Visualisation of Pharmaceutical Material Surface Stability as a Function of Mechanical Processing

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Introduction

In most pharmaceutical dry powder formulations, crystalline drugs or excipients must exhibit a specific functionality that requires a high-energy processing such as milling or micronisation which could induce regions of amorphous state in the material (1). In general, amorphous materials are thermodynamically unstable and may re-crystallise, if the molecular mobility within the region is high enough to allow such re-ordering (2). The differences in physical properties between crystalline and amorphous material can be of importance when affecting the mixing and aerosolisation properties of the active material (3).

Current methods for determining amorphous content in crystalline materials tend to be bulk measurement techniques (XRPD, DSC, DVS). However, the amount of amorphous material present within a processed bulk powder is usually very small and would most likely be present on the surface. The atomic force microscope (4) (AFM) may provide a means of directly visualising amorphous regions present on the surface of mechanically processed crystalline materials.

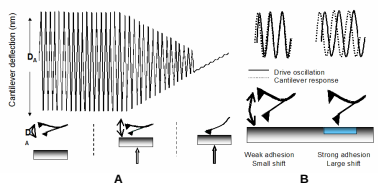

Figure 1: diagrammatic representation of tapping mode ™ method and phase imaging method

Unlike other microscope techniques, the AFM is able to record detailed information without any sample pre-treatment. In simple terms, topographical information obtained by Tapping mode™ is achieved by scanning an oscillating micro-fabricated cantilever tip across a surface at constant amplitude. The amplitude of the oscillating tip is recorded by measuring the deflection of a laser off the tip on a photo-detector. As the distance between the tip and the sample changes, a variation in the amplitude will occur. A feedback loop will therefore correct the height of the scanner in order to keep the amplitude of the tip constant. A diagrammatic representation of tapping mode ™ method is shown in Figure 1A.

Phase imaging is an auxiliary method measuring the degree of phase shift in the oscillation of the tip. As the oscillating cantilever tip encounters regions on a surface containing different physical properties, such as hardness or elasticity, a shift in phase will occur (lag in oscillation). A diagrammatic representation of phase imaging method is shown in Figure 1B. Since it is expected that crystalline regions will have high packing density, the phase difference upon interaction with the scanning tip is expected to be very small. However, for disordered, amorphous regions, a high phase lag is expected due to a high surface free energy (large adhesion), and high deformation of the contact area. By measuring the degree of phase shift in unison with topography it becomes possible to identify variations in surface structure.

Method

Salbutamol sulphate, commonly used in a range of pharmaceutical inhalation products, was chosen as a model drug for investigation as it is well characterised in terms of amorphous-crystalline physical stability (5). A 10% w/w saturated solution of salbutamol sulphate (Beckpharm Ltd) in 50/50 ethanol/water was filtered then stirred at 20°C in a sealed crystallisation vessel. Ethanol was added at a rate of 15ml/hour using a computer controlled syringe driver until the solvent mass ratio was 80/20 ethanol/water. Recovered crystalline material was filtered and dried at 40°C. Mechanical damage to the salbutamol sulphate crystals was achieved by milling the drug material with stainless steel balls (7mm) in a Turbula (Glen Creston Ltd, Middlesex, UK). The crystalline material was milled for 24 minutes, with samples being taken every 6 minutes. Care was taken not to remove more than 2% of the total mill material during this process.

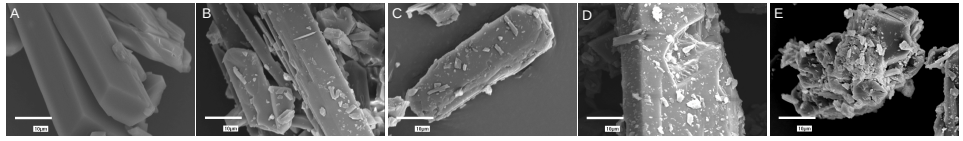

Figure 2: Representative SEM images of salbutamol sulphate after successive milling times

Representative electron micrographs of the re-crystallised salbutamol sulphate, shown in Figure 2A, suggested a needle like morphology with relatively smooth undamaged surfaces. In contrast, electron micrographs of the salbutamol sulphate taken after 6,12,18 and 24 minutes milling times (shown in Figure 2B, C, D and E respectively) indicated an apparent increase in surface damage, non-uniformity in shape and decrease in particle size.

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AFM experiments

Surface stability of the salbutamol sulphate was investigated using a commercially available multimode AFM with nanoscope 3a controller and extender electronics module (Di, Cambridge, UK). Samples were immobilised on steel AFM stubs using tempfix™ (SPI Supplies, West Chester, USA) at 40°C using a custom built pelletier connected to a thermocouple temperature controller (SE5000, Marlow Industries, Dallas, Texas). Surface morphology was investigated using TESP Olympus tips (Di, Cambridge, UK) in tapping mode™ at a scan rate of 0.75 Hz. In addition, intermittent contact force produced as a result of tip oscillation, was minimised by maintaining a low drive amplitude and relative setpoint.

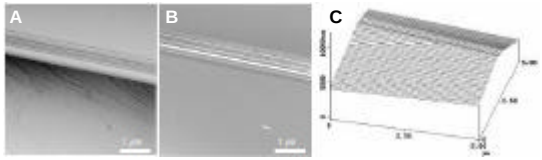

Figure 3: Representative AFM amplitude image (A), corresponding phase response (B) and topographical height image (C) of re-crystallised salbutamol sulphate surface

Re-crystallised salbutamol sulphate topography is shown in Figure 3. A clear distinction between two crystal faces can be observed due to the clear edge. Irregular and parallel steps observed on the lower crystal face in Figure 3A suggested atomic-unit crystal planes. Furthermore, the corresponding phase image shown in Figure 3B indicated no significant differences (>30° phase shift) in the physico-mechanical properties on the crystal surface, apart from linear striations between the two crystal faces. Cross sectional analys is of the AFM height image shown in Figure 3C, were taken perpendicularly to the observable edge and indicated an apparent angle of 99°. According to the salbutamol sulphate crystal system, this suggested that the picture was taken between the {001} and {100} faces.

Representative AFM amplitude (α) and phase (φ) images taken after 6,12, 18 and 24 minutes milling time are shown in Figure 4A, B, C and D respectively. To maintain consistency during AFM imaging, care was taken to identify and image on either the {001} or {100} crystal face of the milled salbutamol sulphate samples (i.e. the two elongated needle faces).

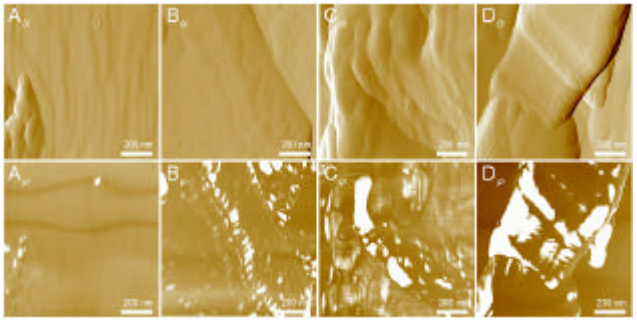

Figure 4: Topographical amplitude images (α) and corresponding phase shift (φ) for salbutamol sulphate crystal surfaces after 6 minutes (A), 12 minutes (B), 18 minutes (C) and 24 minutes (D) milling times.

Simultaneous AFM topographical and phase images of the milled samples indicated an increase in surface disorder as a function of milling time. Specific regions on the milled samples, independent of topography, showed large variations in phase shift (>30°). These regions (not observed on the crystalline salbutamol sulphate) suggested large differences in the physical properties on the surface. Their presence may be due to mechanically induced crystal lattice damage, resulting in surface activation (i.e. amorphous regions). It is important to note, however, that AFM phase imaging is used as a visualisation tool, not as a mean of determining the nature of a crystal structure. Such surface activation may subsequently affect surface stability and ultimately drug delivery efficiency.

Conclusions

The use of AFM phase shift data suggests a relationship between milling time and surface stability. As precedent studies show mechanical process induces amorphous material, results would therefore suggest that the regions observed during phase images might be mechanically induced amorphous material on the surface The presence of such regions will directly affect the stability of a formulation, as the surface energetics will become unpredictable. Such surface activation may subsequently affect surface stability and ultimately drug delivery efficiency.

References

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