Space Chamber devices in vitro performance evaluation at constant flow

R F Oliveira[1], S F C F Teixeira[2], H M Cabral-Marques[3] & J C F Teixeira[1]

[1]CT2M R&D Centre, University of Minho, 4800-058 Guimarães, Portugal
[2]ALGORITMI R&D Centre, University of Minho, 4800-058 Guimarães, Portugal
[3]iMed.ULisboa R&D Centre, Universidade de Lisboa, 1649-003 Lisboa, Portugal

Summary

The use of spacers is advisable for asthma treatment in younger patients (< 5 years). This work aims to evaluate such devices in terms of performance when compared against the use of pressurized metered-dose inhaler (pMDI) solo. For that purpose an experimental *in vitro* assessment of four valved holding chambers (VHC) and one tubular spacer was performed using a Multi-Stage Liquid Impinger at 60 L/min. The add-on 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. Results showed that the highest VHC mass deposition was found in the Volumatic®, while the valveless tubular spacer (i.e. Compact Space Chamber Spacer®) has the lowest deposition. Add-on devices throat deposition was found to be lower than the pMDI solo (≈45 µg). Only between the Compact Space Chamber® and the Space Chamber® were not found statistically significant differences in throat deposition ($p>0.05$). The mass median aerodynamic diameter (MMAD) is lowest for the Volumatic® and highest (2.3±0.1 µm) for the valveless tubular spacer (3.2±0.3 µm), with statistical differences between the add-on devices ($p<0.001$). The MMAD for VHCs with leaflets valve type showed no significant differences ($p>0.05$). Fine particle mass (FPM) between the add-on devices showed no differences ($p>0.05$). The highest FPM is provided by Volumatic® (36.5±2.4 µg) and the lowest Compact Space Chamber Anti-static® (32.9±3.2 µg). The pMDI solo emits lower FPM (29.3±3.4 µg). The calculation of the coarse/fine/extra-fine particle fractions and coarse/fine/extra-fine ratios showed that all the add-on devices have similar performance results for all the calculated metrics, being within the reference values. Add-on devices provide the reduction of the coarse fraction of the pMDI plume and, subsequently, the reduction of the throat deposition. The existence (or not) of a valve, even the type of valve, has influence in the mass deposited inside the VHC and in the throat.

Introduction

The asthma treatment consists in the delivery of an anti-inflammatory and/or bronchodilator drug downstream the oropharynx, in order to increase the airways' inner diameter[1]. Although the inhalation therapy is proven to be one of the preferable ways to control asthma symptoms, the usability of the conventional devices, such as the pressurized metered-dose inhaler (pMDI) is limited for young children and people with coordination problems[2]. The valved holding chamber (VHC), a specific type of spacer, is an add-on device for pMDI, which mitigates this problem and potentiates the drug delivery by removal of the coarse part of the pMDI plume. Many studies state that the VHC material plays an important role in terms of drug delivery[3–5]. 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[3]. Since the VHC geometrical and dimensional parameters also affect drug delivery to the patient[6], it is important to analyse the effect of these parameters on their efficiency. This study aims to the evaluation of four spacer devices upon several metrics of interest, such as the fine particle mass (FPM), mass median aerodynamic diameter (MMAD) and throat deposition.

Experimental Methods

Devices

Five add-on devices were tested using a commercial pMDI HFA-134a containing a salbutamol sulphate formulation (Ventolin® from GlaxoSmithKline®). A tubular spacer - CSCS (similar in shape to the Compact Space Chamber Plus®) and four VHC were evaluated against the MDI solo. The VHC's tested were: the Space Chamber Plus® - SC (from Medical Developments International®); Compact Space Chamber Plus® - CSC (from Medical Developments International®); the Antistatic Compact Space Chamber Plus® - CSCA (from Medical Developments International®) and the Volumatic® - VOL (from GlaxoSmithKline®). The add-on devices volumes are: CSCS - 160 mL; CSCA - 160 mL; CSC - 160 mL; SC – 230 mL and VOL – 750 mL. Each add-on device was submerged in an anionic soap aqueous solution (1:250) during one hour and left drying out for 24 hours, prior to the experimental procedure, based on published procedures[2]. This pre-treatment method was discussed and supported by Mitchell and Nagel[7], proving that electrostatic charge in VHC devices can be mitigated (mainly in the non-dissipative materials). This procedure will set a baseline for all the different devices and reduce the inconsistency of the total emitted mass (TEM).

Experimental Setup

The experimental setup was composed by the pMDI and the VHC attached to a silicon universal adapter fitted in a USP throat[8]. The latter was connected to a 5-stage MSLI (calibrated in 2014 by Westech, UK), using a filter paper on last stage (MN 619 from Macherey-Nagel, Germany). The MSLI was then coupled to a vacuum system constituted by two pumps (GS-6 from General Europe Vacuum, Italy). At the beginning of each experiment, the flow passing through the MSLI, was calibrated by means of a mass flow meter (Model 4043 from TSI, USA) adjusted to a value of 60.0 ± 0.5 L/min.

The corresponding value was marked in a rotameter (D10A11 from ABB, Switzerland) placed between the MSLI and the vacuum system, which was used to monitor the vacuum pump flowrate during the experiment by adjusting it for the increasing pressure drop in the filter. This adjustment was made possible by a ball valve. Due to the fact that MSLI was the equipment available to perform this study, a flowrate of 60 L/min was used in this study, since it provides more accurate results than 30 L/min[9]. Authors are aware that target patient inspiration peak is situated around 20 L/min. Although for comparison purposes, the flowrate value is not a major issue.

Methodology

At the beginning of each experimental test, the pMDI canister was shaken during 5 seconds and fired twice to waste from the MDI original actuator. Subsequently, the canister was placed in the service actuator, already attached to the VHC. A total of 40 puffs were made (20 puff for the case where the pMDI was tested alone), while shaking the canister for 5 seconds between each puff. Before shutting off the pump, a 30 seconds suction time starting from the last puff was allowed. To minimize operator procedure errors, a Java application for Android was developed. A minimum of six repetitions of each test were made, in order to reduce protocol errors and the results uncertainty. Every stage of the apparatus was washed, with 0.01M NaOH[10], into volumetric flasks. To improve the drug solubility and its release from the filter, this was placed into an ultrasonic shaker for 10 minutes. Each washing solution absorbance (λ=244 nm[10]) was measured in triplicate by means of a UV-Vis spectrophotometer (UV-2401PC from Shimadzu Corporation®, Japan). These solutions concentration were estimated through the use of a calibration curve for salbutamol sulphate in NaOH 0.01M (R^2= 0.99996 from 0.01 to 2.0 AU). The determination of the mass retained allowed an extensive analysis of the distribution of mass deposition for each VHC device, as well as, the drug emitted by each device and its aerodynamic characteristics. Values of the total mass collected in each test were also determined and used to evaluate the accuracy of the test. Experiments were conducted at an average temperature of 20.4 ± 0.1 ºC and an average relative humidity of 47 ± 1 %, measured with a weather station (W.155 Weather station from Ventus, Denmark). The large number of puffs executed during experimental procedure is related to the fact that UV-Vis spectrophotometry required a certain level of mass in the MSLI stages to be above the limit of quantification. Nonetheless, the results are normalized for one actuation.

Data analyses

Data obtained were normalized for the mass of one actuation. All data are presented with error bars, which are representative of the standard error of the mean values with an expanded uncertainty based on the t-student distribution for a confidence interval of 95%[11]. Due to the small size of the samples and lack of similarity with a normal distribution, data were evaluated by the nonparametric Kruskal–Wallis H test (SPSS v21.0 from IBM, USA). In all statistic tests, the level of significance considered was 5%. The analysis of the experimental was done in terms of indices that compare the efficiency of the VHCs in comparison to the use of pMDI solo. The procedure for the calculation of such indices is presented below. The formulae described originates in the US Pharmacopeial Forum as a stimulus for the USP revision: <1602> Spacers and valved holding chambers used with inhalation aerosols (USP38-NF33)[12]. The TEM of the device, is the sum of the drug mass present in all zones of the setup right downstream the device under testing. This includes the throat and all the stages of the impactor.

The FPM is the amount of mass present in the stages of the impactor with a cut-off point below 5 µm. In the case that no stage cut-off point coincides with the 5 µm value, it is necessary to proceed with the construction of the cumulative mass-weighted aerodynamic particle size distribution (APSD) and interpolate it from there. That was the case for the MSLI used in this study. The coarse particle mass (CPM) is calculated as the difference between TEM and FPM. This assumes that the mass in the throat is all composed by coarse particles, although not the correct assumption is considered as acceptable. The extra-fine particle mass (EPM) is calculated as the mass of particles bellow 1 µm of diameter. The procedure used for the calculation was similar to the one used for the FPM calculation. The coarse particle fraction (CPF) is calculated in percentage as presented in Eq. 1. A similar equation was used for the calculation of fine particle fraction (FPF) and extra-fine particle fraction (EPF).

$$CPF = \left[\frac{CPM}{TEM}\right] \times 100 \qquad \text{(Eq.1)}$$

The guidelines state that a properly functioning VHC shall have its FPF value above 60%, and CPF below 40%. The EPF is strongly related to the drug formulation APSD, however its value can vary from < 20% FPF to 50% FPF. The following indices are used to evaluate the use of a VHC when compared to a MDI solo. These ratios compare the coarse mass (Rc) presented in Eq. 2. Similar equations were used to calculate the fine mass ratio (Rf) and extra-fine ratios (Re).

$$Rc = \frac{CPM_{VHC}}{CPM_{MDI}} \qquad \text{(Eq.2)}$$

Results

Table 1 presents the mass deposition results (per actuation) for salbutamol in each zone of the apparatus, including the expanded uncertainty associated. Figure 1 represents the cumulative mass fraction emitted by each device tested per aerodynamic cut-off diameter, where the total corresponds to the TEM value. The aerodynamic diameter lower bound was considered as 0.1 µm since the MSLI present a limited resolution for very small particles. Table 2 shows the values for the performance metrics described above, along with the MMAD for all tested devices. Figure 2 presents the scatter plot of the TEM versus FPM, for the devices tested. The diagonal dashed grey line represents the ideal result, where the emitted mass of a device is fully composed by fine particles.

Table 1 – Salbutamol mass deposition results for the tested devices per zone, normalized for one actuation (100 µg).

	Actuator	VHC	Throat	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5 (filter)
MDI	11.5 ± 0.7	-	45.5 ± 2.7	6.1 ± 0.9	5.1 ± 0.5	11.8 ± 1.2	8.9 ± 1.3	15.3 ± 1.8
CSCS	10.0 ± 0.4	27.6 ± 3.5	10.4 ± 0.6	3.1 ± 0.4	4.3 ± 0.4	14.5 ± 0.8	14.3 ± 1.2	18.9 ± 2.1
CSCA	10.1 ± 0.5	44.1 ± 3.4	6.2 ± 0.5	2.8 ± 0.6	3.4 ± 0.4	11.7 ± 0.8	11.3 ± 0.8	16.5 ± 2.2
CSC	9.7 ± 0.8	40.1 ± 1.8	5.2 ± 0.4	2.3 ± 0.5	3.1 ± 0.1	12.6 ± 1.3	12.7 ± 1.0	18.1 ± 1.9
SC	11.0 ± 0.6	37.8 ± 2.5	5.4 ± 0.3	2.4 ± 0.4	3.5 ± 0.5	12.7 ± 1.3	12.8 ± 1.3	18.3 ± 1.3
VOL	10.0 ± 0.8	50.2 ± 4.5	2.8 ± 0.2	1.5 ± 0.2	2.5 ± 0.3	11.3 ± 1.0	12.6 ± 1.0	19.0 ± 1.5

Table 2 – Calculated performance metrics (based in the APSD) for the tested devices.

	MDI	CSCS*	CSCA	CSC	SC	VOL
TEM [µg]	92.6 ± 1.2	65.4 ± 2.3	51.9 ± 3.5	54.1 ± 3.8	55.0 ± 2.1	49.6 ± 2.9
EPM [µg]†	8.6 ± 1.0	10.6 ± 1.2	9.3 ± 1.2	10.2 ± 1.1	10.3 ± 0.7	10.7 ± 0.8
FPM [µg]	29.3 ± 3.4	39.4 ± 3.0	32.9 ± 3.2	36.3 ± 2.7	36.5 ± 1.3	36.5 ± 2.4
CPM [µg]	63.3 ± 2.3	26.0 ± 0.9	19.0 ± 1.3	17.8 ± 1.3	18.5 ± 1.4	13.1 ± 0.8
EPF [%]†	9.3 ± 1.0	16.2 ± 1.3	17.8 ± 1.4	18.8 ± 1.1	18.7 ± 1.9	21.5 ± 0.9
FPF [%]	31.6 ± 3.3	60.1 ± 2.6	63.2 ± 3.0	67.1 ± 0.9	66.4 ± 1.6	73.5 ± 1.2
CPF [%]	68.4 ± 3.3	39.9 ± 2.6	36.8 ± 3.0	32.9 ± 0.9	33.6 ± 1.6	26.5 ± 1.2
Re [-]†	-	1.2 ± 0.1	1.1 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1
Rf [-]	-	1.3 ± 0.1	1.1 ± 0.1	1.2 ± 0.1	1.2 ± 0.0	1.2 ± 0.1
Rc [-]	-	0.4 ± 0.0	0.3 ± 0.0	0.3 ± 0.0	0.3 ± 0.0	0.2 ± 0.0
MMAD [µm]	19.6 ± 4.6	3.2 ± 0.3	2.9 ± 0.3	2.7 ± 0.1	2.7 ± 0.1	2.3 ± 0.1

† Extra-fine mass metrics have low accuracy due to the fact that MSLI has a low number of stages and poor resolution for the extra-fine fraction.
* The application of the metrics is not advisable to valveless tubular spacers.

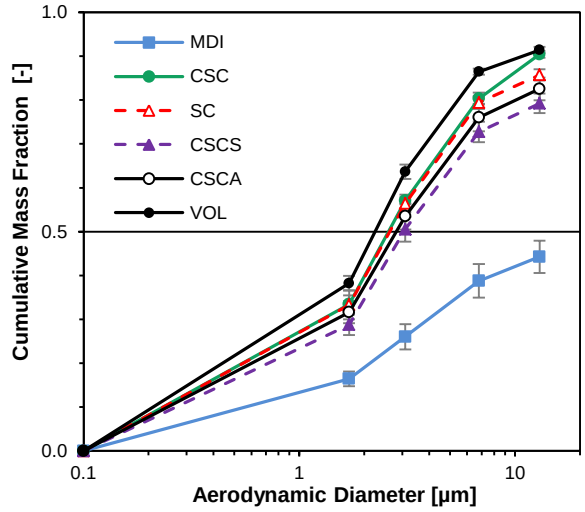

Figure 1 - Cumulative mass fraction from the TEM of each device tested.

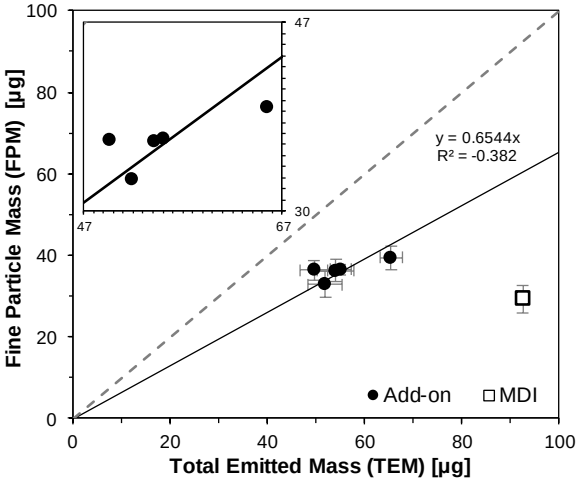

Figure 2 - Correlation plot for the FPM vs. the TEM.

Discussion

Results from Table 1 show the deposition of mass in each zone, where can be observed that the actuator's mass value is very similar for all of the devices (≈10 µg). The CSCS has the lowest VHC mass deposition, related to the fact that no valve is present. Whereas the VOL presents the highest, this might be due to the high internal surface area of the device and to the valve geometry (i.e. Coin type) that has a small and annular aperture area. The Coin valve provides a large obstacle to the particle movement, leading to a greater impact of the bigger particles. Mass deposition (in VHC and throat) is highly related to the flowrate of 60 L/min, although deposition results at 30 L/min show lower values[9]. Mass deposition in throat for the tested add-on devices ranks as following: CSCS > CSCA > SC > CSC > VOL. Statistical significant differences, in the throat deposition, were perceived regarding the valve existence ($H(4)=26.23$, $p<0.001$). Throat deposition is statistically different when comparing VOL with any other add-on device ($p<0.01$), due to the fact that a finer plume exits the VHC, it leads to lower deposition in the throat. Looking to the SC throat deposition versus the other add-on devices it was found statistically significant differences ($p<0.05$), except for the CSC ($H(1)=1.26$, $p>0.05$)

Figure 1 points out that the mass cumulative curve for the MDI solo is significantly different from the add-on devices, as expected. This is related to the fact that a high amount of mass is lost by throat deposition, contrary to the add-on devices that emit a finer plume. The VOL shows slightly higher amount of mass deposited in the lower stages of the MSLI, than the other add-on devices. This fact is surely related to its capacity to remove the coarse fraction of the plume, a finer plume will provide a higher amount of drug to the patient lungs. The represented error bars show that uncertainty is low for all the tested devices.

The MMAD results are shown in Table 2 and rank as following: CSCS > CSCA > SC > CSC > VOL, with statistically significant differences between them ($H(4)=20.94$, $p<0.001$). However there are no significant differences between the valved spacers using Leaflets valve ($H(2)=4.53$, $p>0.05$). The Coin valve device (i.e. VOL) present significant differences when compared to the other valved devices ($H(3)=14.23$, $p<0.01$). Fine particle mass (see Table 2) emitted by the add-on devices show no statistically significant differences ($H(4)=9.17$, $p>0.05$). CSCS ranks highest followed by VOL > SC > CSC > CSCA. The use of an add-on devices proven to increase the available FPM to the patients (>32 µg) when compared to the use of MDI solo (≈29 µg). The EPM obtained with the use of add-on device is slightly higher than the one when MDI was used solo. The values of FPF for the add-on devices were found to be above the advisable[12] value of 60%, with significant differences between them ($H(4)=23.07$, $p<0.001$). All Rc values were below 0.6 and the Rf was slightly above 1.0, which is in agreement with the referenced values[12]. No statistically significant differences were observed between the add-on devices in terms of reported Rf metric ($H(4)=9.10$, $p>0.05$).

Figure 2 results point out that the use of MDI solo emits a higher amount of mass than when it is coupled to any add-on device, although it does not mean that a higher amount of FPM is present. Otherwise, the VHC are all grouped in a region of TEM between ≈50 and ≈65 µg, with the FPM ranging from ≈33 to ≈39 µg. A linear trendline was calculated with these results, solid black line, for the VHCs. It is suggested that such trendline is closely related to the technology itself (e.g. VHC, nebulizer, dry powder inhaler). Likewise, other inhalation treatment devices shall possess another linear trendline with its characteristic slope.

Conclusion

Add-on devices provide the reduction of the coarse fraction of the pMDI plume and, subsequently, the reduction of the throat deposition. The existence (or not) of a valve, even the type of valve, has a strong influence in the mass deposited inside the VHC and in the throat. Results point out that Volumatic® has a good capacity to reduce the MMAD (lower the value, finer the plume and more drug available to the lungs) of the emitted plume, which results in lower throat deposition. This is likely related to the type of valve and high volume of the Volumatic®. The tubular spacer emits the highest FPM within the add-on devices; however its plume is coarser (i.e. highest MMAD) and shows highest throat deposition. Volumatic® emits the second highest FPM. All devices showed performance metrics values within the reference values.

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