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Pulverization Method for Sulfamethizole and Its Physicochemical Properties[1)]

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Sulfamethizole was pulverized by recrystallization from glycols or their derivatives, and correlation of difference in the degree of pulverization with the solvent was studied. Crystalline properties of the pulverized crystals of sulfamethizole thus obtained were also studied.

The degree of pulverization of sulfamethizole by recrystallization from glycols and their derivatives decreased with increase in the number of carbon atoms in the hydrophobic chain of these solvents.

When the pulverized sulfamethizole were examined by IR, X-ray diffraction, and DSC-TG, two kinds of hydrate and one kind of anhydride were detected. The form I (anhydride) was transformed into form III (hydrate; 1 mol H_2O) in the artificial gastric juice of 37°, but not in water.

Keywords——sulfamethizole; pulverization; glycols; glycol derivatives; mean particle diameter; heat of fusion; dissolution behaviour

It is generally known that absorption of drugs is often influenced by the physicochemical property and dosage form, and it has been reported in many papers that practically insoluble preparations show high serum concentration when administered in the pulverized form.[3-5)]

Although one of the authors (Y. Kato), had previously reported increased serum concentration and urinary excretion of the pulverized aspirin,[6,7)] and also the pulverization of aspirin[8)] and phenobarbital,[1)] we report herein some findings obtained from the current investigations on the pulverization of sulfamethizole through recrystallization with glycols and alcohols.

Experimental

Method of Pulverization——A solution of 6 g of sulfamethizole (with a crystal size of 100—150 μ) dissolved in 60 ml of a solvent was heated in a flask at about 75°, filtered while hot, and the filtrate was placed immediately in about 600 ml of cold water of 3°. The solution was stirred at 870 rpm, for 3 min and the precipitated crystals were collected by filtration under suction. The crystals were washed thoroughly with cold water, and dried in a desiccator to obtain finely pulverized crystallized sulfamethizole in about 85% yield. The solvent used for the recrystallization are shown in Table I.

Materials——Sulfamethizole of Japanese Pharmacopoeia IX grade was used. The solvents used for the recrystallization were distilled and purified in the usual way.

Measurement of Particle Diameter——The particle diameters were measured by the sedimentation method (light scanning method) using PSA-Hitachi Model II particle diameter distribution measurement

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Table I. Solvents used for Recrystallization

Solvents	Number of carbon atoms in hydrophobic chain
Water	
Acetone	
Methanol	
Ethanol	
n-Propanol	
Isopropanol	
n-Butanol	
n-Pentanol	
Ethylene glycol (E.G.)	
Diethylene glycol (D.E.G.)	
Triethylene glycol (T.E.G.)	
Ethylene glycol monoethyl ether (Cellosolve)	2
Ethylene glycol isopropyl ether (Isopropyl cellosolve)	3
Ethylene glycol monobutyl ether (Butyl cellosolve)	4
Diethylene glycol monomethyl ether (Methyl carbitol)	1
Diethylene glycol monoethyl ether (Carbitol)	2
Diethylene glycol monobutyl ether (Butyl carbitol)	4
Propylene glycol (P.G.)	3
Dipropylene glycol (D.P.G.)	6
Tripropylene glycol (T.P.G.)	9
Propylene glycol monomethyl ether	4
Dipropylene glycol monomethyl ether	7
Tripropylene glycol monomethyl ether	10
Hexylene glycol (H.G.)	

apparatus. As a disperse, liquid paraffin was used for the pharmacopoeial sulfamethizole and a mixture of liquid paraffin and hexane for the microcrystals of sulfamethizole.

X-Ray Powder Diffraction——A Geigerflex Model 2012 made by Rigakudenki Co., Ltd. was used (Ni filter, Cu-Kα ray).

Infrared Spectroscopy (IR)——IR spectra by KBr method were determined with a Hitachi Model 225 Grating Infrared Spectrophotometer.

Differential Scanning Calorimetry-Thermogravimetry (DSC-TG)——A Rigakudenki DSC-TG (CN.-8085-DI) was used, with the heating rate 10K/min, carrier gas N_2 was employed.

Dissolution Rate Measurements——Distilled water was used as a solvent and a solution of 0.1 N HCl (gelatin was added to 0.1% concentration) as an artificial gastric juice. A 500 ml flask containing 400 ml of a solvent was maintained at 37°±0.1°, 63—88 μ of a sample powder, approximately twice as much as the saturated concentration, was added, the mixture was stirred at 50 rpm, and the solution was filtered through a Millipore filter of 0.45 μm pore size. Sulfamethizole in the solution was determined with HCl–KCl buffer at pH 1.5, and appropriately diluted before the measurement of absorbance at 267 nm.

Results and Discussion

The possible effect of stirring time and speed on the crystal diameter of recrystallized sulfamethizole was examined. Although the stirring speed was made constant and the time

Table II. Effect of Stirring Time on the Recrystallization of Sulfamethizole

Stirring time (min)	Mean particle diameter (μ)	Standard deviation
1	18.42	7.48
30	18.03	6.36
60	17.86	6.05
120	16.90	6.21

Solvent: Isopropyl cellosolve.
Stirring speed: 870 rpm.

varied for 1, 30, 60, and 120 min, almost no effect was recognized as the volume surface mean diameter was approximately 17—18 μ (Table II). Table III shows the volume surface mean diameter at stirring speeds of 0, 50, 200, 400, and 800 rpm with the constant stirring time, and indicates that the mean diameter increased gradually up to 200 rpm, slightly decreased

Table III. Effect of Stirring Speed on the Recrystallization of Sulfamethizole

Stirring speed (rpm)	Mean particle diameter (μ)	Standard deviation
0	18.38	6.04
50	18.88	6.79
200	25.80	7.70
400	23.00	9.51
800	15.01	5.03

Solvent: Isopropyl cellosolve.
Stirring time: 3 min.

Table IV. Mean Particle Diameter by Sedimentation Method of Pulverized Sulfamethizole

Solvents	Crystalline form	Mean particle diameter (μ)	Standard deviation
—(J.P.[a])	I	102.12	45.10
Water	II	12.31	4.80
Acetone	I	25.12	7.48
Methanol	I	21.09	10.14
Ethanol	I	13.14	3.81
n-Propanol	I	9.40	2.25
Isopropanol	I	16.83	5.80
n-Butanol	I	22.57	7.17
n-Pentanol	I	17.24	6.24

a) Commercial sulfamethizole.

Table V. Mean Particle Diameter by Sedimentation Method of Pulverized Sulfamethizole

Solvents	Crystalline form	Mean particle diameter (μ)	Standard deviation
E.G.	I	7.60	2.00
D.E.G.	III	25.91	9.49
T.E.G.	III	26.54	8.44
Cellosolve		25.42	19.40
Isopropyl cellosolve	II	41.44	13.20
Butyl cellosove	III	57.73	17.86
Methyl carbitol	III	26.28	10.36
Carbitol		36.20	12.33
Butyl carbitol	II	56.20	23.82
P.G.	I	34.42	14.48
D.P.G.	III	48.28	13.90
T.P.G.	III	63.11	23.39
Propylene glycol monomethyl ether	I	18.44	4.90
Dipropylene glycol monomethyl ether	I	32.49	6.80
Triprolpylene glycol monomethyl ether		38.60	19.90
H.G.	I	13.83	4.25

at 400 rpm, and considerably decreased to 15 μ at 800 rpm. This trend is probably attributable to the impact, shear force, and size reduction caused by the stirrers.

As for the microcrystals obtained by recrystallization using various kinds of solvents with the stirring speed fixed at 870 rpm and the time to 3 min, the volume surface mean diameters measured by the sedimentation method are given in Tables IV and V. Compared with sulfamethizole of J. P. IX, a difference was noted in a pulverized degree depending

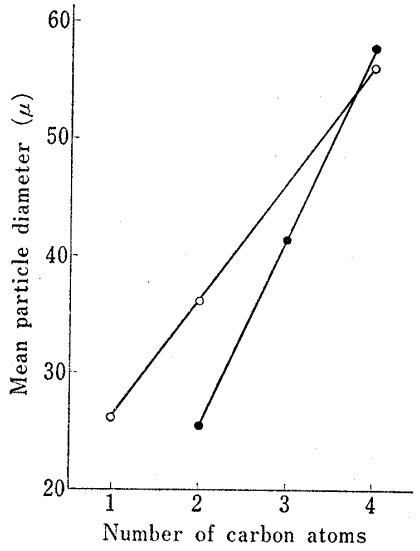


Fig. 1. Relationship between Mean Particle Diameter and Number of Carbon Atoms in Hydrophobic Chain of Glycols and Their Derivatives used for Recrystallization

—●—: E.G. and its derivatives,
—○—: D.EG. and its derivatives.

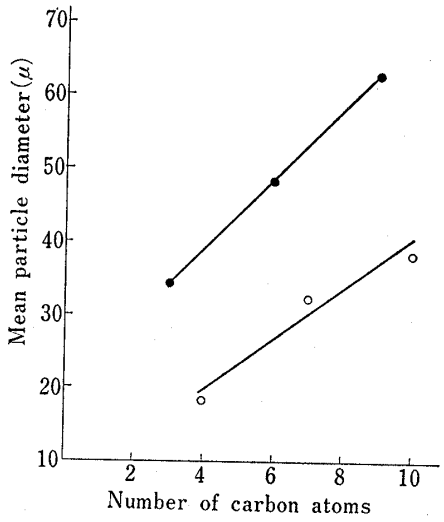


Fig. 2. Relationship between Mean Particle Diameter and Number of Carbon Atoms in Hydrophobic Chain of Glycols and Their Derivatives used for Recrystallization

—●—: P.G. and its derivatives.
—○—: P.G. monomethyl ether and its derivatives

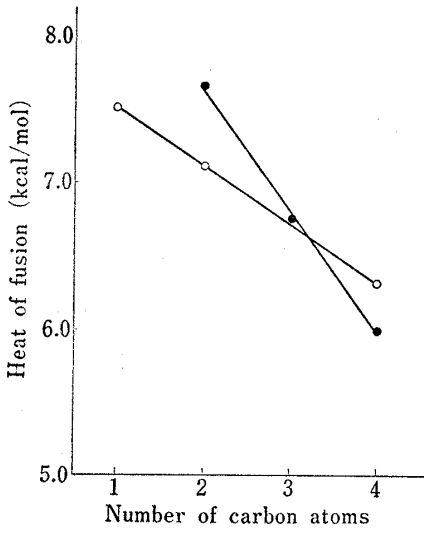


Fig. 3. Relationship between Heat of Fusion and Number of Carbon Atoms in Hydrophobic Chain of Glycols and Their Derivatives used for Recrystallization

—●—: E.G. and its derivatives.
—○—: D.E.G. and its derivatives.

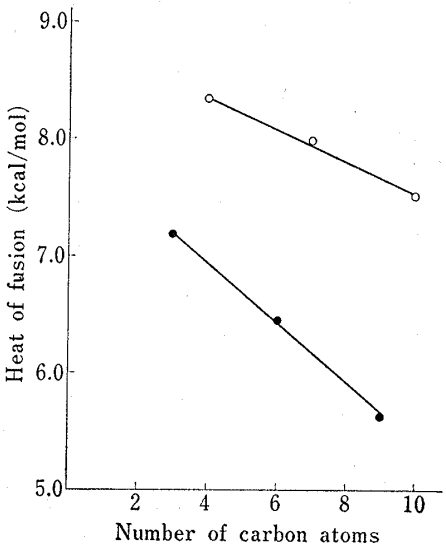


Fig. 4. Relationship between Heat of Fusion and Number of Carbon Atoms in Hydrophobic Chain of Glycols and Their Derivatives used for Recrystallization

—●—: P.G. and its derivatives.
—○—: P.G. monomethyl ether and its derivatives.

on the solvent used, and the particles were pulverized to as small as 1/2 to 1/15 of sulfamethizole of J. P. Crystal forms obtained with each solvent are described later.

Figure 1 shows the volume surface mean diameters of the pulverized crystals of sulfamethizole plotted against the number of carbon atoms in hydrophobic chain of the solvents of both E.G. and D.E.G. systems. The particle diameter was 26.28 μ in the D.E.G. system when pulverized with methylcarbitol with one carbon atom in the hydrophobic chain, 36.20 μ with carbitol with 2 carbon atoms, and 56.20 μ with butylcarbitol with 4 carbon atoms, and the same results were obtained in the E.G. system.

Thus, it was found that the particle diameter became gradually larger in proportion to increase in the number of carbon atoms, indicating a linear relationship and that the larger the number of carbon atoms in hydrophobic chain, the lower was the degree of pulverization.

On the other hand, the particle diameter became larger with increasing number of carbon atoms in the hydrophobic chain in both P.G. and P.G. monomethyl ether systems as well, and the results similar to that in the E.G. and D.E.G. systems were obtained (Fig. 2).

The microcrystals of sulfamethizole were measured with DSC–TG, and the heat of fusion was calculated from the peak area of DSC curves. As shown in Fig. 3 and 4, the number of carbon atoms in the hydrophobic chain of solvents was plotted against the heat of fusion. Fig. 3 and 4 equally show a decrease in the heat of fusion with increasing number of carbon atoms in the hydrophobic chain. Since the specific surface area and heat of fusion change in parallel, decrease in the specific surface area was found to result in larger particle diameter.

The solubility of sulfamethizole in a mixture of these solvents and water 10% (w/w) at 3° was plotted against the number of carbon atoms in the hydrophobic chain of each solvent, as shown in Fig. 5 and 6. These graphs suggest that the larger the number of carbon atoms, the more was soluble sulfamethizole, resulting in the increased particle diameter. Thus, the results obtained from the pulverization of phenobarbital[1] were equally confirmed in the E.G., D.E.G., P.G., and P.G. monomethylether systems in that the increasing number of carbon atoms in the hydrophobic chain reduced the degree of pulverization.

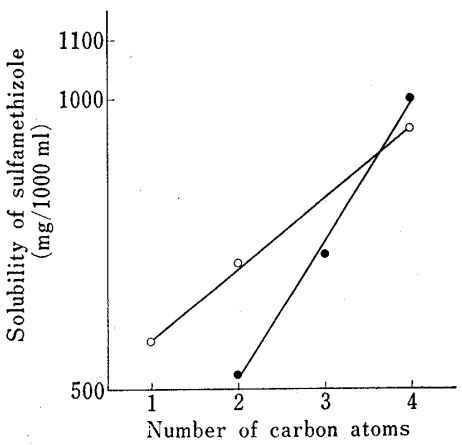


Fig. 5. Relationship between Solubility of Sulfamethizole at 3° and Number of Carbon Atoms in Hydrophobic Chain of Glycols and Their Derivatives used for Recrystallization

—●—: E.G. and its derivatives.
—○—: D.E.G. and its derivatives.

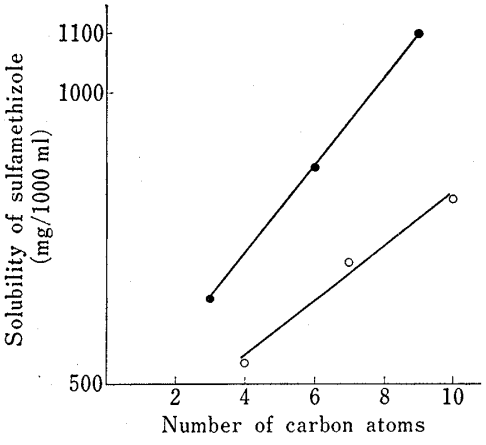
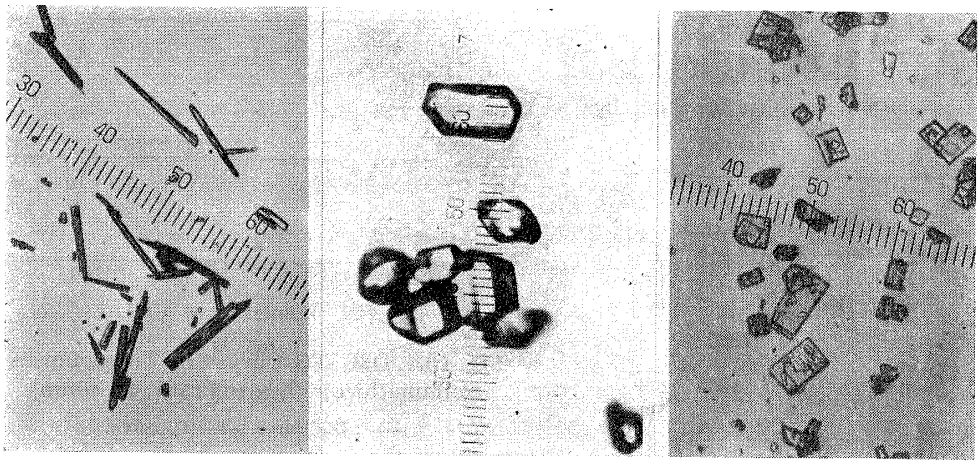


Fig. 6. Relationship between Solubility of Sulfamethizole at 3° and Number of Carbon Atoms in Hydrophobic Chain of Glycols and Their Derivatives used for Recrystallization

—●—: P.G. and its derivatives.
—○—: P.G. monomethyl ether and its derivatives.

Properties of microcrystals of sulfamathizole recrystallized from various kinds of solvents were examined. The measurements made by X-ray diffraction, DSC–TG, and IR proved the presence of 3 types of crystals.

Form I crystals obtained from alcohol such as methanol and ethanol, as well as from acetone, E.G. and P.G., were needles while form II from water and isopropylcellosolve were plates, and form III from butylcellosolve and methylcarbitol were also plates (Fig. 7).



form I form II form III

Fig. 7. Photomicrographs of Three Forms of Sulfamethizole (×67)

The pharmacopoeial crystals were proved to be form I. Form I, II, and III crystals remained stable with no change in their crystalline form when allowed to stand at room temperature for one year. X-Ray diffraction pattern, IR spectrum, and DSC–TG of form I, II, and III crystals are shown in Fig. 8, 9, and 10, respectively.

X-Ray diffraction patterns were apparently different in these 3 forms of crystals, and it was presumed that there was a considerable difference in their crystal structure. When IR spectra were measured, slight differences were recognized in these 3 kinds of crystal forms at 3520 cm^{-1}, 1440—1280 cm^{-1}, and 860 cm^{-1} for form I, II, and III, respectively. Measurements with DSC–TG proved the release of water of crystallization in the DSC curves of the

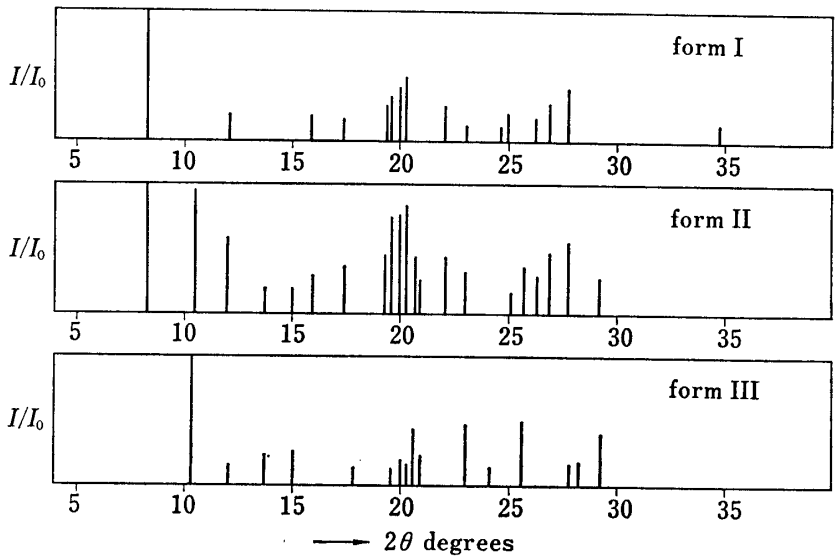


Fig. 8. X-Ray Diffraction Patterns of Three Forms of Sulfamethizole

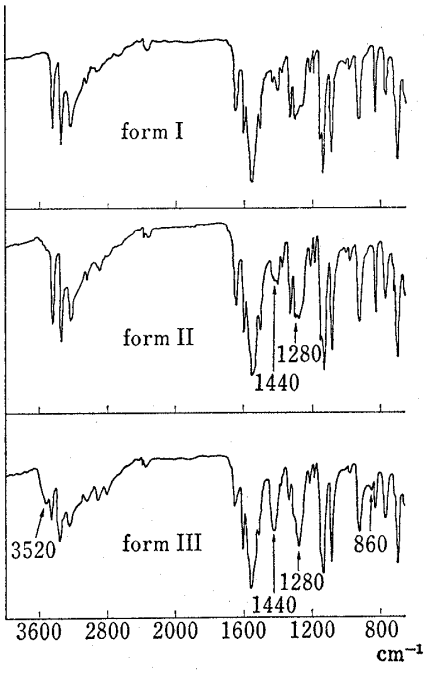


Fig. 9. IR Absorption Spectra of Three Forms of Sulfamethizole in KBr Tablet

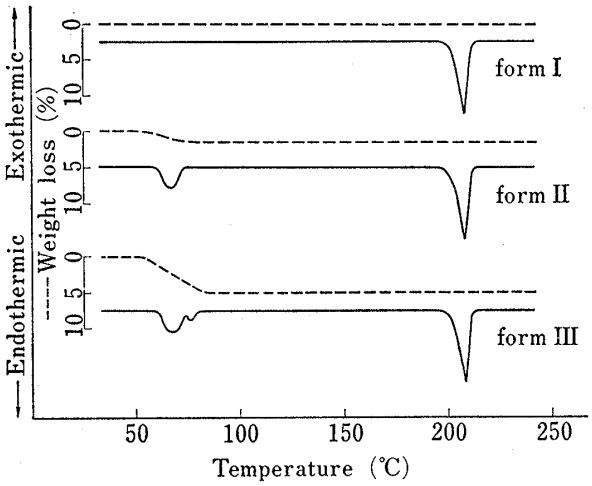


Fig. 10. DSC–TG Curves of Three Forms of Sulfamethizole (heating rate: 10 k/min)

——: DSC curve, ——: TG curve.

Table VI. Analyses of the Composition of Three Forms of Sulfamethizole

Form	Formula	Elemental analysis (%) Calcd. C	H	N	S	Found C	H	N	S
I	$C_9H_{10}N_4O_2S_2$	40.00	3.70	20.73	23.73	39.99	3.44	20.93	23.72
II	$C_9H_{10}N_4O_2S_2 \cdot 1/6H_2O$	39.55	3.81	20.50	23.46	39.46	3.77	20.32	23.24
III	$C_9H_{10}N_4O_2S_2 \cdot H_2O$	37.49	4.19	19.43	22.24	37.55	4.28	19.55	22.08

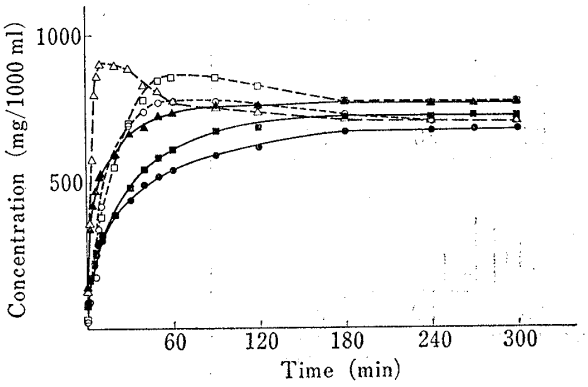


Fig. 11. Dissolution Curves of Different Forms of Sulfamethizole in 0.1 N HCl–0.1 % Gelatin and Water at 37°

—▲—: form I in water, —■—: form II in water, —●—: form III in water —△—: form I in 0.1 N HCl–0.1% gelatin, —□—: form II 0.1 N HCl–0.1% gelatin, —○—: form III in 0.1 N HCl–0.1% gelatin.

form II and III, an endothermic peak presumably caused by the evaporation at about 70°, and a peak of fusion in the vicinity of 208°.

The change in weight of about 1% in form II and about 5% in form III, as against a dehydrating peak in the DSC curves, was observed in the TG curves as well; when the results of elemental analysis (Table VI) are taken into consideration, it is presumed that about 1/6 and about 1 mol of H_2O is present in forms II and III, respectively. Neither a dehydrating peak nor weight loss was noted in form I, which is an anhydride with a peak of fusion almost the same as that in forms II and III.

It is well known from polymorphism and psudopolymorphism of drugs that the solubility or dissolution rate depends on a difference in crystalline form. The dissolution rate of 3 different crystalline forms of sulfamethizole was examined with water and artificial gastric juice at 37° and compared to obtain dissolution curves, which are shown in Fig. 11.

The dissolution curve of the form I (anhydride) showed a decrease after reaching a maximum in the artificial gastric juice, but finally agreed with that of form III (hydrate; 1 mol H_2O). This may probably be due to supersaturation of form I against the solubility of hydrate, which allowed the form III (hydrate) to precipitate with lapse of time, and this was confirmed by DSC–TG.

Thus, the anhydride had seemingly transformed into the hydrate after having been dissolved. However, the initial solubility in water was equally lower compared with that in the artificial gastric juice, and no transformation from the anhydride into the hydrate was recognized. It is generally known that the solubility of anhydride of drugs having water of crystallization is higher.[9–11] A similar trend was observed in the dissolution behavior of the above-mentioned 3 forms of crystals.

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