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Crystallization Control and Physicochemical Properties of Polymorphic Forms of the Factor Xa Inhibitor KFA-1982

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Supporting Information

ABSTRACT: Many polymorphs of KFA-1982, an orally active factor Xa (fXa) inhibitor, have been identified and their physicochemical properties have been investigated. Form B was selected as the oral API form because of its superior stability and solubility characteristics. Crystallization conditions for form B were thoroughly investigated including the role of water in hydrate formation and the use of antisolvents and supersaturation in polymorph control.

INTRODUCTION

Most low-molecular-weight drugs have many polymorphs and pseudopolymorphs due to their complex molecular structures and conformations.[1] Selection of an appropriate crystal form of an active pharmaceutical ingredient (API) is important for drug development because polymorphs and pseudopolymorphs influence the physicochemical properties of an API, such as solubility, stability, density, and hygroscopicity.[2−4] In particular, it is important that all polymorphs and pseudopolymorphs that may emerge during the manufacturing process and beyond are discovered, because late discovery of new crystal forms of the API can lead to product marketing delays and even product withdrawal.[5,6] Moreover, crystal forms that have good physicochemical properties can be beneficial to a pharmaceutical company by expanding intellectual property rights, possibly extending the lifetime of a drug product.

Recently, in-depth and rapid searches of polymorphic forms by robotic high-throughput crystallization systems have been carried out in many pharmaceutical companies or in contract companies.[7−9] However, more detailed studies are still necessary because there are some polymorphisms that cannot be understood using routine techniques like robotic screening systems. Additionally, process chemistry studies are needed to reproducibly manufacture the selected crystal form for the API.[10]

In this contribution, we describe the physicochemical characterization of polymorphic forms of KFA-1982, an orally active fXa inhibitor (Figure 1), and the detailed approach used to control the API crystal form.

Factor Xa Inhibitor KFA-1982. Thromboembolic diseases, such as deep vein thrombosis, pulmonary embolism, myocardial infarction, and thromboembolic stroke, are major causes of morbidity and mortality in developed countries. Currently available anticoagulants, such as warfarin, heparin, and low-molecular-weight heparins, are widely used in the treatment and prevention of thromboembolic diseases. However, these anticoagulants have many therapeutic limitations. For example, heparin is administered intravenously, and frequent monitoring is needed with warfarin administration.

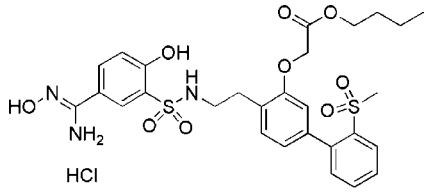

Figure 1. Chemical structure of KFA-1982.

Thus, there is a continuing need for convenient, orally active anticoagulant drugs. Activated blood coagulation factor X (fXa) is a trypsin-like serine protease. It resides at the juncture of the intrinsic and extrinsic pathways in the blood coagulation cascade and plays a critical role in thrombus formation. Recently, some low-molecular-weight factor Xa inhibitors with oral activity have proceeded into late-phase clinical studies or new drug applications, and rivaroxaban and edoxaban have been launched.

We focused on new sulfonamide derivatives, and discovered KFA-1982 free base through a structure-activity relationship study and a pharmacokinetic study.[11] Excellent stability and high solubility are desirable properties in solid-state KFA-1982 free base for use as an oral drug.

RESULTS AND DISCUSSION

Physicochemical Properties of Each Polymorphic Form. The free base of KFA-1982 formed dihydrate crystals, and the crystalline form showed very low solubility. Salt

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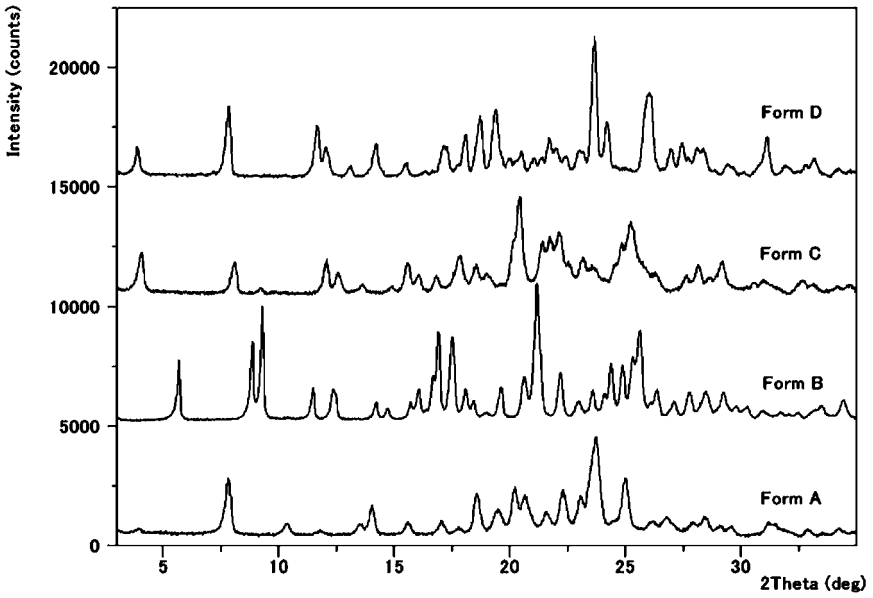

Figure 2. XRPD patterns of polymorphic forms.

screening was carried out to improve the solubility and stability. As a result, crystals of the sodium salt, trifluoroacetate, methanesulfonate, hydrobromide, and hydrochloride were obtained. The hydrochloride salt was selected for the API because of good stability.

The polymorphism was investigated as a step in the drug discovery process. Crystallization studies using various solvents were carried out. Three anhydrous forms (form A, form B, and form D) and a monohydrate (form C) were found at that time (Figure 2). The crystallization solvent systems and melting points of these polymorphs were shown in Table 1. The physicochemical properties of the three polymorphic forms and a pseudopolymorphic form were studied in detail.

Table 1. Crystallization solvent systems and melting points of each polymorph

polymorphs	crystallization solvent systems	melting points, °C
form A[a]	1-butanol/*i*-PrOAc	129
form B	methanol/EtOAc, ethanol/EtOAc 1-butanol/MeOAc	155
form C	solvent systems containing water	76 (transition point) /114
form D	1-butanol/*n*-hexane, 1-butanol /diisopropylether	149

[a]Form A was identified first in the drug discovery stage. However, form A has not been prepared reproducibly without seeds.

Solid Stability. Stability testing of each polymorphic form in open vessels was performed at 40, 60, and 40 °C/75% RH for 1 month. The amounts of relative substances were measured by HPLC. The structure of the major degradation product isolated by column chromatography was identified as a urea derivative (Figure 3) by proton nuclear magnetic resonance (^{1}H NMR) spectroscopy. It was considered that the urea compound arose from an intramolecular rearrangement of the benzamidoxime unit due to heating and moisture. Stability data are shown in Table 2. Form B was found to be stable with the less urea formation than other forms. Forms A and D and the hydrate C showed moisture instability.

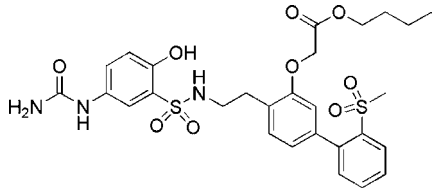

Figure 3. Structure of the urea derivative, the major degradation product.

Table 2. Increase in the major degradation product after storage for 1 month

	increase (area %)		
polymorphs	40 °C	40 °C/75% RH	60 °C
form A	0.00	0.45	0.12
form B	0.01	0.08	0.15
form C	0.20	1.52	5.02
form D	0.02	0.53	0.27

Solubility in Aqueous Solvent. The solubilities of each polymorphic form in water, pH 1.2 buffer, and pH 6.8 buffer at 37 °C were assessed by HPLC. The solubility of KFA-1982 at 1 h from the start of the test is shown in Table 3. The solubility values of forms A, B, and D in water and pH 1.2 buffer were good, 1000−2000 μg/mL. The solubilities of forms A, B, and D in pH 6.8 buffer were below 100 μg/mL due to free base formation. Form C solubility was poor in all systems. On the basis of this data form B was selected as the API form.

Table 3. Saturated solubility of each polymorphic form in aqueous solvent at 37 °C

	saturated solubility (μg/mL)		
polymorph	water	pH 1.2	pH 6.8
form A	1284	1599	63
form B	1532	1845	85
form C	240	247	2
form D	1542	1376	43

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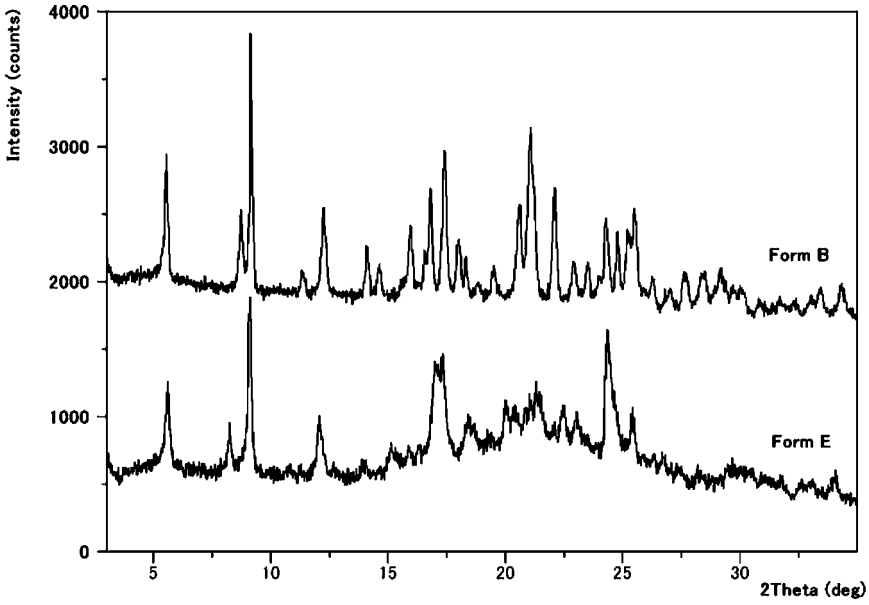

Figure 4. XRPD patterns of forms B and E.

Crystallization Studies in Selected Solvents. Generally, polymorphism can be influenced by all parameters of the crystallization process: solvent type and the mixed composition, crystallization temperature, supersaturation, concentration of specific impurities, stirring rate, and pH values. Because solvent type and composition are typically the most important factors, they should be selected carefully.

A solubility screen of polymorphs was conducted prior to crystallization studies. KFA-1982 showed good solubility in alcoholic solvents. Only 1-butanol was considered acceptable due to the possibility of transesterification in the API. *n*-Heptane, EtOAc and *i*-PrOAc were screened as appropriate antisolvents as recovery from 1-butanol was poor.

Characterization of Polymorphic Behavior in Each Mixed Solvent System. Behaviors of KFA-1982 polymorphs in the selected solvents were analyzed by XRPD. Analysis of dried solids identifies the thermodynamically stable forms. Thus, wet crystals were analyzed by XRPD just after filtration to detect transient forms.[12]

Initially, recrystallization in 1-butanol only was carried out, and then recrystallizations with the selected antisolvents were conducted. As a result, a new form, named form E, arose in the antisolvent nonadditive system (Figure 4). Also, form E was generated under all conditions of EtOAc-added systems and some conditions of *i*-PrOAc systems. On the other hand, form D was confirmed in all *n*-heptane systems (Table 4).

The thermal behavior of form E was measured by XRPD with heating, and form E transformed into form B at 70 °C. Additionally, form E transformed into form B crystals after drying in vacuo at room temperature.

Table 4. Polymorphic forms crystallized in mixed solvents

solvent ratio[a]	polymorphs		
1-butanol/antisolvent	*n*-heptane	*i*-PrOAc	EtOAc
4/1	D	E	E
4/4	D	E	E
4/16	D	D	E

[a]Amount of solvent is shown as solvent volume (mL) to compound weight (g) (e.g. 1-butanol amount: 0.04 mL/0.01 g = 4, *n*-heptane amount: 0.01 mL/0.01 g = 1; 1-butanol/*n*-heptane = 4/1).

Nucleation of Form E and Crystal Structure. It has been reported recently that aggregates form in solution before nucleus generation, which involves an intermolecular interaction in the resulting crystal structure.[13]

First, single-crystal X-ray structural analysis of form E was conducted to understand the molecular conformation of the crystals (Figure 5) and to estimate the crystal nucleation mechanism of form E. On the basis of the form E crystal structure, an interaction between two molecules in a unit cell was confirmed. It was considered that a $\pi-\pi$ stacking

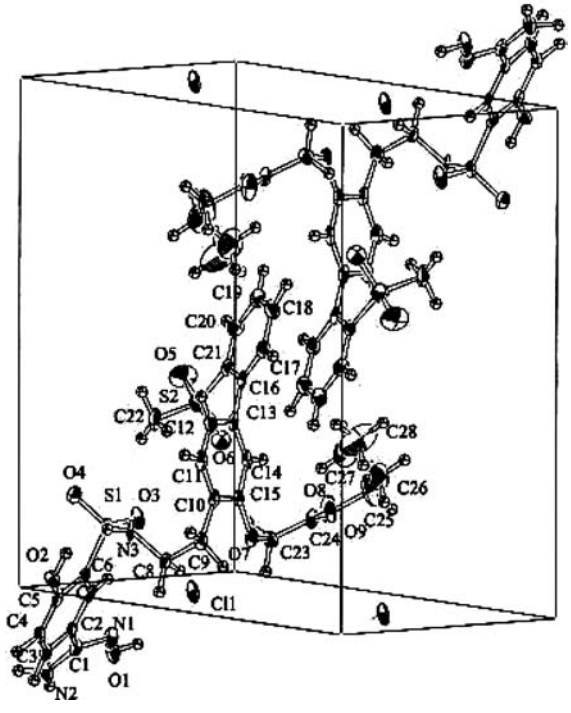

Figure 5. X-ray crystal structure of form E.

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Table 5. Polymorphs that crystallized in mixed solvents with addition of various antisolvents

		polymorphs								
solvent ratio	1-butanol/antisolvent	*n*-heptane	IPE[a]	MTBE[a]	toluene	EtOAc	*n*-PrOAc	*i*-PrOAc	*n*-BuOAc	*s*-BuOAc
	4/1	D	E	E	solvate	E	E	E	E	E
	4/4	D	E	E	solvate	E	E	E	E	E+D
	4/16	D	D	D	solvate	E	E	D	E	D

[a]IPE: diisopropyl ether, MTBE: methyl *tert*-butyl ether.

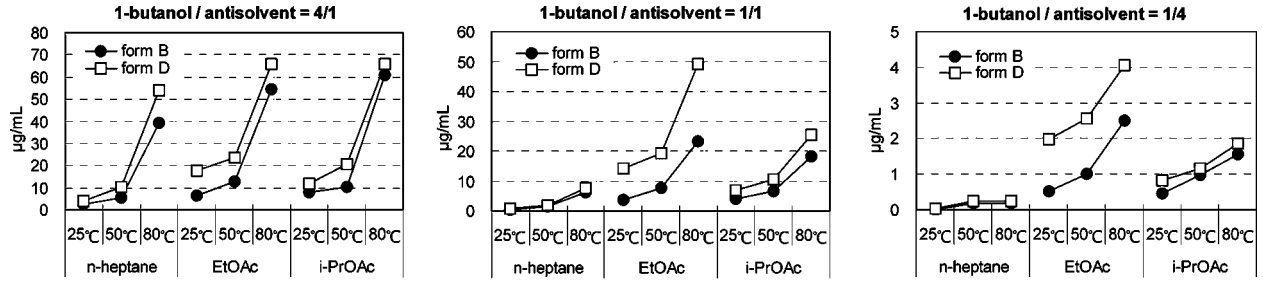

Figure 6. Solubility in mixed solvents.

interaction (interplanar distance = 3.9 Å) exists between the methane-sulfonylated benzene rings. It was confirmed that a butyl group was located near the methane-sulfonylated benzene ring of the other molecule. It was also shown that form E did not form a solvate structure.

Effect of Solvent Structure on Polymorphism. Generally, van der Waals forces and hydrogen bonding contribute to solute−solvent interactions.[12,16−18] As described previously, the antisolvents influenced the generation of each polymorphic form. To study the effect of antisolvent structure on polymorphism, recrystallization in 1-butanol alone was conducted first. Then, a variety of antisolvents were screened as detailed in Table 5. As a result, it was confirmed that recrystallization in an antisolvent, nonadditive system generated form E. In the recrystallization systems with added ether or secondary alkyl acetate, form D was obtained with increasing antisolvent content. In the systems with added *n*-heptane, form D crystals were obtained in the solvents of all mixing ratios. In contrast, form E was obtained independently of the primary alkyl chain length in systems with added acetate. Interestingly, a 1:1 toluene solvate was obtained in solvents with added toluene. This toluene solvate transformed into form B with drying in vacuo and heating. On the basis of the results of recrystallizations in various solvents and the single crystal X-ray structural analysis of form E, the polymorphism was interpreted as follows. Because *n*-heptane is hydrophobic and has affinity for the biphenyl unit, *n*-heptane may inhibit the π-π stacking interaction that served as a basis for the form E crystalline structure. In contrast, it was confirmed that the addition of primary alkyl acetate did not raise the degree of supersaturation versus the other antisolvents and yielded form E without inhibiting the π-π stacking interaction.

Thermodynamic Relationship between the Polymorphs. Enantiotropic and monotropic systems represent different thermodynamic relationships between polymorphs.[14] In an enantiotropic system, the relationship between free energy and solubility reverses at a specific temperature. On the other hand, the relationship is temperature-independent in a monotropic system.

The solubilities of forms B and D in some mixed solvents were measured to investigate the thermodynamic relationships between them. As a result, the solubility of form D was found to be higher than that of form B (Figure 6). Thus, the thermodynamic relationship between forms B and D was considered to be a monotropic system, and form B was the more stable form at every temperature in mixed solvents.

After a solubility test was conducted in mixed solvents (1-butanol/antisolvent =1/1) at room temperature for 3 days, crystal forms of precipitates were measured immediately after filtration by XRPD. Eventually, form B transformed into form E in the three mixed-solvent systems. Form D transformed into form E in 1-butanol/EtOAc but did not transform in *n*-heptane or *i*-PrOAc mixed solvents (Table 6). From these results, it was confirmed that solvent-mediated transformations of each polymorph depended on the type of antisolvent.

Table 6. Polymorphs after suspending in mixed solvents at 25 °C

	polymorphs after solubility studies		
initial form[a]	*n*-heptane	*i*-PrOAc	EtOAc
form B	E	E	E
form D	D	D	E

[a]Each form was suspended in 1-butanol/antisolvent mixed solvents (ratio = 4/4) at 25 °C. (Concentration of compound: 10 mg/80 μL.)

Effect of Supersaturation on Polymorphism. The driving force of crystallization at a given temperature is defined by eq 1, with σ as the supersaturation[15] ratio. The effect of supersaturation was studied on the basis of the added amount of antisolvent and the appearance of polymorphic forms.

$$\sigma = \frac{C - Cs}{Cs} \quad (1)$$

The saturated solubility (Cs) was measured at 80 °C by suspending excess form B crystals in mixed solvents. The σ values were calculated by eq 1 with the concentration (C) of solute and the saturated solubility (Cs) at the same temperature.

As a result, the supersaturation ratio range that precipitated specific polymorph differed according to solvent type (Figure 7). That is, the supersaturation ratios that can precipitate form E crystals cover a wide range in the EtOAc-added system and a

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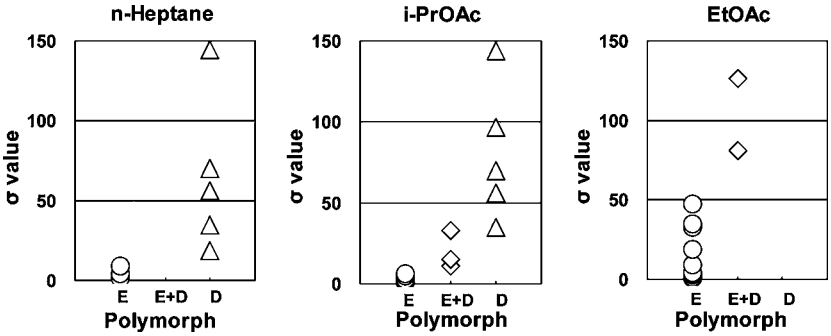

Figure 7. Graph of σ values and polymorphs in mixed solvents.

Table 7. Polymorphs for each σ value in mixed solvent

		n-heptane		*i*-PrOAc		EtOAc	
C (mg/mL)	solvent ratio 1-butanol/antisolvent	σ value	polymorph	σ value	polymorph	σ value	polymorph
200.0	4/1	1.5	E	0.6	E	0.8	E
100.0	8/2	4.1	E	2.3	E	1.7	E
125.0	4/4	8.9	E	2.4	E	2.7	E
62.5	8/8	18.9	D	4.9	E	3.3	E
83.3	4/8	35.0	D	5.9	E	4.4	E
41.7	8/16	70.9	D	10.8	D+E	7.6	E
50.0	4/16	144.2	D	15.1	D+E	9.0	E
25.0	8/32	289.3	D	31.2	D+E	19.0	E
35.7	4/24	458.7	D	56.5	D	32.6	E
27.8	4/32	488.8	D	96.7	D	47.3	E
19.2	4/48	808.2	D	151.5	D	81.6	D+E[a]
14.7	4/64	1777.4	D	168.8	D	126.0	D+E[a]

[a]D+E: mixture of polymorphs.

narrow range in systems with *n*-heptane or *i*-PrOAc addition (Table 7). Thus, EtOAc was added as an antisolvent to generate form E in good yield. It is likely that aggregates of solute molecules already formed in solution before nucleation.[13] It was considered that antisolvent addition was shown to influence the generation of aggregates and polymorphs.

Control of Form C Monohydrate. The monohydrate, form C, showed very low solubility in water and pH 6.8 buffer. When a drug suspension of form C was administered orally to rats, low adsorption and reduced drug efficacy were evident. Generation of monohydrate crystals often results from crystallization experiments in undried solvents. Thus, a detailed investigation of the conditions required to avoid monohydrate generation and in manufacture of form B was conducted.

Crystallization studies were conducted with addition of 0.5–6.0 mol equiv of water into each mixed solvent (good solvent/antisolvent = 4/4). The precipitated polymorphs are shown in Table 8. According to these results, form C crystals were generated by addition of just one molar equivalent of water in *n*-heptane or *i*-PrOAc mixed solvents. In contrast, form C crystals were not generated even with 4 mol equiv of water in EtOAc mixed solvents. Thus, it was confirmed that water did not inhibit the intermolecular hydrophobic interaction of form E in EtOAc mixed solvent. However, it was considered that strictly controlling the amount of water was necessary to manufacture form B crystals in an EtOAc mixed-solvent system.

Manufacturing Process of Form B. From the studies it was clear that using the mixed solvent of 1-butanol and EtOAc enable the control of form B. However, when KFA-1982 was dissolved in a restricted quantity of 1-butanol to obtain high yield, high temperature or long time heating was necessary.

Table 8. Polymorphs crystallized in mixed solvents with addition of water

	1-butanol + antisolvent		
additive water (equiv)	*n*-heptane	*i*-PrOAc	EtOAc
0	D	E	E
0.5	D	E	E
1	C	C	E
2	C	C	E
3	C	C	E
4	C	C	E
5	C	C	C
6	C	C	C

Dissolution of KFA-1982 at 90 °C for 5 h caused about 1% of decrease of chemical purity and coloring of product cystals. Therefore, a small amount of THF as a solubilizing agent was mixed with 1-butanol to dissolve crude KFA-1982. That is, crude KFA-1982 was dissolved in mixed solvent of 1-butanol (4.0) and THF (0.6) at 85 °C in half an hour. (The solvent amount was shown as a ratio of solvent volume (kg) to compound weight (kg).) Subsequently, EtOAc (7.0) was added into the solution, and form B was obtained as expected. This process was successfully implemented in producing several kilograms of acceptable quality API.

■ CONCLUSIONS

Physicochemical studies of respective polymorphs of KFA-1982 were conducted. Form B showed the best solid stability and solubility and was selected as the API crystalline form.

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According to the crystallization studies, form B transformed into form E in acetate/1-butanol mixed solvents, and form E transformed into form B with drying. To recognize the thermodynamic relationships between forms B and D, the solubility of each was measured in mixed solvents. The solubility of Form D was higher than that of form B, indicating a monotropic system.

The solvent structure and supersaturation ratio were the important factors in controlling the polymorphic form of KFA-1982. Because the supersaturation ratio that produced form E was very broad when using EtOAc as the antisolvent, EtOAc was chosen as the most appropriate antisolvent for the production of form B, the desired API form. As mentioned above, we have found the optimal antisolvent to control for the desired polymorph and the threshold amount of antisolvent by investigating solvent effect for polymorph formation and the supersaturation ratio based on antisolvent amount. Currently, the method for industrial crystallization of KFA-1982 is optimized, and KFA-1982 API has been manufactured reproducibly on a pilot scale.

EXPERIMENTAL SECTION

Materials. *Preparation of KFA-1982.* The compound was synthesized by a literature method.[11]

Preparation of Form A Crystals. KFA-1982 (1.0 g) was dissolved in 1-butanol (5.5 mL) at 80 °C. Isopropyl acetate (*i*-PrOAc; 5.5 mL) was added, and the mixture was stirred at room temperature. The precipitated crystals were collected by filtration and dried in vacuo at 50 °C, to obtain 0.82 g of white solids.

Preparation of Form B Crystals. KFA-1982 (1.0 g) was dissolved in 1-butanol (5.5 mL) at 80 °C. Ethyl acetate (5.5 mL) was added, and the mixture was stirred at room temperature. The precipitated crystals were collected by filtration and dried in vacuo at 50 °C, to obtain 0.89 g of white solids.

Pilot-Scale Crystallization of Form B. Crude KFA-1982 (2.57 kg) was dissolved in mixed solvent 1-butanol (11.57 kg) and THF (1.54 kg) at 85 °C. EtOAc (17.99 kg) was added at 30 °C, and the mixure was stirred at 1 h. After solids were precipitated, the slurry was stirred at 50 °C for 3 h and at room temperature for 4 h.

The product solids were isolated by filtration and washed with EtOAc. The solids were dried under reduced pressure at 40 °C for 2 h and at 60 °C for 3 h, yielding 2.26 kg (88%) of KFA-1982 (form B) with 99.5 Area % (A%) chemical purity.

^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.79 (t, J = 7.4 Hz, 3H), 1.22 (sextet, J = 7.4 Hz, 2H), 1.49 (quintet, J = 7.4 Hz, 2H), 2.72 (s, 3H), 2.82 (t, J = 7.2 Hz, 2H), 3.11 (td, J = 7.2, 5.7 Hz, 2H), 4.06 (t, J = 6.5 Hz, 2H), 4.78 (s, 2H), 6.90−6.96 (m, 2H), 7.19 (d, J = 7.5 Hz, 1H), 7.33 (d, J = 8.7 Hz, 1H), 7.36−7.44 (m, 2H), 7.66 (td, J = 7.5, 1.2 Hz, 1H), 7.75 (td, J = 7.5, 1.2 Hz, 1H), 7.82 (dd, J = 8.7, 2.4 Hz, 1H), 8.04−8.10 (m, 2H), 8.5−9.8 (br, 2H), 11.21 (br s, 1H), 12.12 (br s, 1H), 12.5−13.3 (br, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 13.3, 18.3, 29.9, 30.0, 42.2, 43.1, 64.1, 64.7, 113.4, 115.1, 117.5, 122.5, 126.6, 126.9, 127.5, 128.1, 129.6, 129.7, 132.4, 133.1, 133.5, 137.6, 139.2, 140.3, 154.6, 158.4, 159.4, 168.6. Anal. Calcd for $C_{28}H_{34}N_3O_9S_2Cl_1$ (656.17): C, 51.07; H, 5.25; N, 6.40. Found: C, 51.25; H, 5.22; N, 6.40.

Preparation of Form C Crystals. KFA-1982 (1.0 g) was suspended in acidic buffer (10 mL) at room temperature for 16 h (acidic buffer: Japanese Pharmacopeia XVI dissolution testing solution I, pH 1.2). The precipitated crystals were collected by filtration and dried in vacuo at 50 °C, to obtain 0.92 g of white solids.

Preparation of Form D Crystals. KFA-1982 (1.0 g) was dissolved in 1-butanol (5.5 mL) at 80 °C. *n*-Heptane (5.5 mL) was added, and the mixture was stirred at room temperature. The precipitated crystals were collected by filtration and dried in vacuo at 50 °C, to obtain 0.86 g of white solids.

Crystallization Protocol. All of the organic solvents for the crystallization study were dried using 3 Å molecular sieves. Amorphous powder of KFA-1982 was used as the starting material for the crystallization studies. Crystalline powder (10 mg) of KFA-1982 in a vial was dissolved in 1,4-dioxane/water mixed solvent (ratio = 1/1, 250 μL), and the solution was lyophilized using a freeze-dryer (Tokyo Rika Kikai, Japan). The amorphous powder was suspended in 1-butanol and dissolved at 80 °C. An antisolvent was added to the solution at 80 °C. The mixture was stirred at 80 °C for 10 min, cooled at a rate of 1 °C/min to 0 °C, and stirred at 0 °C for 1 h. The precipitated crystals were collected by filtration, and wet crystals were analyzed by XRPD.

ASSOCIATED CONTENT

Supporting Information

Analytical methods. TG/DTA data for each polymorph. Thermal transformation of form C. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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