Remarkable decrease in stiffness of aspirin crystals upon reducing crystal size to nanoscale dimensions via sonochemistry

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Nano-dimensional single crystals of acetylsalicylic acid (aspirin) Form I are generated through sonocrystallization and are shown to exhibit Young’s modulus values in the MPa range, which is significantly softer (5-fold reduction) than macro-dimensional single crystals. The change is attributed to structural consequences of the size-dependent surface-to-volume ratio effect, particularly as related to intermolecular forces.

Understanding and modifying mechanical properties of organic crystalline solids is important in the design of materials with applications in areas such as flexible electronics,1 pharmaceuticals,2 and energy storage.3 Effects of packing on properties of organic solids are prone to the inherent anisotropy of molecules, whereas organization in inorganic materials tends to be more isotropic with properties being less directionally dependent. Recently, crystalline materials that span macro- to nano-dimensions have been shown to exhibit properties based on crystal size.4 Metal-organic nanowires have been reported, for example, to be mechanically softer than macro-dimensional single crystals of the same material.5 In our work, we have shown that nano-dimensional organic cocystals can be either stiffer or softer than macro-dimensional counterparts.6 Macro-sized samples of diamond have also been reported to exhibit a nearly 2-fold reduction in stiffness upon reduction to the nanoscale.7 Nano-dimensional materials exhibit an extremely high surface-to-volume ratio compared to macroscopic solids, which results in an exceedingly dominant contribution of surface energy towards total free energy of a nano-sized solid.8 Indeed, the prediction of size-dependent properties of solid-state materials can be difficult,9 while experimental characterization can provide insight for designing materials with size-specific properties. The issue is particularly relevant for pharmaceutics where crystal size can alter solubility, bioavailability, and absorption properties.10

Aspirin is a common analgesic that exists in up to four polymorphs (Form I-IV).10 The crystal packings of the reported structures (Forms I, II, IV) are defined by carboxylic acid dimers, with packing of adjacent dimers involving acetyl groups engaged in C-H…O hydrogen bonds. Form III is stable only at high pressures and a structure has not been reported. Form II is metastable and converts to Form I under ambient conditions or through mechanical grinding.11 High-quality tablets of aspirin can be readily generated through direct compression,12 and use of smaller aspirin particles (i.e. 300-600 µm in size) for tablet formation has been shown to increase tablet strength (i.e. hardness).13 Studies regarding mechanical properties of aspirin crystals have been described for macro-dimensional crystals. To the best of our knowledge a preparation of nano-dimensional aspirin single crystals has not been reported.14

Here, we report the first synthesis of nano-dimensional aspirin crystals, which is achieved via sonocrystallization. We show that the effective reduction in size of millimetre-sized crystals to the nanoscale results in an approximate 5-fold reduction in crystal stiffness from ca. 2.5 GPa to 550 MPa as determined by atomic force microscopy (AFM) nanoindentation technique (Scheme 1).6 15 The remarkable decrease in crystal stiffness of nano-sized aspirin is attributed to consequences of the surface-to-volume increase effect as related to hydrogen-bonding of the molecules.

**Scheme 1** Mechanical properties (stiffness) of aspirin (Form I) upon reduction of crystal size.

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Electronic Supplementary Information (ESI) available: Experimental details, X-ray analysis, DLS analysis, and AFM measurements. See DOI: 10.1039/x0xx00000x
Macro-dimensional single crystals of aspirin (Form I) were synthesized through slow evaporation from acetone as reported (Fig. 1). Powder X-ray diffraction (PXRD) revealed structurally-pure Form I (see ESI). The macro-dimensional crystals exhibited prism morphologies with base sizes on the order of 3.3 × 1.5 mm and heights of 0.5 mm. AFM nanoindentation measurements were performed on the (100) and (-100) crystallographic faces (Figs. 1a,b). The aspirin molecules interact via O-H⋯O hydrogen bonds as centrosymmetric dimers along the faces (Fig. 1c,d). The hydrogen-bonded dimers lie canted ca. 50° to the planes. The dimers assemble into sheets parallel to the (100) planes. For AFM nanoindentation experiments, repeated force-displacement curves were recorded at ca. 20 positions on both the (100) and (-100) faces. Average Young’s modulus values (mean ± 1 standard deviation) were determined to be 2.4 ± 0.4 GPa and 2.6 ± 0.3 GPa for the (100) and (-100) planes, respectively (Fig. 1b). Young’s modulus values for the planes have been reported to range between 1.3 and 5.9 GPa,9,11,17 thus, our values lie within the reported ranges.

The decrease in stiffness of aspirin with size is remarkable and may be attributed to the surface-to-volume increase effect.5,22 Mechanical properties of a material can be microscopically related to bond lengths and interatomic and intermolecular potentials.23 When the size of a particle is decreased, the ratio of surface-to-volume increases. Moreover, when reduced to the nanoscale, a particle surface will experience structural reorganizations to minimize surface energy. The reorganizations will impact bonding, as well as interatomic and intermolecular forces. A decrease in elastic moduli with a decrease in crystal size has been reported for CdSe nanocrystals.24 The decrease was attributed to surface reconstruction owing to weakening of covalent bonds of the lattice.24 The decrease in stiffness for GaN nanowires has also been reported. The decrease was similarly attributed to a larger loss of covalent bonding versus gains in cohesive energy at the surface.25,26 For aspirin, a change in the ratio of intermolecular bonds at the surface compared to the bulk may account for the lower stiffness. The surface of aspirin, in contrast to the interior, consists of both hydrogen-bonded dimers and ‘free’ acid molecules.27 As the size of an aspirin particle is reduced, the ratio of free molecules to dimers on a per particle basis is expected to increase. Molecular dynamics studies on nanocrystalline aspirin indicate that free molecules at the surface will produce a higher energy structure composed of disordered molecules.22,27,28 We postulate that a loss of long-range order supported by hydrogen bonding at the
surface of the nanosized aspirin crystals likely accounts for the lower stiffness, although further studies to elucidate the nature of the surface are needed.\textsuperscript{23,29} Given that the nucleation mechanism of molecular crystals subjected to sononchemistry also remains poorly understood,\textsuperscript{30} an additional factor may involve an increase in grain boundaries along the surfaces of the nanosized aspirin crystals (cf. diamond).\textsuperscript{7}

We have demonstrated that aspirin single crystals exhibit size-dependent mechanical properties wherein a reduction in size results in significantly softer crystals. We are expanding our studies to other pharmaceutically-relevant compounds to establish strategies to design crystals with targeted physical properties. The approach can have implications in optimizing pharmaceutical properties and preparing materials.

Conflicts of interest
There are no conflicts to declare.

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Significance: Nano-dimensional crystals of aspirin generated through sonochemistry exhibit Young's modulus values an order of magnitude softer than macro-dimensional crystals.