Plume Temperature Measurement of MDIs

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Summary

Methods to determine the temperature of plumes emitted from chlorofluorocarbon (CFC) and hydrofluoroalkane (HFA) metered dose inhalers (MDIs) have been previously been published[1-3]. This paper presents data obtained using a new experimental set-up (Plume Temperature Tester Model PTT 1000, Copley Scientific, UK) that measures plume temperature within a sampling tube constructed to the USP induction port entrance dimensions (USP 35, Apparatus 1, 2, 4 & 5). The temperature of each plume sampled is measured at distances of 25, 50, 75 and 100mm from the MDI's mouthpiece and the data obtained compared to previously published values.

The temperature of a plume emitted from an MDI is dependent upon the sampling distance from the actuator's mouthpiece. The plume is coldest in the proximity of the actuator mouthpiece where rapid flashing and evaporation of the formulation's propellant and volatile excipients causes cooling. Plume temperatures emitted from HFA MDIs vary between marketed products, in some cases being significantly below ambient temperatures (i.e. -46 ± 3°C); this can be attributed to choice of hardware (orifice diameter) and formulation excipients.

Methods

Temperature measurements were conducted within USP Induction Port Entrance Geometry (USP 35, Apparatus 1, 2, 4 & 5) at a sampling flow rate of 28.3l/min (see Figure 1). The apparatus contained four centrally aligned K-Type thermocouples mounted 25, 50, 75 and 100mm from the inlet of the apparatus (see Section A-A, Figure 1). Each thermocouple had an exposed 0.25mm stainless steel tip and a response time of 3ms. The thermocouples were linked to an analogue to digital Interface box and linked by USB cable to a PC using a controller card. Measurements were conducted by firing doses into the sampling apparatus which automatically detected the lowest temperatures within each 30 second sampling period. Data was collected at a sampling rate of 120Hz using the associated data acquisition software, recording temperature profiles from each of the four thermocouples at 3.9ms intervals (i.e. <1ms between thermocouple readings). Mean minimum plume temperature (MMPT) was reported as the average (± standard deviation) of the lowest recorded temperature observed from each of five 30s sampling periods for each MDI. All MDIs were purchased from a local pharmacy and actuated in accordance with patient instruction leaflets; each product was evaluated in duplicate. To address the dynamic nature of the plume in the close proximity of the mouthpiece (sampling distances 25mm and 50mm) two doses were fired into the sampling apparatus during each 30s sampling period. Drug build-up on the thermocouples was removed following the sampling period of each MDI by rinsing the thermocouples (in situ) with methanol and air drying.

Results and Discussion

Initial measurements were conducted upon two MDIs previously reported to have different plume temperature profiles[3]. Figure 2 presents the MMPT (± standard deviation, n = 5) as a function of sampling distance for a) Ventolin 100 and b) Qvar 100; the data is in good agreement with previously published data obtained within delivered dose uniformity apparatus (USP 35, Apparatus A)[3]. The two temperature profiles are markedly different, reflecting the formulation and hardware differences. Addition of excipients and/or reducing the actuator orifice diameter produces an inherently warmer plume: Qvar contains ethanol, and has an orifice diameter of 0.30mm, whereas Ventolin contains no additional excipients, and also has a larger 0.5mm diameter orifice[3].

These trends also follow for the eleven marketed products evaluated (presented in Table 1). For each product evaluated the MMPT (± standard deviation, n = 5) is shown in Figure 3. The greatest difference is observed at a sampling distance of 25mm where the lowest MMPT was -46 ± 3°C (Ventolin) and the highest was 6 ± 1°C (Qvar). The products evaluated with no additional excipients and larger orifice diameters (Flixotide, Seretide and Ventolin) remained the lowest MMPTs at a distance of 50mm, with temperatures ranging between -8 ± 2 to -18 ± 7°C. As the sampling distance was increased to 75mm the difference between the MMPTs for all products reduced, ranging between -2 ± 3ºC (Ventolin) and 7 ± 1ºC (Symbicort). Comparatively, MMPTs were similar for all products (6 ± 1°C to 11 ± 1°C) at the sampling distance of 100mm.

The increase in plume temperature with sampling distance indicates that the majority of the flashing and evaporation of propellant and volatile excipients occurs close to the actuator mouthpiece exit. Stein and Gabrio have previously highlighted that drug deposition is greatest within the first 2-3cm of the USP induction port entrance[4]. Thus the denuded plume is likely to have less of an influence on the plume temperature as the plume travels along the USP induction port. The build-up of drug on the thermocouples is a clear indication that in addition to measuring local gas phase temperature; droplet deposition followed by evaporation and cooling of each thermocouple is an intrinsic characteristic of the measurements presented in this paper. It also follows that more drug is expected to deposit on the thermocouples closest to the actuator mouthpiece exit; and this is evident visually if the thermocouples are not cleaned following multiple product evaluations.

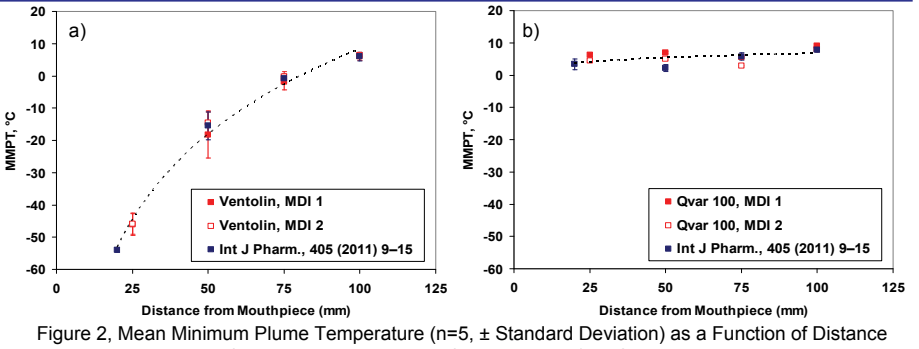

Figure 2, Mean Minimum Plume Temperature (n=5, ± Standard Deviation) as a Function of Distance from the MDI Mouthpiece for a) Ventolin & b) Qvar 100

Introduction

The temperature of the cloud emitted from a metered dose inhaler (MDI) may result in patient discomfort and inconsistent or non-existent dose delivery to the lungs[1]. This is due to rapid formulation flashing and evaporation in the proximity of an MDI's mouthpiece. Cooling of the plume is dependent upon both device and formulation characteristics; MDI's with large metering volumes and actuator orifices emit the coldest plumes, however, plume temperature may be increased by adding excipients (such as ethanol) to the formulation to suppress propellant evaporation rate and cooling[3]. A previously published experimental methodology[2-3] has been developed and data is presented for a number of marketed products.

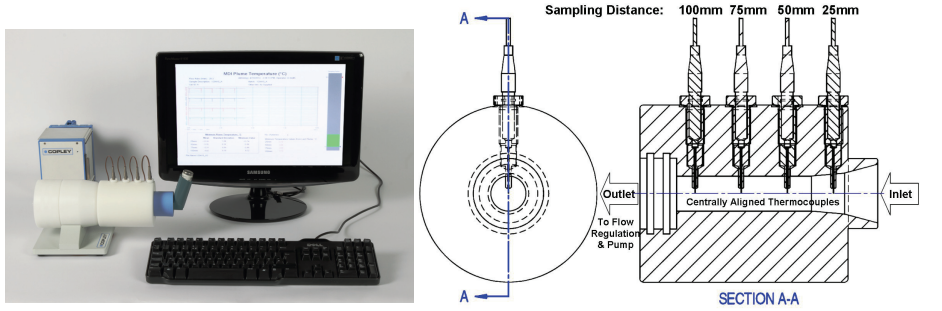

Figure 1, Plume Temperature Set-up Showing Central Positioning of Thermocouples within USP Induction Port Entrance Geometry

Table 1, Device and Formulation Details for the Eleven Marketed Products Evaluated

Product	Metered Dose (µl)	Actuator Orifice Diameter (mm)	Formulation	Propellant	Other Excipients
Clenil 50	50	0.30	Solution	HFA 134a	Ethanol, Glycerol
Clenil 100	50	0.30	Solution	HFA 134a	Ethanol, Glycerol
Clenil 200	50	0.30	Solution	HFA 134a	Ethanol, Glycerol
Clenil 250	50	0.30	Solution	HFA 134a	Ethanol, Glycerol
Flixotide 50	63	0.50	Suspension	HFA 134a	None
Flixotide 250	63	0.50	Suspension	HFA 134a	None
Fostair 6 + 100	63	0.30	Solution	HFA 134a	Ethanol, HCl
Qvar 100	50	0.25	Solution	HFA 134a	Ethanol
Seretide 25 + 250	63	0.50	Suspension	HFA 134a	None
Symbicort 160 + 4.5	50	0.40	Suspension	HFA 227	Povidone K95, PEG 1000
Ventolin 100	63	0.50	Suspension	HFA 134a	None

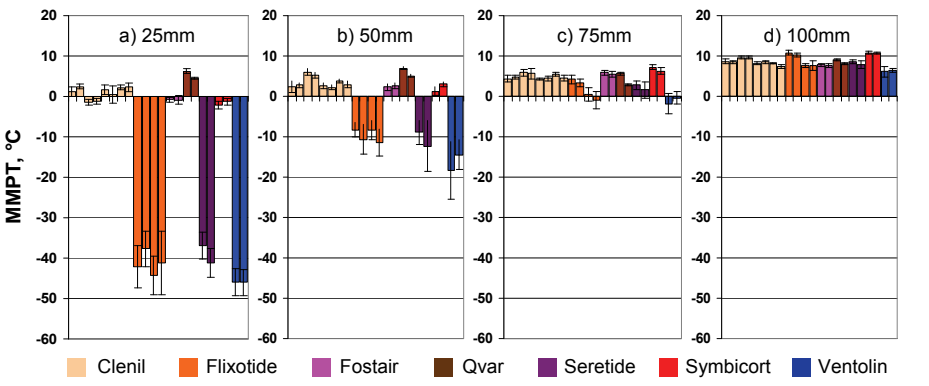

Figure 3: Minimum Plume Temperature (MMPT) for Marketed Products as a Function of Thermocouple Distance from the Actuator Mouthpiece (Error Bars = Standard Deviation, n = 5)

Conclusion

A previously published method for measuring the MMPT emitted from an MDI has been developed such that measurements at four sampling distances are obtained from each sampled plume. The new experimental set-up also utilises the geometry of the USP induction port entrance (USP 35, Apparatus 1, 2, 4 & 5). Experimental data obtained is in good agreement with previously published data.

The temperature of a plume emitted from an MDI is dependent upon the sampling distance from the actuator's mouthpiece. The plume is coldest in the proximity of the actuator mouthpiece where rapid flashing and evaporation of the formulation's propellant and volatile excipients causes cooling. Plume temperatures emitted from HFA MDIs vary between marketed products, in some cases being significantly below ambient temperatures (i.e. -46 ± 3°C); this can be attributed to choice of hardware (orifice diameter) and formulation excipients.

The method developed allows rapid assessment of the MMPT emitted from an MDI. Although the methodology presented is not a simple reflection of gas phase cloud temperature, it is considered to be a useful tool for understanding the relative sensations that maybe encountered by a patient during dose inhalation.

References

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3.Brambilla G; Church T; Lewis D; and Meakin B (2011). 'Plume temperature emitted from metered dose inhalers'. Int J Pharm., 405 (2011) 9–15.

4.Stein, S.W. and Gabrio, B.J. (2000), "Understanding throat deposition during cascade impactor testing," Proc. RDDVII, 287-290.