

Aerosol Deposition Measurements with ODAPT Mask Adapter

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Abstract

Background: Aerosol is commonly used to deliver therapeutic drugs to patient suffering from asthma and chronic obstructive pulmonary disease (COPD). The purpose of this in vitro study is to characterize the effect of using the EcoMask facemask and the ODAPT adapter with the Spiriva Respimat Soft Mist Inhaler (SMI) in different environments.

Methods: An 8-stage Andersen cascade impactor, enclosed in a controlled environment, was connected in-line with a flow meter and a vacuum pump to simulate the steady inhalation of a healthy adult. The Spiriva Respimat SMI was tested at a flow rate of 28.3 L/min, with and without the use of the add-ons (ODAPT adapter and EcoMask facemask). The facemask was mounted on a 3D printed face which was modeled after an adult subject. The experiment was performed in normal (40-50% relative humidity) and humid (>90% relative humidity) environments. The aerosol depositions were then analyzed using a UV-visible spectrophotometer to obtain the particle size distribution of the medication in the cascade impactor.

Results: The particle size distribution was found to shift towards larger aerosol diameters with increasing relative humidity as a result of different water evaporation rates. Furthermore, a maximum of 10% drug delivered via the Respimat SMI was lost when using the add-ons. However, the aerosol deposition in the lungs was found to be 38.8-34.1%, which is similar to measurements without the use of add-ons.

Conclusions: For patients requiring a mask, the use of the EcoMask facemask and the ODAPT adapter is considered to be effective to help administer the medication, as this results in a difference in aerosol deposition of only approximately 7% under normal conditions.

Keywords: Chronic Obstructive Pulmonary Disease (COPD), Spiriva Respimat, Soft-Mist Inhalers (SMIs), ODAPT soft-mist adapter, UV-visible Spectrophotometry, Aerosols, Particle Size Distribution

Introduction

Lung diseases such as asthma and chronic obstructive pulmonary disease (COPD), affect the respiratory system causing breathing difficulties. Therapeutic drugs, which are prescribed for the treatment of lung diseases, are commonly delivered by means of aerosols. The amount of drug deposited in the lungs is largely influenced by the characteristic of the aerosol, the delivery method, the mode of inhalation, and the architecture of the airways.^{1,2} There are several methods of delivering the drugs: pressurised metered-dose inhalers (pMDIs), dry powder inhalers (DPIs), nebulisers, and soft-mist inhalers (SMIs). The Respimat SMI (Boehringer Ingelheim, Ingelheim, Germany) is a new generation of inhaler, which generates an aerosol cloud suitable for inhalation using mechanical power from a spring in comparison to the liquid-gas propellant typically used in pMDIs.³ The soft mist travels much slower (initial droplet velocity is approximately 10 m/s)⁴ and lasts much longer (approximately 1.5 seconds),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 (~40% of the inhaled medication)⁵ to be delivered to the lungs.⁶⁻⁸

Aerosol particles below 5.8 microns are normally regarded as the fine particle fraction, which refers to the particle mass that is able to be inhaled past the mouth-throat region. It was shown that particles between 1 to 5 microns is the optimal size for pharmaceutical aerosols to reach the lower respiratory tract whereas particles larger than 5 microns tend to impact in the upper respiratory airways and are generally swallowed.^{9,10} Several previous studies were performed to characterize aerosol deposition in the lungs using the Respimat SMI. In 1998, Newman et al.¹¹ conducted two randomized studies using the Respimat SMI, where 12 non-smoking adult subjects were administered 100 µg of fenoterol in one study and 250 µg of flunisolide in another. The whole lung deposition, which was measured using gamma scintigraphy, was found to be 39.2% and 44.6% when administered with fenoterol and flunisolide, respectively. Pitcairn et al. (2005)¹² studied the lung deposition of 200 µg of budesonide administered to 14 mild-to-moderate asthmatic patients using the Respimat SMI. The study revealed that 51.6% of the budesonide was deposited in the lungs. A similar study was performed by Brand et al. (2008),⁵ where 13 male and female subjects were administered radiolabelled Berodual (fenoterol hydrobromide 50 µg/ipratropium bromide 20 µg) using the Respimat SMI. It was found that 37% of the inhaled drug deposited in the lungs.

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Figure 1 shows the ODAPT soft mist adapter and the EcoMask facemask used in this study. 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., UK). In this paper, the particle size distribution of the aerosols generated by the Spiriva Respimat SMI was studied in an in vitro set up to investigate the effect on medication delivery resulting from the addition of the ODAPT adapter and EcoMask facemask. The Spiriva Respimat SMI used in this study, contains 2.5 mcg of tiotropium bromide monohydrate, per puff, which is used in the treatment of COPD. To study the effect of the add-ons (ODAPT adapter and EcoMask facemask) on delivering inhaled pharmaceutical drugs to the lungs, the soft mist particle deposition was measured at a steady inhalation flow rate and two humidity levels (40-50% and >90%), using UV-visible spectrophotometry.

Figure 1. Add-on devices tested in this study: ODAPT soft mist adapter (left) and EcoMask facemask with ODAPT adapter (right).



Materials and Methods

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 using commercially available Spiriva Respimat (2.5 mcg tiotropium bromide per puff). Table 1 outlines the four test cases carried out in the current study.

Table 1. Controlled parameters used in this study.

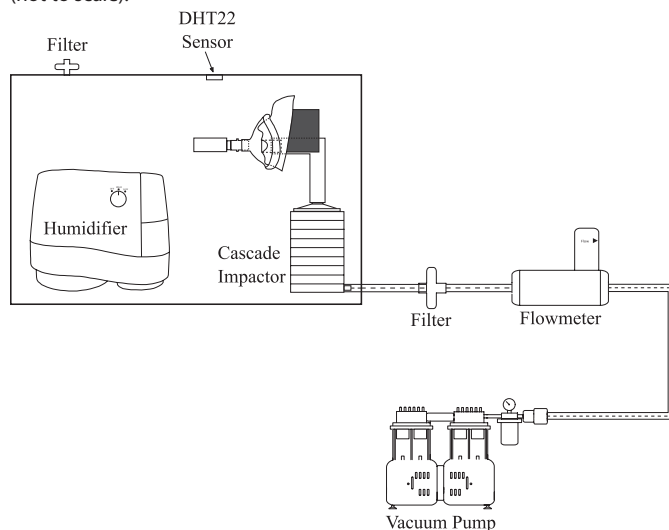
Test Case	Flow Rate [L/min]	Facemask	Relative Humidity [%]
1	28.3	No	40-50
2	28.3	Yes	40-50
3	28.3	No	>90
4	28.3	Yes	>90

Experimental Apparatus

Figure 2 shows a schematic of the experimental setup used in this study. As described in Table 1, for test cases 1 and 3, the inhaler was connected directly to the induction port (IP) simulating the upper airway of an 8-stage Andersen Cascade Impactor (ACI, stages 0 to 7) (MSP Corporation, Shoreview, MN), as can be seen in Figure 3. For test cases 2 and 4, the inhaler was connected in sequence to an ODAPT soft-mist adapter (EcoMask facemask) a 3D printed face, a tubing coupler, and finally to the IP of the ACI as seen in Figure 3. The face was modeled by overlapping multiple photographs of an adult face to generate a three dimensional (3D) mesh using Autodesk Meshmixer and

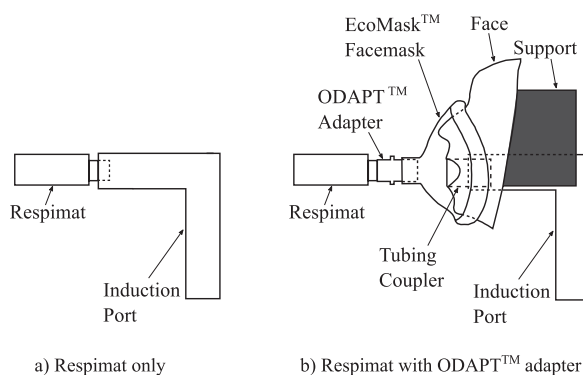
fabricated using the Dimension BST 3D ABS printer (Stratasys, Eden Prairie, MN). The attachment between the 3D printed face and the tubing coupler was carefully sealed to ensure no medication was released to the surroundings. In addition, a block of high density foam was mounted between the face and the IP thereby adding rigidity to the face as well as keeping proper alignment between each device.

Figure 2. Schematic of the experimental setup used in this study (not to scale).



As seen in Figure 2, the entire setup was placed in a sealed, temperature-and-humidity-controlled environment. The temperature was kept constant ($22 \pm 2^\circ\text{C}$) throughout the entire experiment and the humid environment was created using a Duracraft DCM200 2 Gallon Cool Mist Humidifier. 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 both the temperature and humidity of the environment. The DHT22 sensor was placed directly at the mouth level of the 3D printed face to measure the humidity of the air entering the system. To simulate the inspiratory flow rate of a healthy male subject, the method used by Alhegagi,¹³ and Ogronnik et al.,¹⁴ was utilized, through which the ACI was connected in series to a Vital Signs RespirGard II 303 bacterial/viral filter (Vital Signs, Inc., Englewood, CO), a Brooks Mass Flow Meter 5863S (Brooks Instrument, LLC., Hatfield, PA), and a Welch Dry Vacuum Pump 2585B (Welch-

Figure 3. Schematic of the experimental setup used for (a) Respimat only (Test cases 1 and 3) and (b) Respimat with the ODAPT soft mist adapter and the EcoMask facemask (Test cases 2 and 4).



Ilmvac, Niles, IL). The filter was placed between the ACI and the flow meter to collect any unwanted particles leaving the ACI. 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.

Experimental Procedure

Prior to each experiment, each device under test was washed with dish soap, rinsed with water, and allowed to air dry. The cascade impactor was assembled and the experiments were connected as described previously. The Spiriva Respimat inhaler was primed by releasing 5 puffs in open air for first time use, and loaded onto the respective device. For test case 2 and 4, 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 a 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 prepared for washing. 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 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 3) or the IP and the tubing coupler (for the test case 2 and 4) were washed with 15 mL of distilled water. Each component was left in their respective solution for 2 hours to allow for a consistent dissolution of the medication.

Absorbance Measurement

The deposition of the tiotropium bromide monohydrate for each test case was then determined by measuring the absorbency of each wash solution using the Agilent 8453 UV-Visible Spectrophotometer (Agilent Technologies, Santa Clara, CA). A calibration curve was necessary to relate the measured absorbency to the concentration of tiotropium bromide monohydrate. To generate such curve, a stock solution of tiotropium bromide monohydrate and distilled water (using 25 mL) was prepared from 13.9 mg of pure tiotropium bromide monohydrate (Sigma Aldrich Canada, Oakville, Canada). The stock solution was then diluted to known concentrations and the absorbency of these standard solutions was obtained using the Agilent spectrophotometer. It was found that the tiotropium bromide monohydrate has an absorption wavelength of 237 nm.

Prior to measuring the absorbency of the wash solutions, each cuvette was washed 3 times with distilled water and primed 3 times with 0.5 mL of the wash solution under test. At least 2 absorbency readings were taken for each sample of the wash solutions. The concentration of tiotropium bromide could then be found using the calibration curve. The mass deposition and particle size distribution can therefore be calculated.

Data and Statistical Analyses

The drug deposition results were expressed as a percentage of the total recorded medication. The mean \pm SD of the drug deposition were evaluated from at least 5 repeats for each test case. To ensure the reported results were statistically significant,

t-tests were conducted for the drug deposited in the lung. For each test case, a t-value was calculated using the following equation:

$$t = \frac{\bar{X} - \mu}{S / \sqrt{n}}$$

where n is the number of samples, \bar{X} is the sample mean, and S is the sample standard deviation. The hypothesis variable μ is assumed to be the expected percentage drug delivered to the lung ($\mu = 40\%$). P-values of <0.05 were considered statistically significant. Calculations were done with MATLAB R2014b software (MathWorks, Natick, MA).

To characterize the particle size distribution (PSD), the mass median aerodynamic diameter (MMAD) and the geometric standard deviation (GSD) were used. MMAD, which is based on a model that assumes a log-normal distribution of the particle size mass, is determined at the diameter corresponding to the 50th mass percentile (D_{50}). GSD describes the spread of the data in the distribution and is evaluated under the log-normal distribution using the following equation.

$$GSD = D_{84}/D_{50} = D_{50}/D_{16} = (D_{84}/D_{16})^{1/2}$$

where D_{16} and D_{84} are the diameters corresponding to the 16th and 84th mass percentile, respectively. It should be noted that all the PSD data were converted in terms of percentage of the total mass recovered at the different stages and IP of the ACI as well as at the respective add-ons used during the experiment.

Results and Discussion

Particle size distribution

Aerosol size measurements, released from the Spiriva Respimat inhaler (without mask), were compared under normal and humid conditions. Figure 4 shows the cumulative aerosol distribution (the value at the cut-off of 10 μm represents the mass fraction of all particles below 10 μm) for both conditions with their associated standard deviation displayed as error bars. As can be seen, larger amount of fine particles with diameters less than 4.7 microns (representing stages 3 to 7 in the Andersen Cascade Impactor, ACI) are obtained at the lower relative humidity. This shift in particle distribution, which was also observed by Ziegler and Wachtel,¹⁵ and Martin and Finlay,¹⁶ is due to evaporation or condensation where the particles gain or lose mass from their surface.⁹ It is conjectured here that the droplet size distribution measured at 90% RH (relative humidity) closely resembles the distribution generated by the inhaler. For the 40-50% RH conditions, generated inhaler droplets will experience a different evaporation rate, thus changing the measured size distribution.

Table 2. Particle size distributions of aerosol from Spiriva Respimat inhaler under normal and humid conditions.

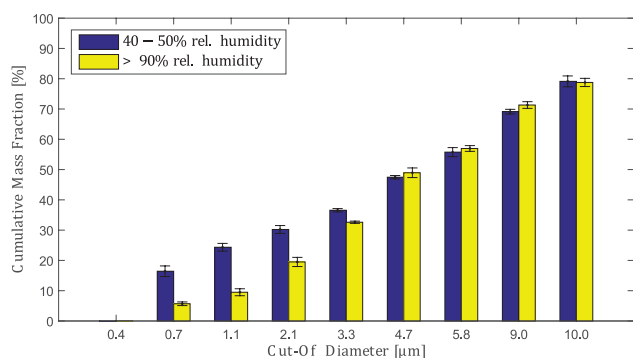
Condition	Relative Humidity [%]	MMAD [μm]	GSD [-]
Normal	40-50	5.0 ± 0.5	7.5 ± 0.5
Humid	>90	4.8 ± 0.2	2.8 ± 0.2

Table 2 summarizes the MMAD and GSD results for both normal and humid conditions, and their respective standard errors. Although there is a shift in the PSD due to the humidity effect, the difference in MMAD under normal (5.0 ± 0.5) and

humid condition (4.8 ± 0.2) was negligible (4.0%). In contrast, humidity had a greater impact on the GSD (7.5 ± 0.5 under normal condition compared to 2.8 ± 0.2 under humid condition) resulting in larger amount of fine particles, therefore, more drug was delivered to the alveoli.

Similarly, as can be observed in Figure 4, about 48% (48.9% for RH>90% and 47.5% for 40-50% RH) of the medication delivered by the Respimat SMI deposited in the tracheo-bronchial and alveolar regions (aerosol with diameters between 0.4 μ m and 4.7 μ m, ACI stages 3 to 7), which are sometimes referred to as the lung.¹⁸ During the clinical study performed by Newman et al.,¹¹ on average 39.2% and 44.6% of fenoterol and flunisolide deposited in the lung, respectively. The slight difference in deposition obtained was mainly due to the steady inhalation rate (in addition to the usage of the induction port to simulate the medication losses on the actual mouth-throat-trachea geometry of patients) used in the current study as compared to the inhalation technique described in Ref.,¹¹ where the subjects inhaled slowly and deeply with a targeted rate of 30 L/min, and held their breath after inhalation for at least 10 seconds.

Figure 4. Aerodynamic particle size distribution under normal and humid conditions.



Aerosol deposition on ODAPT add-ons

To assess the effect on medication delivery when using the ODAPT add-ons, aerosol deposition measurements were conducted via the Spiriva Respimat SMI. Figure 5 shows the effect of the facemask as percentage deposition of tiotropium bromide monohydrate at an inspirational flow rate of 28.3 L/min for the normal (Figure 3(a)) and humid (Figure 3(b)) environments. Each test case was performed at least 5 times with the error bars representing \pm one standard deviation (SD) of the experimental measurements. The aerosol depositions were measured at normal (40-50%) and humid (>90%) conditions, as shown in Figure 5(a) and Figure 5(b), respectively. As can be observed, the percent aerosol deposition on the walls of the ODAPT add-ons is about 23% and 20% of the medication delivered at the normal and humid conditions, respectively. However, when taking into account the decrease in aerosol deposition along the IP (simulated upper airway) walls, the medication loss was no more than 10% when using the ODAPT add-ons.

The amount of tiotropium bromide monohydrate deposited in the lungs (ACI stages 3 to 7 combined) is summarized in Table 3 as percent deposition (PD), where the relative percent loss was calculated with respect to the measurements without add-ons, given as $([PD_{\text{nomask}} - PD_{\text{mask}}] / PD_{\text{nomask}}) \times 100$. In spite of the medication losses on the walls of the add-ons, 44.1% and 38.8% of

the medication was delivered to the lung (with mask) under the normal and humid conditions, respectively, which corresponds to previous studies.^{8,11,12} Therefore, based on the lung deposition measurements, minimal therapeutic drug loss is achieved when using the ODAPT facemask and adapter. Furthermore, the addition of the ODAPT add-ons affected the inhaled drug delivery to the lungs by 7.0% under normal conditions and 20.7% under humid conditions when compared against the experiments without the mask (see again Table 3). Also, under normal conditions there was a greater percent deposition of medication in the stages 6 and 7 lung segments when using ODAPT at normal humidity conditions (see Figure 5(a)). The reason for the larger difference under humid conditions is due to the change in aerosol size distribution (same MMAD but different GSD, with more fine particles, $d_p < 4.7 \mu$ m). This increases the chance of aerosol deposition on the ODAPT add-ons and thus lowering proportionally the deposition in the lungs.

Figure 5. Percent deposition of medication with and without add-ons at a constant temperature of $22 \pm 2^\circ\text{C}$ and relative humidity levels of (a) 40-50% and (b) >90%.

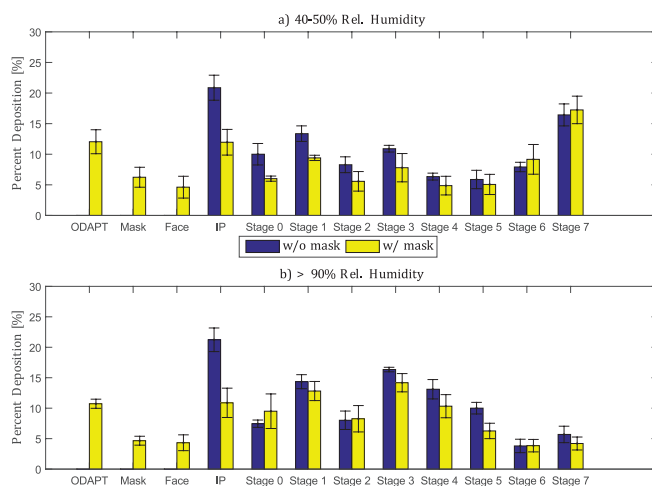


Table 3. Percent and mass deposition comparison with and without add-ons.

	No Mask	Mask	% loss
Percent deposition in lungs at relative humidity of 40-50% (SD) [%]	47.5 (4.0)	44.1 (3.2)	7.0
Percent deposition in lungs at relative humidity of >90% (SD) [%]	48.9 (2.0)	38.8 (3.5)	20.7

Conclusion

The current study showed a change in the Respimat SMI particle size distribution in a humid environment (>90% relative humidity, RH) when compared against normal conditions (indoors, air conditioned environment, 40 to 50% RH) due to droplet evaporation differences. The addition of the ODAPT adapter and facemask, to help deliver the medication to patients requiring a mask, was found to be effective under normal conditions (44.1% lung delivery with mask compared against 47.5% without mask). Increase in humidity levels (to >90% RH) will reduce lung delivery from 48.9% (without mask) to 38.8% (with mask). Nonetheless, 39-45% of the inhaled medication was delivered to the lungs, which is still quite significant when compared against common pressurized metered dose inhalers.

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