# Hollow Porous Particles in Metered Dose Inhalers

**Luis A. Dellamary,[1] Thomas E. Tarara,[1] Dan J. Smith,[1] Christopher H. Woelk,[1] Anastasios Adractas,[1] Michael L. Costello,[2] Howard Gill,[1] and Jeffry G. Weers[1,3]**

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***Purpose.*** To assess the physical stability and aerosol characteristics of suspensions of hollow porous microspheres (PulmoSpheres™) in HFA-134a.

***Methods.*** Cromolyn sodium, albuterol sulfate, and formoterol fumarate microspheres were prepared by a spray-drying method. Particle size and morphology were determined via electron microscopy. Particle aggregation and suspension creaming times were assessed visually, and aerosol performance was determined via Andersen cascade impaction and dose uniformity studies.

***Results.*** The hollow porous particle morphology allows the propellant to permeate freely within the particles creating a novel form of suspension termed a homodispersion™, wherein the dispersed and continuous phases are identical, separated by an insoluble interfacial layer of drug and excipient. Homodispersion formation improves suspension stability by minimizing the difference in density between the particles and the medium, and by reducing attractive forces between particles. The improved physical stability leads to excellent dose uniformity. Excellent aerosolization efficiencies are also observed with PulmoSpheres formulations, with fine particle fractions of about 70%.

***Conclusions.*** The formation of hollow porous particles provides a new formulation technology for stabilizing suspensions of drugs in hydrofluoroalkane propellants with improved physical stability, content uniformity, and aerosolization efficiency.

**KEY WORDS:** asthma; pulmonary drug delivery; metered dose inhaler; particle engineering; spray-drying; suspensions; HFA-134a.

## INTRODUCTION

Pressurized metered dose inhalers (pMDIs) are the mainstay of drug delivery devices for the treatment of asthma (1). In 1996, approximately 500 million inhaler units were sold world-wide; we expect that figure to grow to more than 700 million units by the year 2000. In spite of this growth, formulations of pMDIs have remained virtually unchanged since their initial introduction in the mid-1950s (2). They consist of either micronized drug suspended in liquified propellant, or drug dissolved in liquified propellant plus co-solvent. pMDIs have traditionally utilized chlorofluorocarbon (CFC) propellants. These materials are being phased out, however, due to their implication in stratospheric ozone depletion (3). Two non-CFC hydrofluoroalkane propellants have now been approved: HFA-134a (1,1,1,2-tetrafluoroethane), and HFA-227 (1,1,1,2,3,3,3 heptafluoropropane). Unfortunately, the transition to the new more environmentally acceptable HFA propellants has been difficult, due in large part to the poor solvency of the HFA, which limits the solubility of approved surfactants (i.e. oleic acid, lecithin and sorbitan trioleate) (4–6). The solubility of these surfactants can be increased by the use of cosolvents such as ethanol, but the presence of a cosolvent in substantial quantities is regarded by many as highly undesirable. Some of the potential problems with cosolvents include: chemical instability of the drug substance, extraction of elastomeric components from the valve, enhanced Ostwald ripening, and an alcohol taste not to the liking of some patients.

Alternatively, novel surfactants that have good solubility in HFA-134a and 227 could be developed, but these would require complete toxicological testing programs equivalent to that required for a new drug for inhalation. To date, no technology has been developed that is compatible with a wide range of drugs and that is able to meet the increasingly stringent regulatory standards proposed for pMDIs.

Currently, suspension pMDIs are comprised of micronized drug particles. Micronization leads to broad particle size distributions, and little control over particle morphology and density. In contrast, spray drying affords excellent control over particle size and distribution, particle shape and morphology, and particle density. In this paper we introduce a new particle engineering technology for pMDIs based upon spray dried particles that have been specially designed to be both hollow and porous (PulmoSpheres™).

## MATERIALS AND METHODS

### Preparation of Engineered Particles

Cromolyn sodium PulmoSpheres were manufactured by a spray drying process. An aqueous feed solution was prepared by mixing two solutions A and B, immediately prior to spray-drying. Solution A consisted of a fluorocarbon-in-water emulsion in which 50 g of perfluorodecalin (Air Products, Allentown, PA) was dispersed in 314 g of distilled water with the aid of 2.04 g of saturated egg phosphatidylcholine, EPC-3 (Lipoid KG, Ludwigshafen, Germany) emulsifier. The emulsion was prepared by first dispersing the phospholipid in hot deionized water (T = 50–60°C) with a Tekmar tissumizer at 8,000 rpm for ca. 5 min. The perfluorodecalin was then added dropwise under mixing. The coarse emulsion was homogenized under high pressure (18,000 psi) for 5 discrete passes with an Avestin Emulsiflex-C5 (Ottawa, Canada). The resulting emulsion had a median particle size of 0.2 μm as determined by photosedimentation (Horiba CAPA-700, Irvine, CA). Solution B contained 2.08 g of cromolyn sodium (Sigma, St. Louis, MO) dissolved in 20 g of deionized water with 0.04 g poloxamer 188 (BASF Corporation, Parsippany, NJ). The combined feed solution was spray-dried with a B-191 Mini Spray-Drier (Büchi,

[1] Alliance Pharmaceutical Corp., 3040 Science Park Road, San Diego, California 92121.
[2] Electron Microscopy Services, 1380 Garnet Ave. E-219, San Diego, California 92109.
[3] To whom correspondence should be addressed. (e-mail: jgw@allp.com)

**ABBREVIATIONS:** CFC, chlorofluorocarbon; DSPC, distearoylphosphatidylcholine; FPF, fine particle fraction; GSD, geometric standard deviation; HFA, hydrofluoroalkane; HPLC, high performance liquid chromatography; MMD, mass median (geometric) diameter; MMAD, mass median aerodynamic diameter; PC, phosphatidylcholine; pMDI, pressurized metered dose inhaler; RH, relative humidity; SEM, scanning electron microscopy; TEM, transmission electron microscopy.

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Flawil, Switzerland) equipped with a standard two-fluid nozzle under the following conditions: inlet temperature = 85°C, outlet temperature = 61°C, aspirator = 100%, pump = 2.5 ml $min^{-1}$, nitrogen flow = 2,800 L $hr^{-1}$. The final composition on a weight basis was: 49.5% cromolyn sodium, 49.5% egg phosphatidylcholine, 1.0% poloxamer 188.

Albuterol sulfate PulmoSpheres were prepared by a similar procedure. In this case, solution A contained 194 g of perfluorooctyl bromide (perflubron, LiquiVent®, Alliance Pharmaceutical Corp., San Diego, CA) dispersed in 208 g of distilled water, with the aid of 4.8 g of distearoylphosphatidylcholine, DSPC (Genzyme Pharmaceuticals, Cambridge, MA). Solution B contained 5.2 g albuterol sulfate (FDC Limited, Mumbai, India) dissolved in 46 g of deionized water. A third solution (solution C) containing 0.44 g of calcium chloride dihydrate (Fisher Scientific, Pittsburgh, PA) dissolved in ca. 5 g of deionized water was also prepared. The three solutions were then mixed sequentially, and the resulting mixture used as the feedstock for the spray-drier. The homogenization and spray drying conditions were similar, except the aspirator was set at 82%, the feed pump at 2.3 ml $min^{-1}$, and the nitrogen flow at 2400 L $hr^{-1}$. Some perflubron was retained in the albuterol sulfate powder. The overall powder composition was not determined although the total content of albuterol sulfate was found to be 35%.

For formoterol fumarate PulmoSpheres, solution A contained 15.43 g perfluorooctyl ethane (F-Tech, Tokyo, Japan), dispersed in 142.15 g of distilled water, with 0.714 g DSPC. Solution B contained 0.046 g formoterol fumarate (Betachem Inc., Upper Saddle River, NJ) dissolved in 13.86 g deionized water, along with 0.717 g lactose monohydrate (Sigma Chemical Co., St. Louis, MO), and 0.082 g calcium chloride dihydrate. The spray-drying conditions were: inlet temperature = 85 °C; outlet temperature = 55 °C; aspirator = 87%, pump = 1.5 ml $min^{-1}$. The final formoterol fumarate concentration in the spray-dried powder was 1.8%.

The principal excipient in PulmoSpheres, phosphatidylcholine (PC), is the main component of both endogenous human lung surfactant and approved synthetic lung surfactant preparations (e.g. ExoSurf® Glaxo-Wellcome, Research Triangle Park, NC). It is also the major component of soy lecithin, currently approved for use in pMDI formulations. The choice of other excipients is formulation dependent, and ultimately will be determined by several factors including difficulty in achieving regulatory approval, suspension stability, drug stability, dose reproducibility, fine particle fraction, etc.

### Preparation of Metered Dose Inhalers

Spray-dried powders were hand-filled into aluminum or glass canisters and dried in a vacuum oven at 40°C (25 mm Hg) for 3–4 hr. The pMDI valves were crimp-sealed onto the canisters and the canisters 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. A DF30/50act 50 μL valve (Valois of America, Greenwich, CT) was utilized for the cromolyn sodium PulmoSpheres, and the DF30/50act, A66172 (3-M, St. Paul, MN), and BK357, RB700 (Bespak Inc., Apex, NC) valves were utilized for the albuterol sulfate PulmoSpheres studies. The RB700 valve was also utilized for the formoterol fumarate PulmoSpheres studies. The powder was dispersed in the propellant by first sonicating the canisters for 10–15 s in an 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. Final suspension concentrations were 1.64%, 0.50%, and 0.93% for the cromolyn sodium, albuterol sulfate, and formoterol fumarate PulmoSpheres, respectively. The actuator supplied with the Proventil HFA product was used for all PulmoSpheres testing.

Intal® (Rhône-Poulenc-Rorer, Loughborough, England), and Proventil HFA® (Key Pharmaceuticals, Kenilworth, NJ) were purchased from a local pharmacy.

### Electron Microscopy

Visualization of particle size and morphology was achieved via electron microscopy. For scanning electron microscopy (SEM) studies, the particles were first treated with osmium tetroxide vapor, and then affixed on double sticky graphite tape to an aluminum stub. The sample was sputter-coated with a 250 Å layer of gold/palladium, and imaged on a Steroscan 360 SEM (Cambridge, United Kingdom) operated at an accelerating voltage of 20 Kev and a probe current of 250 pAmps. For the transmission electron microscopy (TEM) studies, particles were embedded with Araldite 502 resin (Ted Pella Inc., Redding, CA). Unstained silver thin sections were imaged with a Zeiss EM 902 (Jena, Germany) at 80 Kev and photographed on Kodak 4489 film (Rochester, NY). Final magnifications were determined from photographs of replica grating standards and negatively stained catalase crystals (Ted Pella Inc.).

### Particle Size Analysis by Laser Diffraction

A Sympatec laser diffraction analyzer (HELOS H1006, Clausthal-Zellerfeld, Germany) equipped with a RODOS type T4.1 vibrating trough was used to characterize the volume-weighted mean geometric diameter (VMD) of the spray-dried powders. Approximately 1–3 mg of powder was placed in the powder feeder, which was subsequently atomized through a laser beam using 1 bar of air pressure, 60 mbar of vacuum, 70% feed rate and 1.30 mm funnel gap. Data was collected over an interval of 0.4 s, with a 175 μm focal length, triggered at 1% obscuration. Particle size distributions were determined using a Fraunhofer model.

### Dose Uniformity

Dose uniformity over the entire contents of the albuterol sulfate and formoterol fumarate PulmoSpheres inhalers were assessed via the current USP test method ⟨905⟩. Accordingly, selected doses were collected in a dose unit sampling apparatus, DUSA (manufactured at Alliance according to specifications provided in the USP test method). Doses not tested were actuated to waste at intervals of 1 min between shots. Between actuations, canisters were mixed on a wrist-action shaker. Prior to actuation the canister was shaken by hand, inverted and immediately fired. For shake-pause-fire testing, the canister was not shaken for a period of 30 s prior to actuation.

For the albuterol sulfate PulmoSpheres, each DUSA and filter were extracted with 10 mL of deionized water. A 2 mL aliquot of the extract was combined with 0.25 mL of 1N NaOH, which is used to convert the albuterol to the phenolate form.

The albuterol sulfate content in each extract was quantified by absorption spectroscopy using a Beckman DU640 (Fullerton, CA) spectrophotometer. The absorption of the solution at 243 nm was determined and compared to an external standard curve with a deionized water/NaOH blank.

For the formoterol fumarate PulmoSpheres, each DUSA and filter were extracted with 10 mL of methanol. Formoterol content was quantitated by high performance liquid chromatography (HPLC). A Beckman System Gold chromatographic system was used (Beckman, Palo Alto, CA). It consisted of a model 126 pump module, a model 168 UV-Vis diode array detector, and a model 507 autosampler. A 100 × 3.0 mm (i.d.) column packed with Spherisorb™ 3 μm C-8 and a 10mm × 4mm (i.d.) safeguard™ column packed with Spherisorb™ 3 μm C-8 (MetaChem, Torrance, CA) were utilized. Isocratic separation was achieved using an acetonitrile:methanol:water:trifluoroacetic acid 640:200:160:0.5 (v/v) solvent system over 10 min. The flow rate was at 0.5 mL/min. Quantitation was done by detection at 214 nm in comparison with an external standard curve. The column and solvents were maintained at ambient temperatures.

### Andersen Cascade Impactor

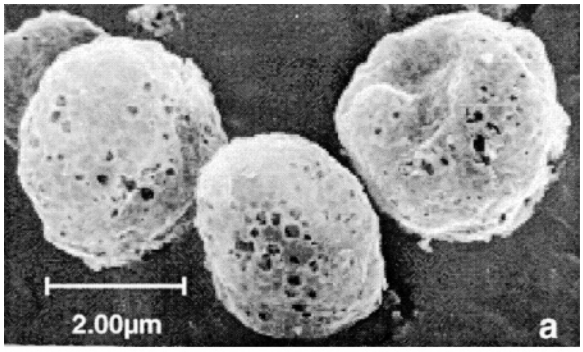
Impaction studies were performed on an eight-stage Andersen cascade impactor (Andersen Instruments, Smyrna, GA), at a flow-rate of 28.3 L $min^{-1}$. The standard USP induction port with an internal volume of 60 ml was utilized. Initially, 5 shots were sent to waste, and the next 10–20 shots (depending on the drug) were made into the impactor. The interval between shots was at least 30 s, to prevent cooling of the canister and resulting moisture condensation. After the last dose was discharged, the inhaler was removed from the impactor. The valve stem and actuator were rinsed separately with a known volume of water (cromolyn sodium), 0.1 N NaOH (albuterol sulfate), or methanol (formoterol fumarate). The impactor was then disassembled with each plate placed in a separate container with the appropriate solvent. The extraction was allowed to proceed for 1 hr at room temperature. Drug concentrations were quantitated against an external standard curve by absorbance spectroscopy or HPLC as detailed above. The filter was installed but not assayed, because the polyacrylic binder interfered with the analysis. The material balance and particle size distribution trends indicated that deposition on the filter was negligibly small. The impactor data reported in this study are for deposition onto uncoated plates. No differences in deposition were noted, however, when the impactor plates are coated with silicone oil.

## RESULTS

To assess the merits of hollow porous particles in pMDIs, we've formulated three drugs frequently used in asthma therapy (cromolyn sodium, albuterol sulfate, and formoterol fumarate).

### Physical Characteristics of the PulmoSpheres Powders

Representative PulmoSpheres particles incorporating the mast cell stabilizer, cromolyn sodium, are shown in Fig. 1. The thin-walled porous particles exhibit a translucent appearance on SEM photomicrographs (Fig. 1A) with a geometric diameter of about 4 μm. The geometric diameter of the cromolyn sodium PulmoSpheres was confirmed by laser diffraction (Sympatec),



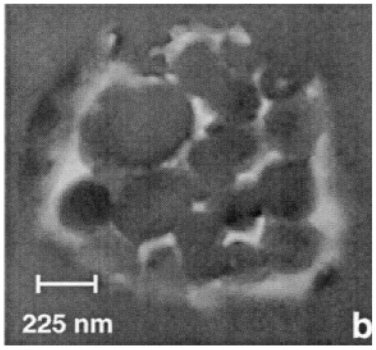




**Fig. 1.** Electron microscopy images of (a) hollow porous cromolyn sodium PulmoSpheres by SEM, and (b) by TEM.

where a volume-weighted mean diameter (VMD) of 4.5 ± 1.4 μm was found (Table 1). Morphologically, the particle walls have a sponge-like appearance, with pores on the order of 50–300 nm. The hollow nature of the particles was confirmed by examining particle cross-sections via TEM (Fig. 1B). Here, the hollow domains in the particle interior were found to be approximately 100–600 nm in size. The sponge-like structure provides excellent mechanical strength to the particles, and neither sonication nor actuation through the pMDI valve were found to alter particle morphology.

The hollow porous nature of the particles was further confirmed by measurement of the bulk density, ρ, of the cromolyn sodium PulmoSpheres powder by a tap method (Van Kel Industries Inc., Edison, NJ). The bulk density was found to be 0.06 g $cm^{-3}$, significantly less than the 0.5–1.0 g $cm^{-3}$ values typically found for micronized powders (Table 1).

The physical characteristics (tap density and geometric size) observed for the PulmoSpheres formulations of the bronchodilators albuterol sulfate and formoterol fumarate are similar

**Table 1.** Physicochemical Characteristics of PulmoSpheres Powders

| Drug | Lot # | Valve | Tap density (g $cm^{-3}$) | VMD (GSD) (μm) |
|---|---|---|---|---|
| Cromolyn sodium | 742-100 | DF30/50 | 0.06 | 4.47 (1.37) |
| Albuterol sulfate | 906-05 | DF30/50 | 0.12 | 3.80 (1.80) |
| | 906-13 | DF30/50 | 0.11 | 3.98 (1.77) |
| | 906-21 | DF30/50 | 0.12 | 3.66 (1.76) |
| | Average | | 0.12 | 3.80 (1.78) |
| | SDEV | | 0.01 | 0.16 (0.02) |
| Formoterol fumarate | 906-25 | RB700 | 0.19 | 2.36 (1.60) |

to that found for cromolyn sodium, i.e. VMD values of about 2–4 μm, and tap densities of about 0.05–0.2 g $cm^{-3}$ (Table 1).

Because of their hollow porous character, PulmoSpheres particles have smaller aerodynamic diameters than their corresponding geometric diameters, viz: $VMAD = VMD\sqrt{\rho_e}$, where VMAD is the volume-weighted mean aerodynamic diameter, and $\rho_e$ is the envelope mass density of the particles. For spherical particles with narrow particle size distributions, the bulk density is a reasonable approximation of the envelope mass density of the particles (7). Based on the measured values in Table 1, the cromolyn sodium, albuterol sulfate, and formoterol fumarate *PulmoSpheres* have estimated VMAD values of 1.1, 1.3, and 1.0 μm, respectively.

### Physical Stability of PulmoSpheres Suspensions

To assess the improvements in physical stability afforded by the hollow porous particle design, we visually compared the sedimentation rates of the PulmoSpheres dispersed in HFA-134a, with micronized particles in the commercial Intal CFC and Proventil HFA formulations. Whereas noticeable sedimentation was observed for the Intal and Proventil HFA products in just seconds, remarkably little sedimentation was observed for the PulmoSpheres suspensions over periods of hours. This is illustrated for albuterol sulfate PulmoSpheres in comparison with Proventil HFA via time-lapse photography (Fig. 2). Creaming times on the order of hours are also observed for the formoterol fumarate *PulmoSpheres* formulation.

### Dose Uniformity of PulmoSpheres Particles

Rapid physical separation of the drug and propellant may lead to a lack of dose uniformity per actuation. The problem of separation of the suspension is generally addressed by vigorously shaking the pMDI immediately prior to use. Patient compliance with even this simple task is difficult to control, however, and slight delays between shaking and administration can affect dose uniformity for poorly stabilized suspensions.

To test the dose uniformity over the entire contents of the inhaler, we utilized the current USP test method ⟨905⟩. The method stipulates that >90% of the delivered doses be within ±25% of the label claim, with less than 10% of the doses ±35%. It is recommended that doses at the beginning, middle, and end of the canister be tested. Accordingly for a 100 shot canister containing albuterol sulfate PulmoSpheres (2 shots per dose), shots (3,4), (5,6), (27,28), (29,30), (50,51), (52,53), (74,75), (76,77), (97,98), and (99,100) were assayed. For dose uniformity studies with formoterol fumarate PulmoSpheres single shots (1,25,50,75,100) were quantitated.

A 1998 FDA draft guidance on metered dose inhaler and dry powder inhaler drug products proposes that the limits be tightened, such that >90% of the delivered doses be within ±20% of the label claim, with none outside of ±25%. Statistically speaking, an RSD of 6% would be required to meet the proposed FDA specifications.

Typical dose uniformity results obtained for albuterol sulfate PulmoSpheres are shown in Fig. 3. Not only are the results within the current guidelines, but they are also within the limits of the proposed guidelines, a strong testament to the improved stability afforded by this form of particle engineering. The relative standard deviation (RSD) for all the doses tested with the three different metering valves was 4.7%. No differences were found if the pMDI was actuated immediately after shaking or 30 s later (i.e. shake-pause-fire testing), as would be expected for suspensions with poor physical stability. As well, the formulation remains within compliance after storage under accelerated conditions (40°C / 75% RH) for 3 months.

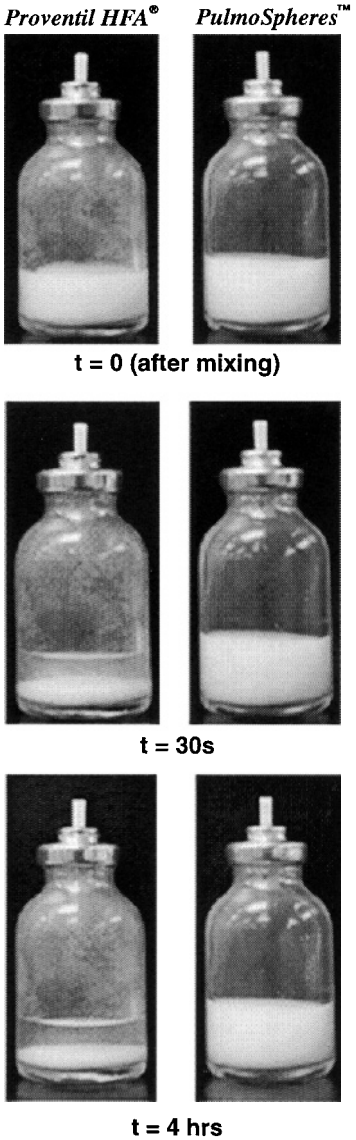



**Fig. 2.** Time-lapse photography of albuterol sulfate pMDI suspensions; a comparison of the commercial Proventil HFA® formulation with a corresponding fomulation of hollow porous particles in HFA-134a, illustrating the improved physical stability afforded by homodispersion formation.

For traditional formulations based on micronized drugs, the RSD is expected to increase significantly as the delivered dose is decreased. For low dose delivery, deposition of drug on the container walls or on the metering valve can negatively impact dose uniformity. Dose uniformity results for the formoterol fumarate PulmoSpheres (label claim ≈ 9 μg) is shown in Fig. 4. Again the RSD is less than 5%, and in compliance with the proposed regulatory requirements.

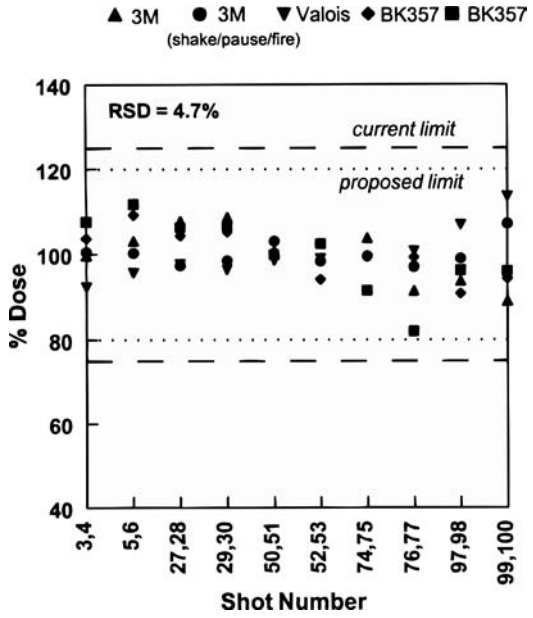



**Fig. 3.** Dose uniformity achieved with albuterol sulfate PulmoSpheres (n = 5 cans).

### Aerosol Characteristics of PulmoSpheres Particles

An eight-stage Andersen cascade impactor was used to determine the aerosol properties of the pMDI formulations. The cascade impactor provides an in vitro system for estimating the potential depth of penetration of aerosols into the human lung. The device consists of a series of flat plates arranged perpendicular to an airflow, such that particles deposit stagewise in accordance with their aerodynamic diameter, which is critically dependent on the cross-sectional area, density, and morphology of the particles. After deposition onto the stages of the impactor, particles are collected and the total mass of drug assessed stagewise; the fine particle fraction (FPF) was determined as the percent of the drug mass on the respirable stages of the impactor (i.e. stages 2-F), divided by the total mass of drug leaving the device (i.e. stages −1-F), where stage −1 corresponds to the induction port, and F to the filter. The fine particle dose (FPD) is the mass of drug on the respirable stages (i.e. $< 5.8$ μm). Obviously, the impactor is only an in-vitro tool useful in predicting in-vivo lung deposition. Ultimately, lung deposition and formulation performance must be assessed clinically.

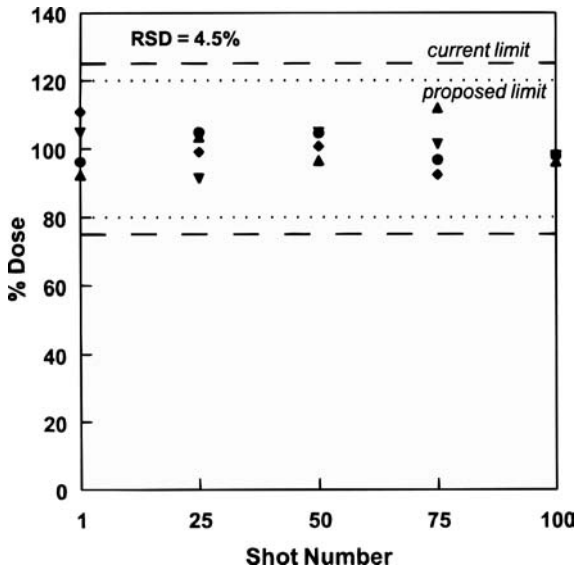



**Fig. 4.** Dose uniformity achieved with formoterol fumarate PulmoSpheres (n = 4 cans).

Typical micronized cromolyn sodium particles present in the Intal product had a FPF of 24.3 ± 2.1%, whereas 68.1 ± 5.9% of the cromolyn sodium in the hollow porous PulmoSpheres was respirable (Table 2). The increases in FPF observed are the result of a shift from impactor stages corresponding to *in vivo* oropharyngeal deposition (stages −1 to 1) to those corresponding to deposition in the bronchial airways of the lung (Fig. 5). The Intal product delivered a dose from the mouthpiece of ca. 800 μg of which only about 200 μg was respirable. An equivalent 200 μg fine particle dose was delivered with a total dose from the mouthpiece of only 300 μg of the cromolyn sodium PulmoSpheres formulation. Finally, the mass median aerodynamic diameter (MMAD) was decreased from 4.7 ± 0.5 μm to 3.4 ± 0.2 μm, with comparable geometric standard deviations (GSD). Numerous studies have confirmed that 2–3 μm particles, as found in the cromolyn *PulmoSpheres* formulation, are optimal for deep lung penetration, and clinical benefit for asthmatic patients (8–11). To assess the stability of the cromolyn sodium PulmoSpheres formulation to water ingress, we placed canisters at 40°C and 80% relative humidity. Aerosol performance was not adversely affected with measured FPFs of 68% at 1 month and 70% after 3 months.

Significant improvements in aerosolization efficiency (Table 2) were also observed for PulmoSpheres containing the short-acting bronchodilator albuterol sulfate, relative to its chosen commercial standard, Proventil HFA® (Key Pharmaceuticals, Kenilworth, NJ). Proventil HFA is the only HFA-based pMDI currently on the market in the United States, and contains a small percentage of an ethanol cosolvent to solubilize the oleic acid surfactant. This comparison is particularly illustrative since in addition to being formulated in the same propellant, both test formulations utilized the Proventil HFA actuator. The albuterol sulfate PulmoSpheres achieved a FPF approaching 67% vs. 48% for Proventil HFA, leading to a potential decrease in label claim by 30%. No change in FPF or MMAD was noted following storage for 3 months at 40 °C / 75% RH. Similar fine particle fractions of about 70% have also been achieved in albuterol sulfate PulmoSpheres formulations prepared in the same fashion where the drug makes up 80–90% of the composition (data not shown).

Equivalent FPFs of about 70% were also obtained for the formoterol fumarate PulmoSpheres formulation (Table 2).

## DISCUSSION

We have engineered hollow porous particles containing bioactive drugs for metered dose inhalers. The hollow porous particles are prepared by a two step process. In the first step, a submicron fluorocarbon-in-water emulsion is prepared by high pressure homogenization. The emulsion is stabilized by a monolayer of phospholipid (e.g. distearoylphosphatidylcholine) at the fluorocarbon/water interface. The fluorocarbon in the

**Table 2.** Comparison of the Andersen Cascade Impactor Data for Commercial Standards and PulmoSpheres

| Formulation | FPF (%) | FPD (μg) | OD (μg) | MMAD (μm) | GSD (μm) |
|---|---|---|---|---|---|
| Intal® (n = 4) (dose = 846 μg) | 24.3 ± 2.0 | 204 ± 27 | 642 ± 143 | 4.7 ± 0.5 | 1.9 ± 0.06 |
| Cromolyn PulmoSpheres™ (n = 3) (dose = 300 μg) | 68.1 ± 5.9 | 201 ± 11 | 95 ± 22 | 3.4 ± 0.2 | 2.0 ± 0.3 |
| Proventil® HFA (n = 3) (dose = 95 μg) | 47.5 ± 3.0 | 45.1 ± 4.1 | 49.8 ± 2.1 | 2.6 ± 0.1 | 2.1 ± 0.3 |
| Albuterol PulmoSpheres™ (n = 8) (dose = 70 μg) | 66.9 ± 0.6 | 47.1 ± 3.8 | 23.1 ± 0.6 | 3.4 ± 0.1 | 1.7 ± 0.05 |
| Formoterol PulmoSpheres™ (n = 3) (dose = 7 μg) | 68.7 ± 3.5 | 5.0 ± 0.1 | 2.3 ± 0.4 | 3.6 ± 0.1 | 1.7 ± 0.03 |

*Note:* Values reported represent mean values ± SDEV for n experiments; Reported dose represents dose leaving the pMDI mouthpiece; FPF = fine particle fraction; FPD = fine particle dose; OD = *in-vitro* oropharyngeal deposition; MMAD = mass median aerodynamic diameter; GSD = geometric standard deviation.

emulsion droplets serves as a "blowing agent" or "inflation agent" during the spray-drying step, and is utilized to create the hollow porous morphology. Particularly preferred fluorocarbons have high boiling points (ca., 140°C). Lower boiling inflation agents yield hollow particles, but the particles are not significantly porous. The porosity and bulk density of the powders are easily controlled by varying the ratio of fluorocarbon to phospholipid in the emulsion. The emulsion is then combined with a second aqueous phase containing the drug to be delivered and any wall-forming excipients (e.g. carbohydrates, salts) desired. In the second processing step, the aqueous dispersion is spray-dried under mild processing conditions. The process is flexible, with the ability to incorporate several excipients with multiple functions into a single particle. Further, the process affords excellent control over particle size, density, and porosity. Finally, the hollow porous morphology can be achieved with relatively high levels of solids (>20%) in the spray-feed.

The resulting powders are easily dispersed in the new hydrofluoroalkane propellants. Penetration of the propellant inside the hollow porous particles results in formation of a novel form of suspension, which we term a homodispersion™, wherein both the continuous and dispersed phases are identical, separated by a thin insoluble shell of drug and excipient. Homodispersion formation improves suspension stability in two important ways.

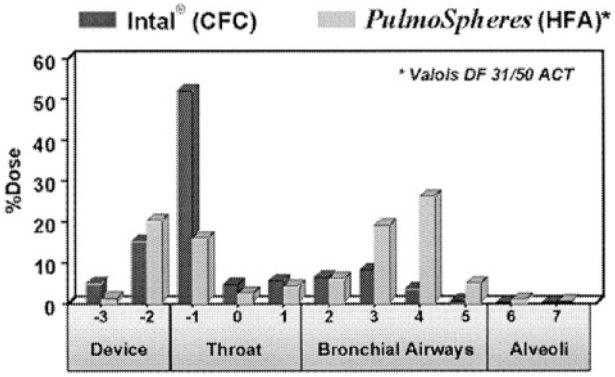



**Fig. 5.** Comparison of Andersen cascade impactor data for Intal® and a formulation of hollow porous particles containing cromolyn sodium in HFA-134a. Stages −3, −2, and −1 refer to the valve stem, actuator (mouthpiece), and induction port, respectively. A large reduction in deposition in the induction port is observed for the hollow porous particles, with the drug mass transferred to stages corresponding to improved airway and alveolar delivery (i.e. stages 2–7).

First, the dispersed particles are composed in large part of the propellant in which they are dispersed. Thus, the differences in density between the fluid-filled particles and the continuous phase are minimized, resulting in a decreased tendency for the particles to cream or sediment. This is illustrated in Fig. 2, where sedimentation times for cromolyn sodium PulmoSpheres are on the order of hours versus seconds for the commercial Proventil HFA inhaler.

Second, van der Waals attractive forces are minimized by making the particles spherical with fluid-filled pores. For two spherical particles, the magnitude of the van der Waals potential, $V_A$, can be approximated by $V_A = \frac{-A_{\text{eff}}}{6H_0}\frac{R_1 R_2}{(R_1 + R_2)}$; where $A_{\text{eff}}$ is a proportionality constant termed the effective Hamaker constant which accounts for the nature of the particles and the medium, $H_0$ is the distance between particles, and $R_1$ and $R_2$ are the radii of spherical particles 1 and 2. The effective Hamaker constant is proportional to the difference in the polarizabilities of the particles and the HFA medium, and scales closely with the difference in their refractive indices: $A_{\text{eff}} = (\sqrt{A_{\text{HFA}}} - \sqrt{A_{\text{PART}}})^2$ where $A_{\text{HFA}}$ and $A_{PART}$ are the Hamaker constants for the propellant and the particles, respectively. As the particles and the propellant become similar in nature (i.e. as occurs during homodispersion formation) $A_{\text{HFA}}$ and $A_{\text{PART}}$ become closer in magnitude, and $A_{\text{eff}}$ and $V_A$ become smaller in magnitude. Having fluid-filled pores may also decrease capillary forces by reducing the interfacial tension (contact angle) between the particles and the medium.

The reduction in interparticle attractive forces leads to decreased particle aggregation. No aggregates were visible in the formulations utilized in the current study. Since aggregates have a larger size than do the primary particles, the reduction in attractive forces also contributes to the reductions in sedimentation rates observed.

Suspension stability plays a critical role in achieving reproducible drug dosing from the pMDI device. This is a challenge that has proven increasingly difficult with the CFC to HFA conversion, and one which is becoming increasingly important in light of the tighter guidelines on dose uniformity being proposed by the FDA. Achieving dose uniformity is especially difficult for low-dose formulations (e.g. formoterol), where deposition of drug on the walls of the container and the valve stem is problematic. Due to their low bulk density and ability to incorporate higher excipient concentrations into the formulation, the total volume of powder in the canister is significantly increased for low-dose PulmoSpheres formulations. This likely

will lead to decreased loss of drug via deposition on the container walls and valve stem, thereby improving dose uniformity. Chemical instability resulting from oxidation of the drug substance after deposition on the valve stem should also be reduced. The excellent dosage uniformity achieved with the physically stable PulmoSpheres formulations is illustrated in Figs. 3 and 4.

The high aerosolization efficiency of the hollow porous particles as compared to the commercial standards can be attributed to: (a) the higher vapor pressure of the HFA-134a propellant relative to CFCs; (b) the smaller orifice diameter of the actuator; (c) effects of the particle engineering. The large differences in aerosolization efficiency observed between Intal and cromolyn PulmoSpheres are due in large part to factors (a) and (b). It is likely that micronized cromolyn sodium formulations in the new HFA propellants will have higher FPFs than the corresponding CFC formulations, simply because of the higher propellant vapor pressure. The differences in FPF observed between Proventil HFA and albuterol PulmoSpheres are more intriguing since the same propellant and actuator are utilized. In this case the effects of particle engineering likely contribute, at least in part, to the increased efficiency observed. The magnitude of the differences between Proventil HFA and albuterol PulmoSpheres could be amplified, however, by the desire of Schering-Plough to maintain the same clinical dose as the CFC-based Proventil product, in order to shorten the regulatory approval time. Achieving equivalent potencies could likely be accomplished by increasing the percentage of the less volatile ethanol co-solvent utilized in the HFA formulation.

Nonetheless the high FPFs achievable with the new HFA propellants, valves, and actuators may lead to decreased clinical doses for some new chemical entities. As well, the potential exists that these new formulations may reduce oropharyngeal deposition. This could be especially important for corticosteroids, where oropharyngeal deposition increases the incidence of local side-effects including throat irritation, coughing and wheezing, and the potential for opportunistic infections (e.g. candidiasis). The correlation between the *in-vitro* behavior of the hollow porous particles and their *in-vivo* deposition, will be examined in an upcoming gamma scintigraphy study in human subjects.

There is a poor correlation between the aerodynamic diameters obtained by Andersen cascade impaction (ca. 3 μm), and those estimated from the geometric diameter and bulk density (ca. 1 μm). The larger size observed by impaction is likely due to particle aggregation resulting from multiple occupancy of propellant droplets as the aerosol is being generated. Multiple occupancy of aerosol droplets is accentuated in the *PulmoSpheres* formulations by the greater volume fraction of powder being delivered. Alternatively, retention of propellant in the hollow porous particles could also result in increases in MMAD. The differences noted could also be due in part to differences between the measured bulk densities and the actual envelope mass densities of the particles.

*PulmoSpheres* suspensions have been prepared over a broad range of drug concentrations (ca., 10 μg—1 mg), assuring their potential for the delivery of low dose formulations of steroids or long-acting bronchodilators, and for high dose drugs such as cromolyn sodium. Overall, their potential for superior physical stability, improved dose uniformity, and high aerosolization efficiencies makes *PulmoSpheres* ideally suited as a platform formulation technology for metered-dose inhalers in HFA propellants.

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