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

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Shortened Title: Performance of DPIs from IGC and Blending Studies

Abstract

The Purpose of these studies was to investigate the ability of surface energy measurements and rates of mixing in dry powder inhaler 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/m2K) and surface enthalpy (103.2 vs. 79.2 mJ/m2) compared to 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 of blending rates correlated positively with aerosol dispersion performance. Both techniques have potential utility in routine screening dry powder inhaler formulations.

Introduction

The performance of dry powder inhalers (DPI) 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 (1-5μm) and carrier particles smaller than 100μm (Larhrib, Zeng, Martin, Marriott, & Pritchard, 1999). It is known that for particle sizes of 10 μm diameter or less, gravitational forces acting on the particles transition to thermodynamic forces such as van der Waals forces between particles (Hickey, 2003). As a result, particles designed for inhalation (generally less than 5 μm) experience high degrees of cohesion. For this reason, the carrier particles are introduced into the system to modulate the interactive forces between drug particles. This type of formulation is termed an interactive mixture.

Accordingly, the performance of interactive mixtures are controlled by relative magnitudes of cohesive (drug-drug) and adhesive (drug-excipient) interparticulate forces. On one hand, the ability to generate homogenous mixtures of drug and carrier particles will depend on the ability of the drug to adhere to the lactose carrier. Alternatively, 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, very strong adhesive forces may result in rapid and uniform mixing but may also prevent the release of the respirable drug particles from the carrier particles during inhalation (Hickey,

Concession, Van Oort, & Platz, 1994). Conversely, strong cohesive forces may cause particle segregation and heterogeneity during mixing but facilitate carrier-drug deaggregation during inhalation.

Understanding and being able to predict interparticulate forces in DPI systems is a major focus of research, 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 (Bérard et al., 2002; Louey, Mulvaney, & Stewart, 2001; Planinξek et al., 2003; Shekunov, Feeley, Chow, Tong, & York, 2003; M. D. Ticehurst, P. York, R. C. Rowe, & S. K Dwivedi, 1996). So far, these methods have been either poor predictors of aerosolization behavior or are technically challenging to perform. We hypothesize that a simple direct approach of evaluating cohesive/adhesive forces in DPI formulations can be studied via mixing kinetics. It is proposed that temporal mixing behavior should correlate 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 & Methods

Materials

Lactose, both milled (Wyndale USP 100 Mesh) and spray dried (Super-Tab Spray Dried), were purchased from Lactose New Zealand (Lactose New Zealand, Hawera, New Zealand). 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 phosphate (HPLC grade) was purchased from VWR, West Chester, PA USA. The alkane probes used for dispersive free energy determination were hexane (99+%, Aldrich), heptane (99+%, Aldrich), octane (99.5+%, Fluka), nonane (99+%, Aldrich), and decane (99+%, Aldrich). Polar probes used were tetrahydrofuron (THF) (EM Science, 99.99%), chloroform (100%, Mallinkrodt), acetone (99.7%, Mallinkrodt), ethyl acetate (99.9%, Mallinkrodt), diethyl ether (99%+, Acros), and ethanol (100%, Aaper).

Lactose Carrier Preparation

Significant preliminary and 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 45μm mesh openings) using a Gilson Gilsonic Autosiever (Gilson Inc, Ohio, USA). The sieve was operated using a combination of tap and vibration modes for 2

minutes at a vibration amplitude of 40. The powder used as carrier lactose in subsequent studies was collected from the 63µm sieve and used in all studies below.

Micronization

Fluorescein sodium was micronized using a lab scale jet mill to reduce the particle size. The parameters used for milling were Pusher Pressure 100psi, Grinding 1 and Grinding 2 Pressures at 100 and 110psi respectively. Particle size was verified using scanning electron microscopy.

Blending

20mg of micronized budesonide or fluorescein sodium was pre-blended with 0.98g of sieved lactose by geometrical addition and dilution in a 6ml vial. The total vial volume occupied by the powder was approximately 40%. Three replicates of each lactose type (spray dried & milled) with budesonide or fluorescein sodium were prepared. The rates and extent of blending were observed over time by sampling the blends at times up to 60 minutes while being mixed using a Turbula orbital mixer at 42rpm (WAB, Switzerland). At each time point 4mg samples were taken from each of the vials (n=4) by micro-thief sampling at predetermined locations within the mixing vial. Samples were placed in HPLC vials containing 2ml 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 by determining the slope of the blend uniformity curves. Due to the oscillation of blending rates in both the positive and 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 rates 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 variate *x* is given by the following formula:

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

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, MN). Briefly, 20mg 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, Germany). The flow rate (60L/min) was pre-calibrated using a Gilmont Flowmeter Base Model F-4001 (Barnant Company, Barrington, IL, USA). The temperature during the study was 22ºC ± 1ºC and the relative humidity at 17% ± 2%.

The fine particle dose (FPD) was determined as the mass of drug deposited in the NGI with aerodynamic diameters less than 4.6μm. Inertial impaction data was 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 *et al* (Gupta & Bhargava, 2006). Briefly, HPLC was performed using a Hitachi Elite LaChrom (Hitachi, CA USA) with UV detection at 244nm using a Kromasil C_8 column (150mm x 4.6mm i.d., Column Engineering, CA USA). The mobile phase consisted of acetonitrile-phosphate buffer (pH 3.2, 25mM, 55:45v/v) at a flow rate of 1.1ml/min, injection volume 10µl and quantification was by peak area using a standard curve in the range 50µg/ml-1µg/ml. HPLC analysis of fluorescein sodium was performed using the same column. UV detection was at 490nm and the mobile phase consisted of methanol:de-ionized water (60:40) at a flow rate of 1.0ml/min.

Particle Size analysis of lactose

Particle size characteristics of the lactose powders were determined using a Sympatec Helos laser diffraction instrument (Sympatec GmbH, Germany). Briefly sieved lactose (Spray dried & milled) was dispersed using compressed nitrogen gas at 150psi. The aerosol was drawn through the laser sensing region with a relative pressure of 95mbar using the Inhaler™ attachment and the detector was activated at a minimum optical concentration of between 4% and 5%. The size distribution was expressed by the volume

mean diameter (VMD). Morphology and particle size were also analyzed using S.E.M (JEOL 5800LV Scanning Electron Microscope) in low pressure mode.

Surface Area analysis of lactose

The surface area of sieved lactose (spray dried & milled) was determined using BET gas adsorption method. Powders were prepared under vacuum for 1 h at 40ºC and then analyzed using a Gemini Surface Area Analyzer (Micromeritics, Norcross, 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 described by Telko and Hickey and does not assume the entropic contributions to Gibb's free energy of adsorption can be neglected (Telko & Hickey, 2007). Inverse gas chromatography (IGC) experiments were conducted with a Hewlett-Packard 5890 Series II GC equipped with flame ionization detector. The instrument was modified to allow installation of 205mm, 4mm ID glass columns. Carrier gas employed was dry nitrogen at a flow rate of 30mL/min. Oven temperatures used were 60^{o}C, 48^{o}C, 36^{o}C, and 26^{o}C. Previous experiments had shown that 60^{o}C is the highest feasible temperature for analyzing lactose; prolonged exposure to higher temperatures can bring about polymorphic transitions. 26^{o}C is the lowest temperature that can reliably be maintained in the GC oven used. 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 hours 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 3 times and averaged; the relative standard deviations in the retention times of these injections were <1% in each case. Each batch was examined with two separate packed columns. Since 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).

Thermal properties of lactose

The thermal properties of sieved lactose (spray dried & milled) were analyzed using a modulated differential scanning calorimeter (Model 2920, TA instruments, New Castle, DE, USA). Samples of approximately 10mg were sealed in aluminum pans and scanned at a rate of 10ºC/min from 35 to 280ºC. The modulation signal was set at 1.592ºC/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, 2.5g of spray dried and milled lactose was added to the Ultrapycnometer and the true density analyzed using compressed helium at 17psi for 10 minutes. The average of six sample runs was performed. Powder flow characteristics were characterized using bulk/tap density, powder compressibility index, and Flodex measurements (Hansen Research, USA). Briefly, Flodex measurements involved adding approximately 20g 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-t test with two-tailed comparison. Differences of $p<0.05$ 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

Dispersive surface free energy was calculated at each temperature based on the method of Schultz et al., 1987 (Schultz, Lavielle, & Martin, 1987). Plots of $RT\ln V_N$ versus $2\cdot N_A\cdot A\cdot\sqrt{\gamma_L^D}$ were determined at each temperature (26°C, 36°C, 48°C, 60°C), and straight line was fitted to the data as described in Telko and Hickey(Telko & Hickey, 2007) . The fit was excellent in each case ($R^2 > 0.999$). Table 2 shows the dispersive free energies determined at each temperature, and are in agreement with previous studies (Ahfat, Buckton, Burrows, & Ticehurst, 2000; Newell, Buckton, Butler, Thielmann, & Williams, 2001a, 2001b; Planinsek et al., 2003; M. D. Ticehurst, P. York, R. C. Rowe, & S. K. 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^2K) 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. K_A and K_B values obtained are 0.186 and 0.338 for spray dried, and 0.159 and 0.235 for milled. The differences between spray dried and milled samples are evident with each probe and result 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.

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 to 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 (Figures 4a and 4b). The mixing rates shown in figures 4a and 4b 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). In contrast, oscillating periods of mixing and segregation were observed for the milled lactose:budesonide powders. Similarly, the fluorescein experiments showed that the milled lactose had greater fluctuations from periods of mixing to periods of segregation compared to the spray dried lactose. We also characterized the average root mean square (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 and allows 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 fine particle dose to that of the higher performing milled lactose from the budesonide system.

Figures 6a and 6b show the emitted doses from each formulation. No differences in emitted dose were detected, indicating that any differences in powder flow properties (i.e. fluidization of the powder from the inhaler) was not responsible for differences in dispersion efficiencies observed with the fine particle dose 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 fine particle dose efficiencies. This emphasizes the strong dependence of dispersion efficiency on interparticulate forces (drug:carrier) compared to low dependency on flow properties.

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 fine particle dose and the K_a and K_b parameters were also evident (data not shown).

Fine particle dose 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 was particle morphology and surface energetics. As expected spray dried particles were spherical and had higher surface energies. Milled particles of alpha-lactose monohydrate were more crystalline shape and had a corresponding 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 the binary DPI mixtures underwent non-linear mixing. Budesonide mixing with spray dried lactose progressed via stepwise mixing rapidly. 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 obvious. 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 to spray dried. These observations may be due to the significantly less adhesive forces between fluorescein and lactose as evidenced by the significantly higher fine particle dose of fluorescein aerosols compared to 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 fine particle dose) 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 as it pertains to dry powder inhalation formulations exemplifies the difficulties in interpretation of correlations in 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 and cost considerations. As a consequence, only one component of a binary dry powder inhalation formulation will be characterized, limiting the utility of the method.

In 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 system. In particular, the root mean square 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 were 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 minutes up to 60 minutes) 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 should be 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 dry powder inhaler formulations. We have initiated follow-up studies to utilize non-destructive chemical analysis (fiber optic probes in the mixing chamber) for faster real time monitoring of blending dynamics. It is possible 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 dry powder inhaler formulations during blending was positively correlated with aerosol dispersion performance. We quantified this by using the root mean square of mixing rates. Both surface energy measurements and blending studies may be used to predict dry powder inhaler

formulation performance. However, routine use of surface energy measurements via IGC may be limited by time and material constraints. In contrast, blending studies may be easily implemented for formulation screening, but further studies are required for confirmation.

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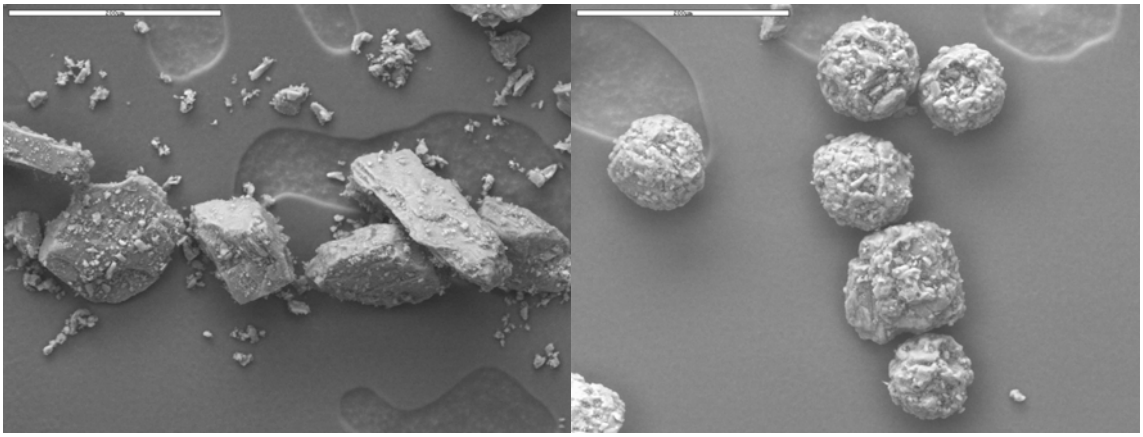
Table 1. Physical characteristics of Spray dried and Milled Lactose

	Spray dried Lactose	**Milled Lactose**
Particle Size (VMD)	69.83µm ± 0.21	70.23µm ± 0.45
Surface Area	1.23 m^2/g	1.21 m^2/g
True Density	1.54g/cm^3± 0.00	1.50g/ cm^3± 0.00
Melting Point	221.47±0.68 ºC	222.74±0.55ºC

Table 2. Dispersive Surface Free Energies (mean ± SD)

T (^{o}C)	Dispersive Surface Free Energy, mJ/m^2	
	Milled	**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



A B

Figure 1. Representative scanning electron micrographs of carrier particles (A: Lactose Milled; B: Lactose Spray dried), Scale bar is 200µm

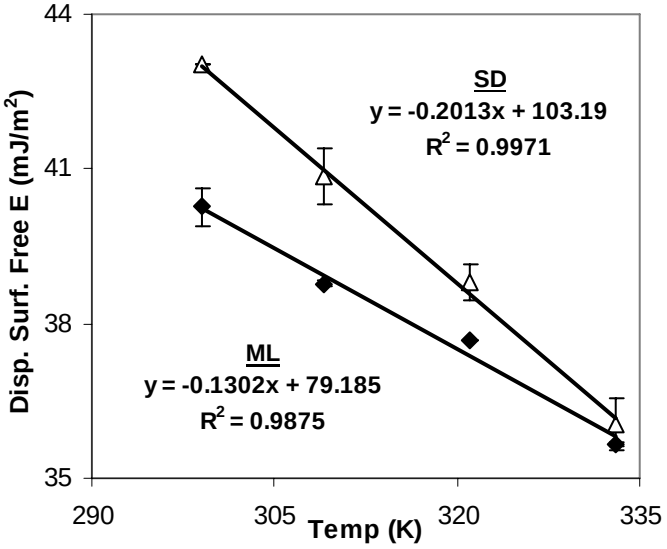


Figure 2. Dispersive surface free energy of Spray dried (SD) and Milled (ML) lactose vs. temperature. The Spray dried material's free energy varied more strongly with temperature, resulting in higher entropy and enthalpy values.

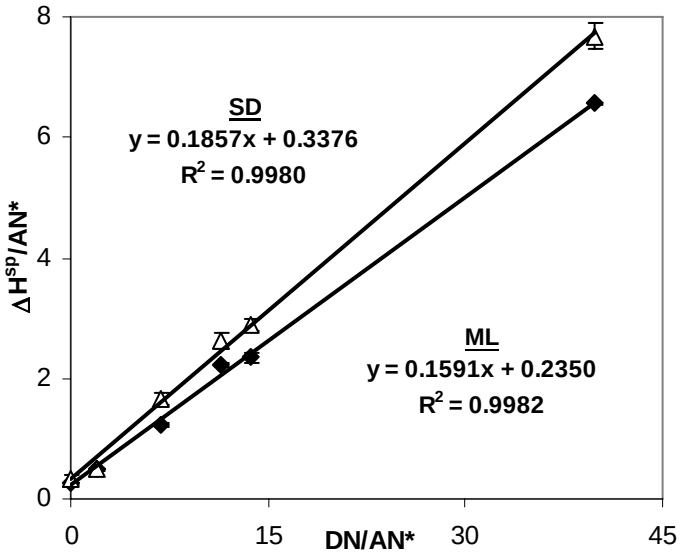


Figure 3. Determination of K_A and K_B values from $\Delta H^{sp}/AN^*$. Triangles represent Spray dried (SD) lactose; diamonds represent Milled (ML) lactose. Each point is average ± standard deviation. The best-fit lines pass through all points and clearly differentiate spray dried from milled material. The correlation is very strong in each case ($R^2 \geq 0.998$).

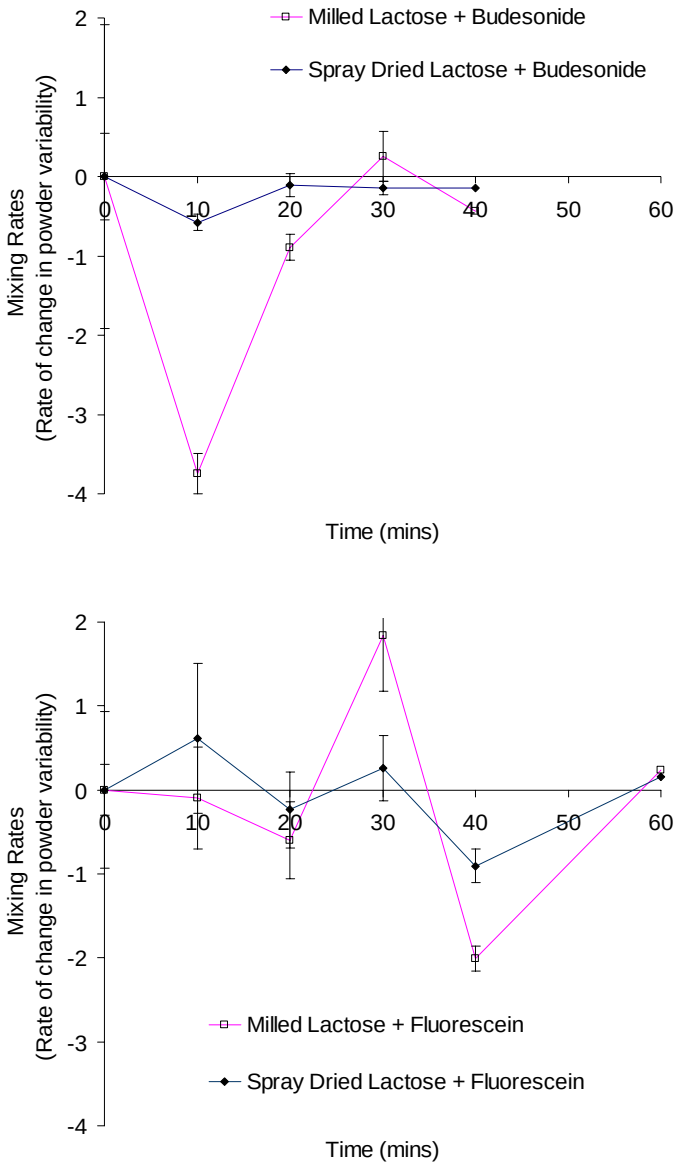
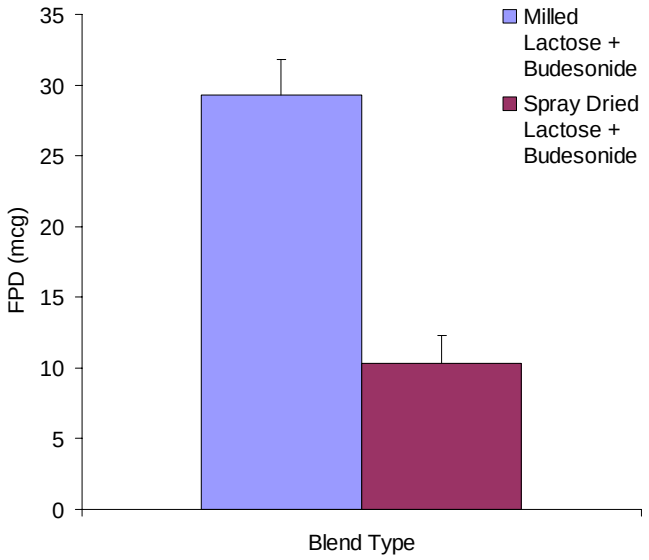
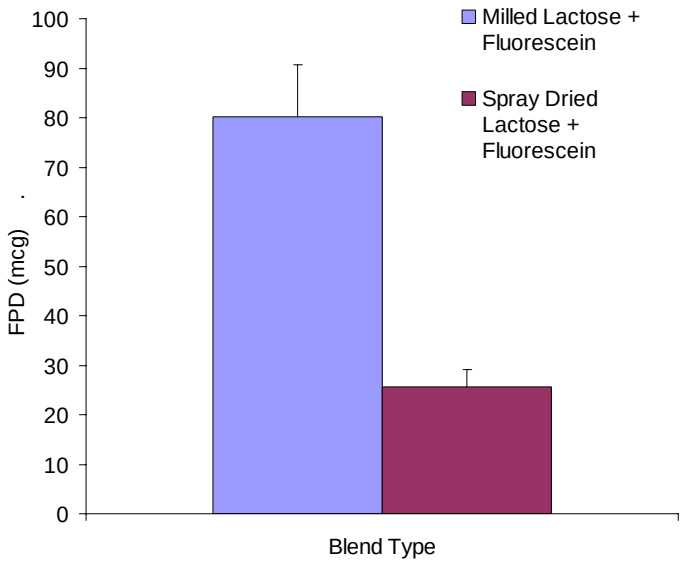


Figure 4a and 4b. Mixing rates determined throughout the blending experiment for both budesonide and fluorescein, using the milled and spray dried lactose carrier powders. Mixing and segregation rates are determined from the coefficients of variation of samples taken at each time point. Positive values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

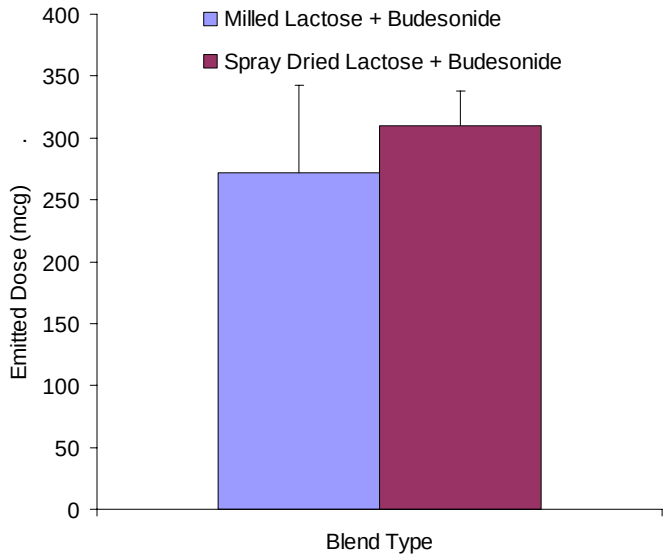


A

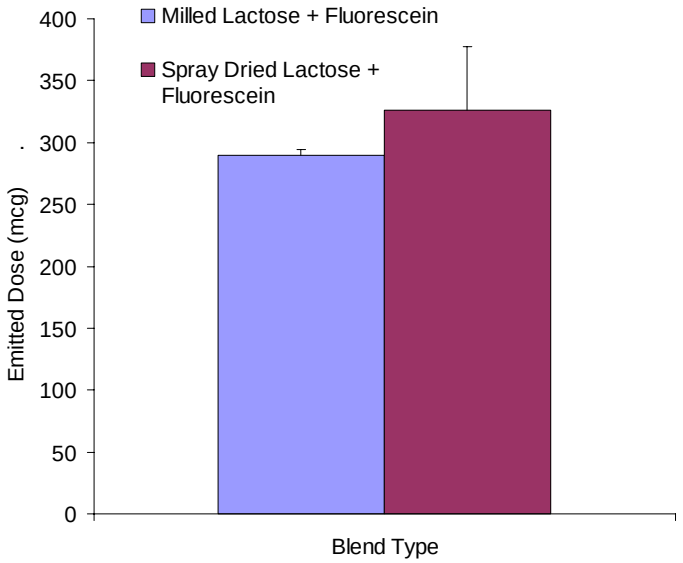


B

Figure 5. Average Fine Particle Dose (FPD) of micronized budesonide (A) and fluorescein (B) from Milled and Spray dried Lactose (n=9)



A



B

Figure 6a and 6b. Emitted dose characteristics for each powder blend (n=9).

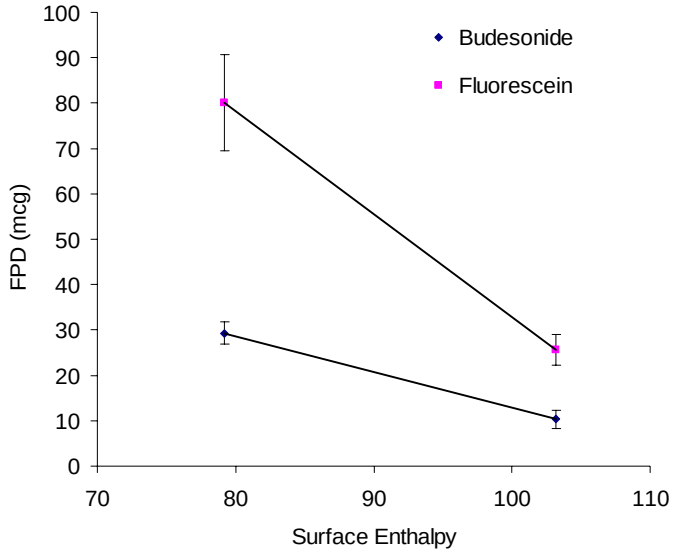


Figure 7. Fine particle dose as a function of surface enthalpy for each formulation type.

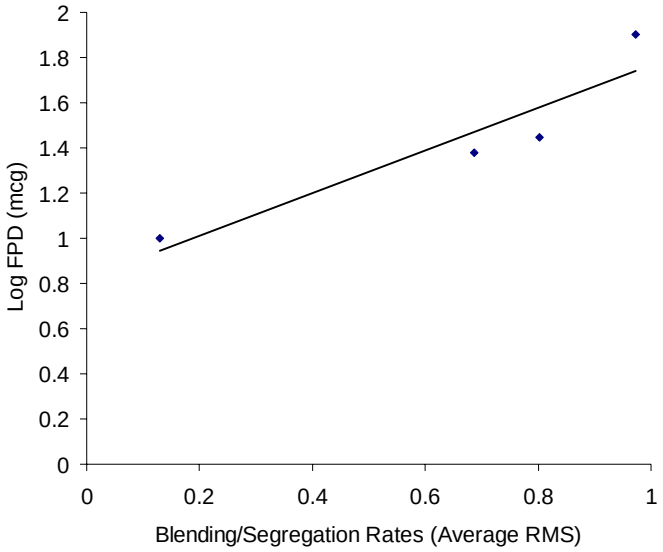


Figure 8. Log of the fine particle dose as a function of the average RMS of mixing rates.