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A novel aerosol inhalation device for pressurized metered dose inhalation aerosols: gammascintigraphic evaluation of pulmonary deposition profiles and comparison with commercial inhalation devices

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Abstract

A cylindrical shape prototype aerosol inhalation device that was previously shown to enhance pulmonary deposition from a nebulizer was evaluated for its performance in conjunction with a pressurized metered dose inhalation aerosol (MDI). Gammascintigraphic studies in human volunteers using radiolabeled technetium Tc 99m sulfur colloid (TSC) MDI showed this prototype to enhance sulfur colloid deposition in the lungs and minimize oropharyngeal deposition. A second in vivo study conducted with a new compact prototype designed for commercial development showed similar pulmonary deposition profiles with the radiolabeled TSC MDI. Data from these studies with the radiolabeled MDI show that both the prototypes enhanced pulmonary deposition and minimized oropharyngeal deposition in comparison with commercial inhalation devices.

Keywords: Pressurized metered dose aerosol; Radiolabeled aerosol; Technetium Tc 99m sulfur colloid; Inhalation device; Gammascintigraphy; Pulmonary deposition

1. Introduction

Inhalation devices are used with pressurized metered dose inhalation aerosols (MDI) to enhance the pulmonary deposition of drugs. Pulmonary deposition efficiency of MDIs is only about 10% due to the turbulence caused by the propellant and oropharyngeal retention of large particles as well as large unevaporated propellant droplets containing particles (Davies, 1975; Short et al., 1981; Newman et al., 1981; Dolovich et al., 1981; Davies, 1982). Several inhalation devices that are interposed between the patient's mouth and MDI were developed and shown to enhance

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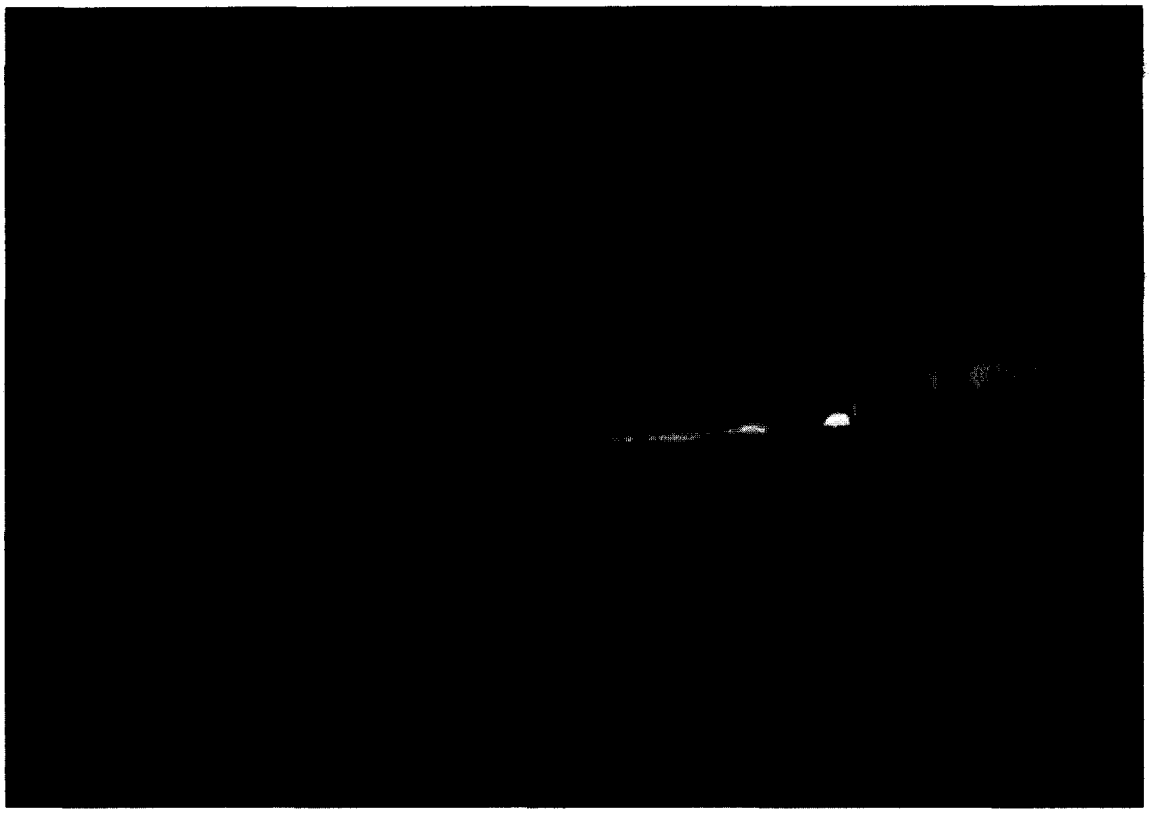

Fig. 1. Prototype I inhalation device: 1. Inspir-Ease® mouth piece 2. Three-piece acrylic cylindrical chamber 3. Rubber 'O' rings. 4. End plate with flow rate limiting orifices.

pulmonary deposition and minimize oropharyngeal deposition (Moren, 1978; Sciarra and Cute, 1978; Newman et al., 1981b; Sackner et al., 1981; Corr et al., 1982; Tobin et al., 1982; Toogood et al., 1982).

Commercial inhalation devices used with MDIs include (i) compact spacer devices (e.g. Aerochamber™, and Brethancer™), and (ii) large reservoir type devices (e.g. Inspir-Ease®, and Nebuhaler®). Spacers are first generation inhalation devices designed to enhance pulmonary deposition by allowing propellant expansion prior to its inhalation. Second generation devices use rigid or collapsible reservoirs with a fixed chamber volume. Both the spacer and chamber devices were shown to enhance pulmonary deposition, while chamber type devices offer an advantage over spacers in minimizing the oropharyngeal deposition via gravitational sedimentation of large particles within the device chamber. However, chamber devices are usually large (e.g. 700 ml chamber for Inspir-Ease®; 850 ml chamber for Nebuhaler®) and cannot be used in a discrete manner.

The purpose of this study was (i) to design a device for MDIs that offers portability like a spacer and the advantages of the chamber design and (ii) to compare the pulmonary deposition performance of this device with commercial inhalation devices by gammascintigraphy using a radiolabeled MDI. Previous pulmonary deposition studies (Newman et al., 1981b and Newman et al., 1981, Vidgren et al., 1987, 1989 and Vidgren et al., 1990; and Zainudin et al., 1989) using radiolabeled MDIs required administration of several sprays to obtain an adequate dose for

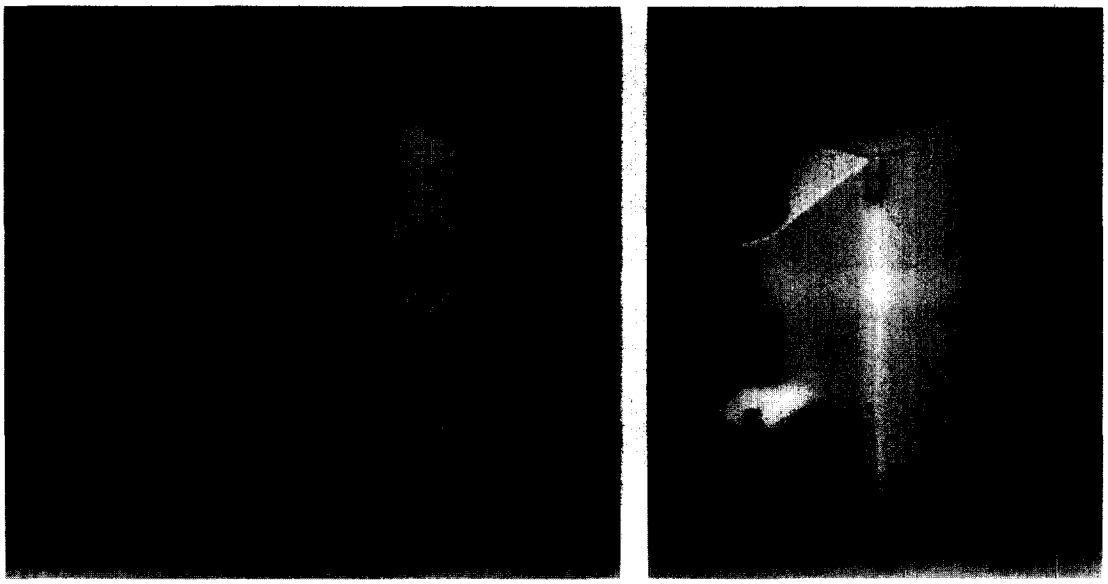

Fig. 2. Prototype II inhalation device: 1. Storage condition. 2. Use condition. 3. Inhalation chamber that houses mouth-piece and MDI during storage. 4. MDI. 5. Mouth-piece. 6. Cap to secure MDI during storage.

imaging. Technetium Tc 99m labeled sulfur colloid (TSC) MDI (Gaddipati et al., 1993) delivers adequate radioactive dose for imaging by a single spray administration which would be more reflective of typical MDI usage. Pulmonary deposition profiles of two prototypes and three commercial inhalation devices were evaluated by gammascintigraphy in human volunteers using the TSC MDI. Data from these gammascintigraphic studies are presented in this report.

2. Materials and methods

2.1. Materials

TSC Kit for the preparation of technetium Tc 99m sulfur colloid (TSC) injection was obtained from Medi-Physics Inc. (Paramus, NJ). Dichlorodifluoromethane (Freon 12) was obtained from Dupont (Deepwater, NJ). Aerosol valves (100 μl, Model DF10) and 19 ml Presspart

Table 1
In vivo study I - distribution of technetium Tc 99m sulfur colloid delivered from an MDI with different inhalation devices

Device	% Distribution[a]			
	Lung	Stomach	Mouth	Trachea
Prototype I	65.3 (1.5)	3.0 (1.0)	18.7 (5.5)	13.0 (4.4)
InspirEase®	45.0 (8.9)	6.0 (4.0)	18.0 (8.5)	31.0 (17.8)
Azmacort™	25.7 (10.5)	21.3 (20.1)	34.7 (13.7)	18.3 (14.0)

[a]Values in parenthesis are S.D., $n = 3$.

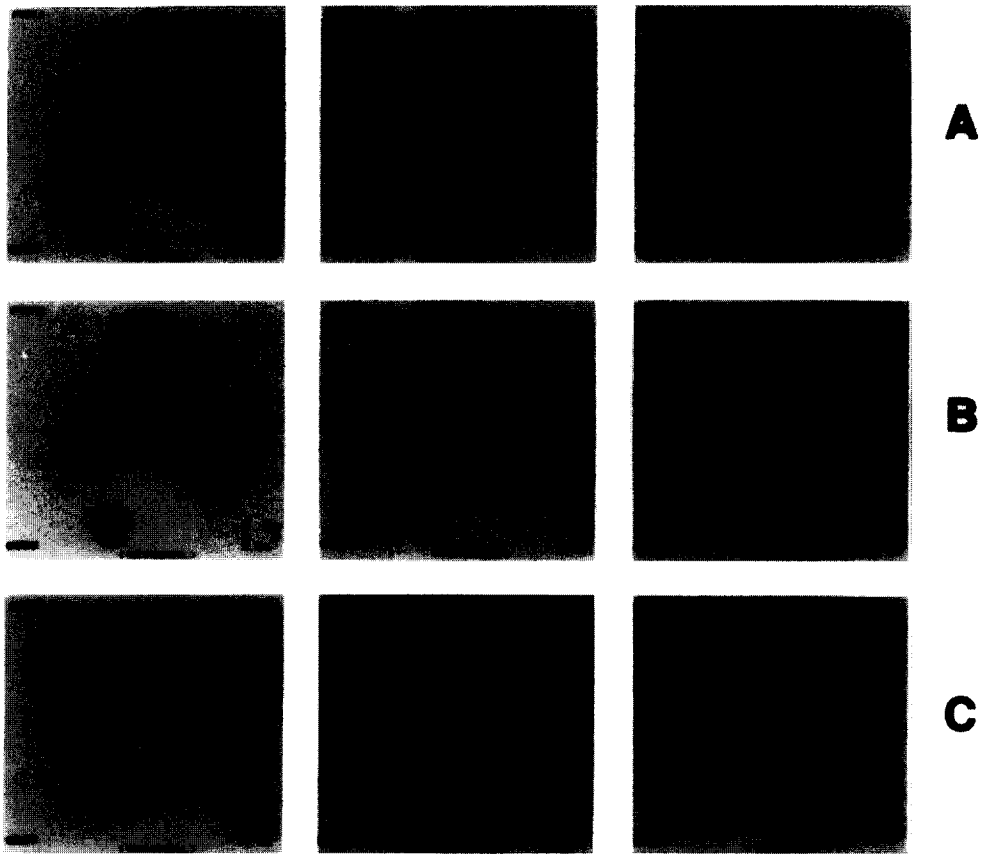

Fig. 3. In vivo study I - Lung deposition from technetium Tc 99m sulfur colloid MDI: row A, prototype I; row B, InspirEase® and row C, Azmacort™ spacer in three different volunteers for each device.

anodized aluminum cans were obtained from Valois (France). Technetium generator (Mo-99/Tc99m) used to prepare sodium pertechnetate solution was obtained from Mallinkrodt Medical Inc. (Maryland Heights, MO).

2.2. Methods

2.2.1. Radiolabeled MDI preparation.

Technetium Tc 99m labeled sulfur colloid MDI was prepared by suspending lyophilized TSC in Freon 12. The manufacturing procedure, dose delivery from the valve and particle size distribution of TSC MDI aerosol are described elsewhere (Gaddipati et al., 1993).

2.2.2. Inhalation dose delivery.

Non-smoking male volunteers (age 18–50) with no history of prior lung disease were evaluated by spirometry. Individuals with FVC and $FEV_1 \geq 80\%$ of predicted value were selected for the study. Prior to the administration of the radiolabeled aerosol inhalation dose, each volunteer was instructed in the use of the device and was allowed to practice the inhalation technique using a placebo aerosol canister containing Freon 12. For the inhalation technique no time restraints were imposed for the length of inhalation and after completing the inhalation a 10 s breath holding time was followed. Each volunteer was administered a single dose of radiolabeled TSC aerosol using one of the test devices and each device was tested in three subjects.

2.2.3. Measurement and calculation of deposition.

Immediately after dose inhalation, each volunteer was scanned with a large field of view gamma

Table 2
In vivo study II - distribution of technetium Tc 99m sulfur colloid delivered from an MDI with different inhalation devices

Device	% Distribution[a]			
	Lung	Stomach	Mouth	Trachea
Prototype I	69.3 (4.6)	13.2 (5.2)	7.8 (5.1)	9.7 (6.4)
Prototype II	75.0 (13.7)	4.8 (5.0)	12.3 (7.6)	7.9 (2.8)
Conventional actuator	7.7 (2.5)	43.3 (15.0)	34.7 (2.9)	14.3 (14.4)

[a]Values in parenthesis are S.D., $n = 3$.

camera (Dyna 4/15, Picker International, Highland Heights, OH) connected to a computer system (System IV, ADAC Laboratories, Milpitas, CA). Images were acquired with a low energy all purpose collimator in a 64 × 64 matrix format. The energy setting used was a 15% window Tc 99m energy peak centered at 140 keV. The data were obtained for the thorax (anterior and posterior views) and the oropharyngeal region by scanning each view in a sitting position. Counts were obtained in the regions of interest delineating the lungs, mouth, stomach and trachea. The data were normalized based on total counts determined in each subject and the results were expressed as percentages of the total sulfur colloid distribution in the lung, mouth, stomach and trachea. This standard trial protocol was accepted by the University of Florida Health Center's Internal Review Board (Gainesville, FL).

2.3. Inhalation devices

2.3.1. Prototype I.

A cylindrical shape prototype inhalation device (Fig. 1) was shown to enhance pulmonary deposition and minimize oropharyngeal deposition of Technetium Tc 99m labeled sulfur colloid injection aerosolized from a nebulizer (Laube et al., 1988 and Zoltan et al., 1990). This device was never tested in conjunction with an MDI, and it would be valuable if pulmonary deposition from an MDI can be improved using this device.

The design features of the above cylindrical prototype (Fig. 1) include a telescopic design made up of three acrylic rings interlocked with two rubber 'O' rings to form a 225 ml inhalation chamber. The exterior chamber length is approximately 7 cm when fully extended. The far end of the chamber is closed with an acrylic plate containing 9 × 1 mm orifices that control the inhalation flow rate. The inhalation end of the device was closed with another acrylic plate designed to fit the mouth-piece from Inspir-Ease® (distributed by Schering Corporation, Kenilworth, NJ). The rubber 'O' rings present between the acrylic rings form an air-tight seal during inhalation.

2.3.2. Prototype II.

The ineptness of the prototype I design for commercial development required further improvements to make the device more compact and easy-to-use. In an attempt to develop a commercially viable design, a variety of inhalation chambers with different shapes and sizes were evaluated by in vitro testing (Gaddipati et al., 1995). These in vitro studies suggested that the cylindrical and rectangular chambers with a 225 ml chamber show similar inhalable fractions. A rectangular shape was selected based on manufacturability considerations and device compactness.

The final design of prototype II consisted of a compact rectangular chamber with a 225 ml chamber volume similar to prototype I. The dimensions of prototype II device are 55 × 35 × 120 mm and the device with an MDI readily fits in a coat pocket or purse. The schematics of this device under use and storage conditions are shown in Fig. 2 (prepared by GR Technical Services, Mountainside, NJ). The device use is a two step operation: (a) open cap (b) pull the MDI holder to lock it in place for inhalation. After inhalation the MDI holder along with the canister can be pushed back into the inhalation chamber and the cap closed for storage. The MDI holder can fit aerosol canisters up to 10 ml size for storage in the inhalation chamber and a 17 ml canister is shown in Fig. 2. The end plate of the

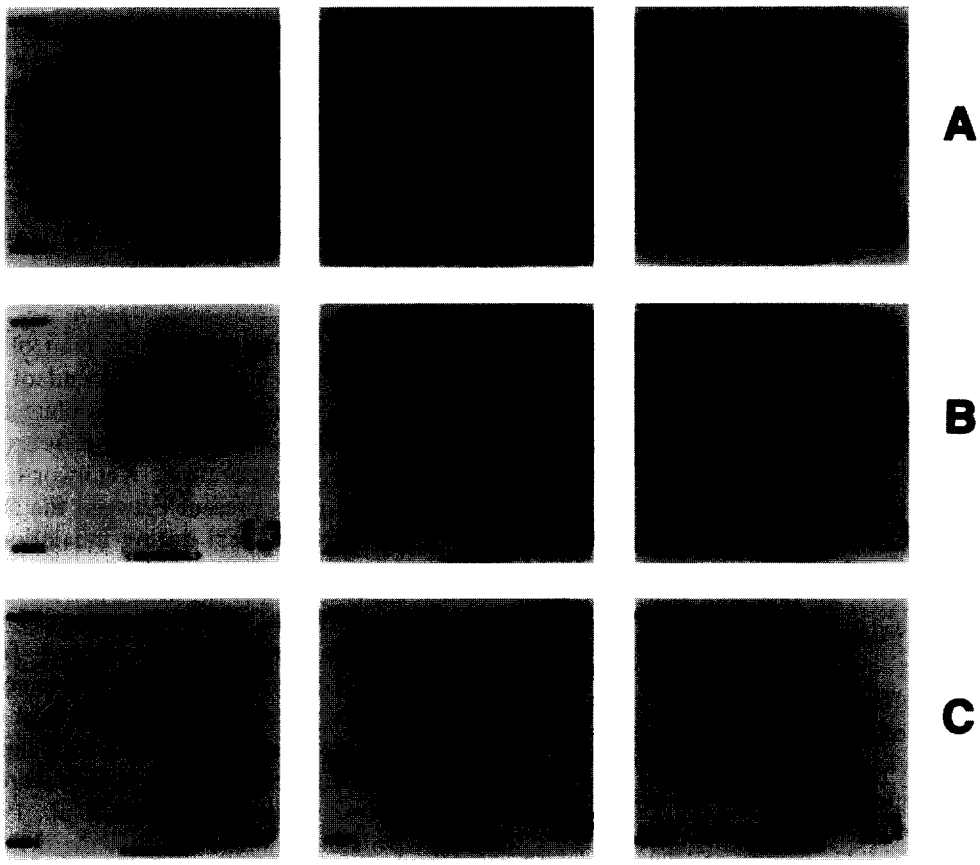

Fig. 4. In vivo study II - Lung deposition from technetium Tc 99m sulfur colloid MDI: row A, prototype I; row B, prototype II; and row C, conventional actuator in three different volunteers for each device.

prototype containing 9 × 1 mm diameter flow rate limiting orifices (not shown in Fig. 2) can be removed to clean the inhalation chamber. The spray orifice was designed to deliver a spray similar to the Inspir-Ease® mouth piece. The spray characteristics evaluated by laser light scattering (Malvern 2600C Droplet and Particle Sizer Equipped with PS51 Pulsed Spray Synchronizer, Malvern, UK) using a Freon 12 MDI showed mean particle size diameters of 2.3 and 2.1 microns for the prototype II and Inspir-Ease® mouth piece respectively. The distance between the actuator spray tip and the laser beam was set at 12 cm and the spray duration was set at 30 ms for the particle size measurements.

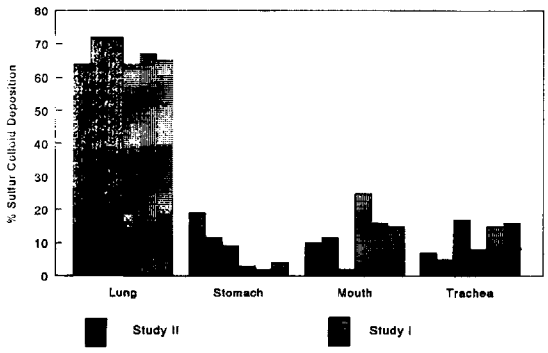

Fig. 5. In vivo pulmonary deposition profiles of all subjects tested with prototype I in studies I and II.

2.4. Commercial devices

Commercial devices included in the studies were Inspir-Ease® which has a cylindrical shape col-

lapsible chamber, a spacer device used with Azmacort™ (Rhone Poulenc Rorer, Collegeville, PA), and a conventional actuator (Model KN3 Valois, France) that delivers the spray directly into the mouth.

3. Results and discussion

3.1. In vivo study I

Prototype I, Inspir-Ease®, and Azmacort™ devices were tested in this study. The gammascintigraphic data of nine subjects from this study are summarized in Table 1 and the gamma images indicating the pulmonary deposition are shown in Fig. 3. The gamma images from the first two columns were generated on day 1 using the same sulfur colloid MDI. The gamma images from the third column were prepared on day 2 using a freshly prepared MDI. The MDI prepared on day 2 contained 10% more radioactivity and the valve delivery was close to the upper specification limit (125%) which resulted in much more intense gamma images for the volunteers tested on day 2.

The images for prototype I (row A) show deeper lung penetration of sulfur colloid for all subjects with an average of 65% inhaled fraction in the lungs. The images for Inspir-Ease® (row B) show deeper lung penetration of sulfur colloid for two subjects and one subject showed large deposition in the trachea and main bronchi. The Inspir-Ease® device produced an average of 45% inhaled sulfur colloid in the lungs. Azmacort™ device (row C) produced an average of 26% inhaled fraction in the lungs, and the images clearly show poor lung deposition of sulfur colloid for all subjects. Oropharyngeal depositions for the prototype I, Inspir-Ease®, and Azmacort™ devices were 35, 55, and 74% respectively.

3.2. In vivo study II

Pulmonary deposition of prototype II was tested in a second gammascintigraphic study. A conventional actuator commonly used with commercial MDIs and prototype I (as a control) were included in this study. Gammascintigraphic data of nine subjects from this study are summarized in Table 2 and the gamma images indicating the lung deposition are shown in Fig. 4.

The images for prototype I (row A) produced an average of 69% inhaled fraction in the lungs. The images of prototype II (row B) show major fraction of inhaled sulfur colloid in the lungs (mean, 75%). The image for one subject (row B - center) shows only a faint image for the lung deposition as a result of the reduction of inhalable fraction (by settling of suspended particles in the device chamber) due to a 20 s delay in inhalation caused by the subject. The distribution of sulfur colloid for this subject was 60% in the lungs despite the reduction in the inhalable fraction. The images (row C) for the conventional actuator clearly show poor lung deposition (mean, 8%) for all subjects. The oropharyngeal depositions for the prototype I, II and conventional actuator were 31, 25, and 92% respectively.

3.3. Comparative evaluation of devices

3.3.1. Pulmonary deposition.

The data from the above in vivo studies (Tables 1 and 2) show enhanced pulmonary deposition from both the prototypes in comparison with a conventional actuator, Azmacort™ spacer and Inspir-Ease® inhalation devices. The enhanced pulmonary deposition observed for the prototypes is attributable to (i) control of inhalation flow rate by the flow rate limiting orifices and (ii) flow through design of the device permits continuous inhalation of the suspended particles to the maximum vital capacity of the subject. The Inspir-Ease® device showed enhanced pulmonary deposition in comparison with Azmacort™ spacer and a conventional actuator. However it showed smaller fraction of sulfur colloid in the lungs in comparison with the prototypes and this might be due the entrapment suspended particles within the collapsing chamber prior to inhalation.

3.3.2. Oropharyngeal deposition.

As expected for the chamber devices, both prototypes and the Inspir-Ease® minimized oropharyngeal deposition in comparison to the

Azmacort™ spacer and conventional actuator. With the Azmacort™ spacer and conventional actuator the spray is delivered directly toward the mouth which results in a majority of the inhalable fraction deposited in the oropharynx.

When an MDI is used with the Inspir-Ease® or prototype devices, the spray is delivered directly into the inhalation chambers where a portion of the spray is retained due to impaction and settling of larger particles. Thus, the elimination of larger un-inhalable particles via the device helps to minimize the oropharyngeal deposition.

3.4. Reproducibility of In vivo studies

The above in vivo studies were conducted approximately 1 year apart. Each study was conducted for 2 days and a freshly prepared radiolabeled TSC MDI was used on each day. In vivo data from six subjects for prototype I from both the studies presented in Fig. 5 clearly show the pulmonary deposition data from the TSC MDI aerosol to be reproducible irrespective of the time of testing and the batch of aerosol used. These data clearly suggest that TSC MDI can be utilized to evaluate the pulmonary deposition profiles of inhalation devices.

4. Conclusions

A new compact rectangular prototype has been developed for use in conjunction with MDIs. In vivo studies using a radiolabeled TSC MDI show that the prototypes I and II enhanced pulmonary deposition and minimized oropharyngeal deposition in comparison with Inspir-Ease®, Azmacort™ spacer and a conventional actuator.

The gamma images and data presented show that the radiolabeled TSC aerosol with a single spray administration showed reproducible pulmonary deposition profiles for each device. These data indicate that the TSC MDI discriminates between devices and can be utilized to characterize the pulmonary distribution profiles of different inhalation devices.

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