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# A new method to evaluate plume characteristics of hydrofluoroalkane and chlorofluorocarbon metered dose inhalers

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**Abstract**

Two concerns raised when comparing metered dose inhalers (MDIs) to other inhalation devices are their relatively high throat deposition and the 'cold-Freon' effect seen in a small number of patients. The cold-Freon effect is presumed to be a result of the cold, forceful MDI plume impacting on the back of a patient's throat. This in vitro study uses a new plume characterization method to determine the spray force and plume temperature of various MDIs. Spray force measurements were made for 28 marketed products consisting of bronchodilators, steroids, press-and-breathe, breath-actuated and nasal inhalers. Results show that chlorofluorocarbon (CFC)-containing MDIs produce extremely forceful and cold plumes. Several hydrofluoralkane (HFA)-containing MDIs produced much softer and warmer plumes, but two HFA products had spray forces similar to the CFC products. Although the type of propellant used can affect spray force, actuator orifice diameter is the most important factor. Data obtained from marketed products and experimental inhalers show that MDIs that have a low spray force also have low throat deposition. 

*Keywords:* Cold-Freon effect; Deposition; Metered dose inhaler; Plume force; Plume temperature; pMDI

## 1. Introduction

Metered dose inhalers (MDIs) have long been a reliable and inexpensive medication delivery form for the treatment of asthma. Two concerns raised when comparing MDIs to other inhalation devices are their relatively high throat deposition (Newman et al., 1981) and the cold-Freon effect seen in a small number of patients (Crompton, 1982; Pedersen et al., 1986). The cold-Freon effect is a result of a forceful blast of cold, liquid propellant impacting on the back of the patient's throat. In addition to being uncomfortable for the user, this can result in an inconsistent or non-existent dose delivered to the lung. Both adverse conditions, high throat deposition and the cold-Freon effect, share a common cause: a high-velocity, forceful blast of formulation exiting the

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device. The forceful plume can be especially uncomfortable when using nasal devices.

With the redesign of MDIs to contain hydrofluoroalkane (HFA) propellants instead of the ozone-depleting chlorofluorocarbons (CFCs), system improvements have resulted in MDIs with much lower throat deposition (Leach et al., 1996) and qualitatively different plume characteristics, such as reduced plume force (Purewal et al., 1998).

In this paper, a new method of quantifying the force and temperature of MDI plumes is described. These measurements provide an in vitro method for determining whether an MDI exhibits the plume characteristics associated with the cold-Freon effect and high throat deposition. Several marketed products were tested, including bronchodilators, steroids, press-and-breathe, breath-actuated and nasal MDIs. Spray force measurements are shown to be a good indicator of the amount of drug deposition occurring in the throat. The effects of some MDI design changes on plume dynamics are also discussed.

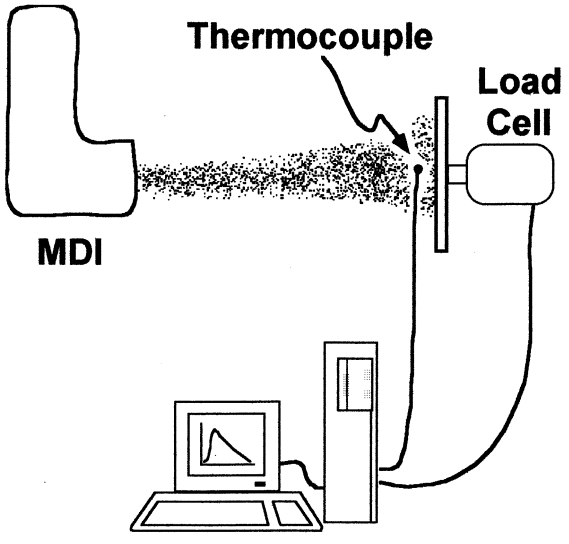


Fig. 1. Experimental set-up for plume force and temperature measurements of MDIs.

## 2. Materials and methods

### 2.1. Description of the data acquisition system

A test apparatus was developed (Fig. 1) to measure the impact force, duration and temperature of an MDI plume as would be sensed by a patient. The MDI was actuated such that the plume would strike the center of a 4.5-cm square plate (0.5 g) located 5 cm from the end of the MDI mouthpiece. A customized data acquisition system (Power Macintosh 8100/80 with NB-MIO-16L DAQ board; National Instruments, Austin, TX) captured the output from a precision miniature load cell (Model 34; Sensotec, Columbus, OH) attached to the plate. The sampling rate was 50 kHz.

In a separate test, a quick-response thermocouple (Model CO2-E; Omega, Stamford, CT) was placed at the center of the plate to measure the plume temperature as a function of time. The thermocouple is constructed of a thin foil (0.0127 mm) to achieve a time constant on the order of 5 ms. Because of the small transducer size, the measurements represent the temperature in the center of the plume only and not an overall plume average. The sampling rate for the temperature measurements was 10 kHz.

The acquisition software (LabVIEW; National Instruments, Austin, TX) recorded the transducer output and processed the data to obtain maximum impact force, spray duration and the minimum temperature of the plume.

### 2.2. Evaluation of marketed products

Comparative spray force and plume temperature measurements were made for several marketed products. Six press-and-breathe bronchodilators, 11 steroid press-and-breathe MDIs, five breath-actuated MDIs, and six nasal MDIs were evaluated (Table 1). Included in these were nine devices that use HFA propellants and two aqueous nasal pump devices.

A single measurement from a randomly selected product was taken with the sample being shaken for approximately 5 s before the test. Each MDI was manually actuated 5 cm from the sensor such

Table 1
Plume impact force, temperature and duration of marketed products[a]

| Product | Maximum impact force (mN) | Minimum plume temperature (°C) | Plume duration (ms) |
|---|---|---|---|
| *Press-and-breathe products* | | | |
| *Bronchodilators* | | | |
| Maxair™ | 93.6 (6.8) | −2.9 (5.5) | 184.1 (9.2) |
| Proventil®HFA[b] | 29.3 (2.3) | 7.8 (3.4) | 180.1 (9.6) |
| Proventil® | 82.1 (3.7) | −25.7 (9.4) | 192.1 (18.7) |
| Sultanol® | 94.9 (5.6) | −30.2 (5.0) | 153.6 (9.3) |
| Sultanol®N[b] | 104.4 (8.0) | −9.2 (10.2) | 154.6 (12.9) |
| Ventolin® | 95.4 (7.9) | −29.1 (7.4) | 95.4 (7.9) |
| *Steroids* | | | |
| Beclazone™ 50 CFC-Free[b] | 45.6 (3.1) | −1.9 (1.1) | 510.8 (52.8) |
| Beclazone™ 250 CFC-Free[b] | 45.8 (1.8) | −4.2 (1.1) | 351.4 (24.4) |
| Beclovent® | 101.3 (6.0) | −16.0 (12.9) | 203.6 (3.4) |
| Becotide™ 100 | 106.1 (8.1) | −32.2 (5.7) | 185.2 (8.6) |
| Flixotide™ | 102.4 (6.5) | −21.3 (11.1) | 191.6 (6.2) |
| Flutide®N[b] | 116.8 (8.8) | −16.7 (9.8) | 134.7 (4.5) |
| Pulmicort | 80.7 (3.4) | n/a | 161.9 (8.9) |
| QVAR™ 50 mcg[b] | 34.3 (2.6) | 3.7 (1.4) | 278.5 (11.4) |
| QVAR™ 100 mcg[b] | 31.9 (2.5) | 3.0 (1.4) | 282.3 (14.2) |
| Vanceril® | 103.1 (6.3) | −19.4 (8.5) | 172.6 (6.6) |
| Vanceril®DS | 79.7 (6.0) | −6.7 (7.1) | 198.8 (8.3) |
| *Breath-actuated products* | | | |
| AeroBec™ 100 Autohaler™ | 105.6 (8.7) | 6.0 (2.3) | 145.0 (25.1) |
| Beclazone™ 100 Easi-Breathe™ | 97.3 (7.9) | −9.4 (8.0) | 209.8 (13.1) |
| Maxair™ Autohaler™ | 85.3 (9.3) | 11.8 (1.8) | 102.0 (5.6) |
| QVAR™ 50 mcg Autohaler™[b] | 39.7 (2.0) | 2.8 (1.1) | 277.7 (9.8) |
| QVAR™ 100 mcg Autohaler™[b] | 39.1 (1.7) | 2.2 (0.9) | 292.5 (22.6) |
| *Nasal products* | | | |
| Beconase | 86.3 (4.3) | n/a | 200.2 (5.1) |
| Beconase AQ[c] | 55.0 (6.1) | n/a | 112.9 (14.9) |
| Nasacort | 171.0 (13.2) | n/a | 103.0 (7.8) |
| Rhinocort | 56.2 (2.5) | n/a | 141.6 (6.4) |
| Vancenase | 178.5 (9.0) | n/a | 52.1 (4.8) |
| Vancenase AQ[c] | 60.0 (8.3) | n/a | 110.6 (16.7) |

[a] Data are given as mean (S.D.); $n = 15$ for force data; $n = 10$ for temperature data. n/a, not applicable.
[b] Products use HFA propellants.
[c] Products are aqueous nasal pumps.

that the plume would strike the center of the plate. Breath-actuated devices were triggered manually. A single inhaler of each product was tested.

After the force measurements were taken, the thermocouple was placed in front of the sensor and the tests repeated to obtain the temperature data.

### 2.3. Spray force measurements and throat deposition of experimental actuators

Spray force and cascade impactor (CI) measurements were made to determine the delivery characteristics of HFA-134a beclomethasone dipropionate MDIs with actuators having various orifice diameters. Actuators with five different

orifice diameters were tested. CI tests were conducted using a USP induction port ('USP throat') and a replica of a human throat ('biological throat'; Velasquez and Gabrio, 1998). Tests using the biological throat were included because it was believed that these tests would provide a more accurate representation of throat deposition during patient use than would be obtained using the USP throat.

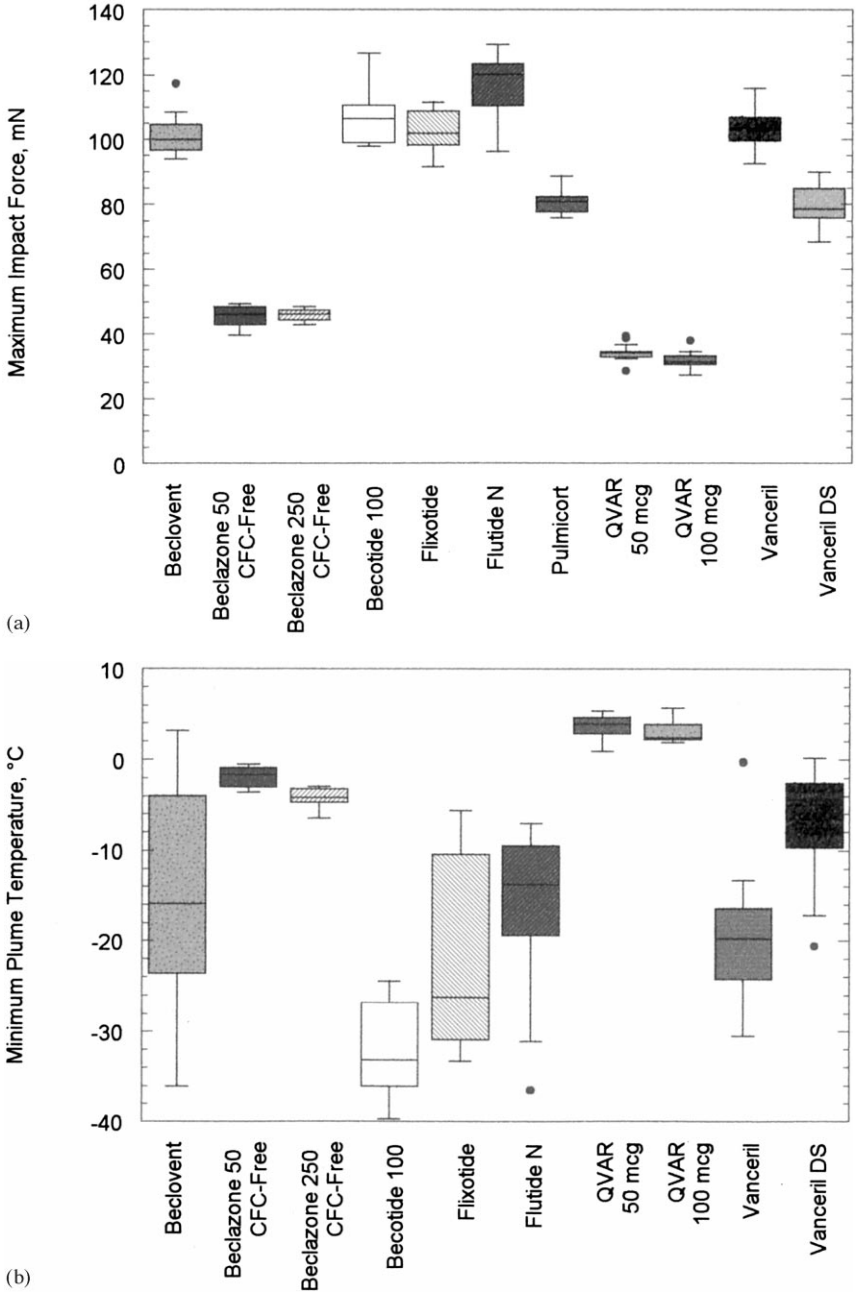


Fig. 2. (a) Plume impact force produced by steroid-containing press-and-breathe MDIs. (b) Minimum plume temperature produced by steroid-containing press-and-breathe MDIs. (c) Plume duration of steroid-containing press-and-breathe MDIs.

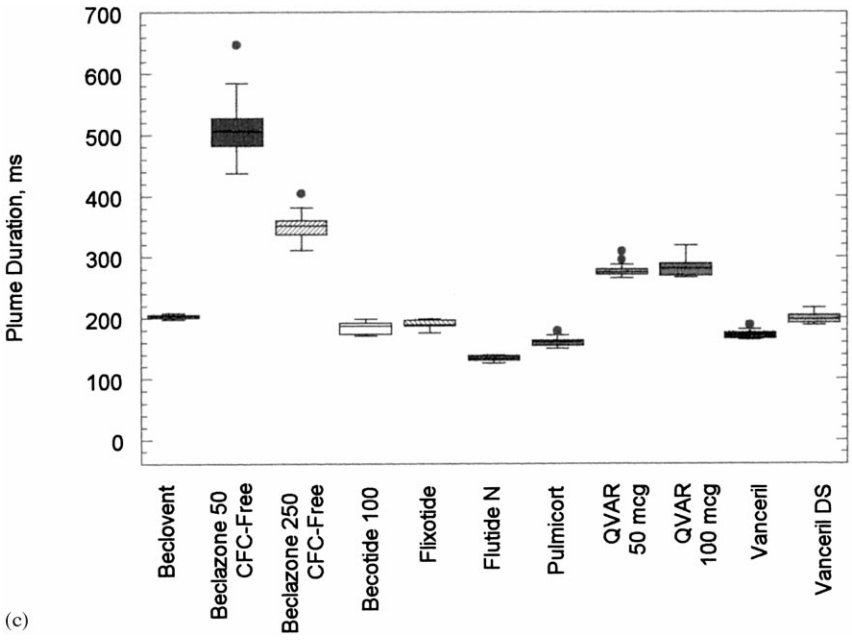


Fig. 2. (*Continued*)

The MDIs tested were formulated to deliver approximately 100 μg (mcg) of beclomethasone dipropionate (BDP) per dose and used 50-μl (mcl) Spraymiser™ valves. Actuators with orifice diameters ranging from 0.29 to 0.56 mm were examined. All actuator dimensions other than orifice diameter were identical.

Five actuators at each orifice diameter were selected for CI testing. Each actuator was tested once with the USP throat and once with the biological throat. The throat was coupled to an Andersen Mark-II cascade impactor operating at a flow rate of 28.3 l/min. The MDI was then actuated into the system five times. The amount of beclomethasone dipropionate depositing on each component of the system was analyzed using reversed-phase high-performance liquid chromatography (HPLC). Ten spray force measurements of each MDI were made using the previously described procedure.

### *2.4. Spray force measurements and throat deposition of marketed products*

CI measurements were made to determine the delivery characteristics of various MDI products currently on the market. At least ten spray force measurements were made for each MDI examined using the previously described procedure. CI tests were conducted using a USP induction port coupled to an Andersen Mark-II cascade impactor operating at a flow rate of 28.3 l/min. The MDI was then actuated into the system five times and was shaken for approximately 5 s before each actuation. At least three tests were conducted for each product examined.

### *2.5. Effect of MDI components on spray force measurements*

The effects of propellant and valve size on spray force were investigated. MDIs filled with only propellant (CFC-12, HFA-134a, or HFA-227) were fitted with metered valves of 25, 50 and 63 μl, and tested using prototype actuators with orifice diameters of 0.32 and 0.48 mm following the procedure described above. All actuator dimensions, other than the orifice diameter, were similar in design to the QVAR™ and Proventil®HFA actuators.

## 3. Results and discussion

### 3.1. Evaluation of marketed products

The results show that all of the CFC products tested have forceful plumes, with forces ranging from 80 to 117 mN (Table 1). The nasal devices span an even larger range, 55–179 mN. The impact force, temperature and spray duration measurements of the steroid press-and-breathe MDIs are shown in Fig. 2. The results are shown in the form of box plots. Box plots are useful for showing the entire distribution of the data. A line is drawn across each box at the median. The bottom of the box represents the first quartile of the distribution, and the top represents the third

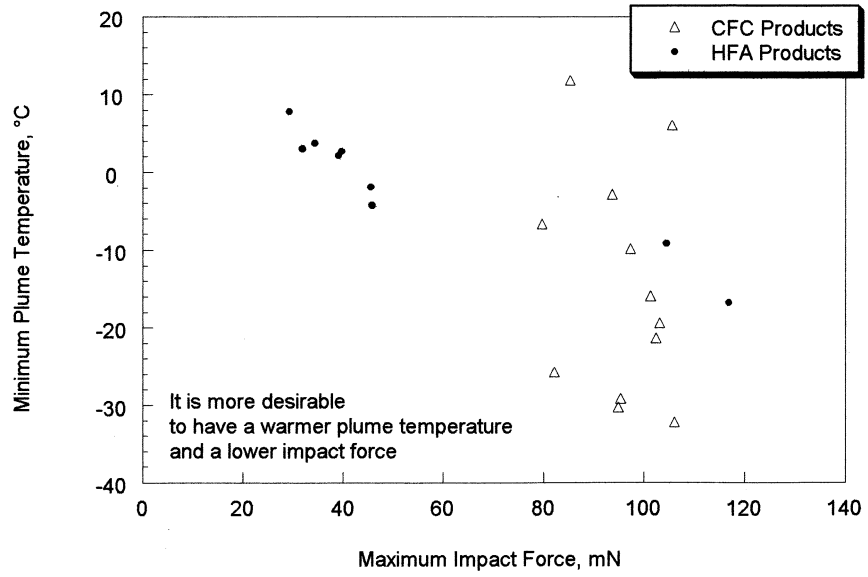


Fig. 3. Plume force and temperature of marketed MDI products.

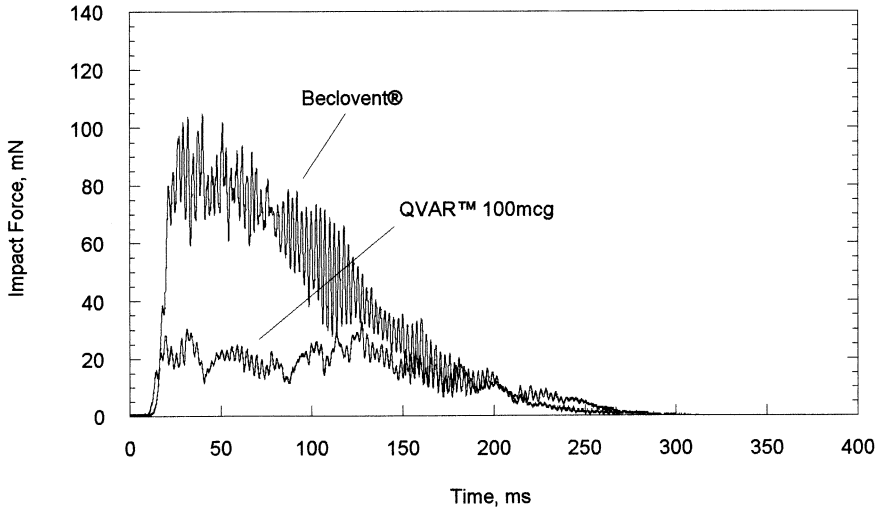


Fig. 4. Plume impact force profile produced by Beclovent® and QVAR™ MDIs.

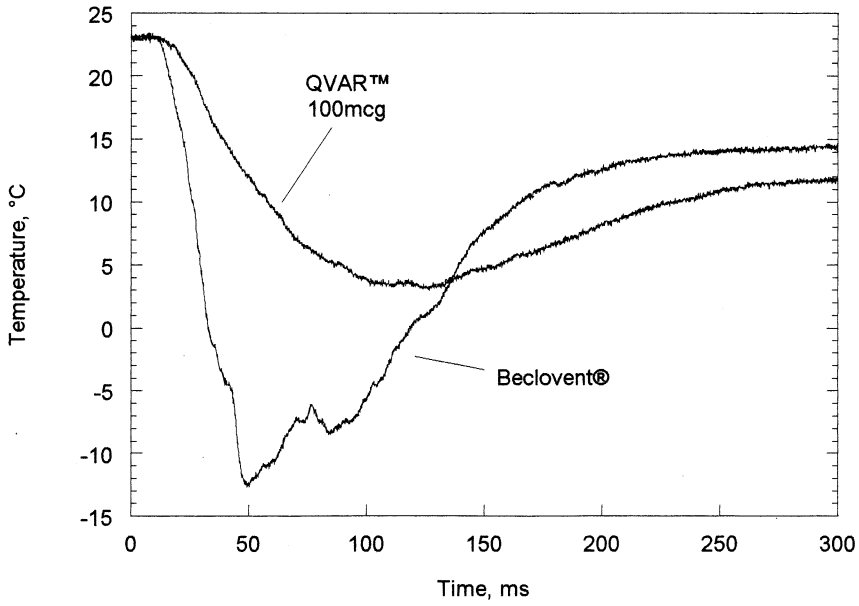


Fig. 5. Plume temperature profile produced by Beclovent® and QVAR™ MDIs.

quartile. The lines extending from the top and the bottom of the box show the range of the data that fall within an acceptable range. Outliers, represented by the open circles, are sufficiently greater or less than the appropriate quartile limits. For example, if a value is greater than the upper quartile limit by more than 1.5 times the difference between the upper and lower quartile limits, that value is considered an outlier.

While some HFA systems produced softer plumes, the use of HFA propellant does not guarantee better results. For example, Proventil®HFA, Beclazone™ CFC-free and QVAR™ produced significantly softer plumes, yet Sultanol®N and Flutide®N did not. In these studies Proventil®HFA was the softest bronchodilator, QVAR™ was the softest press-and-breathe steroid MDI and QVAR™ Autohaler™ was the softest breath-actuated product. For nasal devices, Rhinocort® was the softest pressurized product and had a plume force similar to the aqueous products.

Products tested in multiple dosing strengths did not necessarily produce identical plumes. Vanceril® and Vanceril®DS produced significantly different plume forces and temperatures. Beclazone™ 50 CFC-Free produced a plume that was approximately 45% longer in duration than the 250 mcg product. However, QVAR™ 50 mcg and QVAR™ 50 mcg Autohaler™ had plume characteristics that were similar to their respective 100 mcg dose products.

The plume force and temperature of the 28 products are shown in Fig. 3. To minimize the likelihood of patients experiencing the cold-Freon effect, a softer and warmer plume is desirable. The seven products that are most desirable in this respect use HFA propellant.

The data acquisition system was able to measure the plume characteristics with sufficient resolution to allow product-to-product comparison. Using Beclovent® and QVAR™ for comparison, two examples of an impact force profile and temperature profile are shown as a function of time (Figs. 4 and 5).

### *3.2. Spray force measurements and throat deposition of experimental actuators*

Spray force and Andersen cascade impactor measurements were made for the 100 mcg/dose HFA-134a beclomethasone dipropionate MDIs

with various orifice diameters. The spray force measurements and the amount of drug depositing in the throat during Andersen tests are summarized in Fig. 6. The 'throat deposition %' is defined as the amount of drug collecting in the throat as a percent of the total drug exiting the valve each actuation. Throat deposition results are presented for tests using the USP and biological throats. Spray force measurements of these MDIs were shown to be highly sensitive to the orifice diameter of the actuators, and cascade impactor throat deposition was sensitive to orifice diameters up to approximately 0.4 mm.

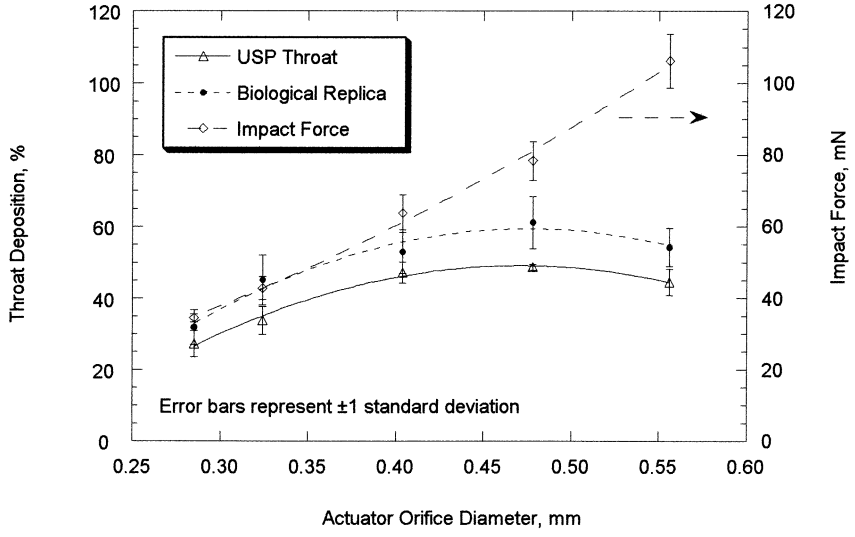


Fig. 6. Plume force and throat deposition as a function of actuator orifice diameter.

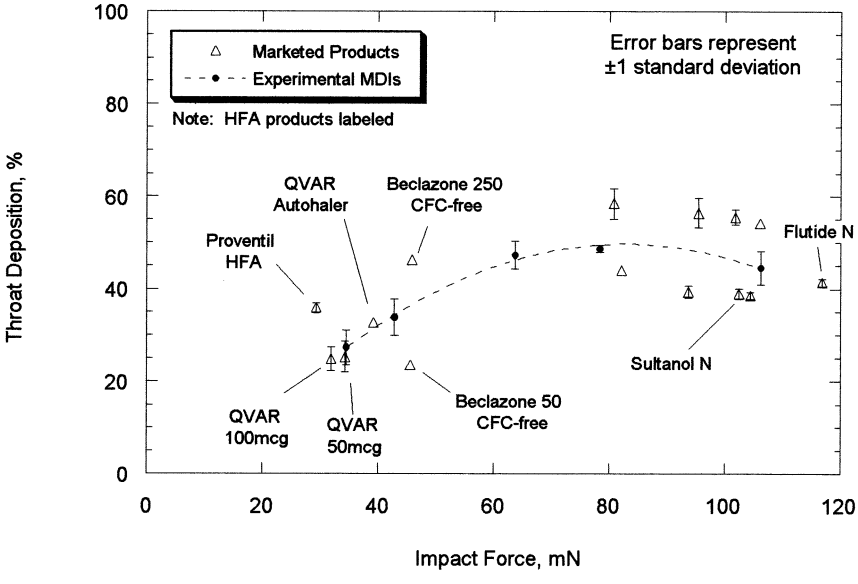


Fig. 7. Throat deposition and plume force for marketed and experimental MDIs.

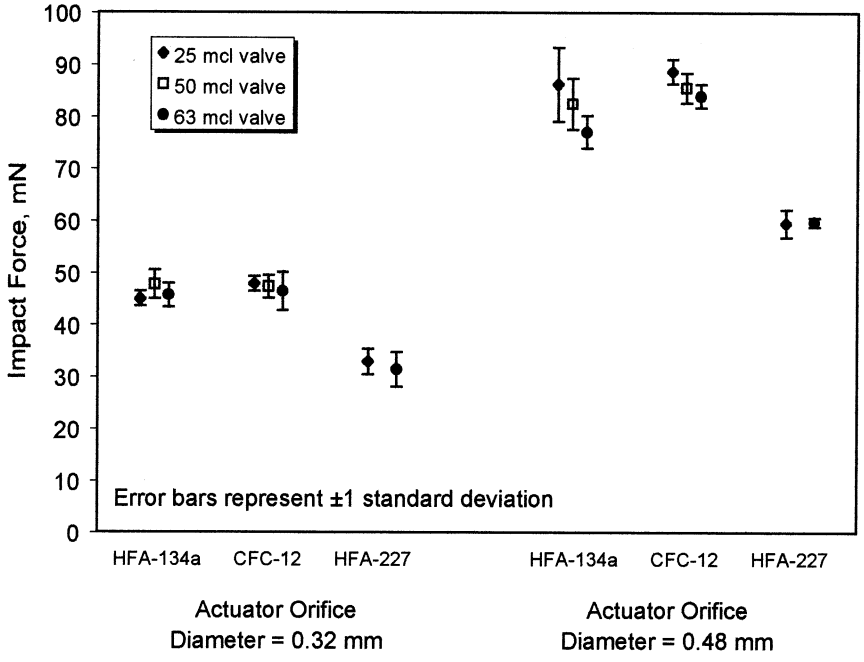


Fig. 8. Effect of propellant type and valve size on plume impact force.

The results indicate that spray force increased significantly with increasing actuator orifice diameter, increasing from 35 to 115 mN as the orifice diameter increased from 0.29 to 0.56 mm. The amount of drug depositing in the throat increased significantly as the orifice diameter increased from 0.29 to 0.40 mm. However, the throat deposition appeared to decrease slightly above 0.48 mm. This difference was small, but was statistically significant ($P = 0.019$). This trend was evident for data collected with both the biological and USP throats; this phenomenon is not yet understood. On average, the biological throat collected approximately 9 mcg/dose more than the USP throat. This difference was statistically significant ($P < 0.001$).

### *3.3. Spray force measurements and throat deposition of marketed products*

Spray force and Andersen cascade impactor measurements were made for various experimental and marketed MDIs. Spray force measurements and the amount of drug depositing in the throat during Andersen tests are summarized in Fig. 7.

There is a correlation between the spray force measurements and the throat deposition from CI tests for the MDIs. Undesirable throat deposition is lowest for MDIs with the lowest spray force. Throat deposition appears to reach a plateau at a spray force of around 60 mN and may actually decrease for MDIs with higher spray forces. In general, MDIs that use HFA propellants have significantly lower spray force and throat deposition than MDIs that use CFC propellants. Notable exceptions to this trend are Flutide®N and Sultanol®N, which had measured spray forces of 116.8 and 104.4 mN, respectively. However, these products had measured orifice diameters of 0.54 and 0.52 mm, respectively, which is more than 55% larger than for any of the other HFA products tested.

### *3.4. Effect of MDI components on spray force measurements*

The effects of propellant and valve size on spray force were investigated by filling vials with

only propellant (CFC-12, HFA-134a, or HFA-227) and measuring the spray force when used with actuators having orifice diameters of 0.32 and 0.48 mm. In the configurations tested, the spray force was relatively insensitive to valve size for all three propellants (Fig. 8). However, the spray force was highly sensitive to the orifice diameter. The spray force dependence on orifice diameter agreed with the results shown in Fig. 6.

There was no significant difference in measured spray force between MDIs using HFA-134a and CFC-12; however, HFA-227 consistently produced a softer plume. The differences seen among the spray forces of HFA-227, CFC-12 and HFA-134a are consistent with the differences in vapor pressure. The vapor pressure of HFA-227 at 25°C is 456 kPa, which is significantly lower than HFA-134a and CFC-12 which have vapor pressures at 25°C of 666 and 652 kPa, respectively.

## 4. Conclusions

A new method of quantifying the force and temperature of MDI plumes has been described. This method provides an in vitro technique for determining whether an MDI exhibits the plume characteristics associated with the cold-Freon effect and high throat deposition.

Spray force and plume temperature measurements were made on marketed bronchodilators, steroids, press-and-breathe, breath-actuated and nasal MDIs. CFC and HFA products were tested. Spray force measurements ranged from 29 to 179 mN among the products tested. Similarly, a wide range in minimum plume temperatures was observed (12–32°C).

All of the CFC products tested had forceful plumes, ranging from 80 to 117 mN. While most HFA systems produced softer plumes, the use of HFA propellants does not guarantee better results. For example, Proventil®HFA, Beclazone™ CFC-Free, QVAR™ and QVAR™ Autohaler™ produced significantly softer plumes than all of the CFC products. However, Sultanol®N and Flutide®N, which also use HFA propellants, had very high spray forces due to their use of large orifices. This illustrates that the force of the plume is dependent on the entire MDI system. Spray force was determined to be particularly sensitive to orifice diameter. Propellant type was shown to affect the spray force and appears to be related to the vapor pressure of the propellant. Valve size was found to have minimal impact on the spray force.

Spray force and throat deposition measurements were correlated for experimental and marketed MDIs. Undesirable throat deposition is lowest for MDIs with the lowest spray force. Throat deposition appears to reach a plateau at a spray force of around 60 mN and may actually decrease for MDIs with higher spray forces. In general, MDIs that use HFA propellants have significantly lower impact force and throat deposition than MDIs that use CFC propellants. Of the 15 products for which CI tests were conducted, the five products with the lowest throat deposition all used HFA propellants.

The measurements presented in this paper demonstrate that there are significant differences in the spray force and plume temperatures of MDIs. These measurements also demonstrate that it is possible to design MDI systems that minimize the spray force and maximize the plume temperature. Products that have these plume characteristics should minimize undesirable throat deposition and reduce the likelihood that patients will experience the cold-Freon effect.

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