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# Plume temperature emitted from metered dose inhalers

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ABSTRACT

The temperature of the drug cloud emitted from a pressurised metered dose inhaler (pMDI) may result in patient discomfort and inconsistent or non-existent dose delivery to the lungs. The effects of variations in formulation (drug, propellant, co-solvent content) and device hardware (metering volume, actuator orifice diameter, add-on devices) upon the temperature of pMDI plumes, expressed as replicate mean minimum values (MMPT), collected into a pharmacopoeial dose unit sampling apparatus (DUSA), have been investigated. Ten commercially available and two development products, including chlorofluorocarbon (CFC) suspensions and hydrofluoroalkane (HFA) solutions or suspensions, were examined together with a number of drug products in late stage development and a variety of HFA 134a placebo pMDIs. Plume temperatures were observed to be lowest in the proximity of the product's actuator mouthpiece where rapid flashing and evaporation of the formulation's propellant and volatile excipients cause cooling. The ability to control plume temperature by judicious choice of formulation co-solvent content, metering volume and the actuator orifice diameter is identified. An ethanol based HFA 134a formulation delivered through a fine orifice is inherently warmer than one with 100% HFA 134a vehicle delivered through a coarse actuator orifice. Of the 10 commercial products evaluated, MMPTs ranged from −54 to +4 °C and followed the formulation class rank order, HFA suspensions < CFC suspensions < HFA solutions. For all systems examined it was possible to raise pMDI plume temperature to that of the ambient surroundings by use of an add-on or integrated spacer device.



## 1. Introduction

The temperature of the cloud emitted from a pressurised metered dose inhaler (pMDI) may result in patient discomfort ("cold Freon effect") and consequent inconsistent or non-existent dose delivery to the lungs (Crompton, 1982). However, there is limited published information on the effects of formulation and device hardware on the temperature of clouds emitted from pMDIs. Gabrio et al. (1999) described methodology in which a PC was used to record the temperature at the centre of a "free" plume using a "quick" response (5 ms) thermocouple positioned at the centre of a 45 $mm^2$ target plate mounted 50 mm from the exit of a pMDI's mouthpiece. No attempt was made to examine potential perturbation from thermal conduction by the target. The experimental conditions used in this study differ significantly in that the expelled cloud is constrained within a pMDI dose unit sampling apparatus (DUSA; EP/USP), thus more closely mimicking the *in vivo* scenario; also the thermocouple sensing tips were at least 10 mm away from the walls of the DUSA.

The plume temperatures of the commercial products previously evaluated by Gabrio et al. (1999) were re-assessed to compare results for the two techniques. Using our technique, the effects of ethanol, widely used as cosolvent, in the formulation vehicle and pMDI hardware variables upon the temperature of plumes emitted from HFA 134a solution based pMDIs were then studied using model placebo pMDI systems together with an extended range of commercial suspension and solution products. The effects of add-on "spacer" and "holding chamber" devices on cloud temperature were also determined.

## 2. Experimental

### 2.1. Measurement of plume temperature

Plumes were collected into a pMDI DUSA constructed from polyethylene terephthalate (PET) in compliance with EP/USP dimensional specifications, operated at a flow rate of 28.3 l $min^{-1}$. Temperature profiles were recorded by thermocouples (Omega, UK, K-Type, response time 3 ms) mounted 20 mm from the inlet of the apparatus with their exposed 0.25 mm stainless steel tips

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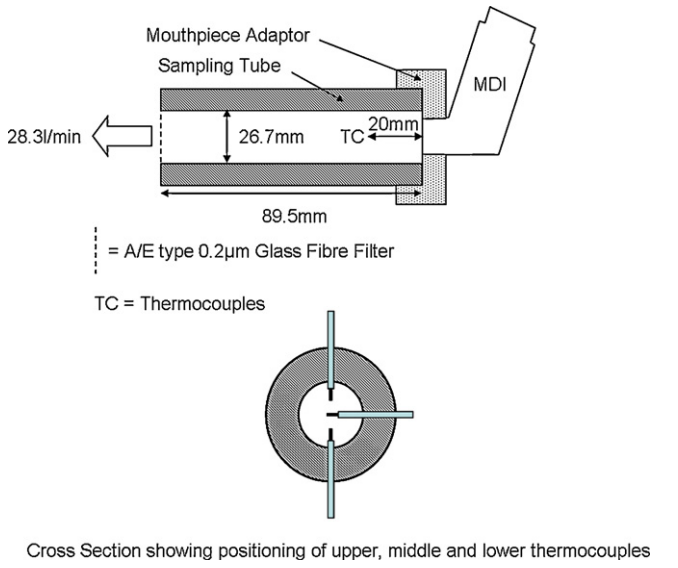


**Fig. 1.** Schematic of plume temperature sampling apparatus.

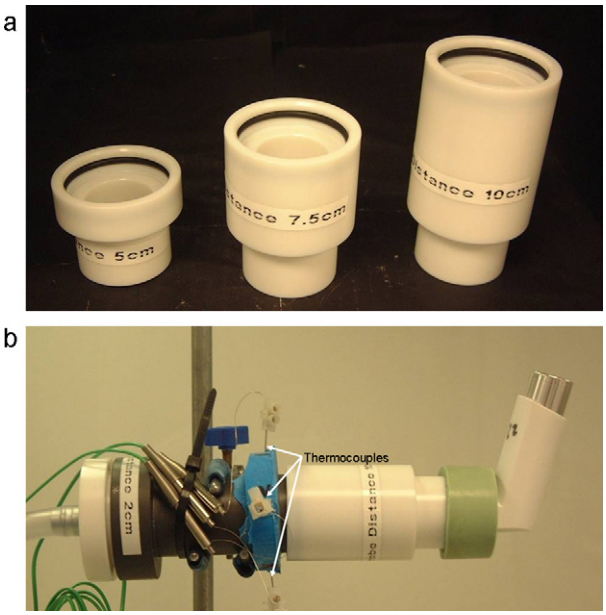


**Fig. 2.** Plume temperature sampling apparatus. (a) Sampling apparatus extensions and (b) sampling apparatus fitted with extension.

vertically aligned. Following initial experiments using a single axially central thermocouple, the apparatus was further modified to incorporate three vertically aligned thermocouples (Fig. 1) to allow confirmation of central axial alignment for the pMDI plume by comparison of the data individually collected from the upper, middle and lower thermocouples. It was observed that MDI plume alignment was of particular importance in the proximity of the actuator where the cloud was highly dynamic and centrally localised; poor MDI alignment would result in failure to axially sample the plume in a representative manner.

The thermocouples were linked to an INET-100, instruNet external analogue to digital Interface box (Omega, UK), which in turn was linked to a PC using an INET-200 PCI controller card (Omega, UK). Central alignment of a pMDI's plume within the sampling apparatus was confirmed by comparing the temperature data collected from the upper, middle and lower thermocouples and ensuring the coldest temperature profile was registered on the middle, i.e. central, thermocouple. For each test condition, measurements were conducted by discharging individual doses into the sampling apparatus at 30 s intervals. Data was collected by the PC at a sampling rate of 231 Hz using Dasylab Data Acquisition Software (extended version), resulting in a plume temperature profile being individually recorded from each of the three thermocouples over a test period of about 7 min, at 4.3 ms intervals. Data aquisition was continuous to ensure that the entire plume temperature profile was captured. Minimum plume temperature (MMPT), for each test condition is reported as the mean ± standard deviation ($n = 10$) of the lowest temperatures from each of five replicate plumes discharged from duplicate units of each batch of product. For pMDIs containing "actives", the sampling apparatus was rinsed with methanol and air-dried after each five replicate dose collection sequence to remove drug deposits formed on the thermocouple sensing tips.

To investigate sampling distance effects, inlet extensions, fabricated from PET and machined to have a flush finish with the sampling apparatus were introduced to allow evaluation of plume temperature at distances of 20, 50, 75 or 100 mm from the actuator's mouthpiece. Joints between the apparatus and extensions were made air-tight using countersunk O-rings (Fig. 2).

### 2.2. Commercial and development pMDI systems

All systems were within their expiry dates at the time of measurement.

*CFC based suspensions*: Becotide® 100, Allen and Hanbury, Batch No. 0426R, and Beclazone® 250, Ivax, Batch No. ACX60A; both products contain beclometasone dipropionate, BDP.

*HFA based suspensions*: Flixotide® 125 Evohaler®, fluticasone propionate, Batch No. 9214, and Ventolin® 100 Evohaler®, salbutamol sulphate, Batch No. 1780, both Allen and Hanbury.

*HFA based solutions*: Qvar® 50, Batch No. ACX60A, Qvar® 100, Batch No. CHG054A, both Ivax, contain BDP. Chiesi Modulite® products; Clenil® 50[a], Batch 050516, Clenil 250[a], Batch 046177, both contain BDP; Budiair® 200[a], budesonide, Batch 076437 and budesonide 400[b], Batch A50522/T; Atimos®/Forair® 12[a], formoterol fumarate, Batch 078024 and formoterol 6, Batch 0309060 Modulite® products were taken from industrial[a] or pilot-scale development batches[b], and fitted with either their conventional Bespak BK630 series actuators with or without add-on spacer devices, Aerochamber Plus®, Trudell Batch No. 060064, Volumatic® Allen and Hanbury, Batch. No. L0387 GW 1297 or an integral spacer device, Chiesi Jet®, Batch No. 05844. Further details of the pMDI formulations and hardware are given in Tables 1 and 2.

### 2.3. HFA 134a—cosolvent vehicle, placebo pMDIs

Pre-determined amounts of ethanol were weighed into tared, cut edge aluminium cans (Presspart). Using Pamasol 2016 laboratory scale, crimping and filling equipment, the cans were sealed with 25, 50, 63 or 100 µl BK 357 valves (Bespak, UK) and filled with a known weight of HFA 134a propellant to a total formulation volume of approximately 12 ml. Final ethanol concentrations were 0–20% (w/w). Cans were fitted with Bespak type BK630 standard actuators with orifice diameters of 0.22, 0.30, 0.36, 0.42 or 0.58 mm.

## 3. Results and discussion

The build-up of drug on the thermocouples is a clear indication that, in addition to the local gas phase temperature, cooling of each thermocouple also arises from droplet deposition and propellant evaporation, the resultant is an intrinsic characteristic of the measurements presented in this paper. Furthermore, since impaction mechanisms are dependent upon momentum, it is assumed that thermocouple deposition will be greatest in the proximity of the

**Table 1**
Formulation and mean minimum plume temperature (±standard deviation, °C) for marketed products: effect of sampling distance.

| Product (actuator orifice diameter, metered dose volume) | Formulation | Surfactant | Propellant | Other excipients | Gabrio et al. (1999), "still air", 50 mm | This study, sampling distance (mm) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 20 | 50 | 75 | 100 |
| Becotide® 100 (0.50 mm, 63 μl) | Suspension | Oleic acid | CFC 11/12 | None | −32.2 ± 5.7 | −31.2 ± 2.1 | −14.0 ± 3.8 | 1.0 ± 0.8 | 8.2 ± 1.3 |
| Beclazone® 250 (0.50 mm, 63 μl) | Suspension | Oleic acid | CFC 11/12 | None | Not measured | −31.3 ± 3.7 | −6.3 ± 2.2 | 3.0 ± 1.3 | 7.7 ± 0.9 |
| Qvar® 50 (0.25 mm, 50 μl) | Solution | None | HFA 134a | Ethanol | 3.7 ± 1.4 | 4.1 ± 0.9 | 2.3 ± 0.4 | 5.1 ± 1.1 | 8.0 ± 0.7 |
| Qvar® 100 (0.25 mm, 50 μl) | Solution | None | HFA 134a | Ethanol | 3.0 ± 1.4 | 3.4 ± 1.7 | 2.2 ± 1.1 | 5.8 ± 1.1 | 7.8 ± 0.6 |
| Flixotide® 125 Evohaler (0.50 mm, 63 μl) | Suspension | None | HFA 134a | None | −21.3 ± 11.1 | −51.1 ± 2.0 | −15.7 ± 5.0 | −0.3 ± 1.2 | 6.4 ± 0.8 |
| Ventolin®/Sultanol® Evohaler (0.50 mm, 63 μl) | Suspension | None | HFA 134a | None | −30.2 ± 5.0 | −54.0 ± 0.7 | −15.5 ± 4.3 | −0.8 ± 1.3 | 6.0 ± 1.4 |

**Table 2**
Mean minimum plume temperature (±standard deviation, °C) of Chiesi Modulite® solution formulations emitted from add-on devices. (All contain HFA 134a as propellant and ethanol as cosolvent. Sampling distance 20 mm from mouthpiece.).

| Product (actuator orifice diameter, metered dose volume) | Actuator/add-on device (device volume) | | | |
|---|---|---|---|---|
| | BK630[a] | BK630[a] + Volumatic (750 ml) | BK630[a] + Aerochamber Plus (149 ml) | Chiesi Jet[b], 0.40 mm orifice diameter (125 ml) |
| Budesonide 200[c] (0.42 mm, 50 μl) | −5.4 ± 2.6 | 18.4 ± 0.2 | 12.5 ± 0.3 | 13.4 ± 0.2 |
| Budesonide 400[c] (0.36 mm, 100 μl) | −7.5 ± 1.1 | 16.6 ± 0.3 | 9.5 ± 0.3 | 9.7 ± 0.4 |
| Formoterol 6[d] (0.30 mm, 50 μl) | −2.7 ± 0.3 | 19.1 ± 0.1 | 11.1 ± 0.4 | 15.3 ± 0.7 |
| Formoterol 12[d] (0.30 mm, 63 μl) | −4.8 ± 1.2 | 18.1 ± 0.1 | 10.3 ± 0.1 | 12.6 ± 0.7 |
| BDP 50[c] (0.30 mm, 50 μl) | −2.0 ± 1.9 | 18.8 ± 0.1 | 13.3 ± 0.3 | 13.3 ± 0.4 |
| BDP 250[c] (0.30 mm, 50 μl) | −1.1 ± 2.4 | 19.1 ± 0.1 | 13.0 ± 0.3 | 13.7 ± 0.5 |

[a] Bespak BK630 series actuator.
[b] Integrated actuator-spacer.
[c] Contains glycerol.
[d] Contains HCl.

mouthpiece where momentum is highest, and will also be dependent upon pMDI formulation and device characteristics (Lewis et al., 2006). The authors consider that although the methodology presented is not, therefore, a simple reflection of gas phase cloud temperature, it is a useful tool for understanding the relative thermal sensations that maybe encountered by a patient during dose inhalation.

### 3.1. Effects of formulation vehicle and pMDI hardware variants on mean minimum plume temperature

Plume temperatures of the placebo HFA 134a solutions were initially studied at a distance of 20 mm from the exit of the actuator's mouthpiece. Fig. 3 presents two representative examples of temperature profiles of individual plumes from propellant only systems, recorded from the central thermocouple. Plume A, discharged from a 25 μl metering chamber via a 0.22 mm orifice Bespak BK630 series actuator exhibits a small initial fall in temperature from ambient to +12 °C ($\Delta T \sim -8$ °C) with little change thereafter over the test period of 400 ms. In contrast, when 100 μl of HFA 134a was discharged through the largest actuator orifice, 0.58 mm, there was a rapid, marked fall in the temperature of plume B which has a well defined minimum of −48 °C ($\Delta T \sim -70$ °C) at ∼90 ms before increasing again to reach ∼−5 °C at the end of the test period. These results are consistent with expectations since the four-fold increase in liquid volume demands greater thermal energy for the liquid → gas transition and the coarser orifice increases the discharge rate, allowing less time for droplet evaporation prior to arrival at the thermocouple sensors. The introduction of ethanol co-solvent results in plume temperature profiles intermediate between the extremes shown in Fig. 3.

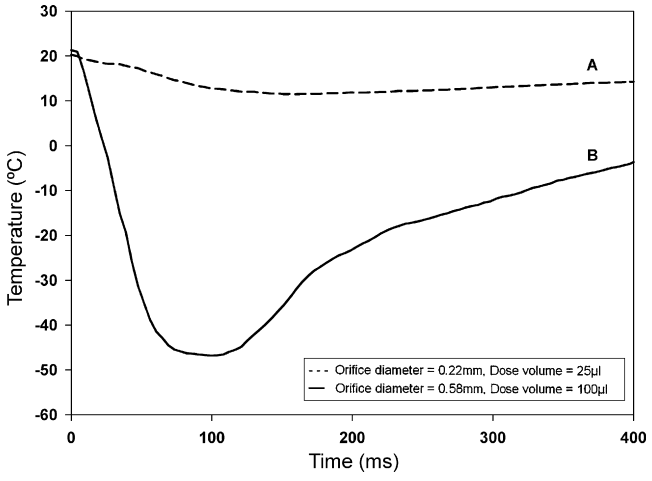


**Fig. 3.** Plume temperature typical profile for HFA 134a placebo MDIs (20 mm from actuator mouthpiece).

MMPTs for placebo pMDIs containing up to 20% (w/w) ethanol co-solvent, packaged with 25–100 μl metering valves and discharged through Bespak BK630 series actuators with orifice diameters ranging from 0.22 to 0.58 mm are presented in Fig. 4a–d. The lowest and highest MMPTs (−48 to +12 °C) were observed for HFA 134a in the absence of co-solvent when delivered via 100 μl/0.58 mm or 25 μl/0.22 mm metering valve/actuator orifice combinations respectively (see also Fig. 3). The data demonstrates that reducing the valve volume and/or actuator orifice diameter results in warmer plumes. Fig. 4 also shows that increasing the ethanol content of a given pMDI system may increase or decrease MMPTs dependent upon the metered volumes/actuator orifice diameters employed and that the addition of ethanol progressively reduces the influence that metering volume has upon MMPT values obtained for a given orifice diameter to the point where they become very similar (Fig. 4a).

The effect of thermocouple sampling distance from the actuator's mouthpiece on MMPT is illustrated in Fig. 5a–c for combinations of three placebo pMDI formulations (0, 10, 20% (w/w) ethanol) and three metering valve/actuator orifice diameter hard-

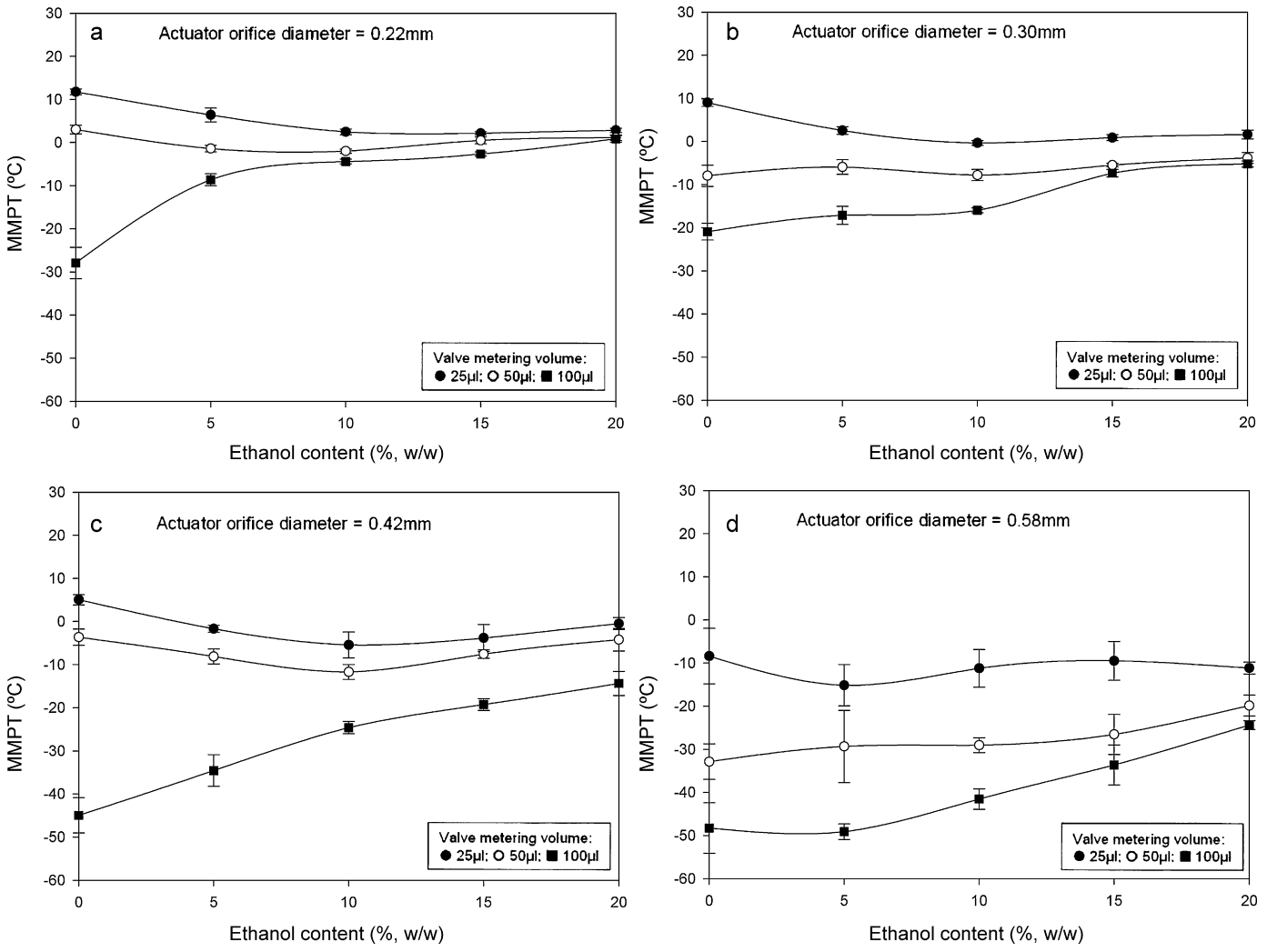


**Fig. 4.** MMPT for placebo ethanol/HFA 134a formulations fitted with 25, 50 or 100 μl metering valves ($n = 5$, mean ± standard deviation).

ware variants (25 μl/0.22 mm, 63 μl/0.58 mm, 100 μl/0.58 mm). Overall, the data confirms the expectation that plumes are coldest in the proximity of the actuator's mouthpiece exit where rapid flashing and evaporation of the propellant and any volatile excipients occur.

Fig. 5a demonstrates, that when 25 μl of HFA 134a without cosolvent is delivered through a Bespak 0.22 mm actuator, there is an approximately linear increase in MMPT from +12 °C to +20 °C ($\Delta T = 8$ °C) over a sampling distance range of 20–100 mm, i.e. distances pertinent to the proximity of the oral cavity from an inhaler mouthpiece. The maximum value observed approximates to the controlled ambient laboratory temperature of +21 ± 3 °C. This would indicate either that propellant evaporation is essentially complete within 100 mm of the actuator's mouthpiece exit and/or the droplet size of any residual liquid propellant is sufficiently small to minimise impaction on the thermocouple. The addition of 10% (w/w) or 20% (w/w) ethanol to the formulation suppresses evaporation of the residual droplets, MMPTs consequently varying from +2 to +12 °C, again approximately linearly, over the same sampling distances; at 100 mm from the actuator mouthpiece MMPT is +8 to +9 °C below the ambient laboratory temperature.

Fig. 5b shows that increasing the metering volume to 63 μl and the actuator orifice diameter to 0.58 mm largely eliminates the influence of ethanol content, MMPT rising from −24 to −19 °C at 20 mm to +11 °C at 100 mm distance from the actuator's mouthpiece exit ($\Delta T \sim 33$ °C); the relationship between MMPT and distance is now non-linear however.

Fig. 5c demonstrates that a further increase in metering volume to 100 μl results in MMPTs which, at 20 mm from the mouthpiece exit, exhibit a wide range (−48 to −24 °C) and also decrease with increasing ethanol content. However, between 50 and 100 mm, MMPT values again become relatively independent of ethanol content, whilst increasing in a linear manner to a consistent value at 100 mm (+1 to +4 °C). One proposed explanation for these observations is that liquid phase HFA 134a is present within the plume's droplets over the whole distance range. Since, at 20 mm from the exit of this 0.58 mm orifice actuator, the formulation with the highest ethanol content has the warmest plume, it is apparent that the presence of ethanol has significantly increased the saturation temperature of the residual formulation such that its evaporation and cooling rate are suppressed compared to that of HFA 134a propellant alone. An alternative hypothesis is that the distinctive results at 20 mm may be driven by droplet impaction on the thermocouple, which could account for their ethanol dependency, but that this driver reduces with increasing droplet distance when the overall gas phase temperature dominates the thermocouple response.

The general conclusion to be drawn from this series of experiments is that aerosol plumes emitted from ethanol based HFA 134a formulations delivered through fine orifices, which have lower impact forces (Bell and Newman, 2007; Gabrio et al., 1999), are

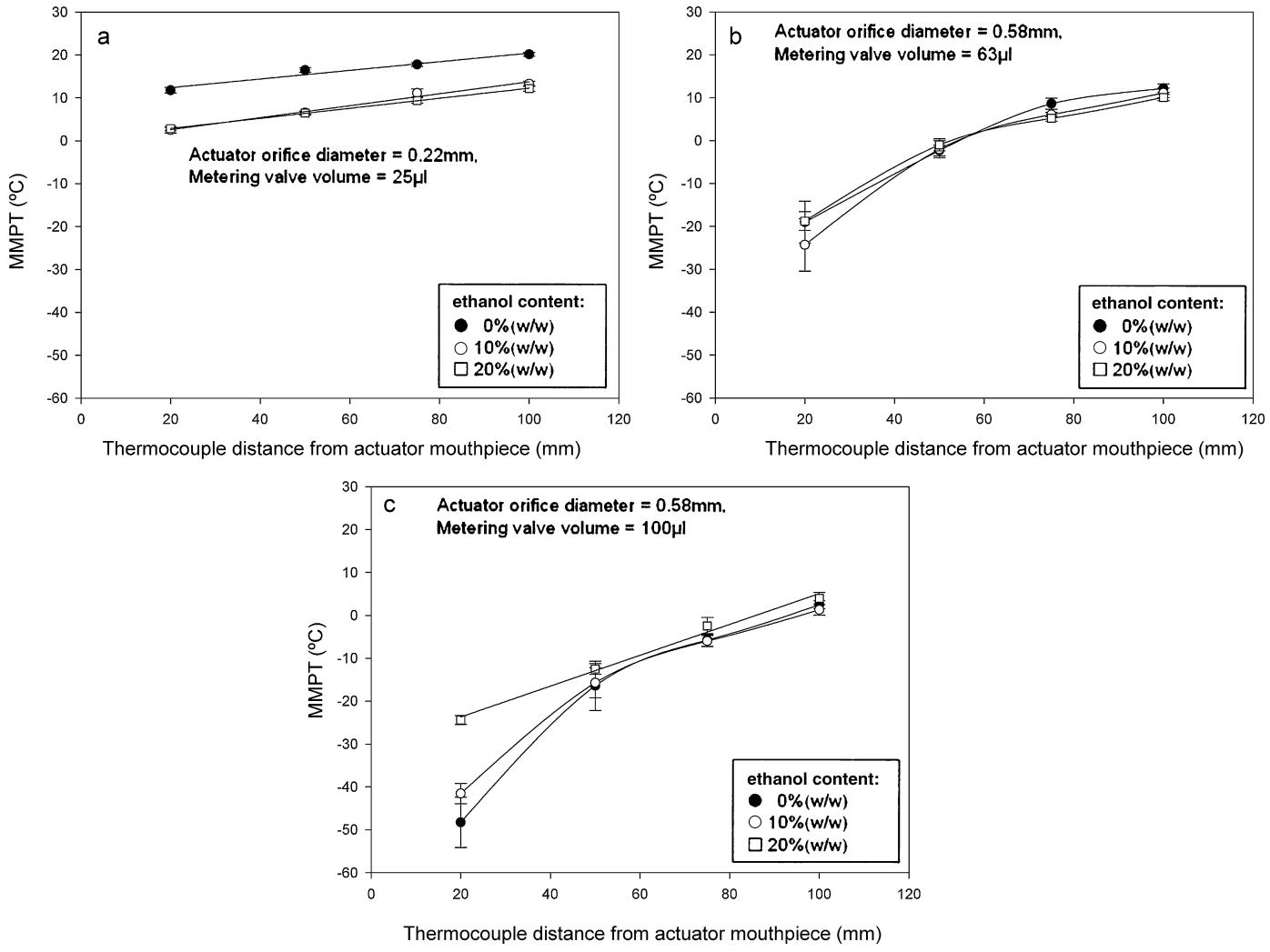


**Fig. 5.** MMPT for placebo ethanol/HFA 134a formulations as a function of thermocouple distance from the actuator mouthpiece ($n = 5$, mean ± standard deviation).

inherently warmer than propellant only formulations delivered through coarse actuator orifices. This is an important observation as such difference is likely to be typical of the "mouth-feel" characteristics for the two principal types of commercial pMDI inhalation products (solution and suspension) currently being developed and marketed (see Table 1). This is in agreement with Bell and Newman (2007), who highlighted the reduction in the "cold feel" of many HFA MDIs compared to CFC MDIs, but emphasized that differences are product specific.

### 3.2. MMPT—sampling distance profiles for commercial products

Table 1 presents MMPT data for six products, two CFC P11/P12 suspensions, two HFA 134a suspensions and two HFA 134a solutions; temperatures for the centre of "free" plumes previously reported for five of these (Gabrio et al., 1999) are included for comparison. Corresponding MMPT—sampling distance profiles are plotted in Fig. 6. Individual values for the duplicate cans within each product/formulation category were similar for a given sampling distance, reflecting their similarity with respect to metered volume and ethanol co-solvent content (Table 1). MMPTs in the proximity of their actuator's mouthpiece exit (20 mm) follow the rank order HFA suspension < CFC suspension < HFA solution; the markedly colder plumes from the HFA suspensions of approximately −50 °C against those from CFC suspensions of approximately −30 °C, are associated with the former's lower boiling points and higher vapour pressures (Meakin et al., 2000). Comparison of the data obtained at equivalent 50 mm distances from the actuator exit for free (Gabrio et al., 1999) and constrained (this study) plumes shows the MMPTs of the former are generally colder, the difference being most apparent for CFC suspension products. This seems likely to result from lower propellant evaporation rates imposed by the non-sink conditions of the constraining DUSA. The MMPT-distance profiles for the ethanol based HFA 134a solution products, Qvar 50 and 100 (Fig. 6b), are similar to those presented in Fig. 5a for analogous ethanol based placebo formulations. MMPTs for the ethanol-free HFA 134a suspension products Flixotide and Ventolin are much lower (−51, −54 °C) at 20 mm, than observed with the Qvar products (+3, +4 °C) which contain ethanol. This is associated with the relative differences in hardware (actuator orifice diameter and metering volume), and formulation (±ethanol). The former's subsequent rise in temperature between 50 and 100 mm from −16 °C to +6 °C is comparable to the profile seen for the non-ethanol based placebo formulation in Fig. 5c.

### 3.3. Modulite® products with and without add-on devices and integrated spacers

Modulite® formulations are drug solutions in HFA 134a containing 12–15% (w/w) ethanol with up to 1.3% (w/w) non-volatile excipient. The ability of the Modulite® technology to generate drug clouds with pre-determined characteristics has been published

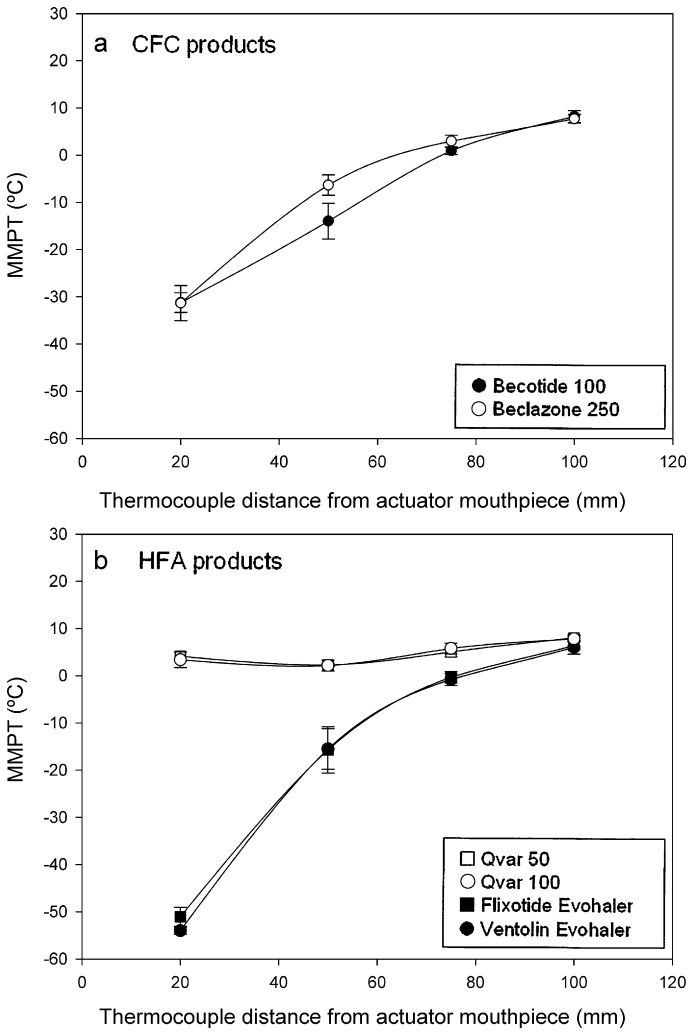


**Fig. 6.** MMPT for marketed products as a function of thermocouple distance from the actuator mouthpiece ($n = 5$, mean ± standard deviation).

(Brambilla et al., 1999, 2003; Ganderton et al., 2002, 2003; Lewis et al., 2005; Piccionno et al., 2006).

Table 2 presents the MMPT data determined at a distance of 20 mm from the exit of the device mouthpiece for six Modulite® products used in conjunction with standard BK630 actuators, with or without Volumatic® or Aerochamber Plus® add-on devices or the Chiesi Jet® integrated actuator-spacer device (Brambilla et al., 2004). Using BK630 actuators alone gave values ranging from −8 °C to −1 °C, which are close to those for their corresponding placebo formulations fitted with similar valve-actuator combinations of −6 °C to −7 °C (derived from Fig. 4). This data demonstrates that the inclusion of actives and small quantities of non-volatile excipients in a formulation does not materially affect the temperature of the corresponding basic propellant-co-solvent plumes.

Spacers and holding chambers are 'add-on' devices commonly used in conjunction with MDIs to reduce undesirable oropharyngeal drug deposition and optimise drug delivery performance by allowing patients to inhale from a slow moving cloud. The use of an add-on device can be expected to increase the temperature of the plume inhaled by the patient since, for the majority of formulations, propellant and volatile excipients will have evaporated from the cloud prior to being inhaled. Table 2 also shows that when the Modulite® products were used in association with either Aerochamber Plus® or Chiesi Jet®, internal volumes 149 and 125 ml respectively, MMPTs were increased (+10 °C to +15 °C) over those observed when standard actuators were used alone (−8 °C to −1 °C). A further increase (+17 °C to +19 °C), tending towards ambient laboratory temperature (18–24 °C), was obtained when the large 750 ml volume Volumatic® device was used. The effects of the add-on devices are analogous to the data shown in Fig. 5, which resulted from the introduction of sampling tube extensions between the actuator and the inlet of the plume sampling apparatus. It is not therefore surprising that warmer plumes are observed when the axial sampling distance is increased from 20 mm (BK630 actuator alone) to 130 mm (Chiesi Jet®) 160 mm (Aerochamber Plus®) and 240 mm (Volumatic®) by means of these various devices.

### 3.4. Refrigeration of pMDI products

In some instances (e.g. formoterol products), there is a requirement for a pMDI to be stored at low temperature (3–5 °C), until being dispensed to the patient. It was therefore of interest to evaluate the effect of such storage on the plume temperature in the event that a patient inhales a dose immediately following acquisition. MMPTs were determined at a distance of 20 mm from the actuator mouthpiece for the two formoterol Modulite® products when actuated immediately upon removal from refrigeration at 3 °C, these were slightly cooler (−7 ± 2 °C and −11 ± 2 °C), than for the same products pre-equilibrated to room temperature (18–24 °C), after removal from the refrigerator (−3 °C and −5 °C), demonstrating that refrigeration for these products does not reduce their MMPTs temperature significantly when compared to the range of plume temperatures observed during this study.

## 4. Conclusions

This study has identified formulation and device variables which can influence the temperature of plumes emitted from pMDIs. The coldest plumes result from use of large valve metering volumes and large actuator orifices. Plume temperature may be raised by increasing drug concentration so that the metering volume can be reduced; by reduction of actuator orifice diameter and/or adding excipients such as ethanol to the formulation which suppress propellant evaporation and cooling rates. Alternatively, use of a large volume add-on device such as Volumatic® results in the MMPT approximating to ambient. Use of smaller add-on devices, such as the Aerochamber Plus® or Chiesi Jet® also significantly increases the temperature of the emitted plume. The ability to elevate plume temperature by judicious choice of these variables has potential for reducing patient discomfort when using a pMDI and result in improved compliance and dose delivery to the lungs.

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