

## Efficiency of valved holding chambers: experimental full dose assessment

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### Summary

Asthma treatment by inhalation in young children, or elderly people with poor coordination, is advisable to be made through a Valved Holding Chamber (VHC) device when a pressurized Metered-Dose Inhaler is prescribed. An analysis of the Emitted Dose (ED) from VHC devices is of utmost importance to infer about the best market option for a certain patient. A full dose Setup was used to test the VHC devices at constant flow and under a breath profile. The devices were tested with Ventolin HFA-134a (salbutamol sulphate as API), and the drug deposited in the Setup was recovered with NaOH 0.01M. Solutions concentrations were estimated by UV-Vis spectrophotometry at 244 nm. At constant flow (26 L/min) results unveils that the ED ranking is the following: Vortex<sup>®</sup> > AeroChamber Plus<sup>®</sup> > NebuChamber<sup>®</sup> > SpaceChamber Plus<sup>®</sup> > OptiChamber Diamond<sup>®</sup> > A2A Spacer<sup>®</sup> > Volumatic<sup>®</sup> > Compact SpaceChamber Plus<sup>®</sup>. The breath profile lead to a different ED ranking: SpaceChamber Plus<sup>®</sup> > Compact SpaceChamber Plus<sup>®</sup> > NebuChamber<sup>®</sup> > AeroChamber Plus<sup>®</sup> > OptiChamber Diamond<sup>®</sup> > Vortex<sup>®</sup> > Volumatic<sup>®</sup> > A2A Spacer<sup>®</sup>. Device material, valve design and body length are the most relevant parameters. Evaluation of the emitted Fine Particle Mass is required to provide a meaningful comparison.

### Introduction

The main purpose of the asthma treatment consists in the delivery of an anti-inflammatory and/or bronchodilator drug beyond the oropharynx, in order to increase the airways' inner diameter<sup>(1,2)</sup>. Although the inhalation therapy is proven to be a way to control asthma symptoms, the efficiency of the conventional devices, such as the pressurized Metered-Dose Inhaler (pMDI) is, yet, inadequate, especially when considering young children and people with coordination problems<sup>(3)</sup>. The VHC, a specific type of spacer, appears as an add-on device for pMDI, which mitigates part of its problems. Many studies state that the VHC material plays an important role in terms of drug delivery. Anti-static coated devices have proven to be more effective than those manufactured in polycarbonate, due to the presence of electrostatic attraction of small drug particles to the walls<sup>(4,5)</sup>. Since the VHC geometrical and dimensional parameters also affect drug delivery to the patient<sup>(6)</sup>, it is important to analyse the effect of these parameters on their efficiency. The correct usage of a VHC device is also known to be determinant to the patient's treatment efficiency<sup>(7)</sup>.

### Experimental Methods

#### Devices

The experimental tests were performed using a commercial pMDI HFA-134a containing a salbutamol formulation (Ventolin<sup>®</sup> from GlaxoSmithKline<sup>®</sup>) coupled with the VHC device. A total of 8 VHC devices were assessed throughout this experimental study (see Figure 1).

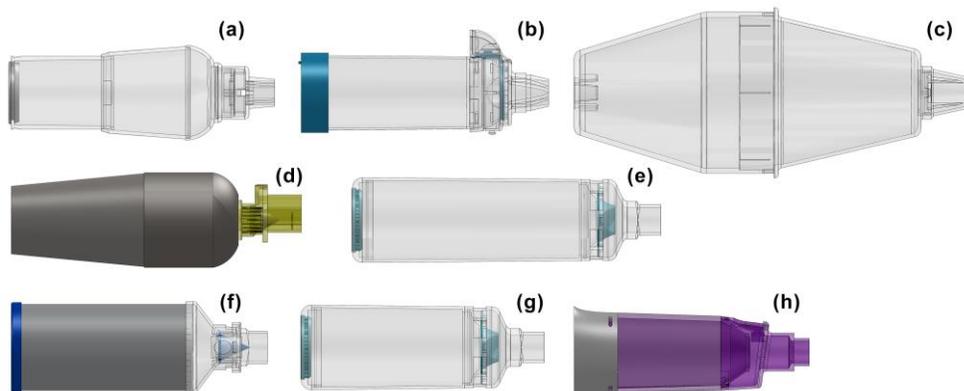


Figure 1 - Representation for each VHC device used in this study.

Being them: (a) *A2A Spacer*<sup>®</sup> from Clement Clarke International<sup>®</sup>, (b) *AeroChamber Plus*<sup>®</sup> from Trudell Medical International<sup>®</sup>, (c) *Volumatic*<sup>®</sup> from Glaxo SmithKline<sup>®</sup>, (d) *NebuChamber*<sup>®</sup> from AstraZeneca<sup>®</sup>, (e) *SpaceChamber Plus*<sup>®</sup> from Medical Development International<sup>®</sup>, (f) *Vortex*<sup>®</sup> from PARI<sup>®</sup>, (g) *Compact SpaceChamber Plus*<sup>®</sup> from Medical Development International<sup>®</sup> and (h) *OptiChamber Diamond*<sup>®</sup> from Philips<sup>®</sup>.

### Experimental Setup

As depicted in Figure 2, the pMDI and each VHC were attached to a plastic adapter fitted on the edge of an aluminum filter housing (containing a filter paper MN 1674 from Macherey-Nagel). In Setup 1, this component was coupled to a vacuum pump, which was calibrated to an output of 26 L/min. A flow meter was used to monitor the vacuum pump flow rate, which was controlled by a needle valve. In Setup 2, the filter housing was directly connected to a breathe simulator, which was based in a closed-form cam-follower mechanism.

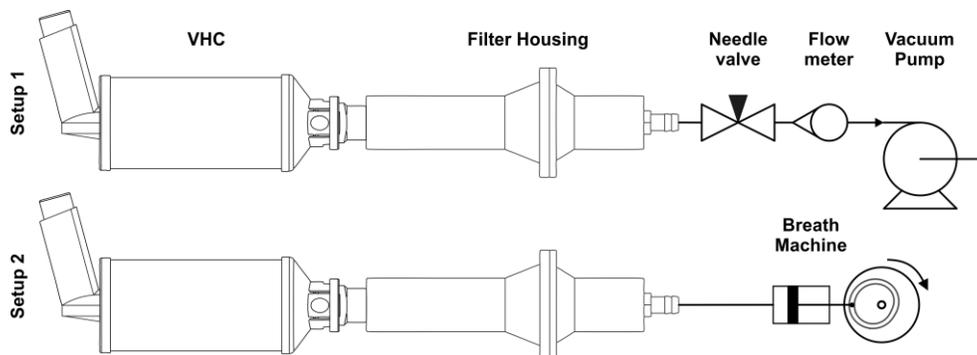


Figure 2 - Schematic of the experimental setup: Setup 1 – constant flow; Setup 2 – breath profile.

### Breathe Pattern

An asthmatic child breathing profile shows certain characteristics that are somehow different from a healthy child. As the holding chamber use is intended for children and elders without the capacity for breathing-actuation coordination, the breathing cycle used is based in data for asthmatic children around 7 years old. According to the Canadian normative for holding chamber testing, a good simplified approach for the shape of the respiratory cycle (flow vs. time) is a sinusoidal function<sup>(8)</sup>. Also other authors presented experimental data that support this assumption<sup>(9)</sup>. The following values were assumed to be the most adequate: breathing frequency of 30 (breaths per minute - BPM), duty cycle of 0.33 and tidal volume of 150 mL. Detailed data sources used is described elsewhere<sup>(10)</sup>. The breathing cycle used is represented in Figure 3. The amplitude of the inspiratory sinus (21 L/min) was obtained by fitting the integral of a sine function to the tidal volume. The same procedure was applied for the exhalation phase. A pause of 4 s after inspiration was added, to allow for the sedimentation of drug particles in the lung. This delay is recommended for improved efficacy in drug delivery. After the exhalation phase, a 2 s pause was also added. This delay is intended to simulate the poor coordination of an asthmatic patient using a VHC device<sup>(11)</sup>.

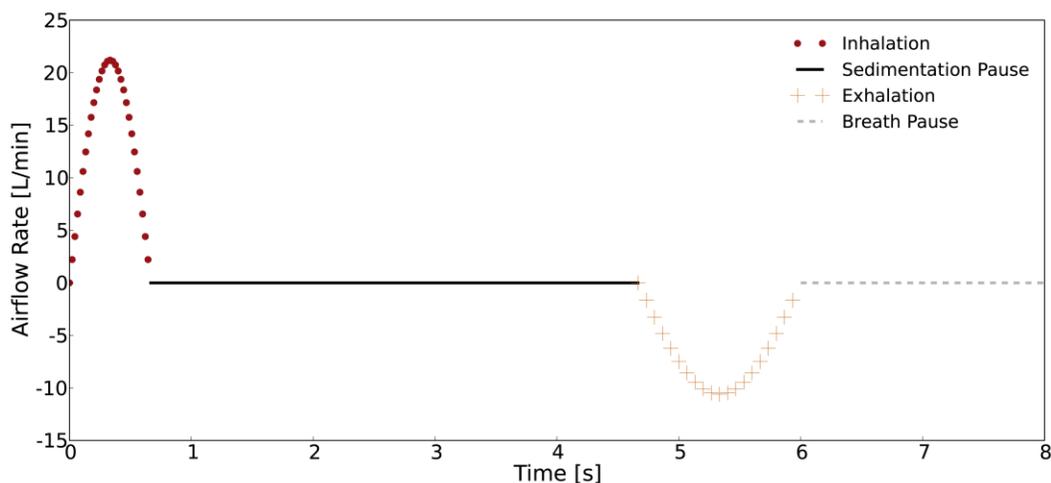


Figure 3 - Asthmatic child breathe profile used in Setup 2.

## Methodology

Each VHC was submerged in an anionic soap solution (1:250) for a period of 1h and dried for at least 12h, prior to the experimental procedure, based on reported findings<sup>(5,12)</sup>. The pMDI canister was then shaken for 5 seconds and fired twice to waste in its original actuator. In Setup 1, the canister was placed in the service actuator, already attached to the VHC. A total of 20 puffs were discharged, being the canister shaken for 5 seconds between each puff. Prior to shutting off the pump, it was allowed a 30 seconds suction time starting from the last puff. In Setup 2, the actuations were made at the beginning of the inspiratory phase (equivalent to 0 s delay studies) during 20 cycles, shaking the canister between puffs. A minimum of three repetitions of each test were made, in order to reduce protocol errors and increase the result's significance. Every stage of the Setup was washed, with NaOH 0.01M<sup>(13)</sup>, into volumetric flasks: primarily, the pMDI into a 25 ml flask, then the VHC device into a 100 ml flask and, finally, the filter paper and the filter housing into 50 ml flasks. To improve the drug solubility and its release from the filter paper, the solution was initially placed into an ultrasonic shaker for 10 min. The washing solutions absorbance ( $\lambda = 244 \text{ nm}^{(13)}$ ) was measured in triplicate by means of a UV-Vis spectrophotometer (UV-2401PC from Shimadzu Corporation<sup>®</sup>). A small addition of NaOH to the distilled water allows the stabilization of pH value, nullifying the absorption peak shifting effects. Using a calibration curve of known absorbance for specific concentrations of salbutamol sulphate, the washing solutions concentration was estimated, which allows the determination of mass retained in each stage. In order to provide a more meaningful data, the mass deposition in the filter paper and its housing were added. In this way it was possible to obtain results for pMDI actuator, VHC and filter deposition, thus allowing a better understanding of the total emitted dose of each of the tested devices. Values of the total mass collected in each test were also determined and used to evaluate the accuracy of the test. Only tests with mass recovery between 85% and 120% of the mass injected were considered as valid.

## Results

Table 1 shows the experimental results obtained in terms of Emitted Dose (ED) at constant flow (using Setup 1) and using a breath simulated profile (using Setup 2) with 0 s delay. In Figure 4 the results comparison for all VHCs at constant and unsteady flow, are depicted.

Table 1 – Emitted dose results, for constant flow and breath profile, with different VHC devices.

VHC Device (Acronym)	Emitted Dose (Ex-actuator) [mcg]	
	Setup 1	Setup 2
Compact SpaceChamber Plus <sup>®</sup> (CSCP)	26.0 ± 3.2 (n=3)	23.0 ± 2.0 (n=3)
Volumatic <sup>®</sup> (VOL)	32.2 ± 4.1 (n=3)	16.1 ± 1.1 (n=3)
A2A Spacer <sup>®</sup> (A2A)	35.8 ± 3.6 (n=4)	10.5 ± 2.0 (n=3)
OptiChamber Diamond <sup>®</sup> (OCD)	40.7 ± 1.0 (n=3)	20.8 ± 0.5 (n=3)
SpaceChamber Plus <sup>®</sup> (SCP)	43.7 ± 1.6 (n=3)	24.3 ± 0.8 (n=3)
NebuChamber <sup>®</sup> (NC)	43.9 ± 2.1 (n=3)	21.6 ± 1.3 (n=3)
AeroChamber Plus <sup>®</sup> (ACP)	46.9 ± 1.3 (n=3)	21.4 ± 0.2 (n=3)
Vortex <sup>®</sup> (V)	52.7 ± 1.8 (n=3)	18.2 ± 1.8 (n=4)

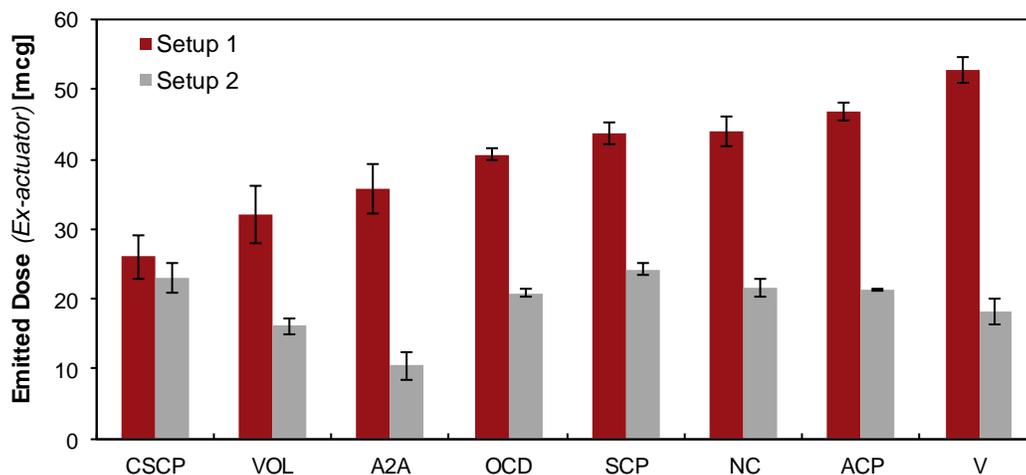


Figure 4 - Representation of the ED results for the different VHCs at constant and unsteady flow.

## Discussion

Results show that, among all VHC tested for 26 L/min, the V presents the highest emitted dose, being twice higher than the CSCP. Ranking top are V and ACP, two non-electrostatic devices, followed by a metal VHC, the NC, which obviously is the best charge dissipative device. Although SCP is made of Polycarbonate, a non-dissipative polymer, the ED is slightly higher than OCD; this is most likely due to the difference in volume (230 vs. 140 mL) and body length (150 vs. 97 mm). A comparison between SCP and CSCP, two geometrically identical devices, shows that the higher the body length, the higher the ED, Barry<sup>(14)</sup> reported the same conclusion for spacers. Valve design is also an important factor; take for instance the VOL case, its valve design is the equivalent to a vertical wall for drug particles passage. The device emitted dose is very low; despite it has the best combination of known geometrical factors<sup>(14)</sup>: high volume (750 mL), high body length (192 mm) and high body diameter (52 mm). Generally speaking the non-electrostatic devices show higher ED than non-dissipative polymers, keeping in mind that results are based in total ED and that all VHC had the same charge reduction soapy water treatment.

Results (based in Setup 2) for a breath profile are distinct from the ones at constant flow. For the tested VHC under this Setup, the results rank as follows: SCP > CSCP > NC > ACP > OCD > V > VOL > A2A. The SCP ranks top with 2.3 times higher emitted dose than A2A. Ranking next are the CSCP and NC, showing similar values. In this Setup, the valve function is the most important factor. And since the spray plume rests in the VHC during certain cycle periods, the non-electrostatic characteristics shall play a very important role. In general, the ED values are quite lower than at constant flow, which is highly expectable, with a reduction from 1.1 to 3.4 times.

## Conclusion

Considering emitted dose (ED) results, the V is the best VHC device at constant flow and the SCP at unsteady flow. The NC and ACP maintain a constant comparative performance at both experimental setups. Body length, valve design and device material seems to be the most influential design characteristics. Fine particle dose studies shall be made to provide a more meaningful insight.

## References

1. National Heart Lung and Blood Institute: *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*. Bethesda; pp. 417, 2007.
2. Bisgaard H, O'Callaghan C, and Smaldone GC: *Drug Delivery to the Lung*. Marcel Dekker, Inc., New York, USA; pp. 536, 2002.
3. Finlay WH, and Zuberbuhler P: In Vitro Comparison of Beclomethasone and Salbutamol Metered-Dose Inhaler Aerosols Inhaled During Pediatric Tidal Breathing From Four Valved Holding Chambers. *Chest*. 1998;114:1676–1680.
4. Janssen R, Weda M, Ekkelenkamp MB, Lammers J-WJ, and Zanen P: Metal versus plastic spacers: an in vitro and in vivo comparison. *Int J Pharm*. 2002;245:93–8.
5. Wildhaber JH, Devadason SG, Hayden MJ, James R, Dufty AP, Fox RA, Summers QA, and LeSouëf PN: Electrostatic charge on a plastic spacer device influences the delivery of salbutamol. *Eur Respir J*. 1996;9:1943–1946.
6. Oliveira RF, Teixeira SFCF, Marques HMC, and Teixeira JC: Efficiency evaluation of VHC: a CFD comparison study at constant flow. In: *Proceedings of the 2014 International Conference on Mechanics, Fluid Mechanics, Heat and Mass Transfer*. EUROPEMENT, Interlaken, Suisse; 2014.
7. Foss SA, and Keppel JW: In Vitro Testing of MDI Spacers: A Technique for Measuring Respirable Dose Output with Actuation In-Phase or Out-of-Phase with Inhalation. *Respir Care*. 1999;44:1474–1485.
8. CAN/CSA-Z264.1-02(R2008): *Spacers and Holding Chambers for Use with Metered-Dose Inhalers*. Canadian Standards Association, Toronto, Canada; pp. 94, 2008.
9. Janssen LL, Anderson NJ, Cassidy PE, Weber RA, and Nelson TJ: Interpretation of Inhalation Airflow Measurements for Respirator Design and Testing. *J. Int. Soc. Respir. Prot*. 2005;22:122–141.
10. Oliveira RF, Teixeira JC, Marques HMC, and Teixeira SF: An Experimental Setup for API Assessment of a Valved Holding Chamber Device. In: *Volume 3A: Biomedical and Biotechnology Engineering*. ASME, San Diego, California, USA; pp. V03AT03A074, 2013.
11. Mitchell JP, and Dolovich MB: Clinically relevant test methods to establish in vitro equivalence for spacers and valved holding chambers used with pressurized metered dose inhalers (pMDIs). *J Aerosol Med Pulm Drug Deliv*. 2012;25:217–42.
12. Piérart F, Wildhaber JH, Vrancken I, Devadason SG, and Le Souëf PN: Washing plastic spacers in household detergent reduces electrostatic charge and greatly improves delivery. *Eur Respir J*. 1999;13:673–8.
13. Finlay WH: Inertial sizing of aerosol inhaled during pediatric tidal breathing from an MDI with attached holding chamber. *Int J Pharm*. 1998;168:147–152.
14. Barry PW, and O'Callaghan C: The Optimum Size and Shape of Spacer Devices for Inhalational Therapy. *J Aerosol Med*. 1995;8:303–305.