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Novel Temperature Controlled Surface Dissolution of Excipient Particles for Carrier Based Dry Powder Inhaler Formulations

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ABSTRACT The surface of lactose monohydrate was modified by solution phase variable temperature dissolution. Lactose monohydrate crystals were added to a known volume of a saturated solution of lactose monohydrate at 25°C. The temperature of the mixture was then ramped to either 30, 35, 40, or 50°C to produce lactose monohydrate batches with reduced levels of fines and lower surface roughness. A dramatic decrease in surface roughness with increasing dissolution temperature was visually observed using scanning electron microscopy. Particle size analysis suggested that the level of lactose fines was reduced after treatment at the lowest dissolution temperature, 30°C. Evaluation of the samples' drug aerosolization using a twin stage impinger, after blending with salbutamol sulphate, suggested that even though there were dramatic changes in roughness and particle size distribution after surface dissolution at 30°C, there was no significant difference in aerosolization as measured by fine particle fraction. However, after surface dissolution at 35°C, there was an increase in fine particle fraction. Surface dissolution at even higher temperatures did not result in any further increase in fine particle fraction. These observations suggest that surface roughness and fines play an important role in the aerosolization of salbutamol sulphate, but the inter-relationships are not straightforward.

KEYWORDS Lactose, Surface dissolved, Dry powder inhaler

INTRODUCTION

The successful development of carrier based dry powder inhaler (DPI) products has been achieved through the design of ever increasingly elaborate devices and an improved understanding of the role of the interactions between the inhaler components, namely drug, carrier, and device. Generally, a DPI is developed and optimized based on iterative observations using in vitro testing. Lactose carriers, from different suppliers, exhibiting different particle characteristics, are

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invariably blended with a micronized drug, again of various particle sizes/shapes and doses. The formulation is then studied using, for example, a twin-stage impinger (TSI), a multi-stage liquid impinger (MSLI), or an Anderson cascade impactor and the aerosolization behavior described in terms of respirable fraction, emitted dose, etc. The characteristics of the carrier and drug and processing parameters are then iterated to produce a formulation which exhibits a reproducible and acceptable dosage profile. This approach has proved very successful since there are a plethora of products on the market which satisfy the stringent requirements of the relevant regulatory authorities (Smith & Parry-Billings, 2003). However, there are still many questions surrounding the nature and effect of particle interactions in a DPI formulation and it is clear that one lactose or drug type or batch or device will not provide universally optimal DPI performance due to, for example, inter- and intra-batch and supplier "equivalence" of lactose and the properties and characteristics of batches of the micronized drug. Indeed, it has been reported that inter-batch variations of lactose can influence formulation performance, especially for low dose drugs (Steckel et al., 2004). This can, in part, be explained in terms of particle size and roughness and, importantly, how accurately the particle descriptors characterize the lactose and drug.

The relationships between particle size, distribution, shape and roughness, and aerosolization have been investigated for both carriers and drugs. There have been reports of the effect of lactose source and particle characteristics on the efficiency of DPI formulations (Kawashima et al., 1998; Larhrib et al., 1999; Louey et al., 2003). Recently, attention has focused on the nature and role of the fine lactose particles in the formulation, and it has been suggested that the efficiency of a formulation can be optimized at a certain level of fines (Zeng et al., 1998; Islam et al., 2004). However, the number of reports describing the relationship between the properties of the carrier and apparent formulation performance can be contradictory (Louey et al., 2003).

In view of the difficulties in understanding, predicting, and comparing the relationships between carrier properties and drugs, lactose and drugs have been further processed to produce modified surfaces/particle size distributions which offer improved, and importantly, more reproducible performance. Additionally, such approaches may allow the production of carriers which exhibit improved batch to batch consistency and stability. A similar approach has been used for drugs where drugs such as salbutamol sulphate have been evaluated after engineering using crystallization processes (Larhrib et al., 2003a) and by supercritical fluid technology (Schiavone et al., 2004; Young & Price, 2004).

The modification of lactose can be divided into three general areas: crystallization, where lactose is crystallized from a lactose solution; solution phase processing, where lactose is exposed to a liquid media and does not completely dissolve so partial dissolution/etching may occur; and dry processing, where lactose is "treated", for example, by co-processing in the absence of a liquid. These methodologies attempt to increase the aerosolization of drug via geometric and morphological modifications. The relationships between lactose surface roughness, crystal aspect ratio and geometry, and drug aerosolization have been studied by crystallization of lactose from water (Zeng et al., 2000), water/acetone (Larhrib et al., 2003b), and carbopol/water/ethanol (Zeng et al., 2001; Larhrib et al., 2003a). These investigations reported an increase in aerosolization of salbutamol sulphate and terbutaline sulphate with decreasing lactose roughness compared to "as supplied" lactose which is in agreement with a study of the relationship between the roughness of sieved lactoses and aerosolization of terbutaline sulphate (Flament et al., 2004). Also, it has been reported that increasing the surface roughness of lactose increases the emitted dose, but reduces the respirable dose, in this case particles below 6.4 μm in size (Heng et al., 2000). Solution phase processing of lactose has been achieved by treating lactose with liquids. Aqueous alcohol has been used to partially dissolve surface asperities resulting in an increase in the aerosolization of salbutamol sulphate (Iida et al., 2003). Lactose has also been treated by decantation with alcohol to remove lactose fines which resulted in a decrease in the aerosolization of salmeterol xinofoate which was restored after re-addition of fines (Islam et al., 2004). Additionally, lactose has been treated or "smoothed" with a suspension of Mg stearate in water/ethanol which resulted in an improvement in the performance and efficiency of a DPI formulation (Young et al., 2002). Such processes may result in some dissolution or etching of lactose and detachment/dissolution of fines from the crystal surfaces and it was not clear if part of any apparent improvement in aerosolization

performance was due to modification of the particle size or fines distributions since a reduction in carrier particle size is reported to improve drug aerosolization (Steckel & Müller, 1997; Louey et al., 2003). Non-liquid based treatment of lactose has been achieved by dry blending with leucine to improve functionality (Staniforth, 1997; Lucas et al., 1999). It can also be argued that addition of lactose in the form of fines to lactose is a form of dry co-processing.

One problem with these types of investigations is that "modification" of a lactose sample invariably results in a change in the particle size and surface characteristics. It is practically impossible to absolutely classify particles in terms of particles size and distribution and surface roughness. This has obvious implications for both carrier and drug and explains the difficulties for quantitative comparisons of formulation performance. The relationship between modification and particle size distribution is further complicated by the possible methodology dependence of apparent particle size descriptors (Larhib et al., 1999).

The previously described reports suggest that for single dose devices, a decrease in lactose surface roughness together with an optimal level of fines should result in an improved lactose carrier performance, which again will be drug and device dependent. Additionally, the production of a lactose carrier which would facilitate classification would be attractive since it would reduce the effect of any possible batch to batch differences. In our efforts to develop multipurpose DPI lactose carriers, this article describes the use of a novel controllable particle surface dissolution process to produce well characterized lactose carriers. The influence of carrier modification, and the potential applications of such carriers in DPI's, has been initially evaluated by studying the delivery of salbutamol sulphate from a conventional DPI formulation and device.

MATERIALS AND METHODS

Materials

Lactose monohydrate (Lactochem® crystals) was supplied by Borculo Whey (Chester, UK). The lactose was vibrated through a nest of sieves to obtain a 63–90 μm sieve fraction, which was used throughout the study. Micronized salbutamol sulphate was supplied by Aventis Pharma (Cheshire, UK). Water was purified by reverse osmosis (MilliQ, Molsheim, France).

Lactose Solubility Profile

A water-temperature solubility profile for lactose monohydrate was determined. A saturated solution of lactose in water was prepared by the continued addition of lactose monohydrate to 20 mL of water. The solution was placed in a controlled temperature water bath at a variety of temperatures (Haake, DC5, Fisons Scientific Equipment, Loughborough, UK) and vigorously shaken for 48 h. Each equilibrated sample was rapidly filtered under vacuum through a 0.2 μm filter. The recovered solution was weighed and dried in an oven at 50°C. The resulting dry mass was re-weighed and the solubility calculated. The solubility of lactose monohydrate was measured between 20°C and 45°C at 5°C intervals. The resulting solubility curve is shown in Fig. 1. The relationship between solubility (S) and temperature (T) was fitted to a third order polynomial (Eq. 1), with an correlation coefficient, R^2, of 0.999.

$$S(T) = 19.892 - 0.2937T + 0.0138T^2 + 0.00003T^3 \quad (1)$$

This gives predicted solubilities of 24.33% and 43.49% at 30°C and 50°C, respectively, which are in agreement with literature values of 24.8% at 30°C and 43.5% at 50°C (Rajah & Blenford, 1998). With prior knowledge of the temperature dependence of the solubility of lactose monohydrate, the undersaturation conditions and degree of dissolution, or "etching" ($\%M_{dissolved}$), of the sieve fractioned crystals could be directly quantified. If the mass of added sieved lactose

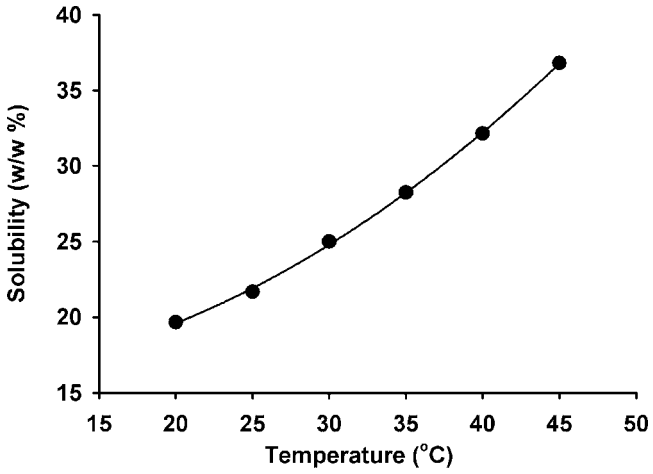

FIGURE 1 **Temperature vs. Solubility Profile for Lactose Monohydrate.**

monohydrate is greater than the "dissolution capacity" of the liquid, the percentage dissolved lactose monohydrate, in terms of mass of the sieved lactose monohydrate added, can be quantified via the following expression:

$$\%M_{dissolved} = \Delta C_T(\%)V_L(ml)/M_{initial}\ (g) \quad \text{for } M_{initial}\ (g) \geq \Delta C_T(\%)V_L(ml)/100 \quad (2)$$

where ΔC_T is the difference in the solubilities of lactose monohydrate at 25°C and the dissolution temperature; the units are g/100 g water or percent. $M_{initial}$ is the mass of the added sieve fractioned lactose monohydrate added to a known volume of the saturated lactose solution (V_L). $\Delta C_T(\%)V_L/100$ is the "dissolution capacity". This quantitative relationship is industrially scalable and requires only a limited number of additional steps to current industrial production and processing. It should be noted that, unlike crystal growth at conditions of low supersaturation, the kinetics of dissolution are rapid. Furthermore, once saturation conditions have been achieved at the dissolution temperature, further dissolution and crystal growth is inhibited.

Preparation of Surface Dissolved Lactose Monohydrate

In simple terms, the surface dissolution of lactose monohydrate was achieved as follows. A saturated solution of lactose in water was prepared and continually stirred at a constant temperature of 25°C. The temperature within the vessel was controlled to within 0.1°C via a refrigerated controlled water bath (Haake, DC5, Fisons Scientific Equipment, Loughborough, UK). A volume of the saturated solution (V_L), 100 mL in this work, was removed from the vessel, filtered, and transferred to a dissolution cell which was maintained at the saturation temperature, i.e., 25°C. A predetermined amount of 63–90 μm sieved lactose monohydrate ($M_{initial}$), 50g in this work, was then added to the saturated solution in the dissolution cell. Surface controlled "dissolution" of the lactose monohydrate particles surfaces was achieved by ramping the temperature within the dissolution vessel at a controlled rate ($0.5°C.min^{-1}$). After surface dissolution, the crystals were separated by filtration and washed with ethanol saturated with lactose. The crystals were allowed to dry at ambient conditions (approximately 20–23°C, 40–50% relative humidity) for 7–10 days. The degree of dissolution can be directly quantified via Eqs. 1 and 2.

Scanning Electron Microscopy

Particle morphology was investigated using scanning electron microscopy (SEM) (Jeol 6400; Jeol, Tokyo, Japan) at 10 keV. Samples were mounted on carbon sticky tabs and gold-coated before imaging (Edwards Sputter Coater, Crawley, UK).

Specific Surface Area

The surface area of the untreated and surface dissolved lactose monohydrate was determined by a Brunauer-Emmett-Teller (BET) adsorption method (Gemini; Micromeritics Ltd., Norcross, GA, USA) using nitrogen and helium gas. Samples were dried under a stream of dry nitrogen at 40°C for 48 h prior to analysis.

Powder Bulk and Tapped Density and Flow

Powder flowability was represented by bulk and tap density measurements. The bulk and tap density of each lactose monohydrate sample was determined by adding 50–100 mL of powder sample into a 100 mL measuring cylinder. The initial volume and mass were recorded, and the sample was then subjected to 100 standard taps using a jolting volumeter (J. Engelsmann, Ludwigshaven, Germany), and the tapped volume recorded. The volumes after subsequent 100 tap sets were recorded until <2% volume change was observed across three consecutive readings. Bulk and tap densities and Carr's compressibility indices (Carr, 1965) were calculated in triplicate.

X-ray Diffraction

X-ray diffraction of untreated and 50°C surface dissolved lactose monohydrate samples were obtained using an x-ray powder diffraction system (D5000, Bruker AXS, Cheshire, UK). Settings were as follows: 2 to 39.960 degrees 2θ, step size 0.036 degrees 2θ, step time 0.5 seconds, temperature 25°C.

Particle Size Analysis

The particle size distributions of the untreated and surface dissolved lactose monohydrate samples were determined by laser light scattering (Mastersizer X; Malvern, UK), using a small volume sample dispersion cell. Samples were dispersed in 0.1% w/w lecithin/cyclohexane before analysis. Each sample was analyzed prior and post ultrasonication (5 min) to assess the fine particulate content. All samples were prepared and analyzed in triplicate.

In Vitro Aerosolization Studies

The relationship between carrier surface dissolution and the in vitro performance of drug–carrier blends was investigated using the TSI. Micronized salbutamol sulphate, the most common β-antagonist used in asthma therapy, was used as a model drug. In simple terms, micronized salbutamol sulphate (median diameter, d_{50} 4.79 μm) was geometrically blended with the untreated and surface dissolved lactose monohydrate samples at a ratio of 67.5:1 w/w using a Whirlymixer (Fisons Scientific Equipment, Loughborough, UK) for 50-second periods. Each final blend was then placed in a Turbula (Bachofen, Basel, Switzerland) and mixed at 46 rev.min^{-1} for 30 min. The final blend was stored in a sealed container with a saturated salt solution of potassium carbonate which produced a relative humidity of 44% RH at 25°C. Prior to in vitro studies, content uniformity was investigated by analyzing 30.0 ± 2 mg samples (n = 10) of each blend. Sample analysis was conducted using a calibrated fluorescence spectroscopy method described elsewhere using water as a dilution solvent (Young & Price, 2004). Content uniformity for all blends gave a relative standard deviation of less than 3%.

Hard gelatine capsules (size 3) were filled with 33 ± 4 mg of powder blend such that each capsule contained a nominal dose of 482 ± 58 μg of salbutamol sulphate. The aerosolization of salbutamol sulphate from each capsule was investigated using apparatus A (British Pharmacopoeia), the TSI (Copley Instruments Ltd, Nottingham, UK) containing 7 mL of water in stage one and 30 mL of water in stage two, which at 60 L.min^{-1} produces a cut-off mass median aerodynamic diameter of 6.4 μm between the two stages (Hallworth & Westmoreland 1987). Each capsule was tested using the Cyclohaler® (Novartis, Surrey, UK) at 60 L.min-1 for 5 sec. The flow rate was achieved using a rotary vein pump and solenoid-valve (Copley Scientific, Nottingham, UK), and calibrated using a reference flow meter. The pump was allowed to run for 4 sec prior to and post solenoid-valve actuation to allow the pump time to equilibrate. The concentration of drug in each stage/device was determined by washing into a volumetric flask with water before analyzing in a calibrated fluorescence spectrophotometer using methods described elsewhere (Young & Price, 2004). Each in vitro test was repeated for each drug–lactose monohydrate blend for a minimum of five capsules.

The aerosolization characteristics were described as: loaded dose (LD), total drug recovered from the capsule, mouthpiece, throat and stages 1 and 2; emitted dose (ED), drug emitted from the device into stages 1 and 2, throat and mouthpiece adapter; fine particle dose (FPD), drug in stage 2 of the TSI; fine particle fraction (FPF), percentage of FPD to LD; delivered dose, percentage ED to LD.

RESULTS

The effect of surface dissolution of lactose monohydrate on the aerosolization of salbutamol sulphate was investigated. Prior to aerosolization studies, the untreated and surface dissolved lactose monohydrate were first characterised in terms of particle morphology, surface area, flowability, crystallinity, and particle size.

Physical Characterization

Scanning Electron Microscopy

Representative scanning electron micrographs of the untreated 30°C and 50°C surface dissolved lactose monohydrate samples are shown in Fig. 2a, b, and c, respectively. Clear morphological variations between the untreated and surface dissolved lactose monohydrate could be observed. Most noticeably, a visual decrease in the level of fines, accompanied by a dramatic decrease in apparent surface roughness, was observed when comparing the untreated and 30°C surface dissolved lactose monohydrate. This apparent degree of dissolution increased with increasing dissolution temperature. This was most noticeable with the 50°C surface dissolved lactose monohydrate, Fig. 2c, where the macroscopic crystal morphology appeared

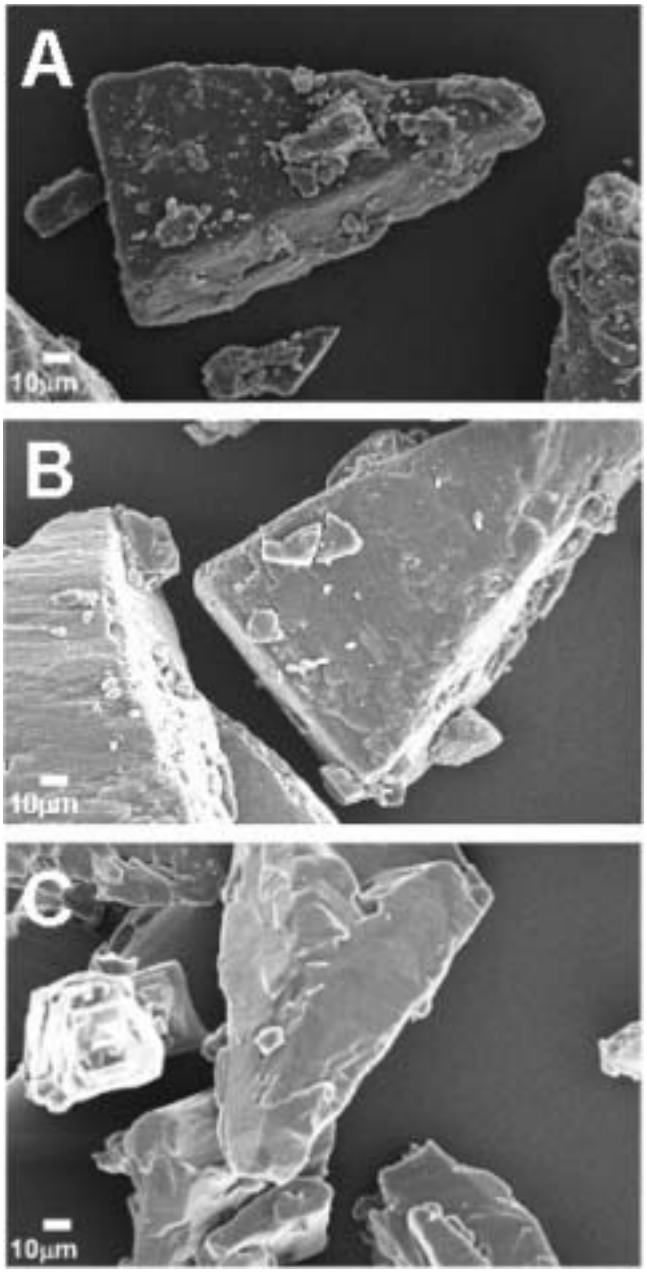

FIGURE 2 **Scanning Electron Micrographs of A, Untreated B, 30°C and 50°C Surface Dissolved Lactose.**

altered. However, such observations are to be expected, since a 25°C solubility temperature difference would result in approximately 50% of the initial mass being dissolved.

Bulk and Tapped Density

The powder flow of the blends, as represented by Carr's compressibility index, is shown in Table 1. In general, the blends exhibited similar (ANOVA, $p < 0.05$) Carr's compressibility indices of 21% ± 3 suggesting that the dissolution process does not dramatically change the flow of the powders. There were no significant differences between the bulk and tapped densities of the samples (not shown). Commercially available sieved lactose monohydrates of different mesh sizes (d_{50} 135 to 55 μm) also exhibit similar Carr's compressibility indices and powder densities (Kibbe & Weller, 2003).

Surface Area

The surface areas of the unmodified and surface dissolved samples are shown in Table 1. It can be seen from Table 1 that all the samples exhibited similar (ANOVA, $p < 0.05$, $n = 3$) surfaces areas of approximately 0.11 m^2g^{-1} suggesting that dissolution does not have a dramatic effect on the bulk surface area of the lactose monohydrate.

X-ray Diffraction

Analysis of the X-ray diffraction patterns for both untreated and 50°C surface dissolved lactose monohydrate (Fig. 3) suggested no modifications of crystal structure and were typical for α-lactose monohydrate. Such observations are to be expected since the processing method does not induce crystal growth and α-lactose monohydrate is the only stable lactose that could be present under the experimental conditions. The changes in the relative intensity of the diffraction lines are due to the geometry of the crystals in the equipment and the removal of fines.

Particle Size Distribution

Cumulative particle size distributions for the untreated and surface dissolved lactose monohydrate samples (after sonication) are shown in Fig. 4. For the untreated lactose monohydrate, it appears that the material contains a significant level of fines. The data suggests that, as expected, the surface dissolution method modifies the particle size distribution with a reduction in the level of fines, which is confirmed by the previously mentioned SEM observations (Fig. 2). However, the surface area of the lactose monohydrates (see Table 1), remained unchanged (ANOVA, $p < 0.05$). As previously stated, any apparent change in functionality may, in part, be a consequence of this removal of fines. These observations also confirm that sieving of lactose monohydrate does not remove all

TABLE 1 **Summary of Lactose Monohydrate Blend Characteristics and In Vitro Performance**

	Dissolution Temperature				
	Untreated	30°C	35°C	40°C	50°C
Particle Size, d_{10}, d_{50}, d_{90} (μm)	7, 78, 145	12, 79, 146	15, 87, 154	20, 85, 164	15, 83, 183
Mass Lactose Dissolved (%)	0	5	12	21	47
Lactose Surface Area (m^2g^{-1})	0.13 ± 0.01	0.10 ± 0.01	0.10 ± 0.01	0.11 ± 0.01	0.11 ± 0.01
Blend Carr's Compressibility Index (%)	19 ± 1	19 ± 1	24 ± 1	18 ± 1	24 ± 1
Emitted Dose (μg)	351 ± 26	348 ± 45	360 ± 48	371 ± 17	435 ± 18
Delivered Dose (%)	82 ± 4	83 ± 2	72 ± 22	82 ± 2	85 ± 3
Fine Particle Dose (FPD) (μg)	56 ± 15	62 ± 2	84 ± 9	88 ± 11	103 ± 10
Fine Particle Fraction (FPF) (%)	13 ± 2	14 ± 5	17 ± 2	19 ± 2	20 ± 2

The degree of dissolution was calculated for 50 g of lactose in 100 mL of saturated lactose solution. ± Values are standard deviations.

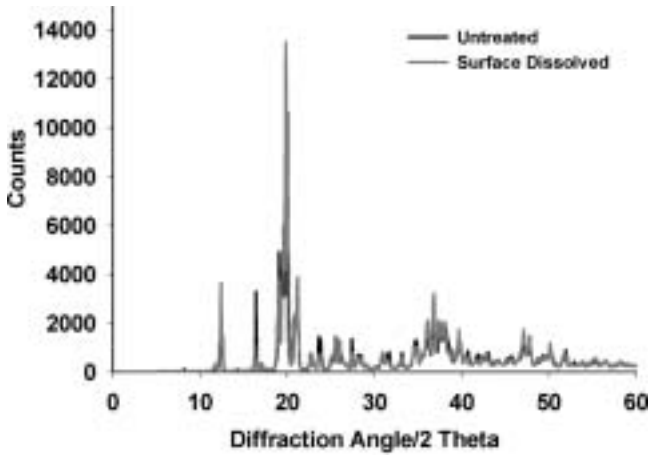

FIGURE 3 **X-ray Powder Diffraction Patterns for Untreated and 50°C Surface Dissolved Lactose Monohydrate Samples.**

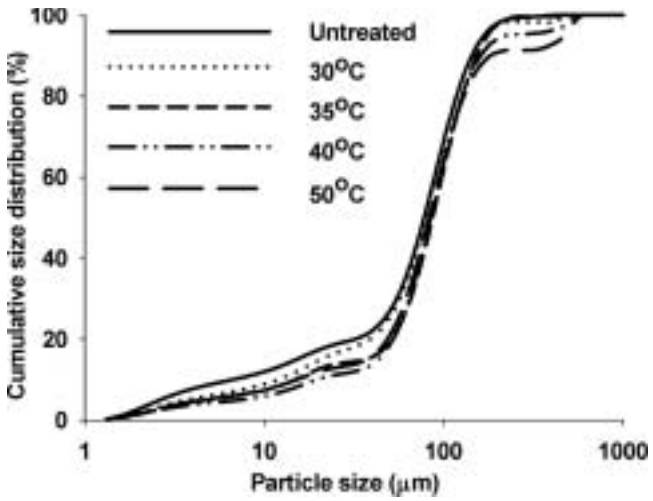

FIGURE 4 **Particle Size Distributions for Untreated and Surface Dissolved Lactose Monohydrate Samples.**

surface bound fine particles (Flamert et al., 2004). The presence and level of fines in lactose carriers is widely reported as an important factor for DPI performance (Zeng et al., 1998; Zeng et al., 1999; Louey et al., 2003; Islam et al., 2004).

In Vitro Aerosolization Studies

The twin-stage impinge (TSI) aerosolization efficiency of salbutamol sulphate from blends of untreated and surface dissolved lactose monohydrate carriers, as represented by FPD and FPF, is summarized in Table 1 and Fig. 5. No significant differences (ANOVA, $p < 0.05$) in either ED (452 μg ± 59 μg) and delivered dose (~81%) were observed. In comparison, analysis of the FPD and FPF suggested that surface dissolution at 35°C had a significant effect on drug liberation (Fisher's pairwise analysis, $p < 0.05$). There were no significant differences between the same parameters for untreated and 30°C surface dissolved samples. Similarly, no significant differences in functionality between samples treated at temperatures of 35–50°C were observed.

DISCUSSION

As previously stated, there are conflicting reports about the inter-relationships between lactose based carriers, micronized drugs, and apparent formulation efficiency. It was reported that increasing the "smoothness" of lactose improved the performance of inhalation formulations (Ganderton & Kaseem, 1992). Presently, it is generally accepted that particle size, roughness, and the level of fines are important. Lactose has been modified using a variety of processes to produce

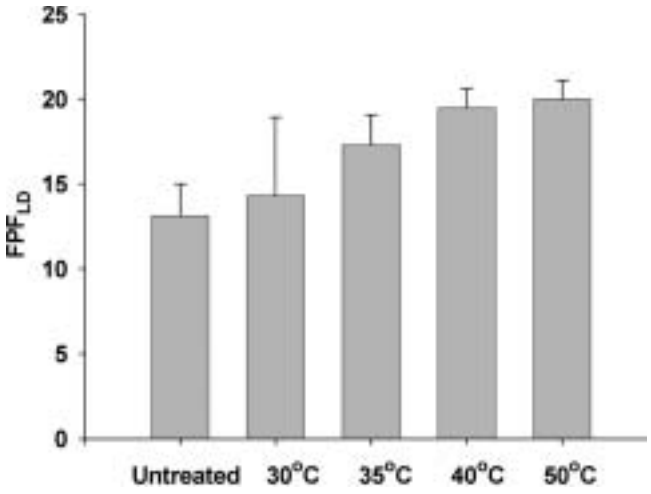

FIGURE 5 **Effect of Dissolution Temperature on Fine Particle Fraction.**

materials which exhibit improved aerosolization properties by crystallization techniques to produce "smooth" crystals with well-defined size descriptors (Zeng et al., 2000; Larhrib et al., 2003b); "smoothing" by solution phase treatment of lactose with a ternary agent, Mg stearate (Young et al., 2002); and dry co-processing with leucine (Lucas et al., 1999). All these methods were reported to result in an improvement in drug aerosolization. Recently, lactose monohydrate has been "wet-smoothed" using a high shear mixer to reduce surface roughness (Ferrari et al., 2004). This present work also suggests that decreasing the surface roughness of the lactose monohydrate carrier results in an increase in FPD and FPF without affecting the ED. However, this is not a simple relationship since the dissolution process also results in modifications of the particle size distribution, in particular, a decrease in the level of fines. Additionally, in this present work, it is interesting to note that the 30°C surface dissolved sample exhibited a reduction in fines but no increase the aerosolization of the drug. This is in agreement with a "smoothing" study which also included an aqueous method which, as well as smoothing the lactose monohydrate, also reduced the level of fines (Young et al., 2002). However, as observed for the 30°C surface dissolved sample in this study, this did not result in any improvement in lactose monohydrate functionality. This would, in part, agree with the proposal that the presence of a certain level of fines improves the functionality of lactose (Staniforth, 1997; Lucas et al., 1998; Louey et al., 2003; Islam et al., 2004) and agrees with the suggestion that removing fines and reducing the surface roughness of sieved lactose increases the performance of a DPI formulation (Flament et al., 2004). However, there are limitations, for example, even though crystallization processes can produce lactose with improved aerosolization, increases in the crystal aspect ratio can be detrimental to formulation characteristics such as content uniformity and flow (Lahrib et al., 2003b).

These observations suggest that it may not be possible to derive simple relationships between apparent surface roughness and fines, and there may be a optimal balance between these two variables which would be expected to be lactose batch and brand dependent. Consequently, quantitative comparisons of literature are difficult due to the lactoses employed and the methodology of particle size and roughness analysis. For example, the classification of a lactose sample based on sieving can be misleading since adhesion of fines to larger particles will always occur due to simple physics. This also confirms that the apparent particle size distribution of lactose may differ depending on the method of determination (Larhib et al., 1999). These have obvious formulation implications. This was exemplified in a study, not shown, to determine the relationship between sonication time and the apparent particle size of untreated sieved lactose monohydrate. Clear differences between the particle distributions of the untreated lactose monohydrate were observed. In general, sonication resulted in an increase in smaller particle fractions, most likely due to the separation of fines from the larger particulates. As expected, this was not observed for the surface dissolved lactose monohydrate samples, correlating with the previously described SEM images. Minor differences in the particle size distribution were observed with increased dissolution temperature but the distribution profiles were essentially similar. These observations show that a sieved lactose sample should be considered as a pseudo-ordered or interactive mix rather than a material defined by some experimentally determined size descriptor and that the particle sizing method should be developed to maximize the information form any particle size descriptors obtained. The production of a modified lactose, such as the "surface dissolved" lactose monohydrate in this study, may offer improved arosolization of drug and formulation characteristics and facilitate a better understanding of particle size and functionality relationships by reducing the effect of the methodology of particle size determination.

CONCLUSIONS

Overall, it appears that there is a relationship, albeit a complex one, between lactose monohydrate nominal particle size and size descriptor, particle size distribution (including fines), and surface topography. This present study suggests that treatment of lactose monohydrate with a suitable liquid can control the particle surface dissolution and the removal of fines to produce materials which increase the aerosolization of salbutamol sulphate from a single dose inhaler. Additionally, such materials may exhibit particle size characteristics which are less dependent on sizing methodology. Further studies are underway investigating the role and effect of fines when combined with smoothed lactose substrates in relation to drug aerosolization and formulation stability.

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