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Towards the understanding and prediction of material changes during micronisation using atomic force microscopy

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ABSTRACT

In this study we aim to explore the potential links between the mechanical properties, micronisation behaviour and surface energy of carbamazepine polymorphs using atomic force microscopy (AFM) measurements of material properties at the nanoscale. Carbamazepine Forms I, II and III were prepared and confirmed using X-ray powder diffraction (XRPD). AFM measurements of indentation hardness, Young's modulus and surface energy were made on the starting material. In addition, the surface energy was measured immediately after micronisation and after storage for four weeks. Carbamazepine polymorphs could be ranked by Young's modulus and hardness. Surface energy measurements showed an increase after micronisation in all cases, and a varying relaxation after storage for four weeks. Form I showed a smaller particle size distribution, indicating more complete micronisation. A promising correlation was observed between the hardness/Young's modulus ratio and the micronisation behaviour, in terms of particle size reduction and surface energy change. The results show potential for the predictive capacity of such an approach, and help to provide a greater understanding of material behaviour and properties during micronisation.

1. Introduction

It is widely accepted within the pharmaceutical industry that the developability of a new compound will depend upon its physicochemical properties (Huang and Tong, 2004; Hlinak et al., 2006; Saxena et al., 2009). In general, when considering the selection of an optimal form of a drug substance, a multi-tiered approach is taken to select candidates that have not only the appropriate efficacy, bioavailability and toxicity but also suitable crystallinity, solubility and stability. At this stage of candidate selection, a developability assessment may also begin to highlight candidates that can be ruled out due to inappropriate physiochemical characteristics (Saxena et al., 2009). However, at this point little focus is placed on other material properties such as surface energy, Young's modulus and hardness. These are potentially equally important properties, since they will influence how the material will behave upon processing and may ultimately dictate the route of formulation (Hlinak et al., 2006). Whilst these attributes may not totally exclude a compound from selection, it clearly is more time and cost effective to be able to select at the earliest possible stage of development the form of a drug that has the most appropriate material properties. For example, two salt forms of a drug may have comparable solubility and stability but may have contrasting physical properties making one more suitable for processing and manufacture.

To fully utilise such secondary parameters as criteria for material selection it is important to understand the correlation between these parameters and their influence on the outcome of material processing. The processing of a drug substance will depend on the route of formulation that has been selected, however, a particularly common process applied to the majority of materials is particle size reduction (Rasenack and Muller, 2004). When considering drugs for the oral route of delivery, particle size reduction is used to achieve solubility enhancement (Chaumeil, 1998; Kim et al., 2008), whereas in the case of inhalation formulation a mean aerodynamic particle size of <5 μm is required for efficient delivery to the lungs (Timsina et al., 1994).

There are many ways of deriving micron size drug particles for optimised formulations (Oh et al., 1995; Feeley et al., 1998a; Rasenack et al., 2003; Rasenack et al., 2004), with the most common method being micronisation, the mechanical comminution of

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particles in a jet air mill (Rasenack and Muller, 2004). During this process a large amount of mechanical stress is applied to the materials that can lead to significant changes in the surface properties, often in an uncontrolled manner. One such change that has been well documented is the creation of disorder or amorphous material at the surface of the micronised particles, a process which continues to be of significance to the pharmaceutical industry, since such physical modifications can lead to materials with markedly different surface properties, with consequent changes in processability (Chikhalia et al., 2006; Wildfong et al., 2006; James et al., 2008). In particular the surface energy of the materials is known to increase upon particle size reduction (Feeley et al., 1998b; Newell et al., 2001a; Chikhalia et al., 2006; Heng et al., 2006). Although this phenomenon is quite widely accepted, it is rarely discussed in detail and little literature exists. As such there is a lack of information surrounding factors that affect surface energy changes. In particular it would be of great value during developability assessment if the potential for undesirable surface property changes could be understood and ultimately predicted.

Currently, information relating to parameters such as surface energy, Young's modulus and hardness are derived at the later stages of formulation. This is the point at which a candidate has been selected and a sufficient amount of material becomes available for testing. This is partly due to a lack of techniques that can routinely derive this information from the quantities of material typically available (∼mg) (Saxena et al., 2009). Over the past two decades, atomic force microscopy (AFM) has shown promise for determining the nanoscale physicochemical properties of pharmaceuticals from minute quantities of materials (Begat et al., 2004; Bunker et al., 2005; Young et al., 2006; Turner et al., 2007). In particular the increased understanding of the force sensing capabilities of the instrument has lead to the development of methodologies for quantitative determination of parameters such as Young's modulus (Davies et al., 2005; Ward et al., 2005; Perkins et al., 2007), surface energy (Zhang et al., 2006; James et al., 2008) and cohesion and adhesion (Begat et al., 2004; Young et al., 2006). In addition the ability of the technique to probe the surface on the nanoscale can help understand any spatial heterogeneity that exists in the material (Roberts, 2005).

In this study we use an AFM approach to explore the relationships between the mechanical properties of a material and the changes observed in the surface energy following micronisation in a jet air mill, on a single particulate level. Three polymorphs of carbamazepine (CBZ) were used as model materials, since its crystalline forms are well characterized and some information on the bulk properties of this material exists in the literature (Roberts and Rowe, 1996; Roberts et al., 2000; Sunkersett et al., 2001; Grzesiak et al., 2003). In addition the study of a polymorphic series allows the comparison of the structure-property relationship more readily since the variability between forms is due to crystal structure and not chemistry (Roberts and Rowe, 1996).

2. Methods

2.1. Preparation of CBZ polymorphs

All forms of CBZ were prepared from commercial material (Sigma, UK). Form I was prepared by heating recrystallized Form III at 170 °C for 2 h. Form II was obtained by slow evaporation of a 100 mg ml^{-1} solution of CBZ in dichloromethane at room temperature. Finally, Form III was obtained by heating a 100 mg ml^{-1} solution of CBZ in ethanol to 80 °C. The solution was allowed to slowly cool at room temperature and left for a further 24 h. The resultant crystals were collected by vacuum filtration. All forms were confirmed by powder X-ray diffraction (PXRD) prior to further experimental analysis.

2.2. Micronisation of CBZ polymorphs

Micronisation was performed by jet milling in a Sturtevant qualification micronizer (Hannover, USA) with a feed pressure of 80 psi and a grind pressure of 100 psi for 10 min. The micronisation conditions were kept constant to allow a direct comparison of post-micronisation parameters between forms, and were therefore not necessarily the optimum conditions for complete particle size reduction. All materials were micronised immediately prior to any subsequent analysis. A proportion of the micronised material from each form was analysed immediately after micronisation, the remainder was stored under ambient conditions (approximately 20 °C and 40% relative humidity) for four weeks.

2.3. Scanning electron microscopy

Scanning electron microscopy (SEM) was carried out using a Leo 1430VP Electron microscope. The accelerating voltage was 10 kV, at a working distance of ∼10 mm. Samples were gold coated prior to imaging.

2.4. Powder X-ray diffraction

Powder X-ray diffraction was performed on Bruker D8 Advance equipped with a CuKα source (λ = 1.5406 Å). Diffractograms were acquired between 5° and 40° 2Θ with a step size of 0.25°. Samples were mounted on a zero background silicon holder and rotated throughout the analysis.

2.5. Particle size measurement

Particle size distributions were recorded on a Malvern Mastersizer 2000 (Malvern, UK) equipped with a Scirocco 2000 dry powder feeder. A vacuum feed was used to both disperse and remove the analysed particles.

2.6. Atomic force microscopy

AFM Young's modulus and hardness measurements were performed on a MultiMode AFM with a NanoScope IIIa controller (Veeco, CA, USA). Surface energy measurements were performed on an EnviroScope AFM with a NanoScope IV controller (Veeco) equipped with humidity control (Triton Technology, UK).

The spring constants of the probes for Young's modulus and surface energy were calibrated prior to use using the method outlined by Sader et al. (1995). The accuracy of this method is taken to be between 5% and 10% (Burnham et al., 2003) which is considered the most significant source of error in the AFM measurements, although here Young's modulus and surface energy measurements were performed with multiple cantilevers to minimise this influence. As such we consider the spread of results from any one experiment to be representative of the true surface variability (Roberts, 2005).

Young's modulus measurements were performed using TESPD probes (Veeco) and followed the methodology previously described by Perkins et al., 2007. Force curves were taken on the surfaces of individual particles in a 5 × 5 array with 500 nm lateral spacing and a maximum loading of 200 nN. This was repeated for at least 10 particles of each polymorphic form. Force curves that showed poor contact or evidence of the probe slipping were disregarded.

Surface energy measurements were performed using FESP probes (Veeco) and followed the methodology previously described