Use of Valved Holding Chambers Without Pre-Conditioning and the Influence of Anti-Static Materials

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Summary

Background: In recent years 'anti-static' Valved Holding Chambers (VHCs) have become more widely available. They enable use directly out of packet without pre-treatment, as pre-washing with detergent followed by drip-drying in air is time-consuming and not always followed. This laboratory study sought to investigate whether fine particle (<4.7 µm) drug delivery efficiency was similar from four commercially available VHCs, two of which were 'anti-static', the others being non-conducting, when pre-washing was not performed.

Materials and Methods: Each VHC (n=3 or 5/group) was evaluated with Seretide® 250 pMDI (fluticasone propionate (FP)/25 salmeterol xinafoate (SX)), sampling the emitted aerosol at 28.3 L/min via an abbreviated Andersen impactor connected to a PhEur/USP induction port. A 5 s delayed inhalation was mimicked using a proprietary apparatus. Recovered FP and SX were assayed by validated HPLC-based methods.

Results: The $FPM_{<4.7\mu m}$ for the non-conducting devices (**Compact SpaceChamber Plus®** and **A2A™ Spacer)** were greatly reduced compared with the anti-static devices with as low as 6% of the medication delivered in some cases compared to the best performing Anti-Static VHC. The two Anti-Static VHCs (***AeroChamber Plus® Flow-Vu®*** Anti-Static VHC and **OptiChamber® Diamond®**) delivered consistently more medication as therapeutically beneficial $FPM_{<4.7\mu m}$, however even for these two devices, the performance was not equivalent, with the former device exhibiting significantly higher values (1-way ANOVA, $p < 0.001$).

Conclusions: The results indicate that if pre-conditioning is not performed for non-conducting VHCs then there is likely to be greatly reduced medication delivered to the patient and therefore under-dosing until VHC conditioning occurs. The use of 'anti-static' VHCs improves the reliability of medication delivery from pMDI-VHC combinations, although there are still differences in performance, and other factors, such as chamber design can also affect the fine particle delivery. Care should be taken by prescribers in the selection of these devices.

Introduction

VHCs are widely prescribed for use with pressurized metered dose inhalers (pMDIs) for patients with poor coordination or for the infant, small child or adult who cannot use a mouthpiece to inhale their medication [1-3]. In recent years, manufacturers of these add-on devices have introduced materials that do not retain electrostatic charge, as a means both to improve medication delivery efficiency and reliability [4, 5]. These 'anti-static' VHCs do not require pre-conditioning, by washing / drying, prior to first use. Such pre-conditioning is instructed to be performed on non-conducting VHCs however this may not always be remembered by the patient or care provider. The purpose of this laboratory-based investigation was to examine the impact on *in-vitro* performance when two anti-Static VHCs were compared to two standard non conducting VHCs, used out of packet and by simulating poor coordination of inhalation with inhaler actuation. This approach conforms to current guidance from European regulatory authorities that testing of VHCs should always simulate delayed inhalation [6].

Materials and Methods

Four different commercially available VHCs were compared using a widely prescribed combination corticosteroid/ long-acting beta agonist pMDI (Seretide 250 µg: fluticasone propionate (FP)/ 25 µg salmeterol xinafoate (SX) per actuation ex metering valve, GSK plc):

(1) ***AeroChamber Plus® Flow-Vu®*** anti-Static VHC with mouthpiece (Trudell Medical International, London, Canada, [**AC Plus AS**], n=5 devices/group**;**
(2) **OptiChamber® Diamond®** anti-Static VHC with mouthpiece (Philips Respironics Inc., Parsippany, NJ, USA); [**OD**], n=5 devices/group
(3) **Compact SpaceChamber Plus®** VHC with mouthpiece (Medical Developments UK Ltd, Ashford, Kent, UK); [**cSC Plus**], n=3 devices/group;
(4) **A2A™ Spacer** with mouthpiece (Clement Clark International Ltd., Harlow, Essex, UK) [**A2A Spacer**], n=3 devices/group.

All VHCs were tested directly after removal from the package. An abbreviated Andersen 8-stage non-viable cascade impactor operated at 28.3 L/min ± 5% was equipped with a Ph.Eur//USP induction port to which the VHC-on-test was fitted via a proprietary 'delay' apparatus [7].

In each instance, actuation of the pMDI took place immediately followed by coupling the mouthpiece to the entry port of this apparatus so that the available aerosol within the VHC was withdrawn by the vacuum to the impactor once the shutter opened access to the VHC after a 5 s delay interval had elapsed. Five actuations were delivered to the impactor per measurement to ensure adequate mass of each active pharmaceutical ingredient was captured.

Recovery and assay for FP and SX components of the drug product was undertaken by validated methods involving HPLC-UV spectrophotometry (FP) and HPLC-fluorescence detection (SX). Fine Particle Mass <4.7 µm ($FPM_{<4.7\mu m}$) was subsequently determined as the measure of the therapeutically beneficial portion of the dose emitted from the VHC on test.

Results

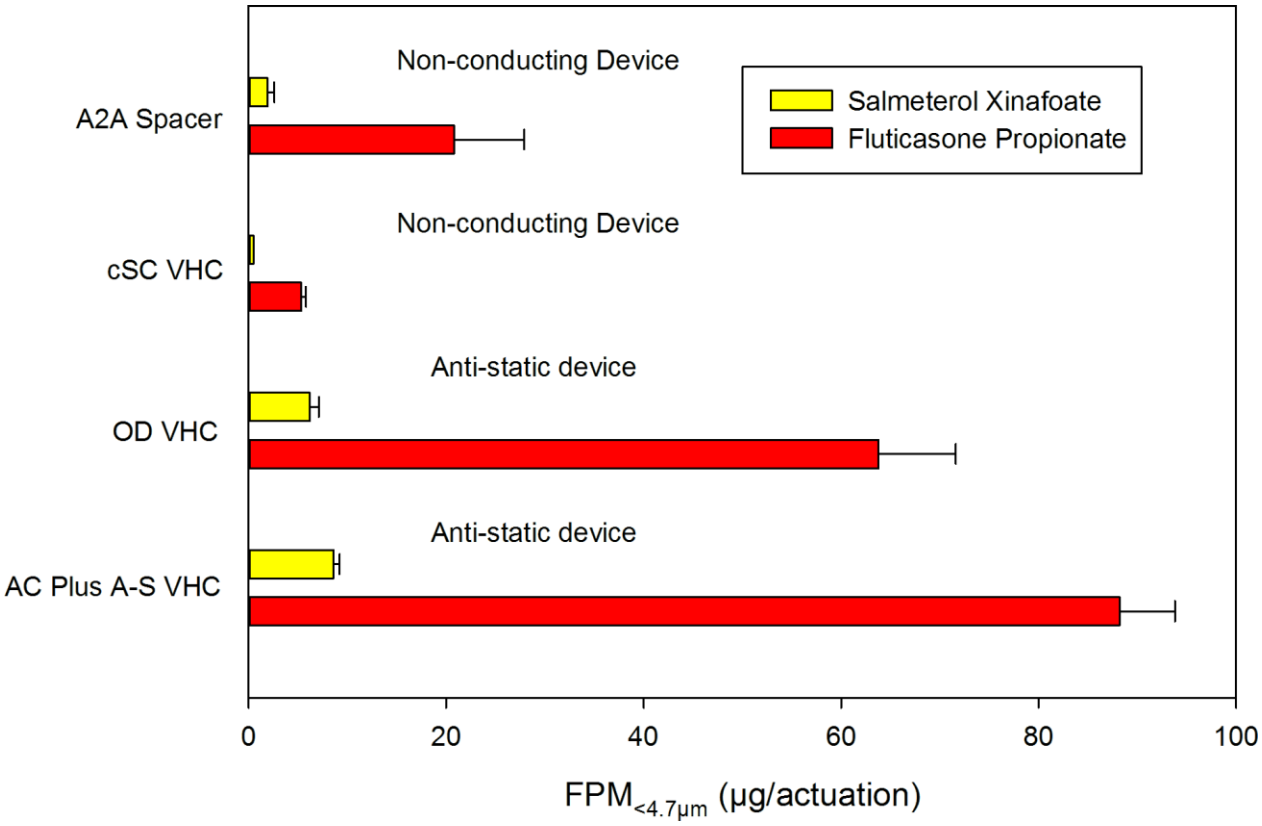
The total masses of FP and SX recovered from each measurement with each VHC type were within ±20% label claim (Table 1), even allowing up to 5% internal losses within the impactor system (8), indicating that both active pharmaceutical ingredients had been properly accounted for.

There were very large differences in the magnitude of the therapeutically beneficial $FPM_{<4.7\mu m}$ between the VHC types for both FP and SX components (Table 1 & Figure 1). The values when using the non-conducting devices (**cSC Plus** and **A2A Spacer)** were greatly reduced compared with either of the anti-static device groups. Compared to the **AC Plus A-S**, the **cSC** produced values of approximately 6% for both FP and SX and the **A2A** produced values of 22-24%. Although significantly higher than the non-conducting devices the two Anti-Static VHCs also exhibited differences with the **AC Plus A-S** group delivering significantly more medication than the next most efficient device group (**OD**) (1-way ANOVA, $p < 0.001$).

Table 1: Out of Package Performance Measures (mean ± SD) with Seretide® for VHCs with 5 s Delay

VHC	API Component	Total Mass Recovered (µg)	$FPM_{<4.7\mu m}$ (µg)
A2A Spacer	FP	239.6 ± 6.4	20.8 ± 7.1
	SX	22.5 ± 1.2	1.9 ± 0.7
cSC Plus VHC	FP	240.8 ± 17.1	5.3 ± 0.5
	SX	21.6 ± 0.7	0.5 ± 0.0
OD VHC	FP	211.6 ± 15.4	63.8 ± 7.8
	SX	20.3 ± 0.3	6.2 ± 0.9
AC Plus A-S VHC	FP	213.4 ± 4.4	88.2 ± 5.6
	SX	21.3 ± 0.3	8.6 ± 0.6

Figure 1: Comparison of *FPM*$_{<4.7\mu m}$ for the Four Types of "Anti-Static' VHC



Conclusions:

As may have been expected, the use of 'anti-static' VHCs enabled significantly higher fine particle mass to be delivered from the pMDI when the VHCs were used direct from packet without pre-conditioning. In all likelihood, the reason for this observed behavior is that with the non-conducting devices the acquired electrostatic charges during manufacture and packaging due to tribo-electrification are not able to dissipate effectively during storage, whereas the addition of 'anti-static' materials enables the charge dissipation to take place. The extent of the reduced delivery from the non-conducting devices was highly significant and would likely reflect under-dosing for the patient until such time as VHC conditioning took place. This underlines the absolute necessity for pre-washing to be performed for these 'non anti-static' VHCs in order to remove surface charges. Although the use of anti-static VHCs has undoubtedly improved the reliability of medication delivery from pMDI-VHC combinations, and removes the need for pre-washing, differences in performance were still observed between the two devices tested and this points towards other factors, such as overall chamber design [9, 10] affecting aerosol transport from the device to the user. In summary, care needs to be taken by prescribers in the selection and preparation of these devices to avoid the risk of under-dosing the patient.

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