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The Influence of Lactose Pseudopolymorphic Form on Salbutamol Sulfate–Lactose Interactions in DPI Formulations

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A series of 63- to 90-μm sieve-fractioned lactose pseudopolymorphs were investigated in terms of carrier functionality for dry powder inhaler (DPI) formulations. Stable α-anhydrous, α-monohydrate, and β-anhydrous were chosen as model pseudopolymorphs. In addition, the β-anhydrous was further purified to remove residual α-monohydrate content (β-treated). The carriers were investigated in terms of morphology, particle size, crystallinity, and surface energy using inverse gas chromatography. Furthermore, the lactose samples carrier performance was evaluated by studying the aerosolization efficiency of the model drug, micronized salbutamol sulfate, from drug–carrier blends using a next generation impactor (NGI). In general, the aerosol performance of drug from carrier followed the rank order α-monohydrate>β-anhydrous>β-treated>α-anhydrous. Significant difference in carrier size was observed, specifically with relation to the amount of fines (where a rank order of β-treated>β-anhydrous>α-monohydrate>α-anhydrous. No direct relationship between fine content and particle morphology was observed. In comparison, an inverse relationship between surface energy and aerosolization efficiency was found, where a plot of fine particle fraction (aerodynamic diameter < 4.46μm) against total surface energy resulted in R^2 = .977. Such observations are most likely due to increased particle carrier adhesion and reduced drug liberation during the aerosolization process, indicating surface chemistry (in this case due to the existence of different pseudopolymorphs) to play a dominating role in DPI systems.

Keywords lactose; polymorph; IGC; in vitro; DPI; dry powder inhaler

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INTRODUCTION

Polymorphism of pharmaceutical drugs and excipients, defined as the ability to crystallize in different crystalline structures, is a long-term problem in the pharmaceutical industry with implications that extend to formulation, therapy, and patenting. The concept of polymorphism was first introduced by Klaproth in 1788, when two different forms of calcium carbonate (defined as calcite and aragonite) were identified (Haleblian & Mccrone, 1969). In simple terms, polymorphs of the same compound have different unit cell arrangements, which subsequently give rise to differing lattice energies and thus different thermodynamic, spectroscopic, surface, and mechanical properties such as solubility, melting point, hardness, density, crystal shape, and vapor pressure (Brittain, 1999; Haleblian & Mccrone, 1969). Subsequently, the investigation and control of structural properties of a crystalline material is a crucial aspect in the development process of drugs, excipients, and pharmaceutical formulations.

Because the formation of a polymorph is dependent on the free association of molecules in a solvent, it is not surprising that a very large number of pharmaceuticals exhibit the phenomenon of polymorphism. In general, 70% of barbiturates, 60% of sulfonamides, and 23% of steroids are estimated to exist in different polymorphic forms (Haleblian, 1975). When left uncontrolled, variation in polymorphism of a particular crystalline material may contribute to a significant variability in the product characteristics (Miller, Raw, & Yu, 2006). For pharmaceutical materials, the regulatory authorities have already recognized the need to limit polymorphic impurities since the presence of differing crystal phases in a formulation can accelerate the conversion process, leading to different polymorphs with unwanted physical and chemical properties. Excipients are ubiquitous in pharmaceutical formulations and are required, for example, as diluents, flow aids, or to improve compactability. Clearly, as with drug molecules, the variation in particular excipients functionality will be dependent on the solid

form used. For example, lactose (Edge, Kibbe, & Kussendrager, 2006a, 2006b), one of the most common excipients used in pharmaceutical formulation, exists in multiple crystalline forms: α-lactose monohydrate (Beevers & Hansen, 1971; Fries, Rao, & Sundaral, 1971), anhydrous β-lactose (Buma & Wiegers, 1967; Hirotsu & Shimada, 1974), stable and unstable anhydrous α-lactose (Platteau, Lefebvre, Affouard, & Derollez, 2004; Platteau et al., 2005), and anhydrous crystals with α and β lactose in molar of ratios of 5:3 and 4:1 (Bushill, Wright, Fuller, & Bell, 1965; Jouppila, Kansikas, & Roos, 1998; Lefebvre et al., 2005; Simpson, Parrish, & Nelson, 1982). Although lactose cannot be considered as a classical polymorph the existence of different stereoisomers and the monohydrate (pseudopolymorphism) could have similar implications as discussed for polymorphs above.

In terms of excipient suitability, β-anhydrous lactose has low moisture content and is widely used for direct compression tableting as well as a capsule filler. Commercial β-anhydrous lactose usually contains a percentage of α-anhydrous lactose (of the order 20–30%) (Edge et al., 2006a). In comparison, the α-lactose monohydrate is most typically used as binding agent, wet granulation, and as a diluent and flow aid in dry powder inhaler (DPI) formulations.

Arguably, the greatest effect of varying forms of excipient on formulation performance will occur when using low-dose active pharmaceutical ingredients and/or where physical interactions between the drug and excipient are critical to the formulation performance. Conventional dry powder inhaler (DPI) formulations, that use large crystalline excipients as carriers, fall within this category. To achieve local delivery of a DPI therapeutic agent to the respiratory tract, the drug particles are engineered to have a size less than 6 μm (to avoid impaction and deposition in the upper thoracic region) (Pritchard, 2001). Subsequently, these drug particles have a high surface area to mass ratio and are highly cohesive/adhesive. Furthermore, the dose regime of such molecules is generally less than 400 μg/dose, making accurate metering difficult. Subsequently, the drug molecules are blended with larger lactose carrier material, to act as a diluent and aid metering. However, it is critical that the adhesion forces between the drug and carrier are overcome during inhalation to allow drug liberation and respiratory penetration. Clearly, variations in anomeric composition and hydration may have a significant impact on the relative adhesion between the contiguous surfaces and directly influence performance.

Although previous studies have investigated the influence of carrier material (Steckel & Bolzen, 2004; Traini, Young, Jones, Edge, & Price, 2006) and lactose morphology (Hickey, 2005; Kawashima, Serigano, Hino, Yamamoto, & Takeuchi, 1998; Louey, Mulvaney, & Stewart, 2001; Steckel, Markefka, teWierik, & Kammelar, 2004; Young et al., 2002; Zeng, Martin, Marriott, & Pritchard, 2001a, 2001b) on the aerosolization performance of blended drug material, little has been reported with regard to the lactose pseudopolymorph used (Larhrib, Zeng, Martin, Marriott, & Pritchard, 1999). Here, the effect of lactose form, α-lactose anhydrous (stable form), α-lactose monohydrate, and β-lactose, on the physicochemical properties, and aerosolization performance were investigated. Specifically, the relationship between surface energy, measured by inverse gas chromatography (IGC) and aerosolization efficiency is investigated.

MATERIALS AND METHODS

Materials

Micronized salbutamol sulfate (Avocado, Italy, UK), was chosen as the model drug, as it is commonly used in the commercial DPIs (Ventolin®, GSK). α-lactose monohydrate and β-lactose anhydrous were supplied by Mallinckrodt Baker (Phillipsburg, NJ, USA). All lactose samples were stored in sealed containers (at 0% relative humidity [RH]) over phosphorus pentoxide. α-lactose anhydrous was obtained by exposing α-lactose monohydrate to methanol vapor using methods reported previously (Platteau et al., 2005). The as supplied β-lactose anhydrous sample is reported as typically containing around 20–30% anhydrous α-lactose and was therefore further purified/treated by refluxing in hot methanol (Holsinger, 1999). Prior to analysis, the four lactose samples were sieved through a nest of sieves (Retsch, Düsseldorf, Germany) to produce a 63- to 90-μm fraction.

Unless otherwise stated, α-lactose anhydrous, α-lactose monohydrate, β-lactose anhydrous, and treated/purified β-lactose anhydrous shall hereafter be referred to as α-anhydrous, α-monohydrate, β-anhydrous, and β-treated, respectively.

Particle Size Analysis

Particle size distributions of the salbutamol sulfate and sieve-fractioned lactose pseudopolymorph samples were analyzed by laser diffraction (Malvern Mastersizer 2000, Worcestershire, UK). Approximately 200 mg of each lactose form or salbutamol sulfate was dispersed in about 10 mL of chloroform, sonicated for 5 min, and added dropwise into a small volume stirred sampling unit containing chloroform. Size distributions were based on 2,000 sweeps for each sample with an obscuration between 10 and 30%. Each sample was analysed in triplicate.

Optical Microscopy

Variation in particle shape was investigated optically using a microscope at 100× magnification (CX41 microscope with DP12 digital camera, Olympus, Tokyo, Japan). Particles were deposited on a microscope slide and dispersed in paraffin oil before a cover slip was added. Wide field images were collected and exported to Image-J software (www.NIH.gov).

Images were processed by threshold analysis to produce a particle length *L* and particle width *W*. The data were analyzed (n = 40 for each carrier), and the elongation ratio (L/W) calculated.

X-Ray Powder Diffraction

X-ray powder diffraction (XRPD) diffractograms for the different lactose samples were collected using Cu Kα radiation, on a Scintag XDS 2000 θ/θ diffractometer (Cupertino, CA, USA), equipped with liquid-nitrogen-cooled solid-state germanium detector. An angular range from 2° to 35° in 2θ was covered in steps of 0.03° at a scan speed of 1°/min. In addition, the β-anhydrous and treated samples were analysed at a lower scan speed to improve the signal-to-noise ratio and thereby increase the detectability of α-lactose monohydrate. The angular range covered was from 9.6° to 13.4° with a step size of 0.02° and a scan rate of 0.1°/min.

Inverse Gas Chromatography

The variation in the surface (free) energy of the lactose samples may affect the force of adhesion between drug and carrier and subsequent aerosolization efficiency. Inverse gas chromatography (IGC) is a powerful tool capable of measuring the surface free energy components of an "unknown" sample packed into a column (the stationary phase) by measuring the retention time of probes, with known energetic properties, as they pass through the column and interact with the sample in the gas (mobile phase) (Lloyd, Ward, & Schreiber, 1989; Thielmann, 2004).

The surface energy can be divided into a dispersive and specific contribution. In simple terms, the dispersive component of the solid surface energy (γ_s^d) may be calculated by measuring the retention time (volume) of a series of *n*-alkanes injected at an infinite dilution using the following relationship (Equation 1):

$$RT \ln V_N = 2N\sqrt{\gamma_s^d a}\sqrt{\gamma_l^d + c}, \quad (1)$$

where R is the gas constant, T the temperature, N the Avogadro number, a the projected surface area of the sample probe, (γ_l^d) the dispersive surface tension of the probe, and V_N the net volume of carrier gas required to elute the probe molecules from the column (corrected for column dead volume and compression factors). Subsequently, the dispersive surface energy of a sample (γ_l^d), may be determined from the slope of the straight line that is obtained by plotting the retention volume ($RT\ln V_N$) against $a\ (\gamma_l^d)^{0.5}$ (Schultz, Lavielle, & Martin, 1987). For the determination of the specific surface energy, various polar probes are injected. The distance between the position of each polar probe (in the same plot as mentioned above) and the alkane straight line is a direct measure for the specific Gibbs free energy (ΔG). To convert the specific free energy into a specific surface energy, an acid–base concept has to be applied. Usually IGC data are analyzed by using the Gutmann concept. However, the disadvantage of this theory is that the obtained numbers are dimensionless and cannot be directly correlated with the dispersive surface energy. For this reason the van Oss (1994) concept was used. Van Oss divides the specific surface energy into an acid (Lewis acceptor), γ_s^+ and base (Lewis donor), γ_s^- contribution. They can be directly obtained from the specific free energy (Equation 2).

$$\Delta G = N_A \times a \times 2 \times ((\gamma_l^+ \times \gamma_s^-)^{1/2} + (\gamma_l^- \times \gamma_s^+)^{1/2}). \quad (2)$$

If monopolar probes are used only two injections are required using one acidic γ_l^+ and basic γ_l^- component. With knowledge of the acid and basic parameters, the specific surface energy γ_s^{AB} may be calculated using Equation 3:

$$\gamma_s^{AB} = 2\sqrt{\gamma_s^+ \gamma_s^-}. \quad (3)$$

The total surface energy (γ_s^T) can then be obtained from the summation of the dispersive (γ_s^d) and specific contributions (γ_s^{AB}).

The surface energetics of each lactose sample was measured using a commercially available IGC system (IGC 2000, Surface Measurement Systems Ltd., London, UK). Approximately 1 g of sample was weighed into silanized IGC columns (300 mm × 3 mm i.d.), plugged with glass wool and tapped for 5 min using a tapping apparatus (Surface Measurement Systems Ltd., London, UK). Each column was purged with dry nitrogen (0% RH) at 318 K prior to measurement for 5 h. The retention time of dispersive probes (*n*-hexane, *n*-octane, *n*-nonane, and *n*-decane) and polar probes (ethyl acetate and chloroform) were measured at infinite dilution conditions using a flame ionization detector with a gas flow rate of 10 mL/min. Dead volume calculations were based on the elution time of methane.

Preparation of Salbutamol Sulfate–Lactose Blends

Formulations containing the different sieve-fractioned lactose samples and micronized salbutamol sulfate were prepared in a mortar by geometrical hand mixing in the ratio 67.5:1 (wt/wt) (excipient/drug). The subsequent blend was transferred into a glass vessel (25 cm^3) with the total sample mass being approximately one third of the vessel volume. The final blend was mixed in a Turbula (Bachofen, Basel, Switzerland) at 46 rpm for 30 min. Blends were stored d in tightly sealed containers with phosphorous pentoxide (0% RH) for a minimum of 24 h prior to analysis. Prior to the in vitro studies, blend content uniformity were investigated by analyzing twenty 33 ± 1.0 mg samples (n = 5) according to the

method described in Appendix XII H (Test B) of the British Pharmacopoeia (2004). Sample analysis was conducted using high-performance liquid chromatography (HPLC). Content uniformity for all blends gave a relative standard deviation of less than 5%.

Chemical Analysis of Salbutamol Sulfate

Quantification of salbutamol sulfate, in content uniformity or in vitro samples, was conducted by HPLC. The HPLC configuration was as follows: Waters 717+ autosampler, 600 pump, 486 detector, 600 controller with millennium software and NovaPak 3.9 mm × 150 mm C18 column (Waters Ltd., Sydney, Australia). Mobile phase used was 0.1% (wt/vol) sodium dodecyl sulfate in a 60:40 (vol/vol) ratio of methanol:water. Standards and samples were prepared in water. Standard linearity was obtained between 0.5 and 12.5 μg/mL (R^2 = .999) with a retention time of approximately 6 min.

In Vitro Analysis

The aerosolization efficiency of salbutamol sulfate from each of the salbutamol–lactose form capsule blends was investigated using Apparatus E, the NGI (Appendix XII F, British Pharmacopoeia). The specific configuration included eight sample collection cups, a preseparator, and United States Pharmacopoeia (USP) throat. All in vitro measurements were conducted at 60 L/min (obtained using a Rotary vein pump and solenoid valve timer), which was set using a calibrated flow meter. Prior to testing, the eight collection cups were coated with silicon oil to eliminate particle bounce and the NGI preseparator was accurately filled with 15 mL of water.

Samples of each blend (33 ± 3 mg) were accurately weighed into size 3 gelatine capsules (Capsugel, Sydney, Australia) and inserted into a Aerolozer® DPI device (Novartis, Sydney, Australia). The DPI was connected to a mouthpiece adapter, inserted into the NGI, and tested for 4 s at 60 L/min. After actuation, the device, capsule, throat, preseparator, and all sample stages were washed into separate volumetrics using water and adjusted to volume. The NGI was washed with methanol and air dried before reuse. Each lactose blend was tested in triplicate. Temperature and humidity throughout the testing were 25ºC and 45% RH. The drug deposition samples collected from each NGI experiment were analyzed by HPLC and processed to produce the following descriptors of drug aerosolization efficiency; loaded dose (LD) (drug recovered from the capsule, mouthpiece, throat, preseparator, NGI stages, and filter); emitted dose (ED) (as LD but omission of device and capsule); fine particle dose (FPD) (drug with an aerodynamic cutoff diameter <4.46 μm); fine particle fraction (FPF) (FPD/LD × 100).

RESULTS AND DISCUSSION

Particle Size Analysis

Particle size distributions for the 63- to 90-mm sieve fraction lactose pseudopolymorph and salbutamol sulfate are shown in Figure 1. From Figure 1 it appears all lactose samples to exhibit similar size profiles with the majority of particles being within the sieve classification range. It is interesting to note, however, that statistical analysis of the median particle size ($d_{0.5}$) and 10th percentile undersize ($d_{0.1}$) of the lactose samples indicated significant differences (ANOVA, $p < .05$). In general, the samples exhibited median diameters of 83.5 ± 2.1, 76.8 ± 0.6, 66.8 ± 1.6, and 56.8±1.6μm for α-anhydrous, α-monohydrate, β-anhydrous, and β-treated, respectively. Furthermore, analysis of the fine $d_{0.1}$ suggested 10% of the particles had a volumetric diameter less than 45.4 ± 6.4, 16.6 ± 1.4, 9.5 ± 0.7, and 5.7 ± 0.1μm for α-anhydrous, α-monohydrate, β-anhydrous, and β-treated, respectively. Such observations are important as recent studies have suggested the presence of fine carrier material are a dominating factor effecting aerosol performance (Islam, Stewart, Larson, & Hartley, 2004; Young et al., 2007). In comparison to the lactose samples, the particle size distribution of the salbutamol sulfate was indicative of a material that had been micronized. In general, the micronized sample had a $d_{0.5}$ of 1.39 ± 0.02 μm with 90% of the particles having a diameter less than 4.85 ± 0.06 μm, thus making the drug suitable for respiratory applications (Pritchard, 2001).

Optical Microscopy

Representative optical micrographs of α-anhydrous, α-monohydrate, β-anhydrous, and β-treated lactose samples are shown in Figure 2A, B, C, and D, respectively. In general, all lactose samples were of similar size, correlating well with

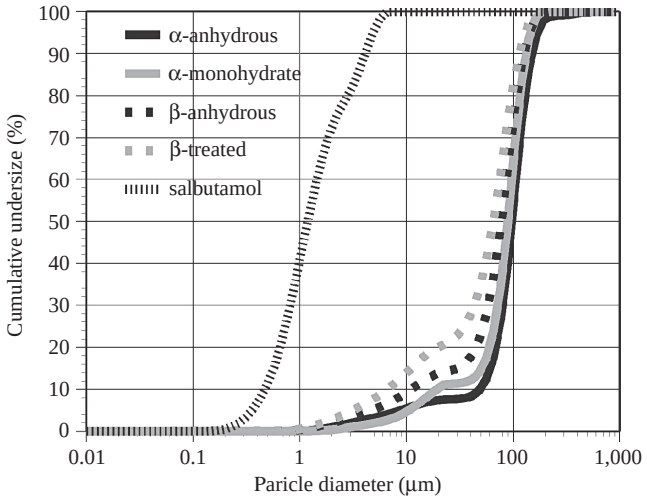

FIGURE 1. Particle size distributions of the sieve fractioned lactose samples and micronized salbutamol sulphate.

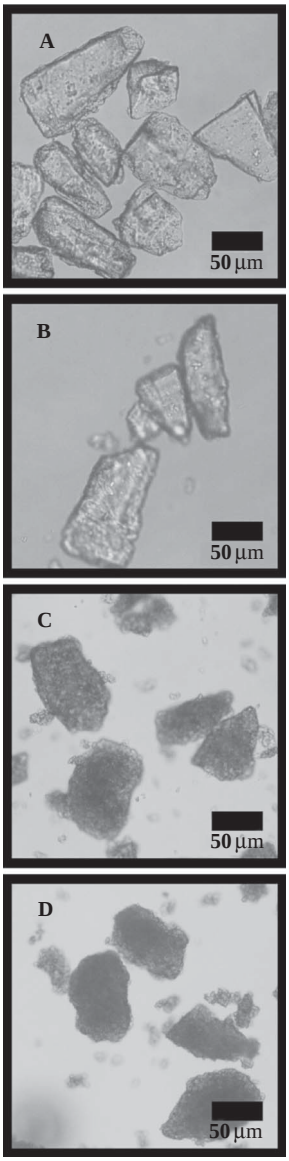

FIGURE 2. Optical micrographs of (A) α-anhydrous, (B) α-monohydrate, (C) β-anhydrous, and (D) β-treated lactose samples.

particle size data measured by laser diffraction, and exhibited irregular crystal morphology. Furthermore, the degree of fine material followed a similar rank order to that of the particle size data, with the β samples having a greater quantity of smaller particles. Particle shape has also been shown to influence the aerosolization performance of drug particles from drug–carrier blends (Zeng, Martin, Marriott, & Pritchard, 2000). Subsequently, the elongation ratio of each sample was calculated and compared. In general, analysis of $n = 40$ particles over five different fields of view, indicated elongation ratios of 1.6 ± 0.6, 1.7 ± 0.6, 1.6 ± 0.4, and 1.5 ± 0.3 for α-anhydrous, α-monohydrate, β-anhydrous, and β-treated lactose samples, respectively. Analysis of the elongation ratio indicated that there was no significant differences between samples (ANOVA, $p < .05$).

X-Ray Powder Diffraction

X-ray diffraction patterns for the α-anhydrous, α-monohydrate, and β-anhydrous lactose samples are shown in Figure 3A, B, and C, respectively. In general, the diffractograms were in good agreement with previously published data for each crystal modification (Kirk, Dann, & Blanchford, 2007). Analysis of the 2θ values for each crystal modification indicated characteristic angles of 9.0°, 12.6°, and 10.6° corresponding to α-anhydrous, α-monohydrate, and β-anhydrous lactose, respectively. Interestingly, the β-anhydrous sample had a small peak at 12.6° indicating the presence of α-monohydrate. Integration to give the α-monohydrate 12.6° peak area and comparison to the integrated area of the 10.6° β-anhydrous peak from slow scans of the β-anhydrous lactose (Figure 4A), suggested the α-monohydrate content to be equivalent to around 20% (wt/wt). This estimation is based on data from a set of calibration mixtures prepared from pure α-lactose monohydrate and β-lactose samples (K Jarring, personal communication, 2007). Such observations are in good correlation with that reported for commercially available β-anhydrous lactose (Edge et al. 2006a). Analysis of the β-treated sample showed a α-monohydrate content of approximately 5%, suggesting that the β-anhydrous sample had been purified to a reasonable extent. The diffraction pattern of this sample also indicated traces of α-anhydrous lactose.

Inverse Gas Chromatography

Analysis of the IGC data for the *n*-alkane series gave dispersive energy values of 46.2, 36.4, 40.3, and 42.5 mJ/m^2 for α-anhydrous, α-monohydrate, β anhydrous, and β-treated lactose, respectively. Similar trends were observed when calculating the specific surface energy components, γ_s^- and γ_s^+ where γ_s^- values of 83.0, 64.9, 74.0, and 77.7 mJ/m^2 and γ_s^+ values of 88.0, 27.4, 47.4, and 64.8 mJ/m^2 were observed for α-anhydrous, α-monohydrate, β-anhydrous, and β-treated lactose, respectively The dispersive as well as the specific surface energies for the β-treated lactose were higher than for β-anhydrous. However, it would be expected that a reduced α-anhydrous content would result in a lower total surface energy for β-treated, when comparing the rank orders of the lactose psuedopolymorphs. One possibility may be that the β-treated lactose is more thermodynamically unstable, resulting in a higher specific energy than for the β-anhydrous sample.

In Vitro Aerosolization Performance Analysis

As previously stated, the aerosolization efficiency of the DPI formulations was assessed using the NGI. Analysis of the total drug content from all stages (and device) suggested no significant difference in salbutamol sulfate across all blends

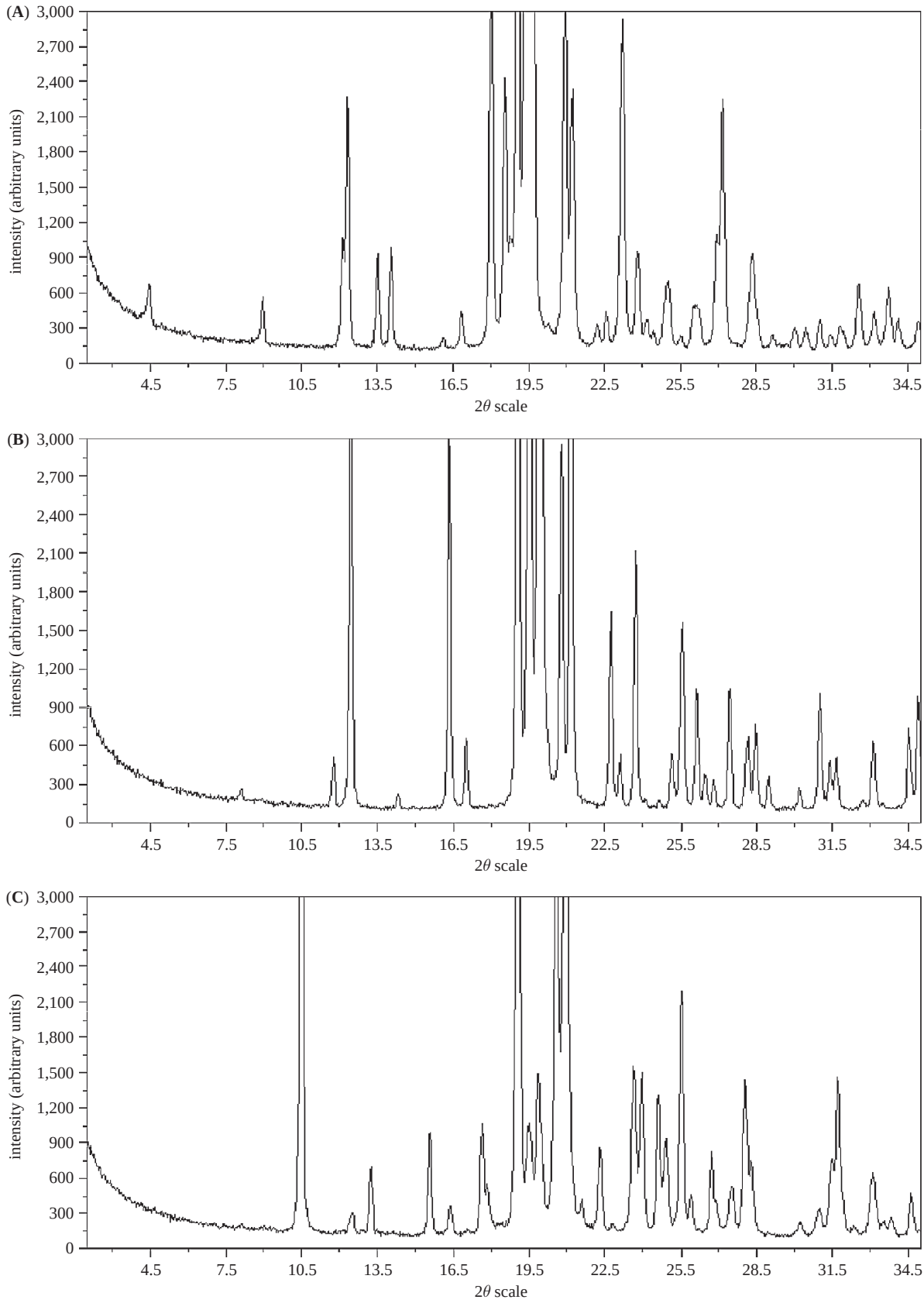

FIGURE 3. X-ray powder diffraction patterns for (A) α-anhydrous, (B) α-monohydrate, and (C) β-anhydrous lactose samples (scan rate 1°min^{-1}).

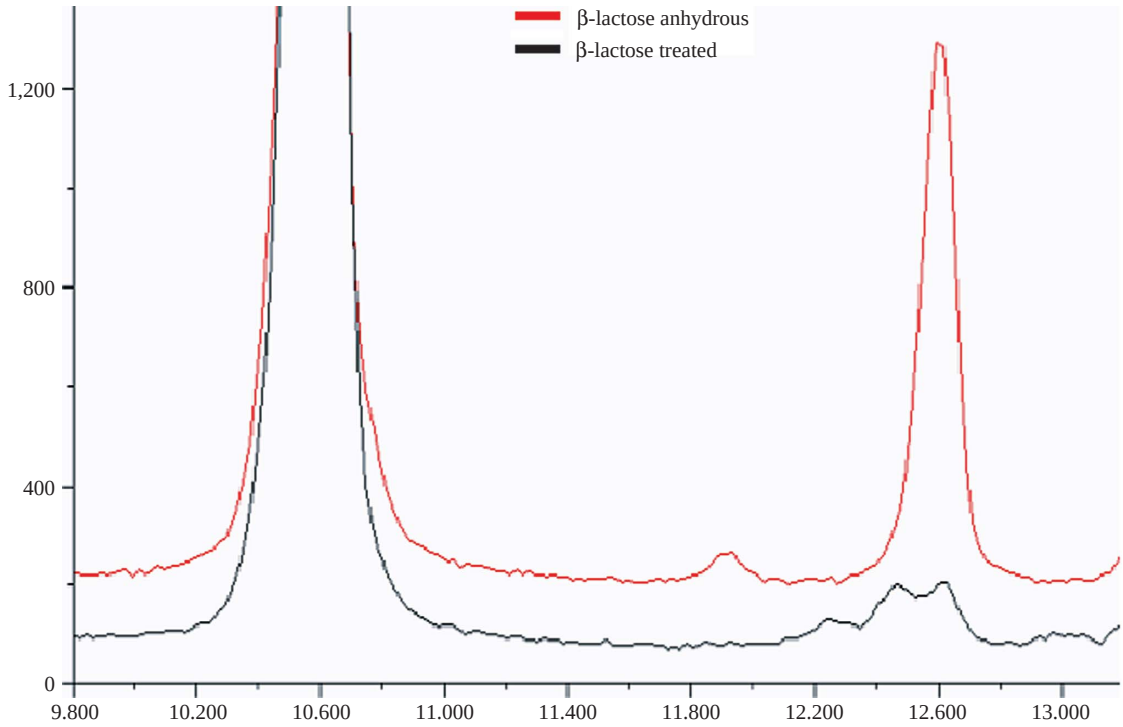

FIGURE 4. Slow XRPD scan (0.1°min^{-1}) of β-anhydrous (top) and β-treated lactose (bottom).

(ANOVA, $p < .05$) (where a mean total dose of 460.6 ± 35.9μg was observed across all blends). As with the total LD, analysis of the ED suggested no significant difference (ANOVA, $p < .05$) (379.1 ± 40.4μg across all blends) in drug emitted from the DPI containing different pseudopolymorphic blends. Such observations are indicative of an ordered mix, in which the drug particles are predominantly adhered to the larger carrier and are liberated upon aerosolization (Young, Traini, & Edge, 2007).

To investigate the influence of lactose type on the aerosolization efficiency of salbutamol from salbutamol–lactose carrier blend, the percentage drug deposition on each stage of the NGI was calculated and plotted in Figure 5. From Figure 5 it can be seen each of the lactose formulations produced different deposition profiles in the various stages of the NGI. Interestingly, one of the most noticeable differences was the percentage drug deposited in the NGI preseparator. The preseparator is designed to capture the carrier component of the formulation (>10 μm), and it may be assumed that any drug captured in this stage is still adhered to the carrier and has not been liberated during the delivery process. Further analysis of the deposition data suggests that a concurrent decrease in the drug deposited on the lower stages of the NGI was observed when higher preseparator and/or throat deposition occurred. To rank the aerosolization efficiency of salbutamol from each of the carrier systems, the FPF was calculated. Salbutamol sulfate FPF values of 5.5 ± 1.2, 19.8 ± 1.1, 14.2 ± 2.9, and 8.1 ± 0.7 % were observed for α-anhydrous, α-monohydrate, β-anhydrous, and β-treated lactose, respectively. Statistical analysis of the FPF data indicated that lactose type had a significant influence on salbutamol sulfate aerosolization efficiency (ANOVA, $p < .05$).

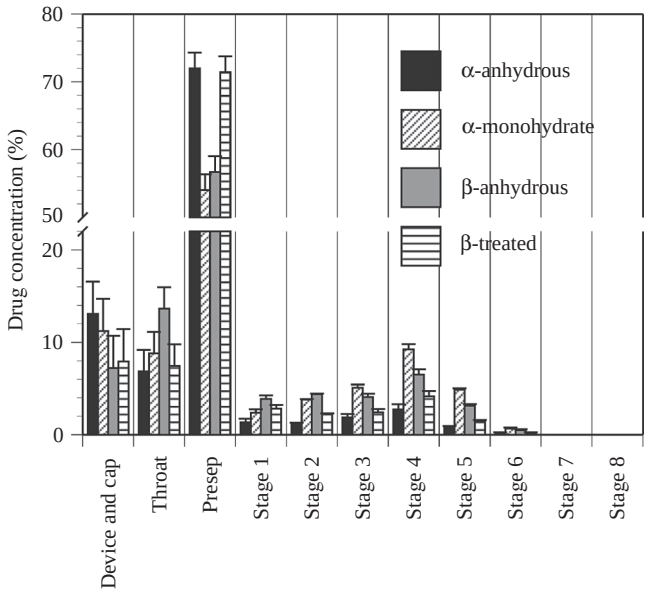

FIGURE 5. Deposition of salbutamol sulphate in the NGI after aerosolization from different lactose blends (error bars indicate standard deviations, $n = 3$).

Relationship Between In Vitro Aerosolization Efficiency and the Physical Properties of the Lactose Carriers

Clear variations in the physical properties of the lactose pseudopolymorph and the aerosolization efficiency of salbutamol sulfate from lactose–drug blends were observed. Previous studies have suggested the presence of intrinsic carrier fines improve drug aerosolization performance from carrier systems (Islam et al., 2004; Jones & Price, 2006; Young et al., 2007). As previously discussed, analysis of the particle size distributions of each sieve-fractioned lactose sample indicated significant difference in the 10th percentile undersize ($d_{0.1}$). Comparison of the $d_{0.1}$ data suggested a rank order of α-anhydrous> α-monohydrate > β-anhydrous > β-treated. When, comparing the α-forms, the large difference in intrinsic fines would suggest that the α-monohydrate ($d_{0.1}$ = 16.6 ± 1.4 μm) to perform better than the α-anhydrous sample ($d_{0.1}$ = 45.4 ± 16.6 μm). Analysis of the FPF data for these two forms, indeed show this to be the case, where the α-monohydrate (FPF = 19.8 ± 1.1%) and α-anhydrous (FPF = 5.5 ± 1.2%) show the extremes in drug aerosolization performance for the lactose series. Interestingly, the α-monohydrate blend showed similar drug aerosolization performance to previously reported for α-lactose monohydrate–salbutamol sulfate blends using similar ratios and formulation methods (Young et al., 2005; Young & Price, 2004). In comparison, previous reports by Larhrib et al. (1999) indicated α-monohydrate and α-anhydrous to have an opposite performance profile to that observed here (α-anhydrous FPF was 13.4±4.2 in comparison to FPFs between 3.9 and 7.9% for α-monohydrate samples, when measured by multistage liquid impinger). Reasons for such disparities are most likely due to the difference in carrier size distribution, where α-anhydrous had a higher percent of fine particles and the variation in ED, indicating complex device–formulation interactions (Larhrib et al., 1999).

The β-anhydrous and β-treated formulations had drug aerosol performance that lay between that of α-anhydrous and α-monohydrate. This is interesting because the β-samples had a significantly higher percentage of fine particles than the α-samples and therefore would be expected to produce the highest performing formulations. Furthermore, comparison of the β-anhydrous ($d_{0.1}$ = 9.5 ± 0.7μm) and β-treated ($d_{0.1}$ = 5.7 ± 0.1μm) would suggest β-treated to have the better performance, where data suggest the converse (β-anhydrous FPF = 14.2 ± 2.9% and β-treated = 8.1 ± 0.7%). Such observations suggested that particle size distribution might not be a primarily dominating role when surface chemistry (through pseudopolymorphic composition) alters dramatically.

Analysis of the surface energy suggested that both the dispersive and specific acid–base components suggested a rank order of α-anhydrous > β-treated > β-anhydrous > α-monohydrate. Interestingly, the drug aerosolization efficiency showed an inverse relationship where FPF could be ranked α-monohydrate > β-anhydrous > β-treated > α-anhydrous. This is interesting as an increase in carrier surface energy would be expected to result in a concurrent increase in drug particle–carrier adhesion and thus decrease the FPF. To further evaluate the influence of surface free energy on the aerosolization performance of salbutamol sulfate from each carrier formulation the in vitro FPF data was plotted against dispersive and total surface energy parameters (Figure 6). The total surface energy was obtained by applying Equation 3. It is interesting to note that the total surface energies are unusally high in terms of the absolute values when compared with typical values from wettability experiments.

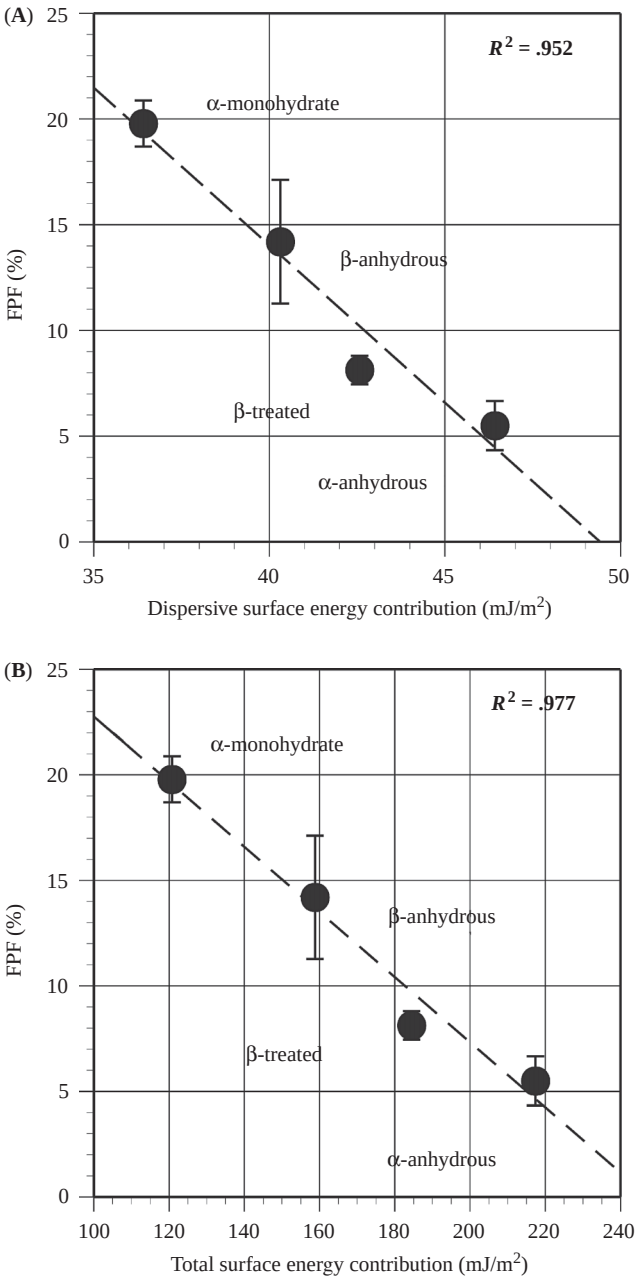

FIGURE 6. Plot of aerosolization efficiency (FPD and FPF) as a function of (A) dispersive and (B) specific surface energy components.

This is due to the overestimation of the specific contribution to the surface energy by IGC. The reasons for this overestimation are lying in the infinite dilution conditions as well as in the overestimation of the input parameter based on the van Oss scale. For wettability experiments, the later problem can be eliminated by using the input parameters suggested by della Volpe et al. Unfortunately, these are not available for probes suitable for gas phase measurements yet (Thielmann, 2004). However, despite the overestimation of the absolute values the trends observed here should not be affected. Analysis of the relationship between the dispersive surface energy component and FPF (Figure 6A) indicated an inverse relationship where linear regression gave an R^2 = .952. Furthermore, analysis of the relationship between the total surface energy and the in vitro aerosolization data showed a similar inverse relationship with higher R^2 of .977, suggesting the polar component to play a significant role in particle carrier adhesion.

CONCLUSIONS

The role of surface chemistry plays a dominating role in particle adhesion. In carrier formulations for dry powder inhalation, variation in the carrier pseudopolymorphic composition may result in large variations in surface energy and thus particle adhesion. Here, four lactose forms were investigated in terms of surface energy and drug aerosolization efficiency. In general, a linear inverse relationship between surface energy and FPF was found that could be attributed to the degree of drug–carrier particle adhesion within the particulate blend.

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REFERENCES

Beevers, C. A., & Hansen, H. N. (1971). Structure of alpha-lactose monohydrate. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem., B 27*(July 15), 1323–1325.

Brittain, H. G. (1999). *Polymorphism in pharmaceutical solids*. New York: Marcel Dekker.

Buma, T. J., & Wiegers, G. A. (1967). X-ray powder patterns of lactose and unit cell dimensions of beta-lactose. *Neth. Milk Dairy J. -Nederlands-Nederlands Melk En Zuiveltijdschrift, 21*(3–4), 208–213.

Bushill, J. H., Wright, W. B., Fuller, C. H. F., & Bell, A. V. (1965). Crystallisation of lactose with particular reference to its occurrence in milk powder. *J. Sci. Food Agric., 16*(10), 622–628.

Edge, S., Kibbe, A., & Kussendrager, K. (2006a). Anhydrous lactose. In R. C. Rowe, P. J. Sheskey, & S. C. Owen (Eds.), *Handbook of pharmaceutical excipients* (pp. 385–388). London: Pharmaceutical Press.

Edge, S., Kibbe, A., & Kussendrager, K. (2006b). Lactose monohydrate. In R. C. Rowe, P. J. Sheskey, & S. C. Owen (Eds.), *Handbook of pharmaceutical excipients* (pp. 389–395). London: Pharmaceutical Press.

Fries, D. C., Rao, S. T., & Sundaralingam, M. (1971). Structural chemistry of carbohydrates.3. crystal and molecular structure of 4-O-beta-d-galactopyranosyl-alpha-d-glucopyranose monohydrate alpha-lactose monohydrate. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem., B 27*(May 15), 994–1005.

Haleblian, J., & Mccrone, W. (1969). Pharmaceutical applications of polymorphism. *J. Pharm. Sci., 58*(8), 911–929.

Haleblian, J. K. (1975). Characterization of habits and crystalline modification of solids and their pharmaceutical applications. *J. Pharm. Sci., 64*(8), 1269–1288.

Hickey, A. J. (2005). Carriers in drug powder delivery. *Am. J. Drug Delivery, 3*(2), 117–132.

Hirotsu, K., & Shimada, A. (1974). Crystal and molecular-structure of beta-lactose. *Bull. Chem. Soc. Jpn., 47*(8), 1872–1879.

Holsinger, V. H. (1999). Lactose. In N. P. Wong, R. Jenness, M. Keeney, & W. H. Marth (Eds.), *Fundamentals of dairy chemistry* (3rd ed.). Gaithersburg: MD: Aspen Publishers.

Islam, N., Stewart, P., Larson, I., & Hartley, P. (2004). Lactose surface modification by decantation: Are drug-fine lactose ratios the key to better dispersion of salmeterol xinafoate from lactose-interactive mixtures? 2. *Pharm. Res., 21*(3), 492–499.

Jones, M. D., & Price, R. (2006). The influence of fine excipient particles on the performance of carrier-based dry powder inhalation formulations. *Pharm. Res., 23*(8), 1665–1674.

Jouppila, K., Kansikas, J., & Roos, Y. H. (1998). Crystallization and X-ray diffraction of crystals formed in water-plasticized amorphous lactose. *Biotechnol. Prog., 14*(2), 347–350.

Kawashima, Y., Serigano, T., Hino, T., Yamamoto, H., & Takeuchi, H. (1998). Effect of surface morphology of carrier lactose on dry powder inhalation property of pranlukast hydrate. *Int. J. Pharm., 172*(1–2), 179–188.

Kirk, J. H., Dann, S. E., & Blatchford, C. G. (2007). Lactose: A definitive guide to polymorph determination. *Int. J. Pharm., 334*(1–2), 103–114.

Larhrib, H., Zeng, X. M., Martin, G. P., Marriott, C., & Pritchard, J. (1999). The use of different grades of lactose as a carrier for aerosolised salbutamol sulphate. *Int. J. Pharm., 191*(1), 1–14.

Lefebvre, J., Willart, J. F., Caron, V., Lefort, R., Affouard, F., & Danede, F. (2005). Structure determination of the 1/1 alpha/beta mixed lactose by X-ray powder diffraction. *Acta Crystallogr., Sect. B: Struct. Sci., 61*, 455–463.

Lloyd, D. R., Ward, T. C., & Schreiber, H. P. (1989). *Inverse gas chromatography: characterisation of polymers and other materials*. Washington DC: American Chemical Society.

Louey, M. D., Mulvaney, P., & Stewart, P. J. (2001). Characterisation of adhesional properties of lactose carriers using atomic force microscopy 1. *J. Pharm. Biomed. Anal., 25*(3–4), 559–567.

Miller, S. P. F., Raw, A. S., & Yu, L. X. (2006). Scientific considerations of pharmaceutical solid polymorphism in regulatory applications. In R. Hilfiker (Ed.), *Polymorphism* (pp. 385–395). Weinheim: Wiley-VCH.

Platteau, C., Lefebvre, J., Affouard, F., & Derollez, P. (2004). Ab initio structure determination of the hygroscopic anhydrous form of a-lactose by powder X-ray diffraction. *Acta Crystallogr., Sect. B: Struct. Sci., 60*, 453–460.

Platteau, C., Lefebvre, J., Affouard, F., Willart, J. F., Derollez, P., & Mallet, F. (2005). Structure determination of the stable anhydrous phase of alpha-lactose from X-ray powder diffraction. *Acta Crystallogr., Sect. B: Struct. Sci., 61*, 185–191.

Pritchard, J. N. (2001). The influence of lung deposition on clinical response. *J. Aerosol Med., 14*, S19–S26.

Schultz, J.; Lavielle, L.; Martin, C. (1987). The role of interface in carbon fibre-epoxy composites. *J. Adhes., 23*,.45–51.

Simpson, T. D., Parrish, F. W., & Nelson, M. L. (1982). Crystalline forms of lactose produced in acidic alcoholic media. *J. Food Sci., 47*(6), 1948–1951.

Steckel, H., & Bolzen, N. (2004). Alternative sugars as potential carriers for dry powder inhalations. *Int. J. Pharm., 270*(1–2), 297–306.

Steckel, H., Markefka, P., teWierik, H., & Kammelar, R. (2004). Functionality testing of inhalation grade lactose. *Eur. J. Pharm. Biopharm., 57*(3), 495–505.

Thielmann, F. (2004). Introduction into the characterisation of porous materials. *J. Chromatogr., A, 1037* (1–2), 115–120.

Traini, D., Young, P. M., Jones, M. D., Edge, S., & Price, R. (2006). Comparative study of erythritol and lactose monohydrate as carriers for inhalation: Atomic force microscopy and in vitro correlation. *Eur. J. Pharm. Sci., 27*(2–3), 243–251.

van Oss, C. J. (1994). *Interfacial forces in aqueous media*. New York: Marcel Dekker.

Young, P. M., Cocconi, D., Colombo, P., Bettini, R., Price, R., Steele, D. F., et al. (2002). Characterization of a surface modified dry powder inhalation carrier prepared by "particle smoothing". *J. Pharm. Pharmacol., 54*(10), 1339–1344.

Young, P. M., Edge, S., Traini, D., Jones, M. D., Price, R., El-Sabawi, D., et al. (2005). The influence of dose on the performance of dry powder inhalation systems 1. *Int. J. Pharm., 296*(1–2), 26–33.

Young, P. M., & Price, R. (2004). The influence of humidity on the aerosolisation of micronised and SEDS produced salbutamol sulphate. *Eur. J. Pharm. Sci., 22*(4), 235–240.

Young, P. M., Traini, D., Chan, H. K., Chiou, H., Edge, S., & Tee, T. (2007). The influence of mechanical processing dry powder inhaler carriers on drug aerosolisation performance. *J. Pharm. Sci*., *96*(5), 1331–1341.

Young, P. M., Traini, D., & Edge, S. (2007). Advances in pulmonary therapy. In R. O. Williams, D. R. Taft, & J. T. McConville (Eds.), *Advanced drug formulation design to optimize therapeutic outcomes*. New York: Informa Healthcare.

Zeng, X. M., Martin, G. P., Marriott, C., & Pritchard, J. (2000). The influence of carrier morphology on drug delivery by dry powder inhalers. *Int. J. Pharm., 200*(1), 93–106.

Zeng, X. M., Martin, G. P., Marriott, C., & Pritchard, J. (2001a). Lactose as a carrier in dry powder formulations: The influence of surface characteristics on drug delivery. *J. Pharm. Sci., 90*(9), 1424–1434.

Zeng, X. M., Martin, G. P., Marriott, C., & Pritchard, J. (2001b). The use of lactose recrystallised from carbopol gels as a carrier for aerosolised salbutamol sulphate. *Eur. J. Pharm. Biopharm., 51*(1), 55–62.