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APPLICATION NOTE

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Crystal Polymorphism Study with Nanoindentation

Countering the Limits of X-Ray Crystallography

Introduction

Studies involving elucidation of physico-chemical and biological properties of various crystal forms belonging to one crystal structure of the same compound is impetus to noteworthy strides in crystal engineering and pharmaceutical sciences. The phenomenon of polymorphism is of particular interest to crystal engineering community and solid state chemists in both academia and industrial segments. Typically various X-ray scattering crystallographic methodologies such as Powder X-ray diffraction (XRD), Single-crystal X-ray diffraction, Small angle X-ray scattering (SAXS) and Wide angle X-ray scattering (WAXS) are used to illustrate crystal orientations to ultimately determine the overall crystal structure. This article highlights the need for employing nanoindentation as a complementary nanomechanical testing technique to X-ray crystallography. Although polymorphism is also relevant to other industries such as agrochemical, food technology, chemical dye and pigment, liquid crystal display, and energy technology, this article discuses the use of nanoindentation to quantify the nanoscale mechanical properties and its plausible variations between the two polymorphic crystal forms (shown in Fig. 1) of the commercially available pharmaceutical compound, namely, Aspirin. Nanoindentation and its capabilities may have direct relevance to the pharmaceutical industry due to the following aspects:

Figure 1: Crystal structures of the aspirin polymorphs: (a) form I, (b) form II.

- **Drug Design & Formulation**: The limits of X-ray crystallography is continuing to be explored in trying to decipher intricate crystal structures and also the possibly underlying crystal forms that appear identical in structure but possess drastic differences in properties. Other complimentary techniques having the capability to quantitatively characterize submicron to micron sized crystal forms to help elucidate differences in inherent physical properties of polymorphic forms with crystallographic isometry might be of high value to the pharmaceutical industry, especially in this phase of production.
- **Process Control & Automation**: Formation of certain crystals forms could either be a spontaneous or a gradual process that is specific to certain environmental conditions or specific to a certain chemical process. It may be desired to constantly monitor (or at least at regular intervals) such key developments within the compound's crystal structure for signature properties, at certain selected phases along the rigorous drug production process, which is generally believed to be expensive.
- **R&D - Crystal Engineering**: Frontier research in crystal engineering involves adopting the principles of intermolecular interactions to design and synthesize chemical compounds with not only unique solid-state structures but also with unique physico-chemical properties. However, oftentimes there is a need to compare properties obtained at the macroscale to that at the submicron scale.
- **IP Protection**: Pharmaceutical drug industry relies on potential complimentary analytical techniques to stay clear from legal aftermaths involved in false reporting of certain health or medicinal benefits and also patent infringement. New compound patent disclosures do not cover the presence or formation of new crystal forms if they are not expounded during the research phase and all crystal forms do not entail regulatory approval.

Procedure

Hysitron **TI 950 TriboIndenter**® equipped with *in-situ* SPM imaging, advanced feedback controller and automation capabilities is suitable for performing nanoindentation on Aspirin crystals. Lab-grown crystals of few mm3 dimensions can be considered for the study and mounted onto the testing stage by adhering the crystals to a sample puck with a cyanoacrylate glue such that the crystal face orientation facilitates nanoindentation tests. A three-sided pyramidal Berkovich diamond indenter probe with a radius of curvature of ~ 100nm can be used to perform indents on the crystals.

Nanoindentation

Nanoindentation is a technique where in a diamond indenter probe with a known radius of curvature is guided to apply a force (or load, *P*), onto the chosen sample surface to attain a displacement (or depth, *h*), into the sample surface. The technique can be performed either with a chosen force as a constant (force control mode) or chosen displacement as constant (displacement control mode). This allows the researchers to test samples with intricate geometries, volume limitations and submicron scale thicknesses. A plot of force versus displacement is obtained as the probe approaches the sample surface and retracts back (observe Fig. 2). Properties such as material stiffness,*K*, Hardness, *H* and elastic modulus, *E* can all be readily determined from the plot. The nature of the plot is the mechanical fingerprint of the particular material and highlights the aspects of plasticity (permanent deformation) and elasticity (non-permanent deformation), which in-turn is the result of the material's intermolecular interactions due to the external stress applied by the indenter probe.

Results

Plot shown in Fig. 2 is the mechanical fingerprint relating to the varying properties of the two crystal forms of Aspirin as attained by Varughese et al. It can be understood from the table shown below Fig. 2 that the elastic modulus between the two crystal forms was about 48%. The arrows marked on the {100} of form I are referred to as displacement bursts that were characteristic only to this form due to sporadic material deformation. Most important observation in this study was the presence of domains of single crystals of form I within form II, which was oblivious to XRD that in-turn only suggested a pure form II.

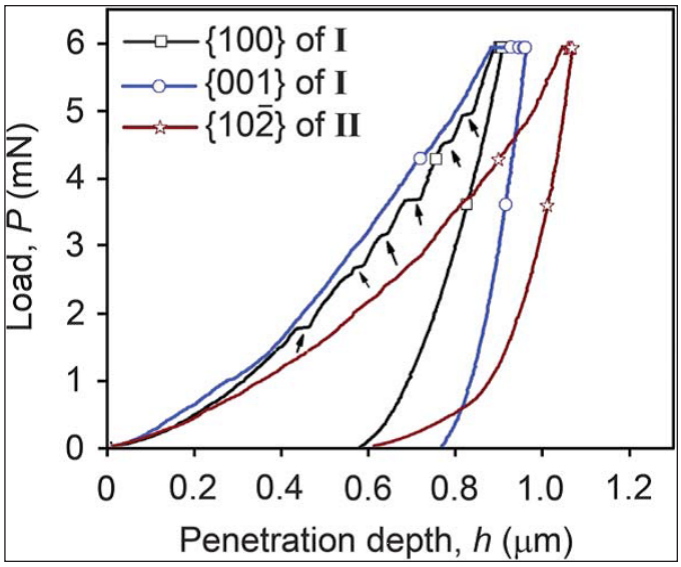

Figure 2: Representative load versus depth curves for all three faces examined, with popins indicated by arrows for the loading curve of {100} of I.
[Chem. Sci., 2011, 2, 2236–2242] – Reproduced by permission of The Royal Society of Chemistry.

	H (GPa)	*E* (GPa)
{100} of **I**	0.257 ± 0.007	5.97 ± 0.291
{001} of **I**	0.240 ± 0.008	9.57 ± 0.201
{102} of **II**	0.152 ± 0.004	4.96 ± 0.226

Table 1: *[Chem. Sci., 2011, 2, 2236–2242]* – Reproduced by permission of The Royal Society of Chemistry.

Conclusion

The magnitude and resolution at which the crystal deformations were recorded is indicative of the techniques sensitivity to material behavior due to controlled external stress, which can easily be further validated for its accuracy and repeatability.

References:

1. Interaction anisotropy and shear instability of aspirin polymorphs established by nanoindentation, Sunil Varughese, M. S. R. N. Kiran, Katarzyna A. Solanko, Andrew D. Bond, U. Ramamurty and Gautam R. Desiraju, Chem. Sci., 2011, 2, 2236-2242.
2. N. Hall. Predicting Polymorphism. Pharmaceutical Formulation & Quality, Feb/Mar 2000.

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