

Polymorphs and a Hydrate of Furosemide–Nicotinamide 1:1 Cocrystal

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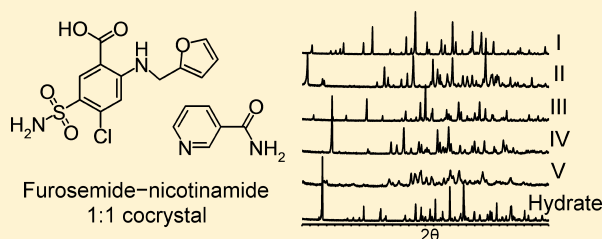
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Supporting Information

ABSTRACT: Five anhydrous polymorphs (forms I–V) and one hydrate of furosemide–nicotinamide 1:1 cocrystal were discovered, and their solid-state properties were characterized using X-ray powder diffraction and differential scanning calorimetry. The crystal structures of forms I–IV were determined from the X-ray powder diffraction data and showed the structural differences between forms, which are mainly attributable to molecular conformations and supramolecular synthons. The slurry conversion experiments revealed that the order of thermodynamic stability of the polymorphs at 25 °C is I > III > II > V > IV. Dynamic vapor sorption analysis and X-ray single-crystal structure determination of the hydrate were conducted to study the dehydration mechanism. We observed structural similarities between the hydrate and its dehydrate, form IV, such as lattice parameters (except the *a*-axis length), synthons between furosemide and nicotinamide molecules, and the molecular conformation of furosemide; after dehydration, however, the *a*-axis contracted and nicotinamide molecules were displaced, along with the pyridine ring twisting.



1. INTRODUCTION

An active pharmaceutical ingredient (API) can exist in various solid forms and often shows polymorphism when the solid form is crystalline.^{1,2} Polymorphism is defined as the ability of a substance to exist in two or more crystalline forms, with different arrangements and/or conformations of the molecule in the crystal lattice.³ Moreover, an API often forms a hydrate with water molecules because of their small size and multidirectional hydrogen-bonding capabilities.⁴ Individual polymorphs and hydrates possess unique physicochemical properties, such as solubility, stability, and hygroscopicity.⁵ Furthermore, in the case of hydrates, the water molecules can escape from the crystal lattice, and the physicochemical properties of the dehydrated form differ from those of the hydrate. Therefore, screening polymorphs and hydrates, evaluating their physicochemical properties, and investigating the dehydration mechanism of hydrates are of particular importance for pharmaceutical research and development.

Recently, cocrystals have been a focus of attention as valuable API forms with the potential to improve physicochemical properties.^{6–21} Pharmaceutical cocrystals can be defined as multicomponent assemblies made up of an API and a coformer with noncovalent interactions.¹⁸ Cocrystals also show polymorphism, and examples of polymorphs of pharmaceutical cocrystals have been reported, comparing their structure^{22–37} and physicochemical stability.²² However, to our knowledge,

the maximum number of polymorphs associated with a pharmaceutical cocrystal reported so far is three, which can be found in barbituric acid–urea 1:1 cocrystal,²⁸ pimelic acid–4,4′-bipyridine cocrystal,²⁹ and ethenzamide–gentisic acid 1:1 cocrystal,³³ although a higher number (four or more) of polymorphs have been reported for single-component crystals or crystalline salts.³⁷ Cocrystal hydrates also exist and several studies have been conducted on them, such as screening,³⁸ dissolution behavior,³⁹ and structure–stability relationships,⁴⁰ but published reports on them are still few. In particular, previous reports on the dehydration mechanism of cocrystal hydrates have been limited.

As polymorphs individually have different crystal structures giving rise to different physicochemical properties between polymorphs, crystal structure determination is useful for investigating polymorphism. In addition, information on the crystal structures of hydrates and their dehydrates is essential for a deep understanding of the hydration/dehydration mechanism. X-ray single-crystal diffraction is a powerful tool and is widely employed to determine the crystal structure, but it is sometimes difficult to prepare suitable single crystals, which are essential for measurement. In particular, a single crystal of

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the hydrate often changes into a polycrystalline powder following dehydration, and, therefore, the crystal structure of the dehydrate cannot be determined. On the other hand, X-ray diffraction data obtained from powder instead of a single crystal can also be used for crystal structure determination. Although X-ray powder diffraction (XRPD) data contain less information than X-ray single-crystal diffraction data because the Bragg peaks overlap,⁴¹ recent advances have increased the opportunities to determine the crystal structure from XRPD data,⁴² particularly through the development of direct-space methods for structure solution.⁴³

Furosemide (FS), 4-chloro-2-[(2-furanylmethyl)amino]-5-sulfamoylbenzoic acid, is a loop diuretic drug⁴⁴ and has suitable hydrogen bonding moieties for cocrystallization such as carboxyl and sulfonamide groups. In this contributing paper, we characterize five polymorphs (forms I–V) and a hydrate of FS–nicotinamide (NCT) 1:1 cocrystal, which were identified through cocrystallization studies between FS and various pharmaceutically acceptable cofomers. The thermodynamic relationship of the polymorphs has been investigated by slurry conversion experiments. Crystal structures of five of the forms (forms I–IV and the hydrate) have been determined from X-ray single-crystal or powder diffraction data to discuss the structural differences of the polymorphs and the dehydration mechanism of the hydrate.

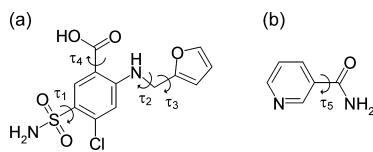


Figure 1. Chemical structures of FS (a) and NCT (b) and the five torsion parameters (τ) in the molecules.

2. EXPERIMENTAL SECTION

2.1. Materials. FS and NCT were purchased from Sigma-Aldrich Japan (Tokyo, Japan) and Wako Pure Chemical Industries (Tokyo, Japan), respectively, and used without further purification. All other chemicals were obtained from various commercial suppliers and used as received.

2.2. Cocrystallization of FS–NCT 1:1 Cocrystals. **2.2.1. Cocrystal Screening.** Slurry method was applied for the cocrystal screening. FS and NCT were dissolved in *tert*-butanol at a 1:1 molar ratio and 50 mg/mL. An 80 μ L measure of the solution was dispensed to each of several glass vials, and then each was lyophilized at -20 °C. Twenty microliters of each crystallization solvent was added to the vials, and then the slurries were shaken at 100 rpm for 1 week at room temperature. Obtained solids were observed by optical microscopy and analyzed by XRPD. The details of the screening method were described in our previous report.⁴⁵

2.2.2. Cooling Crystallization. **Form I.** FS (99 mg) and NCT (37 mg) were dissolved in 1.5 mL of ethanol under reflux. The solution was cooled to room temperature and seeded with 1 mg of form I crystals obtained from the cocrystal screening. The solution was shaken for 15 h at 100 rpm. The crystals were filtered and dried in vacuo at room temperature.

Form II. FS (330 mg) and NCT (122 mg) were dissolved in a mixture of 2.26 mL of ethanol and 0.45 mL of tetrahydrofuran under reflux. The solution was cooled to room temperature and seeded with 1 mg of form II crystals obtained from the cocrystal screening. The solution was shaken for 15 h at 100 rpm. The crystals were filtered and dried in vacuo at room temperature.

Form III. FS (66 mg) and NCT (24 mg) were dissolved in a mixture of 0.53 mL of ethanol and 0.13 mL of acetone under reflux.

The solution was cooled to room temperature and shaken for 15 h at 100 rpm. The crystals were filtered and dried in vacuo at room temperature.

Hydrate. FS (132 mg) and NCT (49 mg) were dissolved in a mixture of 0.9 mL of acetonitrile and 0.1 mL of water under reflux. The solution was cooled to room temperature and seeded with 1 mg of hydrate crystals obtained from the cocrystal screening. The solution was shaken for 1.5 h at 100 rpm. The crystals were filtered and dried under ambient conditions.

Form IV. Form IV was obtained by drying the hydrate in a desiccator containing silica gel at room temperature for 2 days.

Form V. FS (99 mg) and NCT (73 mg) were dissolved in 1.5 mL of 2-propanol under reflux. The solution was cooled to room temperature and seeded with 1 mg of form V crystals obtained from the cocrystal screening. The solution was shaken for 2 h at 100 rpm. The crystals were filtered and dried in vacuo at room temperature.

2.3. XRPD. A Rigaku SmartLab diffractometer, equipped with an incident-beam Ge(111) Johansson monochromator to obtain Cu K α radiation and a Rigaku D/teX Ultra high-speed, position-sensitive detector, was used in the Bragg–Brentano geometry. The X-ray generator was operated at 45 kV and 200 mA. The divergence slit was set at 1/3°. Other experimental conditions were continuous scan, experimental 2θ range from 5° to 35°, scan speed of 5°/min, and step size of 0.02°.

XRPD data for crystal structure determination of forms I, II, III, and IV were collected on the same system in transmission mode using Debye–Scherrer geometry. The incident beam was focused with an ellipsoidal multilayer mirror. The samples were introduced into a 0.7 mm diameter borosilicate glass capillary. For the sample of form IV, the capillary was sealed with an epoxy bonding agent to prevent rehydration. The XRPD data were collected with the specimen rotating. Other experimental conditions are given in Table 1. All the processes in structure determination were

Table 1. Experimental Conditions for X-ray Powder Diffraction

	form I	form II	form III	form IV
2θ range (deg)	4–100	4–100	4–98	3–100
step size (deg)	0.008	0.005	0.008	0.005
scan speed (°/min)	0.5	0.5	0.4	0.1
total data collection time (h)	3.2	3.2	3.9	16.2

performed using a Rigaku PDXL structure analysis software package. To obtain the diffracted peaks, the XRPD patterns were decomposed by the Pawley method, and the diffracted peaks were indexed with DICVOL06⁴⁶ and N-TREOR⁴⁷ programs. The molecular geometries of the FS and NCT molecules were generated from the crystal structures in CSD data (ref code FURSEM01 and NICOAM02) and described by Z-matrix coordinates. The initial structures were determined using direct-space methods with the parallel tempering algorithm. After the direct-space method process, the coordinates of all atoms of the molecules were converted to fractional coordinates, and the structural parameters were refined by the Rietveld method with some restraints on bond lengths and angles. Planar restraints were also applied to a phenyl ring, a furan ring, a pyridine ring, a carboxyl group, and an amide group. The hydrogen atoms were placed geometrically and fixed during the refinement.

2.4. X-ray Single-Crystal Diffraction. X-ray single crystal diffraction data of the hydrate were collected on a Rigaku R-Axis RAPID II with a VariMax Cu diffractometer including a Rigaku MicroMax-007HF microfocus generator with a Cu anode operating at 40 kV and 30 mA, Rigaku VariMax HF optics, and a Rigaku R-Axis RAPID II image plate detector at room temperature. The crystal structure was solved by direct methods using SIR2004⁴⁸ and refined using SHELXL-97.⁴⁹ The furan rings were found to be disordered over two positions and were refined isotropically. The other non-hydrogen atoms were refined anisotropically. No hydrogen atoms were placed

on the furan rings or the water molecules. The other hydrogen atoms were positioned geometrically. All hydrogen atoms were refined using the riding model.

2.5. Differential Scanning Calorimetry (DSC). DSC was performed using an SII NanoTechnology EXSTAR 6200R DSC. Samples were placed in aluminum pans and sealed. The measurements were carried out at the heating rates of 5 °C/min under a nitrogen flow. A total of three runs were performed on each sample.

2.6. Optical Microscopy. Optical microscopy was carried out using a Nikon Eclipse TE2000-U inverted microscope.

2.7. Hot-Stage Optical Microscopy. Hot-stage optical microscopy was performed using a Japan High Tech 10002 hot stage and a Nikon OPTIPHOT2-POL microscope. The heating rate was 5 °C/min.

2.8. Dynamic Vapor Sorption (DVS) Analysis. Water desorption and sorption isotherms for the hydrate were obtained using a Surface Measurement Systems DVS-1 dynamic vapor sorption instrument. Desorption and sorption data were collected between 95 and 0% RH at 25 °C with an equilibrium criterion of less than 0.002%/min weight change or of a maximum equivalent time of 6 h.

2.9. NMR Spectroscopy. ¹H NMR spectra were collected on a JEOL ECP400 spectrometer operating at 400 MHz. Samples were dissolved in DMSO-*d*₆ containing TMS as an internal standard.

2.10. Slurry Conversion Experiment. Slurry conversion experiments of polymorphs were carried out using 2-propanol, 1-propyl acetate, and methyl isobutyl ketone as solvents. A mixture of two polymorphs (2 mg each) was suspended in 40 μL of each solvent. The slurries were shaken at 2000 rpm for 1 day at 25 °C. The resultant solids in the slurries were analyzed using XRPD. Experiments were carried out for all paired combinations of polymorphs.

3. RESULTS AND DISCUSSION

3.1. Cocrystal Screening and Identification. The cocrystal screening for FS and NCT was conducted using the slurry method, and three nonsolvated polymorphs, forms I, II, V, and a hydrate were screened (Table 2). In the course of

Table 2. Forms Obtained in Cocrystal Screening of FS and NCT

crystallization solvent	obtained form
ethanol	II
2-propanol	I + II
1-butanol	I
acetonitrile	S ^a
ethyl acetate	S ^a
1-propyl acetate	II
1-butyl acetate	II
acetone	S ^a
methyl ethyl ketone	S ^a
methyl isobutyl ketone	V
<i>tert</i> -butylmethyl ether	V
tetrahydrofuran	S ^a
toluene	S ^a
<i>N,N</i> -dimethylformamide	-
water	hydrate
dichloromethane	S ^a

^aSolvates of FS–NCT cocrystal. These solvates have not been well characterized.

scale-up studies for forms I, II, V, and the hydrate using a cooling method, form III was identified. Form IV was identified by dehydrating the hydrate. As a consequence, five anhydrous polymorphs, forms I, II, III, IV, and V, and one hydrate were discovered. These polymorphs and the hydrate have different morphologies (Figure 2).

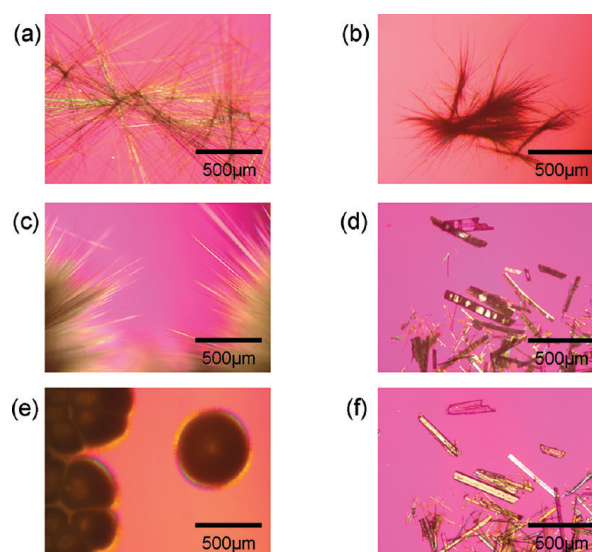


Figure 2. Crystals of FS–NCT 1:1 cocrystal, forms I (a), II (b), III (c), IV (d), V (e), and hydrate (f).

pK_a values of each component are used as indicators of salt or cocrystal formation.^{50,51} When ΔpK_a (pK_a of base – pK_a of acid) is greater than 3, the crystal probably forms a salt, and when ΔpK_a is negative, the crystal very likely forms a cocrystal. In the ΔpK_a range from 0 to 3, the crystal can be a salt or a cocrystal. The pK_a values of FS and NCT are 3.56 (acid) and 3.43 (base) respectively,⁵² so ΔpK_a between FS and NCT is –0.13. Therefore, the forms we found are classified as cocrystals. In addition, ¹H NMR measurements revealed that the stoichiometries of FS and NCT in these forms are 1:1 (see Figure S1 in the Supporting Information). From these findings, the identified forms can be determined to be FS–NCT 1:1 cocrystal.

3.2. Solid-State Characterization of Polymorphs. The identified polymorphs were characterized using XRPD, DSC, and a hot-stage optical microscopy. Each form exhibits a unique XRPD pattern that differs from the starting materials of FS and NCT (Figure 3). The melting points of the polymorphs were determined from the onset temperatures of DSC endothermic peaks and verified by hot-stage microscopy (Figure 4 and Table 3). All the polymorphs show unique melting points that differ from those of the starting materials, FS (213.6 °C ± 1.1 °C) and NCT (127.8 °C ± 0.1 °C). The order of melting points is I (154.9 ± 0.1 °C) > III (153.6 ± 0.3 °C) > II (147.4 ± 0.1 °C) > V (144.2 ± 0.6 °C) > IV (95.9 ± 0.2 °C). In addition, the order of the values for heat of fusion is also I (46.6 ± 0.8 kJ/mol) > III (40.6 ± 0.9 kJ/mol) > II (37.3 ± 0.6 kJ/mol) > V (32.6 ± 0.7 kJ/mol). After form IV melts at approximately 96 °C, it immediately crystallizes to form I, and the endothermic melting peak of form IV overlaps with the exothermic crystallization peak of form I. No other peaks except the melting peaks were observed in the DSC curves of forms I, II, III, and V.

3.3. Solid-State Characterization of the Hydrate. The hydrate was characterized using XRPD and DVS analysis. The hydrate has a unique XRPD pattern that differs from those of the starting materials of FS and NCT, and from the polymorphs of FS–NCT 1:1 cocrystal (Figure 3). In particular, the difference in XRPD patterns between the hydrate and its

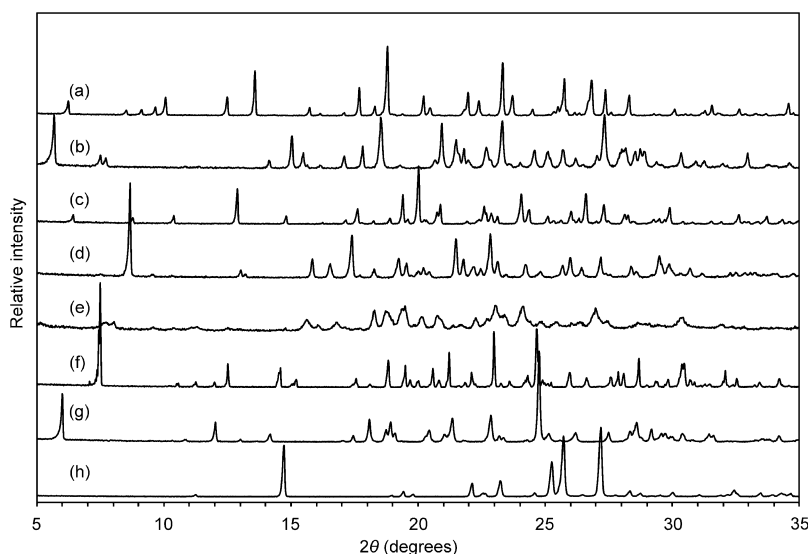


Figure 3. XRPD patterns of FS–NCT 1:1 cocrystal, forms I (a), II (b), III (c), IV (d), V (e), and hydrate (f), and starting materials of FS (g) and NCT (h).

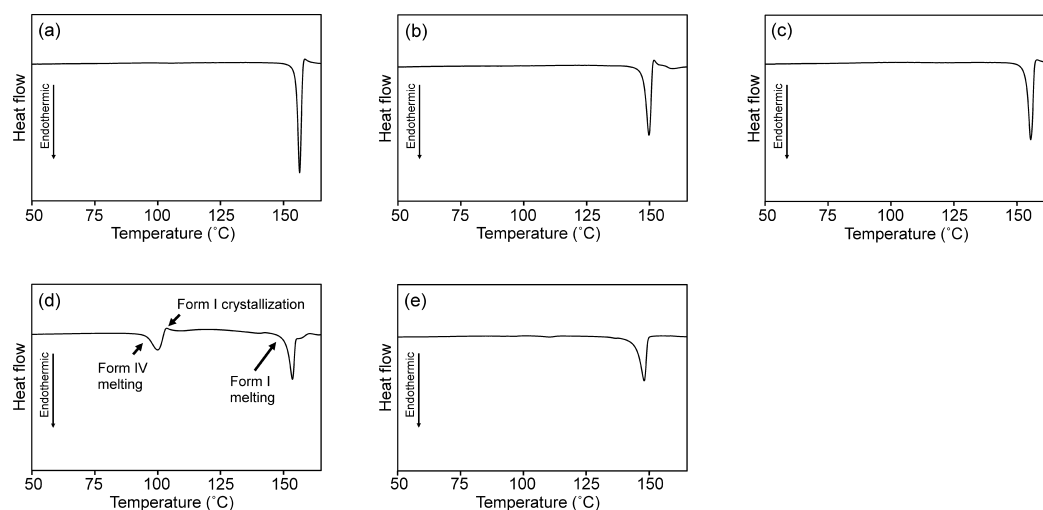


Figure 4. DSC curves of FS–NCT 1:1 cocrystal, forms I (a), II (b), III (c), IV (d), and V (e). After form IV melts, it immediately crystallizes to form I.

Table 3. Melting Points and Heat of Fusions of FS–NCT Cocrystal Polymorphs

form	melting point (°C)	heat of fusion (kJ/mol)
I	154.9 ± 0.1	46.6 ± 0.8
II	147.4 ± 0.1	37.3 ± 0.6
III	153.6 ± 0.3	40.6 ± 0.9
IV	95.9 ± 0.2	N.D.
V	144.2 ± 0.6	32.6 ± 0.7

dehydrate, form IV, suggests that they are not in an isostructural relationship. The water desorption and sorption isotherms of the hydrate show a reversible phase transformation between the hydrate and form IV (Figure 5). The hydrate transforms to form IV under <20% RH in the desorption process, and form IV transforms to the hydrate under >20% RH in the sorption process. The solid form in each process was confirmed by XRPD. The difference of the sample mass between the hydrate

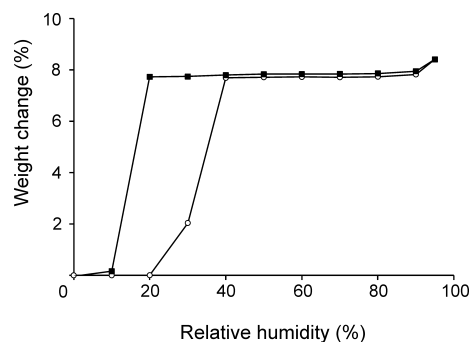


Figure 5. Water desorption (■) and sorption (○) isotherms of FS–NCT 1:1 cocrystal hydrate.

and form IV is ca. 8% w/w, and the hydration number of the hydrate is calculated to be 2.

3.4. Determination of the Thermodynamic Relationship between Polymorphs. Slurry conversion experiments for all combinations of pairs of polymorphs were carried out in 2-propanol, 1-propyl acetate, and methyl isobutyl ketone at 25 °C. The results are summarized in Table 4. Forms II, III, IV,

Table 4. Forms Obtained in Slurry Conversion Experiments of FS–NCT Cocrystal Polymorphs

starting form	solvent		
	2-propanol	1-propyl acetate	methyl isobutyl ketone
I + II	I	I	I
I + III	I	I	I
I + IV	I	I	I
I + V	I	I	I
II + III	III	III	III
II + IV	II + III	II	III
II + V	II	II	II
III + IV	III	III	III
III + V	III	III	III
IV + V	V	V	solvate

and V in the slurries containing form I transformed into form I, while forms II, IV, and V in the slurries containing form III transformed into form III, indicating that form I is the most stable form of the five polymorphs and form III is more stable than forms II, IV, and V at 25 °C. Likewise, other relationships were determined: form II is more stable than forms IV and V, and form IV is the least stable of all five polymorphs. The order of thermodynamic stability of the polymorphs at 25 °C is I > III > II > V > IV.

The thermodynamic relationship of two polymorphs can be either monotropic or enantiotropic. In the monotropic system, only one form is stable at all temperatures below the melting

point. In the enantiotropic system, the thermodynamic stability order of polymorphs changes above or below a transition temperature.⁵ As stated by the heat of fusion rule, a higher melting form has a higher heat of fusion in a monotropic system and a lower heat of fusion in an enantiotropic system.⁵³ In the case of FS–NCT cocrystal forms I, II, III, and V, as the higher melting forms have higher heats of fusion, these four polymorphs are monotropically related. Therefore, the order of thermodynamic stability of forms I, II, III, and V at all temperatures below their melting points is I > III > II > V, which agrees with the thermodynamic relationship at 25 °C determined by slurry conversion experiments. The thermodynamic relationship between form IV and the other four polymorphs was not determined because the heat of fusion of form IV could not be measured.

3.5. Crystal Structure Determination. The crystal structure of the hydrate was determined by X-ray single-crystal diffraction. Crystal structure determination of forms I, II, III, and IV was carried out from XRPD data, as no suitable single crystals could be obtained. The good agreements between the experimental and calculated XRPD patterns in the final Rietveld refinement indicate the correctness of the structures (Figure 6). The crystal structure of form V could not be determined because a suitable single crystal could not be prepared and the space group could not be determined from XRPD data. Details of the crystallographic data for these forms are summarized in Table 5. Hydrogen bonds are one of the most important interactions for cocrystal formation, and, in these crystal structures, we observed a total of 11 kinds of supramolecular synthons, which are defined as structural units within the molecules that can be formed and/or assembled by known or conceivable intermolecular hydrogen bonding (Figure 7, Tables 6 and 7).⁵⁴ The synthons A–E are formed between FS and NCT molecules, synthon F between FS molecules, and synthon

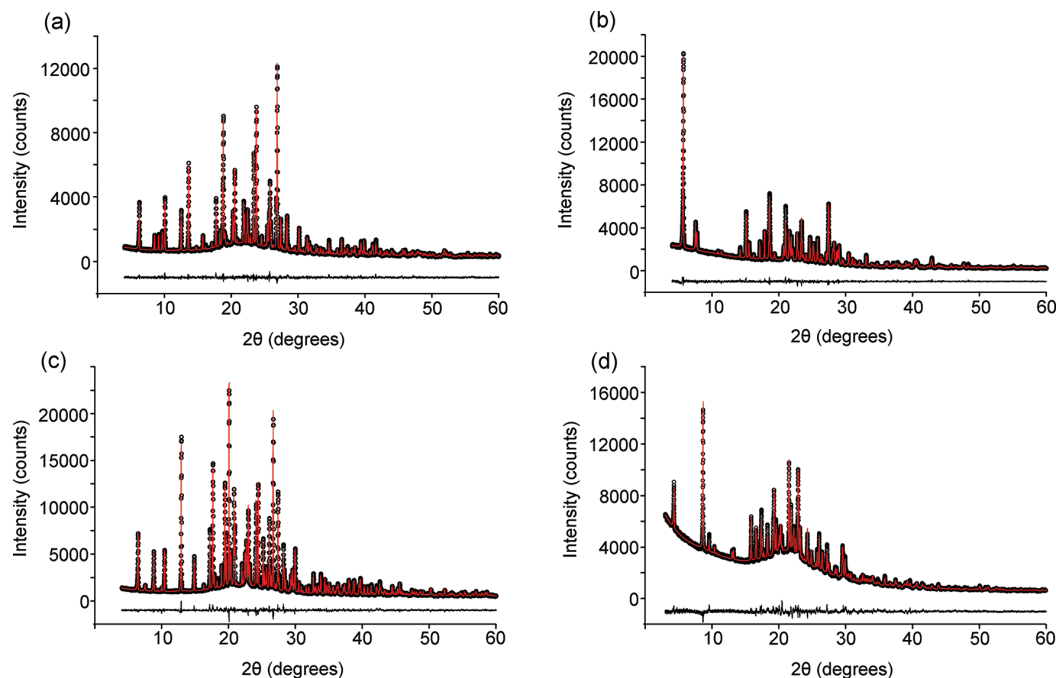
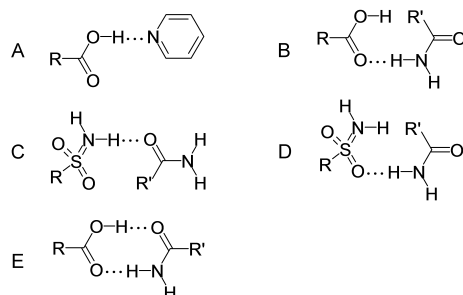


Figure 6. Final Rietveld fit for FS–NCT 1:1 cocrystal, forms I (a), II (b), III (c), and IV (d) showing the experimental (○), calculated (red line), and difference (black line) profiles.

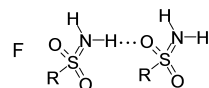
Table 5. Crystallographic Data for FS–NCT Cocrystal Forms I–IV and Hydrate

phase designator	form I	form II	form III	form IV	hydrate
empirical formula	C ₁₈ H ₁₇ N ₄ O ₆ SCl	C ₁₈ H ₁₇ N ₄ O ₆ SCl	C ₁₈ H ₁₇ N ₄ O ₆ SCl	C ₁₈ H ₁₇ N ₄ O ₆ SCl	C ₁₈ H ₁₇ N ₄ O ₆ SCl·2(H ₂ O)
formula weight	452.87	452.87	452.87	452.87	488.90
temperature (K)	298	298	298	298	298
sample formulation	powder	powder	powder	powder	single crystal
crystal system	monoclinic	monoclinic	monoclinic	monoclinic	monoclinic
space group	<i>P</i> 2 ₁ / <i>n</i>	<i>P</i> 2 ₁ / <i>n</i>	<i>P</i> 2 ₁ / <i>n</i>	<i>C</i> 2/ <i>c</i>	<i>C</i> 2/ <i>c</i>
<i>a</i> (Å)	4.86286(13)	16.4686(4)	5.22828(4)	40.6357(13)	46.9784(16)
<i>b</i> (Å)	20.7109(6)	5.01253(14)	18.71272(17)	5.36051(15)	5.09800(15)
<i>c</i> (Å)	19.3632(5)	24.7963(7)	20.12138(18)	18.3727(5)	18.1866(6)
α (°)	90	90	90	90	90
β (°)	92.4168(6)	108.8400(6)	94.8246(5)	92.5034(13)	92.5680(18)
γ (°)	90	90	90	90	90
volume (Å ³)	1948.42(9)	1937.26(9)	1961.61(3)	3998.3(2)	4351.2(3)
<i>Z</i>	4	4	4	8	8
ρ_{calc} (g/cm ³)	1.54	1.55	1.53	1.50	1.49
no. of reflections collected	2007	1972	1916	2067	21761
refinement method	Rietveld	Rietveld	Rietveld	Rietveld	full-matrix least-squares on <i>F</i> ²
no. of unique reflections	2007	1972	1916	2067	3958
no. of parameters	88	78	91	45	288
goodness-of-fit	1.1616 (on <i>y</i> _{obs})	1.1583 (on <i>y</i> _{obs})	1.4711 (on <i>y</i> _{obs})	1.3955 (on <i>y</i> _{obs})	0.931 (on <i>F</i> ²)
final <i>R</i> indices [<i>I</i> > 2σ(<i>I</i>)]					<i>R</i> ₁ = 0.0661
<i>R</i> indices (all data)	<i>R</i> _{wp} = 0.0476 <i>R</i> _{exp} = 0.0409 <i>R</i> _p = 0.0365	<i>R</i> _{wp} = 0.0449 <i>R</i> _{exp} = 0.0387 <i>R</i> _p = 0.0338	<i>R</i> _{wp} = 0.0446 <i>R</i> _{exp} = 0.0303 <i>R</i> _p = 0.0348	<i>R</i> _{wp} = 0.0357 <i>R</i> _{exp} = 0.0256 <i>R</i> _p = 0.0261	<i>wR</i> ₂ = 0.1456

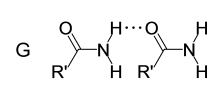
FS and NCT



FS and FS



NCT and NCT



Water related

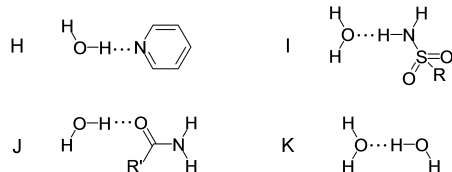


Figure 7. Synthons formed in FS–NCT 1:1 cocrystals.

G is found between NCT molecules. Water molecules in the hydrate form four kinds of hydrogen bonds by bonding with FS, NCT, or another water molecule (synthons H–K).

Form I. Form I is monoclinic with the space group *P*2₁/*n*. The asymmetric unit of form I consists of one FS molecule and

one NCT molecule. The FS and NCT molecules form a pair sustained by the carboxylic acid–pyridine hydrogen bond (synthon A) (Figure 8a). The pairs stack along the *a*-axis and interact with each other through the sulfonamide–sulfonamide and the amide–amide hydrogen bonds (synthons F and G) (Figure 8b).

Form II. Form II is monoclinic with the space group *P*2₁/*n*. The asymmetric unit of form II contains one FS molecule and one NCT molecule. Two FS and two NCT molecules create a planar ring motif stabilized by carboxylic acid–pyridine and carboxylic acid–amide hydrogen bonds (synthon A and B) (Figure 9a). The planar rings stack along the *b*-axis and connect to each other by the amide–amide hydrogen bond (synthon G). The planar rings in the stacks also connect to other rings in adjacent stacks by the sulfonamide–sulfonamide hydrogen bonds (synthon F) (Figure 9b).

Form III. Form III crystallizes in the monoclinic space group *P*2₁/*n* with one FS molecule and one NCT molecule in the asymmetric unit. The FS and the NCT molecules form a chain motif stabilized by carboxylic acid–pyridine and sulfonamide–amide hydrogen bonds (synthon A and D) (Figure 10a). The chains align parallel to the *b*-axis and form a herringbone packing arrangement sustained by the sulfonamide–amide, sulfonamide–sulfonamide, and the amide–amide hydrogen bonds (synthon C, E, and G) (Figure 10b).

Hydrate. The hydrate is monoclinic with the space group *C*2/*c*. The asymmetric unit of the hydrate consists of one FS molecule, one NCT molecule, and two water molecules, in agreement with the stoichiometry of water determined by DVS analysis. The furan rings of the FS molecule are disordered over two sites with occupancies of 0.54 and 0.46. The FS and the NCT molecules form a pair sustained by carboxylic acid–amide hydrogen bonds (synthon E). The pairs align parallel to the *c*-axis and form corrugated sheets stabilized by sulfonamide–amide hydrogen bonds (synthon D). The sheets stack along

Table 6. Synthons Formed in FS–NCT 1:1 Cocrystals^a

form	synthon										
	A	B	C	D	E	F	G	H	I	J	K
I	✓					✓	✓				
II	✓	✓				✓	✓				
III	✓		✓	✓		✓	✓				
IV					✓	✓					
hydrate				✓	✓	✓		✓	✓	✓	✓

^aThe symbol ✓ represents observation of the synthon in the form.

Table 7. Intermolecular Hydrogen Bonds in FS–NCT 1:1 Cocrystals

form	synthon	hydrogen bond	H...A (Å)	D...A (Å)	∠DHA (deg)
I	A	O–H...N	1.69	2.506	175
	F	N–H...O	2.07	2.852	146
	G	N–H...O	2.30	3.061	143
II	A	O–H...N	1.72	2.535	174
	B	N–H...O	2.01	2.884	168
	F	N–H...O	1.92	2.715	148
	G	N–H...O	2.06	2.943	172
III	A	O–H...N	1.82	2.621	166
	C	N–H...O	2.81	3.066	98
	D	N–H...O	2.03	2.922	177
	F	N–H...O	2.21	2.861	130
	G	N–H...O	2.25	2.961	137
IV	E	O–H...O	1.80	2.602	168
		N–H...O	2.12	2.986	164
	F	N–H...O	2.63	2.976	105
hydrate	D	N–H...O	2.22	3.055	164
	E	O–H...O	1.81	2.615	167
		N–H...O	2.11	2.943	163
	F	N–H...O	2.45	2.829	106
	H	O–H...N	^a	2.894	^a
	I	N–H...O	2.07	2.911	157
	J	O–H...O		2.893	
	K	O–H...O		2.900	
		O–H...O		2.964	

^aNo hydrogen atoms were placed on the water molecules.

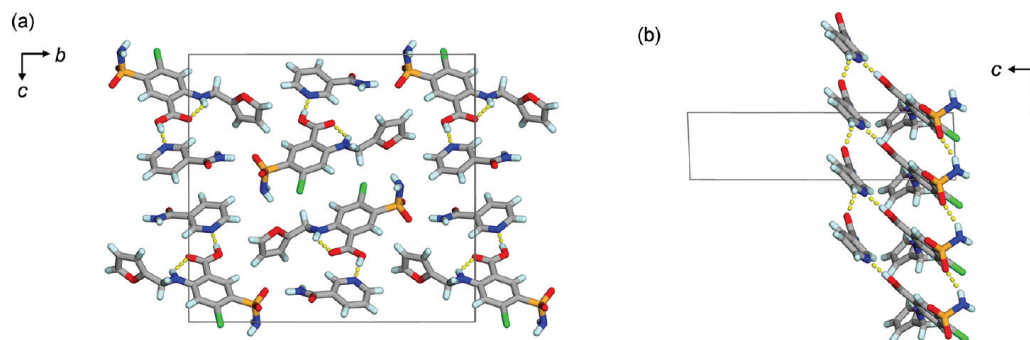
the *b*-axis and interact with each other through the sulfonamide...sulfonamide hydrogen bonds (synthon F) (Figure 11a,b). The two water molecules bind to each other by hydrogen bonding (synthon K) and link to the sulfonamide of one FS and to the pyridine and the amide of one NCT

molecule by hydrogen bonding (synthon H, I, and J), shown in Figure 11c. The water molecules are located in channels parallel to the *b*-axis.

Form IV (Dehydrate of the Hydrate). Form IV is monoclinic with the space group *C2/c*. The asymmetric unit of form IV contains one FS molecule and one NCT molecule. The FS and the NCT molecules form a pair sustained by carboxylic acid...amide hydrogen bonds (synthon E). The pairs stack along the *b*-axis and interact with each other through the sulfonamide...sulfonamide hydrogen bonds (synthon F) (Figure 12).

3.6. Structural Comparison of Polymorphs (Forms I–IV). In every form of which the crystal structure could be solved, the rotation of carboxylic acid in the FS molecule (τ_4) is fixed, which is attributed to the intramolecular hydrogen bonding between the secondary amine and the carbonyl group. The differences in molecular conformation of the FS molecules among the polymorphs are mainly the torsion angles of the sulfonamide group (τ_1) and the orientations of the furan rings (τ_2 , 3). In addition, individual polymorphs have a different torsion angle (τ_5) of the NCT molecules (Table 8).

The synthons observed in these polymorphs are listed in Table 6. Not every possible synthon has been found (e.g., the synthon formed by carboxylic acid...carboxylic acid hydrogen bond was not observed), and in total seven kinds of synthons (synthon A–G) exist in the polymorphs. The synthon F (sulfonamide...sulfonamide) is observed in every form. Forms I, II, and III have synthon A (carboxylic acid...pyridine) and synthon G (amide...amide) in common, but form IV does not have these synthons. Synthons B, C, D, and E are found in only one form each. These significant varieties of hydrogen bonds can explain the structural diversity of the polymorphs. Interestingly, the amount of hydrogen bonds does not correlate with the thermodynamic stability of these polymorphs (e.g.,

Figure 8. Packing diagrams of FS–NCT 1:1 cocrystal form I viewed along the *a*-axis (a) and the *b*-axis (b).

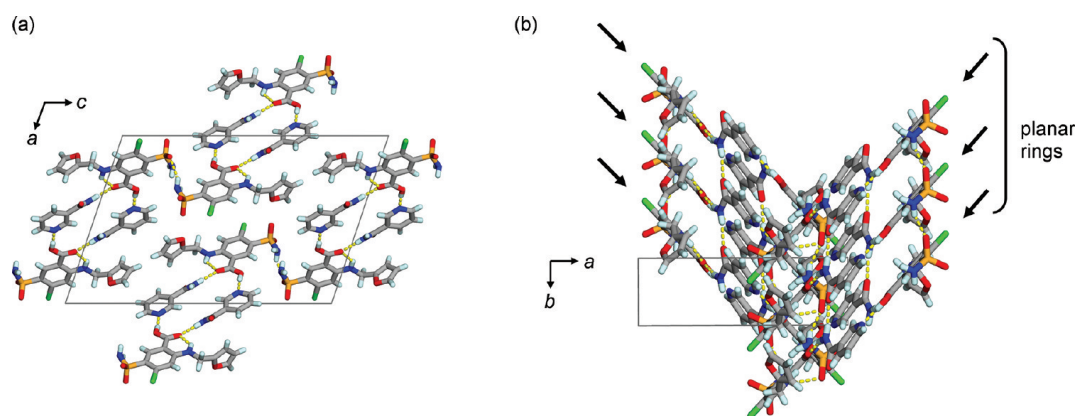


Figure 9. Packing diagrams of FS–NCT 1:1 cocrystal form II viewed along the *b*-axis (a) and the *c*-axis (b).

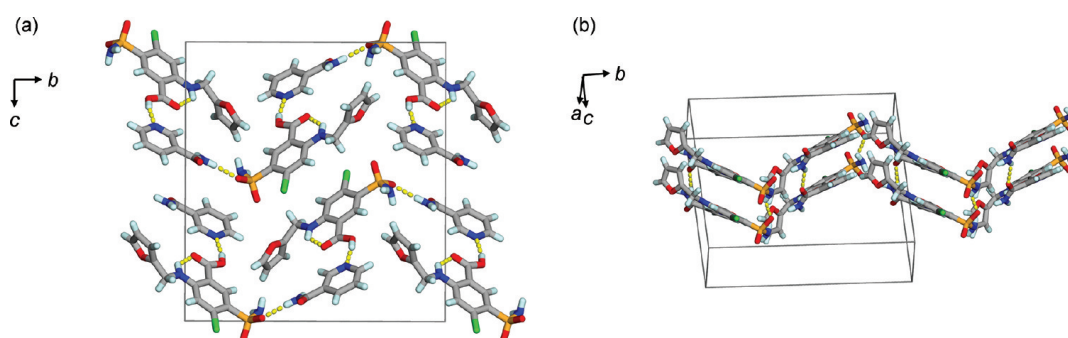


Figure 10. Packing diagrams of FS–NCT 1:1 cocrystal form III viewed along the *b*-axis (a) and showing the herringbone packing arrangement (b).

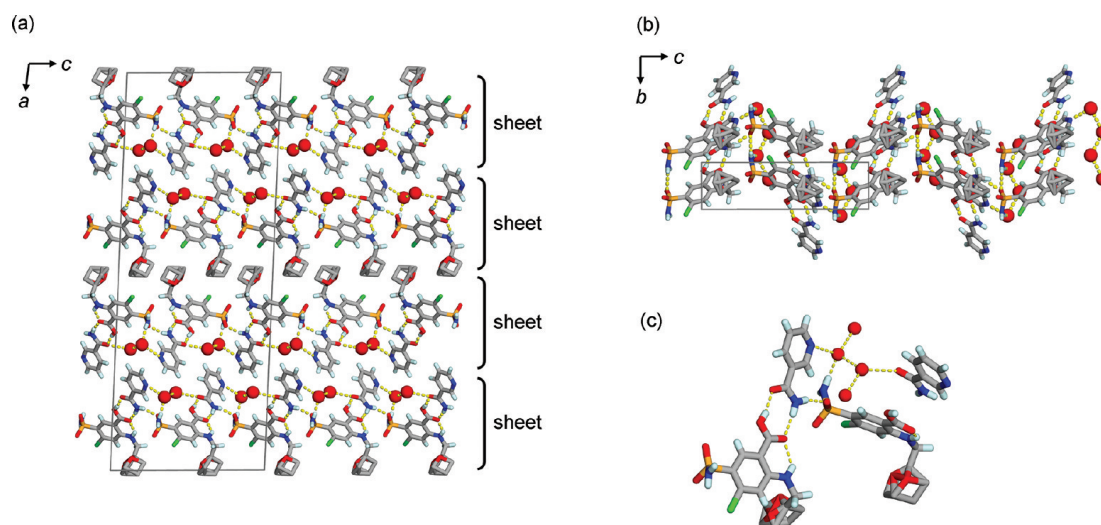


Figure 11. Packing diagrams of FS–NCT 1:1 cocrystal hydrate viewed along the *b*-axis (a) and the *a*-axis (b). Hydrogen bonding network in the hydrate (c).

form I is the thermodynamically most stable form but has fewer hydrogen bonds than forms II and III).

3.7. Dehydration Behavior of the Hydrate. The dehydrated hydrate, form IV, belongs to the same space group, $C2/c$, as the hydrate and has similar lattice parameters except for the *a*-axis length (Table 5). The *a*-axis of form IV is

shorter than that of the hydrate due to a contraction of the unit cell. FS molecules have similar conformations in the hydrate and form IV. On the other hand, a large difference of the torsion angles (τ_5) in the NCT molecules is observed between the hydrate (9.2°) and form IV (54.1°) (Figure 13a). Two of the three synthons between FS and NCT molecules, synthons

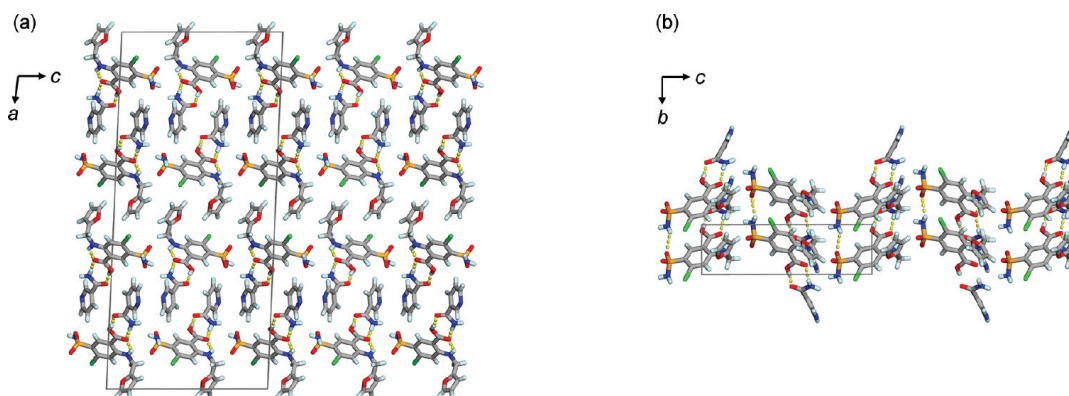


Figure 12. Packing diagrams of FS–NCT 1:1 cocrystal form IV viewed along the *b*-axis (a) and the *a*-axis (b).

Table 8. Torsion Angles in FS–NCT 1:1 Cocrystals

form	τ_1 (deg)	τ_2 (deg)	τ_3 (deg)	τ_4 (deg)	τ_5 (deg)
I	78.6	171.7	77.2	9.3	27.2
II	173.7	155.3	74.2	4.5	34.8
III	174.9	166.8	66.9	5.0	28.6
IV	57.6	85.3	93.5	4.3	54.1
hydrate	67.5	77.4	-74.5^a	5.5	9.2
			37.4^a		

^aThe furan rings of the FS molecule in the hydrate are disordered over two sites.

E and F, remain after dehydration, but synthon D is broken. In addition, the channels in which water molecules are located disappear and the *a*-axis of the unit cell contracts. Although these structural changes are observed, the crystal structure is maintained to some extent after dehydration (Figure 13b). From the above observations, the dehydration mechanism of the hydrate can be explained as follows: under drying conditions, the hydrogen bonds engaged by water molecules in the hydrate disappear when the water molecules escape, and the channels of the hydrate which held the water molecules become empty. The vacant channels are occupied by the NCT molecules along with the pyridine ring twisting. This displacement of the NCT molecules results in the unit cell shrinkage along the *a*-axis.

4. CONCLUSION

We have found five anhydrous polymorphs (forms I–V) and one hydrate of FS–NCT 1:1 cocrystal. The crystal structures of forms I–IV and the hydrate have been determined from the XRPD data and X-ray single-crystal diffraction data, respectively. By using XRPD data to determine the crystal structure, we could investigate the structure even when a suitable single crystal could not be prepared. The structural differences of the polymorphs lie mainly in the conformations of the FS and NCT molecules and supramolecular synthons. This variety results in the diversity of the crystal structures of the polymorphs. The fact that a higher number of polymorphs exist in cocrystals suggests the importance of polymorph screening and characterization of cocrystals, as well as other solid forms of APIs. Slurry conversion experiments were conducted to determine the most stable form at 25 °C, and the results agree with the order of thermodynamic stability determined by the heat of fusion rule. Slurry conversion is a useful method to determine the most stable form even for cocrystals, which is of critical importance for pharmaceutical development.

The hydrate has channels for water molecules and dehydrates to form IV with the structural contraction and conformational change of NCT molecules. Crystal structure determination reveals the structural relationship between the hydrate and the dehydrate, and can explain the dehydration mechanism of the hydrate.

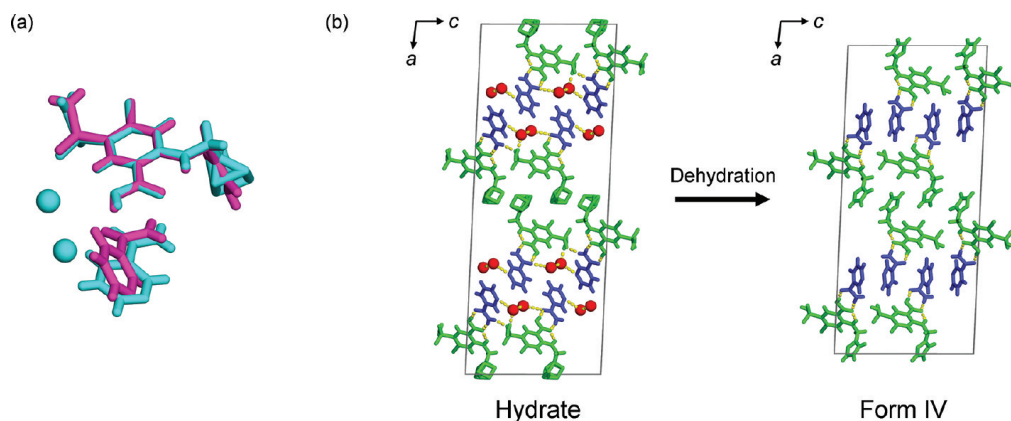


Figure 13. Structural comparison between FS–NCT 1:1 cocrystal hydrate and form IV. Overlay of molecular conformation (cyan: hydrate, magenta: form IV) (a). Packing diagrams before and after dehydration (green: FS molecules, blue: NCT molecules, red: water molecules) (b).

■ ASSOCIATED CONTENT

■ Supporting Information

X-ray crystallographic information files (CIF) and ^1H NMR spectra are available free of charge via the Internet at <http://pubs.acs.org>.

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