Overcoming differences in pMDI actuator resistance to create a standardised training tool

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Summary

The In-Check Flo-Tone® is an approved dual spacer and pressurised metered dose inhaler (pMDI) patient training device that indicates the optimal pMDI actuation point during the inhalation manoeuvre. The device fits many but not all pMDI actuators. A development programme has been undertaken to tailor the existing device to a range of pMDIs that vary in mouthpiece configuration and actuator resistance. In this study Flutiform® Landmark® pMDI (FL, 5μg formoterol fumarate/125μg fluticasone propionate, Napp Laboratories) was tested alone or in combination with machined or moulded adaptors paired with either standard Flo-Tone or Flo-Tone development devices: anti-static plastic, a short device, and a short, flared mouthpiece single unit prototype (the Flo-Tone*CR*™). Aerosol particle size distribution and dose characteristics were derived from Next Generation Impactor experiments conducted at 30 L/min. In all assessments, formoterol and fluticasone data trends were the same. Fine particle fraction (FPF) and fine particle dose (FPD) data were comparable between FL alone and the moulded adaptor plus short Flo-Tone device combinations. The formoterol FPF (%) and FPD (μg) values were 50.43±2.14 and 2.19±0.14 for FL; 50.75±1.04 and 2.13±0.06 for the short Flo-Tone; and 50.22±3.10 and 2.43±0.03 for Flo-Tone*CR*. Preliminary data with the Flo-Tone*CR* to determine reed whistle vibration and detectable whistle flow rates, across a range of commonly used pMDIs, suggest that the actuation indicator sounded at 20-25 L/min. This programme has shown that it is possible to tailor an existing audible training aid to a broader range of pMDIs and actuator designs without drug delivery compromise.

Introduction

In-Check Flo-Tone® (Clement Clarke International Ltd) is a simple, dual small spacer and pressurised metered dose inhaler (pMDI) patient training device, approved for use in the UK, that indicates the appropriate inspiratory flow rate and, therefore, the optimum actuation point for the pMDI during the inhalation manoeuvre. The device currently fits many but not all pMDI actuators, with actuator mouthpiece design limiting the suitability of many add-on training devices. The aim now is to develop a Flo-Tone-type device suitable for these remaining pMDIs. The combination therapy formoterol fumarate (formoterol) plus fluticasone propionate (fluticasone) Flutiform® Landmark® pMDI (FL, Napp Laboratories Ltd.) dose indicating actuator (Figure 1) has been selected for this development programme. The FL actuator mouthpiece has a greater top-to-bottom dimension than the majority of pMDIs, and is also of a sufficiently low resistance that the standard Flo-Tone does not provide the correct audible signal. During patient inhalation, the inspiratory air is drawn through both the low resistance air channels around the canister and through the whistle, resulting in a high inspiratory flow rate before the whistle sounds. The potential for actuator resistance differences between pMDIs is underappreciated and, with training aids vulnerable to resistance effects, patient technique errors can occur. We describe here the development and testing of a suitable training aid via assessments of the *in vitro* performance of FL with and without various forms of Flo-Tone, the overall objective being to improve patient use technique irrespective of pMDI actuator design.

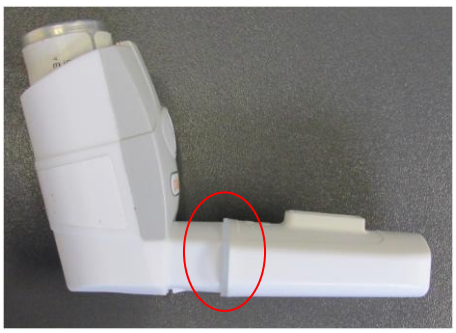


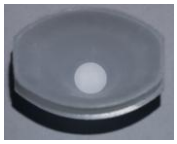
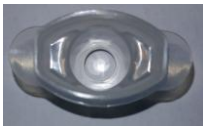
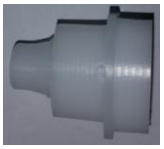
Figure 1 – Flutiform Landmark pMDI plus dummy-adaptor location (red oval) plus Flo-Tone device.

Experimental Methods

A series of six comparative assessments of the aerosol characteristics of 5μg formoterol fumarate/125μg fluticasone propionate pMDI (4.5/115μg ex-actuator respectively) have been carried out using the Next Generation Impactor (NGI, Copley Scientific Ltd.) operated at 30 L/min. Each pMDI was primed according to the patient information leaflet. NGI collection cups were coated, with polyethylene glycol 400 in acetone 2% v/v, to prevent particle-bounce.

The comparisons were between the FL alone, and the aerosol dose characteristics of FL tested via the standard Flo-Tone and the Flo-Tone development devices. The Landmark pMDI mouthpiece dimensions required an adaptor in order to achieve a good fit with the Flo-Tone (Figure 1). Three adaptors (machined, n=2 and moulded, n=1) were created (Table 1), and coupled to three types of Flo-Tone device: the standard commercially available device (Figure 1), a replica in anti-static plastic, and a short device (Figure 2, left, with moulded adaptor).

Table 1 – Adaptors (fitting Flo-Tone to Landmark pMDI)

	Machined adaptor-1 (Ma1)	**Machined adaptor-2 (Ma2)**	**Moulded adaptor (Mo)**
Plan view			
Side view			

The standard Flo-Tone was paired with the machined and moulded adaptors. The anti-static plastic and shorter versions were paired with the moulded adaptor only, creating five delivery assessments. Prior to assessment, standard and short Flo-Tones and adapters were washed with 25°C soapy water, submerged and gently agitated for 30s before allowing to air dry overnight. The audible Flo-Tone whistle, which guides users to actuate the pMDI at the appropriate inspiratory flow rate**,** was not part of these assessments. Indeed, the short device (Figure 2, left) was truncated ahead of the standard Flo-Tone reed-whistle.

Figure 2 – Moulded adaptor plus short Flo-Tone without reed (left), and Flo-Tone*CR* prototype with rotated reed and flared mouthpiece (right).

An additional assessment was carried out with a prototype of the Flo-Tone*CR*™ device: a single unit device, consisting of the adaptor and short Flo-Tone, with a function-tested (data not shown) reed-position rotated through 90° compared with standard (Figure 1 and Figure 2, right) and incorporating mouthpiece flaring.

All least three replicates of each combination were completed (see Table 2). Drug quantitation from the actuator, adaptor(s), Flo-Tone(s), induction port and NGI was by HPLC analysis (Agilent® 1200 quaternary system and ChemStation® LC software). Separation and quantitation were performed on a Waters Spherisorb® S5ODS2 column using isocratic elution of an aqueous mobile phase consisting of acetonitrile:5.0 mM sodium phosphate buffer (pH 3.2) (75:25, v/v) at 1 mL/min. UV detection of fluticasone and formoterol was performed at 240±4 nm and 215±4 nm respectively. The key parameters determined from the NGI tests were metered dose (µg) including actuator deposition, emitted dose ex actuator (µg), fine particle dose (FPD, µg < 5.0 µm), fine particle fraction (FPF, % < 5.0 µm) and mass median aerodynamic diameter (MMAD, µm).

Results

Metered and emitted dose data were comparable between FL alone and FL with the Flo-Tone devices irrespective of adaptor plus device combination. In the comparative assessments, the formoterol and fluticasone data trends were the same, with FPF, FPD and MMAD data given in Table 2. With the exception of the moulded adaptor plus short Flo-Tone combination (+Mo+shFT), the FPF and FPD data were inferior to the FL data (in the shaded cells). Overall, the addition of the adaptor(s) and full-size Flo-Tone device(s) resulted in lower deposition of drugs within the NGI owing to greater retention in the device components (Figure 3). Deposition within the +Mo+shFT (white bars) was less than 20% of the other Flo-Tone types, and induction port deposition was greater. Using the +Mo+shFT, overall NGI deposition was comparable to FL. Similar results were observed for formoterol.

Table 2 - Fine Particle Fraction (FPF), Fine Particle Dose data (FPD) and Mass Median Aerodynamic Diameter (MMAD)

pMDI + device (n=no. of replicates)	Key to Fig. 3	FPF (% < 5.0 µm)		FPD (µg < 5.0 µm)		MMAD (µm)	
		formoterol	fluticasone	formoterol	fluticasone	formoterol	fluticasone
Flutiform Landmark (n=5)	FL	50.43±2.14	44.80±2.04	2.19±0.14	46.85±0.76	2.95±0.07	3.33±0.11
FL + machined adaptor-1 + standard Flo-Tone (n=5)	+Ma1 +stFT	38.57±1.87	36.73±0.75	1.66±0.13	37.34±1.48	2.93±0.04	3.29±0.07
FL + moulded adaptor + standard Flo-Tone (n=3)	+Mo +stFT	39.79±1.68	36.00±1.76	1.62±0.15	38.02±3.97	2.84±0.09	3.23±0.07
FL + moulded adaptor + anti-static Flo-Tone (n=3)	+Mo +asFT	37.42±0.15	34.43±1.04	1.64±0.05	36.88±1.95	2.91±0.10	3.35±0.05
FL + machined adaptor-2 + standard Flo-Tone (n=3)	+Ma2 +stFT	36.12±1.90	33.05±2.72	1.51±0.17	34.53±3.02	2.79±0.08	3.20±0.15
FL + moulded adaptor + short Flo-Tone (n=3)	+Mo +shFT	50.75±1.04	44.59+1.35	2.13±0.06	46.42±1.83	2.94±0.04	3.25±0.08
FL + Flo-Tone*CR* (n=3)	+FT*CR*	50.22±3.10	40.93+1.54	2.43±0.03	47.56±0.10	2.61±0.04	3.10±0.05

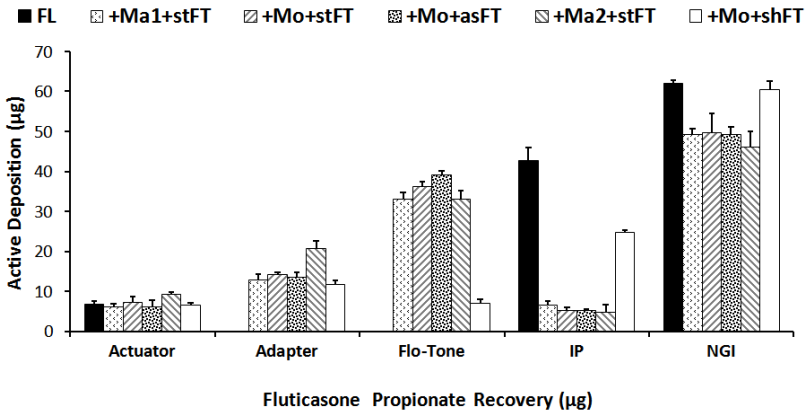


Figure 3. The deposition profile of fluticasone within test components, mean values ± SD (key to legend in column 2 of Table 2)

The data from FL and FL +Mo+shFT have been compared with data generated with a functioning reed device, i.e. a prototype Flo-Tone*CR* (+FT*CR*, see Figure 2, right). FL +Flo-Tone*CR* FPF, FPD and MMAD data are given in the final (bold outline) row of Table 2, and particle size distribution data are shown in Figures 4a and 4b. The data for FL +Mo+shFT and FL +FT*CR* were similar. The key difference between FL and FL plus these two Flo-Tone devices was that the spacer function of the Flo-Tone devices removed larger particle sizes providing smaller MMAD particularly in the case of +FT*CR*. We now have preliminary data with the +FT*CR*, determining reed whistle vibration and detectable whistle flow rates across a range of commonly used pMDIs, that suggest that the actuation indicator is sounding at 20-25 L/min.[1]

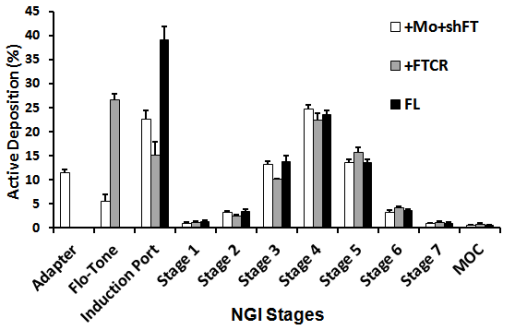


Figure 4a. Formoterol fumarate NGI distribution

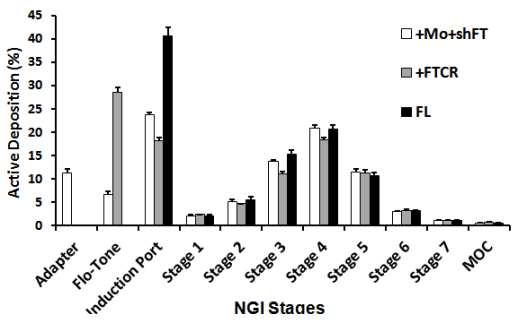


Figure 4b. Fluticasone propionate NGI distribution

Discussion

The standard Flo-Tone device is an established training aid,[2] which does not affect drug aerosol characteristics compared with pMDI alone.[3] The challenge was to design a similarly effective device for 'non-standard' pMDIs. The Landmark actuator necessitated the use of an adaptor, which fitted inside the mouthpiece, in order to effectively couple the Flo-Tone(s) to the actuator. We established that machined and flexible moulded adaptors resulted in similar aerosol characteristics when coupled with a standard Flo-Tone, but performance of these configurations did not match the reference product, Flutiform. Furthermore the use of an anti-static plastic for the Flo-Tone did not change performance. The wash/dry cycle protocol used on the standard Flo-Tone may have reduced the likelihood of detecting a difference but the comparative assessment eliminated the possibility of an advantage via an anti-static effect.

The decision to make a structural change to the size of the Flo-Tone was based on an investigation into a plastics-volume effect: the necessary inclusion of the adaptor increased the overall quantity of plastic that the aerosol plume encountered when combined with the standard Flo-Tone. Both the shortened Flo-Tone plus adaptor and single unit prototype Flo-Tone*CR* do not add any additional plastic compared with standard Flo-Tone, and these two configurations resulted in fine particle fraction and fine particle dose characteristics similar to Flutiform alone, with the benefit of reduced throat deposition.

Mouthpiece configuration can significantly affect particle impaction, with cone angle and plume spray angle being one of a number of factors.[4] *In vitro* research into pMDI particle entrance angle and inhaler insertion angle indicate that maximum aerosol efficiency is reached at a maximum 20°, with effects dependent on plume velocity, aerosol size and formulation.[5-6] The Landmark actuator of the Flutiform pMDI has a slightly outward-flared mouthpiece, with a cone angle of 13°,[7] and the Flo-Tone*CR* has been designed with a cone angle of 20°.

The data indicate that the training aid and spacer attributes of the Flo-Tone device[8] are retained in the new *CR* configuration with a likely reduced throat dosage, whilst retaining aerosol particle size distributions and the key fine particle parameter data.

Conclusion

This development programme has shown that it is possible to tailor an existing audible training aid to a broader range of pMDIs, enabling an audible tone at an appropriate inspiratory flow rate without drug delivery compromise, and retaining the small spacer effect. We are currently extending this prototype research to create a standardised device suitable for a range of pMDIs in popular use that vary in mouthpiece configuration and actuator resistance.

References

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