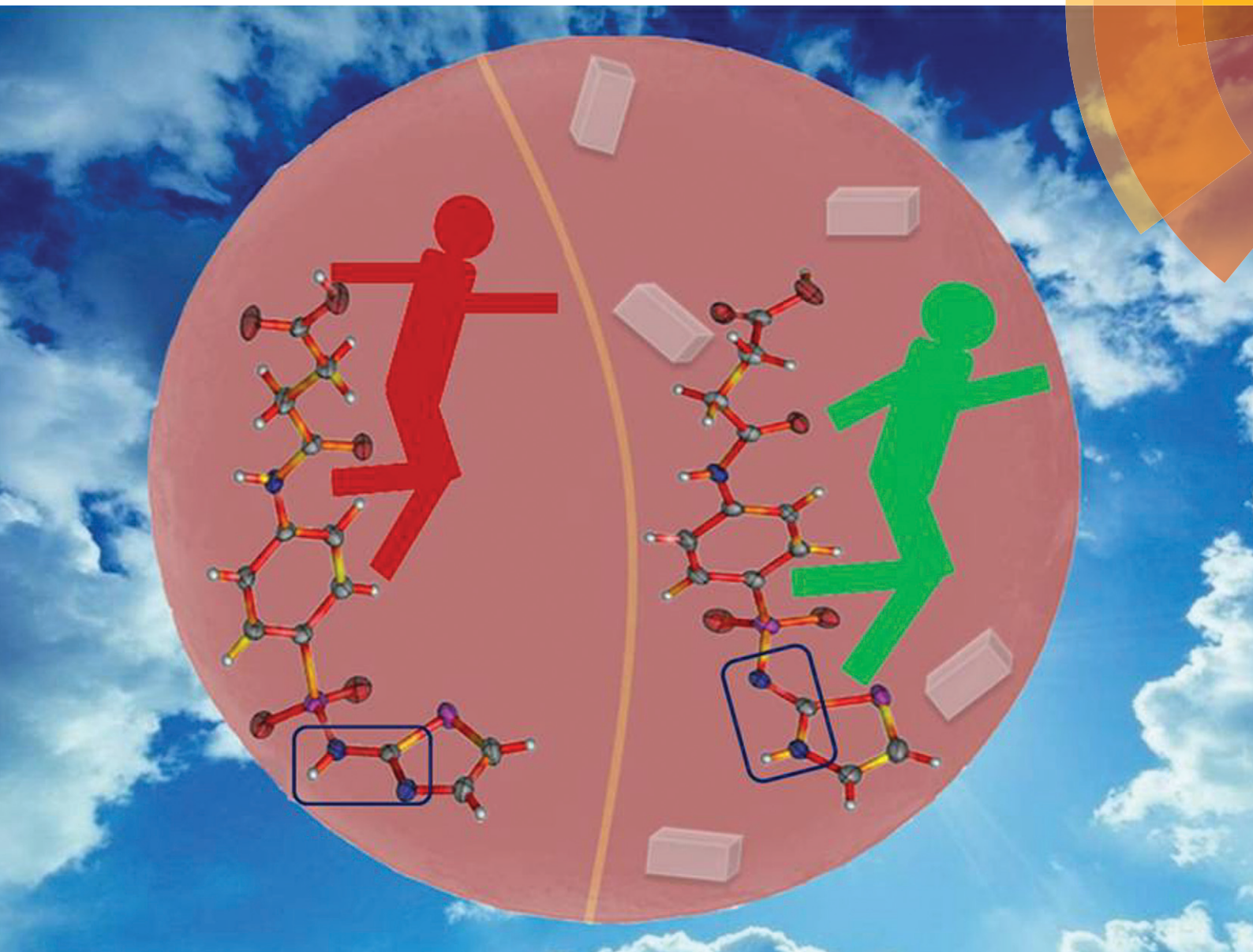


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## PAPER

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Tautomeric preference in polymorphs and pseudopolymorphs of succinylsulfathiazole: fast evaporation screening and thermal studies

# Tautomeric preference in polymorphs and pseudopolymorphs of succinylsulfathiazole: fast evaporation screening and thermal studies†

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Succinylsulfathiazole (SST) is known to exist in seven different crystalline forms, namely two unsolvated polymorphic forms (SST-I, SST-II), a monohydrate (SST/H<sub>2</sub>O), dihydrate (SST/2H<sub>2</sub>O) and solvates of butanol (SST/But), pentanol (SST/Pnt) and dioxane (SST/Diox). Most of these forms have been characterised only by IR and PXRD, while the single crystal structures have been determined for SST/But, SST/Pnt, SST/H<sub>2</sub>O and SST/Diox solvates. Previous studies also noted a lack of reproducibility in preparation of these different forms. Here, we employed a fast evaporation (FE) crystallization method and identified two new solvates from acetone (SST/AcMe) and tetrahydrofuran (SST/THF), as well as determined the single crystal structures for SST-I, SST-II, SST/AcMe and SST/THF. This revealed that SST exclusively adopts the *imidine* tautomeric form in all its solid form structures, but never the *amidine* form. The succinyl group of SST shows a conformational flexibility and adopts either *anti*- or *syn*-geometry to facilitate hydrogen bonding in the different structures. The study also allowed us to rationalize the hydrogen bonding preferences of various functional groups in all the forms. Notably the neat grinding and liquid assisted grinding methods resulted in only SST/H<sub>2</sub>O from various solvents, while the FE method produced polymorphs or pseudopolymorphs from different solvents.

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Succinylsulfathiazole (SST), also known as sulfasuxidine, is a sulfonamide drug and classified as an ultra long acting drug. According to BCS<sup>1</sup> it belongs to either the class II or class IV drug molecules.<sup>2</sup> SST is used for the prevention and treatment of gastrointestinal infections. This drug has solubility problems and shows unfavourable absorption.<sup>3,4</sup> According to Moustafa *et al.*,<sup>5</sup> aqueous suspensions of succinylsulfathiazole exhibit physical instability which causes caking, formation of cement-like precipitates and difficult resuspendability. Hence, SST has been a topic of interest to solid-state pharmaceutical chemists since the 1940s and many attempts have been made to identify its alternative solid forms with superior properties. SST is known to exist in several solid forms, I–VI, as named in previous studies, along with an amorphous form.<sup>5</sup> Among them, reportedly, forms I and IV are true polymorphs, forms II and III contain two and one moles of water, respectively, form V contains one mole of butanol and form VI contains one mole of pentanol.<sup>5a</sup> In due course the single crystal structures of the monohydrate and

solvates, butanol, pentanol along with a new form 1,4-dioxan were reported,<sup>6</sup> while the rest have been characterized only by IR and powder XRD. The lack of reproducibility in the preparation and confusion over the solvent ratios, as noted in some previous studies, makes the structural determination of these forms significant.<sup>5</sup> As the naming of the forms (forms I–VI) in previous studies was also somewhat inconsistent, here we rename them as SST/H<sub>2</sub>O (monohydrate), SST/2H<sub>2</sub>O (dihydrate), SST/AcMe (acetone), SST/THF (tetrahydrofuran), SST/But (butanol), SST/Pnt (pentanol), SST/Diox (dioxane) and the true polymorphs of SST, SST-I and SST-II.

This study has also allowed us to examine the tautomerism and hydrogen bonding preferences in the SST solid forms and their selective preparation by using the fast evaporation (FE) method, which we have exploited recently in the context of polymorphs and co-crystal screening.<sup>7</sup> The solid forms of succinylsulfathiazole have been characterized by powder and single crystal X-ray diffraction techniques, FTIR, differential scanning calorimetry and thermogravimetric analysis.

## 1. Experimental section

### Materials

Succinylsulfathiazole drug (monohydrate form) was purchased from Sigma-Aldrich. Commercially available solvents were used as received without further purification.

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### Fast evaporation method

A sufficient amount of SST was dissolved in various boiling solvents, taken in separate conical flasks. The solutions were filtered into round bottom flasks (rbf) and warmed once again gently to achieve dilute and clear solutions with no solid particles, thus to prevent self-seeding of the original form.<sup>6</sup> The clear solutions in the rbf were dried rapidly using a rotovapor by setting an appropriate reduced pressure, water bath temperature (50 °C) and revolution speed of the rbf (130 rpm). Upon the completion of the solvent evaporation, a continuous vacuum was applied, in order to reach the minimum possible pressure, (9–10 mbar) and held there for about 5 min before collecting the dry solids for characterization. As the solvates can convert to other forms over time, the characterization was done immediately after their preparation without much delay. The phase purity of the solids was established by DSC and comparing the experimental PXRD patterns with those calculated from the corresponding single crystal data (Fig. S3†). IR spectroscopy was also performed using the same batches of samples (Fig. S1†).

### Single crystal preparation

Succinylsulfathiazole drug was dissolved in the boiling solvents acetonitrile (MeCN), ethyl acetate (EA), water (H<sub>2</sub>O), acetone (AcMe) or tetrahydrofuran (THF). The resulting clear solutions were boiled for 10 min before being filtered into a fresh conical flask. The filtrate was left to evaporate slowly at ambient conditions. Single crystals suitable for X-ray diffraction studies were obtained in 4–6 days.

### Powder X-ray diffraction (PXRD)

The PXRD patterns were collected on a Rigaku SmartLab with Cu K $\alpha$  radiation ( $\lambda = 1.540 \text{ \AA}$ ). The tube voltage and amperage were set at 40 kV and 50 mA, respectively. Each sample was scanned between 5 and 70° 2 $\theta$  with a step size of 0.02°. The instrument was previously calibrated using a silicon standard.

### Crystallography

Crystals of the SST forms were individually mounted on a glass pip. Intensity data were collected on a Bruker's KAPPA APEX II CCD Duo system with graphite-monochromatic Mo K $\alpha$  radiation ( $\lambda = 0.71073 \text{ \AA}$ ). All the data were collected at 100 K. Data reduction was performed using Bruker SAINT software.<sup>8a</sup> The crystal structures were solved by direct methods using SHELXL-97 and refined by full-matrix least-squares on  $F^2$  with anisotropic displacement parameters for non-H atoms using SHELXL-97.<sup>8b</sup> Hydrogen atoms associated with carbon atoms were fixed in geometrically constrained positions. Hydrogen atoms associated with oxygen and nitrogen atoms were included in the located positions. Structure graphics shown in the figures were created using the X-Seed software package version 2.0.<sup>9</sup>

### Differential scanning calorimetry (DSC)

DSC was conducted on a Mettler-Toledo DSC1 STAR<sup>c</sup> instrument. Accurately weighed samples (2–3 mg) were placed in hermetically sealed aluminium crucibles (40  $\mu\text{L}$ ) and scanned from 30 to 300 °C at a heating rate of 5 °C min<sup>-1</sup> under a dry nitrogen atmosphere (flow rate 80 mL min<sup>-1</sup>). The data were analyzed using STAR<sup>c</sup> software.

### Thermogravimetric analysis (TGA)

TGA was performed on a Mettler-Toledo TGA/SDTA 851<sup>c</sup> instrument. Approximately 10–15 mg of the sample was added to an aluminium crucible and heated from 30 to 500 °C at a rate of 10 °C min<sup>-1</sup> under continuous nitrogen purging.

### IR spectroscopy

Transmission infrared spectra of the solids were obtained using a Fourier-transform infrared spectrometer (PerkinElmer 502). KBr samples (2 mg in 20 mg of KBr) were prepared and 6 scans were collected at 4 cm<sup>-1</sup> resolution for each sample. The spectra were measured over the range of 4000–400 cm<sup>-1</sup>.

### Computational details

Geometry optimization of the SST tautomers was performed with Gaussian 03<sup>10</sup> using the B3LYP method<sup>11</sup> with the 6-31G(d) basis set,<sup>12</sup> followed by single point energy calculations at the 6-311++G(2df, 2p) level, in a density functional theory (DFT) type calculation. The initial atomic coordinates for the molecules were always taken from the crystal structures.

## 2. Results and discussion

### Screening by fast evaporation technique

Fast evaporation method was employed to conduct a screening for identifying possible new solid forms and to prepare all the known forms of SST from suitable solvents (Table S2†). In our recent reports we established the efficiency of the FE method for screening of co-crystals, co-crystal polymorphs<sup>7a</sup> and single component polymorphic systems.<sup>7b</sup> Here our reinvestigation of the old drug, succinylsulfathiazole, allowed us to test the utility of the FE method for identification and preparation of the API solvates (Table 1). Characterization of FE products by PXRD, IR spectroscopy, DSC and TGA confirmed the formation of pure solids of previously known polymorphic forms, SST-I and SST-II, a monohydrate and two new solvates, SST/AcMe and SST/THF.

Commercial SST sample contained the monohydrate form (SST/H<sub>2</sub>O). The FE product obtained from water had a mixture of two hydrated forms (Fig. S2a†) and also a possible unidentified form (in the PXRD two new peaks were observed at 27° and 29° which did not match with any known form). The PXRD pattern of SST/2H<sub>2</sub>O obtained by a slow evaporation method showed a good agreement with the previously identified dihydrate form (Fig. S2a†). As reported in previous studies SST formed cake like particles in water.<sup>13</sup> Despite several



**Table 1** A comparison table of the present and previous crystallization studies employed for preparing various solid forms of succinylsulfathiazole

Previous study		Present study		
Slow evaporation		Fast evaporation		
Used condition	Resulted form	Used condition	Used condition	Resulted form
Evaporation of AcMe solution to dryness on a water bath —	Polymorph I (earlier name, form I) <b>SST/AcMe</b> (new)	Slow evaporation from MeCN at r.t. Slow evaporation from AcMe at r.t.	50 °C, 130 r.p.m., 250 mbar from EA solvent 50 °C, 130 r.p.m., 400 mbar from AcMe solvent	Polymorph I <b>SST/AcMe</b> (new)
Suspension of any of the other crystal forms in water Crystallization from H <sub>2</sub> O, MeOH or EtOH (or) precipitation from a solution in NaOH by the addition of HCl	<b>SST/2H<sub>2</sub>O</b> (earlier name, form II) <b>SST/H<sub>2</sub>O</b> (earlier name, form III)	— Crystallized from H <sub>2</sub> O, MeOH or EtOH	50 °C, 130 r.p.m., 30 mbar from H <sub>2</sub> O solvent 50 °C, 130 r.p.m., 300 mbar from MeOH solvent	Mixture of <b>SST/H<sub>2</sub>O</b> and <b>SST/2H<sub>2</sub>O</b> <b>SST/H<sub>2</sub>O</b>
Evaporate on a water bath of a AcMe solution until the first crystals separated, followed by evaporation at r.t. —	Polymorph II (earlier name, form IV) <b>SST/THF</b> (new)	Slow evaporation from EA at r.t. Slow evaporation from THF at r.t.	50 °C, 130 r.p.m., 250 mbar from EtOH solvent 50 °C, 130 r.p.m., 250 mbar from THF solvent	Polymorph II <b>SST/THF</b> (new)
Slow evaporation from <i>n</i> -butanol	<b>SST/But</b> (earlier name form V)	—	—	—
Slow evaporation from <i>n</i> -pentanol	<b>SST/Pnt</b> (earlier name form VI)	—	—	—

attempts, we could not obtain single crystals suitable for SCXRD. It was also observed that all the forms of SST converted to SST/H<sub>2</sub>O on long exposure to the atmosphere (Fig. S4†), but not to SST/2H<sub>2</sub>O which is contrary to findings in previous reports. However, SST-II converted to SST/2H<sub>2</sub>O powder.

In the case of polymorphs, the solvent used was different for the slow and fast evaporation methods. The single crystals of SST-I and SST-II were obtained from MeCN and EA, respectively, by slow evaporation but for the same, EA and EtOH were used in the FE method. In case of the solvates, the same solvent was used for both slow and fast evaporation methods. The FE product from MeCN, a mixture of MeCN–MeOH, and MeOH resulted in only SST/H<sub>2</sub>O (Fig. S3b†). The two new solvate forms, SST/AcMe and SST/THF (see Fig. S1†), obtained by the FE method, could not be prepared by the liquid assisted grinding (LAG) method (Fig. S5†). LAG<sup>14</sup> always resulted in SST/H<sub>2</sub>O. Probably, the intake of moisture during the LAG promoted the exclusive formation of SST/H<sub>2</sub>O. The results of the FE method suggest that a closed environment and faster kinetics during the evaporation of the solvent probably helped to prevent water intake, thus resulting in the solvates, instead of hydrates. This study proves the unique advantage of the FE method for quick screening of solvates. Hence the FE method, which is complementary to the existing screening techniques, has potential to become a regular screening tool in solid state pharmaceutical laboratories.

### Crystal structure analysis

Single crystal structures were determined for the two polymorphic forms, SST-I and SST-II, and two solvates, SST/AcMe

and SST/THF. The structure of the monohydrate (SST/H<sub>2</sub>O) is a redetermination. Crystallographic data are listed in Table 2.

A hydrogen bond table (Table S1†) and the ORTEP diagrams (Fig. S6–S10†) for all the solid forms are included in the ESI.† Examination of all the structures revealed a tautomeric preference in the polymorphs and pseudopolymorphs where the SST molecule adopts the *imidine* tautomeric form. The structure determination also allowed us to study the hydrogen bonding or synthon<sup>15</sup> competition among various functional groups in the different forms.

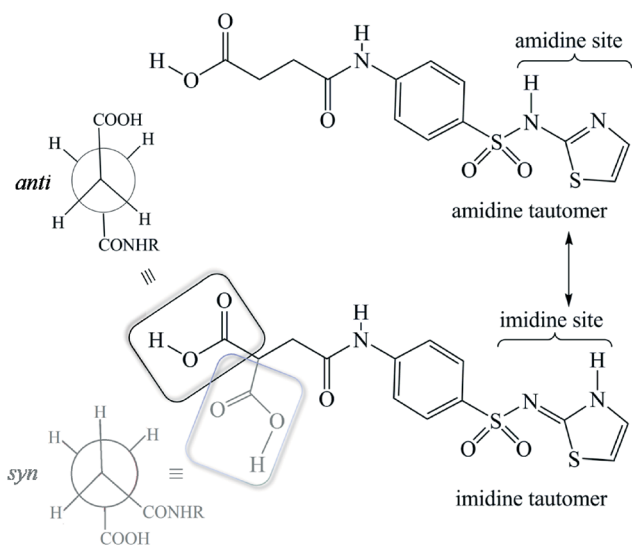
### Polymorph-I (SST-I)

SST-I crystallizes in the triclinic *P* $\bar{1}$  space group with two molecules in the asymmetric unit. Both the SST molecules adopt an L-shape conformation and exist in the *imidine* tautomeric form. Tautomerism, a common phenomenon in sulphonamide drugs,<sup>16–20</sup> occurs *via* transfer of the proton from sulfonamide NH to the thiazole ring N as shown in Scheme 1. Notably, –CH<sub>2</sub>–CH<sub>2</sub>– of succinyl group in both the SST molecules adopts the *anti* geometry (Fig. 1). Two independent SST molecules interact *via* two separate O–H⋯O hydrogen bonds by involving the hydroxyl of CO<sub>2</sub>H and SO<sub>2</sub> groups by synthon 1 (see Scheme 2; O(6)–H(6A)⋯O(9); *d*/Å, *θ*/°: 1.9 Å, 160° and O(2)–H(2C)⋯O(4): 1.97 Å, 155°) to form linear chains which are further connected by (amide)<sub>N</sub>–H⋯O=C(carboxyl) hydrogen bonds *via* synthon 2 (Scheme 2; N(4)–H(4)⋯O(1)=C(1): 2.09 Å, 160° and N(1)–H(1)⋯O(7)=C(14): 2.04 Å, 174°) leading to a ladder type network (Fig. 1b). Adjacent ladders arranged in an antiparallel fashion are connected *via* (imidine)<sub>N</sub>–H⋯O=C(amide) hydrogen bonds. Because of the L-shape conformation of SST molecules, the thiazole rings lie nearly perpendicular to the direction of the ladder network.



**Table 2** Crystallographic data and structure refinement parameters of different forms of SST

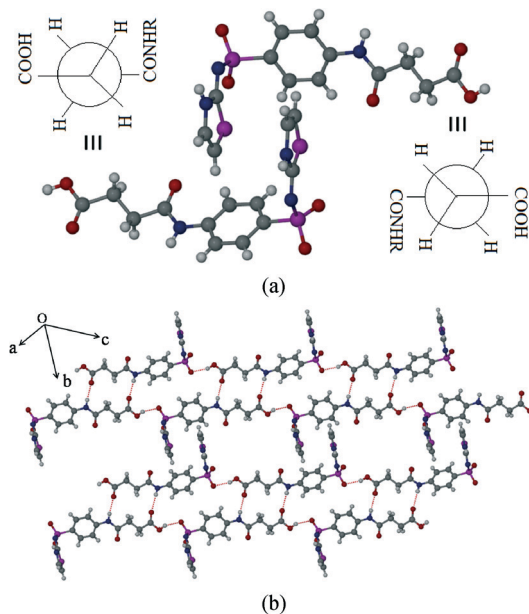
	SST-I	SST-II	SST/H <sub>2</sub> O	SST/AcMe	SST/THF
Chemical formula	C <sub>13</sub> H <sub>13</sub> N <sub>3</sub> O <sub>5</sub> S <sub>2</sub>	C <sub>13</sub> H <sub>13</sub> N <sub>3</sub> O <sub>5</sub> S <sub>2</sub>	C <sub>13</sub> H <sub>13</sub> N <sub>3</sub> O <sub>5</sub> S <sub>2</sub> , H <sub>2</sub> O	2(C <sub>13</sub> H <sub>13</sub> N <sub>3</sub> O <sub>5</sub> S <sub>2</sub> ), C <sub>3</sub> H <sub>6</sub> O	2(C <sub>13</sub> H <sub>13</sub> N <sub>3</sub> O <sub>5</sub> S <sub>2</sub> ), C <sub>4</sub> H <sub>8</sub> O
Formula weight	355.38	355.38	373.40	768.85	782.87
Cryst sys	Triclinic	Monoclinic	Monoclinic	Triclinic	Triclinic
Space group	<i>P</i> $\bar{1}$	<i>P</i> 2 <sub>1</sub> / <i>c</i>	<i>P</i> 2 <sub>1</sub> / <i>c</i>	<i>P</i> $\bar{1}$	<i>P</i> $\bar{1}$
<i>a</i> (Å)	8.8478(4)	11.351(3)	16.190(6)	8.5229(4)	8.7032(2)
<i>b</i> (Å)	13.3523(6)	8.577(2)	5.1460(14)	14.5887(7)	14.5604(5)
<i>c</i> (Å)	14.1584(6)	16.684(3)	19.449(7)	15.2327(7)	15.5676(5)
$\alpha$ (°)	67.9870(10)	90	90	64.7770(10)	64.602(2)
$\beta$ (°)	77.1140(10)	107.483(5)	94.028(17)	78.1610(10)	77.240(2)
$\gamma$ (°)	74.6120(10)	90	90	82.0860(10)	83.635(2)
Vol (Å <sup>3</sup> )	1480.77(11)	1549.4(6)	1616.4(9)	1674.27(14)	1737.79(9)
<i>D</i> <sub>calcd</sub> (g cm <sup>-3</sup> )	1.594	1.523	1.534	1.525	1.496
$\mu$ (mm <sup>-1</sup> )	0.390	0.373	0.365	0.353	0.342
$\theta$ range (°)	1.57–27.00	1.88–27.00	1.26–26.50	1.50–25.14	1.48–26.96
<i>Z</i>	4	4	4	2	2
Range <i>h</i>	–11 to +11	–14 to +14	–20 to +19	–10 to +10	–11 to +11
Range <i>k</i>	–17 to +17	–10 to +10	–6 to +6	–17 to +17	–18 to +17
Range <i>l</i>	–18 to +13	–21 to +11	–24 to +24	–18 to +17	–19 to +17
Reflns collected	25 736	14 705	13 143	24 403	27 707
Independent reflns	6458	3370	3322	5957	7527
Obsd reflns	5701	2241	2672	5375	5176
<i>T</i> (K)	100	100	100	100	100
<i>R</i> <sub>1</sub>	0.0344	0.0428	0.0391	0.0718	0.0440
<i>wR</i> <sub>2</sub>	0.1132	0.1170	0.1016	0.1465	0.1250
GOF	0.873	0.895	1.018	1.044	0.882
CCDC no.	943847	943848	943849	943850	943851

**Scheme 1** Schematic representation of the tautomerism and conformational flexibility in succinylsulfamethazole (SST). Notice the alternate conformations, *anti* (black) or *syn* (grey) geometries, which can be adopted by the succinyl group.

These thiazole rings from adjacent antiparallel ladders close pack as shown in Fig. 1a.

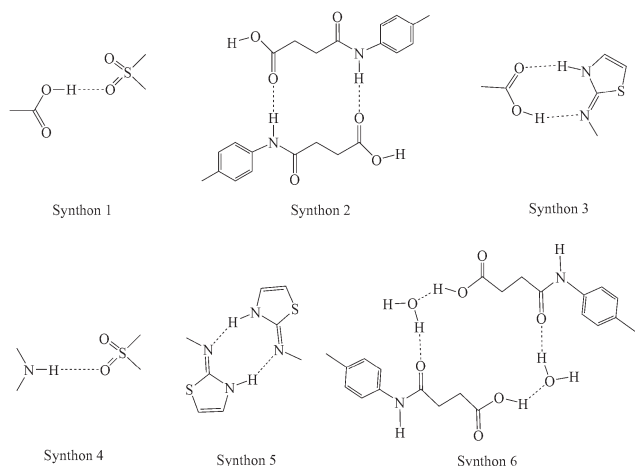
### Polymorph-II (SST-II)

SST-II crystallizes in the monoclinic *P*2<sub>1</sub>/*c* space group with one molecule in the asymmetric unit. The *head-to-tail* interaction by *imidine* and the carboxylic acid groups (N3–H3···O1, 1.96 Å, 174°; O2–H2C···N2, 1.94 Å, 166°) of the adjacent SST

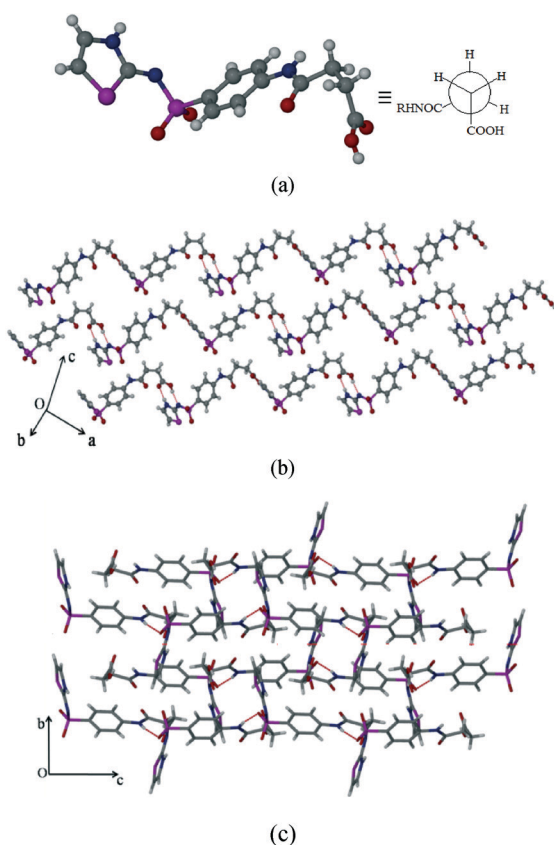
**Fig. 1** Polymorph I of succinylsulfathiazole (SST-I). (a) L-shape molecular geometry of two independent SST molecules with the *anti* –CH<sub>2</sub>–CH<sub>2</sub>– conformation. (b) Ladders formed by the combination of synthons 1 and 2 (see Scheme 2).

molecules *via* a heterodimer, synthon 3, forms wave like chains (Fig. 2b). Interestingly, the formation of the heterodimer is facilitated by the S-shape conformation of SST molecules due to the *syn* geometry of the –CH<sub>2</sub>–CH<sub>2</sub>– group. The parallel wave like chains are orthogonally connected by (sulfonamide)N–H···O(sulfoxy) hydrogen bonds *via* synthon 4





**Scheme 2** Synthons observed in the SST polymorphs, hydrate and solvates.



**Fig. 2** Polymorph II of SST (SST-II). (a) *Syn* geometry of the SST at the  $-\text{CH}_2-\text{CH}_2-$  group. (b) Formation of wave like chains. (c) Interlocked 3D packing viewed along the  $a$ -axis.

( $\text{N}(1)-\text{H}(1)\cdots\text{O}(5)$ ;  $2.15 \text{ \AA}$ ,  $170^\circ$ ), leading to a 2D network. Thiazole rings of one 2D layer fill the voids in another adjacent layer resulting in interdigitation.

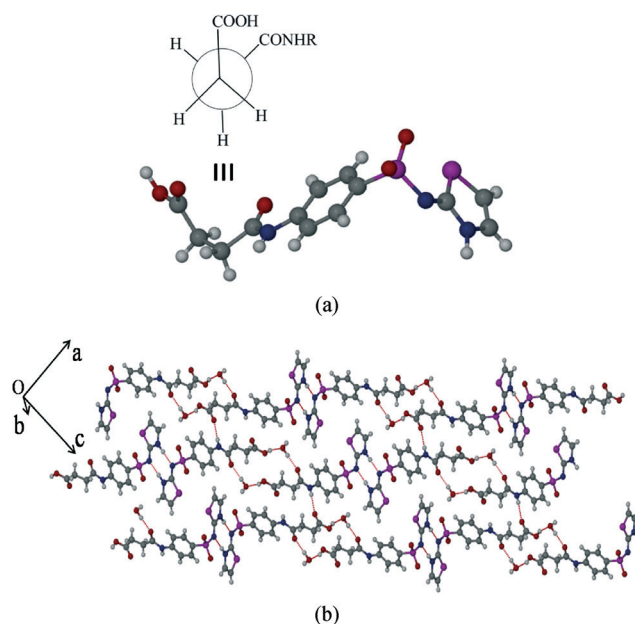
### Succinylsulfathiazole/monohydrate (SST/ $\text{H}_2\text{O}$ )

The hydrated form of SST crystallizes in the monoclinic  $P2_1/c$  space group with one molecule of SST and a water molecule

in the asymmetric unit. SST is in the *syn* or S-type conformation. Here the *imidine* sites of SST molecules primarily form a centrosymmetric homodimer by  $\text{N}-\text{H}\cdots\text{N}$  hydrogen bonds *via* synthon 5 ( $\text{N}(3)-\text{H}(3)\cdots\text{N}(2)$ :  $1.8 \text{ \AA}$ ,  $166^\circ$ ). The water molecules bridge the  $-\text{CO}_2\text{H}$  and amide carbonyl  $\text{O}-$  atom *via* synthon 6 ( $\text{O}(1)-\text{H}(1\text{A})\cdots\text{O}(6)$ :  $1.74 \text{ \AA}$ ,  $158^\circ$  and  $\text{O}(6)-\text{H}(6\text{A})\cdots\text{O}(3)$ :  $1.84 \text{ \AA}$ ,  $174^\circ$ ) as shown in Fig. 3b. The second proton of the water is linked to the sulfoxy group of the next layer, thus the strong hydrogen bonds are extended in all three dimensions.

### Succinylsulfathiazole/acetone solvate (SST/AcMe)

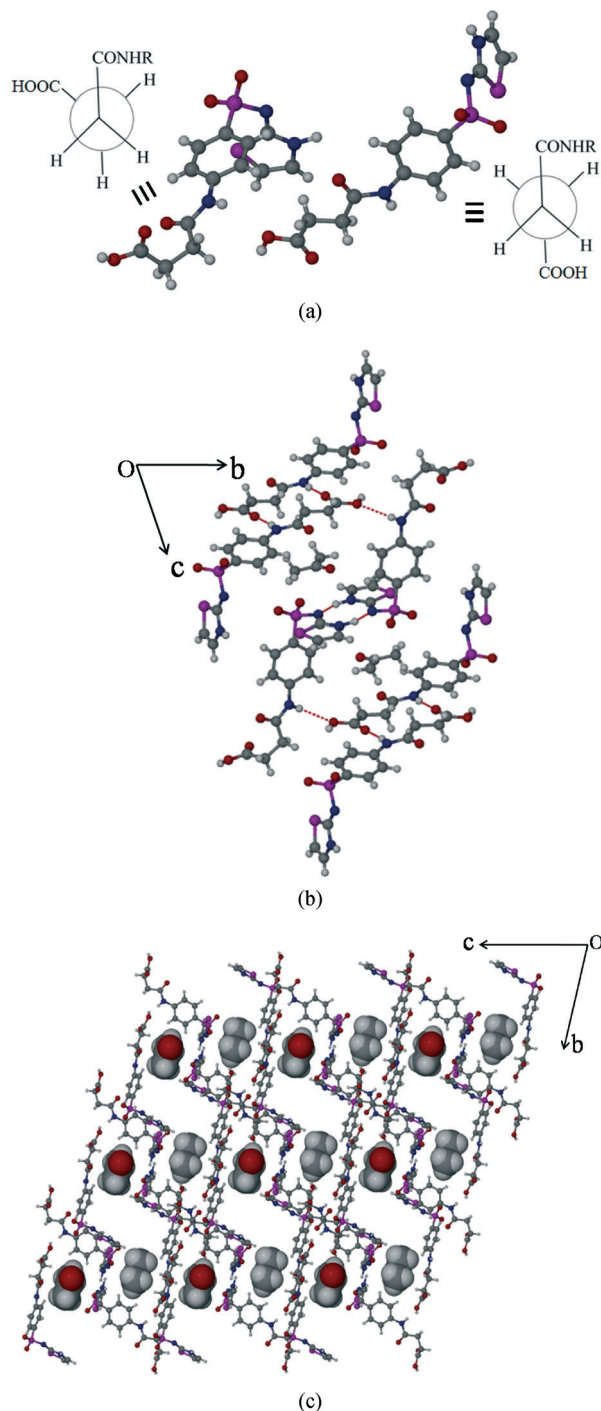
The SST/AcMe solvate crystallizes in the monoclinic  $P\bar{1}$  space group with two molecules of SST and one molecule of AcMe in the asymmetric unit. Interestingly, in this structure the two independent SST molecules adopt different conformations at the succinyl group; the first SST molecule is in the *anti* (L-shape) geometry whereas the second is in the *syn* (S-shape) geometry. Hence, both the conformational variants of SST are simultaneously seen in this structure. The SST molecules of the same symmetry form synthon 5 homodimers involving their *imidine* sites *via*  $\text{N}-\text{H}\cdots\text{N}$  hydrogen bonds ( $\text{N}(3)-\text{H}(3)\cdots\text{N}(2)$ :  $2.0 \text{ \AA}$ ,  $176^\circ$  and  $\text{N}(6)-\text{H}(6)\cdots\text{N}(5)$ :  $1.77 \text{ \AA}$ ,  $154^\circ$ ). The two different conformers facilitate the carboxylic acid groups to form different synthons. Two linear SST molecules are connected through  $(\text{amide})\text{N}-\text{H}\cdots\text{O}=\text{C}(\text{acid})$  hydrogen bonds, in an antiparallel fashion, *via* synthon 2 ( $\text{N}(1)-\text{H}(1\text{A})\cdots\text{O}(2)=\text{C}(1)$ :  $2.1 \text{ \AA}$ ,  $171^\circ$ ). The leftover OH group of the acid is linked to the amide  $\text{C}=\text{O}$  of the bent SST conformers. Whereas the acid OH of the bent



**Fig. 3** SST/monohydrate (SST/ $\text{H}_2\text{O}$ ). (a) *Syn* geometry adopted at  $-\text{CH}_2-\text{CH}_2-$  group of SST. (b) Packing of two adjacent chains, showing the interactions formed by bridging water molecules between two SST molecules.



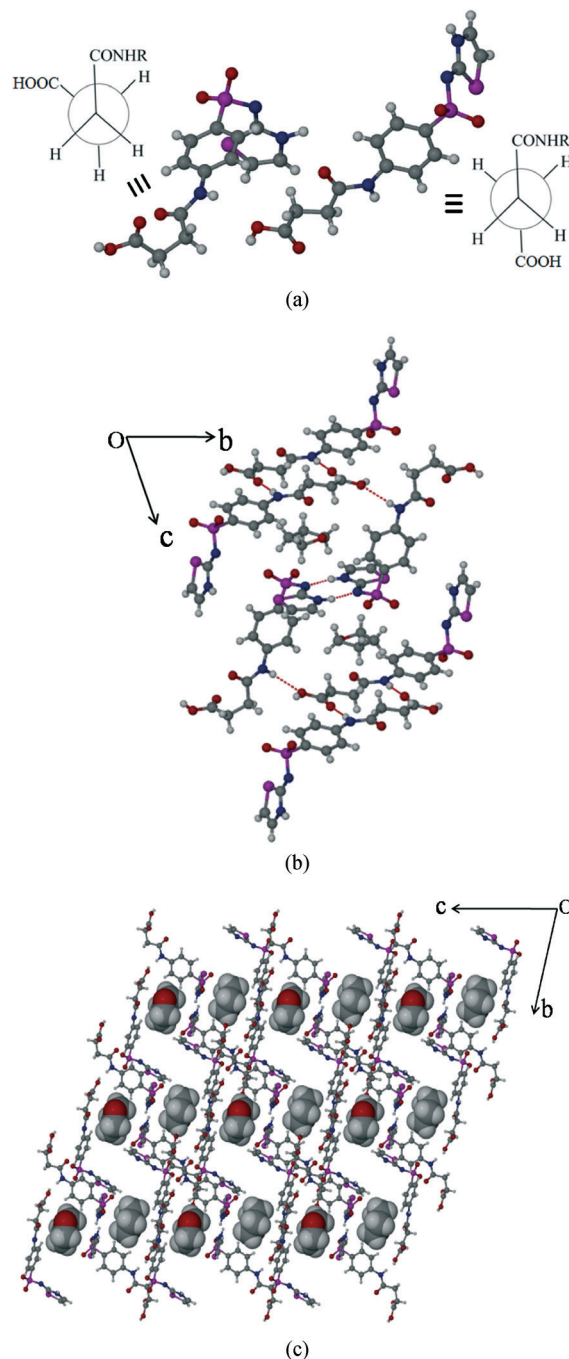
SST molecule is linked to the amide C=O of the linear SST to complete the loop by O–H...O [O(1)–H(1)...O(8): 1.9 Å, 159° and O(6)–H(6B)...O(3): 2.07 Å, 136°]. The solvent AcMe molecules are linked to the two S-shape SST dimers *via* bifurcated C–H...O interactions, and occupy channels formed by the host molecules along the *a*-axis (Fig. 4b).



**Fig. 4** Packing of SST/AcMe solvate. (a) *Syn* and *anti* geometries of two independent SST molecules at  $-\text{CH}_2-\text{CH}_2-$ . (b) Crystal packing showing the different types of interactions present in the structure. (c) Occupation of solvent molecules, AcMe, in channels formed by host SST molecules.

### Succinylsulfathiazole/tetrahydrofuran solvate (SST/THF)

SST/THF also crystallizes in the triclinic  $P\bar{1}$  space group with two molecules of SST and one molecule of THF in the asymmetric unit. Indeed, this is isostructural<sup>16</sup> to SST/AcMe, hence the synthons formed are the same, except some minor differences in the solvent THF interactions with the neighbouring molecules (Fig. 5b).



**Fig. 5** Packing of SST/THF solvate. (a) *Syn* and *anti* geometries of two independent SST molecules at  $-\text{CH}_2-\text{CH}_2-$ . (b) Crystal packing showing the different types of interactions present in the structure. (c) Occupation of solvent molecules, THF, in channels formed by host SST molecules.



### Tautomeric preference: density functional theory calculations

Both tautomerism and polymorphism are common phenomena in sulfonamide drugs.<sup>17–21</sup> In this series of succinyl-sulfathiazole polymorphs and pseudopolymorphs, the API exists only in the *imidine* tautomeric form, in that the proton transfer occurs from the sulphonamide N-atom to the thiazole N-atom (Scheme 1). Hence, the *amidine* tautomeric form of SST is not seen in any of the structures, including in the earlier reported solvates of butanol and pentanol.<sup>6</sup> A search in the Cambridge Structural Database (CSD) (V 5.34) for sulfonamide drugs, with at least >3 hits (exclusively) of the *imidine* tautomeric form, revealed that such a preference is present only in two other cases, sulfathiazole and sulfapyridine (Scheme S1†). To rationalize the tautomeric preference in the solid forms of SST, we performed DFT calculations using Gaussian software. In all cases, the molecules were taken from their corresponding crystal structures and a geometry optimization was performed, before proceeding to the single point energy calculations. The calculated energy difference between the *amidine* and corresponding *imidine* tautomeric forms revealed that the *imidine* tautomeric form is more stable than the *amidine* tautomeric form by 0.1816 kcal mol<sup>−1</sup>, which is consistent with the observed tautomeric preference of the former. It is to be noted that this energy difference between the two tautomeric forms corresponds to the isolated gaseous state molecules, but in the crystalline environment, with stabilizing hydrogen bonds, the difference could increase further to promote the *imidine* form. A more detailed computational study may unravel the fundamental reasons behind the *imidine* tautomeric preference in the solid forms of SST and other sulphonamide drugs.

### Thermal properties of the SST solid forms

The thermal behaviour of all the polymorphs and pseudopolymorphs of SST, were studied by DSC and TGA experiments (Fig. 6 and 7). The DSC thermograms for SST-I and SST-II show a single endothermic transition peak each at 207.6 °C and 192.5 °C, respectively, corresponding to melting. The DSC thermogram of SST/H<sub>2</sub>O showed two endotherms; a minor peak at 148.33 °C, corresponding to the loss of a water molecule, and a major peak at 193.02 °C, corresponding to melting. The two solvates, SST/AcMe and SST/THF, also showed two endotherms each. Major endotherms corresponding to melting were observed at 191.7 °C and 189.5 °C for the SST/AcMe and SST/THF solvates, respectively, while minor endotherms appeared at 169.08 °C (for the loss of AcMe) and 173.94 °C (for the loss of THF). The analyses of the DSC results suggest that SST-I is thermodynamically more stable compared to all the other forms.

The TGA experiments of the two polymorphic forms showed a single weight loss associated with decomposition after melting. In the case of hydrate and solvates, two weight losses were observed. For the SST monohydrate, the first small endotherm corresponding to loss of water (~4.99% of

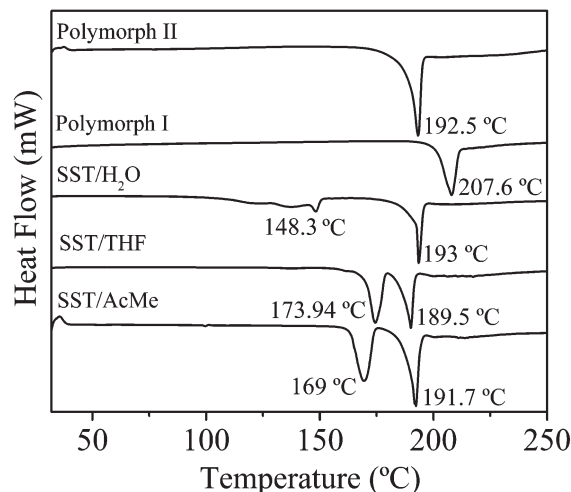


Fig. 6 Differential scanning calorimetry plots of different forms of SST.

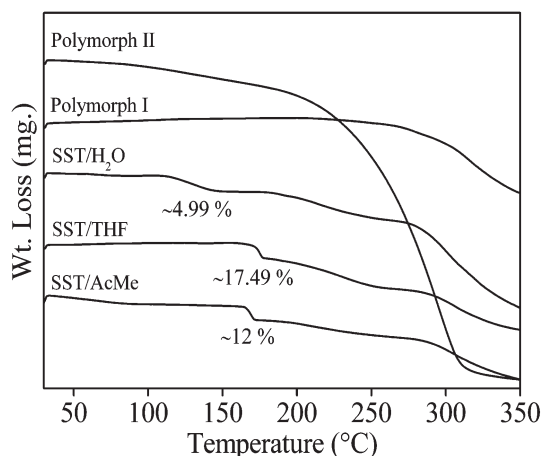


Fig. 7 Thermogravimetric analysis plots of different forms of SST.

the total weight) matched approximately to one mol of water. The slurry product of SST/H<sub>2</sub>O in water also showed a similar weight loss (4.82%), suggesting that there is no conversion of SST/H<sub>2</sub>O to SST/2H<sub>2</sub>O. The weight loss of the solid obtained from the slow evaporation method is (9.12%), equivalent to two moles of water (Fig. S2b†). For the SST/THF and SST/AcMe solvates, the first broad weight loss corresponding to the loss of solvent molecules (~17.49% and ~12.0% of the total weight, respectively) is equivalent to one mol of THF and AcMe, respectively.

### Synthon competition study

SST has a total of three strong hydrogen bond donors, from its acid (–OH), amide (–NH) and *imidine* (–NH) groups, and five strong acceptors, namely from its acid (C=O), amide (C=O), SO<sub>2</sub> (two S=O) and *imidine* (N-atom) groups. Hence, there is an imbalance of acceptors and donors, which can potentially lead to multiple solid forms. Analysis of the synthons formed in the current and previously reported SST/But, SST/Pnt and SST/H<sub>2</sub>O suggests the following. The



most popular interaction is synthon 5, a homodimer between the *imidine* groups, which is observed in all of the five solvates (or pseudopolymorphs), but absent in both the polymorphs. The second most popular is synthon 2, which is formed between the acid (C=O) and amide (NH) groups when there is at least one SST conformer in the anti geometry. As can be expected, the most dominating groups are the *imidine* site and the carboxylic acid group. But synthon 3, formed between these two groups, is observed only once in SST-II. The remaining synthons 1, 4 and 6, which are seen occasionally, involve the less effective SO<sub>2</sub> and amide (C=O/NH) groups. However, notably, the most stable form, SST-I, with synthon 1 and 2, and anti geometry at the -CH<sub>2</sub>-CH<sub>2</sub>- groups, has the highest density of crystal packing. The balance among the large number of competing functional groups in a conformationally flexible molecule can easily be influenced by different solvent conditions. Hence the formation of several solid forms of SST is in line with general observations in the solid state pharmaceutical chemistry and crystal engineering.

## Conclusions

Screening of succinylsulfathiazole by a fast evaporation (FE) method for possible new solid forms and to prepare all the known forms of SST from various solvents, demonstrated the efficiency of the technique for the identification and preparation of API solvates. Two new solvate forms, SST/AcMe and SST/THF were identified successfully by the FE method, which could not be obtained by the liquid assisted grinding (LAG) method. Probably, the intake of moisture during the LAG promotes the exclusive formation of SST/H<sub>2</sub>O. Hence the study demonstrates the complementary nature of the FE method to existing screening techniques and its potential to become a good screening tool in solid state pharmaceutical laboratories. In contrast to previous studies, we observed that the SST/H<sub>2</sub>O is more stable under ambient conditions than SST/2H<sub>2</sub>O. The DSC study revealed that SST-I is thermodynamically the more stable form compared to any other form. In this study, all the solid forms of SST were seen exclusively in the *imidine* form which was rationalized by performing DFT calculations. The energy difference between the two tautomeric forms is consistent with the *imidine* preference in the structures. Crystal structure analysis revealed that the homodimer formed by the *imidine* sites is the most popular synthon, which is observed in all of the SST solvates.

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