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ORIGINAL RESEARCH

Comparison of tiotropium delivery with the ODAPT adapter and a valved holding chamber

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ABSTRACT

RATIONALE: Facemasks are commonly used by certain patients requiring assistance for aerosol medication delivery. Adapters are used as connectors between facemasks and inhalers. The valved holding chamber (VHC) is commonly prescribed with pressurized metered dose inhalers (pMDIs) to improve medication delivery. Recently, the VHC has been used with the Respimat Soft Mist Inhaler (SMI), which is a propellant-free inhaler. The ODAPT soft mist adapter was previously designed to serve as a connector for facemasks used with the Respimat SMI.

OBJECTIVE: The purpose of this in vitro study is to compare the Respimat medication delivery and losses using facemasks when connected separately to 1) the VHC and 2) the ODAPT adapter.

METHODS: Tiotropium was delivered via the Spiriva Respimat SMI with add-ons (either ODAPT adapter or VHC) and without add-ons under different humidity levels (40–50% and >90%) at 28.3 L/min using an 8-stage Andersen cascade impactor. The particle deposition was assessed via UV-visible spectrophotometry.

MEASUREMENTS AND MAIN RESULTS: Under ambient humidity conditions, 7.39% and 19.10% loss of fine particle fraction (FPF) were found using the ODAPT adapter and VHC, respectively. However, for higher humidity, mimicking humidity levels in the lungs, a loss of medication of 16.74% and 30.20% was found using the ODAPT adapter and VHC, respectively. Significant differences were found in medication delivery using the two different connectors, where higher medication losses were found using the VHC.

CONCLUSION: The ODAPT adapter connected to the Respimat SMI was shown to provide higher medication deposition and to minimize drug losses.

RÉSUMÉ

JUSTIFICATION: Les masques faciaux sont couramment utilisés par certains patients nécessitant une assistance pour l'administration de médicaments en aérosol. Des adaptateurs sont utilisés comme connecteurs entre les masques faciaux et les inhalateurs. La chambre de retenue valvée est couramment prescrite avec des aérosols doseurs pressurisés pour améliorer l'administration des médicaments. Récemment, la chambre de retenue valvée a été utilisée avec l'inhalateur Respimat Soft Mist, un inhalateur sans propulseur. L'adaptateur ODAPT Soft Mist a été conçu pour servir de connecteur pour les masques faciaux utilisés avec l'inhalateur Respimat Soft Mist.

OBJECTIF: Le but de cette étude in vitro était de comparer l'administration de médicaments par Respimat à l'aide de masques faciaux lorsqu'ils sont connectés séparément à 1) la chambre de retenue valvée et 2) l'adaptateur ODAPT.

MÉTHODES: Le tiotropium a été administré à l'aide de l'inhalateur Spiriva Respimat avec un accessoire (adaptateur ODAPT ou chambre de retenue valvée) et sans accessoire à différents niveaux d'humidité (40 - 50 % et > 90 %), à 28,3 L / minute, en utilisant un impacteur en cascade Andersen à huit étages. Le dépôt de particules a été évalué par spectrophotométrie UV-Visible.

MESURES ET PRINCIPAUX RÉSULTATS: Dans des conditions d'humidité ambiante, la perte de fractions de particules fines se situait à 7,39 % avec l'adaptateur ODAPT et à 19,10 % avec la chambre de retenue valvée.

CONCLUSION: Il a été démontré que l'adaptateur ODAPT connecté à l'inhalateur Respimat Soft Mist permettait un plus grand dépôt de médicament tout en en minimisant la perte.

KEYWORDS

Spiriva Respimat Soft Mist Inhaler; ODAPT soft mist adapter; valved holding chamber; particle size distribution; face-mask; humidity

Introduction

Aerosol drug therapy has been used to treat lung diseases, such as Chronic Obstructive Pulmonary Disease (COPD). Pharmaceutical aerosols are delivered by means of different types of inhalers depending on the disease and drug used; metered dose inhalers, dry powder inhalers, nebulizers, and soft mist inhalers. Pressurized metered dose inhalers (pMDIs) have been extensively prescribed in the past and remain one of the most used devices for pharmaceutical aerosol delivery.[1] These pMDIs rely on the use of a propellant to deliver the medication at high speeds (2.0–8.4 m/s, 10 cm away from the nozzle) in a short amount of time

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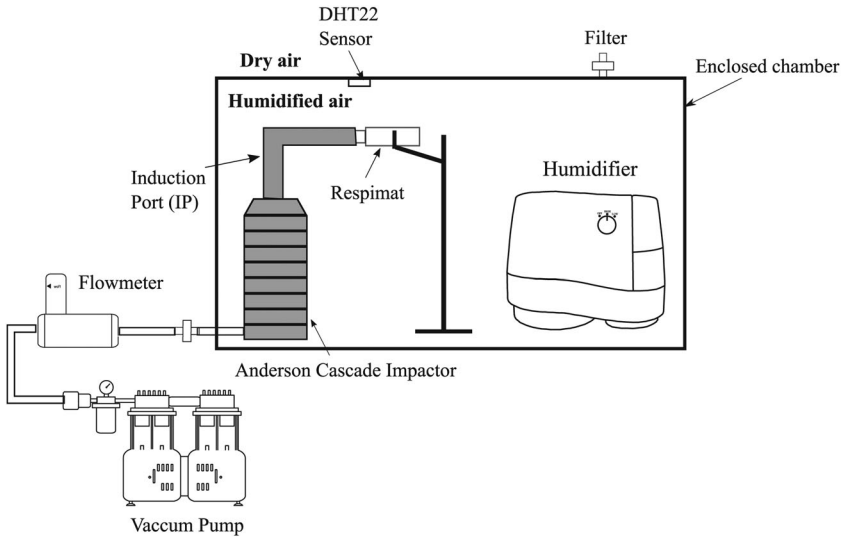

Figure 1. Setup I with no add-ons.

(0.15 to 0.36 sec).[2] As a result, due to particle inertia and turbulent dispersion, a large amount of medication deposits in the mouth-throat region and enters the gastrointestinal tract, hence engendering possible side effects[3] and affecting drug deposition in the lungs. In fact, particle size distribution and aerosol velocity are the most important factors dictating lung deposition. Therefore, a new generation of soft mist inhalers has emerged and is currently commercially available. The Respimat Soft Mist Inhaler (SMI) is a propellant-free inhaler that generates a long lasting aerosol mist (approximately 1.5 s)[4,5] at slower velocities (0.8 m/s, 10 cm away from the nozzle),[2] allowing a higher dose of medication.[5–8] The Respimat Inhaler is intended to be used daily and, therefore, is not intended to be used in intensive care or with the addition of adapters or connectors. However, for patients requiring assistance for medication delivery, such as elderly patients and children, a facemask is often used.

The valved holding chamber (VHC, AeroChamber Plus Flow-Vu, Trudell Medical International, London, ON, Canada), is commonly prescribed with pMDIs to improve medication delivery.[9,10] Using the valved holding chamber in conjunction with pMDIs facilitate the coordination of actuation and breathing.

The use of the VHC with the Respimat SMI has been recently investigated. Kushnarev et al.[11] investigated the fine particle mass, using multiple drug formulations for the Respimat (Combivent, Inspiotto, and Spiriva) using a valved holding chamber via a Next Generation Pharmaceutical Impactor. The authors concluded that the differences in medication delivery with and without the VHC are likely to be clinically insignificant. However, the effect of facemasks was not investigated in this study. Ogasawara et al.[12] investigated, in vivo, the effect of delivering tiotropium via Respimat SMI to elderly patients with and without a VHC on the forced expiratory volume in 1 second (FEV_1). The authors found that the FEV_1 increased with and without the VHC and that no significant difference was found in the FEV_1. In another study, Wachtel et al.[13] investigated, in vitro, the use of a VHC in 1 to 5 year old patients with asthmatic symptoms by analyzing the tiotropium dose delivered and particle size distribution for normal (adult) and low (pediatric) inhalation flow rates.[14] The authors reported lower amounts of medication when delivered using the VHC at lower flow rates, however, the dose delivered to the lungs in μg/Kg is adequate and corresponds to the dose delivered under normal inhalation flow rates (adult) without holding chamber or mask. The authors also reported a loss on medication using the VHC with a 79% delivered dose with VHC compared to no VHC at 30 L/min.

These previous studies show minimal effect on medication delivery using a valved holding chamber. However, large medication losses were also reported. A previous study by Mehri et al.[15] introduces and investigates a new adapter, the ODAPT soft mist adapter (McArthur Medical Sales Inc., Rockton, ON, Canada), for the Respimat SMI designed to fit commercially available facemasks. The authors show the efficacy of the ODAPT adapter when used with the Respimat SMI, reporting maximum medication losses of 16.23% and 18.84% at 28.3 L/min and 60 L/min, respectively, when using the ODAPT adapter.

In this paper, the performance of the valved holding chamber for medication delivery was assessed in vitro and compared to the performance of the ODAPT adapter, under different humidity conditions. The results were compared to the tests performed without connectors. For this purpose, the Spiriva formulation (tiotropium bromide monohydrate) was delivered via the Respimat SMI with add-ons (ODAPT adapter with facemask or VHC with facemask) and without add-ons, to investigate the medication losses under different humidity levels (40–50% and >90%) at 28.3 L/min via an Andersen Cascade Impactor (ACI) and spectrophotometry.

Material and methods

Experimental setup

For this study, Tiotropium was delivered via the Spiriva Respimat SMI with a 2.5 μg of tiotropium per actuation. In order to evaluate medication delivery that can reach the

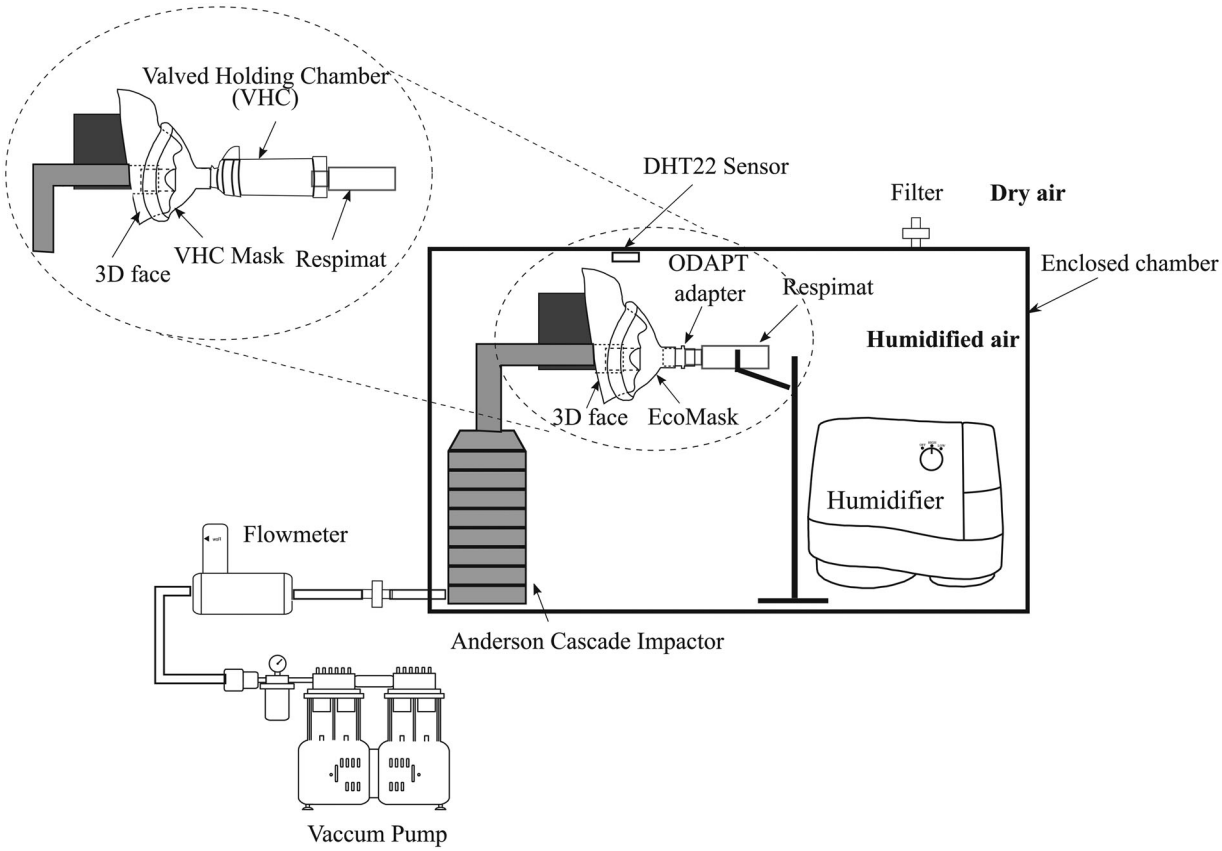

Figure 2. Setup II with add-ons: The ODAPT adapter (encircled with dotted lines) was replaced with the valved holding chamber (VHC) as shown in the larger dotted circle.

lungs, an 8-stage Anderson Cascade Impactor (ACI, stages 0 to 7, Copley Scientific Limited, Nottingham, UK), connected to a vacuum pump (Welch Dry Vacuum Pump 2585B, Welch-Ilmvac, Niles, IL, USA) was used to determine the aerodynamic particle size distribution. The flow rate within the ACI was monitored via a Brooks Mass Flowmeter (5863S Brooks Instrument, LLC, Hatfield, PA) with a 1% full-scale accuracy. The flow meter was connected to a National Instruments Data Acquisition USB-6009 device (National Instruments Corporation, Austin, TX) and the readings were recorded with LabVIEW™ software. The flow rate was monitored and maintained at 28.3 ± 0.3 L/min.

Two different experimental setups were used in this study. Using the first experimental setup (Setup I), The Spiriva Respimat SMI is directly connected to the induction port (IP) of the ACI, hence obtaining a baseline test, without additional components, as shown in Figure 1. In the second Setup (Setup II), The Spiriva Respimat SMI is connected in sequence to an ODAPT soft mist adapter (McArthur Medical Sales Inc., Rockton, ON, Canada), an EcoMask™ facemask (Intersurgical Ltd., UK), a three dimensional (3 D) printed face and tubing that is in turn connected to the IP of the ACI, as shown in Figure 2. The face used in this study was a replica of an adult subject modeled by combining multiple photographs of this subject's face to generate a 3 D mesh using Autodesk Remake and Autodesk Meshmixer and fabricated using the Dimension BST 3 D ABS printer (Stratasys, Eden Prairie, MN). In order to test and compare the efficacy of the valved holding chamber (VHC, AeroChamber Plus Flow-Vu, Trudell Medical International, London, ON, Canada) to the ODAPT adapter under similar conditions, the ODAPT adapter was replaced by the valved holding chamber and tested under the same conditions in Setup II (as shown in Figure 2).

Both setups were placed in a sealed, temperature-and-humidity-controlled environment. The temperature was maintained at 22 ± 2 °C throughout the entire experiment and the humid environment was created using a humidifier (Natural Cool Moisture™, Duracraft Massachusetts, USA). A DHT22 temperature-humidity sensor (Adafruit Industries, LLC., New York, NY) connected to an Arduino UNO Rev3 (Arduino, LLC., Somerville, MA) was used to measure the temperature and humidity of the environment. The DHT22 sensor (with a ± 2-5% accuracy in humidity and ± 0.5% accuracy in temperature) was placed directly at the mouth level of the 3 D printed face to measure the humidity of the air before entering the ACI. For each experimental setup, the experiments were performed in both normal (40–50% relative humidity (RH)) and humid (>90% RH) air to study the aerosol deposition on the ODAPT soft mist adapter and the VHC and medication delivery to the lungs.

Experimental procedure

Prior to each experiment, the Spiriva Respimat inhaler was primed by releasing 5 puffs in open air for first time use. The components were assembled as previously described and shown in Figure 2.

Table 1. Experimental conditions for the different tests performed using Setup I (Figure 1) and II (Figure 2).

Test #	Flow rate (L/min)	Humidity (%)	Add-ons	Setup
Test 1	28.3	40–50	No	I
Test 2	28.3	>90	No	I
Test 3	28.3	40–50	With ODAPT	II
Test 4	28.3	>90	With ODAPT	II
Test 5	28.3	40–50	With VHC	II
Test 6	28.3	>90	With VHC	II

VHC, valved holding chamber.

Table 1 describes the different experimental conditions for test 1 through test 6. For test case 2, 4 and 6, the humidifier was turned on for 30 minutes to allow the relative humidity to reach a steady 98–99%. The vacuum pump was then run at a flow rate of 28.3 ± 0.3 L/min for at least 15 minutes to allow the flow to settle before starting the experiment. Twenty actuations of the Respimat were used with 30 second intervals between each actuation. The vacuum pump was left running for an additional 60 seconds to allow the medication to properly deposit on the plates of the ACI.

The experimental setup was then disassembled and washed separately to quantify the amount of medication deposited within each component. All the different components were washed using distilled water to dissolve the medication. The ACI deposition plates were placed into separate Petri dishes with 15 mL of distilled water and were shaken for 1 minute each. The face, facemask, and ODAPT adapter (for test case 3 and 4) were carefully cleaned with 10 mL, 10 mL and 8 mL of distilled water, respectively. The induction port (IP) only (for test case 1 and 2) or the IP and the tubing coupler (for the test case 3, 4, 5 and 6) were washed with 15 mL of distilled water. For test case 5 and 6, the VHC was washed using 25 mL of distilled water. Each component was left in their respective solution for 2 hours to allow for a consistent dissolution of the medication. Spectrophotometry was used to obtain the concentration of each solution at 237 nm (8453 UV-Visible Spectrophotometer, Agilent Technologies, Santa Clara, CA). Further details on the spectrophotometry methodology are provided in Mehri et al.[15] Three repeats of each test were performed.

Data analysis

Based on the absorbance measurements, the mass of the drug deposited on each component of the experimental setup and the ACI were expressed as a percentage of the total mass recorded. In order to characterize the particle size distribution (PSD), the mass median aerodynamic diameter (MMAD) and the geometric standard deviation (GSD) were assessed. The MMAD and the GSD are calculated based on the particle cumulative distribution (assuming a log-normal particle size mass distribution) as follows:

$$\mathrm{MMAD} = D_{50}$$

$$\mathrm{GSD} = (D_{84}/D_{16})^{0.5} \quad (1)$$

where D_{50}, D_{84} and D_{16} represent the diameters for which 50%, 84% and 16% of the aerosol mass are contained, respectively. Each experiment was repeated three times and the results are shown as an average with the associated standard error. The aerosols deposited on the induction port were included in the determination of the MMAD and GSD with a cutoff diameter of 10 µm.

The Fine Particle Fraction (FPF), defined as the mass percentage of aerosol particle less than or equal to 5 µm, was also determined to further characterize the particle size deposition.

To ensure the reported results were statistically significant, t-tests were conducted. For each test case, a two sample t-value was calculated using the following equation:

$$t = (\bar{x} - \bar{y}) / \sqrt{\frac{S_x^2}{n} + \frac{S_y^2}{m}} \quad (2)$$

where n and m are the number of samples, $\bar{x}$ and $\bar{y}$ are the sample means, and S_x and S_y are the sample standard deviations. The hypothesis is assuming that the two samples have an equal mean. P-values less than 0.05 were considered statistically significant. Calculations were done with MATLAB R2014b software (MathWorks, Natick, MA, USA).

Results

Aerosols generated from the Spiriva Respimat SMI were tested and compared under different humidity conditions. The use of add-ons was also evaluated by comparing the medication delivery and fine particle fraction using the ODAPT adapter and the valved holding chamber in combination with a facemask.

Figure 3 shows the particle size distribution without add-ons, with the ODAPT adapter and with the VHC at 40–50% relative humidity (Figure 3a) and >90% relative humidity (Figure 3b). The results in Figure 3 are shown in terms of the medication deposition relative to the total medication measured. For both humidity levels, the highest deposition without the use of add-ons (Without Adapter/Mask) was found in the induction port (IP). Using the ODAPT adapter combined with the facemask, the highest deposition was found for the particles ranging between 0.4 and 0.7 µm at ambient humidity levels and within particles ranging between 2.1 and 4.7 µm at high humidity levels.

Figure 4 shows the cumulative mass fraction using the add-ons (ODAPT adapter) as a function of the cutoff diameter at ambient (40–50%) and high (>90%) relative humidity. It can be noted that, at ambient relative humidity, larger cumulative mass fraction is obtained for the smaller particles, which highlights larger depositions on the lower stages of the ACI and smaller deposition for the larger particles at ambient relative humidity. The same trend was found when using the VHC as shown in Figure 5.

Figure 6 shows the cumulative mass fraction using the ODAPT adapter and the VHC as a function of the cutoff diameter at ambient (40–50%) relative humidity. These results show a similar cumulative mass fraction for the particles smaller than 2.1 µm. However, differences in the cumulative mass fraction were found between the ODAPT and the VHC for larger particles. In fact, lower drug deposition levels were found on each of the ACI plates using the VHC, whereas larger deposition amounts were found on the

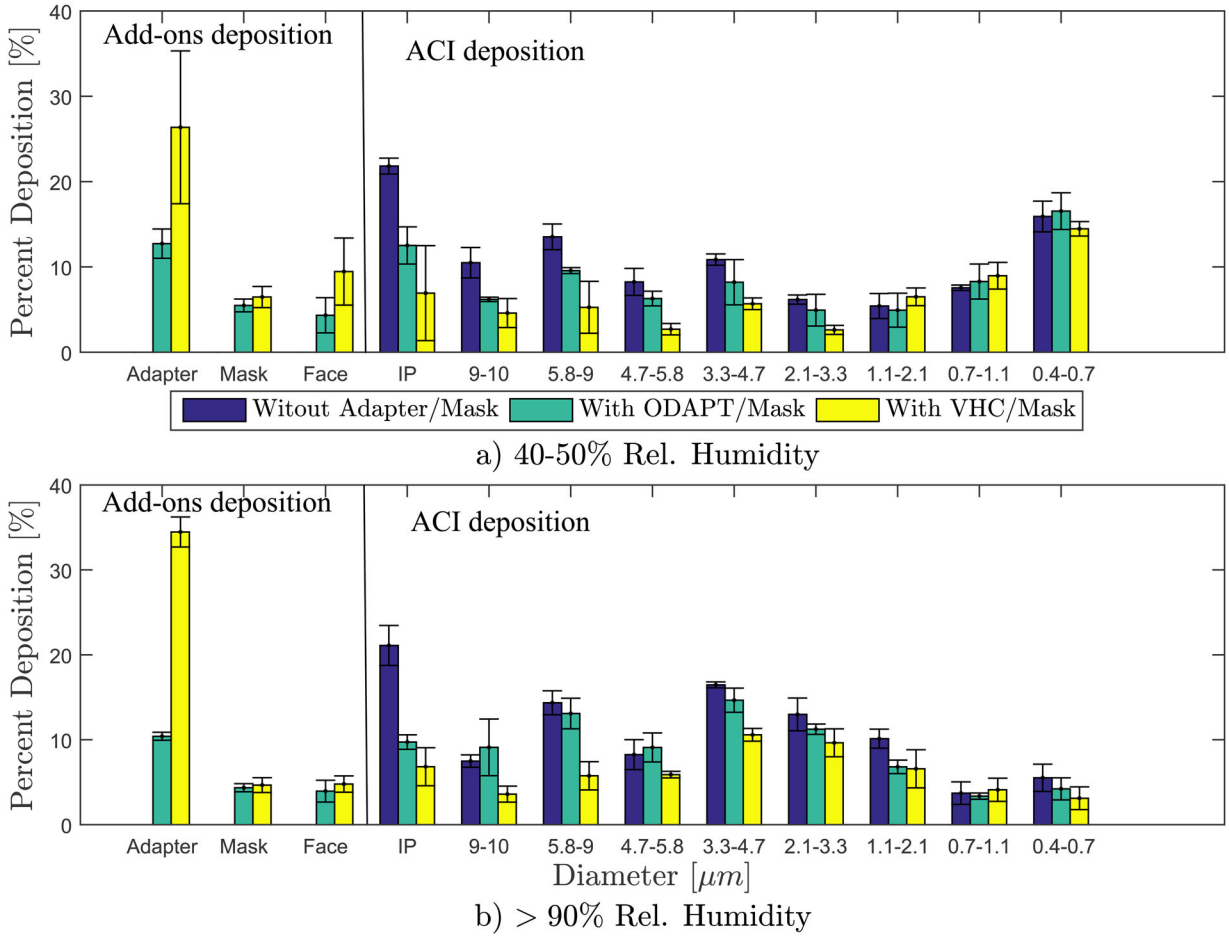

Figure 3. Comparison of drug deposition in the adapter (ODAPT or VHC), mask, face, induction port (IP) and the Andersen Cascade Impactor at 28.3 L/min at (a) 40–50% relative humidity and (b) >90% relative humidity levels. The results are shown as average values of three replicas with the associated standard deviation as the error bars. Legend of the figures refer to the results without add-ons (adapter, mask and face) as shown in Setup I, with the ODAPT adapter (Setup II) and with the valved holding chamber (VHC) as shown in Setup II.

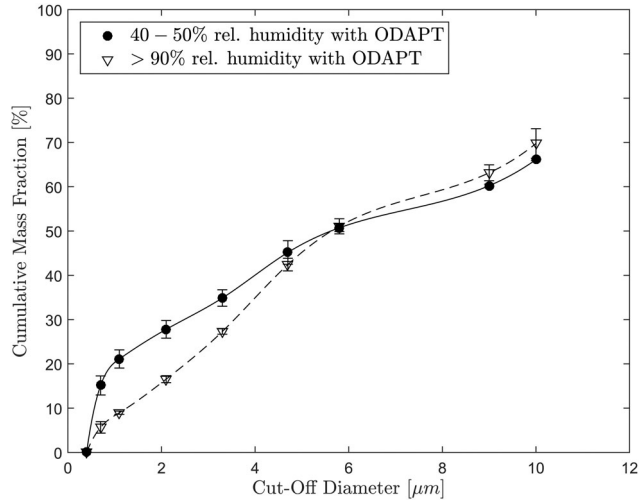

Figure 4. Cumulative mass fraction using the add-ons (ODAPT adapter) as a function of the cutoff diameter at ambient (40–50%) and high (>90%) relative humidity.

add-ons using the VHC ($P < 0.05$), as shown in Table 2. The results observed are also shown in Table 2. These results suggest higher losses of medication using the VHC. Using the ODAPT adapter with the facemask, higher drug depositions were found on each of the ACI plates, when compared to the VHC. In fact, the FPF results, shown in Table 2, show a lower medication delivery to the lungs using the VHC ($P < 0.05$).

The MMAD and GSD are provided in Table 2 for the different tests performed with and without add-ons (ODAPT adapter or VHC) at the different humidity levels. The fine particle fraction measured (particles < 5 μm) was also reported in Table 2 as well as the loss in medication (loss in FPF) when using the ODAPT or VHC (Setup II) compared to the tests performed without add-ons (Setup I). The amount of medication lost in the add-ons is also reported in Table 2. The data reported in Table 2 without add-ons and using the ODAPT adapter have been previously reported elsewhere.[15] The MMAD was found to decrease when using the VHC compared to the ODAPT adapter, for the different humidity levels tested. However, no statistical difference ($P > 0.05$) was found in the MMAD found using the ODAPT adapter and VHC. The GSD was found to decrease at higher humidity with and without add-ons. These results demonstrate a larger spread of PSD at lower humidity that was previously reported.[15] In order to assess the drug deposition using the VHC, the fine particle fraction was used, as shown in Table 2. At ambient humidity levels (40–50% RH), 44.60% ± 2.26% and 38.96% ± 1.90% of

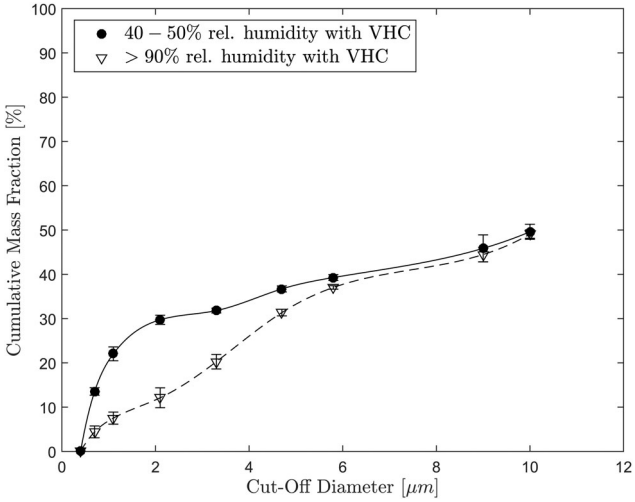

Figure 5. Cumulative mass fraction using the add-ons (valved holding chamber (VHC)) as a function of the cutoff diameter at ambient (40–50%) and high (>90%) relative humidity.

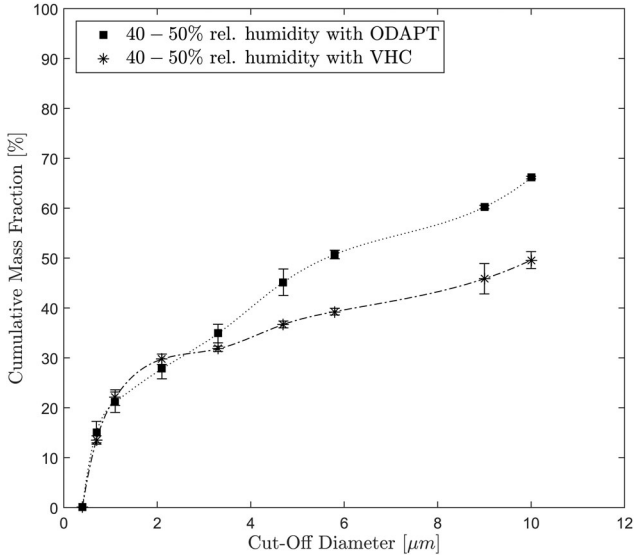

Figure 6. Cumulative mass fraction using the ODAPT adapter and the valved holding chamber (VHC) as a function of the cutoff diameter at ambient (40–50%) relative humidity.

Table 2. Mass Median Aerodynamic Diameter (MMAD), Geometric Standard Deviation (GSD), Fine Particle Fraction (FPF), percentage of FPF loss (% Loss FPF) and medication loss in the add-ons obtained using the Spiriva® Respimat® soft mist inhaler with and without add-ons for the ODAPT and valved holding chamber (VHC) at normal (40–50%) and high (>90%) relative humidity (RH) at 60 L/min.

Test #	Humidity (%)	Add-ons	MMDA (μm) ± SD	GSD (μm) ± SD	FPF (%) < 5μm	% Loss FPF	Add-ons (%)
Test 1	40–50	No	5.37 ± 0.57	9.28 ± 0.62	48.16 ± 2.70	N/A	N/A
Test 2	>90	No	4.73 ± 0.43	2.79 ± 0.22	51.05 ± 2.19	N/A	N/A
Test 3	40–50	ODAPT	3.77 ± 0.48	8.02 ± 0.70	44.60 ± 2.26	7.39	22.54 ± 1.12
Test 4	>90	ODAPT	4.66 ± 0.57	2.55 ± 0.2	42.50 ± 2.50	16.74	18.70 ± 1.48
Test 5	40–50	VHC	2.13 ± 1.17	4.82 ± 2.47	38.96 ± 1.90	19.10	42.29 ± 6.02
Test 6	>90	VHC	3.75 ± 0.44	2.75 ± 0.13	35.63 ± 3.27	30.20	43.90 ± 1.25

N/A, Not Applicable. The results are shown as an average of three replicas with the corresponding standard deviation (SD).

medication were found to be within the range of particles that can reach the lungs using the ODAPT adapter and VHC, respectively, while, at higher humidity levels, 42.50% ± 2.50% and 35.63% ± 3.27% of the total medication were measured using the ODAPT adapter and VHC, respectively. The loss of FPF, shown in Table 2, demonstrate higher medication losses when using the VHC (19.10% and 30.20% for the VHC at 40–50% RH and >90% RH, respectively and 7.39% and 16.74% for ODAPT at 40–50% RH and >90% RH, respectively).

Discussion

The performance of both adapters combined with their respective masks was compared to the direct medication delivery without adapters. Significant differences were found in medication delivery between the different adapters, where greatest medication loss was found using the valved holding chamber. A significant shift in the particle size distribution was noted when increasing the humidity level, where larger depositions were noted for larger particles (2.1–4.7 μm). It can be suggested that this shift in particle distribution is more prominent for the small particles, causing larger cumulative mass fraction for particles smaller than 1.1 μm at ambient relative humidity. This shift in particle size distribution was previously reported by Mehri et al.[15] as well as observed by Ziegler and Wachtel,[16] and Martin and Finlay.[17] In fact, the different humidity conditions engender different condensation rates, hence changing the particle sizes flowing within the ACI, shifting the measured size distribution.

The results obtained shows larger medication delivery using the ODAPT adapter under different humidity levels. It is also suggested that higher medication losses were found in the VHC adapter. Lower medication delivery to the lungs found using VHC is caused by the large volume of the valved holding chamber compared to the ODPAT adapter. The larger volume of the valved holding chamber promotes particle recirculation and deposition on the walls of the chamber. In fact, larger amounts of medication was collected in the add-ons, where 42.29% ± 6.02% (VHC) and 22.54% ± 1.12% (ODAPT) were found at ambient humidity levels and 43.90% ± 1.25% and 18.70% ± 1.48% at high humidity levels using the VHC and ODAPT adapter, respectively.

Although higher medication deliveries and lower medication losses were found using the ODAPT adapter, it is believed that each adapter is intended to be used under different conditions and for different inhalers. The ODAPT adapter showed higher performance compared to the VHC when used with the Spiriva Respimat inhaler. However, the VHC was designed to be used with pMDIs, hence eliminating the need for coordination between breathing and

inhaler's actuation. Therefore, the choice of add-on remains at the clinician's discretion.

The results presented in this study show *in vitro* medication deposition using a Cascade impactor, mimicking or modeling clinical settings. However, this *in vitro* data does not perfectly represent *in vivo* medication deposition, primarily due to differences in lung anatomy and breathing pattern when compared to the experimental setup used. Newman et al.[18] investigated lung particle deposition *in vitro* and *in vivo*. The authors found that the *in vitro* FPF (Fine Particle Fraction) was found to overestimate the *in vivo* lung deposition for the different inhalers tested, but showed similar results for particles less than 3 µm. Although the results found in this present study are expected to predict the particle behavior in the lungs, differences with the whole-lung medication deposition are expected. The results of this study could, therefore, be used to assess *in vivo* medication deposition for proper usage of the Respimat inhaler in intensive care.

Conclusion

In this study, a comparison of the Spiriva medication delivered via the Respimat SMI was performed with add-ons using two different types of adapters (the ODPAT adapter and a valved holding chamber) combined with a facemask. The results were compared to direct medication delivery without add-ons. Significant differences were found in medication delivery between the different adapters, where greatest medication loss was found using the valved holding chamber. Under humid conditions, a 19% increase in FPF and a 57% decrease in deposition to the add-ons were achieved when using the ODAPT vs. VHC for facemask application. The valved holding chamber with the Respimat SMI, would provide efficient drug delivery to the lungs, however, the ODAPT adapter was shown to provide higher medication deposition and to minimize drug losses.

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Declaration of interest statement

No conflicts of interest exist. The authors have nothing to declare.

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