Characterization of Suspension-Based Metered Dose Inhaler Formulations Composed of Spray-Dried Budesonide Microcrystals Dispersed in HFA-134a

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Purpose. To assess the physicochemical characteristics and aerosol properties of suspensions of lipid-coated budesonide microcrystals dispersed in HFA-134a.

Methods. Lipid-coated budesonide microcrystals were prepared by spray-drying an emulsion-based feedstock. Physicochemical characteristics of spray-dried particles were assessed by electron microscopy, laser diffraction, and differential scanning calorimetry. Purity and content were determined by reverse-phase HPLC. Particle aggregation and suspension stability were assessed visually, and aerosol performance was assessed by Andersen cascade impaction and dose content uniformity.

Results. Spray-drying of micronized budesonide microcrystals in the presence of phospholipid-coated emulsion droplets results in the production of low-density lipid-coated microcrystals with low surface energy. These spray-dried particles form stable suspensions in HFA-134a. This translates into good uniformity in the metered dose across the contents of the inhaler and acceptable aerodynamic particle size distributions (MMAD = 3.2 to 3.4 μm). The formulation was observed to maintain its performance over 6 months at 40°C/75% RH and 16 months at 25°C/60% RH. No effect of storage orientation was observed on the content of first sprays following storage (i.e., no Cyr effect). The fine particle dose was found to be linear out to suspension concentrations of about 2% wt/vol, and $FPD_{4.7\mu m}$ values approaching 400 μg can be delivered in a single inhalation.

Conclusions. Engineered particles comprised of lipid-coated microcrystals may provide an acceptable alternative formulation technology for metered dose inhalers in the new hydrofluoroalkane propellants.

KEY WORDS: aerosol; corticosteroid; hydrofluoroalkane; metered dose inhalers; pulmonary drug delivery.

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ABBREVIATIONS: ACI, Andersen cascade impaction; COPD, chronic obstructive pulmonary disease; DCU, dose content uniformity; DSC, differential scanning calorimetry; DSPC, distearoylphosphatidylcholine; FDA, Food & Drug Administration; FPD, fine particle dose; FPF, fine particle fraction; GSD, geometric standard deviation; HFA-134a, 1,1,1,2-tetrafluoroethane; HPLC, high-performance liquid chromatography; HPMC, hydroxypropylmethylcellulose; PFOB, perfluorooctyl bromide; pMDI, pressurized metered dose inhaler; PSD, particle size distribution; RH, relative humidity; RP-HPLC, reverse-phase high-performance liquid chromatography; RSD, relative standard deviation; SEM, scanning electron microscopy; Tm, phospholipid gel to liquid crystal phase transition; UV, ultraviolet; ×50, volume-weighted median diameter.

INTRODUCTION

It has been hypothesized that hollow porous (PulmoSphere) particles provide advantages with respect to suspension stability and dose content uniformity in metered dose inhalers relative to traditional suspensions of micronized drug (1–4). The concept revolves around the formation of a "homodispersion," wherein propellant is able to permeate within the core of the hollow porous particles such that the "dispersed" phase of propellant in the particle core, and the "continuous" phase of propellant which makes up the medium, are the same (2). The formation of a homodispersion is expected to decrease sedimentation/creaming and flocculation via a density matching and a reduction in interparticle attractive forces, respectively. Indeed, excellent physical stability of PulmoSphere suspensions have been noted in HFA-134a, and this has translated into good dose content uniformity, even for very potent drugs like formoterol (1). Even extreme tests with a 30-s pause are able to easily pass the proposed FDA guidance on dose content uniformity with an RSD of 5% or less (3). As well, no effect of storage orientation has been noted on the drug content of the first spray (i.e., no Cyr effect) in studies with albuterol PulmoSphere formulations (2,5). Clinical studies with an albuterol PulmoSphere formulation have shown that the powder is efficiently delivered to the lung, with adsorption about twice that of the Ventolin Evohaler at an equivalent dose (4).

The hollow porous particles detailed in these studies were prepared by spray-drying an emulsion-based feedstock with the active agent dissolved in the continuous phase of the emulsion (i.e., the solution-based PulmoSphere manufacturing process). Hence, the process has been restricted to active agents that have sufficient solubility in water to enable formulation. In the present study, we dispersed fine microcrystals of a water insoluble corticosteroid (budesonide) in the continuous phase of the emulsion (i.e., the suspension-based PulmoSphere manufacturing process). This study will detail the physicochemical properties of the resulting phospholipid-coated budesonide microcrystals, as well as their aerosol properties following dispersion in HFA-134a, and stability thereof.

MATERIALS AND METHODS

Materials

The budesonide PulmoSphere particles were manufactured by the suspension-based PulmoSphere manufacturing process, which involves high pressure homogenization to form a complex dispersion of emulsion droplets and microcrystals, followed by spray-drying (1).

Feedstock Preparation

The emulsion-based feedstock was prepared by first dispersing distearoylphosphatidylcholine, DSPC (Genzyme Pharmaceuticals, Cambridge, MA), and calcium chloride dihydrate (EM Science, Hawthorne, NY) in hot water (T = 70°C to 80°C) with an Ultra-Turrax mixer (IKA Labortechnik, Cincinnati, OH). The mixer was operated at 11,000 rpm for ≈3 min. The ratio of DSPC/Ca was 2:1 mol:mol, a ratio that has been found to be optimal in reducing the moisture

sensitivity of the spray-dried powder (data not shown). While mixing, perfluorooctyl bromide, PFOB (Atofina, Paris, France) was added dropwise at a rate of 20–50 ml/min, to create micrometer-sized PFOB-in-water emulsion droplets. The weight ratio of PFOB/DSPC was 24.3. After PFOB addition was complete, the coarse emulsion was mixed for an additional period of ca. 5 min, and subsequently homogenized at high pressure using an Avestin C-5 homogenizer (Ottawa, Canada) to create submicron emulsion droplets (median diameter is 0.19 μm, as measured via photosedimentation, Horiba CAPA-700, Irvine, CA). The homogenization process consisted of two discrete passes at 12 kpsi, a single pass at 16 kpsi, and 2 passes at 21–22 kpsi.

Micronized budesonide (Industiale Chimica s.r.i, Milan, Italy) was then added to the fine emulsion, and the resulting complex dispersion was mixed on the UltraTurrax for 30 s, and homogenized on the C-5 for an additional 2 passes at 16 kpsi and 2 passes at 20–22 kpsi. Homogenizing the micronized budesonide microcrystals has been shown to further reduce crystal size (data not shown). The concentrated dispersion was further diluted by roughly 4-fold with water. The processing of a more concentrated dispersion aids in the particle size reduction process. The final feedstock concentration (% solids) was 1.1% wt/wt. The theoretical composition (based on the solid components) is 46.1% wt/wt DSPC, 3.9% wt/wt $CaCl_2$, and 50.0% wt/wt budesonide.

Spray-Drying to Produce Engineered Dry Powder

In the second process step, the multi-particulate dispersion was spray-dried on a Niro Mobile Minor (model RM 142, Copenhagen, Denmark), equipped with a proprietary cyclone (ambient temperature) and atomizer. Spray-drying conditions were: inlet temperature = 110°C; outlet temperature = 64°C; atomization pressure = 120 psi; pump flow rate = 31 ml/min; total gas flow = 110 SCFM. The final composition of the spray-dried powder (58.2% wt/wt budesonide, 38.5% wt/wt DSPC, 3.3% wt/wt $CaCl_2$) differed slightly from the theoretical composition, due to fractionation of free DSPC liposomes during the drying process. Residual levels of PFOB and water were also present.

Metered Dose Inhaler Preparation

The spray-dried powder was hand-filled into aluminum canisters (Presspart Incorporated, Cary, NC, item number NC128P) or explosion proof glass vials (visual examination) and dried in a vacuum oven at 40°C (–25 mmHg) for 1 hr. A Valois DF30/63 RCU 63 μl metering valve equipped with a nylon desiccating ring (Valois Pharmaceuticals, Marly-le-Roi, France) was crimp-sealed onto the canister, and the canisters were filled with HFA-134a (DuPont, Wilmington, DE) by overpressure through the valve stem. A Pamasol (Pfäffikon, Switzerland) model 2005 small scale production plant complete with a model 2008 propellant pump was used for this purpose. The powder was dispersed in the propellant by first sonicating the canisters for 10–15 s in a FS-30 bath sonicator (Fisher Scientific, Pittsburgh, PA) and then placing them on a wrist-action shaker (Burrell Scientific, Pittsburgh, PA) for ca. 30 min. The average fill mass of budesonide PulmoSphere bulk powder and HFA 134a per canister was 77.44 ± 0.27 mg and 11.53 ± 0.17g, respectively (0.67% wt/wt or 0.83% wt/vol). The resulting charged pMDIs metered approximately 313 μg of budesonide ex-valve per actuation. The budesonide PulmoSphere formulation was tested using the Proventil HFA actuator (Key Pharmaceuticals, Kenilworth, NJ). The effect of fill mass was also explored independently.

Methods

Scanning Electron Microscopy

Visualization of particle size and morphology was achieved via scanning electron microscopy (SEM). The powder was deposited onto an aluminum stub, and sputter-coated with a 200 Å layer of gold/palladium. The particles were imaged on a Phillips XL30 ESEM LaB6 (FEI Company, Hillsboro, OR), operated at an accelerating voltage of 20 kV, filament current of 1.75 μA, beam current 30–40 mA, and probe current of 250 pA. Randomly selected photomicrographs were digitally captured from 5,000× to 20,000× magnification.

Particle Size Distribution of Dry Powder

The particle size distribution of the spray-dried dry powder was determined by laser diffraction (Sympatec laser diffraction analyzer (HELOS H1006, Clausthal-Zellerfeld, Germany, equipped with a RODOS type T4.1 vibrating trough and disperser). Approximately 5–10 mg of powder was placed directly in the RODOS, and subsequently atomized through a laser beam using 1 bar of air pressure, 50 mbar of vacuum, 70% feed rate, and a 1.30-mm funnel gap. Data was collected over an interval of 0.4 s, with a 175-μm focal length lens, triggered with 1% obscuration. Particle size distributions were determined using a proprietary Sympatec high-resolution Fraünhofer model. The PSD data is expressed in terms of the volume-weighted median diameter (×50), and geometric standard deviation (GSD).

Powder Bulk Density

Bulk densities of the spray-dried powders were estimated by filling a known volume (370 μl) of a size #2 hydroxypropylmethylcellulose (HPMC) capsule (Shionogi, Nara, Japan) with powder and measuring the change in mass gravimetrically using an AT20 balance with a measuring range of 2 μg–22 g (Mettler, Toledo, OH). Care was taken to not compress the powder during filling.

Differential Scanning Calorimetry

The phospholipid gel to liquid crystal phase transition was determined by differential scanning calorimetry, DSC, using a DSC-2920 (TA Instruments Inc., New Castle, DE). Due to the low bulk density of PulmoSphere powders, it was difficult to load more than 1 to 4 mg of powder in a standard aluminum DSC pan. To increase the sample mass and sensitivity, discs of powder (10–20 mg) were prepared using a 5/32″ diameter custom stainless steel press in a 40%RH controlled laboratory. The compressed powder discs were then hermetically sealed in a DSC pan. In a typical DSC experiment, the sample is first cooled to –20°C, equilibrated, and then heated at a rate 5°C/min to 200°C. The gel to liquid crystal phase transition temperature (T_m) is defined as the onset tempera-

ture of the first endothermic transition from each reversing heat flow thermogram.

Powder Moisture Content

Moisture content of the budesonide PulmoSphere bulk powder was determined by Karl Fischer analysis using a Mitsubishi CA-160 (Tokyo, Japan) analyzer equipped with a VA-100 vaporizer set at 140°C. A typical sample size of 20–30 mg was used.

Chemical Identity, Quantity, and Purity

Chemical identification, quantity and purity of budesonide in the PulmoSphere powder was determined by reverse phase high performance liquid chromatography (RP-HPLC) with detection at 240 nm. Samples and standard solutions were prepared in methanol at an approximate concentration of 0.5 mg/ml of budesonide. Samples were analyzed on a Waters HPLC system (Milford, MA) using an isocratic method with a Symmetry C18, 5 μm, 4.6 mm × 150 mm column. The mobile phase was mixed online using 68% phosphate buffer (pH 3.2) and 32% acetonitrile. The analysis was performed with a flow rate of 1.0 ml/min, a column temperature of 25°C, an autosampler temperature of 4°C, and a run time of 45 min. Samples and standards were quantified by summing the peak areas of the (r) and (s) epimer peaks. Budesonide content was calculated using a linear fit standard curve. Impurities greater than or equal to 0.1% of the total integrated peak area were reported. Identity of budesonide was confirmed by comparison of the retention time of the budesonide (s) epimer peak in the reference standard with the retention time of the budesonide (s) epimer peak in the sample solutions.

Aerodynamic Particle Size Distributions

Aerodynamic particle size distributions (PSD) were measured using an Andersen Cascade Impactor, ACI (Copley Instruments, UK), which was fitted with a USP induction port (throat), and operated at a flow rate of 28.3 $L \cdot min^{-1}$. Budesonide captured on the actuator, throat and stages was extracted with methanol. The PSD was determined by analyzing each of the collected samples for budesonide content by UV spectroscopy with detection at 242 nm. Quantitation was by comparison to an external standard curve (absorptivity = 29.40 $L \cdot cm^{-1} \cdot g^{-1}$, $r^2 = 0.9999$). The percentage of the metered dose deposited from stage 3 to the terminal filter (corresponding to particles less than 4.7 μm) is defined as the fine particle fraction ($FPF_{4.7\mu m}$), while the mass of budesonide on stages 3 to filter is defined as the fine particle dose ($FPD_{4.7\mu m}$). The percentage of the metered dose from stage 4 to the filter, i.e., $FPF_{3.3\mu m}$ is also reported, as this has been found to provide a more realistic estimate of the percentage of dose deposited in the lungs (6).

Dose Content Uniformity

Dose content uniformity measurements were collected by actuation of the pMDI canister into a sample bag (Nasco, whirl-pak 18 oz bags). The actuator was placed in the bag, and the walls of the bag and actuator were rinsed with 10 ml of methanol (EM Science, HPLC grade). Rinse samples were quantitated for budesonide by UV spectroscopy. After priming, shots at the beginning (shot 1), middle (shot 50), and end (shot 100) of the canister were quantitated. Waste shots 2 through 49 and 51 through 99 were performed using a pMDI FD-10 robot (InnovaSystems, Inc., Pennsauken, NJ). We chose to monitor the content uniformity in the metered dose (ex-valve), because we wanted to examine the performance of the formulation without complications from actuator performance, since selection of an actuator has not been optimized for this formulation.

Cyr Testing

Emitted doses were determined for ten canisters in three storage orientations: valve-up, valve-down, and valve-horizontal. The pMDIs were primed prior to testing by actuating five shots to waste. At least 30 s was allowed to pass between actuation, and a 5 s manual agitation with the canister held in the valve-down position was used prior to firing. Single actuations were collected across the entire contents of the canister (i.e., at the beginning, middle, and end). Collections were taken for shots 1, 2, 3, 49, 50, 51, 98, 99, and 100. Shots 4 to 48 and 52 through 97 were sent to waste. The time period between the first, second, and third collection sprays was about 3 min. The canisters were placed in their respective storage orientations after shots 48 and 97, and let stand for 24 h The ex-valve dose for this study was 150 μg.

RESULTS

Bulk Powder Analysis

SEM images of the neat micronized budesonide microcrystals and the spray-dried budesonide PulmoSphere powder are shown in Fig. 1. The micronized material (Fig. 1a) is characterized by smooth plate-like crystals, with a broad particle size distribution (PSD) from tens of nanometers to a few micrometers. The microcrystals are highly agglomerated, with smaller microcrystals (less than 1 μm) adhering to larger microcrystals with a high area of contact, owing to their planar shape. The agglomerates are often several microns in size. In contrast, the spray-dried particles (Figs. 1b and 1c) appear to be spheroidal in shape, with geometric sizes between about 1 and 3 μm, and a fairly uniform distribution of particle sizes (narrow PSD). Further, the spray-dried particles are characterized by a rough surface, and exhibit little tendency to agglomerate. The high degree of surface rugosity and absence of free microcrystals provides evidence that the phospholipid is able to effectively coat the active during the spray-drying process. The adsorption of phospholipid on the surface of the particles provides a hydrophobic coating of low surface energy, likely contributing to the diminished degree of particle agglomeration noted.

The morphology of the particles prepared by the suspension-based PulmoSphere manufacturing process differ dramatically from the morphology observed when the active is dissolved in the emulsion continuous phase (e.g., Fig. 1d). The solution-based PulmoSphere process generally leads to hollow/porous particles that resemble a child's whiffle ball, while the suspension-based process leads to particles with more of a crumpled-paper morphology.

The particle sizes noted visually in the SEM images correlate well with the geometric particle size distributions

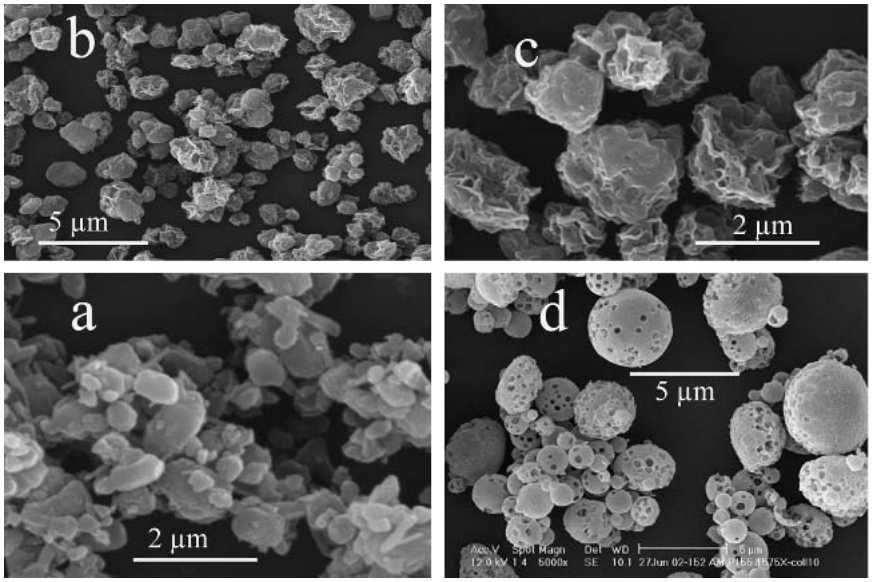

Fig. 1. SEM photomicrographs of various powder preparations: (a) neat micronized budesonide microcrystals; (b) spray-dried budesonide PulmoSphere microcrystals at a magnification of 5,000×; (c) spray-dried budesonide PulmoSphere microcrystals at a magnification of 15,000×; (d) a spray-dried tobramycin PulmoSphere powder prepared by the solution-based manufacturing process.

(PSD) determined by laser diffraction at a driving pressure of 1 bar (Fig. 2). As expected, the PSD for the budesonide PulmoSphere formulation is significantly narrower than for the micronized drug, with the median diameter shifted to smaller sizes. The median geometric size (×50) and geometric standard deviation (GSD) of the spray-dried budesonide powder was found to be 1.7 μm and 1.6, respectively. In contrast, the neat budesonide microcrystals exhibit an ×50 of 2.5 μm, and a GSD of 2.3. The larger sizes noted for the micronized drug are likely the result of incomplete dispersion of the agglomerates noted in the SEM photomicrographs in the RODOS disperser. This is not surprising, given the large cohesive forces expected for the fine micronized drug particles and their planar morphology. Additional milling of the microcrystals during high-pressure homogenization may also contribute, in part, to the decreases in median size noted following spray-drying.

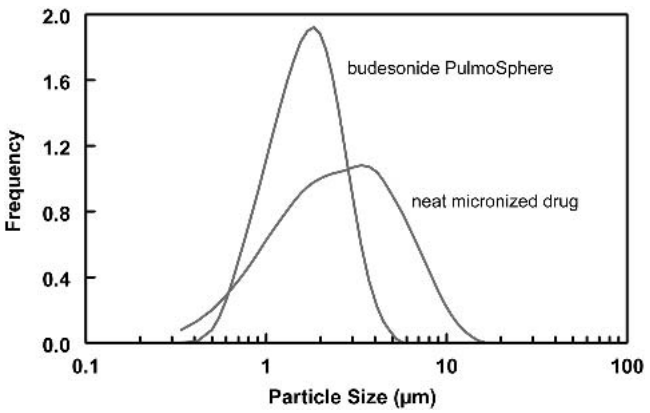

Fig. 2. Particle size distributions observed for neat micronized budesonide microcrystals and the spray-dried budesonide PulmoSphere powder as determined by laser diffraction (Sympatec).

Both PulmoSphere manufacturing processes (solution-based and suspension-based) lead to powders with a low bulk density (<0.2 g/cm^3). In the present instance, the spray-dried budesonide particles exhibit a bulk density of 0.16 g/cm^3, indicative of the significant porosity and high degree of surface rugosity. As well, the low degree of particle aggregation noted in the spray-dried powder leads to increases in interparticle voids, further contributing to the low bulk densities noted.

A DSC thermogram for the budesonide PulmoSphere bulk powder reveals an endotherm at around 85°C related to the change in the acyl chain order of the DSPC (data not shown). This transition is referred to as the T_m, and is indicative of the gel to liquid crystal phase transition in which acyl chains formerly in an all-trans configuration melt to become more liquid-like, with an associated increase in gauche conformer content. Another endothermic transition around 140°C related to drug substance is also observed. The crystalline nature of budesonide in the spray-dried powders was confirmed by X-ray diffraction (data not shown). It is postulated that the phospholipid DSC transitions are predicative of the powder's long-term storage stability, and that it is preferable that the phospholipid T_m be ca. 50°C higher than the storage temperature (7). The high Tm value noted is expected to provide excellent long-term physical stability provided the powder is adequately protected from the deleterious effects of moisture. The average moisture content of the budesonide PulmoSphere powder post-manufacturing was found by Karl Fischer analysis to be 0.55% wt/wt.

The identity, content and purity of budesonide in the formulated PulmoSphere powder were determined by RP-HPLC. The budesonide content in the PulmoSphere formulation was determined to be 58.2 ± 2.5% wt/wt. The two large peaks observed in the RP-HPLC chromatograms at 23.1 min and 25.4 min, correspond to the R and S epimers of budesonide, respectively. Two smaller peaks at 14.6 min and 38.6

min were also observed. The identity of these impurities is unknown, however both of the impurities account for less than 0.1% of the total composition. The purity of the spray-dried budesonide powder post-production was 99.9% wt/wt.

A summary of the physicochemical properties of the spray-dried budesonide PulmoSphere bulk powder are compiled in Table I.

Metered Dose Inhaler Performance

Suspensions of the budesonide PulmoSphere powder at a total suspension concentration of 0.82% wt/vol were prepared. This corresponds to a theoretical metered dose of about 300 μg of budesonide per shot from a 63 μl metering valve. Visual examination of the pMDI suspension formulation in glass vials revealed creaming times on the order of 20 min or more, characteristic of porous formulations prepared by the solution-based PulmoSphere manufacturing process.

Figure 3a presents a comparison of the aerodynamic particle size distributions obtained for the budesonide PulmoSphere powder from the Turbospin (PH&T, Italy) dry powder inhaler at a flow rate of 28.3 L/min. Drug quantitation was performed both gravimetrically and by the drug specific RP-HPLC method. Excellent agreement was observed between the two quantitation methods with respect to drug deposition on the various impactor stages, indicating that the drug and phospholipid form a homogeneous mixture across the entire particle size distribution. This is consistent with the uniform nature of the particles noted via SEM. A dry powder inhaler was used for this purpose in order to obtain sufficient powder on the impactor stages for accurate gravimetric quantitation.

The aerodynamic particle size distributions for the budesonide PulmoSphere pMDI aerosols obtained by Andersen cascade impaction at a flow rate of 28.3 L/min, are plotted in Fig. 3b. The MMAD was found to be 3.4 μm, with a $FPF_{4.7\mu m}$ and $FPF_{3.3\mu m}$, of 39.7% and 22.9%, respectively (n = 4). This corresponds to a $FPD_{4.7\mu m}$ of 125 μg.

Dose content uniformity across the contents of the inhaler was determined for a total of four canisters. Sample collections were made at the beginning (shot #1), middle (shot #50), and end (shot #100) of canister life. The results are shown in Table II.

The metered dose had a mean value of 313.7 μg with an RSD of 3.6% (n = 4). Individual metered dose values ranged from 295.1 to 334.4 μg, or about 6% on either side of the mean value. Hence, the suspension formulations easily passed the proposed FDA Guidance on content uniformity, which stipulates that 90% of the dose be within ±20% of the label claim, with none outside of ±25% (8). There is a slight trend toward increases in metered dose across the contents of the inhaler. The trend is considered insignificant with respect to the FDA mandated specifications for dose content uniformity, however.

Table I. Physicochemical Properties of Spray-Dried Budesonide PulmoSphere Bulk Powder

Physical property	Technique	Value
Identity	RP-HPLC	Conforms
Budesonide content	RP-HPLC	58.2% wt/wt
Budesonide purity	RP-HPLC	99.9% wt/wt (no single peak >0.1%)
Budesonide crystallinity	X-ray diffraction	Confirmed
Particle morphology	SEM	Spheroidal with high rugosity
×50	Laser diffraction	1.7 μm
GSD	Laser diffraction	1.6
Bulk density	Capsule fill mass	0.16 g/cm^3
Moisture content	Karl Fisher	0.55% wt/wt
Tm (phospholipid)	DSC	85°C

Storage Stability

The storage stability of the 0.82% wt/vol budesonide PulmoSphere powder in HFA-134a was assessed over a period of 6 months at 40°C/75% RH and 16 months at 25°C/60% RH (Table III).

The purity and aerosol performance were largely maintained over the storage period, although significant increases in the error about the metered dose were noted after 6 months at 40°C/75% RH and 16 months at 25°C/60% RH. Interestingly, there was no trend in the DCU data at the beginning, middle, and end of canister life, as might be expected if the significant moisture-induced particle agglomeration had occurred for these formulations. As well, no significant trends were noted in the aerodynamic particle size distributions or FPD, with the possible exception of the 6 month data at 40°C/75% RH, where a small increase in the MMAD and drop in $FPD_{4.7\mu m}$ were observed.

Effect of Suspension Concentration

The effect of suspension concentration on the aerodynamic particle size distribution, expressed in terms of the $FPD_{4.7\mu m}$ and $FPD_{3.3\mu m}$ is captured in Fig. 4. Good linearity in the fine particle dose is observed out to total solids concentration of 2% wt/vol, corresponding to a $FPD_{4.7\mu m}$ of about 300 μg. Hence, the technology should be able to handle the typical range of doses for corticosteroids currently administered to asthma and COPD patients.

Cyr Effect

Cyr *et al.* (5) found that the drug content of the first spray after a period as short as one hour was substantially less than that of subsequent sprays for generic albuterol pMDIs. This was ascribed to prime loss on storage, an issue that is related both to the characteristics of the metering valve and the nature of the formulation. Figure 5 presents the results of Cyr testing for the 0.4% wt/vol budesonide PulmoSphere pMDI formulation at a metered dose of 150 μg.

Shots 1–3 represent the first three shots from the canister immediately after priming. Excellent uniformity in the metered dose is noted for the fifteen canisters with an RSD of 2.7%. At this point, shots 4–47 were fired to waste and the canisters were stored in the valve-down, valve-up, and valve-horizontal orientations for a period of 24 h The canisters were then shaken and shots 48–50 were fired in succession. There is no evidence for a decrease in metered dose following storage, even for canisters stored in the valve-up configuration. Although the RSD for the canisters has increased following storage, all of the doses are still within ±20% of the mean dose (i.e., within the proposed FDA Guidance). The procedure was then repeated with shots 51–97 sent to waste, and

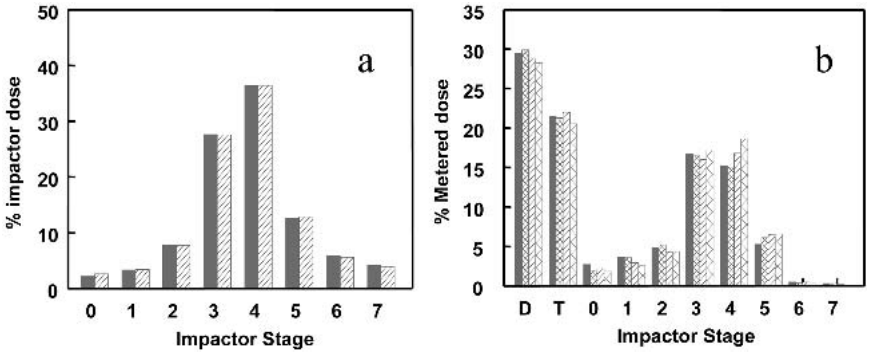

Fig. 3. Aerodynamic particle size distribution of the budesonide PulmoSphere pMDI formulation. (a) Comparison of the deposition on impactor stages quantitated gravimetrically (solid bar) or by a drug specific method (cross-hatch bar); (b) aerodynamic particle size distributions obtained by the drug specific quantitation method for four independent canisters. D and T refer to deposition in the device (valve stem and actuator) and USP throat, respectively.

shots 98–100 fired and collected in succession following a storage period of 24 h. Again, there is no evidence for a Cyr effect, and the RSD for the final three actuations is similar to the shots collected from the middle of the canister. There is a slight trend toward increasing metered dose over the contents of the inhaler, although this trend is not expected to impact DCU to a significant extent.

DISCUSSION

In traditional pMDI formulations, drug is either dissolved in the liquefied propellant, with or without the aid of a less volatile co-solvent, or suspended in the form of micronized drug particles, with the aid of a dispersing agent (9,10). The three dispersants typically used with chlorofluorocarbon (CFC) propellants (i.e., sorbitan trioleate, oleic acid, and lecithin) are no longer soluble in the more environmentally friendly hydrofluoroalkane (HFA) propellants, necessitating that new formulation strategies be developed for suspension-based pMDI products (10–12). One formulation approach has been to increase the solvency of the dispersants by adding a co-solvent (11). Often these suspensions still cream within a matter of seconds, however, placing increased importance on the patient using the device correctly (i.e., shaking the canister, and rapidly inhaling following shaking). Even a minor pause between shaking and firing of the canister can impact the dose that the patient receives (13). Given that FDA is mandating more stringent control on dose content uniformity (8), the need for improved suspension stability is becoming increasingly important. As well, the presence of a co-solvent can impact chemical stability of the dispersed drug substance, and increase extraction of leachables, leading to decreases in aerosol performance over time (14). The present study details a new particle engineering strategy to improve suspension stability and performance in suspension-based pMDIs. In particular, the present paper examines the flexibility of the PulmoSphere process technology to formulate poorly soluble drugs into engineered particles for aerosol delivery in a pressurized metered dose inhaler.

Table II. Dose Content Uniformity for Budesonide PulmoSphere pMDI Formulation (Suspension Concentrations Varied from 0.666% wt/wt to 0.670% wt/wt for Various Canisters as a Result of Inherent Variability in Hand-Filling)

	Metered dose (μg)/(% mean dose)		
pMDI no.	Shot no. 1	Shot no. 50	Shot no. 100
21	312.6 (99.6)	322.2 (102.7)	334.4 (106.6)
22	302.7 (96.5)	295.1 (94.1)	315.8 (100.7)
23	313.4 (99.9)	315.0 (100.4)	330.0 (105.2)
24	309.7 (98.7)	312.2 (99.5)	301.3 (96.0)
Mean (SD)	309.6 (4.9)	311.1 (11.4)	320.4 (15.0)
Grand mean (SD)		313.7 (11.3)	
		RDS = 3.6%	
Range		295.1–334.4	
(% from mean)		(–5.9% to +6.6%)	

The spray-dried budesonide PulmoSphere particles exhibit a spheroidal shape and a high degree of surface roughness. The increases in surface rugosity noted may have a significant impact on the agglomeration properties of the dispersed particles, as asperities prevent close approach of particles to within van der Waals contact (15). The low surface energy of the hydrophobic phosphatidylcholine also contributes to decreasing interparticle attractive forces (2). These morphologic features and surface characteristics likely contribute to the excellent suspension stability noted for these particles in HFA-134a. The slow creaming times noted (on the order of minutes), contributes to the acceptable performance in dose content uniformity measurements across the contents of the inhaler, where RSDs of 2–4% are noted on release. Acceptable metering performance is maintained on storage, although errors increase at the end of study (6 months at 40°C/75% RH and 16 months at 25°C/60% RH). As well, metering performance is maintained for single dose shots following storage in different orientations (i.e., no Cyr effect) (2,5,16). No significant variations in the mass median aerodynamic diameter or fine particle dose are noted on storage. These results suggest that particle engineering may be able to improve suspension stability and aerosol performance for suspension-based pMDI formulations, thereby improving the probability of passing FDA-mandated stability criteria over the lifetime of the product.

Traditional CFC pMDIs exhibit lung deposition of only 10–20% of the metered dose (9). New suspension-based HFA formulations are not significantly improved. For example, only about 14.5% of the emitted albuterol sulfate dose is

Table III. Changes in Purity and Aerosol Properties of Budesonide PulmoSphere Formulation on Storage

Property	Initial (n = 4)	t = 3 mo 25/60 (n = 3)	t = 3 mo 40/75 (n = 3)	t = 6 mo 25/60 (n = 3)	t = 6 mo 40/75 (n = 3)	t = 9 mo 25/60 (n = 2)	t = 16 mo 25/60 (n = 4)
Purity	99.9%	99.8%	99.7%	99.9%	99.7%	99.7%	99.2%
Metered dose (RSD)	313.3 μg (3.4%)	320.5 μg (5.9%)	318.8 μg (6.9%)	318.9 μg (6.1%)	321.1 μg (9.0%)	307.4 μg (5.4%)	332.6 μg (9.9%)
MMAD	3.4 μm	3.2 μm	3.3 μm	3.3 μm	3.6 μm	3.4 μm	3.3 μm
$FPF_{4.7\mu m}$	39.7%	43.6%	42.8%	42.2%	35.8%	39.5%	42.0%
$FPD_{4.7\mu m}$	116 μg	127 μg	121 μg	121 μg	103 μg	112 μg	122 μg

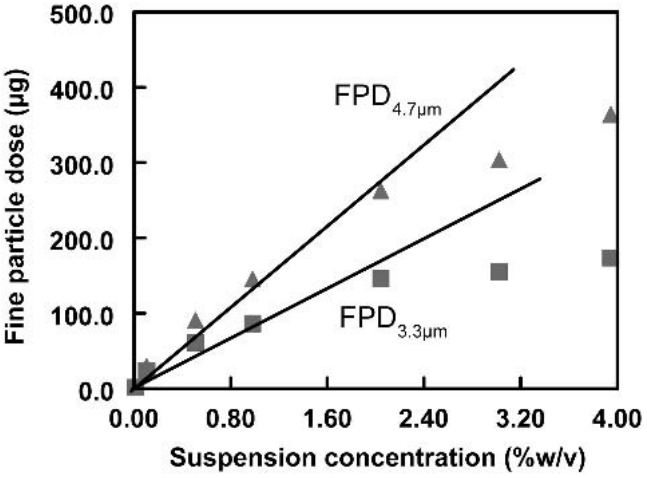

Fig. 4. Effect of suspension concentration on the fine particle dose in a budesonide PulmoSphere pMDI formulation.

deposited in subject's lungs with the Ventolin Evohaler (GSK, London, U.K.) (4). The corresponding albuterol PulmoSphere formulation deposited 28.5% of the metered dose in subject's lungs (4). Based on in-vitro aerosol testing it is anticipated that the budesonide PulmoSphere formulation will meet or exceed the deposition achieved with the albuterol PulmoSphere formulation. A similar budesonide PulmoSphere formulation delivered 58% of the nominal dose in a capsule to the lungs of volunteers from a portable, passive, dry powder inhaler (17). This value is comparable to the lung delivery achieved with a solution-based pMDI formulation of beclomethasone dipropionate, where the MMAD was 1.1 μm (18–20).

The preferred MMAD and GSD values for corticosteroids remain controversial, although there is a growing body of evidence that delivery to both large and small airways is beneficial (21–24). On the flip side, alveolar deposition leads to more rapid systemic absorption, potentially increasing the potential for systemic side-effects. This might favor a slightly higher MMAD than that found with solution-based pMDIs, so as to reduce alveolar deposition. The high lung delivery efficiency noted with solution pMDIs does decrease oropharyngeal absorption, thereby decreasing local side-effects (e.g.,

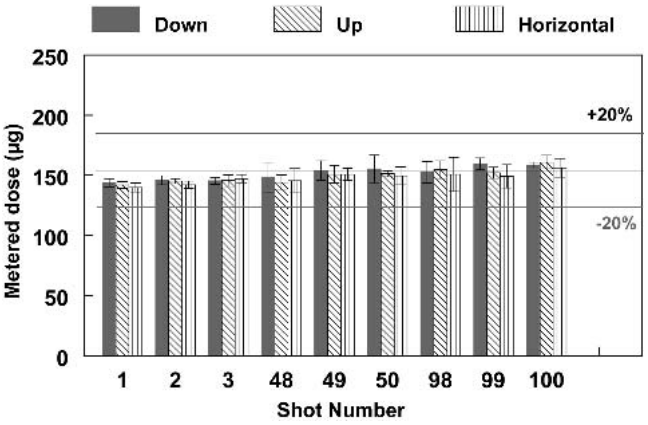

Fig. 5. Effect of storage orientation on metering performance in 0.4% wt/vol budesonide PulmoSphere particles in HFA-134a (n = 15 canisters, 5 at each storage orientation).

candidiasis) (18–20). The suspension-based PulmoSphere formulations represent an intermediate in terms of delivery efficiency between the traditional micronized drug suspension formulations (10–15%), and the solution-based formulations (ca. 50%). Although solution pMDIs work effectively for highly potent asthma drugs, they may be limited for high dose delivery. This is due to the fact that aerosol performance decreases with increasing solute and co-solvent content (25,26). As well, most drugs have limited solubility in HFA or HFA/co-solvent mixtures. Hence the linearity in $FPD_{4.7\mu m}$ out to doses of 400 μg with a 63 μl metering valve, lends hope that lung doses approaching 1 mg can be delivered in a single puff with a 150 μl metering valve, potentially opening the door to the delivery of less potent actives in a pMDI (27).

CONCLUSIONS

- Initial characterization of a budesonide PulmoSphere pMDI formulation in HFA-134a suggest that the suspension is very stable (creaming time >20 min), and that this stability translates into low RSD values (3.6%) in dose content uniformity testing at release
- The high Tm (85°C) noted for the formulation suggests that the physical stability of the suspension should be good unless significant water ingress occurs into the canister. This is confirmed by the small impact in aerosol performance noted on storage.
- The drug substance survived the spray-drying process, and exhibited high purity (>99.9%) at release, which was maintained on stability

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