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RESEARCH ARTICLE

Characterising the surface adhesive behavior of tablet tooling components by atomic force microscopy

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Abstract

Purpose: The aim of this study is to develop an atomic force microscopy (AFM) based approach to study the adhesive forces between tabletting punches and model formulation ingredients, that can ultimately be used to understand and predict issues such as sticking during tabletting compression.

Methods: Adhesive interactions were studied between single lactose particles and coated tablet punches. The adhesion was measured at varying relative humidities (RHs) and the influence of surface roughness was investigated. Roughness parameters were measured with AFM imaging and a modeling approach used to predict the influence of roughness on adhesion.

Results: Surface roughness was found to play a significant role in the observed lactose-punch adhesion and the variation of this adhesion across the punch surface. Such differences between punches can be correlated to observations from industrial use. Adhesion forces were spatially mapped to indentify "hot spots" of high adhesion. A modeling approach can predict the relative adhesion of different surfaces from roughness data. The adhesion was also significantly affected by RH, for one type of punch causing a greater than 3× increase in adhesion between 30 and 60% RH. Interestingly, different punches showed different RH-adhesion behavior, relating to their hydrophilicity.

Conclusions: The work introduces a new method for screening tablet punch materials and tabletting conditions. Important factors to be considered when evaluating adhesive interactions in tablet compression have been highlighted. Correlations are observed between AFM adhesion results and tabletting behavior during manufacture. This provides a promising basis for a predictive approach toward combating tabletting issues.

Keywords: Tablet tooling, tablet manufacture, atomic force microscopy, particle adhesion, sticking, lactose

Introduction

Understanding particle–particle and particle-surface interactions is important in many areas of drug development, formulation and delivery in the pharmaceutical industry[1–3]. Perhaps less well acknowledged, is the role of such interactions in manufacturing processes such as tablet compression. Commonly encountered problems in tabletting such as "sticking," whereby material transfers onto the surface of the tablet punch after removal of the load[4–6], are inherently related to the way in which particles in the formulation interact with the tablet punch. It is therefore of great interest to be able to understand these interaction forces, and their possible influence on tablet manufacture in more detail.

Problems such as sticking arise from the interactions between formulation ingredients and the punch faces used to compress tablets. However, there are complex contributions to this process including the mechanical and compaction properties of the formulation ingredients (elastic and plastic deformation), the type of excipients[7], the parameters used during tabletting, the environmental conditions[4,8–12] and additional factors such as the presence of low-melting-point drugs or solid dispersions[13]. In particular, the properties of the punch faces themselves are directly associated with the quality of the fully formed tablet. Specific types of problems during tablet compression have been indentified and investigated including sticking[6,14], picking[15] and capping[16]. There is an increasing

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interest in using punches with a range of surface treatments and coatings offering improved wear and non-stick properties over uncoated metals. An example is the early work of Schumann and Searle[17] on chromium nitride tablet tooling and later Roberts et al.[14], who have demonstrated the influence of chrome plated tooling on tablet sticking at various loads.

It would be beneficial to be able to quantify the adhesive potential of solid dosage formulation ingredients to punch materials. In this way, methods could be developed to help understand, and predict, problems in tablet manufacture earlier in the drug development process. There are inherent advantages associated with reducing the financial and material costs due to a production failure.

Conventionally, problems like sticking in tabletting manufacture are addressed by costly trial-and-error processes involving prior knowledge of which solutions will work in particular situations[11]. An alternative is the use of specialist *in situ* equipment for direct measurements of tablet adherence such as a tablet process analyzer[13] or stain gauge based apparatus[18]. There appears to be a lack of understanding regarding the fundamental mechanisms underpinning sticking. In this article, we suggest that a more proactive approach can be employed based on assessing the interaction forces of major formulation ingredients with punch faces. Since this can be performed in isolation of large scale tabletting manufacture, the analysis can be performed first, allowing any potential problems to be anticipated and circumvented.

In this article, we outline research using atomic force microscopy (AFM) to investigate such interactions. AFM is being found increasingly useful to directly assess particle–particle and particle-surface interactions in pharmaceutical research[3,19]. In particular, the so-called "colloidal probe" technique, whereby a single particle is attached to the AFM cantilever, has demonstrated great potential. It has already been applied to a wide range of pharmaceutical areas. Examples are ranking particulate interactions in inhalation formulations[20–25], surface energy measurements[26,27], mechanical property measurements[28–30] and packaging issues[31].

One of the advantages of the AFM technique is its ability to quantify interaction forces at a single particle level, accessing information not possible using bulk scale techniques such as the centrifugal technique[10]. AFM can also operate in a range of experimental geometries and environmental conditions. Due to its high force sensitivity it is possible to study the nature of various forces involved such as van der Waals, electrostatic and capillary forces and how these respond to environmental effects, for example, under different relative humidities (RHs).

Two previous publications have used AFM based techniques to address the issue of sticking in tablet compression. Wang et al.[11] utilized an iron-coated AFM tip as a model for the interaction with a punch face. They determined a ranking of three profen compounds in terms of work of adhesion. In a similar approach, Lee[32] used a steel sphere attached to an AFM probe to measure the difference in adhesion between different formulation ingredients. Both articles therefore model the tablet compression by having a metallic probe to represent the punch face and using the pharmaceutical materials as substrates. Additionally, Weber et al.[33] used an AFM approach to investigate the influence of lubricant (magnesium stearate) on the adhesion behavior of particles to a steel surface, chosen as model for a tablet die.

In this article, we use a different approach whereby real tablet tooling punch faces are employed as substrates and challenged by AFM probes functionalised with lactose particles (as an example of a common tablet excipient). In this manner the properties of punch faces that contribute to sticking issues can be investigated "*in situ*" using real tooling, providing a more realistic experimental geometry.

Adhesion forces between particle and surfaces are often considered to be a sum of van der Waals, capillary and electrostatic forces[22]. The contribution from each of these components varies as a function of conditions in which they are measured. The ubiquitous van der Waals forces depend upon surface energy and ultimately the Hamaker constants of materials[19]. They act over a short range and are therefore affected by the surface roughness and the effective contact area[34–37]. Capillary forces are generated when moisture condenses into the gap between a particle and surface causing a liquid bridge. The strength of these forces therefore depends heavily upon the RH, gap geometry and surface chemical condition[22,38–40]. Electrostatic forces arise when tribocharging occurs between contacting materials. The resulting force can be relatively strong and long ranged. However, these forces are difficult to manipulate and quantify[41] and are not the focus of this study.

In particular, the influence of RH and roughness on particle interactions has been studied by a number of authors using the AFM single particle approach[19]. Generally speaking, experiments have shown that an increase in RH leads to an increase in adhesive tendency. This is caused by the formation of capillary forces, whereby moisture condenses to form a liquid meniscus resulting in an attractive force[42]. Early studies by Young et al.[43,44] measured the cohesion and adhesion behavior of various drugs as a function of RH. Bérard et al.[45,46] carried out studies using lactose and drug particle probes and observed increases in adhesion as a function of RH. Hooton et al. showed in more detail how the adhesion-RH profile can depend on the precise contract geometry of the particle probe, with a "peak" effect also observed, whereby above a certain RH value the adhesion begins to decrease[22]. This peak effect has also been observed and explained elsewhere[40,47,48].

It was recognized early in the development of AFM single particle measurements that roughness plays a key role in determining adhesion due to the importance of the true contact area at the nanoscale[19]. Many studies have shown how roughness influences the strength of

adhesion forces[49–51]. In tabletting, bulk scale studies have shown that the punch surface roughness is a significant factor in the sticking behavior of a model ibuprofen-lactose formulation[14].

There have been attempts to model the influence of roughness on adhesion. Rabinovich et al.[52,53] built on the work of Rumpf[54] and proposed on a model based on measuring two scales of roughness. Further details are given in the theory section of this article. Beach et al.[34] conducted an interesting study comparing the adhesion behavior of peptide material, lactose particles and colloid probes on surfaces of varying roughness. The authors applied the Rabinovich model to their results and found a good correlation for the lactose particles on most surfaces.

This study aims to investigate the interactions of a common formulation ingredient (lactose) with different punch face coatings using a single particle AFM approach. Emphasis is placed on understanding the influence of punch face material, RH and surface roughness on particle adhesion. The ultimate aim is to develop our understanding such that a proactive approach to tabletting issues like sticking can be used before a final selection of both formulation materials and processing parameters is made.

Theoretical approach for particle adhesion to a rough surface

In order to predict the attractive forces between a spherical particle and flat plane, Hamaker developed the following model by integrating the London-van der Waals attractive forces at solid interfaces that occurs as a result of fluctuating dipoles at the atomic level[36],

$$F_{ad} = \frac{AR}{6h_0^2} \tag{1}$$

Where A is the Hamaker constant; R is the radius of the spherical particle, and h_0 is the distance of closet approach between two surfaces and is taken to be equal to 0.3 nm (radius of an atom).

The Hamaker constant can be calculated according to equation 2, where γ_s^{LW} refers to the Lifshitz-van der Waals component of the surface free energy[34].

$$A = 1.44 \times 10\text{-}18\gamma_s^{LW} \tag{2}$$

For contact between dissimilar materials, a combining rule approximation[55] can be used to estimate the effective Hamaker constant, A_{12} (in our case between a lactose particle and a coated punch face). Table 1 details the data used in the calculations for the current study.

Table 1. Hamaker constants and surface free energies for the materials used in this study.

Materials	Hamaker constant ($\times 10^{-20}$ J)	Surface free energy γ_s^{LW} (mJm^{-2})
Lactose monohydrate (A_{11})	7.20[a]	—
Chromium nitride (A_{22})	5.46[b]	37.93[c]
Lactose-CrN (A_{12})	6.27[d]	—

$$A_{12} = \sqrt{A_{11}}\sqrt{A_{22}} \tag{3}$$

Equation 1 only applies to an idealized flat surface. To account for the effect of rough surfaces on adhesion forces, Rumpf modified the Hamaker model to account for hemispherical surface asperities[54]. Later, Rabinovich et al.[52] further modified Rumpf's formula by introducing both the peak-to-peak distance and the rms roughness to describe a series of asperities. This was further advanced by the same authors by assuming two superimposed length scales of roughness as follows[53]. Equation 4 predicts the adhesion force based on this model.

$$F_{ad} = \frac{AR}{6h_0^2}\left[\frac{1}{1+\left(\frac{58R(rms_2)}{\lambda_2^2}\right)} + \frac{1}{\left(1+\frac{58R(rms_1)}{\lambda_1^2}\right)\left(1+\frac{1.82(rms_2)}{h_0}\right)^2}\right] \tag{4}$$

Where rms_1 and l_1 are the rms surface roughness and peak-to-peak distance on the larger scale (i.e. surface undulations), whereas rms_2 and l_2 are measured from asperities on a smaller length scale.

It should be noted that this equation only considers the dispersive van der Waals attraction between surfaces, and does not allow for other forces or elastic deformation of the surfaces, which may occur and would cause an increase in adhesion[52]. The equation consists of two principle terms. The first term is present to describe the contact interaction of the particle with an asperity on the surface, while the second term accounts for the non-contact interaction with the average surface plane.

In this article, we use this model to calculate predicted adhesion forces between a lactose particle and tablet tooling with measured roughness parameters based on AFM imaging data.

Experimental

Sample preparation

Five types of flat punch faces were prepared at I Holland Limited (Nottingham, UK). To facilitate AFM analysis, flat disks of base metal (in two grades of steel, HPG-S and HPG-P) ~15 mm in diameter and 4 mm in thickness were prepared. Four different types of coating materials were then applied onto the surface in the same fashion as for commercially available tooling components. The details of the punches used in this article are given in Table 2.

Prior to collecting AFM force data, the punches were washed in an ultrasonic ethanol bath for 5 min. The surface was then rinsed with deionized water and dried thoroughly under nitrogen before being stored in a desiccator between measurements.

To more closely mimic the use of tablet punches in an industrial environment, selected punches were

Table 2. Specifications of the materials used in the tablet punches studied.

Nominal name	HPG-S	HC	CN	CN+	DLC
Coating components	N/A	Hard chromium	Chromium nitride	Chromium nitride	Diamond-like carbon
Base material	HPG-S	HPG-S	HPG-P	HPG-P	HPG-S
Coating thickness (μm)	—	3–6	2–4	2–4	2–4
Surface polished	No	No	No	Yes	No

additionally treated with a 3% aqueous solution of Tickopur R33 (DR H. Stamm GmbH, Germany) by ultrasonication for 5 min. This surface treatment agent is commonly used on tablet tooling for anti-corrosion purposes. Treated samples were subsequently dried and stored as before prior to use.

AFM imaging

Punch face surfaces were imaged using AFM in contact mode on a Nanoscope IIIa MultiMode instrument (Veeco, Santa Babara, CA). Images were taken at 1 μm, 3 μm, 10 μm, 30 μm, and 120 μm scan sizes with 512 × 512 pixel resolution. Other imaging parameters were adjusted to maximize resolution. At least three sampling locations were taken from each punch face. The root mean squared (*rms*) roughness was measured from these images using the instrument software and averaged for each sample type and image size.

Modeling adhesion forces

In order to use the Rabinovich model as described in the theory section by additional measurements were taken of the distances between asperities (l), on both the large (l_1) and small (l_2) scale for the chromium nitride (CN) and chromium nitride+ (CN+) punches. The choice of which length scales to use for taking measurements of l_1, l_2, rms_1, and rms_2 are somewhat arbitrary and so different combinations of these parameters were measured from different image sizes. Predicted adhesion forces are calculated from equation 4. The contact radius of the lactose particle asperity, *R*, was determined from images of the contacting asperities as ~150 nm. The Hamaker constant for the system was estimated to be 6.27 × 10–20 J (A_{12} in Table 1).

Adhesive force measurement

The spring constants of tip-less contact mode AFM cantilevers were calibrated using the thermal method[56]. α-Lactose monohydrate (Respitose, ML003, DMV, Veghel, Netherlands) was used as an example formulation ingredient. AFM probes were functionalised with single lactose particles using a method described elsewhere[21]. Particle placement on each probe was confirmed using optical and scanning electron microscopy.

In order to exclude possible electrostatic forces from the interactions, all the punch face surfaces were briefly scanned with a Static Line II (Agar Scientific, Stansted, UK) immediately prior to adhesion force measurements. Measurement of adhesion forces was carried out against the punch faces using an EnviroScope AFM (Veeco) with the maximum press-on force kept between 10 and 20 nN. In all the tests, the humidity was accurately controlled using an integrated humidity generator (Triton Technology, Nottingham, UK).

For studies investigating the influence of surface roughness, the RH was maintained at 10% throughout. An array of adhesion measurements were taken in a 50 × 50 grid covering an area of 10 × 10 μm on the punch face surfaces (i.e. measurements spaced laterally by 200 nm). This was repeated on CN and CN+ punch faces, which differ only in their surface roughness, using the same particle probe.

For the variable humidity studies, the RH was increased from 10 to 30% and then 60%, taking adhesion measurements at each RH in a 12 × 12 grid over an area of 5 × 5 μm. The RH was then reduced back to 30 and 10% recording further measurements to investigate repeatability and any possible hysteresis. The system was allowed to equilibrate for at least 30 min at each RH. These measurements were conducted on three coated tablet punches, chosen for their different surface chemistries; CN+, hard chromium (HC) and a diamond-like carbon coating (DLC), details are given in Table 2. The surfaces were pre-treated with R33 solution to mimic use in an industrial setting. For each punch face, the same particle probe was used at all RH values to ensure a valid comparison. All the adhesion measurements on each tablet punch type were repeated with a second particle probe to ensure repeatability and that trends were not caused by one particular particle.

AFM force curves were analyzed and processed using customized software to extract adhesion forces. The particle probes were additionally examined before and after the adhesion force measurements using a tip characterisation grating (TGT1, Moscow, Russia) to image the contacting asperities of the particle[22]. This ensures that no changes have occurred to particle morphology which would invalidate adhesion comparisons and allows the measurement of asperity radius necessary for the modeling.

Contact angle measurements

To investigate the relationship between the adhesion behavior at different RHs and the surface properties of tablet punches, static water contact angle measurements were conducted. The sessile drop method (CAM 200, KSV Instruments, Helsinki, Finland) was used to record triplicate measurements on the punches used for RH studies; CN+, HC, and DLC punches. Measurements were recorded on punches that had been washed and treated with R33 solution (as described in sample preparation).

Results

Surface topography and roughness

Four coated punch faces, DLC, HC, CN, and CN+ and one uncoated steel punch face (HPG-S), were imaged using AFM in contact mode. Example 10 × 10 μm topographic images are displayed in Figure 1A–1E and show that different surface treatments result in very different surface morphologies. The uncoated punch face, shows a high density of striations on the surface (Figure 1A). The HC coating lessens the definition of such striations and the surface is covered with a high density of nanoscale pores or pits (Figure 1B), ~100–300 nm in diameter. In general, DLC presents a smoother surface with straight grooves which arise from the underlying base material (Figure 1C). In addition, there are some voids ~300 nm in size, with occasional small particulates on the surface.

Tablet punches coated in CN and CN+ differ only by a surface polishing process (Figure 1D and 1E, respectively). The CN tablet punch shows a series of circular features connected together to form a networked surface. In comparison, the polished CN+ surface appears smoother (Figure 1E) and the sharp edges around those circular features have been removed. However, the presence of circular surface depressions from the CN surface remains.

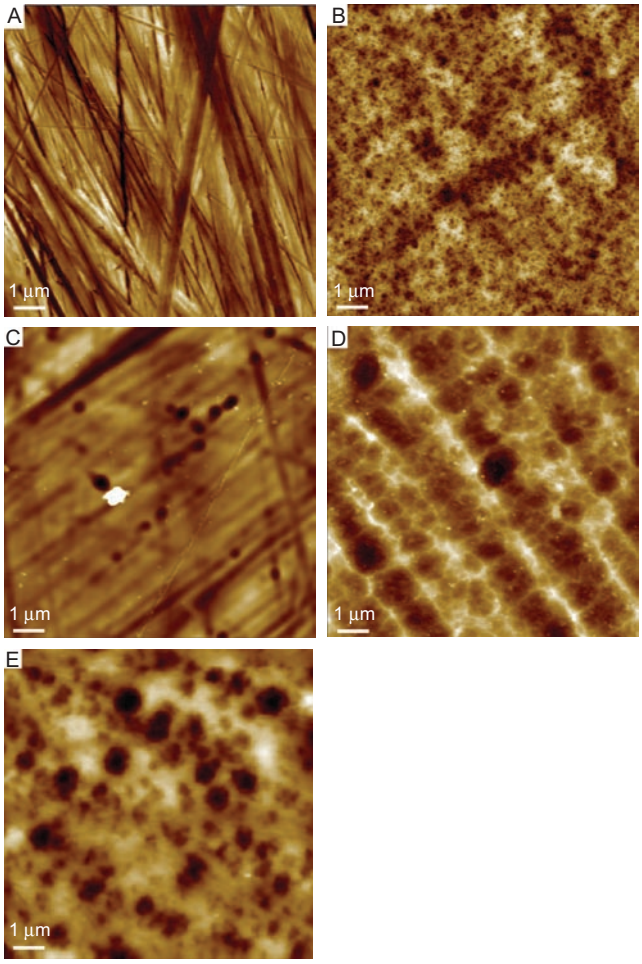

Figure 1. AFM topography images of tablet punch surfaces (A) HPG-S, z-range = 70 nm (B) HC, 70 nm (C) DLC, 100 nm (D) CN, 200 nm, and (E) CN+, 100 nm.

Figure 2 plots the surface roughness (*rms*) as a function of imaging size for all five punches. The roughness increases with imaging size as expected, and tends to stabilize at ~30 μm (with the exception of CN+ which shows a large increase between 30 and 120 μm). The data shows that the polishing process has significantly lowered the roughness of the CN+ in comparison to the CN. The roughness values of the other three punch faces, DLC, HC, and HPG-S are of a similar level, and are significantly smoother than both the CN and CN+.

Influence of roughness on adhesion

Figure 3A and 3B shows the adhesion force distributions measured on the CN+ and CN punches, respectively, which differ only in surface roughness. Each represents the variation in adhesion measured across a 10 × 10 μm area of the surface ($n = 2500$). The data is reasonably well fitted with a Gaussian distribution (solid lines) for both samples. The corresponding mean adhesion forces are 14.2 nN for the CN+ and 19.2 nN for the CN. Note that the same lactose particle probe was employed for both CN and CN+ punches in order to eliminate a possible variation in contact area induced by different particle probes and to allow direct comparison of the distributions. Since the adhesion data was recorded in a defined grid pattern across the surface, it is also possible to plot the data as an adhesion force map, as shown in Figure 4.

Modeling the influence of roughness on adhesion

To further understand the influence of roughness on adhesion forces, a modeling approach was also considered. As detailed, the Rabinovich model predicts the adhesion force between a particle and a surface based upon the presence of two scales of roughness[52,53]. The choice of image sizes from which to obtain the necessary input values (*rms* and λ) values for small and large scales is important and should reflect the scale of observation and the scales over which surface roughness varies significantly. Different combinations of image sizes were

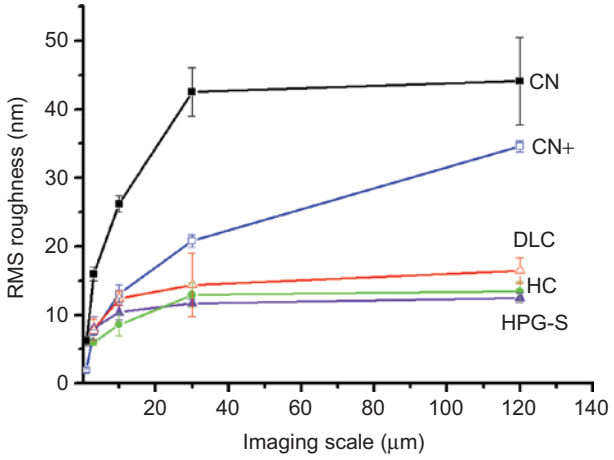

Figure 2. Tablet punch surface roughness (rms) as a function of image size.

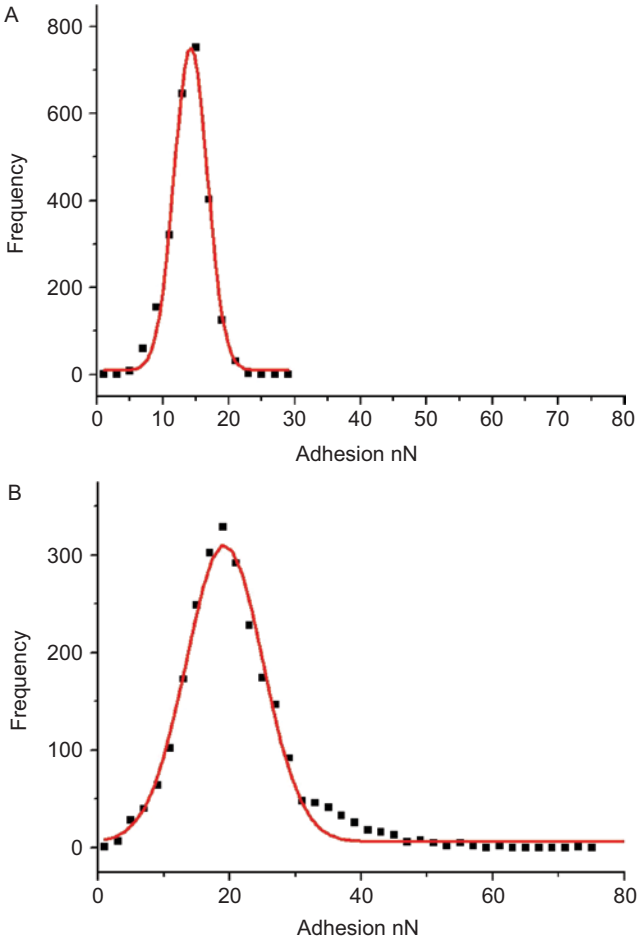

Figure 3. Adhesion force distribution (solid squares) and Gaussian fit (solid line) for (A) CN+ and (B) CN tablet punches ($n = 2500$).

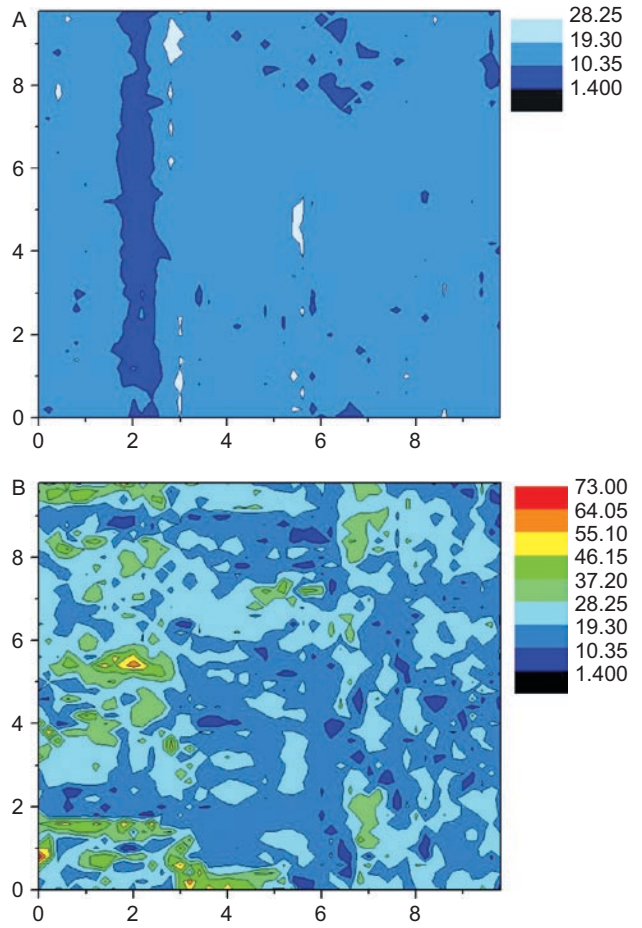

Figure 4. Adhesion force maps for (A) CN+ and (B) CN tablet punches. X, Y scale is in m, forces are in nN and scaled the same for both maps.

used to derive these measurements and are shown in Table 3 alongside the predicted adhesion forces.

Table 3 indicates that the values of the adhesion forces predicted by the model. Although these absolute values will depend on the accuracy of the parameters used, and on the applicability of the model itself, it is of particular interest to consider predicted ratio of the adhesion forces on the two surfaces, $F_{ad}CN+/F_{ad}CN$. This ratio will only depend on the *rms* and λ measurements obtained from the images, and provides a robust comparative approach.

Influence of humidity on adhesion

Adhesion forces were determined for three different punches (CN+, HC, and DLC) as the RH was varied between 10 and 60%. A series of adhesion measurements were recorded in a grid on the surface at each RH and the mean adhesion force (± the standard deviation as a measure of the variation across the surface) was then plotted as a function of RH for each tablet punch. The results are shown in Figures 5–7 for CN+, HC and DLC, respectively.

For the CN+ tablet punch (Figure 5), there is no change between 10 and 30% RH, but the adhesion increases sharply between 30 and 60% RH. The data for the HC tablet punch shown in Figure 6 demonstrates a less pronounced peak effect at 60% RH.

The effect RH on the DLC tablet punch (Figure 7) shows a different behavior, only a subtle increase in adhesion was observed when RH was increased from 30 to 60%. Interestingly, the change in the adhesion with RH was not reversible in this case; remaining high after the RH was decreased.

Contact angle measurements

The static water contact angles measured on the CN+, HC, and DLC tablet punches are displayed in Figure 8, both after cleaning and after treatment with R33 solution. The data reveals that surface treatment with the Tickopur R33 solution improves the surface wettability through increased hydrophilicity of all the punches, leading to a decrease in contact angle. The HC punch has a notably more hydrophilic surface than the CN+ and DLC.

Discussion

The use of AFM as a tool for predicting and understanding the adhesive interactions between particle and tablet punch faces has been demonstrated. The

Table 3. A summary of the predicted adhesion forces of lactose on the CN+ and CN punches and their ratio based on the Rabinovich model which accounts for surface roughness over different length scales.

Image size (μm)							Predicted	
Large (1)	Small (2)	Punch	rms_1 (nm)	λ_1 (nm)	rms_2 (nm)	λ_2 (nm)	F_{ad} (nN)	$F_{ad}CN^+/F_{ad}CN$
30×30	3×3	CN+	20.8	2500	7.5	620	14.9	1
		CN	29.4	2500	12.5	840	15.1	
30×30	10×10	CN+	20.8	2500	13.1	1200	16.1	1
		CN	29.4	2500	20.9	1500	16.1	
10×10	3×3	CN+	13.1	1200	7.5	620	14.9	1
		CN	20.9	1500	12.5	840	15.1	
3×3	1×1	CN+	7.5	620	1.9	120	8.2	0.7
		CN	12.5	840	6.2	330	11.7	
30×30	1×1	CN+	20.8	2500	1.9	120	8.2	0.7
		CN	29.4	2500	6.2	330	11.7	
10×10	1×1	CN+	13.1	1200	1.9	120	8.2	0.7
		CN	20.9	1500	6.2	330	11.7	

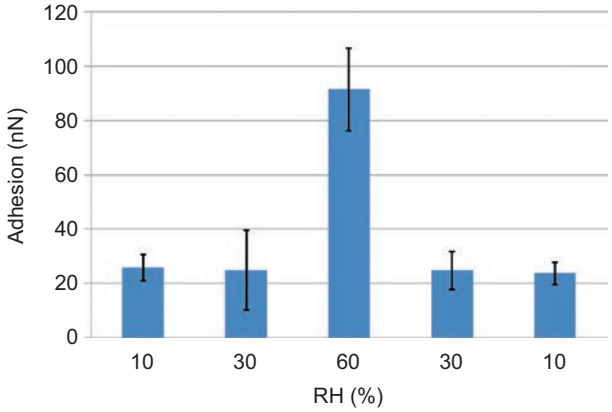

Figure 5. Adhesion forces as a function of relative humidity for CN+ tablet punch.

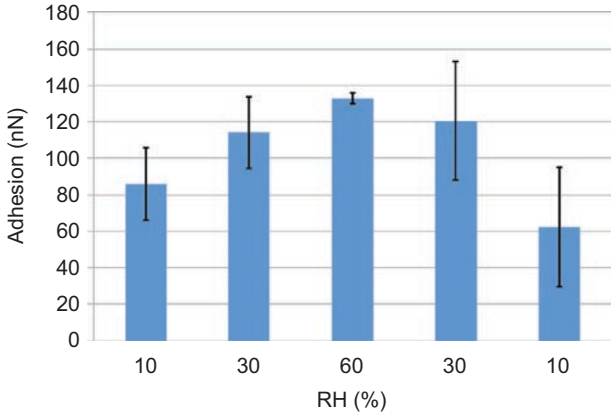

Figure 6. Adhesion forces as a function of relative humidity for HC tablet punch.

technique is sensitive to influences such as surface roughness and RH which can impact on issues such as sticking during tablet manufacture. It is proposed that this approach can be extended to screen materials and punch faces or highlight a possibly problematic ingredient in a formulation.

The influence of tablet punch surface roughness on the adhesion force has been investigated by comparing two punch faces differing only in surface morphology, CN and CN+. The difference in surface morphology and roughness has been highlighted in Figures 1D, 1E, and 2, respectively. It is clear from Figure 2 that the polished CN+ surface gives a lower *rms* roughness value across the length scales, as would be expected. The adhesion force distributions obtained on these surfaces (Figure 3A and 3B) clearly reveal the influence of surface roughness on the adhesion force magnitude and distribution. Surface roughness is well known to affect particle adhesion by determining the contact area of the asperities (or the number of asperities) over which van der Waals forces can act[10]. These experiments were conducted at low RH to remove the influence of capillary forces and ensure that van der Waals forces were dominant.

Compared to CN+, the CN has a rougher surface with more asperities to interact with the contacting particle, causing a statistically greater average adhesive force (CN = 19.2 nN and CN+ = 14.2 nN). This is consistent with the practical observation that the CN+ can help reduce sticking issues in an industrial setting[57].

In addition, the rougher surface also promotes a more heterogeneous distribution of the adhesion (Figure 3). Using the standard deviation as a measure of distribution width, the CN sample (SD = 5.8 nN) is much boarder than that of the CN+ (SD = 2.5 nN). Interestingly, for the CN punch there is a distinct additional shoulder adjacent to the main peak of the distribution with high values of adhesion forces being more frequently recorded. It is hypothesised that this could be related to problematic interactions that act as the nucleation sites for sticking during tablet compression. It is clear from Figure 4B that there are "hot spots" of high adhesion forces on the CN surface which are related to the shoulder observed in the distribution plot in Figure 3B.

These measurements on the CN and CN+ tablet punches correlate with practical observations regarding their tabletting performance, where the CN+ is used as a "low sticking" alternative for difficult formulations[57]. This link between single particle measurement and bulk scale observation provides clear evidence that this

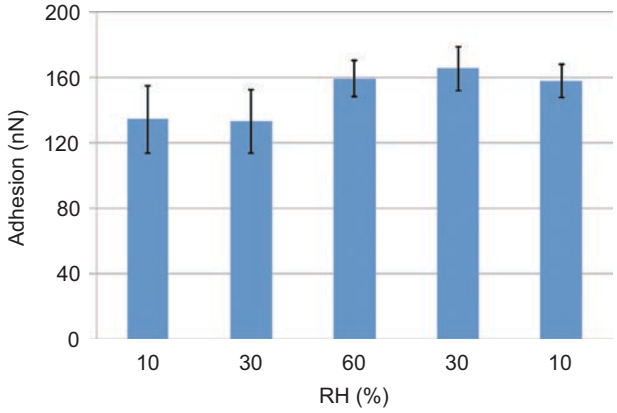

Figure 7. Adhesion forces as a function of relative humidity for DLC tablet punch.

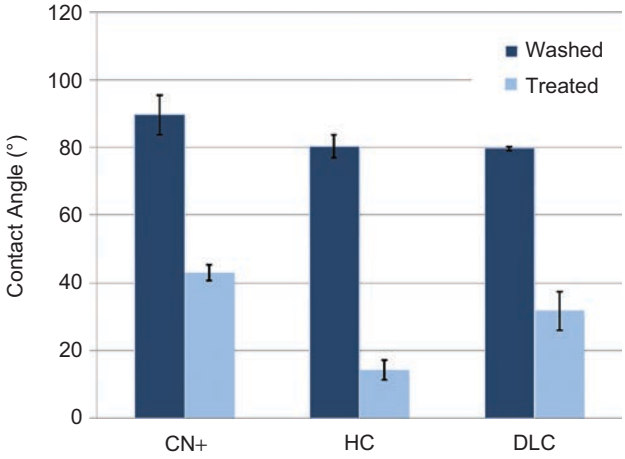

Figure 8. Static water contact angles for CN+, HC, and DLC tablet punches.

AFM approach can be used predicatively or as a trouble shooting tool for avoiding sticking issues.

The model proposed by Rabinovich et al.[52,53] has been used to try and predict the forces obtained on the CN and CN+ tablet punches. The model takes inputs of the *rms* roughness and the distance between asperities, λ. It is intuitive that the scale at which these parameters are measured for the model should reflect the scale at which adhesion event take place on the real surface. The model assumes an idealized surface profile of super imposed spherical asperities and troughs, which is obviously a simplification of the real engineered surface as we study here. In addition, the model neglects deformation of the particle on contact which will increase contact area, and the possible contributions of forces other than van der Waals (although we have tried to minimize these experimentally). Despite these factors, the model offers an improvement on previous attempts to match theory with experiment[53]. Here we find the absolute values of adhesion predicted by the model (8–16 nN) are in general close to those determined experimentally by AFM for CN and CN+ punches.

Perhaps of more relevance is the adhesion force ratio (F_{ad}CN+/F_{ad}CN), which reflects only the relative difference in surface roughness of the two tablet punches tested here. This is calculated as a function of different parameters and compared to the experimentally determined value (0.7). The strongest correlation is seen in the last three rows of Table 3, where the parameters rms_2 and λ_2 were derived from the smallest image size (1 × 1 μm). It appears that with the parameters used here for the CN and CN+ surfaces, the model is dominated by the terms for the smaller image size. It is suggested that the model is more accurate in this case because the particle itself only contacts the surface with a small asperity (radius ≈ 150 nm) and so measurements based on smaller length scales more closely reflect the interaction. Despite the assumptions inherent in the model, the success of this approach to predict the relative adhesion of CN and CN+ tooling provides encouragement that it could be used predicatively to assess the relative sticking propensity of different surfaces based on knowledge of surface morphology and roughness.

In this study, we have simulated interactions during the tablet compression process by bringing a single particle into and out of contact with a punch surface using an AFM cantilever as a "force probe." It is worth considering how this process compares to real tablet compression in terms of applied loads. Typical compaction forces during compression of a tablet in industry are around 20 kN[5], which is equivalent to a pressure of ≈250 MPa acting over a tablet of 1 cm diameter. Here the pressure exerted during an adhesion measurement is estimated at 10 MPa (calculated from a force of 20 nN and an estimation of contact area from AFM imaging of the particle probe). It is clear that under higher loads, particles may undergo elastic or plastic deformations and thus have a larger contact area with a surface. In contrast at the loads experienced in AFM, only elastic deformation typically takes place (indeed plastic deformation can be easily identified in the AFM data if it occurs). The resulting contact area with the tablet punch and therefore the attractive van der Waals forces are proportionally reduced. Nevertheless this difference does not affect the effectiveness of using the method to predict the intrinsic adhesive tendency of a tooling component based on roughness, a similar acknowledgement is made by Lee[32]. Bulk scale tabletting studies have shown that the roughness of the tablet punch can influence the amount of sticking[14]. Here the measured AFM result successfully predicts the difference in adhesion between CN and CN+.

The ability of RH to affect particle adhesion is well documented in the AFM literature, however the possible influence of such changes on tablet compression are not so well widely discussed. Our experiments highlight how the RH can have a dramatic influence on the adhesion of particles to tablet punches, which could impact tabletting performance if not properly controlled.

Figures 5–7 indicate the different responses to the changes in humidity from the CN+, HC, and DLC punches,

respectively. For the CN+ surface there is a sharp rise in adhesion force between 30 and 60% (increasing by a factor of 3.7) which we attribute to the formation of capillary forces. Above a certain critical RH, water from the surrounding air can form liquid bridges in the gaps between the lactose particle and the tablet punch surface[22,47,48,58]. It is evident from the data that this critical RH for the lactose-CN+ system is between 30 and 60%. As would be expected, the formation of these capillary forces is reversible and the adhesion returns to lower levels as the RH is reduced.

Different behavior is observed on the HC tablet punch, whereby a less pronounced increase is observed between 10 and 60% RH. One explanation for this is that capillary forces are acting even at 10% RH on this surface (i.e. the adhesion starts off higher at 10% RH). Increasing the RH further increases the magnitude of this effect. It is interesting to note the significant reduction in the variation of adhesion across the surface at 60%. This might suggest that at 60% RH capillary forces are dominant and mask variability introduced in van der Waals forces from the underlying surface roughness.

The DLC tablet punch shows different behavior again, with a very subtle increase in adhesion between 30 and 60%. Given the small variations observed at different RHs, this could again be explained by the interpretation that capillary forces contribute at all RHs. It is interesting to note that the adhesion in this case does not appear be reversible, at least on the timescales used in this experiment (the system was left to equilibrate for at least 30 min at each RH level). This suggests that the DLC punch surface behaves very differently from the CN+ and HC in the way the surface interacts with water moisture in the air.

Hooton et al.[22] discuss the onset of capillary forces in terms of the spreading coefficient of a surface, which in turn depends on its surface energy. The point of formation of liquid films necessary for capillary forces will vary on surfaces with different surface properties. In the present study, the different RH-adhesion profiles that we see on the tablet punches can be related to their surface hydrophilicity as measured by water contact angle. It is intuitive that the more hydrophobic a surface is, the more difficult it will be for capillary forces to form and the critical RH will be higher. This has been shown theoretically and discussed by Pakarinen et al.[59] This hypothesis is backed up by the contact angle data for the treated surfaces (Figure 8). The data shows the CN+ has the most hydrophobic surface, correlating with the observation that capillary formation appears at higher RH (causing the abrupt jump in adhesion between 30 and 60%). In contrast, for the more hydrophilic DLC and HC surfaces, it is possible that capillary forces are significant even at 10% RH, and that this increases gradually with a further RH increase due to an increase in the thickness of water layer.

It is also interesting to consider the possible influence of roughness on the RH-adhesion behavior. As noted by Hooton et al.[22], the wetting of a surface is hindered by its roughness. In our study, the CN+ surface is notably rougher than the HC and DLC surfaces, and also shows the highest onset of capillary forces.

Conclusions

This study has demonstrated an approach for measuring the adhesive interactions of a typical excipient with the surfaces of tablet punches at the single particle level using AFM. This provides a better understanding of the interactions that cause tabletting issues such as sticking during tablet compression and manufacture. This study has focused on the role of surface roughness and RH on adhesion and has shown that it is possible to quantify and map the punch face adhesion, and to detect key parameters which influence adhesion behavior.

A correlation has been shown between the surface morphology and roughness measured from AFM imaging and the resulting adhesion force distributions. High adhesion sites, which could contribute to sticking have been quantified and mapped. A theoretical approach has shown promise for modeling the influence of roughness on particle-punch adhesion.

The influence of RH on the adhesion has been shown to vary greatly between different tablet punches, depending on the level of capillary interactions that occur. The different RH-adhesion profiles observed have been related to the surface hydrophilicity of the punches, measured from water contact angle. The importance of surface hydrophilicity and its potentially dramatic impact on particle adhesion to tablet punch surfaces has been demonstrated. This highlights the need to carefully consider environmental conditions during tablet manufacture.

The work introduces a new method for screening punch materials and tabletting conditions and highlights important factors which need to considered when evaluating adhesive interactions in tablet compression and how potential sticking problems may be affected. This provides a promising basis for a predictive approach toward combating tabletting issues.

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Declarations of interest

The authors report no declarations of interest.

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