Pharmaceutical Research, Vol. 24, No. 6, June 2007 (© 2007)
DOI: 10.1007/s11095-006-9230-z

Short Communication

Direct Observation of Single Particle Electrostatic Charging by Atomic Force Microscopy

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Received August 2, 2006; accepted December 22, 2006; published online March 21, 2007

Purpose. To show that atomic force microscopy (AFM) can be used to directly study the electrostatic charging and dissipation of single pharmaceutical particles.

Materials and Methods. Particles of lactose attached to AFM cantilevers were charged on a glass surface at a relative humidity (RH) of 0.1%. By recording force-distance curves, we use a measurement of the long range electrostatic interaction to compare the generation of charge by contact charging and tribocharging and to study the effect of RH on charge dissipation.

Results. As expected, tribocharging by scanning the particle across the glass surface generates considerably more charge than repeated local contacts. Increasing the RH from 0.1 to 5% over a period of 37 min dissipates the tribo-generated electrostatic charge.

Conclusions. Using a combination of the abilities of AFM to scan in contact mode and record force-distance curves, we have shown a novel method to study electrostatic charging of particles. By measuring the length of the long range electrostatic interaction, we are able to compare different mechanisms of generating charge and to study the effect of RH on charge dissipation.

KEY WORDS: atomic force microscopy; electrostatic charging; lactose; particle interactions.

INTRODUCTION

The influence of atomic force microscopy (AFM) as a technique to study single particle interactions in inhalation formulations has grown in recent years (1,2). The ability to study adhesion on a single particle level has allowed a greater understanding of the fundamental processes involved in these interactions. Here we provide a novel extension to these studies to examine electrostatic charging and dissipation of single particles. To the best of the authors' knowledge, only two papers have noted an observed electrostatic force between a particle and a surface in a pharmaceutical system using AFM (3,4).

Electrostatic charging of pharmaceutical powders is important in the manufacture and handling of bulk powders as well as in other areas such as inhalation delivery from dry powder inhalers (DPIs) (5–7). It arises from the transfer of electrons between materials with different work functions. The term 'tribocharging' is often used to refer to two different processes, contact charging (touching the surface at a direction normal to the surface) and friction charging (dragging along the surface) (8). Here we will use the term tribocharging only to refer to the later process.

AFM studies of particle electrostatic charging have been employed in the field of electrophotographics (9,10) and when using model spherical particles (11,12). Methods used to initially charge the particles vary from simple contact with the surface (12), to applying electric fields to the particle (9) and charging with the beam in a scanning electron microscope (SEM) (10).

The inherent ability of the AFM to measure forces as a function of separation (in the form of force-distance curves (13)) means it is possible to study the dependence of the electrostatic force on particle-surface separation. The ubiquitous van der Waals force between a particle and a surface is very short ranged, acting up to separation distances of tens of nanometres (14); by contrast the electrostatic force is long ranged (10,15). A clear experimental conformation of this contrast was presented by Gady *et al.* (12). When recording force-distance curves with AFM the presence of electrostatic interactions gives a distinctive curvature in the cantilever response on the approach trace (the 'jump in' region) due to this long ranged nature (3,10).

For pharmaceutical powders, electrostatic charging behaviour has traditionally been studied on the bulk scale using the Faraday pail technique, amongst others, to determine the specific charge (charge per unit mass) (16,17). In this method the powder can be charged by a variety of mechanisms, commonly by agitation in a cyclone (16,17), by simply pouring directly from a chosen surface (18) or by deposition directly from a DPI (5,6).

Despite Faraday pail based techniques being used for over 20 years, little development in the methodology or technology appears to have taken place. Most studies have focused on making comparisons of the charge generated by different

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ABBREVIATIONS: AFM, atomic force microscopy; DPI, dry powder inhaler; Min, minutes; RH, relative humidity.

contacting surfaces and powders (5,16,17,19–21) and on the effect of particle size (19,22). Recently it has been acknowledged in the literature that further research into electrostatic charging of pharmaceutical powders is needed, particularly as applied to inhalation formulations (8,23).

A new technique is presented to study the electrostatic charging and dissipation of single pharmaceutical particles. We utilise the ability of AFM to both scan across (contact mode imaging), and measure interaction forces (force-distance curves) with a surface. Particles of lactose attached directly to AFM cantilevers were charged by two different mechanisms, contact charging and tribocharging. The length of the jump in region was measured from force-distance curves as a relative indication of the amount of charge present. The generation and decay of electrostatic charge is compared at a range of relative humidities (RHs).

It is widely known that the presence of humidity, and hence surface water layers, decreases the significance of electrostatic forces (24,25). The absorbed moisture increases the electrical conductivity of the surfaces involved and leads to rapid dissipation of charge. A more detailed study of this mechanism has been reported (26). An AFM study with micronised drug particles has previously reported a decrease in cohesion force due to the decreasing contribution of electrostatic forces, as evident in the shape of force-distance curves (4).

An inherent problem with Faraday pail based methods, is that particles adhere to the walls of the charging device after which particle-particle contacts dominate, often generating less charge (22,27). The technique presented here avoids this problem, and provides direct control over the contacting surfaces. Additionally the details of the charging contact, press on force, scan distance and speed, can all be precisely controlled.

MATERIALS AND METHODS

Sample Preparation

Silicon nitride v-shaped cantilevers (Park Scientific Instruments, Sunnyvale, CA, USA), were calibrated for their normal spring constants using the thermal method (28). Lactose particles (Sigma-Aldrich, Dorset, UK) approximately 10–20 μm in diameter were attached to these cantilevers by AFM using a method described previously (3), and attachment was confirmed by SEM.

A glass surface was made by cutting a small square from a microscope slide (Agar Scientific, Essex, UK). The glass was cleaned before each experiment by sonication in acetone, rinsing with distilled water and cleaning in a UV-ozone cleaner (Bioforce Nanosciences, Ames, IA, USA) for 20 min.

AFM Studies of Particle Electrostatic Charging

All AFM work was conducted using an EnviroScope instrument (Veeco, Santa Barbara, CA, USA) equipped with a Triton humidity controller (Triton Technologies, Keyworth, Nottinghamshire, UK). In this setup the sample stage and scanner are sealed in a small chamber through which a flow of air is continually passed. The RH of the air is precisely controlled over a range of 0–80%, with an accuracy of 0.1%, by being either passed through desiccant or bubbling through water.

The experiment consisted of two main parts, charging the particle and then measuring the amount of charge. Two methods of charging the particle on a glass surface were compared, termed contact charging and tribocharging. A relative measurement of the charging is then made by studying the approach trace of force-distance curves.

The first charging method, contact charging, consists of repeatedly contacting the particle with the surface in the normal direction by taking force-distance curves. At each stage in this study, 16 force-distance curves were taken, spaced over 3 μm × 3 μm areas on the glass surface, each separated by approximately 5 s and with a press on force of 5 nN. Both the time between force curves and the press on force are likely to affect the build up of electrostatic charge and are kept constant throughout. This method was used at RHs of 0.1% and 40% (at each RH, the system was left to equilibrate for 20 min before making measurements). As well being used to *generate* charge, these same force-distance curves were also analysed to *measure* the charge, the details of which are given later.

An equilibration time of 20 min was chosen based on observation of the laser deflection from the cantilever. Initially, when the humidity is changed, the deflection varies as moisture is absorbed on to the particle and cantilever, 20 min was found to be sufficient to ensure this process had finished and the deflection had stabilised. Dey *et al.* (29) have observed using AFM studies of moisture film thickness that surface water layers reach equilibrium almost instantaneously.

The second method of charging the particle, tribocharging, involves scanning the particle across the surface using contact mode imaging. The particle was scanned at a RH of 0.1% over a 5 μm × 5 μm area on the glass for 256 lines at a press on force of 5 nN and a scan speed of 0.5 Hz. This is equivalent to a total distance of 2.56 mm at a speed of 5 μms^{-1}.

Immediately after the particle was charged by the tribocharging method, a further series of 16 force-distance curves were recorded in order to examine the charge that had been generated (still at a RH of 0.1%). These were taken with the same parameters as with the contact charging.

Once completed, the particle was lifted from the surface and the humidity was ramped up to 1%. It took approximately 1 min to reach this humidity with an overshoot of 0.2%. This was left to equilibrate for 20 min after which another series of 16 force-distance curves were recorded to examine the dissipation of charge. Following this the humidity was increased to 5%, taking about 2 min to reach this level with a 0.5% overshoot. The particle was lifted clear of the surface and left to equilibrate for a further 17 min and a final set of 16 force-distance curves were recorded.

In order to compare the amount of charge generated, we have developed a method that utilises the long range electrostatic interaction that can be seen in the approach trace of a force-distance curve, commonly termed the 'jump in' region. An example is shown in Fig. 1, where a charged and an uncharged force-distance curve are shown for comparison.

We have measured the length of this jump in region as a qualitative indication of the amount of charging present. This was done by summing the contributions from the *y*-axis (cantilever deflection), and the *x*-axis (Z piezo movement) between the free level (the last point at which the particle feels no surface forces) and the point at which the particle establishes solid–solid contact with the surface. A similar analysis has been

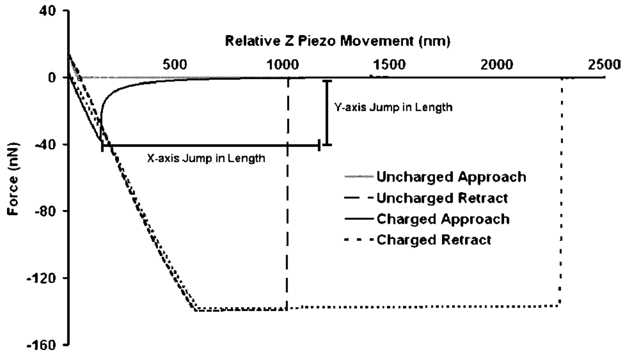

Fig. 1. Example force curves, showing both approach and retract traces for a charged and an uncharged particle-surface contact. *Construction lines* show how the length of the jump in region is measured.

used elsewhere to measure the thickness of absorbed water layers (29). The cantilever deflection was converted to a distance by multiplying with the deflection sensitivity, i.e., the gradient of the contact region of a force-distance curve on a non-compliant surface (glass).

To summarise, the measured quantity represents the distance at which the electrostatic force between the particle and surface can be first detected, providing a relative indication of the strength of the electrostatic force acting. A comparative approach is then adopted to investigate the effect of RH on charge dissipation. This measurement procedure is also depicted in Fig. 1 (although here the *y* axis is in units of force, only different by a factor of the cantilever spring constant). In comparison, the jump in length for non-electrostatic forces is very small, as also shown in Fig. 1. Force-distance curves were analysed in this way using SPIP AFM analysis software (Image Metrology ApS, Lyngby, Denmark). Finally, adhesion values from each force curve were calculated using the previously determined spring constant, 0.38 Nm^{-1}, and custom written software.

RESULTS AND DISCUSSION

We have shown that AFM can be used to study the electrostatic charging of a single lactose particle on a glass surface. The electrostatic force is evident from the approach traces of force-distance curves, where the long range interactions cause a large jump in region, an example is shown in Fig. 1.

One of the potential advantages of using AFM to investigate particle charging is that the relationship between force and separation can be studied. Various models have been employed to predict the force-separation dependence in the jump in region for spherical particles (10,12,30). These are typically based on summing two charge distributions, one localised in the region around the contact area and one spread over the whole particle. In the case of the lactose particles used here, these models gave poor fits to the data, indicating that the charge distributions are more complicated in form. This is expected since the particles are irregularly shaped, and assumptions of sphericity at the appropriate scale are not valid.

The inability to fully characterise the complex contact geometry and associated charge distribution, and hence quantify electrostatic charging, is, at present, a significant drawback of this technique. It is therefore limited to a strictly comparative approach which isn't easily related to any fundamental quantity, in contrast to existing techniques such as the Faraday pail which can quantify specific charge. Future progress towards a more quantitative approach may involve modelling approaches for the charge density on surface asperities (31) or the use of electrostatic force microscopy techniques (EFM) to probe local electrostatic variation (32).

Results showing examples of measured jump in lengths are plotted in Fig. 2a, where an average over each set of 16 force curves was taken, and the standard deviation used as the error. The length of the jump in region is plotted as a function of the experimental variables, RH and time after the tribocharging. Several observations are immediately apparent from the results. Firstly, at 40% RH electrostatic contributions are negligible, the jump in part of the force curve here is caused by the contact between the thin water layers present on both on the particle and the glass (29) and the short range van der Waals forces. In this case the jump in region is also noticeably different in shape with a much steeper gradient (data not shown). The value for 40% RH on Fig. 2a can therefore be considered a reference for an uncharged particle-surface contact.

It is clear from Fig. 2a that the tribocharging process at 0.1% RH has been effective causing an increase in jump in length from 15 ± 1 nm (uncharged 40% RH) to 681 ± 228 nm immediately after. As the RH was increased from 0.1 to 5% the electrostatic interaction decreased as the charge was dis-

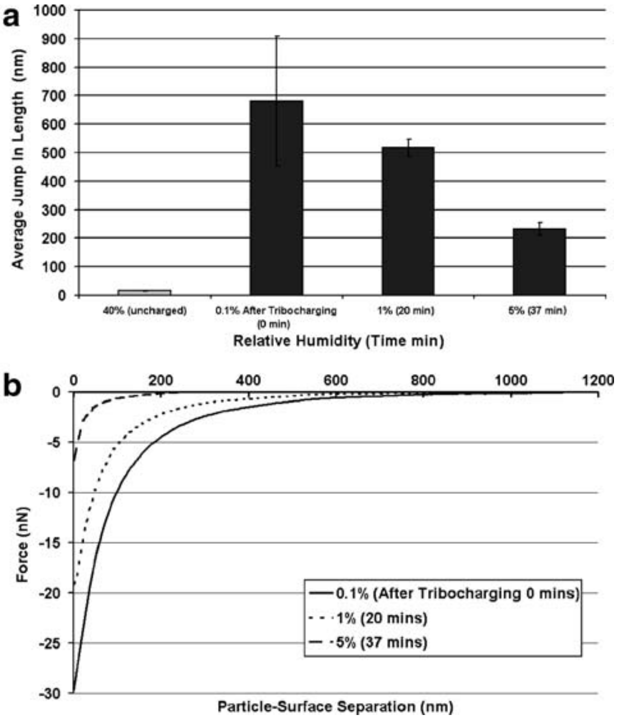

Fig. 2. (**a**) Processed results showing the length of the jump in region for the different stages of the experiment. A larger jump in length is indicative of a greater electrostatic interaction between the lactose particle and the glass surface. (**b**) Example force-separation curves showing approach traces for the lactose particle contacts with the glass surface at different RHs. Relative positioning of the curves on the *x*-axis have been adjusted to ease comparison.

sipated. The observed dissipation is caused by the increasing presence of water vapour which raises the conductivity of the surfaces. Charge may also be lost to the surrounding air due to the presence of water ions in humid air (26). In addition to modifying the surfaces, the change in water content of the air in the gap between surfaces may influence the force observed, although the dielectric constant of air changes by only $3 \times 10^{-4}\%$ between dry and saturated air (33), so this effect would be expected to be very small.

It should be pointed out that in this experiment the contributions to charge dissipation from time and RH have not been separated; isolating these is the subject of ongoing work. It should also be noted that the process of recording force curves in order to measure the dissipation would be expected to generate some charge due to contact charging (as discussed in more detail below). However, we have found that the charge generated by such contacts is much smaller than by tribocharging, and small compared to the changes seen due to dissipation. A significant effect on the dissipation behaviour observed in Fig. 2a is therefore not expected.

Jump in regions have been isolated from the approach traces of example force-distance curves at different RHs and plotted together in Fig. 2b to visually show how the long range electrostatic interaction decreases with RH and time. To ease comparison the free level region of each approach trace has been removed, leaving only the region over which electrostatic forces act. In addition the relative positioning has been adjusted so that each curve reaches minimum force at precisely zero particle-surface separation.

The contact charging method used at 0.1% RH has caused a build up of charge that increased with the number of contacts made, this is shown in Fig. 3, where the jump in length is plotted as a function of the number of force curves taken. With the parameters used here the tribocharging process was much more effective at generating charge, causing a maximum jump in length of 681 ± 228 nm compared with a maximum of 196 nm after 15 normal contacts. Intuitively, this would be expected since the contact time and opportunity for electron exchange is much greater when the two materials are dragged past each other (a similar result has been reported elsewhere (34)).

The adhesion force between the particle and the surface was also calculated for each force-distance curve taken. To clearly see the effect of electrostatic charging on adhesion it is necessary to compare the adhesion at 0.1% RH both before and after tribocharging. In this manner the contribution to the adhesion due to capillary forces, which would be more significant at higher RHs, is removed. The average adhesion from the 16 force curves increased after tribocharging from 217 ± 91 nN to 829 ± 52 nN (where the standard deviation is taken as the error). This confirms that electrostatic interactions can dramatically increase not only the range over which particle-surface forces act (as seen in the increase in jump in lengths), but also the strength of adhesion between materials.

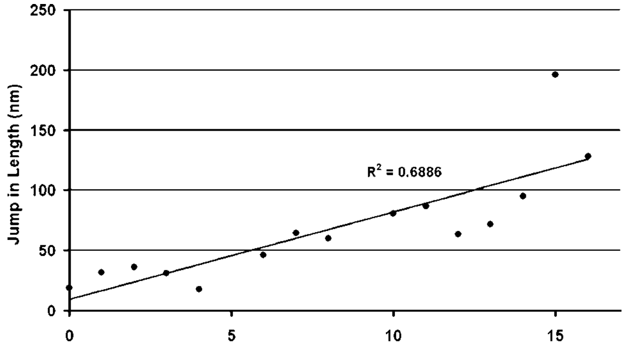

Fig. 3. Jump in length as a function of the number of repeated normal contacts between the lactose particle and glass surface.

The results presented here are taken using a single lactose particle. If the experiment was repeated with different particles of varying size, contact area and asperity geometry, potentially large differences in electrostatic charging and dissipation behaviour would be expected. Hence it is important to emphasise the comparative nature of this approach. These experiments make a valid comparison of charging mechanisms and dissipation at different humidities, but could not be directly compared with results taken using further particles and different cantilevers. Further developments might permit a more quantitative approach by normalising for contact area and asperity shape. Similar developments are taking place with AFM single particle adhesion measurements, where initial comparative studies (3) are being eclipsed by more recent attempts to allow for contact area (2).

This technique has potentially useful applications in pharmaceutical research of particle interactions where electrostatic forces can be studied for a range of materials at varying RH. The opportunity to study the impact of surface engineering treatments, particle roughness and morphology also clearly exists. In the case of DPIs, where relatively little is known about the electrostatic adhesion of particles, the propensity of certain materials to charge in contact with specific device components could be investigated.

CONCLUSIONS

A new method has been developed to study the electrostatic charging of single pharmaceutical particles. Using AFM, single particles of lactose attached to cantilevers were charged against glass by repeated contacts and by scanning across the surface (tribocharging) at 0.1% RH. The build up of electrostatic charge was clearly evident as a long range interaction in the approach trace (jump in region) of force-distance curves. The length of this jump in region was used as a relative measurement of the charge present.

We have demonstrated this technique by charging particles by both contact charging and tribocharging. The later causes the jump in length to increase by a factor of six. The particle-surface adhesion force was also observed to increase, here by a factor of four after the particle was tribocharged. As the relative humidity was increased, the generated charge was gradually dissipated over time. This technique has the potential to help further understand electrostatic contributions to particle interactions in pharmaceutical formulations.

ACKNOWLEDGMENTS

MJB acknowledges GSK and EPSRC for funding of studentship. MJB would like to thank Xinyong Chen for continuing help and support with AFM instrumentation.

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