



Surface energy changes and their relationship with the dispersibility of salmeterol xinafoate powders for inhalation after storage at high RH

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ABSTRACT

This study investigated the relationship between surface energy of micronized lactose, coarse lactose and salmeterol xinafoate and dispersibility from a mixture after storage at 75% RH. Surface energies, dispersibility, morphology, and the presence of amorphous domains were determined by inverse gas chromatography, twin stage impinger, scanning electron microscope and dynamic vapour sorption, respectively. The fine particle fraction of mixture decreased significantly in 4 weeks ($P < 0.05$), reaching a static level in 3 months. Amorphous content was not detected in the micronized lactose, coarse lactose and salmeterol xinafoate. After conditioning stored samples at 75% RH for 2 h, dispersive surface energy of both micronized and coarse lactose significantly decreased ($P < 0.05$), while the polar surface energy of all significantly increased ($P < 0.05$) resulting in significant increase in total surface energy after storage. After conditioning stored samples at 0% RH for 2 h, no significant difference was observed in any surface energy parameter. This study concluded that the total surface energy increased during storage at high RH due to the adhered surface moisture. The mechanism of decreased dispersibility was related to increased capillary/solid bridging interactions and to possible increased interaction of contiguous particles due to increased polar surface energy.

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1. Introduction

The ideal goals in the development of powders for inhalation are high efficiency, low variability and aerosol dispersibility stability during the shelf-life of the product. Dispersibility is affected by storage RH, and this issue has been a subject of research (Braun et al., 1996; Hindle and Makinen, 1996; Johnson et al., 1996; Geuns et al., 1997; Mackin et al., 1997; Maggi et al., 1999; Harjunen et al., 2003; Young et al., 2003a, 2007; Young and Price, 2004; Lida et al., 2004; Borgstrom et al., 2005; Zeng et al., 2007; Glaab et al., 2008). In general, storage at high relative humidity adversely affected dispersibility. However, these studies did not relate dispersibility to fundamental interparticulate interactions which are important factors in changing dispersibility upon storage. Separation energies or adhesion forces at different relative humidities were measured by Young et al. (2006) using atomic force microscopy (AFM) and by Zhu et al. (2008) using an annular ring shear tester to relate them to dispersibility. Several other studies measured adhesion forces or separation energies at different

RHs for materials commonly used in dry powder inhaler formulations either using a centrifuge technique (Podczeck et al., 1996, 1997) or using AFM (Berard et al., 2002a,b; Price et al., 2002; Young et al., 2003b, 2004), although their relationship with dispersibility was not reported.

A relationship between dispersibility and surface energy (γ) should be expected as the interparticulate interactions are influenced by the individual surface energies of the components (Mukhopadhyay and Schreiber, 1995). The interparticulate interactions or adhesion force (F_{ad}) between particles in a vacuum can be calculated using either the Johnson–Kendall–Roberts (JKR) model (Eq. (1)) (Johnson et al., 1971) or the Derjaguin–Muller–Toporov (DMT) model (Derjaguin et al., 1975) (Eq. (2)) from the surface energy:

$$F_{ad} = \frac{3}{2} \gamma \Pi r \quad (1)$$

$$F_{ad} = 2\gamma \Pi r \quad (2)$$

where r is the radius of the particles. Both models are applicable based on interacting material properties and their geometries. The JKR model is best suited to large particles having high surface energy and low elastic moduli while the DMT model is best fit for small particles having low surface energies and high elastic

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moduli. Thus, the adhesion or interparticulate forces are directly proportional to surface energy.

The surface free energy or surface energy (γ) is defined as the energy per unit area of surface. Materials may have both non-polar forces, van der Waals' forces and polar forces such as, acid–base interaction forces or hydrogen bonding (Fowkes, 1964, 1983; Grimsey et al., 2002). The total surface energy (γ) is the additive result of the dispersive (γ^D) and polar contributions (γ^P) (Fowkes, 1964, 1983; Van Oss et al., 1988; Traini et al., 2006):

$$\gamma = \gamma^D + \gamma^P \quad (3)$$

Surface energy can be easily measured using inverse gas chromatography (IGC). IGC is regarded as a fast, accurate and non-destructive method for surface energy measurement (Voelkel, 2004). IGC can measure surface adsorption below monolayer coverage (Ticehurst et al., 1996) which is very important because the first adsorbing layer controls processes like surface wetting (Brunauer et al., 1938). The relationship between dispersibility and surface energy using IGC was investigated in a number of studies mentioned in the following: a negative correlation was observed between aerosol dispersibility (expressed as fine particle fraction, FPF or fine particle dose, FPD or emitted dose, ED) and dispersive surface energy. This correlation was observed with the following materials: micronized and SEDS salbutamol sulphate (SS) and salmeterol xinafoate (SX) (Feeley et al., 2000), R-PLGA (rifampicin loaded poly(lactide-co-glycolide) microparticles) from mixtures with lactose and maltodextrin (Sethuraman and Hickey, 2002), micronized and SEDS budesonide or albuterol from blends with Pharmatose 325M (Schivone et al., 2004), a drug in development (IFNa-2b) (Ronggao et al., 2005) and three SX samples (micronized SX, SX-I and SX-II) (Tong et al., 2006). All the above studies mainly attempted to relate dispersive surface energy with dispersibility. However, dispersive surface energy is only one surface energy component. Some studies have addressed the relationship between dispersibility and both dispersive and specific or total surface energy components. For example, Thielmann et al. (2006) showed that the FPF of binary mixtures containing salbutamol sulphate with lactoses (α -lactose monohydrate, β -lactose, β -lactose purified and α -lactose anhydrous) decreased with increasing dispersive surface energy or specific surface energy or work of adhesion/cohesion ratio. Saleem et al. (2008) reported a negative correlation between dispersive surface energy or acid–base parameters of carrier lactose (spray dried and milled lactose) and FPD using budesonide or fluorescein. Recently, Traini et al. (2008) have reported an inverse relationship between FPF of salbutamol sulphate from mixtures with four lactose pseudopolymorphs (α -anhydrous, α -monohydrate, β -anhydrous and β -treated) and the surface energies (both dispersive and total) of the lactoses. Bernhard and Steckel (2005) also found a correlation between surface energy and FPF, but was not as distinct as they had expected. On the other hand, a positive correlation was found by other researchers (Cline and Dalby, 2002). However, dispersibility of powders is a complex process and will be dependent not only on surface energy of interacting materials when particles are in contact, but will also be influenced by other factors such as packing fraction (Kendall and Stainton, 2001; Adi et al., 2006) which will depend on particle size, particle size distributions and roughness (Sohn and Moreland, 1967; Brouwers, 2006). Therefore, it is important to understand all other contributing factors to realize the effect of surface energy on dispersibility.

A variation in humidity can affect the surface energy of a powder. The dispersive surface energy has been shown to either decrease or remain unchanged with an increase in RH. A decrease in dispersive surface energy with increasing RH was observed for cellulose (Sooben et al., 2000), amorphous lactose and milled

lactose (Newell et al., 2001), clays (Balard et al., 1997), tolbutamide though it remained constant for acetaminophen and carbamazepine (Sunkersett et al., 2001). No change in net retention volume was observed for four α -lactose monohydrate samples (Ticehurst et al., 1996). There does not seem to be a general relationship between specific surface energy and RH. For example, Sunkersett et al. (2001) did not find a significant change in the specific surface energy of carbamazepine though they observed a decrease in interactions of acetaminophen with acetone and THF with increasing humidity. In another study, Ticehurst et al. (1996) found that the net retention volume of polar probe (the retention volume of the probe minus the retention volume for a non-interacting probe) for four α -lactose monohydrate samples decreased in presence of moisture. Thus, surface energy (dispersive and polar) can change during storage at high RH.

Hence the purpose of this current study was to investigate the surface energy changes and their relationship with aerosol dispersibility during storage at high RH. Specifically, the authors' focus was on the use of IGC to determine the surface energy changes (dispersive, specific and total) of salmeterol xinafoate, micronized lactose and coarse lactose immediately before storage and after storage at high relative humidity. Furthermore, the authors examined how the aerosol dispersibility changes related to the surface energy of those materials.

2. Materials and methods

2.1. Materials

Inhalation grade micronized salmeterol xinafoate (SX) was generously supplied by GlaxoSmithkline (Victoria, Australia). Inhalac[®] 120 (Meggler AG, Wasserburg, Germany) and its micronized form produced by micronization using a fluid energy mill (K-tron Soder, NJ, USA) were used as coarse lactose (CL) and micronized lactose (ML), respectively. High performance liquid chromatography (HPLC grade), methanol (CH₃OH, Merck KGaA, Darmstadt, Germany), milli-Q grade water (Millipore Corporation, Melsheim, France) and ammonium acetate (BDH Laboratories, Victoria, Australia) were used in HPLC analysis. Sodium chloride (BDH Laboratories, Victoria, Australia) was used to generate 75% RH conditions. Nitrogen (Linde Gas Pty Ltd., NSW, Australia) was used for dynamic vapour sorption analysis. GC grade undecane, decane, nonane, octane, heptane, dichloromethane and ethyl acetate (all from Sigma–Aldrich GmbH, Steinheim, Germany); methane (Linde Gas Pty Ltd., NSW, Australia) and helium (Core Gas Pty Ltd., NSW, Australia) were used in the IGC experiments.

2.2. Methods

2.2.1. Preparation of powder formulations

A SX (2.5%)–CL mixture containing 20% micronized lactose (M20F) (batch size, 5 g) was prepared according to a previously validated mixing method (Alway et al., 1996; Liu and Stewart, 1998). The micronized SX and ML were placed between equal amounts of CL in a test tube (10 cm long and 3 cm inner diameter). Powder occupied around 25% of the test tube volume. Three ceramic beads (approximately 10 mm diameter) were placed inside, the test tube was stoppered and inverted several times to prevent the drug from sticking to the sides of the test tube. The test tube was then shaken vigorously for 5 min by hand. The ceramic beads provided a ball-milling effect to break up agglomerates.

2.2.2. Homogeneity of powder mixtures

Twenty samples (20 ± 0.5 mg each), accurately weighed using an analytical balance (Mettler AT 261 Deltarange, Greifensee-

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