Improving Mechanical Properties of Crystalline Solids by Cocrystal Formation: New Compressible Forms of Paracetamol

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Control of the solid-state arrangement of molecules within a crystal is a central challenge for organic materials chemistry. In the context of solid pharmaceuticals, addressing this challenge results in significant investment (of research time and finance) in methods for the discovery and the prediction of solid-state properties of new solid forms, such as polymorphs or salts. There are, however, limitations on the ability of salts and polymorphs to produce functional pharmaceutical materials. Salt formation is limited to molecules containing ionizable groups, and the pharmaceutical use of polymorphs is not preferred due to the danger of a polymorph transformation affecting a formulated product, as illustrated by the anti-HIV drug ritonavir.[1] Cocrystallization[2] is a recent approach in pharmaceutical materials science, and is recognized as a general strategy toward expanding the number of solid forms available to an active pharmaceutical ingredient (API). While cocrystals have already been proven useful in improving the stability,[3] solubility, and dissolution rate[4] of a variety of APIs, we now demonstrate cocrystallization as a means of generating solid forms of APIs with improved mechanical properties.[5] In particular, we have generated layered cocrystal forms of the nonionizable API paracetamol (**pca**, Fig. 1a) through liquid-assisted grinding (LAG).[6] We have additionally analyzed how the improved mechanical properties may be related to specific crystallographic features.

There are two well-known polymorphs of **pca**, forms **1** and **2**,[7] as well as a highly unstable third polymorph that has not yet been fully characterized.[8] The parallel packing of flat hydrogen-bonded layers in the metastable form **2**[9] results in superior compaction properties to the thermodynamically stable form **1**, which is composed of corrugated hydrogen-bonded layers of molecules (Fig. 1b, c). Although form **2** would, therefore, be preferred in an industrial tableting process, its lower thermodynamic stability prevents harvesting its use commercially. As a result, marketed **pca** tablets are a compromise involving form **1** accompanied by a large loading of a binder that prevents chipping and disintegration.[10]

Consequently, the development of a layered, thermodynamically stable, and pharmaceutically acceptable form of **pca** with properties similar to form **2** is an interesting challenge to (pharmaceutical) crystal engineering.[11–14] The challenge is further increased by the lack of acidic or basic functionalities on the **pca** molecule, preventing the synthesis of salts as alternative solid forms.[15]

We, therefore, decided to use cocrystallization as a strategy to generate layered solid forms of **pca** that would be thermodynamically stable and exhibit tablet-forming properties resembling form **2**. We were encouraged in this by a recent report by Sun and Hou, who reported that cocrystal formation can modify mechanical properties of caffeine.[16] As suitable cocrystal formers for the construction of a layered structure,[14] we selected molecules of comparable size to **pca** that have, or can readily adopt, a flat shape.[17] Having in mind the pharmaceutical relevance of our product, we utilized compounds generally recognized as safe (GRAS): malonic acid (**mal**), succinic acid (**suc**), adipic acid (**adi**), nicotinamide (**nic**), ascorbic acid (**asc**), saccharin (**sac**), theophylline (**thp**), theobromine (**thb**), and caffeine (**caf**), along with molecules we felt were required to fully explore the role of molecular shape and functionality in cocrystal formation: oxalic acid (**oxa**),[12c,13] naphthalene (**nap**), anthracene (**ant**), and phenazine (**phe**).

To achieve the highest efficiency of cocrystal screening, we selected mechanochemical methods, LAG and neat grinding.[6] These methods have been demonstrated to provide improved results compared to the more frequently used methods of thermal or solution-based cocrystallization. Cocrystal (**pca**)·(**thp**), previously obtained from solution by Childs et al.,[14] provided a suitable target to verify the efficiency of our screen. Furthermore, to ensure the completeness of our screen, as well as to obtain single crystals suitable for subsequent crystal-structure determination via X-ray diffraction, we additionally pursued cocrystallization from solution. Mechanochemical screening revealed four

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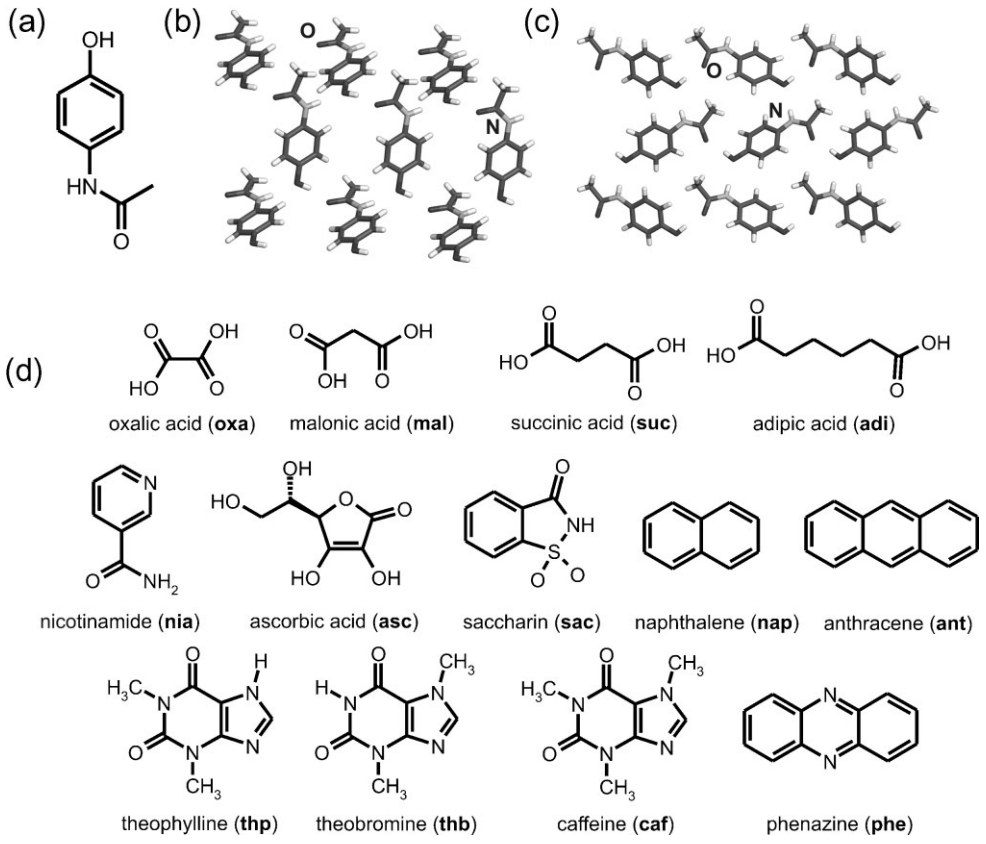

Figure 1. a) Molecular diagram of paracetamol (**pca**). b) Fragment of the crystal structure of **pca** form **1**. c) Fragment of the crystal structure of **pca** form **2**. d) Molecular diagrams of explored potential cocrystal formers for **pca**.

Table 1. Relevant mechanical properties of forms **1** and **2** and cocrystals. Diagonal elements S_{ij} of the calculated elastic compliance tensor and highest eigenvalue of the compliance matrix (λ)[d][e]

Material	**pca** form **1**	**pca** form **2**	(**pca**) · (**oxa**)	(**pca**) · (**thp**)	(**pca**)$_2$ · (**nap**)	(**pca**) · (**phe**)$_2$
Tablet thickness [mm]	–[a]	–[b]	2.54	2.37	2.71	2.89
Tablet diameter [mm]	–[a]	–[b]	5	5	5	5
Breaking force [N]	–[a]	–[b]	40	52	45	40
Tensile strength [MPa]	–[a]	–[b]	1.15	2.79	2.11	1.76
E_{latt} [kJ mol^{-1}][c]	−113.76	−109.56	−206.12	−231.79	−298.38	−322.09
S_{11} [GPa^{-1}][d]	0.113	0.031	0.293	0.350	0.091	0.142
S_{22} [GPa^{-1}][d]	0.198	0.074	0.032	0.040	0.048	0.167
S_{33} [GPa^{-1}][d]	0.088	0.102	0.295	0.322	0.068	0.176
S_{44} [GPa^{-1}][d]	0.188	0.336	0.425	0.634	0.117	0.704
S_{55} [GPa^{-1}][d]	0.202	1.034	0.076	0.380	0.362	0.543
S_{66} [GPa^{-1}][d]	0.132	0.098	0.353	0.325	1.011	0.254
λ [GPa^{-1}][e]	0.292	1.034	0.683	0.908	1.015	1.200

[a] Pure **1** did not form tablets; [b] The difficulties in preparing pure **2** prevented tabletting experiments on this material; [c] The calculated lattice energies, refer to a mol of one formula unit; [d] The reference axes for the elastic constants are defined as: **x**//**a**, **y**//**b**, **z**//**c** for the orthorhombic **pca** form **2**, **x**//**a***, **z**//**c**, **y** ⊥ **x**,**z** for the monoclinic and triclinic crystal structures; [e] The highest eigenvalue of the elastic compliance tensor.

new crystalline solids with **oxa**,[18,19] **nap**, and **phe**, as well as the known cocrystal (**pca**) · (**thp**). The cocrystal involving **oxa** has to date only been obtained mechanochemically.

The testing of compression properties (Table 1) demonstrated that all four cocrystals, (**pca**) · (**oxa**), (**pca**) · (**thp**), (**pca**)$_2$ · (**nap**), and (**pca**) · (**phe**)$_2$, are superior to form **1** in tablet formation. In particular, while form **1** could not be compressed into a tablet without extensive chipping, all four cocrystallization products readily formed tablets (Fig. 2a). The comparison of tensile strengths (Table 1) measured for the resulting tablets allowed ranking the tablets in the following order: (**pca**) · (**oxa**) < (**pca**) · (**phe**)$_2$ < (**pca**)$_2$ · (**nap**) < (**pca**) · (**thp**).

To rationalize the observed improvement in mechanical properties at the molecular level, the crystal structures of

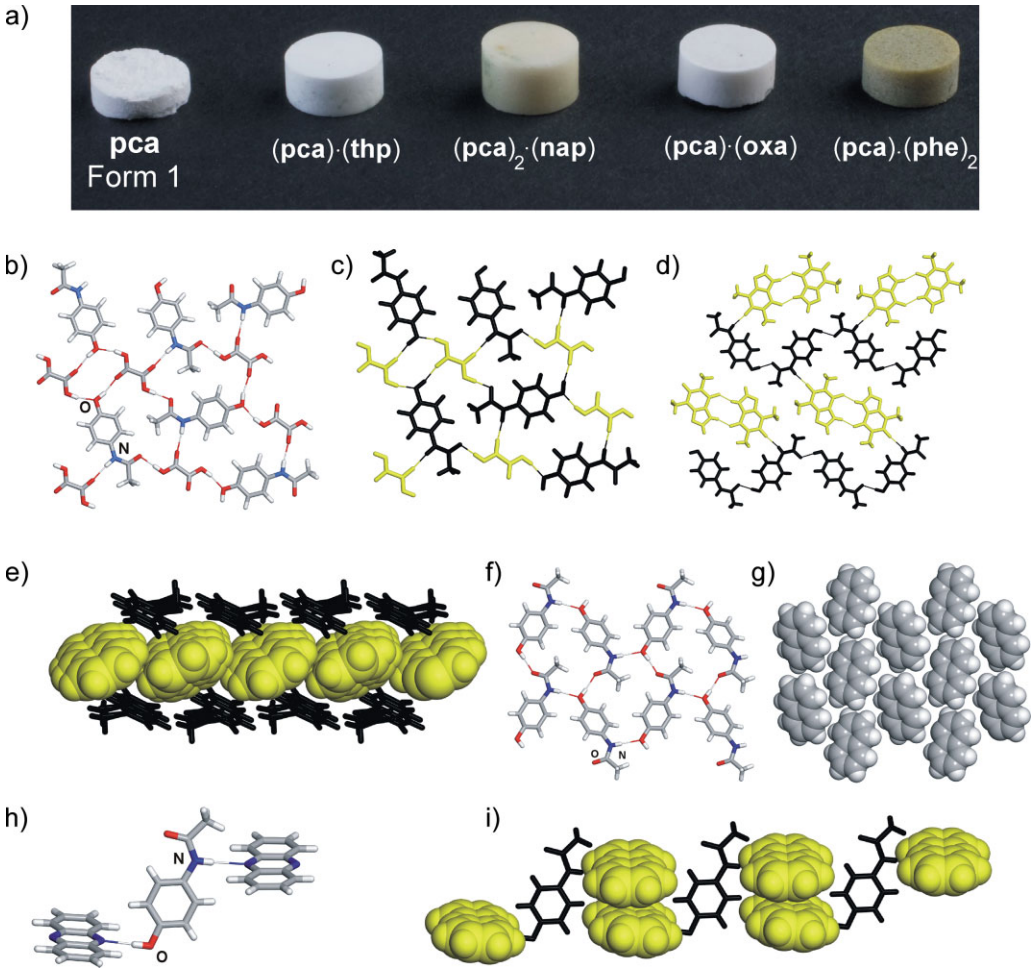

Figure 2. a) Tablets resulting from compression experiments involving **pca** form **1** and the four derived cocrystals. b) A hydrogen-bonded layer in (**pca**) · (**oxa**). c) The same layer fragment with **pca** and **oxa** molecules shown in black and yellow, respectively. d) A hydrogen-bonded layer in (**pca**) · (**thp**) with **pca** and **thp** molecules shown in black and yellow, respectively. e) Fragment of the $(\mathbf{pca})_2 \cdot (\mathbf{nap})$ structure, viewed along the crystallographic *b*-axis, with **pca** and **nap** shown in black and yellow, respectively. f) and g) Single layers of **pca** and **nap** in $(\mathbf{pca})_2 \cdot (\mathbf{nap})$, respectively. h) Molecular assembly in the cocrystal $(\mathbf{pca}) \cdot (\mathbf{phe})_2$. i) Molecular tape in $(\mathbf{pca}) \cdot (\mathbf{phe})_2$, with **pca** shown in black and **phe** in yellow.

(**pca**) · (**oxa**), $(\mathbf{pca})_2 \cdot (\mathbf{nap})$ and $(\mathbf{pca}) \cdot (\mathbf{phe})_2$ were determined. Structural analysis confirmed that (**pca**) · (**oxa**) was a cocrystal, composed of hydrogen-bonded **pca** and **oxa** molecules which form hydrogen-bonded layers (Fig. 2b,c). In each layer, **pca** acts as a two-fold hydrogen-bond donor through amide NH and phenol OH functionalities, and as a two-fold acceptor via the amide CO and phenol OH groups (Fig. 2b). Thus, each **pca** molecule is hydrogen-bonded to four neighboring **oxa** molecules and, conversely, each **oxa** molecule to four **pca** molecules (Fig. 2c). The outcome is a layered structure achieved by two-dimensional tiling of 0D (unimolecular) motifs of **pca** and **oxa**. The structure of (**pca**) · (**oxa**) is different to the layered structure observed in (**pca**) · (**thp**), which is formed by a combination of 0D dimer motifs of **thp** and 1D tape motifs of **pca** (Fig. 2d). The dimers of **thp** in each layer are formed through a pair of N−H···O (O···N separation 2.73 Å) hydrogen bonds joined in an $R_2^2(10)$ motif.[20] Molecules of **pca** form zigzag tapes held together by O−H···O hydrogen bonds (O···O separation 2.72 Å) with OH donors and imide C=O acceptors. The **pca** tapes link to **thp** dimers via N−H···O bonds between amide NH groups of **pca** and imide C=O groups of **thp**. In addition to classical O−H···O and N−H−O hydrogen bonds, **pca** and **thp** also connect via C−H···O (C−O separation: 3.29 Å) interactions[21] involving the OH group of **pca** as the acceptor and the imidazole CH group of **thp** as the donor.

In the $(\mathbf{pca})_2 \cdot (\mathbf{nap})$ cocrystal, the layered structure involves stacking of alternating layers of **pca** and **nap** (Fig. 2e). The **pca** layers in $(\mathbf{pca})_2 \cdot (\mathbf{nap})$ (Fig. 2f) strongly resemble those in form **2**. In particular, N−H···O and O−H···O hydrogen-bond separations in form **2** are 2.94 and 2.71 Å, respectively,[7a] while corresponding distances in $(\mathbf{pca})_2 \cdot (\mathbf{nap})$ are 2.93 and 2.64 Å. The structure of a **nap** layer in $(\mathbf{pca})_2 \cdot (\mathbf{nap})$ resembles the {101} layer in pure **nap** (Fig. 2g).[22]

In contrast to (**pca**) · (**oxa**) and (**pca**) · (**thp**), the structure of $(\mathbf{pca})_2 \cdot (\mathbf{nap})$ does not involve strong hydrogen bonding between the API and the cocrystal former. Instead, the layers are connected by weak C−H···π and π···π interactions, suggesting that $(\mathbf{pca})_2 \cdot (\mathbf{nap})$ could be regarded as a layered inclusion compound

of **pca** form **2**. However, the layers in (**pca**)$_2$ · (**nap**) are not robust to the loss of **nap**, as demonstrated by in situ powder X-ray diffraction (PXRD) measurements on a (**pca**)$_2$ · (**nap**) sample, such that when heated from 30 to 180 °C, a simultaneous loss of **nap** by sublimation and formation of form **1** takes place.

The inability of **ant** to form a cocrystal with **pca** suggests that (**pca**)$_2$ · (**nap**) resulted from a serendipitous fit of molecular shapes and sizes. To explore if incompatibility of **pca** with **ant** may be overcome by hydrogen bonding, we utilized **phe** as an analog of **ant** substituted with two nitrogen atoms as hydrogen-bonding "handles."[23] The resulting (**pca**) · (**phe**)$_2$ cocrystal is composed of finite Z-shaped assemblies held together by O−H···N (2.84 Å) and N−H···N (3.00 Å) hydrogen bonds. In each assembly, **pca** acts as the hydrogen bond donor, whilst pairs of **phe** join neighboring assemblies into supramolecular tapes via π-stacking interactions (Fig. 2h,i).

The layered structures of (**pca**) · (**oxa**), (**pca**) · (**thp**), and (**pca**)$_2$ · (**nap**) provide a tentative explanation for the observed enhanced ability to form tablets. To further explore the relationships between crystal packing and mechanical properties, we have estimated the elastic constants of each cocrystal from the second derivatives of their calculated lattice energies, using the program DMAREL.[24] Such calculations have previously been used to rationalize the mechanical property differences between **pca** forms **1** and **2**.[9d] As a measure to compare the four cocrystals and the two polymorphs of pure **pca**, we have calculated the eigenvalues of the elastic compliance tensor, *S*. The value of the highest eigenvalue, λ, is a measure of the compliance of the crystal to its most facile distortion. We find that crystals with weak shear planes have a high compliance eigenvalue, corresponding to a shearing stress. This is illustrated by the values calculated for the two polymorphs of **pca** (Table 1): form **1**, with its corrugated layers of molecules, has a low compliance, while the highest eigenvalue of the form **2** compliance tensor is much higher, and corresponds to S_{55}—shearing of {010} crystal planes along [100]. This ability of **pca** form **2** to be compressed into tablets is attributed to this compliance to shear, leading to plastic deformation during compaction.[9]

Comparing all six crystals, λ increases in the order: **pca** form **1** < (**pca**) · (**oxa**) < (**pca**) · (**thp**) < (**pca**)$_2$ · (**nap**) ≈ **pca** form **2** < (**pca**) · (**phe**)$_2$, and the cocrystals are expected to have tableting properties more similar to those of **pca** form **2** than form **1**. While we did not measure properties of pure **pca** form **1** tablets due to its inability to form a tablet, there is a relationship between our calculated λ and the measured tensile strengths of the tablets made with each cocrystal. Analysis of the elastic compliance tensors also indicated that the weakest shear planes in the layered crystals are nearly parallel to the planes of molecular layers: {104} in (**pca**) · (**oxa**), {103} in (**pca**) · (**thp**), and {100} in (**pca**) · (**nap**)$_2$, supporting the expected relationship between layered structure and improved tabletability. Of the layered cocrystal structures, (**pca**) · (**oxa**) is calculated to be the least compliant to shear stress and, indeed, is the cocrystal that leads to tablets with the lowest tensile strength.

Although the structure of (**pca**) · (**phe**)$_2$ is not layered, the cocrystal demonstrated superior mechanical properties to **1**, in agreement with the comparison of calculated λ values. A possible explanation for this improvement may be found in the crystal structures of **pca** form **1** and (**pca**) · (**phe**)$_2$. Whereas **1** is built of corrugated and extensively hydrogen-bonded layers, the Z-shaped molecular assemblies in (**pca**) · (**phe**)$_2$ interact only by weak forces, such as π–π stacking and C−H···N interactions. Consequently, the structure of (**pca**) · (**phe**)$_2$ suggests an alternative approach to improve mechanical properties of APIs, by forming cocrystals composed of weakly interacting molecular assemblies. In such a scheme, the cocrystal former resembles a molecular-level binder, segregating API molecules that would otherwise interconnect via hydrogen bonds.

In summary, we have demonstrated, by an appropriate crystal-engineering strategy, the ability to construct stable **pca** cocrystals with layered structures, and with mechanical properties resembling those of form **2**. Indeed, **pca** is surprisingly versatile and robust in the formation of layered structures, acting as a four-connected building block that can assemble into 0-, 1-, or 2D motifs with a suitable cocrystal former. Engineering of mechanical properties via cocrystallization can provide materials suitable for pharmaceutical applications such as in the case of (**pca**) · (**thp**),[14] a layered cocrystal of high tensile strength that consists of pharmaceutically acceptable components. We believe that the results presented herein illustrate how cocrystallization, even in the absence of a synthon-based design, can be utilized together with modern experimental and theoretical techniques to provide solutions and innovations to technologically important problems.

Experimental

Details of cocrystal preparation, compression experiments, solid-state analysis, and computational methods are given in the Supporting Information, along with relevant PXRD, differential scanning calorimetry (DSC), and Fourier-transform (FT)-IR data and the complete calculated elastic compliance tensors.

[CCDC 720365–720368 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.]

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