Available online at www.sciencedirect.com
ScienceDirect
International Journal of Pharmaceutics 325 (2006) 163–171
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Pharmaceutical Nanotechnology

A nanoscale study of particle friction in a pharmaceutical system

Matthew J. Bunker [a], Clive J. Roberts [a,*], Martyn C. Davies [a], Michael B. James [b]

[a] *Laboratory of Biophysics and Surface Analysis, School of Pharmacy, University of Nottingham, Nottingham NG7 2RD, UK*
[b] *Inhaled Product Development, GlaxoSmithKline, Ware SG12 0DP, UK*

Received 8 March 2006; received in revised form 13 June 2006; accepted 17 June 2006
Available online 23 June 2006

Abstract

Studies of single particle interactions in dry powder inhaler (DPI) formulations using atomic force microscopy (AFM) have recently grown in popularity. Currently, these experiments are all based on measuring particle adhesion forces. We broaden this approach by presenting a novel AFM friction study of single particles in a pharmaceutical system, to examine forces acting parallel to a surface. The sliding friction signal of lactose particles attached to AFM cantilevers was recorded in lateral force (LF) mode over 5 μm × 5 μm areas on five different surfaces chosen to represent both relevant inter-particle and particle–surface interactions. A ranking of friction forces was obtained as follows: glass ≈ zanamivir > zanamivir–magnesium stearate (99.5%/0.5%, w/w) blend ≈ magnesium stearate ≈ PTFE. The addition of magnesium stearate to the zanamivir surface dominated and significantly reduced the friction (Kruskal–Wallis test, $P < 0.001$). AFM images of the contacting asperities of the lactose particles show changes in contact morphology due to two processes. Firstly the asperity wears flat due to abrasion and secondly small magnesium stearate particles transfer onto the asperity. It is proposed that in combination with AFM particle adhesion measurements, this method could be used to screen new formulations and the effectiveness of tertiary components in modifying carrier–drug interactions.

Keywords: Atomic force microscopy; Dry powder inhaler; Particle interactions; Friction; Lactose

1. Introduction

The performance of dry powder inhalers (DPIs) is to a large extent dictated by the particle interactions that take place during manufacture, storage and use. A typical formulation consists of a mixture of micronised drug particles (typically < 5 μm) and an excipient such as lactose (typically 60–90 μm) to act as a carrier and diluent. The purpose of the carrier particles is to aid removal of the drug from the reservoir in the device. Upon mixing, the drug particles adhere to the carrier surface and are separated by the aerodynamic forces created on inhalation, the smaller drug particles are then free to penetrate the deep lung region.

The addition of a tertiary excipient component has shown promise to improve performance by modifying the interaction between the carrier surface and the drug particles (Frijlink and de Boer, 2004). A common example is magnesium stearate which is often used in pharmaceutical solid dosage forms as an adhesion modifier and a lubricant (Swaminathan and Kildsig, 2002). In the case of DPIs it has been shown to increase aerosolisation of the drug by reducing adhesion (Young et al., 2002a).

It is clear that the interactions that take place between drug and carrier particles, and any surfaces in the device they may contact, will play a critical role in determining the efficiency of a DPI. The atomic force microscope (AFM) has become an increasingly popular technique for studying such interactions on a single particle level (Bunker et al., 2005). In such experiments a particle is attached to an AFM micro cantilever and the adhesion force required to remove it from a surface in the normal direction is measured. This technique has provided formulation relevant information such as the ranking of adhesion forces to various surfaces (Young et al., 2002a; Eve et al., 2002; Sindel and Zimmermann, 2001; Young et al., 2003a), the cohesive-adhesive nature of a powdered mixture (Begat et al., 2004), the humidity dependence of adhesion (Berard et al., 2002a,b; Hooton et al., 2004) and the surface free energy of particles (Davies et al., 2005). In addition, some correlation has been shown between single particle adhesion information and aerodynamic bulk removal methods (Young et al., 2002a).

In reality, particles are separated from each other and surfaces they contact by turbulent air streams acting in many directions

* Corresponding author. Tel.: +44 115 9515048; fax: +44 115 9515110.
E-mail address: clive.roberts@nottingham.ac.uk (C.J. Roberts).

0378-5173/$ – see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2006.06.024

(Labris and Dolovich, 2003; Wang et al., 2004) and therefore particle friction is likely to be as important to powder behaviour as adhesion forces (Jones et al., 2004; Podczech and Newton, 1995). It would hence seem that measuring normal adhesion forces as currently done in an AFM study represents a somewhat limited view of the real situation. Here we broaden the approach by presenting the first investigation of particle friction in a pharmaceutically relevant system, increasing the amount of information that can be gained on a single particle level using AFM.

It has long been known that the AFM is capable of measuring friction by recording the lateral force (LF) signals from the cantilever as it twists in response to being traced along a surface (sometimes known as lateral force microscopy or friction force microscopy) (Mate et al., 1987). Whilst the fundamentals of friction have been examined in detail using model and colloidal particles (Carpick, 1997) the study of friction in 'real' particulate systems in the literature has been limited. Examples include the work of Meurk et al. who studied the friction behaviour of a ceramic powder granule (Meurk et al., 2001) and Ecke et al. who developed new instrumentation called the particle interaction apparatus that allowed easier frictional studies (Ecke et al., 2001). A comprehensive study of the frictional behaviour of various industrially important powder particles was carried out by Jones et al. who studied particle–particle and particle–surface friction and related the results to data from bulk shear testers (Jones et al., 2004). The methodology for these experiments forms the basis for that employed in this work, and will be explained in the following sections.

In this paper, we present what the authors believe to be the first AFM investigation of single particle friction using pharmaceutically relevant materials. We have studied the friction of a lactose particle probe on five surfaces, two chosen to represent particle–surface interactions and three to represent particle–particle interactions. In this way we were able to produce a ranking of friction on the different surfaces.

2. Materials and methods

2.1. Materials and sample preparation

Silicon nitride v-shaped cantilevers (Park Scientific Instruments, Sunnyvale, CA, USA), were calibrated for their normal spring constant, typically 0.3 N m^{-1}, using the thermal method (Hutter and Bechhoefer, 1993). α-Lactose monohydrate was obtained from Sigma–Aldrich (Poole, Dorset, UK). Four particles, designated A–D and approximately 10–20 μm in diameter were attached to these cantilevers after calibration by AFM using a method described previously (Eve et al., 2002), an example is shown in Fig. 1. Details of the five surfaces chosen for friction measurements, along with justifications for their choice are given below.

Glass and polytetrafluoroethylene (PTFE) were chosen as examples for particle–surface interactions. PTFE is well known for its low surface energy, 'non-stick' properties and is commonly used to minimise powder adhesion to canister walls. Glass is a material frequently used in the handling of pharmaceutical

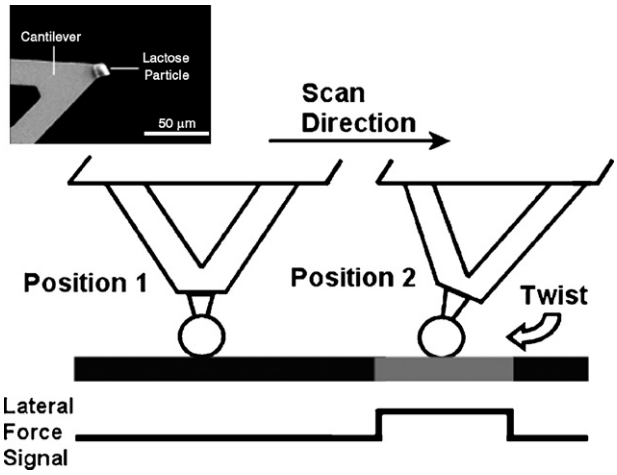

Fig. 1. Schematic of AFM particle friction setup. Position 1: low friction surface causes very small lateral force on cantilever. Position 2: high friction surface causes large lateral force and cantilever twists. Inset: SEM image of lactose particle attached to cantilever.

powders, and serves as an example of a highly flat surface. AFM studies of the particle adhesion behaviour on these two surfaces has previously been reported (Eve et al., 2002; Young et al., 2003a). PTFE surfaces were prepared by stretching PTFE tape (BASF, UK) flat over a piece of silicon. A glass surface was made by cutting a small square from a microscope slide (Agar Scientific, Essex, UK) which was cleaned before each experiment by sonication in acetone.

We have used single crystals of un-micronised zanamivir, supplied by GSK (Ware, UK), in order to study the particle–particle friction with the lactose probe. Zanamivir is a drug administered by the inhalation route and its crystals in its un-micronised form are prismatic in shape and typically 100 μm × 500 μm in size. This makes it an excellent choice for this study, because it is relatively easy to find flat areas suitable for AFM work. The adhesion behaviour of zanamivir has also been previously studied by AFM (Berard et al., 2002a,b).

Magnesium stearate (Sigma–Aldrich) has been chosen as an example of a tertiary component which can be added to the surface of the zanamivir. The particle size varies greatly from <1 up to 25 μm, but was further reduced in size as large particles were broken up during blending with the zanamivir (this was confirmed by AFM imaging of the zanamivir–magnesium stearate blend as described in Section 3.1). It is well known for its properties as a glident and a lubricant and so here we would expect it to lower friction in the interaction between the lactose probe and the zanamivir crystal. Magnesium stearate has previously been found to lower the adhesion of a drug probe to a lactose surface (Young et al., 2002a).

Zanamivir was blended with 0.5% (w/w) of magnesium stearate (Turbula mixer, Willy A. Bachofen AG, Basel, Switzerland) for 15 min at a rotation rate of 72 min^{-1}. Small amounts of the as prepared zanamivir and the zanamivir–magnesium stearate blend were added directly onto a sticky carbon tab (Agar Scientific) with a spatula and secured onto a steel AFM stub; loose crystals were removed under a stream of dry nitrogen gas.

Lastly a surface of magnesium stearate alone was constructed to act as a reference by loosely compacting the powder down onto a sticky carbon tab with a plastic petri dish.

2.2. AFM Imaging of surfaces

Tapping mode AFM images were taken using a D3000 AFM (Veeco, Santa Barbara, CA, USA) to examine the surface topology of the five surfaces used in this experiment, PTFE, glass, zanamivir, zanamivir–magnesium stearate blend and magnesium stearate. Representative average roughness (R_a) values were determined by measurement from at least three 5 μm × 5 μm images using the software supplied with the instrument and averaged. The R_a roughness parameter measures the average height difference between all the sampled points on a surface and an assumed centre line (Podczech, 1997).

2.3. AFM friction measurements

It is worth clarifying an issue of terminology at this point. The term 'lateral force' will be used here to refer to the signal recorded by the AFM in either the forward or reverse scan directions. Only when data has been processed as described below will the term 'friction' be used to describe the measurement. Lateral force images were recorded by scanning the lactose particles in contact mode across a 5 μm × 5 μm area of each surface using an EnviroScope AFM (Veeco). These images were recorded in both forward and reverse scan directions simultaneously, at 256 × 256 pixel resolution, equivalent to 256 adjacent 5 μm length scan lines, each separated by 19.5 nm. The scan speed was maintained at 8.72 μm s^{-1}. A schematic of an AFM particle friction measurement is shown in Fig. 1. To ensure the normal load was kept constant, the deflection sensitivity of each cantilever was found by taking a force–distance curve on glass. For each surface the normal load was maintained between 16 and 18 nN by taking force–distance curves and monitoring the difference between the free level and the imaging set-point.

The experiment was repeated in triplicate, using lactose particles A–C. For the measurements on zanamivir and zanamivir–magnesium stearate blend, a crystal that was lying flat with its dominant crystal face facing upwards was first located. All friction measurements were performed on this same crystal face. Areas that appeared smooth under the optical microscope of the AFM, with no large visible fines were then chosen for the experiments. Measurements on these two surfaces were taken on at least two different crystals and averaged. All measurements were taken at 25 °C and 40% relative humidity.

It is inevitable that the contacting asperities on the particles will be subject to some change during these experiments. To prevent the possibility of particle wear biasing friction data, measurements were performed on the different surfaces in varying sequential order for each of the triplicate measurements. It was anticipated that some magnesium stearate would adhere to the lactose particles on contact and hence possibly affect subsequent friction measurements on other surfaces. To avoid this problem, all experiments on the zanamivir–magnesium stearate blend and magnesium stearate were carried out last.

To investigate this possibility of transfer of magnesium stearate to the lactose, a further measurement was undertaken with particles A, C and D on glass after contact with the magnesium stearate surface. In this way we can study any changes in the friction behaviour of the lactose particles by comparing to the previous measurement on glass. Measurements could not be completed with particle B due to damage incurred to the cantilever. To compensate for this loss of data, a further lactose particle D was used, and friction measurements performed on glass before and after a measurement on the magnesium stearate.

2.4. Particle asperity imaging

Both before and after the friction experiments, the lactose particles attached to the cantilevers were imaged by scanning in contact mode across a calibration grating (TGT01 NT-MDT, Moscow, Russia) consisting of a regularly spaced array of sharp spikes (Hooton et al., 2002). This allowed the contacting asperities to be examined for any changes during the experiment and was an indication of any wear that may have occurred.

2.5. Data processing

Much has been published on the calibration of AFM lateral signals into units of force. Despite considerable effort (Lantz et al., 1997; O'Shea et al., 1992; Cain et al., 2000; Carpick et al., 1997), there is no universally accepted method and errors of around 30% are reported (Gibson et al., 1997). Attempts have been made to develop calibrations based on cantilever geometry and material bulk properties (Neumeister and Ducker, 1994; Schwarz and Wiesendanger, 1996) whilst other methods rely on measurements of lateral signals on slopes of known angles (Ogletree et al., 1996; Varenberg et al., 2003). For the purposes of this paper, friction signals remained un-calibrated and presented in arbitrary units of volts, but remain directly proportional to friction force. Useful information can be obtained without the calibration into Newton's; this is done by making relative comparisons of the friction signal on different surfaces. A similar 'semi-quantitative' approach has been used in numerous studies elsewhere (Beake et al., 1998; Carpick et al., 2004; Kim et al., 2001; Xu et al., 1998; Putman et al., 1995).

Each pixel in the lateral force images represents the amount of twisting or lateral force on the cantilever at that particular point on the surface. A histogram was plotted from each image to show the distribution of these lateral forces. The mean signal was calculated for each image and the difference between corresponding forward and reverse mean signals was taken as a quantitative representation of the friction force (Jones et al., 2004). Subtracting the lateral force signals from both scan directions in this way ensures that contributions from slopes on the surface are significantly reduced, leaving a true indication of friction force. Statistical analysis was performed using InStat software (GraphPad Software, San Diego, CA, USA) to examine the differences in friction between the surfaces.

3. Results and discussion

3.1. AFM images of surfaces

Examples of 5 μm × 5 μm topographic AFM images of each surface used for friction measurements are shown in Fig. 2A–E along with the *z*-range (i.e. height of surface features) for each image. Calculated roughness values are given in Table 1. The glass, Fig. 2B, presents a flat surface, $R_a = 0.687$ nm, with some visible particulate contamination not removed by the cleaning process. The PTFE, Fig. 2A, is a lot rougher, $R_a = 28.7$ nm. The magnesium stearate, Fig. 2E presents the roughest surface, $R_a = 38.5$ nm and consists of compressed individual particles with cracks and pits in between. The zanamivir crystals, an example is shown in Fig. 2C, are generally flat with small fines consistently distributed on the surface. The addition of the magnesium stearate to the zanamivir is evident from Fig. 2D, where small particles, less than 1 μm in size, are distributed on the surface and the R_a roughness has increased from 3.24 to 6.20 nm.

Table 1
Roughness values from 5 μm × 5 μm AFM images of surfaces

Surface	Average roughness, R_a (nm) ± S.D.
PTFE	28.7 ± 13.2
Glass	0.687 ± 0.190
Zanamivir	3.24 ± 1.40
Zanamivir–magnesium stearate	6.20 ± 2.01
Magnesium stearate	38.5 ± 6.25

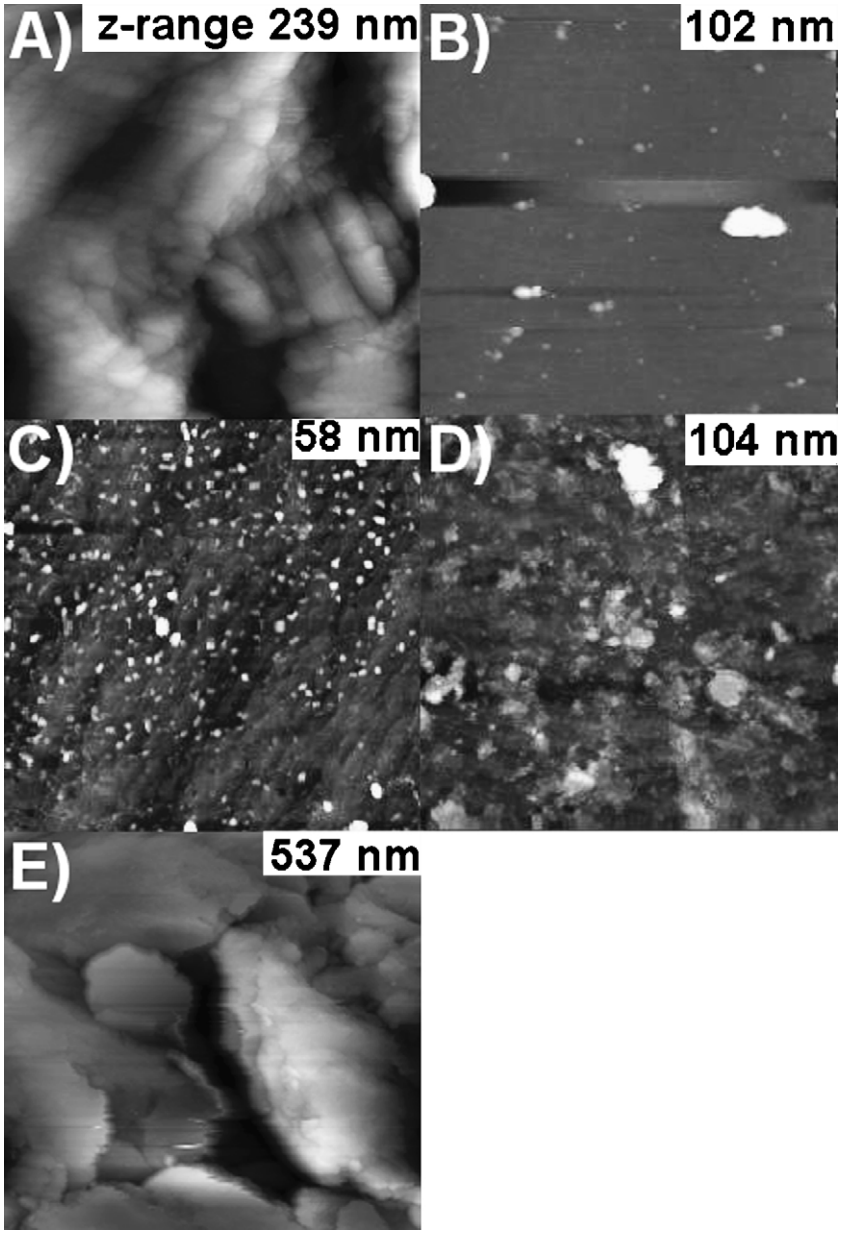

Fig. 2. 5 μm × 5 μm topographic AFM images of surfaces showing *z*-ranges. (A) PTFE; (B) glass; (C) zanamivir; (D) zanamivir–magnesium stearate blend; (E) magnesium stearate compact.

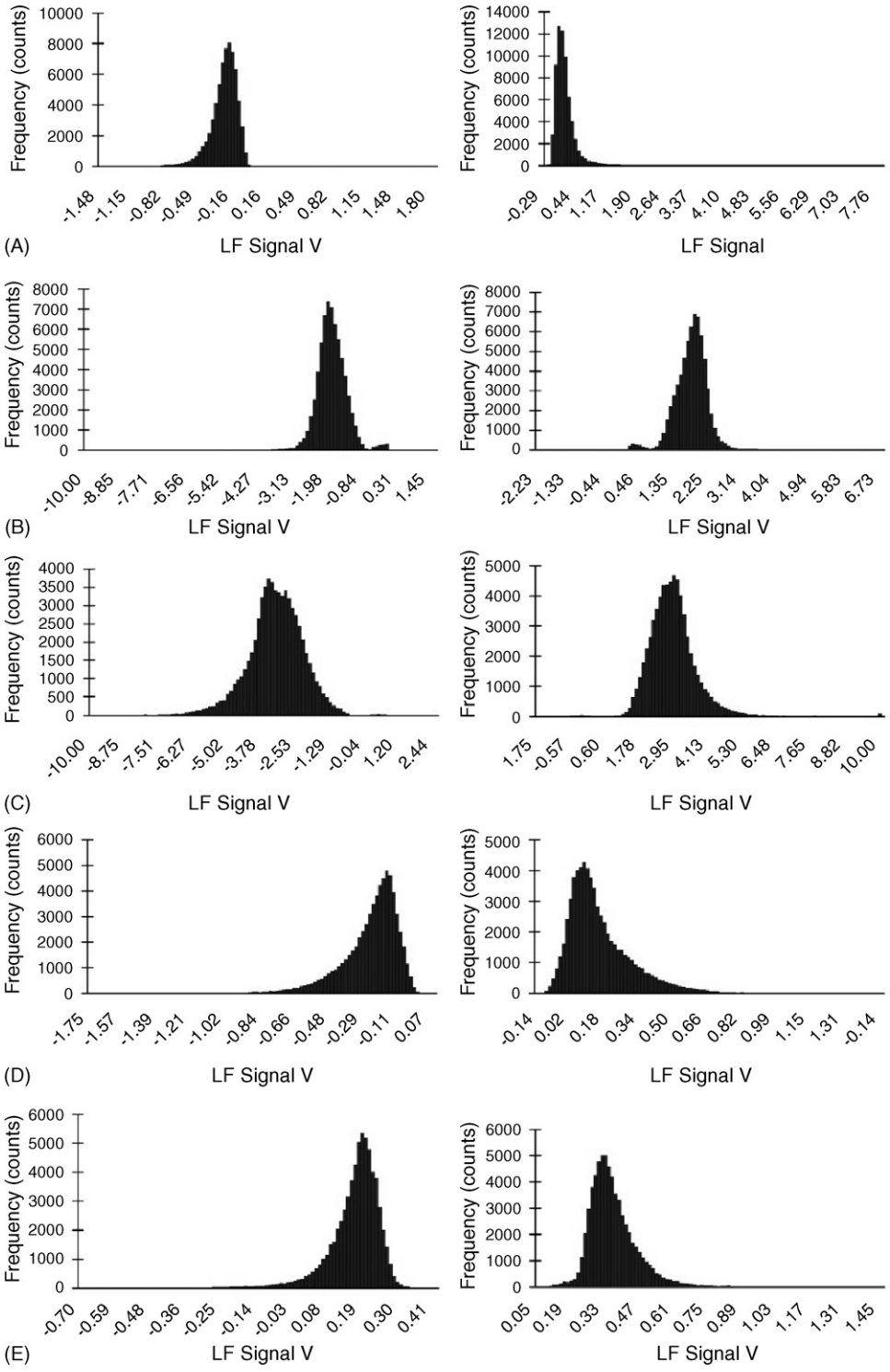

Fig. 3. Lateral force histograms first column forward scan direction, second reverse. (A) PTFE; (B) glass; (C) zanamivir; (D) zanamivir–magnesium stearate blend; (E) magnesium stearate compact.

3.2. AFM friction measurements

Lateral force histograms for each scan direction on all five surfaces are shown in Fig. 3. They are all offset from zero indicating true friction information is being obtained. This is because if slope effects are dominating, the histogram will straddle zero since real friction forces cannot act in two directions in a single scan direction (Jones et al., 2004). All histograms are nearly symmetrical, allowing the mean signal to be taken as reliable indication of the average.

The distributions of lateral force signal on the glass and PTFE are narrower than the other surfaces. The second smaller peak in the histogram on glass (Fig. 3B) corresponds to friction over some contamination on the surface (this was checked using

AFM image analysis software by examining the signal at specific points on the lateral force image). Such data, along with aberrant any scan lines on the images were removed from the calculation of the average signal. There is a second peak apparent in the histograms for zanamivir (Fig. 3C) which is caused by the heterogeneity on the surface as seen in the AFM topographic image in Fig. 2C. There are contributions from both the small fines on the surface and the background crystal plane.

Representative lateral force images for the five surfaces and both scan directions are shown in Fig. 4. These images show considerable surface detail and are similar to the topographic data shown in Fig. 2. This is because the lactose particles are in contact with a small number of relatively sharp asperities. Little evidence is present for slip-stick type behaviour and it has been suggested that it is nanoscale roughness and variations in adhesion that give such images detail (Jones et al., 2004).

The processed friction data for particles A–C is shown in Fig. 5. A ranking of friction forces between the lactose particles and the surfaces can be drawn up as follows: glass ≈ zanamivir > zanamivir–magnesium stearate blend ≈ magnesium stearate ≈ PTFE. The significance of this ranking was checked by performing a Kruskal–Wallis test, where the difference between the friction on glass or zanamivir and the three other surfaces for all three particles was shown to be significant ($P < 0.001$). This ranking is only valid for lactose particles as used here, as other materials could interact differently. In order to further understand this ranking it is necessary to consider various factors which influence friction forces, including surface roughness and surface energy.

Two factors are likely to contribute to the high friction seen on glass. Firstly, since glass has such a low surface roughness (R_a roughness = 0.687 nm), it offers a large contact area for the interaction with the particle, which will act to increase friction. Secondly, due to the hydrophilic nature of glass, capillary forces are likely to be present. Although the exact humidity at which capillary forces become significant varies depending on the materials in contact, they have been reported to affect particle adhesion at similar or lower values to the 40% used here (Berard et al., 2002a; Hooton et al., 2004; Tsukada et al., 2004; Young et al., 2002b, 2003b) for example, high particle adhesion on glass has previously been attributed to capillary forces at 25% (Eve et al., 2002).

PTFE is well known for its low friction properties, and the same can be seen in these experiments, where its low surface energy leads to low friction. A similar pattern has been observed elsewhere in an AFM investigation of adhesion forces with a salbutamol particle, where a ranking of glass > lactose > PTFE was found (Eve et al., 2002).

It should be noted that the effect of surface roughness on contact area and hence adhesion and friction processes is greatly dependant on the relative scales of the roughness and the contacting asperities of the particle. For very smooth surfaces, a small increase in roughness can act to lower the contact area and hence lower adhesion and friction forces. However, beyond a certain roughness, the space between, and the height of, the surface asperities will be comparable to the particle size and the effective friction could increase due to multiple points of contacts

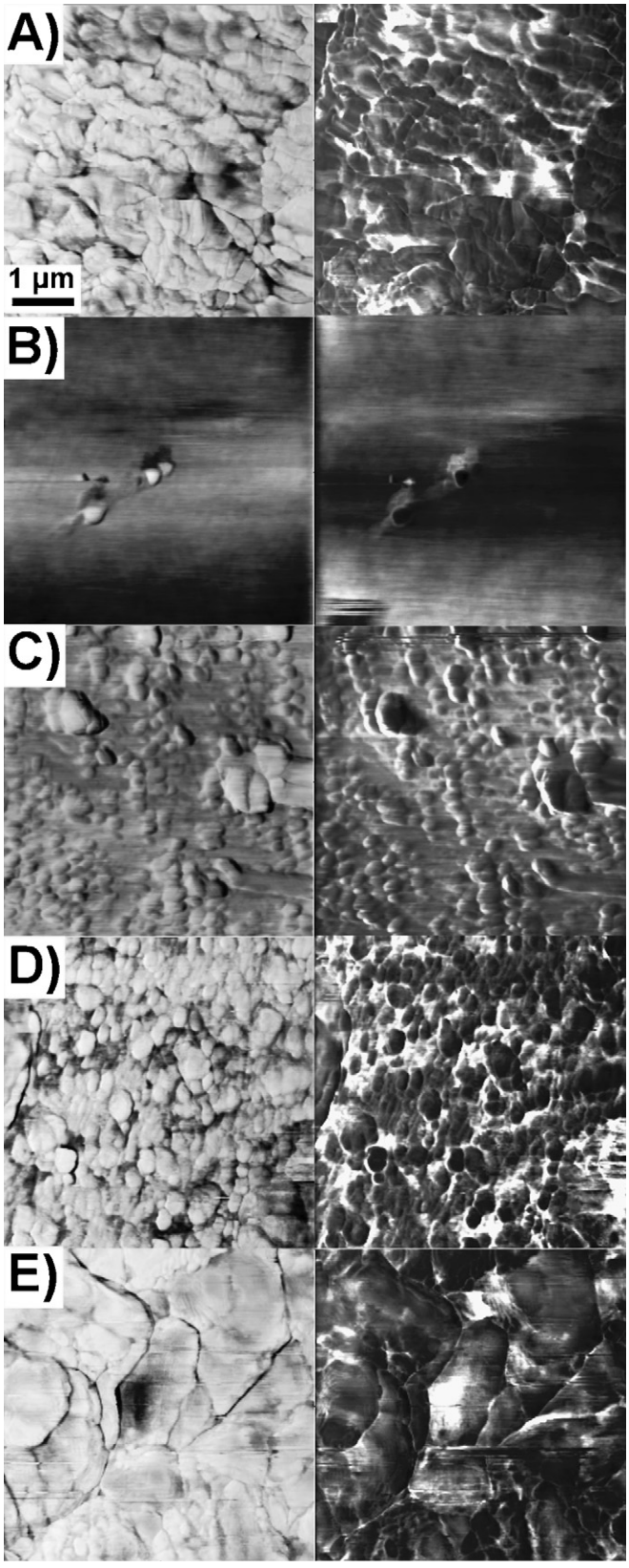

Fig. 4. Lateral force images, first column forward scan direction, second reverse. (A) PTFE; (B) glass; (C) zanamivir; (D) zanamivir–magnesium stearate blend; (E) magnesium stearate compact.

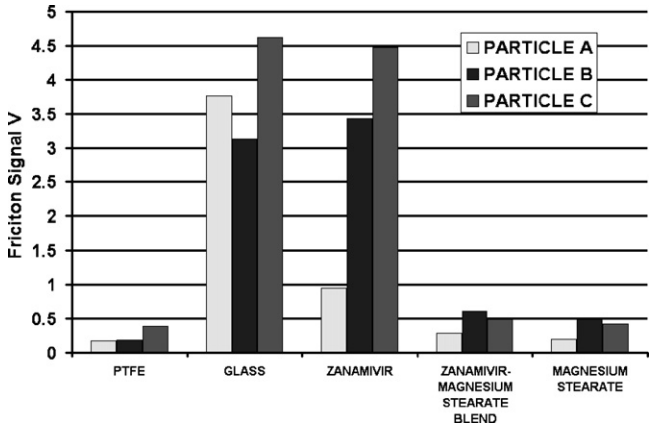

Fig. 5. Processed data showing friction signal on all surfaces for lactose particles A–C.

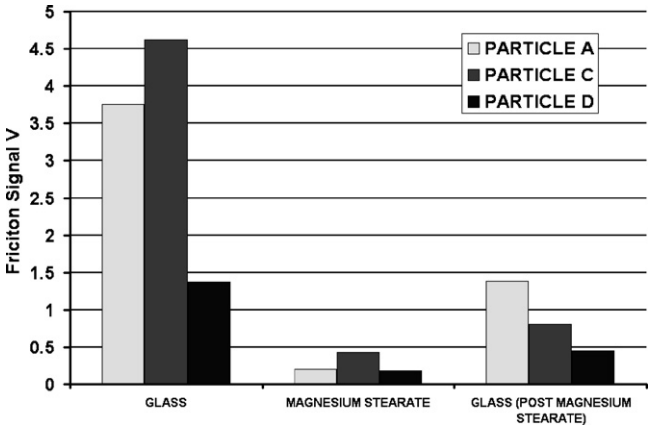

Fig. 6. Processed data showing friction signal on glass both before and after contact with magnesium stearate compact for lactose particles A, C and D.

and the ratchet mechanism (Bhushan, 2005). Such roughness scaling effects are well documented in the AFM particle adhesion literature (Bunker et al., 2005; Podczech, 1997; Islam et al., 2005), and similar arguments are applied here.

Changes in contact area due to surface roughness and the presence of significant topography can influence friction images (Meyer et al., 1998). The approximate size of a contacting asperity on one of the lactose particles used here can be taken as 1 μm × 1 μm (from typical asperity images, Section 3.3). Examination of line profiles taken the across the topographic images (Fig. 2) reveal that for the PTFE and magnesium stearate samples, the surface roughness is of a large enough scale so that the asperity can fit into the valleys. The contact area would then vary depending on whether the asperity touches a peak (small contact area) or valley (multiple contact points) or the surface. This also depends on the extent to which the surface can be deformed and since it is expected that the magnesium stearate is easily displaced by the particle, topography may not be so important in this case. For the PTFE sample it might be expected that the ratchet mechanism will contribute due to the presence of significant topography, but the friction signal remains low, indicating that intrinsic material properties such as the low surface energy, dominate over topographic effects and comparisons between different surfaces are therefore valid.

The friction on the zanamivir surface is similar in magnitude to that on glass except in the case of particle A where it is much lower. This exception is most likely due to differential wearing of asperities or heterogeneity on the zanamivir surface. Although absolute friction signals on glass and zanamivir are similar, they can be distinguished by the distributions of friction across the surface. The histograms in Fig. 3B and D show that zanamivir has a broader distribution.

Interestingly, the addition of magnesium stearate to the zanamivir surface appears to have reduced the friction to approximately the same level as on the magnesium stearate surface alone, indicating that it is dominating the friction behaviour of the blend. Although only 0.5% (w/w) was added, we have shown that the presence of the magnesium stearate has a dramatic effect on the friction behaviour of the zanamivir surface. This result is not difficult to comprehend when the evidence that magnesium stearate is sticking to the lactose particle is considered. Magnesium stearate has previously been shown to increase aerosolisation from a DPI by reducing adhesion (Young et al., 2002a), and this data is consistent with this role in aiding particle separation, possibly by reducing friction.

It was speculated that magnesium stearate would adhere to the surface of the lactose particles during these experiments. The friction on glass both before and after contact with the magnesium stearate surface is shown in Fig. 6 for particles A, C and D, and has been significantly reduced ($P < 0.001$, Kruskal–Wallis test) in all cases. This indicates that some magnesium stearate has transferred to the lactose particles and is reducing friction in subsequent measurements. In one case, particle D, there was a dramatic change in friction during the first friction image on glass after contact with the magnesium stearate. At the beginning of the image, the friction signal was low as expected due to the presence of magnesium stearate. However, after several scan lines, the friction suddenly increased, suggesting that some magnesium stearate that fallen off the particle and the contact was now more like that between lactose and glass alone. More evidence for this material transfer is provided by the LF histograms. The histogram for the zanamivir–magnesium stearate blend is very similar to the one for magnesium stearate blend in breadth (Fig. 3D and E); both are narrower than the zanamivir alone, indicating that the magnesium stearate masks some of the greater variation in friction seen on the unmodified zanamivir surface.

3.3. Particle asperity imaging

With all three particles used in these experiments the shape of the contacting asperities visibly changed during the experiment. Images of the contacting asperity on particle B both before and after all the friction measurements are shown in Fig. 7. It can be seen that several of the small peaks have been replaced by a flat area. Intermediate images taken after measurements on glass only (not shown) have clearly shown that asperity wear does occur. Although it is not possible as yet to discriminate between the wearing down of asperities and the addition of new material (magnesium stearate) from these images, we conclude

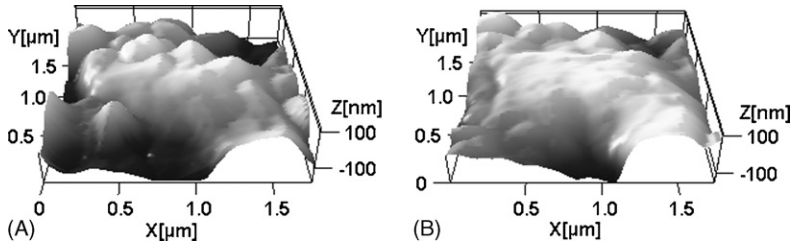

Fig. 7. AFM images of the contacting asperities on particle B (A) before, and (B) after, all friction measurements were made.

that a combination of these two factors changes the morphology. The future use of a chemically specific technique such as time of flight secondary ion mass spectroscopy (ToF-SIMS) or Raman spectroscopy could potentially distinguish between these possibilities.

Clearly the change in morphology during friction experiments will lead to changes in friction forces, but for this case we have shown that any such changes are small compared to differences in friction between various surfaces. By changing the order in which the surfaces were used, it has been shown that consistent rankings on different surfaces can be made. A related consideration with this new approach is the potential asymmetry introduced by the particular asperity or asperities contacting the surface. It is possible that the particle will show greater friction in one scan direction than the other. Such an effect would be apparent when comparing forward and reverse lateral force signals; however no significant asymmetry has been observed here.

4. Conclusions

For the first time, single particle friction in a model pharmaceutical system has been studied using AFM. Using a lactose particle, a consistent ranking of friction signals was found as follows: glass $\approx$ zanamivir > zanamivir–magnesium stearate blend $\approx$ magnesium stearate $\approx$ PTFE. We have shown that the addition of a small amount of magnesium stearate (0.5%, w/w) to the zanamivir surface significantly ($P < 0.001$) reduces interparticle friction.

Evidence has been presented that magnesium stearate readily adheres to the lactose probe and that this can lower friction in subsequent interactions. AFM imaging of the particle asperities reveals changes in the contact morphology caused by the friction experiments, which can be explained by a combination of wear and the collection of magnesium stearate. These changes do not contribute significantly to the differences in friction we observe.

Significant progress has been made in recent years using AFM to study particle adhesion forces. In real DPI systems, friction has an important role to play in the particle interactions which directly influence device performance. We believe that particle friction studies as presented here could be used in conjunction with adhesion measurements to examine the potential physical stability of DPI formulations, test the suitability of container materials and screen the effectiveness of tertiary components on altering the carrier–drug interaction.

Acknowledgments

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

References

Beake, B.D., Ling, J.S.G., Leggett, G.J., 1998. Correlation of friction, adhesion, wettability and surface chemistry after argon plasma treatment of poly(ethylene terephthalate). J. Mater. Chem. 8, 2845–2854.

Begat, P., Price, R., Staniforth, J.N., Morton, D.A.V., 2004. The cohesive–adhesive balances in dry powder inhaler formulations. I. Direct quantification by atomic force microscopy. Pharm. Res. 21, 1591–1597.

Berard, V., Lesniewska, E., Andres, C., Pertuy, D., Laroche, C., Pourcelot, Y., 2002a. Dry powder inhaler: influence of humidity on topology and adhesion studied by AFM. Int. J. Pharm. 232, 213–224.

Berard, V., Lesniewska, E., Andres, C., Pertuy, D., Laroche, C., Pourcelot, Y., 2002b. Affinity scale between a carrier and a drug in DPI studied by atomic force microscopy. Int. J. Pharm. 247, 127–137.

Bunker, M.J., Roberts, C.J., Davies, M.C., 2005. Towards screening of inhalation formulations: Measuring interactions with atomic force microscopy. Expert Opin. Drug Deliv. 2, 613–624.

Bhushan, B., 2005. Nanotribology and Nanomechanics An Introduction. Springer, Berlin.

Cain, R.G., Biggs, S., Page, N.W., 2000. Force calibration in lateral force microscopy. J. Colloid Interf. Sci. 227, 55–65.

Carpick, R.W., 1997. Scratching the surface: fundamental investigations of tribology with atomic force microscopy. Chem. Rev. 97, 1163–1194.

Carpick, R.W., Ogletree, D.F., Salmeron, M., 1997. Lateral stiffness: a new nanomechanical measurement for the determination of shear strengths with friction force microscopy. Appl. Phys. Lett. 70, 1548–1550.

Carpick, R.W., Flater, E.E., Sridharan, K., 2004. The effect of surface chemistry and structure on nano-scale adhesion and friction. Polym. Mater.: Sci. Eng. 90, 197–198.

Davies, M., Brindley, A., Chen, X., Marlow, M., Doughty, S.W., Shrubb, I., Roberts, C.J., 2005. Characterization of drug particle surface energetics and Young's modulus by atomic force microscopy and inverse gas chromatography. Pharm. Res. 22, 1158–1166.

Ecke, S., Raiteri, R., Bonaccurso, E., Reiner, C., Deiseroth, H., Butt, H.-J., 2001. Measuring normal and friction forces acting on individual fine particles. Rev. Scientific Instrum. 72, 4164–4170.

Eve, J.K., Patel, N., Luk, S.Y., Ebbens, S.J., Roberts, C.J., 2002. A study of single drug particle adhesion interactions using atomic force microscopy. Int. J. Pharm. 238, 17–27.

Frijlink, H.W., de Boer, A.H., 2004. Dry powder inhalers for pulmonary drug delivery. Exp. Opin. Drug Deliv. 1, 67–86.

Gibson, C.T., Watson, G.S., Myhra, S., 1997. Lateral force microscopy—a quantitative approach. Wear 213, 72–79.

Hooton, J.C., German, C.S., Allen, S., Davies, M.C., Roberts, C.J., Tendler, S.J.B., Williams, P.M., 2002. Characterization of particle–particle interactions by atomic force microscopy: effect of contact area. Pharm. Res. 20, 508–514.

Hooton, J.C., German, C.S., Allen, S., Davies, M.C., Roberts, C.J., Tendler, S.J.B., Williams, P.M., 2004. An AFM study of the effect of nanoscale contact geometry and surface chemistry on the adhesion of pharmaceutical particles. Pharm. Res. 21, 952–960.

Hutter, J.L., Bechhoefer, J., 1993. Calibration of atomic-force microscope tips. Rev. Scientific Instrum. 64, 1868–1873.

Islam, N., Stewart, P., Larson, I., Hartley, P., 2005. Surface roughness contribution to the adhesion force distribution of salmeterol xinafoate on lactose carriers by atomic force microscopy. J. Pharm. Sci. 94, 1500–1511.

Jones, R., Pollock, H.M., Geldart, D., Verlinden-Luts, A., 2004. Frictional forces between cohesive powder particles studied by AFM. Ultramicroscopy 100, 59–78.

Kim, S.H., Marmo, C., Somorjai, G.A., 2001. Friction studies of hydrogel contact lenses using AFM: non-crosslinked polymers of low friction at the surface. Biomaterials 22, 3285–3294.

Labris, N.R., Dolovich, M.B., 2003. Pulmonary drug delivery. Part II. The role of inhalent delivery devices and drug formulations in therapeutic effectiveness of aerosolized medications. Br. J. Clin. Pharm. 56, 600–612.

Lantz, M.A., O'Shea, S.J., Hoole, A.C.F., Welland, M.E., 1997. Lateral stiffness of the tip and tip-sample contact in frictional force microscopy. Appl. Phys. Lett. 70, 970–972.

Mate, C.M., McClelland, G.M., Erlandsson, R., Chang, S., 1987. Atomic-scale friction of a tungsten tip on a graphite surface. Phys. Rev. Lett. 59, 1942–1945.

Meurk, A., Yanez, J., Bergstrom, L., 2001. Silicon nitride granule friction measurements with an atomic force microscope: effect of humidity and binder concentration. Powder Technol. 119, 241–249.

Meyer, E., Overney, R.M., Dransfeld, K., Gyalog, T., 1998. Nanoscience Friction and Rheology on the Nanometer Scale. World Scientific Publishing Co. Pte. Ltd., London.

Neumeister, N., Ducker, W., 1994. Lateral, normal, and longitudinal spring constants of atomic force microscopy cantilevers. Rev. Scientific Instrum. 65, 2527–2531.

Ogletree, D.F., Carpick, R.W., Salmeron, M., 1996. Calibration of frictional forces in atomic force microscopy. Rev. Scientific Instrum. 67, 3298–3306.

O'Shea, S.J., Welland, M.E., Rayment, T., 1992. Atomic force microscope study of boundary layer lubrication. Appl. Phys. Lett. 61, 2240–2242.

Podczech, F., 1997. Particle–particle Adhesion in Pharmaceutical Powder Handling. Imperial College Press, London.

Podczech, F., Newton, J.M., 1995. Development of an ultracentrifuge technique to determine the adhesion and friction properties between particles and surfaces. J. Pharm. Sci. 84, 1067–1071.

Putman, C.A.J., Igarashi, M., Kaneko, R., 1995. Single-asperity friction in friction force microscopy: the composite-tip model. Appl. Phys. Lett. 66, 3221–3223.

Schwarz, U.D., Wiesendanger, R., 1996. Quantitative analysis of lateral force microscopy experiments. Rev. Scientific Instrum. 67, 2560–2567.

Sindel, U., Zimmermann, I., 2001. Measurement of interaction forces between individual powder particles using an atomic force microscope. Powder Technol. 117, 247–254.

Swaminathan, V., Kildsig, D.O., 2002. Effect of magnesium stearate on the content uniformity of active ingredient in pharmaceutical powder mixtures. AAPS PharmSciTech 3.

Tsukada, M., Irie, R., Yonemochi, Y., Noda, R., Kamiya, H., Watanabe, W., Kauppinen, E.I., 2004. Adhesion force measurement of a DPI size pharmaceutical particle by colloid probe atomic force microscopy. Powder Technol. 141, 262–269.

Varenberg, M., Etsion, I., Halperin, G., 2003. An improved wedge calibration method for lateral force in atomic force microscopy. Rev. Scientific Instrum. 74, 3362–3367.

Wang, Z., Lange, C.F., Finlay, W.H., 2004. Use of an impinging jet for dispersion of dry powder inhalation aerosols. Int. J. Pharm. 275, 123–131.

Xu, L., Bluhm, H., Salmeron, M., 1998. An AFM study of the tribological properties of NaCl (1 0 0) surfaces under moist air. Surf. Sci. 407, 251–255.

Young, P.M., Cocconi, D., Colombo, P., Bettini, R., Price, R., Steele, D.F., Tobyn, M.J., 2002a. Characterisation of a surface modified dry powder inhalation carrier prepared by particle smoothing. J. Pharm. Pharmacol. 54, 1339–1344.

Young, P.M., Price, R., Tobyn, M.J., Buttrum, M., Dey, F., 2002b. Investigation into the effect of humidity on drug–drug interactions using the atomic force microscope. J. Pharm. Sci. 92, 815–822.

Young, P.M., Price, R., Lewis, D., Edge, S., Traini, D., 2003a. Under pressure: predicting pressurized metered dose inhaler interactions using the atomic force microscope. J. Colloid Interf. Sci. 262, 298–302.

Young, P.M., Price, R., Tobyn, M.J., Buttrum, M., Dey, F., 2003b. The influence of relative humidity on the cohesion properties of micronised drugs used in inhalation therapy. J. Pharm. Sci. 93, 753–761.