Research Paper

The Interaction Between the Oropharyngeal Geometry and Aerosols via Pressurised Metered Dose Inhalers

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Purpose. This study investigated the effect of oropharyngeal geometry on inhaled aerosol characteristics via pressurised metered dose inhalers (pMDIs), both with or without spacers.

Methods. Seven adult oropharyngeal models with different centreline lengths, total volumes, and degrees of constriction were employed as induction ports for a laser diffraction particle size analyser and cascade impactor. Particle size change over time, mass median aerodynamic diameter (MMAD), average median volume diameter (D_V50), inhaled doses, and oropharyngeal depositions (percentage of the nominal dose) for aerosols via suspension and ultrafine pMDIs with or without spacers at 30 l/min airflow were determined.

Results. Variations in oropharyngeal geometry caused significant variations in inhaled particle size distributions, doses, oropharyngeal drug depositions, and particle size change over time when pMDIs were used without spacers. However, inhaled aerosol characteristics had marginal variations for the ultrafine pMDI plus large volume spacer (MMAD range: 0.69–0.78 μm, D_V50 range: 1.27–1.36 μm, inhaled dose range: 46.46–52.92%). It was found that the amounts of inhaled aerosol particles with aerodynamic size of less than 0.83 μm via pMDIs plus large volume spacer were slightly affected by the oropharyngeal geometry.

Conclusion. Inhaling ultrafine aerosols via spacers may reduce the effect of oropharyngeal geometry on inhaled aerosol properties.

KEY WORDS: acute asthma exacerbations; inter-subject inhaled dose variability; oropharyngeal models; pressurised metered dose inhalers; ultrafine aerosols.

INTRODUCTION

Pulmonary drug delivery has been employed not only for treatment of respiratory diseases, such as asthma, but also delivery of peptides, such as insulin, for systemic effects and vaccines for immunization (1). Amongst the inhalers, pressurised metered dose inhalers (pMDIs) are used extensively by patients due to their portability, low airflow resistance, and generation of suitable aerosols independent of patient inspiratory flow rate. The presence of these properties has resulted in using pMDIs (with spacers) as first line drug delivery device in treatment of acute asthma exacerbations (2,3). However, a subgroup of patients has been identified

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who had poor responses to inhaled drugs (corticosteroids and bronchodilators) via these devices (2,4), which could not be attributed to the poor inhalation technique, as pMDIs were used with spacers. To achieve goals of therapy in these patients, increasing the drug dose was considered, but this resulted in increased drug systemic side effects (4), or the patients were required intense monitoring and hospitalisation (2). Furthermore, it has been shown that variability in oropharyngeal drug deposition caused variability in amounts of drug reaching the lungs via inhalers (5–8), and consequently resulted in variable clinical responses (5). Therefore, these observations suggest that reduction in the amount of drug reaching the lungs could have played an important role for poor responses to the inhalation therapy.

Attempts have been made to reduce the oropharyngeal drug deposition by increasing inhaler airflow resistance (8) and elongating the inhaler mouthpiece (9). However, these approaches were not successful. This is because inhalers with a high airflow resistance were not suitable for young children and elderly patients (10). Furthermore, elongating inhaler mouthpiece was not sufficient to significantly reduce oropharyngeal drug deposition compared to the normal oropharyngeal drug depositions (9). In fact, recent studies using oropharyngeal models have indicated that differences in the oropharyngeal geometries would cause variation in the amounts of drug delivered to the lungs via conventional suspension pMDIs with or without spacers (11,12). However, ultrafine pMDIs (devices that generate aerosols with mass

median aerodynamic diameter less than 1 μm), which have markedly different aerosol performance compared to conventional suspension pMDIs (13,14), have not been investigated.

The primary goal of this study was to compare an ultrafine pMDI with a suspension pMDI with regard to the effect of oropharyngeal geometry on the inhaled aerosol particle size, particle size time profile, dose, and oropharyngeal drug deposition. In this study, physiologically faithful oropharyngeal models were employed, and spacers with different sizes were considered. A corticosteroid inhaler and a bronchodilator inhaler, which are commonly used in treatment of acute asthma exacerbations, were chosen. The secondary goal of this study was to estimate aerodynamic particle size, which would make the inhaled dose relatively independent of the oropharyngeal geometry.

MATERIAL

Brij®35 (polyoxyethylene lauryl ether) and beclometasone dipropionate were purchased from Sigma-Aldrich (Chemie GmbH, Steinheim, Germany). Glycerol was obtained from BDH Laboratory Supplies (Poole, England), salbutamol sulphate micronised powder was a gift from GlaxoSmithKline (Ware, UK), Decan 90 detergent solution was obtained from Decan Laboratories Ltd (Sussex, UK), and HPLC-grade methanol was purchased from Fisher Scientific (Loughborough, UK). Salbutamol sulphate suspension pMDI (Ventolin™ Evohaler™ GlaxoSmithKline Ltd, London, UK, 100 μg per actuation), and beclometasone dipropionate solution pMDI (Qvar™ Ivax Pharmaceuticals, London, UK, 50 μg per actuation) were employed.

METHODS

The Oropharyngeal Models and Add-On Spacers

Three-dimensional reconstructions of the mouth and throat of healthy adult subjects inhaling at 30 l/min via the Bricanyl pMDI (AstraZeneca, Kings Langley, UK) and NebuChamber mouthpiece (AstraZeneca, Kings Langley, UK) were considered. These data were obtained in a previous study using magnetic resonance imaging (MRI) (15). The subjects' age range was 23–35 years. In total, seven three-dimensional reconstructions were employed. For the purpose of this study, oropharyngeal shapes with different centreline lengths and configurations were used. The oropharyngeal geometries were ranked between 1 and 7 according to their volumes (by rank, 1 being the smallest volume and 7 the largest one). Also, similar to a previous study (8), the oropharyngeal configurations were categorised into three groups. The grouping was based on the severity of the airway narrowing (due to the oropharyngeal posture) in the oropharynx section of the throat. The groups were

A. Wide open space
B. Moderate narrowing
C. Marked constriction.

Fig. 1A illustrates the three-dimensional surface rendering of the reconstructed mouths and throats, their midsagittal sections, and designations (1C, 2C, 3A, 4A, 5A, 6B, 7B).

Fig. 1B depicts a typical head and neck MRI image illustrating the centreline in the mouth and throat, and the region of the airway (starting from the back of the upper lip to 2 cm below the vocal cords) that was considered to calculate the oropharyngeal volume. The midsagittal head and neck MRI images of the subjects and cross-sectional areas of the oropharyngeal reconstructions (along the centreline) are provided as "Online Supplementary Material." Table I presents the oropharyngeal lengths, volumes, and their designations. The oropharyngeal plastic (acrylnitrile-butadiene-styrene) models were prepared according to the previously reported method (16). The 1C, 2C, 3A, and 5A models were employed in previous studies (12,16). The inhalers tested in this study had low airflow resistances similar to those that were used in the MRI study (15); similar inspiratory airflow rates via the inhalers were also employed. Furthermore, the circular shape and cross-sectional diameter of the Qvar mouthpiece were similar to the shape and dimensions of the oral cavity inlets of 2C, 4A, 5A, and 6B models. Similarly, the rectangular shape and cross-sectional diameter of the Ventolin Evohaler mouthpiece were comparable with shape and dimensions of the oral cavity inlets of 1C, 3A, and 7B models. Therefore, marked differences in the oropharyngeal geometries due to switching from the original inhalers that were used in the MRI study (15) to those that were employed in this study were not expected.

The AeroTrach Plus™ spacer (Trudell Medical International) was used as a large-valved holding chamber (large volume spacer, 149 ml space volume). In addition, the Optimiser (Norton Healthcare and Glaxo-SmithKline Ltd, Harlow, UK,) was used with the Ventolin as small volume spacer. Furthermore, a high-density polyethylene tube with 2 cm internal diameter (2.2 cm outer diameter) and 8 cm length (denoted as "long tube") was used with the Qvar. To reduce the electrostatic charge in the spacers, these were soaked for 2 h in 2% (w/v) Decan 90 solution and left to drip-dry.

The following inhaler devices were employed: the Qvar, Qvar with the large volume spacer, Qvar with the long tube, and Ventolin with the large volume spacer, which had circular mouthpieces, so these were used with the 2C, 4A, 5A, and 6B oropharyngeal models (which also had circular cross section at the inlet of the oral cavity part and diameter similar to the inhalers' mouthpieces). Combinations of the Ventolin pMDI with or without the Optimiser had rectangular mouthpiece shape, so these were used with 1C, 3A, and 7B models (which also had rectangular cross section at the inlet of the oral cavity part and diameter similar to the inhalers' mouthpieces). In this study, it was possible to match commercially available ultrafine pMDI (the Qvar with circular mouthpiece) with the oropharyngeal models that also had circular oral cavity inlet. The rectangular mouthpiece of bronchodilator suspension pMDI necessitated using oropharyngeal models with rectangular oral cavity inlets. The matching of the inhalers with the corresponding oropharyngeal models was performed to ensure suitable connections between the inhalers and models. However, by considering employed airflow rate (30 l/min) and aerosol particle diameter (mostly less than 3 μm) in this study, based on a previous work, a considerable change in the oropharyngeal drug deposition due to variations in the mouthpiece diameter and shape was not expected (17).
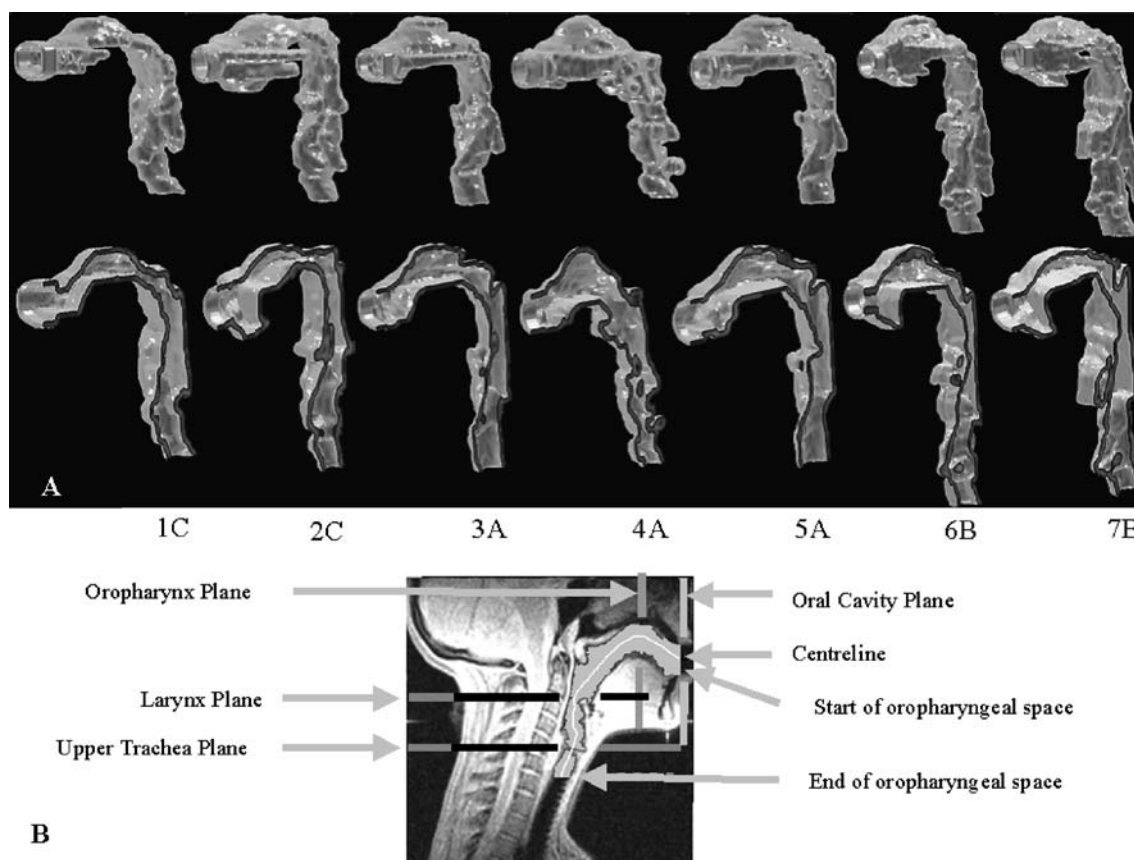
Fig. 1. A Three-dimensional reconstructions of the oropharyngeal geometries that were employed in this study; the 2C, 4A, 5A, and 6B are oropharyngeal geometries by inhaling via the circular mouthpiece, and the 1C, 3A, and 7B are oropharyngeal geometries via the rectangular mouthpiece. In this panel the midsaggital sections of the reconstructed geometries are also presented. **B** A typical midsaggital MRI image of a subject inhaling via an inhaler, illustrating different regions of the mouth and throat, and the region that was considered to calculate the oropharyngeal volume.

Laser Diffraction Particle Size Measurements

A Sympatec HELOS BF/MAGIC® system (Sympatec GmbH, Clausthal-Zellerfeld, Germany) equipped with a modular inhaler adapter (INHALER® 2000) and R2 lens (size range from 0.25–87.5 µm) was used to obtain laser diffraction angles and intensities. The Fraunhofer model operated within the WINDOX 5 software was employed to calculate the particle size distributions of the samples. Aerosols were directed to the inhaler module either via an oropharyngeal model (connected to the inlet of the inhaler module from its upper trachea part) or by directly connecting the inhaler device to the instrument. In this study the counter flow was not used. However, the windows that the laser beam passed through were cleaned regularly.

To deliver aerosols to an oropharyngeal model, a pMDI with or without a spacer was connected to the oral cavity part of the corresponding model and sealed using flexible Parafilm M. Then the airflow through the inhaler device and oropharyngeal model was set to 30 l/min and the device was actuated once. When the suspension pMDI was evaluated, the device was shaken before each actuation. The particle size measure-

Table I. The Oropharyngeal Characteristics and Configurations

Oropharyngeal designation[a]	Oropharyngeal volume/cm^3	Oropharyngeal opening[b]	Oropharyngeal centreline length/cm	Gender	Oral cavity inlet cross-section shape
1C	37.6	C	17.1	F	Rectangular
2C	53.4	C	18.7	F	Circular
3A	55.9	A	19.9	M	Rectangular
4A	61.8	A	17.8	F	Circular
5A	68.4	A	19.9	M	Circular
6B	75.1	B	21.6	M	Circular
7B	80.8	B	22.3	M	Rectangular

[a] The designation sequence is rank of oropharyngeal volume/oropharyngeal configuration category
[b] A: wide open space; B: a moderate narrowing; C: a marked constriction; F: female; M: male

ments were performed at 1 ms time slices with trigger conditions of either optical concentration greater than 0.3% or real time duration of 0.2 s. As the duration of aerosol delivery via an inhaler with or without attaching to a model had a distribution, for simplicity, general trends are reported in this study. The airflow rate was set at 14 l/min when pMDIs were used with the large volume spacer and connected directly to the inhaler module (without using any oropharyngeal model). This allowed a suitable number of sample data points to be obtained. Based on a previous study, marked differences in the aerosol performances of the pMDIs used with the large volume spacer (reduced electrostatic charge) caused by switching the airflow rate from 30 l/min to 14 l/min were not expected (18). Prior to each experiment, the oropharyngeal models were wetted with a solution of 0.7 g Brij 35 in 100 ml of glycerol to simulate the wet mucosa that naturally occurs in the throat.

The particle size distributions were compared statistically by the average median volume diameter D_v50, defined as 50% of the cumulative volume undersize (this parameter was indicated as X_{50} by the manufacturer). The relative span, $(D_v90-D_v10)/D_v50$, for each particle size distribution was calculated to present the dispersity of the distribution. Particle size measurements for each experimental setting were replicated six times.

Aerodynamic Particle Size Measurements

The oropharyngeal models using suitable adaptors were connected to the Next Generation Impactor (Copley Scientific, Nottingham, UK). Then, a glass microfibre filter at the outlet of the impactor was used to capture particles that were not collected by the impactor. A high capacity pump (Copley Scientific, Nottingham, UK) was used to draw air through the oropharyngeal models and impactor at 30 l/min. Based on previously published data, the impactor plates were not coated with any adhesive agents (19). An inhaler device (pMDI with or without attaching to a spacer) was connected to the oral cavity of the respective model, and the connection was sealed using Parafilm M flexible film. When the required airflow through the device and model, was established, the pMDI was actuated once, and the airflow rate was maintained for 8 s. The suspension pMDI was shaken before each actuation. For each particle size measurement, the pMDIs were actuated ten times. Then, the oropharyngeal model, spacer, impactor cups, and filter were washed with either distilled water for the salbutamol pMDI, or methanol/water mixture (70/30% v/v) for the beclometasone dipropionate pMDI. The amount of deposited drug in each section was determined using spectrophotometric analysis at 276 nm for salbutamol sulphate and 239 nm for beclometasone dipropionate from the relevant standard curves. Drug depositions within the impactor or oropharyngeal models are reported as percentage of nominal dose via the pMDIs. Oropharyngeal models before each aerosol deposition experiment were wetted by the corresponding washing solution to simulate the wet condition in the mouth and throat.

Since the oropharyngeal models were considered as the induction port for the impactor, the total amount of drug deposited in the impactor and attached filter was considered as the inhaled dose. The mass median aerodynamic diameter (MMAD) of aerosol particles for each experimental setting was calculated by plotting cumulative percentage of mass less than stated aerodynamic diameter (probability scale) *versus* aerodynamic diameter (log scale). Each deposition study was replicated six times. The experiments were performed at the local ambient conditions (typically 20°C temperature and 70% relative humidity). In the Results, section the Qvar pMDI is referred to as the ultrafine pMDI, and the Ventolin Evohaler pMDI as the suspension pMDI.

Statistical Analysis

Kruskal–Wallis tests followed by two-tailed Mann–Whitney U-tests for all cases were conducted. Then, by considering total number of comparisons, the Bonferroni correction was applied to the α level. Therefore, as the number of comparisons was 6 for each experimental setting in the group of 2C, 4A, 5A, and 6B models, the significance level for this group was considered as $P<0.008$. Similarly, since the number of comparisons was 3 for each experimental setting in the group of 1C, 3A, and 7B models, the significance level was set as $P<0.016$.

RESULTS

Particle Size Analysis

Laser Diffraction

Fig. 2 presents cumulative volume percent size distribution curves of aerosol particles at the exit of oropharyngeal models via the inhalers. In the figures, representative particle size distributions via the inhalers without using an oropharyngeal model are also plotted. It can be seen that particle size distributions were affected considerably by the oropharyngeal geometry when pMDIs were used alone (Fig. 2A and B), or when suspension pMDI were used with spacers (Fig. 2C and D). When the large volume spacer was used with the ultrafine pMDI, the deviation from the original particle size distribution was minimal (Fig. 2E).

Fig. 3 illustrates particle size distribution parameters, D_V10, D_V50, D_V90, and span changes over time. It can be seen that when the oropharyngeal models were used with pMDIs only (Fig. 3A–C), duration of aerosol delivery was longer for the ultrafine pMDI than the suspension formulation. This may be explained due to entrapping of ultrafine aerosol particles in air recirculations (within the models) for a longer time than larger aerosol particles via the suspension formulation. Also, within each formulation, the duration of aerosol delivery was increased by increasing the oropharyngeal volume. Furthermore, all particle size distribution parameters changed significantly over time for models that had constrictions in the oral cavity (the 1C, 2C, 6B, and 7B models). Taking pMDI formulation into account, decrease in particle size was more significant for the ultrafine pMDI (containing alcohol) than the suspension formulation.

The emission of aerosols with relatively constant particle size distribution via the oropharyngeal models with wide openings in the oral cavity (the 4A and 5A models in Fig. 3A and B) by using the ultrafine pMDI may be explained by rapid ventilation of the models and consequently faster
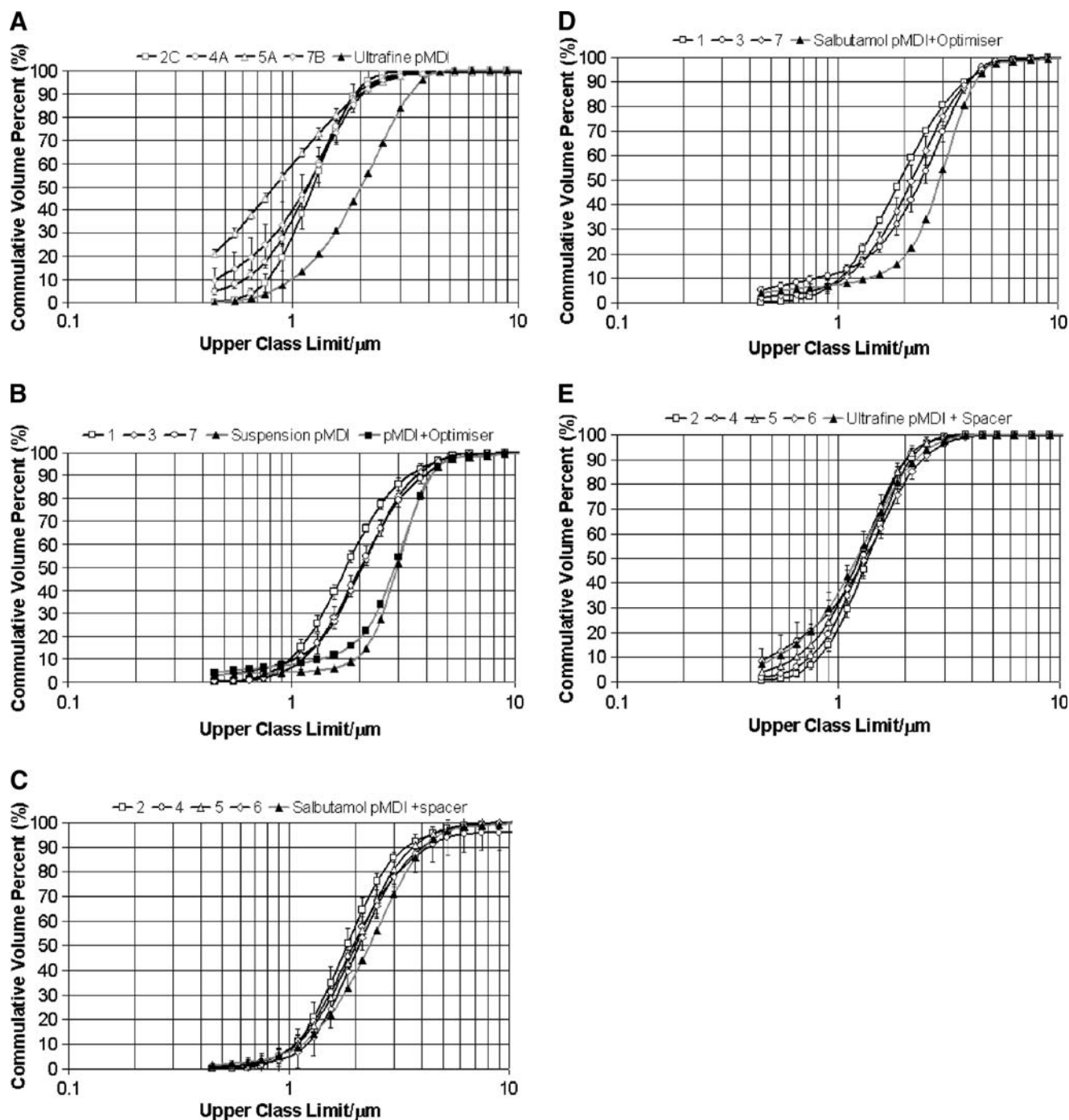
Fig. 2. Cumulative undersize volume percent particle size distributions of aerosol particles that passed the oropharyngeal models via the ultrafine pMDI alone (panel **A**), suspension pMDI alone (panel **B**), suspension pMDI with the large volume spacer (panel **C**), suspension pMDI with the small volume spacer (panel **D**), and ultrafine pMDI with the large volume spacer (panel **E**). In these figures, typical particle size distributions via the inhalers only (without attaching to a model) are presented by *black filled symbols*. *Error bars* present standard deviations (*n*=6).

evaporation of the propellant and excipient. However, a relatively steady state situation in particle size was observed around 2 s after actuation for models with large oropharyngeal volumes (the 5A and 6B models). Particle size change over time for pMDIs without connecting to the models did not follow the above patterns (data not shown).

Using the large volume spacer plus pMDIs alleviated particle size change over time for D_v50 (Fig. 3F) and D_v90

(Fig. 3G), but not for D_v10 (Fig. 3E) values for aerosols that pass through the models. Similar trends (Fig. 3E–G) were also observed for aerosols via the pMDIs plus the large volume spacer only (without connecting to models). It can be seen from Fig. 3E that for these aerosols, D_v10 values initially increased then decreased. This may be due to saturation of the laser measuring chamber with the propellant and excipient, consequently delaying evaporation of aerosol
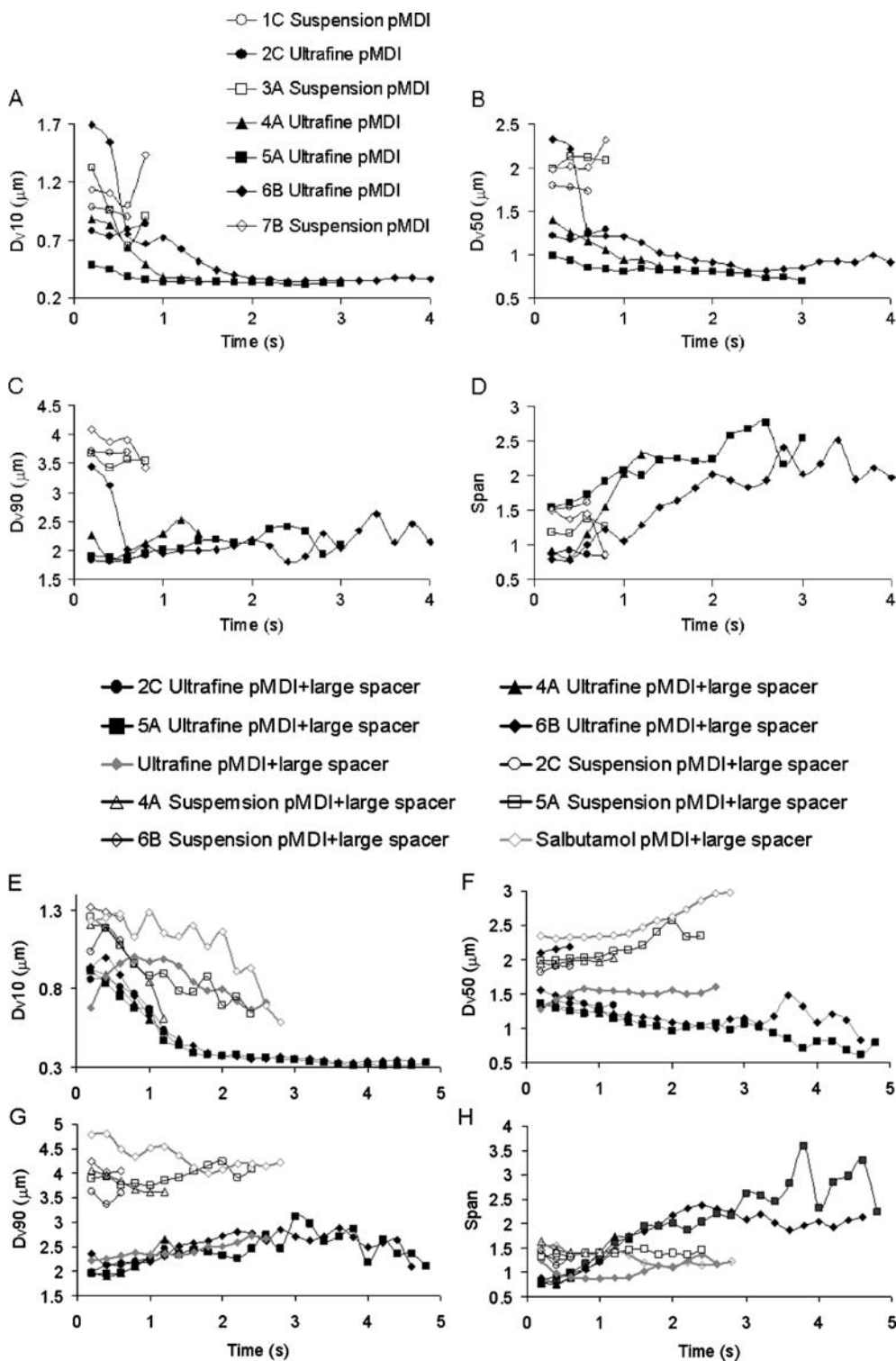
Fig. 3. Over time change of particle size distribution parameters, D_V10, D_V50, D_V90, and span via inhalers. Panels **A** to **D** are for pMDIs without spacers, and **E** to **H** for pMDIs with the large volume spacer. *Open circular symbols* show the 1C geometry, *filled circular symbols* show the 2C geometry, *open square symbols* depict the 3A geometry, *filled triangle symbols* depict the 4A geometry, *filled square symbols* illustrate the 5A geometry, *filled diamond symbols* present the 6B geometry, and *open diamond symbols* illustrate the 7B geometry. In Figure **E** to **H** *grey curves* present particle size distributions for the pMDIs with the large volume spacer but without attaching to an oropharyngeal model. *Open grey circle* symbols depict the suspension pMDI, and *filled grey diamond symbols* show the ultrafine pMDI. For the *grey plots*, the airflow was set at 14 l/min.

particles. Similarly, gradual evaporation of propellants and excipients from the aerosol particles within the models might cause a gradual decline in particle size when the models were employed.
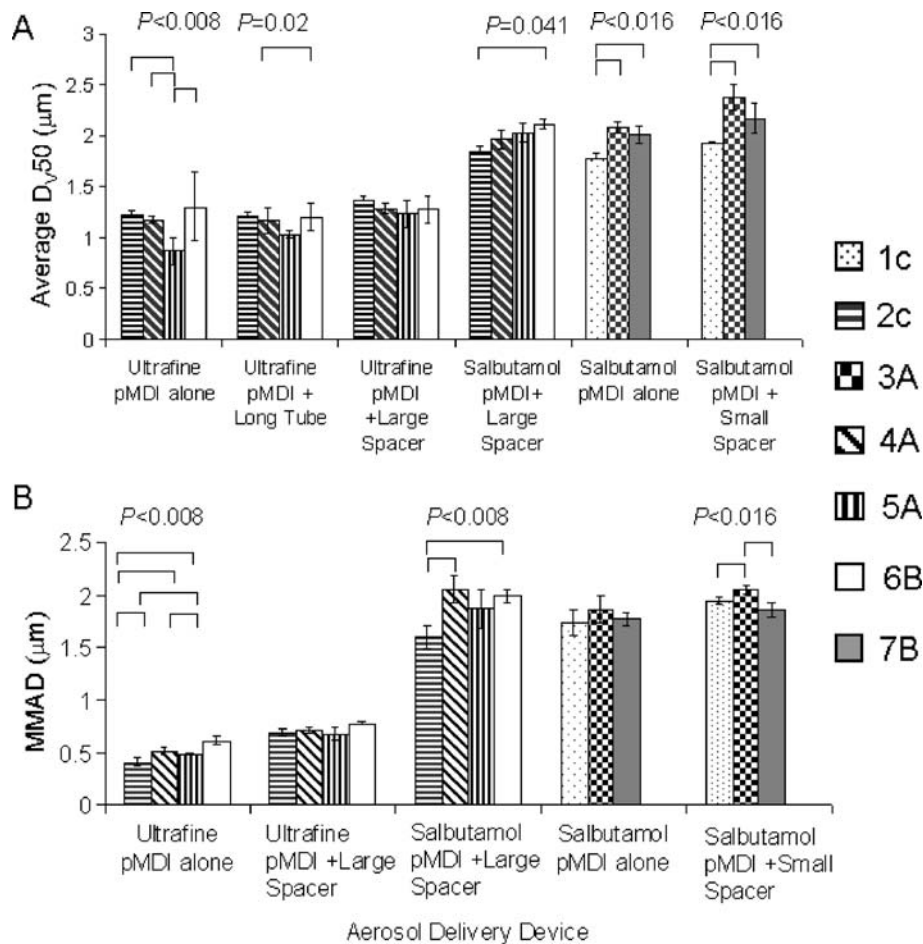
The average volume median diameters (D_v50) of the aerosol particles via the pMDIs with or without spacers are illustrated in Fig. 4A. In this figure, data are presented as ascending oropharyngeal volume on the x-axis. It can be seen that from using the ultrafine pMDI without a spacer, D_v50 decreases significantly from 1.24 ± 0.09 μm to 0.82 ± 0.01 μm as the oropharyngeal volume increases from 53.4 cm^3 to 68.4 cm^3 (oropharyngeal models: 2C, 4A, and 5A). However, average D_v50 increases significantly to 1.10 ± 0.13 μm despite increasing the oropharyngeal volume (75.1 cm^3) for the 6B model. A similar trend in average D_v50 but with less severity can also be seen for the ultrafine pMDI that was used with the long tube. This observation may be explained by referring to Fig. 3A to C, indicating that the presence of constrictions in the oral cavity might delay evaporation of the propellant and

excipient, which resulted in initial larger aerosol particles emitting from the model, and this increased the average value of D_v50.

Using the ultrafine pMDI with the large volume spacer increased average D_v50 compared to the ultrafine pMDI without using the spacers (Fig. 4A), but the variability of these values between the oropharyngeal models decreased (1.27 ± 0.06 μm to 1.36 ± 0.13 μm). In contrast, average D_v50 changed considerably for the suspension pMDI (with or without spacers) as a function of total oropharyngeal volume and presence of constrictions in the oral cavity (Fig. 4A).

Aerodynamic Particle Size

Cumulative mass aerodynamic distribution curves for aerosol particles that passed through the models via the inhalers are illustrated in Fig. 5. A clear effect of oropharyngeal geometry on the distribution curves can be seen when pMDIs used without spacers (Fig. 5A for the ultrafine pMDI,

Fig. 4. Panel **A** average median volume diameters, D_v50, of aerosol particles that passed through the models via the ultrafine pMDI without a spacer, with the large volume spacer, and with the long tube, also the salbutamol pMDI without a spacer, with the large volume spacer, and the small volume spacer (the Optimiser). Panel **B** MMAD of the aerosol particles that passed through the models via the above inhalers, apart from the ultrafine pMDI with the long tube. *Dotted white bars* show the 1C model, *horizontally hatched bars* show the 2C model, chequered bars indicate the 3A model, *diagonally hatched bars* depict the 4A model, *vertically hatched bars* present the 5A model, *white bars* show the 6B model, and *grey bars* designate the 7B model. In each device category, data are presented as ascending oropharyngeal volume (from *left* to *right*). *Horizontal brackets* show significant differences between pairs. *Error bars* present standard deviations ($n=6$).

and 5C for the suspension pMDI). Using the large volume spacer (Fig. 5B and C) or the small volume spacer with the suspension formulation (Fig. 5E) reduced the effect of oropharyngeal geometry on aerodynamic particle size distributions (at least up to 90% cumulative mass). The data in Fig. 5 also show a non-linear relationship between cumulative mass under size and aerodynamic particle size in the probability-log scale for aerosols that passed through the models, in particular for the ultrafine pMDI.

Particle deposition distributions within the impactor for the pMDIs used with the large volume spacer are illustrated in Fig. 6 (Fig. 6A for the ultrafine pMDI and 6B for the suspension pMDI). It can be seen that amount of inhaled aerosol particles with aerodynamic diameter less than 0.83 μm (stage 7, MOC and filter) became relatively independent of the oropharyngeal geometry.

Estimated mass median aerodynamic particle diameters for aerosols via the inhalers attached to the models are presented in Fig. 4B. Significant differences between MMAD values were found for the ultrafine pMDI without spacer (MMAD range: 0.41 ± 0.04 μm to 0.61 ± 0.04 μm, $P<0.008$), salbutamol pMDI with the large volume spacer (MMAD range: 1.86 ± 0.18 to 2.05 ± 0.13 μm $P<0.008$), and salbutamol pMDI with the small volume spacer (MMAD range: 1.86 ± 0.07 μm to 2.05 ± 0.04 μm, $P<0.016$). However, the differences in MMAD values of the models for the salbutamol without

spacer, despite the large variations, did not reach the significance level (range: 1.73 ± 0.12 μm to 1.85 ± 0.13 μm). On the other hand, using the ultrafine pMDI with the large volume spacer resulted in less variation in the MMAD values (MMAD range: 0.69 ± 0.03 μm to 0.78 ± 0.02 μm) with no significant differences amongst them.

Inhaled Dose and Oropharyngeal Drug Deposition

The inhaled doses and oropharyngeal drug depositions, as percentage of the nominal dose, via the pMDIs with or without spacers are shown in Fig. 7. In this figure, data are presented as ascending oropharyngeal volume on the x-axis. A general positive correlation can be seen between volume of the oropharyngeal model and inhaled dose (Fig. 7A) for the ultrafine pMDI without spacer ($15.99 \pm 4.95\%$ to $42.50 \pm 3.68\%$), and salbutamol pMDI with or without spacers. Statistical analysis showed significant differences amongst those values. However, inhaled doses for the ultrafine pMDI with the large volume spacer despite a small increase ($46.46 \pm 2.77\%$ to $52.92 \pm 4.92\%$) were relatively independent of the oropharyngeal geometry and showed no significant differences amongst the models. Data in Fig. 7A also indicate that inhaled doses via the suspension pMDI plus the large volume spacer were comparable to those through the small volume spacer.
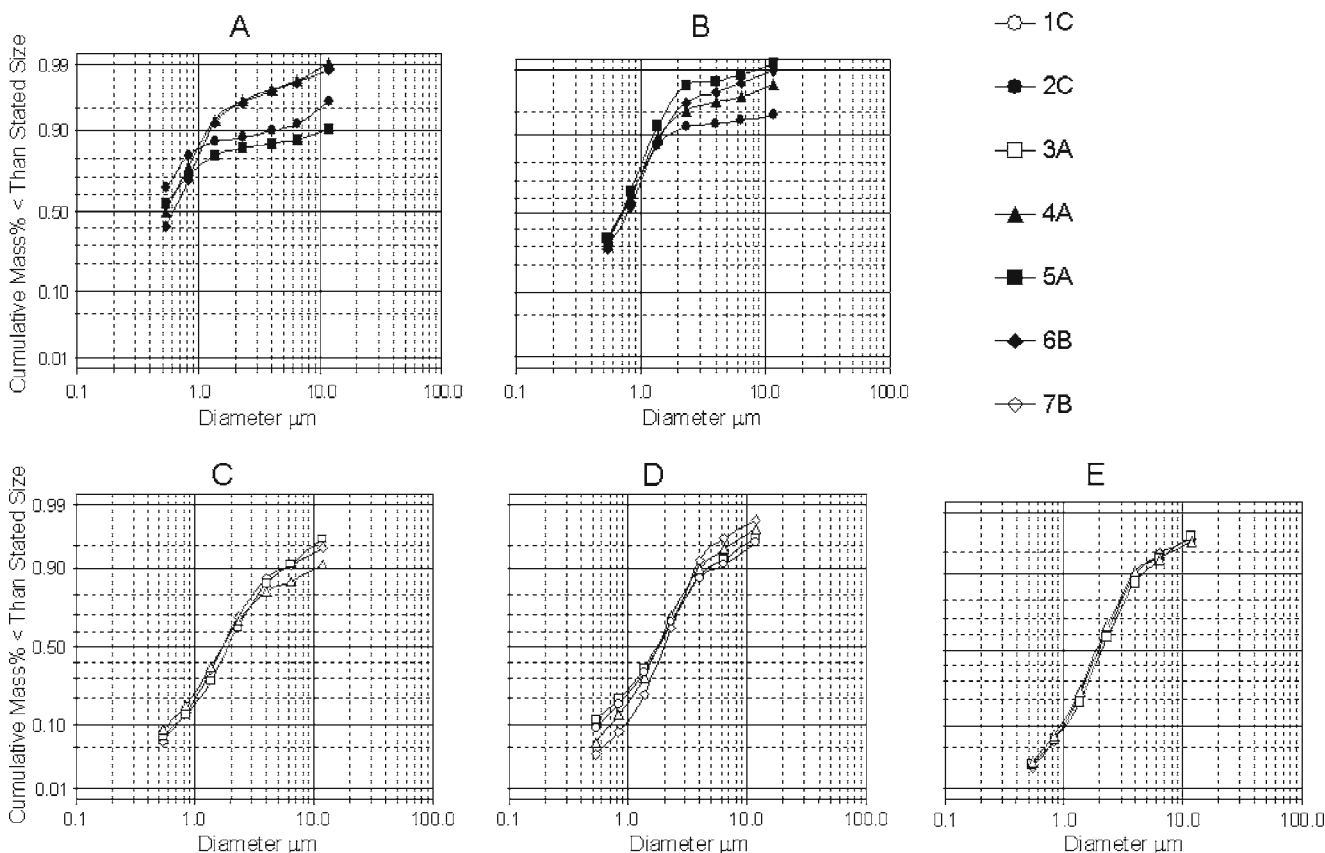
Fig. 5. Cumulative mass percent less than stated size distributions in probability-log scale for aerosol particles passed through the models via the ultrafine pMDI alone (Panel **A**), ultrafine pMDI with the large volume spacer (Panel **B**), salbutamol pMDI alone (Panel **C**), salbutamol pMDI with the large volume spacer (Panel **D**), and salbutamol pMDI with the Optimiser (Panel **E**). *Open circular symbols* show the 1C geometry, *filled circular symbols* show the 2C geometry, *open square symbols* depict the 3A geometry, *filled triangle symbols* depict the 4A geometry, *filled square symbols* illustrate the 5A geometry, *filled diamond symbols* present the 6B geometry, and *open diamond symbols* illustrate the 7B geometry ($n=6$).
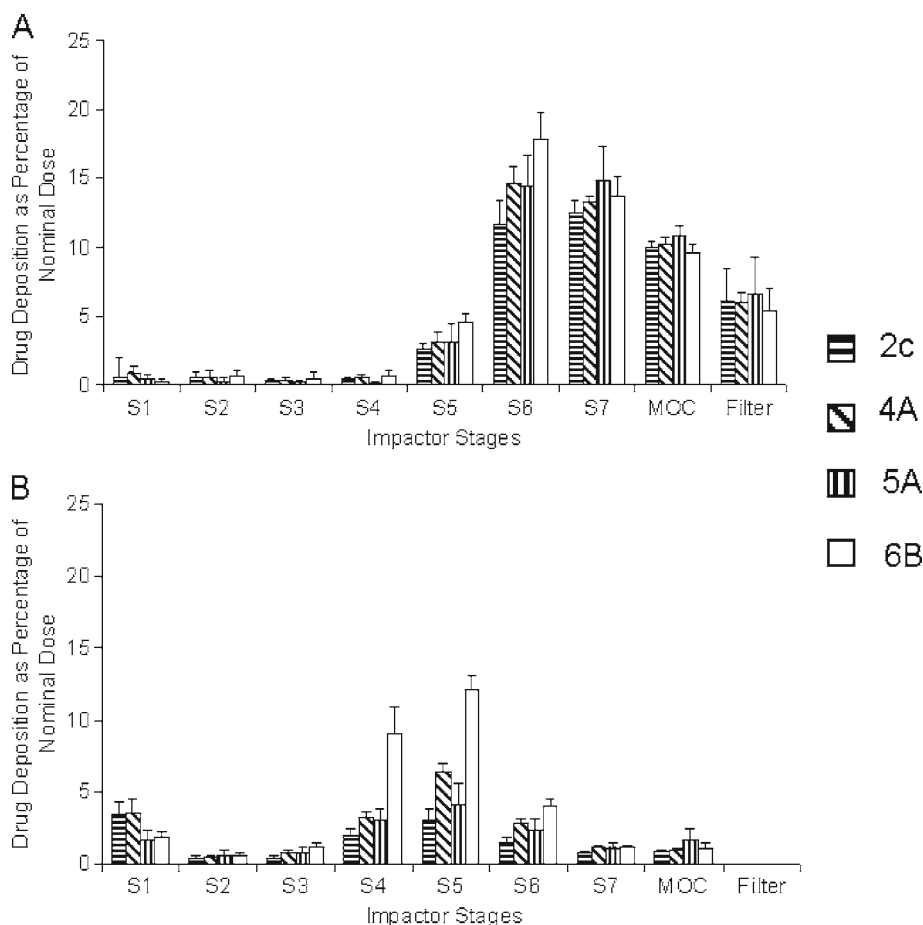
Fig. 6. Drug deposition distributions within the impactor for aerosols passed through the models via the ultrafine pMDI (panel **A**) and suspension pMDI (panel **B**) used with the large volume spacer. *Horizontally hatched bars* show the 2C model, *diagonally hatched bars* depict the 4A model, *vertically hatched bars* present the 5A model, and *white bars* show the 6B model. *Error bars* present standard deviations (*n*=6).

Increasing oropharyngeal volume reduced oropharyngeal drug deposition for the ultrafine pMDI with or without the large volume spacer, and suspension pMDI with the large volume spacer (Fig. 7B). However, oropharyngeal drug depositions via the suspension pMDI with or without the small volume spacer were dependent on the oropharyngeal volume and presence of constrictions within the airway. Drug deposition, as percentage of the nominal dose, within the large volume spacer was 14.94±1.32% for the ultrafine pMDI, and 64.79±4.35% for the suspension pMDI.

DISCUSSION

The results of this study suggest that inhaled doses of aerosol particles with aerodynamic size less than 0.83 μm from large volume spacers at a rate of 30 l/min would not be significantly affected by the oropharyngeal geometry. Also, the presence of constrictions in the oral cavity may affect evaporation rate of aerosol particles via pMDIs.

Treatment with high and repeated doses of brochodilators and corticosteroids in management of acute asthma exacerbations have been indicated in the literature (20,21). Delivering high and less variable inhaled doses of these drugs would be crucial in an effective treatment of acute asthma exacerbations. Therefore, based on the results of this study, to achieve high and less variable lung doses, development of ultrafine or nanosuspension pMDI formulations should be expanded (22,23).

The results of this study further demonstrate that although ultrafine pMDIs may produce aerosol particles with MMAD of 1 μm (14), time and space should be given for evaporation of propellant and cosolvent from the initial generated aerosol particles. Then the inhaled dose may become independent of oropharyngeal geometry. It should be noted that in this study the ambient conditions (humidity and temperature) were used for the inhaled air, whereas the results of this study may not be valid if air with a high level of humidity, which may increase the size of inhaled particles, is inhaled (24). Furthermore, as particle size may change due to hygroscopic growth in the lungs (25), then depending on the change in the particle size, despite the similarity of inhaled doses, the same regions of the lungs may not be targeted (26).

The results of this study agree well with a previous *in vitro* study showing a negative correlation between total oropharyngeal volume and aerosol deposition in the throat via a suspension pMDI (11). In addition, the current study
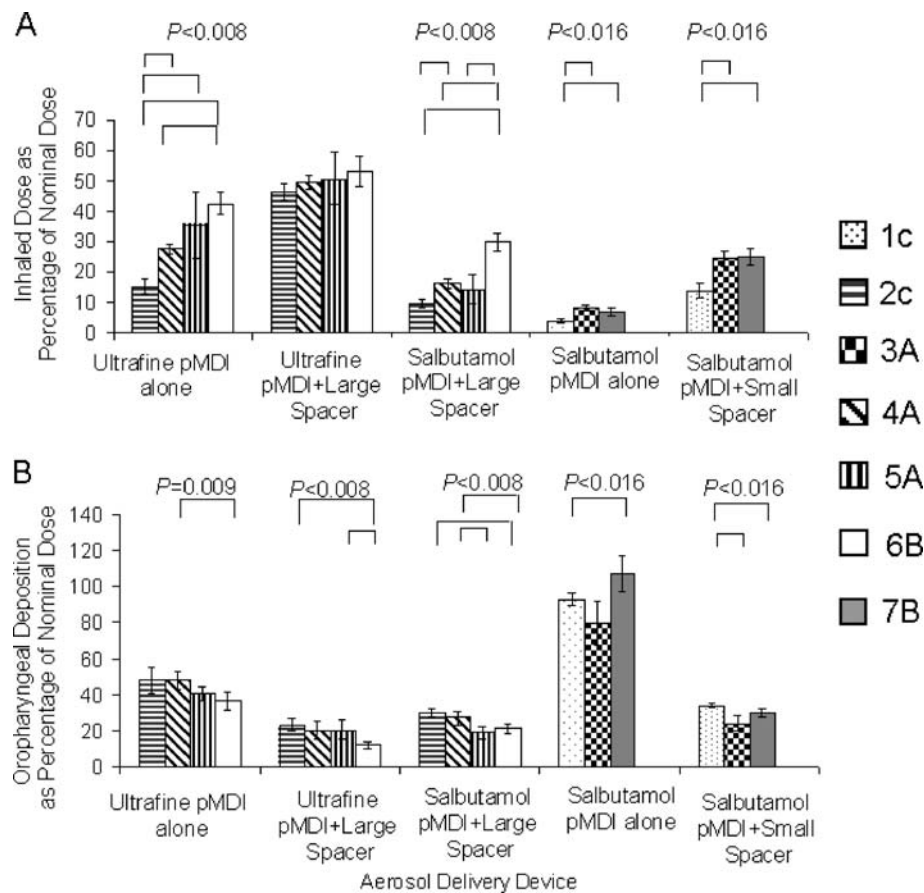
Fig. 7. Inhaled dose (panel **A**) and oropharyngeal drug deposition (panel **B**) as percentage of the nominal dose via the inhalers. *Dotted white bars* show the 1C model, *horizontally hatched bars* show the 2C model, *chequered bars* indicate the 3A model, *diagonally hatched bars* depict the 4A model, *vertically hatched bars* present the 5A model, *white bars* show the 6B model, and *grey bars* designate the 7B model. In each device category, data is presented as ascending oropharyngeal volume (from *left* to *right*). *Horizontal brackets* indicate significant differences between pairs. *Error bars* present standard deviations (*n*=6).

shows that the presence of constrictions should be considered, since smaller throats with wide openings in the airway may result in similar aerosol depositions as do larger throats but with constrictions. Furthermore, the relationship between the total oropharyngeal volume and inhaled dose or oropharyngeal drug deposition may be eliminated if ultrafine aerosols are inhaled via a large volume spacer at 30 l/min.

Despite the important role of corticosteroids in management of acute asthma exacerbations, a study has found no benefit of doubling inhaled corticosteroid amounts in the management plan (27). This observation may be partly explained by the results of this study that as the inhalers in the above study were suspension pMDIs, then the inhaled doses might have been extensively affected by the oropharyngeal geometry and posture.

The results of this study regarding variation in the oropharyngeal aerosol deposition via pMDIs may be applicable to adult subjects with stable asthma, as differences in oropharyngeal aerosol depositions between these asthmatic and healthy adult subjects have not been shown before (28). However, it should be noted that the oropharyngeal models employed in this study were based on healthy adult subjects. This may not completely represent patients with acute asthma exercitations.

As it seems impossible to determine the oropharyngeal configurations of these patients using conventional methods such as MRI, then it was anticipated that employing oropharyngeal models with different configurations would illustrate the possible range of oropharyngeal geometries that may occur in these patients. Additionally, it may be argued that elements other than suitable particle size distribution and dose of aerosols are required in an effective treatment of acute asthma exacerbations. Therefore, clinical studies will be required to establish the results of the current study.

The results of this study are also in good agreement with data from clinical studies showing large intra-subject and inter-subject variations of lung doses for aerosol particles with MMAD >2μm (29–32). In addition, the results of this study agree with the data of a clinical study showing high lung doses (approximately 58% of the ex-actuator dose) with little variability via the Qvar with a large volume spacer in children aged 5–17 years old (33). Age-dependent drug lung deposition via a suspension pMDI plus spacer has been shown before (34).

Another limitation of this study is comparing the aerosol performances of two pMDI formulations with different actuator designs. As it has been shown that the actuator design, such as the orifice size, could have effect on the plume

geometry (35), then the results of this study may not be valid if significant changes are applied to the actuators or formulations of employed pMDIs.

In conclusion, the present study suggests that delivery of aerosol particles with MMAD less than 0.83 μm to the lungs via large volume spacers at 30 l/min inhalation flow rate would not be affected significantly by the variations in the oropharyngeal geometry. The results of this study are in good agreement with clinical data. Therefore, in formulation of pMDIs, the ability of a product to generate ultrafine aerosol particles may be considered an important feature when fast speed and a precise amount of inhaled drug is necessary.

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