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Single particle friction on blister packaging materials used in dry powder inhalers

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ABSTRACT

Using atomic force microscopy (AFM) the adhesion and sliding friction behaviour of single lactose particles attached directly to AFM cantilevers has been studied. Measurements were made on the two sides of a blister packaging material used in dry powder inhalers (DPI). Although no significant differences in adhesion were observed, clear differences in particle friction were evident, where one side offers consistently greater friction across the range of loads studied here. The packaging samples were characterised by time-of-flight secondary ion mass spectrometry (ToF-SIMS) and X-ray photoelectron spectroscopy (XPS) and found to have different surface chemistries. The observed difference in friction behaviour is discussed in the context of the differences seen in surface chemistry, topography and hardness. It is reasoned that in this case hardness has the largest influence, and on one sample soft surface layers are displaced by the particle. A clear relationship between friction and load was only observed with one of the three particles tested; this was attributed to multiple asperities being brought into contact, illustrating the important role of nanoscale contact geometry in determining friction behaviour.

1. Introduction

A typical formulation in dry powder inhalers (DPIs) uses a mixture of micronised active component and larger carrier particles. The role of these carriers, typically lactose, is to collect drug particles on their surface, aiding their removal from the device (Zeng et al., 2001) and helping avoid agglomeration. The powder is stored in the inhaler in a reservoir, either in bulk or in individual doses. Upon inhalation, the powder is removed from the reservoir and the smaller drug particles separate from the carriers and are then free to penetrate the deep lung region where they are therapeutically more effective (Taylor and Kellaway, 2001). It is apparent that the interactions between both kinds of particle and the surfaces they contact in the device are of critical importance to the efficiency of the device.

The atomic force microscope (AFM) has grown in influence as a means to investigate particle interactions in inhalation formulations on a single particle level (Bunker et al., 2005). By attaching particles directly to cantilevers, the adhesion force in the direction normal to the surface can be measured by recording force–distance curves (Ibrahim et al., 2000). There are many examples of formulation relevant studies including the ranking of adhesion forces (Sindel and Zimmermann, 2001; Eve et al., 2002; Young et al., 2002, 2003a), the cohesive–adhesive tendencies of drug–carrier mixtures

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(Begat et al., 2004), the effect of relative humidity on adhesion (Berard et al., 2002a,b; Hooton et al., 2004) and the calculation of particle surface free energy (Davies et al., 2005; Zhang et al., 2006).

Despite these useful advances based on the measurement of adhesion forces, it has been suggested that particle friction could be as important to powder behaviour as adhesion (Podczech and Newton, 1995; Jones et al., 2004). This is intuitive since in the case of a DPI, particles will be removed from the device by turbulent air streams acting in many directions (Labris and Dolovich, 2003; Wang et al., 2004); measuring normal removal forces would then seem to represent a limited view. In parallel with such experimental approaches, there is considerable interest in attempting to model particle interactions and removal from surfaces. Removal by an air stream can be initiated by either a lifting, rolling or sliding mechanism (Burdick et al., 2001, 2005), which although difficult to measure explicitly on a single particle level, may benefit from appropriate study of sliding friction forces.

The AFM has long been used to study friction on flat surfaces by recording the lateral force (LF) or sideways twisting movements of the cantilever as it is scanned across a surface (Mate et al., 1987). Commercial AFMs normally use a four segment photodiode detector capable of monitoring this signal (commonly termed left–right or horizontal). Although various aspects of friction have been studied extensively since the advent of AFM, only a few publications have detailed studies on particle friction (Ecke et al., 2001; Meurk et al., 2001). The most comprehensive of these is a study on various industrial powders by Jones et al. (2004). In a recent study we showed that comparisons of friction can be made on different surfaces using pharmaceutical materials (Bunker et al., 2006).

Calibration of LF signals into units of friction force remains a difficult problem. There is much published work on the subject and approaches vary from calibrations based on cantilever geometry and material bulk properties (Neumeister and Ducker, 1994; Schwarz and Wiesendanger, 1996) to methods that use measurements of LF signals on known slopes (Ogletree et al., 1996; Varenberg et al., 2003). However, useful information can be obtained by studying friction without this calibration, by making relative measurements and comparisons (Xu et al., 1998; Kim et al., 2001; Carpick et al., 2004).

In this paper we present single particle friction and adhesion measurements between lactose and the two sides of a DPI blister packaging material using AFM, the authors believe this is the first study of its kind on such materials. The two sides of the blister pack are shown to be different by both surface chemical and physical characterisation. We demonstrate that meaningful comparisons of friction behaviour can be made. We propose that such measurements could be used in conjunction with adhesion studies to gain further information on single particle interactions with AFM. Such an approach has the potential to screen the effectiveness of candidate packaging materials and carrier particles and to provide data for computational models being developed to simulate particle from surfaces.

2. Materials and methods

2.1. Materials

DPI blister packaging materials were supplied by GlaxoSmithKline (GSK, Ware, UK). This consists of two strips of polymer coated metal foil, one is flat (termed sample 1) and the other has a series of pockets punched in a line (termed sample 2). The two sides are glued together to hold the individual doses of powder in place in the pockets. As described in the following sections, surface chemical characterisation shows the two sides are made from different materials. When the device is activated the pocket is pierced open and the powder is removed. The samples used in these experiments were supplied blank and have not had previous contact with any powders. α-Lactose monohydrate was obtained from Sigma–Aldrich (Poole, Dorset, UK).

2.2. Methods

2.2.1. Sample preparation

V-shaped silicon nitride cantilevers (Park Scientific Instruments, Sunnyvale, CA, USA) were calibrated for normal spring constant using the thermal method (Hutter and Bechhoefer, 1993). Particles of lactose, typically 10–20 μm, were attached directly using an AFM, details of this method have been published previously (Eve et al., 2002). Five particles were prepared for adhesion measurements designated A–E and three were used for friction work, numbered 1–3.

To prepare the DPI packaging samples, small squares (approximately 1 mm^2 in area) were cut from both the bottom of the pocket in sample 2 and the part of sample 1 which would normally be in contact with the powder. These were attached to AFM stubs with a two part commercial epoxy adhesive (Araldite Precision, Huntsman Advanced Materials, Everberg, Belgium). Samples for time-of-flight secondary ion mass spectrometry (ToF-SIMS) and X-ray photoelectron spectroscopy (XPS) analysis were prepared in a similar way, with small sections cut and secured to clean silicon wafers with double sided tape.

2.2.2. AFM imaging

Both samples were imaged by AFM in both contact and tapping mode prior to friction measurements to examine the surface topography. All images were taken on a Nanoscope IIIa Multimode AFM equipped with an E scanner (Veeco, Santa Barbara, CA, USA). Images were taken at scan sizes of 10 μm $\times$ 10 μm and average roughness R_a values were calculated using SPIP AFM image processing software (Image Metrology ApS, Lyngby, Denmark) from at least three different areas.

2.2.3. ToF-SIMS

ToF-SIMS is a highly surface specific spectroscopic technique that allows recognition of chemical species by identifying ionised mass fragments released from the surface by the impaction of primary ions (Belu et al., 2003). A ToF-SIMS IV (IONTOF, Münster, Germany) instrument was used with a gallium ion source and spectra were collected from both positive and negative ions. Once characteristic peaks have been identi-