SPECIAL ISSUE: Celebrating the 100th Anniversary of Nankai University

Mechanical properties of coordination polymer-based dietary supplements

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In the past two decades, coordination polymers (CPs) have been studied intensively in materials science due to their chemical diversity and unique hybrid nature integrating both the organic and inorganic components at the molecular level [1–3]. Recently, considerable efforts have been dedicated to investigating their physical properties, which include gas adsorption and separation [4], drug delivery [5], catalysis [6], ferromagnetism [7], ferroelectricity and multiferroicity [8]. Despite extensive studies on numerous properties of CPs, there is a major lack of knowledge about their applications as food dietary supplements and additives, which are commonly consumed in our daily life to provide mineral nutrition [9]. In terms of composition, CP-based dietary supplements have better bioactivity and less side-effects than conventional purely inorganic food supplements, and play a significant role in the food and pharmaceutical industry [10]. CP-based supplements and additives cover a wide range of materials, including calcium (e.g., calcium gluconate, calcium aspartate, calcium fumarate), copper (e.g., copper glycinate), magnesium (e.g., magnesium malate), zinc (e.g., zinc glycinate, zinc acetate), iron (e.g., ferrous fumarate), and potassium (e.g., potassium citrate) derivatives [9,11–15].

In the industrial-scale pharmaceutical manufacturing, for molecule drug crystals, the tablet form is often preferred as the dosage form among liquid, soft gel, powder, and capsule [16], because of its excellent product specifications such as long term stability, low cost, good portability, ability to resist tampering, high production throughput, flexibility with a unique product image (shape, size, and color) and easy usage [16–18]. However,

the confronting challenge is that the successful development of a tablet dosage form should consider the solubility, stability, bioavailability, and mechanical properties of the product. Fortunately, crystal engineering is widely utilized in designing active pharmaceutical ingredients (APIs) to solve above problems, and it can also be used to tune the mechanical properties such as grindability and tabletability. For example, there are many studies for adopting the optimum measures of constructing tablet product, such as cocrystallization [19–21], hydrates [22,23], salt formation [24] and multicomponent crystals [25].

Notably, one of the significant physicochemical properties of APIs is their mechanical properties (e.g., plasticity and elasticity). During tableting process of pharmaceutical powder, the crystals are milled and compacted, and the elastic and plastic properties during this complex process directly influence the powder tabletability [9,21,25–27]. For example, strong elastic recovery (the extent of slight recover during the decompression and ejection phases) after compression is considered as the main reason of adverse phenomena such as capping or delamination of tablets [17,18,25]. Furthermore, a better plasticity (the ability for a material undergoing permanent shape change, local structural distortion and irreversible deformation under the stress) *via* slipping in a crystal may result in more facile milling and better tabletability, which usually originates from the motions of dislocation along some specific slipped planes [25,27]. So it is of fundamental importance to understand the relationship between the crystal structure and mechanical properties of API crystals.

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However, comparing with the common pharmaceutical molecule drug crystals, food dietary supplements CPs present a significant lack of available knowledge on the elastic and plastic properties. Only few systematic studies involving zinc acetate dihydrate, zinc glycinate hydrate and calcium fumarate trihydrate have been investigated in the literatures [9,14,15]. It is worth noting that many CPs and coordination complexes (e.g., calcium gluconate [28], vitamin B₆ [29] and ferrous fumarate [28,30]) have been served as APIs in tablet form, for example, calcium gluconate (CHCaO) tablet is not only a mineral supplement and medication, but also used as a source of Ca²⁺ ion to regulate the drug release with the change in the concentration of calcium gluconate in alginate matrix tablets [31]. However, little has been known about the structure-mechanical property relationship of these CP crystals though it is of vice importance for their formulation and tableting, such as understanding the disintegration, dissolution and release [31,32]. This perspective highlights the latest advances in mechanical properties of CP-based dietary supplements, and discusses their determining influences in pharmaceutical manufacturing by comparing with small molecule drug crystals and inorganic dietary supplements.

The quantitative characterization of the mechanical properties of crystals can be facilitated by the nanoindentation technique, which has been successfully demonstrated for both metal-organic frameworks and organic crystals (including many small molecular pharmaceuticals such as APIs) [9,20,24,26,27]. Elasticity and plasticity of known CPs can be reflected by conventional mechanical metrics such as Young's modulus (E) and hardness (H). Fig. 1 demonstrates the structures of some selected CP-based food supplements, inorganic dietary supplements and small molecule drug crystals, and their E and H are plotted in Fig. 2.

For inorganic food dietary supplements, the mechanical properties of magnesium oxide (MgO, $Fm-3m$, cubic), zinc oxide (ZnO, $P63mc$, hexagonal wurtzite structure), and calcium carbonate (CaCO₃, $R-3c$, trigonal, Fig. 1a) crystals have been studied using a nanoindentation technique [33–35]. Caceres *et al.* [34] reported the H and E of pure MgO single crystals and for MgO crystals doped with H, Li, Ni or Co impurities, subjected to different thermal treatments. The results show that a constant value of 300 GPa for E was obtained in all cases, signifying that the elastic properties are not influenced by impurities or intrinsic defects. Moreover, the pure MgO crystals have a hardness of 9.2(2) GPa, and the enhancing hardness of doped crystals originated from impurities,

point defects, cavities and metallic precipitates, which indicates that impurities and thermally caused intrinsic defects significantly modifies the hardness of MgO single crystals. Kucheyev *et al.* [35] reported the deformation behavior of bulk ZnO single crystals by nanoindentation in combination with atomic force microscopy. Nanoindentation results reveal that plastic deformation has been observed with relatively low loads (≥ 4 –13 mN) and an ~ 4.2 μm radius spherical indenter, and the average values of the H and E are ~ 5.0 and ~ 111.2 GPa, respectively. Remarkably, the elastic-plastic threshold has been found to be dependent on the loading rate, and faster loading can result in larger threshold values, on average. Furthermore, slip has been identified as the major mode of plastic deformation in ZnO, which is responsible for the pop-in events witnessed during loading. In addition, Merkel *et al.* [33] reported the mechanical properties of calcite (CaCO₃) by nanoindentation on shell of the rhynchonelliform brachiopod *Mergerlia truncate*, the H and E are ~ 4.6 and ~ 80 GPa for the calcitic shell of *Mergerlia truncate*, respectively.

Turning attention to molecular crystals which are often brittle, their mechanical performance in the situation of crystal packing, slip, and defects plays an important role in pharmaceutical manufacturing. Moreover, molecular crystals are usually stabilized by weak interactions, such as hydrogen bonds and van der Waals interactions. As shown in Fig. 2, we plot the data of E and H for small molecule drug crystals, e.g., theophylline-methyl gallate [21], aspirin [36], saccharin [38], sodium saccharin [39], felodipine [37], voriconazole [24], omeprazole [40], sulfa drug [41], curcumin, *L*-alanine and caffeine:4-chloro-3-nitrobenzoic acid [21,42,43]. When comparing with the inorganic dietary supplement compounds ($E \sim 80$ –300 GPa and $H \sim 5$ –9 GPa for MgO, ZnO and CaCO₃), the E and H of these drug crystals are significantly lower and the ranges of E and H are ~ 3.79 –25.1 GPa and ~ 0.01 –1.14 GPa, respectively, which indicates the mechanical properties of molecular solids significantly differ from these inorganic compounds.

Molecular crystals can also exhibit the characteristic structural anisotropy in mechanical behavior. For example, aspirin is a mild drug that reduces pain and fever. Varughese *et al.* [36] reported the interaction anisotropy and shear instability of the two polymorphs of aspirin (polymorphs I and II exhibited similar crystal structures). The results of nanoindentation experiment on single crystals show that {001} face of polymorphs I is stiffer and harder than {10-2} face of polymorphs II, with a difference of 48% for the elastic moduli and 37% for the

Figure 1 (a) The crystal structures of three inorganic dietary supplements (MgO, ZnO and CaCO₃) [33–35]. (b) The typical small molecule drug crystals (aspirin-polymorphs I, felodipine-form II and voriconazole) [36]. Reproduced with permission from Ref. [37], Copyright 2014, Wiley-VCH and Ref. [24], Copyright 2015, American Chemical Society. (c) Zinc and calcium dietary supplements (zinc acetate dihydrate, zinc glycinate hydrate and calcium fumarate trihydrate) [14,15]. Reproduced with permission from Ref. [9], Copyright 2015, ACS.

hardness indices for indentation along the potential shearing direction, and slip in II occurs more readily for nanoindentation on {10-2} face of II compared with {001} of I, which indicates plastic deformation occurs *via* slip. Additionally, they also found that the stress-induced solid-state II→I transformation can be fetched rapidly by mechanical milling, and proceed *via* a slip mechanism. On the basis of the earlier work on aspirin, Mishra *et al.* [37] further reported the other intergrowth polymorphism crystal, API felodipine (form II, including two different unit cells), confirmed that this microstructure can lead to a clear bimodal response to nanoindentation on the {100} face of form II, but the other indented faces of forms I and III, including the {001} face of form II, only

showed a standard unimodal response, and the variances of E and H were comparable to the variances obtained for the unimodal indents on all of the other crystal forms, which indicated that these crystals represented distinct, well-defined responses. Moreover, Mishra *et al.* also found that the response labelled {100}₍₁₎ was harder and stiffer than {100}₍₂₎ on the intergrowth polymorphism crystal, demonstrating distinct properties for two polymorphic forms within the same crystal. API crystals are often tuned to improve their mechanical properties for a better manufacturability. A typical example is voriconazole (VOR) crystal, an antifungal drug, which is too soft for tableting and compacting, so crystal engineering is used to make co-crystals and salts with modified me-

Figure 2 Overview of E vs. H plots of CPs, several well-known inorganic food dietary supplements and small molecule drug crystals (x and y -axes are in log scale). Among these CPs, E and H lie in the ranges of about 4.3–33.4 GPa and 0.01–1.36 GPa, respectively. Comparing with inorganic compounds, such as MgO ($E \sim 300$ GPa and $H \sim 9$ GPa, Ref. [34]), ZnO ($E \sim 111.2$ GPa and $H \sim 5$ GPa, Ref. [35]) and CaCO_3 ($E \sim 80$ GPa and $H \sim 5$ GPa, Ref. [33]), these CPs are much softer and possess more excellent flexibility.

chanical properties. Sanphui *et al.* [24] reported the tuning mechanical properties of VOR salts (VOR-HCl (1:2), VOR-OXA1 (1:1.5), VOR-OXA2 (1:1)) and co-crystals (VOR-FUM (1:1), VOR-PHB (1:1), VOR-PAB (1:1)) characterized by single crystal X-ray diffraction and nanoindentation. The results show that the salts exhibit better hardness than the drug and co-crystals in the order salts $\gg$ drug $\gg$ co-crystals. Comparing with drug and co-crystals of VOR, the hardness property of the salts is explained by the reason of stronger ionic interactions, other noncovalent interactions, and lack of slip planes. The presence of a critical number of slip planes and a smaller number of intermolecular interactions make co-crystals softer than VOR. Linked to VOR drug, the API paracetamol (pca) shows improved mechanical properties via co-crystal formation. Karki *et al.* [19] reported the compression properties of four co-crystals, (pca)·(oxa), (pca)·(thp), (pca)₂·(nap), and (pca)·(phe)₂ (oxalic acid, oxa; theobromine, thb; naphthalene, nap; phenazine, phe), and the comparison of tensile strengths measured for the resulting tablets gave the ranking in the order: (pca)·(oxa) < (pca)·(phe)₂ < (pca)₂·(nap) < (pca)·(thp), as shown in Fig. 3. Crystal structure analysis confirmed that co-crystals of (pca)·(oxa), (pca)·(thp), and (pca)₂·(nap) have layered structures, which can enhance the ability to form tablets. Interestingly, (pca)·(oxa) and (pca)·(thp) have strong hydrogen bonds between the APIs and co-

crystal formers. However, the structure of (pca)₂·(nap) shows significant difference, i.e., the layers in this co-crystal are connected by weak C–H... π and π ... π interactions. Moreover, the non-layered (pca)·(phe)₂ is composed of finite Z-shaped assemblies held together by O–H...N and N–H...N hydrogen bonds. And the calculations indicate (pca)·(oxa) has the least compliance to shear stress, which gives relevant tablets with the lowest tensile strength. Furthermore, Ainurofiq *et al.* [25] reported a multicomponent crystal of desloratadine (DES-BA, a salt crystal) with improved mechanical properties (desloratadine is an anti-histamine drug, BA is benzoic acid). The compaction measurements show that the tablets' tensile strength of DES-BA (> 2 MPa) has been attained at compaction pressures > 200 MPa, which is higher than DES (< 1 MPa) at pressures < 150 MPa (the proposed minimum tensile strength is 2 MPa for ensuring integrity of a pharmaceutical tablet). And a tendency of capping is observed in the DES tablets with the pressure increasing higher than 250 MPa, but DES-BA could be made into good tablets up to 350 MPa (neither capping nor lamination tendency was observed), as shown in Fig. 3f, g. Their studies show this multicomponent crystal has better tableability and plasticity profiles than the parent drug, which is attributed to the presence of a layered structure and slip planes.

In contrast to the research of mechanical properties in organic pharmaceutical molecules, there are very few reports on the fundamental mechanical properties of CP-based food supplements and additives. Sun *et al.* [9] reported the mechanical properties of calcium fumarate trihydrate ($\text{Ca}(\text{C}_4\text{H}_2\text{O}_4) \cdot 3\text{H}_2\text{O}$, one dimensional (1D) coordination polymer shown in Fig. 1c, a calcium source for food and beverage) using nanoindentation and high-pressure X-ray diffraction. The ranges of E , H , yield stress and creep behavior are 16.7–33.4 GPa, 1.05–1.36 GPa, 0.70–0.90 GPa and $0.8\text{--}5.8 \text{ nm s}^{-1}$, respectively, which are influenced by the directionality of the inorganic Ca–O–Ca linkages, O–H...O hydrogen bonding and the orientation of the fumarate ligands. Notably, the E and H of calcium fumarate trihydrate are significantly lower than the values for inorganic food supplements, while being much higher than those of organic pharmaceutical molecules, as shown in Fig. 2. Moreover, the results of high-pressure single-crystal X-ray diffraction experiments reveal a bulk modulus of 20 GPa, which indicates it is elastic recovery intermediate between organic pharmaceutical (~ 13 GPa) crystals and inorganic dietary supplements (MgO, ~ 73 GPa; CaCO_3 , ~ 160 GPa) [9].

Feng *et al.* [15] first reported the negative area com-

Figure 3 (a) The tablets resulting from compression experiments in pca form I and the four derived cocrystals. (b, d) The hydrogen-bonded layer in (pca)·(oxa) and (pca)·(thp). (c) A single layer of pca in (pca)₂·(nap). (e) Molecular assembly in (pca)·(phe)₂. Reproduced with permission from Ref. [19], Copyright 2014, Wiley-VCH. (f) Tablets of DES and DES-BA at a compaction pressure of 350 MPa. (g) A layered structure constructed by a 1D hydrogen bonding chain between DES-BA pairs. (h) The packing layers along the *c* axis enabled slip planes parallel to (001). DES and BA are plotted in capped stick and spacefill types, respectively. Reproduced with permission from Ref. [25], Copyright 2018, Elsevier.

pressibility (NAC) of zinc acetate dihydrate ($\text{Zn}(\text{CH}_3\text{COO})_2 \cdot 2\text{H}_2\text{O}$, food supplement and drug for treating cold) using high-pressure synchrotron powder X-ray diffraction (HP-PXRD). $\text{Zn}(\text{CH}_3\text{COO})_2 \cdot 2\text{H}_2\text{O}$ crystallizes in the monoclinic space group and shows a hydrogen-bonded layered supramolecular architecture (Fig. 1c). The results of HP-PXRD reveal the large NAC ($K = -8.1(8) \text{ TPa}^{-1}$) over a wide pressure range of 0.15–4.44 GPa, which ranks the third largest in all hitherto known 8 NAC materials, and the largest if excluding those with phase transitions and metastable high-pressure NAC. Interestingly, the microscopic mechanism of the NAC behavior arises from the complex cooperation of intra-layer coordination and hydrogen-bonding interactions, and inter-layer van der Waals forces. In addition, the isothermal bulk modulus of 20(2) GPa is comparable to that of calcium fumarate trihydrate. Furthermore, the

average values of E and H values are 4.3(2) and 0.37(2) GPa for (100) face, and 5.8(3) and 0.58(5) GPa for (001) face, respectively. The E modulus shows medium anisotropy with $E_{(001)}/E_{(100)} = 1.35$ in elastic deformation, while the hardness exhibits large anisotropy with $H_{(001)}/H_{(100)} = 1.57$ in plastic deformation. The difference (26%) in the elastic moduli for the crystal faces indicates possible dissimilarities in the interaction features. And the much larger anisotropy in hardness (36%) suggests significant differences in the micro-mechanisms of plasticity. Therefore, the H and E values obtained on the two different natural facets for the (100) and (001) faces manifest significant mechanical anisotropy of $\text{Zn}(\text{CH}_3\text{COO})_2 \cdot 2\text{H}_2\text{O}$.

Azeem *et al.* [14] recently reported the elastic and hydrostatic behaviour of a zinc dietary supplement, zinc glycinate hydrate ($\text{Zn}[\text{O}_2\text{CCH}_2\text{NH}_2]_2 \cdot \text{H}_2\text{O}$, a pseudo 2D

structure with monoclinic space group), *via* the density functional theory (DFT) calculations and HP-PXRD. The range of E is in 13.84–36.11 GPa by the DFT calculations, indicating significant elastic anisotropy, and the B/G ratios of 1.30–3.83 (B and G are bulk modulus and shear modulus, respectively) reveal the crystal could be brittle under uniaxial stress according to the Pugh's criterion. Furthermore, the bulk modulus is ~ 31 GPa, which is slightly higher than that of $\text{Zn}(\text{CH}_3\text{COO})_2 \cdot 2\text{H}_2\text{O}$ and lies in the middle of the values between inorganic dietary supplements and organic pharmaceutical crystals.

The manufacturing process of tablets can vary with the product requirement but typically includes milling, blending, granulation and tableting, as shown in Fig. 4, which can be significantly influenced by the crystalline structure and mechanical properties of API and excipient particles. Therefore, it is necessary to clarify the influence factors of crystal structure and material properties on the formulation and manufacture of pharmaceutical tablets. For the milling process, the brittleness of crystals plays a significant role. If a material shows a good deformability, it may hinder the milling process. For example, soft voriconazole becomes paste-like upon grinding, which makes it difficult to mill, but the hard sildenafil citrate is easier to handle [24]. Blending and granulation processes are also highly influenced by crystal morphology, mechanical and surface properties. The segregation in mixtures (e.g., API and excipient) is commonly induced by the difference of particles size, density and surface energy [44,45]. The segregation of API and excipient can result in undesired product qualities, such as over- or under-dosing. The tableability of the bulk powder is significantly determined by the crystal plasticity and elasticity. The plasticity of CP crystals can be influenced by several crystal features, such as crystal packing, slip, dislocation motion, twinning, kinking, and perturbation of lattice stability. For example, introducing more slip planes is a valid strategy for plasticity enhancement in crystal engineering, which facilitates the compaction of powders with poor tableability [20]. And the motions of intrinsic dislocations can contribute to crystal plasticity, which generally weakens the lattice and enables plastic deformation under neglecting work hardening. The crystal elasticity can cause the elastic recovery of tablets during decompression. A strong elastic recovery can even break the tablet and causes capping or delamination after tablet ejection [46]. Therefore, both high elasticity and low plasticity of crystal can lead to poor tableting performance. On the other hand, the mechanical operations on the crystal particles during the manufacturing process can

Figure 4 The manufacturing process scheme of typical pharmaceutical tablets. (a) 1D and 2D APIs are milled to form nanorod and nanosheet shape powders, respectively. (b) Blending and granulation for the mix of the APIs powder and excipients is performed. (c) A standard in-die compaction process.

change the properties of the particles. Notably, the phase transitions can appear among APIs during production processes (e.g., milling, handling, and tableting), which further results in the rearrangement of intermolecular interactions and local molecular movements under mechanical loading [47]. For example, in the two co-crystal polymorphs of caffeine:4-chloro-3-nitrobenzoic acid (Form I and Form II), Form I is more brittle and harder than Form II, and can convert readily to Form II upon mechanical grinding [21]. Furthermore, various manufacturing operations may have different requirements of crystal properties, such as the crystal plasticity for milling and tableting as discussed above. Therefore, it is of fundamental importance to properly control and optimize the crystal properties for further manufacturing operations.

In summary, the mechanical properties are critical in the applications of CP crystals, especially in pharmaceutical manufacturing. Compared with other research of small molecule drug crystals, it is vital to draw the interrelations between the material properties and the underlying crystal structures of CP-based supplements and additives in the context of crystal engineering. However, systematic investigations and quantitative understanding of the mechanical properties at the molecular level remains rare, which may be ascribed to the difficulty in preparing crystals, the absence of suitable characterization techniques, and the complex nature of the crystal

structures themselves. Thus, it is still a key challenge to establish correlations between crystal structure and mechanical response for advancement in this area.

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polymers and hybrid organic-inorganic perovskites.

interests in powder and multi-phase technologies, using numerical methods and experimental characterization methods, for applications in heterogeneous catalysis, pharmaceutical engineering and relevant chemical engineering areas.

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配位聚合物基膳食补充剂的力学性质研究

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摘要 由于温和的口服性能和良好的生物相容性, 配位聚合物基膳食补充剂一直在市场上广受欢迎。这类膳食补充剂通常都是以片剂的形式销售, 其片剂的加工和制造过程与其力学性质密切相关。本文系统总结了配位聚合物膳食补充剂的晶体结构与力学性质之间的内在关系, 并与小分子药物晶体和无机膳食补充剂进行比较, 为其片剂加工制造过程提供参考。