

# ***In-vitro* measurement of aerosol generated by Respimat SMI penetrating through upper airways**

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**Abstract.** Respimat soft mist inhaler (SMI) is an inhaler producing a soft mist with low velocity. The liquid drug solution is emitted by the mechanical energy of compressed spring, so the device is propellant-free. This paper describes the measurement of particle fraction penetrating through the model of the upper respiratory tract (mouth cavity, pharynx, larynx trachea). The solution inside the cartridge was marked by fluorescein in order to evaluate the regional particle deposition in the model. After the exposition, segments of the model, as well as the filter, were washed out and the deposited fluorescein was extracted into water. The analysis showed that the fraction of particles penetrating through the upper respiratory tract was 64.7±6.7 %. However, the real inhalation pattern was not simulated and measurement was provided with continual “inhalation” without “exhalation”.

## **1 Introduction**

An inhalation treatment grew in popularity in the last decades. It is a non-invasive and effective way of drug delivery and it is attractive for patients as well as caregivers. Today the inhalation therapy is commonly used for the treatment of pulmonary diseases but there are already developed inhalation systems delivering the therapeutic aerosol into the circulatory system via alveoli as well [1]. Chronic Obstructive Pulmonary Disease (COPD) was the fifth most frequent cause of death in 2002 and according to the World Health Organisation (WHO), it will be the fourth one in 2030. COPD nowadays affects approximately 210 million people [2].

The efficacy of the inhalation treatment obviously depends on the amount of drug deposited in the patient lungs. This can be influenced by parameters of pharmaceutical aerosols, such as its velocity and particle size [3]. The commonly used inhalation systems are divided into 3 main categories: Dry Powder Inhalers (DPI), Metered Dose Inhalers (MDI) and nebulizers [4]. The DPIs are portable inhalers used for inhalation of drug formulation in a powder form. They are passive devices, it means, it is necessary to create a forced deep inspiration to suck the powder from the inhaler. A patient needs to create a sufficient inspiration flowrate to ensure the proper deagglomeration of particles. It can be complicated for children, old people or patients in the late stage of the disease. On the other hand, the passivity of DPIs makes the coordination of inspiration and particle dispersion easier in comparison with MDIs [5].

The nebulizers are usually a bit larger devices nebulizing the liquid drug solution. Commonly, they are not portable because they need to be plugged into electricity. The most common technology used for

nebulization of liquid drug solution is the compressed air. However, there are other nebulization technologies, such as vibrating mesh or ultrasonic vibrations [6]. However, the using of nebulizers is more time-consuming in comparison with MDI and DPI; one dosing takes approximately 7 minutes [5].

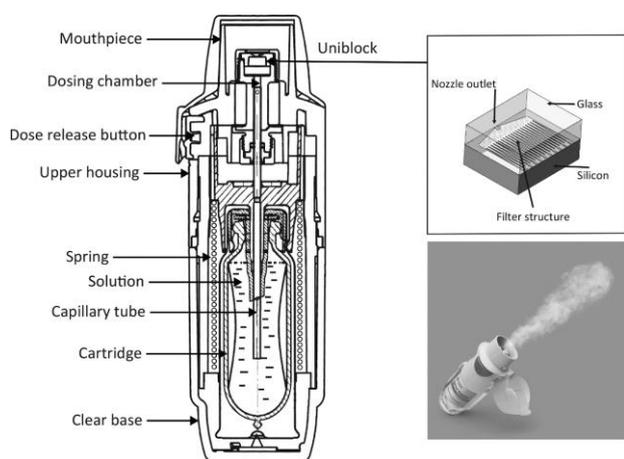
The MDIs are also portable devices emitting a precisely metered dose of the drug formulation. MDIs use a propellant (nowadays Hydrofluoroalkanes – HFA) to disperse the formulation into the aerosol form. MDIs contain a reservoir with a mixture of drugs, liquidized propellant, and other components. After actuation, this pressurized formulation (metered in the metering valve system) is emitted through the nozzle [7]. It creates an aerosol with high velocity, where many compounds of formulation evaporate immediately after dispersion [8]. A major fraction of particles generated by these devices deposits in upper airways (mouth cavity, pharynx larynx) due to the significant effect of inertial impaction. It is gaining in importance with the increase of particle size and particle velocity. This aerosol is often cold and it can decrease the effectivity of treatment in patients with cold air induced bronchospasm [9]. The small deposition fraction within the lungs in case of MDI was shown many times. *Newman et al.* [10] in a wide-frame study of fenoterol particles deposition found that the deposition fraction (a mass of particles deposited in selected area expressed as a percentage of total deposited mass) in the lungs using the pMDI is lower than 20 %. Similar results were acquired also in his previous study [11] comparing lung deposition with and without using the auxiliary devices (spacers) [11]. According to the *Egan's Fundamentals of Respiratory Care* [9], in general,

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approximately 80 % of aerosol emitted by MDIs deposit in the oropharynx.

This was the reason for the development of the Respimat SMI. Low aerosol velocity and longer time of aerosol emission should cause lower oropharyngeal deposition. The Respimat SMI (Boehringer Ingelheim, Germany) is a propellant-free inhaler applied for asthma and COPD therapy. This system is very popular nowadays and it is becoming the preferable inhaler over the pressurized Metered Dose Inhalers (pMDI) or Dry Powder Inhalers (DPI) [12]. The Respimat uses a special system for nebulizing the drug solution, which enables to produce the aerosol stream with low velocity. The drug solution is stored in an aluminium cartridge. By rotation of the clear base of the Respimat by 180°, the spring compresses, moves the cartridge against the capillary tube and transfers the precisely metered amount of drug solution from the cartridge into the dosing chamber through the capillary tube [12]. A most important part of this device is the uniblock. It consists of two nozzle outlets placed in extremely fine filter channels. After pressing the dose release button, the liquid is forced through these nozzles, it means the solution is split into two streams within two nozzles converging in the precisely controlled angle. The collision of these two streams causes the atomization of the liquid into slow-moving aerosol – it means 0.8 m/s [13,14]. This device produces a high fine particle fraction 65 – 80 % (particles with diameter < 5.8 µm) [3]. The time period of the aerosol emission is much longer than in the case of pMDIs. It facilitates the coordination of actuation of the device and inspiration.

Pitcairn *et al.* [15] performed measurements with radiolabelled aerosol produced by Respimat SMI and selected DPI and pMDI. The aerosol was inhaled by fourteen patients with mild to moderate asthma and ages between 19 and 65 years. The flow rate of 30 L/min was used for all devices except for DPI, for which the study was provided in both 30 and 60 L/min flowrates [15]. In the case of Respimat SMI was the dose deposited in lung determined to be 51.6 (46–57) %, then 19.3 % of the dose deposited in the oropharynx, and 17.7 % in the device. The fraction exhaled from the respiratory system



**Fig. 1:** Scheme of Respimat SMI [12].

was 10 % [15]. For cases of DPI (60 L/min), was the percentage of the dose deposited in lungs 28.5 %, for DPI (30 L/min) it was 17.8 % and for pMDI only 8.9 % [15]. These data show very good effectivity of the Respimat SMI device in comparison with commonly used inhalers.

This contribution reports similar measurements of Respimat SMI, however, our experimental setup included a mechanical model (replica) of human upper airways created by *Lizal et al.* [16]. This approach is supposed to provide better repeatability of the results and hence can be suitable for validation of potential computational simulations.

## 2 Methods

Firstly, the liquid was removed from the canister of the Respimat SMI placebo and replaced by fluorescein solution with a concentration of 3 mg/ml. Because number of doses was limited the concentration had to be so high. [17]

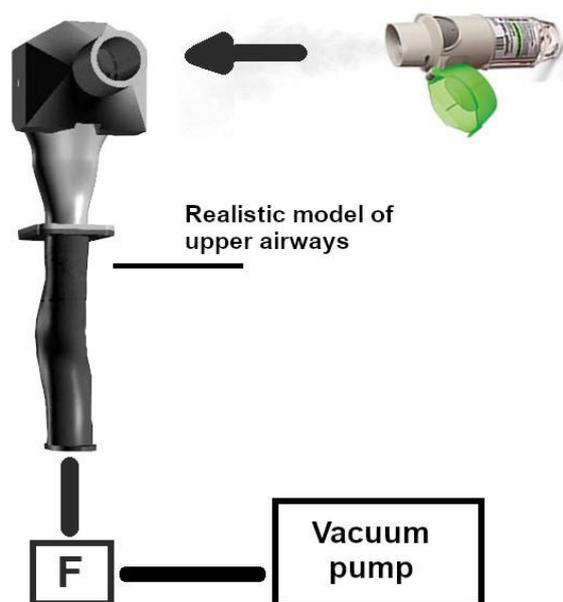
For the measurements of aerosol deposition the Respimat SMI Placebo with refilled cartridge was used. The parameters of aerosol produced by this device with the labelled formulation were validated by Laser Doppler Anemometry/Phase Doppler Anemometry (LDA/PDA) and compared with parameters of Respimat SMI Spiolto (the real drug formulation) measured by the same methods. The differences between parameters (velocity and particle size distribution) of aerosols generated from these two formulations were negligible. Since the differences between parameters of these two solutions were negligible the measurements of aerosol deposition could be provided [17].

Subsequently, the experimental rig for the measurement of the particle deposition was set. It consisted of the oropharyngeal region segment and trachea segment connected together (illustrated in Figure 2 and in [16]), the hose with a nitrocellulose membrane filter connected to a vacuum pump and all the contacts were sealed well. [17]

The flow rate was set to 30 L/min. This flow rate was steady, it means the inhalation and exhalation were not simulated. [17]

The Respimat SMI was placed coaxially with the cylinder on the front side of the mouth cavity. Two series consisting of three consecutive repeated measurements were performed. In the first series, 10 doses were emitted per one measurement. In the second series, 20 doses were emitted per one measurement [17].

After the exposure described above, it was necessary to extract the deposited aerosol into distilled water. The membrane filter was placed into the ultrasonic cleaner for 5 minutes. The concentration of fluorescein was determined by fluorimeter (Quantus™ Fluorometer, Promega) and deposited mass was calculated according to the fluorescein concentration and sample volume. [17]

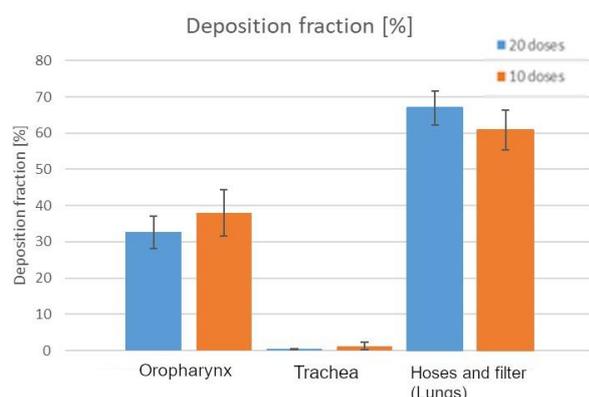


**Fig. 2 :** Scheme of the assembly.

### 3 Results

The deposited particle mass in each segment was determined. This mass was transformed into the deposition fraction defined as the mass of particles deposited in one segment divided by the total deposited mass. From the acquired results it is visible that the marginal part of aerosol was able to penetrate into the tracheobronchial tree. The fraction measured on hoses and filter (it means in the parts after oropharyngeal region and trachea) in all of the measurements exceeded 50 % and it was higher than 60 % in most of the measurements. The fraction of particles deposited within the model of the trachea was very low in comparison with the oropharyngeal region and hoses with filters, as expected.

Results of the deposition fraction in the oropharyngeal region and in the last segment (hoses and filter) were quite variable as can be seen from standard deviations shown in Table 1. However, although the average results of deposition fraction in the last segment differ between measurements with 10 doses and 20 doses, it seems the number of actuations did not have a



**Fig. 3:** Measured fractions of deposited particles.

significant impact on the results. In order to test the effect of the number of used doses, it would be necessary to repeat the measurement much more times. If we assume that the experiments with 10 and 20 doses are equivalent, the average value of deposition fraction in segments below oropharyngeal region is  $64.7 \pm 6.7$  %.

### 4 Discussion

Data gained by measurements presented in this paper show a significant difference in comparison with the oropharyngeal deposition of common MDI. The oropharyngeal deposition in these measurements was approximately 35% and fraction penetrating into lower airways approximately 63 %. Even better deposition data were gained during *in vitro* measurements presented in the source [18], where the oropharyngeal deposition fraction was determined as 27 — 29 %.

During the *in vivo* measurement performed using radiolabeling provided by *Pitcairn et al.* [15], the lungs deposition fraction was a bit lower - 51,6 % (46-57 %) than in the measurements described in this paper. However, during our measurements, the aerosol was delivered into the model by steady airflow of 30 l/min, whereas during the above mentioned *in vivo* measurements, the whole inhalation and exhalation were provided.

### 5 Conclusion

Since the Respimat SMI is an important novel device for an inhalation treatment, measurements of oropharyngeal aerosol deposition of particles produced by this device were performed on the realistic model of upper airways. The liquid solution of fluorescein was atomized by Respimat SMI and inhaled into the model with constant flow rate of 30 l/min. In general, current results are in good agreement with previous measurements. The deposition fraction published in *Delvadia* thesis of dissertation [19] measured with the same steady flowrate (30 l/min) was even a bit higher. However, the *in vitro* measurements performed on Alberta throat model [20] compared the lung deposition of Respimat aerosol using different breathing cycles (moderate and very severe COPD) and significant variability between breathing patterns were shown. Certain differences were found after comparison with previously published measurements of *Pitcairn et al.* [15], who measured (*in vivo*) the whole unsteady inhalation - exhalation cycle. Nonetheless, in their case, the exhaled fraction was approximately 10 %, which accounts for the difference between the our measurements. For more accurate determination of the lung deposition within the human lungs, the model with breathing simulator created at the Brno University of Technology (BUT) [16] will be used. The measurements described in this paper form the basis for the future measurement of regional lung deposition of aerosol generated by Respimat SMI.

### 6 Acknowledgement

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