In vitro validation of the use of a spacer with an extrafine Beclomethasone/Formoterol formulation

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Introduction

Lung deposition of aerosolized drugs is dependent on inhalation technique, device and formulation[1] (Figure 1). Valved holding chambers (VHC) are accessories often needed for proper drug distribution with pMDIs (pressurized metered-dose inhaler). However, because changes to devices can be associated with negatives outcomes, characterization of the resulting aerosol particles is essential, especially with fixed combinations for which data with VHC are limited. The performance of an extrafine formulation (Innovair®, Chiesi) of a β2 adrenergic agonist (Formoterol Fumarate/FF) combined with a corticosteroid (Beclomethasone dipropionate/BDP) via pMDI was characterized *in vitro* with or without a VHC (Tips-haler®, Protec'Som).

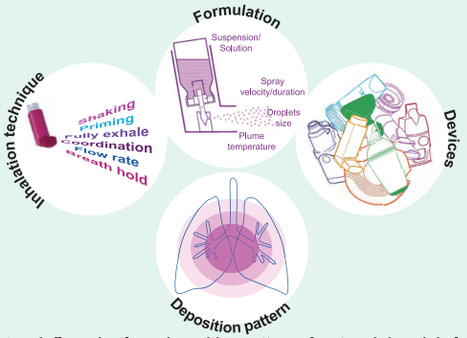

Figure 1: Factors influencing lung deposition pattern of metered-dose inhalers aerosols.

Methods

Analyses were performed with 10 puffs from the Innovair pMDI (BDP 100µg per dose/FF 6µg per dose) with or without VHC (used according to the manufacturer's instructions). Particle size distributions were measured using a cascade impactor (Next Generation Impactor, Copley Scientific) with the USP induction port at 30 L/min. All components were tested for drug deposition. Samples were HPLC analyzed (Ultimate 3000 system, Dionex) for the simultaneous detection of BDP and FF. Six independent replicates were performed for each condition (with and without VHC). Values are reported as means ± standard deviation. When applicable, values were normalized to 1 puff. Statistical analyses were performed using the open source software JASP. Differences were considered significant at p values < 0.005.

Results

Total doses delivered were equivalent for the pMDI used alone or with VHC (Table 1). There was a 33% FF and a 18% BDP decrease of the impactor mass (representing the mass delivered to the patient) when the VHC was used, mostly due to the mass of drug retained by the VHC, reducing the dose in the trachea (Figure 3). Drug ratios (BDP/FF) were found to be unchanged: 17.04 for the pMDI alone and 17.14 for the pMDI + VHC (the nominal dose ratio of the fixed combination is 16.7). A 10% increase of the fine particle fraction (FPF) was found for both drugs when the VHC was used (Figure 2), bringing the FPF to over 50% of the total dose and over 80% of the impactor mass.

Table 1: Influence of the VHC on delivered dose and particle size of Formoterol and Beclomethasone aerosols from Innovair.

	Formoterol		Beclomethasone	
	pMDI	pMDI + VHC	pMDI	pMDI + VHC
DD µg (± SD)	4.23 (0.40)	4,3 (0.19)	71.94 (5.98)	73.73 (5.44)
IM µg (± SD)	3.77 (0.10)*	2.52 (0.28)	63.44 (5.77)**	52.28 (4.03)
MMAD µm (± SD)	1.14 (0.04)	1.09 (0.03)	1.25 (0.04)	1.15 (0.04)*
GSD (± SD)	1.79 (0.04)	1.66 (0.03)	1.93 (0.06)	1.79 (0.03)
$FPD_{5µm}$ µg (± SD)	1.68 (0.10)	2.24 (0.28)*	32.66 (2.38)	41.80 (3.94)*
$FPF_{5µm}$ %DD (± SD)	39,93 (4.04)	52.11 (6.73)*	45.59 (4.08)	57.08 (8.10)**
$FPF_{5µm}$ %IM (± SD)	44.96 (5.06)	88.94 (4.68)	51.74 (4.73)*	80.45 (9.01)*

SD: Standard deviation; DD: Delivered dose (total mass delivered by pMDI); IM: Impactor mass (mass recovered from the impactor's stages and USP port); MMAD: Mass Median Aerodynamic Diameter; GSD: Geometric Standard Deviation; $FPD_{5µm}$: Fine particle (aerodynamic diameter<5µm) dose; $FPF_{5µm}$: Fine particle (aerodynamic diameter<5µm) fraction, expressed as % of total dose or as % of the impactor mass; *p value <0.001; **p value <0.005.

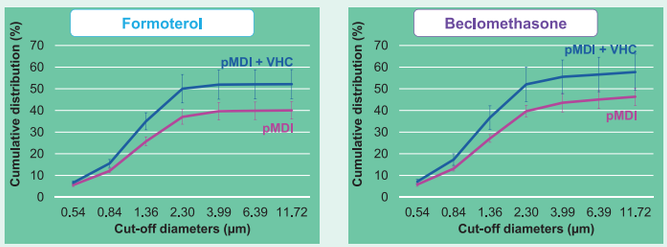

Figure 2: Cumulative distributions with or without VHC of Formoterol and Beclomethasone aerosols from Innovair.

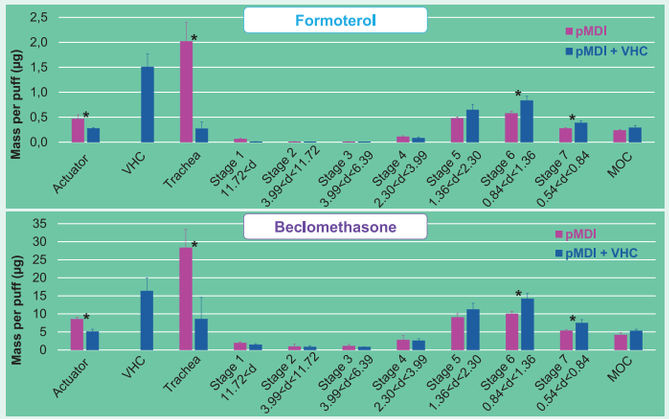

Figure 3: Mass distribution of Formoterol and Beclomethasone aerosols from Innovair.
d: diameter (µm); * pvalue < 0.001

Conclusion

MDIs emitting fine particles provide higher lung deposition and improved clinical benefits.[2] *In vitro* characterization of MDIs used with VHC is a necessary step towards ensuring that those advantages are preserved. We showed that the VHC used here with an extrafine formulation maintains DD and increases FPF. It has been shown that an increase in lung deposition accompanied by a decreased oropharyngeal deposition leads to no overall systemic exposure changes,[3] ensuring that the safety and efficacy profile of the fixed combination pMDI is maintained when used with this VHC.

References

[1] De Backer, W. *et al.* Lung Deposition of BDP/Formoterol HFA pMDI in Healthy Volunteers, Asthmatic, and COPD Patients. *Journal of Aerosol Medicine and Pulmonary Drug Delivery* **23,** 137–148 (2010).
[2] Nicolini, G., Scichilone, N., Bizzi, A., Papi, A. & Fabbri, L. M. Beclomethasone/formoterol fixed combination for the management of asthma: patient considerations. *Ther Clin Risk Manag* **4,** 855–864 (2008).
[3] Kuna, P. *et al.* Pharmacokinetics and pharmacodynamics of an extrafine fixed pMDI combination of beclometasone dipropionate/formoterol fumarate in adolescent asthma. *Br J Clin Pharmacol* **80,** 569–580 (2015).