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ORIGINAL RESEARCH

Respimat soft mist inhaler (SMI) in-vitro aerosol delivery with the ODAPT adapter and facemask

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ABSTRACT

INTRODUCTION: The Respimat Soft Mist Inhaler (SMI) is a propellant-free inhaler that generates a fine aerosol mist suitable for inhalation. For patients requiring facemasks for medication delivery, the presence of the facemask influences the lung deposition. The purpose of this study was to assess, in vitro, the effect of the attachment of add-ons (ODAPT soft mist adapter with facemask) to the Respimat SMI on the medication delivery under different conditions and evaluate the efficacy of the ODAPT with facemask.

METHODS: The Spiriva Respimat SMI was tested twice (with and without add-ons) at 28.3 L/min and 60 L/min in 40%–50% and >90% relative humidity environments, using an 8-stage Andersen cascade impactor, enclosed in a sealed temperature-and-humidity-controlled chamber. The particle deposition was assessed by UV-visible spectrophotometry.

RESULTS: Increasing relative humidity shifts the particle size distribution toward larger particles due to the evaporation rate difference. At higher humidity levels, 18.7% and 20.3% of the medication delivered was lost in the add-ons at 28.3 L/min and 60 L/min, respectively. However, the fine particle fraction (FPF) was found to range between about 42% and 51% for 28.3 L/min and 41% and 50% for 60 L/min. No significant difference in FPF was found at different flow rates.

CONCLUSION: Minimal impact therapeutic drug delivery was achieved when using the ODAPT adapter with facemask for the Spiriva Respimat SMI with a loss of medication deposition of 7.39% and 16.23% under normal and high relative humidity, respectively, at 28.3 L/min and 18.84% and 9.64% under normal and high relative humidity, respectively, at 60 L/min.

RÉSUMÉ

INTRODUCTION: L'inhalateur Respimat Soft Mist est un inhalateur sans agent propulseur qui libère un fin nuage d'aérosol favorable à l'inhalation. Chez les patients qui nécessitent des masques faciaux pour l'administration du médicament, la présence du masque facial influence le dépôt dans les poumons. Le but de cette étude était d'analyser, *in vitro*, l'effet de l'ajout d'accessoires, soit l'adaptateur ODAPT et le masque facial pour inhalateur Respimat, sur l'administration du médicament dans différentes conditions. L'étude visait aussi à évaluer l'efficacité de l'ODAPT avec un masque facial.

MÉTHODES: L'inhalateur Spiriva Respimat a été testé deux fois, avec et sans accessoires, à 28,3 L/min et 60 L/min, dans des milieux où l'humidité relative était de 40-50 % et > 90%, en utilisant un impacteur en cascade Andersen à huit étages inséré dans un réservoir hermétique où la température et l'humidité étaient contrôlées. Le dépôt de particules a été analysé par spectométrie UV-visible.

RÉSULTATS: En raison de la différence dans le taux d'évaporation, la taille des particules augmentait avec l'augmentation de l'humidité relative. À des niveaux d'humidité plus élevés, 18,7 % et 20,3 % de la médication administrée était perdue dans les accessoires à 28,3 L/min et 60 L/min, respectivement. Toutefois, la fraction de particules fines se situait entre 42 % et 51 % à un débit de 28,3 L/min et entre 41 % and 50% à un débit de 60 L/min. Aucune différence significative dans la fraction des particules fines n'a été observée à différents taux de débit.

CONCLUSION: L'impact minimal de l'administration thérapeutique du médicament a été atteint lorsque l'adaptateur ODAPT était utilisé avec un masque facial pour inhalateur Spiriva Respimat, soit une perte de dépôt de la médication de 7,39 % et de 16,23 % dans des conditions d'humidité normale et élevée, respectivement à 28,3 L/min, et 18,84% et 9,64 % dans des conditions d'humidité normale et élevée, respectivement, à 60 L/min.

KEYWORDS

Aerosols; chronic obstructive pulmonary disease (COPD); ODAPT soft mist adapter; particle size distribution; soft mist inhalers (SMIS); Spiriva Respimat

Introduction

Inhaled pharmaceutical aerosols are commonly used as therapeutic drugs for patients with lung diseases such as asthma and chronic obstructive pulmonary disease (COPD). The Respimat Soft Mist Inhaler (SMI; Boehringer Ingelheim, Ingelheim, Germany) is a propellant free inhaler that

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generates and deliver pharmaceutical aerosols suitable for inhalation using mechanical power from a spring at a slower velocity (0.8 m/s 10 cm away from the nozzle),[1] in comparison to the liquid–gas propellant typically used in pMDIs (pressurized metered dose inhalers), and lasts much longer (approximately 1.5 seconds),[2,3] thereby facilitating the coordination of actuation with inhalation for proper medication delivery. Furthermore, SMIs generate finer particles than pMDIs, thus allowing a higher dose of medication.[3–6] The Spiriva formulation for the Respimat SMI consists of a solution of tiotropium bromide monohydrate contained in a 4-mL cartridge. The Spiriva Respimat inhaler delivers a metered dose (10–15 µL) of the solution per puff,[3] hence delivering 2.5 µg of tiotropium per actuation (daily dose of 5 µg).

The Respimat SMI has been the focus of numerous studies in order to assess the particle size distribution delivered by the device as well as the dynamics of the aerosols generated. The fine particle fraction (FPF) with multiple medications delivered by the Respimat SMI was extensively investigated in vitro[7,8] and in vivo.[5,6,9] Ciciliani et al.[8] compared the medication deposition experimentally (collected downstream of the Alberta throat model using a next generation impactor or a filter) and numerically (obtained from four different inhalers using idealized breathing patterns from patients with moderate and severe COPD). The authors found that the Respimat SMI, using Spiriva medication, showed the lowest amount of medication depositing in the mouth–throat model and the highest amount of particles reaching the lungs, with an FPF (< 5 µm) of 44.7% and a modeled dose to the lung of 59% and 67% for moderate and severe COPD breathing patterns, respectively.[8]

Newman et al.[5] conducted two randomized studies using the Respimat SMI in vivo using two different medications (fenoterol and flunisolide). The whole lung deposition, which was measured using gamma scintigraphy, was found to be 39.2% and 44.6% with fenoterol and flunisolide, respectively. Brand et al.[6] explored the effect of inhaler technique on lung deposition using the Respimat SMI and a pMDI. For this purpose, 13 male and female subjects with COPD and poor pMDI technique were administered radiolabeled Berodual (fenoterol hydrobromide 50 µg/ipratropium bromide 20 µg) using the Respimat SMI or hydrofluoroalkane (HFA)-MDI, before and after training. The study revealed that proper inhaler technique improved lung deposition for the Respimat SMI, with 37% and 53% medication depositing in the lungs for untrained and trained subjects, respectively. However, the authors found no statistical difference in lung deposition using pMDIs before and after training (21% for untrained and trained subjects).

The Respimat inhaler is intended to be used without add-ons. In order to properly use the Respimat inhaler, the patient is required to place their mouth on the mouthpiece, creating a seal around the mouthpiece without closing the side vents of the inhaler. The inhaler should be actuated while the patient is taking a slow deep breath (recommended inspiratory flow rate of about 30 L/min[5,6]) with a 10 second hold of breath after inhalation. Proper inhaler technique is crucial for efficient medication delivery to the lungs. However, Brand et al.[6] showed that misuse of the inhaler and poor technique resulted in a reduction in particle deposition in the lungs, which is common among elderly patients and children. Moreover dementia patients are not capable of using inhalers to deliver the dose of medication. Therefore, for these patients, facemasks are required. Since the Respimat inhaler is not intended to be used with a facemask, or in intensive care, soft mist adapters are necessary. However, the effect of the addition of a facemask and adapters on drug delivery using the Respimat SMI is not known. Furthermore, higher average and peak inspiratory flow rates were found with patients misusing the inhaler and were shown to affect lung deposition.[6] Therefore, it is important to determine the effect of the inhalation flow rate on drug deposition using the add-ons.

Figure 1. Illustration of the ODAPT soft mist adapter and EcoMask facemask.

The ODAPT soft mist adapter (McArthur Medical Sales Inc., Rockton, ON) was designed to deliver inhaled medication via Respimat SMIs to patients requiring a facemask or tracheostomy application. ODAPT allows for the use of standard masks such as the EcoMask facemask (Intersurgical Ltd., Wokingham, Berkshire, UK). Figure 1 shows the ODAPT soft mist adapter and the EcoMask facemask used in this study.

In this paper, the effect of the presence of the ODAPT soft mist adapter with facemask on medication delivery was assessed. For this purpose, the Spiriva Respimat inhaler was tested, in vitro, initially without add-ons (ODAPT soft mist adapter with facemask) to investigate the particle size distribution and medication losses under different humidity levels (40%–50% and >90%) and different steady inhalation flow rates (28.3 and 60 L/min) using an Andersen Cascade Impactor and a UV-visible spectrophotometer. Additional comparison tests were conducted as well (under same humidity and inhalation flow rate conditions) with the Spiriva Respimat inhaler attached to the add-ons (facemask and the ODAPT soft mist adapter).

Material and methods

Experimental setup

For this study, experiments were performed varying humidity levels and flow rates in order to assess deposition of

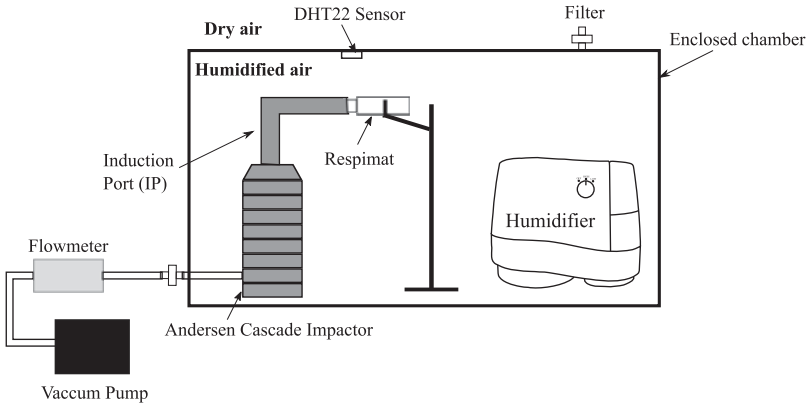

Figure 2. Experimental setup without add-ons (setup I).

tiotropium bromide monohydrate within the add-ons (ODAPT adapter, facemask and the 3 D printed faces) and evaluate medication delivery under different conditions. For this purpose, an 8-stage Andersen Cascade Impactor (ACI, 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, USA) with a 1% full-scale accuracy. The flowmeter was controlled via LabVIEW (National Instruments, Austin, TX, USA) using a National Instruments Data Acquisition system (USB-6009, National Instruments Corporation, Austin, TX, USA). A Vital Signs RespirGard II 303 bacterial/viral filter (Vital Signs, Inc., Englewood, CO) was placed between the ACI and the flowmeter in order to collect particles prior to entering the flowmeter. In order to mimic different inspiration levels, the flow rate was varied for the different experiments and maintained at 28.3 ± 0.35 L/min and 60 ± 0.35 L/min to mimic normal and high inhalation flow rates.

Two different experimental setups were used in this study. Using the first experimental setup (Setup I), as shown in Figure 2, a baseline test can be obtained by connecting the Spiriva Respimat SMI directly to the induction port (IP) of the ACI. In the second setup (Setup II), shown in Figure 3, the Spiriva Respimat SMI was connected in-line to the ODAPT soft mist adapter, a facemask, a three dimensional (3D) printed face and a tubing coupler directly connected to the IP of the ACI. The face used in this study was an anatomically correct replica of an adult subject modeled by combining multiple photographs of this subject's face to generate a 3D mesh using Autodesk Remake and Autodesk Meshmixer and fabricated using the dimension BST 3D ABS printer (Stratasys, Eden Prairie, MN, USA). To ensure no medication loss in the surroundings and proper apparatus alignment, the in-line connections were carefully sealed and a block of high density foam was mounted between the face and the IP.

Both setups are enclosed in a sealed temperature-and-humidity-controlled chamber. Relative humidity (RH) and temperature in the chamber were measured via a DHT22 sensor (with a ± 2%–5% accuracy in humidity and ± 0.5% accuracy in temperature) controlled by an Arduino software (Arduino, USA). The DHT22 sensor was placed directly above the IP of the ACI, hence measuring the relative humidity and temperature of the particles entering the ACI. Through the experiment, the temperature was maintained at 22 ± 0.2 °C. The humid environment in the enclosing was created using two humidifiers (Natural Cool Moisture, Duracraft, Southborough, MA, USA and Crane Ultrasonic Cool Mist Humidifier, Chemotec by Crane Canada, Montreal, QC, Canada). For this study, the aerosol particle size distribution in the ACI was investigated under two relative humidity levels. For the experiments at ambient levels, the relative humidity was maintained between 40% and 50%, while for the experiments at high humidity levels, the relative humidity was increased and maintained above 90%.

Experimental procedure

The Spiriva Respimat SMI was actuated five times before each first usage to prime the device prior to connecting it to the experimental setup. Prior to each experiment, the different components were connected in-line as previously described and shown in Figures 2 and 3. Table 1 describes the different experimental conditions for test 1 through test 8. Tests 1 through 4 represents the tests performed at a flow rates of 28.3 L/min, while test 5 through 8 represent the tests performed at 60 L/min, The add-ons (ODAPT adapter, facemask and 3D printed face) are used for tests 2 and 6 at ambient humidity levels (40%–50% RH) and for tests 4 and 8 at high humidity levels (>90% RH) using setup II as shown in Figure 3.

In order to ensure constant and controlled humidity levels, the humidifier is turned on and allowed to run for 15 minutes within the enclosed chamber prior to the experiment. Once the humidity remains within the desired range, the vacuum pump was activated and allowed to run for 10 minutes to allow the flow rate (28.3 ± 0.3 L/min and 60 ± 0.2 L/min) and humidity level (40%–50% RH or >90% RH) to stabilize. The medication was delivered via the Respimat using 20 actuations with a 30 second interval between each actuation. The pump was left running for an additional 60 seconds after the last actuation to allow proper

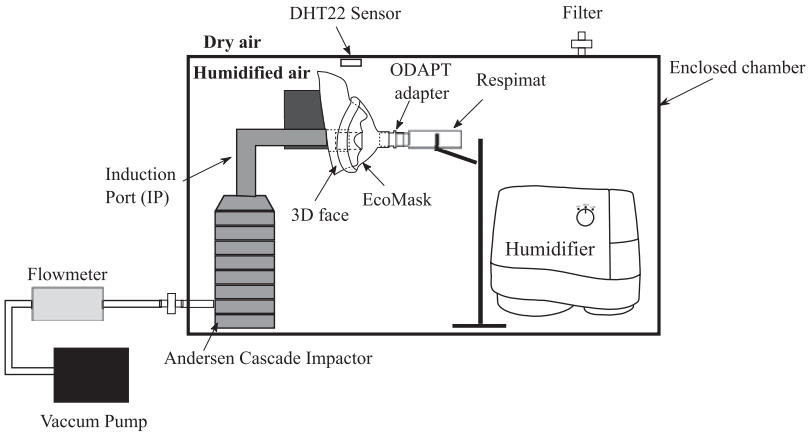

Figure 3. Experimental setup with add-ons (setup II).

Table 1. Experimental conditions for the different tests performed suing setup I (Figure 2) and II (Figure 3).

Test #	Flow Rate (L/min)	Humidity (%)	Add-ons	Setup
Test 1	28.3	40–50	No	I
Test 2	28.3	40–50	Yes	II
Test 3	28.3	>90	No	I
Test 4	28.3	>90	Yes	II
Test 5	60	40–50	No	I
Test 6	60	40–50	Yes	II
Test 7	60	>90	No	I
Test 8	60	>90	Yes	II

medication deposition in the components and cascade impactor plates.

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 plates were placed in petri dishes with 15 mL of distilled water for an hour, allowing the medication to properly dissolve. With Setup II (Figure 3), the ODAPT adapter, the facemask and the 3D face were washed with 8 mL, 10 mL and 10 mL of distilled water, respectively, while the tubing coupler and the IP were washed with 15 mL. With Setup I (Figure 2), only the IP was washed using 15 mL of distilled water. The concentration of each solution was determined using spectrophotometry. Three repeats of each test (Table 1) were performed. The medication deposited on the SMI was not considered in this study. In order to avoid altering the performance of the SMI, frequent cleaning of the mouthpiece was performed: the mouthpiece was thoroughly rinsed with distilled water and was allowed to air dry before each use.

Spectrophotometry

The absorbance of each solution was measured using a UV-visible spectrophotometer (Agilent Technologies, Santa Clara, CA, USA) with a wide range of wavelengths varying from 190 nm to 1100 nm.

A full spectrum scan was performed to determine the absorption wavelength of the Spiriva medication (tiotropium bromide monohydrate). It was found that the tiotropium bromide monohydrate has an absorption wavelength of 237 nm. A calibration curve is required in order to relate the solution concentration to the absorbance measurements. The calibration curve was obtained by measuring the absorbance of different solutions with known concentrations. The solutions were diluted from a stock solution prepared with pure tiotropium bromide monohydrate (Sigma Aldrich Canada, Oakville, Canada) with a concentration of 0.54 mg/mL. Using a linear regression to fit the absorbance data, the relationship between the absorption and the solution concentration was found. Therefore, the mass deposition in each component can be calculated.

The cuvettes used for the absorbance measurements were thoroughly washed with distilled water prior to the measurements and primed three times with the solution to be measured. An average of 3 readings was used for the absorbance measurements for the ACI plates and the IP, whereas an average of 2 readings was used for the absorbance measurements for the ODAPT adapter, 3D printed faces and the facemask.

Data analysis

The mass of drug deposited on each of the components and the ACI plates (based on the absorbance measurements) was expressed in terms of percentage of the total mass measured experimentally. Therefore, the particle size distribution (PSD) was determined based on the drug deposition in the ACI plates. In order to assess the PSD and ensure a significant fraction of the particles generated fell within the inhalable range, the mass median aerodynamic diameter (MMAD) and the geometric standard deviation (GSD) were used. 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 is repeated three times and the results are shown as an average with the associated

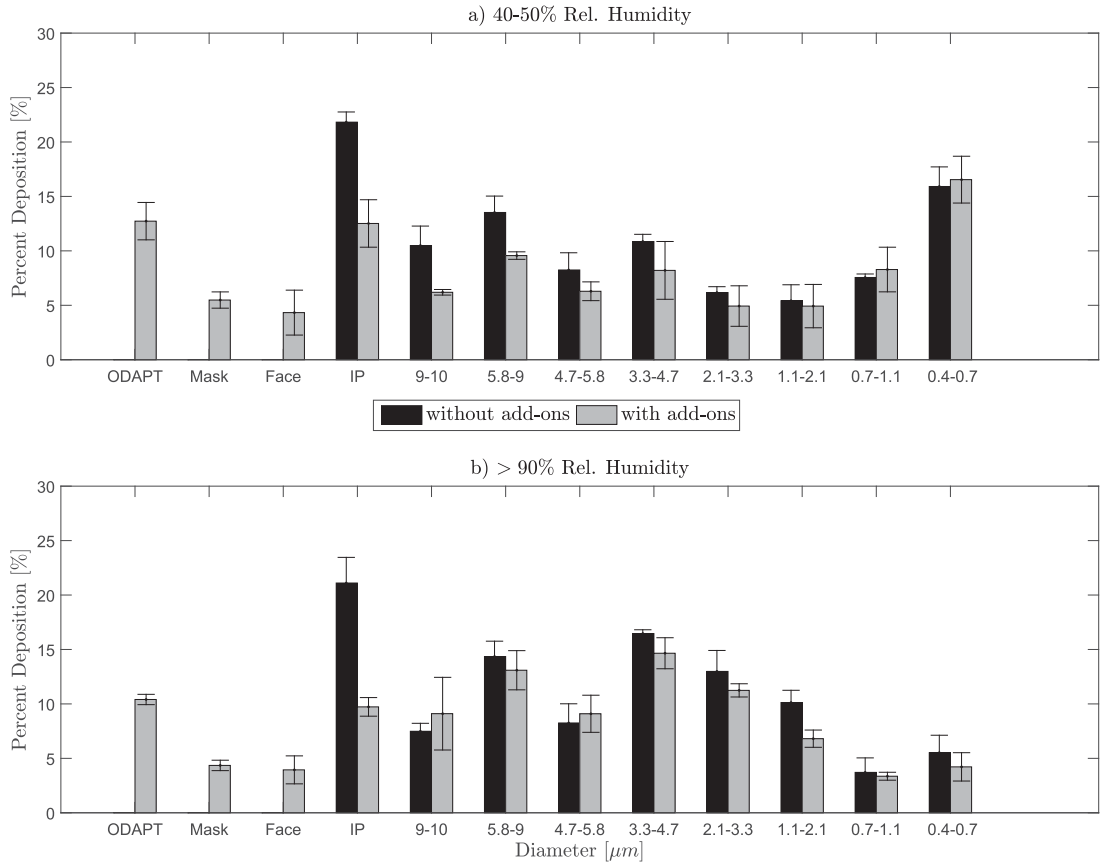

Figure 4. Drug deposition in the ODAPT adapter, mask, face, induction port (IP) and the Andersen Cascade Impactor at 28.3 L/min at (a) 40%–50% relative humidity and (b) >90% relative humidity levels. The results are shown as average values of three replicas with the associated standard deviation as the error bars. Legend of the figure refers to the results without add-ons and with add-ons.

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.

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:

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

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 of <0.05 were considered statistically significant. Calculations were done with MATLAB R2014b software (MathWorks, Natick, MA, USA).

Results

To assess the effect of the ODAPT add-ons on medication delivery, the particle deposition on the different components of Setup I and II was analyzed with and without the add-ons. Figure 4 shows the tiotropium bromide monohydrate deposition (expressed as a percentage of the total drug deposited) on the ODAPT adapter, the facemask, the 3D printed face and the stages of the cascade impactor at an inspirational flow rate of 28.3 L/min at 40%–50% relative humidity (Figure 4a) and >90% relative humidity (Figure 4b). Figure 4 also shows a comparison of drug deposition with (grey bars) and without (black bars) the add-ons. The deposition values are shown as average values of three consecutive tests with the error bars demonstrating the standard deviation associated with the measurements. It can be observed that at ambient relative humidity levels (40%–50% RH) that highest depositions were found within the IP (Induction Port) and the last stage of the ACI (0.4–0.7 µm), while less deposition was found for the larger particle. However, increasing the relative humidity (>90% RH) caused a shift in the PSD where the highest particle deposition was found for particles between 3.3 and 4.7 µm. It is also important to note that lower deposition is found in the ACI stages when using the add-ons.

Figure 5 compares the tiotropium bromide monohydrate deposition within the different components of the experimental setup with and without add-ons at an inspirational flow rate of 60 L/min at 40%–50% relative humidity (Figure 5a) and >90% relative humidity (Figure 5b). The results are shown as average values of three replicas with the associated standard deviation as shown as the error bars. A similar trend to the results at 28.3 L/min (Figure 4) was found for the PSD at a higher inspiratory flow rate. The highest deposition was found on the last stage of the ACI (0.25–0.54 µm). However, at higher humidity a shift in the PSD is noted and highest depositions were found for larger particles (4.4–6.5 µm). In fact this shift is also noted when looking at Figures 6 and 7, which represent the cumulative

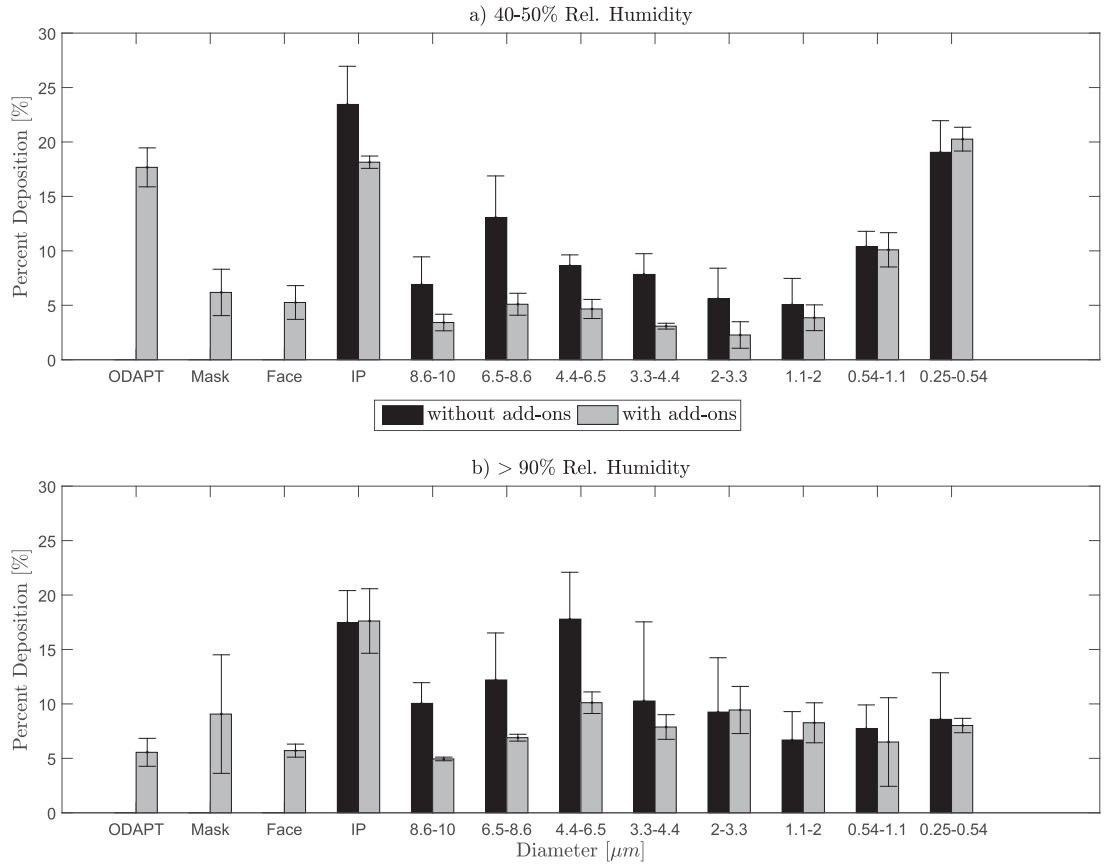

Figure 5. Drug deposition in the ODAPT adapter, mask, face, induction port (IP) and the Andersen Cascade Impactor at 60 L/min at (a) 40%–50% relative humidity and (b) >90% relative humidity levels. The results are shown as average values of three replicas with the associated standard deviation as shown as the error bars. Legend of the figure refers to the results without add-ons and with add-ons.

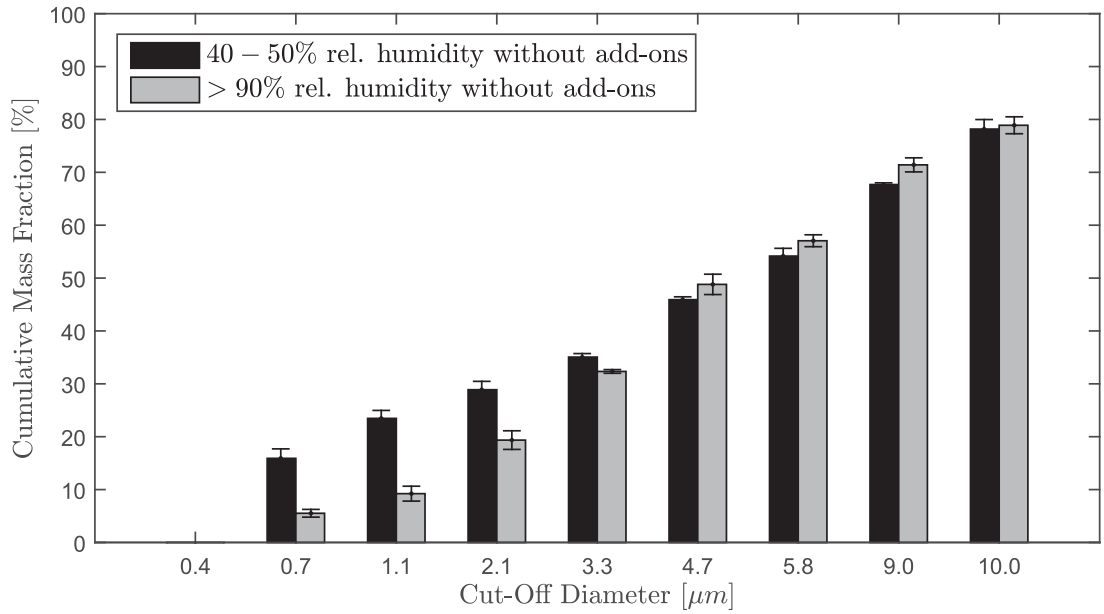

Figure 6. Cumulative mass fraction of medication without the add-ons at 28.3 L/min. The results are shown as average values of three replicas with the associated standard deviation as shown as the error bars. Legend of the figure refers to the results at 40%–50% and >90% relative humidity without add-ons.

mass fraction of the aerosol particles for flow rates of 28.3 L/min and 60 L/min, respectively, as a function of the cutoff diameter at various impactor stage for the Spiriva medication at 40%–50% relative humidity and >90% relative humidity. Each result is presented as the average of three replicas with the error bars depicting the standard deviation associated with the measurements. As can be seen, a larger amount of fine particles is present at lower relative humidity.

Tables 2 and 3 summarize the results obtained at 28.3 L/min (Test 1–4) and 60 L/min (Test 5–8) with and without the

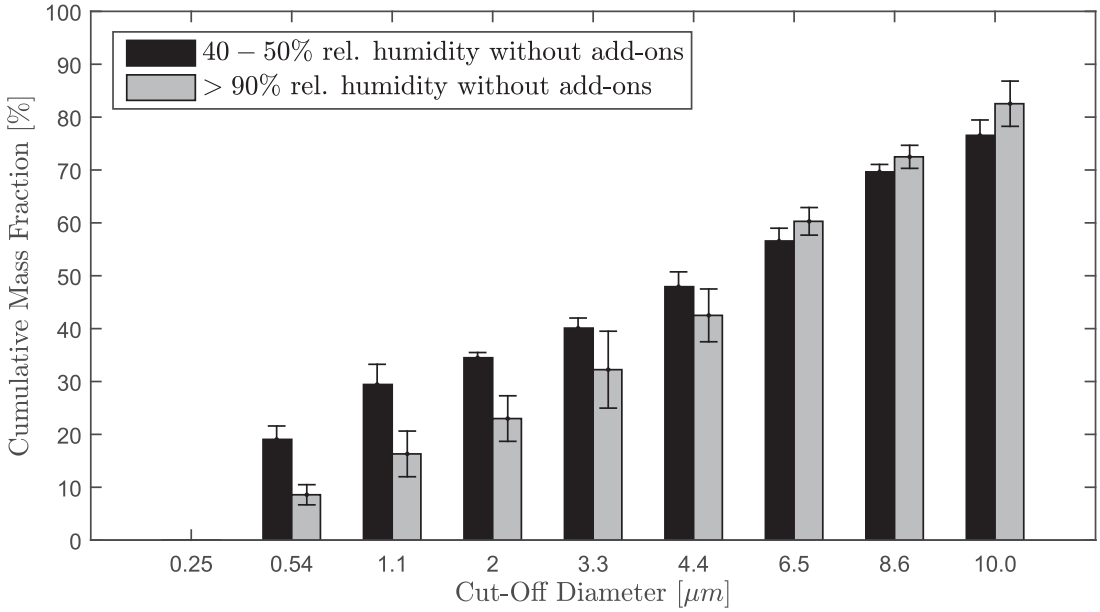

Figure 7. Cumulative mass fraction of medication without the add-ons at 60 L/min. The results are shown as average values of three replicas with the associated standard deviation as shown as the error bars. Legend of the figure refers to the results at 40%–50% and >90% relative humidity without add-ons.

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 at normal (40%–50%) and high (>90%) relative humidity (RH) at 28.3 L/min.[a]

Test #	Humidity (%)	Add-ons	MMDA (μm) ± SD	GSD (μm) ± SD	FPF (%) < 5 μm	% Loss FPF	Add-ons (%)
Test 1	40–50	No	5.21 ± 0.30	7.18 ± 0.33	48.16 ± 2.70	7.39	N/A
Test 2	40–50	Yes	3.90 ± 0.61	6.21 ± 0.77	44.60 ± 2.26		22.54
Test 3	>90	No	4.85 ± 0.25	2.76 ± 0.27	51.05 ± 2.19	16.23	N/A
Test 4	>90	Yes	4.79 ± 0.36	2.52 ± 0.23	42.76 ± 2.50		18.7

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

Table 3. 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 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 5	40–50	No	4.96 ± 0.83	10.02 ± 2.05	50.40 ± 3.27	18.84	N/A
Test 6	40–50	Yes	2.78 ± 0.57	7.78 ± 1.64	40.90 ± 2.92		29.1
Test 7	>90	No	5.37 ± 0.90	4.55 ± 2.10	47.58 ± 6.43	9.64	N/A
Test 8	>90	Yes	4.56 ± 0.98	4.41 ± 0.14	42.99 ± 9.38		20.3

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

add-ons under different conditions. In order to better assess the particle size distribution, the MMAD and GSD for each test were calculated based on the cumulative mass fraction results in Figures 6 and 7 using Equation (1). The IP deposition results were included in the calculation of the GSD and MMAD. The Fine Particle Fraction (FPF), defined as the mass percentage of aerosol particle less than or equal to 5 μm, is also presented in Tables 2 and 3 for the different tests. Therefore, the percentage of FPF loss, due to the presence of the add-ons, the amount of drug deposited in the IP and add-ons (ODAPT adapter, facemask and 3D face) are also calculated and shown in Tables 2 and 3 at 40%–50% relative humidity and >90% relative humidity. The results are shown as an average ± standard deviation (SD) of three replicas. It was found that MMAD ranges between 3.90 ± 0.61 μm and 5.21 ± 0.30 for a flow rate of 28.3 L/min and varies between 2.78 ± 0.57 μm and 5.37 ± 0.90 for a flow rate of 60 L/min. The values obtained are within the inhalable range (1–5 μm[10–12]). As can be seen from Figures 4 and 5, the percentage of medication delivered by the Spiriva Respimat SMI that could reach the lungs (FPF) was found to vary between 42.76 ± 2.50% and 51.05 ± 2.19% for the tests performed at 28.3 L/min (Table 2) and between 42.99 ± 9.38% and 50.40 ± 3.27% for the tests performed at 60 L/min (Table 3). Lower FPF was found when using the add-ons as noted in Figures 4 and 5. In order to assess the effect of the add-ons on the tiotropium bromide monohydrate delivery using the Respimat SMI, the relative percentage loss was calculated with respect to the measurements without add-ons, given as $([FPF_{nomask} - FPF_{mask}]/FPF_{nomask}) \times 100$, as shown in Tables 2 and 3 for inspiratory flow rates of 28.3 and 60 L/min, respectively. As can be observed, maximum medication losses (18.84%) were found for the test performed at ambient RH at 60 L/min, while smallest losses (7.39%) were found at ambient

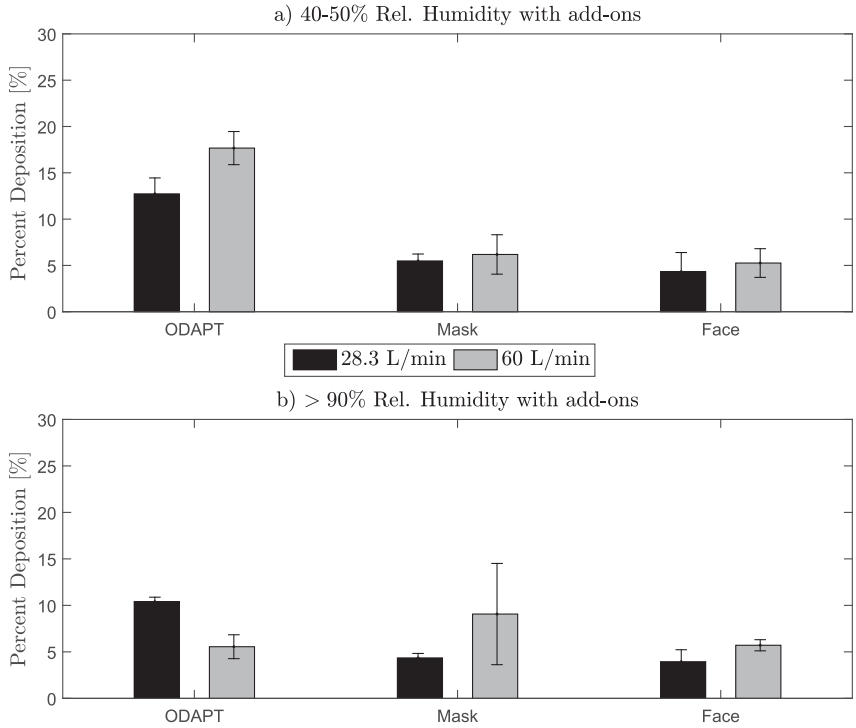

Figure 8. Percentage (%) of particle deposition collected from the ODAPT soft mist adapter, the facemask and 3D printed face at 28.3 and 60 L/min at (a) 40%–50% relative humidity and (b) >90% relative humidity levels. The results are shown as average values of three replicas with the associated standard deviation as shown as the error bars.

RH and 28.3 L/min. The percentage drug deposition in the add-ons (ODAPT adapter, facemask, and the 3D printed faces) is also reported in Tables 2 and 3. It was found that 22.54% and 18.7% were collected on the walls of the add-ons at 40%–50% RH and 90% RH, respectively, for an inhalation flow rate of 28.3 L/min, while 29.1% and 20.3% were collected on the walls of the add-ons at 40%–50% RH and 90% RH, respectively, at 60 L/min.

In order to investigate the effect of the flow rate on the medication deposition within the add-ons, a comparison of the tiotropium bromide monohydrate collected on the add-ons (ODAPT adapter, facemask and the 3 D face), expressed as a percentage of the total medication deposition at 28.3 L/min and 60 L/min for normal and high relative humidity is shown in Figures 8a and b, respectively. It can be observed that, at normal relative humidity (40%–50% RH, Figure 8a), the highest deposition was found within the ODAPT adapter for both flow rates, whereas at high relative humidity (>90% RH), highest depositions was found within the ODAPT adapter at 28.3 L/min and in the mask at 60 L/min. However, a larger standard deviation was found when analyzing medication collected on the mask for the different tests performed. The statistical analysis performed showed a significant difference in medication deposition within the ODAPT adapter for the flow rate tested, while no significant difference in deposition in the facemask and 3D printed face was found.

Discussion

In this study, the effect of humidity, the presence of the add-ons and flow rate on the MMAD, GSD, FPF and deposition are discussed.

Analyzing the particle size distribution within the ACI through Figures 4 and 5 (for flow rates of 28.3 and 60 L/min, respectively), a shift in particle size distribution was noticed, where higher deposition was found for smaller particles at ambient relative humidity. The humidity effect can also be noticed when analyzing the MMAD and GSD results (see Tables 2 and 3). The MMAD was found to increase when increasing the humidity in the presence of the add-ons. However, no significant difference was found for the MMAD using Setup I without the add-ons. Larger GSD values were found for the normal ambient relative humidity, which indicates a broader particle size distribution and hence larger amounts of fine particles. It is suggested that the humidity affects the particle size distribution (MMAD and GSD) mostly with the presence of the add-ons. This shift in particle distribution was previously observed by Ziegler and Wachtel[13] and Martin and Finlay[14] and is attributed to the differences in condensation rate (depending on the temperature of the droplet and surrounding environment), thus changing the measured size distribution.

The presence of the add-ons was shown to affect the aerosol behavior and medication deposition. Tables 2 and 3 show the MMAD decreases when using the add-ons. A significant difference was found at 40%–50% RH, while no significant difference was observed for higher relative humidity for both flow rates. Through Tables 2 and 3, it can be observed that large amounts of medication were collected on the walls of the add-ons. However, in spite of medication losses on the walls of the add-ons and the resulting slight decrease in the inhalable FPF (Fine Particle Fraction with diameters $< 5.0\,\mu$m), $44.60 \pm 2.26\%$ and $42.76 \pm 2.50\%$ of the medication was found to be within the inhalable range at

28.3 L/min, while 40.90 ± 2.92% and 42.99 ± 9.38% of the medication was delivered at 60 L/min (with the mask and adapter) under the normal and humid conditions, respectively. Therefore, the presence of the ODAPT adapter and mask do not greatly affect the amount of medication within the inhalable fraction (FPF varying approximately from 40% to 51% in the present work), a range which was found to be similar to results obtained by Ciciliani et al.[8] in vitro experiments using the Spiriva Respimat formulation and Newman et al.[5] in vivo using the Respimat SMI with fenoterol and flunisolide. Tiotropium bromide Monohydrate (Spiriva Respimat) was used in this study to test the effect of the add-ons on drug delivery. However, these add-ons can be used with different drug combination such as tiotropium bromide and Olodaterol (Stiolto Respimat) and Iprotropium bromide and Albuterol (Combivent Respimat). Slight differences in particle deposition are expected when using different drug combinations.

A slight decrease in MMAD was noted when comparing both flow rates tested (28.3 and 60 L/min Tables 2 and 3, respectively); however, no statistical significant difference was found ($P > 0.05$). The FPF was found within the same range for the different inspiration flow rates tested with no significant statistical difference for all the different tests (with and without a mask, under normal and high relative humidity) with $P > 0.05$. These results agree with the previous findings of Ciciliani et al.[8] where it was found that deposition of tiotropium bromide monohydrate did not vary significantly with the air flow rates tested with a COPD breathing pattern. Brand et al.[6] showed that the medication deposition in the lungs for trained patients (with mean inspiratory flow rates of 86.6 ± 33.1 L/min) differed from the deposition with untrained patients (with a mean inspiratory flow rates of 35.2 ± 10.6 L/min), conjecturing that the inspiratory flow rate affects the lung deposition. However, in the study of Brand et al.,[6] the duration of inhalation and the duration of a breath hold also differed for the trained and untrained patients which could have contributed to the difference on lung deposition. Although it is recommended to use the Spiriva Respimat SMI at a flow rate of about 30 L/min,[5,6] it was found that increasing the inhalation flow rate was shown to have no major effect on the amount of medication that could deposit in the lungs.

The results presented in this study were obtained using in vitro experimental set ups mimicking environmental clinical settings. Newman et al.[15] investigated lung particle deposition in vitro (using the aerodynamic particle size distribution) and in vivo. The authors found that the in vitro FPF was found to overestimate the whole lung deposition for all 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 whole lung drug deposition are expected.

In summary, the effect of the ODAPT adapter with facemask addition on the medication delivery using the Spiriva Respimat SMI was investigated and compared to direct conventional medication delivery using the SMI (no add-ons). It was found that, under humid conditions (mimicking the humidity levels in the lungs), 16.23% and 9.64% loss in the "lung" deposition at 28.3 L/min and 60 L/min respectively, while 7.39% and 18.84% loss in the "lung" deposition was found at 28.3 L/min and 60 L/min respectively under normal humidity levels. Despite the medication losses, it was found that the tiotropium bromide monohydrate delivered ranges between about 42% and 51% for 28.3 L/min and 41% and 50% for 60 L/min, which was found to agree with lung deposition in previous studies.[5,6,8]

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Disclosure

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

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