Substantial *In Vitro* Equivalence Exists for Anti-Static and Non-Static Versions of the Same Valved Holding Chamber (VHC) Family Provided Pre-Washing of the Non-Static Version is Undertaken to Mitigate Electrostatic Charge

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Summary

Washing of VHCs in detergent followed by drip-drying is an effective means to mitigate electrostatic charge associated with non-conducting devices. Recently, manufacturers have developed VHCs manufactured from charge-dissipative materials as a means of avoiding this preparation step to improve compliance. We report the outcome from measurements of total emitted mass (TEM) and fine particle mass ($FPM_{<4.7\ \mu m}$) from non-conducting and anti-static versions of the ***AeroChamber Plus*****/mouthpiece VHC family with nine widely prescribed HFA pressurized metered dose inhaler-based formulations. Values of either TEM or $FPM_{<4.7\ \mu m}$ for the two VHC variants were within 10% of each other for every formulation evaluated, demonstrating substantial *in vitro* equivalence, provided that the manufacturer's instructions for device preparation are followed.

Introduction

The performance of spacers and VHCs used in conjunction with pressurized metered-dose inhaler (pMDI)-generated aerosols is known to be influenced by the interaction of electrostatic charge associated with the formulation before and during aerosol formation (1, 2), and also acquired by interior surfaces of these add-on devices during manufacture (3, 4). Electrostatic charge accumulates on non-conducting surfaces, where it attracts incoming particles emitted by the inhaler at actuation, retaining a significant portion of those particles that would otherwise be inhaled as therapeutically beneficial aerosol (5). The overall effect is to reduce clinical efficacy in an unpredictable manner (6).

The practice of pre-treating these devices by washing in mild ionic detergent, followed by drip-drying in air has been validated in the laboratory (7, 8) and also demonstrated clinically (9, 10). This procedure appears to mitigate the effect of electrostatic charge by coating internal surfaces in the pathway of the aerosol with a conducting layer of surfactant (11). This process is particularly important when using the new HFA-based formulations, many of which do not contain surfactant as an excipient to aid in uniform operation of the metering valve of the inhaler (12). At least one clinical guideline now recommends washing as part of device care (13).

Recently, a new generation of VHCs manufactured from charge-dissipative and transparent materials has been developed with the intention of retaining visibility of the aerosol plume during generation (14, 15), that is recognised as an important patient feedback aid (16). At the same time the use of these materials should avoid the need to pre-treat the device, as this practice may not always happen under time pressure in either hospital or home environments.

We report the outcome of an *in vitro* study of the behaviour of two universal (*i.e.* mechanically compatible with almost all pMDI inhalers), non-conducting and charge-dissipative, anti-static versions of the ***AeroChamber Plus****/mouthpiece VHC family (Trudell Medical International, London, Canada; n=5 VHCs/group) having similar internal geometry. Both groups of VHCs were evaluated with a range of widely prescribed HFA pressurized metered dose inhaler-based formulations, after pre-treatment in accordance with the manufacturer's instructions.

Materials and Methods

Non-conducting (NC; Figure 1) and anti-static (AS; Figure 2) versions of the ***AeroChamber Plus****/mouthpiece VHC (n=5 VHCs/group) were evaluated by Andersen 8-stage non-viable cascade impactor (ACI) equipped with USP/Ph.Eur. induction port, using nine widely prescribed HFA pressurized metered dose inhaler-based formulations (Table 1). The procedure followed was in accordance with the methodology described in the European Pharmacopeia (17).

The devices were prepared before use in accordance with manufacturer's instructions (wash/drip-dry for non-conducting VHCs, use directly out-of-package for the anti-static devices). In each case, measurements of total emitted mass (TEM) and fine particle mass < 4.7 µm aerodynamic diameter ($FPM_{<4.7\ \mu m}$), regarded as indicative of the therapeutically-beneficial portion of the emitted dose (18), were determined. Assay for each active pharmaceutical ingredient (API) was undertaken by HPLC-UV/fluorescence spectrophotometry using validated methods.

Figure 1: Non-Conducting *AeroChamber Plus VHC/mouthpiece (NC)**

Figure 2: Anti-Static *AeroChamber Plus VHC /mouthpiece (AS)**

Results

The outcome of the measurements of TEM and $FPM_{<4.7\ \mu m}$ (mean ± SD) from the two ***AeroChamber Plus**** VHC types is summarized in Table 1.

Table 1: *In Vitro* Performance Metrics for Non-Conducting and Anti-Static *AeroChamber Plus VHCs**

pMDI Formulation by Product Name	Active Pharmaceutical Ingredient ex Valve (µg)	TEM (µg/actuation)		$FPM_{<4.7\ \mu m}$ (µg/actuation)	
		NC	AS	NC	AS
Advair*	50 – fluticasone propionate	29.6 ± 1.6	26.6 ± 1.4	**26.6 ± 1.4**	**23.7 ± 1.4**
	25 – salmeterol xinafoate	15.3 ± 0.9	15.0 ± 1.0	**13.9 ± 0.9**	**13.7 ± 1.0**
Alvesco*	100 – ciclesonide	68.2 ± 2.7	68.3 ± 1.8	**68.1 ± 2.8**	**68.2 ± 1.8**
Atrovent*	20 – ipratropium bromide	10.7 ± 0.2	9.3 ± 0.3	**10.0 ± 0.2**	**9.2 ± 0.3**
Clenil*	100 – beclometasone	53.5± 3.4	54.6 ± 1.8	**45.0 ± 2.3**	**45.0 ± 1.9**
Flovent*	125- fluticasone propionate	72.3 ± 2.7	68.3 ± 3.1	**64.6 ± 3.0**	**62.1 ± 3.8**
Fostair*	100 – beclometasone	74.3 ± 1.8	74.2 ± 0.8	**72.3 ± 1.9**	**72.6 ± 1.1**
	6 – formoterol fumarate	3.9 ± 0.3	3.8 ± 0.5	**3.8 ± 0.3**	**3.7 ± 0.5**
Qvar*	100 – beclometasone	69.4 ± 4.8	65.4 ± 4.5	**67.2 ± 5.8**	**63.1 ± 6.0**
Symbicort*	80 – budesonide	61.6 ± 2.9	61.3 ± 2.7	**48.6 ± 2.2**	**50.6 ± 2.3**
	4.5 - formoterol fumarate	3.5 ± 0.2	3.6 ± 0.3	**3.1 ± 0.2**	**3.2 ± 0.2**
Ventolin*	100 – salbutamol (base)	53.6 ± 5.0	55.2 ± 3.8	**48.6 ± 4.6**	**49.5 ± 3.0**

Discussion

Values of either TEM or $FPM_{<4.7\ \mu m}$ for the two VHC variants were within 10% of each other for every formulation evaluated, demonstrating substantial *in vitro* equivalence. This outcome was in accordance with expectations, since Kwok et al., using a 3-mm square-section probe located within a non-conducting ***AeroChamber Plus**** VHC/mouthpiece and connected to a sensitive electrostatic voltmeter, had demonstrated a reduction in electric field potentials induced by electrostatic charges localised at various regions within the chamber to the point at which they were almost non-detectable (19). Likewise, Piérart et al. obtained a substantial increase in emitted mass of fine particles from a salbutamol pMDI when Volumatic* VHCs (GSK, plc), manufactured from non-conducting polycarbonate polymer were pre-washed in various types of ionic detergent (7). The formation of a monolayer of charge-conducting surfactant after evaporation of water on the interior surfaces exposed to detergent appears to be an effective means of dissipating charge from these devices (5).

The data from the present study confirm previous *in vitro* work with another VHC (***AeroChamber Max****) also manufactured from similar transparent, charge dissipative polymer, that such VHCs are fully effective when used direct from their packaging (20). The use of such materials for the antistatic ***AeroChamber Plus**** VHCs is as effective at mitigating adverse effects associated with electrostatic charge as pre-washing the non-conducting version. However, because the electrostatic charge dissipation property is 'built-in' to the construction of the anti-static VHCs, charge acquisition and accumulation do not take place during manufacture and shipping to the customer, making them more user-friendly, as well as providing more consistent medication delivery compared with non-conducting devices (20).

Conclusions

An extensive comparative *in vitro* evaluation of non-conducting and anti-static ***AeroChamber Plus**** VHCs has confirmed that substantial equivalence exists between the two device families as long as the manufacturer's instructions are followed in their preparation before use. The ability to be able to obtain medication from new anti-static VHCs without having to pre-wash them is an important clinical benefit in cases where facilities to prepare devices in this way are not readily available, or where time-pressure may result in non-compliance with instructions to pre-wash.

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