Effect of crystal habits on the surface energy and cohesion of crystalline powders

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A B S T R A C T

The role of surface properties, influenced by particle processing, in particle–particle interactions (powder cohesion) is investigated in this study. Wetting behaviour of mefenamic acid was found to be anisotropic by sessile drop contact angle measurements on macroscopic (>1 cm) single crystals, with variations in contact angle of water from 56.3° to 92.0°. This is attributed to variations in surface chemical functionality at specific facets, and confirmed using X-ray photoelectron spectroscopy (XPS). Using a finite dilution inverse gas chromatography (FD-IGC) approach, the surface energy heterogeneity of powders was determined. The surface energy profile of different mefenamic acid crystal habits was directly related to the relative exposure of different crystal facets. Cohesion, determined by a uniaxial compression test, was also found to relate to surface energy of the powders. By employing a surface modification (silanisation) approach, the contribution from crystal shape from surface area and surface energy was decoupled. By "normalising" contribution from surface energy and surface area, needle shaped crystals were found to be ∼2.5× more cohesive compared to elongated plates or hexagonal cuboid shapes crystals.

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1. Introduction

The role of the physicochemical properties of particulate pharmaceutical materials on their cohesion and powder flow properties has attracted extensive research interest in the past four decades (Feng et al., 2007; Kaerger et al., 2004; Lam and Nakagawa, 1994; Podczeck and Mia, 1996; Podczeck and Révész, 1993; Ridgway and Morland, 1977). Understanding the role of physicochemical properties on cohesion and the development of strategies to control cohesion by tailoring the properties of pharmaceutical materials may be critically important for efficient and cost effective processing (Hou and Sun, 2008). The effect of particle shape and size on powder flow and cohesion is referred extensively in the literature (Jones et al., 2003). Moreland and Ridgway were the first to report the effect of particle shape on bulk density (Ridgway and Morland, 1977). Podczeck and Mia reported the effect of particle size and shape on the Hausner ratio and angle of internal friction (Podczeck and Mia, 1996). They found particles with higher aspect ratio (needle shaped crystal), showed a higher angle of internal friction. Kaerger et al. investigated the effect of particle shape and size on flow and compaction behaviour of blends, reporting that blends containing spherical paracetamol particles (prepared using crystallisation by sonication) with microcrystalline cellulose had improved flow properties compared to micronised particles (Kaerger et al., 2004). Gamble et al. investigated the effect of different sub-populations e.g. agglomerates and primary particles, highlighting the effect of the presence of agglomerates in enhancing the flow properties of bulk primary particles (Gamble et al., 2011). Di Martino et al. studied the effect of different crystal shapes of ibuprofen on compression and flow properties, highlighting improved densification of the smooth coin type crystal habit compared to other crystals habits, which were attributed to the increase in powder bed porosity.

Crystals of the same polymorphic form with different crystal shapes (habits) can be obtained by varying the relative growth rates of the different crystals facets. This in turn can be dependent

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on material intrinsic properties or be affected by properties of the crystallisation solvent, crystal growth inhibitors or additives (Berkovitch-Yellin, 1985; Bourne and Davey, 1976; Lovette et al., 2008). Crystal habits not only determine the main bulk properties of the crystalline material (e.g. bulk density, flowability and mechanical strength) but also alter the surface energy (Ho et al., 2012).

Surface energy of crystalline pharmaceutical materials has been shown to be anisotropic (Heng et al., 2006a, 2007; Ho et al., 2008, 2010). Facet specific surface energy of organic crystalline material was directly correlated with the chemical functional groups exposed on the crystal facet surfaces using contact angle and X-ray photoelectron spectroscopy (XPS) measurements. Considering the facet specific surface energy of a crystalline material, it is postulated that surface energetics of the crystalline powders depend on the relative surface energy contributions of the different crystal facets. Using D-mannitol as a model system, Ho et al. demonstrated that decreasing the aspect ratio of needle shaped crystals resulted in a decreasing shift in the overall contribution of the dispersive component of the surface energy. This was attributed to the increasing contribution of the facet showing lowest dispersive component of surface energy (facet (0 1 1)) (Ho et al., 2012). The ability to tailor crystal habits will result in the change in the relative contribution of different crystal facets. This change will result in a dissimilar surface energy of the crystalline powders, which may have an impact on powder cohesion.

Although it is well known that particle–particle interactions, e.g. cohesion/adhesion, are governed by the surface, the effect of crystal shapes on powder flow properties have not considered the impact of the anisotropic surface properties of the crystals. Considering that particle shape, surface energy and surface area can influence flow properties, it is essential to understand the contribution of each of these factors.

This study aims to firstly study the effect of crystal habit on surface energy and cohesion of crystalline pharmaceutical powders. Secondly, an approach to decouple the contributions of surface energy and particle shape is presented. Mefenamic Acid, a non-steroidal, anti-inflammatory drug, is used as a model compound. Macroscopic single crystals of mefenamic acid are grown and used for determining facet specific surface energies. This is then correlated to the surface energy heterogeneity measurements of crystalline powders of mefenamic acid crystallised in different crystal habits. Cohesion values of different shape mefenamic crystal were measured using a uniaxial compression test. Results were correlated with surface energy and crystal shape to elucidate their respective effect on cohesion. Further, the effect of surface energy on cohesion was "normalised" with silanisation of mefenamic acid, allowing de-coupling the contribution of crystal shape on cohesion from that of surface energy and surface area.

2. Materials

Mefenamic acid (2-(2, 3-dimethylphenyl) amino benzoic acid) (99.0% Sigma–Aldrich, Dorset, UK), acetone (>99.5%) and methanol (>99.5%) were obtained from VWR BDH Prolabo, Lutterworth, UK and used for growth of a macroscopic single crystal of mefenamic acid. Toluene (>99.5%), diethyl ether (>99.5%), ethyl acetate (>99.5%), dichloromethane (>99.0%), acetone (>99.5%), isopropyl alcohol (>99.5%) and methanol (>99.5%) were all received from VWR BDH Prolabo, Lutterworth, UK and used without further purification for crystallisation of different crystal habits of mefenamic acid. Deionised water, ethylene glycol (>99.0%, Sigma Aldrich, Dorset, UK), formamide (>99.5%, Acros Organics, Loughborough, UK) and diiodomethane (>99.0%, Acros Organics,

Loughborough, UK) were used as probe liquids for contact angle measurements. n-hexane (>99.0%), ethyl acetate (>99.5%) and dichloromethane (>99.5%) were obtained from VWR BDH Prolabo, Lutterworth, UK), whereas n-heptane (≥99.0), n-octane (≥99.0%), n-nonane (≥99.0%) and n-decane (≥99.0%) were obtained from Sigma–Aldrich, Dorset, UK and used without further purification as probe liquids in inverse phase gas chromatography.

3. Methods

3.1. Growth of mefenamic acid macroscopic single crystal

Mefenamic acid seed crystals of a few millimetres in size were obtained from slow evaporation of a supersaturated solution of mefenamic acid in acetone or methanol at room temperature. Macroscopic single crystals were obtained by slow solvent evaporation from saturated methanol solution at room temperature. A saturated solution of mefenamic acid in methanol was prepared under constant stirring. A single seed of mefenamic acid crystal was tied with an aramid fibre and suspended in the saturated solution, which is kept without stirring. Slow evaporation of the solvent was maintained resulting in the crystal growth. The saturated solution of mefenamic acid in methanol was periodically changed. Macroscopic single crystals of mefenamic acid obtained were dried under ambient conditions and used for further characterisation and contact angle measurements.

3.2. Crystallisation of mefenamic acid from different solvent systems

Saturated solutions of mefenamic acid in seven different organic solvents with varying polarity were prepared at 50 °C. A single step cooling profile was adopted. Saturated solutions of mefenamic acid at 50 °C were transferred to an incubator (Surface Measurement Systems Ltd. London, UK) maintained at 4 °C. Mefenamic acid crystals obtained after 24 h were filtered through general-purpose laboratory filter paper (Whatman, UK) and dried under ambient conditions. Dried crystals were stored in the glass container and used for further characterisation.

3.3. Silanisation of mefenamic acid powders

Recrystallised mefenamic acid powders were silanised using a protocol reported in the literature (Al-Chalabi et al., 1990). In a typical process, 500 mg of mefenamic acid powder was added to a 50 mL 5% (v/v) solution of dichlorodimethylsilane in cyclohexane. The mixture was refluxed at 80 °C for 24 h. Then, the reaction mixture is allowed to cool down to room temperature and filtered using general-purpose laboratory filter paper (Whatman, UK) followed by drying in a vacuum oven at 80 °C for 4 h. Post silanisation, the silanised mefenamic acid powders were stored in a glass vial at ambient conditions.

3.4. Single crystal X-ray diffraction for crystal facet indexing

The indexing of the crystal faces was performed using an Oxford Diffraction Xcalibur 3 E diffractometer (Agilent Technologies, Oxford, UK) equipped with ceramic XRD C-tech tube and Oxford Diffraction Sapphire detector. Single crystal X-ray diffraction data was obtained at 50 kV and 40 mA. Based on the single crystal X-ray diffraction data crystal facets were indexed using Agilent CrysAlisPro (Agilent Technologies, Oxford, UK) software system.

3.5. Contact angle measurements of a macroscopic single crystal

A Krüss Drop Shape Analyser DSA 10 (Krüss GmbH, Hamburg, Germany) was used for the static sessile drop contact angle