**The *in vitro* effects in aerosol performance of poor lip sealing around the mouthpiece of a pressured metered dose inhaler**

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**Summary**

**Background:** A problem associated with the use of pressurised metered dose inhalers (pMDI) is the inappropriate seal between a patient's lips and the inhaler mouthpiece. Such incorrect use of inhaler may affect its aerosol performance due to unpredicted changes of the flow dynamics in the inhaler. **Methods**: The current study investigates the *in vitro* aerosol performance of a Ventolin® suspension pMDI using cascade impaction method, at different experimental setups to simulate conditions where the correct/incorrect use of inhalers occurs. In addition, effects of modified Ventolin® actuators with high and low flow resistances on the pMDI aerosol performances with the above configurations were also evaluated. **Results:** This study demonstrated that different seal conditions with a normal Ventolin® actuator did not significantly affect the aerosol performance of the formulation ($p>0.05$). No significant change ($p>0.05$) in fine particle dose was observed under different combinations of actuators and mouthpiece adaptors. The aerodynamic diameter and distribution of emitted particles from all experimental conditions did not show any significant change ($p>0.05$), probably due to the similar size of pre-engineered particles in the suspension formulation. **Conclusion:** It is hypothesized that the additional airflow induced by improper seals between patients' lips and actuator mouthpiece may not influence the aerodynamic performance of suspension pMDIs. Resistance of air flowing through the actuator influences particle deposition in the actuator mouthpiece and USP induction port, possibly due to different degree of flow turbulence at the exit of the actuator mouthpiece. However the particle deposition profiles in the cascade impactor did not exhibit any significant changes.

**Introduction**

There are two recommended ways for patients to correctly use a pMDI[1]: (1) closed mouth technique – the inhaler is placed in a patient's mouth and (2) open mouth technique – the inhaler is activated an inch or so in front of a patient's mouth[1]. The common problem associated with the former is the 'leaky mouth' – inappropriate seal between a patient's lips and the actuator mouthpiece[2]. Previous research has shown that up to ~30% of the asthmatic patients[3] do not seal lips around the inhaler mouthpiece properly. Although the error percentage dropped to <10%[3] after proper patient training, the impact of the poor lip-sealing condition on the inhaler performance is not fully investigated. Such incorrect use of the inhaler may cause a reduction in aerosol deposition in the respiratory region due to an additional airflow introduced at the mouthpiece exit from the space created between lips and actuator mouthpiece[4]. The aim of the current study was to investigate the aerosol performances of a commercial suspension pMDI formulation (Ventolin®) using 'leaky' and 'non-leaky' mouthpiece adaptors (Figure 1) to simulate correct and improper inhaling techniques. In addition, the influence of modified Ventolin® actuators with high and low resistances on pMDI aerosol performances was also investigated.

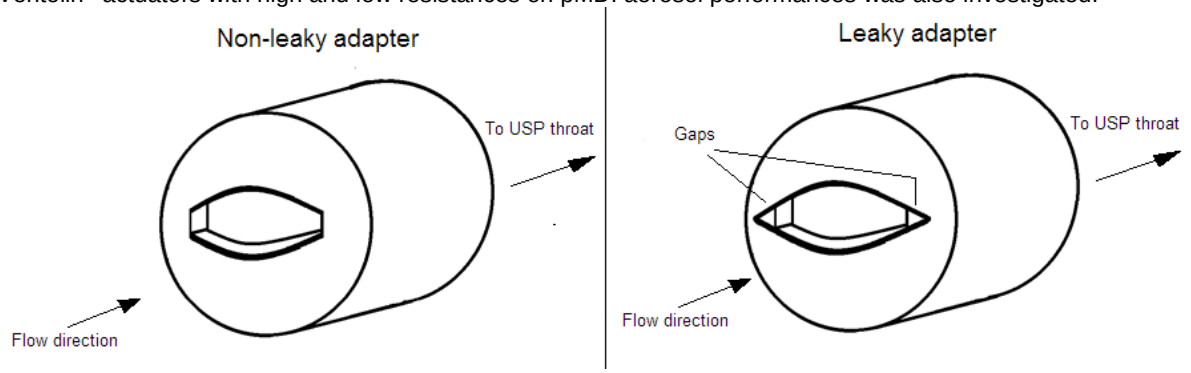


**Figure 1 Schematic overview of the used adapters**

**Experimental methods**

The aerosol performances of Ventolin® suspension pMDI formulation (100 µg/dose salbutamol sulphate) were evaluated with different combination of mouthpiece adaptors and actuators according to Table 1 using an Andersen Cascade Impactor (ACI, Copley Scientific, UK) at 28.3 L/min.

In brief, 10 doses were actuated into the ACI at 28.3 L/min with a 5 second shaking in between each actuation. The impactor assembly was disassembled for chemical quantification using high performance liquid performance chromatography (HPLC). Prior to sample analysis, the HPLC method was validated using a C18 column (Luna, Phenomenex, US), mobile phase of 8% (v/v) buffered acetonitrile aqueous solution (0.05M $K_2HPO_4$, PH 4.5) at a flow rate 1mL/min, detection wavelength 270 nm and injection volume 100 µL. The actuator, mouthpiece adaptor and each stage of the ACI were rinsed with acetonitrile aqueous solution (8%, v/v) into proper volumetric flasks.

The collected samples were quantified using freshly prepared standard solutions and linearity was confirmed in between the concentration range of 0.1-10 µg/ml ($R^2$ > 0.999).

**Table 1 Combinations of different mouthpiece adaptors and actuator setups**

| Condition | Actuator | Mouthpiece adapter |
|---|---|---|
| A | Standard | Non-leaky |
| B | Standard | Leaky |
| C | High resistance (custom made) | Non-leaky |
| D | High resistance (custom made) | Leaky |
| E | Low resistance (custom made) | Non-leaky |
| F | Low resistance (custom made) | Leaky |

The airflow resistances of the different actuators under leaky and non-leaky conditions were determined using a TSI flowmeter (Model 4040, TSI instruments, USA) with a flow simulator (1120, Hans and Rudolph Inc., USA) at different air velocities (30, 60, 90,120 and 150 L/min). The airflow resistance was calculated as the square root of the difference in kPa at each flow rate divided by the flow rate.

Analysis of variance (ANOVA) followed by Tukey's multiple comparisons was performed to determine the significance. Differences were deemed significant for *p* value <0.05. Unless otherwise stated data are presented in terms of mean (n=3) ± standard deviation.

## Results

Table 2 summarizes the aerodynamic performance of different experimental combinations according to Table 1. Aerosol performance for suspension pMDIs is mainly determined by the initial size of pre-engineered particles suspended in the liquefied propellant[5]. Therefore, the mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) under different experimental configurations did not exhibit any significant change (p<0.05). This was consistent to previously published results[6]. Using the high resistance actuator (C and D, Table 3), the emitted dose was significantly lower than the other actuators (A, B, E and F), due to a high actuator deposition caused by a change in the ex-orifice plume geometry, presumably due to a higher degree of airflow turbulence.

**Table 2 Emitted aerosol results with different actuators and mouthpiece adaptors conditions (n=3 ± Standard deviation)**

| Condition | MMAD (µm) | GSD | Total dose (mg) | Emitted Dose (mg) | FPD (mg) |
|---|---|---|---|---|---|
| A | 3.11 (±0.24) | 1.76 (±0.11) | 1.23 (±0.08) | 1.08 (±0.07) | 0.40 (±0.03) |
| B | 3.24 (±0.09) | 1.80 (±0.17) | 1.27 (±0.02) | 1.13 (±0.09) | 0.40 (±0.03) |
| C | 2.94 (±0.11) | 1.69 (±0.02) | 1.12 (±0.08) | 0.85 (±0.02)* | 0.33 (±0.02) |
| D | 3.09 (±0.12) | 1.69 (±0.03) | 1.07 (±0.06) | 0.81 (±0.03)* | 0.36 (±0.04) |
| E | 3.38 (±0.33) | 1.63 (±0.10) | 1.27 (±0.07) | 1.09 (±0.05) | 0.37 (±0.03) |
| F | 3.10 (±0.07) | 1.67 (±0.02) | 1.17 (±0.08) | 1.02 (±0.01) | 0.45 (±0.04) |

* Significantly different from condition A, B, E and F (p<0.05)

Table 3 shows the airflow resistance and pressured drop for different actuators and mouthpiece adaptors combinations at 28.3 L/min. The airflow resistances of standard and low-resistance actuators (A and B, E, Table 3) were similar with identical values of pressure drop, indicating similar flow conditions at the mouthpiece exit. The pressure drop of condition F (low-resistance adaptor and leaky mouthpiece) was below the detection limit, suggesting that such combination may have minimal effect on the airflow. A significant increase in the flow resistance and pressure drop for the high-resistance actuator (C and D, Table 3) was noticed, possibly resulting in different flow patterns in the mouthpiece.

Figure 2 shows the particle mass deposition profiles of the different experimental configurations. The stage deposition profiles showed similar patterns for all the experimental conditions, which is reflected in the MMAD and GSD having no statistical differences. However, condition C and D showed different actuator and throat deposition profiles (p<0.05), causing a decrease in emitted dose (Table 2) and thus reduction in the mass of particles impacted on the ACI stages. This observation supports the hypothesis that airflow with high-degree of turbulence may be introduced at this condition, leading to a distinct deposition pattern. In addition a reduction in the total ACI stage deposition under such conditions (p<0.05) was observed. However, a lower degree of throat deposition was observed for condition D (leaky mouthpiece adaptor) compared to that of condition C, possibly due to "shielding" laminar flows along the walls of the USP induction port introduced by the leaky mouthpiece adaptor. No significant differences in stage mass deposition (p<0.05), as well as the actuator and throat deposition (p<0.05) among other conditions were observed.

**Table 3 Air resistances of the different conditions (n=5)**

| Condition | Air resistance ($mmH_2O^{0.5} * L/min^{-1}$) | Pressure drop at 28.3 L/min ($mmH_2O^{0.5} * L/min^{-1}$) |
|---|---|---|
| A | 4.94 | 10.20 |
| B | 4.51 | 10.20 |
| C | 10.26 | 30.59 |
| D | 6.50 | 10.20 |
| E | 4.71 | 10.20 |
| F | 4.78 | N/A* |

* Below limit of detection

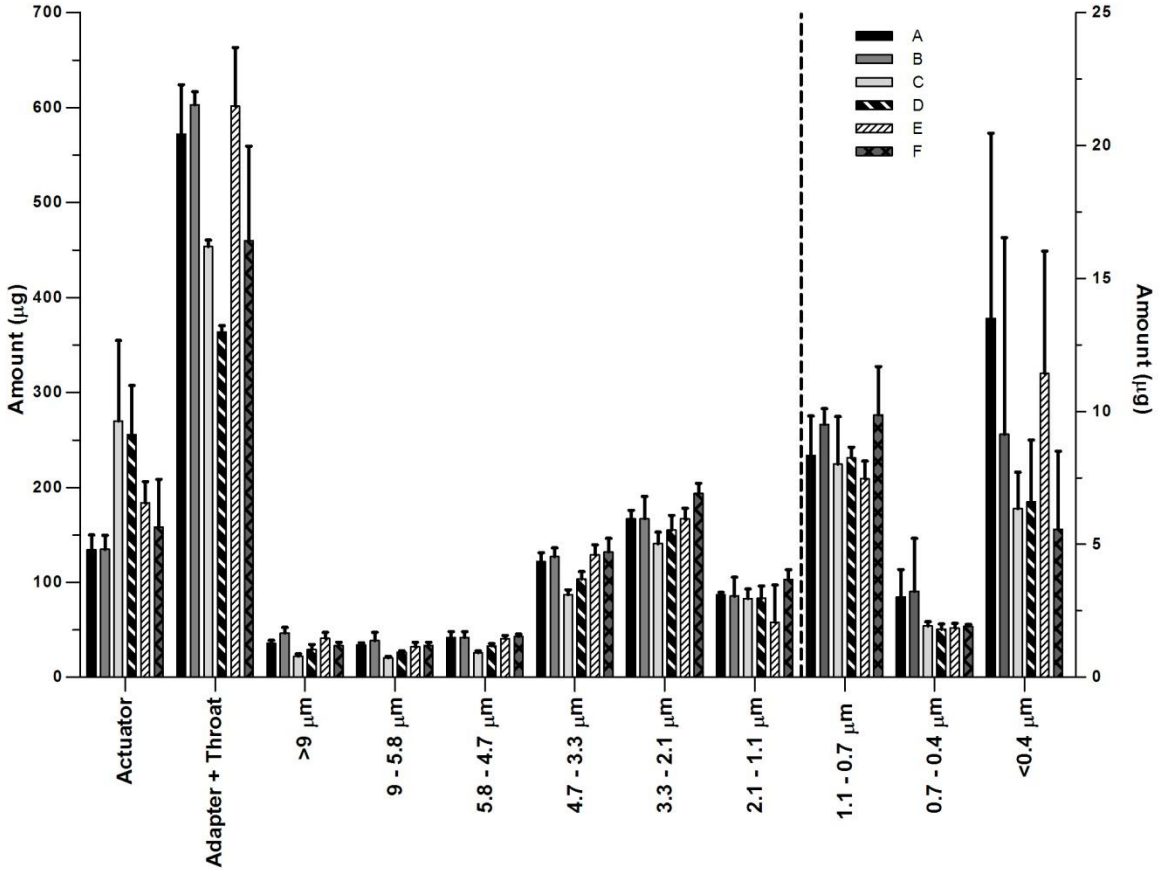


**Figure 2 Mass deposition profiles of emitted particles from Ventolin® suspension formulation with different actuators and mouthpiece adaptors combinations (results on the left axis). Due to low mass deposition results from 1.1- 0.4 µm (at the right of the dotted line, results on the right Y-axis (n=3, ± standard deviation).**

## Discussion and conclusion

This study demonstrated that the improper seal between patients' lips and actuator mouthpiece did not significantly influence the aerosol performance of Ventolin® suspension pMDI formulation, when a standard or low-resistance actuator was used. Using a high-resistance actuator may reduce the FPD, due to the high-degree of flow turbulence at the mouthpiece exit; however, additional flows introduced by the leaky mouthpiece adaptor may serve as 'protective' flow sheets to contain the ex-valve plume geometry in the USP induction port, resulting in a low throat deposition profile.

All the experimental conditions did not show significant difference in the MMAD and GSD of emitted particles. The major momentum in a pMDI formulation is from propellant evaporation once a formulation is actuated[3]; therefore, the airflow resistance and pressure drop of actuator and mouthpiece adaptor combination may not be the main determinants in influencing the aerosol performance of a given suspension formulation. The ex-valve plume characteristics may also not be greatly affected when a mild change in flow dynamics is applied, resulting in almost identical aerosol performance among the different conditions studied.

However, the modified actuators, in either non-leaky or leaky adapters conditions, introduced significant variations (~32%) between the triplicate experiments performed for the mass deposition profile of the actuator and up to ~11% in the cumulative deposition in the throat and actuator.

In conclusion, the aerosol performance of a suspension pMDI formulation is mainly determined by the formulation composition. Difference in actuator resistance may introduce increased variability between individual experiments; however, the aerosol performance may not be significantly affected. The inappropriate seal between patients' lips and actuator mouthpiece may also have limited influences on the aerosol performance. It would be of interest to investigate the effects of abovementioned variables on the aerodynamic performance of solution-based pMDIs. In addition, since for breath actuated pMDIs a leak increases the flow rate necessary for triggering quite significantly, probably imparting more velocity on those particles, also this aspect should be investigated in the future.

**REFERENCES**


1. Sheth, P., Bertsch, M. D., Knapp, C. L., & Myrdal, P. B. (2014). In vitro evaluation of nonconventional accessory devices for pressurized metered-dose inhalers. Annals of Allergy, Asthma & Immunology : Official Publication of the American College of Allergy, Asthma, & Immunology, 113(1), 55–62. doi:10.1016/j.anai.2014.04.006

2. Roy, A., Battle, K., Lurslurchachai, L., Halm, E. a & Wisnivesky, J. P. Inhaler device, administration technique, and adherence to inhaled corticosteroids in patients with asthma. Prim. Care Respir. J. 20, 148–54 (2011).

3. Rasool, F. *et al.* Evaluation and Training of Inhaler Techniques among Asthmatic Patients. **30,** 518–520 (2014).

4. Fadl, A., Wang, J., Yang, P., Zhang, Z., & Cheng, Y. S. (2007). Balloon-based in vitro MDI aerosol deposition experiments on the effects of mouthpiece diameter. Inhalation Toxicology, 19(6-7), 505–15.

5. Smyth, H. D. C. (2003). The influence of formulation variables on the performance of alternative propellant-driven metered dose inhalers. Advanced Drug Delivery Reviews, 55(7), 807–28.

6. Haghi, M., Traini, D., & Young, P. (2014). In Vitro Cell Integrated Impactor Deposition Methodology for the Study of Aerodynamically Relevant Size Fractions from Commercial Pressurised Metered Dose Inhalers. Pharmaceutical Research. doi:10.1007/s11095-013-1282-2