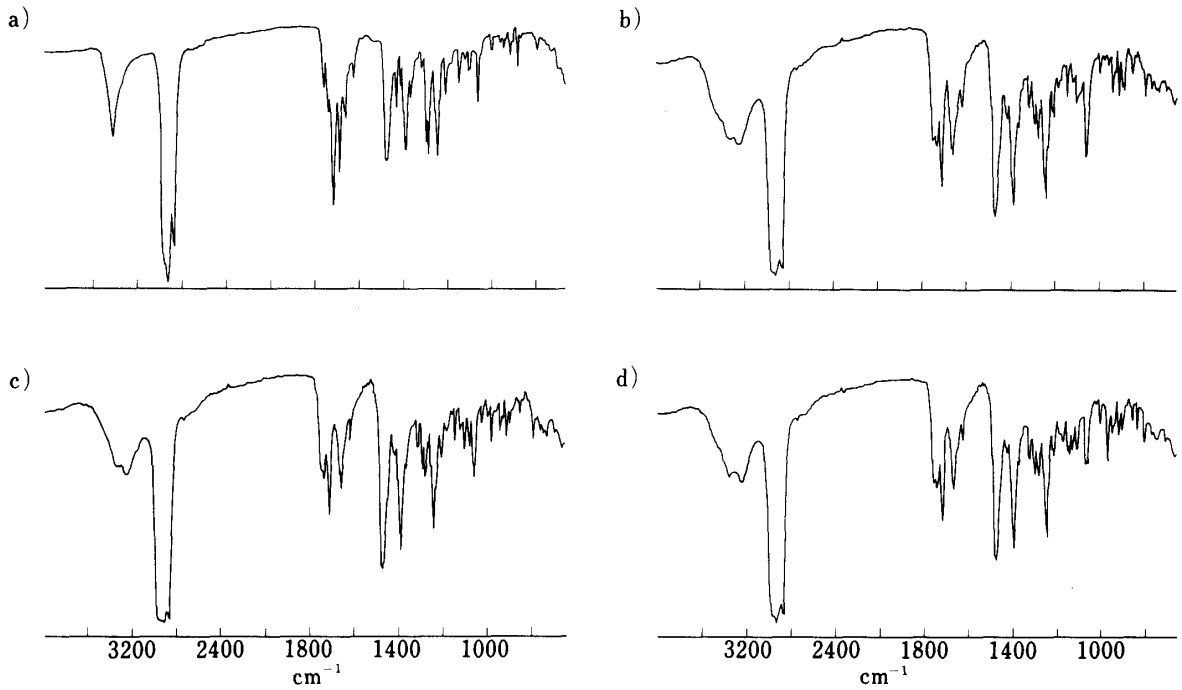

Fig. 2. IR Spectra of Cortisone Acetate and Its Alcohol Solvates

a) cortisone acetate form II, b) the ethanol solvate,
c) the *n*-propanol solvate, d) the isopropanol solvate.

were formed between the steroid and ethanol, *n*-propanol and isopropanol. Accordingly, these crystals were examined by DSC, TG, IR, NMR and X-ray diffraction analysis in order to confirm solvate formation.

1) **IR and NMR Spectra and X-Ray Powder Diffraction**——The results are shown in Figs. 2—5. The solvate crystals gave IR spectra and X-ray patterns significantly different from those of the three polymorphs of cortisone acetate in the literature.[2-4] In the NMR spectrum

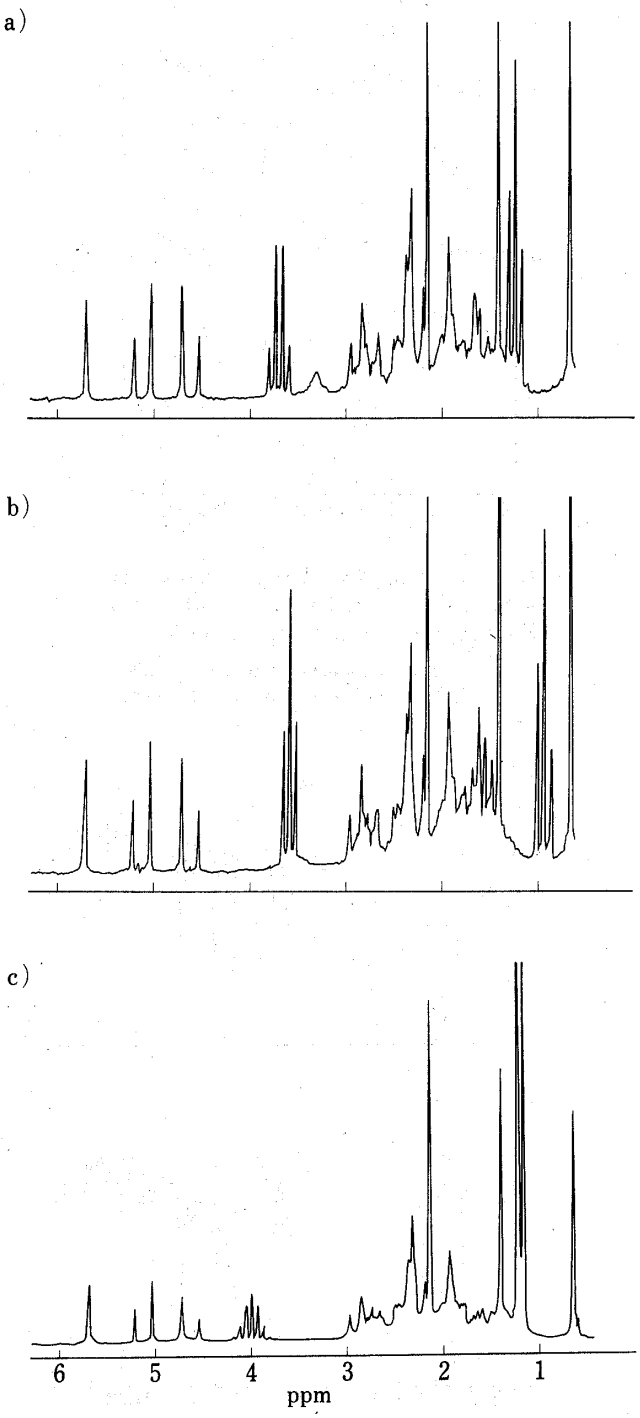

Fig. 4. NMR Spectra of Cortisone Acetate Alcohol Solvates

a) the ethanol solvate, b) the *n*-propanol solvate, c) the isopropanol solvate.

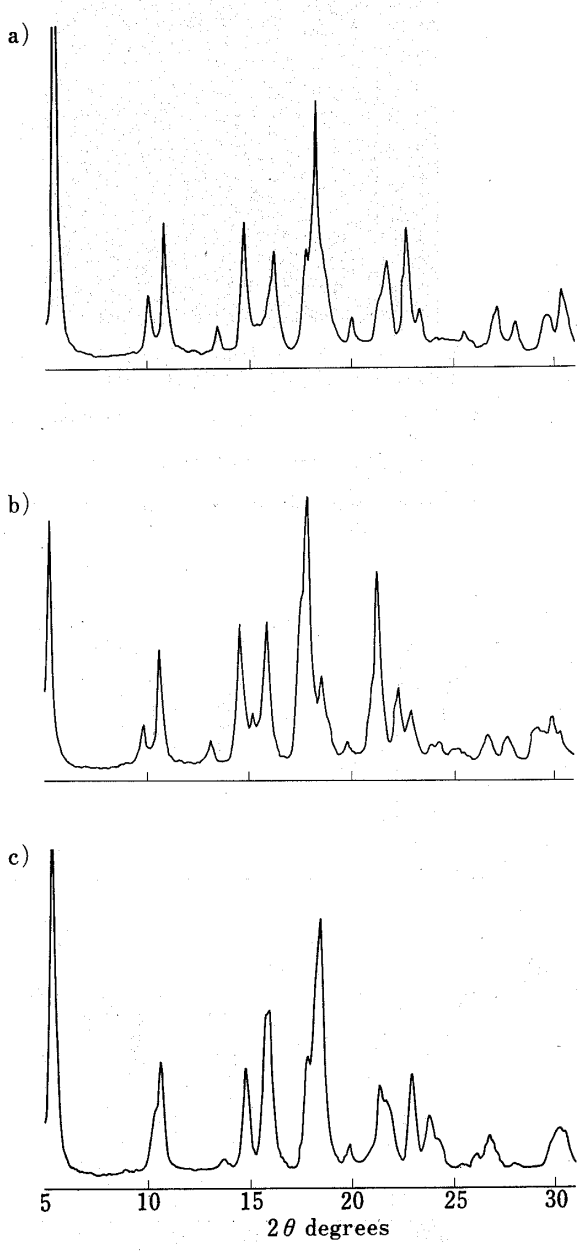

Fig. 5. X-Ray Powder Diffractograms of Cortisone Acetate Alcohol Solvates

a) the ethanol solvate, b) the *n*-propanol solvate, c) the isopropanol solvate.

of the ethanol solvate, there appeared a quartet and a triplet at 3.69 and 1.24 ppm, respectively, ascribable to the resonances of the $-CH_2-$ and $-CH_3$ protons of the ethanol component. In the case of the *n*-propanol solvate, the resonance of the $-CH_3$ protons appears at 0.92 ppm as a triplet. Another triplet is also found at 3.58 ppm due to the methylene protons of the $-CH_2OH$ group. Further, in the spectrum of the isopropanol solvate solution, the doublet at 1.19 ppm and the septet at 4.0 ppm can reasonably be assigned to two $-CH_3$ protons and the $-CH-$ proton of the contained isopropanol, respectively. In no case was a chemical shift due to protons of water detected. These findings confirm that the three kinds of solvates were really formed. It was also evident from the changes in IR patterns on heating that these solvates were ultimately converted to the polymorphic form II of the steroid.

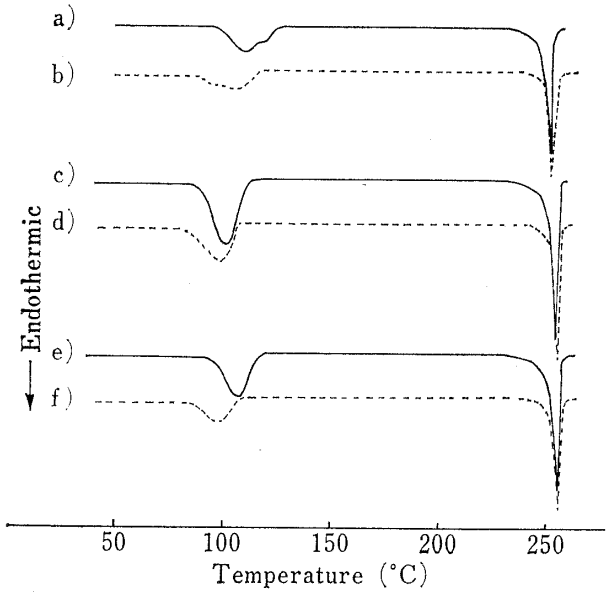

Fig. 6. DSC Curves of Cortisone Acetate Alcohol Solvates

a) the ethanol solvate, prepared by recrystallization: heating rate, 16°C/min; sample weight, 5.244 mg.
b) the ethanol solvate prepared by sorption: heating rate, 16°C/min; sample weight, 4.866 mg.
c) the *n*-propanol solvate prepared by recrystallization: heating rate, 16°C/min; sample weight, 8.521 mg.
d) the *n*-propanol solvate prepared by sorption: heating rate, 16°C/min; sample weight, 6.112 mg.
e) the isopropanol solvate prepared by recrystallization: heating rate, 16°C/min; sample weight, 7.506 mg.
f) the isopropanol solvate prepared by sorption: heating rate, 16°C/min; sample weight, 4.581 mg.

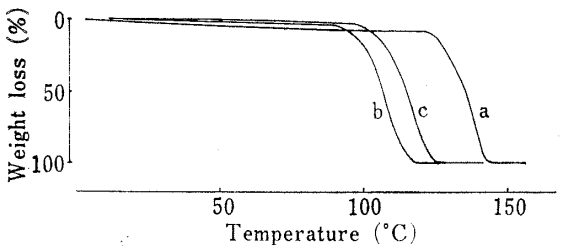

Fig. 7. TG Curves of Cortisone Acetate Alcohol Solvates prepared by Recrystallization

a) the ethanol solvate; 2.388 mg→2.139 mg (cortisone acetate: ethanol=1: 1.02),
b) the *n*-propanol solvate; 2.132 mg→1.862 mg (cortisone acetate: *n*-propanol=1: 0.96),
c) the isopropanol solvate; 2.255 mg→1.976 mg (cortisone acetate: isopropanol=1: 0.93).

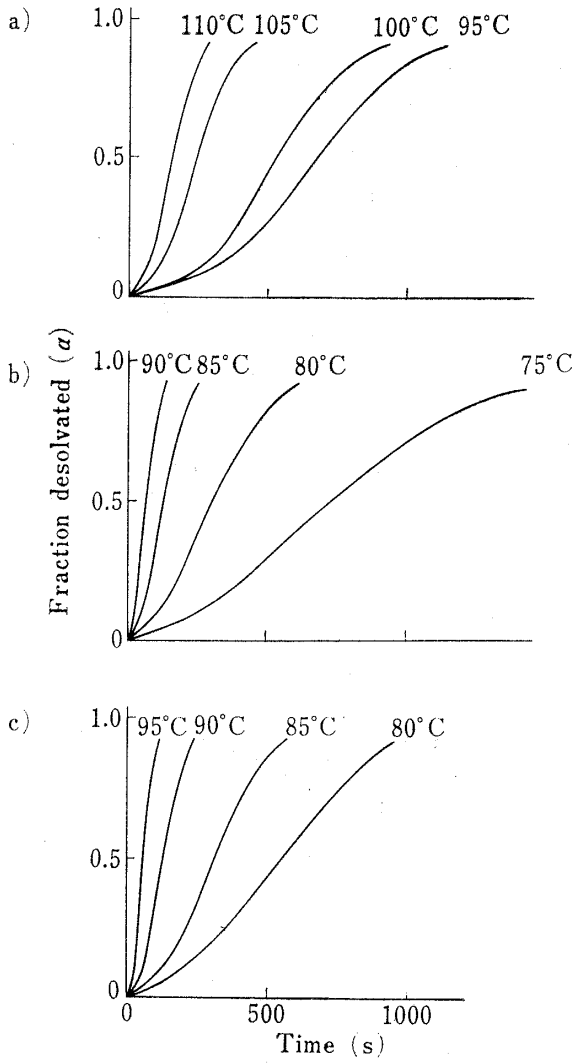

Fig. 8. Isothermal Desolvation Curves of Cortisone Acetate Alcohol Solvates prepared by Recrystallization

a) the ethanol solvate, b) the *n*-propanol solvate, c) the isopropanol solvate.

2) **DSC and TG Curves**——DSC under the closed condition could not be done because of early rupture of the sample pan; therefore, the curves in Fig. 6 are those under the semiclosed condition. In the DSC curves of the three solvates, the first endothermic peak is assigned to desolvation of alcohol, while the second sharp one at about 250°C is assigned to melting of cortisone acetate. Although the desolvation peaks of the sorbed samples appeared at appreci-

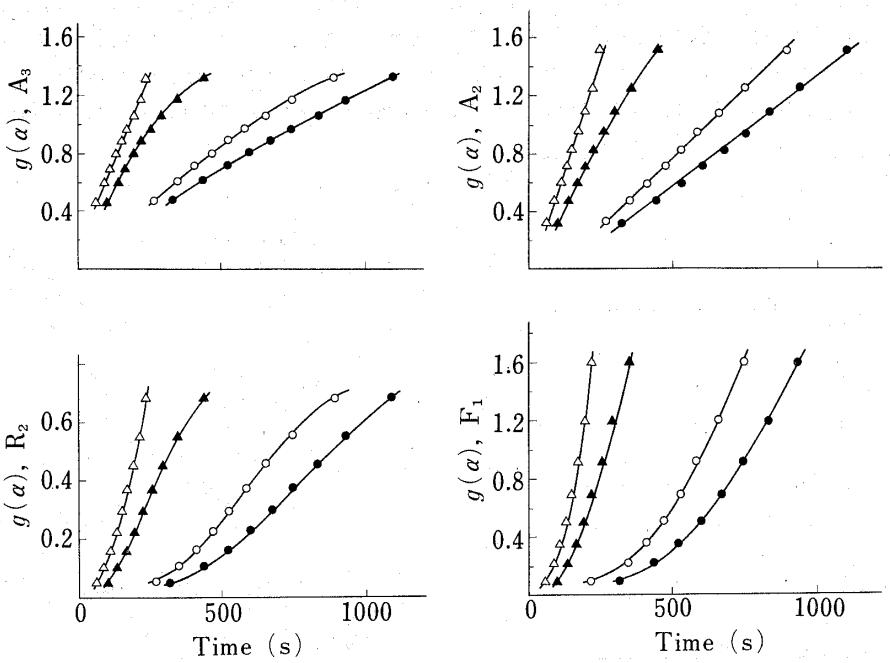

Fig. 9. Dependence of $g(\alpha)$ on Time for the Isothermal Desolvation of the Cortisone Acetate Ethanol Solvate (See Table I)

●: 95°C, ○: 100°C, ▲: 105°C, △: 110°C.

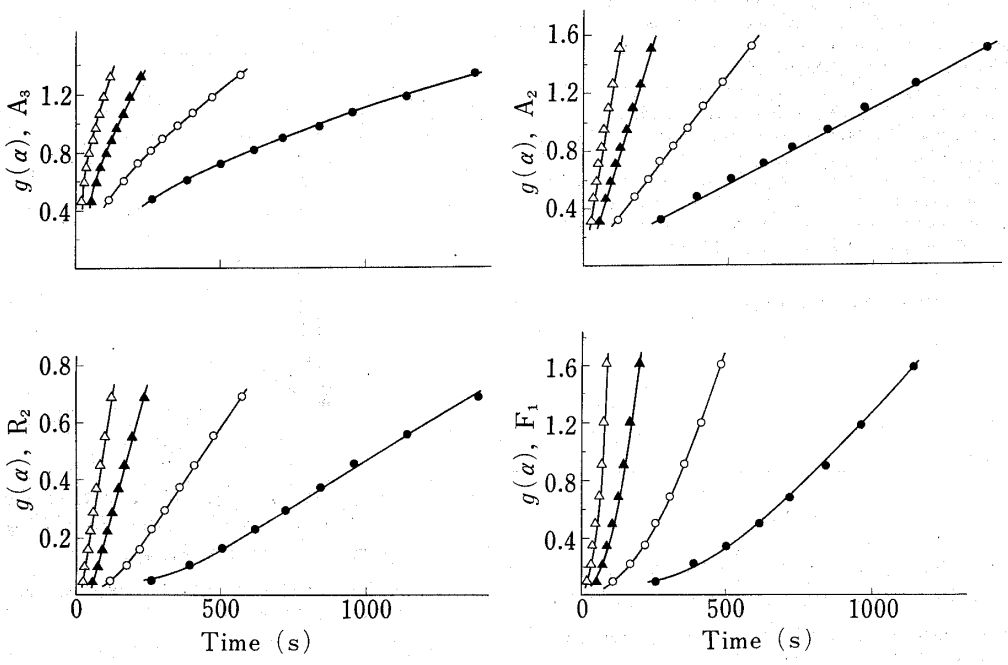

Fig. 10. Dependence of $g(\alpha)$ on Time for the Isothermal Desolvation of the Cortisone Acetate *n*-Propanol Solvate (See Table I)

●: 75°C, ○: 80°C, ▲: 85°C, △: 90°C.

ably lower temperatures, the endothermic heats were found to be nearly the same as those of the recrystallized samples. Accordingly, the same solvates are formed by recrystallization and by sorption.

When the recrystallized sample of the ethanol solvate was heated rapidly, desolvation was often represented by two successive DSC peaks. This result suggests that partial fusion occurred, presumably due to peritectic decomposition; however, it is clear that unless the heating rate is too rapid, the alcohol component can be easily removed without preliminary liquefaction.

As shown in Fig. 7, the TG curves of the three solvates each exhibited a single step at temperatures corresponding to the desolvation DSC peaks. The combining ratios of all the solvates were determined to be 1 : 1 from the weight changes in the TG curves.

Activation Energies of Desolvation and the Mechanisms involved

The isothermal desolvation curves in Fig. 8 were drawn from the original TG data at constant temperatures by taking the fractions α desolvated as the ordinates. From the values of α, the functions $g(\alpha)$ in Table I were calculated and the curves in Figs. 9—11 were obtained by plotting $g(\alpha)$ against time t, On comparing these curves, the best linearity was found with those according to the Avrami–Erofeev equation (A_2), and kinetically reliable values of the rate constants k for the desolvation of the three solvates can be determined from the slopes of the lines. Thus, the activation energies for the ethanol, *n*-propanol and isopropanol

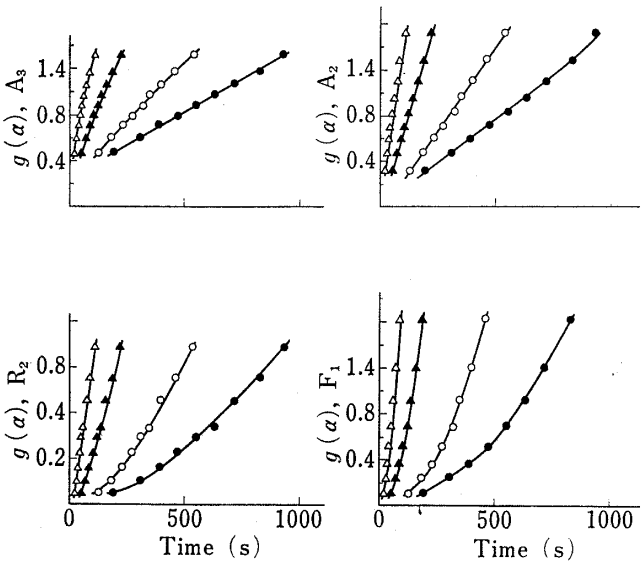

Fig. 11. Dependence of $g(\alpha)$ on Time for the Isothermal Desolvation of the Cortisone Acetate Isopropanol Solvate (See Table I)

●: 80°C, ○: 85°C, ▲: 90°C, △: 95°C.

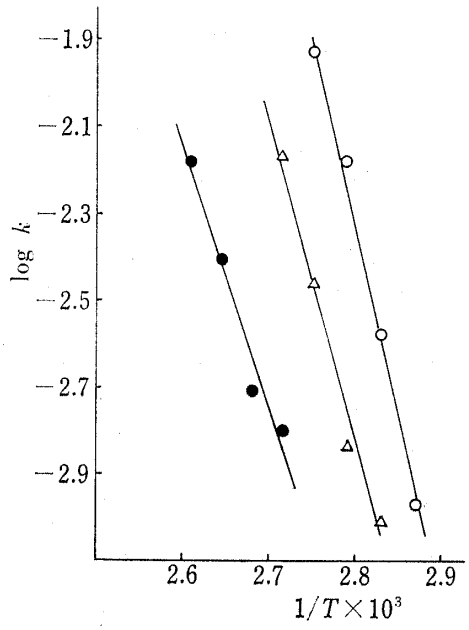

Fig. 12. Plots of log k against $1/T$ for the Thermal Desolvation of Cortisone Acetate Alcohol Solvates

●: the ethanol solvate,
○: the *n*-propanol solvate,
△: the isopropanol solvate.

TABLE II. Specific Surface Areas and Pore Volumes for Desolvated Particles

Desolvated particles	Specific surface area (m^2/g)	Adsorbed N_2 volume at $P/P_s=0.967$ (ml/g, S.T.P.)	Total pore volume (ml/g)
via Ethanol solvate	3.2	7.8	0.012
via *n*-Propanol solvate	3.5	6.5	0.010
via Isopropanol solvate	3.3	5.8	0.009

Table III. Densities of Cortisone Acetate and Its Alcohol Solvates[a)]

Cortisone acetate recrystallized from benzene	1.251
Ethanol solvate	1.214
n-Propanol solvate	1.222
Isopropanol solvate	1.216

a) The densities were determined by the floatation method.

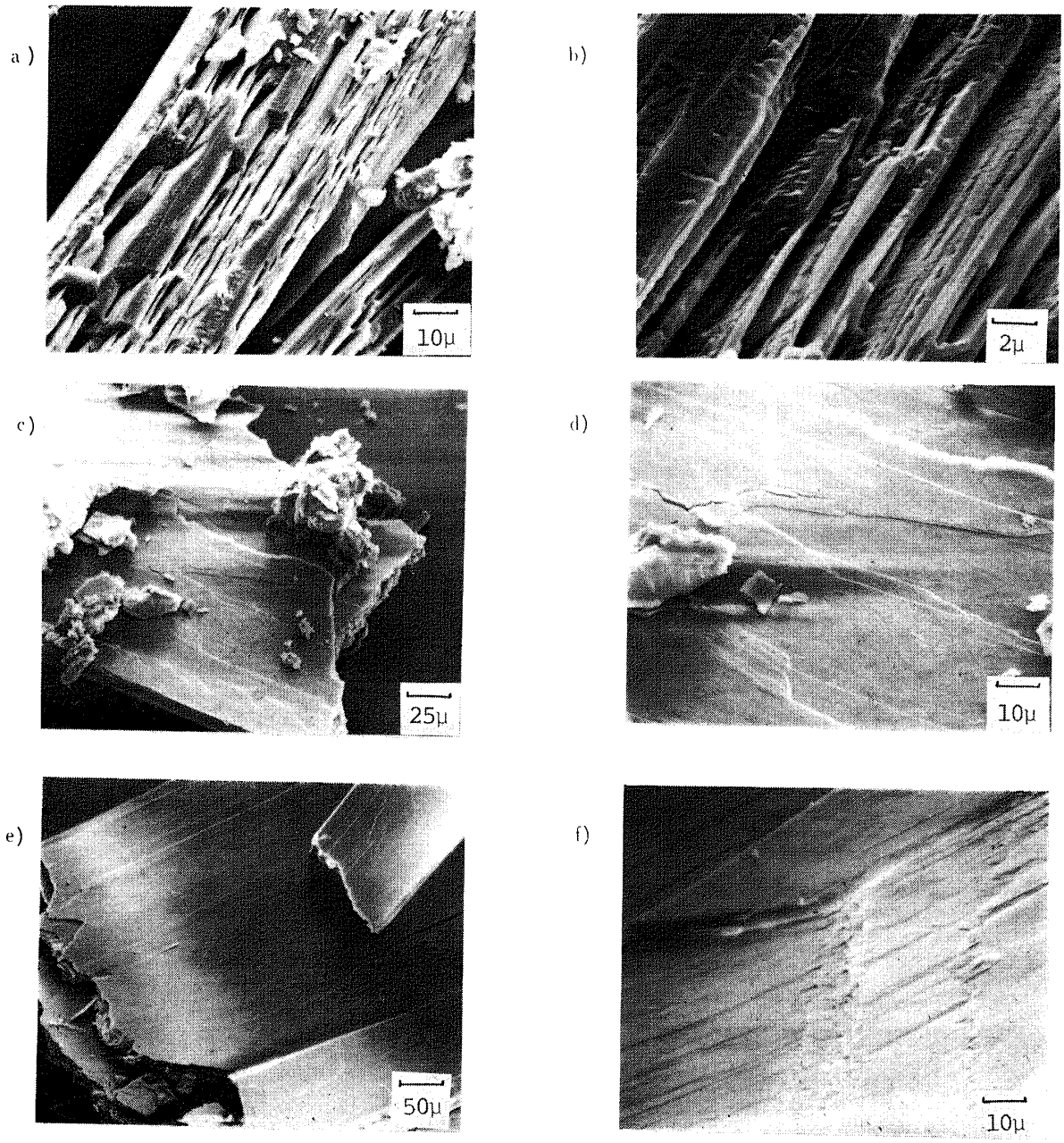

Fig. 13. Scanning Electron Microphotographs of Cortisone Acetate recovered from Its Alcohol Solvates

a) recovered from the ethanol solvate; ×1000,
b) recovered from the ethanol solvate; ×5000,
c) recovered from the *n*-propanol solvate; ×400,
d) recovered from the *n*-propanol solvate; ×1000,
e) recovered from the isopropanol solvate; ×200,
f) recovered from the isopropanol solvate; ×1000.

solvates were calculated to be 27, 40 and 37 kcal/mol, respectively, from the slopes of the Arrhenius plots (Fig. 12).

Although the above results were obtained by mechanical application of kinetic equations deduced theoretically, it appears that under the experimental conditions adopted, desolvation from these solvates will proceed by the mechanism of random nucleation and two-dimensional growth of the nuclei, and not by others such as the diffusion-controlled or the phase boundary reaction mechanisms.

Micromeritic Properties of the Desolvated Products

The effects of conditions during desolvation on the micromeritic properties of the recovered steroid were examined by scanning electron microscopy and by BET measurement. As shown in Fig. 13, when the crystals of the solvates were heated at a temperature below 80°C under a reduced pressure of 2—3 mm Hg, they became opaque and under the scanning electron microscope exhibited very small striae distributed all over the surface. However, the recovered particles were easily divided into fine powder by only slight trituration.

The specific surface areas and the total pore volumes of these particles, which were sieved to below 35 mesh in size, were determined from their adsorption isotherms. As shown in Table II, the values of the two properties were both comparatively large even without further grinding, and were similar for the products derived from all three solvates. Since the densities of the three solvates were found to be almost the same (Table III), the similar values of specific surface area and total pore volume probably indicate that nearly the same changes in molecular volume had occurred during desolvation of all these solvates.

Conclusion

Several crystalline forms of cortisone acetate have hitherto been reported by a number of authors but considerable discrepancies exist among their results. Such discrepancies are not only attributable to arbitrary designation by the authors but also to the lack of strict distinction among polymorphs, hydrates and solvates.

In the present study, three physical forms of cortisone acetate were isolated by recrystallization from its ethanol, *n*-propanol and isopropanol solutions or by vapor sorption of these alcohols. It was confirmed that they were not polymorphs but were solvates of the steroid each having a molecular combining ratio of 1 : 1.

Like other solvates of solid drugs, they were not stable on standing and yielded the original steroid with a loose structure by releasing their solvent components. Therefore, attempts were made to obtain basic data on these solvates as possible intermediates for the particle size reduction of cortisone acetate. It became clear that aggregates of the recovered steroid having a large specific surface area were formed by heating these solvates under reduced pressure and that the aggregates were easily disintegrated into very fine primary particles merely by slight trituration. Also, it was found that the desolvation processes followed the two-dimensional random nucleation mechanism as represented by the Avrami–Erofeev equation.

References and Notes

1) This forms part XIII of "Studies of Methods of Particle Size Reduction of Medicinal Compounds." Part XII: Y. Tsuda and K. Sekiguchi, *Yakugaku Zasshi*, **101**, 55 (1981).
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