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Evaluation of SCF-engineered particle-based lactose blends in passive dry powder inhalers

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Abstract

The objective of this study was to assess the performance of SCF-engineered budesonide and albuterol sulfate powder blends in passive dry powder inhalers (DPI) relative to micronized drug blends. A number of lactose grades for inhalation were screened and the appropriate carrier and drug-to-lactose blending ratio were selected based on drug content and emitted dose uniformity. Aerosol performance was characterized by Andersen cascade impaction. Blend formulations of SEDS (solution enhanced dispersion by supercritical fluids) budesonide and albuterol exhibited a significant drug content uniformity (7–9% RSD) improvement over micronized drug blends (16–20% RSD). Further, the SEDS formulations demonstrated higher emitted dose and reduced emitted dose variability (10–12% RSD) compared to micronized powders (21–25% RSD) in the Turbospin, albeit without significant enhancement of the fine particle fraction. In contrast, SEDS powders exhibited increased fine particle fractions over micronized blends in the Clickhaler; improvements were more pronounced with albuterol sulfate. The performance enhancements observed with the SEDS powders are attributed to their increased surface smoothness and reduced surface energy that are presumed to minimize irreversible drug–carrier particle interactions, thus resulting in more efficient drug detachment from the carrier particle surface during aerosolization. As demonstrated for budesonide and albuterol, SEDS may enhance performance of lactose blends and thus provide an attractive particle engineering option for the development of blend formulations for inhalation delivery.

Keywords: Supercritical fluids; Micronization; Lactose blends; Dry powder inhaler; Pulmonary delivery

1. Introduction

The increased need for improved and efficient inhalation delivery of new therapeutic agents requires sophisticated delivery systems that maximize patient benefit while improving convenience and compliance. The preparation of microparticle-based dosage forms of therapeutic molecules for dry powder (DPI) or metered dose (MDI) inhalation delivery presents significant challenges. Despite recent advances in particle engineering approaches, micronization, or fluid energy/jet milling, remains the process of choice in inhalation product development, owing to its relative simplicity, established scale up and conformity to existing manufacturing and development operations. Notwithstanding its widespread use, this particle

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formation methodology suffers from many drawbacks that challenge product development (Ward and Schultz, 1995). Micronization generally provides limited control over the size, shape and morphology of particles, while small changes in particle characteristics may result in unacceptable variability in aerosol performance. Micronized particles are often highly charged and cohesive, resulting in significant downstream processing and poor product performance.

To reduce cohesion between the primary drug particles and improve formulation flowability, a common industry practice is to prepare physical blends of the drug microparticles with larger carrier particles, most namely α-lactose monohydrate (Bell et al., 1971; Malcolmson and Embleton, 1998). During inhalation, the drug particles are detached from the carrier particle surface by the energy of the inspired flow. The larger carrier particles presumably impact in the oropharynx and the upper airways, whereas the respirable drug particles penetrate into the lungs. Blend systems significantly enhance drug particle flowability, thus improving dosing accuracy and minimizing the dose variability observed with neat drug formulations, while making them easier to handle during manufacturing operations (Timsina et al., 1994; Vidgren et al., 1994). Lactose blending is a well-established approach that has been employed in development of numerous inhalation products, such as Ventolin Rotacaps® (0.8% (w/w) albuterol sulfate in the Rotahaler) (Steckel and Müller, 1997a), Flovent RotaDisk® and Becodisks® (0.2–1% (w/w) fluticasone propionate and 0.4–1.6% (w/w) beclomethasone dipropionate in the Diskhaler) (Vachon and Chulia, 1998; Larhib et al., 1999) and Foradil® (formoterol in the Cyclohaler) (Zeng et al., 2000).

Supercritical fluid (SCF) technologies have advanced over the past decade (Tom and Debenedetti, 1991; Jung and Perrut, 2001), driven by the need for high purity, chemically stable particles with controlled physical properties of drug compounds manufactured in a more consistent and reliable manner. Their development was motivated by the high solvent power of supercritical fluids and their flexible physical and solvation properties. One such approach, the Nektar SCF technology, which is based on the principle of *solution enhanced dispersion by supercritical fluids* (SEDS), has demonstrated significant capabilities in controlling particle physical properties (Hanna and York, 1994). In this process, a solution of the drug material is fed with a stream of supercritical fluid (e.g. CO_2) through a specially designed nozzle under controlled conditions of temperature and pressure. The supercritical fluid disperses, mixes and rapidly extracts the solvent from the drug solution, leading to the formation of particles, which are retained in a particle formation vessel (Hanna and York, 1994; Palakodaty et al., 1998). Manipulation of the operating conditions of pressure, temperature, solution concentration and flow rates in the nozzle enables accurate control of particle size, shape and morphology, which renders the process particularly attractive for use in pulmonary delivery.

This report describes efforts undertaken to evaluate the suitability of SEDS powders in development of lactose-blended formulations for inhalation delivery in passive, unit-dose and reservoir DPIs. Budesonide and albuterol, two frequently formulated inhalation products, were selected on the basis of their diverse physicochemical properties. A range of lactose carriers was evaluated and the most suitable ones were selected for formulation. SCF and micronized drug powders were formulated as lactose blends and their aerosol performance was assessed. Finally, the physicochemical properties of the powders were investigated in an effort to establish an understanding of the underlying phenomena controlling the behavior of the SCF powders in the blend systems.

2. Materials and methods

2.1. Materials

Bulk micronized budesonide was provided by Astra Zeneca (Södertälje, Sweden); albuterol was purchased from ACETO Corporation (Lake Success, NY). Inhalation-grade α-lactose monohydrate powders were obtained from Chr. Hansen (Mahwah, New Jersey) and Meggle (Wasserburg, Germany). The selected lactose grades, which had been manufactured by different processing methods, spanned a range of particle sizes, size distributions and morphologies (Table 1). The commercial sieved and milled samples comprised crystals ranging from 10 to 450 μm in size. All materials were stored at ambient conditions, shielded from light. Hexane, heptane, octane, nonane,

Table 1
Particle size, size distribution and particle surface area of the lactose grades used in preparation of the blend formulations

Lactose grade	VMD (μm)	Fines (% <5 μm)	Surface area (m^2/g)
Prismalac 40	450	–	–
Spherolac 100	114	1.5	–
Inhalac 70	220	–	–
Inhalac 120	150	–	–
Inhalac 230	97.1	1.4	–
Granulac 230	27.2	16.9	1.0[a]
Sorbolac 400	9.8	30.5	1.3[a]
Pharmatose 325M	61.3	3.2	0.233 ± 0.007[b]

[a] Certificate of analysis from manufacturer.
[b] Kawashima et al. (1998).

decane, chloroform, tetrahydrofuran, ethyl acetate and acetone (all 99+% purity) were purchased from Aldrich Chemical Co. (St. Louis, MO).

The Clickhaler (Innovata Biomed Ltd., Tewkesbury, UK) is a medium resistance ($0.1\,(cmH_2O^{1/2})/(L\,min^{-1})$, data not shown) multi-dose, reservoir-type device, which incorporates a low turbulence dispersion mechanism and is powered by a patients' inspiratory effort. It has demonstrated reproducible performance in lactose blend formulations and has gained regulatory approval in many European countries for bronchodilators and other anti-inflammatory drugs (Barrowcliffe et al., 1998).

The Turbospin (PH&T; Milan, Italy) is a medium resistance DPI, with a resistance of $0.09\,(cmH_2O^{1/2})/(L\,min^{-1})$ (Meakin et al., 1996). The powder is released from a size #2 capsule through vibration induced by the patient's inspiration. The Turbospin utilizes shear during rattling of the capsule, generated by the airflow through vents along the side of the capsule chamber, and jetting of the airstream at the restriction in the mouthpiece to deagglomerate and disperse the powder. Size-2 HPMC capsules were purchased from Shionogi Qualicaps, Inc. (Whitsett, NC) for use with the Turbospin device.

2.2. SEDS powder manufacturing

SEDS albuterol sulfate powders were manufactured on a SCF pilot plant, by pumping a 1% (w/v) solution of the drug in methanol using a reciprocating pump (Jasco, UK) at 10 mL/min. The CO_2 was liquefied and then introduced at 150 mL/min into the 2-L precipitation vessel via a coaxial nozzle. Dichloromethane was added as an anti-solvent modifier to the CO_2 stream at a flow rate of 20 mL/min. The pressure in the vessel was maintained at 200 bar by a back-pressure regulator (BPR) (Tescom, USA). After removal of the solvent into the CO_2 phase, the dry albuterol sulfate particles were collected in a PTFE filter bag at the base of the precipitation vessel.

SEDS budesonide was prepared on the SCF GMP manufacturing plant (Palakodaty et al., 2000), which is a scaled up version of the pilot plant, with a 10-L atomization vessel and a 60-kg/h capacity CO_2 pump. A 2% (w/v) solution of budesonide in acetone was pumped at 0.6 kg/h along with CO_2 at 50 kg/h into a co-axial nozzle, both using diaphragm pumps (LEWA). A pressure of 100 bar was maintained by a back-pressure regulator (Tescom, USA) and the vessel temperature was maintained at 70 °C. The powder was collected in a PTFE filter bag.

2.3. Blend preparation

The blending process may impact the performance of aerosol blends. However, in order to enable a comparative performance evaluation of SCF versus micronized powders, their blends were prepared at the same conditions, without optimization for each type of powder. Lactose blends were prepared by geometrically (Hersey, 1975; Yeung and Hersey, 1979) mixing a total weight of 3 g of lactose and active drug in 20-mL glass scintillation vials. The carrier was always added first in order to coat the vial walls and reduce drug adhesion. Between powder additions, the mixing vessel was inverted 15 times to facilitate blending. Final blending was carried out in a Turbula Shaker Mixer® Type T2 F (Glen Mills Inc., Clifton, NJ), which is a low energy tumbler, for 33 min at a mix-

ing speed of 59 rpm. Blend ratios were varied between experiments and are reported in the appropriate experimental sections.

2.4. Drug content uniformity

After blending, five samples of approximately 16-mg each (twice the final capsule fill weight to reduce sampling errors; Lord, 1993) were taken using a dosage unit sample apparatus from each of the top, middle and bottom sections of the powder-mixing vessel. Samples were reconstituted in the appropriate solvent and were analyzed for drug content, using the methods described in Section 2.6. The percent relative standard deviation (%RSD) of the drug content for all 15 samples was calculated and used as an indication of drug content uniformity.

2.5. Emitted dose and aerodynamic particle size analysis

Emitted dose (ED), defined as the relative amount of drug powder loaded in the capsule that leaves the device, was determined in the Turbospin device at conditions of 'comfortable' and 'forceful' inhalation (28.3 and 60 LPM, respectively) at a total inspired volume of 2 L. EDs were determined by chemical analysis of the powder collected on a glass fiber filter; all filters were washed with 2 mL of the appropriate mobile phase (water for albuterol and water: acetonitrile (50:50, v/v) for budesonide). After vigorous vortexing, the samples were analyzed by the methods described in Section 2.6.

Mass median aerodynamic diameter (MMAD) was determined via chemical analysis by inertial impaction with an eight-stage Andersen cascade impactor (Andersen Instruments, Smyrna, GA) equipped with a pre-separator, special adaptors to fit the device mouthpieces and retrofitted to compensate for the high flow rate. For Turbospin testing, 8-mg doses of drug:lactose blends (5% (w/w) active) were filled in size-2 HPMC capsules and sampled at 60 L/min for a total inspiratory volume of 2 L. For the Clickhaler (25 mm^3 reservoir) particle size analysis was performed at a flow rate of 49 L/min (a forceful inhalation) with a total inspiratory volume of 4 L; a total of eight doses were discharged into the impactor per determination and each determination was carried out twice. The stage cut-offs were calculated using a modified Stokes' equation (Van Oort et al., 1996). Fine particle fraction ($FPF_{\leq 5\,\mu m}$), defined as the fraction of emitted drug mass in the respirable size range ($\leq 5\,\mu m$), was determined by interpolation of the Andersen deposition profiles. In all cases, the $FPF_{\leq 5\,\mu m}$ was corrected for drug deposition in the induction port, pre-separator and on top of the first stage. All aerosol tests were performed at room temperature and controlled relative humidity (RH) conditions of 35–40%.

2.6. Drug content analysis

Budesonide was analyzed via reverse-phase HPLC using a Hewlett Packard (Palo Alto, CA) model 1100 HPLC. Budesonide was eluted isocratically through a Symmetry C_{18} column (Waters, Inc.) using a mobile phase consisting of a 45:55 acetonitrile:water mixture at a flow rate of 1 mL/min. Budesonide elution was monitored at 246 nm using a variable wavelength detector. Concentrations of the sample were determined by extrapolation to a standard curve constructed by injections of a known concentration solution of the bulk material ($R^2 = 0.99965$). Albuterol content was determined via UV detection using a model V-560 Jasco UV/VIS Spectrophotometer (Easton, MD), using an extinction coefficient of 622 L mol^{-1} cm^{-1} at 224 nm. All samples were diluted with HPLC-grade water to bring the absorbance within the linear range of the spectrophotometric assay (between 0.5 μg/mL and 1 mg/mL). Drug concentrations were determined by extrapolation to a standard curve constructed by serial dilutions of known concentration solutions of the bulk material ($R^2 = 0.99875$).

2.7. Particle morphology

Powder morphology was determined on a Philips XL 30 Electronic Scanning Electron Microscope (E-SEM) (FEI Company, Hillsboro, OR), operated at an accelerating voltage of 20 kV, filament current of 1.75 μA, beam current of 30–40 mA and probe current of 250 pA. Samples were prepared by mounting approximately 0.5 mg of powder onto a 5 mm × 5 mm silicon wafer affixed via graphite tape to an aluminum stub. The powder was then sputter-coated for 40 s

at beam current of 38–42 mA with a 200 Å layer of gold/palladium alloy. Samples were visualized at 30–50 mA at magnifications of 2500–10,000×.

2.8. Particle size analysis

The volume-weighed mean geometric diameter (VMD) was determined with a Sympatec laser diffraction analyzer (HELOS H1006, Clausthal-Zellerfeld, Germany) equipped with a RODOS type T4.1 vibrating trough disperser. Approximately 2 mg of bulk powder ($n = 2$) was placed into the RODOS vibrating trough and dispersed through the laser beam using settings of 1 bar of air pressure, 53 mbar of vacuum, 70% feed rate, 1.30 mm funnel gap, and an R2 lens for scattered light collection. Data was collected over an interval of 0.4 s, with a 175-μm focal length lens. Particle size distributions were calculated using a Fraünhofer model.

2.9. Surface energy analysis

The surface energies of the drug powders were determined by inverse gas chromatography (IGC) using a Surface Measurement Systems (London, UK) iGC-2000 equipped with thermal conductivity and flame ionization detectors, as described previously (Feeley, 2002; Feeley et al., 1998). The dispersive component of the surface energy (γ_s^D) was calculated from the interaction data for *n*-alkanes by (Schultz et al., 1989; Ticehurst et al., 1994; Smith et al., 1978):

$$RT \ln V_N = 2N(\gamma_s^D)^{1/2} a (\gamma_L^D)^{1/2} + C \quad (1)$$

where N is the Avogadro's number, γ_s^D the dispersive component of surface free energy of the solid, a the surface area of the probe molecule, γ_L^D the dispersive component of surface free energy of the liquid and C a constant.

3. Results and discussion

As shown in the SEM photographs in Fig. 1a, SEDS budesonide consisted of small, uniform particles of approximately 1–2 μm. The particles were homogeneous and appeared to have a smooth surface texture without significant irregularities. The SEM images revealed a few agglomerates (approximately 4–6 μm). Laser diffraction analysis indicated a symmetric, monomodal size distribution with a mean diameter of 2.7 μm, thus confirming the presence of agglomerates. In contrast, the micronized powder (Fig. 1b) consisted of highly irregular particles (<1–4 μm) containing a significant amount of 'fines'. Most particles formed larger agglomerates, which however did not appear to be bridged; the observations were in agreement with the laser diffraction data, which indicated a VMD of 2.4 μm and a wide distribution span. The SEDS albuterol batch, shown in Fig. 1c, comprised irregular, diamond-shaped particles with a VMD of 3.1 μm, which form loose agglomerates ranging between 3 and 6 μm. In contrast, the micronized drug (Fig. 1d) was highly heterogeneous, typical of this manufacturing process, and consisted of loosely packed agglomerates; the VMD was determined at 2.8 μm.

In interactive or ordered drug–carrier mixtures, the fine drug particles adhere to the surface of the carrier (Hersey, 1975). The adhesion force must be sufficient to avoid demixing during metering, but small enough to allow detachment during aerosolization (Ganderton and Kassem, 1992). Drug adhesion to the carrier can be influenced by the surface of both drug and carrier, drug to carrier ratio, carrier particle size, mixing time and method, moisture and electrostatic behavior. Thus, the choice of a suitable lactose type is critical in development of inhalation blends, as the lactose particle characteristics, such as particle size, morphology, surface energetics, shape and surface rugosity, can affect performance (Staniforth et al., 1982; Staniforth, 1996). Further, the device-lactose combination is critical, as it may influence the aerosol performance; devices employing high-efficiency dispersion systems have been able to produce high respirable fractions from powder blends containing coarse carrier particles, while devices that do not subject powders to turbulent air paths might require carrier formulations containing a large amount of fine particles in order to obtain an effective dispersion (Malcolmson and Embleton, 1998).

To evaluate the aerosol performance of the blend formulations of the SCF-processed drugs, the suitable lactose types were first identified for each device and the effect of drug to carrier ratio on performance was assessed.

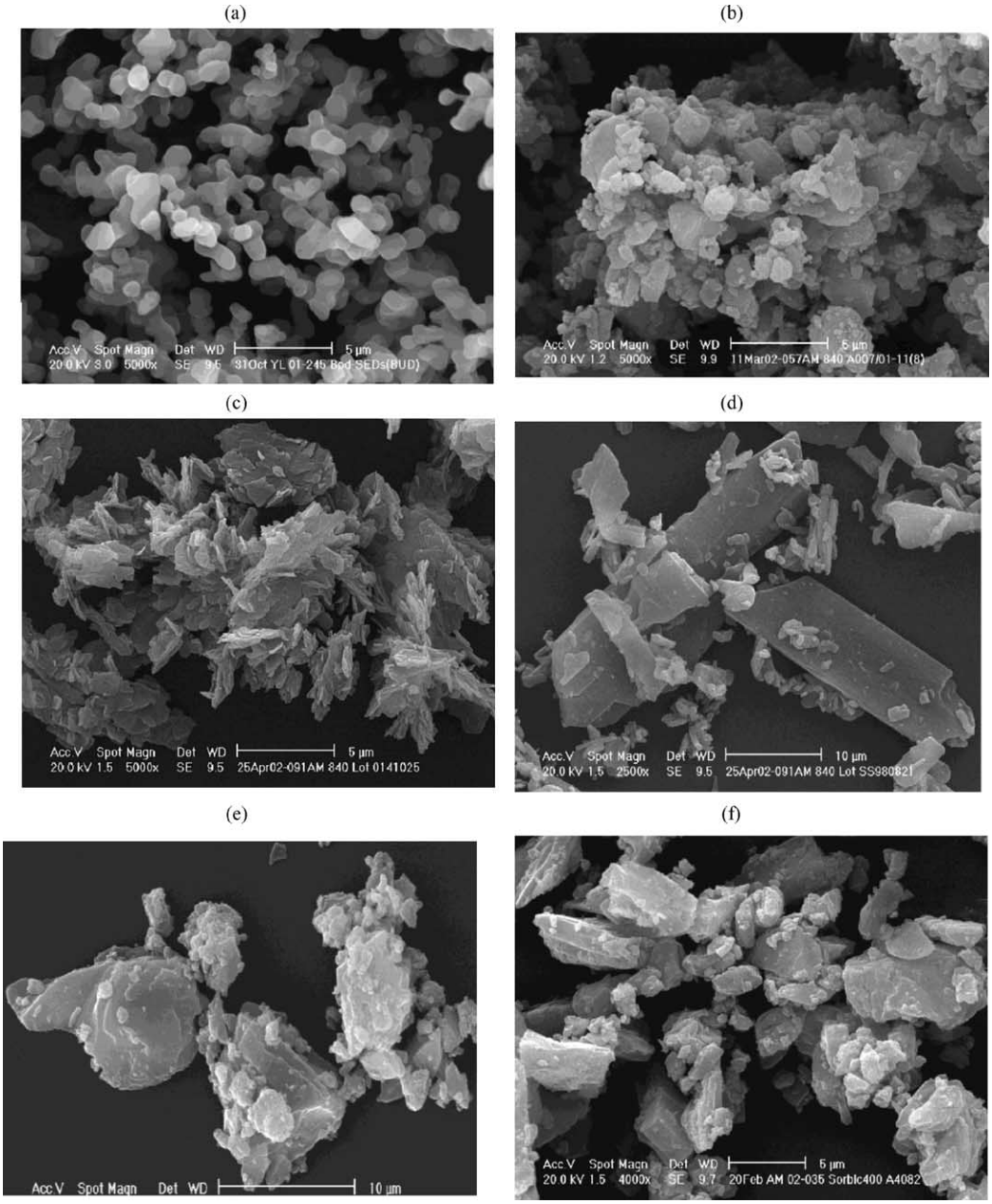

Fig. 1. Scanning electron micrographs of (a) SEDS budesonide, (b) micronized budesonide, (c) SEDS albuterol, (d) micronized albuterol, (e) Granulac 230, and (f) Sorbolac 400.

3.1. Lactose carrier selection

The appropriate carrier for each device was selected on the basis of its emitted dose and ED variability from each device. As shown in Fig. 2, the smaller-sized lactose carriers (<30 μm) performed best in the Turbospin, providing the highest emitted dose with the lowest ED variability: 81 ±

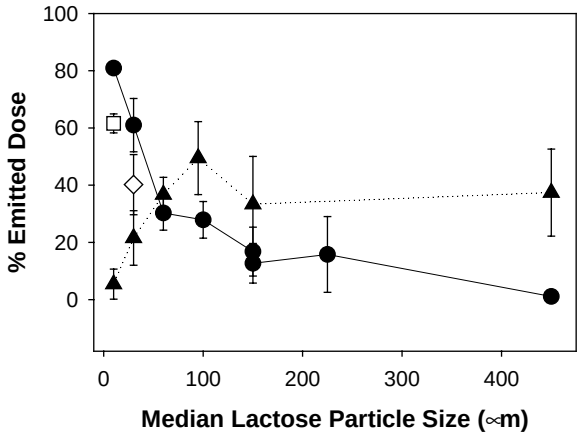

Fig. 2. Emitted dose for non-tumbled lactose tested using Turbospin (60 LPM) and Clickhaler (49 LPM). Emitted dose results for Clickhaler were calculated based on powder density and metering scoop volume. Circles with solid lines (–●–): Turbospin non-tumbled lactose ED; triangles with dotted lines (···▲···): Clickhaler non-tumbled lactose ED; open square (□): emitted dose of SorboLac 400 after tumbling at 59 rpm for 33 min; open diamond (◇): emitted dose of GranuLac 230 after tumbling at 59 rpm for 33 min.

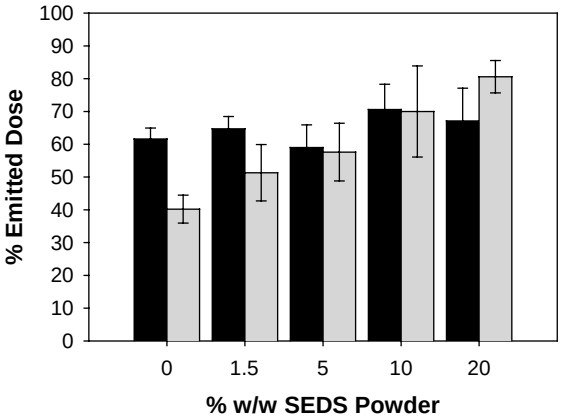

Fig. 3. Emitted dose analysis of SorboLac 400 (solid bars), and GranuLac 230 (shaded bars) blends of SEDS budesonide at increasing drug mass ratios in the Turbospin. Data presented with % standard deviations.

1.3% and 61 ± 15% for SorboLac-400 (VMD of 9.8 μm) and GranuLac-230 (VMD of 27.2 μm), respectively. To assess the impact of tumbling, the ED of the above lactose grades was determined following tumbling in the Turbula mixer. As shown in Fig. 2, tumbling resulted in approximately 20% drop of the ED for both lactose types. For GranuLac 230, the ED drop was accompanied by a significant increase in variability (26% RSD), while there was a rather minor effect on the variability observed with Sorbolac 400 (5–6% RSD). In contrast, the best dispersion from the Clickhaler was achieved with coarse lactose particles of mean diameter ≥60 μm; further increase of lactose size did not improve emitted dose. This may be related to the gravitational-based dose metering mechanism employed in this device, indicating that only the larger carriers provided adequate particle flowability required to reproducibly fill the metering dimple, in agreement with literature studies (Zeng et al., 1998, 2000). From these results, the Pharmatose 325M grade was selected for all subsequent evaluation in the Clickhaler.

3.2. Effect of blend ratio

The blending ratio of the formulation components can significantly impact aerosol performance. It has been suggested (Staniforth et al., 1982; Dunbar et al., 1998) that this may be due to the presence of ‘high energy’ sites on the carrier particle surface that preferentially bind drug particles in an irreversible manner and compromise emitted dose. Further, mechanical interlocking, which occurs when the smaller drug particles are ‘forced’ into cavities on the carrier surface, can significantly reduce drug detachment during aerosolization and further lower the drug emitted dose. To determine the impact of possible “high energy” sites on SorboLac 400 or GranuLac 230 surfaces, blend formulations were prepared at increasing drug-to-carrier mass ratios (0.5, 5, 10, and 20% (w/w) SEDS) and their emitted dose was evaluated. The results for SorboLac 400 blends, which are shown in Fig. 3, indicate that there is no effect of blend ratio on emitted dose or ED variability. In contrast, GranuLac 230 blends appear to exhibit a small, but measurable drug ratio dependence, as the emitted dose increased with increasing SEDS content, reaching approximately 80% at a drug weight fraction of 20% (w/w). This may indicate that the excess drug particles possibly mitigate strong binding carrier–drug and carrier–carrier interactions, thus allowing for more efficient aerosolization. These findings are in general

agreement with studies by Steckel and Müller (1997b), who observed a small increase of the delivered dose of budesonide from Granulac 200 blends above 5% (w/w) drug content in both the Spinhaler and Easyhaler DPIs. Based on these results, SorboLac 400 was selected for all performance assessments with the Turbospin device.

The small ED differences observed in the Turbospin between the Sorbolac 400 and Granulac 230 cannot be explained on the basis of their particle size differences. It is possible that the exhibited behavior is due to the presence of a large population of fines ($X_{<5\,\mu m}$ ~20%) in the raw Granulac 230 material, which is not significantly different from that in Sorbolac 400 ($X_{<5\,\mu m} = 30\%$). Fines have been clearly shown to enhance respirable fractions of blended actives (Steckel and Müller, 1997b; Zeng et al., 1998, 2000; Kassem and Ganderton, 1990). They are thought to act as drug–coarse carrier interaction modifiers, by coating the high-energy sites on the larger carrier particles and promoting drug deagglomeration by establishing reversible interactions with the drug particles. However, their role in powder flow and drug emitted dose is rather unclear. Much of their effects may be related to their increased surface roughness, which appears to have a pronounced and dichotomous influence on particle adhesion. Kawashima et al. (1998) demonstrated that rough carriers improved emitted drug dose from the Spinhaler. However, the reverse trend was observed with the respirable fractions: a relatively smooth crystalline lactose (Pharmatose 325M) produced the highest respirable fraction over the higher rugosity, fluid bed granulated and spray dried lactose particles.

3.3. Dose content and emitted mass uniformity

Drug content uniformity was evaluated with 5% (w/w) blends of drug powders with Sorbolac 400. The results, shown in Table 2, indicate that SEDS blends exhibit significant uniformity improvements over micronized blends: 7.4% versus 16.3% RSD for budesonide and 9.2% versus 19.1% RSD for albuterol. Similar, albeit smaller, dose content uniformity enhancements were observed with the Pharmatose 325M blends. As will be discussed later, the improved content uniformity exhibited by the SCF powders is attributed to their smoother particle morphology and reduced surface energy (Feeley et al., 1998).

Table 2
Drug content uniformity, expressed as % RSD, of the SEDS and micronized powders following blending with lactose carriers

Drug	Process	Drug content uniformity (% RSD)	
		Sorbolac 400	Pharmatose 325M
Budesonide	SEDS	7.4	7.2
	Micronized	16.3	11.2
Albuterol	SEDS	9.2	10.4
	Micronized	19.1	13.3

3.4. Aerosol performance evaluation

The ED performance of lactose blends of both SEDS and micronized powders prepared at 5% (w/w) active, were evaluated in the Turbospin at 60 LPM. Both albuterol and budesonide SCF powders emptied well from the Turbospin, demonstrating similar emitted doses (~60%) with similar ED variability (7–9% RSD) (Fig. 4). In contrast, the micronized budesonide blend exhibited a significantly lower ED (44%), while the performance of the micronized albuterol was statistically similar to that of its SCF counterpart. However, for both drugs examined, the micronized powder blends exhibited two-fold larger emitted dose variability compared to the SCF powders (11.7% versus 21.2% for budesonide, and 12.6%

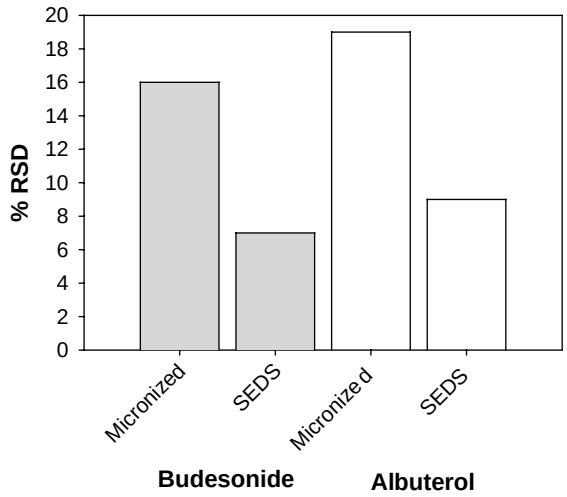

Fig. 4. Relative standard deviation of ED dose of 5% (w/w) SEDS and micronized budesonide and albuterol blends with SorboLac 400 using Turbospin at 60 LPM.

Table 3
Fine particle fraction and fine particle dose analysis for 5% (w/w) SEDS and micronized budesonide and albuterol blends with SorboLac 400 in the Turbospin

Drug	Formulation	$FPF_{\leq 5\,\mu m}$ (%)	$FPD^{a}_{\leq 5\,\mu m}$ (μg)
Budesonide	SEDS	38	92.0 ± 10.1
	Micronized	44	77.4 ± 17.3
Albuterol	SEDS	22	57.3 ± 7.2
	Micronized	25	58.3 ± 14.5

[a] Nominal dose is 400 μg for both (SEDS and micronized) formulations of both drugs.

versus 24.8% for albuterol). The reduced variability observed with the SCF powders may partially be attributed to the improved dose content uniformity obtained with these powders, but also the improved powder characteristics.

As illustrated in Table 3, both SCF and micronized powders exhibited similar fine particle fractions. The $FPF_{<5\,\mu m}$ were between 38 and 44% for budesonide and between 22 and 25% for albuterol powders. In all cases, significant powder deposition was observed in the induction port and the pre-separator (Fig. 5a and b), which reduced the particle fraction deposited on the impactor stages. This could be due to the presence of particle agglomerates, as observed in the scanning electron micrographs or, alternatively, it may signify strong drug adhesion on the lactose particles that does not permit drug separation during aerosolization.

In contrast, in the Clickhaler, both SCF powders exhibited somewhat higher $FPF_{<5\,\mu m}$ over micronized blends (Table 4). The improvements were more pronounced with albuterol sulfate, for which the SEDS powder exhibited a significantly higher $FPF_{<5\,\mu m}$ (30%) over the micronized drug blend (12%), resulting in doubling of the fine particle dose (FPD). Similar but less pronounced trends were observed with budesonide, probably owing to the very high

Table 4
Fine particle fraction and fine particle dose for budesonide and albuterol blends with Pharmatose 325M in the Clickhaler

Drug	Formulation	$FPF_{\leq 5\,\mu m}$ (%)	$FPD_{\leq 5\,\mu m}$ (μg)
Budesonide	SEDS	18	74.5 ± 17.7
	Micronized	11	46.4 ± 6.2
Albuterol	SEDS	30	74.8 ± 2.3
	Micronized	12	27.9 ± 1.6

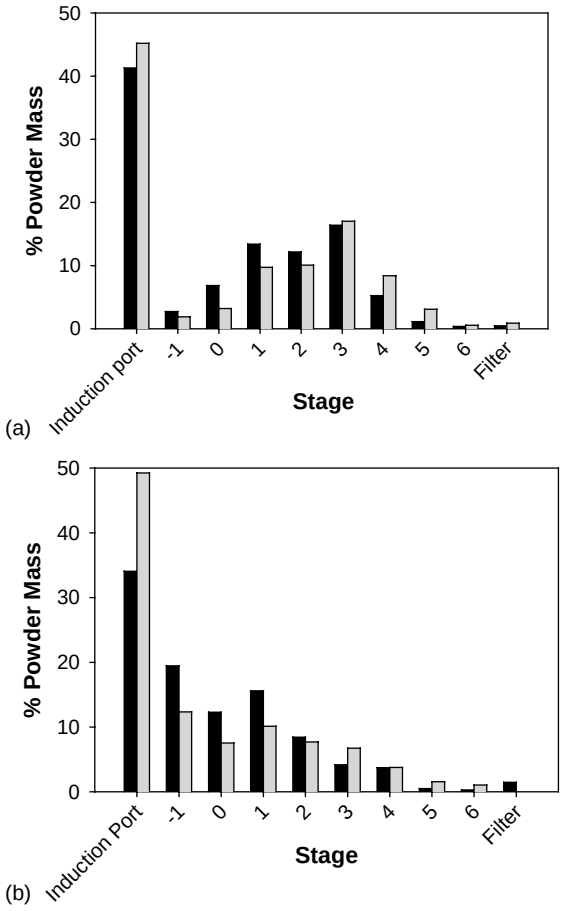

Fig. 5. Fractional powder deposition in the Andersen impactor stages for (a) 5% (w/w) budesonide- and (b) 5% (w/w) albuterol-Sorbolac 400 blends delivered with the Turbospin. Dark bars represent SEDS and light-shaded bars represent micronized blends.

proportion of drug (over 85%) lost in the induction port and pre-separator, thus decreasing the $FPF_{<5\,\mu m}$. Although sorbed moisture can significantly impact aerosol performance (Price et al., 2002), the small differences in water content between SCF and micronized powders at the experimental relative humidity conditions (35–40% RH) cannot fully account for the aerosol performance differences. The small $FPF_{<5\,\mu m}$ may be attributed to the relatively high drug content in the Pharmatose 325M blends. Clarke et al. (2001) reported poor aerosol performance of nedocromil sodium from high drug mass blends with coarse lactose particles, independent of blend-

Table 5
Surface energy parameters of albuterol sulfate and budesonide powders

Sample	γ_s^D (mJ/m^2)	K_A	K_D
Unprocessed albuterol[a]	49.1	0.46	0.61
SEDS albuterol	39.3 ± 0.4	0.24	0.46
Micronized albuterol[a]	58.6 ± 0.3	0.31	0.64
SEDS budesonide	51.3 ± 0.8	–	–
Micronized budesonide	59.8 ± 0.2	–	–

[a] Feeley (2002).

ing conditions. The authors hypothesized that, in the absence of a pre-screening process, the poor performance was due to deposition of drug multilayers on the coarse carrier particles and formation of cohesive drug particle agglomerates independent of the carrier component. Because of the high budesonide content in our blends, we similarly hypothesize that the formulation may be dominated by interactions between agglomerates and ordered units of the drug and the coarse carrier, whether single- or multi-particle carrier coverage. Presumably, these interactions could be largely impacted by the shear forces during blend preparation; however, this aspect was not investigated in this report.

The improved drug content uniformity and reduced emitted dose variability observed with the SEDS powders in the Turbospin may partially be explained by their surface characteristics. The role of surface energy is particularly pronounced in dry powder inhalation systems due to the large surface area to volume ratio of the particles. Previous studies using inverse gas chromatography (IGC) have demonstrated that micronization increases the particle surface energy, as indicated by the increase of the dispersive component of the surface free energy γ_s^D (Feeley, 2002). Further, micronized powders exhibit a more cohesive nature, demonstrated by the increases in mean avalanche time and flow irregularity (Feeley, 2002). To test the above hypothesis, the surface energy of the powders was assessed via IGC. As illustrated in Table 5, after micronization the surface of albuterol particles becomes more energetic, as indicated by the increase in the dispersive component of surface free energy. In contrast, SEDS processing of albuterol resulted in lower free energy (39.3 mJ/m^2) compared to both micronized drug and unprocessed material. Similarly, SEDS budesonide exhibited lower surface energy (51.3 ± 0.8 mJ/m^2) compared to the micronized drug (59.8 ± 0.2 mJ/m^2). Based on the ΔG^{SP} values, the micronized budesonide exhibits a stronger interaction with the basic and amphoteric polar probes, which was also apparent from the non-gaussian nature of their elution peaks (not shown). Further, acid (K_A) and base (K_D) parameters of the powders were calculated based on the powder interaction energetics with the polar probes. These calculations are based on theories developed by Draco et al. (1971) and Gutmann (1978), and enable measurement of the acid–base surface properties of powders using the interaction energies of the powders with the polar probes. The analysis (Table 5) demonstrates that micronization rendered albuterol more electron donating, as shown by the increased K_D and decreased K_A. These results are also supported by previous findings that functional groups on micronized surfaces were activated towards electrophilic substitution (Feeley et al., 1998). In contrast, the SEDS albuterol powders exhibited a reduced electron donating character, as indicated by the reduced K_D. These findings are in good agreement with previous findings with SEDS-processed albuterol and salmeterol xinafoate (Feeley, 2002; Feeley et al., 1998).

The reduced surface energy of the SCF powders may represent a lower energetic barrier to powder blending with lactose carrier particles, thereby resulting in superior powder homogeneity and better dose uniformity, as demonstrated in this study. This is further supported by the reduced electrostatic charges exhibited by the SEDS albuterol–lactose blends (+16.4 nC/g compared to +25.9 nC/g for micronized blends (Feeley, 2002)).

Another parameter that has a significant impact on particle adhesion, and thus powder dispersion from lactose blends, is the contact geometry between drug and substrate particles, i.e. their surface roughness (Price et al., 2000). It is generally accepted that increased surface roughness will reduce detachment of the drug particles, as the latter are less likely to be separated from the clefts and pits on a rough surface (Podczeck, 1998; Kawashima et al., 1998). Atomic force microscopy studies have suggested that SEDS albuterol powders exhibit a smoother surface compared to micronized drug, as indicated by the decreased surface roughness (R_{rms}, root mean square deviation of the asperity height distribution) of 0.1 nm versus

1.2 nm, respectively (York, 2003). Based on the above axiom, by virtue of their smoother surface, SCF particles would be expected to exhibit improved dissociation from the carrier particle surface. Yet, neither the reduced particle surface energy nor the relative surface smoothness alone can explain the equivalent or reduced $FPF_{<5\,\mu m}$ (compared to micronized drug blends) of the SCF powders in the Turbospin. For both drugs, this may be partially attributed to the formation of 'irreversible' agglomerates of the neat SEDS particles, which cannot be dispersed by this low resistance device. This is supported by observations (Lobo et al., 2003) that aerosolization of neat SCF powders of both drugs in the Turbospin resulted in similar or lower $FPF_{<5\,\mu m}$ compared to micronized materials. It is possible that this is due to the higher interparticulate forces exhibited by particles comprising smoother surfaces (Dunbar et al., 1998). We hypothesize that the increased surface smoothness, albeit enables separation of the drug particles from the carrier, it also contributes to stronger drug interparticle interactions, thus leading to incomplete deagglomeration following aerosolization. Such effects are not evident in the Clickhaler, probably owing to the different dispersion mechanism employed by this device, the coarse lactose carrier selected for this device, the testing conditions or even the significantly lower $FPF_{<5\,\mu m}$ exhibited in this device. This device-dependence has been well demonstrated in the literature, as the powder fluidization and dispersion mechanisms employed by different DPIs may have a profound effect on particle adhesion and cohesion in blend systems (Dunbar et al., 1998).

This study highlighted some performance differences of SCF over micronized drug powders in lactose blend formulations in passive unit- and multi-dose DPIs. Despite improvements in drug content uniformity and emitted dose afforded by SCF-engineered particles, probably driven by the reduced surface energetics, further formulation optimization work is required to improve deagglomeration of primary particles. Such efforts need to be directed towards achieving a balance between drug and carrier properties that will maximize performance. Further, the comparative evaluation of powder ED and $FPF_{<5\,\mu m}$ after blending under optimal conditions for each powder would be warranted. The surface topography of the particles seems to be a key optimization parameter. It is also important to note that, owing to their fundamental design, SCF processes may provide formulation enhancements outside of aerosol performance, including improvements relating to the solid-state characteristics, such as control and selection of the polymorph type (Tong et al., 2002) and minimization of high-energy amorphous sites, thus making them an attractive particle engineering tool for DPI product development. These attributes may be particularly useful when formulating stability-challenged, labile or hard to process molecules, for which other processing methods may fail.

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