Screening for crystalline salts *via* mechanochemistry†

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Neat grinding and solvent-drop grinding methods are found to be effective screening tools for indicating the potential for crystalline salt formation involving a given acid–base pair, as demonstrated with two model pharmaceuticals.

The formation of crystalline ionic complexes, or salts, is of fundamental importance to the development of many active pharmaceutical ingredients (APIs), where the approach is used for both reaction purification and physical property optimization.[1] A salt screen that reveals the maximum number of salt forms of a given API allows researchers to achieve an optimal physical property profile prior to formulation development. A great deal of effort, increasingly using high-throughput robotics, is currently expended in revealing available salt forms of a given API.[2,3]

Salts are typically formed by crystallization from solution. In attempting to maximize the number of salts obtained from a solution-based salt screen, the total number of experiments can be extensive. Variables include temperature and concentration gradients, solvent system selection, and crystallization method (*e.g.* solvent evaporation, cooling, and antisolvent addition). As an example, a solution-based high throughput crystal form screen of the API sertraline involved 3600 experiments in order to reveal a total of 18 crystalline salts.[4] The large number of variables coupled with the urgent pace of drug development suggests that a more efficient and selective approach to pharmaceutical salt screening would provide immediate value to researchers in this field.

Performed manually with a mortar and pestle or mechanically with a mill, solid-state grinding[5] is a mechanochemical alternative to solution-based crystallization as a means of obtaining crystalline complexes (*e.g.* charge-transfer complexes,[6] salts[7] and cocrystals[8]) and offers an advantage in ease of experimental design. The standard solvent-free 'neat grinding' method was recently modified to provide rate enhancement and added selectivity in certain cases *via* the addition of sub-stoichiometric amounts of solvent to the grinding mixture; this has been termed 'solvent-drop grinding'.[9–12]

The aim of the current study was to evaluate whether screening for salts of APIs by grinding could provide increased effectiveness, in terms of both screening efficiency and ability to reveal new forms. The Cambridge Structural Database[13] (CSD) was searched for APIs with a large number of reported crystal structures of pharmaceutically-acceptable[1] salts. In order to validate the use of grinding as a screening tool for pharmaceutical salts, the methods of neat grinding and solvent-drop grinding were employed to attempt a 'salt screen' for the known CSD salt forms.

Two structurally similar APIs, the antibacterial drug trimethoprim (**T**) and the antimalarial drug pyrimethamine (**P**), were identified as appropriate candidates for this initial pilot study; both are weak nitrogenous bases. Salts under present consideration were limited to those of the API with pharmaceutically-acceptable carboxylic acids. Chemical structures of APIs and CSD reference codes for crystal structures of salts are provided in Table 1. All salt structures were reported to have been solved by single-crystal XRD on crystals grown by solvent crystallization. The reported salts were of 1 : 1 API : acid stoichiometry with the exception of the 2 : 1 **P** : fumarate salt. Also of note is that the reported **T** : salicylate salt is a methanol solvate, and the reported **P** : acetate salt is a monohydrate. Salts of **T** : fumarate and **T** : succinate were not available in the CSD, but were included in the grinding salt screen to provide continuity with experiments involving **P**. All grinding experiments were performed mechanically with ingoing 1 : 1 API : acid stoichiometry, and identical grinding conditions were maintained for each experiment, with the exception of the addition of solvent for solvent-drop grinding.‡ Analysis by PXRD was used to determine the existence of new crystalline phases; for each material representing a new phase, solution ^{1}H and ^{13}C NMR data confirmed that the new phase did not represent a chemical reaction other than salt formation between starting components.‡

Results of the mechanochemical salt screening experiments, as determined by PXRD analysis and summarized in Table 1, demonstrated several possible outcomes: grinding was shown to produce either (1) no reaction, as judged by the presence of a physical mixture of starting materials; (2) the known CSD salt form; or (3) a new crystal form, see Scheme 1.

Upon neat grinding (in the absence of solvent), reaction was achieved in 6 of the 14 possible cases. Of the 6 experiments that produced phases not corresponding to starting materials, 2 grinding experiments (**T** : glutarate; **P** : formate) resulted in materials with PXRD patterns matching the known CSD salt forms. Other experiments (**T** : formate; **T** : acetate; **P** : glutarate) represented the synthesis of new crystalline salts, including the experiment involving **P** : acetate, which produced a PXRD pattern that was tentatively identified as a new salt.§ That a number of the materials produced by neat grinding represented new salt forms of **T** and **P** demonstrated that neat grinding provides a specific advantage over solution-based salt synthesis, in agreement with a finding from a related study.[7]

To evaluate whether the method of solvent-drop grinding could enable additional improvements in screening effectiveness, methanol was added in small quantities to the grinding jars prior to repeating each grinding experiment.‡ Methanol was selected on

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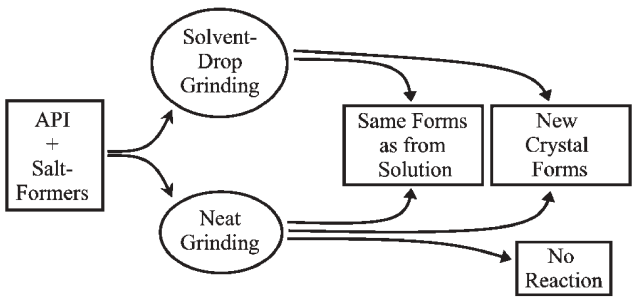
† Electronic supplementary information (ESI) available: Literature references for CSD crystal structures and overlay of PXRD patterns of each material obtained by grinding. See DOI: 10.1039/b512626f

Table 1 Results of solid-state grinding salt screen

	Trimethoprim (**T**) salt screen			Pyrimethamine (**P**) salt screen		
Counterion	Known crystalline salt[a]	Neat grinding[b]	Solvent-drop grinding[b]	Known crystalline salt[a]	Neat grinding[b]	Solvent-drop grinding[b]
formate	TMPFOR01	+	+	UHAYIL	√	√
acetate	FUWVAU	+	+	*CIVDIU*	+	++
maleate	QIKDIX	x	√	ULAXOU	x	√
fumarate	(None)	x	+	ULAXIO	x	+
succinate	(None)	x	+	ULAYAH	x	√
glutarate	CACBOY	√	√	UHAYEH	+	+
salicylate	*MIFWUT*	x	+	CIVDOA	x	+

[a] Crystal structure CSD reference codes are provided here; literature references provided as ESI.† 'None' indicates crystal structure of salt not reported in the literature. Italicized reference codes indicate structure also contains solvent of crystallization (see text). [b] Symbols indicate the following: **x** = no salt formation occurred on grinding (physical mixture observed by PXRD); √ = grinding produced material with PXRD pattern matching that simulated from known CSD salt form; **+** = grinding produced a PXRD pattern distinct from starting materials and known CSD salt form; **++** = a new PXRD pattern resulted that was different from neat grinding product (*i.e.* the likely generation of an alternate crystal form). Solvent-drop grinding experiments were conducted with methanol.



Scheme 1 Diagram showing results from salt screening *via* grinding.

the basis that this solvent showed success in previous solvent-drop grinding cocrystallization studies.[9,11] Furthermore, methanol is commonly used in the pharmaceutical industry and was a reported crystallization solvent of several of the CSD salts of compound **P**.

All 14 solvent-drop grinding experiments resulted in the formation of crystalline forms distinct from starting materials (as determined by PXRD). Five of the 14 experiments resulted in the known CSD salts. The products of the other 9 experiments did not match those from the CSD, suggesting that new salts had formed.

In 3 of the instances where neat grinding resulted in no reaction (**T** : maleate; **P** : maleate; **P** : succinate), solvent-drop grinding produced the known CSD salt form. An illustrative example is provided as Figure 1. In several other cases where neat grinding resulted in no reaction (**T** : fumarate; **T** : succinate; **T** : salicylate; **P** : fumarate), solvent-drop grinding produced materials with PXRD patterns not corresponding to a known CSD salt form. In addition, the experiment involving **P** : salicylate produced a new phase upon solvent-drop grinding that did not unambiguously match the CSD entry.§ Furthermore, the solvent-drop grinding experiment involving **P** : acetate appeared, on the basis of a tentative assignment, to have produced a second new salt form, distinct from the neat grinding product.§

In the case involving **T** : succinate, where a crystal structure for the salt was not in the CSD, evidence of salt formation by solvent-drop grinding prompted solution growth experiments that yielded

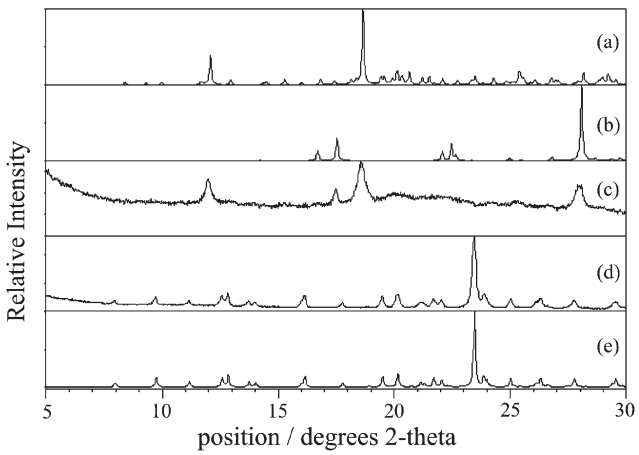


Fig. 1 Overlay of PXRD patterns: (a) **P**, simulated from CSD structure MUFMAB; (b) maleic acid simulated from CSD structure MALIAC11; (c) product from neat grinding of **P** and maleic acid; (d) product from solvent-drop grinding of **P** and maleic acid; (e) **P** : maleate salt, simulated from CSD structure ULAXOU.

single crystals by slow evaporation from DMSO. The good agreement between the PXRD pattern of the new phase produced by solvent-drop grinding and the pattern simulated from the subsequent single-crystal XRD structure of a 2 : 1 **T** : succinate salt is shown in Figure 2, together with the 'no reaction' result from neat grinding. Crystal structure data for this salt is provided as ESI.† The fact that several salt forms resulted exclusively from solvent-drop grinding indicates an enhanced ability of this approach to reveal new crystal forms over both neat grinding and solution-based crystallization.

In summary, neat grinding provided *ca.* 40% overall screening efficiency, measured as the percentage of experiments that generated crystalline products distinct from physical mixtures of starting materials. Upon performing the grinding salt screen with methanol addition, overall screening efficiency increased from *ca.* 40% for neat grinding to a remarkable 100% for solvent-drop grinding.

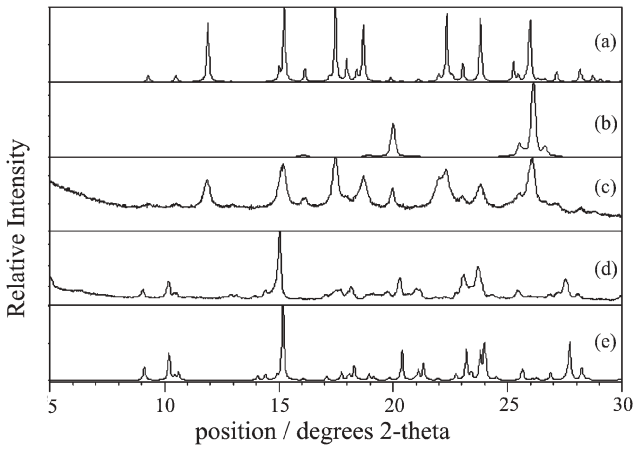


Fig. 2 Overlay of PXRD patterns: (a) **T**, simulated from CSD structure AMXBPM10; (b) succinic acid β-polymorph simulated from CSD structure SUCACB06; (c) product of neat grinding of **T** and succinic acid; (d) product from solvent-drop grinding of **T** and succinic acid; (e) **T** : succinate salt, simulated from single crystal data obtained in this study.

Neat grinding, which contains inherent benefits in terms of green chemistry application and experiment design free of solvent considerations, demonstrated overall utility as a salt screening technique, having produced several known CSD salts and a number of new crystal forms. The implementation of solvent-drop grinding with methanol provided significant benefit in terms of overall screening effectiveness, including revealing salts of two API : acid combinations not known to form prior to this study. It is noteworthy that several CSD salts were not reproduced in this preliminary grinding screen, suggesting that maximum salt form diversity will be achieved through a combination of solid-state grinding and solution-based techniques.

We note that the tendency for an API to lose crystallinity upon grinding may not necessarily reduce its potential for use in salt screening *via* solid-state grinding. While grinding of either **T** or **P** alone resulted in significantly reduced crystallinity, several of the salts obtained, particularly those obtained by solvent-drop grinding, possessed a good degree of crystallinity, as judged by relative intensities of PXRD peaks.

Additional investigation is necessary to determine whether other solvents will produce similar effects as those observed to result from solvent-drop grinding with methanol. In an indication that solvent choice may be an important factor in salt synthesis outcome, recent reports showed that solvent choice in solvent-drop grinding cocrystal syntheses dictated polymorphic[10] and stoichiometric[11] outcome.

To better understand the structural features and physical properties of the new crystal forms obtained in this study, full crystal structure data will be necessary. While single-crystal XRD is not possible on materials prepared directly by grinding, alternative means of obtaining crystal structures include structure determination from PXRD data as well as the use of material from grinding as seeds in subsequent solution growth experiments.[14–16] As it is possible that several of the new crystal forms described here are polymorphs of the known CSD salts of **T** and **P**, the mechanochemical approach will be of particular interest in terms of its ability to generate new polymorphs of salts.

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Notes and references

‡ Grinding was performed with a Retsch Mixer Mill model MM200 using 10 ml stainless steel grinding jars with two 7 mm stainless steel grinding balls at a rate of 30 Hz for a total time of 30 min. 250 mg API was used with an equimolar amount of acid. In the case of solvent addition, 2 drops from a pipette (*ca.* 0.03 ml) of methanol was added to the ingoing powder mixture prior to beginning grinding. Solution NMR (^{1}H and ^{13}C, DMSO-d_6 solvent) was performed on a Bruker Avance 500 MHz TCI spectrometer. PXRD patterns were collected on a Philips X'Pert Pro diffractometer using Ni-filtered CuKα radiation (λ = 1.5418 Å) at 40 kV and 40 mA using an X'Celerator RTMS detector. Each sample was analyzed between 2.5 and 50.0° 2θ with a step size of *ca.* 0.02° 2θ and a total scan time of 4.0 min. PXRD patterns were simulated from single crystal data using the software *Mercury* (version 1.4, CCDC, Cambridge, UK). PXRD pattern comparison was performed using the software *X'Pert Highscore* (version 1.0f, PANalytical B.V., Almelo, the Netherlands). Single-crystal XRD data were collected on a Nonius Kappa CCD diffractometer and structure solution and refinement were carried out using the *SHELXS-97* software package (University of Göttingen, Germany). Crystal structure data for **T** : succinate salt: $C_{14}H_{19}N_4O_3{\cdot}0.5(C_4H_4O_4)$, M = 349.37, monoclinic, *C*2/*c*, a = 17.343(4), b = 11.672(2), c = 16.835(3) Å, β = 91.95(3)°, V = 3405.8(12) Å^3, T = 180(2) K, Z = 8, D_c = 1.363 g cm^{-3}, Mo-Kα, μ = 0.103 mm^{-1}, 3434 independent data with $I > 2\sigma(I)$, R = 0.0390, Rw = 0.1025. The acidic hydrogen was located on the base in the X-ray difference map and refined isotropically, all other hydrogen atom positions were calculated and refined using a riding model. CCDC 283624. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b512626f

§ The CSD entries for **P** : acetate (CIVDIU) and **P** : salicylate (CIVDOA) lacked 3D atomic coordinates; hence, experimental PXRD patterns could be compared only to the simulated line positions from these entries. As a result, these comparisons contained a degree of uncertainty regarding the overall agreement between experimental patterns and CSD entries.

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