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Decoupling the contribution of dispersive and acid-base components of surface energy on the cohesion of pharmaceutical powders

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ABSTRACT

This study reports an experimental approach to determine the contribution from two different components of surface energy on cohesion. A method to tailor the surface chemistry of mefenamic acid via silanization is established and the role of surface energy on cohesion is investigated. Silanization was used as a method to functionalize mefenamic acid surfaces with four different functional end groups resulting in an ascending order of the dispersive component of surface energy. Furthermore, four haloalkane functional end groups were grafted on to the surface of mefenamic acid, resulting in varying levels of acid-base component of surface energy, while maintaining constant dispersive component of surface energy. A proportional increase in cohesion was observed with increases in both dispersive as well as acid-base components of surface energy. Contributions from dispersive and acid-base surface energy on cohesion were determined using an iterative approach. Due to the contribution from acid-base surface energy, cohesion was found to increase ~11.7× compared to the contribution from dispersive surface energy. Here, we provide an approach to deconvolute the contribution from two different components of surface energy on cohesion, which has the potential of predicting powder flow behavior and ultimately controlling powder cohesion.

1. Introduction

Inter-particle interaction is argued to be governed by the material surface properties. Mechanisms for inter-particle interaction can be classified as two broad categories, physical and chemical interactions. Chemical interactions involves mainly covalent, ionic, metallic or electrostatic bonds, whereas physical interactions are a result of intermolecular forces, for example van der Waals and hydrogen bonding (Kendall, 1994). In addition to chemical and physical interactions, mechanical interlocking and diffusion are other two mechanisms widely discussed in the literature (Maeda et al., 2002). In industrial particle processing, instantaneous formation of menisci in capillaries between adhered particles is unavoidable and in such scenarios capillary forces of adhesion and inter-particle contact area becomes increasingly important (Rabinovich et al., 2002). For the purpose of this study, the discussion is focused on different intermolecular forces based on inter-particle interaction mechanisms. Furthermore, the analysis is limited to the surface energetic heterogeneity/homogeneity not taking into consideration role of any structural or compositional heterogeneity.

In the current literature, focusing on the cohesion of pharmaceutical materials, a number of reports have considered the role of surface energy on cohesion and powder flow properties (Barra et al., 1996, 1998; Bhandari and Howes, 2005; Chen et al., 2010; Deng and Davé, 2013; Han et al., 2013; Jallo et al., 2011; Kilbury et al., 2012; Moreno-Atanasio et al., 2005; Spillmann et al., 2008; Traini et al., 2005; Young et al., 2003, 2004). Barra et al. investigated the effect of the surface energy and cohesion parameters proposed by Wu (Wu, 1973) and Rowe (Rowe, 1989a,b) to predict the maximum value of interaction parameters or strength of interaction between particles of binary mixture. Furthermore they also studied the influence of polar and dispersive fractions of two interacting materials on prediction (Barra et al., 1996; Barra et al., 1998). Moreno-Atanasio et al. used distinct

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element method (DEM) to simulate the effect of surface energy on unconfined yield stress (UYS), revealing that an increase in surface energy by an order of magnitude produced similar increase in simulated UYS (Moreno-Atanasio et al., 2005). Traini et al. used atomic force microscopy as a tool to investigate adhesion–cohesion balance in pressurized metered dose inhalers, demonstrating a linear correlation between theoretical work of cohesion/adhesion calculated from contact angle, inverse phase gas chromatography and atomic force microscopy measurements (Traini et al., 2005). Chen et al. and Jallo et al. used surface modification, either using silanization of aluminum particles or using dry-coating method to coat surface using silica particles, to reduce cohesion. Reduction in cohesion was attributed to the reduction in surface energy; silanization of aluminium was found to result in a reduction of the surface energy, and subsequently measured cohesion values of silanized aluminum were observed to be lower, compared to unsilanized aluminum (Chen et al., 2010; Jallo et al., 2011). On the basis of the findings of Chen et al., Han et al. investigated effect of dry coating on passivating the high energy sites of micronized ibuprofen for improving flowability recently. Surface energy heterogeneity was observed to reduce as a result of dry-coating and the surface energy follows a descending trend with increasing coating resulting in reduction in cohesion (Han et al., 2013).

It is apparent from the current literature that surface energy has a major role to play in controlling cohesion. However, whilst recent literature reports have suggested that a higher surface energy may result in higher cohesion and suggested routes to passivate higher surface energy sites, no fundamental understanding on the contribution from surface energy on cohesion compared to other surface attributes have been reported. Recently methodology for de-coupling roles of different surface properties, particularly, particle shape, surface area and surface energy has been established (Shah et al., 2014a,b). Considering that different components of surface energy can contribute towards cohesion on the basis of contribution from intermolecular forces, this study focuses on developing an approach for de-coupling the contribution from dispersive and acid-base component of surface energy on cohesion.

2. Materials

Mefenamic acid (2-(2,3-dimethylphenyl) amino benzoic acid) (99.0%), *n*-heptane (≥99.0%), *n*-octane (≥99.0%), *n*-nonane (≥99.0%), *n*-decane (≥99.0%), dichlorodimethylsilane (>99.5%,), dodecyl triethoxysilane (technical grade), vinyltrimethoxysilane (>97.0%), triethoxyphenylsilane (>98.0%), (3-iodopropyl) trimethoxysilane (≥95.0%), (3-bromopropyl) trimethoxysilane (≥97.0%) and trimethoxy(3,3,3-trifluoropropyl) silane (≥97.0%) were purchased from Sigma Aldrich, Dorset, UK. Methanol (>99.5%), ethyl acetate (>99.5%), dichloromethane (>99.0%), *n*-hexane (>99.0%), and cyclohexane (>99.0%) were received from VWR BDH Prolabo, Lutterworth, UK and (3-chloropropyl) trichlorosilane (>97.0%) was received from Alfa Aesar, Heysham, UK. All chemicals were used as received.

3. Methods

3.1. Silanization of milled mefenamic acid

Milled mefenamic acid powders were silanized 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 appropriate silane 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 silanization, the silanized mefenamic acid powders were stored in a glass vial at ambient conditions.

3.2. Surface energy analysis

Surface energy analyzer (SEA, Surface Measurement Systems Ltd., London, UK) was used for surface energy heterogeneity characterization. Approximately 300 mg of mefenamic acid was packed in pre-silanized iGC columns (Surface Measurement Systems Ltd., London, UK) and conditioned for 2 h at 30 °C followed by pulse injection measurements. Methane was used to determine the column dead time. Helium at a flow rate of 10 sccm was used as a carrier gas for all injections for the columns packed with un-silanized mefenamic acid, whereas 3 sccm helium flow rate was used for columns packed with silanized mefenamic acid. A series of dispersive *n*-alkane probes (hexane, heptane, octane, nonane and decane) at a range of concentrations were injected in order to achieve target surface coverages (n/n_m) ranging from 0.7% to 10%. Net retention volumes were calculated using the commonly applied Schultz method (Schultz et al., 1987). Mono-polar probes (dichloromethane and ethyl acetate) were injected at the same concentrations to determine non-dispersive interactions. The surface energy due to the non-dispersive interactions was calculated using the vOCG method reported in the literature (Das et al., 2010; Van Oss et al., 1988). Principles of the techniques

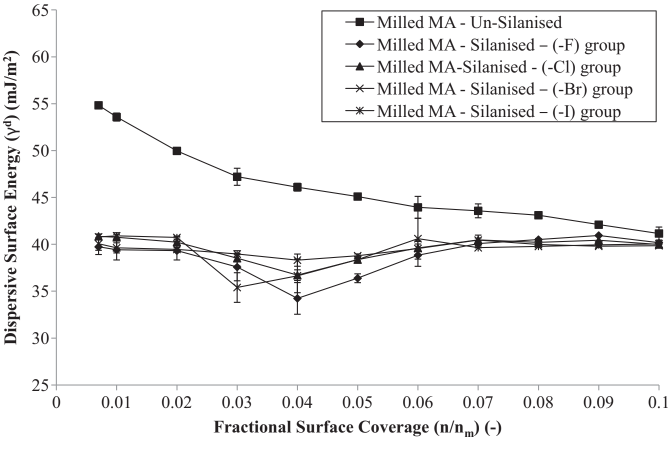

Fig. 1. γ^d profiles for milled mefenamic acid silanized with −F, −Cl, −Br, and −I functional end groups.

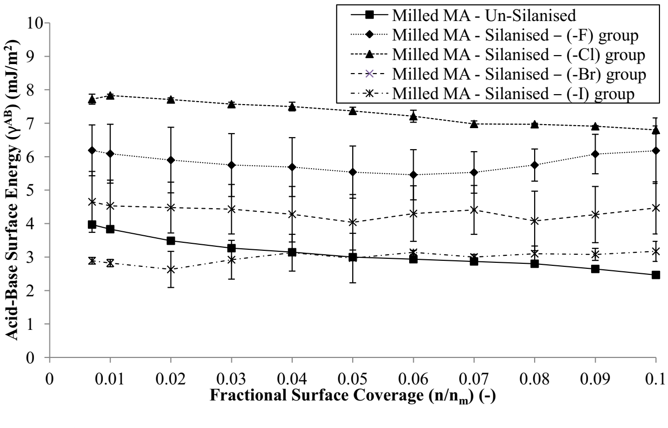

Fig. 2. γ^{AB} profiles for milled mefenamic acid silanized with −F, −Cl, −Br, and −I functional end groups.