

# SOLUBILITIES AND CRYSTALLIZATION BEHAVIOR OF CIMETIDINE POLYMORPHIC FORMS A AND B

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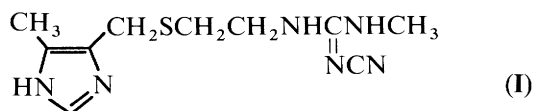
**Key Words:** Crystallization, Polymorphism, Solubility, Selective Crystallization, Nucleation, Mixed Solvent, Surface Energy

For the polymorphic forms A and B of the organic compound cimetidine, their solubilities in H<sub>2</sub>O, 2-propanol (IPA) and H<sub>2</sub>O-IPA mixture and their crystallization behavior, mainly from IPA, were studied. It became apparent that form A is more soluble than form B in any solvent and that the solubilities of both forms increase in the order H<sub>2</sub>O, IPA, H<sub>2</sub>O-IPA mixture. In IPA as a solvent, at high supersaturation ratio ( $S_A \geq 3.6$ ), form A, which is of thermodynamically metastable form, was preferentially crystallized regardless of the presence or absence ( $S_A \geq 4.5$ ) and the form of seeds ( $S_A \geq 3.6$ ). Phase transition from form A to B was not observed. The primary nucleation rate of form A was also measured at  $S_A = 4.8 \sim 6.3$  by the waiting-time method and surface energy  $\sigma_A$  was estimated to be  $8.1 \times 10^{-3} \text{ J} \cdot \text{m}^{-2}$ . At lower supersaturation ratio ( $S_A \leq 2$ ) the form corresponding to that of the seed was crystallized, contrary to results reported in earlier papers that no form B is obtained from IPA solution. The growth rate of form A was also measured at  $S_A = 2.2 \sim 1.3$ , by the light transmittance method, and  $\sigma_A$  was estimated to be  $5.2 \times 10^{-3} \text{ J} \cdot \text{m}^{-2}$ .

## Introduction

Medical substances often have characteristic crystal polymorphs, and hence the crystallization techniques which produce the desired form are important from the viewpoint of bioavailability.

Cimetidine<sup>2)</sup>, N-cyano-N'-methyl-N''-[2-[(5-methyl-1H-imidazol-4-yl)-methyl-thio]-ethyl]-guanidine (I),



is a potent antagonist of histamine H<sub>2</sub>-receptors<sup>1)</sup> and has been known to have four anhydrous forms, A, B, C and D and three monohydrate forms, M<sub>1</sub>, M<sub>2</sub> and M<sub>3</sub>. Among these forms, form A is preferable for medicine. It has been reported that form A is crystallized from non-aqueous media such as 2-propanol (IPA) and the other forms from H<sub>2</sub>O, but

that form B is sometimes crystallized together with form A<sup>3,6,7,10,12)</sup>. Although there are some reports about solubilities and crystallization of cimetidine, forms A and B, with less quantitative analyses, chemical engineering approaches have not been taken at all.

In this work, the solubility curves of cimetidine of forms A and B in H<sub>2</sub>O, IPA and H<sub>2</sub>O-IPA mixture were measured and their crystallization behavior, mainly from IPA, was studied.

## 1. Experimentals

### 1.1 Physical properties and identification of polymorphic form

Identification of polymorphic form was done by the following characteristic infrared band peaks<sup>6)</sup> [cm<sup>-1</sup>]; A: 1204, 1156, 1077, 954; B: 1280, 1192, 1184, 1176; C: 1182, 1066, 948, using a Shimadzu FTIR-4300. The content ratio of forms A and B in mixed crystals was detected in the range of 5~95%, using the typical band peaks of 1204cm<sup>-1</sup> and 1156cm<sup>-1</sup> for form A and 1184cm<sup>-1</sup> for form B. Observations by optical microscope (OLYMPUS IMT-2) and scanning electron microscope (Shimadzu EPM-810) were also

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made.

Cimetidine powder (supplied by Fujimoto Pharmaceutical Co.) and guaranteed reagent grade 2-propanol (Wako Chemicals Co.) were used without further purification. The water used in this study was purified by ion exchange and then by distillation.

The physical properties of cimetidine are as follows:  $MW$  [g/mol] = 252;  $\rho_s$  [g·cm<sup>-3</sup>] = 1.3<sup>3)</sup>;  $v_m$  [cm<sup>3</sup>] = 193.8;  $d$  [nm] ( $= (v_m/N_A)^{1/3}$ ) = 0.69;  $a$  [nm<sup>2</sup>] ( $= d^2$ ) = 0.47;  $mp$ . [K]<sup>10)</sup> = 414~416 (form A), 415~418 (form B), 418~419 (form C).

SEM photographs of commercial products of forms A, B and C are shown in Fig. 1.

## 1.2 Solubility measurements

The equilibrium solubilities were measured in the temperature range of 293.2~323.2 K (in H<sub>2</sub>O), 293.2~338.2 K (in IPA) and 293.2~323.2 K (in H<sub>2</sub>O-IPA mixture), as follows. A jacketed glass vessel of 200 ml (for H<sub>2</sub>O and IPA) or 50 ml (for H<sub>2</sub>O-IPA mixture) in volume was charged with solvent and was adjusted to a given temperature (deviation within  $\pm 0.05$  K). Then excess cimetidine powder of 170~100 mesh was added, and allowed to equilibrate over a period of 5 h under agitation at the rate  $N_r$  [min<sup>-1</sup>] = 340 [path 1]. Samples of solution were obtained by quick filtration of slurry aliquots through a 0.45  $\mu$ m milipore membrane and were diluted to a concentration of about 10<sup>-5</sup> mol/l with distilled water. The concentration of cimetidine was then determined from the intensity of UV absorption at 218 nm, using a Shimadzu UV-140. The relation between solute concentration and the intensity of UV absorption was calibrated prior to the experiments.

Additionally to path 1, which is the approach from undersaturated state, measurements of solubility from supersaturated state [path 2<sup>13)</sup>] were also made by the following procedure to confirm the equilibrium solubility. After obtaining the solubility data at a given temperature, as mentioned above, the slurry used in path 1 was successively cooled down to a one-rank lower temperature and then the solution concentration was measured.

The solid in solution was filtered, air-dried and then subjected to form characterization by the method mentioned in 1.1.

## 1.3 Crystallization

Crystallization experiments were carried out, using H<sub>2</sub>O and IPA as solvent separately. As to H<sub>2</sub>O as a solvent, an aqueous cimetidine solution of about 200 ml or 1000 ml in volume was maintained at an undersaturated temperature,  $T_u$ , and then cooled down to a crystallization temperature,  $T_c$ , without agitation.

As to IPA as a solvent, crystallization experiments were carried out, using a jacketed cylindrical glass vessel of 553 ml volume ( $\phi 80 \times 110$  mm) with a stirrer

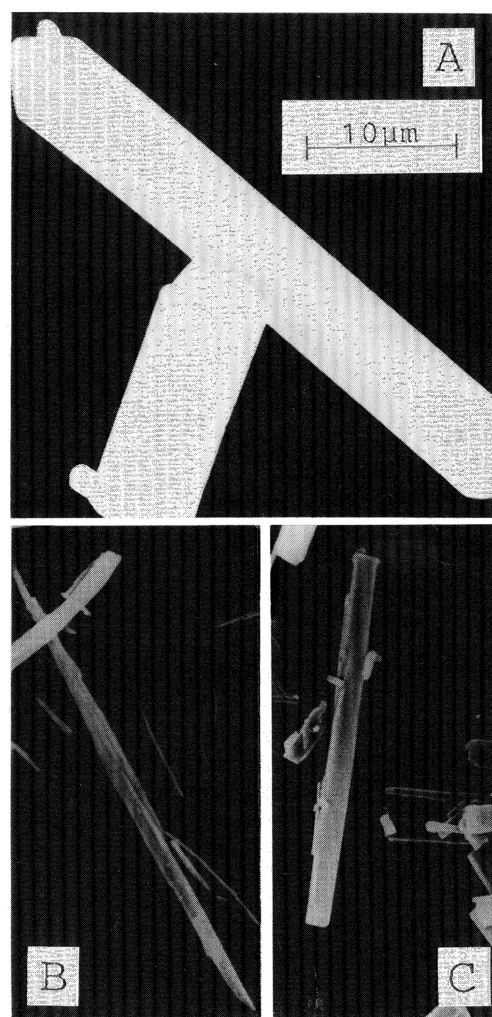


Fig. 1. SEM photographs of forms A, B and C

of glass rod with two paddles of 40 mm length, 10 mm wide and set at a 45° angle. Solution of a given concentration  $C_0$  was added to the vessel and was then cooled down in two ways.

Procedure 1 (Operations at high supersaturated state with supersaturation ratio,  $S$  [—] ( $= C/C_s$ ,  $C_s$ : equilibrium solubility) at initial crystallization  $S_{c,A}$  [—]  $\geq 3.6$ ,  $S_{c,B}$  [—]  $\geq 4.8$ ): Cooling down to  $T_c$  [K] = 293.2 at the rate of 10 K/min, without and with seeds of A (0, 0.2, 1 g) or B (0, 0.01~0.2 g).

Procedure 2 (Operations at low supersaturated state): 1) Cooling down to  $T_c$  = 293.2 or 323.2 at a rate of 10 K/min with seeds of A (0.1, 1.5 g) or B (1.5 g) in the range of  $S_{c,A}$  = 1.4~2.2,  $S_{c,B}$  = 1.8~2.8. To know the crystallization behavior in more detail, the experiment was also carried out by the light-transmittance method<sup>5,15,16)</sup> at  $T_c$  = 293.2 with seeds of A (0.1 g). 2) Stepwise cooling at a rate of 0.2 K/min with seeds of B (1, 2 g), in the range of  $S_A$  = 0.9~1.9,  $S_B$  = 1.5~2.6.

These procedures in IPA are shown schematically in Fig. 2. Arrows in the figure indicate the progress

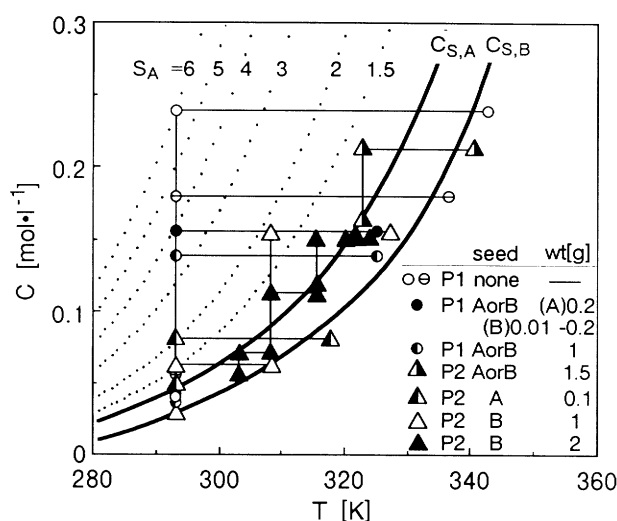


Fig. 2. Crystallization operations (P: procedure)

of crystallization.

All seed crystals were used after washing with unsaturated solution and the solutions were prefiltered through a  $0.45\ \mu\text{m}$  milipore membrane. Experimental conditions were as follows:  $\text{H}_2\text{O}$ -solvent:  $T_u$  [K] = 338, 350;  $C_0$  [ $\text{mol}\cdot\text{l}^{-1}$ ] = 0.19; agitation rate  $N_r$  [ $\text{min}^{-1}$ ] = 0. IPA-solvent:  $C_0$  = 0.136 ~ 0.180;  $S$  at initial  $S_{0,A}$  = 0.7 ~ 0.9;  $S_{c,A}$  = 1.1 ~ 6.3; initially maintained temperature  $T_0$  [K] = 318.2 ~ 343.2;  $T_c$  [K] = 293.2 ~ 323.2;  $N_r$  = 600, 450; cooling rate  $b$  [ $\text{K}\cdot\text{min}^{-1}$ ] = 0.2, 10; size of seed crystals  $d_s$  [ $\mu\text{m}$ ] = 88 ~ 149.

For the primary nucleation measurement, the waiting time method<sup>4)</sup> was applied under the following conditions:  $T_0$  = 336.2 ~ 343.2;  $T_c$  = 293.2;  $C_0$  = 0.18 ~ 0.24;  $S_{c,A}$  = 4.8 ~ 6.3;  $N_r$  = 600.

## 2. Results and Discussion

### 2.1 Solubilities

Figures 3-a and b show time courses of solute concentration in  $\text{H}_2\text{O}$  and IPA respectively during solubility measurement experiments. Arrows in these figures indicate the time when cooling was started in the case of path 2. In  $\text{H}_2\text{O}$  solution, the solubilities of form B obtained by path 1 were identical with those by path 2. However, the values of form A by path 2 were always lower than those by path 1. From the identification of excess suspended crystals it was found that a phase transition from form A to form C occurs. This fact indicates that the solubility of form C is lower than that of form A.

In IPA solution the solubilities of both forms A and B by path 2 were higher than those by path 1. This may be due to the low growth rates of the crystals, especially form B.

As a result, the values obtained by path 1 were taken as the equilibrium solubilities,  $C_s$ . Figures 4 and 5 show the solubility data in  $\text{H}_2\text{O}$  and IPA and

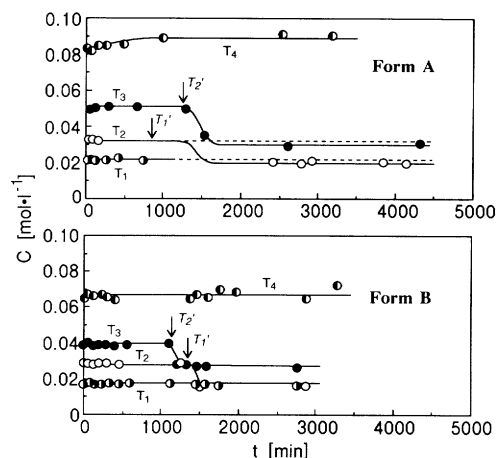


Fig. 3-a. Time course of solute concentration during solubility measurement experiments in  $\text{H}_2\text{O}$ :  $T_1$  (●) = 293.2,  $T_2$  (○) = 303.2,  $T_3$  (●) = 313.2,  $T_4$  (●) = 323.2 K (path 1),  $T_1'$  (○) = 293.2,  $T_2'$  (●) = 303.2 K (path 2)

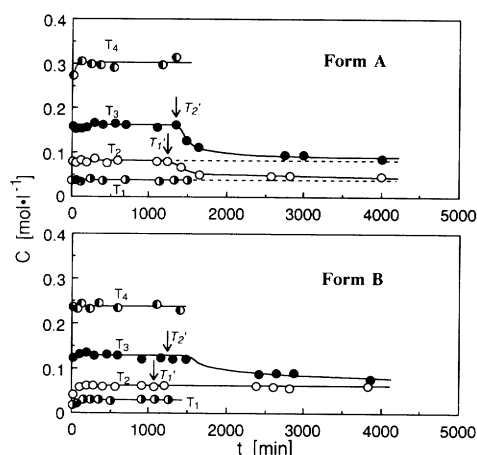


Fig. 3-b. Time course of solute concentration during solubility measurement experiments in IPA:  $T_1$  (●) = 293.2,  $T_2$  (○) = 308.2,  $T_3$  (●) = 323.2,  $T_4$  (●) = 328.2 K (path 1),  $T_1'$  (○) = 293.2,  $T_2'$  (●) = 308.2 K (path 2)

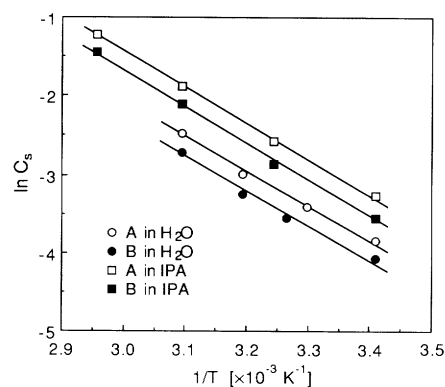
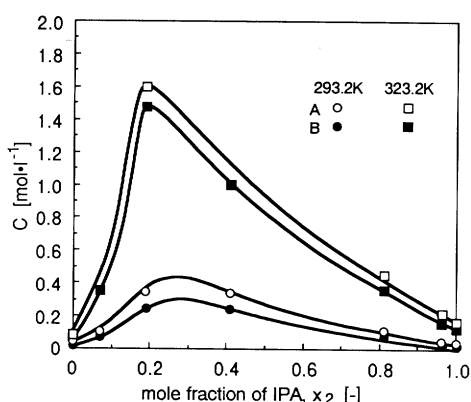


Fig. 4. Equilibrium solubility in  $\text{H}_2\text{O}$  and 2-propanol

$\text{H}_2\text{O}$ -IPA mixture respectively. These figures indicate that form A is more soluble than form B in any solvent ( $C_{s,A}:C_{s,B}$  = 1.3:1 in  $\text{H}_2\text{O}$ , 1.3:1 in IPA, 1.1:1 in  $\text{H}_2\text{O}/\text{IPA}$  = 50/50 (v/v)) and that both forms are more

**Table 1.** Temperature dependency of solubility

Form	Solvent	H <sub>2</sub> O	Mixed solvent, $x_2^{*2}$ ( $v_2/v^{*3}$ )					IPA
			0.07 (0.25)	0.19 (0.50)	0.41 (0.75)	0.81 (0.95)	0.96 (0.99)	
A	$\alpha$	[K]	4260		4387	4357	4589	4521
	$\beta$	[—]	10.7		15.4	12.7	12.7	12.2
	$\Delta H_{sol}^{*1}$	[kJ/mol]	35.4		40.2	36.2	38.2	37.6
B	$\alpha$	[K]	4220	5192	5720	4520	4859	4690
	$\beta$	[—]	10.3	15.0	18.1	14.0	14.0	12.4
	$\Delta H_{sol}^{*1}$	[kJ/mol]	35.1	43.2	47.6	37.6	40.4	36.7

\*<sup>1</sup> apparent heat of dissolution,  $=\alpha \times R$ .\*<sup>2</sup> mole fraction of IPA.\*<sup>3</sup> volume fraction of IPA.**Fig. 5.** Equilibrium solubility in H<sub>2</sub>O-IPA mixture

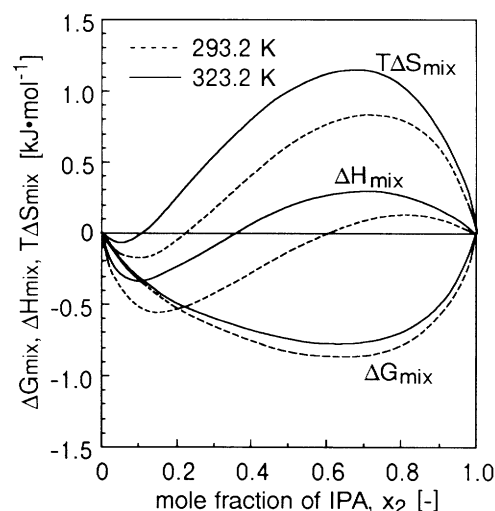
soluble in the order H<sub>2</sub>O, IPA and H<sub>2</sub>O-IPA mixture. For example, the ratio of  $C_{s,A}$  in these solvents at 323.2 K is 1 (in H<sub>2</sub>O):3 (in IPA):32 (in H<sub>2</sub>O/IPA = 50/50 (v/v)). In the mixed solvent, the maximum solubilities were found at volume ratio 1:1 and IPA mole fraction  $x_2=0.19$ , as shown in Fig. 5. These equilibrium solubility data in H<sub>2</sub>O, IPA and H<sub>2</sub>O-IPA mixture well satisfied the following relation (modified Kelvin-Helmholtz equation).

$$\ln C_s = -\alpha/T + \beta \quad (1)$$

The parameters  $\alpha$  and  $\beta$  were obtained as shown in Table 1.

From the solubility data, the surface energy  $\sigma_s$  [J·m<sup>-2</sup>] values were estimated by Nakai's method<sup>8)</sup> to be, for example,  $14.2 \times 10^{-3}$  (A, in H<sub>2</sub>O);  $14.6 \times 10^{-3}$  (B, in H<sub>2</sub>O);  $10.6 \times 10^{-3}$  (A, in IPA); and  $11.1 \times 10^{-3}$  (B, in IPA) at 293.2 K.

It is noted that the H<sub>2</sub>O-IPA mixed solvent dissolves cimetidine remarkably, as mentioned above, compared with H<sub>2</sub>O or IPA alone; that is, this binary solution shows so-called "cosolvency"<sup>14)</sup> for cimetidine. H<sub>2</sub>O-IPA solution deviates greatly from the ideal solution, with large positive excess Gibbs energy  $\Delta G^E$  arising from negative entropy  $\Delta S^E$  in the H<sub>2</sub>O-rich

**Fig. 6.** Thermodynamic functions of H<sub>2</sub>O-IPA mixture

range and from positive enthalpy  $\Delta H^E$  in the IPA-rich range<sup>11)</sup>.

Using the data<sup>11)</sup> on  $\Delta H^E$  and  $\Delta S^E$ , the changes of Gibbs energy, entropy and enthalpy with mixing  $\Delta G_{mix}$ ,  $T\Delta S_{mix}$  and  $\Delta H_{mix}(=\Delta H^E)$  in the binary solution were calculated numerically by the following equations:

$$\begin{aligned} \Delta S_{mix} &= \Delta S^E + \Delta S^{ideal}, \\ \Delta S^{ideal} &= -R(x_1 \ln x_1 + x_2 \ln x_2) \end{aligned} \quad (2)$$

$$\Delta G_{mix} = \Delta H_{mix} - T\Delta S_{mix} \quad (3)$$

and the results are shown in Fig. 6. Though there still remain uncertainties, the high solubility of cimetidine in H<sub>2</sub>O-IPA solution may be due to these solvents being miscible and forming a more stable state with mixing.

## 2.2 Crystallization

From aqueous solution without agitation, at  $T_u=338$  form C alone was crystallized and at  $T_u=350$  form M<sub>1</sub> alone was crystallized, contrary to the previous report<sup>6)</sup> that only form C was crystallized.

These experiments were carried out in a less quantitative way, so no further consideration has been given them.

In IPA solution and in Procedure 1, form A, which is a thermodynamically metastable form, was preferentially crystallized, without seed crystals at  $S_A \geq 4.5$ , and regardless of kind of seed crystals or of thermal history of starting solution at  $S_A \geq 3.6$ . In observation by optical microscope and analysis by FT-IR, no phase transition from A to B was observed over a period in these experiments. Therefore, at this high supersaturation ratio the system was found to obey "Ostwald's Step Law"<sup>9)</sup> concerning the preferential crystallization of the metastable polymorphic form, and the nucleation and/or growth rate of form B appeared to be slower than those of form A at such a high supersaturation.

For the range of  $S_{c,A} = 4.8 \sim 6.3$ , the primary nucleation of form A was measured by the waiting time ( $\theta$ ) method<sup>4)</sup> at  $T_c = 293.2$ ,  $N_r = 600$  and was analyzed by the relation

$$\log(\theta V) = -\log\left(\frac{k_1}{N_{obs}}\right) + \frac{M}{\log^2 S} \quad (4)$$

where, assuming the nucleus to be spherical,

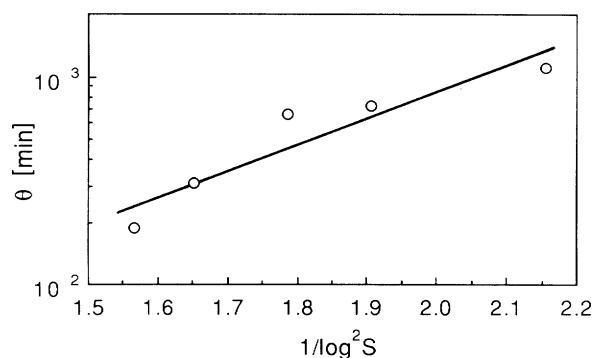
$$M = \frac{16}{3} \pi \left( \frac{\sigma}{2.303 kT} \right)^3 v^2 \quad (5)$$

From the slope of the straight line in **Fig. 7**, the surface energy of  $\sigma$  of form A was estimated to be  $8.1 \times 10^{-3} \text{ J} \cdot \text{m}^{-2}$ . This value is not much different from  $\sigma_s$  obtained from solubility data, described in 2.1. From the  $\sigma$  value, radius  $r_c$  of critical nucleus and number of solute  $m$  in a critical nucleus as model parameters at  $S_A = 5$ ,  $T_c = 293$  were evaluated to be 0.8 nm and 6.7, respectively.

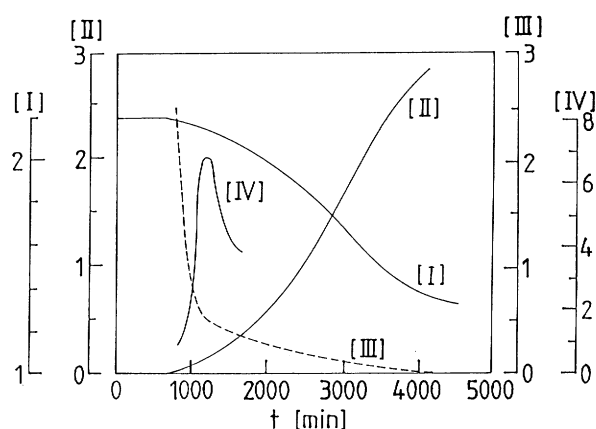
In IPA solution and in Procedure 2, contrary to the results in earlier papers<sup>3,6,12)</sup> that only form A is crystallized from IPA solution, not only form A but also form B was crystallized, corresponding to the form of seed, with good reproducibility.

The crystal growth rate of form A was also measured in this low range of supersaturation ratio ( $S_A = 2.2 \sim 1.3$ ), using a batch crystallizer of 553 ml in volume, by the light transmittance method<sup>5,15,16)</sup>, at  $T_c = 293.2$ ;  $N_r = 600$ ; seed: form A 0.1 g ( $\Delta$  in **Fig. 2**). **Figure 8** shows the time course of supersaturation ratio, total surface area of the suspended particles, linear growth rate and secondary nucleation rate. Since the supersaturation is relatively high, the data on linear growth rate  $dr/dt$  were arranged under the assumption that the rate-determining step is the two-dimensional nucleation rate<sup>4,16)</sup>:

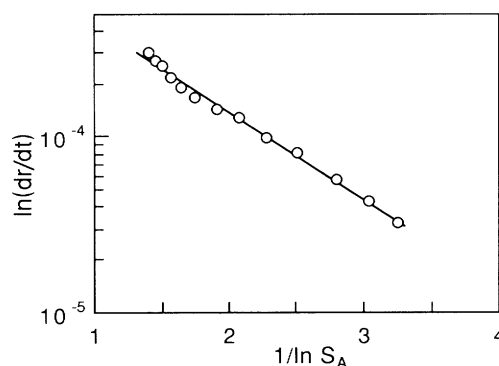
$$\frac{dr}{dt} = k \cdot \exp \left[ -\frac{\pi a \sigma'^2}{(kT)^2 \ln S} \right] \quad (4)$$



**Fig. 7.**  $\theta$  vs.  $\log^{-2} S$



**Fig. 8.** Crystallization of form A from its IPA solution:  $S_0 = 2.2$ ;  $N_r = 600 \text{ min}^{-1}$ ;  $T_c = 293.2 \text{ K}$ ; Seed: form A 0.1 g.  
[I] supersaturation ratio ( $= C/C_{s,A}$ ) [—]  
[II] total surface area of particles [ $\text{cm}^2 \cdot \text{cm}^{-3}$ ]  
[III] linear growth rate [ $\times 10^{-3} \mu\text{m} \cdot \text{s}^{-1}$ ]  
[IV] secondary nucleation rate [ $\times 10^{-2} \cdot \text{cm}^{-3} \cdot \text{s}^{-1}$ ]



**Fig. 9.**  $\ln(dr/dt)$  vs.  $1/\ln S_A$

as shown in **Fig. 9**. It was also attempted to rearrange the linear growth rate data in a ln-ln chart against  $\Delta C (= C - C_s)$  and  $(S - 1)(= (C - C_s)/C_s)$ , but no linear relationships were obtained. From **Fig. 9**, free edge energy  $\sigma'$  and surface energy  $\sigma'_A/d_A$  were estimated to be  $3.5 \times 10^{-12} \text{ J} \cdot \text{m}^{-1}$  and  $5.2 \times 10^{-3} \text{ J} \cdot \text{m}^{-2}$  respectively.

## Conclusions

1) Equilibrium solubilities of cimetidine in H<sub>2</sub>O, IPA and H<sub>2</sub>O-IPA mixture were measured. It was found that form A is more soluble than form B in any solvent, and that both forms are more soluble in the order H<sub>2</sub>O, IPA, H<sub>2</sub>O-IPA mixture.

2) In IPA solution at higher supersaturation ( $S_A \geq 3.6$ ), form A, which is a thermodynamically metastable form, was crystallized preferentially regardless of presence or absence of seed ( $S_A \geq 4.5$ ) and regardless of the form of seed ( $S_A \geq 3.6$ ). No phase transition from form A to the more stable form B was observed.

3) In IPA solution at lower supersaturation ( $S_A \leq 2$ ), the form corresponding to that of seed was crystallized.

4) Contrary to the results in earlier papers<sup>3,6,12</sup>, form B was crystallized with good reproducibility from IPA solution at low supersaturation ( $S_A \leq 2$ ) by using form B crystals as seeds.

## Acknowledgement

The authors wish to thank Fujimoto Pharmaceutical Co. for supplying cimetidine powder.

## Nomenclature

$a$	= area occupied by unit solute in surface, = $d^2$	[nm <sup>2</sup> ]
$b$	= cooling rate	[K · min <sup>-1</sup> ]
$C$	= solute concentration	[mol · l <sup>-1</sup> ]
$d$	= solute diameter	[nm]
$d_s$	= size of seed crystals	[μm]
$\Delta G$	= Gibbs energy change	[J · mol <sup>-1</sup> ]
$\Delta H$	= enthalpy change	[J · mol <sup>-1</sup> ]
$\Delta H_{sol}$	= apparent heat of dissolution (= $\alpha \cdot R$ )	[J · mol <sup>-1</sup> ]
$k$	= Boltzmann constant	[J · m <sup>-2</sup> ]
$k_1$	= nucleation rate constant	[—]
$MW$	= molecular weight	[mol <sup>-1</sup> ]
$m$	= number of solute in a critical nucleus	[—]
$mp.$	= melting point	[K]
$N_A$	= Avogadro number	[mol <sup>-1</sup> ]
$N_{obs}$	= number of nuclei at $t = \theta$	[—]
$N_r$	= agitation rate	[min <sup>-1</sup> ]
$R$	= gas constant	[J · K <sup>-1</sup> · mol <sup>-1</sup> ]
$r_c$	= radius of critical nucleus	[nm]
$S$	= supersaturation ratio (= $C/C_s$ )	[—]
$\Delta S$	= entropy change	[J · K <sup>-1</sup> · mol <sup>-1</sup> ]
$T$	= absolute temperature	[K]
$T_c$	= crystallization temperature	[K]
$T_u$	= initially maintained temperature at undersaturation	[K]

$T_0$	= initially maintained temperature	[K]
$V$	= volume of solution	[cm <sup>3</sup> ]
$v$	= volume of crystal (= $v_m/N_A$ )	[cm <sup>3</sup> ]
$v_m$	= molar volume of crystal	[cm <sup>3</sup> · mol <sup>-1</sup> ]
$x$	= mole fraction	[—]
$\alpha$	= parameters in Eq. (1)	[K]
$\beta$	= parameters in Eq. (1)	[—]
$\rho_s$	= density of crystal	[g · cm <sup>-3</sup> ]
$\sigma$	= surface energy	[J · m <sup>-2</sup> ]
$\sigma'$	= free edge energy of a growth unit in a step	[J · m <sup>-1</sup> ]
$\sigma_s$	= surface energy obtained from solubility data	[J · m <sup>-2</sup> ]
$\theta$	= waiting time	[min]

## <Subscripts>

$A$	= form A
$B$	= form B
$c$	= at crystallization
$s$	= at saturation
$0$	= initial
$1$	= H <sub>2</sub> O in H <sub>2</sub> O-IPA mixture
$2$	= IPA in H <sub>2</sub> O-IPA mixture

## <Superscripts>

$E$	= thermodynamic excess function
$ideal$	= ideal solution

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