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The influence of relative humidity on particulate interactions in carrier-based dry powder inhaler formulations

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Abstract

An atomic force microscope (AFM) colloid probe technique has been used to investigate the effect of relative humidity (RH) on the adhesion properties of pharmaceutical powder surfaces. The adhesion between a model substrate, α-lactose monohydrate, and model particulate drugs, salbutamol sulphate and budesonide, was investigated between RHs of 15 and 75%. The surface topography of the model α-lactose monohydrate was produced by controlling the supersaturation conditions during crystal growth to produce sub-nanometre scale roughness. The adhesion interactions between lactose and drug probes of salbutamol sulphate and budesonide were shown to be significantly increased with each incremental rise in humidity. Capillary forces were significantly more dominant for the adhesion in the budesonide–lactose system up to 60% RH but were more dominant for salbutamol sulphate–lactose above 60% RH. These studies suggested that non-surface-specific capillary forces play a dominant role in the adhesion between drug and carrier, which may significantly reduce the deaggregation and dispersion properties of a dry powder formulation.

Keywords: Relative humidity; Particle adhesion; AFM; Capillary forces; DPI; Formulation

1. Introduction

The delivery of therapeutic drugs via the respiratory tract using dry powder inhalers (DPIs) has become an effective means of treating respiratory ailments and, more recently, systemic disorders. In most cases, a lower dose of drug is required with inhalation devices in achieving a pharmacological equivalence to orally administered medicine. Furthermore, the rich supply of blood and large surface available for absorption in the lower airways provides an effective portal entry to the systemic circulation, while avoiding GI degradation and first pass hepatic metabolism.

DPI systems invariably involve the application of an inspirational energy to a blend of drug and excipients. Blends of drug and excipients are often prepared by mixing a coarse grade carrier, traditionally α-lactose monohydrate, and a micronised drug. The carrier particles act as a diluent and aid in the metering, device filling and fluidisation of a formulation. The formulation is then packaged into a DPI device so that when the blend is

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exposed to a stress (the patients' inspirational energy), it will flow and deagglomerate to deposit the drug in the deep lung. The adhesion between drug and carrier will be a consequence of the manufacturing processes and components, and the fundamental physicochemical properties between the drug and lactose surfaces. However, even though these systems have been successfully employed for the past 30 years, many questions still remain about the fundamental effects of the particles properties and, more importantly, the effect of storage conditions and environments on the adhesion characteristics and efficiency of DPI systems (Jashnani et al., 1995).

In order to try to overcome some of these problems, many modifications have been designed to increase pulmonary deposition. These have mainly concentrated on reducing the force of adhesion by manipulating the macroscopic properties of carrier particles. These include particle shape (Zeng et al., 2000), particle size (Bell et al., 1971; Staniforth, 1995; Zeng et al., 1999), surface rugosity (Ganderton, 1992; Zeng et al., 1997) and surface passivation via addition of ternary components (Staniforth, 1996; Lucas et al., 1998; Zeng et al., 1998). These ill-defined and somewhat uncontrollable modifications, at the microscopic level, are possible sources of the apparent inter- and intra-batch variations in aerolisation behaviour.

Particle adhesion is a dynamic process. Under ambient conditions (ca. 50% relative humidity, RH), and in the absence of any significant triboelectrification, particle adhesion is dominated by a non-surface-specific capillary force (Sedin and Rowlen, 2000), which arises from a thin layer of water molecules adsorbed on the surfaces. As surfaces come into contact, condensed water wicks into the capillary spaces between the contiguous surfaces, forming a concave-shaped meniscus. The theory, developed by Kelvin, has been successfully used to explain the behaviour of effect of capillary force on the interactions between particles in terms of changes in the Laplace vapour pressure for curved liquid surfaces (Israelachvili, 1991). The negative Laplace pressure acting across the meniscus and the surface tensional force at the liquid/air interface induces an attractive force between contiguous surfaces. The capillary forces have been reported to vary from a few nanoNewtons to a few hundred nanonewtons for particles of organic drug crystals over a range of humidities (Price et al., 2000; Dey et al., 2000).

The future advances in inhalation particle engineering will require a greater fundamental understanding of particulate interactions at the mesoscopic level (10^{-6}–10^{-9} m), and the elucidation of specific physicochemical and environmental factors which govern their variability. Therefore, in order to study the effect of RH on the adhesion between particles, a model drug/excipient system was developed. The adhesive forces between a model drug, salbutamol sulphate or budesonide and the surfaces of a α-lactose monohydrate were investigated over a range of humidities using an atomic force microscope (AFM). The AFM provides a simple and sensitive means of probing the adhesion force and separation energy which is required to remove the colloidal particles from specific locations on a substrate surface (Ducker et al., 1991), and may afford information about more complex pharmaceutical systems. The interactive forces are measured as a function of sample displacement, by recording the deflection of a spring-like probe as the substrate is brought into and out of contact with the colloidal particle. The vertical displacement ($\mathrm{d}x$) of the cantilever is converted into force by applying Hooke's law ($F_{\mathrm{ad}} = k\ \mathrm{d}x$), where k is the cantilever spring constant. With a sub-angstrom vertical sensitivity, the AFM can detect forces of the order of picoNewtons (10^{-12} N). In addition, the energy required to separate the particle from the sample surface can be calculated by integrating the area under the retraction portion of an individual force curve. The main advantage of determining the separation energy (e_{sep}) is that it takes into account any variations in mechanical properties between the contiguous bodies. Although the force of adhesion is highly dependent on the contact area between a particle and a flat surface, possibly as a result of deformation at the contact area, its measurement does not directly relate to variations in the elastic moduli of the contacting materials.

2. Materials and methods

2.1. Materials

Micronised salbutamol sulphate and budesonide were used as-supplied. High-purity crystalline α-lactose monohydrate was obtained from Aldrich (Dorset, UK). All solutions were prepared using distilled and deionised 18.2 MΩ cm^{-1} resistivity water (Millipore, Molsheim, France).

2.2. Drug probe preparation

A multi-stage optical micromanipulation system for the attachment of respirable-sized drug particulates to standard v-shaped tipless cantilevers (DNP-020, Digital Instruments, CA) has been adapted from the method described by Preuss and Butt (1998). Briefly, the process involves coating the apex of the silicon nitride cantilever (spring constant, $k = 0.58$ N/m) with a thin layer of epoxy resin (Araldite, UK) prior to attaching an individual micronised particle. A high-resolution, reflective mode microscope was constantly used throughout the procedure to evaluate tip cleanliness, quantity of glue and tip-particle integrity prior to and post-curing. A scanning electron microscope (SEM) micrograph of a salbutamol sulphate drug probe used throughout the study is shown in Fig. 1. Possible variations in spring constant were minimised by obtaining a wafer of tipless cantilevers (> 500), as batch-to-batch thickness concerns were eliminated. Randomly chosen tips ($n = 5$) from across the wafer indicated less than 14% variation in spring constant using the thermal method (Hutter and Bechhoefer, 1993).

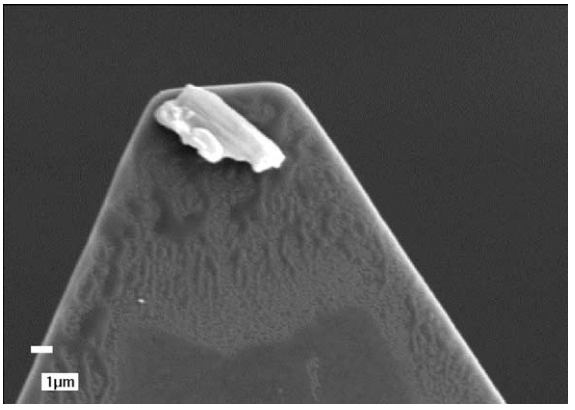

Fig. 1. SEM photomicrograph of the salbutamol sulphate drug probe used throughout the study.

2.3. Preparation of surface-modified α-lactose monohydrate crystals

Nanometre-scale modifications to the surface roughness of $\{0\ \bar{1}\ 1\}$ faces of α-lactose monohydrate crystals were prepared via a temperature-controlled micro-crystallisation system (Ester et al., 1997). Crystals were initially nucleated by evaporation of a small volume of saturated solution on a 15×15 mm^2 glass cover slip. The seed crystals, typically in the size range 10–100 μm, were lowered into a temperature-controlled crystallisation vessel containing a supersaturated solution. By controlling degree of supersaturation, via the solubility–temperature profile of an aqueous α-lactose monohydrate solution (Thurlby, 1976), the surface texture of excipient particles could be controllably modified.

2.4. Atomic force microscopy

Atomic force microscopy measurements were performed in two different modes using a NanoScope IIIa SPM controller, a Multimode AFM head (Digital Instruments, Santa Barbara, CA) and a J-type scanner (lateral scan range of 125 μm, spatial range of 5 μm). The basic modes involved recording the surface texture of the substrate surfaces, and detailed force volume scans of the interaction between the drug probes and substrate.

2.4.1. Topography measurements with AFM

All AFM surface topography images were recorded in TappingMode™ operation (TM-AFM). Tetrahedral-tipped silicon-etched cantilevers (OTSP, Digital Instruments) with a nominal tip radius of curvature < 10 nm, force constant ca. 42 N/m and a resonant frequency 200–400 kHz were utilised for imaging. To quantify the variations in the surface properties of α-lactose monohydrate crystals, root-mean-squared roughness

measurements (Rq) of the average height deviations of surface asperities were computed.

2.4.2. Separation energy measurements with AFM

Multiple force curves for the interactions between the model colloidal probes and {0 $\bar{1}$ 1} faces of α-lactose monohydrate were conducted by AFM in force volume mode. Individual force curves ($n = 4096$) were conducted over a 10×10 μm^2 area with the following settings: scan size 2 μm, scan rate 6.0 Hz and a compressive loading force of 20 nN. The area under each force curve was integrated using a custom-built batch conversion software program. The corresponding separation energy values from the large matrix of data were computed and represented as a frequency distribution histogram and a cumulative frequency plot. Separation energy measurements were performed for each drug probe at 15, 30, 45, 60 and 75% RH.

2.5. Environmentally controlled AFM system

The effect of RH on particle adhesion was investigated using a custom built perfusion unit. The partial vapour pressure of water within the imaging chamber of AFM was controlled by varying a mixture of dry nitrogen gas with the same gas humidified to 100% under constant temperature (25 ± 0.2 °C). A Thermo-Hygro™ sensor continually measured the %RH above the substrate surface. Humidity measurements were generally in good agreement ($\pm 5\%$) with tabulated values for saturated vapour environments of various salts, and thus are the values reported here.

2.6. Scanning electron microscopy

Samples were positioned on SEM holders and coated with a thin layer of gold (Edwards Sputter Coater, UK). Scanning electron microscopy was performed using a JEOL JSM6310 scanning electron microscope (JEOL, Tokyo, Japan).

2.7. Dynamic vapour sorption

Moisture sorption profiles of α-lactose monohydrate, micronised salbutamol sulphate and budesonide were determined using dynamic vapour sorption (DVS) (Surface Measurement Systems Ltd. (DVS-1), London, UK). Approximately 100 mg of sieve-fractioned (63–90 μm) α-lactose monohydrate was weighed into the sample cell. Equilibration mass was determined at each humidity by a dm/dt of 0.02%. Approximately 10 mg of the micronised samples was weighed into the sample cell. The equilibration mass was determined at each humidity by a dm/dt of 0.002%. Each sample was subjected to an incremental increase in RH in steps of 10% RH between 0 and 90%.

3. Results

In order to gain an insight into the effects of particle engineering and storage conditions, it is important to know the topography and the adhesion characteristics of the surfaces and how they vary with humidity. If the apparent changes in particle properties can be related to bulk powder properties, then this may afford valuable information to predict the stability of a formulation. The surface topography and adhesion properties of the lactose carrier were investigated using SEM and AFM. The results were then compared to the bulk response of the powder as determined using DVS.

3.1. Surface characterisation of the controlled crystallisation of α-lactose monohydrate

3.1.1. Scanning electron microscopy

A representative SEM photomicrograph and AFM topographical image of the surface morphology of the dominant {0 $\bar{1}$ 1} growth face of α-lactose monohydrate, nucleated and subsequently grown at low degrees of supersaturation, are shown in Fig. 2a and b, respectively.

3.1.2. Atomic force microscopy

The smooth texture of the α-lactose crystals in the SEM photomicrograph correlates well with the

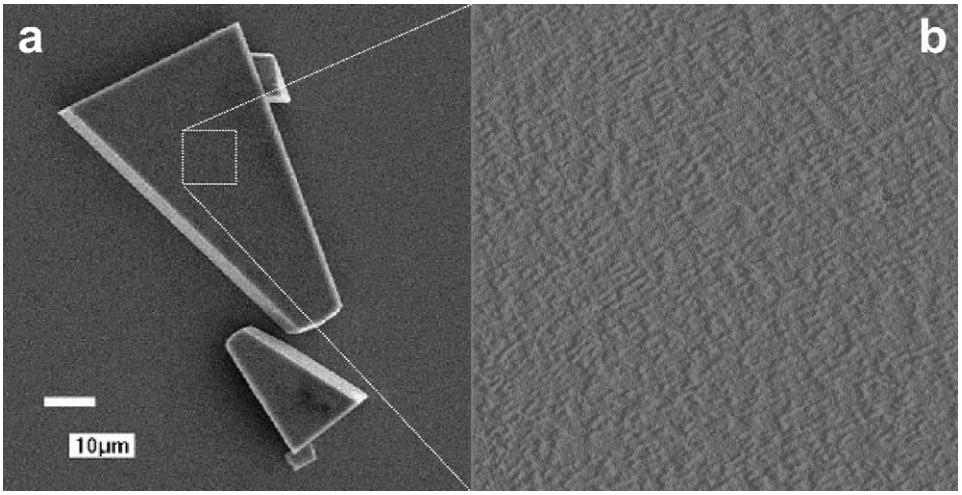

Fig. 2. SEM photomicrograph (a) and high-resolution AFM image (b) of the {0 $\bar{1}$ 1} face of the tailor made α-lactose monohydrate crystal. AFM scan size (10×10 μm^2).

high-resolution AFM image (Fig. 2b), where the root-mean-squared surface roughness over relatively large areas (10×10 μm^2) of a 60–120 μm α-lactose monohydrate crystal was found to be 0.250 ± 0.018 nm ($n = 3$). Exposure of the bespoke α-lactose monohydrate crystals to increasing RH (15–75% RH) did not lead to any observable changes in the surface morphology of the {0 $\bar{1}$ 1} face. The stability of the crystal surfaces, even upon exposure to elevated humidities for extended periods (75% RH for 12 h), were further exemplified by equivalent surface roughness measurements of the crystal surfaces.

3.2. Separation energy measurements

3.2.1. Separation energy distributions

The frequency distribution histograms of the separation energy measurements for a salbutamol sulphate and budesonide particle obtained from multiple contact points ($n = 4096$) on the {0 $\bar{1}$ 1} face of a α-lactose monohydrate crystal, under ambient conditions (%RH = 35%), are shown in Fig. 3a and b, respectively. The atomically smooth lactose surface provided a uniform contact area for particle adhesion. This is illustrated by the narrow distribution of the separation energies. The low dispersion of the separation energy measurements and mesokurtic profiles of the frequency histograms for salbutamol sulphate–lactose and budesonide–lactose adhesive interactions suggested a normal distribution function, allowing very small changes in the force of adhesion and separation energy to be characterised using arithmetic mean and arithmetic standard deviation.

3.2.2. Role of RH

The sensitivity of the AFM colloid probe technique to variations in the adhesion properties of a respirable-sized drug particle as a function of RH is demonstrated in Fig. 4a and b, which show the cumulative frequency separation energy plots for the interaction of a salbutamol sulphate and budesonide drug probe with an atomically smooth {0 $\bar{1}$ 1} lactose surface at 15, 30, 45, 60 and 75% RH, respectively. Significant differences in the adhesion force and separation energy measurements were observed ($P < 0.05$) for both systems for each incremental increase in the environmental partial water vapour pressure. However, with increasing humidity ($> 45\%$ RH), a concomitant increase in the spread of the normally distributed separation energies were observed for the interactive systems. Possible reasons may include incomplete monolayer coverage of condensate water or non-uniform bilayer wetting of the either the substrate surface or the drug particle surfaces. No evidence of attractive or repulsive long-range

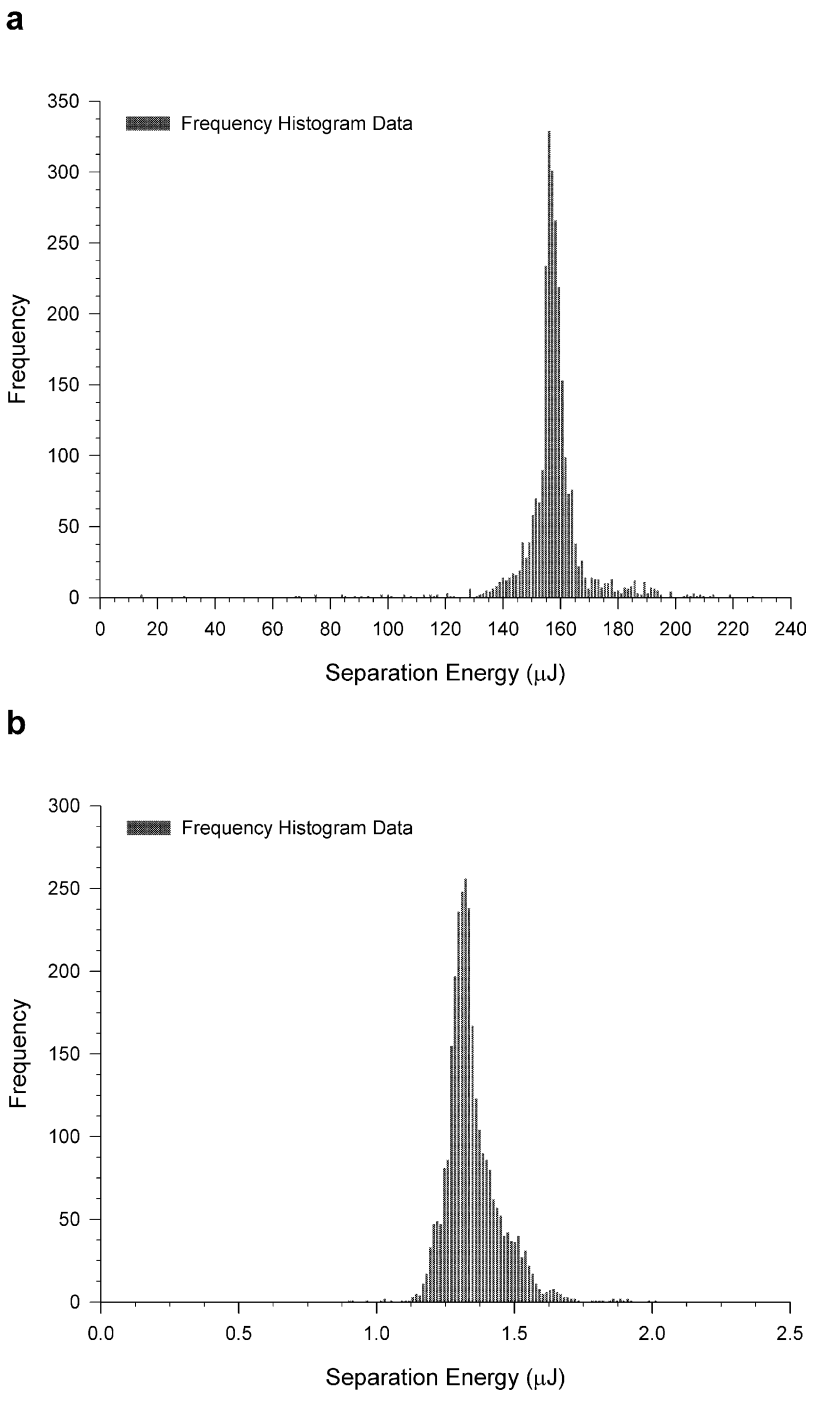

Fig. 3. Frequency distribution histograms of the separation energy measurements recorded over a $10 \times 10\ \mu m^2$ area ($n = 4096$) for the interaction of a salbutamol sulphate drug probe (a) and a budesonide drug probe (b) with an atomically smooth $\{0\ \bar{1}\ 1\}$ surface of a α-lactose monohydrate crystal under ambient conditions (%RH = 35%).

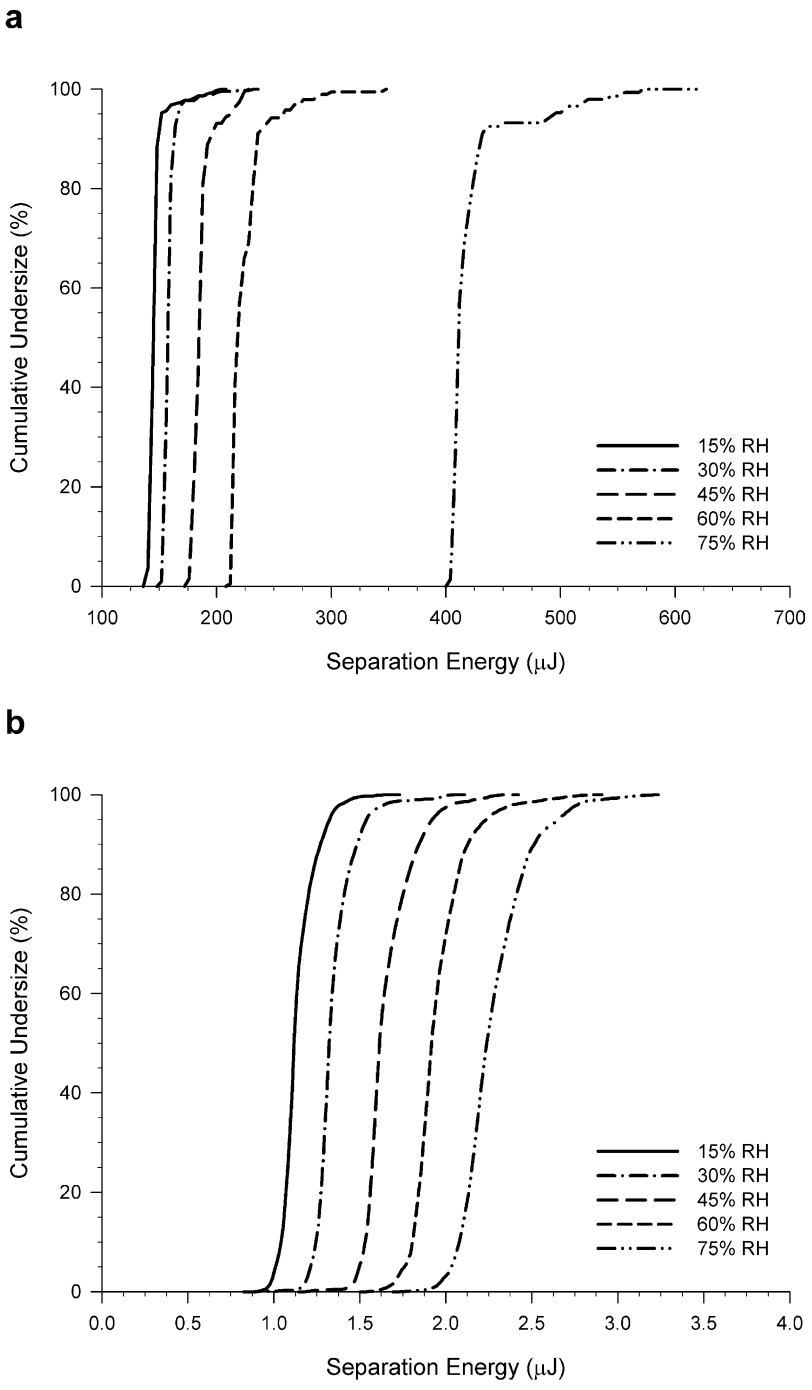

Fig. 4. Cumulative frequency separation energy plots of a salbutamol drug probe (a) and a budesonide drug probe (b) with an atomically smooth {0 $\bar{1}$ 1} surface of a α-lactose monohydrate crystal at 15, 30, 45, 60 and 75% RH.

electrostatic forces in the approach cycles of the force–displacement curves were observed over the entire humidity range for the interactions with lactose of salbutamol sulphate and budesonide.

The specific role of RH on the mean adhesion force (line graph) and separation energy (bar graph) of a micronised salbutamol sulphate drug probe and a budesonide drug probe on an atomically smooth $\{0\ \bar{1}\ 1\}$ face of α-lactose monohydrate are shown graphically in Fig. 5a and b, respectively. The adhesion properties of both salbutamol sulphate and budesonide were significantly different with increasing RH ($P < 0.05$). The data suggested that RH played a dominant role on the adhesion properties between drug and excipient.

3.3. Dynamic vapour sorption measurements

DVS profiles, calculated as percentage of dry mass, for commercial grade α-lactose monohydrate, micronised salbutamol sulphate and budesonide are shown in Fig. 6. Analysis of the sorption profiles for all materials indicated low water adsorption across the humidity range (0–90% RH). Furthermore, there was no indication of moisture absorption or recrystallisation. The linear increase in moisture uptake with increasing RH for the budesonide sample is consistent with an equilibrium adsorption profile, where the adsorbed film produces a partial water vapour pressure equivalent to the environmental partial pressure. Thus, the moisture uptake for the hydrophobic, water-insoluble budesonide is significantly smaller than the water-soluble salbutamol sulphate. Comparisons between the micronised samples and 63–90 μm α-lactose monohydrate sample would not be valid due to the large differences in the surface area available for water adsorption on the surfaces of the micronised samples. It is important to note, however, that the water sorption profile for α-lactose monohydrate was for the raw material, as the engineered lactose yield was not sufficient for bulk analysis. It is envisaged that a similar profile for the engineered lactose would be observed, although there may be slight variations due to a potential decrease in surface area.

4. Discussion

It is widely accepted that RH can affect interparticulate forces through the condensation of water vapour on the interface between a particle and a surface (Coelho and Harnby, 1978). Consequently, it has been accepted that capillary condensation only occurs at high RHs ($> 50\%$), and capillary forces only contribute to particulate interactions above 65% RH (Zimon, 1982). However, with the advent of the AFM and its potential for measuring variations in the adhesion of an individual particle at the mesoscopic level, the onset of capillary interactions has generally been found to occur at a much lower RH. In some cases, the humidity dependence of adhesion forces has been found to be as low as 20% RH (Eastman and Zhu, 1996; Xu et al., 1998).

In this study, the AFM colloid probe technique has suggested that humidity and particle topography play important roles in interparticulate adhesion within carrier-based DPI formulations. For the lactose/budesonide system, humidity plays a significant role on particle adhesion at humidities well below 50%. In the case of lactose/salbutamol, this effect is less pronounced below 50% RH. These observations suggest that, in agreement with previous AFM studies, the general definition of the limiting role of capillary forces on particulate interactions below 65% is not universally applicable.

Controlling the surface texture of the dominant growth face of an α-lactose monohydrate crystal, at the Ångstrom-scale, substantially reduced the influence of substrate surface roughness on particle adhesion. The uniform contact area of the contiguous surfaces over multiple contact points over a relatively wide area of the lactose substrate ($> 10\ \mu m^2$) were characterised by a very small coefficient of variation ($\leq 0.7\%$). As a result, the adhesion energy distributions determined from a whole array of force curves were typically observed to fit a normal distribution. Under controlled environments of humidity, the adhesion measurements were observed to be stable and reproducible upon several repeated experiments. The influence of increasing substrate surface roughness on particle adhesion has been shown

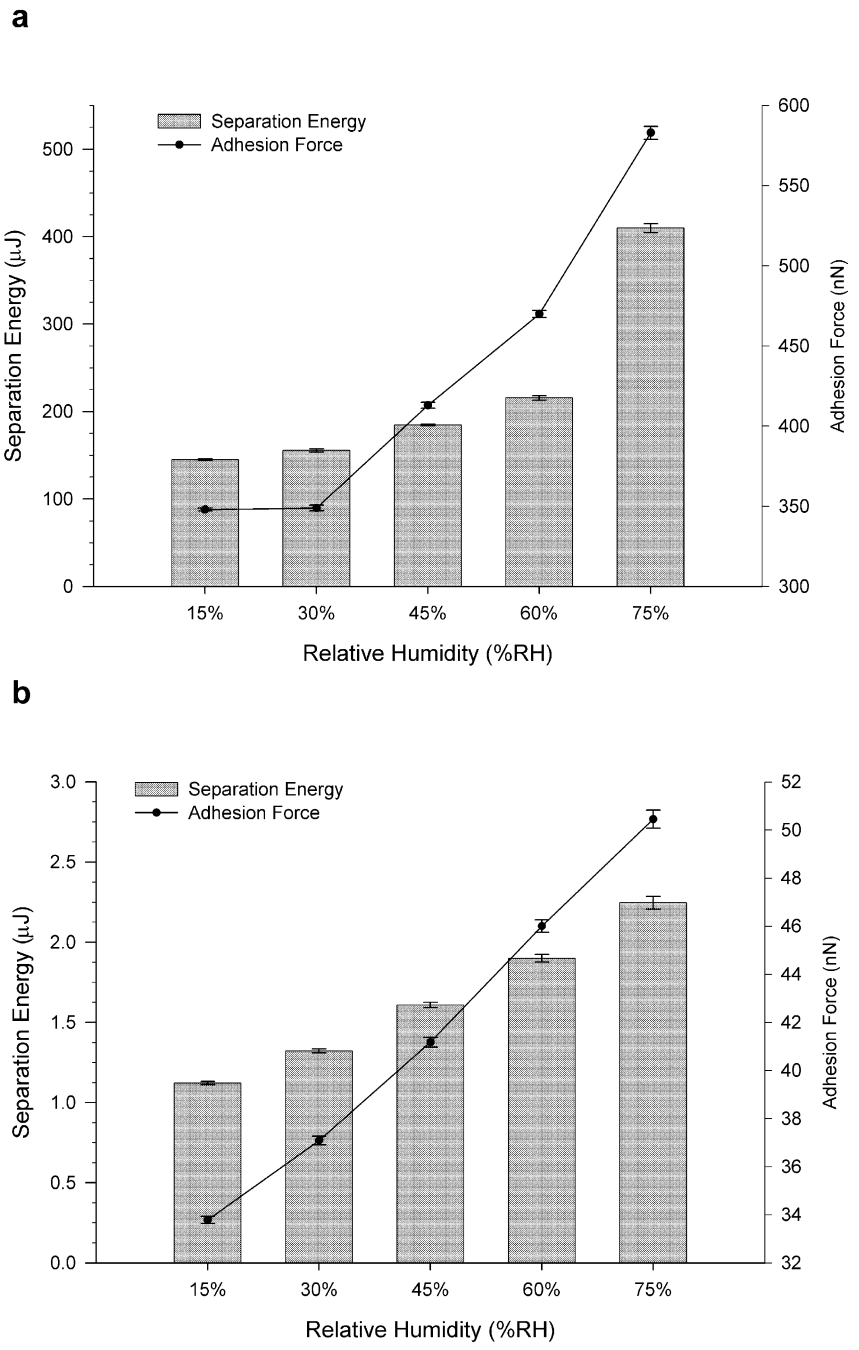

Fig. 5. The mean adhesion force and separation energy of the interaction of a salbutamol sulphate drug probe (a) and a budesonide drug probe (b) with an atomically smooth {0 $\bar{1}$ 1} surface of a α-lactose monohydrate crystal at 15, 30, 45, 60 and 75% RH.

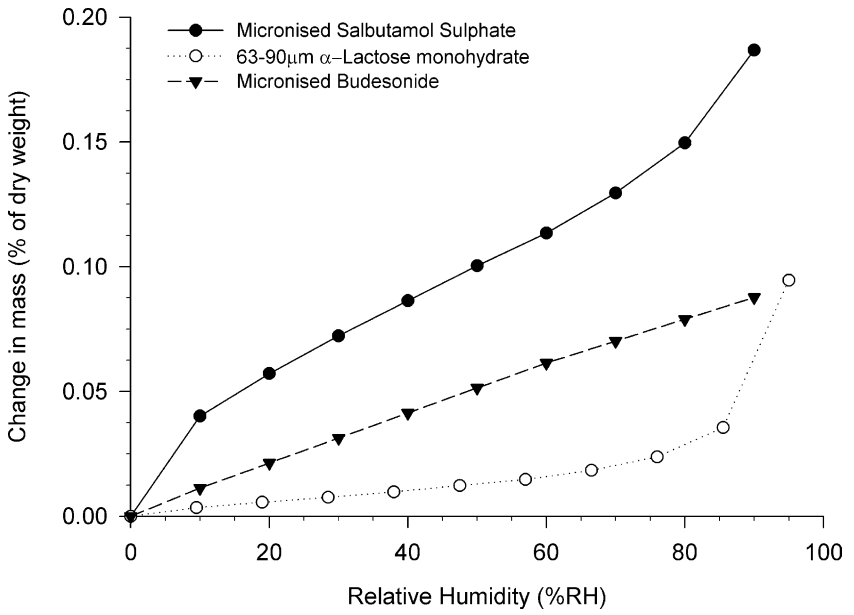

Fig. 6. DVS isotherm for 63–90 μm particle size α-lactose monohydrate, micronised salbutamol sulphate and budesonide with increasing RH.

to lead to high variability in adhesion energy measurements, and the transformation from a normal to a log–normal distribution, which suggests that the contact area between drug and lactose plays a critical role in the adhesion properties between drug and substrate (Louey et al., 2001; Young et al., in press). Additionally, the model surfaces of crystallised α-lactose monohydrate crystals exhibited structural stability with variations in RH, with no surface morphological transformations between 15 and 75% RH. The stability of the crystalline growth face of α-lactose monohydrate is expected, as the water vapour pressure for deliquesce of α-lactose monohydrate was found to be ca. 95% RH. However, recent studies on the surface stability of compacted surfaces of commercial grade α-lactose monohydrate particles have shown surface instability of the compressed particles at RHs above 32% (Bérard et al., 2002). A possible source of the instability and the thermodynamic driving force for Ostwald ripening of the aggregated particles was thought to be the presence of amorphous domains on the surfaces of the lactose particles upon processing and subsequent compaction.

The use of atomically smooth surfaces of α-lactose enabled direct characterisation of the specific role of RH on the variation in adhesion properties of an individual drug particle. However, a quantitative relationship between the measured interparticulate forces and true contact geometry of the contiguous surfaces were practically impossible. The large variations in particle shape, size and surface irregularities of micronised particles give rise to surface asperities with local variations in radii of curvature. As a result, even similar-sized particles will exhibit varying contact geometrics with the underlying substrate. Theoretical estimates of the contact area could be made if the interfacial free energy of the contiguous materials and force of adhesion were known. However, variability in crystal habit and orientation of the contacting drug surface, as well as the difficulty in determining the surface free energy of the contacting surfaces, precluded a quantitative measure of the relationship between the true contact area of the contiguous surfaces and their adhesion properties for the micronised drug particles. The current limitations of the AFM colloid probe technique to the influence of drug probe geometry on particle–

particle interactions may ultimately lead to unpredictable and variable capillary interactions. However, recent AFM measurements of a number of micronised drug particles with increasing RH have demonstrated that although contact geometry is not known, the adhesion properties of such systems retain a general trend (Young et al., in press). These limitations are currently being addressed through advances in particle engineering, computing modelling and the development of novel imaging techniques for mapping the drug probe surfaces.

The specific role of RH on the adhesion properties of individual and multiple micronised drug probes can be qualitatively analysed by normalising the separation energy measurements of the interaction of the drug probe to atomically smooth surfaces of α-lactose at low RHs ($<15\%$), as illustrated in Fig. 7.

The results of this study indicated that an increase in RH resulted in a concomitant increase in the adhesion force and separation energy measurements of the interaction between individual micronised drug particles of salbutamol sulphate and budesonide and the dominant $\{0\ \bar{1}\ 1\}$ growth face of α-lactose monohydrate. Significant differences were observed in the adhesion measurements ($P<0.05$) with each incremental increase in RH. However, the observed trends in the adhesion measurements for the interaction of a micronised salbutamol sulphate particle and a budesonide particle with the dominant $\{0\ \bar{1}\ 1\}$ surface of α-lactose monohydrate crystal as a function of RH were apparently different.

The separation energy measurements of the interaction between salbutamol sulphate and α-lactose monohydrate with increasing RH were discontinuous. Under low RH conditions, the influence of the surface tensional force on the overall adhesion and separation energy of the particle was significant but very small, with an observed 0.3% increase between 15 and 30% RH. This suggested, particularly in the observed absence of any contact electrification charging that below 30% RH salbutamol sulphate–lactose adhesive interactions were dominated by ubiquitous van der Waals forces. With increasing RH, the separation energy and adhesive force increased linearly between 30 and 60% RH. Requiring an additional 29% amount of energy between 30 and

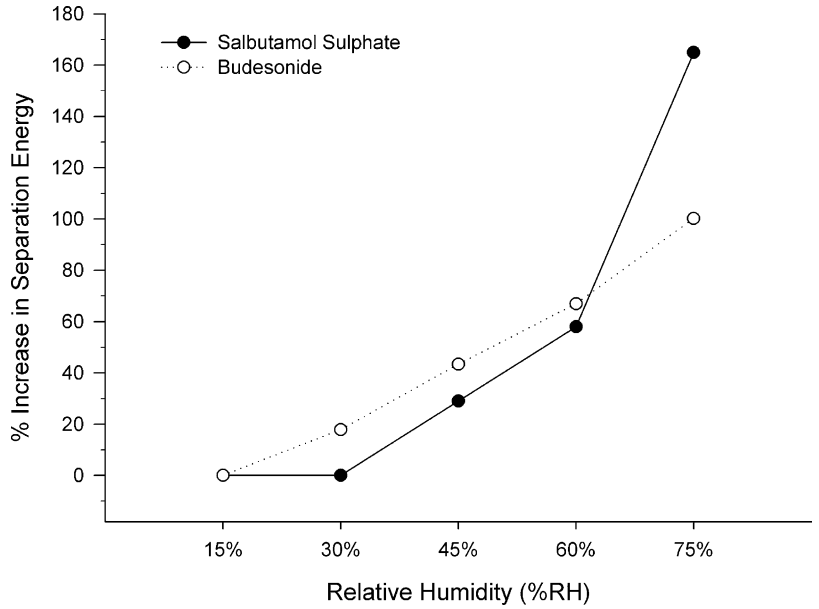

Fig. 7. Normalised separation energy measurements of the interaction of a salbutamol sulphate drug probe and budesonide drug probe with the $\{0\ \bar{1}\ 1\}$ surface of a α-lactose monohydrate crystal.

45% RH and over 58% of separation energy between 30 and 60% RH. Exposure to a high partial water vapour pressures (75% RH) led to a more dramatic increase in particle adhesion, requiring approximately a three-fold increase in energy from the system to separate the salbutamol sulphate particle from the lactose surface at 15% RH. These observations suggest that at low RH ($<30\%$), capillary forces do not contribute significantly to the adhesive interactions between salbutamol sulphate and the dominant growth face of a α-lactose monohydrate crystal. The onset of capillary interactions occurs at a critical RH of 30%, and above which capillary condensation contributes significantly to the overall adhesion properties between a salbutamol sulphate particle and the $\{0\ \bar{1}\ 1\}$ surface of α-lactose monohydrate. The absence of a capillary interaction below a critical RH has been previously been reported by AFM force measurements and scanning polarisation force microscopy (SPFM) studies (Xu et al., 1998), where it was proposed that below a critical water vapour pressure condensating water forms a strongly bound ice-like water layer. Upon saturation of this bilayer at a specific critical RH, additional condensation of water vapour forms a more liquid-like layer, allowing the formation of a capillary meniscus around the contact point of contiguous surfaces.

The separation energy between a budesonide drug probe and the dominant growth face of α-lactose monohydrate increased linearly with increasing RH. Between 15 and 60% RH, the influence of capillary condensation to the adhesion of the hydrophobic budesonide particle to the $\{0\ \bar{1}\ 1\}$ surface of α-lactose monohydrate was more dominant than for the water-soluble salbutamol sulphate. This difference was clearly evident at low RHs, whereby increasing the partial water vapour pressure from 15 to 30% RH led to an 18% increase in separation energy for the budesonide–lactose interaction. The higher sensitivity of the capillary interaction of the hydrophobic steroid to the hydrophilic lactose surface at low and ambient RHs may possibly relate to the possible absence of the formation of a saturated tightly bound ice-like water layer on the surface of the hydrophobic drug. The highly unstable nature of the physisorbed water film on the hydrophobic particle will, therefore, increase the likeliness of forming a stable meniscus bridge at low RHs. Above 60% RH, the capillary force interaction for the salbutamol sulphate–lactose system increased more dramatically than for the budesonide–lactose. The effect of capillary condensation on the interaction between budesonide and lactose is most clearly observed between 15 and 75% RH, requiring a 100% increase in energy to separate the contiguous surfaces.

5. Conclusions

The use of an AFM to probe the inter-particulate interactions at a single particle level provided a fundamental insight into the microscopic interactions that govern bulk properties of dry powder formulations. The normally distributed data between an individual drug probe and an atomically smooth surface of α-lactose monohydrate enabled characterisation of the specific role of RH on particle adhesion. The influence of RH on the adhesion properties of a salbutamol sulphate and budesonide drug probe to the $\{0\ \bar{1}\ 1\}$ surface of α-lactose monohydrate were observed to follow different trends for salbutamol sulphate–lactose and budesonide–lactose interactions. Since an increase in adhesion energy will reduce the dispersion and deaggregation properties of a DPI formulation, the environmental conditions during processing, packaging and storage of DPI's will ultimately influence the aerolisation efficiency and therapeutic efficacy of the respirable drugs to the respiratory tract. In combination with bulk techniques, AFM may potentially play a pivotal role in the future technological advances in the design and modifications of dry powder inhalation formulations.

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