# Measuring the cold freon effect

## In vitro *testing that can support the development of new and generic metered dose inhalers*

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Users of pressurized metered dose inhalers (MDIs) may well be familiar with the cold freon effect—the inadvertent reaction to the chilling sensation that hits the back of the throat following actuation of the device. Caused by impaction of the delivered dose and the rapid evaporation of any remaining propellant (and in some cases, volatile co-excipients as well), the cold freon effect strongly influences the efficiency of drug delivery. It may, for example, cause the patient to abort or be unsuccessful in completing the inhalation manoeuvre. Quantifying this phenomenon is therefore important when aiming to replicate or improve inhalation behavior and MDI performance.

Here we examine reliable measurment of the cold freon effect, introducing a test set-up and new device that streamline the process (Plume Temperature Tester 1000, Copley Scientific, Nottingham, UK). Experimental data illustrate the way measurement supports the successful modification of a device or formulation to achieve development goals.

## The development of MDIs

Convenient for users and inexpensive to manufacture, pressurized MDIs are the established choice for delivering the corticosteroids and bronchodilators used globally to treat respiratory disorders. With MDIs, the motive force for drug delivery is provided by a pressurized propellant expanding and evaporating out of the device, causing rapid acceleration of the therapeutic dose. The impact of the dose hitting the back of throat at considerable velocity—and the chilling effect associated with the evaporation of any residual propellant—prompts the cold freon effect.

Conventionally, chlorofluorocarbons (CFCs) were the propellant of choice for MDIs, but this has changed as a result of the Montreal Protocol, prompting the gradual transition to alternatives—primarily hydrofluoroalkanes (HFAs) such as HFA-134a and HFA-227. Special dispensation was granted to permit the ongoing use of CFCs in MDIs to avoid the potential health impacts of rapid product withdrawal and the difficulties of reformulation. However, over the last decade or so, CFC MDIs have been substantially replaced. HFA-134a combines an acceptable toxicity profile with the required functionality and is now the most popular choice of propellant. It has largely displaced CFCs in many countries,[1,2] although they remain in use in some; a situation likely to persist for several more years.[3]

This reformulation process has necessitated considerable development activity and the evolution of a new generation of products. The cold freon effect is a widely recognized issue within this context and its reduction is seen as advantageous for the development of products that will simultaneously meet new formulation requirements and reduce usage errors.[4,5] Softer, warmer plumes may be produced by:

- Changing the formulation (propellant, excipient or co-solvent)
- Modifying the device (metering volume or actuator orifice diameter)
- Using add-on devices such as spacers or valved holding chambers

In all cases, however, reliable quantification of the cold freon effect is an important precursor to its effective control.

The rising global demand for inexpensive and effective treatments for respiratory illness also makes MDIs a prime market for the generic pharmaceuticals industry. Here, the need to replicate, rather than necessarily enhance, inhalation experience is an important reason for quantifying the combined effect of impaction force and propellant evaporation. In 2006, the United States Food and

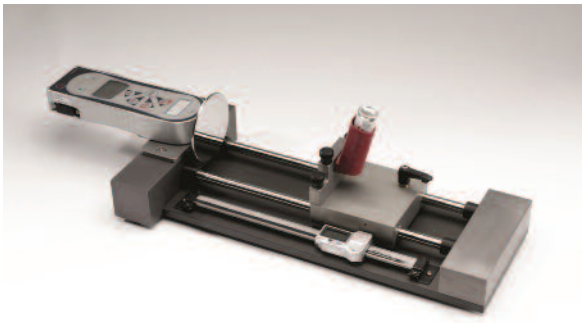
Drug Administration (FDA) released results from an *in vitro* study highlighting the strategy of using maximum impaction force as a way of demonstrating *in vitro* equivalence.[6] Guidance issued by the European Medicines Agency (EMA) in 2009 goes further, specifically stating that to substantiate therapeutic equivalence through *in vitro* testing, it is necessary to confirm that "any qualitative and/or quantitative differences in excipients should not be likely to affect the inhalation behavior of the patient (e.g. particle size distribution affecting mouth and throat feel or "cold freon" effect)."[7]

## Measuring plume temperature

Because the cold freon effect is a reaction to the combined sensation of impaction force and evaporative cooling, efforts to assess it have focused attention in two discrete areas: quantifying the force caused by high velocity impaction and plume temperature measurement. Impaction force can be assessed via leading edge velocity measurements or by direct measurement with an appropriately positioned load cell.[5,6,8] The Spray Force Tester Model SFT 1000 (Copley Scientific, Figure 1), for example, provides a straightforward, robust, commercially-available solution, allowing the measurement of spray force at a range of user-defined distances from the origin of the plume.[4,8]

**Figure 1**

**Measuring spray force is one aspect of assessing the cold freon effect (Spray Force Tester Model SFT 1000, Copley Scientific).**

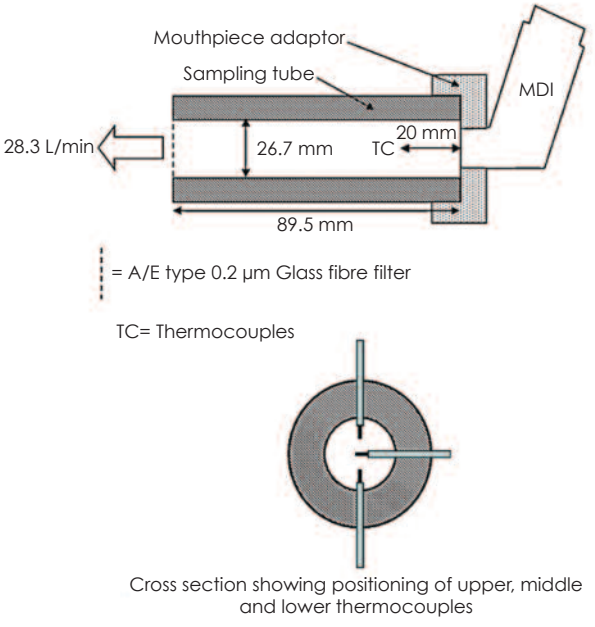


Early reported attempts to measure the temperature experienced during drug delivery were based on positioning a quick response thermocouple at the center of a plate, towards which the device was actuated.[4,5] This method produced useful comparative data for a range of commercially-available products but was recognizably sub-optimal in terms of replicating *in vivo* delivery conditions. An extensive study conducted in 2011 by Brambilla, et al.[9] therefore had the dual aims of establishing a robust method for plume temperature measurement and then using it to assess different strategies for controlling the cold freon effect.

In this study, a trial test apparatus was constructed based on the design of the MDI dose uniformity sampling apparatus (DUSA), modified to include fast response thermocouples for temperature measurement. Initially, a single axially central thermocouple was installed 20 mm from the inlet (Figure 2), but in a subsequent modification, two vertically aligned thermocouples were installed, as shown, to verify central axial alignment of the plume and ensure representative sampling. This modification confirmed that the central thermocouple did indeed record the lowest temperatures, validating the thermocouple positioning and the overall test set-up.

**Figure 2**

**Schematic showing the features of the plume temperature measuring test set-up of Brambilla, et al., which is based on the MDI DUSA apparatus**




For each test, individual doses were discharged into the test apparatus at 30-second intervals. A flow rate of 28.3 L/min was applied during testing, in line with the USP and Ph.Eur. recommendations for DUSA and aerodynamic particle size distribution MDI testing. Continuous data acquisition throughout the discharging process ensured that the entire plume temperature profile was captured, with average minimum plume temperatures (MMPT) reported for each condition, calculated from five duplicate measurements.

A final development in the testing apparatus involved fabricating a polyethylene terephthalate

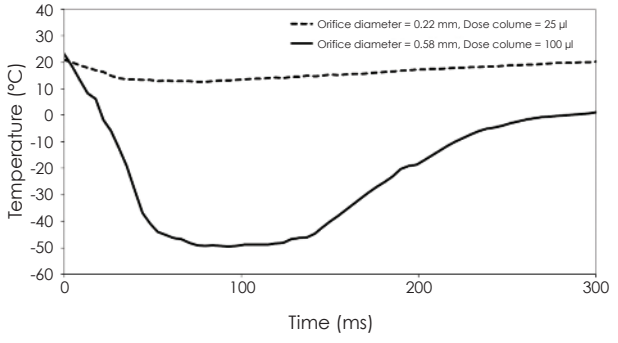
(PET) extension, with a flush finish to the sampling apparatus, to enable the measurement of plume temperature at 20, 50, 75 or 100 mm from the actuator mouthpiece. This modification permitted assessment of the effect of distance on the extent of the cold freon effect, which proved useful for evaluating the practical implications of the measured data.

## Evaluating plume temperature data

Initial tests carried out with HFA-134a placebo solutions demonstrated the ability of this set-up to support MDI development. Figure 3 shows plume temperature data recorded using a single thermocouple set-up. Data set A is for delivery of a relatively small dose volume, 25 µL, through a fine orifice, 0.22 mm, while data set B relates to the delivery of 100 µL through a coarse 0.58 mm orifice. The results show that increasing the dose volume and using a coarser orifice results in cooler temperatures being measured at the thermocouple. This effect is attributable to the greater thermal energy required to flash evaporate larger volumes of HFA propellant released at a faster rate.

### Figure 3

**Data (from a study by Brambilla, et al.) showing how orifice diameter and dose volume influence the plume temperature of an HFA-134a placebo MDI at a sampling distance of 20 mm**




Subsequent tests with commercial products and the four thermocouple system provided further insight into MDI performance. Figure 4 shows how plume temperature varies as a function of distance from the actuator for several HFA-based products. Plume temperatures for the Qvar products are relatively constant across the distance measured, but Flixotide and Ventolin, in sharp contrast, show a very low initial plume temperature that rises quickly, becoming equivalent to the Qvar products at around 100 mm.

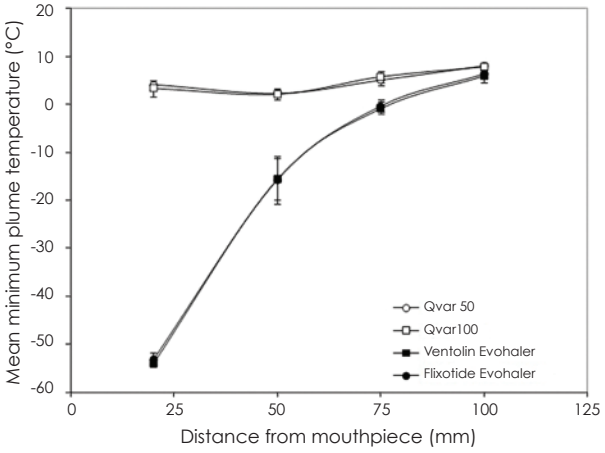
These differences can be attributed as much to the formulations of the products—both of the Qvar products use ethanol as a co-solvent—as to the inhaler design (actuator orifice diameter and metered volume). Their impact on product use may depend on the physiology of the patient but, in this case, for those products that do develop very low initial plume temperatures, propellant loss is sufficiently rapid that temperatures return to relatively benign levels at distance beyond 50 mm from the actuator.

The results obtained for the commercial products were compared with analogous data recorded using the unconfined test set-up described previously (thermocouple installed on an impaction surface),[5] and in general, the temperatures recorded were higher with the constrained system. (Data not shown.) This finding can be explained by lower propellant evaporation rates in the DUSA system, which, more similarly to the mouth and throat, does not present sink conditions for rapid propellant loss. This can be argued as evidence that the DUSA-based set-up provides more representative data than previous alternatives.

Finally, during testing it was observed that drug tended to deposit on the thermocouples. This suggests that the temperatures recorded were influenced not just by the temperature of the gas phase plume but also by droplet deposition and subsequent propellant evaporation. Since thermocouple deposition will tend to depend on momentum, it is likely that this mechanism will be most influential on the thermocouples closest to the mouthpiece and will be affected by the MDI formulation and device characteristics. It can be argued that this

### Figure 4

**Mean minimum plume temperature (MMPT) as a function of distance from the actuator mouthpiece for a range of commercial HFA MDIs**



deviation from simple measurement of the gas phase makes the test set-up and methodologies more representative of *in vivo* behavior as impaction, droplet deposition and subsequent propellant evaporation are all mechanisms that will take place within the mouth and throat during product use, to create the sensation experienced during delivery.

## Streamlining plume temperature measurement

Building on the findings of this experimental study, Copley Scientific has developed the Plume Temperature Tester Model PTT 1000, for routine analysis (Figure 5). Like the experimental set-up used, it has a propylene sampling tube but with the same internal dimensions as the standard Ph Eur/USP induction, rather than those of a DUSA apparatus. It has four centrally-aligned thermocouples mounted vertically at a distance of 25, 50, 75 and 100 mm from the inlet. These are linked to a data acquisition system under the control of a computer and easily removable for cleaning. The outlet of the PTT 1000 can be connected to a waste shot collector or directly to a DUSA tube for representative dose collection at 28.3 L/min.

**Figure 5**

**An automated system for plume temperature testing (Plume Temperature Tester 1000, Copley Scientific)**

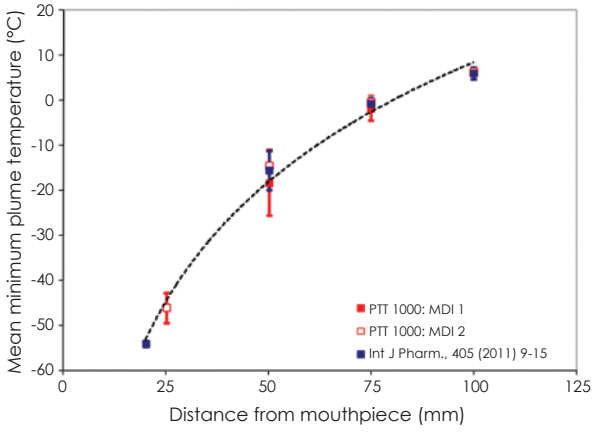

To assess the performance of the PTT 1000, data measurements were made for some of the products tested in the study described above. Figure 6 displays example data showing close agreement between these two sets of data. These data validate the PTT 1000 against the original experimental set-up detailed above, which was extensively studied, and suggest that plume temperature measurements are not overly sensitive to the internal geometry of the test apparatus. They confirm the commercial unit as a proven solution for robust and routine plume temperature measurement within the laboratory, when plume temperature data is essential for effective product development.

## In conclusion

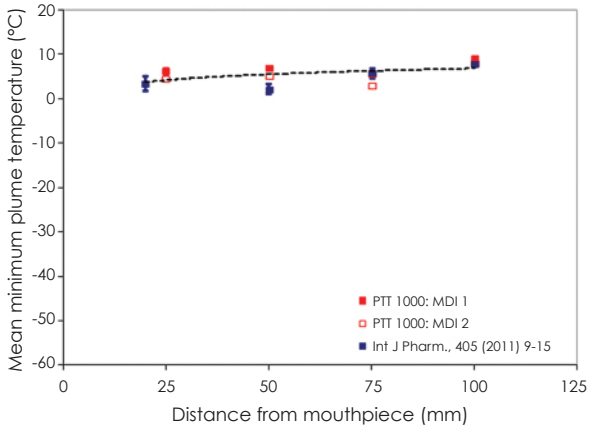
The replication of MDI performance and the development of new products with softer, warmer plumes that encourage patient compliance, call for reliable quantification of the cold freon effect. On the basis of a detailed experimental study, a commercial plume temperature tester has been developed that allows reproducible measurement under conditions closely similar to those used for other *in vitro* MDI test methods. This system enables systematic investigation of the impact of device geometry, formulation and the use of additional devices

**Figure 6**

**Test data showing close agreement between measurements recorded using the PTT 1000 and previously-published experimental data obtained using a DUSA test set-up**




**Plume temperature of Ventolin Evohaler**




**Plume temperature of Qvar 100**

such as spacers, to support the accelerated development of both generic and innovator products and the more efficient application of MDI technology.

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