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In vitro evaluation of nonconventional accessory devices for pressurized metered-dose inhalers

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ARTICLE INFO

Article history:

Received for publication January 9, 2014.

Received in revised form April 4, 2014.

Accepted for publication April 9, 2014.

ABSTRACT

Background: The selection of accessory devices for pressurized metered-dose inhalers (pMDIs) by health care professionals is typically cost driven without consideration of how the device modifies clinical outcomes.

Objective: To evaluate nonconventional accessory devices and the open-mouth technique with and without ideal coordination of actuation and inhalation to identify and understand the considerations for recommending potential inexpensive devices.

Methods: In vitro performance parameters of the beclomethasone dipropionate pMDI were evaluated with several devices (AeroChamber, toilet paper roll, paper towel roll, rolled paper, plastic bottle spacer, bottle-holding chamber, and nebulizer reservoir tubing).

Results: Compared with the pMDI alone, all the accessory devices evaluated have significantly lower drug exposure and throat deposition and higher respirable fractions, with the paper towel roll having the greatest effect of the devices evaluated (exposure decreased from a mean [SD] of 76.1 [4.8] μg to 49.2 [2.0] μg , throat deposition decreased from 32.0 [3.2] μg to 0.8 [0.3] μg , and respirable fraction increased from 49.8% [3.2%] to 96.4% [0.4%]). Introduction of a delay between actuation and inhalation resulted in greater variability in performance metrics for the devices evaluated, and the bottle-holding chamber and paper towel roll were most effective in mitigating the effect of the delay. The open-mouth technique was found to decrease throat deposition and respirable mass compared with the pMDI alone.

Conclusion: In addition to cost, the amount of drug that deposits in the throat and the lungs and the effect of asynchronous actuation and inhalation can vary with the selection of an accessory device, which may affect the therapeutic benefits of the pMDI selected.

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Introduction

Pressurized metered-dose inhalers (pMDIs) are a common drug delivery modality for treating asthma. The pMDI system delivers drug to the lung, decreasing systemic exposure and permitting increased portability compared with nebulizers.¹ The drug delivery efficiency of pMDIs relies on the correct use of the device. Ideally, patients should purse their lips around the actuator and inhale deeply through the mouth at a slow and steady rate while pressing down on the canister (ie, actuating the device) and then holding their breath for 10 seconds. Even with the ideal technique, a considerable proportion of drug from pMDIs deposits in the mouth and throat (50%–80%), with only 10% to 50% of the drug reaching the site of action.² Drug deposition, especially of corticosteroids, in the oropharynx can cause oral candidiasis, dysphonia, and reflex bronchospasm.³ For most pediatric patients, coordination of inhalation and actuation is problematic.^{4,5}

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Disclosures: The author disclose no conflicts of interest.

Some concerns surrounding pMDI administration can be mitigated with the use of accessory devices (also known as add-on devices), which may improve patient adherence.⁶ Accessory devices extend past the pMDI actuator and include simple tube spacers, holding chambers, and “reverse-flow” devices, in which the pMDI is actuated into a chamber, away from the patient, from which the patient then inhales.⁷ Ideally, addition of an accessory device reduces drug deposition in the mouth and throat, while maintaining or increasing drug delivery to the lungs, compared with the use of a pMDI alone (without an accessory device).⁷ Furthermore, accessory devices may minimize drug administration difficulties associated with poor coordination.² The National Institutes of Health’s Guidelines for the Diagnosis and Management of Asthma recommend the use of an accessory device for children younger than 5 years.²

The pMDI atomization process creates a dynamic aerosol plume of droplets. As represented in Figure 1, the changes in overall product performance of pMDIs with an accessory device are dependent on the plume and droplet characteristics.^{8–13} Because of the loss of aerosol particles in the accessory device, there is a marked

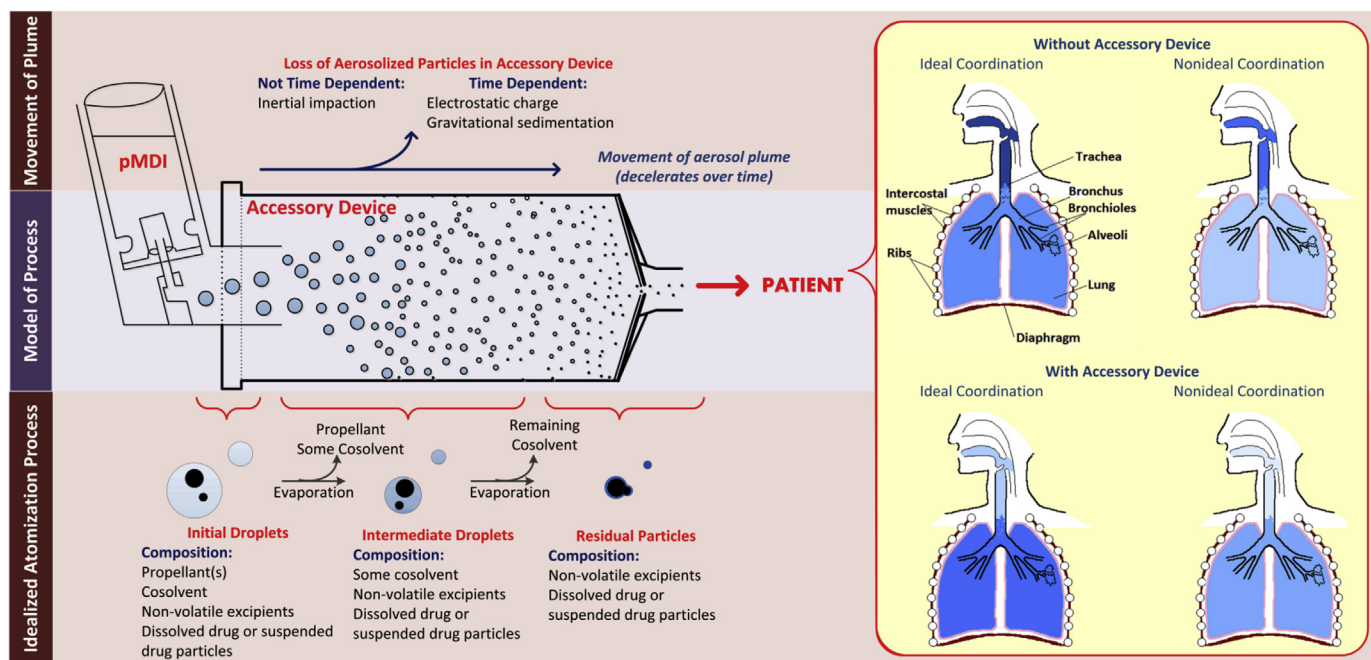


Figure 1. A model of the aerosolization process (left, top and bottom) from a pressurized metered-dose inhaler (pMDI) through a generic accessory device (left, middle) along with the general trends of relative amount of drug deposited in the lungs and oropharynx (yellow box on the right). The shading of the blue in the oropharyngeal cavity and lungs represents the relative amount of drug that deposits compared with the ideal use of pMDIs without an accessory device, where the darker shade of blue represents an increase in deposition in that region and a lighter shade of blue represents a decrease in deposition in the given region.

decrease in total drug exposure. The total drug exposure in this study is defined as the dose of the aerosolized drug theoretically delivered to the patient (ie, oropharynx and upper and lower respiratory tract). In addition, the resulting overall aerodynamic particle size distribution (APSD) of residual particles depositing in the lungs may also be smaller because of the drying process of aerosolized droplets occurring before a patient's inhalation of the aerosol.¹⁰ The changes in APSD may be clinically significant because they can affect regional deposition of the drugs in the lungs.¹⁴ With the stark decrease in throat deposition, the fraction of the total drug exposure that is respirable increases. However, aside from the change in respirable fraction, it is important to also consider the effect of the device on the absolute respirable mass because it is the amount of the drug that renders the therapeutic benefit.¹⁵

Disadvantages of using commercial accessory devices include the requirement of a prescription and additional expense, costing roughly US \$15 to US \$40 in 2013.⁷ These devices are also difficult to obtain in developing countries.^{16,17} Thus, the use of nonconventional accessory devices made out of easily accessible materials, such as a toilet paper roll or plastic drink bottle, could be cost-saving for many patients without sacrificing clinical effectiveness.^{18–24} However, *in vitro* research that determines the variability of pMDI product performance for these devices has been limited. Alternatively, the open-mouth technique, in which the pMDI is actuated 3 to 5 cm away from the open mouth, has been suggested in lieu of an accessory device.²⁵ The use of this technique is thought to decrease drug deposition in the mouth and throat and may eliminate the need for accessory devices. However, like nonconventional accessory devices, few studies have assessed pMDI product performance for this technique.

This study evaluates the *in vitro* effects on product performance using a variety of nonconventional accessory devices and the open-mouth technique with and without asynchronous coordination of actuation and inhalation of a commercial pMDI to further understand the role accessory devices play in asthma therapeutics.

Furthermore, 2 mouth-throat models (the US Pharmacopeia [USP] inlet and the Alberta Idealized Throat [AIT]) are evaluated. The AIT incorporates the curvature and change in lumen diameter associated with the human oropharynx to result in a closer representation of throat drug deposition than the compendial inlet.²⁶

Methods

Materials

Beclomethasone dipropionate (BDP) pMDIs (QVAR hydrofluoroalkane formulation, 80 µg per actuation; 3M Drug Delivery Systems, Northridge, California), actuators, and an AeroChamber Valved Holding Chamber (Forest Pharmaceuticals Inc, New York, New York) were donated by 3M. Toilet paper and paper towel rolls, SoBe LifeWater bottles (PepsiCo, Purchase, New York), and computer paper were purchased from local grocery stores. Corrugated nebulizer reservoirs were obtained from Micro Mist nebulizer tubing kits (Hudson RCI, Durham, North Carolina). High-performance liquid chromatography (HPLC)-grade acetonitrile was purchased from Spectrum Chemicals (Gardena, Georgia), and 200-proof ethanol was purchased from Decon Labs Inc (King of Prussia, Pennsylvania).

Nonconventional Accessory Devices

The nonconventional accessory devices evaluated in this study are depicted in Figure 2. The rolled paper spacer was created by rolling a letter-sized sheet of computer paper lengthwise, with approximately 9.7 cm overlap. The plastic bottle spacer was produced by cutting a hole that fit the mouthpiece of the pMDI in the base of the bottle. The bottle-holding chamber, a reverse-flow device, was crafted by cutting two 1-cm X's into the base of the bottle, which ensured that air flowed freely through the bottle. If the opening of the accessory device was larger than the diameter of the actuator, the actuator was centered within the device with the body



Figure 2. The accessory devices used in this study (not to scale). Pertinent dimensions of each accessory device are given: L, length; D, diameter; and V, volume. Note that the AeroChamber, nebulizer reservoir tubing, bottle-holding chamber, and bottle spacers are made from plastic. The roller paper, toilet paper roll, and paper towel roll are paper products. pMDI indicated pressurized metered-dose inhaler.

of the actuator flush against it, such that the mouthpiece was inserted into the accessory device as far in as possible. The AeroChamber, nebulizer reservoirs, and plastic water bottles evaluated in this study do not contain any antistatic coating and were rinsed using soapy water and air dried.

Experimental Set-up

Impactor inlet and particle size analysis

The performance of each accessory device configuration was evaluated at least in quadruplicate using a TSI model 3306 Respirable Impactor Inlet coupled to a TSI model 3321 Aerodynamic Particle Sizer, collectively referred to as the TSI system (TSI Inc, Shoreview, Minnesota), at 28.3 L/min. Photographs and diagrams of the TSI system can be found elsewhere.²⁷ The respirable impactor inlet was also coupled to 1 of 2 inlets: the USP inlet and AIT (Fig 3^{28–30}), which simulate the human oropharynx. The USP inlet is a standardized inlet used for compendial tests. The AIT was developed using computed tomography, magnetic resonance imaging, and observations of living subjects to serve as an inlet with more humanlike geometry of the oropharyngeal cavity and drug deposition patterns than the USP inlet for the purpose of in vitro–in vivo correlations.³¹ The experimental setup for this study follows the design of the study by Myrdal et al.²⁷ Of note, the respirable impactor inlet has a single-stage impactor with an aerodynamic diameter cut point of 4.7 μm , which serves as the threshold for determining respirable and nonrespirable drug mass.

The aerosol vials were sampled with and without a nominal 1-second delay in inhalation. Testing without a delay simulates ideal inhalation and actuation coordination; for these experiments, once the airflow was commenced, the pMDI was shaken and actuated once every 10 seconds for 3 actuations and then the airflow was turned off after 70 seconds. The introduction of a 1-second delay serves as a surrogate for testing the effect of the accessory device in cases where inhalation and actuation coordination is less than ideal.¹⁵ For experiments with asynchronous actuation and inhalation, the pMDI was shaken and actuated and the vacuum turned on after approximately 1 second and remained on for 10 seconds; this was repeated for all 3 actuations. After the final actuation, the

airflow was turned off after 70 seconds. For all analyses, the valve stem, actuator, inlet, stage, and filter were rinsed with known volumes of 10:90 water:acetonitrile. The amount of drug present on each component was determined by HPLC.

Open-mouth technique

For the open-mouth technique, the pMDI was held approximately 4 cm away from the opening of the USP throat with the mouthpiece centered with the opening. A shield was placed at the opening of the inlet to prevent deposition of aerosol particles on the exterior surface of the inlet. Testing and analyses were conducted in accordance with the methods used to evaluate ideal and nonideal coordination of actuation and inhalation.

HPLC Assay

Samples were analyzed using a Waters 2690 separations module coupled to a 996-photodiode array detector (Waters Corporation, Milford, Massachusetts). The data were collected and processed by Millennium, version 3.20 (Waters Corporation). The HPLC methods used were adapted from the work of Gupta and Myrdal,³² with the only difference being that the mobile phase used was 25:75 water:acetonitrile and the retention time for beclomethasone dipropionate was 4.7 minutes at 240 nm. Quantification was conducted based on a peak area using a 5-point standard curve. Standards were prepared in 10:90 water:acetonitrile and ranged from 1.05 to 50.4 $\mu\text{g/mL}$. The limit of detection and the limit of quantification of the method were determined from the standard deviation (SD) of response for known concentrations of beclomethasone dipropionate. Experimentally, the limit of detection and limit of quantification were 8.40 and 21.0 ng/mL, respectively.

Statistical Analysis

Each accessory device or technique was compared with the pMDI alone. The primary product performance metrics analyzed are total drug exposure (micrograms per actuation), throat deposition (micrograms per actuation), respirable mass (micrograms per actuation), fine particle fraction (FPF), and mass median aerodynamic diameter (MMAD). The total drug exposure is the mass of

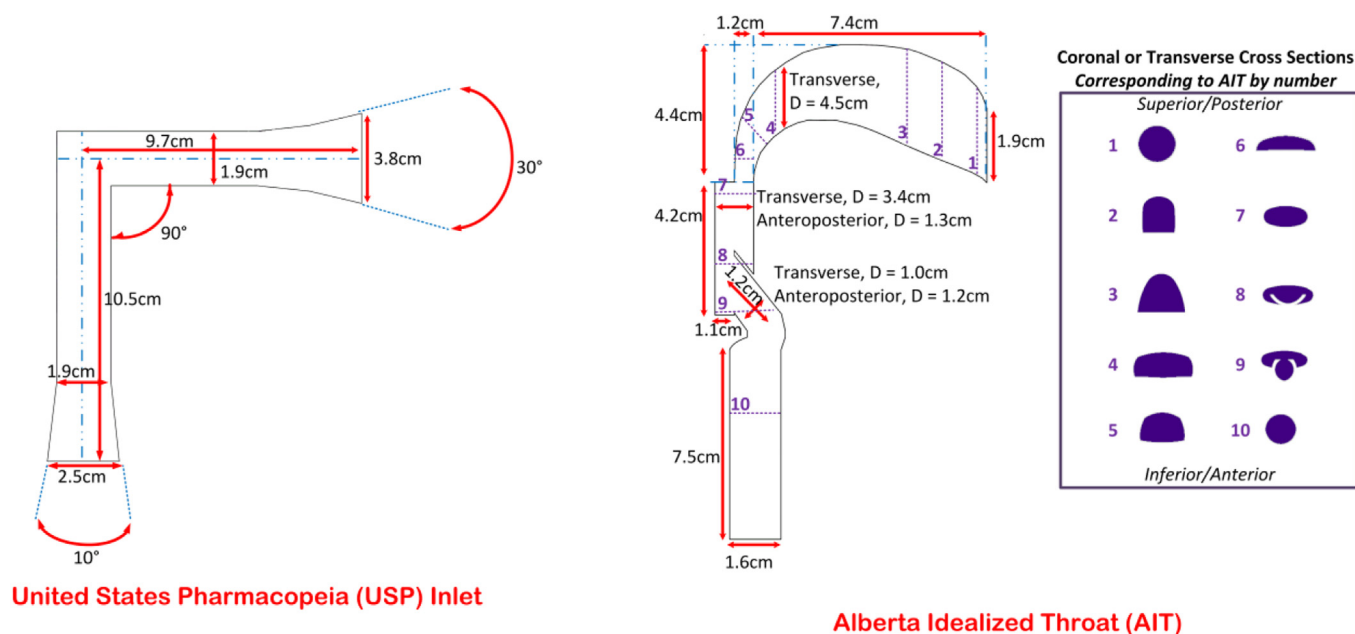


Figure 3. Schematic of the US Pharmacopeia (USP) inlet and Alberta Idealized Throat (AIT) in the sagittal plane. The USP inlet is essentially 2 cylinders (each tapered at one end) connected to each other at the nontapered ends at a right angle. The AIT, presented on the right, models the human oral cavity, pharynx, epiglottis, glottis (larynx), and trachea. It is composed of several elliptical cylinders, which can best be visualized by the cross-sections (purple dotted lines and the corresponding figures in the box on the right).^{26,28,29} Drug deposition within the entire inlet, as presented, is used to determine the throat deposition.

drug collected on throat, stage, and filter of TSI system; it is a surrogate for the total dose of medication delivered to the patient ex-actuator and ex-accessory device, if applicable. Throat deposition is the mass of drug collected on the inlet; this is the amount of drug depositing in the patient's mouth and throat regions. Respirable mass is the mass of drug collected on the filter of the TSI system; this mass of drug has aerodynamic particle sizes of $4.7 \mu\text{m}$ or less and is the amount of drug depositing in a patient's lungs. The FPF is the respirable mass relative to the total exposure of the medication from a specific pMDI and can be calculated using the following equation.

$$\text{FPF (\%)} = \frac{100 \times \text{Respirable Mass } (\mu\text{g})}{\text{Total Drug Exposure } (\mu\text{g})}$$

The MMAD is the diameter at which 50% of the aerosolized drug's mass lies below or above the stated diameter with a correction for the particles' density; it is frequently referred to as *particle size* or *APSD*. Statistical analysis was performed using Stata statistical software, version 10.0 (StataCorp, College Station, Texas). The data were analyzed using multiple independent *t* tests, assuming unequal variances or regression analysis with an a priori α threshold of 0.05.

Results

Overall Effect of Accessory Device

USP inlet in ideal conditions

The accessory device configurations were evaluated using the USP inlet, and the results are presented in Figure 4. For the pMDI alone used in this study, a mean (SD) of 99.2 (3.4) μg of beclomethasone dipropionate was recovered ex-valve and 22.6 (3.2) μg of drug deposited on the actuator. The difference between these 2 values represents the labeled claim of the pMDI. Of the amount of drug recovered, 32.0 (3.22) μg of beclomethasone dipropionate deposited on the throat, 5.0 (1.7) μg was nonrespirable, and 37.9 (3.7) μg was respirable. In the configurations with accessory device, some amount of the drug is deposited in the accessory

device and is not considered to be part of the total drug exposure. For each of the configurations tested, the addition of the accessory device significantly reduced the total theoretical patient drug exposure. The mean total drug exposure of the pMDI alone was 76.1 μg compared with 33.5 to 58.9 μg with an accessory device (44.0%–77.4% of that with pMDI alone). In addition, the use of an accessory device significantly decreased throat deposition by 25.9 to 31.7 μg (0.97%–19.1% of that with pMDI alone). The plastic bottle spacer, rolled paper, and AeroChamber did not significantly affect the respirable mass of BDP. This resulted in a near doubling of the FPF from a mean of 49.8% with pMDI alone to 83.2% to 99.1% with the use of an accessory device. These changes in in vitro performance metrics may result in improved drug deposition in the lower respiratory tract (ie, the lungs) and decreased drug deposition in the oropharynx (ie, the mouth and throat) relative to using the pMDI alone, which potentially could affect clinical response to the inhaled medication and decrease topical adverse effects in the oropharynx. The mean (SD) MMAD for pMDIs alone was 0.991 (0.109) μm , whereas that for pMDIs with the accessory devices was 0.957 (0.078) μm ($P > .05$), with a mean geometric SD of 1.7.

USP ideal in nonideal conditions

In agreement with the work by Dalby et al,¹⁰ the delay in inhalation after actuation has a significant effect on the performance of pMDIs in this study (Table 1). The most notable concern with imperfect coordination is the decrease in respirable mass of the drug, which reduces the amount of drug reaching the site of action and may require a dose increase to achieve the same therapeutic response. Accessory devices may mitigate the decrease in respirable mass (Figure 5). With imperfect coordination and the use of an accessory device, in vitro results suggest that there is a decrease in total drug exposure and an increase in FPF due to a decrease in throat deposition and a potential increase in respirable drug compared with pMDI alone with a delay. Interestingly, with the delay in inhalation, the accessory devices evaluated present a large variability in the total drug exposure (5.0–36.9 μg for nebulizer reservoir and bottle-holding chamber, respectively), which is

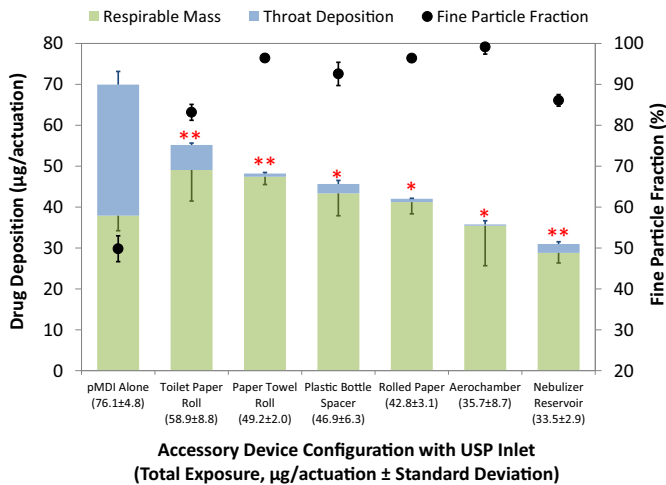


Figure 4. Drug deposition (throat deposition and respirable mass) as a function of accessory device configuration with ideal coordination between actuation and inhalation using the US Pharmacopeia (USP) inlet, corresponding fine particle fraction, and the total exposure of beclomethasone dipropionate. *For the given configuration, exposure, throat deposition, and fine particle fraction are significantly different compared with the pressurized metered-dose inhaler (pMDI) alone ($P < .01$). The respirable mass is not significantly different from that of the pMDI alone configuration ($P = .06-.51$). **For the given configuration, exposure, throat deposition, respirable mass, and fine particle fraction are significantly different compared with the pMDI alone ($P < .01$).

discernible especially when compared with configurations without delay. The only nonconventional holding chamber assessed was the bottle-holding chamber, which functions as well as the paper towel roll in mitigating the effect of imperfect actuation and inhalation coordination (Figure 5). When compared with the use of pMDIs alone with ideal coordination of actuation and inhalation, the accessory devices used in instances of imperfect coordination decrease throat deposition to 0 to 4.2 µg but also decrease respirable mass to 5.0 to 31.8 µm (0%–13% throat deposition and 13.2%–83.9% respirable mass of that achieved with pMDIs alone with ideal use).

The tube spacers evaluated in this study have different internal volumes: nebulizer reservoir, toilet paper roll, rolled paper, and paper towel roll (ranked by increasing volume). Under ideal conditions, there are no trends in respirable mass, throat deposition, or FPF as a function of accessory device volume. However, with the introduction of a delay in inhalation after actuation, there is a dependency of respirable mass on volume of the tube spacer. For each cubic centimeter increase in volume, the respirable mass increased by 0.064 µg ($R^2 = 0.91$, $P = .012$). Throat deposition and FPF were not dependent on the volume of the spacer.

The MMADs for pMDIs with a delay between inhalation and actuation ranged from 0.982 to 1.20 µm (mean [SD], 1.01 [0.11] µm), whereas that for tube spacers with delay ranged from 0.816 to 1.06 µm (mean [SD], 0.925 [0.072] µm). The MMADs from configurations with the pMDI alone were significantly greater than those with tube spacers ($P = .041$), which illustrates that spacers allow for greater evaporation of propellant and cosolvent and may

preferentially filter out larger particles. In addition, the mean MMAD for configurations with the simulated poor coordination were smaller than those with ideal coordination ($P < .001$), suggesting that the increased time between pMDI actuation and inhalation allows for greater evaporation of the excipients, resulting in a finer residual particle size. This change in residual particle size does not affect the FPF for the accessory devices evaluated because this is an “extrafine” formulation, with most of the aerosolized medication particles having an aerodynamic diameter of 4.7 µm or less³³; however, coarse formulations, including suspension formulations, may be affected by this phenomenon.

Alberta Idealized Throat

Under ideal testing conditions, the AIT exhibits greater throat deposition than that seen with the USP inlet (45.2 vs 32.0 µg, Table 2). Furthermore, there is no change in respirable mass of the drug, which results in a decrease in FPF with the AIT compared with the USP throat. With the use of accessory devices, aerosolized particles have greater time to evaporate, resulting in smaller particles being inhaled, thereby mitigating the effect of increased drug deposition in the throat with the AIT. In addition, compared with pMDI alone with the AIT, the effect of the accessory devices tested mimics that seen with the USP inlet. Of note, the respirable mass with the nebulizer reservoir was statistically less than that seen without any accessory devices (by 7.2 µg).

The comparison of the performance metrics for pMDIs with USP inlet vs AIT alone and with various accessory devices are presented in Table 2. Although the throat deposition of BDP is lower with the USP inlet compared with the AIT, this trend is not statistically significant or consistently observed with the accessory devices tested. There is no significant difference in the respirable mass with respect to accessory device, suggesting that nearly the same amount of drug deposits in the respirable region in the lung with both inlets.

Open-Mouth Technique

Compared with pMDI alone, with perfect coordination of actuation and inhalation, the open-mouth technique leads to significantly decreased exposure and increased FPF due to a relatively greater decrease in throat deposition than respirable mass of the drug (Figure 6). In addition, with asynchronous actuation and inhalation, there is a significant decrease in exposure, throat deposition, and respirable mass with the open-mouth technique compared with conventional use of the pMDI.

Discussion

Overall, the use of accessory devices with a beclomethasone dipropionate pMDI decreases the total drug exposure by starkly reducing throat deposition while generally maintaining the amount of drug that could deposit in the respirable region of the lung. These effects clinically may result in decreased risk of topical and/or systemic adverse drug effects due to decreased throat deposition while maintaining the therapeutic efficacy due to no significant change in the respirable mass. Interestingly, the use of certain accessory

Table 1
Comparison of performance metrics for beclomethasone dipropionate pMDI with ideal and nonideal coordination of actuation and inhalation^a

Variable	pMDI without delay in inhalation	pMDI with delay in inhalation	Change relative to ideal coordination, %	P value
Exposure, µg	76.1 (4.8)	46.2 (1.3)	−39.3	<.001
Throat deposition, µg	32.0 (3.2)	37.9 (1.0)	+18.4	.005
Respirable mass, µg	37.9 (3.7)	8.3 (0.4)	−78.1	<.001
FPF, %	49.8 (3.2)	18.0 (0.6)	−63.9	<.001

Abbreviations: FPF, fine particle fraction; pMDI, pressurized metered-dose inhaler.

^aData are presented as mean (SD).

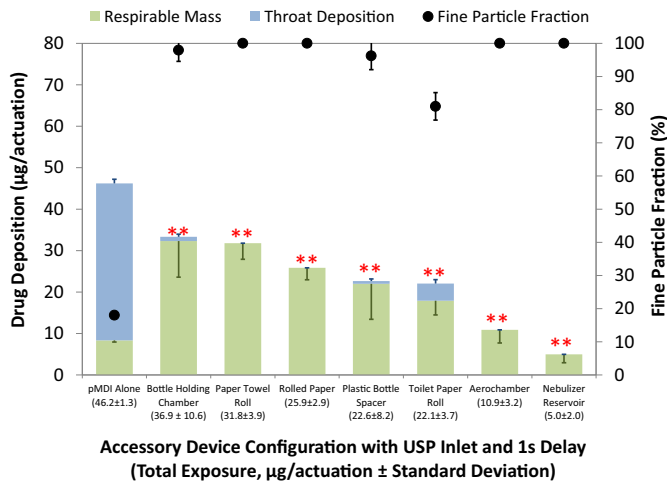


Figure 5. Drug deposition (throat deposition and respirable mass) as a function of accessory device configuration with nonideal coordination between actuation and inhalation using the US Pharmacopeia (USP) inlet (left). The corresponding fine particle fraction can be found on the right for each configuration. The total exposure of beclomethasone dipropionate for a given configuration at the bottom, in the x-axis labels. **For the given configuration, exposure, throat deposition, respirable mass, and fine particle fraction are significantly different compared with pressurized metered-dose inhaler (pMDI) alone ($P < .02$).

devices may alter the amount of drug that deposits in the respirable region of the lung (Figure 4). In cases where the respirable mass of an accessory device configuration is greater than that seen with the pMDI alone (ie, toilet paper and paper towel rolls), more drug may deposit in the respirable region of the lung with the use of the accessory device, which may be therapeutically noteworthy. However, for devices that decrease respirable mass relative to pMDI alone (ie, nebulizer reservoir), disease state control may be adversely affected and an increase in medication dose may be required based on clinical response.

In this study, the effect of the AeroChamber on aerosol behavior serves as a benchmark for the general trends expected with the use of an accessory device. Interestingly, most of the plastic accessory devices have increased variability in performance metrics compared with the paper-based accessory devices. One of the primary causes of inconsistent medication delivery from plastic accessory devices, aside from inertial impaction on the interior surface of the accessory device, is the electrostatic charge of the aerosolized medication and the interior surface of the accessory device.^{15,34} This results in a time-dependent preferential deposition

of the drug on the surface of the accessory device, which becomes especially important in cases of delayed inhalation after actuation.¹⁵ Multiple examples exist that illustrate the effect of electrostatics in decreasing drug delivery efficiency from accessory devices.^{15,34} Antistatic accessory devices, such as the AeroChamber Plus Z Stat and OptiChamber Diamond, are commercially available.

Commercial accessory devices, especially holding chambers, have been marketed to aid patients in effectively using pMDIs by removing the need to coordinate actuation and inhalation. To simulate the difficulty in coordinating inhalation and actuation, a nominal 1-second delay was introduced between actuation of the pMDI and initiating the air flow of the aerosol sampling instrument. If electrostatic interactions between aerosolized particles and the accessory device wall are not a concern, then Stokes' law becomes the governing factor in determining drug deposition on the accessory device. Thus, the longer the delay before inhalation, the more likely it is that a larger portion of the dose will deposit on the accessory device. Furthermore, the larger the interior diameter of the accessory device, the longer the particles will remain airborne and have the potential to be inhaled.¹⁵ An increase in delay to 5 seconds between pMDI actuation and the start of inhalation has been known to result in an incremental loss of drug exiting a commercial valved holding chamber, which results in a decrease in the respirable mass of the aerosolized medication.¹⁰

One criticism of the USP inlet is that it typically underestimates in vivo mouth-throat deposition.²⁶ Data from the AIT, as presented by Zhang et al,²⁶ follow in vivo deposition efficiency curves as a function of aerosolized particle density and size and inhalation flow rate, thus making it an improved in vitro predictor of in vivo drug deposition in the oropharynx. Hence, some of the accessory device configurations were evaluated using the AIT. Pressurized MDI drug deposition in the throat occurs by turbulent deposition, which increases with increase in particle size of the atomized droplets and tortuosity of the aerosol path.¹¹ Compared with the USP inlet, the AIT has a greater number of bends and changes in cross-sectional diameters, which leads to increased turbulence of air flow. The lack of obvious trends when comparing the USP to the AIT indicates that it is reasonable to conduct studies with the USP inlet with satisfactory correlation to that seen with a more anatomically accurate inlet.

Clinical studies have suggested that the use of isoprenaline, albuterol, or fenoterol with the open-mouth technique may have significantly greater response in peak flow or relative bioavailability to the lung than the conventional method of using pMDIs.^{35–37} The open-mouth technique has been recommended over the conventional pMDI inhalation technique based on potential for inhaling more dry residual particles that are finer because of the increased time it takes for particles to travel from the actuator to the patient,

Table 2
Comparison of performance metrics for various accessory devices using USP inlet vs AIT^a

Accessory device configuration and inlet evaluated	Exposure, µg	Throat deposition, µg	Respirable mass, µg	FPF, %
pMDI alone				
USP	76.1 (4.8)	32.0 (3.2)	37.9 (3.7)	49.8 (3.2)
AIT	85.4 (3.1) ^b	45.2 (3.6) ^b	37.5 (4.3)	43.8 (4.3) ^b
Plastic bottle spacer				
USP	46.9 (6.3)	2.3 (0.9)	43.3 (5.5)	92.6 (0.4)
AIT	43.9 (11.0)	1.8 (0.3)	41.4 (10.8)	94.1 (1.0) ^b
AeroChamber				
USP	35.7 (8.7)	0.3 (0.9)	35.4 (9.8)	99.1 (2.8)
AIT	37.3 (9.6)	1.5 (0.6) ^b	35.7 (9.0)	95.8 (0.9) ^b
Nebulizer reservoir				
USP	33.5 (2.9)	2.2 (0.5)	28.8 (2.4)	86.1 (0.5)
AIT	35.0 (1.9)	3.5 (0.5) ^b	30.2 (1.5)	86.3 (1.0)

Abbreviations: AIT, Alberta Idealized Throat; FPF, fine particle fraction; USP, US Pharmacopeia.

^aData are presented as mean (SD).

^bValue is statistically significant ($P < .05$) compared with its corresponding USP inlet value.

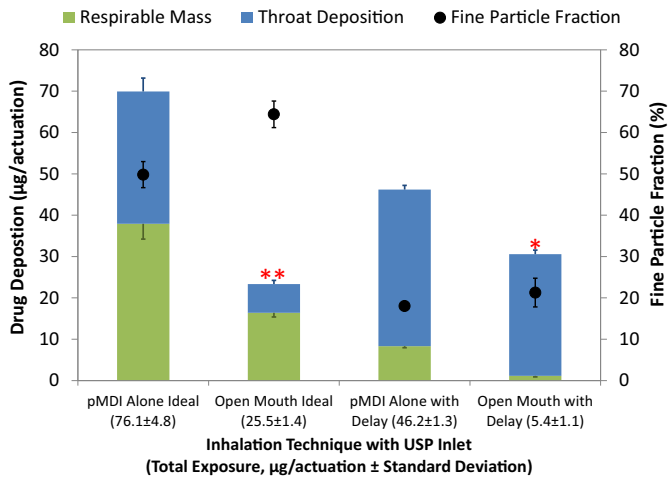


Figure 6. Drug deposition (throat deposition and respirable mass) as a function of open-mouth or conventional techniques with ideal and nonideal (ie, delay) coordination of actuation and inhalation using the US Pharmacopeia (USP) inlet (left). The corresponding fine particle fraction (FPF) can be found on the right for each configuration. The total drug exposure of beclomethasone dipropionate for a given configuration is listed along the bottom, as part of the x-axis labels. *For the given configuration exposure, throat deposition and respirable mass are significantly different compared with pMDI alone with delay ($P < .01$). The FPF is not significantly different from that of the pMDI alone configuration with delay ($P = .12$). **For the given configuration exposure, throat deposition, respirable mass, and FPF are significantly different compared with pMDI alone with ideal coordination of actuation and inhalation ($P < .01$).

resulting in decreased deposition of the drug in the throat.²⁵ Previous studies^{35–37} evaluating the effect of the open-mouth technique compared with conventional use of pMDIs were conducted with chlorofluorocarbon pMDIs, which have a more forceful plume than the current hydrofluoroalkane pMDIs.^{38,39} This may account for the differences seen between the literature and the present study. Overall, although the open-mouth technique decreases throat deposition, it also appreciably decreases respirable mass, which is further accentuated by imperfect coordination of actuation and inhalation, implicating that the technique may not be an effective method for using pMDIs. The decrease in all of the parameters can be associated with misdirection of the aerosol plume as a result of spraying into the air several centimeters away from the patient's mouth.⁴⁰

Given the results of in vitro product performance for a variety of nonconventional accessory devices with beclomethasone dipropionate, these devices should be considered for further clinical testing to be used with pMDIs, especially in developing nations where accessory devices are not readily available. It is expected that this beclomethasone dipropionate pMDI can serve as a model pMDI to represent the direction of changes in performance metrics expected with the use of accessory devices and other pMDIs.^{41,42} Furthermore, for developed nations, this study highlights that the cost of a nonconventional accessory device is one of many factors to consider when recommending an accessory device for a given pMDI. Other factors to be considered in addition to the specific pMDI selected for a particular accessory device include the amount of drug that deposits in the oropharynx and lung, the material and geometric dimensions of the accessory device, and a patient's coordination of actuation and inhalation.

Acknowledgments

We would like to thank Stephen W. Stein (3M Drug Delivery Systems, St Paul, Minnesota) for his technical assistance and providing supplies for this study.

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