How priming of a Large Volumatic® spacer affects the aerosol dose delivered?

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Summary

Background Spacers are commonly used add-on devices for pressurised meter dose inhalers (pMDI) to improve drug delivery to the lungs. Plastic spacers need to be 'prepared' prior to use by priming or washing in order to remove possible electrostatic charge. **Aim:** The study aimed to evaluate the performance of a Volumatic® spacer (GSK) using two types of preparation techniques (primed with multiple actuations without prior washing and, washed with liquid detergent and used without priming) and its effects on the dose available for inhalation following administration of multiple doses of a suspension pMDI formulation. **Experimental Method:** The Volumatic® spacer was tested in three different conditions: new and untreated, washed, and primed. In each condition, twelve doses of salbutamol sulphate pMDI (Ventolin®, GSK) were actuated into the spacer and the emitted doses were collected and chemically quantified. **Results:** Data showed higher average dose of 25.11± 2.92 µg for primed condition, 16.22± 2.72 µg washed and 11.69 ± 1.12 µg new and untreated condition, respectively. **Conclusion:** This study showed that priming a spacer with multiple doses prior to use results in a higher exiting particle mass, indicating that priming a large-volume spacer could be advantageous in a clinical setting, where multiple doses need to be administered to patients.

Introduction

Spacers are holding chambers used as add-on device for pressurized meter dose Inhalers (pMDIs) to facilitate drug delivery to the lungs. Spacers fill a particularly important role in patient groups that suffer from decreased lung function, acute asthmatic exacerbations and/or poor coordination. Using a spacers reduces the velocity of the spray droplets, allowing more time for the patient to inhale, thereby increasing the amount of drug particles available for lung deposition [1].

Plastic spacers are one of the commonly used add–on devices in clinical settings[2]. One main disadvantage with plastic spacers is the build-up of electrostatic charge on the inside surfaces, causing the emitted aerosols to adhere to the spacers due to static interaction, with consequent reduction of the available dose for administration[3]. Previous research has shown that static charge can be avoided by washing the spacer in liquid detergent[4], or priming the spacer with multiple actuations prior to use[5]. The aim of this study was to evaluate the performance of the commercially available large-volume Volumatic® (750mL) plastic spacer with three preparation techniques: (A) new spacer without any preparation, (B) pre-washed in mild liquid detergent and left to air dry, and (C) new spacer primed with 20 doses of salbutamol sulphate Ventolin® pMDI prior to use. Each preparation technique was evaluated as the available mass of aerosols exiting from the spacers up to 12 individual doses, according to procedures for the emergency treatment highlighted in the Global Initiative for Asthma (GINA) [6].

Method and Materials

Each spacer was prepared using the abovementioned techniques. For each testing condition, 12 individual doses of a new Ventolin® pMDI was actuated into the Volumatic® spacer and each dose (effective dose) exiting from the spacer was collected into a Dose Unit Sampling Apparatus (DUSA) at 28.3L/min for 8 sec. Vigorous shaking of the pMDI canister was undertaken in between each shot. The DUSA, spacer and actuator were thoroughly rinsed with acetonitrile aqueous solution (8%, v/v) into proper volumetric flasks and samples chemically quantified using high performance liquid chromatography (HPLC). The sample quantification was performed using a C18 column (Luna, Phemomenex, US) using a standard solution in 0.05-10 µg/mL concentration range with R^2>0.999 and a mobile phase of 8% (v/v) buffered acetonitrile aqueous solution (0.05M K_2HPO_4, PH 4.5) at a flow rate 1mL/min, with a detection wavelength 270 nm and injection volume 100 µL.

Analysis of variance (ANOVA) followed by Tuckey'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) and standard deviation.

Results

Table 1 shows the total dose, emitted dose and mass of particles deposited in the spacers with different preparation techniques after delivering 12 actuations of Ventolin® pMDI. The emitted dose is defined as the mass of particles deposited in the spacer and collected in the DUSA. Total doses from different conditions were in line with Ventolin® nominal dose (100 µg/actuation), according to the pharmacopeia dose requirements (± 25% of label claim) [7]. The mass of aerosols deposited in the spacers accounted for approximate 86% ~ 92% of the emitted doses for the three

spacers preparation techniques, suggesting the amount of aerosols that can be administered by patients from spacers is very limited using a large-volume plastic spacer.

Table 1 Total dose, emitted dose and particle deposition in the Volumatic® spacer prepared with different techniques after 12 actuations

Preparation technique	Total dose (μg)	Emitted dose (μg)	Mass deposition in spacer (μg)	Mass deposition% in spacer
A (new and untreated)	1133.0 ± 27.4	1057.2 ± 28.4	917.0 ± 26.4	86.7 ± 0.3
B (washed and unprimed)	1444.2 ± 29.9	1469.7 ± 14.0	1275.3 ± 9.9	86.8 ± 1.4
C (new and primed)	4002.8 ± 91.2*	3812.8 ± 100.2	3511.4 ± 74.3	92.1 ± 0.9

*: Total dose includes the amount of aerosols from spacer priming (20 actuations)

Figure 2 shows the effective doses of aerosols of 12 individual actuations exiting from the spacer prepared with different techniques. Spacers prepared with condition A (new and untreated) showed the least effective doses, with an average value of 11.69 ± 1.12 μg/actuation. Condition B (washed) and C (new and primed) showed an effective dose, at an average of 16.22 ± 2.27 and 25.11 ± 2.92 μg/actuation, respectively. Although up to 92% of particle deposited in the spacer, results for condition C are significantly higher than those from other preparation techniques ($p<0.05$), suggesting the spacers prepared by priming may be more suitable for patients due to the higher effective doses. The average effective dose from condition B was also significantly higher than the unprepared condition, indicating that washing plastic spacers with mild liquid detergent may effectively reduce the electrostatic charge induced by the plastic material.

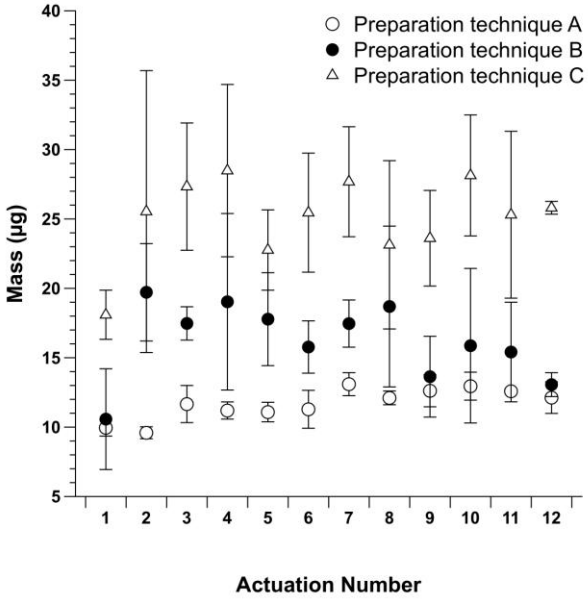

Figure 2 Effective doses of emitted aerosols exiting from spacers prepared using different techniques: (A) new and untreated, (B) washed and (C) primed with 20 actuations according to GINA [6]

In addition, the first two effective doses of condition A were significantly lower than the remaining doses ($p<0.05$), which demonstrates the poor spacer performance if no preparation was conducted, as most of emitted aerosols from initial actuations may adhere to the inside of a spacer due to static charge (Figure 2). There was no significant difference in the effective doses from actuation number 9-12, between condition A and B ($p>0.05$). This observation indicates that the spacer may be 'coated' by the emitted particles from the first 8 actuations, therefore giving similar effective doses. The effective dose from the first actuation of condition B was also lower than the rest, which also suggests the particle adherence onto the spacer surfaces. However, the increase in the effective doses of the remaining actuations may indicate that washing the spacer with mild liquid detergents can effectively reduce the number of actuations required to prepare a large-volume spacer.

An increase in the effective dose can be observed when a spacer was primed with 20 actuations of the Ventolin® pMDI (Preparation technique C, Figure 2). Such an increase may be the result of spacer coating with emitted particles during priming. Although preparing spacers with technique B and C (washing and priming) can effectively increase the administered dose, large variability (~37% in RSD, relative standard deviation) can also be observed. Such high variation between each measurement and actuation may also potentially affect the aerosol lung deposition when a

patient uses the large-volume plastic spacer, since patients may have different lung capacities, possibly introducing additional variability in the effective dose released from the spacers.

Discussion and Conclusion

This study shows the difference in the effective dose of a pMDI that can be delivered when a large-volume (750 mL) plastic spacer (Volumatic®) is prepared using different techniques. Data on the collected effective dose indicated the highest particle lung deposition could be achieved by priming the space with 20 actuations of the suspension pMDI. Washing spacer with mild liquid detergent can also effectively reduce the electrostatic charge built on the spacer, however a reduction in the effective doses was observed. Using this spacer without any pre-treatment resulted in the lowest effective dose, due to the electrostatic interactions between emitted aerosols and spacer.

These observations correlate with previous research showing greater exiting doses from a primed plastic spacer compared to new and untreated ones[5]. Although aerosol delivery efficiency from washed spacers was previously investigated [4, 8], no current literature has compared the effective doses that patients may potentially administrate when spacers are prepared in different methods. Therefore the current study, whilst highlighting the importance of cleaning a spacer properly for general usage, also indicates that priming is the preferred method instead of washing for the large-volume plastic spacers, in order to obtain maximised drug delivery to patients, a valuable information for clinical emergency setting where patient's administration of multiple consecutive doses of medication is required in a short time period. In the future, it would be of interest to investigate the effective doses from spacers with different volumes and materials.

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