IN VITRO EVALUATION OF DRUG PARTICLE SIZE DELIVERED FROM MDIS WITH A BREATH-ACTUATION DEVICE

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BACKGROUND

Metered dose inhalers continue to be widely used by patients despite reported difficulties with their use. Studies show that up to 70% of patients are unable to use their metered-dose inhaler (MDI) correctly (Dolovich, MA et al, CHEST 2005). Much of this failure relates to the patients' inability to coordinate their inhalation with the delivery of the medication from the MDI (depression of the canister in the inhaler boot). As a consequence, patients may not be getting the appropriate dose from the inhaler for management of their disease.

To help patients alleviate this "timing" problem, Respirics is developing a number of devices which function as a result of a patient's inspiratory effort. The company has developed MD Turbo™ (Figure 1), a breath-activated accessory device, to be used with many of currently prescribed MDIs.

We evaluated the use of different MDI's in conjunction with various technologies designed to assist with the delivery of aerosolized medications. We compared the mass median aerodynamic diameter (MMAD) of drug delivered from three separate MDIs when used alone, with a valved holding chamber (Pocket Spacer™, Ferraris Medical Inc.) and with MD Turbo™.

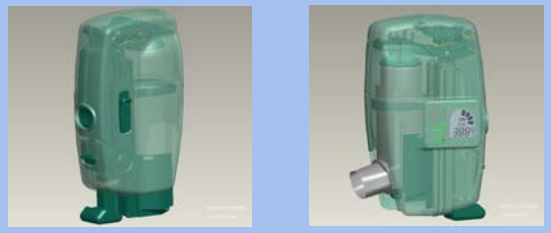

FIGURE 1: MD Turbo™ shown as manufactured (left) and with a standard MDI loaded inside (right).

OBJECTIVE

To compare the particle size distribution (MMAD) for three different metered-dose inhalers when used with the Respirics MD Turbo™, the Pocket Spacer™ and the MDI boot supplied with the medication. This is the particle size that theoretically could be delivered to a patient's airways.

MATERIALS AND METHODS

Three different MDIs, albuterol USP (Warrick Pharmaceuticals), Alupent® (metaproterenol sulfate, Boehringer Inhgelheim) and Flovent® (fluticasone propionate, GSK) were tested by attachment to a throat model, feeding into an Anderson 8-stage cascade impactor (see Figure 2).

Each MDI was tested on the circuit by attachment to an adapter at the throat model under three different configurations: Alone (canister in boot as supplied by manufacturer), with a valved holding chamber and then with the MD Turbo™. Airflow through the impactor was regulated at a constant rate of 28.3 L/min. Each MDI was tested (n=10 actuations) with at least 10 seconds between actuations. Active drug collected on the impactor plates was assayed by HPLC.

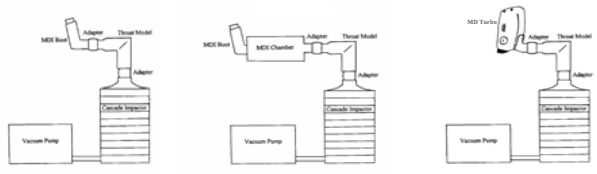

FIGURE 2: Test setups shown with MDI alone (left), MDI attached to a holding chamber (middle) and MDI inside the MD Turbo™ (right).

RESULTS

Particle sizing, as measured by MMAD, for albuterol ranged from 1.73μm ±0.02 to 1.80μm ±0.04. The measurements for metaproterenol and fluticasone ranged from 4.19μm ±0.08 to 4.80μm ±0.17 and 2.26μm ±0.22 to 2.31μm ±0.28 respectively. Geometric standard deviations showed similar particle size uniformity for each drug across the three delivery methods. See Table 1 below.

	MDI + MD Turbo™		MDI + Pocket Spacer™		MDI Alone	
	MMAD (μm ±SD)	GSD	MMAD (μm ±SD)	GSD	MMAD (μm ±SD)	GSD
Albuterol	1.75 ±0.06	1.68 ±0.20	1.73 ±0.02	1.51 ±0.01	1.80 ±0.04	1.57 ±0.01
Metaproterenol sulfate	4.80 ±0.17	1.75 ±0.05	4.19 ±0.08	1.68 ±0.05	4.64 ±0.19	1.75 ±0.03
Fluticasone propionate	2.31 ±0.28	1.69 ±0.11	2.29 ±0.25	1.65 ±0.06	2.26 ±0.22	1.66 ±0.06

Table 1: Study results for albuterol, metaproterenol and fluticasone MDIs for all three test configurations.

DISCUSSION

The MMAD measurements for each delivery method indicate that there was no significant difference in the particle size of the drug deposited in the cascade impactor. One limitation of this study is that *in vitro* results do not necessarily correlate well to *in vivo* lung deposition as individual anatomies and breathing characteristics vary. To the degree that the (*in vitro*) throat model and cascade impactor act as a proxy of what might be delivered to the lungs, with all other variables kept constant, the MMAD measurements were comparable for each drug across delivery methods. Particle size uniformity measurements (GSD) for each method were comparable for all drugs.

The MMADs recorded for the three different drugs show the broad range of particle sizes that are delivered by currently marketed MDIs. The inhaler which delivered the largest particles, metaproterenol, saw the greatest decrease in MMAD when used with the holding chamber. Gravitational fallout in the holding chamber had its greatest impact in the case of metaproterenol, a formulation delivered in the form of larger, heavier drug particles (~ 2x the MMAD of the other drugs).

In summary, there was very little difference between the results produced by the three methods of MDI use.

CONCLUSION

The MMADs of MDIs delivered with the assistance of the MD Turbo™ are consistent with those of the MDIs used on their own or with a holding chamber. We conclude that the MD Turbo™ can accommodate a variety of MDIs, and can assist with the delivery of those aerosolized medications.

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