Crystallization of Selective Polymorph Using Relationship Between Supersaturation and Solubility

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For polymorph screening, the plot of $\Delta C_{met}/C_c$ against C^*/C_c in nucleation kinetics was investigated. The polymorph screening for forms I and II and amorphous form of clopidogrel hydrogen sulfate was carried out according to the nucleation kinetics expressed by this plot. The stability order of polymorphs for famotidin was also predicted successfully by this model. This model was used in the expectation of supersaturation level for polymorphic formation. Two types of polymorphic crystallization: transformation from metastable form to stable form and nucleation and growth of polymorphic form without transformation can be explained. Amorphous form was also expected by this model. Even though polymorphs depend on lots of crystallization parameters such as solvent, temperature, concentration, cooling rate, and so forth, plot of $\Delta C_{met}/C_c$ and the C^*/C_c in various nucleation kinetics gives a guide line for screening of polymorph. © 2015 American Institute of Chemical Engineers *AIChE J*, 61: 1372–1379, 2015

Keywords: crystallization, screening of polymorph, supersaturation, pharmaceutical, solubility

Introduction

Compounds that exist in various solid-state forms, crystalline or amorphous, offer unique challenges in product development and manufacturing.[1] Pharmaceutical development of thermodynamically metastable forms is often desired because of their enhanced biopharmaceutical properties as a result of higher solubilities and faster dissolution rates. In other cases, metastable forms are unacceptable because of crystallization and transformation to a more thermodynamically stable form during processing, storage, or dissolution.[2–4]

Polymorphism is a phenomenon which occurs in crystalline solid states[5] when a molecule packs/conforms in different ways giving rise to two or more distinct crystal structures. Different polymorphs of the same material normally exhibit different properties, such as compressibility, melting point, and solubility, which can have a great influence on the bioavailability of pharmaceuticals. Consequently, it is important to make sure that the desired polymorph is consistently controlled in the production process. As crystallization of active pharmaceutical materials takes place in solution,[6] polymorphic transformation often occurs according to Ostwald's rule of stages,[7] whereby the metastable form is transformed into the stable form. It is very difficult to control the transformation process and to produce the target polymorph; hence, it is essential to grasp which experimental factors affect the transformation kinetics. The solution-mediated mechanism only allows the transition from a metastable form to the stable form. This type of transformation is driven by the difference in solubility between the two forms.

In polymorphic crystallization of clopidogrel hydrogen sulfate (CHS) in various solvents, transformation of polymorphs was monitored successfully by inline measurement.[8–10] Two types of transformations were observed: one when the metastable form nucleated first and then transformed into the stable form, the other was nucleation and growth of the stable form without transformation. Which process occurs depends on the crystallization conditions such as solvent type, temperature, concentration, cooling rate, and so forth. The kinetics of the transformation is determined by solubility difference, solid/solvent ratio, agitation, processing temperature, and seeding. Thus, the polymorph is determined by the kinetics of nucleation and growth, which are functions of supersaturation. The combination of generating different conditions and characterization methods can complete the screen of polymorphism. Previous work on screening of polymorphs focused mainly on making measurements during crystallizations.[8,10–12] However, theoretical work on polymorph screening is relatively rare. In this study, a model is developed which leads to using a plot of supersaturation against solubility for polymorph screening. The polymorph screenings for Forms I and II, and amorphous form of CHS, and for Forms A and B of famotidin were investigated by this model.

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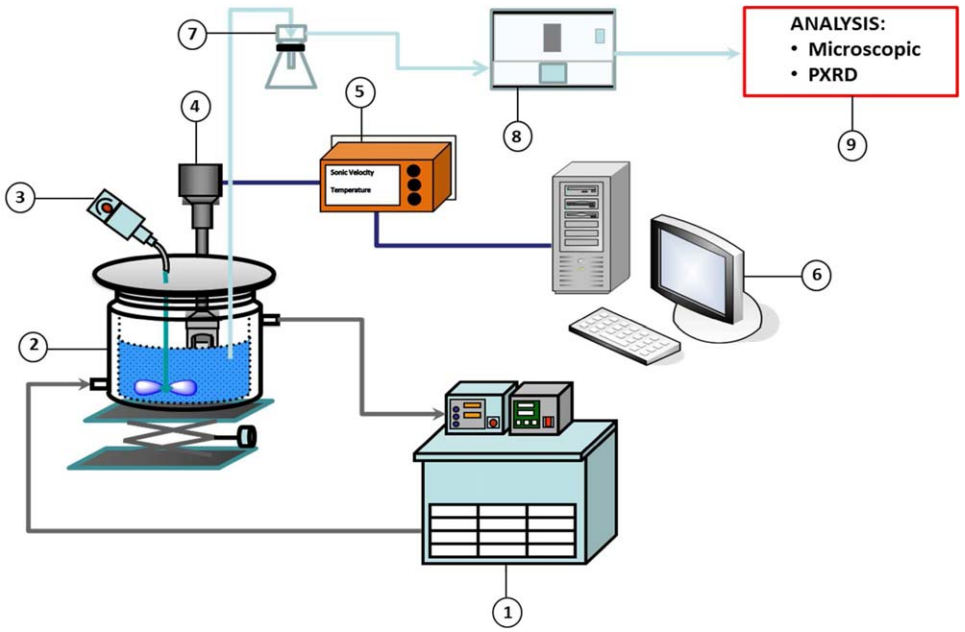

Figure 1. Schematic diagram of experimental setup.

[Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Experimental

Materials and identification of polymorphs

Form I and II crystals of CHS ($C_{16}H_{16}ClNO_2S.H_2SO_4$, MW 419.2, 99.0% pure, supplied by JC Chemical Co.) was used without purification. Formic acid (FA) (solvent) and isopropyl alcohol (IPA; antisolvent) were purchased from Duksan Pure Chemicals Co. Polymorphs of crystals obtained were identified using x-ray powder diffraction (XRPD). XRPD patterns were taken with an x-ray Diffractometer (D/MAX 2500H, Rigaku Co., Tokyo, Japan). The measurement conditions were as follows: target, Cu; filter, Ni; voltage, 60 kV; current, 300 mA; receiving slit, 0.3 mm; scan range, 1°–40° (2θ); step size, 0.02°; and scanning speed, 1°/min. About 50 mg of the sample powder was carefully loaded into a glass holder, and the sample surface was flattened softly to avoid particle orientation using a spatula and glass plate and then the sample weight was accurately measured.

Experimental method

The experimental setup for CHS crystallization in FA–IPA solvents is the same as in the previous study[10] and shown in Figure 1. It consists of a 300-mL double-jacketed crystallizer, a 5-cm marine-type mechanical stirrer, an ultrasonic velocity-measuring system, thermostatic bath, vacuum filter, and vacuum-drying equipment. The experiments were conducted in batch crystallization mode. In all operations, ultrasonic velocity, concentration, and temperature were recorded at 2 s intervals.[8–10] The CHS Form II crystals were dissolved in pure FA solvent at 10°C higher than the saturation temperature. The solution was kept at this constant temperature until all the crystals were fully dissolved, and then slowly cooled to the saturation temperature and maintained there for an hour. The clear solution was then fed to the agitated IPA at a constant temperature using a thermostatic bath. Temperature of IPA was adjusted to the same as crystallization temperature before addition of FA–CHS solution. The FA–CHS solution was fed all at once to IPA solvent. Experiment conditions and results are listed in Table 1.

The solids were sampled at regular intervals using a solid–liquid separator with a glass filter. The polymorphic form was identified by XRPD and scanning electron microscope (SEM) analysis. The solubility of Forms I and II in FA–IPA mixtures was measured in previous studies.[13] Amorphous CHS was prepared in FA–IPA solvent mixtures by vacuum evaporative crystallization. The solubility of amorphous CHS in the FA–IPA mixture was measured by the same method reported in Ref. 13, with results reported below.

Previous work presented successful polymorph screening of CHS in methanol-IPA solvent.[8] Experiment conditions and results for methanol-IPA mixtures are summarized in Table 2. For famotidine experiments, metastable zone widths of Form A (metastable form) and Form B (stable form) in water and methanol were measured by cooling crystallization at various initial concentration and temperature.[12] It was found that the nucleation barrier of Form A of famotidine was larger than that of Form B. Experiment conditions and data for famotidine are summarized in Table 3.

Microscopy study

Microscopy studies using focused ion beam-SEM (FIB-SEM) were carried out to observe specific crystal faces of Form I, transformed crystals (Form I + II) and Form II. Figure 2 shows FIB-SEM photos for Form I crystals, crystals being transformed from Form I into Form II and Form II crystals. The crystals were obtained in FA–IPA mixture. Form I crystals were observed microscopically as polygonal with smooth surface in the bulk solution. Form I + II and Form II were observed as irregular shape with the porous surface. Form II had more pores than Form I + II. This observation confirms that the transformation is induced by the heterogeneous nucleation and growth of Form II on the surface of Form I. Metastable form and stable form can be obtained without transformation by control the crystallization conditions. According to Ostwald's rule of stages,[7] a metastable polymorph is obtained first during this process and then transformed into the more stable polymorph. It proposed that the transformation was occurred by dissolution of

Table 1. Experiment Conditions for FA-IPA

FA Mass Fraction in Solvent	Crystallization Temperature (K)	Feed Concentration (CHS *g*/FA + IPA *g*)	Seeding Point	Polymorph in Nucleation	Final Polymorph	$\Delta C_{met}/C_c$	C^*/C_c	S_{max}
0.100	298.15	0.182	None	Form II	Form II	0.029	0.092	1.10
0.067	298.15	0.122	None	Form II	Form II	0.018	0.063	1.09
0.050	298.15	0.093	None	Form II	Form II	0.010	0.052	1.06
0.200	308.15	0.473	None	Form II	Form II	0.100	0.220	1.12
0.100	308.15	0.258	None	Form II	Form II	0.070	0.100	1.19
0.067	308.15	0.178	None	Form II	Form II	0.070	0.050	1.34
0.050	308.15	0.135	None	Form II	Form II	0.030	0.060	1.16
0.05	308.15	0.135	3.5 wt % 0 s	Form I	Form II	0.0468	0.0433	1.28
0.05	308.15	0.135	3.5 wt % 500 s	Form I	Form II	0.0453	0.0448	1.26
0.05	308.15	0.135	3.5 wt % 1000 s	Form I	Form II	0.0444	0.0457	1.25
0.05	308.15	0.135	3.5 wt % 1500 s	Form I	Form II	0.0437	0.0465	1.24
0.05	308.15	0.135	2.5 wt % 0 s	Form I	Form I	0.0535	0.0348	1.38
0.05	308.15	0.135	2.5 wt % 500 s	Form I	Form I	0.0527	0.0354	1.37
0.05	308.15	0.135	2.5 wt % 1000 s	Form I	Form I	0.0558	0.0327	1.42
0.05	308.15	0.135	2.5 wt % 1500 s	Form I	Form I	0.0546	0.0337	1.40
0.05	308.15	0.135	1.5 wt % 0 s	Form I	Form II	0.0537	0.0346	1.38
0.05	308.15	0.135	1.5 wt % 500 s	Form I	Form II	0.0537	0.0346	1.38
0.05	308.15	0.135	1.5 wt % 1000 s	Form I	Form II	0.0506	0.0374	1.33
0.05	308.15	0.135	1.5 wt % 1500 s	Form I	Form II	0.0496	0.0382	1.32
0.05	308.15	0.739	None	Form I	Form II	0.140	0.360	1.38
0.05	393.15	0.666	None	Amorphous	Amorphous	0.400	0.040	6.34
0.05	393.15	0.954	None	Amorphous	Amorphous	0.560	0.070	4.56
0.05	393.15	0.981	None	Amorphous	Amorphous	0.570	0.090	3.80
0.05	393.15	0.971	None	Amorphous	Amorphous	0.550	0.100	3.45
0.05	393.15	0.990	None	Amorphous	Amorphous	0.600	0.060	5.47

Table 2. Experiment Conditions for Methanol-IPA

Methanol Mass Fraction in Solvent	Temperature (K)	Feed Concentration (CHS *g*/Methanol-IPA *g*)	Seeding Point	Polymorph in Nucleation	Final Polymorph	$\Delta C_{met}/C_c$	C^*/C_c	S_{max}
0.130	298	0.182	None	Form I	Form II	0.1064	0.0186	1.175
0.117	298	0.164	None	Form I	Form II	0.0952	0.0175	1.184
0.107	298	0.15	None	Form I	Form II	0.0841	0.0186	1.221
0.094	298	0.132	None	Form I	Form II	0.0714	0.0191	1.268
0.051	298	0.072	None	Form I	Form II	0.0375	0.0120	1.319

the less stable form, because of different solubilities between metastable form and more stable form. From Figure 2, it was found that transformation was carried out by nucleation in surface of metastable form rather than dissolution of metastable form. Therefore, polymorph can be controlled by understanding the kinetic effect, especially for nucleation, in which main parameter is the supersaturation.

Effect of Supersaturation

In solution-mediated crystallization, supersaturation is a major parameter to affect the polymorph of the crystals. Figure 3 shows the solubility of the stable form (Form II), the metastable form (Form I), and unstable form (amorphous form) of CHS, as a function of FA–IPA composition at a constant temperature of 308.15 K. The solubility curve is unchangeable because it is a thermodynamic property while the metastable zone width is flexible because it is a kinetic property. The metastable zone width depends on rates of cooling, evaporation, addition of nonsolvent, respectively, for cooling crystallization, evaporative crystallization, and drowning-out crystallization. Figures 4A–C show the schematic change of metastable zone width with respect to supersaturation level. Figure 4A shows the case operated at lower supersaturation. In this case, Form II (stable form) only is obtained in the nucleation step and is grown because the other two forms are undersaturated. Thus, it is not possible to be transformed from the metastable form. However, as shown in Figure 4B, at higher supersaturation, nucleation of Form I (metastable form) occurs first, and then Form I can be transformed into Form II. As shown in Figure 4C, at ultrahigh supersaturation, amorphous form (unstable form)

Table 3. Experiment Conditions for Famotidine

Solvent	Temperature (K)	Feed Concentration (Solute *g*/Solution *g*)	Seeding Point	Polymorph in Nucleation	Final Polymorph	$\Delta C_{met}/C_c$	C^*/C_c	S_{max}
Water	273	0.061	None	Form B	Form B	0.0555	9.26×10^{-5}	600
Water	273	0.041	None	Form B	Form B	0.0369	9.26×10^{-5}	399
Methanol	273	0.028	None	Form B	Form B	0.0231	2.77×10^{-3}	9.3
Methanol	328	0.025	None	Form A	Form A	0.0102	1.29×10^{-2}	1.8
Methanol	323	0.021	None	Form A	Form A	0.0093	1.02×10^{-2}	1.9
Methanol	307	0.013	None	Form A	Form A	0.0056	5.56×10^{-3}	2.0

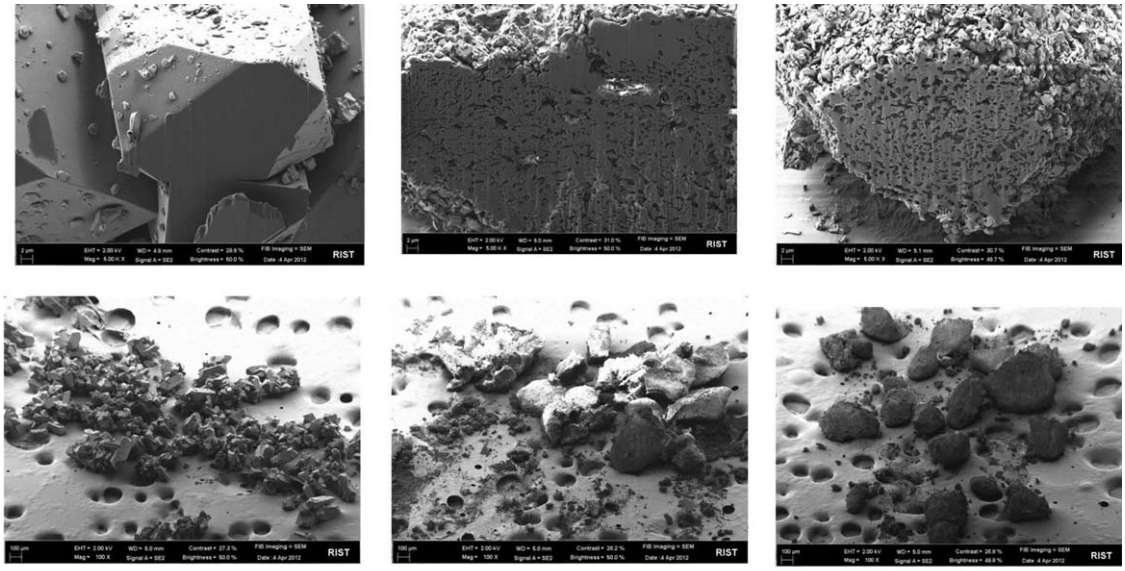

Figure 2. SEM photos for (a) Form I crystals, (b) transformation of Form I into Form II, and (c) Form II crystals of CHS.

was formed and grown. Amorphous form can be transformed into Forms I and II if the operation line passes through the metastable limits of Forms I and II. In fact, to procure the amorphous form a very high supersaturation is necessary. This supports that the amorphous form was obtained by high-supersaturation techniques like spray drying, rapid cooling, and so forth.[14,15]

In cases when the transformation occurs, the supersaturation of each polymorph contributes to the determination of polymorphic form. Figure 5 shows the variation of concentration during the transformation. The ratio of supersaturations for Form II and Form I can be calculated by

$$\frac{S_{\mathrm{I}}}{S_{\mathrm{II}}}=\frac{C_{\mathrm{II}}{}^{*}}{C_{\mathrm{I}}{}^{*}} \tag{1}$$

where S is the relative supersaturation (C/C^*) and C^* the saturation concentration.

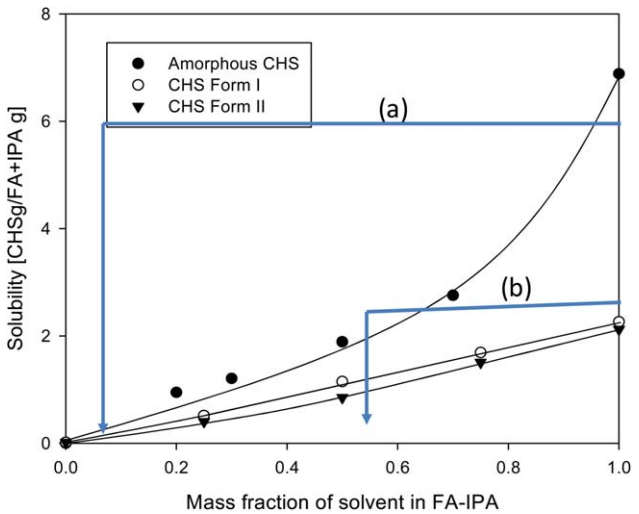

Figure 3. Solubility of Form I, Form II, and amorphous form of CHS in FA-IPA solvent mixtures as a function of mass fraction of FA, at a temperature of 308.15 K, with crystallization conditions: (a) mass ratio of CHS/FA = 6.0 and mass ratio of IPA/FA = 15.6 and (b) mass ratio of CHS/FA = 2.5 and mass ratio of IPA/FA = 0.82.

[Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Results and Discussion

The polymorphic form is determined in the nucleation step. Nucleation kinetics can be expressed by the following classical nucleation equation

$$B_i=A\exp\left(-\frac{\Delta G_i}{kT}\right) \tag{2}$$

where ΔG_i is the activation energy for the nucleation of Form i, and A is the frequency factor.

ΔG_i can be derived by the classical nucleation theory as follows

$$\Delta G_i=\frac{16\pi\gamma_i^3\upsilon^2}{3(kT\ln S_i)^2} \tag{3}$$

where γ, υ, and S are interfacial tension, molecular volume, and relative supersaturation, respectively. The frequency factor A can be obtained by collision frequency between molecules, the interfacial energy and energy barrier for diffusion of solute. Mersmann completed the build of the following nucleation equations.[16] Nucleation rate of Form i is expressed by Eqs. 4 and 5.

For homogeneous nucleation

$$B_{\mathrm{hom},i}=1.5D_{\mathrm{AB}}(C_{\mathrm{c}}N_{\mathrm{A}})^{5/3}\left(\frac{C_i^*}{C_{\mathrm{c}}}\right)^{7/3}S_i^{7/3}\left(K\ln\frac{C_{\mathrm{c}}}{C_i^*}\right)^{1/2}\exp\left(-\frac{16\pi}{3}\left(K\ln\frac{C_{\mathrm{c}}}{C_i^*}\right)^3\left(\frac{1}{\ln S_i}\right)^2\right) \tag{4}$$

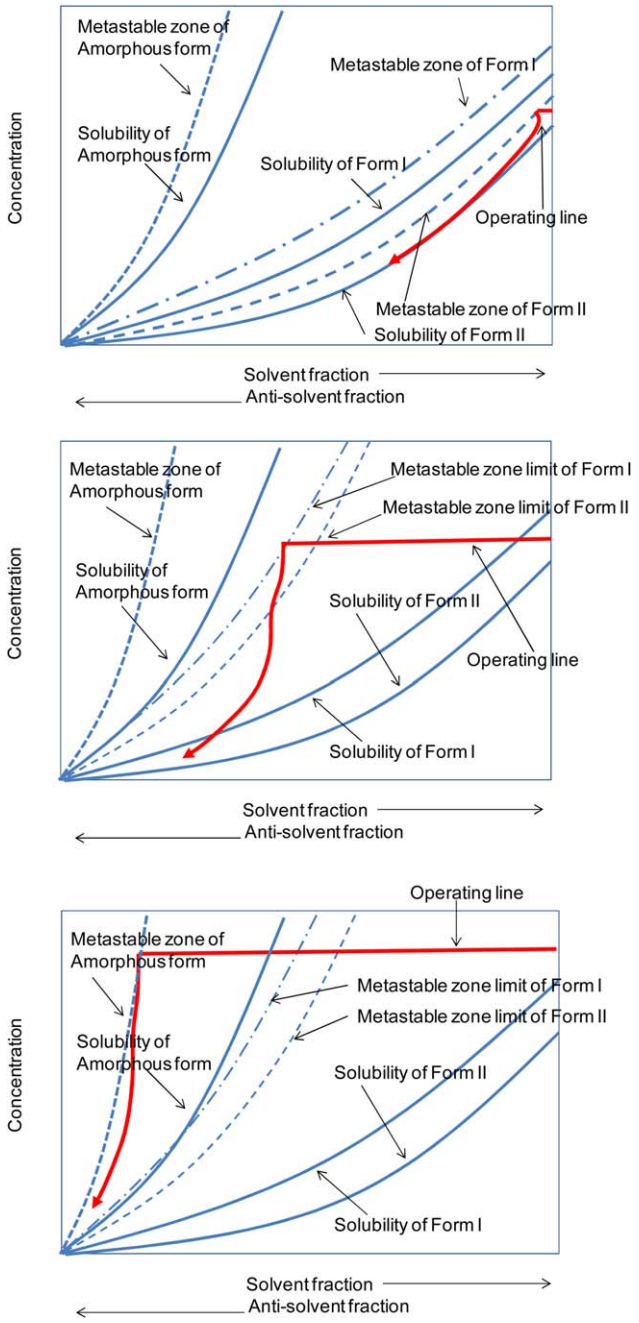

Figure 4. Schematic drawings of solubility, metastable zone widths and operating lines for stable form II, metastable form I, and amorphous form of CHS at fixed temperature.

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where D_{AB}, C, C^*, C_c, N_A, and K means diffusion coefficient, concentration, saturation concentration, molar density of solid, Avogadro' number and dimensionless constant, respectively.

For heterogeneous nucleation

$$B_{het,i}=1.5D_{AB}(C_cN_A)^{5/3}\left(\frac{C_i^*}{C_c}\right)^{7/3}S_i^{7/3}\left(Kf\ln\frac{C_c}{C_i^*}\right)^{1/2}\exp\left(-\frac{16\pi}{3}\left(Kf\ln\frac{C_c}{C_i^*}\right)^3\left(\frac{1}{\ln S_i}\right)^2\right) \quad (5)$$

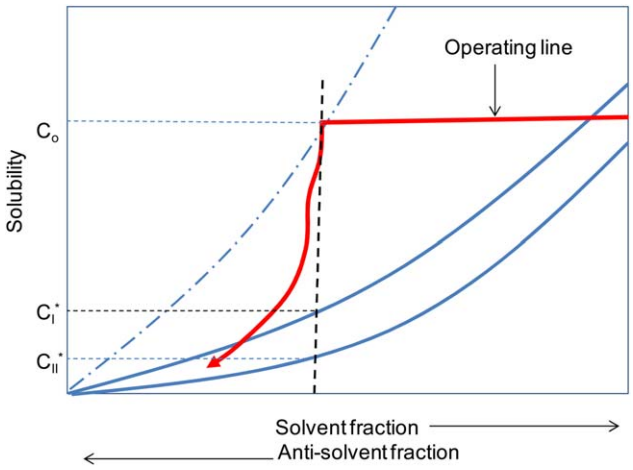

Figure 5. Schematic drawing for supersaturation of stable form, Form II, and metastable form, Form I, where C_o, C_I^*, and C_{II}^*, mean initial concentration, equilibrium concentrations of Form I and Form II, respectively, in case of transformation of Form I into Form II (see operating line).

[Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

For surface nucleation

$$B_{surf,i}=D_{AB}(C_cN_A)^{4/3}\exp\left(-\pi\left(K\ln\frac{C_c}{C_i^*}\right)^2\left(\frac{1}{\ln S_i}\right)\right) \quad (6)$$

f means the reduction factor for the nucleation work. In case that the factor f equals to 1.0, it means homogeneous nucleation equation. The surface nucleation considers the formation of secondary nuclei in case of no attrition nucleation.[16]

The interfacial tension can be calculated in the following equation

$$\gamma=K(C_cN_A)^{2/3}kT\ln(C_c/C^*) \quad (7)$$

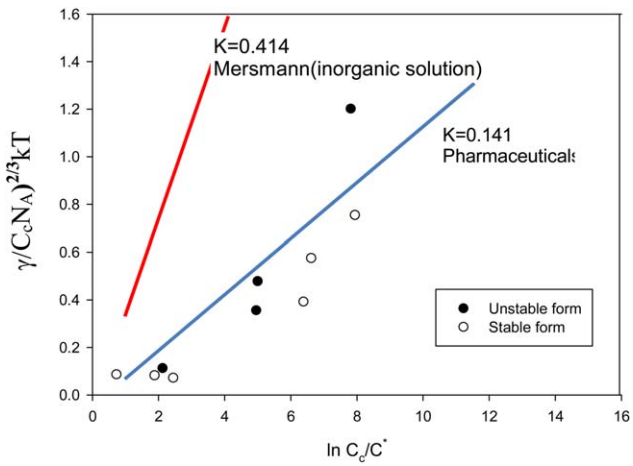

Figure 6. K values for inorganic solution and pharmaceuticals using the interfacial tension published for clopidogrel,[11] famotidine,[13] and paracetamol.[12]

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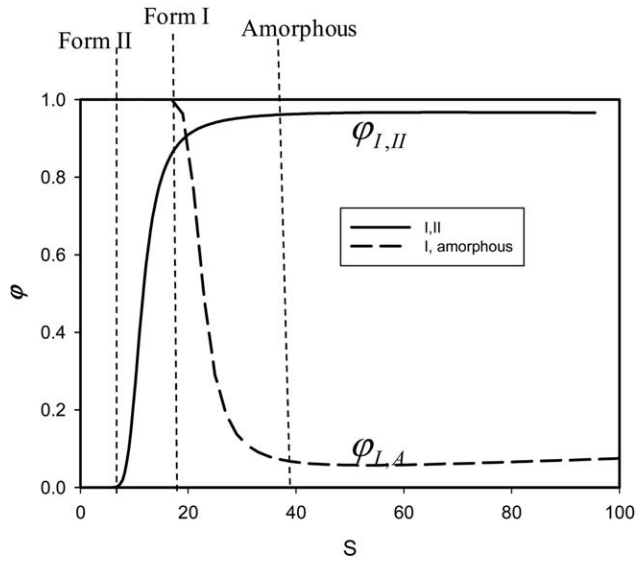

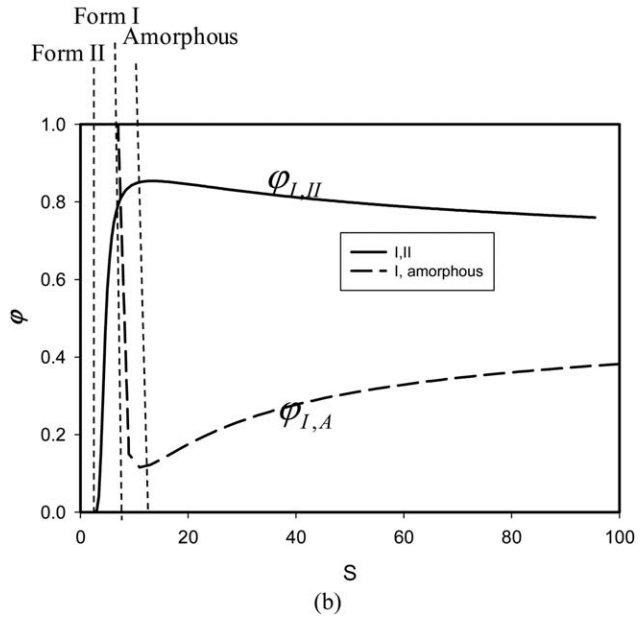

Figure 7. Effect of supersaturation on polymorphic form.

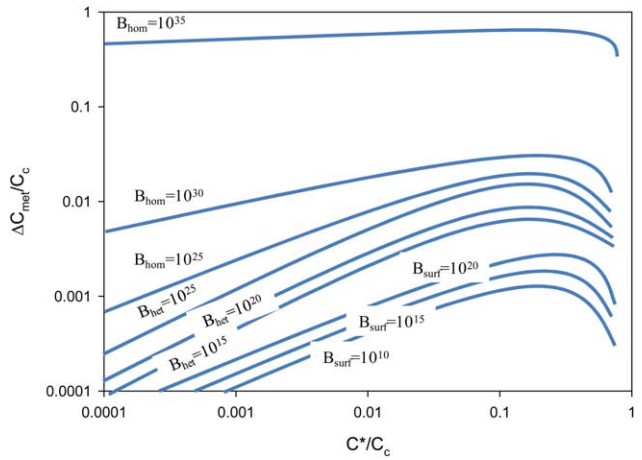

Figure 8. Plot of $\Delta C/C_c$ vs. C^*/C_c for nucleation rates.

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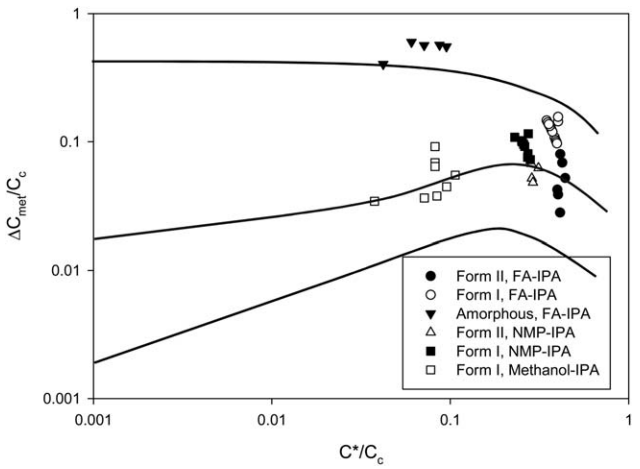

Figure 9. Expectation of polymorphic form by plot of $\Delta C/C_c$ vs. C^*/C_c.

The dimensionless constant K can be derived by the interfacial geometry and the experimental data.[17] Mersmann correlated interfacial tension with its solubility for inorganic soluble in water. In result, $K = 0.414$ was obtained. K value for pharmaceuticals was correlated with the experimental data[8,11,18] and was obtained as 0.141. A few data of interfacial tension were published for clopidogrel,[10] famotidine,[12] and paracetamol.[11] These data are shown in Figure 6.

When the metastable polymorphic form is nucleated first, it is then transformed into the stable form. The level of supersaturation is an important parameter determining the first generated form. The polymorphic composition can be calculated by the nucleation rate of polymorphic forms. The fraction of polymorph can be expressed in the competition of polymorphic nucleation. The fraction of polymorph A in polymorphs A and B mixture, $\varphi_{A,B}$ is expressed as

$$\varphi_{A,B} = \frac{B_A}{B_A + B_B} \tag{8}$$

Figure 7 shows results of calculation using Eqs. 4 and 8 for the cases (a) and (b), as shown in Figure 3. In the case (a) shown in Figure 3, in the higher initial supersaturation, Form II is generated at $S = 8.2$ and Form I is generated at $S = 17.5$, and amorphous form is at $S = 40$. In the case (b) shown in Figure 3, in the lower initial supersaturation, Form II is generated at $S = 3.1$ and Form I is generated at $S = 9.3$, and amorphous form is at $S = 13.6$. Thus, the higher supersaturation leads to the lower stable form. In comparison with experimental data, Form II, Form I, and amorphous form were obtained when S values are about 1.1, 1.35, and 5.0, respectively. Even though this result is not matched with the experimental data, dependence of supersaturation on polymorph screening can be expected.

As seen in Eqs. 4 and 5, primary nucleation can be expressed as a function of C^*/C_c and $\Delta C_{met}/C_c$.[16] ΔC_{met} means the supersaturation at the metastable zone width

$$B = f(C^*/C_c, \Delta C_{met}/C_c) \tag{9}$$

Table 4. Conditions for Three Forms of CHS

	Form I	Form II	Amorphous
C_c (kmol/m^3)	3.341346	3.413462	2.884615
C^* (kmol/m^3)	0.023567	0.021463	0.480769
C_o (kmol/m^3)	0.218531	0.178063	2.185315

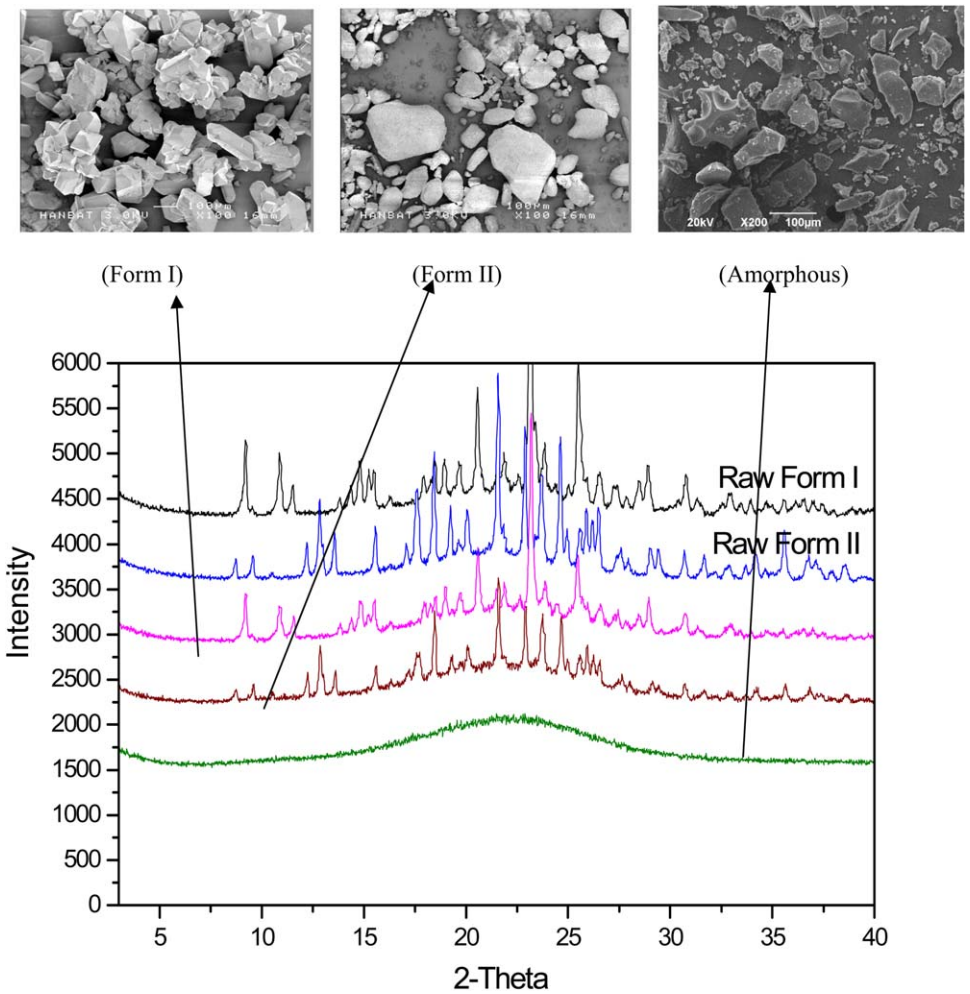

Figure 10. SEM photos and XRPD patterns of CHS obtained in the experiments.

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To grasp the polymorphic nucleation, the plot of the dimensionless metastable supersaturation against dimensionless solubility can be considered. By Mersmann,[16] the relationship between $\Delta C_{met}/C_c$ and the C^*/C_c for various nucleation mechanisms has been shown in Figure 8. These plots are valid for $D_{AB} = 1.21 \times 10^{-9}$ m^2/s and $C_c = 3.4$ kmol/m^3 for CHS in FA/IPA.[10] The solubility of CHS in the solvent investigated is in the range of $3 \times 10^{-4}-1.5$ kmol/m^3, and its dimensionless solubility is, therefore, $C^*/C_c = 10^{-4}-0.5$ with C_c=3.4 kmol/m^3. In Figure 8, the nucleation mechanism can be distinguished by homogeneous nucleation rate (B_{hom}) $> 10^{25}$ nuclei/m^3 s and 10^{25} nuclei/m^3 s <heterogeneous nucleation (B_{het}) $< 10^{15}$ nuclei/m^3 s. Plots of $\Delta C/C_c$ against C^*/C_c for Form I, Form II, and amorphous form are shown in Figure 9. The conditions for three forms are confirmed by the experiments (see Table 4). Form I and amorphous form are driven by the homogeneous nucleation equation, and Form II is driven by the heterogeneous nucleation equation. These conditions are applied to Eq. 4. Factor f is assumed as 0.1. The calculation results are shown in Figure 9. The lines show the calculation results for Form I, Form II, and amorphous. The calculated lines were compared to the experimental data. The data published for

Table 5. Conditions for Two Forms of Famotidine

	Form B	Form A
C_c (kmol/m^3)	3.204748	3.204748
C^* (kmol/m^3)	0.017698	0.02938
C_o (kmol/m^3)	0.083068	0.053899

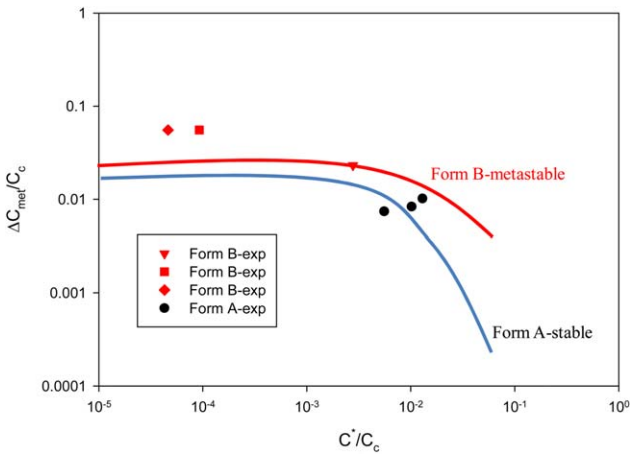

Figure 11. Plots of $\Delta C/C_c$ against C^*/C_c for Form A and Form B of famotidine.

[Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

polymorphic crystallization in N-methylpirrolidone–IPA solvents are shown.[10] Even though data are scattered, similar trends to the calculation results are suggested. One possibility for the scattering data is due to effect of secondary nucleation. Ferrari and Davey suggested that the secondary nucleation was dominated for the transformation of metastable form into stable form.[19] In this study, seeding was used for nucleation of Form I by adjusting supersaturation within metastable zone limit of Form I at 12 experimental runs. Roughly speaking, it gives information about the supersaturation to be selected for screening of polymorphs. Figure 10 shows the XRPD patterns and SEM photographs of CHS obtained in three experiments. It was found that Form I, Form II, and amorphous were formed successfully.

This model was extended to famotidine, which was studied previously with regard to polymorphic forms. Form B (metastable form) and Form A (stable form) were obtained under various conditions.[12] Cooling and seeding were induced in various solvents. Crystallization of famotidine in methanol was sampled. Table 5 lists conditions for two forms of famotidine. Figure 11 shows plots of $\Delta C/C_c$ against C^*/C_c for Form A and Form B of famotidine. From this figure, Forms A and B can be selected by supersaturation.

Conclusions

The relationship between $\Delta C/C_c$ and the C^*/C_c was introduced for the screening of polymorphs. The polymorph screening for Forms I and II, and amorphous form of CHS was expected by the nucleation mechanism expressed by plot of $\Delta C/C_c$ vs. the C^*/C_c. Famotidin was also applied successfully by this model. This model can be used in the expectation of supersaturation level for polymorphic formation. Two types of polymorphic crystallization: transformation from metastable form to stable form, and nucleation and growth of stable form without transformation can be explained by this model. The amorphous form was also expected by this model. Even though lots of crystallization parameters like solvent, temperature, concentration, cooling rate, and so forth affect to the polymorphic formation, plot of $\Delta C/C_c$ and the C^*/C_c in different nucleation mechanisms gives a guide line for screening of polymorph.

Notation

B = nucleation rate, nuclei/m^3 s
C_o = initial concentration, kmol/m^3
C^* = equilibrium concentration, kmol/m^3
ΔC = supersaturation, kmol/m^3
C_c = crystal molar density, kmol/m^3
D_{AB} = diffusion coefficient, m^2/s
ΔG = activation energy, J/mol
K = constant of Eq. 7
N_A = Avogadro' number, mol^{-1}
S = relative supersaturation

Greek letters

γ = interfacial tension, J/m^2
κ = Boltzmann constant
v = molecular volume, m^3
φ = mass fraction of polymorph

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