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Challenges of Working with Active Pharmaceutical Ingredients to Measure Adhesion Forces by Atomic Force Microscopy

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Atomic force microscopy (AFM) is a powerful technique used to help fundamentally understand the interaction between two materials. In addition to nanometer-scale imaging, numerous physical properties such as surface energy, adhesion, conductivity, and hardness can be elucidated. Sticking and picking, which is of interest in formulation development and pharmaceutical manufacturing, is fundamentally connected to a balance between adhesion and cohesion forces [1]. AFM is well suited to measure these forces, as has been shown in the literature [2]. Determination of these properties will also contribute to the fundamental understanding of materials.

Measurement of interaction forces by AFM between surfaces (*i.e.*, particle-particle and particle-substrate) first requires attaching individual particles of various sizes and at various orientations to AFM cantilevers and then obtaining force curves. Cohesion/adhesion forces can be extracted from these curves and used to establish correlations to previously generated material properties (*e.g.*, surface energy (inverse gas chromatography)) in an attempt to predict whether or not a material (*e.g.*, API or excipient) will adhere to manufacturing surfaces. Additionally, this information can be used to evaluate how materials within a formulation interact with one another.

Sample preparation and knowledge of key sample attributes are critical to obtaining meaningful determination of adhesion forces. Some of the main sample attributes are particle shape, surface contact area, chemical surface structure, and affect of environmental humidity on samples. We have developed methods to attach individual particles to AFM cantilevers and studied the impact of how particles were oriented on the substrate (*e.g.*, individual particles, compacts, whole tablets [1]). Examples of compacts of two different compounds are illustrated in Figure 1. Some challenges we encountered working with compounds included particle size, presence of adherent fines, and crystals that appeared to deliquesce in a high relative humidity environment (Figure 2). Since compounds generally have different properties, we found that no single method suited all systems.

As these challenges were overcome, force measurements were obtained. Two compounds, referred to as Compound A and Compound B, are known to be “sticky”. Compound B was generally considered to be more sticky than Compound A, based on observed tablet defects [1] and analytical experiments measuring compound content on punch faces. The AFM force measurements obtained indicate that particles in a compact of pure Compound A have a higher average adhesion force with a silicon nitride AFM tip than particles in compact of pure Compound B (Table 1). These results are not consistent with previous observations; however, the standard deviations suggest no difference in the adhesion force between the compounds and a bare AFM tip. Additional work is ongoing to improve the measurements and to determine if there is a difference in adhesion force between these two compounds as well as between other systems determined to be sticky.

AFM is a powerful technique that is being used to help understand particle-particle and particle-substrate interactions of interest in to Pharmaceutical development; however, the nature of the compounds typically studied create additional challenges in obtaining reliable data. Understanding particle-particle and particle-substrate interactions will aid chemists and formulators on developing APIs and formulations with physical and material attributes that minimize detrimental affects associated with manufacturing.

References
[1] Vogt et al., *Microsc. Microanal.* 15 (Suppl. 2) (2009) 380-381.
[2] Begat et al., *Pharmaceutical Research,* 21(9) (2004) 1591-1597.

Table 1. Adhesion forces between API and Bare AFM tip

Compound	**Force**
A	45.9 nN ± 7.7
B	41.0 nN ± 5.2

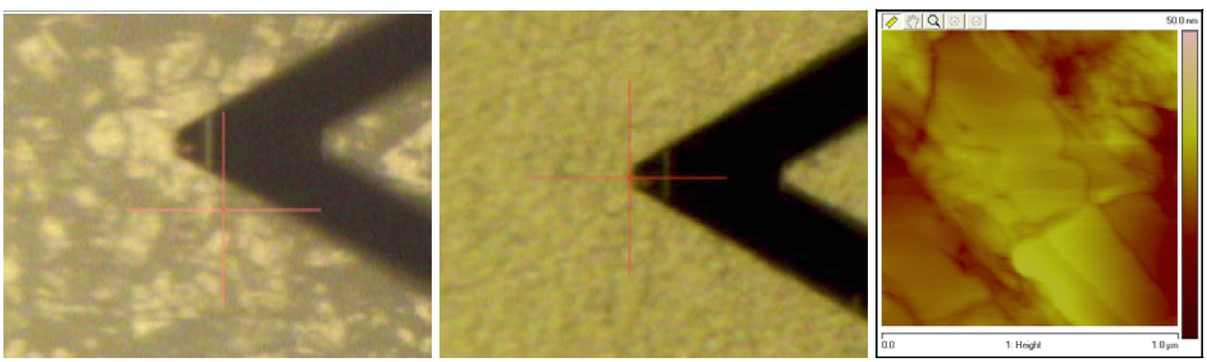

Figure 1. Optical images (left and middle) of compacts from two different APIs. Dark triangular feature is the cantilever. AFM contact mode height image (right) of compact shown in middle image depicting flat area for making force measurement. Note the light and dark regions in the right image compared to the finer structure in the left image.

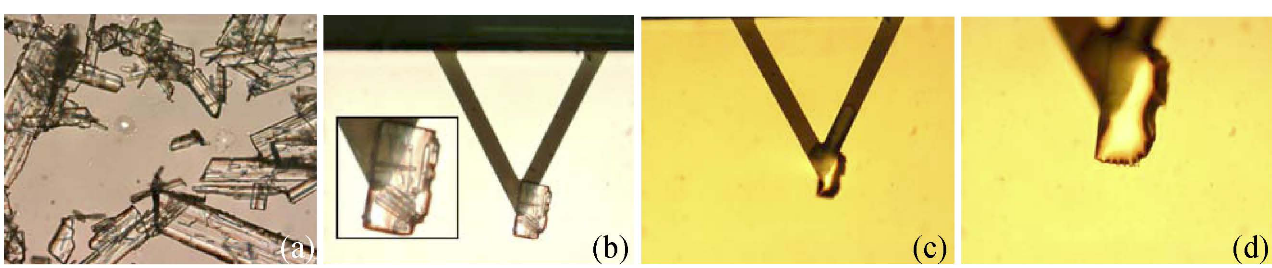

Figure 2. Optical micrographs of (a) API on a glass slide, (b) API particle on AFM cantilever, and (c,d) API particle shown in (b) exposed to higher relative humidity (> 50%). Particle on cantilever appears to deliquesce in presence of high RH. Inset in (b) shows adherent fines on API particle.

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