Investigation into the in vitro Performance of Anti-static vhcs by Particle Size Distribution using the next Generation Pharmaceutical Impactor (ngi)

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Summary

Aerodynamic particle size distribution and total delivered dose (TDD) performance testing of several Anti-static Valved Holding Chambers (VHCs) has been conducted with a series of selected pMDI drugs using the Next Generation Impactor (NGI) at a flow rate of 30 L/min. The main body of the Antistatic VHCs tested is made from three distinctively different types of materials of construction – including aluminium (VORTEX Non Electrostatic Holding Chamber), Acrylonitrile Butadiene Styrene , ABS (OptiChamber Diamond Anti-static chamber) and a Polypropylene Blend Polymer (Medical Developments Internationals Anti-static Compact Space Chamber Plus & AeroChamber Plus Flow-Vu Anti-static VHC). Results have shown that the VHCs made from the polypropylene blend polymer outperform the other VHCs tested for overall TDD and FPD/EFPD deliveries over all drugs tested, with total performance ranking over all three platforms being AS-CSCP > ACP-FV > VOR-NE > OCD-AS.

Introduction

Valve holding chambers are designed to act as a reservoir for medication that has been delivered from an inhaler, or pMDI, before it is inhaled by a patient. As a result of using a VHC in combination with an inhaler, it does not require patient-coordinated actuation and inhalation for maximum drug delivery efficiency. VHCs which exhibit anti-static properties have been reported to require no pre-priming of the chamber to enable maximum and consistent delivery of the therapeutically beneficial dose (fine particle dose, FPD) to the patient by minimizing static charge build-up of the device.[1,2] It is also believed that anti-static VHCs will have an influence on the efficient delivery of therapeutically beneficial dose (≤ 4.7µm) due to the greater effects that static charge have upon the attraction of smaller drug particle sizes.[3,4]

The purpose of this study was to compare the Total Delivered Dose (TDD) and Fine Particle Doses (both FPD ≤4.7µm, and EFPD ≤1.0µm) from 4 pMDI's with a series of antistatic VHCs of similar size but different materials of construction.

Experimental Methods

Testing was conducted on four unique VHCs as outlined in Table 1 using four different pMDIs as outlined in Table 2.

Table 1: List of anti-static VHCs tested, VHC abbreviation, and testing matrix conducted.

VHC	Abbrev.	No. of samples	No of tests /sample	Total No. of tests
None (pMDI only)	pMDI	2	3	6
Anti-static Compact Space Chamber Plus	AS-CSCP	3	3	9
AeroChamber Plus Flow-Vu Anti-static VHC	ACP-FV	3	3	9
OptiChamber Diamond Anti-static Chamber	OCD-AS	3	3	9
VORTEX Non Electrostatic Holding Chamber	VOR-NE	3	3	9

Table 2: List of pMDIs used, including actuation amounts, total actuations/pMDI and total available drug per test run.

Drug Tested (pMDI)	Dose /actuation (µg)	No. pMDIs used	Actuations /pMDI	Total dose available (µg)	Flowrate (L/min)
Salbutamol sulfate (VENTOLIN)	100	3	2	600	30
Beclomethasone dipropionate (QVAR)	100	3	2	600	30
Ipratropium bromide (ATROVENT)	21	3	6	378	30
Fluticasone propionate (FLIXOTIDE)	125	3	2	750	30

All pMDIs were primed according to manufacturer's recommendations before use in testing. All VHCs were used either straight from the original packaging without priming (AS-CSCP, ACP-FV & OCD-AS) or washed before use (VOR-NE) as per manufacturer's instructions. Particle size measurements were made using a Copley NGI impactor at a flowrate of 30L/min (±5%) for all VHCs and drugs tested. Aerosol passing through the NGI impacts on the impactor throat and various cascade stages on the basis of its aerodynamic size. Aerosol residue deposited at each stage is collected and quantified by HPLC assay against a linear standard curve plotted from standard solutions.

Results were processed into aerosol size distributions using the validated Copley Inhaler Testing Data Analysis Software (CITDAS), from which relevant aerosol size parameters were generated. Total delivered dose (TDD) is calculated as the sum of drug aerosol residue collected in the NGI impactor stages, including the NGI throat and final filter. Fine particle dose (FPD) is the cumulative dose ≤ 4.7µm in particle size (excluding the final filter). Extra fine particle dose (EFPD) is the cumulative ≤ 1.0µm in particle size (excluding the final filter).

Results

Experimental results for each VHC tested using 4 different pMDIs including total delivered dose (TDD), fine particle dose (FPD), extrafine particle dose (EFPD), and MMAD are summarised in Table 3, with Standard Error Margins (SEM) in parenthesis. Table 4 includes summarised data for %TDD, %FPD and %EFPD for each VHC with respect to the pMDI only.

Table 3: Comparative aerosol size & total output results obtained for various Anti-static VHCs and pMDIs @ 30L/min.

Device	Mean TDD µg /actuation	Mean FPD µg /actuation	Mean EFPD µg /actuation	Mean MMAD (µm)	Mean GSD of MMAD
Salbutamol Sulfate @30L/min					
pMDI only	100.4 (3.4)	44.4 (2.1)	4.1 (0.9)	2.51 (0.05)	2.02 (0.05)
AS-CSCP	62.3 (2.0)	48.7 (1.7)	4.4 (0.2)	2.32 (0.02)	1.72 (0.04)
ACP-FV	61.1 (3.4)	49.4 (2.9)	3.3 (0.1)	2.36 (0.01)	1.65 (0.01)
OCD-AS	60.3 (2.7)	45.8 (2.2)	3.7 (0.2)	2.18 (0.02)	1.66 (0.01)
VOR-NE	62.4 (5.2)	46.9 (4.9)	3.1 (0.3)	2.33 (0.02)	1.65 (0.02)
Fluticasone Propionate @30L/min					
pMDI only	117.6 (5.0)	54.3 (3.0)	2.8 (0.1)	2.87 (0.04)	1.89 (0.04)
AS-CSCP	85.7 (4.2)	74.1 (3.4)	3.2 (0.1)	2.57 (0.02)	1.56 (0.01)
ACP-FV	79.7 (1.4)	65.0 (0.9)	3.5 (0.2)	2.72 (0.01)	1.65 (0.02)
OCD-AS	72.1 (3.2)	56.5 (3.0)	2.9 (0.2)	2.49 (0.01)	1.60 (0.01)
VOR-NE	90.5 (2.5)	75.1 (2.5)	3.2 (0.1)	2.57 (0.01)	1.56 (0.01)
Beclomethasone Dipropionate @30L/min					
pMDI only	77.0 (1.5)	54.6 (1.3)	26.1 (0.5)	1.05 (0.01)	1.77 (0.01)
AS-CSCP	75.0 (1.7)	68.1 (1.7)	33.2 (1.1)	1.03 (0.01)	1.68 (0.01)
ACP-FV	77.4 (2.5)	70.5 (2.5)	33.2 (1.4)	1.05 (0.01)	1.66 (0.01)
OCD-AS	62.7 (0.9)	47.9 (0.8)	37.4 (0.6)	0.74 (0.01)	1.60 (0.02)
VOR-NE	62.3 (0.9)	56.6 (0.9)	26.2 (0.4)	1.06 (0.01)	1.64 (0.01)
Ipratropium Bromide @30L/min					
pMDI only	15.9 (1.0)	5.1 (0.5)	3.0 (0.2)	1.03 (0.01)	3.52 (0.35)
AS-CSCP	9.3 (0.3)	6.3 (0.3)	3.4 (0.1)	1.00 (0.02)	2.23 (0.12)
ACP-FV	8.0 (0.4)	5.4 (0.4)	3.1 (0.2)	0.93 (0.02)	1.93 (0.08)
OCD-AS	9.2 (0.4)	5.4 (0.3)	2.8 (0.2)	1.24 (0.05)	4.79 (0.38)
VOR-NE	6.6 (0.1)	4.8 (0.1)	2.6 (0.1)	0.97 (0.07)	1.78 (0.07)

TDD = Total Delivered Dose; FPD = Fine Particle Dose (≤ 4.7µm); EFPD = Extra Fine Particle Dose (≤ 1.0µm)
Numbers in parenthesis = Standard error margins (SEM)

Figure 1 compares the mean total delivered dose (TDD) results for all antistatic VHCs over all four drugs tested @30L/min. For salbutamol, TDD results across all VHCs tested are quite consistent with doses only ranging from 60% (OCD-AS) to 62% (AS-CSCP & VOR-NE) of the TDD of the pMDI only. Similarly for fluticasone, TDD results are shown to range from 61% (OCD-AS) to 77% (VOR-NE) of the pMDI only. For beclomethasone & Ipratropium, TDD results were observed to be slightly more varied with doses ranging from 81% (OCD-AS & VOR-NE) to 101% (ACP-FV) and 41% (VOR-NE) to 59% (AS-CSCP) respectively.

Figures 2 & 3 compares both the fine particle (FPD ≤4.7µm) and extra fine particle (EFPD ≤1.0µm) doses for all antistatic VHCs over all four drugs tested.

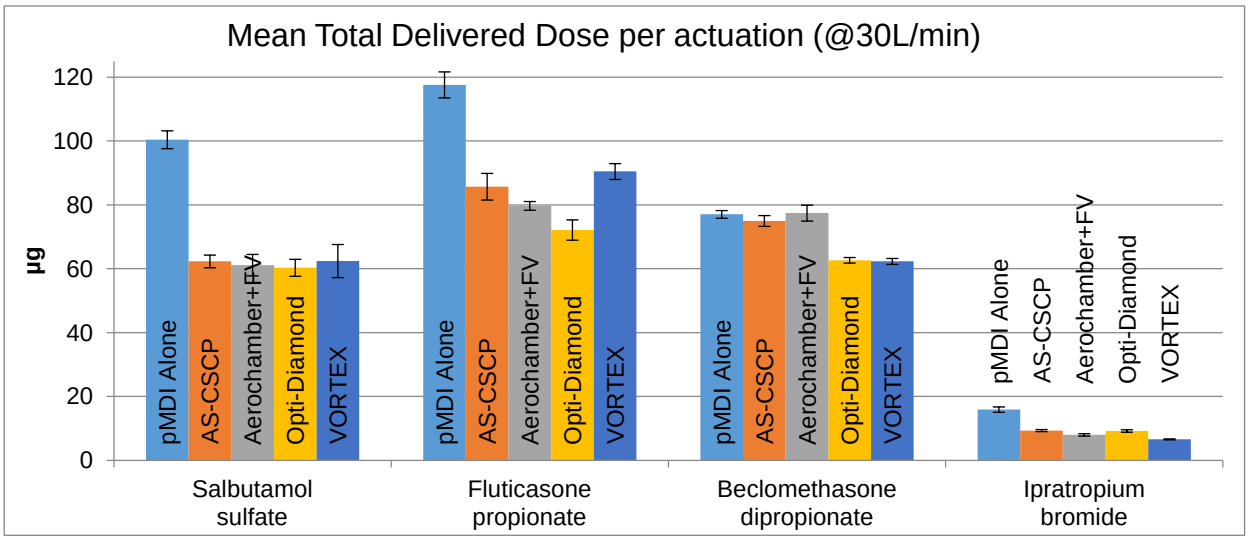

Figure 1 – Mean total delivered dose (TDD) for all VHCs and drugs tested.

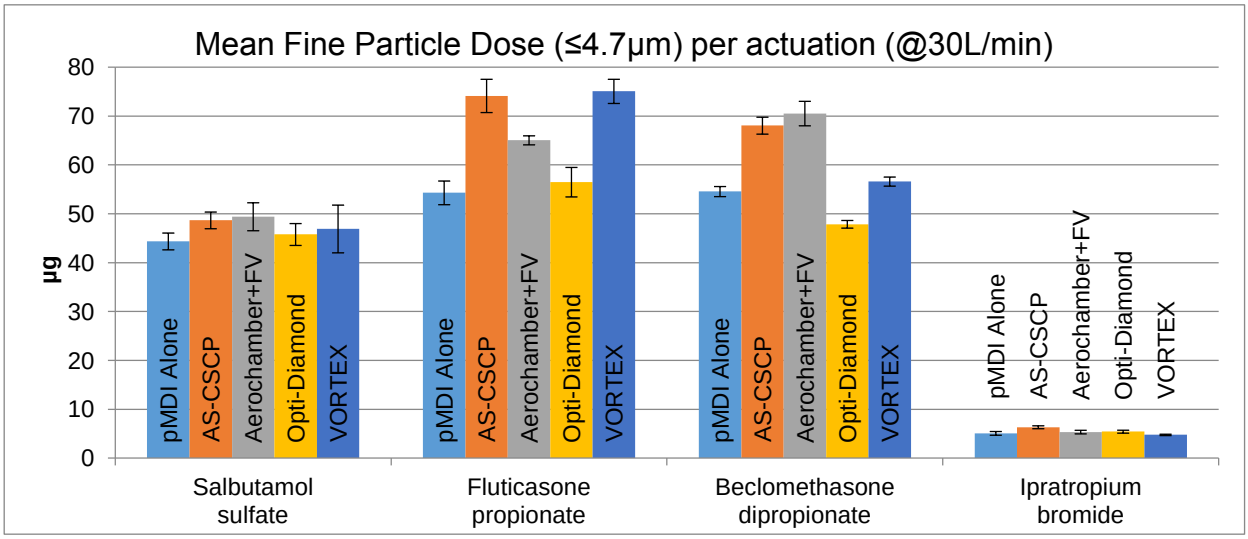

Figure 2 – Mean fine particle dose (FPD) for all VHCs and drugs tested.

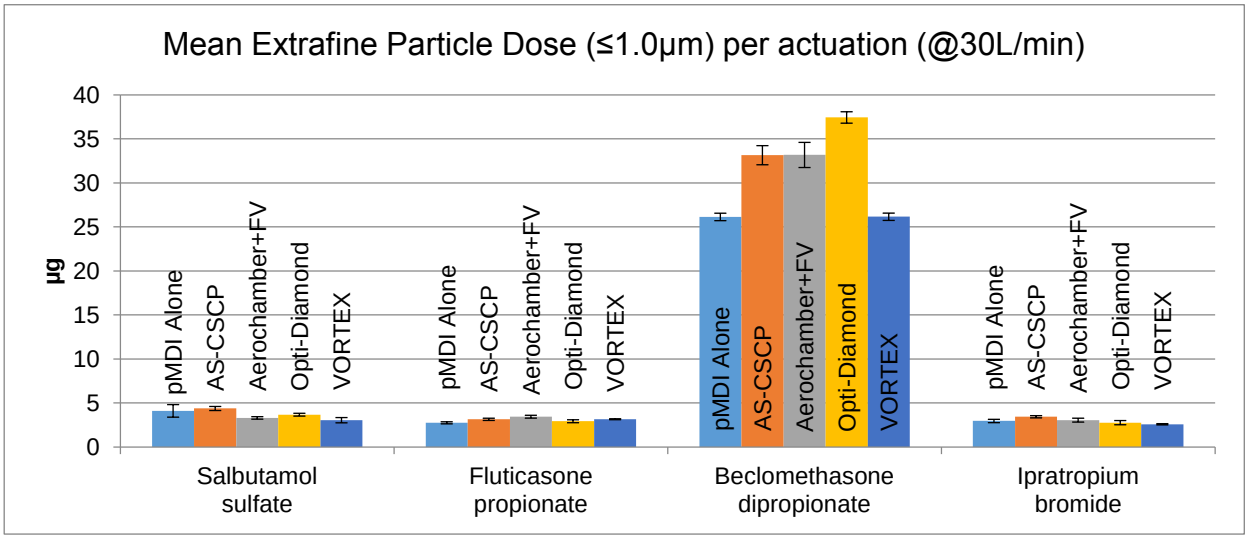

Figure 3 – Mean extra-fine particle dose (EFPD) for all VHCs and drugs tested.

Results show that for the FPD, all spacers delivered ≥100% of all 4 drugs tested when compared to the pMDI only. The only two exceptions to this were OCD-AS in conjunction with belcomethasone (88%) and VOR-NE in conjunction with Ipratropium (94%).

Table 4 - %Total Delivered Dose, %Fine Particle Dose and %Extra Fine Particle Dose for all VHCs tested as a percentage of the same fraction from the pMDI only.

Device	Salbutamol sulfate	Fluticasone propionate	Beclomethasone dipropionate	Ipratropium bromide	Avg % across all Drugs
% Total Delivered Dose (to pMDI only)					
AS-CSCP	62%	73%	97%	59%	**73%**
ACP-FV	61%	68%	101%	50%	**70%**
OCD-AS	60%	61%	81%	58%	**65%**
VOR-NE	62%	77%	81%	41%	**65%**
% Fine Particle Dose (to pMDI only)					
AS-CSCP	110%	137%	125%	125%	**124%**
ACP-FV	111%	120%	129%	105%	**116%**
OCD-AS	103%	104%	88%	107%	**100%**
VOR-NE	106%	138%	104%	94%	**110%**
% Extra Fine Particle Dose (to pMDI only)					
AS-CSCP	107%	115%	127%	116%	**116%**
ACP-FV	81%	125%	127%	103%	**109%**
OCD-AS	90%	107%	143%	94%	**108%**
VOR-NE	74%	115%	100%	87%	**94%**

Discussion

Overall results show that among all VHCs tested for at 30 L/min, the AS-CSCP affords the highest average TDD, FPD and EFPD percentage when measured against the respective pMDI alone. For average TDD & FPD % over all drugs tested, the performance ranks as AS-CSCP > ACP-FV > VOR-NE > OCD-AS. This ranking only changes for the average EFPD % over all drugs tested, with AS-CSCP > ACP-FV > OCD-AS > VOR-NE. These rankings are supported through the comparison of results for each data set using ANOVA, with the visually obvious difference seen in Fig's 1-3 being seen as statistically significant. Both the AS-CSCP and ACP-FV provide the highest performance outputs over all three aerodynamic platforms tested, with each antistatic VHC being constructed from proprietary polypropylene polymer blends Importantly, the AS-CSCP VHC ranks highest for the average %FPD (AS-CSCP/pMDI) across all three classes of drugs, demonstrating consistent delivery of respirable mass, the proportion of actuated dose comprising particles sufficiently small ($\leq$ 4.7 µm) to reach the patient's airways during inhalation to deliver the required therapeutic dose. The aluminium body of the VOR-NE and ABS body of the OCD-AS show lowest performances on average. It is noted that other VHC parameters such as valve design cannot be ruled out in influencing the overall results observed, however, using a static flow rate for this experiment is expected to minimize these potential effects.

Conclusions

Aerodynamic particle size distribution and total delivered dose performance testing of several Anti-static VHCs has been conducted using a series of selected drugs (pMDIs) using the Next Generation Impactor (NGI) at a constant flow rate of 30 L/min. These results were then compared as a percentage of the pMDI only and ranked for total performance over each individual drug, giving an average performance % across all drugs. Results have shown that the VHCs made from the polypropylene blend polymer outperform the other VHCs tested for overall TDD and FPD/EFPD deliveries over all drugs tested, with total performance ranking over all three platforms being AS-CSCP > ACP-FV > VOR-NE > OCD-AS.

References

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