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4-Aminosalicylic Acid Adducts

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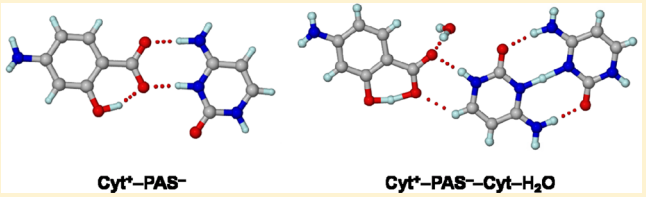
Supporting Information

ABSTRACT: 4-Aminosalicylic acid (*p*-aminosalicylic acid, PAS), an antituberculosis drug, is a model active pharmaceutical ingredient to study salt and cocrystal formation in a multiple hydrogen-bonding functionality molecule with carboxylic acid, amine, and phenol groups. A cytosine salt CYT^+-PAS^-, salt cocrystal hydrate $CYT^+-PAS^--CYT-H_2O$, and nicotinamide cocrystal hydrate $PAS-NAM-H_2O$, are described in this article. Furthermore, X-ray crystal structures of PAS sodium dihydrate, sulfate, and mesylate salts and dehydration/rehydration behavior of the sodium salt by powder X-ray diffraction are discussed.



INTRODUCTION

4-Aminosalicylic acid, commonly known as *p*-aminosalicylic acid (abbreviated as PAS, Figure 1), is a second-line drug used in the treatment of multidrug-resistant tuberculosis (MDR-TB)[1] and is on the World Health Organization Model List of Essential Medicines.[2] PAS was found to be also effective toward ulcerative colitis[3] and Crohn's disease,[4] but the more potent drug in these latter ailments is its isomer 5-aminosalicylic acid[4,5] (5-ASA, common name mesalazine or mesalamine, Figure 1). Both these aminosalicylic acids are amphoteric molecules, and surprisingly, there are no polymorphs reported for these classic drugs. Interestingly, PAS exists in an unionized state as 4-$NH_2C_6H_3(OH)COOH$, whereas 5-ASA is a zwitterion/inner salt 5-$NH_3^+C_6H_3(OH)COO^-$ in the crystal structure[6] (Figure 1). In buffer solutions, PAS is known to exist in different ionic states: (a) as a diprotic acid ($NH_3^+C_6H_3(OH)COOH$) below its pK_{a1} (= 1.79), (b) as a zwitterion ($NH_3^+C_6H_3(OH)COO^-$) at its isoelectric point (p*I* = 2.71), and (c) as a diprotic base ($NH_2C_6H_3(OH)COO^-$) above its pK_{a2} (= 3.63).[7] PAS decarboxylates to 3-aminophenol ($NH_2C_6H_4OH$) through the zwitterionic species[7] and also upon melting.[8]

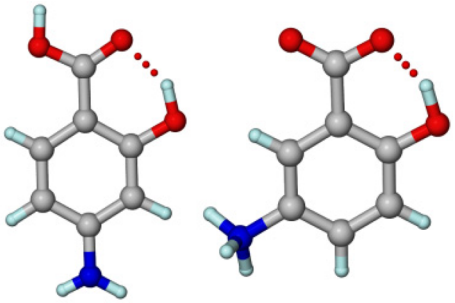


Figure 1. (a) 4-Aminosalicylic acid (PAS) exists in an unionized neutral form and (b) 5-aminosalicylic acid (5-ASA) is a zwitterion in the crystal structure. Intramolecular O–H···O hydrogen bond is present in both structures. The molecular structure of 4-ASA is extracted from the CSD (refcode AMSALA01).[6] The reported structure of 5-ASA (refcode SAQJAV) has no H atoms, and hence, its X-ray crystal structure was redetermined with 3D coordinates (.cif file is deposited to CCDC).

There is a renewed interest in the chemistry of *p*-aminosalicylic acid. It was recently shown that PAS inhibits dihydropteroate synthase in M. tuberculosis by acting as a replacement substrate and a prodrug that releases active forms by the enzymes that they eventually inactivate.[9] Cocrystals of PAS with pyrazinamide, isoniazid,[10] and sulfadimidine[11] are examples of drug–drug cocrystals, which can become multi-drug, fixed-dose formulations in the future. An amorphous form,[12] several salts (sodium,[8b] potassium, hydrochloride, sulfate, mesylate, ammonium, etc.),[13] molecular salts[14] (piperazinium, morpholinium), and a dioxane solvate[15] of PAS were reported by different groups, and among these, the ammonium salt is polymorphic.[16] However, crystal structures of many of these salts are not reported. Because of its rich functionalities (carboxylic acid, amine, and phenol), PAS could form a multitude of adducts[17] with coformers depending on the pK_a,[18] and thereby offer a better understanding of salt and cocrystal supramolecular assembly.[10,14b,18,19] Salts, cocrystals, and salt cocrystal hydrate of PAS with pyrdine coformers were

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Table 1. X-ray Crystallographic Parameters

adduct	$Na^+-PAS^--2H_2O$	$2PAS^+-SO_4^{2-}$	$PAS^+-CH_3SO_3^-$	Cyt^+-PAS^-	$Cyt^+-PAS^--Cyt-H_2O$	$PAS-NAM-H_2O$
empirical formula	$C_7H_{10}NNaO_5$	$C_{14}H_{16}N_2O_{10}S$	$C_8H_{11}NO_6S$	$C_{11}H_{12}N_4O_4$	$C_{15}H_{19}N_7O_6$	$C_{13}H_{15}N_3O_5$
formula weight	211.15	404.35	249.24	264.25	393.37	293.28
crystal system	monoclinic	orthorhombic	monoclinic	monoclinic	monoclinic	triclinic
space group	$P2_1/c$	$Pba2$	$P2_1/c$	$P2_1/c$	$P2_1/n$	$P\bar{1}$
Z^a	16	12	8	16	16	6
T (K)	298(2)	298(2)	298(2)	100(2)	298(2)	100(2)
a (Å)	8.790(4)	15.7940(16)	5.3525(5)	12.6069(17)	7.4285(6)	6.750(2)
b (Å)	14.615(7)	19.897(2)	17.8159(12)	13.6925(18)	22.0769(18)	7.060(2)
c (Å)	6.955(3)	5.5179(6)	11.0537(10)	14.595(2)	10.9219(10)	14.809(4)
α (deg)	90	90	90	90	90	95.977(4)
β (deg)	97.799(8)	90	99.057(8)	110.973(3)	101.461(9)	97.899(5)
γ (deg)	90	90	90	90	90	104.722(4)
VÅ^3	885.3(8)	1734.0(3)	1040.93(15)	2352.5(5)	1755.5(3)	668.9(3)
D_{calc} (g cm^{-3})	1.584	1.549	1.590	1.492	1.488	1.456
μ (mm^{-1})	0.174	0.246	0.325	0.116	0.118	0.114
reflns collected	9005	3402	4343	24058	6349	5351
unique reflns	1749	3402	2132	4667	2992	2206
observed reflns	1558	3244	1420	3233	1367	1653
R_1 [$I > 2\sigma(I)$]	0.0434	0.0443	0.0426	0.0856	0.0517	0.0400
wR_2 [all]	0.1015	0.1110	0.0982	0.1405	0.0664	0.0967
goodness-of-fit	1.103	1.135	0.968	1.142	0.851	1.040
diffractometer	Bruker Smart-Apex	Bruker Smart-Apex	Oxford Xcalibur Gemini	Bruker Smart-Apex	Oxford Xcalibur Gemini	Bruker Smart-Apex

$^aZ = Z''$ (no. of crystallographically nonequivalent molecules of any type in the asymmetric unit)[23] × no. of independent general positions of the space group.

recently reported by Goswami et al.[20] The absence of polymorphism in PAS encouraged us to carry out a solid form screen for a novel zwitterionic form[21] of PAS or a new polymorph. In this study, two cytosine adducts, CYT^+-PAS^- salt and $CYT^+-PAS^--CYT-H_2O$ salt cocrystal hydrate, and a nicotinamide cocrystal hydrate, $PAS-NAM-H_2O$, were obtained. X-ray crystal structures of the known sodium dihydrate PAS[8b] and its sulfate and mesylate[13] salts are added.

RESULTS AND DISCUSSION

Solid form screening of PAS to study its supramolecular solid form space gave salts and salt cocrystal and cocrystal. Attempts to obtain a zwitterionic form or a polymorph of PAS by different methods such as evaporative crystallization (solvents and temperatures), sublimation,[22] crystallization from aqueous HCl solutions of varying pH, exchange of counterions reaction to give a zwitterion (e.g., $NH_2C_6H_3(OH)COO^-$'C'$^+$ + $X^-NH_3^+C_6H_3(OH)COOH$ → $NH_3^+C_6H_3(OH)COO^-$ + 'C'$^+X^-$, where 'C' is a salt former such as cytosine), etc., were unsuccessful. All the crystallization attempts are summarized in the experimental section.

Sodium-4-aminosalicylate Dihydrate ($Na^+-PAS^--2H_2O$). When PAS was dissolved in NaOH solution and left for crystallization at ambient temperature, a dihydrate of the salt was obtained in the space group $P2_1/c$ (see X-ray crystallographic parameters in Table 1 and hydrogen bonds in Table S1, Supporting Information). The crystal structure is a coordination compound with the sodium (Na^I) residing in a six-coordinate twisted-octahedral geometry. The six ligand positions are occupied by three PAS molecules (through COO^-, OH, and NH_2 groups), one crystallographic unique water molecule, and two waters that are shared by a neighboring Na^I atom (Figure 2a). The sodium ions form a tape with PAS and water molecules and such adjacent tapes propagate through channel water molecules (Figure 2b).

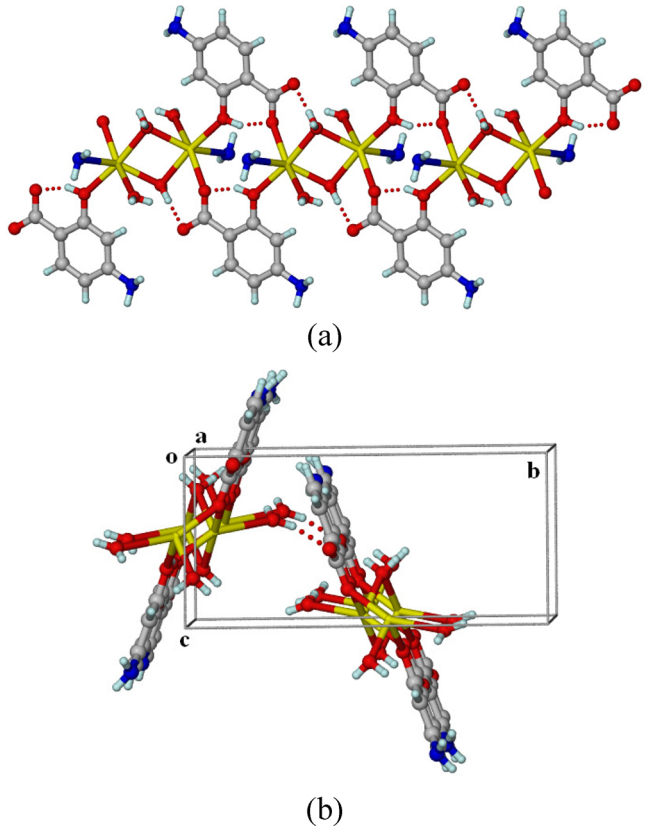

Figure 2. (a) Tape of sodium PAS and water molecules. (b) Adjacent tapes are connected by channel waters along the a axis.

Bis-4-ammonium Salicylic Acid Sulfate ($2PAS^+-SO_4^{2-}$). A 2:1 PAS sulfate salt was crystallized upon slow evaporation of a methanolic solution. Each sulfate moiety

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connects the crystallographic unique PAS molecules, which make a zigzag chain along the *b* axis through N^+–H···O^- and O–H···O bonds (Figure 3a). Such chains extend into a corrugated sheet-like structure (Figure 3b).

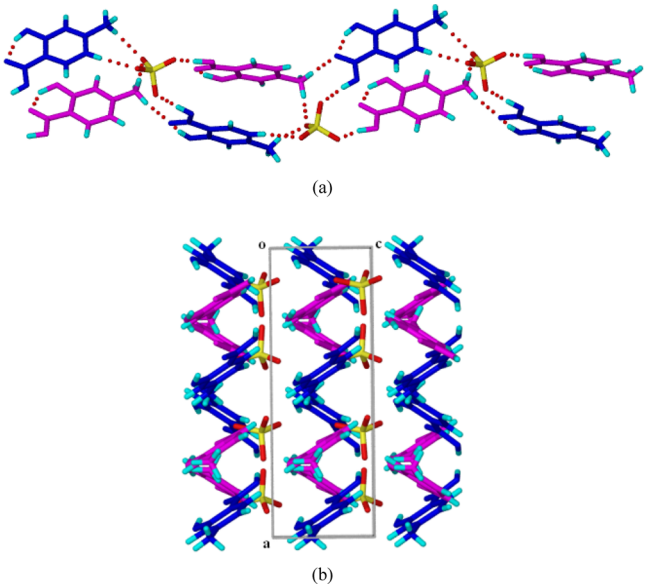

Figure 3. (a) Crystallographic unique PAS molecules (shown in different colors) make zigzag chains through N^+–H···O^- and O–H···O bonds with the sulfate groups. (b) Such molecular chains form a corrugated sheet in the *ab* plane.

4-Ammonium Salicylic Acid Mesylate (PAS^+–$CH_3SO_3^-$). A 1:1 PAS mesylate salt was crystallized upon slow evaporation of a methanolic solution of the components in molar ratio. Parallel tapes of N^+–H···O^- bonded PAS molecules are connected by mesylate ions through N^+–H···O^- and O–H···O hydrogen bonds, which extend into sheets (Figure 4) parallel to the (102) plane. Such sheets are connected by oxygens of the mesylate (orthogonal to the plane) and lie at an interplanar separation of 3.53 Å.

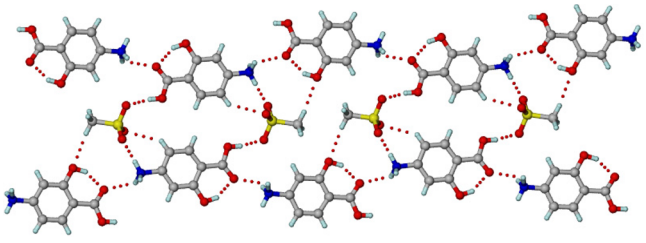

Figure 4. Parallel tapes of PAS molecules connected by mesylate ions through N^+–H···O^-, O–H···O, and C–H···O hydrogen bonds in a layered motif.

Cytosinium-4-aminosalicylate (Cyt^+–PAS^-). Crystallization of PAS and cytosine in a 1:1 ratio from methanol resulted in two different stoichiometry adducts, a 1:1 salt and a 1:1:1:1 salt cocrystal hydrate, in different batches. The crystal structure of the 1:1 salt contains two symmetry-independent PAS and cytosine molecules. The familiar 2-amino-pyrimidinium–carboxylate heterosynthon[24] between cytosine and PAS was observed (Figure 5a). Adjacent heterodimer units propagate perpendicular to each other through N–H···O and C–H···O hydrogen bonds (Figure 5b).

Cytosinium-4-aminosalicylate Cytosine Hydrate (Cyt^+–PAS^-–Cyt–H_2O). Crystal structure of this adduct shows a PAS anion, a cytosinium cation, and cytosine and water molecules, making it a salt cocrystal since cytosine is present in ionized and unionized states. The ions make carboxylate–pyridinium heterosynthon (Figure 6a) instead of carboxylate–aminopyrimidinium present in the previous structure. The amino-pyrimidinium group of cytosinium cation makes a self-complementary 3-point synthon with a neutral cytosine such that the pyrimidinium N–H is shared between the two moieties (N–H distance: cytosinium cation 1.31(4) Å; unionized cytosine 1.52(4) Å). A long covalent bond N–H is typical in a charge-assisted short N^+–H···N hydrogen bond. The 3-point synthon flanked by PAS anions propagates into infinite tapes through $C(6)R_4^2(8)$ graph set[25] motif (Figure 6b). These tapes form a herringbone structure that makes channels parallel to the *a* axis, which is filled with water molecules (Figure 6c). Very recently, Sridhar et al.[26] observed that whenever the cytosine/acid ratio is 2:1 in the crystal structure, the 3-point cytosinium–cytosine synthon involving the amino-pyrimidine group is preferred over the carboxylate–amino-pyrimidinium synthon, and the same situation is observed in our structures.

Generally, grinding technique (neat and/or liquid-assisted) is employed to prepare macroscopic amounts of a multi-component adduct.[27] The cytosine salt and nicotinamide cocrystal hydrate (discussed next) were reproduced by using this technique, the former by ethanol-assisted and the latter by water-assisted grinding, but the cytosine salt cocrystal was not obtained. The PXRD of the ground material (of PAS and cytosine in 1:2 ratio subjected to water-assisted grinding) did not match with the calculated diffraction lines of the salt cocrystal X-ray crystal structure Cyt^+–PAS^-–Cyt–H_2O. It was found to be a mixture of Cyt^+–PAS^- salt and cytosine hydrate by PXRD profile match (Figure S1, Supporting Information). The nonformation of cytosine salt cocrystal in certain cases was noted by Sridhar et al.[26] Crystallization of this salt cocrystal could be due to solution kinetics. The ΔpK_a between cytosine and PAS is 0.77 (pK_a pyrimidine-H^+ 4.4,[28] acid 3.63),[7] a value that is in the 0–3 region in which it is difficult to predict the extent of proton transfer based on solution pK_as.[18] In this situation, both ionized and unionized species can coexist in solution, and the final crystallization product(s) can be salt or cocrystal or even salt cocrystal depending upon the species that precipitate from solution. The products of crystallization are therefore a result of crystallization conditions (temperature, concentration, and solvent) and kinetic effects (the species that is least soluble will precipitate).[18d] Cruz-Cabeza[18c] recently reported that the probability for salt and cocrystal formation is about equal when $\Delta pK_a \approx 1$.

4-Aminosalicylic Acid–Nicotinamide Hydrate (PAS–NAM–H_2O). Similar to the cytosine case, the pK_a difference between nicotinamide (pK_a pyridine-H^+ 4.2)[29] is 0.57. Consistent with the Cruz-Cabeza's study,[18c] which showed increasing tendency for cocrystal formation with ΔpK_a approaching zero, a 1:1:1 cocrystal hydrate of PAS and nicotinamide was crystallized from methanol. The same cocrystal hydrate was reproduced upon water-assisted grinding of the components. Neat grinding of PAS and nicotinamide (to avoid water/moisture) did not afford any anhydrous cocrystal as monitored by PXRD. In the crystal structure, PAS molecules connect the amide dimer of nicotinamide molecules through acid–pyridine synthon and extend into zigzag tapes through

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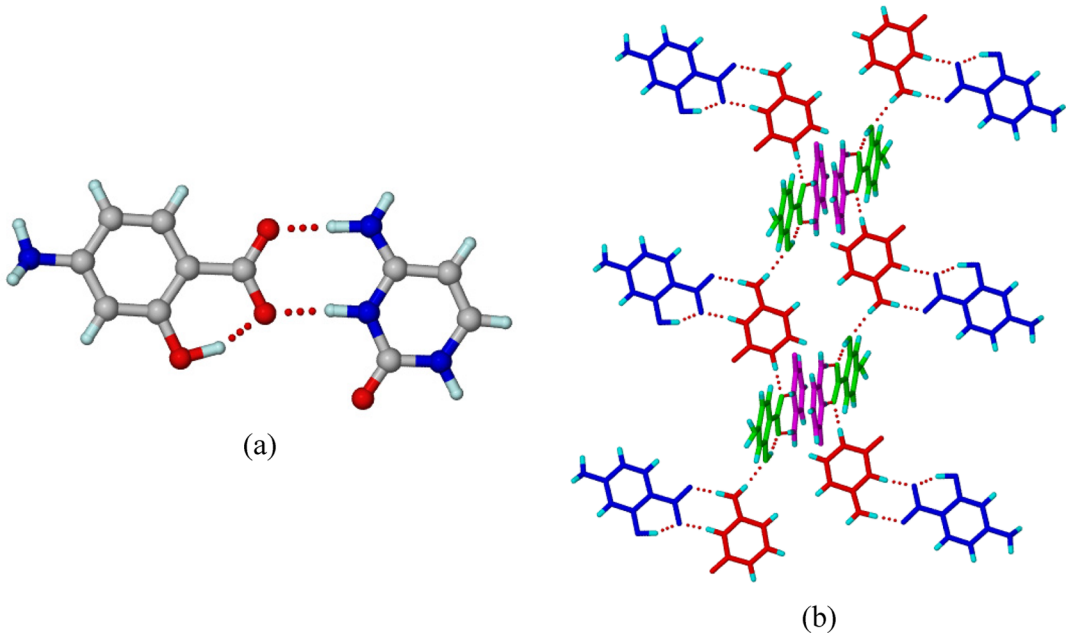

Figure 5. (a) 2-Amino-pyrimidinium−carboxylate synthon of cytosinium cation and PAS anion in the heterodimer. (b) These finite heterodimers between symmetry-independent PAS and cytosine molecules (shown in different colors) propagate in an orthogonal fashion.

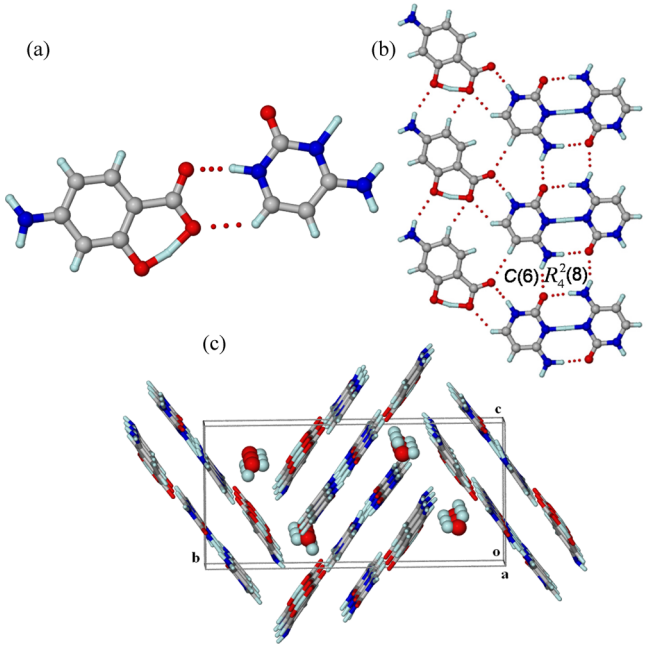

Figure 6. (a) Carboxylate−pyrimidinium synthon between PAS anion and cytosinium cation. (b) Cytosinium cation and cytosine are connected by 3-point synthon of N−H···O and N−H···N hydrogen bonds and extend into infinite tapes through $C(6)R_4^2(8)$ motif. (c) The tapes form a herringbone structure, which makes channels along the *a* axis for water molecules.

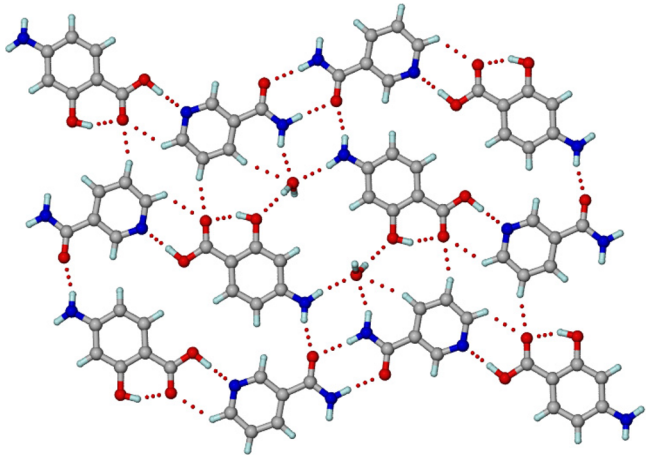

Figure 7. Zigzag tapes formed by amide dimer nicotinamide molecules connected through acid−pyridine synthon with PAS molecules extend into a sheet structure through water molecules.

water molecules (Figure 7) into sheets that lie at an interplanar distance of 3.26 Å. The water molecules form channels along the *a*-axis and connect the sheets through O−H···O hydrogen bonds.

Thermal Analysis. All adducts, except PAS−cytosine salt cocrystal, were obtained in bulk quantity, and their solid form integrity was confirmed by PXRD profile match with the X-ray crystal structure (Figures S2−S6, Supporting Information). Na−PAS dihydrate and 2PAS−SO_4 were obtained from direct synthesis, and PAS−NAM hydrate was prepared through water-assisted grinding. Water of crystallization is present in the sodium and nicotinamide adducts, but the solvent could not be conclusively assigned for the sulfate salt from the difference electron density maps. To find out if these adducts will give anhydrates, their DSC and TGA were recorded to look for thermal transitions and weight loss (Figures 8 and 9). PAS−NAM hydrate turns black upon melting and gave 3-amino-phenol as a byproduct of PAS decomposition.[8] The concomitant release of water was confirmed in TGA (the weight loss of 21.15% matches with one water and one CO_2 molecule, calcd 21.16%, see Figure 8). The dihydrate sodium salt showed a transition at 80−100 °C prior to the melting endotherm at 193 °C in DSC. The weight loss in TGA matched with two water molecules in the dihydrate crystal (calcd 17.06%, obsd 16.43%; Figure 9a). Controlled dehydration of the dihydrate salt at 110 °C for 30 min resulted

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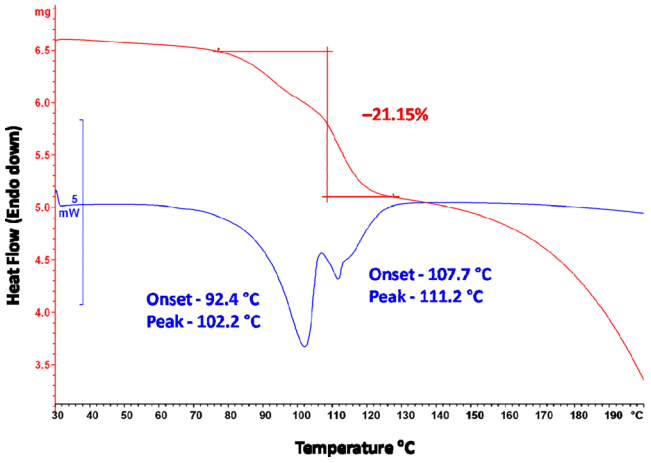
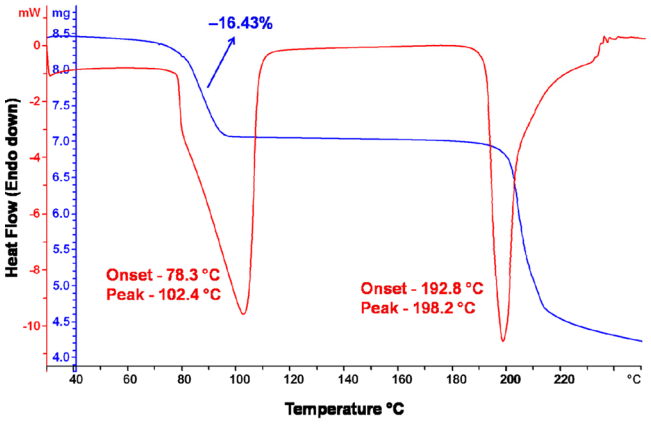
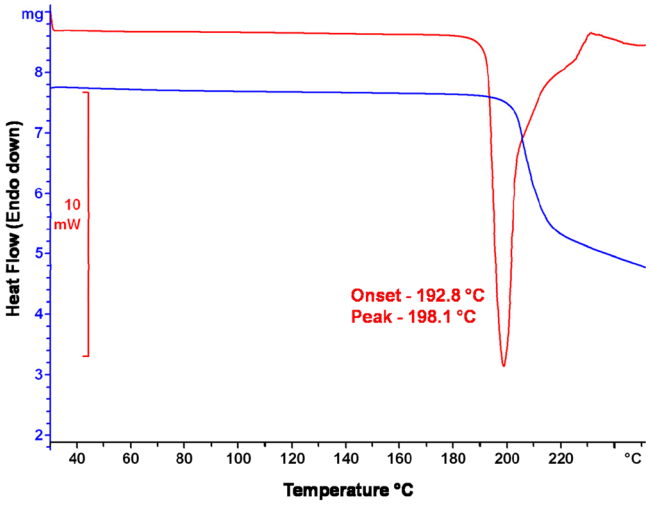


Figure 8. DSC (blue) and TGA (red) of PAS−NAM−H_2O. The two endotherms in DSC are the two weight loss steps in TGA due to melting and decomposition.



(a)



(b)

Figure 9. DSC (red) and TGA (blue) of (a) Na−PAS dihydrate and (b) its anhydrate. The hydrate salt showed water loss at 80−100 °C before melting, and the anhydrate did not exhibit a visible transition before melting at 193 °C.

in an anhydrous material (see DSC and TGA in Figure 9b). Water-assisted grinding of the dehydrated salt gave back the original dihydrate salt, and the hydrate ↔ anhydrate transformation was monitored by PXRD (Figure 10). Thus, the PAS-sodium salt was obtained both in hydrate and anhydrate forms under controlled conditions.

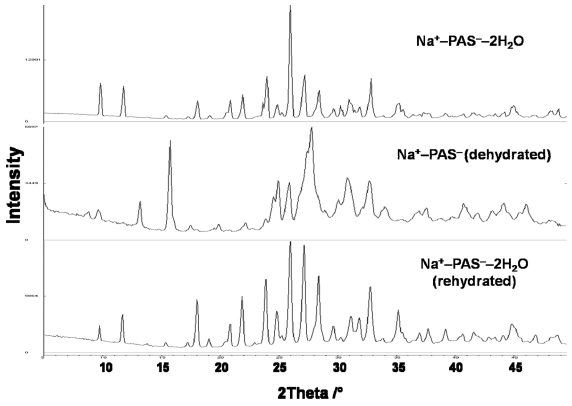


Figure 10. PXRD plots of Na−PAS dihydrate to show the formation of an anhydrate upon dehydration and its conversion to the original dihydrate upon rehydration.

Lack of Polymorphism in API. We were somewhat surprised to note that, despite the presence of three hydrogen bonding functional groups in 4-ASA, COOH, OH, NH_2, neither a zwitterionic form (similar to 5-ASA,[6] see Figure 1) nor a new polymorph was obtained for the active pharmaceutical ingredient (API) in our numerous crystallization attempts (see experimental section). Apart from the lack of polymorphism in these classic drugs, another fact that struck us is that 4-ASA is a neutral molecule and that 5-ASA is zwitterionic in the crystal structure (see Figure 1). Three polymorphs of the ammonium salt of 4-ASA[16] and multiple crystal forms (including a polymorphic cocrystal) of 4-ASA with pyridine coformers[20] were recently reported. A computational study of low energy−high density crystal structures[30] should be informative in the search for polymorphs of these important amino salicylic acids.

CONCLUSIONS

The solid form space of PAS was explored and its variable stoichiometry adducts with cytosine (a salt and salt cocrystal) and sodium (anhydrate and hydrate salts) were obtained. A nicotinamide cocrystal hydrate was also obtained and X-ray crystal structures of a few salts were also determined. PAS has a tendency to form solvate/hydrate adducts (4 out of 6 structures studied in this work). PAS-sodium salt was obtained both in hydrate and anhydrate forms in a controlled and reproducible way. The difficulty of predicting the cocrystallization product as salt, cocrystal, or salt cocrystal in the ΔpK_a range 0−4[18] is complicated in the multifunctional molecule PAS. Cytosine and nicotinamide adducts fall in the borderline zone. The 2-point synthon of carboxylate−aminopyrimidinium in the 1:1 cytosine salt and the 3-point motif of cytosinium−cytosine in the 2:1 cytosine salt cocrystal are consistent with a recent report.[26] However, only the former product could be prepared by the grinding technique. This example highlights the subtle role of crystallization conditions in obtaining a particular product and the necessity of design controls for scale-up processes. These examples add to the diversity of multicomponent crystalline solids of APIs.[17,19]

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EXPERIMENTAL SECTION

Materials and Methods. 4-Aminosalicylic acid was purchased from Shanghai Xunxin Chemical Co., Ltd., China, and used without further purification. All other chemicals were of analytical or chromatographic grade. Water purified from a mixed bed deionizer purification system was used for all experiments.

Synthesis of Adducts. *a. Sodium-4-aminosalicylate dihydrate (Na^+–PAS^-–$2H_2O$).* PAS (153 mg, 1 mmol) was dissolved in aqueous NaOH (40 mg, 1 mmol) solution (3 mL) and left for slow evaporation at room temperature. Brown colored crystals of plate morphology were observed after a few days.

b. Bis-4-ammonium Salicylic Acid Sulfate ($2PAS^+$–SO_4^{2-}) and 4-Ammonium Salicylic Acid Mesylate (PAS^+–$CH_3SO_3^-$). PAS and the sulfonic acid (2:1 molar ratio for sulfuric acid and 1:1 for methanesulfonic acid) were dissolved in acetone in separate flasks and kept at −20 °C. After 10 min, the two solutions were mixed and stirred for 5−10 min in an ice-cold bath. The salt was obtained as a grayish precipitate, which was filtered on a 2.5 μm Whatman filter paper and washed with acetone and dried. Single crystals of the sulfate salt were obtained as brownish needles when 30 mg of the salt was recrystallized from 5 mL of warm methanol at room temperature. Similarly, the mesylate salt crystallized as brownish plates.

c. Cytosinium-4-aminosalicylate (Cyt^+–PAS^-) and Cytosinium-4-aminosalicylate Cytosine Hydrate (Cyt^+–PAS^-–Cyt–H_2O). PAS (30 mg, 0.2 mmol) and cytosine (22 mg, 0.2 mmol) were dissolved in 6−8 mL of warm methanol and left for slow evaporation at room temperature. Adducts of 1:1 and 2:1 stoichiometry (both of brown color) crystallized in plate and needle morphology, respectively, in different batches. The composition and structure was confirmed by single crystal X-ray diffraction.

d. 4-Aminosalicylic Acid–Nicotinamide Hydrate (PAS–NAM–H_2O). PAS (30 mg, 0.2 mmol) and nicotinamide (24 mg, 0.2 mmol) were dissolved in 6 mL of warm ethanol and left for slow evaporation at room temperature. Brown colored crystals of plate morphology were harvested after a few days.

Cogrinding. About 200 mg of the components, combined together as per the stoichiometric ratio in the crystal structure, were ground for 15−20 min using a mortar and pestle. Then, 8−10 drops of the solvent was added during grinding in the case of solvent-assisted grinding. PXRD of the ground material was recorded to confirm complete reaction of the starting materials and formation of a new crystalline phase. The product was matched with the X-ray crystal structure by PXRD line overlay.

Polymorph Screening Experiments of PAS. PAS was crystallized from aqueous HCl solutions in the pH range 1.2−4.0, i.e., near its pK_a values,[7] to induce internal proton transfer with the intent of isolating its zwitterionic form. Also, metathesis reaction of Cyt^+–PAS^- salt with PAS hydrochloride salt (PAS^+–Cl^-, prepared as per the method by Forbes et al.)[13] was carried out by ethanol-assisted grinding to induce crystallization of its zwitterion via the reaction sequence shown in eq 1 ('C' = pharmaceutical salt former). The expectation was that the Cyt^+–Cl^- will precipitate and leave a zwitterionic form of PAS for crystallization by the addition of antisolvent (*n*-hexane). Apart from evaporative crystallization in several solvents and sublimation, the above experiments did not result in any polymorph/zwitterion of PAS as monitored by PXRD.

$$NH_2C_6H_3(OH)COO^-{}'C'^+ + X^-NH_3^+C_6H_3(OH)COOH \rightarrow NH_3^+C_6H_3(OH)COO^- + {}'C'^+X^- \quad (1)$$

X-ray Crystallography. X-ray reflections for sodium, sulfate, and cytosine salts and nicotinamide cocrystal were collected on a Bruker SMART-APEX CCD diffractometer equipped with a graphite monochromator and Mo−Kα fine-focus sealed tube (λ = 0.71073 Å). Data reduction was performed using Bruker SAINT software.[31] Intensities were corrected for absorption using SADABS.[32] Structures were solved and refined using SHELX-97.[33] The sulfate structure contained vaguely resolved peaks possible of a solvent that was removed by using 'squeeze' in PLATON.[34] X-ray reflections for mesylate salt and cytosine salt cocrystal were collected on an Oxford Xcalibur Gemini Eos CCD diffractometer using Cu−Kα radiation (λ = 1.5418 Å). Data reduction was performed using CrysAlisPro (version 1.171.33.55),[35] and OLEX2-1.0[36] was used to solve and refine the structure. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms on heteroatoms were located from difference electron density maps, and all C−H hydrogens were fixed geometrically. The final CIF files and hydrogen bond geometries were validated in PLATON.[34] X-Seed[37] was used to prepare packing diagrams: CCDC Nos. 914456−914462.

Powder X-ray Diffraction. PXRD was recorded on a Bruker D8 Advance diffractometer using Cu−Kα X-radiation (λ = 1.5406 Å) at 40 kV and 30 mA. Diffraction patterns were collected over 2θ range of 5−50° at scan rate of 1° min^{-1}. Powdercell 2.4[38] was used to plot the diffraction patterns.

Thermal Analysis. DSC was performed on a Mettler Toledo DSC 1 module calibrated with indium (T_m = 156.60 °C; ΔH_f = 28.45 J g^{-1}) and zinc (T_m = 419.50 °C; ΔH_f = 107.50 J g^{-1}) as per the manufacturer's specifications. TGA was performed on a Mettler Toledo TGA/SDTA 851e module calibrated with indium (T_m = 156.60 °C) and aluminum (T_m = 660.30 °C). The typical sample size is 3−5 mg for DSC and 8−10 mg for TGA. The temperature range used in both DSC and TGA is 30−250 °C at 5 °C min^{-1}. Samples were placed in crimped but vented aluminum pans for DSC, and open alumina pans for TGA and were purged by a stream of dry nitrogen flowing at 50 mL min^{-1}.

ASSOCIATED CONTENT

Supporting Information

Table of hydrogen bonds, PXRD patterns, CIF files. 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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