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 in a processed bulk powder is usually very small and would most likely be present on the surface. The atomic force microscope (AFM) may provide a means of directly visualising amorphous regions present on the surface of mechanically processed crystalline materials.

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 then 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.

Method

Salbutamol sulphate, commonly used in a range of pharmaceutical inhalation products, was chosen as a model drug for investigation as it is well characterized in terms of amorphous-crystalline physical stability (4). A 10% w/w saturated solution of salbutamol sulphate (Blackpharm Ltd) in 0.9% sodium chloride was filtered then sterilised at 120°C in a sealed crystallisation vessel. Ethanol was added at a rate of 15%/hour using a computer controlled syringe driver until the ethanol mass ratio was 6:1, when the solution was cooled to 0°C. Mechanical damage to the salbutamol sulphate crystal was achieved by milling the drug material with stainless steel balls (7mm) in a Turbula (Glen Creston Ltd, Middlesex, UK). The crystal line 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.

AFM experiments

Surface stability of the salbutamol sulphate was investigated using a commercially available multimode AFM with nanoscope 3a controller and scanner electronic module (DI, Cambridge, UK). Samples were immobilised on steel AFM stubs using tempfix™ (SPI Supplies, West Chester, USA) at 40°C using a custom build 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.

Representative AFM amplitude image (A), corresponding phase response (B) and topographical height image (C) of the crystalline salbutamol sulphate surface is suggested that the picture was taken between the {001} and {100} faces.

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 unison with topography it becomes possible to identify variations in surface structure.

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.

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