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Tabletting Science

A SCIENTIFIC APPROACH TO A STICKY PROBLEM

Sticking, the adherence of granule to punch face or die bore, is one of the major issues affecting the manufacture of solid dose pharmaceuticals. As part of I Holland's continuing quest to increase understanding of the science behind tabletting, their Research & Development team have completed a preliminary study in partnership with UK based contract research organisation Molecular Profiles.

The aim of the study is to develop an atomic force microscopy (AFM) based approach to understanding why formulation can sometimes stick to tablet punch tips. It is the intention that this will ultimately be used to understand and prevent sticking.

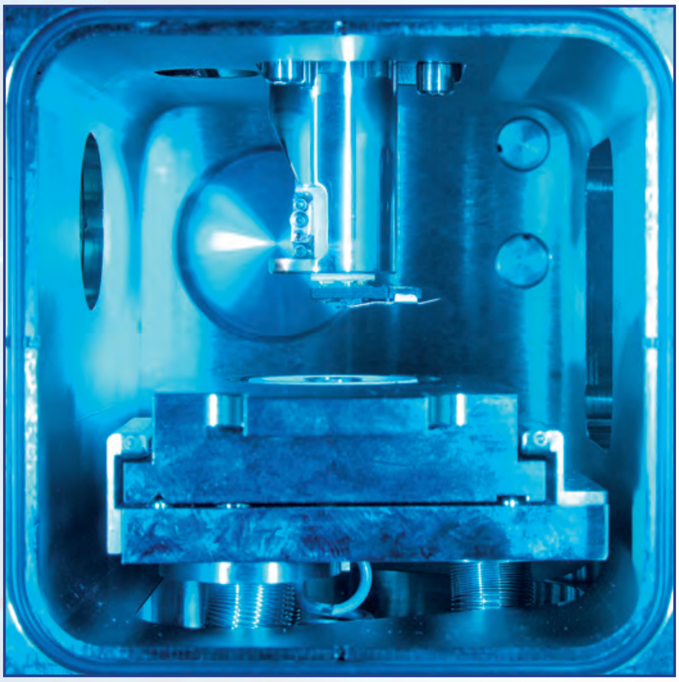
What is Atomic Force Microscopy?

AFM provides an ultra-sensitive force measurement instrument, based on optical detection of the motion of a miniaturised tip attached to a cantilever. By replacing the AFM tip with the particle of interest it is possible to exploit this to measure particle-surface adhesion levels.

Measuring adhesion forces with AFM

The force measuring capabilities of the AFM can be exploited to directly measure the adhesion forces between two surfaces. The AFM probe can be functionalised with a particle of interest (lactose in this case) and its interaction with the tablet punch tip can be measured.

Force-distance curves are recorded by monitoring the deflections of the cantilever as the probe and sample are brought into contact, and then separated. Figure 1 displays an idealised force-distance curve, a plot of cantilever deflection against the distance moved by the cantilever.



AFM Chamber

To begin, the probe and sample are separated by a large distance (as shown in **A** above). As the probe-sample separation is reduced (**B** above), the cantilever can be deflected by long-range forces acting on the probe.

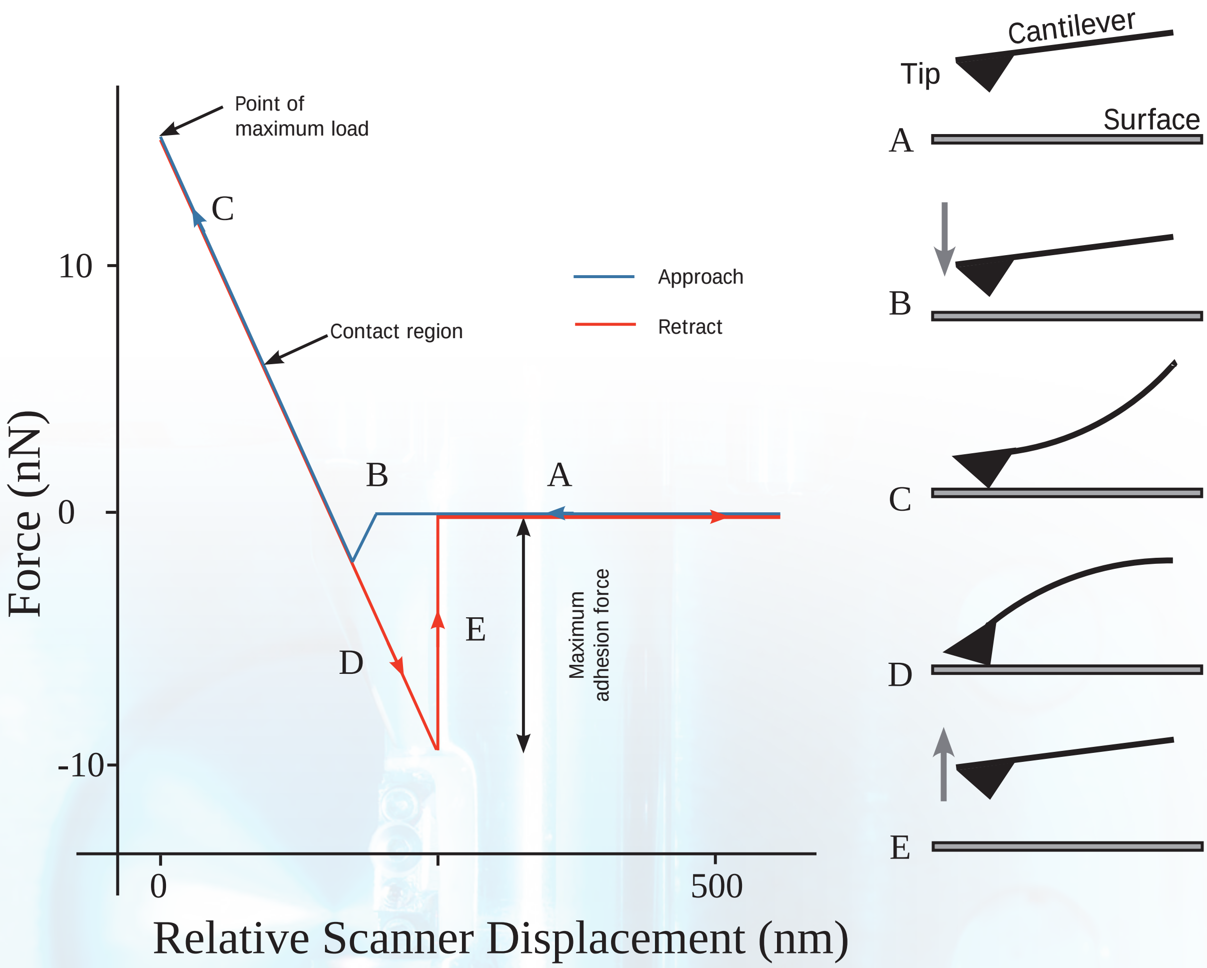


Figure 1. *Idealised force-distance curve showing tip-sample interactions.*

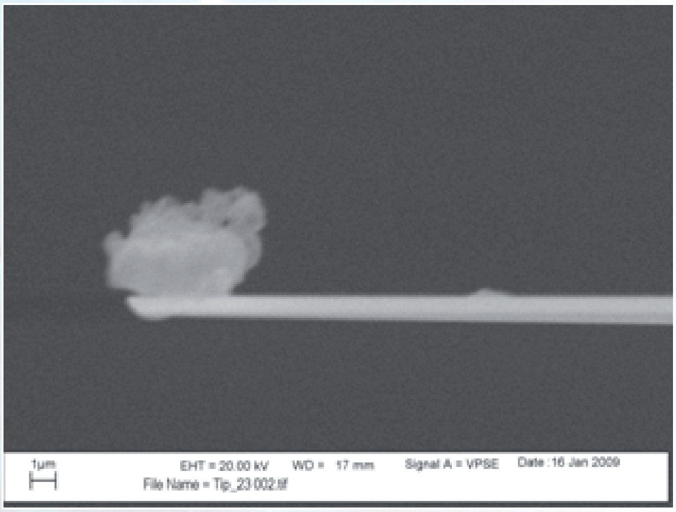
Attractive forces (for example, van der Waals or attractive electrostatic forces) bend the cantilever towards the probe.

Repulsive forces (for example, electrostatic repulsive forces) deflect the probe away from the surface. At a point close to the surface, the probe can 'jump into contact' if it experiences an attractive force greater than the stiffness of the cantilever spring.

Once the probe is in contact with the surface, cantilever deflection will increase (**C**) as the fixed end of the cantilever is moved closer to the sample. This continues until a predetermined point of maximum load is reached. The process is then reversed.

As the cantilever is withdrawn (**D**), the probe may adhere to the surface due to interactions between the probe and sample.

Further retraction overcomes this interaction and the cantilever breaks free from the surface (**E**). This adhesion force (in nanonewtons (nN)) can be calculated from the difference between the maximal cantilever deflection during retraction and the point of zero deflection of the cantilever.



Single lactose particle mounted on AFM probe.

Effect of humidity on adhesion forces

Adhesion forces were determined as a function of relative humidity (RH) using a lactose particle probe and different coated tooling (PharmaCote CN+, Hard Chrome and Diamond Like Carbon (DLC)). Each surface was treated by sonication in 3% R33 (Tickopur – corrosion inhibitor) solution for 10 minutes before use. Adhesion force data was collected from an array of 12 x 12 points across a 6 µm x 6 µm area of the surface. The RH was varied from 10%, 30%, 60%, 30% and 10% and allowed to equilibrate for at least 30 minutes at each level.

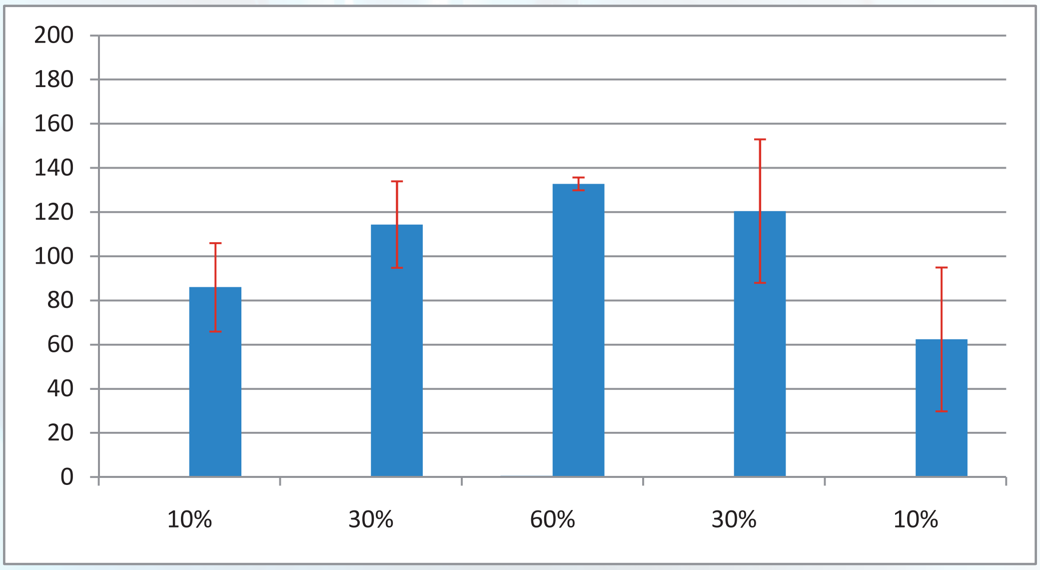


Figure 2. *Adhesion force as a function of relative humidity (RH) for Hard Chrome.*

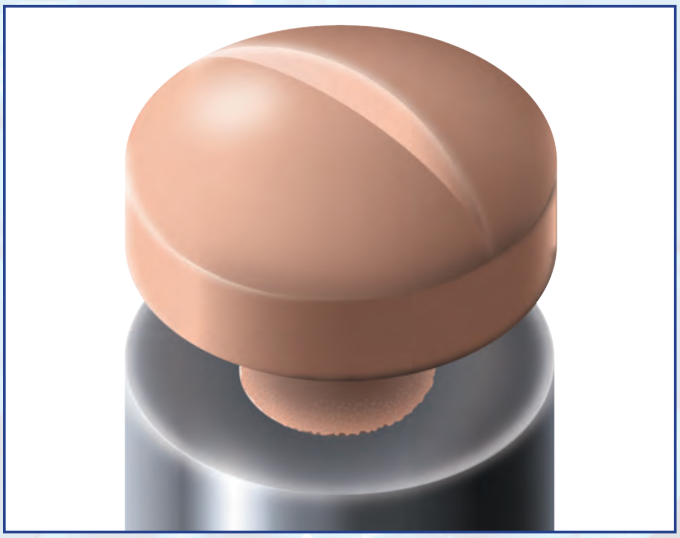


Illustration of sticking.

Adhesion behaviour of typical Hard Chrome

The effect of humidity on the adhesion to the Hard Chrome tooling is shown in Figure 2. The data demonstrates that the humidity dependence is not as strong for the Hard Chrome surface, exhibiting a gentler peak effect at 60% RH. It is interesting to note the dramatically reduced standard deviation (shown as red error bar on graphs) at high RH, possibly suggesting that the water layer and resulting capillary forces at this RH mask any underlying variability.

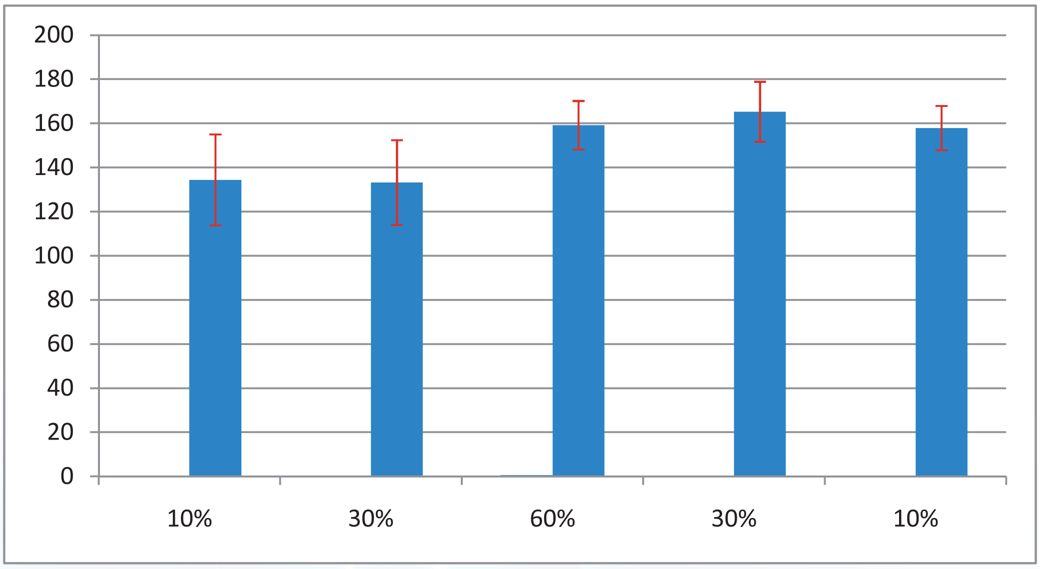


Figure 3. *Adhesion force as a function of RH for DLC.*

Adhesion behaviour of typical Diamond Like Carbon coating (DLC)

The effect of RH on the adhesion of Diamond Like Carbon (DLC) is shown in Figure 3. The data demonstrates that only a subtle increase in adhesion was recorded when the RH was increased from 30%-60%. Interestingly, the change in the adhesion with RH was not reversible in this case; remaining high after the RH was decreased suggesting that the surface of the DLC tooling is behaving differently from PharmaCote CN+ (surface engineered Chromium Nitride) and Hard Chrome.

Adhesion behaviour of PharmaCote CN+

The effect of RH on the adhesion for CN+ is plotted in Figure 4. The data demonstrates that the adhesion increases sharply and reversibly between 30%-60% RH. The sharp rise in adhesion force is probably attributed to the formation of capillary bridges between the particle and the surface at a critical RH.

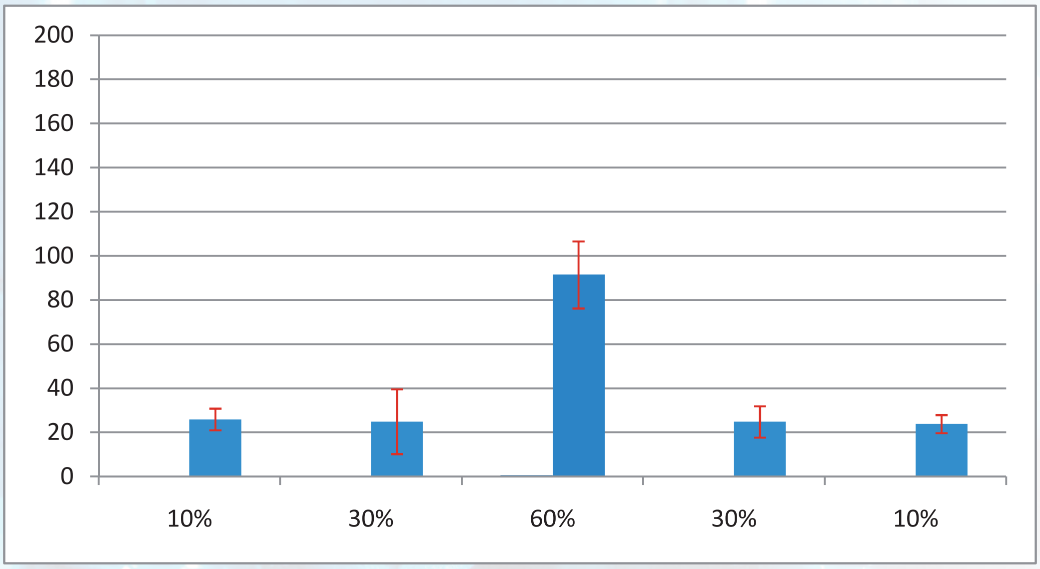


Figure 4. *Adhesion force as a function of RH for CN+.*

Surface roughness (RMS) of standard and surface engineered CN coating.

An array of adhesion force data was collected in a grid of 50 x 50 points using the same lactose particle probe for both surfaces at 10% RH. The lateral spacing between each point is 200 nm, covering a total area of 10 µm X 10 µm. The graph below (Fig 5) shows data from both samples overlaid on the same graph for comparison.

Granulate sticking to punch tip face

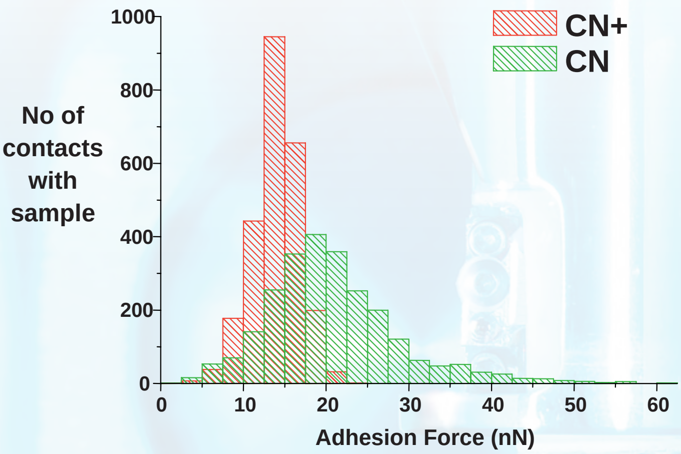


Figure 5. *Combined histogram of adhesion force data measured from CN and CN+ surfaces.*

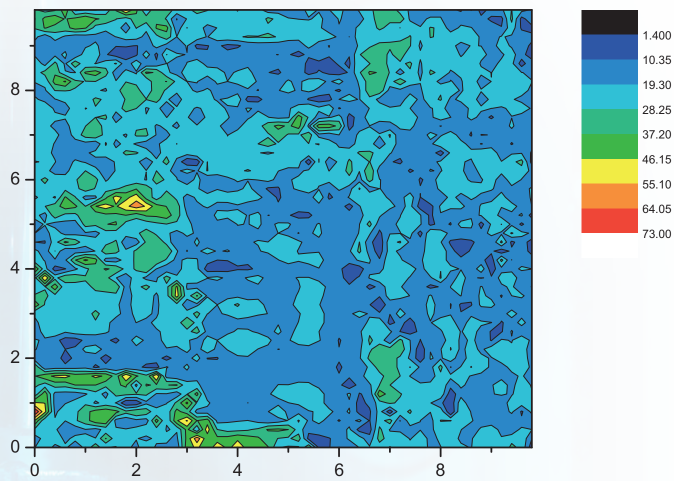


Figure 6. *Force mapping for CN sample (x/y scales in µm).*

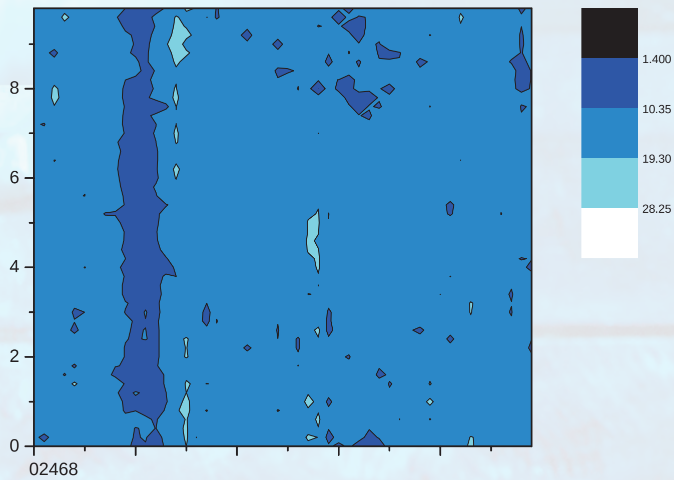


Figure 7. *Adhesion force mapping of CN+ sample (x/y scales in µm).*

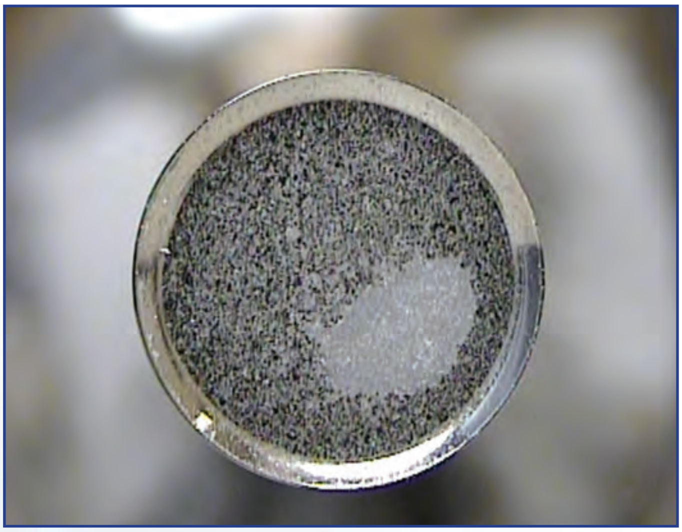
There are some observable differences between the two surfaces. The mean adhesion force measured for CN+ is lower in comparison to CN. Therefore the data suggests that the standard CN surface provides sites of higher adhesion in comparison with the surface engineered CN+.

It is clear from Figure 6 that, on the standard CN surface, there are some “hot spots” with high adhesion forces. It is possible that sticking during tablet compression could occur on these spots. However, Figure 7 shows no such ‘hot spots’ on the surface engineered CN+. Therefore it is likely that this coated surface would cause far less localised sticking. Figure 6. Force mapping for CN sample (x/y scales in µm).

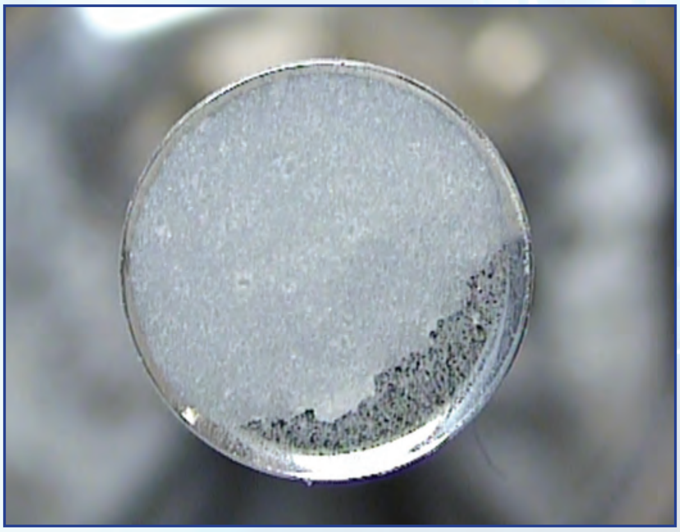
SUMMARY

During this series of experiments it was discovered that the adhesion behaviour of different coatings varies with humidity. In comparison with PharmaCote CN+, it can be seen that typical Hard Chromium and DLC coatings have higher adhesion characteristics across the humidity range tested.

It can also be seen that PharmaCote CN+ is more resistant to capillary action (humidity) than typical HC and DLC. Indeed, CN+ resists adhesion force increases up to 60% RH and then recovers it's lower adhesion characteristics when the RH is reduced.



Granulate sticking to plain punch tip face.



Acute sticking of formulation to punch tip face.

The comparative force mapping of standard and surface engineered (+ process) PharmaCote CN shows that the adhesion forces are not only lower but also more consistent with the + process applied.

This study has shown that the use of atomic force microscopy is a valid tool in the understanding of adhesion interactions between granule and tablet compression tooling.

PharmaCote CN+ Punch.

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