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AFM study of hydrophilicity on acetaminophen crystals

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ABSTRACT

Pharmaceutical powder processing is notoriously subject to unpredictable jamming, sticking and charging disturbances. To unveil the material science underlying these effects, we use atomic force microscopy (AFM) on a common pharmaceutical, acetaminophen (APAP). Specifically, we study surface adhesion and morphology as a function of relative humidity (RH) for monoclinic acetaminophen, using both plain AFM tips and tips functionalized to be hydrophobic or hydrophilic. Results indicate that the (0 0 1) crystal face exhibits significantly higher adhesion (surface potential) than the other crystal faces. For all the faces clear peaks in adhesion occur at 50–60% RH when they are examined using hydrophilic tips. The surface morphology of some facets showed a strong dependence on RH while others showed little or no significant change. In particular, the morphology of the (1 −1 0) faces developed large terraces at high humidity, possibly due to deliquescence followed by recrystallization. These results confirm the hypothesis that different crystal facets exhibit distinct surface potentials and morphology that change with environmental exposure. The work suggests that future studies of powder behaviors would benefit from a more detailed modeling of crystal surface contact mechanics.

1. Introduction

Crystal properties of active pharmaceutical ingredients (APIs) are commonly engineered to produce desirable behaviors such as dissolution and bioavailability. Unfortunately, these properties also affect powder flow, jamming and sticking in unpredictable ways, causing downstream uncertainties during mixing and tableting (Muzzio et al., 2002). Because of these uncertainties, formulations of APIs and excipients for each new drug that is introduced must undergo an extended trial and error process that is sometimes unsuccessful. The aim is to ensure powder flow, mixing, and tableting (Florence and Attwood, 1988; Keel et al., 2004) meet tight specifications designed to ensure the final product performs as expected.

There is a little question that our understanding of the laws of Chemistry and Physics are adequate to predict how molecules, crystals and even particles interact individually under model conditions (Loew et al., 1993; Carlson and McCammon, 2000; Koynov et al., 2011). We are, however, remarkably poor at predicting in advance how powders made of these same components will behave in bulk form. This is in part due to the fact that we have not characterized how common organic crystals behave in even the most basic of practical situations. One example is our very limited knowledge of the behaviors of different crystal facets in the presence of ambient humidity.

To close this gap and enable future detailed simulations of the mechanics of bulk pharmaceutical powders, in this paper we perform surface-force measurements on a common pharmaceutical crystal, acetaminophen (APAP) in the presence of varying relative humidity (RH); which is believed to influence the surface morphology and adhesion of organic crystals, and may result in deliquescence that affects the stability of pharmaceutical materials (Airaksinen et al., 2005). We use atomic force microscopy (AFM), which can directly evaluate interaction forces between two contacting surfaces as well as between surfaces intermediated by a water capillary neck (Butt and Kappl, 2009). We use hydrophilic and hydrophobic AFM probe tips to study the effects of such capillary necks as well as surface morphological changes with RH.

Previous studies have shown that AFM is a powerful technique to measure the hydrophobic and hydrophilic interactions when capillary forces are present (Butt and Kappl, 2009; Farshchi-Tabrizi et al., 2008). The exact contact geometry is believed to be

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critical in determining the humidity dependence of adhesion forces (Butt et al., 2005). These earlier studies have demonstrated that the forces due to a capillary meniscus often increase continuously with increasing humidity to a maximum and then decrease. This was interpreted as being the result of change with RH in contact radius and contact angle for the meniscus when the geometry is a single asperity (Hooton et al., 2004). The experimental studies were supported by theoretical investigations that provided a clear insight into the water meniscus structure (Jang et al., 2004). However, this theory may not be appropriate for nanoscale interactions as several factors may be unknown, such as tip geometry, surface corrugation and contamination (Jang et al., 2004). In addition, environmental and electrostatic factors can also affect the surface properties by modifying the effective potentials. It is often difficult to quantify these interactions, particularly on the surface of organic crystals. Past studies of capillary interactions in pharmaceutical organics provide some evidence that these interactions become more dominant at higher humidity (Young et al., 2003). Such interactions are often considered to give a continuous increasing trend in the adhesion force with increasing RH; contrary to studies for a model single asperity contact (Hooton et al., 2004). In fact evidence available in the literature hints that the geometry of asperity contacts, particle-surface capillary forces and the chemistry of the asperity can all affect such continuous trends with RH (He et al., 2001; Xiao and Qian, 2000; Sedin and Rowlen, 2000; de Lazzer et al., 1999; Harnby et al., 1996a). It is interesting to note that the increasing or decreasing trend of adhesion force with RH has been found to dependent on the size, shape and roughness/flatness of the contacting surface (Harnby et al., 1996b). These factors mean a continuous increase of adhesion with RH is questionable for organic crystals. For instance, varying RH over a range was found to have minimal effect on cellulose nanocrystals (Lahiji et al., 2010), while in contrast it has been found that capillary adhesion forces increase with RH on surfaces with domains of high surface free energy (Matsushige et al., 1995; Zhang et al., 2006). In simple terms, organic crystal surfaces (Chen et al., 2009; Ikai, 1996) have been found to show several disparities with RH, which in turn have been found to depend on their storage and co-crystal phenomena (Cassidy et al., 2009; Yang et al., 2011).

Many studies devoted to the RH dependence of adhesion forces typically do not consider how hydrophobic and hydrophilic forces differ as a function of RH on multi-faceted organic crystals such as acetaminophen (APAP). This study addresses this gap and also examines changes in surface morphology with RH for different crystal facets of APAP. The ability to perform single asperity contact measurements with an AFM is particularly useful when considering the mechanical action of processing pharmaceutical powders. The contacts between individual powder particles are essentially a series of single asperity contacts and, hence, AFM testing can be used as a highly controlled model system to study individual asperity contacts similar to those seen during powder processing. The methodology used should be effective for studies of adhesive force and surface morphology on most multiple faceted organic crystals.

2. Materials and methods

The first stage of experimental investigation involved the preparation of crystals from multiple solvents. Crystals were grown by dissolving acetaminophen (N-acetyl-p-aminophenol or APAP; Mallinckrodt, Raleigh, NC; 19 μm) in solvents including water, methanol, ethanol and acetone. A super-saturated solution of acetaminophen in the above mentioned solvents was prepared and the crystal precipitation was left to occur under ambient temperature (24 °C). A series of experiments were carried out to determine the optimum conditions suitable for growing large crystals in order to perform AFM experiments. Well-faceted single crystals (>2 mm) in multiple batches were nucleated after 72 h and were collected after precipitation and evaporation of solvent at ambient temperature. The crystals were stored in a desiccator until they were used in the AFM studies. The crystal geometry and dimensions were initially examined with an optical microscope. Crystals of various geometries grown from different solvents (Fig. 1) were compared and those with clearly identifiable facets selected.

Table 1
Faces of the single crystal identified from SXRD.

h	*k*	*l*	Distance to the crystal centroid (mm)
1.00	−1.00	0.00	0.310
−1.00	1.00	0.00	0.310
1.00	1.00	0.00	0.600
−1.00	−1.00	0.00	0.600
0.00	0.00	1.00	0.700
0.00	0.00	−1.00	0.700
1.00	1.00	−2.00	0.700

From each batch a crystal was selected and characterized by single crystal XRD (SXRD). The dominant faces were labeled along with the alignment of the faces. The crystals were mounted on a Bruker SMART APEX single crystal diffractometer. A monochromatized Mo K-alpha source was used to determine the unit cell and the orientation matrix for the crystals. The unit cell data matched the un-solvated acetaminophen "*P*2(1)/*a* monoclinic phase" with unique axis *b* = 9.386 Å in the Cambridge Structural Database, Refcode = HXACAN01 (CCDC ID: AI631510). The space group for the chosen crystal, *P*2(1)/*a*, is one of three equally valid monoclinic settings by the use of different *a* and *c* axes. If different axes were chosen, different face indices with respect to those 2 axes would result, namely the *P*2(1)/*c* or *P*2(1)/*n* face indices, that do not match those of *P*2(1)/*a*. A microscopic video camera was used to confirm the faces assigned to the sample. Only small superficial divots and steps were not assigned, as the faces given in Table 1 account for the shape and volume of the sample. The crystal appeared to be single as only a few of the 260 reflections did not fit the matrix. However, some reflections exhibited a "streaky" appearance which is likely due to the crystal contains a significant number of defects.

For the AFM study the crystal was mounted on a disk, which was then mounted onto a magnetic stub and imaged using tapping mode on a Nanoscope IIIa MultiMode AFM (Veeco, Bicester, USA). Silicon tips with a nominal spring constant of 50 N/m were used initially for measuring the adhesion forces on different crystal facets. Tapping mode imaging was used to study the surface topography and forces on the following facets (1 −1 0), (−1 1 0) and (0 0 1) with the specific aim of identifying variations in adhesion forces and morphology on the different crystal facets.

The adhesion forces for tips functionalized with different chemicals (hydrophobic and hydrophilic) were tested on the crystal facets. Silicon AFM tips were gold coated and dipped in 1-carboxy-decanethiol solution for 24 h in order for a self-assembled monolayer (SAM) to form with hydrophilic (OH) terminal groups. Similarly, hydrophobic functionalization of AFM tips was achieved by dipping the AFM tip in a decanethiol solution and allowing a SAM to form. A comparison of the adhesion forces using hydrophobic, hydrophilic and plain AFM tip was performed on all the crystal facets.

To determine the effect of RH on adhesion and surface morphology the forces for plain, hydrophilic and hydrophobic tips on crystal surfaces were measured at different humidities. Modifying air conditioner settings and using silica gel gave a humidity range going from a low of 30% RH to a high of 80–90% RH. The samples were exposed to the given RH conditions for 24 h before performing

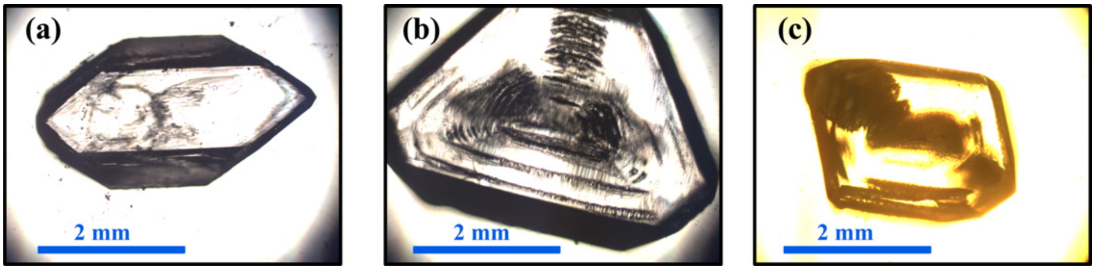


Fig. 1. Optical microscopy of APAP crystals synthesized from different solvents: (a) methanol; (b) acetone; and (c) water.

the AFM experiments. RH was monitored with a Bacharach sling psychrometer and a combined digital radio-signal psychrometer and thermometer (Fisher Scientific).

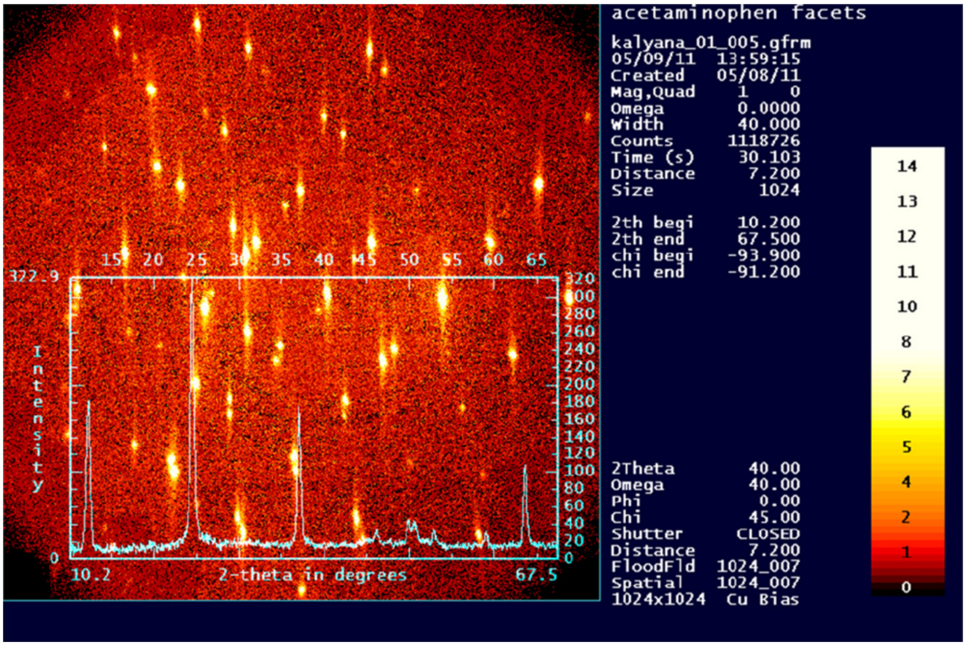
3. Results and discussion

3.1. Surface topography and identification of crystal planes/Miller indices

The morphology and surface topography of the crystals seen in Fig. 1 was observed to be dependent on the synthesis conditions. The crystals seen in Fig. 1(a) and (b), grown from methanol and acetone, respectively, were found to be thick as they were prepared with prolonged growing or deposition time. On the other hand, the crystals of APAP grown from water as the solvent, shown in Fig. 1(c), were found to have a central flat face. After using an optical microscope to analyze several crystals made from multiple solvents, the large organic crystals of APAP, Fig. 1(c), with a smooth surface were found to be the most suitable for XRD and AFM experimental analysis. These APAP crystals made from water were observed to be colorless and transparent. The most accessible crystal facets for AFM studies were identified and the Bruker GADDS software was used to fit the XRD peaks (see Fig. 2). The molecular arrangement of the facets studied and their Miller indices are shown in Fig. 3. The XRD data are consistent with a crystal growing layer-by-layer forming a single monoclinic crystal (Yang et al., 2011). Representative AFM surface morphological images were taken at various locations on each of the largest APAP crystal faces. Examples of the surface morphologies are shown in Fig. 4 for the largest crystal faces. The AFM data indicates that the surfaces are generally smooth, though there is some variation in roughness between the different faces, notably the (0 0 1) surface is smoother than the (1 −1 0) and (−1 1 0) surfaces. The general smoothness of the surfaces indicates a fairly uniform growth rate for the crystal faces, though (0 0 1) is the one that appears to grow most uniformly.

3.2. Adhesion on different crystal faces

Previous investigations have studied the adhesion forces on organic crystals (Zhang et al., 2006; Chen et al., 2009; Ikai, 1996; Cassidy et al., 2009), and for some crystals adhesion has been found to be face specific (Muster and Prestidge, 2002; Li et al., 2010). However, little data exist on the variability of adhesive forces on different crystal faces of APAP. Initially plain AFM silica tips were used to look at adhesion on the surfaces. The uniformity of the adhesion over the crystal surface was assessed by performing multiple force measurements at different locations on each face. To alleviate issues related to the variations in tip geometry the same tip was used on all the facets examined under the same environment conditions. Additionally the experiments on each facet were carried out one after another on the same day to avoid variations in the ambient condition. The relative adhesive forces for the



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acetaminophen facets

kalyana_01_005.gfrm
05/09/11  13:59:15
Created   05/08/11
Mag,Quad    1     0
Omega       0.0000
Width      40.000
Counts    1118726
Time (s)   30.103
Distance    7.200
Size         1024

2th begi   10.200
2th end    67.500
chi begi  -93.900
chi end   -91.200

2Theta       40.00
Omega        40.00
Phi           0.00
Chi          45.00
Shutter     CLOSED
Distance     7.200
FloodFld  1024_007
Spatial   1024_007
1024x1024  Cu Bias
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Fig. 2. Single crystal X-ray diffraction pattern of APAP crystal. The bright spots correspond to diffraction peaks for the layers of the crystal structure. The sharp X-ray intensity peaks correspond to the dominant faces of the crystal. Note that some of the peaks are “streaky” which likely signifies that the crystal contains many defects.

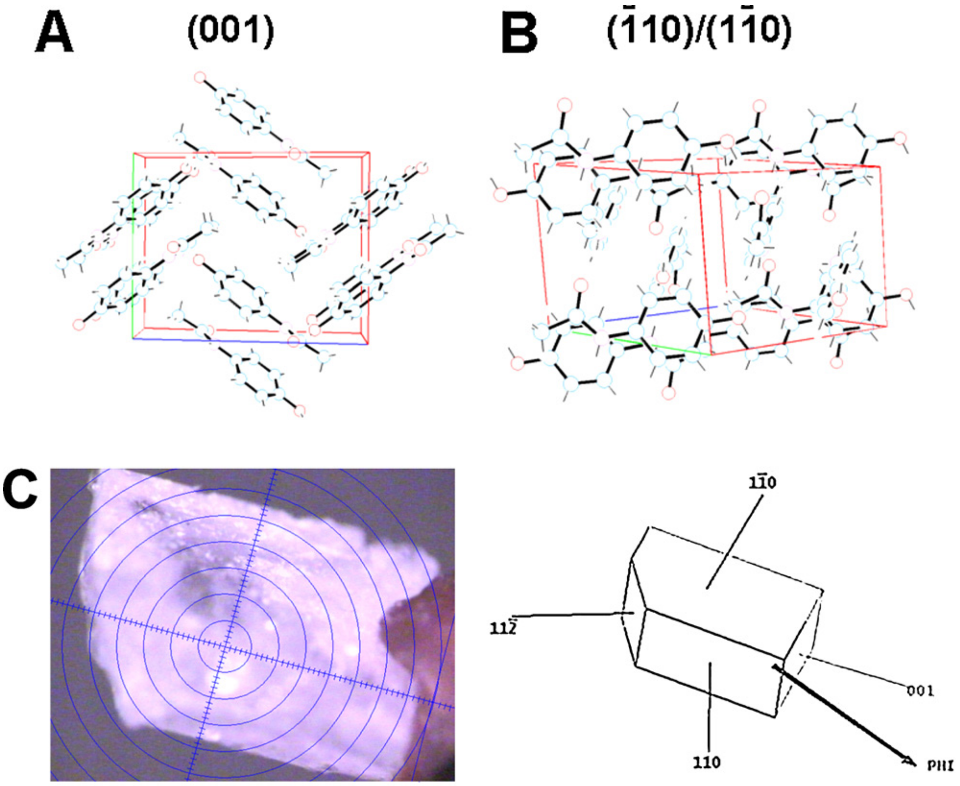

Fig. 3. (a) Projection of the (0 0 1) crystal face for the acetaminophen structure with space group *P*21/*a*. (b) Projection of the (−1 1 0)/(1 −1 0) crystal face. (c) Identification of the Miller indices of the dominant planes on a single crystal using X-ray diffraction.

different faces and tips used are shown in Fig. 5. Using ANOVA it was found that there were no statistically significant variation with location on each of the individual faces and the average adhesion force on the (1 −1 0) and (−1 1 0) faces showed no statistical difference. However, the (0 0 1) face showed a very significant (*p*-value between 0.001 and 0.01), statistically higher adhesion than the other two faces. All of the faces showed very significant increases in adhesion when hydrophilic tips were used when compared to hydrophobic and normal (unfunctionalized) tips. The adhesive forces measured with these latter two types of tips were statistically indistinguishable. The differences in adhesion are unlikely to be due to changes in contact geometry since the adhesion measurements were done on flat regions of the surfaces and further to this all the faces were relatively smooth on the scale of the AFM tip. Also the changes in adhesion due to the tip geometry (radius) being modified by functionalization are minimal since the normal tips had radii of ≈40 nm and the Au and thiol layers are just a few nanometers thick (<5 nm). The negligible impact of functionalization on tip geometry is highlight by the fact that the normal (unfunctionalized) and the hydrophobic (Au layer plus decanethiol) tips gave forces that were statistically indistinguishable. Rather the differences in adhesion with crystal face reflect the presence of different chemical moieties on the respective faces. Note that force curves obtained with AFM can be affected by the transfer of material from the surface to the tip. This typically causes a sudden change in the measured adhesion force. When this was observed the tip was replaced to ensure a clean tip was used during the measurements.

3.3. *Adhesion with chemically modified AFM tips*

The origin of adhesion forces in AFM experiments is diverse and includes Van der Waals bonds, hydrophobic/hydrophilic interactions, electrostatic forces, electrical double layers and various other physical interactions (Butt et al., 2005). When water condenses at the contact between an AFM tip and the surface it is possible for large capillary forces to develop that become the dominate source of adhesion during AFM tests. One distinctive point observed during the current AFM measurements with chemically modified tips was that there was no significant difference between the force measured with a hydrophobic tip and a chemically unmodified plain tip (Fig. 5), which suggests there is no capillary neck formed for either of these tip types. However, the adhesive forces on all the crystal faces measured with the hydrophilic AFM tip were found to be higher than those measured with a hydrophobic tip. This is primarily attributable to the polar groups being present on the hydrophilic tip surface which attract water to form a capillary neck and, hence, generate a strong attractive force between the sample and the probe (Keel et al., 2004). The findings are in agreement with the study conducted by Chen et al. (2009) where the unmodified Si_3N_4 probe surface used was expected to be hydroxylated and have an OH-terminated probe. Others have observed a similar trend, but the behavior of the organic APAP crystal surface is not well known. In this study, we have tried to bridge this gap, by investigating the interactions of hydrophilic and hydrophobic domains on multiple crystal facets. It was interesting to note that the hydrophilic force was higher than the hydrophobic (and plain tip) adhesive force for all the faces, though the highest values were on the (0 0 1) face.

3.4. *Influence of humidity on adhesion forces of APAP crystal faces*

Given the higher adhesion seen with the hydrophilic tips it was expected that the presence of moisture or humidity would play an important role in determining the adhesion between the probe and sample surface. To further investigate this phenomenon the tip-APAP crystal interactions with hydrophilic and hydrophobic tips were studied over a range of humidity conditions. Based on

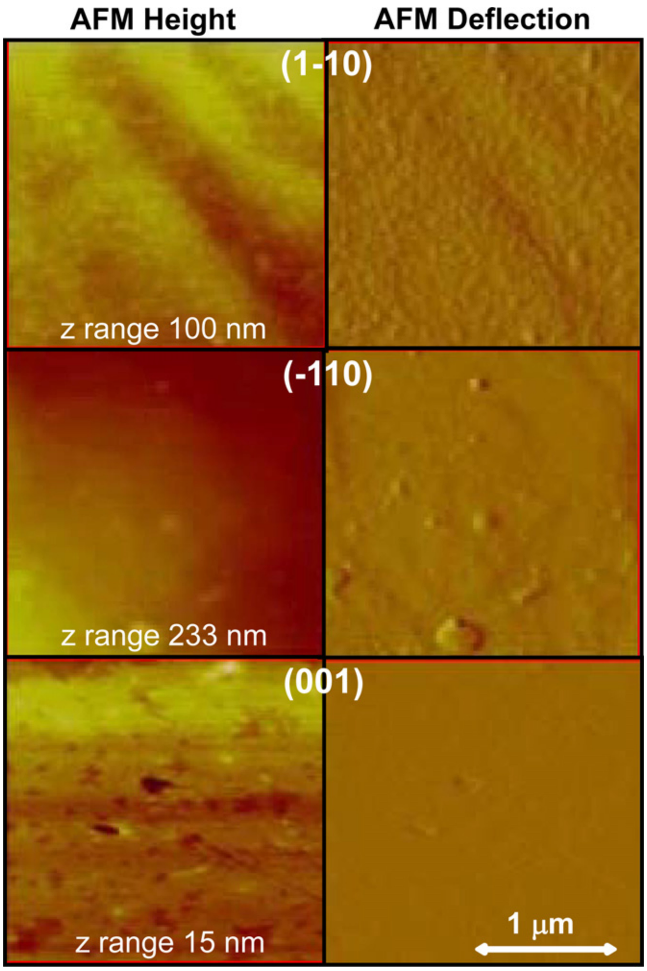

Fig. 4. AFM tapping mode images of the surface morphology of the dominant crystal faces of APAP synthesized using water as the solvent. The RMS roughness of the faces is 45 nm for (1 −1 0), 113 nm for (−1 1 0) and 6.1 nm for (0 0 1).

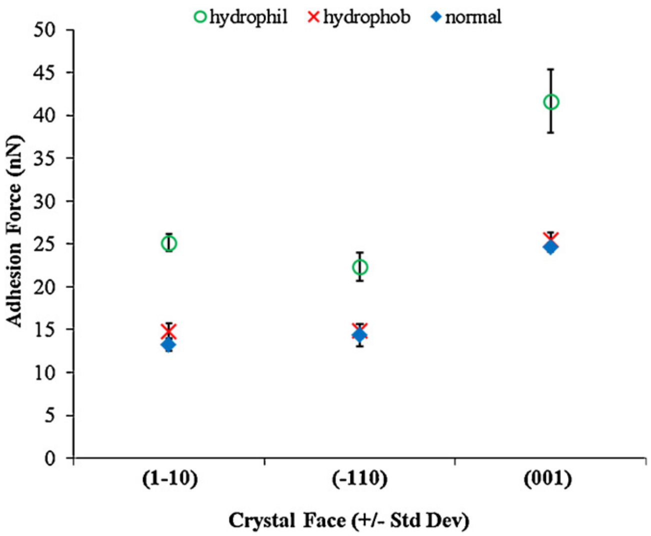

Fig. 5. Variation of adhesion force measured with chemically modified hydrophilic, hydrophobic and unmodified (normal) AFM tips on each APAP face. The error bars are one standard deviation.

the adhesion force measurements already discussed the different facets of the APAP were investigated under varied humidity conditions. The results for the (1 −1 0) and (0 0 1) facets of the APAP crystals in particular are highlighted here.

The increase in adhesion with RH as seen in Fig. 6 is in agreement with contact mechanic models when a capillary force is present. Many studies in the past (Butt and Kappl, 2009; Farshchi-Tabrizi et al., 2008; Butt et al., 2005; Hooton et al., 2004; Jang et al., 2004; Young et al., 2003; He et al., 2001; Xiao and Qian, 2000; Sedin and Rowlen, 2000; de Lazzer et al., 1999; Harnby et al., 1996a,b; Lahiji et al., 2010; Matsushige et al., 1995; Zhang et al., 2006; Chen et al., 2009; Ikai, 1996) showed the role played by the capillary forces in determining the probe–sample interaction under variable RH. Essentially increasing RH will tend to increase adhesion for hydrophilic surfaces and tips due to the presence of a meniscus. This can be attributed to the formation of water meniscus between the probe and sample surface. However, the magnitude of force can be expected to increase or decrease depending upon the thickness or uniformity of the water meniscus which is formed by capillary condensation or by accumulation of adsorbed liquid (Butt et al., 2005). Specifically, the adhesive force shows a dependence on the size of the meniscus and the contact angle of the meniscus with the tip. As RH increases the adhesion initially increases as the meniscus increases in size, but eventually at high RH the contact angle increases and the magnitude of the meniscus forces drops. This analysis is valid for a hemispherical tip (the approximate shape of the AFM tips used in this study) contacting a comparatively smooth surface, which is the case for the faces of APAP studied here. Surface asperities on rough surfaces can give an entirely different response to increasing humidity due to the effect of the asperities on the contact angle. Other interactions such as Van der Waals forces and effects due the polarity of the COOH terminal group on the AFM tip and polar groups on the crystal surface increasing the polar force component (Ikai, 1996) can also affect the adhesion, though the meniscus will tend to dominate for hydrophilic surfaces.

3.5. Surface morphology and humidity for APAP crystal faces

As well as quantifying surface adhesive forces the AFM was used to image the APAP crystal faces and identify changes in surface morphology with RH. As discussed above the forces associated with a meniscus can be dependent on the surface roughness, hence changes in morphology with RH could potentially affect the adhesive forces measured. It was found that one crystal facet (1 −1 0) exhibited a significant change in surface geometry at higher RH as seen in Fig. 7 while the other surfaces examined did not show any significant change in morphology. At higher humidities the (1 −1 0) face showed more plateau like features, with each plateau having a very flat surface. A possible explanation for this is some sort of recrystallization of the sample surface occurring at high humidity as a result of water uptake. It is also possible that the act of scanning the APAP surface with an AFM tip might affect the surface morphology of the samples, particularly under conditions of high humidity. To mitigate this potential problem tapping mode was used during these studies since the relatively small time of contact with the surface reduces the risk of changes in morphology.

Changes in the surface morphology during the dissolution of APAP have been seen in previous studies using AFM (Li et al., 2000, 2001). These changes in morphology with humidity coupled to the humidity dependence of the adhesion are the strong indication that the ability to process APAP into powder compacts and tablets is likely to be highly dependent on the ambient environment.

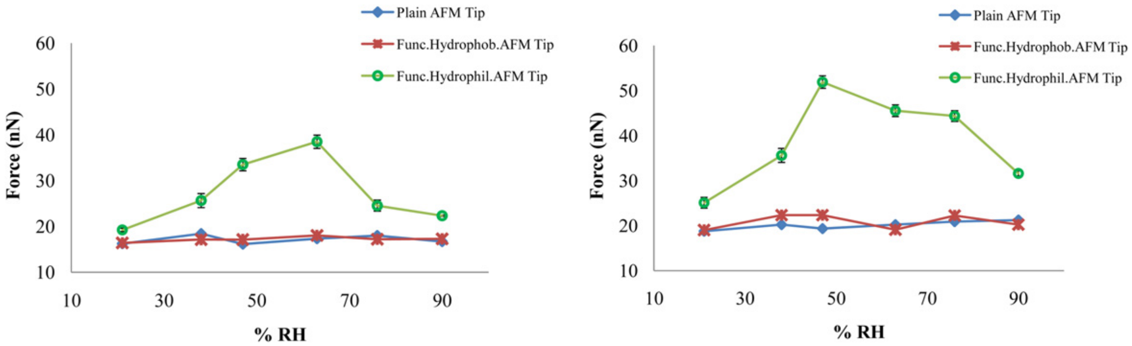

Fig. 6. Effect of humidity on adhesion force on crystal facets of APAP. An increase is seen for a hydrophilic AFM tip with increasing humidity up to 50–60% RH. Above this RH there is a gradual drop in adhesion. Humidity had no effect for tips, which were not hydrophilic.

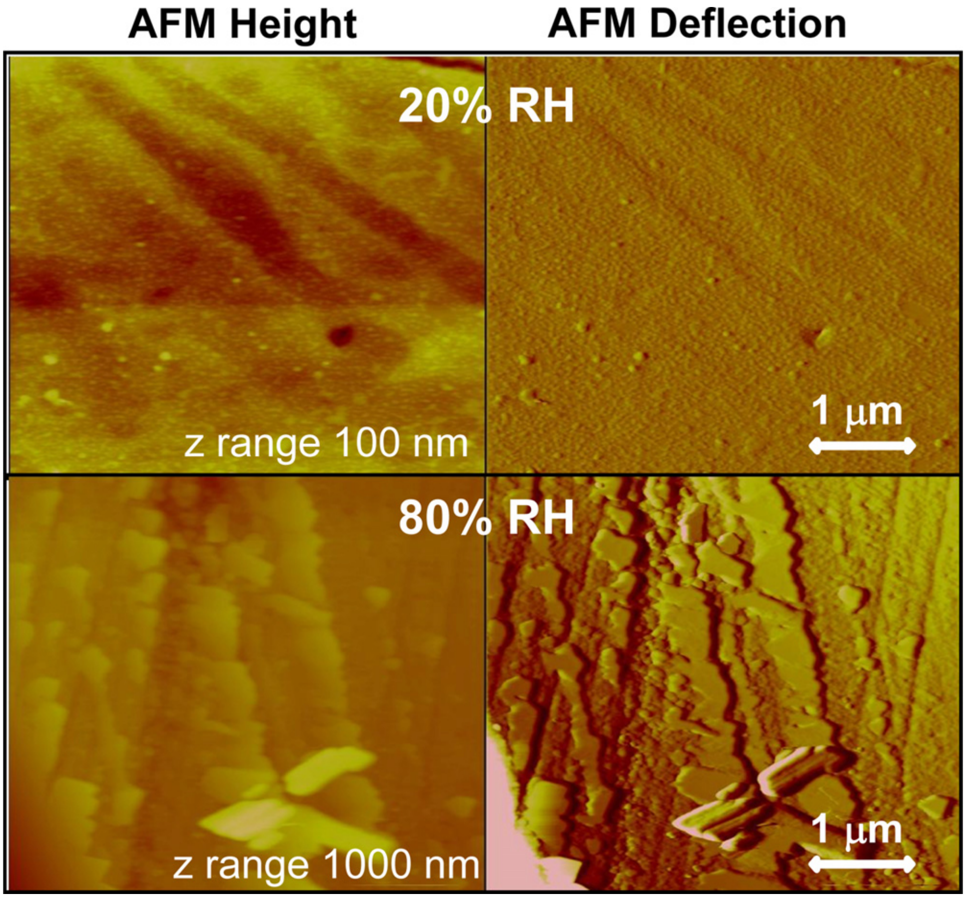

Fig. 7. Change in surface topography with increase in RH. Not all crystal facets exhibited this morphological change. Only the (1 −1 0) crystal facet showed the surface change at higher RH environment.

4. Conclusions

Using AFM and controlling the environmental humidity we have shown that the hydrophilicity of different APAP crystal faces affects surface adhesion. The (0 0 1) face in particularly exhibits higher adhesion than the (1 −1 0) and (−1 1 0) faces. Adhesion on all of the faces peaks at around 50–60% RH, which is expected for relatively flat hydrophilic surfaces. During the processing of APAP this dependence of adhesion on RH could be a factor in the ability to make homogenous formulations during mixing and in the reproducible formation of tablets. The difference in adhesion between faces is likely due to the differences in the chemical moities on the faces as shown in Fig. 3. Specifically, the (0 0 1) APAP face is known to be the most hydrophilic (Heng et al., 2006) due to the high density of OH functional groups when compared to the other crystal faces. RH was also found to affect the surface morphology of the crystal, though these changes were not observed on the hydrophilic (0 0 1) face, but rather than on the (1 −1 0) face which lies normal to the (0 0 1) plane. The changes in morphology with RH, like the changes in adhesion, may affect the interactions between APAP crystals during mixing and tableting.

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