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Research Paper

Effect of Oropharyngeal Length in Drug Lung Delivery via Suspension Pressurized Metered Dose Inhalers

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Purpose. To determine the effect of the oropharyngeal length in adults on the lung dose of a suspension pressurized metered dose inhaler, and whether employing small volume spacers can alter this role.
Methods. Depositions of Ventolin™ Evohaler™ (100) μg in the oropharyngeal models of two healthy adult subjects with 17.1 cm (short cast) and 19.9 cm (long cast) centerline lengths via three small volume spacers [two spacers with 3 cm effective length but one with 6.5 cm^2 (L3) and the other with 24.6 cm^2 (L3W) cross sections, and the Optimiser] were studied.
Results. Without using spacers, lung dose of the long cast (19.52 ± 2.32 μg, mean ± standard deviation) was significantly larger than that for the short cast (8.08 ± 1.01 μg, $p < 0.006$). However, using the L3 spacer with the short cast made the lung dose (18.59 ± 3.33 μg) similar to that for the long cast alone. Lung doses of the short cast (20.43 ± 1.42 μg) and the long cast (30.81 ± 1.84 μg) with the L3W spacer were similar to those with the L3 spacer. However, using the Optimiser spacer increased the lung dose for the short cast (22.27 ± 6.03 μg) and significantly for the long cast (35.61 ± 2.19 μg, $p < 0.006$) compared to those for the L3 spacer. Using spacers increased drug deposition in the oropharynx part of the short cast, and this reduced the lung dose compared to that for the long cast.
Conclusion. The oropharyngeal length in adults may affect the lung dose via the pMDIs, which may not be eliminated by using small volume spacers.

KEY WORDS: oropharyngeal length; orophryngeal models, the upper airway; pressurized metered dose inhaler; small volume spacers.

INTRODUCTION

Pressurized metered dose inhalers (pMDIs) contain chlorofluorocarbons (CFCs) or hydrofluoroalkanes (HFAs) as propellant. Upon activation by a valve system, a metered volume of the drug and propellant suspension/solution is released and exposed to the atmosphere. Then, suddenly, the propellant expands and transforms the metered suspension/solution volume into aerosol particles (1,2). The aerosol particles initially travel at high speeds such as 17 m/s for a CFC formulation or 14 m/s for an HFA formulation (3). However, the aerosol particles rapidly lose their speed due to drag forces applied by the air (4). During the first 100 ms after actuation of the device, the aerosol particles can travel as far as 20 cm for an HFA formulation or 40 cm for a CFC formulation (3). The long fire length of a pMDI results in deposition of a significant amount of the aerosol particles (typically 73% of the administered dose for a suspension formulation and 29% for a solution formulation) in the mouth and throat (5,6). To improve the amount of the drug that can be delivered to the lungs, holding chambers (spacers) have been developed to be used with pMDIs. In principle, these devices increase the distance between the device and the patient's mouth. Then, when the aerosol particles reach the oropharynx, not only have they lost a significant amount of their kinetic energy, their sizes have also decreased, due to evaporation of the propellant. Therefore, their travel path can be deflected by the patient's inhalation flow (7,8), and aerosol deposition in the patient's mouth and throat decreases (9–12). This principle has been used to explain higher aerosol deposition in the upper airways (mouth and throat) of children via pMDIs compared to that for adults (13,14), and may be used to explain increased lung dose via a pMDI by increasing the height in children (15).

Similar to *in vivo* observations, it was shown that extending the vertical length of a model throat (inlet) to a cascade impactor from 7 to 28 cm decreased the mass median aerodynamic diameter (MMAD) of a CFC pMDI from 2.97 to 2.76 μm (16). Also, to correlate the determined MMAD of a pMDI by employing the TSI impactor system 3306/3320 (TSI

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Inc., Shoreview, MN, USA) with those that were determined by using the Anderson Cascade Impactor, the vertical length of the USP inlet needs to be increased by at least 20 cm (17,18). Along with pMDIs, the effect of size of the respiratory tract (19–23), or the lung disease (24), on deposition of simple aerosols or aerosols from nebulizers have been investigated. In these studies, relationships between the age of a child (19–21) or body height (22,23) and lung dimensions have been implemented. In modeling aerosol deposition in these studies, considering the size of the airways in the lungs was necessary because the mechanism of aerosol deposition depends on the geometry of the airways (19–24).

Despite considering the effect of respiratory tract length on aerosol deposition and length of the inlet of a cascade impactor on the MMAD of aerosol particles emitted from a pMDI, a better understanding of the high intersubject variation in the lung dose via pMDIs in adults is required (11,12,25,26). Although lack of coordination between device actuation and inhalation has been accounted for the observed high variation of drug lung dose via pMDIs (26), observing such a high intersubject lung dose variation (up to 9 times) via a pMDI in clinical studies in which subjects were trained well and their inhalation techniques were observed closely (11,12,25,26) remains to be investigated. Our understanding of aerosol delivery via pMDIs can be significantly improved by employing physiologically faithful oropharyngeal models. These models can now be obtained by applying a recently developed method, which allows us to determine the shape of the upper airway (mouth and throat) of a volunteer three-dimensionally while inhaling via inhaler devices (27). Applying this method showed that the intersubject variation in oropharyngeal length while inhaling via a pMDI ranged from 17.1 to 22.3 cm (27). Based on this observation, we investigated the effect of oropharyngeal length on the lung dose of a suspension pMDI by employing oropharyngeal models. This information may help us to better understand aerosol deposition in the mouth and throat via pMDIs, and improve our understanding of the observed high intersubject lung dose variation via pMDIs (11,12,25,26). To further reveal the mechanism of aerosol deposition via pMDIs in the oropharyngeal models, aerosol deposition distributions in the models were determined. We also investigated whether using small volume spacers would reduce intersubject variation of the lung dose via pMDIs.

Although aerosol deposition in the mouth and throat has been estimated from previously developed equations by Rudolf and colleagues (28), these equations are not valid for aerosol deposition via pMDIs (29). And to predict more accurately the performance of a pMDI in clinic, investigators have employed a human airway replica in which the oropharyngeal part of the model was obtained from cadaveric studies (30–32). Although this gives an improvement in our understanding of aerosol deposition in the mouth and throat via pMDIs, the upper airway (oropharyngeal) models that can be obtained from living subjects by applying a magnetic resonance imaging method (MRI) (27) are more physiologically faithful than models obtained from cadaveric studies. Consequently, a more accurate prediction of the performance of an inhaler in the clinic by employing these models is expected.

MATERIALS AND METHODS

Materials

Glycerol was obtained from BDH Laboratory Supplies (Poole, England, UK), salbutamol sulfate micronized powder was a gift from Glaxo Wellcome (Ware, UK), Brij®35 (polyoxyethylene lauryl ether) was purchased from Sigma-Aldrich (Chemie GmbH, Steinheim, Germany), Decan 90 detergent solution was obtained from Decan Laboratories Ltd (Sussex, UK), and Ventolin™ Evohaler™ HFA pMDI 100 μg per actuation (Glaxo-SmithKline Ltd, London, UK) was employed.

Methods

Manufacturing the Oropharyngeal Models

Three-dimensional reconstructions of the upper airways of two healthy adult subjects with different centerline lengths while inhaling via the Bricanyle pMDI (AstraZeneca, Kings Langley, UK), performed in a previous study (27), were considered in this study. The centerline length was defined as the length of the centerline in the upper airway, starting from the back of the upper lip to 2 cm below the vocal cords toward the lungs (27). To exclude the effect of severe constrictions in the mouth and throat on aerosol delivery to the lungs (33,34), in this study the upper airways without considerable constrictions were considered. The minimum and maximum values of the centerline length with the above condition were 17.1 and 19.9 cm (27). Figure 1A illustrates the midsagittal MRI of these subjects while inhaling via the device. The cross-sectional area profiles of these upper airways, calculated according to the previously reported method (27), in different regions are illustrated in Fig. 1B. The gap between cross-sectional area measurements in the oral cavity, larynx, and upper trachea was 5 mm in the imaging direction. In the oropharynx measurements, the right angle toward the oropharynx was divided into sections with 10° gaps, and the sections were extended to intersect with the oropharynx. The measured cross-sectional areas were perpendicular to the centerline (27).

Models of the upper airway were prepared according to the previously reported method (33). Briefly, the upper airway three-dimensional reconstructions were converted into stereolithographic (STL) format files by using computer programs developed in MATLAB 6.0 (MathWorks, Inc., Natick, MA, USA). A Dimension Machine 3D Printer (Stratasys, Eden Prairie, MN, USA) was employed to produce the upper airway models from ABS (acrylnitrile butadiene styrene) plastic by using the STL files. The models were prepared in four parts (oral cavity, oropharynx, larynx, and upper trachea), which were fastened to each other by nuts and bolts to form the complete upper airway model (33). The model of the upper airway with the longer centerline length is denoted by the long cast, and the other by the short cast.

Small Volume Spacers

Two small volume spacers were designed by an in-house computer program developed using C^{++} Builder 3 (Borland Corp., Scotts Valley, CA, USA). One of the spacers was in

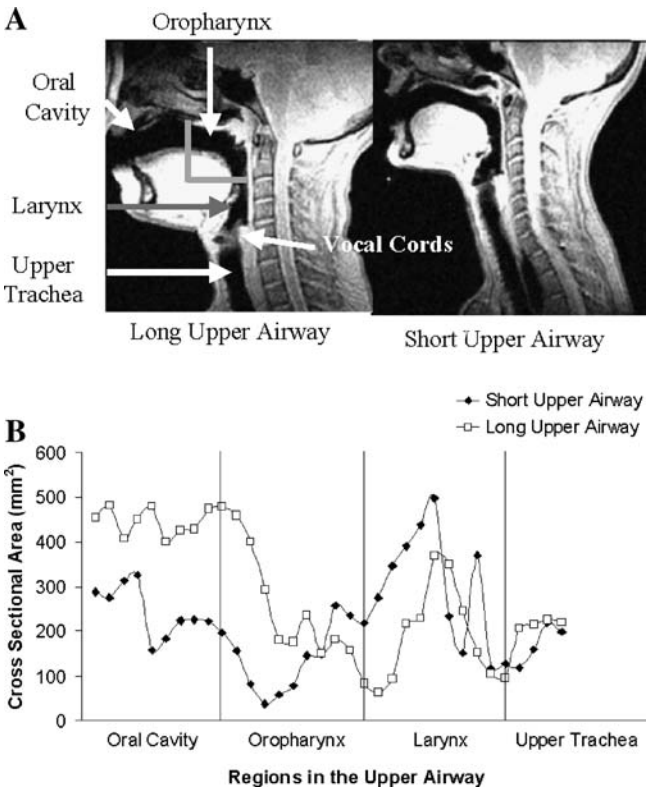

Fig. 1. (A) Midsagittal magnetic resonance images (MRI) of the upper airways of two healthy adult subjects while inhaling via the Bricanyle pMDI without significant constrictions in the upper airways, but with different upper airway centerline lengths. The upper airway centerline length of the subject with midsagittal MRI on the left was 19.9 cm (the long upper airway) and the centerline length of the other upper airway was 17.1 cm (the short upper airway). (B) Cross-sectional area profiles of the upper airways in different regions. Open squares represent the long upper airway and closed diamonds represent the short upper airway.

the form of a straight tube with total length of 5 cm, 5.07 cm^2 cross-sectional area at the spout, and 6.5 cm^2 at the inlet. The outlet cross-sectional shape of this device was similar to the spout of the pMDI that was considered in the MRI study (27). One centimeter of this device inlet was accommodating the pMDI actuator, and for the length of 1 cm from the spout of the device it was considered to locate within the lips of the oral cavity. Then the pMDI actuator, by using this spacer, had approximately 3 cm extra distance from the oral cavity of the cast compared to a situation without using a spacer. This device is denoted by L3 spacer in this paper. The other spacer had the same length, inlet, and spout cross-sectional area and shape as the L3 spacer. However, this device—for the length of 3 cm after the device inlet—had 24.6 cm^2 cross-sectional area with circular cross-sectional shape. This device is denoted by L3W spacer.

The computer-generated designs of the spacers were then converted into STL files for rapid prototyping. The small volume spacers were manufactured from ABS plastic (Fig. 2). As well as these spacers, the Optimiser spacer (Norton Healthcare Ltd, Harlow, UK, and Glaxo-SmithKline) was also considered in this study (Fig. 2). To reduce the electrostatic charge in the spacers (35,36), before the aerosol deposition study, they were soaked for 2 h in 2% solution of Decan 90 and were allowed to drip-dry.

Experimental Setup

Prior to each experiment run, each cast was filled with a solution of 0.7 g Brij® 35 in 100 mL of glycerol (33,37) to simulate the wet mucosa that naturally occurs in the upper airway. Next, the solution was emptied from the cast, and the cast was left upright to drip-dry (33,37)). Afterwards, the studied spacer was connected to the oral cavity of the cast and then the cast was connected to a filter holder (Swinnex® 25, Millipore), which typically contained 137 mg of cotton wool, to collect the aerosol particles that passed through the cast (Fig. 3). Then the filter holder was connected to a vacuum pump (Alcatel, Franklin Electric, Bluffton, IN, USA) to draw air at the rate of 30 L/min through the cast during the experiment run. The airflow rate through the cast was determined via the In-Check Dial (Clement Clarke International Ltd., Essex, UK). Prior to each aerosol deposition run, the Ventoiln™ Evohaler™ pMDI was shaken and primed. For each experiment run, the pMDI was fired 10 times into the cast/small volume spacer. The gap between each pMDI actuation was 10 s, and the device was shaken vigorously during this time (38). The airflow through the casts was maintained just before the first actuation and continued until 10 s after the last actuation.

Aerosol Deposition Measurements

At the end of each experiment run, all parts of the cast and the cotton wool (filter) were washed separately with distilled water. The amount of salbutamol sulfate in each wash was determined by spectrophotometric analysis at 276 nm from a standard curve. In a previous study, it was determined that other ingredients in each experiment run did not interfere

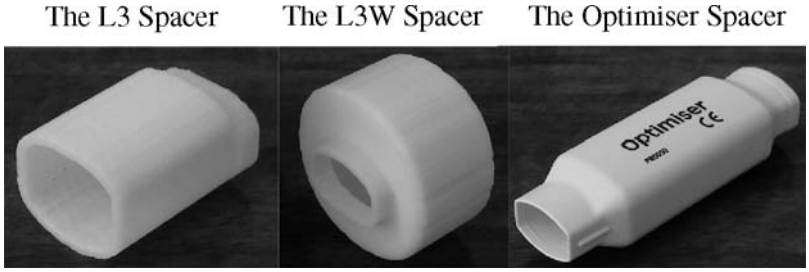

Fig. 2. Photographs of the small volume spacers that were employed in this study: the L3 spacer (left), the L3W spacer (middle), and the Optimiser spacer (right).

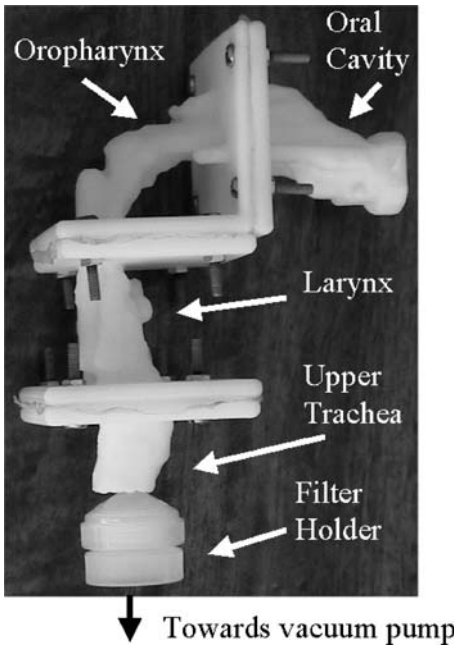

Fig. 3. A photograph of one of the oropharyngeal models that were employed in this study, representing different parts of the model.

with the drug absorbance at 276 nm (33). Each deposition study was replicated six times. About 180 actuations from each pMDI were used for the aerosol deposition study. Without using a spacer, 91% of the nominal dose for the long cast and 82% of the nominal dose for the short cast, on average, were recovered. For the purpose of this study, the recovered dose was defined as the total amount of the drug that was deposited in the cast and filter. In previous studies the particle size distribution of the Ventoiln™ Evohaler™ pMDI was determined (25,39), and it was shown that the fine particle fraction (particles with diameter of less than 3.3 μm) of this product is 27.3% (25).

Statistical Analysis

To compare the aerosol deposition measurements of salbutamol sulfate in the filter and cast, with and without using a spacer, one-way ANOVA tests were initially carried out. For all cases (except one), it was found that the assumption for equality of the variances was not valid (p value for test of homogeneity of variances was less than 0.05). Next, Kruskal-Wallis tests followed by two-tailed Mann-Whitney U tests for all cases with Bonferroni correction to the alpha level ($p = 0.05/8$ for comparisons of aerosol depositions in the filter, $p = 0.05/7$ for comparisons of aerosol depositions in the oral cavity, and $p = 0.05/5$ for comparisons of aerosol depositions in the oropharynx parts of the casts) were conducted (40,41). The values, given in Results, are mean ± standard deviation.

RESULTS

Aerosol Deposition in the Filter without using a Spacer

Drug depositions in different parts of the casts and drug depositions in the filter (lung dose) per device actuation with and without using the spacers are illustrated in Fig. 4. When a spacer was not used, drug deposition in the filter for the long cast (Fig. 4B; 19.52 ± 2.32 μg) was significantly larger than that for the short cast (Fig. 4B; 8.08 ± 1.01 μg, $p < 0.006$). To ensure that the drug depositions were not affected by the variation of delivered dose by the pMDI, percentages of the recovered dose that were deposited in different sections were also calculated and are illustrated in Fig. 5. As can be seen in Fig. 5B, without using a spacer the fraction of the recovered dose that deposited in the filter for the long cast (21.94 ± 4.54%) was significantly larger than that for the short cast (10.05 ± 2.36%, $p < 0.006$).

Effect of the L3 Spacer on Aerosol Deposition in the Filter

Using the L3 spacer with the short cast significantly increased the amount of drug deposition (18.59 ± 3.33 μg, Fig. 4B) and percentage of the recovered dose (Fig. 5B, 27.10 ± 1.32%) in the filter compared to those for the same cast without using a spacer ($p < 0.006$). This made the lung dose for the short cast with the L3 spacer to be comparable with the lung dose of the long cast without using a spacer ($p = 0.589$). Also, the percentage of the recovered dose that deposited in the filter for the short cast by using the L3 spacer was similar to that for the long cast without using a spacer ($p = 0.093$). This observation may be explained that by adding the L3 spacer with the short cast made the distance between the device and the filter to become similar to that for the long cast without using a spacer.

Adding the L3 spacer to the long cast significantly increased the amount of drug deposition (Fig. 4B, 28.87 ± 2.24 μg) and percentage of the recovered dose (Fig. 5B, 36.39 ± 2.51%) in the filter compared to those without using a spacer ($p < 0.006$). Moreover, these values were significantly larger than those for the short cast by using the L3 spacer ($p < 0.006$).

Effect of the L3W Spacer on Aerosol Deposition in the Filter

It can be seen from Fig. 4B that increasing the spacer cross-sectional area did not considerably improve the lung dose for both casts (20.43 ± 1.42 μg for the short cast and 30.81 ± 1.84 μg for the long cast) compared to those by using the L3 spacer. However, the percentage of the recovered dose deposited in the filter improved for the short cast by using the L3W spacer (Fig. 5B, 33.25 ± 1.87%) and made it comparable to that for the long cast (Fig. 5B, 38.84 ± 4.82%) by using the same spacer.

Effect of the Optimiser Spacer on Aerosol Deposition in the Filter

The amount of drug deposited in the filter (Fig. 4B) increased when the Optimiser spacer was used for both casts (22.27 ± 6.03 μg for the short cast and 35.61 ± 2.19 μg for the long cast) compared to values obtained by using the L3 spacer. The difference between the amount of drug deposited in the filter by using the Optimiser spacer and the L3 spacer reached the significance level only for the long cast ($p < 0.006$). The lack of significance difference between the lung dose by using the Optimiser spacer and the L3 spacer for the

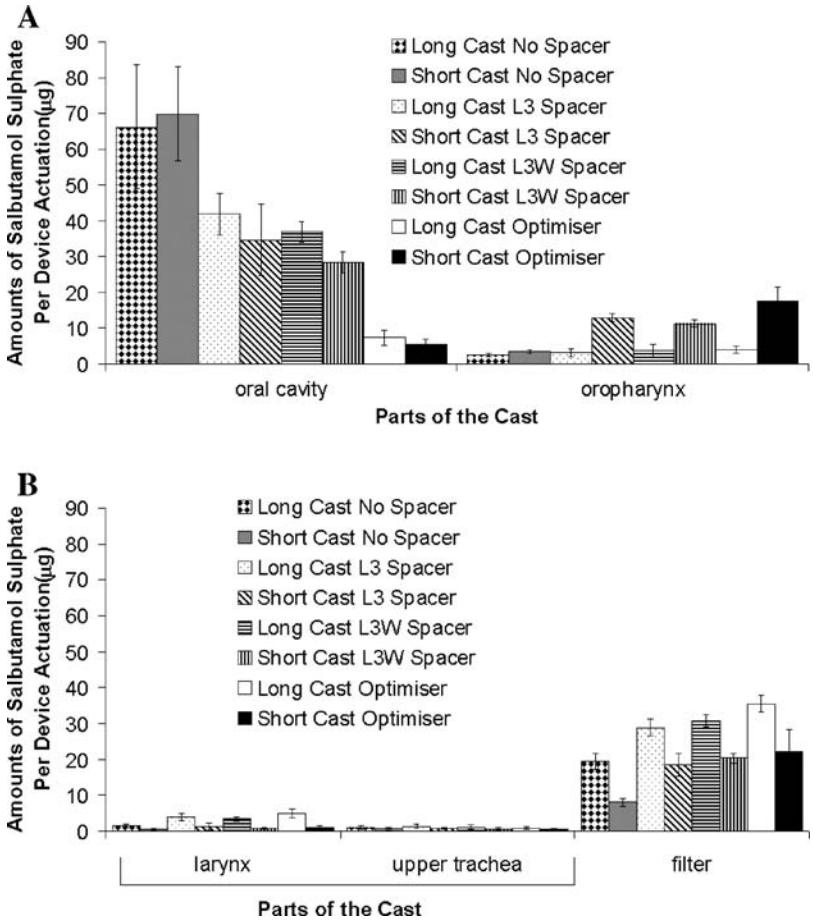

Fig. 4. Deposition of the amount of salbutamol sulphate per device actuation in different parts of the casts and filter with and without using the small volume spacers. (A) Amount of drug deposition in the oral cavity and oropharynx parts of the casts. (B) Amount of aerosol deposition in the larynx and upper trachea parts of the casts and also filter. Checkered bars indicate the long cast without using a spacer; gray bars show the short cast without using a spacer; dotted bars illustrate the long cast with the L3 spacer; diagonally hatched bars represent the short cast with the L3 spacer; horizontally hatched bars show the long cast with the L3W spacer; vertically hatched bars indicate the short cast with the L3W spacer; white bars illustrate the long cast with the Optimiser spacer; black bars represent the short cast with the Optimiser spacer. Error bars indicate standard deviation ($n = 6$).

short cast ($p = 0.699$) was attributed to the considerable deviation in the delivered dose by the pMDI from the nominal dose when the device had delivered most of its drug. However, the percentages of the recovered dose that deposited in the filter by using the Optimiser spacer (Fig. 5B) were significantly larger (46.80 ± 4.9% for the short cast and 67.53 ± 3.64% for the long cast) than those for both casts by using the L3 spacer ($p < 0.006$). The amount of drug and the percentage of recovered dose that deposited in the filter (Figs. 4B and 5B, respectively) by using the Optimiser spacer for the long cast were significantly larger than those for the short cast by using the same spacer ($p < 0.006$).

Effect of Small Volume Spacers on Aerosol Deposition in the Casts

Figure 4A shows that despite the difference in the lengths of casts, the amount of aerosol deposited in the oral cavity of both casts without using a spacer were similar (69.80 ± 13.11 μg of drug for the short cast and 66.25 ± 17.13 μg of drug for the long cast, $p = 0.589$). However, the percentage of the recovered dose deposited in the oral cavity of the short cast (Fig. 5A, 84.24 ± 2.52%) was significantly larger than that for the long cast (Fig. 5A, 71.99 ± 6.58%, $p < 0.007$).

Figures 4A and 5A illustrate that using the L3 spacer significantly decreased aerosol deposition in the oral cavity of both casts (34.77 ± 10.02 μg of drug and 49.85 ± 5.39% of the recovered dose for the short cast, and 41.94 ± 5.75 μg of drug and 52.61 ± 3.67% of the recovered dose for the long cast) compared to those without using a spacer ($p < 0.007$). Aerosol depositions in the oral cavity parts of both casts by using the L3W spacer were slightly smaller than those by using the L3 spacer (Figs. 4A and 5A) (28.45 ± 2.85 μg of drug and 46.18 ± 1.84% of the recovered dose for the short cast, and 36.96 ± 2.85 μg of drug and 50.23 ± 4.97% of the recovered dose for the long cast). However, further significant reduction of aerosol deposition in the oral cavity of both casts (Figs. 4A and 5A) was obtained by using the Optimiser

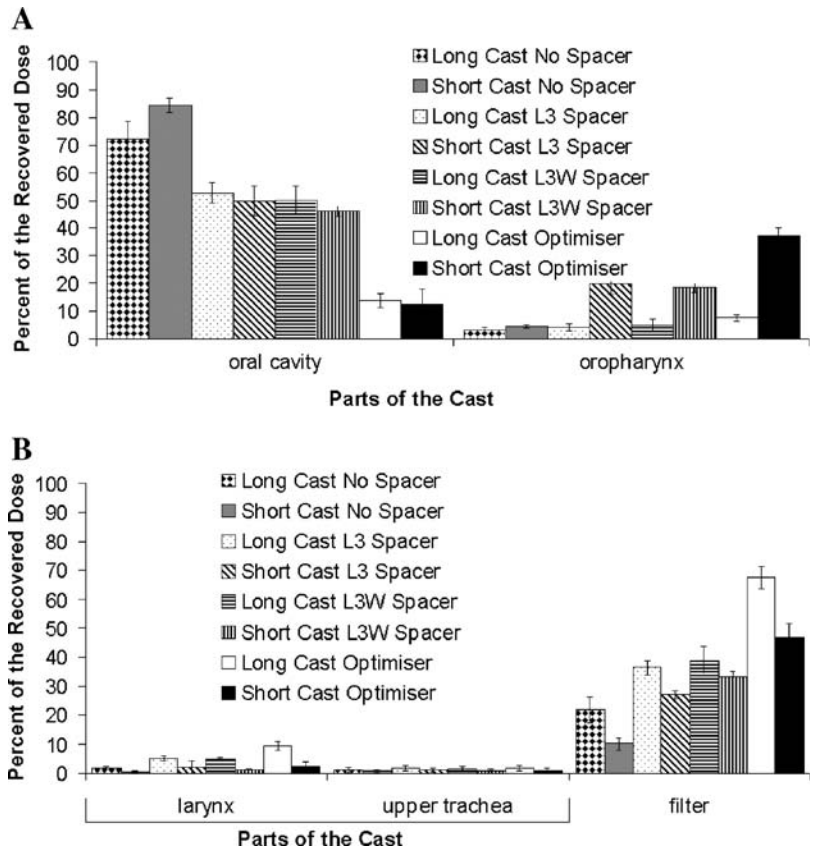

Fig. 5. Deposition of the percentages of the recovered dose in different parts of the casts and filter with and without using the small volume spacers. (A) Deposition of the percentage of the recovered dose in the oral cavity and oropharynx parts of the casts. (B) Deposition of the percentage of the recovered dose in the larynx and upper trachea parts of the casts and also filter. Checkered bars indicate the long cast without using a spacer; gray bars show the short cast without using a spacer, dotted bars illustrate the long cast with the L3 spacer; diagonally hatched bars represent the short cast with the L3 spacer; horizontally hatched bars show the long cast with the L3W spacer; vertically hatched bars indicate the short cast with the L3W spacer; white bars illustrate the long cast with the Optimiser spacer; black bars represent the short cast with the Optimiser spacer. Error bars indicate standard deviation ($n = 6$).

spacer (5.59 ± 1.39 μg of drug and 12.61 ± 5.13% of the recovered dose for the short cast, and 7.34 ± 1.97 μg of drug and 13.73 ± 2.46% of the recovered dose for the long cast) compared to those by using the L3 spacer ($p < 0.007$).

Significant differences between the aerosol depositions in the oral cavity of the short and long cast by using the L3 spacer (for the amount of drug deposition, $p = 0.180$, and for the percentage of the recovered dose, $p = 0.310$), or the Optimiser spacer (for the amount of drug deposition, $p = 0.132$, and for the percentage of the recovered dose, $p = 0.589$) were not observed.

The amount of drug (Fig. 4A) and percentage of the recovered dose (Fig. 5A) deposited in the oropharynx part of the short cast by using the L3 spacer (13.10 ± 1.13 μg and 19.61 ± 3.70%) were significantly larger than those for the long cast by using the same spacer (3.25 ± 1.05 μg and 4.08 ± 1.22%, $p < 0.01$). Similarly, deposition of the amount of drug and percentage of the recovered dose in the oropharynx part of the short cast by using the Optimiser spacer (17.56 ± 3.94 μg and 37.18 ± 3.08%) were significantly larger than those for the long cast by using the same spacer (4.02 ± 0.92 μg and 7.53 ± 1.19%, $p < 0.01$). However, without using a spacer the amount of drug and percentage of the recovered dose deposited in the oropharynx part of the short cast (3.55 ± 0.47 μg and 4.35 ± 0.53%) were similar to those by using the long cast (2.61 ± 0.56 μg and 2.99 ± 0.95%, $p = 0.15$).

Aerosol depositions in the oropharynx part of each cast were also affected by the type of the small spacer (Figs. 4A and 5A), and this was much more evident for the short cast. The amount of drug and percentage of the recovered dose deposited in the oropharynx part of the short cast by using the L3 spacer were significantly larger than those without using a spacer ($p < 0.01$). Although the amount of aerosol deposited in the oropharynx part of the short cast by using the Optimiser spacer did not become significantly larger than that by using the L3 spacer ($p = 0.026$), the significant difference was observed for the percentage of the recovered dose ($p < 0.01$).

Despite a significant increase in the cross-sectional areas of the larynx part in the short cast compared to those for the long cast (Fig. 1A), aerosol depositions in this part for the long cast with and without using a spacer were

slightly larger than those for the short cast (Figs. 4B and 5B). Aerosol depositions in the upper trachea parts of both casts with and without using a spacer were similar (Figs. 4B and 5B).

DISCUSSION

This *in vitro* study suggests that differences in the oropharyngeal length can result in significant variation in drug lung delivery via a suspension pMDI. This could be part of an explanation to the reported large intersubject variation in drug lung delivery via the suspension pMDIs (25,26). Results of this study indicate that the oral cavity is the main part of the upper airway in which aerosol deposition occurs. Therefore, rinsing the mouth after administration of a suspension pMDI would considerably decrease the drug side effects in the mouth for potent active ingredients such as corticosteroids. This finding supports the current practice in the clinic (42,43).

Results of this study suggest that, if the distances between the actuator of a suspension pMDI and the vocal cords of adult patients become similar by employing small volume spacers (which are tailored for each patient), if patients perform their inhalation technique via the pMDI correctly, and if the patients do not make substantial constrictions in their upper airways (mouth and throat) while inhaling via the device, then variation in drug lung delivery via the pMDI should decrease considerably. To determine the correct length of a small spacer for an adult patient, it is required to determine the upper airway length of that patient while the subject is inhaling via the pMDI. One approach could be employing methods such as MRI (27); however, this method would be costly. Results of this study show that using the same small volume spacer by all adult patients may sustain the variation in drug lung delivery via the pMDIs, because of differences in the distances between the device actuator and the vocal cords. However, it should be noted that there might be a small volume spacer with appropriate dimensions, which was not considered in this study, and this device could be used by all adult patients and would decrease the effect of the upper airway length on drug lung delivery via the pMDIs. However, further studies are required to investigate this possibility.

Analysis of drug deposition distributions in the oropharyngeal models indicate that increased drug deposition in the oropharynx part of the short cast, compared to that for the long cast, decreased the amount of drug that would have been delivered to the filter. This observation might be explained by the fact that a combination of small cross-sectional areas of the oropharynx part and shorter length of the oral cavity of the short cast compared to those for the long cast have increased drug deposition in this part of the short cast. Therefore, it may be speculated that using small volume spacers decreased the velocity of aerosol particles that entered the oral cavity of the casts, and thus the aerosol particles were able to follow the airstreams in this part and consequently drug deposition decreased. However, when the aerosol particles arrived in the oropharynx part of the short cast, they did not lose their kinetic energy sufficiently in comparison to that for the long cast. Therefore, higher drug deposition occurred in this part for the short cast. However, at present we can not explain the higher aerosol deposition in the oropharynx part of the short cast by using the Optimiser spacer compared to that for the L3 spacer, where the former was longer than the latter. To better reveal the drug deposition mechanism in the oropharyngeal models, further studies that employ methods such as particle imaging velocimetry (44) are required. This information would also help us to design small volume spacers, which might be used by patients, and would reduce the effect of oropharyngeal length on drug lung delivery via suspension pMDIs.

In a previous clinical investigation, which used the Ventolin™ Evohaler™ pMDI, drug lung deposition ranged from 3.3 to 29.9% of the ex-valve dose (4.0–34.6% of the total dose that deposited in the lungs and oropharynx) (25). Lung doses of the models that were employed in this study without using a spacer (10.05 ± 2.3% of the recovered dose for the short cast and 21.9 ± 4.54% for the long cast) fall within the range of the reported *in vivo* data. However, it should be noted that in the previous MRI study (27), upper airways with longer lengths than the one used for this study were observed. Due to considerable constrictions in those upper airways, those cases were not included in this study. Therefore, based on our results, it may be speculated that the higher lung depositions observed from the suspension pMDI (25) might be because of the longer upper airways than the one considered in this study and the lack of significant constrictions in them.

This study indicates that for the small volume spacers that were investigated, the length of the spacer was more effective in modifying aerosol deposition in the oropharyngeal models via the suspension pMDI than its cross-sectional area. This may be because, for these small volume spacers, the length of the device was not sufficient to allow developing the aerosol plume diagonally (1). In this study, only the volume of the L3 spacer was increased (the L3W spacer), as manufacturing a spacer with the length of the Optimiser spacer, but with a larger cross section, would have resulted in a large chamber in which the aerosol particles may not be inhaled in a single inhalation (one breath).

These results suggest that if a suspension pMDI is used with the Optimiser spacer, a significant improvement in lung delivery via the inhaler (2.75-fold for the short cast and 1.82-fold for the long cast) would be achieved. This is in good agreement with clinical data showing that relative bioavailability of sodium cromoglycate on average increased by 1.80-fold by using the Optimiser spacer with the pMDI compared to using the same pMDI alone (45).

This study indicates that, in developing pharmaceutical aerosols, more than one oropharyngeal model should be employed to accurately predict the performance of a product in the clinic. The advantage of employing a physiologically faithful model is that detailed information such as drug deposition distribution in the model can be obtained, whereas this type of information can not be obtained from clinical studies (46,47). This information may help us to better understand the aerosol deposition mechanism in the upper airway and consequently help to improve the performance of the inhaler.

It has been shown that the formulation of a pMDI has a significant effect on drug lung delivery via the device (6,14). For example, the drug lung deposition via beclome-

thasone dipropionate solution pMDI, on average, is 53% of the ex-actuator dose (6), whereas for a salbutamol suspension pMDI it is 14.5% of the ex-valve dose (25). Therefore, due to the ultrafine particle size of the solution pMDIs (47), results of this study may not be extrapolated to these formulations.

CONCLUSION

This study suggests that drug lung deposition of suspension pMDIs can be affected by the length of the upper airway. The longer upper airways would allow more aerosol particles of the pMDI to pass toward the lungs. Using small volume spacers with the shorter upper airways would reduce the effect of oropharyngeal length on drug lung delivery via the pMDIs. This study also suggests that under the same inhalation conditions (using the same small volume spacer), longer upper airways may allow significantly more drug to be delivered to the lungs than the shorter upper airways via a suspension pMDI.

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