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Salt Selection and Simultaneous Polymorphism Assessment via High-Throughput Crystallization: The Case of Sertraline

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Abstract:

High-throughput (HT) crystallization experiments were conducted with sertraline free base in the presence of mono-, di- and triacidic salt formers. Over 3600 crystallization trials were conducted, leading to the identification and characterization of 18 crystalline salt forms. Due to the large number of crystallization conditions for a given salt type, it was possible to gauge the propensity of a given salt form to exhibit polymorphism. Four salt forms were found to exist (in this limited screen) as monomorphic materials. Unlike the HCl salt in the marketed drug product, the HBr salt appears resistant to polymorphism, crystallizing as a single form from over 140 discrete trials. This observation underscores the lack of predictability of polymorphic behavior of pharmaceuticals even when seemingly minor changes to the composition are made. The experiments highlight the importance of coupling salt selection studies with simultaneous polymorph screening to gain a more comprehensive understanding of solid form diversity as part of the form selection process for pharmaceutical development.

Introduction

Salt selection is a strategy that is commonly employed to improve properties of pharmaceutical compounds.[1,2] Crystalline salts can confer useful attributes such as improved aqueous solubility, chemical stability, and high bioavailability relative to those of the free base or acid of the active compound. Drug delivery options, including parenteral solutions and controlled release technologies, often depend on the ability to modulate physicochemical properties. Furthermore, salts and other crystal forms (e.g. hydrates, solvates, and cocrystals) of drug substances are patentable compositions that enhance the intellectual property estate of a given molecular entity.[3] Due to its central placement in chemical development and pharmaceutical research, salt selection is becoming increasingly automated to meet the need for rapid identification of crystalline salt forms in early development.[2,4−6] Salt selection at earlier stages has also been demonstrated, using high-throughput crystallization.[7]

The sudden appearance of a more stable polymorph of an active pharmaceutical ingredient (API) is an unpredictable and challenging aspect of drug development. Generally, the most stable crystal form of a given compound is desired, and much effort is expended to find it in the early stages of development. When a new form appears late in development, the product must be carefully evaluated to ensure that performance and quality (e.g., content uniformity) have not changed. The process operations or formulation may need to be adapted or changed entirely to restore the original performance. The result can be a significant delay in critical clinical studies, drug approval, and market entry. An even bigger problem is the potential emergence of such a polymorph in a marketed product.[8] In the worst case, the product must be withdrawn from the market for reformulation if specifications of the original product cannot be met. Polymorphism can occur in neutral compounds and salts alike. There is currently no suitably accurate algorithm to predict whether a given composition (e.g. a salt vs free drug) will be more or less polymorphic than another. Extensive experimentation is needed to ensure that all polymorphs and solvates of the selected neutral or salt form are found early in development. In the case of compounds that can make crystalline salts, it may be possible to find salt forms with lesser propensity for polymorphism.

Sertraline HCl (Zoloft) is an example of a salt form that is highly polymorphic and prone to solvate formation. While the polymorphism is not believed to have significantly slowed the development of Zoloft, it has given generic drug companies an opportunity to capture a large amount of intellectual property on the drug. Indeed, data on 28 purported forms of sertraline HCl have been disclosed by

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several companies at the time of this submission.[9] A critical analysis of the polymorphism issue of sertraline HCl has recently been reported.[10] The impact of some of the crystal forms that were discovered by companies other than the innovator on product value (in the form of early generic competition) may prove to be significant.

The extent of polymorphism is currently not a major criterion for selection of development form, but it is worth considering the propensity for polymorphic behavior at the discovery−development interface. In this study, we report the use of high-throughput (HT) salt screening to find a large number of crystalline salt forms for a single API and to quickly identify those salts that are highly polymorphic. Sertraline is used as a model compound because of the high susceptibility of its HCl salt to form polymorphs and solvates.

Experimental Section

Materials. Sertraline HCl (>99%) was obtained from Interchem Corporation (Paramus, NJ) as crystalline form II. The compound was dissolved in water, treated with excess sodium hydroxide, extracted into ether, and crystallized as the free base. The resulting compound was used without further purification (melting point 64−66 °C, HPLC purity >99.9%). Solvents were purchased from Sigma-Aldrich, Spectrum or Fisher, generally as HPLC grade, and were used without further purification. HPLC-grade distilled water (at pH just over 5) was obtained from Fisher. Only borosilicate glass or polypropylene components were allowed to contact the solvents during storage.

Two series of HT crystallization trials were performed using CrystalMax technology. Multiple parallel crystallizations were carried out for each salt former according to methods previously described.[11,12] The first crystallization trial series was carried out in 12 96-well aluminum blocks holding borosilicate tubes containing mixtures of sertraline, 1.05 mol equiv of a monoprotic salt former, and solvents (see Table 1). The second trial was carried out in 24 96-well blocks holding borosilicate tubes containing mixtures of sertraline, 0.55 or 1.05 mol equiv of a polyprotic salt former, and solvents. Sertraline base was dispensed to the tubes in methanol solution, and the methanol was evaporated using a Turbovap 96 (Zymark, Hopkinton MA). The individual mixtures of drug, salt former, and solvent, devised using proprietary design software (Architect), were prepared by combinatorially dispensing the salt formers and water and/or organic solvents using a Cartesian SynQuad 32-channel dispenser (Cartesian Technologies, Irvine, CA). Salt formers were dispensed from 0.5 M stock solutions, and the solvent was removed using a Turbovap 96 prior to addition of the final solvent mixture for crystallization. Duplicates of each composition were prepared; identical samples were located in different arrays in each case. Each tube was sealed with a Teflon-coated crimp top within 15 s of receiving combinatorially dispensed solvents to avoid evaporation of organic solvents. The samples were heated to 65 °C for 2 h and cooled at 1 °C/min to 25 °C. Automated vision checks were performed at the end of the heating cycle, immediately after cooling, and periodically thereafter. Samples containing crystals were quenched by aspiration of the solvent followed by drying under a stream of nitrogen.

Table 1. **Components used in the HT salt screens**

solvents	monoprotic salt formers	polyprotic salt formers
acetonitrile	acetic acid	citric acid
ethanol	benzenesulfonic acid	fumaric acid
iso-propanol	benzoic acid	maleic acid
iso-butanol	ethanesulfonic acid	malonic acid
iso-propyl acetate	hydrobromic acid	phosphoric acid
tetrahydrofuran	methanesulfonic acid	succinic acid
n-heptane	lactic acid	sulfuric acid
propylene glycol	*p*-toluenesulfonic acid	L-tartaric acid
water		

Raman spectra of the solids obtained in the crystallization process were collected on a Nicolet Almega dispersive system fitted with a 30 mW NIR laser at 785 nm. Cluster classification of Raman spectra was performed using proprietary software (Inquire). The software first filters Raman spectra to remove background and to accentuate peaks and shoulders. Then, peaks are picked using standard derivative methods, and amplitudes are calculated. Finally, a hierarchical clustering algorithm is used in conjunction with a distance measure related to the Tanimoto coefficient in order to bin spectra. This method uses peak positions, rather than amplitudes, to discriminate between different patterns. The software allows a user to select a spectral window over which two peaks are considered to be at the same position (a tolerance value, which is generally 2−3 cm^{-1}), as well as a minimum height for a filtered peak to be considered for clustering. Additionally, regions of interest (i.e., wavenumber ranges) can be selected to focus the analysis. With appropriate settings, which can be interactively adjusted by the user, the software is able to identify and bin a Raman spectrum that has only one peak feature in a slightly different location than in other patterns. Samples with spectra that are sufficiently dissimilar to all others to be included in clusters are referred to as "outliers."

Powder X-ray diffraction (PXRD) patterns were measured for at least two samples from each large Raman cluster and at least one sample from smaller clusters and groups of outliers. PXRD on samples in boron-rich glass or quartz capillaries (Charles Supper Co., Natick, MA) was performed in transmission mode on a Rigaku D/MAX Rapid image plate diffractometer (Rigaku/MSC, Woodlands, TX) employing Cu Kα radiation with a 0.3 mm collimator and a 2.0 kW source, operating at 46 kV/40 mA. Preferred-orientation effects were minimized by collecting PXRD data in transmission mode, while oscillating about the ω-axis from 0 to 5° and spinning

(9) Patent information on forms of sertraline hydrochloride was collected from the following documents: (a) (Pfizer). U.S. Patent 5,248,699. (b) (Torcan). EP 0 928 784 A1; (c) (Teva). WO 00/32551 A1. (d) (CIBA Specialty Chemicals Holding Inc.). WO 01/32601 A1. (e) (Teva). WO 01/45692 A1.

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360° about the ϕ-axis at 2 deg/s. PXRD on an array of samples in reflectance mode was performed on a Bruker D8 Discover with GADDS diffractometer with a HI-STAR area detector (Bruker AXS Inc., Madison, WI) employing Cu Kα radiation with a 0.5 mm collimator and a 2.2 kW source. Thermal analyses were performed on a Q1000 mDSC and Q500 TGA (TA Instruments, Wilmington DE). Heating rates of 10 °C/min were employed. The DSC was calibrated with a single-point method using the extrapolated onset of the melting point of a 0.275 sample of indium. Sample sizes used to generate the reported melting points ranged from 0.085 to 0.44 mg. Microscopy was performed and photomicrographs taken on a Zeiss Axioplan microscope and Zeiss Axiocam type 1 SNO641, respectively (Zeiss, Thornwood, NY).

Samples for solubility measurement were prepared by adding deionized water to solids from individual vials, allowing the suspensions to equilibrate for 30 min with gentle agitation, filtration through a Costar Spin-X HPLC microcentrifuge filter with a 0.2 μm nylon filter, and dilution of aliquots with 30/70 acetonitrile/water. The concentration of sertraline base was calculated from HPLC peak areas using a calibration curve generated from sertraline base standards. Sample analysis was performed on a Waters Alliance System HPLC (Waters Corporation, Milford, MA) using a Waters Symmetry C18 column and a 70/30 (v/v) mixture of 10 mM ammonium formate pH 3.0 and acetonitrile. UV detection wavelength was set at 250 nm.

A single crystal of sertraline HBr was selected and mounted on a Pyrex fiber affixed to a brass pin. The crystal was optically centered and placed on an Enraf-Nonius CAD4-U diffractometer. X-ray data were collected using the Enraf-Nonius EXPRESS program (graphite monochromated Cu Kα radiation, $\lambda = 1.54178$ Å) using the $\omega - 2\theta$ technique.[13] The structure was solved by direct methods using SIR-92 and refined using the Oxford CRYSTALS package.[14] Non-hydrogen atoms were refined using anisotropic displacement parameters. The acidic hydrogen atoms were refined using isotropic displacement parameters. Other hydrogen atoms were placed at calculated positions ($D_{C-H} = 0.95$ Å), held fixed during the refinement, and updated after each least-squares cycle.

Results and Disussion

Sertraline free base was subjected to over 3200 crystallization trials with pharmaceutically acceptable acids. The emphasis was placed on finding crystalline salt forms of monoacids, for comparison with the marketed HCl salt. A foray was also made into salt forms of di- and tribasic acids.

Monoionic Salt Former Screen. The forms identified for each salt of sertraline, statistics on the percentage of samples that crystallized, and available physical characterization data are shown in Table 2. Raman spectra of all crystalline samples from the monoionic salt screen were sorted based on similarity (see Experimental Section) and the similarity scores plotted on an *n*-by-*n* matrix to form the diagram shown in Figure 1. The sorting leads to the appearance of clusters; each sample in a given cluster was found to contain the same salt former by analysis of the database entries. However, most sertraline salts produced Raman spectra with sufficient subtle variability that what appears as a single cluster for each form is typically a combination of one large bin and several closely related small bins and "outliers" (based on the value of Tanimoto distances of samples relative to the main cluster). Differences in spectra that can lead to multiple bins are to be expected from any sensitive analytical technique when large collections of crystalline samples are examined. Minor changes in spectra can arise from differences in particle size, purity, and sample orientation. In addition, a number of samples classified as "outliers" in this experiment were found to be damp with residual solvent, which can occur as a result of incomplete quenching. Unlike PXRD, Raman is often sensitive to the presence of the residual solvent in the solid sample. The potential for variability in large datasets suggests that plots such as that in Figure 1 should be examined in conjunction with secondary characterization data and informatics tools.

The tosylate salt cluster in Figure 1 has been annotated to help visualize the smaller clusters and outliers that make up the entire cluster. Visually, the samples appear to fit into a single large cluster in which all samples are clearly related and distinct from those in the rest of the diagram. Although the differences were small, outliers and small bins could result from polymorphs; thus, PXRD samples were measured from each small bin. In all, approximately 6% of all crystalline samples were analyzed by PXRD. White arrows are used to show the presence of three clusters, C1−C3, and two areas containing outliers. Clusters C1 and C2 had no common solvent present in all samples that could account for their differences. Every sample in cluster C3 was crystallized from a solvent mixture that included propylene glycol (PG), but PXRD and thermal analysis provided no evidence of solvate formation. Propylene glycol has a high

Table 2. **Results of HT sertraline salt screen and physical data for select compounds**

salt form	% hits[a]	% dissolved[b]	form	melting temp (°C)	intensity (J/g)	solublity (mg/mL)[c]
acetate	8	0	A	–	–	3.3
hydrobromide	82	7	A	266	57	0.6
benzoate	35	30	A	134	21−43	
			B	155	94	0.4
benzenesulfonate	78	<1	A	150	91	0.3
ethanesulfonate	8	54	A	78−96 (broad)	–	
			B	148	56	1.7
lactate	22	15	A	150	91	1.9
			B	62	42	
methanesulfonate	69	14	A	196	67	
			B	201	88	4.2
			C	–		
p-toluenesulfonate	94	<1	A	265	77	0.1

[a] "% hits" is the percentage of samples containing a given salt former that yielded crystals. [b] "% dissolved" is percentage of crystalline samples in which crystals formed only after cooling from the heating cycle. The remainder of samples clearly contained crystals in photos taken at 65 °C. [c] Solubility was measured at room temperature in deionized water.

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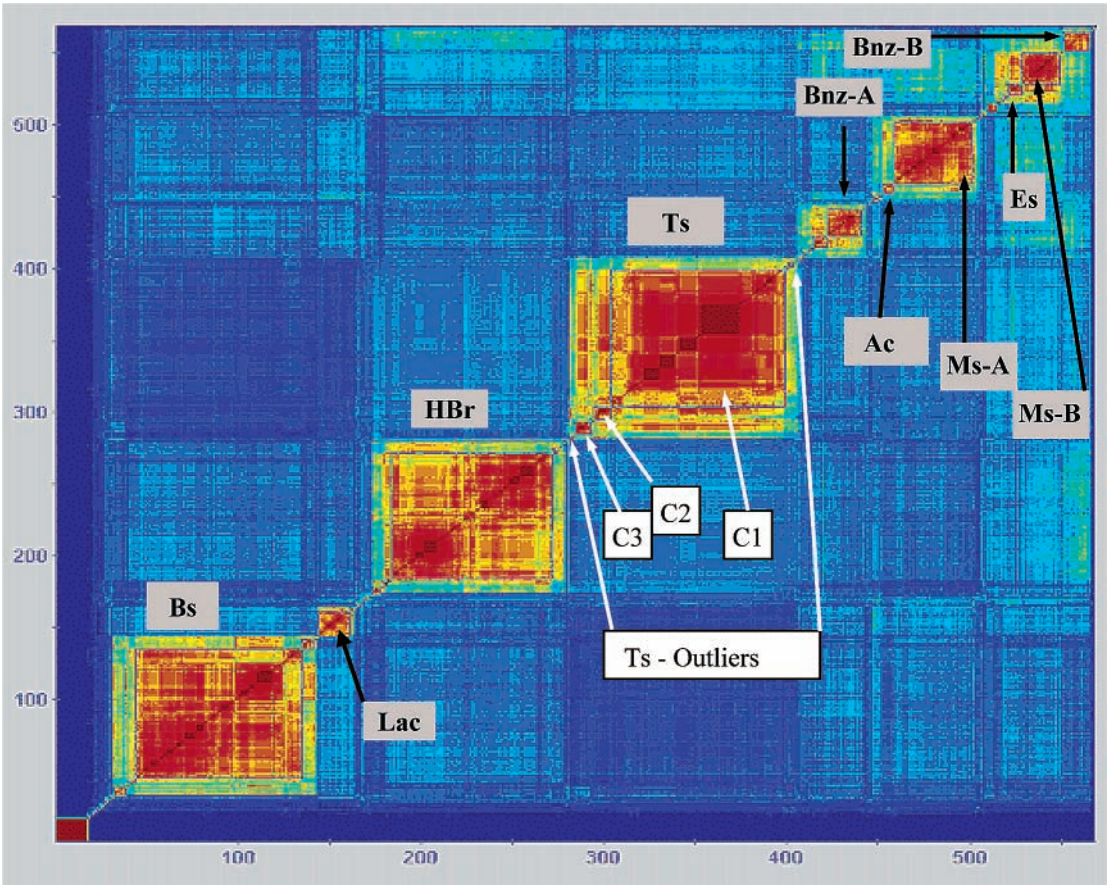

Figure 1. **Cluster analysis of Raman spectra using Tanimoto coefficients (ref 12). The label abbreviations correspond to salts as follows: Ac = acetate; Bnz = benzoate; Bs = benzenesulfonate; Es = ethanesulfonate; HBr = hydrobromide; Lac = lactate; Ts = *p*-toluenesulfonic acid. The white text boxes and arrows show the location of sertraline tosylate samples that clustered in the (C1) main bin, (C2 and C3) smaller but related bins, and (Ts − outliers) as outliers around the main cluster.**

boiling point (188 °C at 1 atm pressure), so it should not be surprising that some will remain after quenching. The presence of the solvent alters the spectra sufficiently to warrant a new cluster, but not so much as to eliminate the correlation to the other *p*-tosylate salt samples.

Raman clusters corresponding to polymorphs of one salt form can be as distinct from one another as different salt forms (Figure 1). The benzoate and mesylate salts each form two distinct clusters that appear to be unrelated in the figure. PXRD analysis confirms that such spatially separated bins correspond to polymorphs of the salts. Of further importance is the relative size of the clusters: the main cluster corresponding to each polymorph is no more than twice the size of the other, suggesting that both forms are relatively easy to make. The solvent systems that yielded polymorphs mesylate-A and mesylate-B were examined to determine whether there was clear guidance for choosing conditions to make each polymorph. Protic solvents had a slight preference for mesylate-A and aprotic solvents for mesylate-B, but there appears to be a high degree of overlap in solvent conditions. Likewise, both mesylate forms were found in samples that crystallized at 65 °C and in those that crystallized after cooling. The melting point and heat of fusion of form B indicate that it is most likely the more stable polymorph. However, it is likely that reliable production of either polymorph would be difficult in the absence of seeds.

Solubility in water and/or organic solvents is a key physical parameter for compatibility with various dosage forms and to evaluate processing options. The number of crystallizations observed for a given salt form may provide early insight into the relative ease of developing some of the forms. Roughly 144 crystallization experiments were used for each salt, but the number of crystalline solids produced varied greatly. Greater than 75% of all samples containing *p*-toluenesulfonic acid, benzenesulfonic acid, or HBr yielded crystals. Since a single polymorph was found for these salt forms, it seems likely that a procedure could be devised for making the form consistently and in high yield, although scale-up efforts are inevitably needed to verify this aspect. These salt forms were also found to have aqueous solubility below 1 mg/mL and should be relatively stable toward conversion to amorphous material during pharmaceutical processing involving aqueous wet granulation. In contrast to the besylate, *p*-tosylate, and HBr salts, fewer than 10% of samples containing acetic or ethanesulfonic acid yielded crystals. The apparently high solubility of these salts in a wide range of solvents may make them the best options (aside from the free base) if a solution formulation is desired.

The ability to compare many PXRD patterns of the same polymorph allows for early detection of potential analytical challenges. The main Raman cluster corresponding to polymorph A of the benzoate salt is grouped with a number

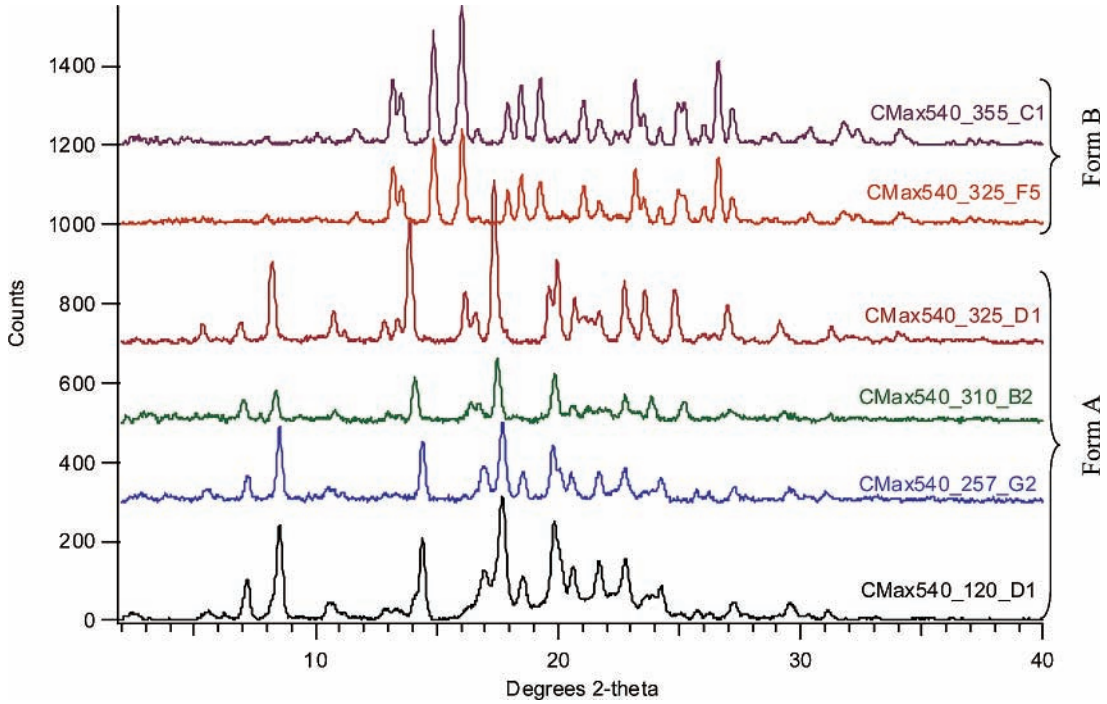

Figure 2. **Overlay of PXRD data for selected sertraline benzoate samples. The bottom four patterns represent form A; the large peaks shift while smaller peaks are present only in some samples.**

of outliers and small clusters, all of which are also benzoate salts (Figure 1). The stacked plot of PXRD patterns (Figure 2) shows patterns for polymorphs A and B of the benzoate salt. Inspection of the PXRD patterns of samples taken throughout the group labeled Bnz-A in Figure 1 reveals an analytical challenge; the PXRD patterns look more or less similar, but many diffraction peaks shift and several small peaks appear and disappear essentially at random. Such variability in PXRD patterns is likely to cause problems for chemical and pharmaceutical development, as well as raising regulatory issues, and therefore such forms are generally not desirable as product candidates.

Physical properties, including melting points and aqueous solubility, were measured for the samples when sufficient material was available. The data are useful for determining whether a given salt form might be used successfully in a product. For sertraline, solubility data show that all salt forms achieve concentrations of at least 0.1 mg/mL in water. The solubility of the acetate and ethanesulfonate salts were sufficiently low to be used in aqueous granulation processes, although more work would have to done to show excipient compatibility prior to use in solid dosage form development. The solubility of the HBr salt is approximately 3-fold lower than the solubility of the most stable polymorph of the HCl salt at room temperature (form I solubility of 1.6 mg/mL was recorded in water at room temperature).

Di- and Triacidic Salt Formers. A screen for salts of di- and triprotic acids was carried out for preliminary comparison to the mono-salts. The 2300 samples in the experiment yielded 1474 hits, approximately 1250 of which crystallized upon addition of the salt former or during the heating step. Six crystalline samples were selected for each ratio of a given salt former based on differences in solvent content and appearance of crystals from the photomicrographs captured as part of the screen. Care was taken to choose samples from diverse solvent conditions. PXRD was used as an initial evaluation to determine whether the salt form was overtly polymorphic or should be studied further. Figure 3 shows an overlay of six PXRD patterns from the selected samples of sertraline with phosphoric acid. Once it became clear that there were multiple forms of sertraline phosphate, no further samples were analyzed. Likewise, citric, fumaric, maleic, malonic, sulfuric, and succinic acids all yielded more than two forms in the initial evaluation. L-Tartaric acid yielded only two forms, one of which was found only in samples containing 0.5 equiv of acid, while the other appeared only when a full equivalent of acid was added. Scale-up of the forms and analysis by HPLC and ^{1}H NMR found that both were hemi-L-tartrate salts, indicating that sertraline-L-tartrate is polymorphic as well.

Single-Crystal Structure of HBr Salt. A single-crystal structure of the HBr salt was obtained to understand the nature of packing and ionic associations in the compound. The structure in Figure 4 shows that sertraline HBr crystallizes in the noncentrosymmetric orthorhombic space group $P2_12_12_1$ and contains four molecules of the salt in the unit cell.[15] Examination of the packing diagram indicates that sertraline HBr is made up of a two-dimensional hydrogen-bonded network. The primary motif results in the formation of hydrogen-bonded chains (N−H···Br) propagating along the *b* axis with graph set C(4), as shown in Figure 4a.[16] Secondary hydrogen bonds (C−H···Cl−C) complete the

(15) Crystallographic data: $a = 6.0937(5)$ Å, $b = 11.1975(11)$ Å, $c = 25.165(2)$ Å, $\alpha = \beta = \gamma = 90°$, $V = 1717.1(3)$, $R = 0.0371$, $R_w = 0.0437$.

(16) Hydrogen bonds involved in the primary motif: N(1)−H(1)···Br(1) [$2 - x$, $^1/_2 + y$, $^3/_2 - z$, 3.320Å, 155°], N(1)−H(2)···Br(1) [x, y, z, 3.301Å, 157°].

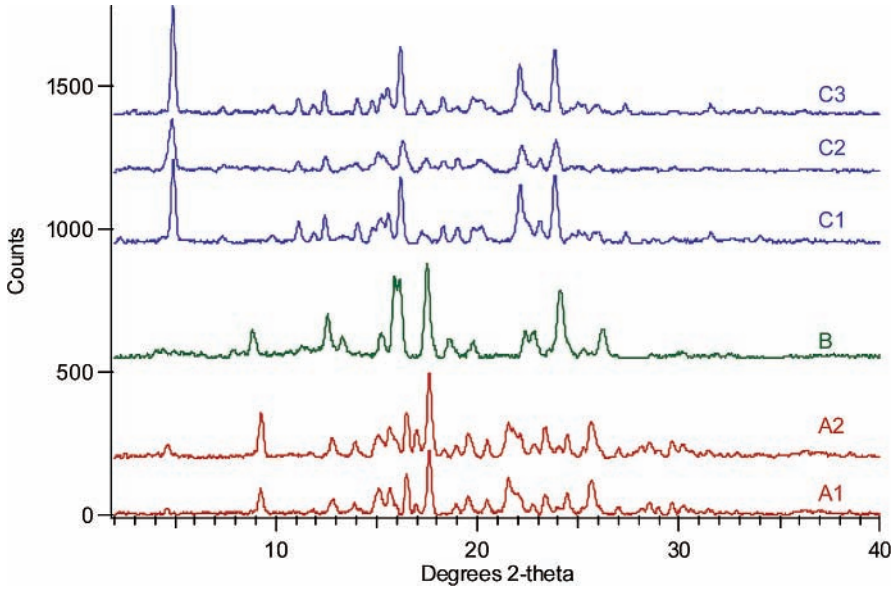

Figure 3. **Overlay of PXRD patterns of sertraline phosphate salt from six samples, selected for analysis based on differences in physical appearance and diversity of solvent content. Three unique forms (A−C) were present in tubes containing sertraline with A1 1.05 equiv of H_3PO_4 in ethanol/water; A2 1.05 equiv of H_3PO_4 in water/acetonitrile; B 0.5 equiv of H_3PO_4 in 2-propanol/water; C1 0.5 equiv of H_3PO_4 in 2-propanol/ethanol; C2 0.5 equiv of H_3PO_4 in *iso*-propyl acetate/tetrahydrofuran; and C3 0.5 equiv of H_3PO_4 in acetonitrile/propylene glycol.**

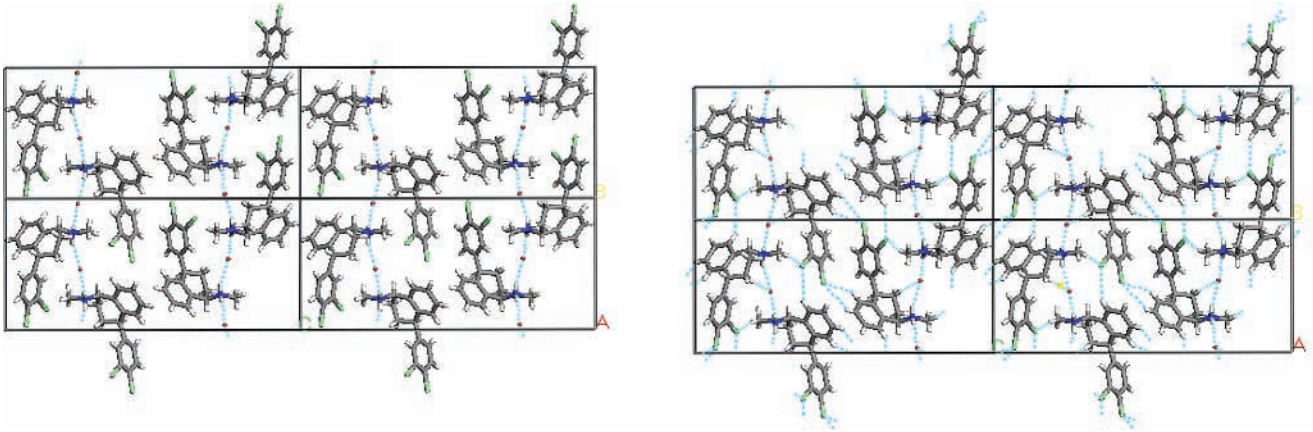

Figure 4. **View along the *a*-axis of the single-crystal structure of sertraline HBr. The compound crystallizes in the noncentrosymmetric orthorhombic space group $P2_12_12_1$ and contains four molecules of the salt in the unit cell. (a) Packing diagram showing the hydrogen-bonded chain. (b) Packing diagram illustrating the full hydrogen−bonded network.**

two-dimensional network and these are indicated in Figure 4b.[17]

Sertraline HCl form I also crystallizes in the noncentrosymmetric orthorhombic space-group $P2_12_12_1$ and is made up of a two-dimensional hydrogen-bonded network.[18] No obvious differences were observed between the sertraline HCl and HBr salts that could explain the increased polymorphism of the HCl salt. In addition, neither compound contained any discernible voids in the unit cell, suggestive of a tendency for formation of solvates. Further analysis of the packing interactions is currently underway. While we cannot definitively prove that the HBr salt is less polymorphic than the HCl salt at this time, initial experiments indicate some difficulty in generating form diversity of sertraline HBr.

In contrast to chloride, bromide ion produces sedation and dermatological problems (19), and doses are limited for toxicity reasons. In the case of sertraline (about 50−200 mg/day) the bromide dose would be unacceptable. The drug example containing the highest amount of bromide is Benylin, for which the adult formula allows up to 0.34 mmol (or 27 mg) of bromide ion to be administered on a daily basis. For a 200 mg dose of sertraline (the current maximum daily dose), about 51 mg would be added as bromide ion. In this case, at least two other salt forms, the besylate and *p*-tosylate, appear to have low form diversity and are pharmaceutically acceptable at the needed dosage.

Conclusions

We have demonstrated that seemingly minor differences in salt former can have profound effects on the number of polymorphs and solvates that can be found in the corre-

(17) Secondary hydrogen bonds: C(17)−H(171)····Cl(2) [3.79 Å, 162°], C(7)−H(71)····Cl(2) [3.83 Å, 147°], C(10)−H(101)····Cl(1) [3.69 Å, 130°].

(18) Caruso, F.; Besmer, A.; Rossi, M. *Acta Crystallogr., Sect. C* **1999**, *55*, 1712.

sponding salts. These effects are quite unpredictable. Hence, a greater extent of experimentation, as achieved by applying HT crystallization in tandem with other chemistry activities, can help highlight or even eliminate the highly polymorphic salts at a very early stage. Such insight allows process chemists, engineers, and pharmaceutical scientists to focus resources on a less polymorphic salt form.

Supporting Information Available

Experimental details (PDF) and X-ray crystallographic file in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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