Improved Lung Delivery from a Passive Dry Powder Inhaler Using an Engineered PulmoSphere® Powder

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Purpose. To assess the pulmonary deposition and pharmacokinetics of an engineered PulmoSphere® powder relative to standard micronized drug when delivered from passive dry powder inhalers (DPIs).
Methods. Budesonide PulmoSphere (PS_{bud}) powder was manufactured using an emulsion-based spray-drying process. Eight healthy subjects completed 3 treatments in crossover fashion: 370 μg budesonide PulmoSphere inhaled from Eclipse® DPI at target PIF of 25 $L{\cdot}min^{-1}$ (PS_{bud25}), and 50 $L{\cdot}min^{-1}$ (PS_{bud50}), and 800 μg of pelletized budesonide from Pulmicort® Turbuhaler® at 60 $L{\cdot}min^{-1}$(TH_{bud60}). PS_{bud} powder was radiolabeled with ^{99m}Tc and lung deposition determined scintigraphically. Plasma budesonide concentrations were measured for 12 h after inhalation.
Results. Pulmonary deposition (mean ± sd) of PS_{bud} was 57 ± 7% and 58 ± 8% of the nominal dose at 25 and 50 $L{\cdot}min^{-1}$, respectively. Mean peak plasma budesonide levels were 4.7 (PS_{bud25}), 4.0 (PS_{bud50}), and 2.2 $ng{\cdot}ml^{-1}$ (TH_{bud60}). Median t_{max} was 5 min after both PS_{bud} inhalations compared to 20 min for Turbuhaler ($P < 0.05$). Mean AUCs were comparable after all inhalations, 5.1 (PS_{bud25}), 5.9 (PS_{bud50}), and 6.0 (TH_{bud60}) $ng{\cdot}h{\cdot}ml^{-1}$. The engineered PS_{bud} powder delivered at both flow rates from the Eclipse® DPI was twice as efficiently deposited as pelletized budesonide delivered at 60 $L{\cdot}min^{-1}$ from the Turbuhaler. Intersubject variability was also dramatically decreased for PS_{bud} relative to TH_{bud}.
Conclusion. Delivery of an engineered PulmoSphere formulation is more efficient and reproducible than delivery of micronized drug from passive DPIs.

KEY WORDS: pulmonary drug delivery; dry powder inhaler; particle engineering; spray-drying; pharmacoscintigraphy; Eclipse®.

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ABBREVIATIONS: AUC, area under the curve; CV, coefficient of variation; DPI, dry powder inhaler; DSPC, distearoylphosphatidylcholine; ECG, electrocardiogram; ED, emitted dose; FEV_1, one-second forced expiratory volume; FPF, fine particle fraction; FRC, functional residual capacity; FVC, forced vital capacity; HPLC, high performance liquid chromatography; MSLI, multistage liquid impinger; P/C, peripheral to central ratio; PIF, peak inspiratory flow rate; PSD, particle size distribution; SD, standard deviation; t_{max} = time to peak serum concentration of budesonide.

INTRODUCTION

Currently all marketed dry powder inhalation products are comprised of micronized drug (either agglomerated or blended) delivered from "passive" dry powder inhalers, DPIs (1,2). These inhalers are passive in the sense that they rely on the patient's inspiratory effort to disperse the powder into a respirable aerosol. Fine powders (<5 μm) generate fine aerosols, but particle adhesion reduces delivery efficiency and leads to flow rate dependent lung deposition (3–7). For example, Borgstrom *et al*., found that lung deposition for the corticosteroid, budesonide, was 27.7% of the metered dose at a peak inspiratory flow rate (PIF) of 60 $L{\cdot}min^{-1}$, but only 14.8% at a PIF of 35 $L{\cdot}min^{-1}$ (3). While this may be acceptable for drugs with a large therapeutic index like budesonide, it may not be for drugs with a narrow therapeutic index (e.g., insulin). Hence, it would be advantageous to develop powder formulations with improved dispersibility from passive DPIs.

In this paper, we present the results of pharmacoscintigraphy studies on a new dry powder formulation technology [pharmacoscintigraphy refers to the fact that both deposition (scintigraphy) and serum pharmacokinetics are both determined for a given subject]. The formulation is comprised of spray-dried particles whose morphology is engineered to be both hollow and porous (PulmoSphere®) (8,9). PulmoSphere powders exhibit excellent flow and dispersion from passive DPIs. *In vitro* characterization of PulmoSphere powders predicts highly efficient lung delivery that is relatively independent of inspiratory flow rate (10). It is postulated that interpatient variability will also be reduced relative to conventional DPI formulations as a result of the improved dispersibility and limited flow rate dependence.

Pharmacoscintigraphy was used to study aerosol performance in a three-way randomized crossover study in eight healthy volunteers. On each study day subjects inhaled one of the following: a budesonide PulmoSphere formulation at a targeted PIF of 25 $L{\cdot}min^{-1}$; a budesonide PulmoSphere formulation at a targeted PIF of 50 $L{\cdot}min^{-1}$; or a single dose of micronized budesonide delivered from the commercial Pulmicort Turbuhaler at a targeted PIF of 60 $L{\cdot}min^{-1}$.

MATERIALS AND METHODS

Materials

The budesonide PulmoSphere formulation was manufactured by a two-step process described previously (8). In short, micronized budesonide crystals (Industriale Chimica S.R.L., Sarono, Italy) are combined with a coarse perflubron-in-water emulsion that is stabilized by a monolayer of distearoylphosphatidylcholine (Genzyme Pharmaceuticals, Cambridge, Massachusetts). The resulting dispersion is passed through a high pressure homogenizer (Avestin, Ottawa, Canada). The drug crystals and submicron emulsion droplets are then combined with a second aqueous phase containing calcium chloride dihydrate (J.T. Baker, Phillipsburg, New Jersey), and lactose monohydrate (Foremost Farms, Rothschild, Wisconsin), and the resulting mixture was spray-dried (Büchi Mini Spray-Drier, Flawil, Switzerland). The perflubron (LiquiVent®, Alliance Pharmaceutical Corp., San Diego, California) serves as a blowing agent in the spray-drying pro-

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cess aiding in the formation of the desired hollow porous particle morphology (Fig. 1).

The PulmoSphere formulation was inhaled from the Eclipse® DPI (Aventis Pharma Ltd., Holmes Chapel, United Kingdom), a passive dry powder inhaler accommodating size #2 capsules. The capsules were comprised of hydroxypropylmethylcellulose, HPMC, and obtained from Shionogi (Nara, Japan). The Eclipse is a high resistance device with a resistance of 0.19 ($cmH_20^{1/2}$)/($L{\cdot}min^{-1}$) (data not shown). The HPMC capsules were filled with 2.5 mg of PulmoSphere powder that contained 3.7% w/w budesonide, corresponding to 92 μg of budesonide per actuation.

A marketed budesonide product, the Pulmicort® Turbuhaler® (Astra AB, Sweden), was used as a pharmacokinetic reference in the third arm of the study. The Turbuhaler is a medium resistance passive DPI with a device resistance of 0.10 ($cmH_20^{1/2}$)/($L\ min^{-1}$) (11). Pelletized drug is contained in a reservoir in the device. The Turbuhaler meters a nominal dose of 200 μg of neat budesonide per actuation.

Radiolabeling Techniques

The PulmoSphere budesonide formulation was radiolabeled with ^{99m}technetium (^{99m}Tc) using a modification of a previously described method (12,13). Briefly, ^{99m}Tc-pertechnetate (Nycomed Amersham, Amersham, United Kingdom) was extracted from a saline solution into an organic solvent (2-pentanone), and subsequently transferred to an empty glass vial. Gentle heating in a stream of air then evaporated the organic phase. The radionuclide was resuspended in Freon-113 and combined with the insoluble budesonide PulmoSphere powder. After flash freezing in liquid nitrogen, the solvent was removed by sublimation via vacuum drying. The resulting radiolabeled budesonide PulmoSphere powder was hand-filled into size #2 HPMC capsules for aerosol performance and clinical testing.

Because a considerable body of literature is available on pulmonary delivery of budesonide from the Turbuhaler (3,14,15), it was not radiolabeled for assessment of deposition. It was used as a comparator for the pharmacokinetic portion of the study.

Validation of Radiolabeling Methods

Before beginning the clinical phase of the study, *in vitro* validation experiments were conducted to demonstrate that: (a) significant alteration of the particle size distribution (PSD) did not occur during the ^{99m}Tc radiolabeling process; (b) the PSD of the radiolabel matched the PSD of the drug. Particle size measurements were performed using a multistage liquid impinger (MSLI, Copley Instruments, Nottingham, United Kingdom) fitted with a USP induction port (16). Despite its decreased resolution relative to cascade impaction, the MSLI was chosen for aerodynamic particle size assessment due to the significant bounce and reentrainment issues experienced with the ultralow density PulmoSphere particles in the cascade impactor. Wash solutions from the MSLI (induction port, stages, and filter) were collected and quantitated for drug and radiolabel content by HPLC and gamma counting, respectively. The percentage of the emitted dose distributed on the induction port, MSLI stages and filter was calculated based on the concentrations of drug and radiolabel on each of the MSLI components.

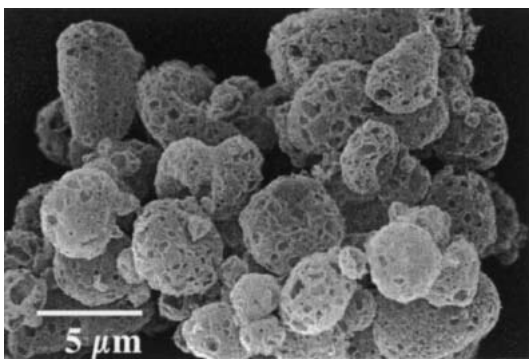

Fig. 1. SEM of PulmoSphere® budesonide formulation.

Validation aerosol testing was performed at flow rates of 30 and 50 $L{\cdot}min^{-1}$. During the clinical phase of the study, the particle size distribution of the radiolabel was determined before subject dosing at a flow rate of 30_$L{\cdot}min^{-1}$. To determine the appropriate flow rates for testing we asked volunteers to breathe both comfortably and forcefully through the Eclipse device. The average peak inspiratory flow was found to be 25 and 50 $L{\cdot}min^{-1}$, for comfortable and forceful inhalation, respectively. To allow comparison of testing in the Andersen cascade impactor and MSLI we chose to test in-vitro at a flow rate of 30 $L{\cdot}min^{-1}$ for comfortable inhalation.

Subjects and Protocol

This was a single center, three-way crossover study conducted in 10 subjects determined to be in good health based on medical history, physical examination, ECG, routine clinical chemistry, hematology, urinalysis, and pulmonary function tests. Subjects with a recent history of smoking or lower respiratory problems were excluded. The study was conducted according to the Declaration of Helsinki on biomedical research in human subjects, and written informed consent was obtained from all subjects before recruitment. The clinical protocol was approved by the Quorn Research Review Committee (Leicestershire, United Kingdom).

One of the following three treatments was administered on each of three separate clinic visits at least 3 days apart, in randomized order: PulmoSphere budesonide powder (4 × 92 μg) inhaled from the Eclipse at a targeted PIF of 25 $L{\cdot}min^{-1}$, PulmoSphere budesonide powder (4 × 92 μg) inhaled from the Eclipse at a targeted PIF of 50 $L{\cdot}min^{-1}$, and budesonide (4 × 200 μg) inhaled from the Pulmicort Turbuhaler at a targeted PIF of 60 $L{\cdot}min^{-1}$. These doses are four times the label claim for Pulmicort and were chosen to provide adequate sensitivity in quantitation of serum budesonide. The PulmoSphere dose was determined from in-vitro MSLI results, by matching the fraction of particles less than 3.3 μm to Pulmicort. Prior to dosing, subjects were trained to inhale to the target PIF using the DPIs connected in series to a Vitalograph spirometer (Vitalograph Ltd., United Kingdom) equipped with a visual feedback monitor. Wearing nose clips, subjects inhaled from the Eclipse or the Turbuhaler from FRC to total lung capacity, held their breath for 5 sec, and then exhaled through a filter that captured any radioactive aerosol in the exhaled air. During aerosol inhalations, each subject's inspiratory flow rate was recorded by the spirometer.

For the budesonide PulmoSphere formulation, 92 μg of

budesonide was administered in four separate inhalations, for a total administered dose of 370 μg. Only the fourth capsule to be inhaled contained the radiolabeled budesonide PulmoSphere powder, together with up to 10 MBq ^{99m}Tc. For the Pulmicort Turbuhaler treatment, subjects performed four inhalations of 200 μg of unlabeled budesonide for a total dose of 800 μg of budesonide. Successive inhalations were performed at 30 s intervals.

Venous blood samples for determination of plasma budesonide concentrations were collected into vacutainer tubes containing EDTA at the following intervals: predose, and 5, 10, 20, 30, 45 min and 1, 1.5, 2, 3, 4, 6, 8, and 12 h after dose administration. After centrifugation, plasma was immediately stored in polypropylene tubes at or below minus 20°C until analysis. To reduce the contribution of extrapulmonary absorption to systemic availability of inhaled budesonide, gastrointestinal (GI) absorption of budesonide was blocked by concomitant administration of an activated charcoal solution (charcoal-block technique) as previously described (14,17). Immediately before inhalation, subjects rinsed their mouths with and swallowed 50 ml of activated charcoal suspension (200 mg·ml^{-1}). An additional charcoal drink was administered 5 min, 1 h, and 2 h after inhalation. No water was permitted from the initial charcoal administration until after the last charcoal drink.

Pulmonary function (FVC: forced vital capacity; FEV_1: one-second forced expiratory volume) and vital signs were recorded before and 30 min after each dose and before discharging the subject from the study center at each visit. Adverse events were monitored throughout the study. In addition, each subject underwent a physical examination, ECG, routine clinical chemistry, hematology and urinalysis, and pulmonary function testing at the end of the study.

Scintigraphy

Immediately following administration of the radiolabeled aerosol, two-dimensional scintigraphic images of the anterior and posterior chest, lateral oropharynx, Eclipse DPI, capsule and exhalation filter were recorded using a gamma camera (General Electric Maxicamera, Milwaukee, Wisconsin). All images were recorded on a Park Medical Micas Xplus computer system (Park Medical, Farnborough, United Kingdom) and were stored on Digital Audio Tape (DAT, Seagate, Amsterdam, Netherlands).

Scintigraphic images were compared with whole lung outlines generated from a ^{81m}Krypton ventilation scan obtained from each volunteer. Regions of interest were drawn around the oropharynx, esophagus, stomach, and whole lung. The counts obtained within these regions were corrected for background radioactivity, radioactive decay and tissue attenuation of gamma rays (18). In regions where both anterior and posterior images were recorded, the geometric mean of counts in both images was calculated. Determination of the percentage of the dose deposited in the oropharynx included activity adhering to the mouth and pharynx together with any swallowed activity detected in the esophagus, stomach and intestine. Counts for each area were expressed as a percentage of the capsule dose, which was determined from the sum of the total body counts in addition to those deposited on the Eclipse, the capsule, and the exhalation filter.

The lungs were divided into central, intermediate and peripheral regions of interest (19). The peripheral lung zone to central lung zone deposition ratio (P/C ratio) was calculated as an index of regional lung deposition.

Analytical Procedures

Plasma samples were analyzed for budesonide concentration at MDS Pharma Services (Montreal, Canada) using a validated high performance liquid chromatography method with mass spectrometric detection. The standard curve ranged from 20–2000 pg·ml^{-1}. The limit of quantitation was 20 pg·ml^{-1}.

Pharmacokinetic parameters (C_{max}, t_{max}, $t_{1/2}$, and AUC) were generated from plasma budesonide concentrations with WinNonlin software (PharSight Corp., Mountain View, California) using standard noncompartmental modeling techniques. Concentrations below the lower limit of quantitation were regarded as zero. AUC values were calculated as the area under the curve from 0 to the last measurable concentration, calculated by the log-linear trapezoidal method, plus extrapolation to infinity based on the observed terminal elimination rate. The bioavailability of each PulmoSphere (PS) treatment, relative to the Pulmicort Turbuhaler (TH) was calculated for each subject as shown:

$$\text{Relative bioavailability} = (AUC_{PS} / AUC_{TH}) * (dose_{TH} / dose_{PS})$$

where $dose_{TH}$ and $dose_{PS}$ are 800 μg and 370 μg budesonide, respectively. Statistical comparisons between treatments were made using a paired, two-tailed Student's *t*-test.

RESULTS

The results of the radiolabeling validation tests for the PulmoSphere budesonide formulation are summarized in Fig, 2. The particle size distribution of budesonide before labeling was compared with that after labeling, and also with the ^{99m}Tc radiolabel. Distributions of budesonide and radiolabel closely matched across all stages of the MSLI. These data demonstrated that the radiolabel deposition patterns would be representative of drug deposition, and that the PulmoSphere drug formulation retained its aerosol properties after the radiolabeling process.

Before administering the ^{99m}Tc-PulmoSphere budesonide formulation to subjects on each study day, the material manufactured that day was tested in the Eclipse DPI to ensure that the PSD of the radiolabel was comparable to that obtained in the radiolabeling validation experiments. PSDs comparable to those obtained during the validation process were observed (data not shown).

Clinical Results

Ten subjects (6 male, 4 female) with a mean age of 34 ± 10 years were enrolled in the study. Mean height and weight were 74 ± 15 kg and 171 ± 9 cm, respectively. Eight subjects completed the study, one withdrew consent before the second dose, and one was withdrawn due to a positive pregnancy test before the third dosing visit.

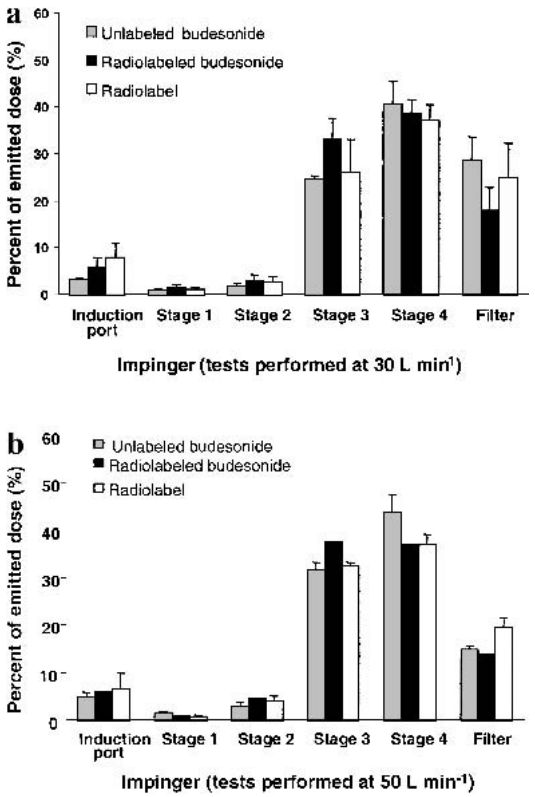

Fig. 2. Particle size distributions for PulmoSphere® budesonide obtained in radiolabeling validation studies at a test flow rate (Q) of 30 L·min^{-1} (a), and 50 L·min^{-1} (b). Unlabeled and radiolabeled budesonide refer to the mass of budesonide on the MSLI as determined by HPLC analysis before and after the radiolabeling process. The ^{99m}Tc radiolabel PSD was determined from the MSLI, with quantitation of radioactivity with a gamma camera. All data are Mean ± SD. Nominal cutoff diameters ($ECD_{50\%,Q}$) of the MSLI in the flow range from 30 to 100 L·min^{-1} are given by (21): Stage 1: $ECD_{50\%,Q} = 13\ (Q/60)^{-1/2}$; Stage 2: $ECD_{50\%,Q} = 6.8\ (Q/60)^{-1/2}$; Stage 3: $ECD_{50\%,Q} = 3.1\ (Q/60)^{-1/2}$; Stage 4: $ECD_{50\%,Q} = 1.7\ (Q/60)^{-1/2}$

Deposition

The targeted PIF values for the budesonide PulmoSphere formulation were 50 L·min^{-1} and 25 L·min^{-1}. The actual PIF values for subjects during the clinical study were 44 ± 5 L·min^{-1} and 29 ± 3 L·min^{-1}. The mean PIF rate when subjects inhaled from the Turbuhaler (target = 60 L·min^{-1}) was 63 ± 9 L·min^{-1}. The relative percentage of the ^{99m}Tc-PulmoSphere budesonide dose remaining in the Eclipse DPI, deposited in the oropharyngeal region, deposited in the lungs, and exhaled are shown in Table I. Scintigraphic data is reported only for the 8 subjects who completed all three arms of the study. The majority (93%) of the PulmoSphere budesonide was emptied from the capsule on inhalation, with approximately 7% of the capsule dose (range 2–11%) being retained in the body of the DPI. Hence, 87% of the powder mass in the capsule was delivered to the volunteer. One third (34%) of the emitted dose was deposited in the oropharyngeal region, and the remaining two-thirds (66%) reached the lung. Whole lung deposition ranged from 45–67% of the nominal capsule dose, and averaged 57.7% and 57.0% for the high and low peak inspiratory flow rates, respectively. Distribution of the ^{99m}Tc-PulmoSphere budesonide within the central, intermediate, and peripheral regions of the lung was similar at both inspiratory flow rates, and was approximately 20% for each of the three lung regions (Table I). The ratio of peripheral lung zone to central lung zone deposition (P/C) was 1.2 ± 0.6 and 1.1 ± 0.5 for the high and low flow rates, respectively. Based on previous observations, the P/C ratios in the present study suggest that 50–55% of the pulmonary dose reached the alveolated regions of the lung (20). The subjects exhaled a negligible amount of radioactivity; 0.1 ± 0.1% and 0.0 ± 0.0% for the high and low flow rates, respectively.

Pharmacokinetics

Systemic exposure to budesonide was comparable after inhalation of the budesonide PulmoSphere powder and the Pulmicort Turbuhaler. Plasma concentrations of budesonide rose rapidly following administration of PulmoSphere budesonide, with peak concentrations observed within 5 to 10 min of dosing (Fig. 3). Plasma levels of budesonide rose more slowly after Turbuhaler administration (median t_{max} 20 min, $P < 0.005$ vs. PulmoSphere), but concentrations were comparable for both treatments starting from 20 min postdose and the terminal half-lives were also comparable. Mean peak plasma budesonide concentrations after inhalation of the PulmoSphere powder at the low or high flow rate were approxi-

Table I. Regional Deposition of a ^{99m}Tc-PulmoSphere Budesonide Formulation

	Percent (%) of nominal dose Mean ± SD	
n = 8[a]	29 L·min^{-1}	44 L·min^{-1}
Capsule	5.8 ± 1.5	6.6 ± 1.9
Eclipse inhaler	7.7 ± 2.3	6.3 ± 3.1
Emitted dose	86.5 ± 3.1	87.0 ± 4.1
Oropharynx[b]	29.4 ± 6.9	29.3 ± 7.1
Whole lung	57.0 ± 6.5	57.7 ± 7.8
Central lung	17.2 ± 2.1	17.9 ± 4.1
Intermediate lung	20.6 ± 2.5	20.0 ± 2.6
Peripheral lung	19.2 ± 5.3	19.7 ± 6.1
Exhalation filter	0.0 ± 0.0	0.1 ± 0.1

[a] Data shown is from the 8 subjects subjects who completed both PulmoSphere treatments.
[b] The oropharynx includes deposition in the mouth, pharynx, esophagus, stomach, and intestine.

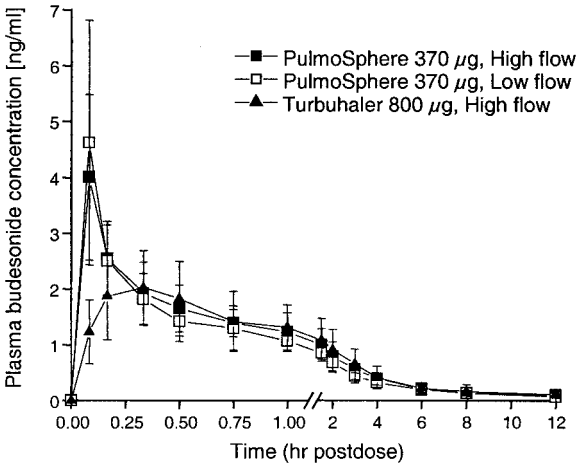

Fig. 3. Plasma budesonide concentrations after inhalation of PulmoSphere budesonide (370 μg budesonide) from the Eclipse DPI at low and high PIFs, and after inhalation of crystalline budesonide (800 μg) from the Pulmicort Turbuhaler at high PIF (Mean ± SD).

mately twice as high as after the Pulmicort Turbuhaler (4.7 and 4.0 $\mu g \cdot ml^{-1}$ vs. 2.2 $\mu g \cdot ml^{-1}$, respectively, $P < 0.05$, Table II). Nevertheless, the extent of budesonide absorption (AUC) was comparable after inhalation of the budesonide PulmoSphere powder (means 5.1 and 5.9 $ng \cdot h \cdot ml^{-1}$) and the Pulmicort Turbuhaler doses (mean 6.0 $ng \cdot h \cdot ml^{-1}$). Since the nominal dose of budesonide PulmoSphere in the Eclipse (370 μg) was approximately half of the dose metered by the Turbuhaler (800 μg), the relative bioavailability of the PulmoSphere/Eclipse combination was 2.1–2.5 times greater than that of Turbuhaler. It should be noted that budesonide in not being given by inhalation to achieve systemic exposure. Further, physicochemical differences in the formulations (see comments later in this paper) may also contribute to these pharmacokinetic differences.

Safety

No abnormalities of lung function or episodes of bronchospasm were observed during the study, and the inhalations were well tolerated. Six of the subjects (60%) reported at least one adverse event, most commonly headache, vomiting or nausea, but all were of mild or moderate severity. Similar gastrointestinal complaints are common after drinking charcoal suspensions.

DISCUSSION

In this study, the pulmonary deposition and systemic bioavailability of a spray-dried budesonide PulmoSphere formulation were examined following inhalation from a passive dry powder inhaler (Eclipse). The PulmoSphere formulation was engineered to have improved powder flow and dispersibility relative to traditional micronized drug. It was hypothesized that the improvement in powder flow and dispersibility would lead to increases in delivery efficiency and a reduction in the inspiratory flow rate dependent deposition seen with micronized powders delivered from passive devices.

In vitro characterization of the PulmoSphere powder (Fig. 2) showed a high fine particle fraction (approximately 60% < 3.7 μm at 50 $L \cdot min^{-1}$) suggesting the potential for high *in vivo* lung deposition. The data also showed that the pattern of deposition on the various stages of the impinger does not change appreciably with flow rate, in spite of the fact that the size cutoffs for each stage change dramatically with flow rate. In so far as the change in cutoff diameters for the impinger stages can be considered to mimic similar changes in inertial capture efficiency of the upper airways with changing flow rate (11,22), these data indicate that only a minor flow rate/deposition dependency should be observed *in vivo*. Indeed both of these "expectations" were validated *in vivo.*

Total lung deposition was measured directly for the budesonide PulmoSphere formulation by gamma scintigraphy, and found to be independent of PIF (57.7% of the nominal dose at 44 $L \cdot min^{-1}$, and 57.0% at 29 $L \cdot min^{-1}$). In contrast to the PulmoSphere formulation, Borgstrom *et al.* (3), found that lung deposition decreased for the Pulmicort Turbuhaler from 27.7% at 58 $L \cdot min^{-1}$, to 14.8% at 36 $L \cdot min^{-1}$ (expressed as a percentage of the metered dose). Other investigators have observed similar efficiencies (10–30%) and flow rate dependence for micronized drugs delivered from the Turbuhaler and other passive dry powder inhalers (3–7,14,15,17).

The increased efficiency of lung delivery noted for the PulmoSphere formulation relative to the Pulmicort Turbuhaler by scintigraphy is also reflected in the measured sys-

Table II. Pharmacokinetic Parameters of Budesonide Formulations after Inhalation

	Mean ± SD (%CV)			
		Budesonide PulmoSphere 370 μg		Pulmicort 800 μg
	n	Eclipse 29 $L \cdot min^{-1}$	Eclipse 44 $L \cdot min^{-1}$	Turbuhaler 63 $L \cdot min^{-1}$
C_{max} $[ng \cdot ml^{-1}]$	8[a]	4.7 ± 2.1 (43%)[c]	4.0 ± 1.5 (37%)[d]	2.2 ± 0.7 (32%)
t_{max} [h][b]	8	0.08 (0.08–0.17)[d]	0.08 (0.08–0.08)[d]	0.33 (0.17–0.5)
$T_{1/2}$ [h]	8	3.3 ± 0.77 (23%)	3.8 ± 1.3 (34%)	2.9 ± 1.0 (35%)
AUC $[ng \cdot h \cdot ml^{-1}]$	8	5.1 ± 0.87 (17%)	5.9 ± 1.0 (17%)	6.0 ± 2.1 (35%)
Relative bioavailability vs Turbuhaler	8	2.1 ± 1.1 (46%)	2.5 ± 1.2 (49%)	

[a] Data shown is from subjects completing all three study periods.
[b] The median (range) is reported for t_{max}.
[c] $P < 0.05$ vs. Pulmicort Turbuhaler 800 μg.
[d] $P < 0.005$ vs. Pulmicort Turbuhaler 800 μg.

temic bioavailability. The relative bioavailability for the PulmoSphere formulation compared to the Pulmicort Turbuhaler was 2.5 with maximal inspiratory effort, and 2.1 under comfortable inhalation conditions. One can also estimate total lung deposition from the pharmacokinetic data, using the Turbuhaler deposition data from Borgstrom *et al.*, (3), and assuming that the metered dose from the Turbuhaler is 89% of the nominal dose (14). This analysis yields a total lung deposition for the PulmoSphere formulation under maximal inhalation conditions of 62% of the nominal dose, in close agreement with the 57.7% value measured via scintigraphy.

Regional deposition can be expressed as the ratio of peripheral to central deposition (P/C ratio) in scintigraphy images. The P/C ratio for budesonide in the PulmoSphere formulation was 1.1 to 1.2. This corresponds to a relatively even distribution for budesonide throughout the lung (20). This is likely preferred for a corticosteroid such as budesonide, since receptors on lung epithelia are evenly distributed throughout the lung. In contrast the P/C ratio is greater (1.7–1.8) for the Pulmicort formulation in volunteers (3).

Improvements in the efficiency of lung deposition also lead to decreases in total oropharyngeal deposition. This may be of importance for corticosteroids, where local and systemic side effects including opportunistic infections (e.g., candidiasis) are often observed. At an equivalent budesonide lung dose, oropharyngeal deposition with the PulmoSphere formulation is decreased approximately 6- to 7-fold.

In addition to the improved efficiency of pulmonary delivery noted, PulmoSphere formulations are expected to reduce interpatient variability relative to current micronized drugs delivered from passive DPIs, due to the decreased dependence of total lung deposition on inspiratory effort. Improvements in reproducibility are reflected in differences in the coefficient of variation (CV) for the AUC data, where a value of 16–17% was observed for the PulmoSphere formulation versus 35% for the Pulmicort Turbuhaler. A similar picture emerges from the gamma scintigraphy data, where the CV values for the PulmoSphere formulation are 11–13% depending on the inspiratory flow rate. In contrast Borgstrom *et al.*, (3) found CV values of 34% and 22% at 58 $L \cdot min^{-1}$ and 36 $L \cdot min^{-1}$, respectively. The CV values obtained in the Borgstrom study underestimate the interpatient variability associated with the Pulmicort Turbuhaler due to: (a) the fact that the errors were measured for a narrow window of PIF, and the strong flow rate dependent deposition observed for the Pulmicort Turbuhaler will only serve to increase the CV in instances where patients are not instructed or compliant with proper breathing technique. This source of error is dramatically reduced for the flow rate independent PulmoSphere formulation; (b) the fact that the Turbuhaler values are presented as a percentage of the metered dose (i.e., errors associated with Turbuhaler metering are not included). Large errors (CV $\approx$ 20–50%) are also noted for a variety of other micronized drug formulations delivered from a various passive DPIs (4–7).

The variability observed for the budesonide PulmoSphere formulation delivered from the passive Eclipse inhaler was reduced in comparison to that obtained following delivery of micronized albuterol sulfate (23) or beclomethasone dipropionate, BDP (24) from the "active" Spiros DPI. For albuterol sulfate delivered from Spiros, the mean lung dose and CV values were 25.8 ± 9.2 (36%) at 15 $L \cdot min^{-1}$, and 19.3 ± 7.3 (38%) at 60 $L \cdot min^{-1}$. For BDP, lung deposition was 40.5 ± 5.8 (14%) at 15 $L \cdot min^{-1}$, and 30.4 ± 8.6 (28%) at 60 $L \cdot min^{-1}$. The Spiros DPI is an active DPI, where powder dispersion is decoupled from the patient's inspiratory effort. Spiros uses a battery-operated electric motor to drive an impeller that disperses the powder. Despite the fact that powder dispersion is decoupled from the patient, lung deposition still varies appreciably with PIF. The dependence of lung deposition on PIF in these active devices is opposite to the dependence with PIF observed for delivery from passive devices, and reflects variations in lung deposition due to differences in inertial impaction as a result of changes in PIF. In contrast, the decreasing deposition with decreasing PIF observed for passive inhalers is driven primarily by variations in powder dispersion with PIF.

The improvements in powder dispersibility noted for PulmoSphere powders are the result of several factors, all of which decrease either the interparticle separation distance, or the area of contact between particles (10). Micronized drug crystals are often comprised of flat surfaces with a large variance in particle size. As a result, the area of contact between particles is large and the attractive forces between them can be strong. The micronization process may also lead to increases in surface energy, thereby increasing particle cohesion. In contrast, PulmoSphere particles are engineered to be both hollow and porous. They are spherical in shape and have geometric sizes of about 3–5 μm. The area of contact between spherical particles is less than is found for flat surfaces, and often can be particle on the edge of a pore, a very weak interaction. In addition, PulmoSphere particles often have rough surfaces (asperites), which effectively increase interparticle separation distances. Their surface is comprised of hydrophobic lipid molecules with a low surface energy, ca., $30 mN \cdot m^{-1}$ (data not shown).

Significant decreases in the time to peak plasma concentrations were noted for the PulmoSphere formulation relative to the crystalline drug in Pulmicort. Examination of the PulmoSphere budesonide formulation via polarized light microscopy revealed significant birefringence indicative of crystalline domains of budesonide. X-ray diffraction and Raman spectroscopic studies indicated that both crystalline and amorphous polymorphs of budesonide are present in the PulmoSphere budesonide formulation (data not shown). It is likely that the amorphous budesonide is solubilized within the phospholipid excipient. The faster absorption of PulmoSphere budesonide observed in the pharmacokinetic data is likely the result of two factors: (a) the decreased particle size of the crystalline drug following wet-milling of the micronized drug crystals in the high pressure homogenizer during production which would allow deeper penetration into the lung; and (b) the increased proportion of amorphous budesonide present in the spray-dried product.

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