VARIATION IN PARTICLE ADHESION DUE TO CAPILLARY AND ELECTROSTATIC FORCES

Robert Price[1], Michael J. Tobyn[1], John N. Staniforth[1], Marian Thomas[2] and Mike B. Davies[2]

[1]Pharmaceutical Technology Research Group, Department of Pharmacyand Pharmacology, University of Bath, Bath, UK. [2] GlaxoWellcome Research and Development, Park Road, Ware, Hertforsdshire, UK.

Objective

To determine, with the use of an Atomic Force Microscope (AFM), a quantitative measurement of the variation in the adhesion between an individual drug particle and a substrate surface, due to capillary and electrostatic forces.

Introduction

The improvement of the therapeutic efficacy of a dry powder formulation requires an increased understanding of the interactive and adhesive forces between micron-sized drug particles and carrier exipient particles. And of the adhesive properties between these particulate materials and inhaler construction materials [1]. An understanding of these interactions, and how they are influenced by physicochemical properties and environmental conditions, may provide the relevant information regarding the range of energies required to detach and aerolise micron-sized drug particles from relevant surface in dry powder inhalers (DPIs). The main contribution to the adhesion of a micron-sized particle to a solid surface is a composite of the ubiquitous van der Waals forces, as well as other contributing electrostatic and capillary forces [2]. Of the well-established techniques, which are capable of measuring the adhesion force of micron size particles [3,4,5], none allow the direct measurement of the interactive and adhesive forces between an individual micronised drug particle and a substrate surface. With the advent of the AFM and the methodology for attaching individual drug particles to atomic force cantilever type springs concerns regarding these fundamental interactions can, for the first time, be addressed. With a force sensitivity of the order of a few piconewtons (10^{-12}N), AFM force measurements can quantitatively measure the interactive and adhesive forces, as well as the separation energies required to liberate the drug particles from the substrate surface. In this investigation, we describe the use of an AFM to probe the interactive forces and the specific role capillary and electrostatic forces play on particle-substrate adhesion energies.

Methods

Drug Probe Preparation: Individual micronised drug particles (nominal diameter ~2µm) were attached to standard V-shaped tipless cantilevers (Nanoprobes, California) using optical micro-manipulation techniques. Figure 1.

Sample Preparation: Atomically flat surfaces of muscovite mica were prepared by cleaving in air, and subsequently exposing to the ambient for 24 hours to dissipate electrostatic charges.

Adhesion Force Measurements: All force measurements were undertaken in "Force Imaging" mode, with a Nanoscope IIIa AFM (Digital Instruments California). Force-displacement curves are generated by measuring the deflection of the drug probe cantilever as a sample is ramped, in a normal direction, towards and away from the drug probe. The small changes in deflection are detected by the reflection of a laser beam, positioned at the free end of the cantilever, onto a four-quadrant photodetector. Figure 2. A typical force-displacement curve and a description of the mechanics involved are represented in Figure 3. For relative humidity studies the microscope was hermetically sealed inside a plexiglass container. The relative humidity inside the container was controlled by the introduction of either dry nitrogen or water vapour.

Software Analysis: A series of custom built software programs have been written. Specifically, to convert the output voltage of the photodiode and the displacement of piezo transducer to absolute force versus substrate displacement, and, subsequent analysis in determining the force of adhesion and separation energy.

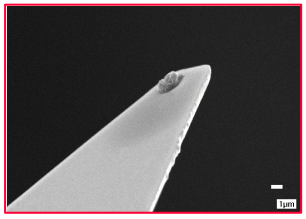

Figure 1: SEM image of a Drug Probe

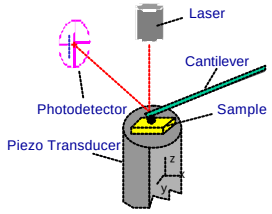

Figure 2: Schematic representation of AFM set-up

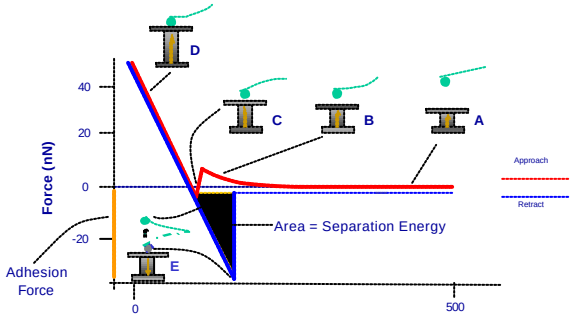

Figure 2: Anatomy of a Force-Displacement curve

A At large separations, the cantilever doesn't deflect as the substrate approaches the particle.

B As the surface approaches the particle, long range electrostatic forces (attractive or repulsive) act between the sample and probe. Repulsive in the example shown!

C As the gradient of attraction, due to the interactive forces, exceeds the spring constant of the cantilever, the drug probe "jumps" into contact with the surface.

D Upon contact, the sample continues to extend causing the cantilever to deflect backwards, while compressively loading the particle to a pre-set value.

E Upon reversal, the load is slowly removed until contact between the drug particle and the substrate surface is broken.

The difference between the minimum of the retraction curve and the probe's resting position is a direct measurement of the adhesion force.

Results and Discussion

Typical force-displacement curves and corresponding frequency distribution histograms of the separation energies of a micronised drug particle under varying relative humidity are represented in Figure 4a. Distributions were generated by analysing the separation energies of four thousand force-distance curves over the substrate surface. Quantitative characterisation of the median separation energy and interquartile range (shown as error bars) for each adhesion energy distribution is summarised in Figure 4b. The data suggests that the presence of capillary forces influences the energy required to remove adherent particles from a mica substrate surface. In addition, the separation energy measurements at low humidity, in the absence of electrostatic forces, suggests that capillary forces plays a dominant role in the adhesion a micron-sized particle to hydrophilic solid surfaces under ambient conditions. By varying the relative humidity (RH) from 13-62 %RH, a six-fold increase in energy is required to liberate the drug particle from the mica surface. This large increase in separation energy with increasing humidity indicates the high degree of protection required for micronised powders in dry powder inhalers. In the case of micron sized particles, the relatively large surface area to volume ratio, acts to promote the attractive capillary force between the particle and substrate surface. This is probably due to the surface tension of the adsorbed liquid layer as it is drawn by capillary action into the interfacial spaces of the contiguous bodies.

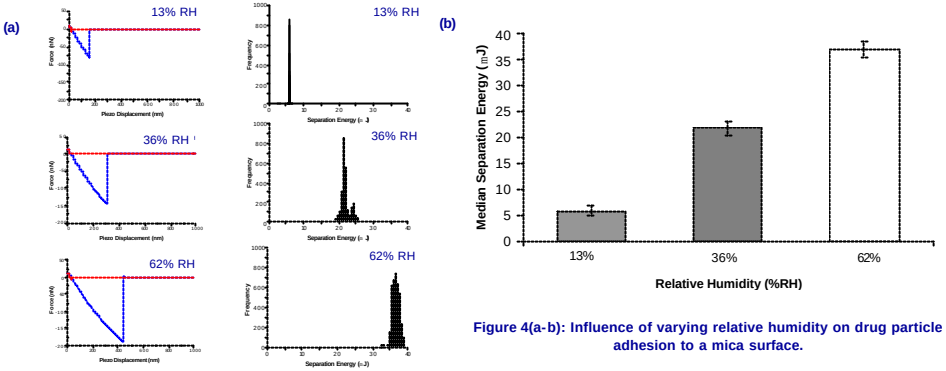

Figure 4(a-b): Influence of varying relative humidity on drug particle adhesion to a mica surface.

During the processing, handling and aerosolisation of dry powders, the continuous movement of particles provides the ideal conditions for the build-up of electrostatic charges [6]. Consequently, electrostatic charge interactions may play a dominant role in the long-range attraction and adhesion between drug and carrier and device surfaces. The influence of an induced electrostatic particle charge on the separation energy to a mica surface, under ambient conditions, is shown in figure 5. The median separation energy data suggests that the presence of an electrostatic attractive force, evident from the approach cycle of a force-distance curve, substantially increases the degree of adhesion of the the charged particle to the mica substrate with respect to the uncharged particle. Due to the high resistivity of organic drug crystals, and the influence attractive electrostatic forces has on particle adhesion, the degree of contact electrification between micronised particles and carrier and device materials needs to be minimised.

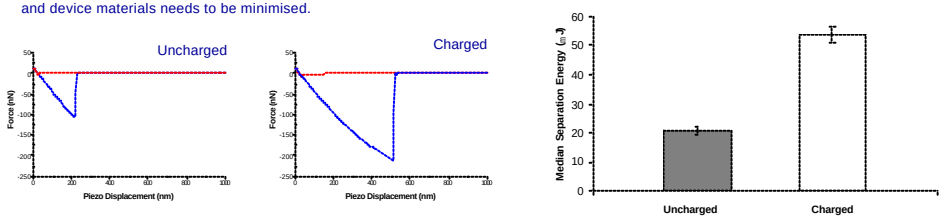

Figure 5: Variation in adhesion between an uncharged and electrostatically charged drug particle on a mica surface.

Conclusions

- Capillary forces appears to have a dramatic effect on the adhesion of micronised drug particles. For hydrophilic surfaces, surface tensional forces are dominant under ambient conditions.
- The potential build-up of electrostatic charges between drug particles and interacting materials, can give rise to a long-range attractive force which influences the movement and adhesive properties of micronised drug particles.
- AFM-based force spectroscopy, a relatively new tool for investigating interactive forces, provides a fundamental insight into the forces of adhesion, and how the individual force contributions influence particle adhesion.

Acknowledgement

We are grateful to GlaxoWellcome, Ware, UK for the support of this project..

References

[1] Staniforth, J.N. (1987) Order out of chaos. J. Pharm Pharmacol., 38, 329-334.

[2] Hinds, W.C. (1982) Adhesion of particles. In Aerosol Technology:Properties, Behaviour and Measurement of Airborne Particles, Wiley, New York, 127-132.

[3] Korecki, M.C and Stewart P.J. (1987) Adhesion of solid particles to solid surface. A.M.A. Arch. Env. Health, 1, 13-21.

[4]. Staniforth, J.N., Rees, J.E., Lai, F.K., Hersey, J.A. (1981) Determination of interparticulate forces in ordered powder mixes. J. Pharm Pharmacol., 33, 485-490.

[5]. Mullins, M.E., Michaels, L.P., Menon, V., Locke, B., andRanade, M.B. (1992) Effect of geometry on particle adhesion. Aerosol Sci andTechnol., 17, 105-118.

[6]. Peart, J., Staniforth, J.N., Byron, P.R. andMeakin, B.J. (1996) Electrostatic charge interactions in pharmaceutical dry powder aerosols. In RDD V, Interpharm Press: Buffalo Grove, IL, 85-94.

email: r.price@bath.ac.uk