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Kinetic Study of the Dehydration of Sulfaguanidine under Isothermal Conditions[1,2)]

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Intact and ground crystals of Sulfaguanidine (monohydrate) were prepared by recrystallization from aqueous solution with or without subsequent grinding. The hydrate was also prepared by sorbing H_2O vapor on the particles of anhydrous sulfaguanidine. By using these as sample materials, the dehydration curves at various temperatures were determined under dry conditions at 1 atm and *in vacuo*, as well as under various conditions of humidity. The applicability of various kinetic equations for solid state decomposition was investigated. It was found that chemically the same hydrate was dehydrated through different mechanisms depending on the crystal properties of the samples and the environmental conditions.

In addition, changes in surface appearance of the intact and the ground crystals were observed during heating at constant temperatures. It is suggested that the differences in the dehydration mechanisms may be attributable to different modes of nuclei growth.

Keywords——sulfaguanidine; dehydration (influencing factors and kinetic mechanisms); activation energy; change in surface appearance during dehydration; heating and isothermal thermogravimetry; differential scanning calorimetry; X-ray powder diffractometry

It is considered that desolvation from a solvate depends on various factors such as particle size, crystal imperfection, temperature, environmental pressure and the presence or absence of the solvent vapor. In order to determine the kinetic mechanism of such a solid phase decomposition, two methods of approach are usually adopted. One is the heating method (increasing temperature) and the other is the isothermal method (constant temperature). Recently, the former method, especially the use of differential scanning calorimetry or thermogravimetry has been popular because of its simplicity; however, the method is insufficient for examining the effects of all the possible influencing factors. Although the isothermal method is in principle considered to be more suitable, no detailed investigations have been done on desolvation from a drug solvate.

In the previous papers,[3,4)] the alcohol solvates of cortisone acetate and the ketone and dioxane solvates of sulfathiazole were isolated and identified. At the same time, the desolvation kinetics of these solvates were determined by checking the fractions desolvated at constant temperatures against the predictions of various kinetic equations hitherto proposed. In the present study, sulfaguanidine (monohydrate) was chosen as a model solvate and its dehydration mechanisms under isothermal conditions, as well as the influences of the above factors, were investigated.

Experimental

Preparation of Samples——1) Intact Crystals: Commercial sulfaguanidine (monohydrate) was recrystallized from twice-distilled water under gradual cooling. The rectangular crystals that formed were well developed and were completely transparent. No visible cracks were found on their surfaces under a magnifying glass. For the kinetic study, these crystals were stored at a relative humidity of about 75%.

2) Ground Crystals: The recrystallized sulfaguanidine was ground lightly and passed through a 150 mesh screen.

3) Sorbed Powder: The recrystallized sulfaguanidine was dehydrated completely by heating at about 130 °C at 2 mmHg pressure. Then, it was reconverted to the hydrate by storage at a relative humidity of 80% at 25 °C, and the powder below 150 mesh in size was used as the test sample.

Examination of Anhydrous and Hydrous Sulfaguanidine——The anhydrous and hydrous sulfaguanidine were examined by differential scanning calorimetry (DSC), thermogravimetry (TG), infrared spectroscopy (IR) and X-ray powder diffractometry. The instruments used were DSC-1B and TGS-1 (Perkin-Elmer Co., Ltd.) and JASCO IRA-1 and JDX-7F (Japan Electron Optics Co., Ltd.), respectively. The analytical procedures were essentially the same as described in the previous papers.[3,4)]

Kinetic Studies by Isothermal Thermogravimetry——A Perkin-Elmer TGS-1 thermobalance was used and an assembly permitting dehydration under reduced pressure in a dry or humid state was constructed as shown in Fig. 1.[5)] The procedures for determining the dehydration rate laws and the activation energies were the same as described previously,[3,4)] but the isothermal gravimetric analyses were done under the following conditions.

1) Under Dry Conditions at 1 atm: The system in Fig. 1 was opened and dry N_2 gas was introduced at a rate of 20 ml/min.

2) Under Dry and Evacuated Conditions: The system was evacuated at a pressure of 1 mmHg. Then, it was closed till the end of each measurement.

3) Under Humid and Evacuated Conditions: H_2O vapor was introduced into the system previously evacuated to 1 mmHg until the total pressure attained 10 mmHg. Then, the system was closed.

Microscopic Observation of Dehydration Process——The changes in appearance of the intact and ground crystals during dehydration at constant temperatures were observed with a Mettler FP-5 hot-stage microscope.

Surface Appearance by Scanning Electron Microscopy——Samples of the ground crystals and the sorbed powder as well as the dehydrated products were coated with gold film in an evacuated chamber at 10^{-5} mmHg and were observed electronmicroscopically. The apparatus used was an MSM-4 scanning electron microscope (Hitachi-Akashi Co., Ltd.).

Results and Discussion

Chemical Identity of the Three Sample Materials and Their Differences in Surface Appearance

As shown in Figs. 2 and 3, the IR spectrum and the X-ray diffraction pattern of the sorbed powder were the same as those of the intact and ground crystals and exhibited no peaks ascribable to anhydrous sulfaguanidine.[6)] Also, as shown in Fig. 4, similar DSC and TG curves were obtained with the three samples except that the small peak at about 156 °C due to polymorphic transition[6)] was not observed in the sorbed powder, and that the peaks and steps due to dehydration appeared at somewhat different temperatures. From the weight decreases, it was determined that each of the samples contained 1 mol of H_2O ($C_7H_{10}N_4O_2S : H_2O = 1 : 0.998 \pm 0.005$ for the intact crystals, $1 : 0.99 \pm 0.01$ for the ground crystals and $1 : 1.00 \pm 0.01$

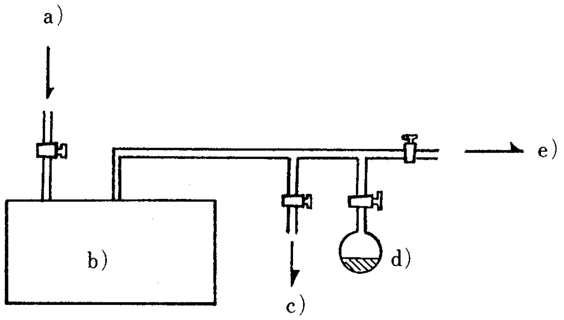

Fig. 1. TG Assembly for Measurement of Dehydration Curves under Various Conditions

a) dry N_2 gas inlet; b) thermobalance; c) pressure gauge; d) degassed water; e) N_2 gas outlet or vacuum pump.

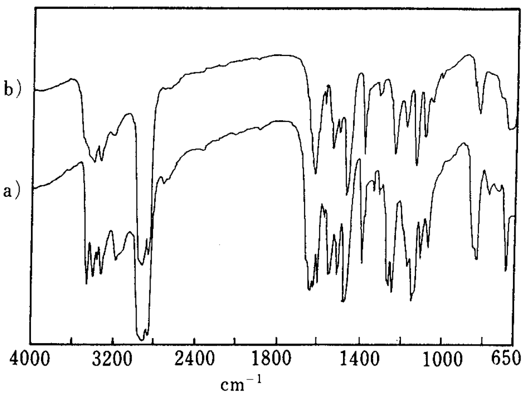

Fig. 2. IR Spectra of Anhydrous Sulfaguanidine and Sulfaguanidine (Monohydrate)

a) anhydrous sulfaguanidine; b) hydrous sulfaguanidine (sorbed powder).

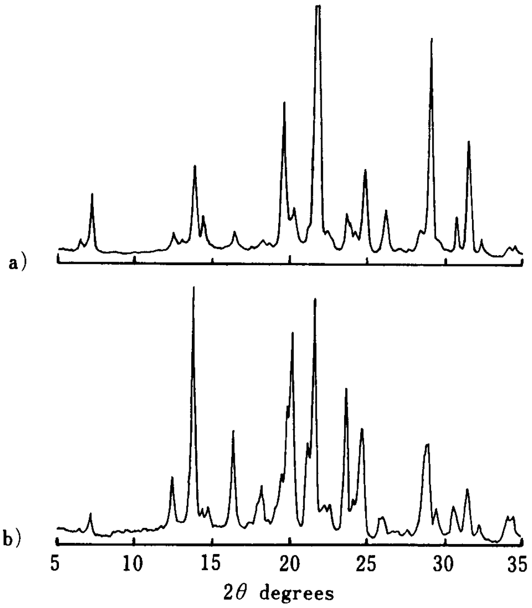

Fig. 3. X-Ray Powder Diffraction Patterns of Sulfaguanidine (Monohydrate)

a) monohydrate prepared by recrystallization; b) monohydrate prepared by sorption.

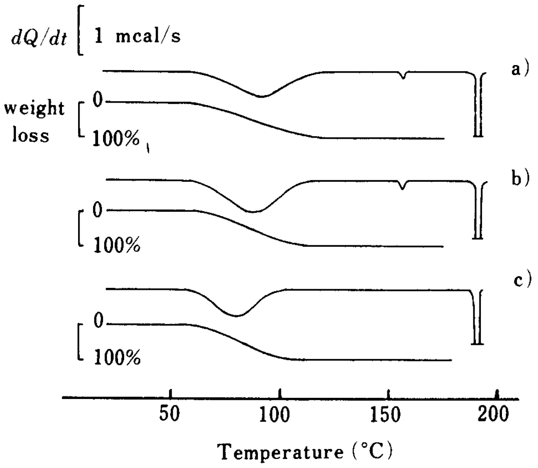

Fig. 4. DSC and TG Curves of Sulfaguanidine (Monohydrate)

a) intact crystals (about 1.5 mm in length) prepared by recrystallization: DSC range, 4 mcal/s; heating rate, 4 °C/min; sample weight, 3.57 mg; weight loss, 3.072→2.833 mg

b) ground crystals: DSC range, 4 mcal/s; heating rate, 4 °C/min; sample weight, 4.08 mg; weight loss, 3.210→2.960 mg

c) sorbed powder: DSC range, 4 mcal/s; heating rate, 4 °C/min; sample weight, 3.00 mg; weight loss, 3.425→3.159 mg.

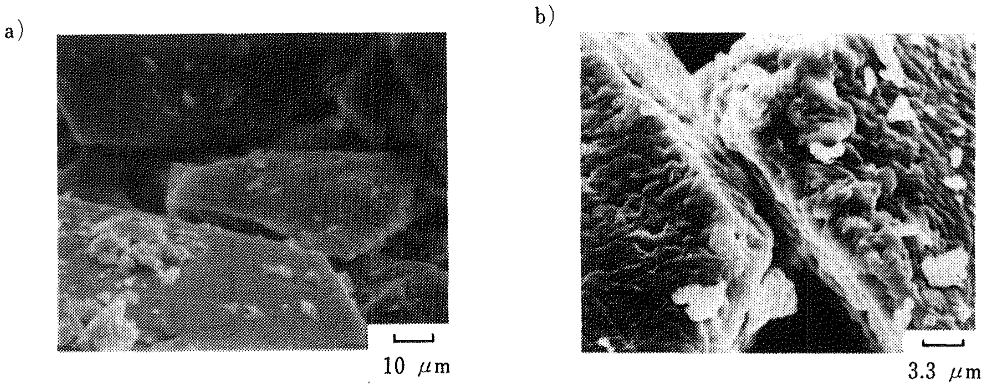

Fig. 5. Scanning Electron Microphotographs of Sulfaguanidine (Monohydrate)

a) ground crystals (×1000); b) sorbed powder (×3000).

for the sorbed powder). Accordingly, all were confirmed to be pure sulfaguanidine.

In spite of the chemicl identity of the samples, the surface appearances under the electron microscope differed distinctly, as shown in Fig. 5. The ground crystals consisted of fragments of single crystals to which some irregular fines adhered. The surface of the sorbed powder showed a porous structure formed by agglomeration of the primary particles produced during preliminary dehydration and subsequent hydration. The fact that the dehydration DSC peak and the corresponding TG step of the sorbed powder began to appear at slightly lower temperature than those of the crystalline samples might be related to such differences in appearance.

Dehydration Curves at Constant Temperatures

The curves in Figs. 6—8 were constructed from the isothermal gravimetry data by plotting the fraction dehydrated α against time t. They represent the differences of

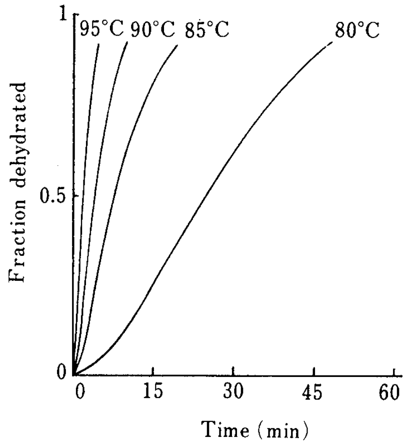

Fig. 6. Isothermal Desolvation Curves of Sulfaguanidine (Monohydrate) Intact Crystals[a] under Dry Conditions at 1 atm

[a] About 1.5 mm in length.

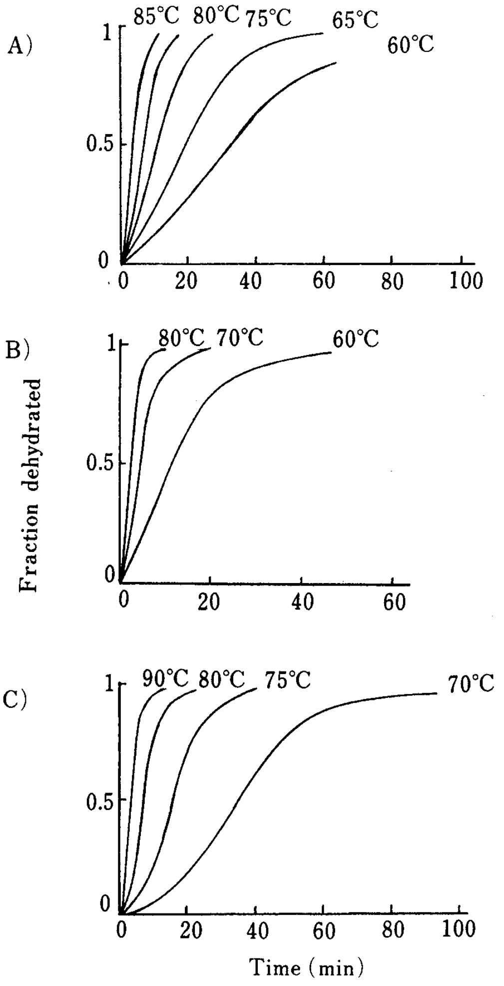

Fig. 7. Isothermal Dehydration Curves of Ground Crystals of Sulfaguanidine (Monohydrate)

A) under dry conditions at 1 atm; B) under dry conditions at 1 mmHg; C) under humid and evacuated conditions.

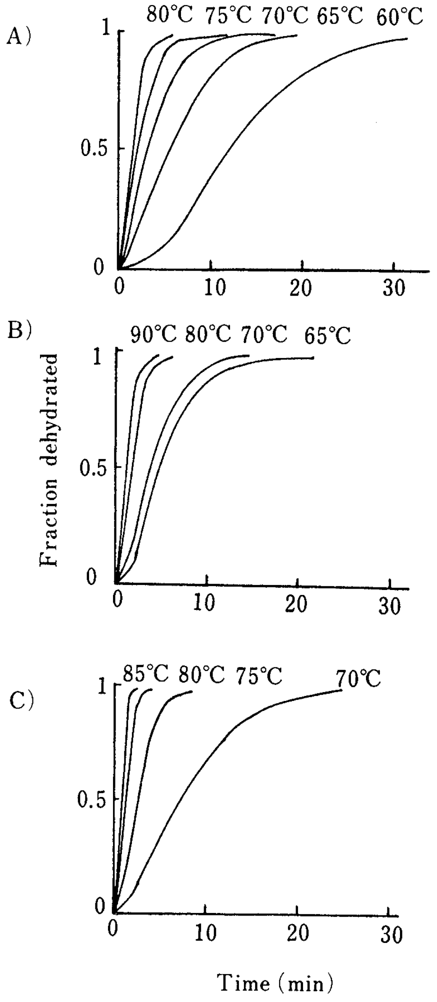

Fig. 8. Isothermal Dehydration Curves of Sulfaguanidine (Monohydrate) Prepared by Sorption

A) under dry conditions at 1 atm; B) under dry conditions at 1 mmHg; C) under humid and evacuated conditions.

dehydration patterns among the three samples under various conditions. It is evident that the intact crystals released the combined H_2O molecules most slowly, while the sorbed powder released them most rapidly. The results indicate that dehydration from the hydrate was dependent on the particle size and on the surface roughness.

At relatively low temperatures, the curves under open conditions at 1 atm rose gradually, then rapidly and finally levelled off. In the case of the ground crystals and the sorbed powder, this sigmoidal character was more marked in the dehydration under humid and evacuated conditions. On the other hand, dehydration under dry and evacuated conditions was not delayed at the beginning and the plots were linear. These results show that the dehydration of sulfaguanidine was affected more by H_2O vapor and less by the pressure.

Mechanisms of Dehydration of the Three Samples under Different Conditions

As described above, the dehydration curves of sulfaguanidine depended on the kinds of samples and the environmental conditions. It was considered therefore that different mechanisms might be followed depending on these influencing factors. As shown in Figs. 9—

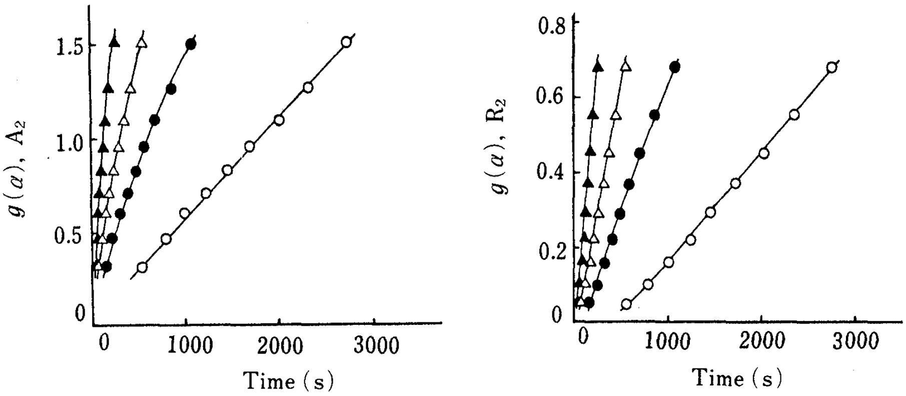

Fig. 9. Dependence of $g(\alpha)$ on Time for the Isothermal Dehydration of Sulfaguanidine (Monohydrate) Intact Crystals

—○—, 80 °C; —●—, 85 °C; —△—, 90 °C; —▲—, 95 °C.

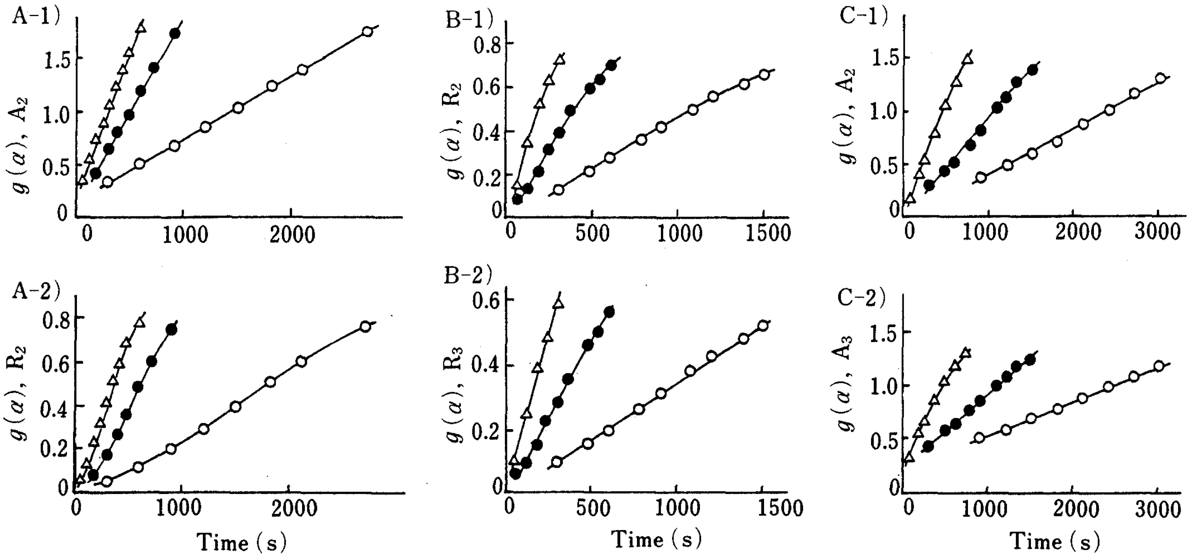

Fig. 10. Dependence of $g(\alpha)$ on Time for the Isothermal Dehydration of Ground Crystals of Sulfaguanidine (Monohydrate)

A-1), A-2); under dry conditions at 1 atm.
—○—, 65 °C; —●—, 75 °C; —△—, 80 °C.
B-1), B-2); under dry conditions at 1 mmHg.
—○—, 60 °C; —●—, 70 °C; —△—, 80 °C.
C-1), C-2), under humid and evacuated conditions.
—○—, 70 °C; —●—, 75 °C; —△—, 80 °C.

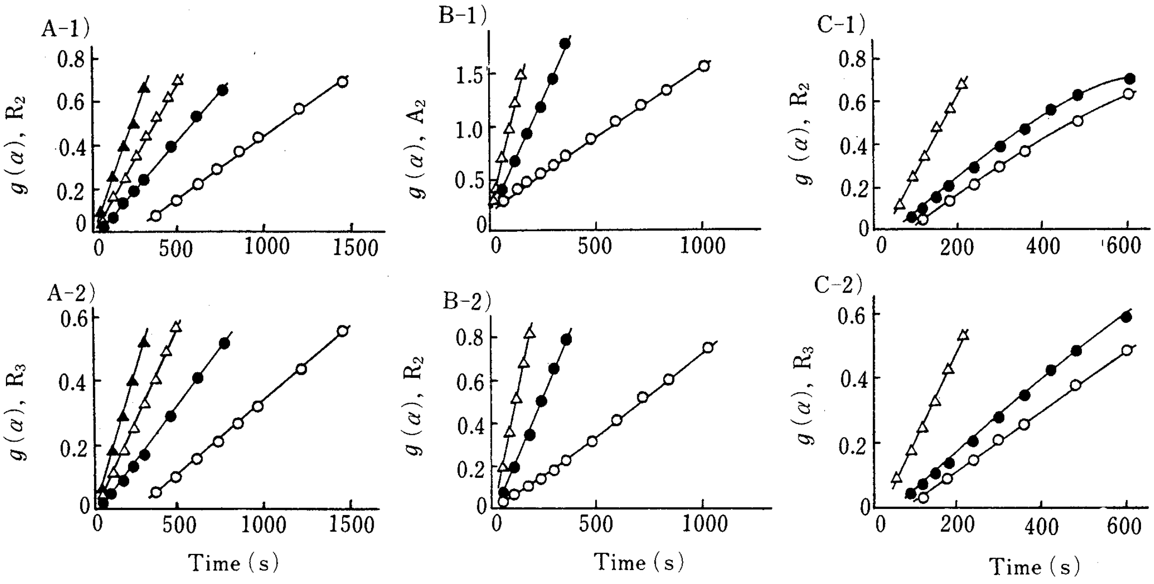

Fig. 11. Dependence of $g(\alpha)$ on Time for the Isothermal Dehydration of Sulfaguanidine (Monohydrate) Prepared by Sorption

A-1), A-2); under dry conditions at 1 atm.
—○—, 60 °C; —●—, 65 °C; —△—, 70 °C.
B-1), B-2); under dry conditions at 1 mmHg.
—○—, 65 °C; —●—, 70 °C; —△—, 80 °C.
C-1), C-2); under humid and evacuated conditions.
—○—, 70 °C; —●—, 75 °C; —△—, 80 °C.

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)

12, examination of conformity[7] to the kinetic equations $g(\alpha)=kt$ proposed for various types of solid state decomposition was carried out by plotting the calculated values of $g(\alpha)$ in Table I against time t.

Under dry conditions at 1 atm, dehydration from the intact crystals conformed at every temperature to the mechanism represented by the equation R_2 for the phase boundary reaction.[8] The Avrami–Erofeev equation A_2[9] was also applicable to the same dehydration at 80 °C, though not at higher temperatures.

When the ground crystals were dehydrated under dry conditions at 1 atm or under humid and evacuated conditions, the best linearity was found with the Avrami–Erofeev equation A_2.

However, under reduced pressure in the absence of H_2O vapor, dehydration of the same sample occurred according to the mechanism of type R_3[8] for the phase boundary reaction.

In the dehydration from the sorbed powder under dry conditions at 1 atm, not one but two kinetic expressions were possible at all temperatures: that is, the $g(\alpha)$–t curves appeared to be linear when equation R_2 or R_3 was chosen as the function $g(\alpha)$. Under dry and evacuated conditions, best linear fits were obtained with equation A_2; however, an equally good linear correlation was found at 70 °C and at 80 °C with equation R_2. Further, in the evacuated and humid environment, the sorbed powder was apparently dehydrated according to the mechanism described by equation R_3.

Thus, chemically the same monohydrate behaved differently during dehydration as a result of complicated interactions among the influencing factors (physical properties of the sample material, environmental temperature, pressure and humidity).

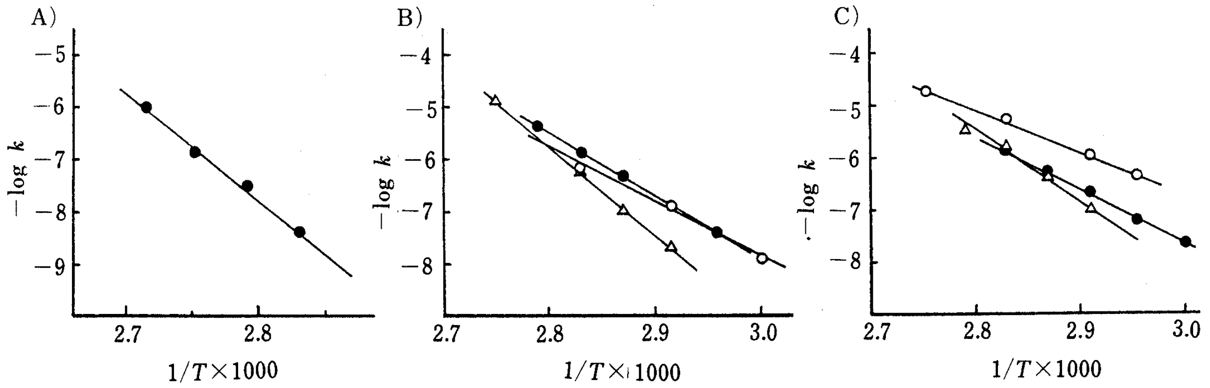

Fig. 12. Plots of log$k$ against $1/T$ for the Thermal Desolvation of Sulfaguanidine (Monohydrate)

A) intact crystals.
—●—, under 1 atm.
B) ground crystals.
—●—, under 1 atm; —○—, under 1 mmHg; —△—, under humid conditions (10 mmHg/H_2O).
C) sorbed powder.
—●—, under 1 atm; —○—, under 1 mmHg; —△—, under humid conditions (10 mmHg/H_2O).

TABLE II. Activation Energies of Dehydration of Sulfaguanidine (Monohydrate) and the Mechanisms Involved

Sample	Condition	Activation energy (kcal/mol)	Mechanism
Intact crystals	1 atm	40.0	R_2
Ground crystals	1 atm	24.5	A_2
	1 mmHg	20.5	R_3
	10 mmHg/H_2O	34.6	A_2
Sorbed powder	1 atm	21.6 (21.5[a])	R_3 (R_2)
	1 mmHg	15.9 (16.1[b])	R_2 (A_2)
	10 mmHg/H_2O	24.3	R_3

a) Calculated from the R_2 equation.
b) Calculated from the A_2 equation.

Activation Energies for Dehydration under Various Conditions

As shown in Fig. 12 and in Table II, the activation energies for dehydration were calculated from the temperature dependencies of the rate constants which were determined from linear $g(\alpha)$–t plots. It is evident that different activation energies were required depending on differences in the crystallinity of the samples as well as in the environmental factors. For example, the energies under dry conditions at 1 atm decrease in the order : intact crystals > ground crystals > sorbed powder. The fact that the energy values for the latter two samples under the three conditions became largest in the presence of H_2O vapor amounting to only 10 mmHg can be explained by the principle of mobile equilibrium. Aslo, in the absence of H_2O vapor, the effect of pressure was significant.

Observation of the Dehydration Processes under a Microscope

Using the hot stage microscope, changes in the surface appearance of the intact and ground crystals were observed during dehydration (Figs. 13 and 14). In the case of the intact crystals, nucleation and growth of anhydrous sulfaguanidine occurred almost exclusively at the apexes and the edges of the crystals. Then the interface thus formed spread horizontally and at the same time shifted inward. It is therefore considered that dehydration by random nucleation did not occur in this case.

Unlike the intact crystals, the ground crystals showed many cracks on their surface as a result of the grinding. On heating under atmospheric conditions, nucleation and growth of the anhydrous sulfaguanidine started mostly around these cracks. Also, dehydration proceeded

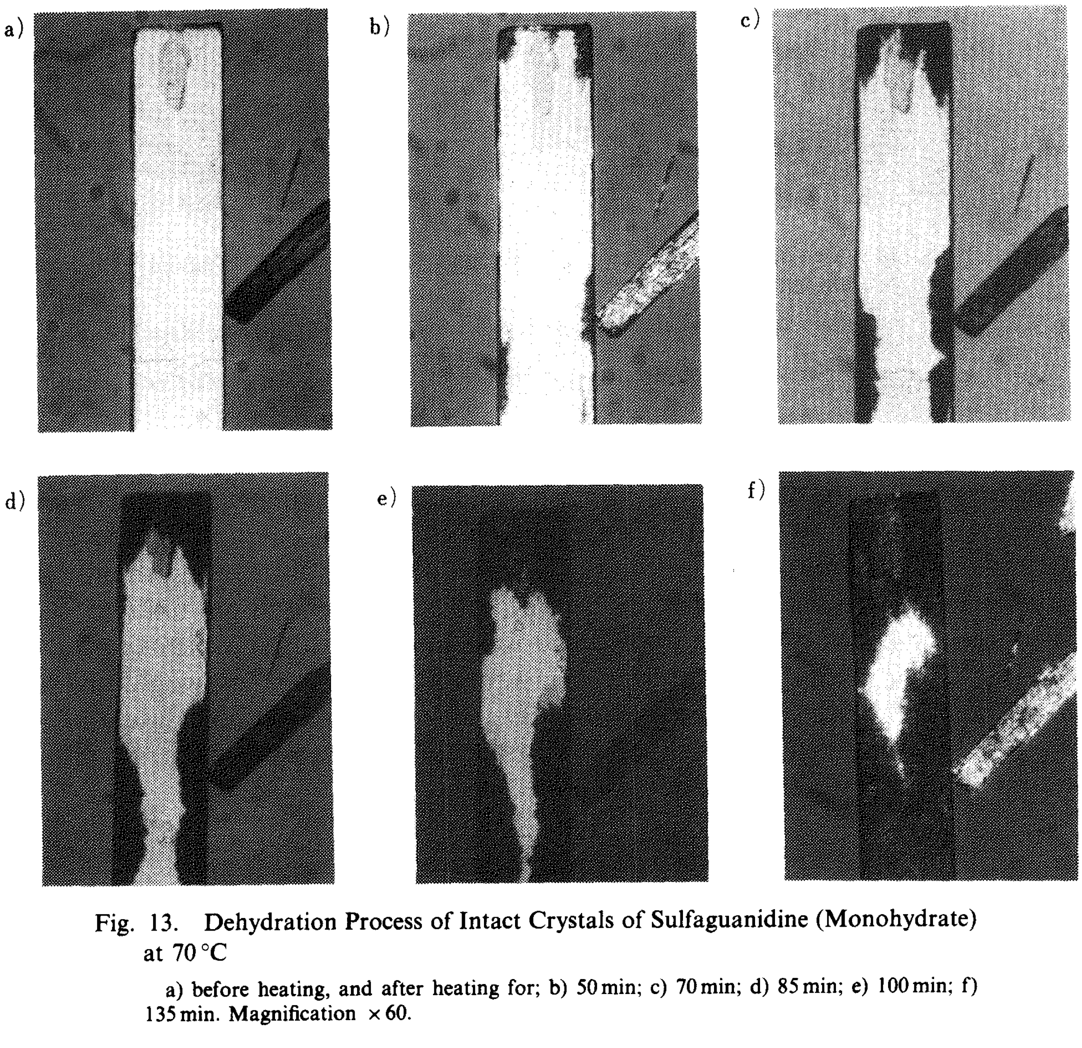

Fig. 13. Dehydration Process of Intact Crystals of Sulfaguanidine (Monohydrate) at 70 °C

a) before heating, and after heating for; b) 50 min; c) 70 min; d) 85 min; e) 100 min; f) 135 min. Magnification ×60.

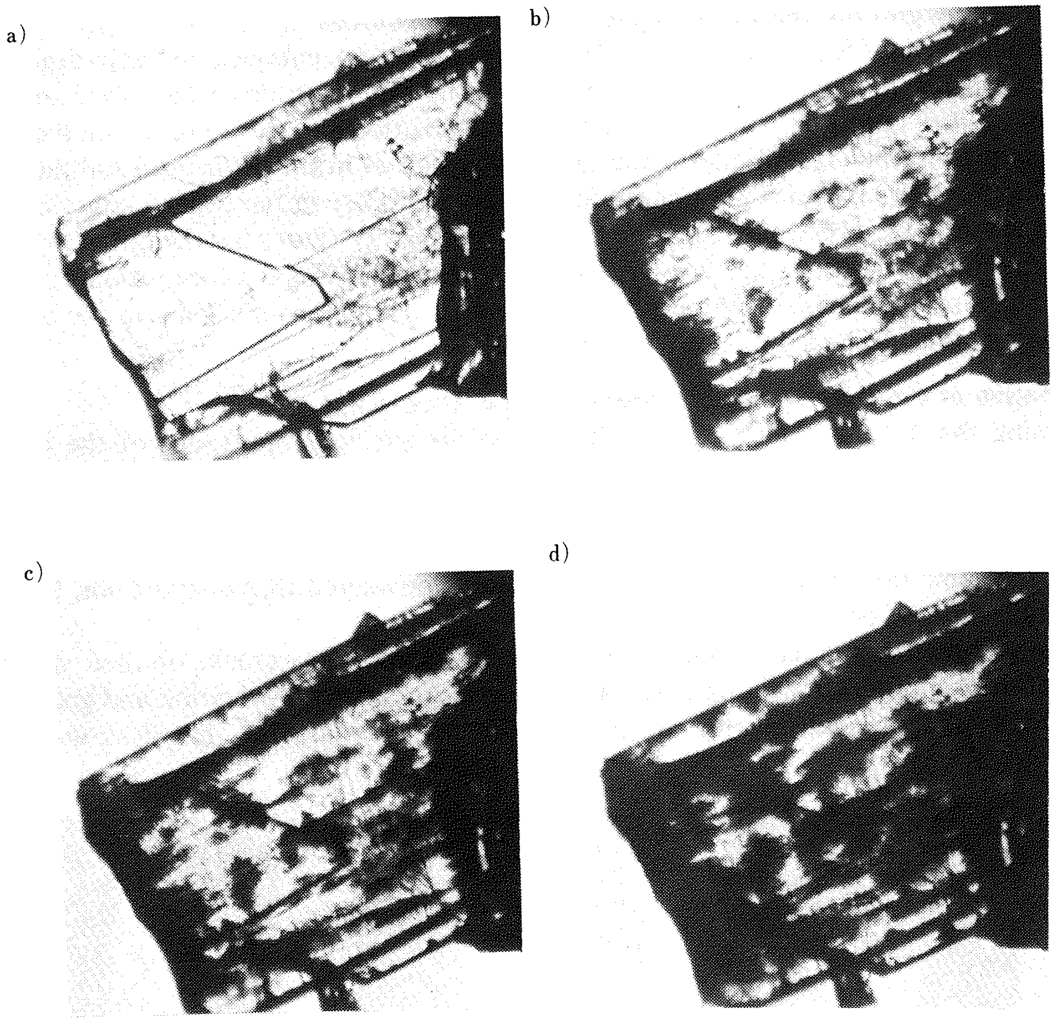

Fig. 14. Dehydration Process of Ground Crystals[a] of Sulfaguanidine (Monohydrate) at 90 °C

a) before heating, and after heating for; b) 0.5 min; c) 2.7 min; d) 3.3 min. Magnification × 60.

a) For microscopic observation, ground crystals remaining on a 150 mesh sieve were used.

much more rapidly than in the intact crystals. Accordingly, it is considered that crystal imperfections where the dehydration reaction could be easily activated were abundant around these cracks. Thus, these observations support the conclusion based on kinetic analyses that the same sample of ground crystals was dehydrated through different mechanisms when the environmental conditions were changed. For example, under conditions unfavorable for rapid dehydration, the nuclei would be formed and would grow exclusively near the cracks. On the other hand, under favorable conditions, nuclei formation and growth would not be confined to these cracks. Probably, nucleic would appear all over the crystal surface and the surface would soon be covered with the dehydrated product. Thus, inward contraction of the reaction interface would become the rate-determining factor.

Conclusion

Previous work on desolvation or dehydration from a drug solvate or a hydrate has paid little regard to the differences between influencing factors intrinsic to the sample material and those related to environmental conditions. This can lead to erroneous conclusions, as is clear from the present results.

Sulfaguanidine (monohydrate) in the present study is easily separable from aqueous solution in well-developed crystalline form and is stable under atmospheric conditions. In addition, it releases on heating at moderate temperatures all of the combined H_2O molecules without passing through a lower hydrate. For these reasons, it was chosen as a model solvate suitable for detailed investigation, and three kinds of sample materials having different physical properties were prepared, so that the reaction kinetics as well as the changes in appearance during isothermal dehydration could be examined as fully as possible.

Thus, it became clear that chemically the same hydrate was dehydrated through different mechanisms, depending on the crystal properties and the environmental conditions such as temperature, pressure and the presence or absence of H_2O vapor. It is suggested that these differences were likely to be attributable to different modes of nuclei growth.

When the hydrate of an active drug is incorporated into various dosage forms, it is often said that the quality of the products is not well controlled but varies from bach to bach. The present results provide some basis for this observation, and suggest that some previously neglected factors will have to be taken into consideration during formulation processes, if the problem is to be overcome.

References and Notes

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