Characterization of the surface physico-chemical stability of materials directly applicable to inhalation therapy

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Abstract— **Atomic force microscopy (AFM) has been used to investigate the surface properties of mechanically processed respirable sized drug particles. Phase imaging, an auxiliary technique of conventional intermittent contact mode (TappingMode™) AFM imaging, was employed to differentiate the physico-mechanical variations on the processed surfaces of model salbutamol sulphate drug crystals. Samples were produced by cumulative milling of crystals formed by conventional batch crystallisation. With increased periods of milling, specific regions on the salbutamol sulphate crystals showed increased variations in phase lag (>30°), which were independent of topographical induced phase changes. These regions, not generally observed on non-milled samples, suggested a surface induced change to the physico-mechanical properties of the processed crystals. The surface regions of increased phase could possibly be associated with the formation of surface disorder, which could be amorphous in nature**.

Keywords—**Atomic Force Microscopy, Amorphous, Crystals**

I. Introduction

The physico-chemical stability of pharmaceutical materials (both active agents and excipients) used for dry powder inhalation therapy play a dominating role on both long-term therapeutic efficacy and delivery characteristics of a specific formulation. Such stability issues are generally affected by variations in environmental conditions upon storage (both relative humidity and temperature). The use of spray-dried materials, for example, which contain a large percentage of amorphous material, would be directly affected by variations in relative humidity and/or temperature. In general, with a sufficient increase in free volume and molecular diffusion, the metastable amorphous system will undergo a phase transition to a more thermodynamically stable crystalline form. Such transitions will potentially generate solid bridging between materials, thus significantly impairing delivery performance (via reduction in respirable fraction). To a lesser extent, the high energy processing of highly crystalline materials (most commonly used in inhalation therapy) to achieve a more conducive respirable particle size range will inevitably induce dislocations, defects and, potentially, regions which are amorphous in nature. Such disorder would be expected to be primarily located on the surface of the processed material. Although such disorder may be several orders of magnitudes less than that of a spray dried material, their presence and apparent instability may cause long term stability issues, subsequently impacting on deaggregation and dispersion efficiency of a formulation.

Current methodologies of determining disorder (i.e. % amorphous content) in pharmaceutical processed materials have been limited to bulk analytical techniques. Although great advancements have been made in such systems (i.e. resolution and sensitivity), there are still severe limitations when detecting very small amount of disorder. For example, techniques such as modulated differential scanning calorimetry [1] (MDSC), dynamic vapour sorption [2] (DVS) and isothermal microcalorimetry [3] are limited to a detection of ≥1% w/w amorphous content. These techniques also lack any information regarding the dynamic stability of amorphous disorder below and above the glass transition temperature prior to the re-crystallisation process. For inhalation material, such information is critical to the overall stability and performance of a formulation.

A potential method for circumventing these limitations would be the direct visualisation of the physico-chemical and physico-mechanical differences between the surface states of processed material. Atomic force microscope [4] (AFM) provides such a means of attaining these goals, enabling high-resolution (sub-nanometre) elucidation of specific changes to the surface properties of materials. Furthermore, the use of an auxiliary phase imaging AFM technique allows specific differentiation between areas where variations in the mechanical properties on the substrate surface and/or physical variations in the adhesion characteristics between the tip and underlying substrate can be observed. For processed materials, the sensitivity of AFM to surface variations may provide a means of visualising and monitoring the stability of surface disorder. Furthermore, by incorporating the whole system in an environmentally controlled unit, it becomes possible to investigate the influence of relative humidity and temperature on surface properties of processed materials.

A schematic representation of the phase imaging technique is illustrated in Figure 1. In phase imaging, the phase lag between the oscillation of a high aspect ratio AFM probe in air and upon interacting with the sample is continually measured. The amount of energy dissipated between the tip and the sample surface is directly proportional to the recorded phase difference. A large phase shift infers areas of high adhesion and/or highly deformable areas on the substrate surface, while a small phase shift would relate to areas of low adhesion and/or non-

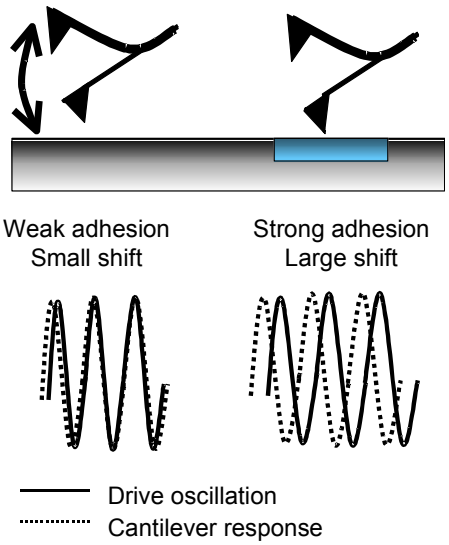

Fig. 1. Diagrammatic representation of phase imaging AFM technique

deformable areas of the surface. In this study, phase imaging AFM was utilized as a means of measuring variations in physico-mechanical properties of crystalline and amorphous regions of mechanically processed pharmaceutical materials.

II. Methodology

The surface properties of pharmaceutical materials were investigated using a commercially available multimode AFM with NanoScope IIIa controller (DI, Cambridge, UK), enclosed in a custom-built environmentally controlled perfusion based unit. Samples were deposited onto a mica surface, which was pre-mounted on an AFM sample stub. Imaging was conducted in Tapping Mode™ with the use of an auxiliary extender module for phase lag measurements. Images were recorded at a scan rate of 1.0 Hz with a high-aspect silicon probe (OTESP, DI, Cambridge, UK).

Salbutamol sulphate was chosen as a model drug since it widely used for the treatment of asthma, and is commonly delivered via the dry powder route. Two forms of the material were produced and characterised by simultaneous topographical and phase AFM imaging: crystalline salbutamol sulphate nucleated and grown from an aqueous solution by adding ethanol as an anti solvent and disruption of the crystalline sample through cumulative periods of milling [5]. All measurements were imaged under controlled environmental conditions (45% RH, 25°C).

III. Results and Discussion

The crystalline {001} and {100} faces of salbutamol sulphate, grown under controlled supersaturation conditions, showed no significant differences (>30° phase shift) in physico-mechanical properties (amplitude and phase images not shown). Representative AFM tapping mode and phase images taken after 12 and 24 minutes milling time of the crystalline samples are shown in Figures 2a,b and 3a,b, respectively. In contrast to the thermodynamically stable crystalline faces, AFM imaging of cumulatively milled crystals showed a decrease in the surface uniformity and the presence of discrete surface domains. These surfaces domains exhibited large increases in phase. The correlation between the induction of these regions and increase in phase suggests these surface domains exhibit different physico-mechanical properties to non-milled, crystalline faces. Furthermore, although not directly quantitative, a clear rank increase in the quantity of such regions was observed as a function of milling time. As these phase shift regions indicate large variations in the physico-mechanical properties of the drug surface, it would be quite logical to conclude that their presence may be due to mechanically induced damage to the crystalline lattice, resulting in the surface activation of highly metastable amorphous regions. These regions may subsequently affect interfacial stability and ultimately the delivery efficiency of the formulated drug.

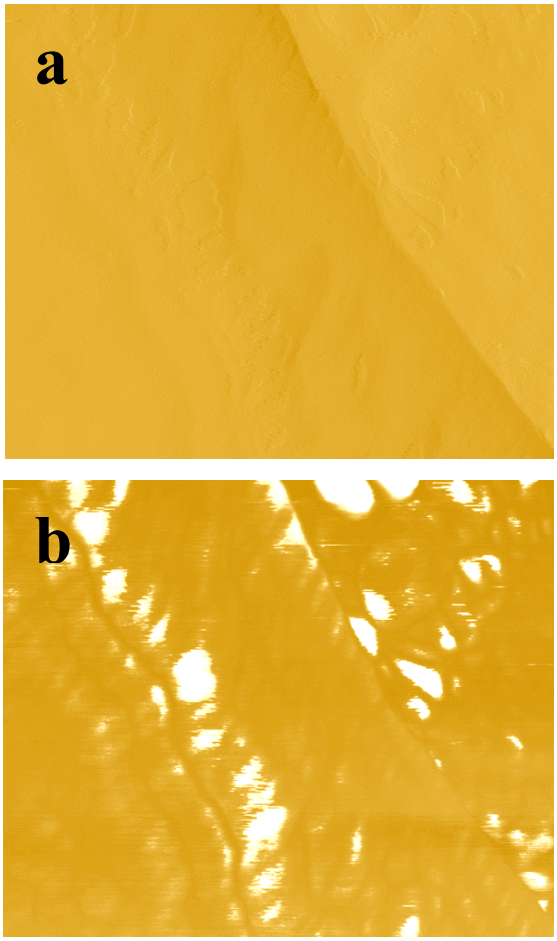

Fig. 2. Surface topography (a) and corresponding phase image (b) of a salbutamol sulphate crystal after 12 minutes milling time exposure.

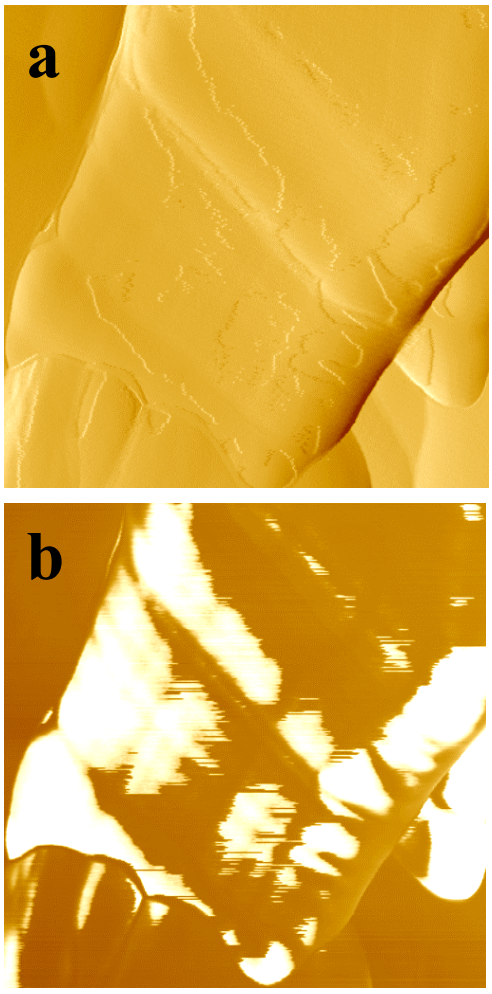

Fig. 3. Surface topography (a) and corresponding phase image (b) of a salbutamol sulphate crystal after 24 minutes milling time exposure.

V. Conclusion

Phase imaging AFM studies of the surface properties of mechanically processed salbutamol sulphate drug crystals suggested a relationship between increase in phase and surface activation of nominally crystalline faces. These discrete surface regions display an apparent difference in physico-mechanical properties with respect to the crystalline state. These regions, which might be associated with mechanically induced amorphous material, will directly affect the stability and aerolisation properties of a dry powder inhalation formulation. In combination with bulk techniques, AFM may provide a valuable tool in visualizing the metastable nature of partially disordered materials and the requirements for post-conditioning of mechanically processed pharmaceutical solids in attaining thermodynamic stability.

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