

PERFORMANCE OF A NEW TOP-MOUNTED DOSE INDICATOR FOR USE WITH PRESSURIZED METERED DOSE INHALERS (pMDIs)

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INTRODUCTION

The integration of dose indicating or counting mechanisms into pMDI-based drug delivery systems is becoming recognized as the most reliable solution to provide accurate information concerning the amount of medication remaining, especially important at prompting the patient to replace the inhaler when the manufacturer-specified number of actuations has been delivered (1). The USFDA has recently published a draft Guidance for Industry (2), in which recommendations are made that dose-indicating equipment be included with pMDI products under development. Dose indicating devices must not interfere with the normal delivery of medication, and the present *in vitro* study was therefore developed to demonstrate normal performance of pMDIs of a widely prescribed HFA-based bronchodilator (Proventil™-HFA, 200 actuations of 108 µg/dose albuterol sulfate equivalent to 90 µg/dose albuterol base ex actuator, Key Pharmaceuticals, Kenilworth, NJ, USA) equipped with a new top-mounted dose indicator (Trudell Medical International, London, Canada (Figure 1)).



Figure 1 Proventil™-HFA pMDI equipped with top-mounted dose indicator (indicator also shown separately below).

MATERIALS AND METHODS

Particle size measurements from pMDIs equipped with and without the dose indicator ($n = 5$ /group) were made using an 8-stage cascade impactor (Thermo Andersen, Smyrna, GA, USA) at 28.3 ± 0.5 L/min in accordance with the US Pharmacopeial procedure (3). Each pMDI canister was tested in the manufacturer's actuator. Five priming doses were actuated to waste, and then the next 5 doses (start-of-life) were delivered to the impactor at 30 second intervals, shaking the canister for 5 seconds immediately before each actuation. Subsequently, a further 90 actuations were delivered to waste followed by 5 more actuations (mid-life) to the impactor in a separate measurement. Finally, 75 more actuations were delivered to waste before the final 5 actuations (near end-of-life) were made to the impactor for a third performance measurement. The canisters were not further emptied to exhaustion, as the purpose of this investigation was to confirm functioning of these pMDIs in normal use containing some medication. Following each measurement, the impactor was disassembled and the contents of each stage and the USP/EP induction port assayed for albuterol base by HPLC-UV spectrophotometry.

RESULTS AND DISCUSSION

Measurements of total emitted dose (TED) and fine particle dose (FPD, particles $< 4.7 \mu\text{m}$ aerodynamic diameter) for each group of pMDIs are summarized in Table 1. FPD is not a release specification for this product, but was selected to provide an up to date metric for comparison.

Table 1

Comparison of pMDI performance with and without top-mounted dose indicator, measured by Andersen 8-stage impactor at beginning, mid-life, and near to end of life.

Performance Measure	Actuations 6 – 10		Actuations 101 – 105		Actuations 181 – 185	
	Dose Indicator	No Dose Indicator	Dose Indicator	No Dose Indicator	Dose Indicator	No Dose Indicator
	TD (μg)	75.8 ± 2.0	76.0 ± 2.5	73.9 ± 3.1	76.3 ± 1.5	75.1 ± 1.9
FPD (μg)	40.9 ± 3.0	40.4 ± 3.0	39.8 ± 3.4	39.1 ± 1.9	41.0 ± 3.0	39.6 ± 2.9

$n = 5$ pMDIs/group, 1 measurement/pMDI
mean \pm SD

Overall values of TED for the three measurements made at the start, middle, and near end of canister life were 74.9 ± 2.4 $\mu\text{g}/\text{dose}$ and 75.8 ± 2.2 μg for the pMDIs with and without dose indicator, and the corresponding values of FPD were 40.6 ± 3.0 μg (with dose indicator) and 39.7 ± 2.5 μg (without dose indicator). Both FPD and TED were equivalent with and without dose indicator present at each of the measurement periods during canister life (un-paired t-test, $p \geq 0.15$). These data indicate that the top-mounted dose indicator did not influence pMDI performance.

REFERENCES

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2. USFDA Draft Guidance for Industry, (2001), "Integration of dose-counting mechanisms into MDI drug products," *CDER*, November 2001.
3. <601> "Aerosols," in *US Pharmacopeia* 24th Edition, 1st Supplement, US Pharmacopeia, Rockville, MD, USA., 2674-2688.

Notes