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Continued Investigation Into the Influence of Loaded Dose on the Performance of Dry Powder Inhalers: Surface Smoothing Effects

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ABSTRACT The aerosolization of salbutamol sulfate, measured as fine particle dose (FPD_{LD}) and fine particle fraction (FPF_{LD}) (<6.4 μm mass median aerodynamic diameter), from two sieved (63–90 μm) lactose monohydrate carriers, one as supplied, one smoothed by controlled surface dissolution, was studied. In general, no significant variation in FPD_{LD} was observed at drug loadings between 10 and 63.5 μg and 10 and 135 μg for the surface dissolved and as supplied lactose monohydrates, respectively. Increasing the drug load above these levels resulted in linear increases in FPD_{LD} with increasing drug load with the surface dissolved lactose monohydrate exhibiting higher FPD_{LD} and FPF_{LD}. This suggests that, at lower drug loadings, areas of the carrier exhibiting higher adhesion, so-called active sites, were being preferentially occupied and filled. Since there was no evidence of drug agglomeration using scanning electron microscopy, the observations suggest that the number and range of such higher energy "active sites" can be reduced by modifying the surface roughness, that is, energies, of the carrier.

KEYWORDS Active sites, Dry powder inhaler, Lactose, Smoothing

INTRODUCTION

The formulations used in dry powder inhaler (DPI) systems invariably consist of an ordered mix of processed drug particulates (~5 μm diameter) and a larger, inert carrier material, typically lactose monohydrate (~100 μm diameter). However, the key to the successful development of a DPI product is the preparation of a formulation that can provide reproducible and acceptable powder flowability, dosing efficiency, and delivery of the drug particulates to the respiratory system. The efficiency of such DPI systems at delivering drugs to the respiratory tract can be related to many factors including the inspirational flow rate (Timsina et al., 1994) and the physico-chemical properties and interactions of the drug (Young & Price, 2004; Chew et al., 2005) and carrier particles (Larhrib et al., 1999; Kawashima et al., 1998; Zeng et al., 2000a,

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2000b). It is clear that an improved understanding of relationships between the properties, interactions and functionality of carriers and drugs will allow issues such as formulation and product consistency to be addressed.

In terms of carrier performance, previous reports have suggested that carrier particles contain areas of high and low adhesion, referred to as active sites (Staniforth, 1996). These active site regions may be attributed to morphological features (e.g., "peaks" and "troughs") and/or chemical properties across the surface (e.g., crystal face and structure and the presence of amorphous material). It was proposed that drug particles may be more difficult to remove from the carrier upon aerosolization due to preferential binding to any active sites on the carrier particles during mixing (Hersey, 1975; Staniforth, 1995). It was also suggested that the presence of active sites would be particularly important for the aerosolization performance for low drug concentrations and would, in part, explain the recently observed relationship between drug/lactose ratio and aerosolization performance of a dry powder (Young et al., 2005). At very low drug concentrations, an increase in drug/lactose ratio resulted in a linear decrease in the percentage of the respirable fraction (sub 6.4 μm particle size) of drug removed during aerosolization. That is to say the actual amount of the sub 6.4 μm drug dose removed from the carrier remained constant and the increased drug loading merely occupied the active sites. However, at a certain critical drug load, further increases in drug/lactose ratio resulted in an increase in both the percentage and the amount of the sub 6.4 μm particle size drug removed from the carrier. Since imaging of the samples showed the absence of drug agglomerates, it was suggested that such observations were due to regions of higher adhesion (active sites) being filled, thereby allowing increased drug liberation with increasing dose.

The logical conclusion from such a hypothesis would be that if the number and/or energy range of active sites was reduced, the minimum point in the relationship between the percentage of the respirable fraction removed with drug load would be decreased to a lower drug load (or drug/lactose ratio), and conversely, by increasing such regions, the point would be increased. To test this hypothesis, and further investigate the phenomenon, the previous drug/lactose ratio study (ratios 1:100 to 1:5000) (Young et al., 2005) was repeated using a "smoothed" (etched) lactose, produced by the controlled surface dissolution of lactose (El-Sabawi et al., 2006).

EXPERIMENTAL

The formulation and testing methodology precisely followed that previously described (Young et al., 2005); however, the commercial grade 63–90 μm lactose, used to prepare the drug/lactose blends in the original study, was replaced with 5% surface dissolved lactose (63–90 μm size fraction) (El-Sabawi et al., 2006). As with the previous study, the same batch of micronized salbutamol sulfate was chosen as the model drug. Content uniformity (50 mg samples, $n = 10$) across each blend indicated coefficients of variations less than 5%. Aerosolization efficiency was determined by analyzing the drug deposition of 50-mg formulations (stored in gelatin capsules) from a Cyclohaler®, at 60 $L.min^{-1}$, using a twin stage impinger (TSI). Samples were randomized for drug/lactose ratio. All experiments were performed in triplicate and results were compared with data produced in the original study (Young et al., 2005). Morphology of the lactose particles was examined by scanning electron microscopy (SEM) (Jeol 6310, Jeol, Tokyo, Japan) at 10 KeV. Samples were gold coated prior to analysis (Edwards Sputter Coater, Surrey, UK).

RESULTS AND DISCUSSION

Representative scanning electron micrographs of untreated and 5% surface dissolved lactose particles are shown in Fig. 1. The temperature controlled surface etching process led to a significant reduction in the amount of intrinsic fines present, and generally increased the degree of surface smoothness, as indicated by SEM microscopy and surface area determinations (El-Sabawi et al., In press). The relationship between the loaded drug dose and emitted dose of the untreated and surface dissolved lactose blends is shown in Fig. 2A. It can be seen from Fig. 2A that, as observed in the previous study, a linear relationship existed between the loaded dose and emitted dose, with a slope for all data of 0.87 (passing through the origin) giving an R^2 of 0.99. Such observations, suggest that the efficiency of the device at removing drug from 50-mg bulk formulations was independent of lactose morphology or drug/lactose ratio.

Analysis of the fine particle dose (based on total recovered dose), that is, drug particles below 6.4 μm, (FPD_{LD}) obtained for the surface dissolved lactose formulations (Fig. 2B) indicated no significant differences in performance between loaded doses of 32.5 ± 2.2 μg

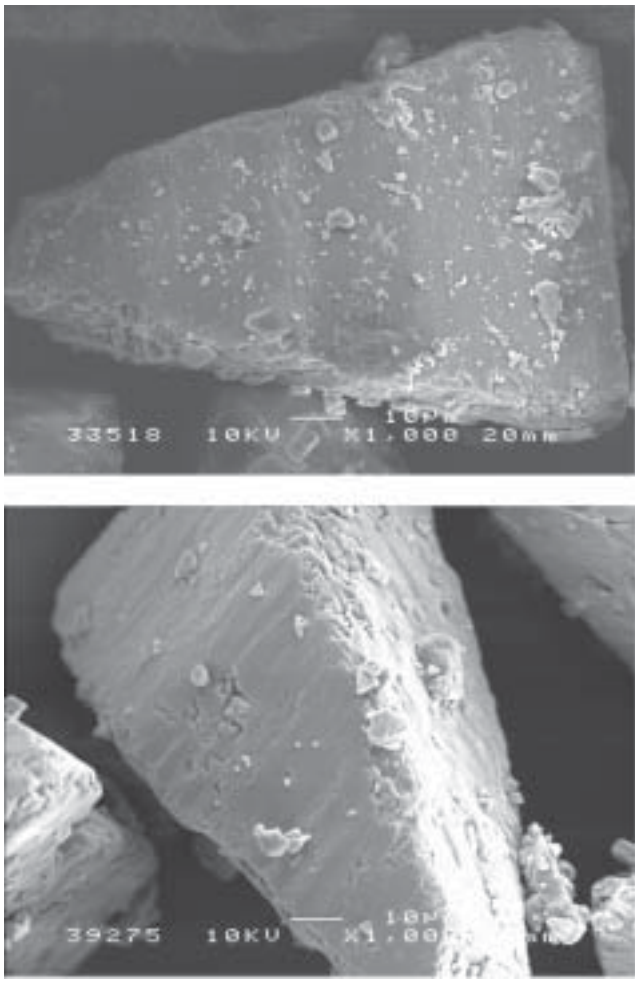

FIGURE 1 **Representative Scanning Electron Micrographs of 63–90 μm (A) Untreated Lactose and (B) 5% Surface Dissolved Lactose.**

and 63.5 ± 0.8 μg. Interestingly, blends using the supplied lactose formulations (reported previously) showed no significant differences until a higher loading dose was achieved (>135 μg dose). Such observations suggest that since both samples were 63–90-μm fractions and exhibited similar particle size distributions, the smoothing of lactose resulted in a decrease in active sites and, thus, an improvement of drug aerosolization at lower doses.

Furthermore, such observations are corroborated when examining the relationship between the fine particle fraction (based on total recovered dose), that is, the percentage drug below 6.4 μm to the total recovered drug (FPF_{LD}), shown in Fig. 2C. As previously discussed, when studying commercial grade 63–90-μm lactose formulations, at lower drug loads, both formulations exhibited a linear decrease in FPF_{LD} with increasing drug load, as the potential active sites were filled (resulting in no significant differenced in FPD_{LD}). At a

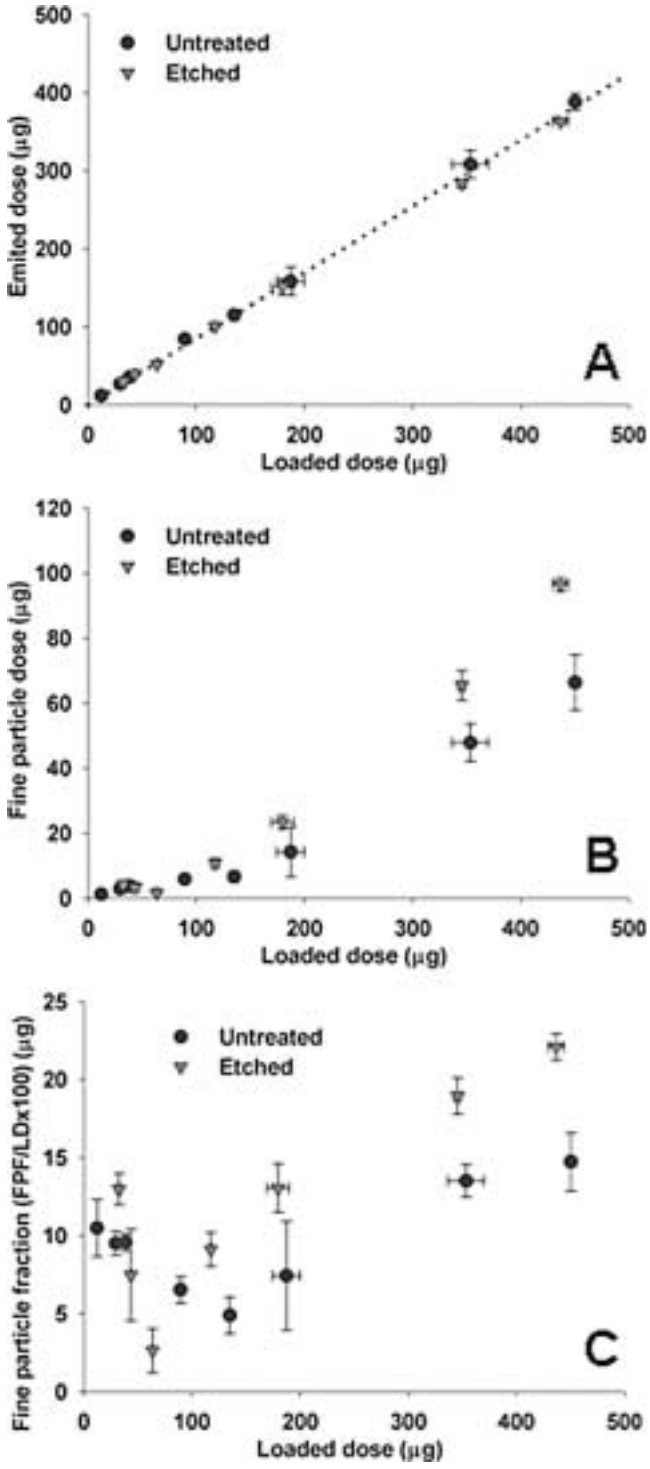

FIGURE 2 **Relationship Between Loaded Dose (A) Emitted Dose, (B) Fine Particle Dose, and (C) Fine Particle Fraction of Salbutamol Sulfate Blended With Untreated and Surface Dissolved Lactose Monohydrate.**

critical drug load, both the FPF_{LD} and FPD_{LD} increased. However, the smoother surface dissolved lactose resulted in a reduction in both the slope and the point of minimum linear decrease (minimum $FPF_{LD} = 64.5$ μg,

slope R^2 0.96; compared to 135 μg, slope R^2 0.98 for the supplied sample).

In general, such observations are expected since it is reasonable to assume that a reduction in active sites by surface smoothing would result in increased aerosolization performance at lower drug concentrations. Although such factors may not significantly affect the majority of current inhalation formulations, which typically contain more than 100 μg of drug, the performance of lower dose formulations will clearly be more vulnerable to the influence of any active sites.

CONCLUSIONS

The observations in this study suggest that smoothing of the surface of lactose monohydrate may afford carriers that offer improved drug aerosolization performance at both low and high drug loads by reducing the number and range of carrier surface active sites.

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