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Nanomechanical testing technique for millimeter-sized and smaller molecular crystals

Michael R. Maughan [a], M. Teresa Carvajal [b], David F. Bahr [a,*]

[a] School of Materials Engineering, Purdue University, West Lafayette, IN, USA
[b] Department of Agricultural & Biological Engineering Purdue University, West Lafayette, IN, USA

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ABSTRACT

Large crystals are used as a control for the development of a mounting and nanoindentation testing technique for millimeter-sized and smaller molecular crystals. Indentation techniques causing either only elastic or elastic–plastic deformation produce similar results in assessing elastic modulus, however, the elastic indents are susceptible to surface angle and roughness effects necessitating larger sample sizes for similar confidence bounds. Elastic–plastic indentations give the most accurate results and could be used to determine the different elastic constants for anisotropic materials by indenting different crystal faces, but not by rotating the indenter about its axis and indenting the same face in a different location. The hardness of small and large crystals is similar, suggesting that defect content probed in this study is similar, and that small crystals can be compared directly to larger ones. The Young's modulus and hardness of the model test material, griseofulvin, are given for the first time to be 11.5 GPa and 0.4 GPa respectively.

1. Introduction

It is desirable to understand the mechanical properties of molecular crystals used for pharmaceuticals and pyrotechnic materials to predict performance under conditions of both processing and service. These mechanical properties play an important role in the handling, stability and performance of pharmaceuticals and pyrotechnics. For instance, compacting pharmaceuticals into tablet form can be adversely impacted by crystal fracture, while concerns over mechanical stability and inadvertent ignition during handling necessitate the need to measure safe processing conditions. A fundamental understanding of the mechanical properties of molecular crystals is essential to advancing these disparate disciplines of mechanical behavior and crystal growth and their respective industrial applications.

Measuring the mechanical properties of molecular crystals has been difficult due to their generally soft, yet brittle, behavior and subsequently there is difficulty in creating shapes or structures amenable for standardized mechanical testing methods to assess the elastic, plastic, or fracture properties used for metals, ceramics, and polymers. Large crystals can be specially grown to multi-millimeter sizes solely for the purpose of assessing the mechanical properties, but since defect density and structure will likely influence plastic deformation or fracture there may be differences between the properties of sub-mm size crystals and the larger crystals based on the growth conditions needed to achieve large sizes leading to either higher or lower defect densities. Growing crystals large enough for traditional mechanical testing techniques is challenging, and they can be damaged by common surface preparation procedures. Electron microscopy techniques for determining the elastic constants can damage any size crystal as well (Kobayashi and Isoda, 1993). Many groups have therefore chosen to utilize small-scale indentation techniques to study the mechanical properties of relatively large crystals for pharmaceutical and energetic applications (Duncan-Hewitt and Weatherly, 1989; Liao and Wiedmann, 2004; Liao and Scott Wiedmann, 2005; Ramos and Bahr, 2007; Perkins et al., 2007; Masterson and Cao, 2008; Tan et al., 2009; Ramos et al., 2009; Cao et al., 2010; Ramos et al., 2011; Varughese et al., 2011; Kiran et al., 2012; Ghosh et al., 2013; Mishra et al., 2014; Chattoraj et al., 2014). However, no study has indicated the viability of the nanoindentation technique for determining the elastic modulus of sub-millimeter sized crystals in this material class, or directly compared the mechanical properties of molecular crystals of much larger size to those at the size scale commonly used in service with statistically relevant sample sizes.

* Corresponding author at: 701 W. Stadium Ave, West Lafayette, IN 47907, USA. Tel.: +1 765 494 4100; fax: +1 765 494 1204.
E-mail address: dfbahr@purdue.edu (D.F. Bahr).

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Here we use the term small to denote crystals smaller than 1 mm and greater than about 250 μm. Perkins et al. used atomic force microscopy (AFM) to study small crystals and compare the results to traditional nanoindentation of large crystals (Perkins et al., 2007), however with a sample size of at most four from each material studied, a more extensive investigation of the factors influencing measurements of mechanical properties on molecular crystals is required. Further, the compliance inherent in AFM based testing means calibration of machine compliance can lead to large uncertainties as the stiffness of materials increases. Wagner et al. conducted an uncertainty quantification study on the use of the AFM technique to measure the elastic modulus of cellulose nanocrystals with mean modulus of 8.1 GPa. They found that for these samples, the uncertainty was 37%, and that "uncertainties in extracting the local modulus of the sample are greater than what would be sampled by multiple replicates of the experiments (Wagner et al., 2011)." While they noted that reducing the modulus would reduce the uncertainty, we expect many pharmaceutical and energetic crystals to have similar moduli, in the 5–50 GPa regime, and hence there is still a need to develop reproducible methods of property measurements in this class of materials.

Additionally, batch-to-batch variability in powder properties is a critical issue affecting processing behavior. Routine analytical methods usually quantify changes at the bulk powder (Ticehurst et al., 1996; Chamarthy et al., 2009) or the agglomerate particulate level (Ely and Carvajal, 2011). However, since differences observed at the macro (bulk powder) level, can easily mask the underlying changes taking place at the micro (structural) scale, attention must be directed to understanding the changes in the material properties of powders subjected to industrial processes. One example of such sources of unintended, and as a result, uncontrolled variation is milling. Recent developments in analytical methodologies can be useful in characterizing the nature of the structural changes widely grouped under the term "activation" (Jing et al., 2011) and reveal subtle differences that cause lot-to-lot differences in raw materials of either active pharmaceutical ingredient (API) or excipients (pharmacologically inactive ingredients).

To address the aforementioned issues, we have chosen to utilize nanoindentation techniques to study the elastic and plastic properties of single crystals of griseofulvin (GSF) by varying sample size, crystallographic orientation relative to the probe direction, and probe geometry with the goal of determining the efficacy of the technique on a model system of small crystals; those of a size scale used in the pharmaceutical industry. Developing such a technique will enable testing those materials where it is difficult to grow large crystals, or enable testing earlier in the development of those materials where it has already been demonstrated that it is possible to produce larger quantities. Further, pharmaceutical compounds frequently exhibit brittle behavior that can influence typical nanoindentation approaches. If the material cracks, the indentation system is sampling the compliance of the crack, rather than the material itself. In this event, these tests should be subject to careful consideration before the test is deemed acceptable. To eliminate this potential pitfall, we investigate the use of spherical indentation in the elastic regime, fitting load-depth curves collected with a probe of known radius to the equation developed by Hertz for elastic contact between two spheres (Hertz, 1896). GSF is an ideal material for such a study. It has only one stable polymorph (Mahieu et al., 2013) and it is hydrophobic thus reducing the possibility of its properties changing with time due to atmospheric moisture absorption (Ramos and Bahr, 2007). It also has a melting temperature above 200 °C, which allows the use of certain temperature sensitive adhesives to be used to secure small crystals to rigid mounting platforms commonly used in nanoindentation (Ahmed et al., 1998). We use a probe with a blunt point, since sharp probes are known to be more likely to cause cracking, and our initial investigations on GSF samples with a sharp Berkovich probe showed cracking behavior even at low depths.

At present, there are no published works reporting the mechanical properties of single crystals of GSF. An order of magnitude estimate for the expected modulus of GSF can be obtained by considering the modulus of similar crystals reported in the literature. The modulus of sucrose is approximately 33 GPa (Duncan-Hewitt and Weatherly, 1989; Ramos and Bahr, 2007), that of acetaminophen is 8.4 GPa (Duncan-Hewitt and Weatherly, 1989), and aspirin in the range of 5–9.6 GPa (Varughese et al., 2011) depending on the orientation of the face tested. Indentation of co-crystals of vanillin isomers have been found to exhibit an elastic modulus between 4.3 and 6.5 GPa (Krishna et al., 2015). All these indentation measurements agree favorably with early measurements produced via uniaxial compression (Ridgway et al., 1969), suggesting that indentation and bulk measurements and indentation measurements are capable of measuring similar properties. Thus, it may be expected that the modulus of GSF will be larger than 1 and less than 100 GPa, and within the range noted previously as becoming problematic for calibrating AFM based indentation techniques.

2. Methods

2.1. Crystal growth and structure

GSF crystallizes in a tetragonal cell, with the P41 space group and lattice parameters of $\alpha = 90.0°$, a = b = 8.9714 Å, c = 19.8848 Å, V = 1600.46 Å^3 and there are four molecules per unit cell (Nirmala et al., 1982). Some physicochemical properties are known; it has a melting point of 220 °C and its water solubility is 8.64 mg/L (at 25 °C) (Dannenfelser and Yalkowsky, 1991).

GSF crystals were grown by slow-cooling a saturated solution. The saturated GSF solution was made by dissolving commercial GSF (Hawkins Pharmaceutical Group) in acetonitrile (Sigma–Aldrich) at 40 °C and stirring the solution for about 2 h. The solution was then filtered and allowed to cool slowly to room temperature, inducing crystallization. After about 72 h, crystal growth was observed. Both large and small crystals were identified by optical microscopy, isolated from the solution, and then air-dried at room temperature and lab-air conditions prior to analysis by nanoindentation.

2.2. Nanoindentation procedure

Two methods for preparing GSF crystals for nanoindentation were investigated. First, for large crystals, a common mounting procedure was used. Here, the crystals were manipulated by hand with tweezers and secured to a 1 mm thick steel disk with a typical adhesive, cyanoacrylate glue (Tan et al., 2009; Ramos et al., 2009, 2011; Varughese et al., 2011; Kiran et al., 2012; Ghosh et al., 2013). For this method, two faces that were nominally parallel were identified, with one of the two being secured to the disk. The alternate face was then left pointing "up" in a direction to be indented. The drawback of this method is that if the two faces deviate appreciably from parallelism, then the indented surface will be angled. Xu and Li have considered this problem and found that angled surfaces can considerably influence the measured indentation hardness and modulus (Xu and Li, 2007). The majority of indentation studies use specimens mounted with this technique, and when it is properly applied, indentation tests on these samples give true measurements of the properties.

For smaller crystals, those with their largest dimension of approximately 1 mm or smaller, it was not possible by manual manipulation with tweezers to easily orient a crystal with a face