Measurement of Process-Dependent Material Properties of Pharmaceutical Solids by Nanoindentation

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ABSTRACT: The purpose of this work was to evaluate nanoindentation as a means to characterize the material properties of pharmaceutical solids. X-ray diffraction of potassium chloride and acetaminophen showed that samples prepared by cooling a melt to a crystalline sample as opposed to slow recrystallization had the same crystal structure. With analysis of the force–displacement curves, the KCl quenched samples had a hardness that was 10 times higher than the recrystallized KCl, while acetaminophen quenched samples were 25% harder than the recrystallized samples. The elastic moduli of the quenched samples were also much greater than that observed for the recrystallized samples. Although the elasticity was independent of load, the hardness increased with load for acetaminophen. With each sample, the flow at constant load increased with applied load. Etching patterns obtained by atomic force microscopy showed that the KCl quenched sample had a higher dislocation density than the recrystallized sample, although there was no evident difference in the acetaminophen samples. Overall, the differences in the observed sample properties may be related to the dislocation density. Thus, nanoindentation has been shown to be a sensitive method for determining a processed-induced change in the hardness, creep, and elasticity of KCl and acetaminophen. © 2004 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 94:79–92, 2005

Keywords: scanning probe microscopy; nanoindentation; acetaminophen; potassium chloride; elastic modulus; hardness; creep

INTRODUCTION

Mechanical properties of pharmaceutical solids play an important role in determining their compaction behavior[1–4] and are influenced by their molecular and crystal structures.[5,6] Thus, there is a need to understand and measure mechanical properties. However, due to technological limitations, precise measurements on individual, small particles are difficult.[5,7,8] Traditional methods[9] not only need a relatively large amount of material but also may include unavoidable complications arising from particle–particle interactions. Therefore, a method that only requires a small amount of material and provides measurements at a nanoscale may be ideal for such a task.

Recently, nanoindentation has emerged as a powerful tool in investigating mechanical properties of materials in small dimensions.[10,11] Successful applications have been made with single inorganic crystals,[12,13] human dentin,[14] silver nanowires,[15] and numerous surface coatings.[16] Our specific interest has been the examination of nanoindentation as a means of characterizing the hardness, creep, and elasticity of solids. The broad goal is to evaluate the usefulness of nanoindentation for investigating pharmaceutical systems.

In this work, the hardness, creep, and elastic modulus were determined as a function of indentation force for acetaminophen (APAP) and potassium chloride (KCl), which were prepared by

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melting with rapid cooling and recrystallization. Significant differences in the properties were found between APAP and KCl. In addition, the same compound prepared by different methods also yielded distinct results. Because the method-dependent materials had the same crystal state as deduced from X-ray diffraction, the unique properties may be related to variances in the dislocation density. Such observed differences may also have potentially significant implications in the preparation of tablets. Finally, the sensitivity of nanoindentation in characterizing these attributes indicates that this technique can serve a unique role in the assessment of pharmaceutical solids.

THEORY

In nanoindentation, an indenter of specified geometry is used. This has included spherical, cylindrical, and triangular and rectangular pyramid shapes. For surface preparation, several different methods are used, such as polishing,[17] chemical etching,[18] and cleaving a crystal surface.[19] In the measurement, the surface is scanned using the indenter as the surface probe from which a microscopic, topographic image is obtained. If the roughness of the sample is deemed sufficiently small, the nanoindenter may then be programmed to carry out indentations with specified conditions for the number of replications, loading, and unloading, as well as an intervening holding phases. The maximum applied force is set along with the time during which the force will rise from zero to the maximum value. The duration of the loading and holding phases is also preset. With initiation of the experiment, the force, displacement, and time of the indentation are simultaneously recorded. Following indentation, the surface may again be scanned, and the accompanying software can be used to analyze the dimensions of the dent. Several methods are available for analyzing the force–displacement curves obtained with nanoindentation.[10] The three specific parameters, related to properties of pharmaceutical interest, that may be determined from the force–displacement curve, are the hardness, elastic modulus and creep.

Indentation Contact Area (A) and Elasticity

In discussing the parameters obtained with nanoindentation, it is important first to define the indentation contact area (A), which is the area at a given penetration depth of the indenter. In the case of a pyramid indenter, it refers to the triangular shape that is level with the surface of the sample. That is, the base of the inverted pyramidal shaped dent. The area, A, is functionally related to the square of the depth of penetration, h,[10]

$$A = f(h^2)$$

With nanoindentation, the true area is unknown because the indenter is not an ideal pyramid shape. Thus, the area is determined experimentally as a function of penetration depth by indenting a surface with known elasticity. The area is then calculated from the known reduced elastic modulus, E_r, and the measured stiffness, S, which is the initial slope of the unloading portion of the force–displacement curve. That is,

$$S = \frac{2\beta E_r \sqrt{A}}{\sqrt{\pi}}$$

where β is the correction factor for the shape function.[10] The reduced elastic modulus may be related to the elastic modulus, E, provided the material is isotropic and deformed in a manner described by Poisson's ratio, ν,

$$\frac{1}{E_r} = \frac{(1-\nu_i^2)}{E_i} + \frac{(1-\nu_s^2)}{E_s}$$

where i refers to the indenter and s refers to the sample. With the use of an indenter composed of diamond, which has a very large elastic modulus (1141 GPa), the second term is often negligible. Experimentally, the area is determined by indenting a silica surface at different applied forces, which yields an array of areas over a wide range of penetration depths. The area function is then obtained by carrying out a second fitting of the areas plotted as a function of the penetration depth.

Hardness

The hardness, H, is defined in terms of the maximal force, F_{max}, and corrected area, A_c, by

$$H = F_{max}/A_c$$

where the area is calculated from the depth of the penetration following correction for elastic recoil and the fitted area function.[10] It should be noted that there is nothing unique about the maximal value of the force, because the force at any given

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