Drug Development and Industrial Pharmacy, 34:1002–1010, 2008
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ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1080/03639040802154905

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healthcare

Prediction of Dry Powder Inhaler Formulation Performance From Surface Energetics and Blending Dynamics

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The purpose of these studies was to investigate the ability of surface energy measurements and rates of mixing in dry powder inhaler (DPI) formulations to predict aerosol dispersion performance. Two lactose carrier systems comprising either spray-dried or milled particles were developed such that they had identical physical characteristics except for surface morphology and surface energies avoiding confounding variables common in other studies. Surface energy measurements confirmed significant differences between the powder systems. Spray-dried lactose had a higher surface entropy (0.20 vs. 0.13 mJ/m^{2}K) and surface enthalpy (103.2 vs. 79.2 mJ/m^2) compared with milled lactose. Mixing rates of budesonide or fluorescein were assessed dynamically, and significant differences in blending were observed between lactose systems for both drugs. Surface energies of the lactose carriers were inversely proportional to dispersion performance. In addition, the root mean square (RMS) of blending rates correlated positively with aerosol dispersion performance. Both techniques have potential utility in routine screening of DPI formulations.

Keywords inverse gas chromatography; mixing; lactose; aerosol

INTRODUCTION

The performance of dry powder inhalers (DPIs) is highly dependent on the interactions of the device and the formulation components. In DPI formulations, the active ingredient is micronized and most often blended with larger carrier particles, such as α-lactose monohydrate (Begat, Morton, Staniforth, & Price, 2004). The function of carrier particles within the DPI formulation is to aid flow, fluidization, and dispersion properties (Hickey et al., 2007; Smyth & Hickey, 2005). Typical DPI formulations are binary mixtures of drug (1–5 μm) and carrier particles smaller than 100 μm (Larhrib, Zeng, Martin, Marriott, & Pritchard, 1999). For particles smaller than about 10 μm in diameter, van der Waals forces between particles predominate over gravitational and fluid dynamic forces (Hickey, 2003). As a result, particles designed for inhalation (generally <5 μm) experience high degrees of cohesion and poor dispersibility. Carrier particles are often introduced into the system to modulate the interactive forces between drug particles. This type of formulation is termed an interactive mixture.

The performance of interactive mixtures is a function of the relative magnitudes of cohesive (drug–drug) and adhesive (drug–excipient) interparticulate forces. On the one hand, the ability to generate homogenous mixtures of drug and carrier particles depends on the ability of the drug to adhere to the lactose carrier. On the other hand, the aerosol dispersion performance of the DPI formulation depends on the forces required to deaggregate and disperse drug particles from the carrier surface. For example, strong adhesive forces may result in rapid and uniform mixing but may also prevent the release of the respirable drug particles from the carrier during inhalation (Hickey, Concession, Van Oort, & Platz, 1994). Conversely, strong cohesive forces may lead to particle segregation and heterogeneity during mixing but may also facilitate carrier–drug deaggregation during inhalation.

Understanding and being able to predict interparticulate forces in DPI systems is a major research objective, as this would lead to the ability to predict and optimize DPI performance. Interparticulate forces have been probed using a number of different approaches including the reductionist approach of looking at individual particle–particle interactions (e.g., atomic force microscopy), as well as composite and bulk powder methods utilizing powder flow indices and inverse gas chromatography (IGC) (Bérard et al., 2002; Louey, Mulvaney, & Stewart, 2001; Planinsek et al., 2003; Shekunov, Feeley, Chow, Tong, & York, 2003; Ticehurst, York, Rowe, & Dwivedi, 1996). So far, these methods have been either poor predictors of aerosolization behavior or have been technically challenging to perform. We present a simple and direct approach of evaluating cohesive/adhesive forces in DPI

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formulations via mixing kinetics. It is proposed that temporal mixing behavior correlates with the interparticulate forces between carrier and drug particles. Mixing studies, as routinely performed for blend uniformity validation, may therefore be employed as screening studies and predictors of powder performance in a passive DPI system.

MATERIALS AND METHODS

Materials

Lactose, both milled (Wyndale USP 100 Mesh) and spray-dried (Super-Tab Spray Dried), was provided by Lactose New Zealand (Hawera, NZ). Micronized Budesonide was purchased from Spectrum Chemicals and Laboratory Products (New Brunswick, NJ, USA). Fluorescein sodium was purchased from Sigma-Aldrich (St. Louis, MO, USA). Acetonitrile (HPLC grade) was purchased from VWR (West Chester, PA, USA). Gelatin capsules were obtained from Capsugel (Greenwood, SC, USA). Monobasic and dibasic potassium phosphates (HPLC grade) were purchased from VWR. The alkane probes used for dispersive free energy determination were hexane (99+%; Sigma-Aldrich), heptane (99+%; Sigma-Aldrich), octane (99.5+%; Fluka, St Louis, MO, USA), nonane (99+%; Sigma-Aldrich), and decane (99+%; Sigma-Aldrich). Polar probes used were tetrahydrofuron (THF) (99.99%; EM Science, Lawrence, KS, USA), chloroform (100%; Mallinkrodt, Hazelwood, MO, USA), acetone (99.7%; Mallinkrodt), ethyl acetate (99.9%; Mallinkrodt), diethyl ether (99+%; Acros, Geel, Belgium), and ethanol (100%, Aaper, Brookfield, CT, USA).

Lactose Carrier Preparation

Significant preliminary optimization studies were performed to obtain a method for generating comparable powder systems for both spray-dried and milled lactose. Five grams of lactose (spray-dried or milled) was sieved with a sieve stack (425-, 212-, 125-, 90-, 63-, and 45-μm mesh openings) using a Gilson Gilsonic Autosiever (Gilson Inc., Lewis Center, OH, USA). The sieve was operated using a combination of tap and vibration modes for 2 min at a vibration amplitude of 40. The powder used as carrier lactose in subsequent studies was collected from the 63-μm sieve and used in all studies below.

Micronization

Fluorescein sodium was micronized using a laboratory scale jet mill. The parameters used for milling were pusher pressure 100 psi, grinding 1 and grinding 2 pressures at 100 and 110 psi, respectively. Particle size was verified using scanning electron microscopy (SEM).

Blending

About 20 mg of micronized budesonide or fluorescein sodium was pre-blended with 0.98 g of sieved lactose by geometrical addition and dilution in a 6-mL vial. The total vial volume occupied by the powder was approximately 40%. Three replicates of each lactose type (spray-dried and milled) with budesonide or fluorescein sodium were prepared. The rates and extents of blending were observed over time by sampling the blends at times up to 60 min while being mixed using a Turbula orbital mixer at 42 rpm (Willy A. Bachofen AG, Basel, Switzerland). At each time point, 4-mg samples were taken from each of the vials ($n = 4$) by micro-thief sampling at pre-determined locations within the mixing vial. Samples were placed in high-performance liquid chromatography (HPLC) vials containing 2 mL mobile phase, and drug content was analyzed using the HPLC method below. Blending uniformity was quantified and plotted by calculating percentage coefficient of variance (%CV) over time for each vial in the experimental matrix. Mixing rates were calculated from the slope of the blend uniformity curves. Because of the oscillation of blending rates in both the positive and the negative direction (i.e., mixing and segregation processes), we calculated the root mean square (RMS), also known as the quadratic mean, as the statistical measure of the magnitude of the varying quantity (mixing rates). The RMS enables quantification of the magnitude of the mixing rate's deviation from zero. Simple averaging of the mixing rates is not applicable because both positive and negative mixing rates were obtained. RMS is a common method of quantifying signal amplitudes in a variety of fields and is easily applied to the dynamics of the mixing of binary powders. This also allows direct comparison of the systems under investigation and description of the mixing process/dynamics using a single number.

The RMS of variable x is given by the following equation:

$$R(x) = \sqrt{\frac{\sum_{i=1}^{n} x_i^2}{n}}.$$

Dispersion and Powder Performance

Dispersion and powder aerosolization performance was determined from cascade impaction studies as per USP/NF guidelines (USP 26, 2003) using a Next Generation Impactor (NGI) (MSP Corp., Shoreview, MN, USA). Briefly, 20 mg of blended powder from each vial containing lactose (spray-dried or milled) and drug were placed in gelatin capsules and placed inside a Handihaler (Boehringer Ingelheim, Ingelheim, Germany). The flow rate (60 L/min) was pre-calibrated using a Gilmont Flowmeter Base Model F-4001 (Barnant Company, Barrington, IL, USA). The temperature during the study was 22 ± 1°C and the relative humidity was 17 ± 2%.

The fine particle dose (FPD) was determined as the mass of drug deposited in the NGI with aerodynamic diameters less than 4.46 μm. Inertial impaction data were also subjected to log-probability analysis to allow the derivation of mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) for each aerosol powder dose (Feddah, Brown, Gipps, & Davies, 2000).

Chemical Analysis

Budesonide was analyzed according to the HPLC method reported by Gupta and Bhargava (2006). Briefly, HPLC was performed using a Hitachi Elite LaChrom (Hitachi, San Jose, CA, USA) with UV detection at 244 nm using a Kromasil C_8 column (150mm × 4.6 mm i.d.; Column Engineering, Chicago, IL, USA). The mobile phase consisted of acetonitrile–phosphate buffer (pH 3.2, 25 mM, 55:45 vol/vol) at a flow rate of 1.1 mL/min, injection volume 10 μL, and quantification was by peak area using a standard curve in the range 50–1 μg/mL. HPLC analysis of fluorescein sodium was performed using the same column. UV detection was at 490 nm and the mobile phase consisted of methanol : deionized water (60:40) at a flow rate of 1.0 mL/min.

Particle Size Analysis of Lactose

Particle size characteristics of the lactose powders were determined using a Sympatec Helos laser diffraction instrument (Sympatec GmbH, Clausthal-Zellerfeld, Germany). Briefly, sieved lactose (Spray-dried and milled) was dispersed using compressed nitrogen gas at 150 psi. The aerosol was drawn through the laser-sensing region with a relative pressure of 95 mbar using the Inhaler™ attachment, and the detector was activated at a minimum optical concentration between 4 and 5%. The size distribution was expressed by the volume mean diameter (VMD). Morphology and particle size were also analyzed using SEM (JEOL 5800LV Scanning Electron Microscope; Jeol, Peabody, MA, USA) in low-pressure mode.

Surface Area Analysis of Lactose

The surface area of sieved lactose (spray-dried and milled) was determined using BET gas adsorption method. Powders were prepared under vacuum for 1 h at 40°C and then analyzed using a Gemini Surface Area Analyzer (Micromeritics, Norcross, GA, USA). Calculation of the specific surface area was done by the BET multipoint method.

Surface Energy Analysis of Lactose

Surface energy measurements were performed using the approach proposed by Schultz, Lavielle, and Martin (1987); the rationale of this approach has more recently been described by Telko and Hickey; it is somewhat different from the more commonly used simplified methodology and includes entropic contributions to Gibb's free energy of adsorption (Telko & Hickey, 2007). IGC experiments were conducted with a Hewlett-Packard 5890 Series II GC equipped with flame ionization detector (GMI Inc., Ramsey, MN, USA). The instrument was modified to allow installation of 205 mm × 4 mm i.d. glass columns. Carrier gas employed was dry nitrogen at a flow rate of 30 mL/min. Oven temperatures used were 60, 48, 36, and 26°C. Previous experiments had shown that 60°C is the highest feasible temperature for analyzing lactose; prolonged exposure to higher temperatures can bring about polymorphic transitions. The lowest temperature that can reliably be maintained in the GC oven used is 26°C. Lactose was packed into deactivated (Mohammad & Fell, 1983) glass columns and plugged with silanated glass wool. After the temperature was changed, the packed column was allowed to equilibrate for 4 h before subsequent injections were made. Injections were made with a 1-μL Hamilton syringe. Injection volumes were <0.01 μL; infinite dilution was ensured. Each injection was made at least three times and averaged; the relative standard deviations in the retention times of these injections were less than 1% in each case. Each batch was examined with two separate packed columns. Because even inert probes, such as methane, can be somewhat retarded (Smith, Haken, & Wainwright, 1978), dead time was calculated using the retention times of heptane, octane, and nonane (Conder & Young, 1979).

Dispersive surface free energy was calculated at each temperature based on the method of Schultz et al. (1987), which correlates net retention volume, V_N, and free energy of adsorption, $-\Delta G_A$, via the following equations:

$$\begin{aligned} -\Delta G_A &= RT\ln V_N + C \\ &= 2\cdot N_A\cdot A\cdot\sqrt{\gamma_S^D}\sqrt{\gamma_L^D} + C, \end{aligned}$$

where N_A is Avogadro's number, A is the effective surface area of the probe molecule, γ_S^D and γ_L^D are dispersive free energies of interacting solid and probe, and C is a constant that depends on the chosen reference state. Given that surface area and γ_L^D increase linearly for a homologous series of *n*-alkanes, dispersive surface energy (or rather the square root of it) is determined from the slope of a $RT\ln V_N$ versus $2\cdot N_A\cdot A\cdot\sqrt{\gamma_L^D}$ plot. Specific free energy is determined from the retention of polar probes by way of the acid/base approach to molecular interactions (Gutmann, 1978), based on which specific interactions are classified as either electron donor- or electron acceptor-type interactions. Using this approach, the surface can be characterized by two constants related to the acid/base interactions via the equation:

$$\Delta H_A^{sp} = K_A DN + K_B AN^*,$$

where ΔH^{sp} is the specific enthalpy of adsorption, *DN* and *AN** the donor and corrected acceptor numbers, and K_A and K_B are the acid (acceptor) and base (donor) parameters of the studied surface, respectively.

Thermal Properties of Lactose

The thermal properties of sieved lactose (spray-dried and milled) were analyzed using a modulated differential scanning calorimeter (Model 2920; TA Instruments, New Castle, DE, USA). Samples of approximately 10 mg were sealed in aluminum pans and scanned at a rate of 10°C/min from 35 to 280°C. The modulation signal was set at 1.592°C/min. The thermograms were analyzed using TA Instruments Universal Analysis Software.

Powder Flow and Density Characteristics of Lactose

True density was measured using an Ultrapycnometer according to manufacturer's directions (Quantachrome Instruments, Boynton Beach, FL, USA). Briefly, 2.5 g of spray-dried and milled lactose was added to the Ultrapycnometer and the true density analyzed using compressed helium at 17 psi for 10 min. Six sample runs were performed and averaged. Powder flow characteristics were characterized using bulk/tap density, powder compressibility index, and Flodex measurements (Hansen Research, Salt Lake City, UT, USA). Briefly, Flodex measurements involved adding approximately 20 g of spray-dried or milled lactose into a chamber and the flow properties determined by the flow under gravity through various orifices of different size until all the powder passed through.

Statistical Analysis

All statistical analysis was performed using the paired Student's *t*-test with two-tailed comparison. Differences of $p < .05$ are considered significantly different.

RESULTS

Physical Properties

The physical characterization of the lactose carrier systems confirmed equivalent particle size distributions, surface areas, true densities, and melting points of the spray-dried and milled powders (Table 1). The electron micrographs (Figure 1) show the different morphologies of milled lactose and spray-dried lactose. Spray-dried particles, as anticipated, were spherical, and milled lactose displayed monoclinic or tomahawk crystal shape.

Surface Energies

Plots of $RT \ln V_N$ versus $2 \cdot N_A \cdot A \cdot \sqrt{\gamma_L^D}$ were determined at each temperature (26, 36, 48, 60°C), and straight lines 8were fitted to the data as described in Telko and Hickey (2007). The fit was excellent in each case ($R^2 > .999$). Table 2 shows the dispersive free energies determined at each temperature, which are in agreement with previous studies (Ahfat, Buckton, Burrows, & Ticehurst, 2000; Newell, Buckton, Butler, Thielmann, & Williams, 2001a, 2001b; Planinsek et al., 2003; Ticehurst, York, Rowe, & Dwivedi, 1996). The spray-dried material has higher surface free energy at each temperature. Moreover, when the dispersive surface free energies are plotted against temperature for the materials (Figure 2), different curves are obtained. The free energy of spray-dried lactose increases more rapidly with temperature, resulting in a higher surface entropy (0.20 vs. 0.13 mJ/m^{2}K) and surface enthalpy (103.2 vs. 79.2 mJ/m^2). Clearly, spray-dried lactose is more energetic with respect to Lifschift–van der Waals forces. Interpretation of polar probes yields further insight. Differences in retention behavior of polar probes between spray-dried and milled were evident throughout the analysis. The specific free energies obtained for each probe were plotted against temperature, and enthalpies were calculated. The column to column reproducibility was very good, and enthalpy values had RSD < 5% on all points. The enthalpies were used to obtain acidic and basic parameters, shown in Figure 3. Acid (acceptor) and base (donor) parameters, K_A and K_B, respectively, were 0.186 and 0.338 for spray-dried and 0.159 and 0.235 for milled lactose. The differences between spray-dried and milled samples were evident with each probe and resulted in significantly different K_A and K_B values. Spray-dried material is more energetic with higher acidic and basic parameters and is thus expected to interact more strongly with acidic and basic molecules.

TABLE 1
Physical Characteristics of Spray-Dried and Milled Lactose

	Spray-Dried Lactose	Milled Lactose
Particle size (VMD)	69.83 ± 0.21 μm	70.23 ± 0.45 μm
Surface area	1.23 m^2/g	1.21 m^2/g
True density	1.54 ± 0.00 g/cm^3	1.50 ± 0.00 g/cm^3
Melting point	221.47 ± 0.68°C	222.74 ± 0.55°C

Powder Flow

The derived characteristics of these powders, powder compressibility (spray-dried 12.1 ± 0.26%, milled 33.9 ± 0.14%), and critical orifice measurements (Flodex) (spray-dried = 7, milled = 22) indicated significantly better flow properties of spray-dried lactose compared with milled lactose.

Blending Dynamics

Mixing rates of budesonide or fluorescein were assessed dynamically, and significant differences in blending were observed between lactose systems for both drugs (Figure 4A and B). The mixing rates shown in Figure 4A and B indicate the dynamic changes in the coefficient of variation of samples taken from each powder system. For both drugs, milled lactose demonstrated the greatest dynamical change and variation in mixing and segregation rates. Spray-dried lactose : budesonide formulations showed the least change in mixing rates. Also, we did not detect periods where powder segregation occurred with the spray-dried lactose : budesonide formulations (all values were negative). By contrast, oscillating periods of mixing and segregation were observed for the milled lactose : budesonide

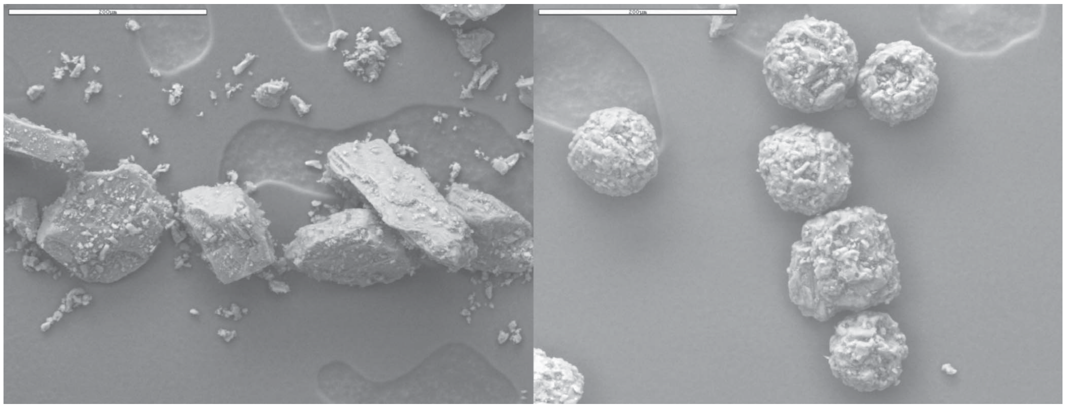
(A) (B)

FIGURE 1. Representative scanning electron micrographs (SEM) of carrier particles: (A) lactose milled; (B) lactose spray-dried. Scale bar is 200 μm.

TABLE 2
Dispersive Surface Free Energies ($M \pm SD$)

T (°C)	Dispersive Surface Free Energy (mJ/m^2) Milled	Dispersive Surface Free Energy (mJ/m^2) Spray Dried
26	40.3 ± 0.04	43.0 ± 0.00
36	38.8 ± 0.00	40.9 ± 0.54
48	37.7 ± 0.06	38.8 ± 0.36
60	35.7 ± 0.37	36.1 ± 0.50

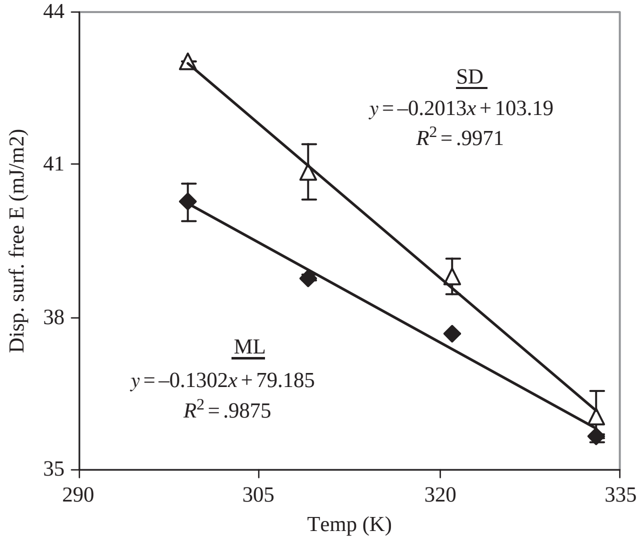

FIGURE 2. Dispersive surface free energy of spray-dried (SD) and milled (ML) lactose versus temperature. The spray-dried material's free energy varied more strongly with temperature, resulting in higher entropy and enthalpy values.

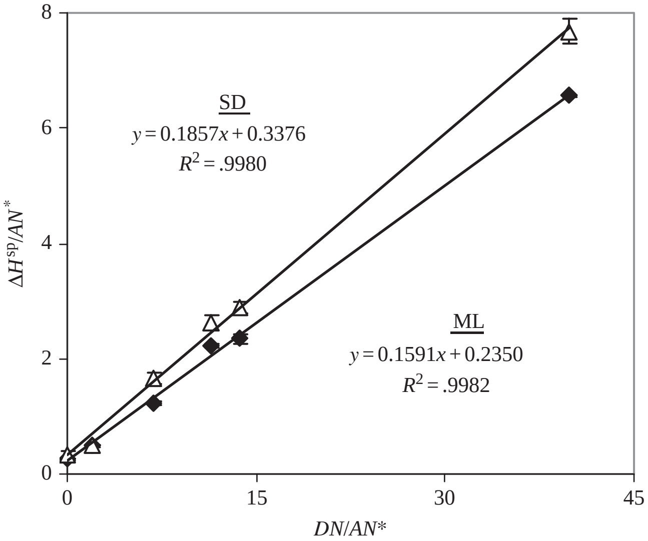

FIGURE 3. Determination of K_A and K_B values from $\Delta H^{sp}/AN^*$. Triangles represent spray-dried (SD) lactose; diamonds represent milled (ML) lactose. Each point is average ± *SD*. The best-fit lines pass through all points and clearly differentiate spray-dried from milled material. The correlation is very strong in each case ($R^2 \geq .998$).

powders. Similarly, the fluorescein experiments showed that the milled lactose had greater fluctuations from periods of mixing to periods of segregation compared with the spray-dried lactose. We also characterized the average RMS of mixing for each powder system. This allows a single number to characterize the overall mixing dynamics for each drug and lactose combination. These data are presented below where correlations between mixing (RMS) and dispersion performance are described.

Dispersion Studies

Aerosol dispersion studies were performed to provide quantitative performance data for each drug : lactose combination

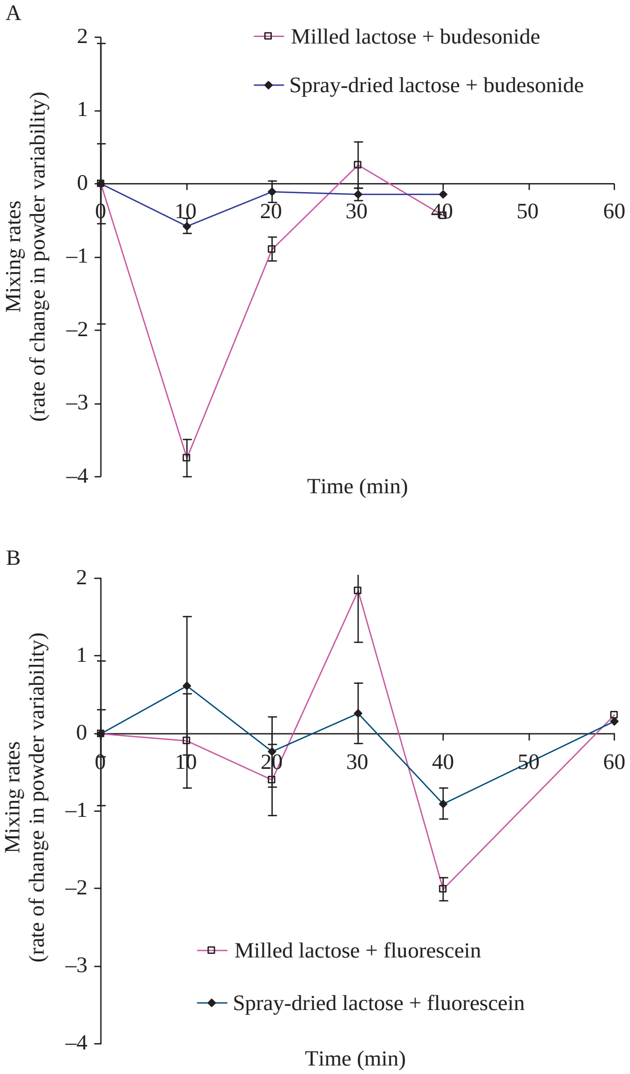

FIGURE 4. Mixing rates determined throughout the blending experiment for both (A) budesonide and (B) fluorescein, using the milled and spray-dried lactose carrier powders. Mixing and segregation rates are determined from the coefficients of variation of samples taken at each time point. Positive values indicate segregation whereas negative values correspond to mixing ($n = 3$).

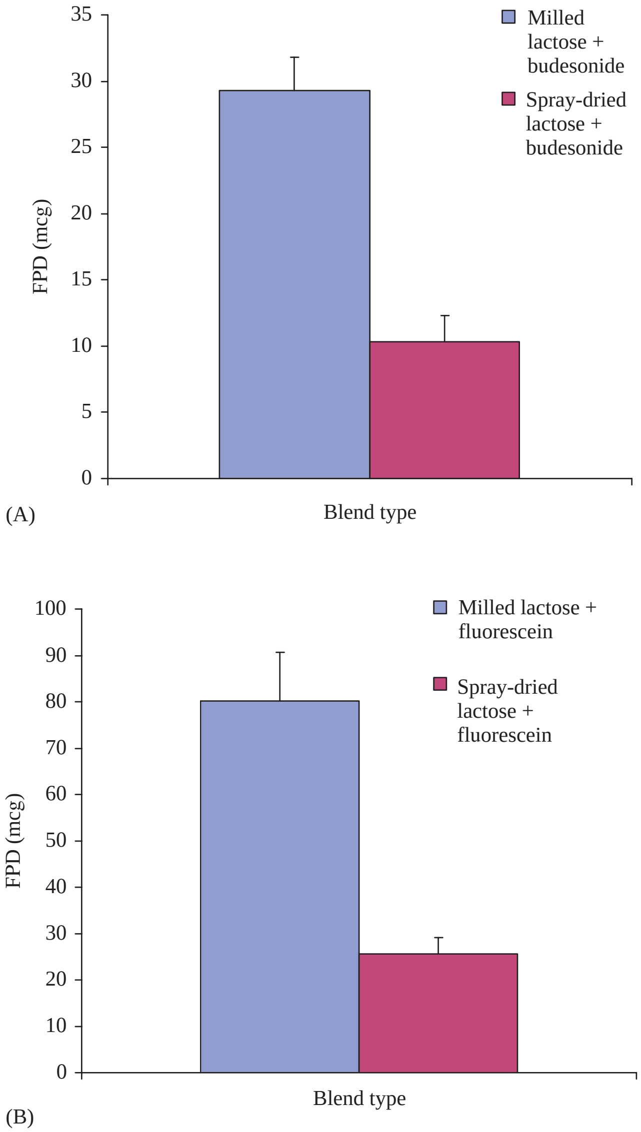

FIGURE 5. Average fine particle dose (FPD) of micronized budesonide (A) and fluorescein (B) from milled and spray-dried Lactose ($n = 9$).

and allow the predictive nature of both surface energy measurements and mixing studies to be determined. As expected, for both budesonide and fluorescein, the milled lactose system provides significantly improved performance over the spray-dried system (Figure 5). This has been described previously and is thought to be related to the higher amorphous content in spray-dried particles that may give rise to higher surface energies of spray-dried particles (Louey, Van Oort, & Hickey, 2004; Newell et al., 2001a; Schiavone, Palakodaty, Clark, York, & Tzannis, 2004). It was also noted that fluorescein aerosol dispersion efficiencies were significantly higher than that observed for budesonide. The poorer performing spray-dried lactose, when used with fluorescein, had an equivalent FPD to that of the higher performing milled lactose from the budesonide system.

Figure 6A and B shows the emitted doses from each formulation. No differences in emitted dose were detected, indicating that any difference in powder flow properties (i.e., fluidization of the powder from the inhaler) was not responsible for differences in dispersion efficiencies observed with the FPD data. Despite the poorer flow performance of the milled lactose, the emitted dose from these formulations was the same as spray-dried systems. In addition, the emitted doses were very similar between the two model drugs evaluated (budesonide and fluorescein) despite their very different FPD efficiencies. This emphasizes the strong dependence of dispersion efficiency on interparticulate forces (drug : carrier) compared with low dependency on flow properties.

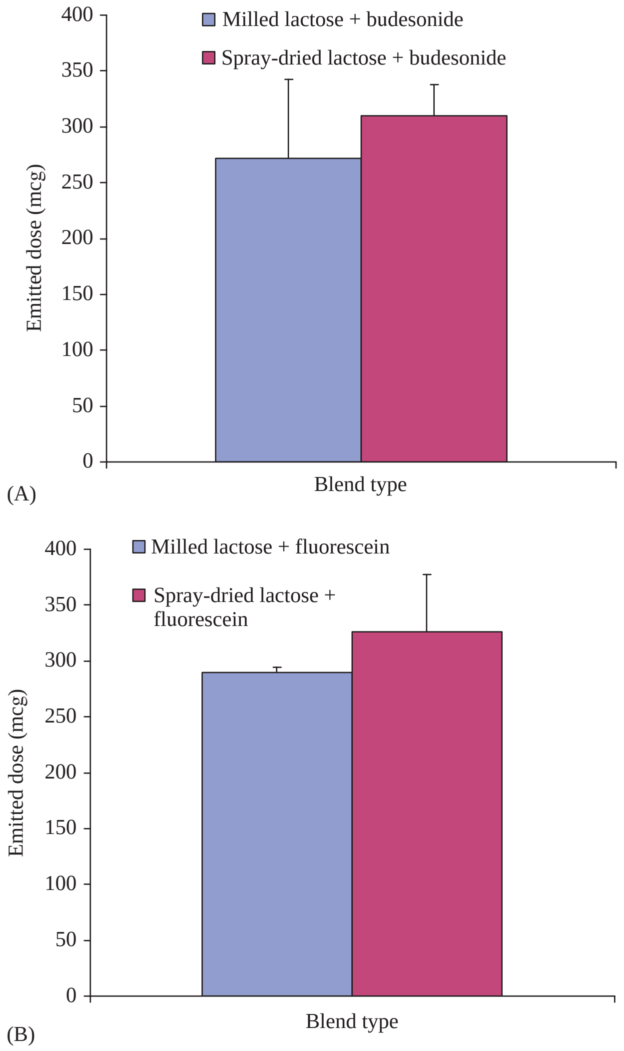

FIGURE 6. Emitted dose characteristics for each powder blend ($n = 9$) (A) budesonide studies and (B) fluorescein studies.

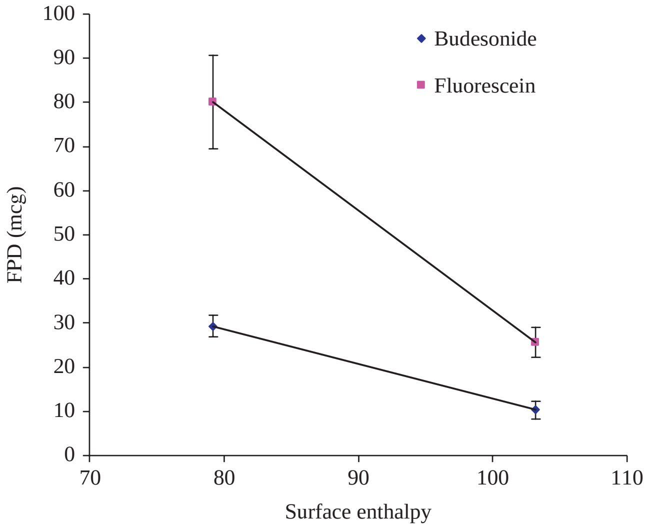

FIGURE 7. Fine particle dose (FPD) as a function of surface enthalpy for each formulation type.

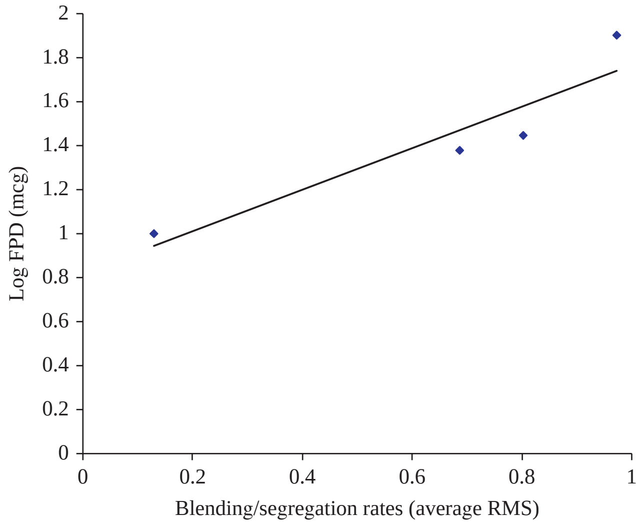

FIGURE 8. Log of the fine particle dose (FPD) as a function of the average root mean square (RMS) of mixing rates.

Aerosolization Performance Correlates with Surface Energies and Mixing Dynamics

Surface energies of the lactose carriers were inversely proportional to dispersion performance (Figure 7). As expected, there were significant differences in the correlation depending on the drug investigated. Similar relationships between the FPD and the K_a and K_b parameters were also evident (data not shown).

FPD was also related to the mixing behavior of each system (Figure 8). In this case, a positive correlation between the average RMS and log (*FPD*) was found. Increasing the RMS indicates greater fluctuations in mixing as a function of time.

DISCUSSION

The development of matched lactose carrier powder systems facilitated the investigation of surface energy and blending dynamics on aerosol performance under controlled conditions. Developing these matched DPI carrier systems was not a trivial task and has not been reported before. The most important differences between the spray-dried and milled lactose powders were particle morphology and surface energetics. As expected, spray-dried particles were spherical and had higher surface energies. Milled particles of α-lactose monohydrate were more crystalline in shape and had a correspondingly lower surface energy. Differences in morphology and surface energies also corresponded to differences in powder flow measurements. Again, as expected, the spray-dried particles had significantly improved flow performance as measured by

Carr’s index and FloDex™ measurements. To minimize these differences in flow performance during the blending studies, we investigated the flow regimes of the powders within the mixing vessels at different speeds of the orbital mixer. The dynamic blending studies were performed at mixer speeds where the powder flow was observed to be in the cascading regime, thus minimizing the influence of flow performance differences during mixing. Blending dynamics were hypothesized to predict dispersion performance on the basis of cohesive and adhesive balances within binary mixtures. In general, the mixing kinetics showed that the binary DPI mixtures underwent nonlinear mixing. Budesonide blends with spray-dried lactose progressed via rapid stepwise mixing. However, budesonide mixing with milled lactose demonstrated both mixing and segregation of the binary components as a function of time. Patterns of fluorescein mixing behavior with spray-dried and milled lactose were less apparent. In both cases, mixing and segregation intervals were identified. Milled lactose had greater changes in mixing rates (i.e., more rapid mixing and segregation) compared with spray–dried lactose. These observations may be due to the significantly less adhesive forces between fluorescein and lactose as evidenced by the significantly higher FPD of fluorescein aerosols compared with budesonide aerosols.

The main objective of these studies was to investigate the predictive nature of both surface energy measurements and mixing dynamics for aerosol dispersion performance. Surface energy measurements were correlated negatively with dispersion performance, as predicted. Higher surface energies of the lactose powder systems resulted in lower dispersion efficiencies (as measured by FPD) for both drugs tested. This was consistent for all surface energy quantification parameters (enthalpy, entropy, and acid and base contributions). Similar observations have been made previously between fine particle fraction and surface energy (Schiavone et al., 2004). However, others have also reported a positive correlation between surface energy and fine particle fraction (Cline & Dalby, 2002). These different findings reported in IGC literature pertaining to DPI formulations exemplify the difficulties in interpretation of correlations for these systems. If the powders that are being compared have different particle sizes, size distributions, surface areas, and other physical characteristics that are different, isolating the influence of surface energy on powder performances can be impossible. In these studies, we are confident that all these confounding variables (with the exception of particle morphology) have been well controlled, and differences in powder performance can be strongly attributed to surface energetics. Further studies are underway using other drugs and additional matched lactose systems to confirm this relationship. Surface energy determinations are quite labor intensive, and the quantity of powder required is relatively large for accurate measurements. As a result, there are limitations to the routine and high throughput screening of carrier systems for inhalation formulation development. Furthermore, surface energy measurements will generally only be applicable to the carrier system and not to the active agent due to sample size, process, and cost limitations. As a consequence, only one component of a binary dry powder inhalation (DPI) formulation will be characterized, limiting the utility of the method.

By contrast, mixing studies should be routinely performed during formulation development and may provide information on the interactions between both carrier and drug particles. We hypothesized that blending studies could be used to gain insight into the cohesive and adhesive balance between carrier and drug particles. Under this hypothesis, strong interactions between drug and carrier would be demonstrated during blending studies as rapid mixing. Alternatively, weak interactions between drug and carrier would result in either poor blending or oscillating periods of mixing and segregation. If blending studies were sensitive to these differences in interparticulate forces, then they should also be a marker for aerosol dispersion performance. In these studies, we observed significant differences in blending behavior depending on both drug and lactose systems. In particular, the RMS of blending rates (i.e., both mixing and segregation rates) appeared to be predictive of aerosol dispersion performance. Increases in the RMS correlated with improved dispersion performance. Thus, greater mixing and segregation rates are associated with improved formulation performance. This finding deviates somewhat from our original hypothesis. However, it appears that mixtures that have periods of both mixing and segregation at the time scales monitored (i.e., every 10 min up to 60 min) performed better. This observation is consistent with our original postulation that weak interactions between drug and carrier would result in either poor blending or oscillating periods of mixing and segregation. In terms of a screening method, blending studies are routinely performed for formulation development independently of predicting aerosol performance. Consequently, blending studies are an attractive quantitative method to probe interactions between drug and carrier in DPI formulations. We have initiated follow-up studies to utilize nondestructive chemical analysis (fiber optic probes in the mixing chamber) for faster real-time monitoring of blending dynamics. It is possible that the sensitivity of this technique will be significantly enhanced by improving both the temporal resolution and accuracy in powder sampling. In addition, we plan to evaluate the effect of differences in triboelectrification and electrostatic charge in different formulations being tested.

CONCLUSION

Under controlled conditions, the relationship between surface energy measurements and dispersion performance is, as anticipated, inversely proportional. However, the relationship between mixing dynamics and dispersion performance was more complex. The observation of periods mixing and segregation in DPI formulations during blending was positively correlated with aerosol dispersion performance. We quantified this by using the RMS of mixing rates. Both surface energy measurements and blending studies may be used to predict DPI formulation performance. However, routine use of surface energy measurements via IGC may be limited by time and material constraints. By contrast, blending studies may be easily implemented for formulation screening, but further studies are required for confirmation.

ACKNOWLEDGMENTS

Authors acknowledge the generosity of Lactose New Zealand (DMV-Fonterra Excipients) for providing lactose samples used in these studies. Martin Telko gratefully acknowledges past support from a U.S. Pharmacopeia Graduate Fellowship and current support from a PhRMA Foundation Pre-Doctoral Fellowship.

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