Exceptional powder tabletability of elastically flexible crystals

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Abstract

Reversible elastic deformation is deleterious to tablet formation by powder compaction. However, highly elastic caffeine and 4-chloro-3-nitrobenzoic acid cocrystal methanolate (CCM) exhibited surprisingly high tabletability, surpassing that of well-known plastically deformable crystals. We show that the exceptional tabletability of CCM powder is due to the activation of the (010) slip planes along the <001> direction during tableting. The same slip system is dormant when the needle-shaped CCM single crystals are bent on the side faces (1-10) or (110). Thus, the successful prediction of tableting performance requires consideration of crystal anisotropy and stress conditions during powder compression instead of the qualitative single-crystal bending behavior.

Keywords: Powder compaction, crystal plasticity, elastic-plastic material, mechanical testing

Mechanically flexible, i.e., elastically and plastically bendable, organic and organometallic crystals have attracted tremendous attention in recent years.[1–12] A fundamental understanding of such intriguing material properties requires studying the compression and elongation as well as breakage and formation of weak non-covalent chemical bonds, such as hydrogen bonds, halogen bonds, and $\pi\cdots\pi$ stacking. Despite the significant progress in designing and understanding the properties of flexible organic crystals, they continue to bring surprises.[1–12] Effective crystal engineering based on an understanding of structure-property relationships has broad applications in improving the performance of a wide range of materials, including pharmaceutics, flexible optoelectronics, explosives, and mechanical actuators.[13] One of the outstanding challenges in the design of functional materials through crystal structure engineering is predicting the behavior of bulk powder samples from single crystals of organic compounds. During powder compaction of crystalline solids in the pharmaceutical industry, particles undergo a complex process involving rearrangement, fragmentation, elastic deformation, plastic deformation, and viscoelastic deformation. Thus, the tableting behavior of crystalline active pharmaceutical ingredients (APIs) is challenging to predict. Recent studies using crystal engineering approaches revealed that understanding the structural basis for mechanical properties can greatly improve our ability to design high-quality pharmaceutical tablets.[14,15]

According to the bonding area-bonding strength (BABS) model,[16,17] inadequate plasticity is the primary reason for poor tableting performance due to the inability of particles to develop a sufficient bonding area (BA) in a tablet through permanent plastic deformation.[13,18] As such, crystalline APIs designed with improved plasticity have been shown to achieve excellent tabletability.[3] High plasticity is closely linked to the presence of unobstructed molecular layers, or slip planes, with low interlayer attractive and steric interactions in a crystal structure.[3,14,15,19]

Consequently, the tabletability of the emerging class of highly elastic crystals may be intuitively expected to be poor because elastic deformation does not contribute to the development of permanent BA in a tablet after compression.[16,20] In fact, the recovery after excessive elastic deformation is responsible for the phenomenon of overcompression, where tablets are weakened by increased pressure above a certain threshold.[21] Until now, however, no systematic studies on powder compaction of elastic crystals have been performed to test this hypothesis.[20] From the list of known elastic crystals,[6,10,12,13,18,22–26] we chose the caffeine:4-chloro-3-nitrobenzoic acid cocrystal methanol solvate (CCM) in this work.[10]

Surprisingly, the CCM powder exhibited exceptional tabletability, which was even better than that of the highly plastic caffeine hydrate (CAH) and the Schiff base of ortho-vanillin with 6-chloro-2,4-dinitroaniline cocrystal (sb-ovan:cda) (Figure 1), which have the best-known tabletability among organic crystals so far.[3,27]

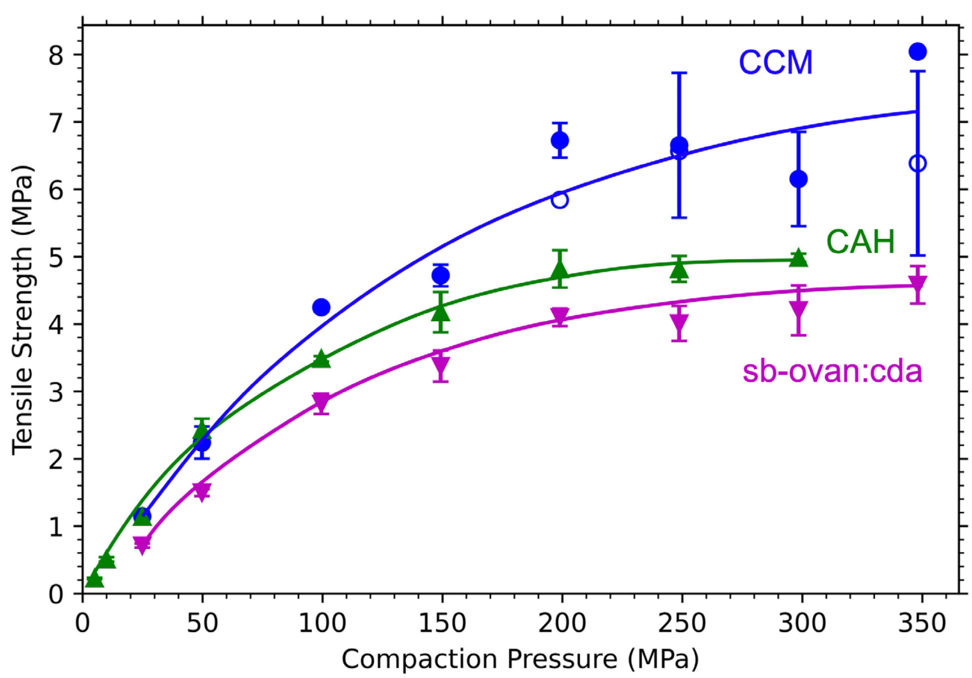

Figure 1. Tabletability profiles of CCM (circles), 2D plastic CAH (up triangles), and sb-ovan:cda (down triangles). Open symbols signify tablet lamination during the diametrical breaking test.

Such exceptionally good tabletability necessitates a large BA in a tablet, which can be achieved only when CCM crystals undergo a significant degree of plastic deformation during compression. However, CCM single crystals exhibited substantial 2D elastic flexibility when bent by a load applied on the side faces of the needle crystal (Figure S1).[28] To reconcile the seemingly contradicting observations between single crystal mechanical behavior and bulk powder compression, we quantified the elastic recovery and plasticity of CCM during compression.

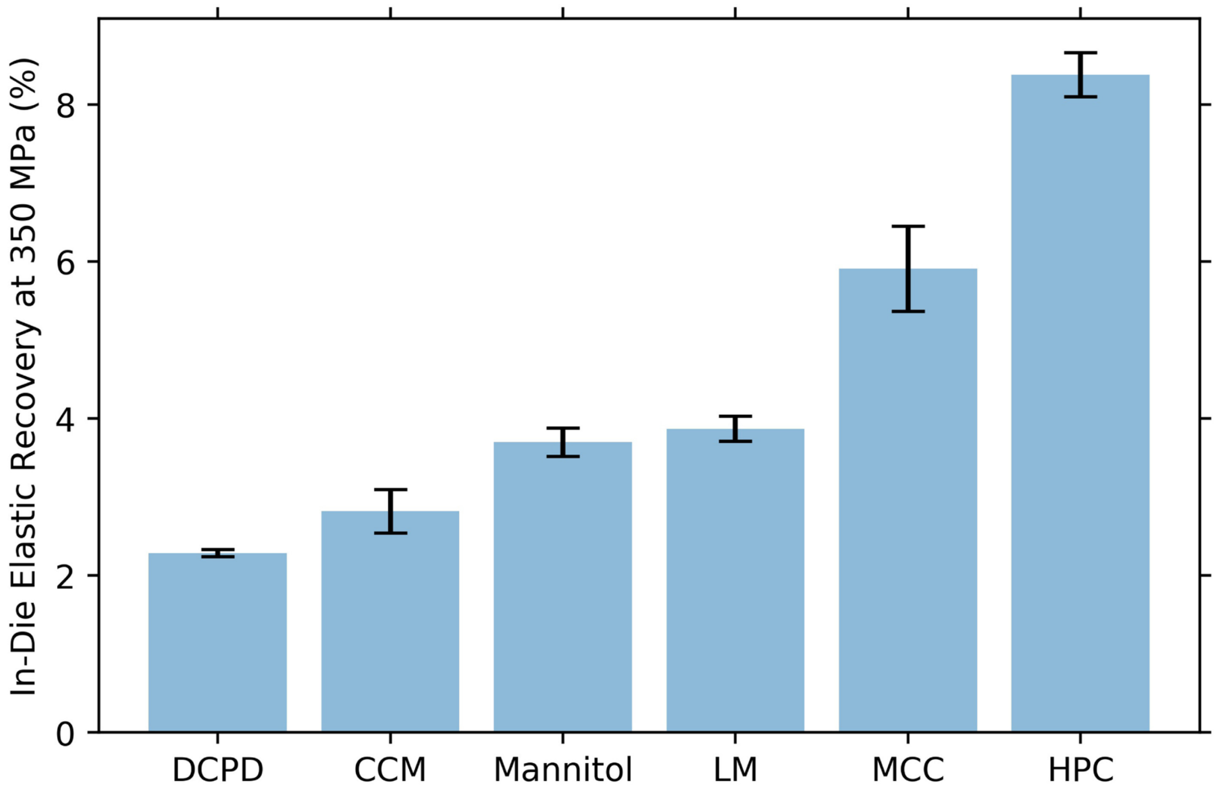

Figure 2. Elastic recovery after compression at 350 MPa of DCPD, CCM, mannitol, LM, MCC, and HPC.

At 350 MPa, which is a relatively high pressure for tablet manufacturing, the in-die elastic recovery of CCM (< 3%) was lower than commonly used excipients, e.g., mannitol, lactose monohydrate (LM), microcrystalline cellulose (MCC), and hydroxypropyl cellulose (HPC),[29] but slightly higher than that of dicalcium phosphate dihydrate (DCPD) (Figure 2). Thus, the extent of elastic recovery of the compressed CCM tablet is far lower than the maximum elastic strain, which approached 12.5% when CCM single crystals were bent on a crystal side face.[10] If the elastic strain of individual CCM crystals were the same as that of the tablet, i.e., the mechanical properties of CCM crystals were isotropic, the strain of CCM would be far below its elastic limit along the crystal needle axis, <001>.[28] In that case, plastic deformation would not have taken place. Therefore, the anisotropy of CCM mechanical properties plays a necessary role in enabling the plastic deformation required to form strong tablets. This data indicates that the mechanical behavior of single crystals during bending is different from bulk powder compression.

From the exponential relationship between tablet elastic modulus and porosity, the elastic modulus at zero porosity (E_0) can be obtained by extrapolating experimental data to zero porosity (Figure S2). The E_0 of the CCM (5.0 ± 0.2 GPa) is about half of the E along the long axis of the crystal obtained from molecular dynamic calculations (~10 GPa).[30] This value is lower than the E_0 of mannitol (11.1 GPa) and potassium chloride (9.2 GPa) but higher than that of aspirin (2.3 GPa) and MCC (4.7 GPa), all of which were determined using similar compressive methods.[31–33] Since potassium chloride, aspirin, and MCC are all plastic, the elasticity of bulk CCM powder, as measured by E_0, is similar to plastic powders during powder compression in die. The data thus far suggest that CCM crystals, despite being exceptionally elastic when bent, actually exhibit high plasticity during compaction, resembling that of well-characterized plastic materials.

The value of one plasticity parameter, *1/C*, of CCM (186 ± 36 MPa) lies between that of plastic MCC (76 ± 7 MPa) and brittle mannitol (455 ± 12 MPa), LM (504 ± 19 MPa), and DCPD (2133 ± 123 MPa) (Figure 3).[29,34] The value of another plasticity parameter, mean yield pressure (P_y), of CCM (54.7 ± 2.1 MPa), extracted from in-die compression data using the Heckel analysis (Figure S3), is similar to MCC (41.1 ± 1.8 MPa) but substantially lower than those of LM (163.5 ± 11.7 MPa), mannitol (143.0 ± 3.0 MPa), and DCPD (408.3 ± 27.3 MPa) (Figure 3).[29,35] Therefore, both plasticity parameters indicate that the CCM powder exhibits plasticity closer to plastic MCC than to brittle LM, mannitol, and DCPD. This is aligned with the large extent of plastic deformation required for the CCM to develop sufficient BA to account for its superior tabletability (Figure 1).

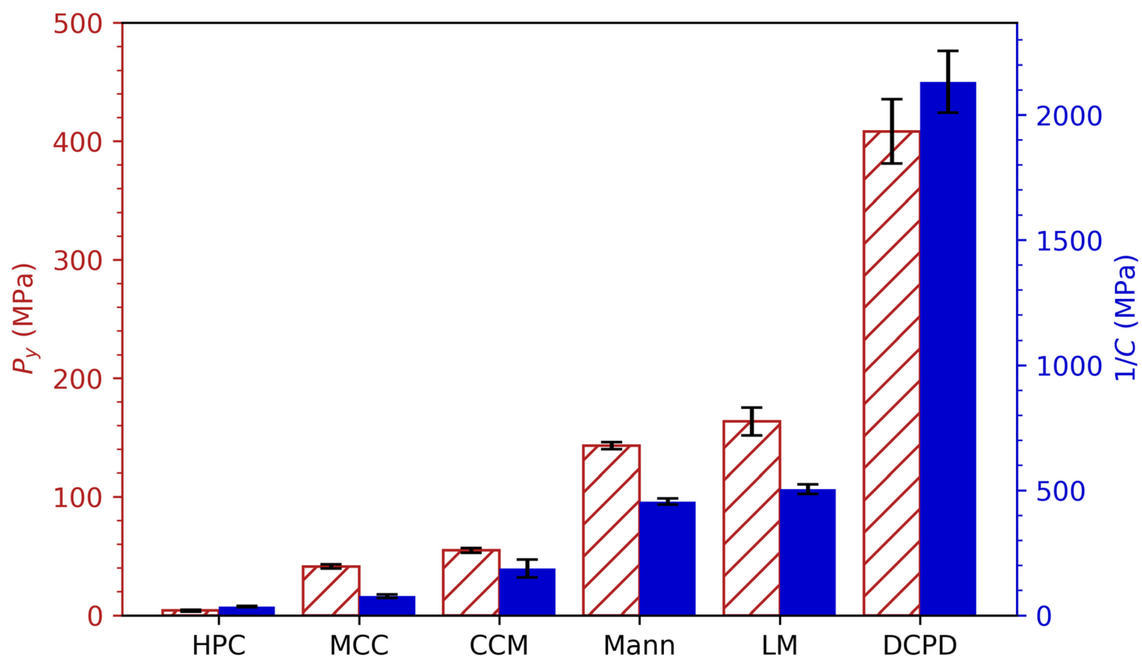

Figure 3. Plasticity parameters of HPC, MCC, CCM, mannitol, LM, MCC, and HPC (patterned bars, P_y; solid bars, *1/C*).

According to the BABS interplay model, in addition to BA, bonding strength (BS) is the other key factor that controls tabletability.[16,17] The apparent BS among different materials can be assessed using the tablet tensile strength value at zero porosity (σ_0), where a higher value of σ_0 indicates a higher apparent BS.[36,37] The σ_0 of CCM (7.7 ± 0.3 MPa) is lower than that of MCC (~11 MPa) and mannitol (12.4 MPa), but slightly higher than that of LM (6.7 MPa).[38,39] Therefore, instead of being a result of high BS, the exceptional tabletability of CCM is mainly a result of a high BA, which dictates a high plasticity.

A reconciliation between the exceptional elasticity of single crystals during bending and high plasticity during die compression can be achieved by considering the different stress conditions in the two scenarios. While the stress applied to single crystals is only along one direction during bending, crystals are subjected to a pseudo-hydraulic stress condition in-die during tableting, where stresses are applied to a given crystal from many directions through contacts with neighboring crystals and air (Figure 4**a**). When the stress is sufficiently high, the crystals will undergo plastic deformation by activating slip planes,[40,41] which remain dormant when a single crystal is bent. From a structural perspective, the most likely activated slip plane for the CCM is the (010) plane because these layers can slide with ease along the unobstructed <001> direction due to the relatively weak interaction energy between (010) planes, as shown by its energy framework (Figure 4**b**).[42,43] This mode of plastic deformation is inactive when the needle-shaped crystal is bent on the side crystal faces, (1-10) and (110),[44] because the slippage of the (010) planes along the <001> direction is effectively hindered, as the (010) planes are at an angle to the shear plane when the crystal is bent on either (1-10) or (110) face (Figure 4**b**).

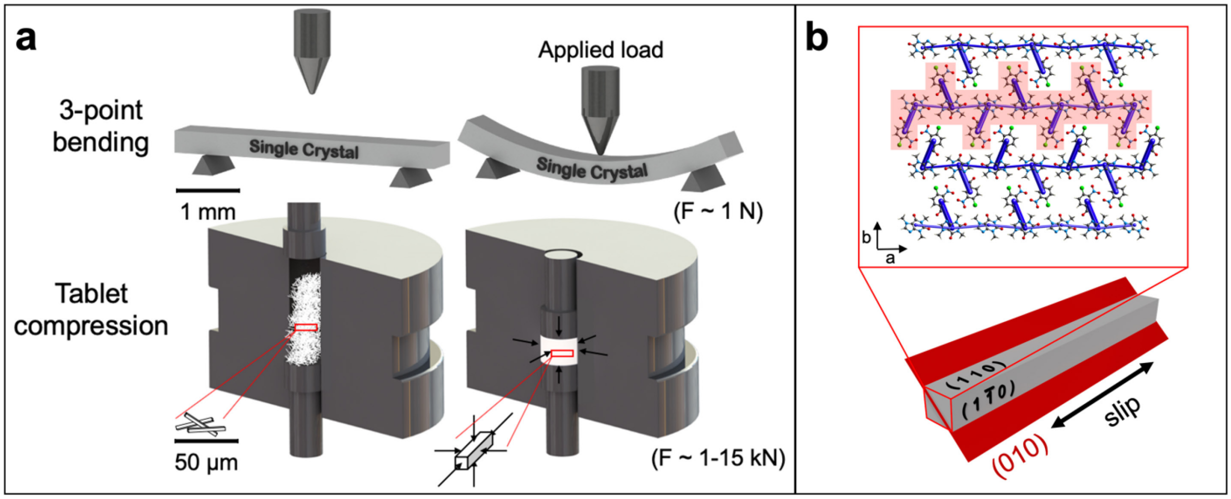

Figure 4. (**a**) Conditional difference between elastic deformation of a single crystal under 3-point bending and the plasticity of the bulk powder during compression, and (**b**) energy framework showing (010) as the most probable active slip plane.

This example shows that, although qualitative bending behaviors of single crystals are intuitively related to mechanical properties and bulk powder tableting performance, high single-crystal elasticity does not necessarily translate to poor tabletability because of distinct stress conditions during the two test scenarios. To further illustrate this point, we also tested the tabletability of desolvated CCM (CCMd, Figure S4), which exhibits brittle fracture instead of elastic flexibility when a stress is applied during a 3-point bending test.[10] The strikingly different bending behavior cannot be attributed to major structure differences because of the structural similarity between CCM and CCMd, indicated by their closely similar powder X-ray diffraction patterns (Figure S5). Therefore, the mechanical properties of these two crystalline phases are expected to be similar. The radically different brittle bending behavior of CCMd could be attributed to the presence of a significantly higher concentration of defects in CCMd crystals arising from the desolvation process, which promotes premature failure of the crystals through crack propagation.[10,45] Such an effect is expected to favor tabletability since more extensive fragmentation of crystals leads to a larger area for bonding among particles. However, the lack of elastic flexibility of CMMd during the 3-point bending experiment does not affect its bulk powder compaction properties, since E_0, P_y, tabletability, particle size, in-die elastic recovery, compressibility, compactibility, and *1/C* are all comparable between CCMd and CCM (Figures S2 – S4, S6 – S12). Therefore, the extent of crystal plastic deformation, which determines the total BA formed during powder compression, is affected by inherent mechanical properties dictated by crystal structure but is independent of the elastic flexibility of single crystals during a bending test.

Thus, in the case of CCM, powder tableting performance is directly linked to crystal structure and corresponding mechanical properties but is decoupled from single-crystal bending behavior. This work expands the potential applications of elastically flexible crystals in tableting. Results from this study highlight the importance of considering both structural origin and external stimuli when studying the properties and performance of organic materials.

Supporting Information

Methods and material details; 2D elastic bending of CCM; elastic modulus versus porosity; in-die Heckel plots, tabletability, PXRD, polarized light microscopy, in-die elastic recovery, compressibility, compactibility, pressure–density fitting using the Sun equation, TGA thermograms, and DSC thermograms of CCM and CCMd (PDF)

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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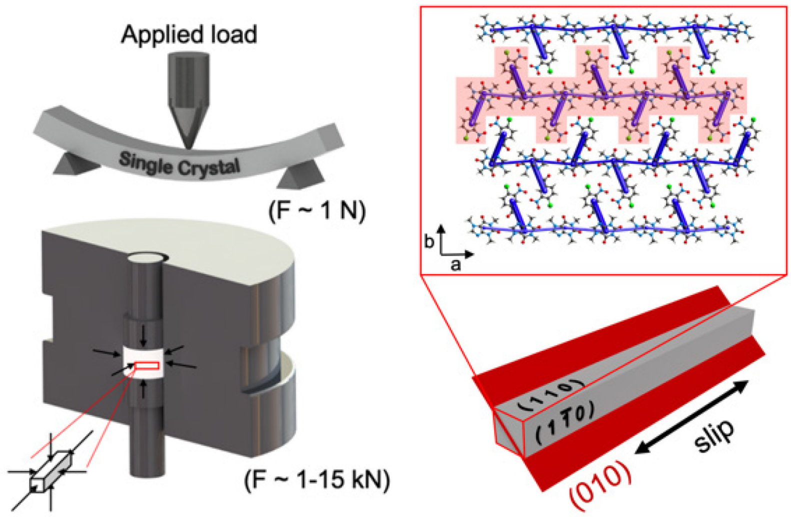

Synopsis

The surprisingly high tabletability of elastically bending caffeine cocrystal is explained by the activation of (010) slip planes along the <001> direction during powder compression.