Characterization and Selective Crystallization of Famotidine Polymorphs

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ABSTRACT: Famotidine crystallizes in two different polymorphic forms: the metastable polymorph B and the stable polymorph A. In this work, solid characterization for both polymorphs has been conducted in detail. The solubility, metastable zone width and interfacial energy of both polymorphs in different solvents have been measured. The influence of solvent, cooling rate, initial concentration and the temperature of nucleation on polymorphism has been investigated. Results show that the nature of polymorph that crystallizes from solution depends on the initial concentration of the solution, solvent, cooling rate, and the temperature of nucleation. Polymorph B preferentially crystallizes only at high concentrations. When acetonitrile or methanol is used as solvent, cooling rate can affect the polymorph of product only at high concentrations. While water is used as solvent, cooling rate has no effect on the polymorph of product, and nucleation temperature is found to be the predominant controlling factor. The effect of crystallization conditions on the polymorph of famotidine can be mainly attributed to the conformational polymorphism. Finally the "polymorphic window" for famotidine crystallized from aqueous solution has been described. © 2006 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 96:2457–2468, 2007

Keywords: famotidine; polymorph; solid state; characterization; crystallization; thermodynamics; solubility; nucleation; polymorphic window

INTRODUCTION

Polymorphism may be defined as the ability of a compound to exist in different crystalline forms in which the molecules have different arrangements (packing polymorphism) and/or conformations (conformational polymorphism) in the crystal lattice.[1] Polymorphism is a widespread phenomena observed for more than half of all drug substances.[2,3] Polymorphs can have different mechanical, thermal, physical, and chemical properties, such as compressibility, melting point, crystal habit, color, density, dissolution rate, and solubility. These can have a great influence on the bioavailability, hygroscopicity, stability, filtration, and tableting processes of pharmaceutical materials.[4]

According to Ostwald's Rule,[5] in a crystallization from the melt or from solution, the solid first formed will be that which is the least stable of the polymorphs, the one with the largest Gibbs free energy. Although it is a useful indicator of a possible sequence of production of crystalline forms, the Ostwald's Rule is not as universal and reliable.[6] The traditional methods, such as varying solvent,[7] temperature,[8] supersaturation,[9] cooling rate,[10] and seeding strategy,[11,12] have been extensively applied to control the polymorphic behavior of a compound during its crystallization process.[13] Recent approaches for discovery and selection of polymorphic forms of a compound include crystallization with tailor-made soluble additives,[14–17] polymer heteronuclei,[18,19]

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crystallization on various substrates and templates,[20–22] laser induced nucleation,[23] solvent-drop grinding,[24] spray drying,[25] supercritical fluid crystallization,[26] capillary crystallization,[27,28] crystallization confined in nanopores,[29] etc. In spite of above great efforts the fundamental mechanisms and molecular properties that drive crystal form diversity, specifically the nucleation of polymorphic forms, are not well understood. As a result, the appearance and disappearance of polymorphs are still experienced as somewhat mysterious and, predictive methods of assessing polymorphic behavior of pharmaceutical compounds remain a formidable challenge.[30,31]

Famotidine which is an excellent histamine H_2-receptor antagonist,[32] has been chosen as the model substance since only a very limited proportion of the literature on anti-histamine agents has been devoted to the problematic issue of polymorphism.[33] Famotidine has two known conformational polymorphs (A and B), but the system is far from well established and understood. According to Overgaard and Hibbs,[33] crystals of polymorph A and polymorph B belong to the monoclinic crystal system. The unit cell dimensions of polymorph A are $a = 11.912$ Å, $b = 7.188$ Å, $c = 16.624$ Å, $\beta = 100.045^\circ$, while the unit cell dimensions of polymorph B are $a = 16.980$ Å, $b = 5.285$ Å, $c = 17.639$ Å, $\beta = 116.416^\circ$. The crystal packings and conformers of polymorph A and polymorph B are shown in Figure 1. The aim of this work was to study the influence of crystallization process parameters on the polymorphism of famotidine. The operating parameters studied were the solvent, cooling rate, initial concentration and nucleation temperature.

MATERIALS AND METHODS

Materials

Form B of famotidine, methanol and acetonitrile were obtained from Sigma-Aldrich (St. Louis, MO). All chemicals were of the highest grade available, and used without further purification.

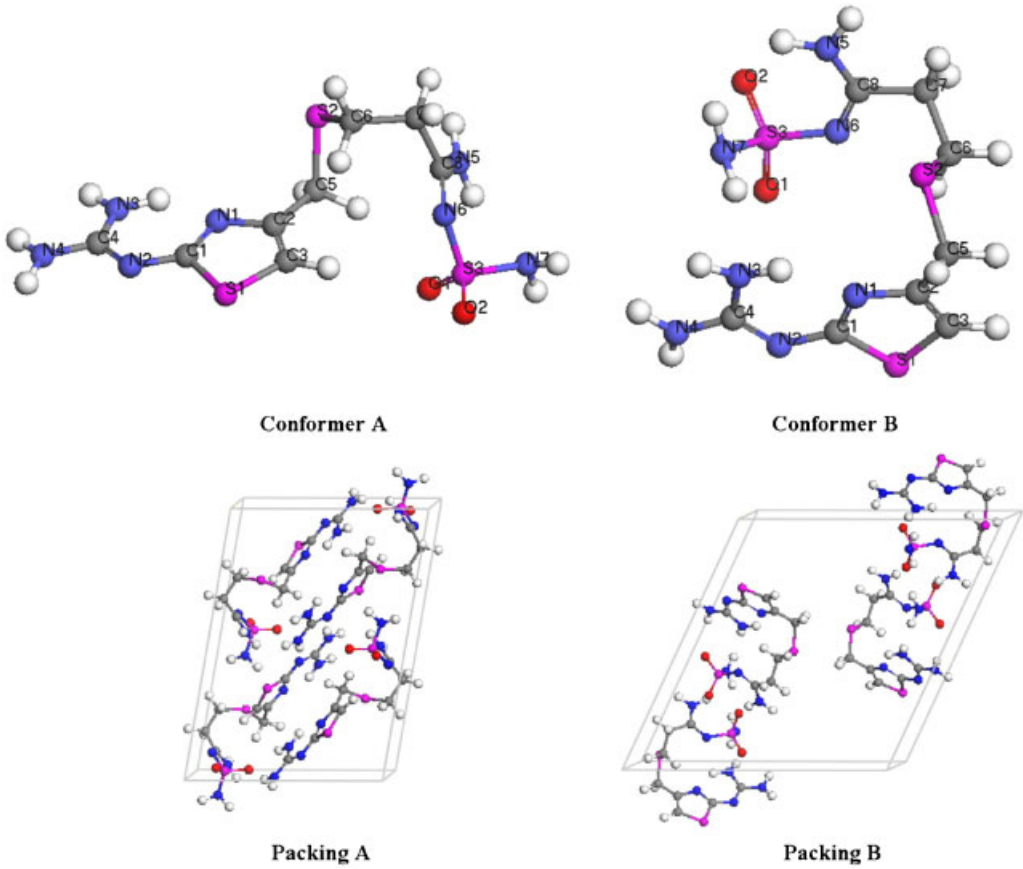

Figure 1. Crystal packings and conformers of famotidine polymorphs.

 DOI 10.1002/jps

The form A was slowly recrystallized from dilute acetonitrile solution. Deionized water was prepared with a Milli-Q water system (Millipore, Billerica, MA).

X-Ray Powder Diffraction

XRPD was conducted by a Bruker D8 Advance diffractometer (Bruker, Karlsruhe, Germany) at 40 kV and 30 mA with a Ni-filtered CuKα radiation source ($\lambda = 1.54$ Å). The samples were scanned from 5° to 40° (2θ) at a step size of 0.05° and at a scanning rate of 3 degrees per minute.

Fourier-Transform Infrared Spectroscopy

FTIR spectra were recorded from KBr disks using a Digilab Excalibur Series FTS-3000 spectrophotometer (Digilab, Canton, MA). Ground KBr powder was used as the background in the measurements. Number of scan was 32 and resolution was 4 cm^{-1}. The measured wavenumber range was from 4000 to 400 cm^{-1}.

Thermal Analysis

Thermal analysis methods used in this study included differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), and hot-stage microscopy (HSM).

DSC was performed using a Mettler-Toledo DSC-822 differential scanning calorimeter (Mettler-Toledo, Columbus, OH). Indium was used for calibration. Accurately weighed samples (5–8 mg) were placed in hermetically sealed aluminum pans and scanned at 10°C/min under nitrogen purge.

TGA was performed with a Shimadzu TGA-50 instrument (Shimadzu, Kyoto, Japan) that was also calibrated with indium prior to analysis. The sample weight was approximately 10–20 mg and heating rate of 10°C/min under nitrogen purge was used.

HSM analysis was carried out with a Linkam THMS 600 hot-stage (Linkam, Surrey, UK) and an Olympus BX51 microscope with an attached CCD video camera (Olympus, Tokyo, Japan), and imagines were recorded and analyzed by software (analySIS™). The powders of A-form and B-form were heated at 3°C/min to 190°C, held for 5 min, cooled at 3°C/min to 70°C, and reheated at 3°C/min to 190°C.

Raman Spectroscopy

Raman spectra were collected using a Renishaw System 1000 micro-Raman spectroscope (Renishaw, Gloucestershire, UK) equipped with an Ar-ion laser (514.5 nm) with an output power of 50 mW. Calibration was performed using a silicon standard. Measurements were made using a 1200 lines/mm grating.

Scanning Electron Microscopy

The morphology of each crystalline form was observed by scanning electron microscopy (SEM). A small amount of samples were scattered on double-sided adhesive carbon tabs mounted on SEM stubs, and were coated with Au/Pd in a Cressington 208 sputter coater (Pelco International, Redding, CA). Thereafter, the samples were examined with a JSM-6700F Field Emission SEM (Jeol, Tokyo, Japan), operating at 15 kV.

Solubility Measurements

The solubility of the two polymorphs of famotidine was measured in water, methanol and acetonitrile at various temperatures. Saturated solution of the pure solid form was prepared in a 30-mL jacketed glass crystallizer. The Teflon-coated magnetic stirring bar ensured proper mixing in the crystallizer. The temperature of the crystallizer was controlled by a heating and refrigeration circulator (PolyScience, Niles, IL), and the solution was stirred for at least 24 h at each temperature. After the equilibration, the agitation was stopped, and the solution was allowed to settle for 6 h. The supernatant in equilibrium with a macroscopically observable solid was then filtered through Millex-VV 0.1-μm filters (Millipore). The concentration of filtered supernatant was determined spectroscopically by measuring absorbance at 280 nm of UV spectroscopy (UV-2450, Shimadzu, Kyoto, Japan). The extinction coefficient obtained through calibration experiments was 35.6 mL/(mg·cm). Calibration curve was determined in pure water. Solubility of each sample was measured in duplicate.

Metastable Zone Width Measurements

The experiments were carried out in a 100-mL jacketed glass crystallizer. The temperature control of the crystallizer was performed by a programmable circulator (Julabo ME, Seelbach,

Germany). For all experiments, the stirring rate was taken equal to 500 rpm. A laser generator (Interlink TS-N, Singapore) generating a laser beam of 660 nm was applied to detect turbidity. The saturated solutions of pure polymorph B prepared at various temperatures were heated above 3°C of the solubility temperatures. Then, the solutions were cooled at the constant rate of 12°C/h. The temperatures at which the solutions became translucent were recorded. After crystallization, the solutions were filtered, and the products were dried for analysis.

Induction Time Measurements

A suspension of the desired amount of the polymorph B of famotidine was heated above 3°C of the equilibrium temperature to dissolve all crystals. It was then filtered through a 0.1-μm membrane filter and added to the 30-mL jacketed glass crystallizer of which temperature was kept at the desired value. When crystals appeared, the induction time t_{ind} was recorded, and the crystals were filtered off immediately and analyzed quantitatively by FTIR for their polymorphic content. Experiments under each set of conditions, defined by supersaturation ratio S and nucleation temperature T, were replicated. The reported induction time t_{ind} is the average of the measured replicates.

Cooling Crystallization Experiments

Saturated solutions were firstly prepared by dissolving required amount of B-form powder in different solvents at various equilibrium temperatures. The solvents were water, methanol and acetonitrile. Then the saturated solutions were filtered, moved to the 100-mL jacketed glass crystallizer pre-heated at the equilibrium temperatures, and then cooled down. The cooling rates employed were 2, 12, 20, 60°C/h, and quench-cooling by use of ice-bath. The crystals that first appeared were filtered off and analyzed quantitatively by FTIR for their polymorphic content. Furthermore, in some experiments the crystals were allowed to remain suspended for continuing cooling before being collected for analysis.

Form–Interconversion Experiments

Suspensions with excess amount of pure polymorph A or B in water, methanol or acetonitrile were firstly prepared at 50°C, and then moved to a wrist-action shaker (Burrell, Pittsburgh, PA) in which the temperature of water bath was kept at either 25°C or 50°C. The shaking rate was about 200 strokes per minute. Small amount of each suspension was periodically withdrawn, filtered, dried and analyzed by FTIR. At the temperatures of 25 and 50°C, and after 4 days, no interconversion was observed in the slurry of pure polymorph.

RESULTS

Solid Characterization of Pure Polymorphs

Each of the pure polymorphs of famotidine has a distinct and characteristic XRPD pattern as shown in Figure 2. For instance, the A-form and B-form have characteristic diffraction peaks at 10.66° and 5.94°, respectively.

There are clear and definite differences between the IR-spectra of the two famotidine crystal forms, as shown in Figure 3. For example, polymorph A and polymorph B have characteristic absorption peaks at 3452 and 3506 cm^{-1}, respectively.

As shown in Figure 4, the measured onset and peak maximum of the melting endotherm of polymorph A are 166.9°C and 173.8°C, respectively, while those of polymorph B are 158.9°C and 65.4°C, respectively. The measured melt enthalpy of polymorphs A and B are 49.7 and

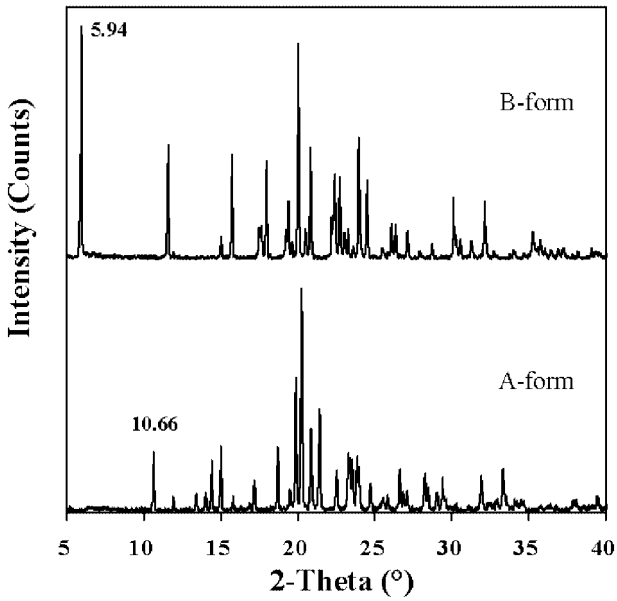

Figure 2. X-ray powder diffraction patterns for A-form and B-form of famotidine crystals.

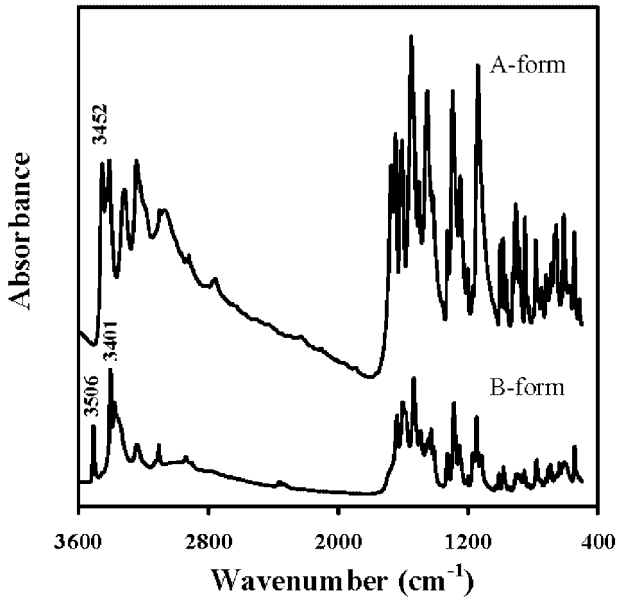

Figure 3. FTIR spectra of A-form and B-form of famotidine crystals.

48.6 kJ/mol, respectively. Results from the HSM experiments confirm that the B-form has a lower melting point, as shown in Figure 5.

Raman spectra of pure A-form and B-form in the range of 300 to 1600 cm^{-1} are presented in Figure 6. Some specific differences between the A-form and the B-form can clearly be observed. For instance, the peaks at 327, 362, 545, 659, 750, 1258, and 1465 cm^{-1} are characteristic for the A-form and the peaks at 353, 549, 684, 740, 1241, and 1455 cm^{-1} are characteristic for the B-form. The region from 300 to 400 cm^{-1} is sensitive to crystal structure and contains peaks due to lattice vibrations. The bulk of the chemical structure details can be obtained from the region 500 to about 1600 cm^{-1}. The large differences in Raman spectra of the two forms of famotidine are mainly caused by the conformational differences of the molecules in the crystal lattice of the A-form and the B-form. The molecular conformations are significantly different through a torsion angle at C6–C7 in the main carbon chain, as shown in Figure 1. The polymorphs of famotidine, therefore, can be discriminated by Raman spectroscopy.

The morphology of each form is shown in Figure 7. Both forms mainly exhibit a rodlike morphology, and thus it is difficult to identify the polymorph by the shape of the crystal. Furthermore, the A-form has smaller size and is apt to aggregate.

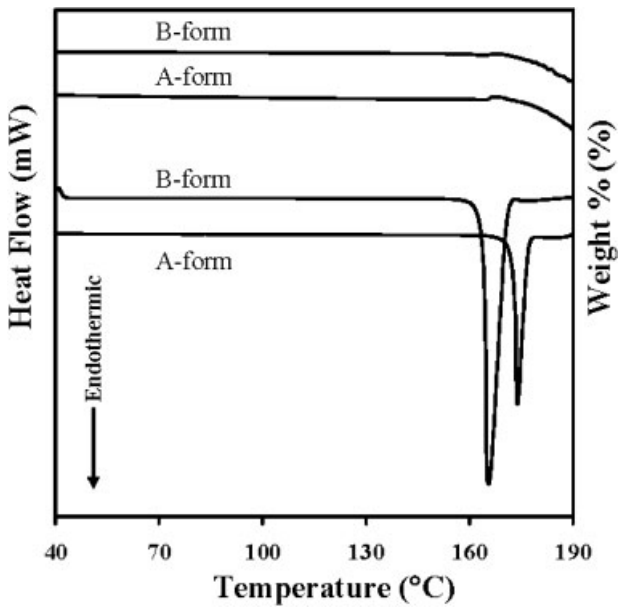

Figure 4. DSC and TGA curves of A-form and B-form.

Solubility of Pure Polymorphs

Figure 8 presents experimental results over the solubility of famotidine polymorphs in water, methanol and acetonitrile at different temperatures. In general, the solubility of both polymorphs increases with the temperature. And the solubilities of polymorph A and polymorph B in methanol are higher than those in water or acetonitrile. The solubility curves expose a monotropic nature of the polymorphs of famotidine. Polymorph A is the thermodynamically favored form (stable form with lower solubility), while polymorph B is the kinetically favored form (metastable form with higher solubility).[34]

Metastable Zone Width

Figures 9–11 show the metastable zone widths of the polymorphs of famotidine in three solvents at a cooling rate of 12°C/h. The average metastable zone widths of polymorph A in methanol, water and acetonitrile are 20.5°C, 15.6°C, and 44.5°C, respectively. On the other hand, the average metastable zone width of polymorph B in water is about 3.0°C, which is narrower than that of polymorph A. The higher the nucleation barrier, the larger the metastable zone width of the polymorph is.[35] Therefore, the nucleation barrier

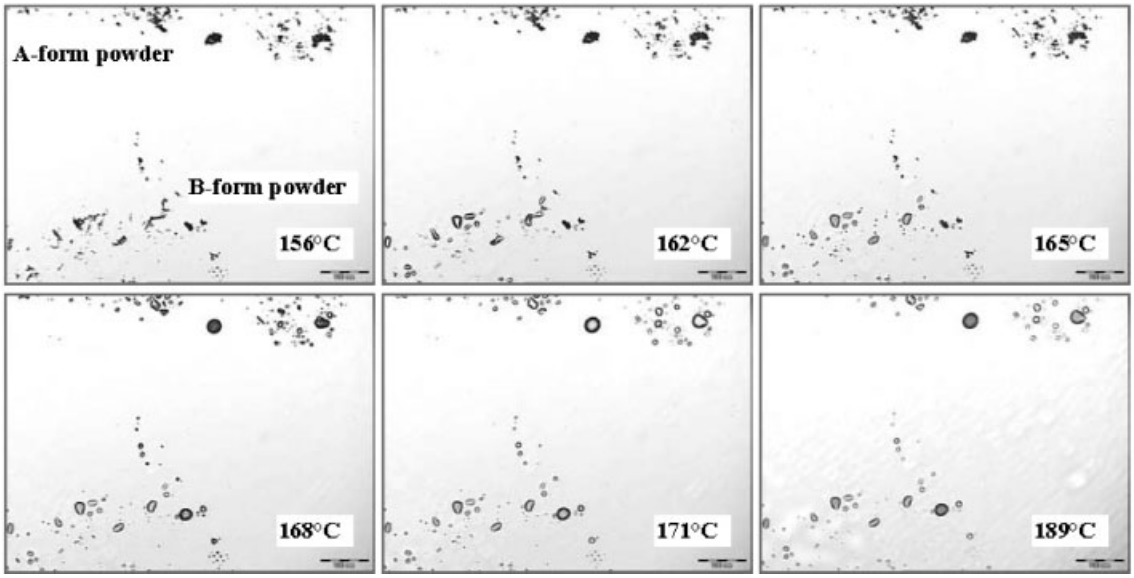

Figure 5. Melting behaviors of A-form and B-form examined under HSM.

of polymorph A of famotidine is larger than that of polymorph B.

Induction Time and Interfacial Tension

When the formation of a stable nucleus is the rate-limiting step, the induction time t_{ind} is inversely related to the nucleation rate J.[36] According to the classical nucleation theory, J can be calculated using Eq. (1):[37]

$$J = \frac{1}{t_{ind}} = A_n \exp\left(-\beta \frac{\gamma^3 v_m^2}{v^2 \kappa_B^3 T^3 (\ln S)^2}\right) \quad (1)$$

where S is the supersaturation ratio, T is the temperature of nucleation, γ is the interfacial tension between the nucleus and the supersaturated solution, A_n is a pre-exponential coefficient, β is a geometric factor, v_m is the molecular volume of the solute, v is the number of ions into which a solute molecule dissociates ($v = 1$ for famotidine molecule), and κ_B is the Boltzmann constant.

Assuming the critical nuclei are spherical, a plot of $\ln(t_{ind})$ against $1/(\ln S)^2$ should yield a straight line of slope $16\pi\gamma^3 v_m^2/3\kappa_B^3 T^3$, from which γ can be calculated. The plots of $\ln(t_{ind})$ against $1/(\ln S)^2$ at 0 and 50°C in three solvents are illustrated in Figure 12, and the calculated γ are list in Table 1.

Figure 12 shows that, at the nucleation temperature of 50°C, the nature of the polymorph that nucleates depends on the concentration of nucleating solution. That is, at low concentration, polymorph A nucleates, while at high concentration, polymorph B nucleates. As shown in Table 1, at the same nucleation temperature, among three solvents studied, the interfacial tension between aqueous supersaturated solution and the nucleus of polymorph A is highest. Meanwhile, the interfacial tension is also found to decrease with

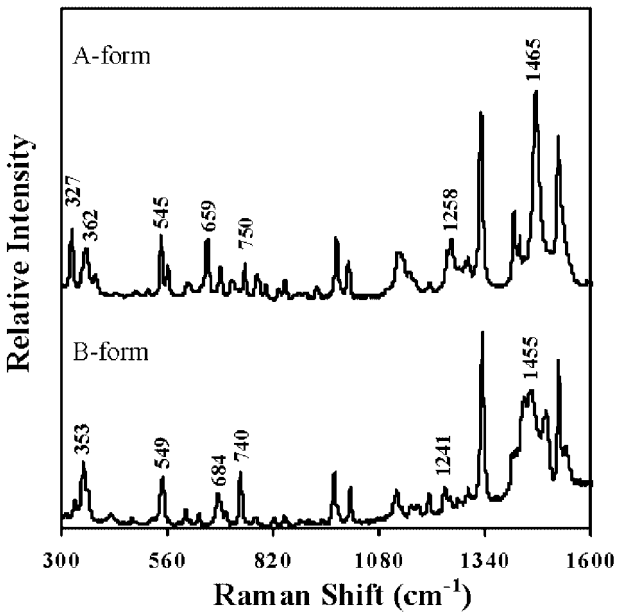

Figure 6. Raman spectra of famotidine polymorphs.

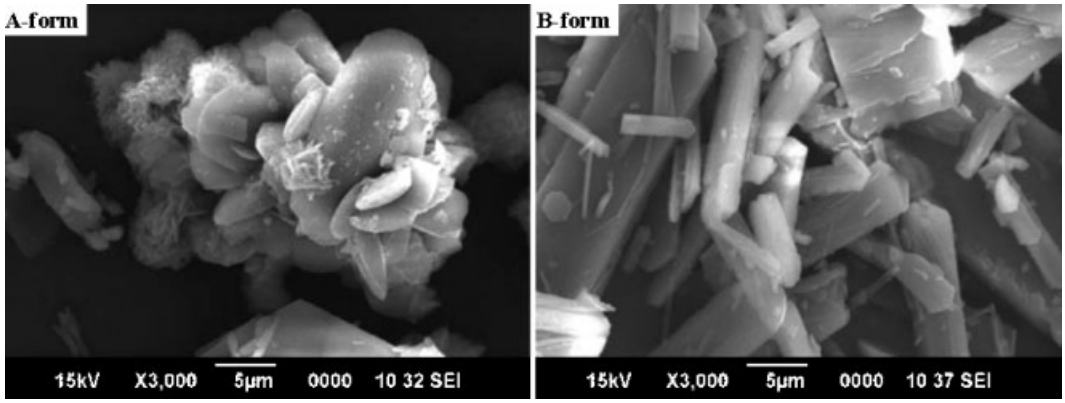

Figure 7. SEM photographs of the two polymorphs of famotidine.

an increase of temperature. Against expectation, the calculated interfacial tension of polymorph B is higher than that of polymorph A. Through inverse gas chromatographic analysis, Tong et al.[38] have demonstrated that the metastable polymorph of salmeterol xinafoate possesses a higher surface free energy, higher surface entropy, and a more polar surface than the stable polymorph.

Polymorphic Window

From the experiments of induction time measurements, the "occurrence domain"[39] of each respective polymorph with respect to nucleation temperature and initial concentration, designated as "polymorphic window" in this work, can be determined. To control a crystallization process to produce the desired polymorph, the "polymorphic window" that is unique for that particular polymorph needs to be delineated. The "polymorphic window" for the crystallization of famotidine from aqueous solution is described in Figure 13.

When a saturate solution at point A is cooled, the polymorph of crystalline product is B-form when nucleation temperature is between T_B and T_C, mixture of A- and B-forms when nucleation temperature between T_C and T_D, and A-form when nucleation temperature lower than T_D.

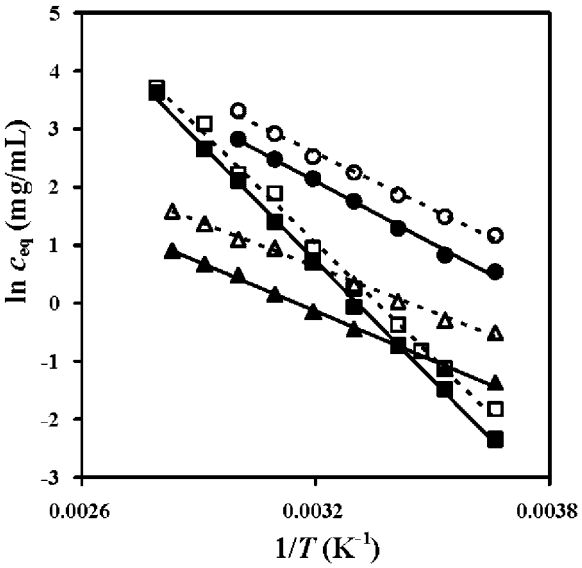

Figure 8. Van't Hoff plots of equilibrium solubility of polymorph A and polymorph B against the reciprocal of absolute temperature. (○) B-form in methanol; (●) A-form in methanol; (□) B-form in water; (■) A-form in water; (△) B-form in acetonitrile; (▲) A-form in acetonitrile.

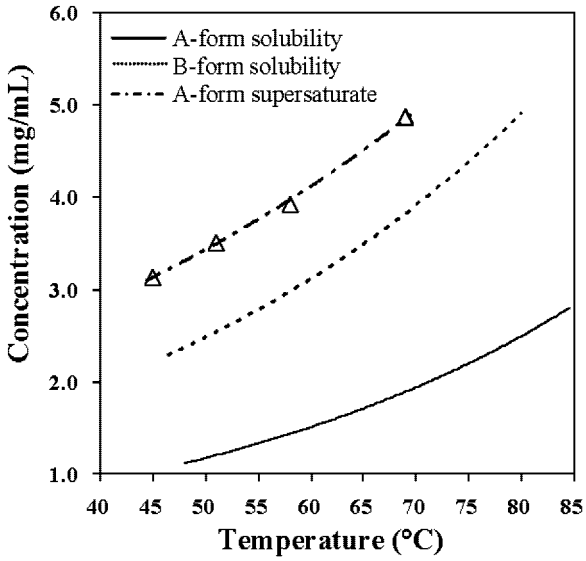

Figure 9. Experimental metastable zone width of polymorph A in acetonitrile.

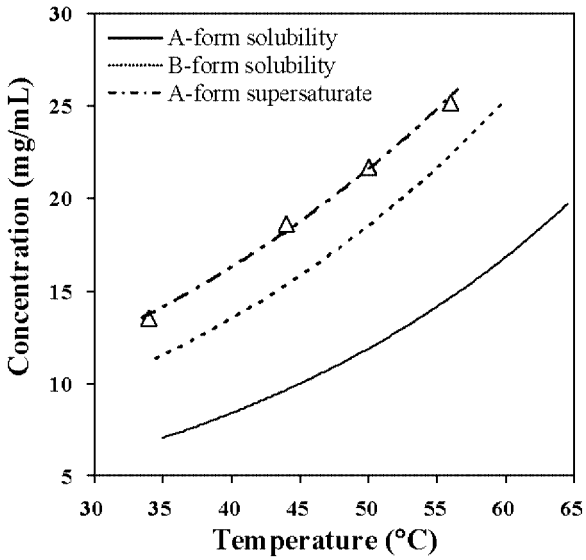

Figure 10. Experimental metastable zone width of polymorph A in methanol.

Cooling Crystallization

Results from the cooling crystallization experiments at different cooling rates and initial concentrations in water, methanol and acetonitrile are presented in Table 2. It is found that, when acetonitrile or methanol is used as solvent, cooling rate can affect the polymorph of product only at high concentrations, that is, fast cooling crystallization from high concentration solution can produce polymorph B. However, when water is used as solvent, cooling rate has no effect on the polymorph of final product.

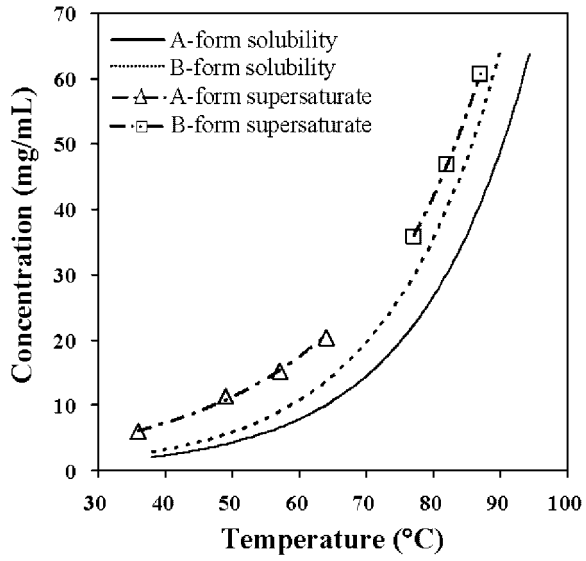

Figure 11. Comparison between experimental metastable zone widths of polymorphs A and B in water.

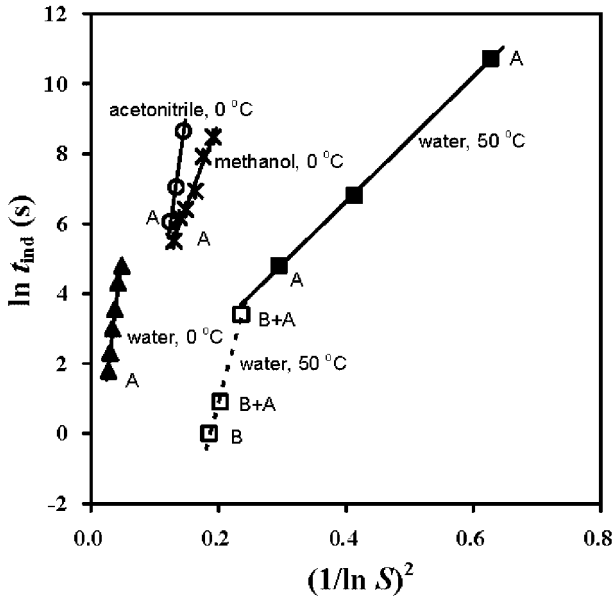

Figure 12. Dependence of the induction time on the supersaturation ratio, the nucleation temperature and the nature of the polymorph that crystallizes.

DISCUSSION

As shown in Figure 1, the crystallization of famotidine has the predominant characteristic of conformational polymorphism. From a thermodynamic viewpoint, the conformer which can assemble in a favorable way to minimize the system's free energy will crystallize.[40] From the viewpoint of structure, the conformer which will crystallize preferentially from a melt or solution will be the one easiest to form (i.e., the one with the smallest energy barrier expressed in kinetic/thermodynamic terms) or the one whose struc-

Table 1. The Calculated Interfacial Tensions Under Different Conditions

Temperature (°C)	Interfacial Tensions (mJ/m^2)			
	Water	Acetonitrile	Methanol	Polymorph
0	15.68	14.88	10.70	A
10	13.08	—	—	A
20	12.37	—	—	A
50	9.16	—	—	A
50	14.36	—	—	B/B+A

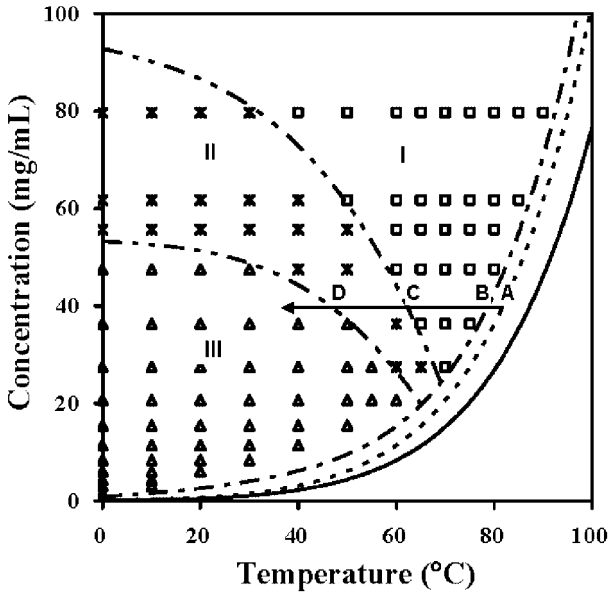

Figure 13. Effects of initial concentration and nucleation temperature on polymorphic crystallization behaviour. Zone I—B-form; Zone II—mixture of B-form and A-form; Zone III—A-form; solubility curve of A-form; solubility curve of B-form; supersaturate curve of B-form (high temperature) and A-form (low temperature).

tural organization is most readily derived from the arrangement in the melt or solution.[41] Besides, such intermolecular forces as ionic, van der Waals, dipole–dipole and hydrogen bonding, can affect the structures and packing behaviors of conformers. Based on above viewpoints, the effect of crystallization parameters on the polymorphism of famotidine is discussed as follows.

As shown in Figure 13 and Table 2, when famotidine is crystallized from the solutions at low initial concentrations, form A normally occurs, whereas form B would crystallize preferentially only at high concentrations. In the dilute solution, the interaction between solute molecules may be weak, so that conformer A extensively exists and preferentially nucleates. At high concentration, the interaction between solute molecules may be quite strong, and solute molecules exist in the conformation of conformer B.

Table 2. Results from Cooling Crystallization Experiments

	Water			Methanol		Acetonitrile	
	Initial Concentration (mg/mL)						
Cooling rate (°C/h)	60.8	40.7	6.6	28.8	18.5	5.0	3.1
2	B	B	A	A	A	A	A
12	B	B	A	A	A	A	A
20	B	B	A	A	A	A	A
60	B	B	A	B+A	A	A+B	A
Ice-bath[a]	B+A	A	A	B	A	B	A

[a]Quench-cooling by ice-bath.

At a certain concentration and a certain nucleation temperature, the supersaturation driving force is higher for polymorph A since it has a lower solubility and, the interfacial energy of the stable polymorph A is lower than that of the metastable polymorph B. From Eq. (1), assuming the pre-exponential coefficient A_n and the geometric factor β are same, the polymorph A should thus be favored. However, when water is used as solvent (Fig. 13), polymorph B normally can occur at high nucleation temperature when initial concentration is high enough. This is because, at high temperature, the collision frequency and interaction between solute molecules are largely increased, so that solute molecules favorably exist in the conformation of conformer B in solution or pre-nucleation aggregates.

As shown in Table 2, when acetonitrile or methanol is used as solvent, cooling rate can affect the polymorph of product only at high concentrations. That is because, when very fast cooling rate is employed, the metastable limit of polymorph B is exceeded, thus polymorph B can be preferentially formatted. In this case, the polymorphic purity of product depends to a high degree on the nucleation rates of both forms.

Dependent on the conditions, crystallization of polymorphs from solvent may be under kinetic or thermodynamic control. In the latter case the nature of the solvent will be immaterial in respect of the polymorph produced.[42] Nevertheless, specific solvent effects, which are related to the solvent-solute interactions and to bulk effects (e.g., interfacial tension) of the concentrated solution, are important in polymorph formation during crystallization.[43] The solvent–solute interactions can affect the nucleation, crystal growth and solvent-mediated polymorph transformation,[44] which consequently affect the appearance of polymorphs. On the other hand, bulk properties of solvents, such as viscosity and surface tension, may also affect the crystallization kinetics and the appearance of polymorphs.[45] The solvent effect on crystallization has also been interpreted in the light of inhibiting nucleation or retarding crystal growth. In this respect, the phenomenon is

Table 3. Solvent Property Parameters of Water, Methanol, and Acetonitrile

Solvent	π^a	$\Sigma\alpha^b$	$\Sigma\beta^c$	Dipole Moment[d]	Dielectric Constant[e]	Cohesive Energy Density[f]	Viscosity [g]	Surface Tension[h]
Acetonitrile	0.75	0.07	0.32	3.92	35.69	522.95	0.37	41.25
Methanol	0.60	0.43	0.47	1.70	32.61	808.26	0.54	31.77
Water	1.09	1.17	0.47	1.87	78.36	2095.93	0.89	104.70

[a]Polarity/dipolarity of the solvent.
[b]Summation of the hydrogen bond donor propensities of the solvent.
[c]Summation of the hydrogen bond acceptor propensities of the solvent.
[d]Dipole moment in the unit of debye.
[e]Dielectric constant.
[f]Cohesive energy density in the unit of J mol/ml.
[g]Viscosity of the solvent at 25°C in the unit of mPa s.
[h]Surface tension of the solvent at 25°C in the unit of cal/(mol Å^2).

analogous to controlling crystal morphology through additives and solvents.[46]

In many case studies in the literature, polar and non-polar terminology has been used to address solvent effect on polymorphism.[47] However, hydrogen bonding may play a major role in that kind of effect. Hydrogen bonding can occur between solute–solute, solvent–solvent, and solvent–solute molecules. A solvent molecule that has greater ability to donate or accept hydrogen bonding than the solute molecules, will establish hydrogen bonding with the solute molecules and may not allow the other solute molecules approach the same site. This will affect the final outcome of crystal structure and may even direct to a solvate formation.[48] Solvents with higher polarity index have more tendencies in disrupting hydrogen bonding between solute molecules.[49]

The solvent properties may be described by solvent property parameters, including hydrogen bond acceptor propensity, hydrogen bond donor propensity, polarity/dipolarity, dipole moment, dielectric constant, viscosity, surface tension, and cohesive energy density, etc. Eight property parameters of three solvents used in this work are listed in Table 3.[50]

Our results show that solvents have effects on solubility, metastable zone width, and interfacial tension. Among three solvents studied, methanol provides highest solubility and lowest interfacial energy, acetonitrile contributes lowest solubility and widest metastable zone width, and water results in largest interfacial energy. On the other hand, from the Table 3, water and methanol are known as dipolar protic solvents, and can act as hydrogen bond donors and acceptors. Acetonitrile is regarded as dipolar aprotic solvent, and can act as hydrogen bond acceptor. Water is more polar and the stronger hydrogen bond donor than methanol. As shown in Figure 1, famotidine molecule has both hydrogen bonding accepting and donating abilities. During cluster formation, the molecules can sit side-by-side and establish intra- and inter-molecular hydrogen bonding between nitro oxygen atoms and the amine nitrogen atoms, such as intermolecular hydrogen bonds: N4···N2, O1···N3, O1···N4, and intramolecular hydrogen bonds: N3···N1 and/or N3···N7.[51] The intramolecular hydrogen bonds play a decisive role in building the folded conformation, that is, conformer B. Water, as the strongest hydrogen bond donor and acceptor, can provide the bridge bonded with the sulfamoyl N atom or O atom and with the guanidino N atom, which thus can further stabilize the folded conformation (conformer B), whereas methanol or acetonitrile can not act as this kind of connector. Experimental results (Tab. 2) indicate that, polymorph B (conformer B) can preferentially crystallize from concentrated aqueous solution, whereas methanol with weak hydrogen bonding propensity but giving a high solubility is preferred to crystallize a more stable polymorph A.

In conclusion, the polymorphism of famotidine possesses a monotropic nature, and polymorph A is the thermodynamically favored form, while polymorph B is the kinetically favored form. The nature of the polymorph of famotidine that crystallizes from solution depends on the initial concentration of the solution, solvent, cooling rate, and the temperature of nucleation. The effect of crystallization conditions on the polymorph of famotidine is mainly attributed to the conformational polymorphism, which results from different types of intermolecular interactions of solute–solute and solute–solvent, for example, van der Waals, hydrogen bonding, etc. Through the

control of the crystallization process, the desired polymorph of famotidine can be produced.

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