Aerosol Dispersion of Respirable Particles in Narrow Size Distributions Using Drug-Alone and Lactose-Blend Formulations

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Purpose. To examine the effect of formulation type on the aerosolization of respirable particles in narrow size distributions.

Methods. Aerosol dispersion of two formulation types (drug alone and 2% w/w drug-lactose blends) containing micronized or spray-dried fluticasone propionate (FP) particles ($d_{50\%}$ = 1.3 to 9.6 μm, GSD = 1.8 to 2.2) were examined using cascade impaction at 60 L/min with low and high resistance inhaler devices: Rotahaler and Inhalator, respectively.

Results. The aerosol dispersion of FP particles was significantly affected by the particle size, particle type, inhaler device, and formulation type. Interactions were observed between all factors. Generally, greater powder entrainment was obtained with smaller $d_{50\%}$. Higher emitted doses were obtained from drug-alone formulations of spray-dried FP particles and lactose blends of micronized FP particles. Greater aerosol dispersion of spray-dried FP particles was obtained using lactose-blend formulations with $d_{50\%}$ around 4 μm. Greater aerosol dispersion of micronized FP particles was obtained using formulations of drug alone. Larger $d_{50\%}$ produced larger mass median aerodynamic diameters.

Conclusions. Small changes in the particle size within the 1–10-μm range exerted a major influence on aerosol dispersion of jet-milled and spray-dried FP particles using drug-alone and lactose-blend formulations.

KEY WORDS: aerosol dispersion; drug-alone formulations; lactose-blend formulations; narrow size distributions; respirable particles.

INTRODUCTION

Drug particles with aerodynamic sizes of 1–10 μm are required for lung deposition (1). Particle size and distribution play an important role in the dispersion of aerosol formulations. The relationship between particle size within the respirable range and aerosol dispersion has previously been examined using powder formulations containing drug alone. The dispersion of spray-dried mannitol and disodium cromoglycate (DSCG) aerosol particles was significantly affected by the particle size (2,3). The aerosol dispersion of jet-milled and spray-dried mannitol particles was significantly affected by the particle size and morphology (4).

A formulation strategy used to improve the flowability and aerosolization of respirable particles includes the use of interactive mixtures, where respirable drug particles are adhered to the surface of larger excipient carrier particles, usually lactose. Dispersion of drug particles as aerosols from the powder formulations, containing either drug alone or lactose blends, is required for lung deposition. Various factors may affect particle dispersion from interactive mixtures including carrier size and distribution (5–7), shape and surface roughness (8,9), drug-carrier ratio (6,7,10), presence of ternary components (10–12), and mixing and storage conditions (10). However, the influence of the size of drug particles on aerosol dispersion from interactive mixtures has yet to be examined.

The objective of this study was to examine the influence of particle size of micronized and spray-dried fluticasone propionate (FP) particles within the respirable range (1–10 μm) on aerosol dispersion using different formulation types (drug alone or lactose blends) in two different devices. It should be noted that optimization of the powder formulations was not attempted as the objective of the study was to examine the influence of particle size on aerosol dispersion of respirable-sized particles rather than improving the aerosol dispersion.

MATERIALS AND METHODS

Materials

Fluticasone propionate (GlaxoSmithKline, Research Triangle Park (RTP); micronized, Batch WC76065) was used as the model drug. Lactose monohydrate was used in the lactose-blend formulations (sieved size fractions of 45–75 μm) (Pharmatose 325M, DMV International, Veghel, The Netherlands; Lot numbers 043200 and 043445).

Methods

Spray-Drying

Spray-dried FP particles were prepared from solutions and suspensions using a Mini Spray-dryer B-191 (Buichi, Flawil, Switzerland) with a two-fluid nozzle. The solvent was acetone and the atomization gas was nitrogen. The particle size distributions were adjusted by varying the following parameters: feed concentration (5–10% w/w), atomization pressure (1–3 bar), and nozzle size (0.5–10 mm). An inlet temperature of 100°C and feed rate of 5 ml/min was used. A thermocycling method was used to produce large particles, where a 10% w/v FP suspension was heated at 50°C for 60 min, cooled in an ice-bath, and then stored at 4°C overnight, prior to spray-drying.

Analytical Method

FP was quantified by ultraviolet (UV) absorbance measured at a wavelength of 238 nm (UV160U UV-Visible Spectrophotometer, Shimadzu Corporation, Columbia, MD, USA). Methanol (70% v/v) was the solvent. Sonication ensured dissolution. A linear range was obtained from 0.25 to 50 μg/ml (r^2 = 0.997). The limits of detection and quantification were 0.25 and 0.5 μg/ml, respectively. The addition of lactose concentrations of up to 200 μg/ml did not affect the FP assay. Previous high-performance liquid chromatography (HPLC)

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data has shown that decomposition of FP does not occur due to the spray-drying process, thus UV analysis was adequate.

Physicochemical Characterization

The particle size distribution was determined by laser diffraction (HELOS Particle Size Analysis H0838, Sympatec GmbH System-Partikel-Technik, Clausthal-Zellerfeld, Germany) using the RODOS dispersing unit with a 40% feed rate and 4 bar pressure differential. The median diameter ($d_{50\%}$) and geometric standard deviation (GSD) was determined.

The surface morphology was examined by scanning electron microscopy (SEM) (JSM-6300 FV, JEOL, Peabody, MA, USA). Samples were attached to sample stubs using double-sided tape, then sputter-coated with gold palladium alloy (Polaron 5200, Polaron Instruments, Agawan, MA, USA) and viewed using an accelerating voltage of 15 kV.

The thermal properties were analyzed using differential scanning calorimetry (DSC) (DSC2010 Differential Scanning Calorimeter, TA Instruments, New Castle, DE, USA) in the range of 30–220°C using a heating rate of 10°C/min, under a nitrogen gas purge.

The crystallinity was examined by X-ray diffraction (XRD; XDS2000 Diffractometer, Scintag Inc., Sunnydale, CA, USA) in angular increments of 0.03° in the range of 2° to 50°, at a scan rate of 1°2θ/min. Samples were dusted onto a petroleum-coated quartz zero background plate.

The true density of FP particles was measured by helium pycnometry (AccuPyc 1330, Micromeritics, Norcross, GA, USA) using a $1cm^3$ sample cell.

The Carr's compressibility index (CI) was determined from the tapped (ρ_{tap}) and bulk densities (ρ_{bulk}):

$$CI = \frac{\rho_{tap} - \rho_{bulk}}{\rho_{tap}} \times 100\% \quad (1)$$

The tapped and bulk densities were measured in a 2.5-ml glass syringe (Hamilton Company, Reno, NV, USA) using an automatic tapper (Vanderkamp tap density tester, VanKel Industries Inc., Cary, NC, USA). The tapped density was determined after 2500 taps. The CI values were used as an estimate of interparticle forces within aggregates.

The dynamic powder flow was characterized using a vibrating spatula method with a strain gauge measurement device (13,14). The mass of powder falling from a vibrating spatula (Mettler LV3, Mettler-Toledo, Columbus, OH, USA), tilted at an angle equivalent to its static angle of repose, was measured (n = 3). Analysis of the mass vs. time profile was performed with various stride lengths to produce a Richardson plot, the logarithm of the curve length plotted as a function of the logarithm of stride length. The fractal dimension (δ) was determined from the linear part of the Richardson plot using the equation $\delta = 1+|m|$, where m was the slope of the curve. Generally, δ values range between 1 and 2, with lower values being indicative of more regular flow behavior.

Powder Blending

Lactose blends containing 2% w/w FP (micronized or spray-dried particles) were prepared in 5-g batches. A pre-blend was prepared in glass vial with a small spatula by geometric dilution. The pre-blend was then mixed at 96 rpm for 25 min (Turbula mixer, Glen Mills, Clifton, NJ, USA). The homogeneity of each blend was examined using random samples (20 × 20 mg). The mean drug content, standard deviation, and coefficient of variation was determined.

Aerosol Dispersion Characterization

The *in vitro* aerosol dispersion was determined using an eight-stage, nonviable cascade impactor with pre-separator (Graseby-Andersen, Smyrna, GA, USA) operating at an airflow rate of 60 L/min. The impaction plates were coated with a 1% w/v solution of silicone oil in hexane and the pre-separator contained 10 ml of methanol (70% v/v) to prevent particle bounce and re-entrainment. Two inhaler devices were used: a low-resistance device (Rotahaler, GSK, Research Triangle Park (RTP), NC) and a high-resistance device (Inhalator, Boehringer Ingelheim, Ingelheim, Germany). The powder formulation (20 mg) was loaded into hard gelatin capsules (size 3, Eli Lily and Co., Indianapolis, IN, USA). A single capsule was used for drug-alone formulations (containing 20 mg FP), and five capsules were used for 2% FP-lactose blend formulations (equivalent to 2 mg FP). Each capsule has air drawn through it for 10 s. Measurements were performed in triplicate. The amount of FP deposited in the inhaler, throat and pre-separator, individual impaction plates and stages was quantified. The temperature and relative humidity of the surrounding environment was measured prior to each impaction.

The emitted dose (ED) was defined as the mass of drug delivered from the inhaler (i.e., total amount excluding the inhaler device and capsule), expressed as a percentage of the total amount of FP collected. The fine particle fraction (FPF) was defined as the mass of drug deposited in stage 2 and lower ($d_{ae} < 4$ μm), expressed as a percentage of the total amount of FP collected. The mass median aerodynamic diameter (MMAD) was calculated as the 50th percentile of the aerodynamic particle size distribution by mass.

In addition, the relative fine particle fraction (FPF_{rel}) was defined as the mass of dispersed drug particles with $d_{ae} <$ 4 μm (particles deposited on stage 2 and lower), expressed as a percentage of the total mass of drug particles with $d_{ae} < 4$ μm. The total mass of drug particles with $d_{ae} < 4$ μm in each sample was estimated graphically from the laser diffraction data, assuming primary particles were measured with the laser diffraction technique used. The equivalent diameter corresponding to d_{ae} of 4 μm was calculated using the following equation (15):

$$d_{ae} = d\sqrt{\rho} \quad (2)$$

where d_{ae} is the aerodynamic diameter, d is the diameter, and ρ is the true density of FP particles. The FPF_{rel} enables the comparison of the dispersion efficiency between the FP samples.

RESULTS

Physicochemical Characterization

The median diameter ($d_{50\%}$) and geometric standard deviation (GSD) of micronized FP particles were 2.1μm and 2.0, respectively. The $d_{50\%}$ of spray-dried particles were 1.3, 2.5, 3.9, and 9.6 μm, and GSD values were between 1.8 and 2.2. Narrow size distributions were obtained with minimal overlap

(Fig. 1). The production of satellite droplets during spray-drying resulted in a bimodal distribution in the spray-dried samples. Although this phenomenon occurred in all samples, it was more evident in the size distribution of smaller sized samples ($d_{50\%}$ = 1.3 and 2.5 μm).

Micronized FP particles (Fig. 2A) were angular in shape, whereas the spray-dried particles were spherical in shape (Fig. 2B). The particle size of primary particles observed by SEM was consistent with the particle size data obtained by laser diffraction. Varying degrees of aggregation were observed in both micronized and spray-dried samples. FP particles were adhered to the surface of the lactose carrier in the FP-lactose blends, indicating the formation of interactive mixtures (Figs. 2C and 2D).

The true density of FP particles ranged between 1.34 and 1.39 g/cm^3. The mean value of 1.37 g/cm^3 was used to determine the geometric diameter (calculated as 3.4 μm using Eq. 2), equivalent to an aerodynamic diameter of 4.0 μm. Equation 2 assumes that the particles are spherical. A shape factor is required to account for nonspherical particles; however, this only becomes important for elongated particles. For example, the shape factor for a sphere is unity and 1.08 for a cube (16). A shape factor was not used in this study, due to the difficulty in assigning the correct shape factor for the angular micronized FP particles. This resulted in minimal differences (less than 10%) in the calculated aerodynamic diameter of micronized FP particles.

All FP samples were isomorphic, consisting of Form I. The micronized and larger spray-dried FP particles ($d_{50\%}$ = 2.5, 3.9, 9.6 μm) were highly crystalline. However, the smallest spray-dried FP particles ($d_{50\%}$ = 1.3 μm) exhibited characteristic peaks corresponding to Form 1 with a halo (Fig. 3). This was suggestive of a slight degree of crystalline disorder or amorphous phase. The amorphous-to-crystalline phase transition at around 100–120°C was observed for the spray-dried sample ($d_{50\%}$ = 1.3 μm) with an enthalpy of transition of 34.07 J/g (Fig. 4). This phase transition was absent in the other FP samples. The presence of some amorphous material in the smallest spray-dried sample ($d_{50\%}$ = 1.3 μm) was likely due to the solution spray-drying and insufficient time required for full crystallization prior to solvent evaporation. All other samples were spray-dried from a suspension. Although the slight amorphous content observed in the smallest spray-dried sample ($d_{50\%}$ = 1.3 μm) may play a role in affecting its aerosol dispersion, the main effects in this study were examined with respect to particle size and morphology.

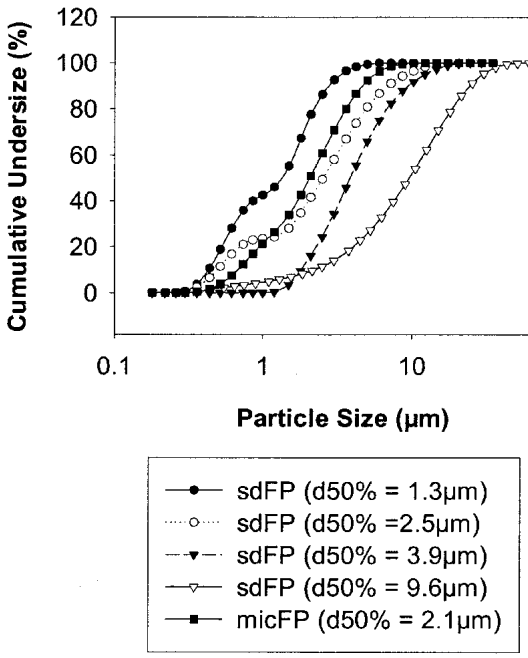

Fig. 1. Particle size distribution of micronized FP (micFP) and spray-dried FP (sdFP) samples determined by laser diffraction using 4 bar pressure differential.

Powder Flow

The bulk and tapped densities, Carr's compressibility index (CI), and fractal dimension (δ) of FP samples are listed in Table I. Micronized FP particles exhibited greater compressibility (higher CI) and higher δ value compared with spray-dried particles. The intermediate-sized spray-dried FP sample ($d_{50\%}$ = 3.9 μm) exhibited the least degree of compressibility. Although distinct differences were not observed between δ values of micronized and spray-dried FP samples ($p = 0.512$, one-way ANOVA, Sigmastat v1.0, Jandel Corporation, San Rafael, CA, USA), minimal differences may be important for powder behavior (17).

Blending Homogeneity

The blend homogeneity of FP-lactose blends was acceptable, with accuracy within 10% of theoretical and coefficient of variance of around 7%.

Aerosol Dispersion Characterization

The cascade impaction studies were conducted under ambient conditions of 21.0–24.0°C and 28–49%RH. The recovery of FP ranged between 86.1% and 110.1%. A summary of the data obtained from cascade impactions is presented in Table II.

Emitted Dose

The ED of FP particles ranged between 28.0% and 93.0% (Fig. 5A). Significant differences were observed in the ED due to particle size, characterized by $d_{50\%}$, for drug-alone formulations using Rotahaler and Inhalator ($p < 0.001$ and $p < 0.0001$, respectively) and for lactose-blend formulations using the Rotahaler ($p < 0.0001$), but not the Inhalator. Generally, higher EDs were obtained with smaller $d_{50\%}$ and with the Inhalator rather than Rotahaler. Significant differences were observed in the ED due to formulation type ($p < 0.05$). Generally, higher EDs were obtained with spray-dried FP particles, irregardless of formulation type. Spray-dried FP particles produced higher ED using drug-alone formulations, whereas micronized FP produced higher ED from lactose-blend formulations.

Fine Particle Fraction

The FPF of FP particles ranged between 0.5% and 9.3% (Fig. 5B). Significant differences were observed in the FPF due to $d_{50\%}$ from drug-alone formulations using the Rotahaler and Inhalator ($p < 0.0001$ and $p < 0.005$, respectively) and from lactose-blend formulations using the Rotahaler and

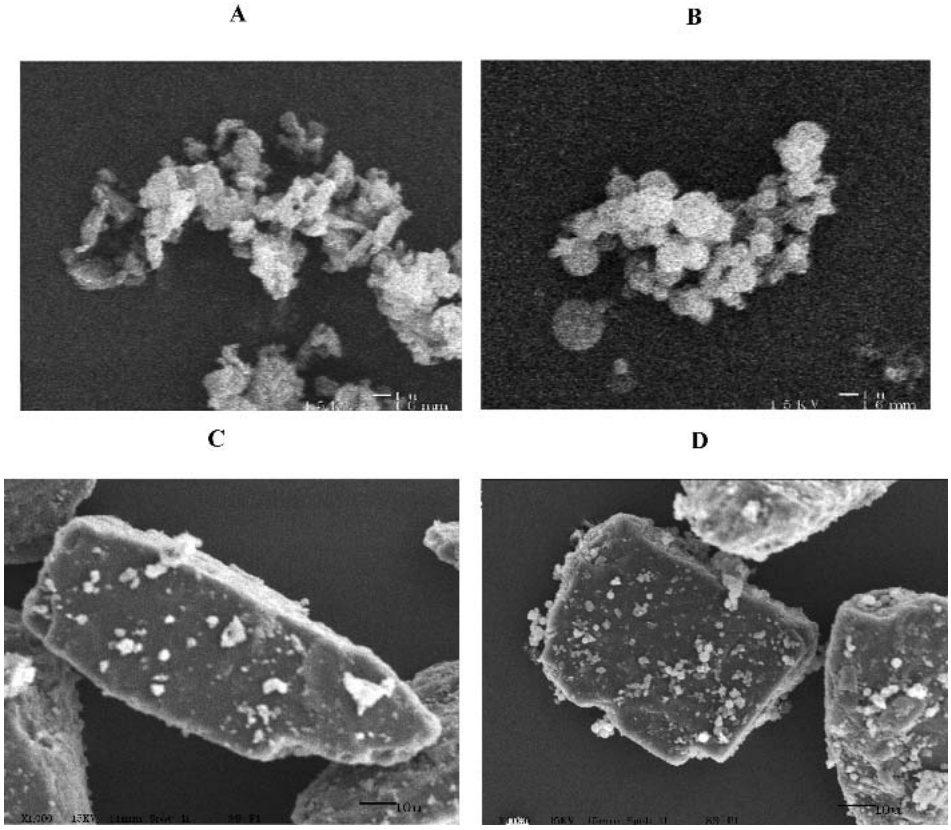

Fig. 2. Scanning electron micrographs of A. micronized FP particles, B. spray-dried FP particles, C. lactose blend containing micronized FP and D. lactose blend containing spray-dried FP.

Inhalator ($p < 0.001$ and $p < 0.0001$, respectively). Using either formulation or either inhaler device, higher FPFs were obtained from the micronized FP ($d_{50\%}$ = 2.1 μm) and smallest spray-dried FP particles ($d_{50\%}$ = 1.3 μm) than the larger spray-dried FP particles. Generally, higher FPFs were obtained from the Inhalator compared with the Rotahaler. Significant differences were observed in the FPF due to formulation type ($p < 0.05$). Spray-dried FP produced higher FPFs from lactose-blend formulations.

Relative Fine Particle Fraction

The FPF_{rel}s of FP particles ranged between 1.9% and 13.3% (Fig. 5C). Significant differences were observed in the FPF_{rel} due to $d_{50\%}$ from drug-alone formulations using the Rotahaler and Inhalator ($p < 0.001$ and $p < 0.05$, respectively); and from lactose blends using the Rotahaler ($p = 0.0001$). However, significant differences were not detected in FPF_{rel} of lactose blends due to $d_{50\%}$ using the Inhalator. This was likely due to the high FPF_{rel} from lactose blends of all samples. Higher FPF_{rel}s were obtained from the intermediate and larger spray-dried FP sample ($d_{50\%}$ = 3.9 and 9.6 μm). Generally, the Inhalator produced higher FPF_{rel}s than the Rotahaler. Significant differences were observed in the FPF_{rel}

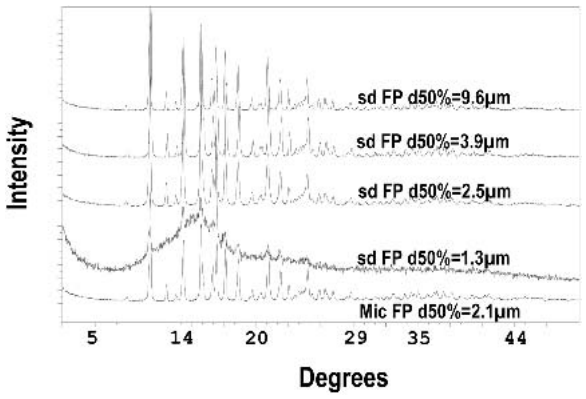

Fig. 3. A micronized powder x-ray diffractograms of micronized FP (micFP) and spray-dried FP (sdFP) samples.

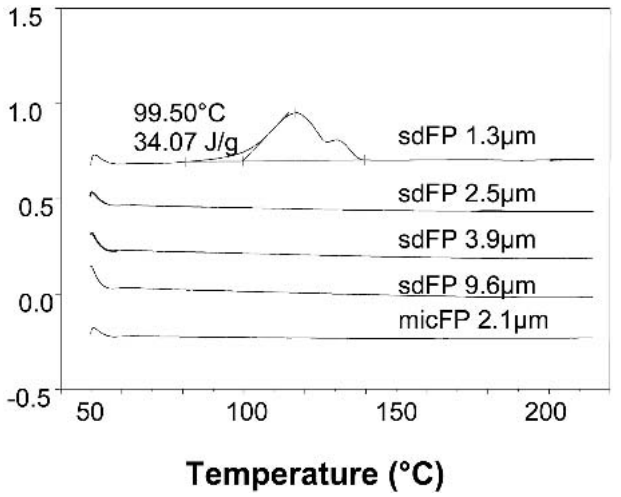

Fig. 4. Differential scanning calorimetry (DSC) thermogram of micronized FP (micFP) and spray-dried FP (sdFP) sample ($d_{50\%}$ = 1.3μm).

Table I. Bulk Density, Tapped Density, Carr's Compressibility Index, and Fractal Dimension (δ) of FP Samples

Sample	Bulk density (g/ml)	Tapped density (g/ml)	CI	δ[a]
Micronized FP				
$d_{50\%}$ = 2.1 μm	0.122	0.227	46.15	1.0195 (0.0126)
Spray-dried FP				
$d_{50\%}$ = 1.3 μm	0.166	0.275	39.47	1.0131 (0.0019)
$d_{50\%}$ = 2.5 μm	0.220	0.362	39.29	1.0122 (0.0002)
$d_{50\%}$ = 3.9 μm	0.250	0.406	38.46	1.0135 (0.0030)
$d_{50\%}$ = 9.6 μm	0.331	0.552	40.00	1.0111 (0.0035)

CI, Carr's compressibility index; FP, fluticasone propionate.
[a] Mean value with standard deviation in parentheses, n = 3.

due to formulation type ($p < 0.05$). Spray-dried particles produced higher FPF_{rel}s from lactose-blend formulations.

Mass Median Aerodynamic Diameter

The MMAD of FP particles ranged between 2.63 and 4.94 μm (Fig. 5D). Significant differences were observed in the MMAD due to $d_{50\%}$ from drug-alone formulations using the Rotahaler and Inhalator ($p < 0.0001$ for either) and from lactose-blend formulations using the Rotahaler and Inhalator ($p < 0.05$ and $p < 0.0005$, respectively). Significantly lower MMADs were obtained from the micronized FP ($d_{50\%}$ = 2.1 μm) and the smallest spray-dried FP sample ($d_{50\%}$ = 1.3 μm) than the larger spray-dried FP samples for both formulation types and both inhaler device. Generally, smaller MMADs were obtained when using the Inhalator than when using the Rotahaler. Significant differences were observed in the MMAD due to formulation type ($p < 0.05$), where lower MMADs were obtained from lactose-blend formulations ($p < 0.05$).

DISCUSSION

Narrow size distributions of spray-dried FP particles were produced in the respirable (1–10 μm) range. The $d_{50\%}$ differed between samples. Minimal differences were observed in the physicochemical properties. All samples were highly crystalline, except the smallest spray-dried FP sample ($d_{50\%}$ = 1.3 μm) in which a small degree of amorphous phase was detected, as indicated in the DSC and XRD data. The particle morphology differed between the micronized and spray-dried FP particles. Micronized particles were angular, whereas spray-dried particles were spherical.

The particle size ($d_{50\%}$), formulation type (drug alone and lactose blend), inhaler device (Rotahaler or Inhalator), and particle type (micronized or spray-dried FP) significantly affected the aerosol dispersion of FP particles.

Significant differences were observed between the aerosol dispersion of FP particles due to the particle size. This effect was dependent on the inhaler device, formulation type, and particle type. Generally, larger particles (characterized by $d_{50\%}$) reduced the ED and FPF and increased the MMAD. Particles with $d_{50\%}$ around 4 μm produced a maximal FPF_{rel}. Similar results were obtained in the previous study examining the effect of particle size using drug-alone formulations of jet-milled and spray-dried mannitol, where increased powder flow and aerosol dispersion was observed in the 2–5-μm range. These results were explained by the formation of intermediate-sized aggregates, which were easily entrained and deaggregated within the airstream. The smaller particles (closer to 1 μm) formed large aggregates with strong cohesion forces, which were easily entrained, but difficult to deaggregate. The larger particles (close to 10 μm) formed weak aggregates or behave as discrete particles, which acted under gravitational forces (4). However, greater aerosol dispersion was achieved for mannitol particles, attributed to differences in physicochemical properties affecting the cohesion/adhesion properties of FP particles. Previously, DSCG particles produced lower aerosol dispersion compared with mannitol particles, attributed to different Hamaker constants affecting the van der Waals forces (2,3).

Significant differences were observed between the aerosol dispersion of FP particles due to the type of powder formulation used. This effect was dependant on the particle type and the inhaler device used. Spray-dried FP particles produced higher EDs from drug-alone formulations, whereas micronized FP particles produced higher EDs from lactose-blend formulations. Higher FPFs and FPF_{rel}s were obtained using lactose-blend formulations for both micronized and spray-dried FP particles, except drug-alone formulations of micronized particles using the Rotahaler. Smaller MMADs were obtained using lactose-blend formulations. The interparticulate forces differ according to the formulation type. Only cohesional forces between FP particles exist in drug-alone formulations, whereas both cohesional forces between FP particles and adhesional forces between FP and lactose particles exist in lactose-blend formulations. The existence of strong cohesional forces between spray-dried FP particles may explain the higher ED and lower FPF obtained using drug-alone formulations. Aggregates with strong cohesion between spray-dried FP particles provide good flow and entrainment, but poor deaggregation, resulting in higher ED and lower FPF. Relatively lower adhesion forces between spray-dried FP particles and lactose carrier would provide better deaggregation, resulting in higher FPF using lactose blend-formulations.

A major limitation was that only one particle size of micronized FP was used in this study. Thus, a direct comparison of micronized and spray-dried FP particles was not possible because the particle size of each was not identical. Technical difficulty in the jet-milling of FP prevented the production of additional size distributions. The examination of other sizes of jet-milled FP samples may allow further distinction between the aerosol dispersion of jet-milled and spray-dried FP particles. From the results of this study, it is uncertain whether micronized or spray-dried FP particles would provide greater aerosol dispersion.

All FP samples flowed from the vibrating spatula as aggregates, rather than individual particles. The low fractal dimensions (δ) obtained for all FP samples were indicative of regular flow properties. Similar results were previously obtained from respirable jet-milled and spray-dried mannitol particles (1–10 μm) (4). The higher δ value obtained for micronized FP particles, although not statistically significant, corresponded with a significantly lower ED obtained using the Rotahaler and Inhalator for drug-alone formulations.

Table II. Summary of Cascade Impaction Data (mean, n = 5)

	ED (%)		FPF (%)		FPF_{rel} (%)		MMAD (μm)	
Sample ($d_{50\%}$)	Rotahaler	Inhalator	Rotahaler	Inhalator	Rotahaler	Inhalator	Rotahaler	Inhalator
Drug alone								
JM 2.1 μm	42.14	56.61	4.64	7.75	5.95	9.94	4.27	3.53
SD 1.3 μm	79.13	86.14	1.97	8.18	2.05	8.54	4.17	3.41
SD 2.5 μm	70.60	88.34	1.23	1.96	1.91	3.06	4.84	4.63
SD 3.9 μm	60.82	93.01	1.42	2.38	3.36	5.63	4.77	4.36
SD 9.6 μm	42.76	90.94	0.50	0.74	3.01	4.48	4.94	4.64
Lactose blend								
JM 2.1 μm	66.52	63.34	3.99	9.32	5.11	11.95	3.50	2.63
SD 1.3 μm	57.46	67.55	3.63	8.62	3.48	9.00	3.73	3.16
SD 2.5 μm	45.16	60.07	3.30	6.95	5.13	10.81	4.09	3.38
SD 3.9 μm	47.67	61.04	3.58	5.61	8.47	13.27	3.98	3.65
SD 9.6 μm	27.95	50.58	1.34	1.74	8.12	10.53	4.13	3.78

JM, jet-milled; SD, spray-dried; ED, emitted dose; FPF, fine particle fraction; MMAD, mass median aerodynamic diameter.

This supports the vibrating spatula technique as a method for the estimation of ED performance, where more irregular flow (higher δ) produce lower ED values (4). The flow properties of lactose-blend formulations were not examined using the vibrating spatula technique.

The Carr's compressibility index provided an estimation of the particle forces within the aggregates of micronized and spray-dried FP particles. In a previous study examining respirable sized particles of mannitol, lower CI values were indicative of aggregates involving strong interparticulate forces able

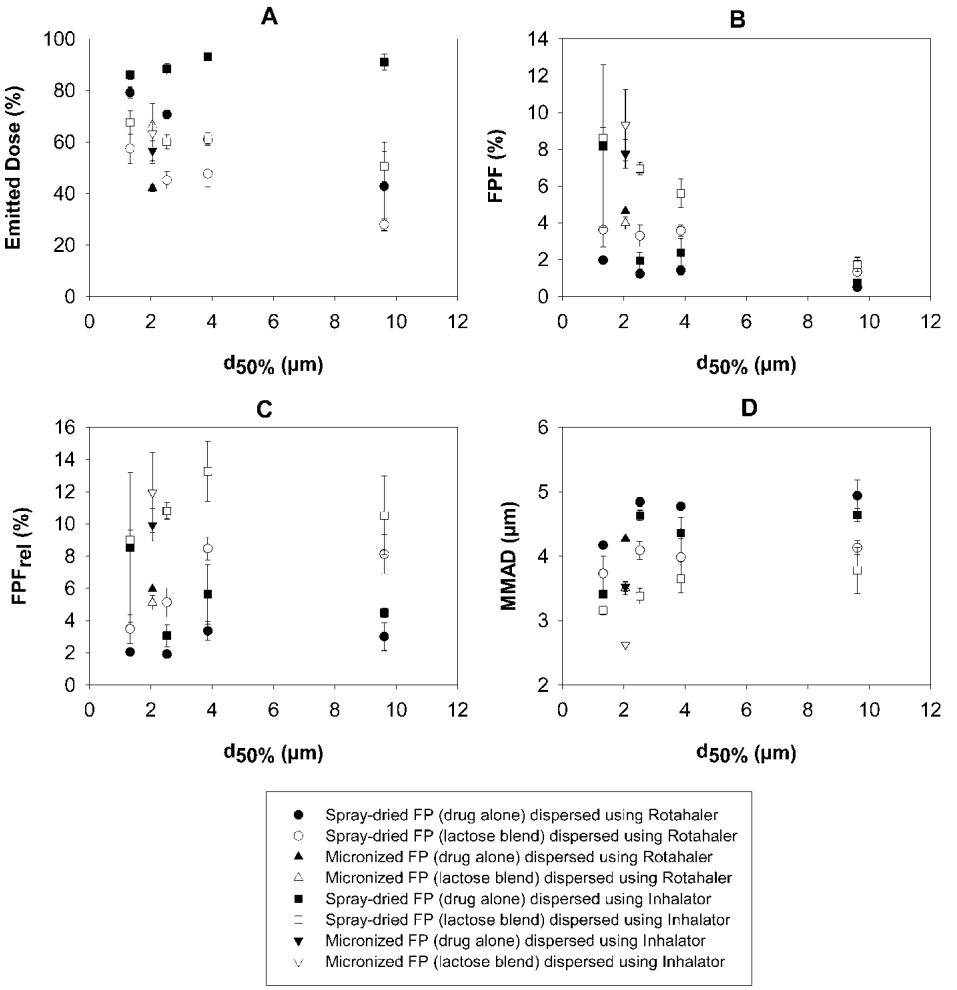

Fig. 5. Relationship between median diameter ($d_{50\%}$) of micronized and spray-dried FP samples (Mean ± standard deviation, n = 3) and A. Emitted Dose, B. Fine Particle Fraction (FPF), C. Relative Fine Particle Fraction (FPF_{rel}) and D. mass median aerodynamic diameter (MMAD) determined by cascade impaction using drug alone and lactose blend formulations, dispersed using the Rotahaler and Inhalator.

to withstand breakdown during tapping. High CI values were indicative of aggregates containing weaker interparticulate forces (4). The lowest CI value obtained from the intermediate-sized spray-dried FP particle ($d_{50\%}$ = 3.9 μm) corresponded with the highest FPF_{rel} value obtained using lactose-blend formulations with both inhaler devices. This result was in agreement with previous results where intermediate-sized mannitol particles (2–5 μm) exhibited better aerosol dispersion, attributed to weaker van der Waals forces leading to easier deaggregation of loose aggregates within the airstream (4).

The pressure drop achieved by the inhaler device significantly affected the aerosol dispersion of micronized and spray-dried FP particles. The Inhalator provides greater pressure drop and higher shear forces at a given airflow, due to its higher specific resistance [0.180 $cmH_2O^{1/2}$/(L/min)], compared with the Rotahaler [0.040 $cmH_2O^{1/2}$/(L/min)] (18). As expected, the Inhalator produced higher ED, FPF, and FPF_{rel} and smaller MMADs than the Rotahaler for most FP samples. In addition, the higher efficiency of the Inhalator was able to negate the differences in aerosol dispersion due to the size of drug particles. For example, high ED and FPF_{rel} results were obtained from lactose-blend formulations using the Inhalator and differences were not observed due to $d_{50\%}$ of drug particles.

The effect of the width of the size distribution was not been examined in this study. Because monodisperse particles were not produced, the effect of very fine particles may play an important role in the powder flow and aerosol dispersion behavior of particles in the 1–10-μm range. Future work to be examined includes the preparation and characterization of particles with similar median diameters but varying distribution widths.

In summary, the particle size, inhaler device, and formulation type significantly affected the aerosol dispersion of micronized and spray-dried FP particles. The effect of particle size on aerosol dispersion was dependent on the inhaler device, formulation type, and particle type. Generally, greater powder entrainment was obtained with smaller $d_{50\%}$. Greater aerosol dispersion of spray-dried FP particles was obtained at $d_{50\%}$ around 4 μm using lactose-blend formulations. Larger $d_{50\%}$ produced larger MMADs. The effect of formulation type on aerosol dispersion was dependent on the inhaler device and particle type used. Better entrainment was achieved using drug-alone formulations of spray-dried FP particles and lactose-blend formulations of micronized FP particles. Better aerosol dispersion was achieved using formulations containing FP-lactose blends, except those containing micronized FP using the Rotahaler, where the drug-alone formulation produced better aerosol dispersion. Small changes in the particle size within the respirable range (1–10 μm) produced a major impact in the aerosol dispersion of powders, using both drug alone and lactose-blend formulations.

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