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 valuable information regarding the range of energies required to detach and aerolise micron-sized drug particles from relevant surfaces. In the case of micronised drug 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 driven by capillary action into the interfacial spaces of the continuous bodies.

Methods

Drug Probe Preparation: Individual micronised drug particles (nominal diameter - 2μm) were attached to standard Vahpeped tipless cantilevers (Nanoprobes, California) to allow optical micro-manipulation techniques. Illustrated in Figure 1.

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

Adhesion Force Measurements: All force measurements were undertaken in “Force Imaging” mode, using a Nanoscope IIIa AFM (Digital Instruments California). Force-displacement curves are generated by measuring the deflection of the 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. Illustrated in Figure 1a. 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 photodetector and the displacement of piezo transducer to absolute force versus substrate displacement, and subsequent analysis in determining the force of adhesion and separation energy.

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 illustrated 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 humidity measurement 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 play a dominant role in the adhesion a micron-sized particle to hydrophilic solid surfaces under ambient conditions. By varying the relative humidity (RH) from 13.6% to 92.4%, 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, due to the 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 driven by capillary action into the interfacial spaces of the continuous bodies.

Conclusions

• Capillary forces appear to have a dramatic effect on the adhesion of micronised drug particles. For hydrophobic 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.

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References