Metered-Dose Inhalers, Dry Powder Inhalers, and Transitions

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Key words: pressurized metered-dose inhaler, spacer, valved holding chamber, dry powder inhaler, chlorofluorocarbon, hydrofluoroalkane, aerosol.

Introduction

Pressurized metered-dose inhalers (pMDIs) are the most common devices, around the world, for therapeutic aerosol delivery, with more than 440 million pMDIs produced in 1998 and production of pMDIs estimated to reach 800 million by the year 2000.[1] Next to the tablet (pill), the pMDI is the most common form of medication. As recently as 45 years ago, the only available option for a portable hand-held system of aerosol therapy was the hand bulb nebulizer. The hand bulb nebulizer was relatively fragile and did not provide consistent aerosol output or multidose convenience.

In 1955, the 13-year-old asthmatic daughter of Dr George Maison, President of Riker Laboratories (a wholly-owned subsidiary of Rexall Drug Company, now 3M Pharmaceuticals) asked her father "why can't they put my asthma medicine in a spray-can like they do hair spray?" Dr Maison asked Mr Irving Porush, the head chemist in Riker's three-person pharmaceutical development lab, to develop a pressurized inhaler for delivery of a bronchodilator. Armed with some propellant from Du Pont (FREON 12 and 114), an old ice cream freezer from the Rexall drug store downstairs, a case of empty soda bottles, and a bottle capper, the first pMDI was born. Within a matter of months, the first pMDIs with salts of isoproterenol and epinephrine were developed, using a 50 μL metering valve developed for perfume aerosols, a 10 mL amber vial, and a 3-inch-long plastic mouthpiece with a molded nozzle.[2] In June of 1955, the first clinical trials at the Long Beach Veterans Administration Hospital showed these first pMDIs to be effective, and new drug approvals filed in January of 1956 (documents 13 mm thick) were approved by March of the same year.[2] In 1957, a suspension of micronized drug in propellant with a surfactant was substituted for the original bronchodilators. It is interesting that, although the suspensions proved to be more effective in all pulmonary measurements, many of the previous pMDI users complained that they were not getting as much medication. Apparently, patients missed the taste of the

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alcohol present in early solution formulations, which they associated with active medication. This era represented much of the technologic innovation we are familiar with in the current chlorofluorocarbon (CFC)-propelled pMDIs. Soon thereafter, the Kefauver amendments to the food and drug laws required more complex new drug approval submissions and clinical trials.[2] This radically curtailed innovative development of pMDI technology for the next 40 years.

In 1974, the Rowland and Molena theory that CFCs were contributing to ozone depletion led to a ban of CFCs in common aerosol products.[3] By the end of the decade the ozone depletion theory was falling into disrepute, and interest in alternative propellants such as perfluoropropane was limited by the expense of toxicity testing and clinical testing. By the mid-1980s, the paperwork for a new drug approval submission for a pMDI of a new bronchodilator had grown from less than 2 cm thick to 17 volumes, and 3.5 years from submission to approval.[1]

In 1987, the Montreal protocol was signed, and refrigerant manufacturers, the primary producers of CFCs, said they would cease production of CFCs by 1996. An exemption was granted for pMDIs to use CFCs until such time as suitable alternatives could be found. This escalated the development of the dry powder inhaler (DPI), as the quest for suitable alternative propellants began in earnest.

The first alternative propellant compound to enter full-term industrial toxicity tests was hydrofluoroalkane (HFA)-134a (tetrafluroethane), which appeared to be a promising replacement for CFC-12.[4] A pharmaceutical consortium was formed to facilitate the testing required by regulatory agencies for HFA-134a and HFA-227 (heptafluoropropane). These propellants have physicochemical properties similar to the three CFCs used in pMDIs (Table 1).[4]

The goals herein are to characterize some of the key issues associated with the use of pMDIs and DPIs and to discuss their evolution in response to the transition to more environmentally benign propellants.
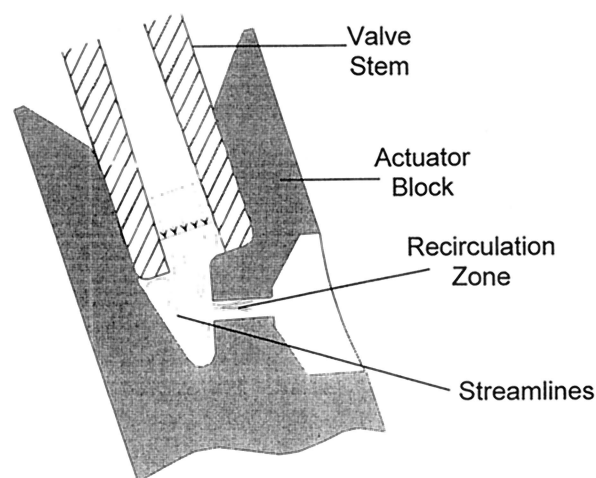

Fig. 1. Path of fluid flow in actuator nozzle of a pressurized metered-dose inhaler (pMDI). Changes in valve stem size and design of the actuator nozzle recirculation zone and actuator orifice can affect plume geometry and aerosol characteristics. The orifice diameter of the chlorofluorocarbon-propelled pMDI Ventolin (0.021 inch) is nearly twice that of the hydrofluoroalkane-propelled pMDI Proventil HFA (0.011 inch), which correlates with differences in mass median aerodynamic diameter and respirable mass. (From Reference 8, with permission.)

Pressurized Metered-Dose Inhalers

The pMDI is the most commonly prescribed method of aerosol delivery.[5] pMDIs are used to administer bronchodilators, anticholinergics, anti-inflammatory agents, and steroids. More formulations of these drugs are currently available for use via pMDI than via other nebulization systems. Properly used, pMDIs are at least as effective as other systems of aerosol generation for drug delivery.[6]

A pMDI is a pressurized canister containing a mixture of propellants, surfactants, preservatives, and flavoring agents, with approximately 1% of the total contents being active drug. This mixture is released from the canister through a metering valve and stem that fits into an actuator

Table 1. Physicochemical and Atmospheric Properties of Propellants Used in Pressured Metered-Dose Inhalers

Propellant	Formula	Common Name	Density (g/mL) at 20° C	Vapor Pressure at 20° C	Boiling Point	Atmospheric Life Years	Global Warming Potential	Ozone-Depleting Potential
HFA-134a	$C_2H_2F_4$	Tetrafluoroethane	1.21	70	−27° C	16	0.26	0
HFA-227	C_3HF_7	Heptafluoropropane	1.41	40	−17° C	33	0.3	0
CFC-11	CCl_3F	Trichlorofluoromethane	1.49	−1.8	24° C	60	1	1.0
CFC-12	CCl_2F_2	Dichlorodifluoromethane	1.33	67.6	−30° C	125	3	0.9
CFC-114	$C_2Cl_2F_4$	Dichlorotetrafluoroethane	1.47	11.9	4° C	200	3.9	0.7

*Ozone-depleting potential is set relative to CFC-11, which is assigned a value of 1.0.
CFC = chlorofluorocarbon. HFA = hydrofluoroalkane.
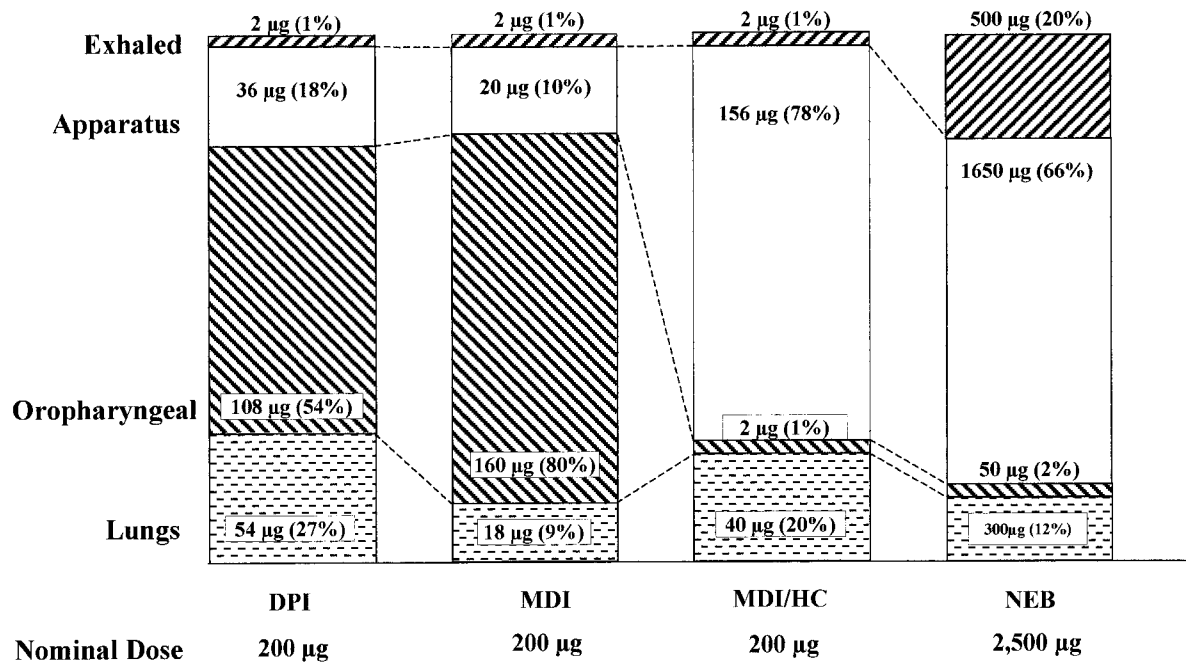(Adapted from Reference 4, with permission).

Fig. 2. Comparison of the quantity and percent of nominal dose of albuterol deposited in the lungs, oropharynx, apparatus, and exhaled, with typical use of a dry powdered inhaler (DPI), a pressurized metered-dose inhaler (pMDI), a pMDI with holding chamber (MDI/HC), and a nebulizer (NEB). Both DPI and pMDI deposit > 50% of nominal dose in the oropharynx, while pMDI/HC and NEB leave 78–80% of the dose in the apparatus. The percent of nominal dose exhaled is 20-fold greater with the nebulizer than with other devices. (Adapted from data in Reference 18 and from Fink JB, Tobin MJ, Dhand R. Bronchodilator therapy in mechanically ventilated patients. Respir Care 1999;44[1]: 53–69.)

boot designed and tested by the manufacturer to work with that specific formulation.[7] Small changes in actuator design can change a pMDI's aerosol characteristics and output (Fig. 1).[8] Dispersing agents are present in concentrations equal to or greater than that of the medication, and in some patients these dispersing agents cause coughing and wheezing.[9] The bulk of the spray (up to 80% by weight) is propellant, commonly a CFC such as FREON.[10,11] Adverse reactions to CFCs are extremely rare.[12,13]

The output volume of a pMDI ranges from 30–100 μL and contains between 20 μg and 5 mg of drug. Lung deposition is estimated at 10–25% in adults, with high intersubject variability, largely dependent on user technique. When proper technique and an accessory device is used, the pMDI delivers substantially more of the nominal dose of medication to the lung than a standard small-volume nebulizer (SVN).

Aerosol production from a pMDI takes approximately 20 milliseconds.[14] Aerosolization of the liquid released from the canister begins as the propellants vaporize or "flash," leaving the actuator in a "plume," and continues as the propellant evaporates.[15] The velocity of the liquid spray leaving the pMDI is about 15 m/s, which falls to less than half the maximum velocity within 0.1 second as the plume develops and moves away from the actuator orifice.[16] The particles produced from the "flashing" of pro-

pellants are initially 35 μm, and rapidly decrease in size because of evaporation as the plume moves away from the nozzle.[17] These aged smaller particles have been associated with a distance of $\geq$ 12 cm from the nozzle.[17] Because of the velocity and dispersion of the jet fired from the pMDI, approximately 80% of the dose leaving the actuator impacts and deposits in the oropharynx, especially when the canister is fired inside the mouth.[11,17] The mass median aerodynamic diameter (MMAD) of aged aerosol particles from a pMDI is 2–6 μm, with lung deposition of about 10–20%.[18] The 80% of dose deposited in the mouth may be a factor in systemic absorption, as opposed to direct aerosol delivery to the lung (Fig. 2), since the pMDI delivers a substantial amount of drug to the mucous membranes of the mouth and stomach. Unfortunately, the actual amount of drug delivered to an individual patient is unpredictable because of substantial interpatient variability.[18]

The nominal dose of medication with the pMDI is much smaller than with the nebulizer (see Fig. 2). The quantity of albuterol from a pMDI exiting the actuator nozzle is 100 μg with each actuation or 90 μg from the opening of the actuator boot (which is how pMDI aerosol output is characterized in the United States). Thus, a dose of 2 to 4 actuations (200–400 μg nominal dose) with 10% deposition of the nominal dose to the lower respiratory tract

Table 2.   Optimal Technique for Using a pMDI

Warm the pMDI canister to hand or body temperature, shake
    vigorously.
Assemble apparatus, uncap mouthpiece and make sure there are no
    loose objects in the device.
Open mouth wide, keep tongue from obstructing the mouthpiece.
Hold the pMDI vertically, with the outlet aimed at mouth.
Place canister outlet between lips, or position the pMDI about 4 cm
    (two fingers) away from mouth.
Breathe out normally.
As you begin to breathe in slowly (<0.5 L/s), actuate (fire) the pMDI.
Continue to inhale to total lung capacity.
Hold breath for 4–10 seconds.
Wait 30 seconds between inhalations (actuations).
Disassemble apparatus, recap mouthpiece.

pMDI = pressurized metered-dose inhaler.
(Adapted from data in Reference 5.)

delivers 20–40 μg to the lung, resulting in the typical
bronchodilator response.

Technique and Patient Education

Effective use of a pMDI is technique-dependent. Up to
two thirds of pMDI users and health professionals who
teach pMDI use do not perform the procedure proper-
ly.[19,20] Table 2 outlines recommended steps for self-ad-
ministering a bronchodilator using a pMDI.[21] Good patient
instruction can take 10–30 minutes and should include
demonstration, practice, and confirmation of patient per-
formance (demonstration placebo units are available from
many manufacturers for this purpose). Repeated instruc-
tion improves performance.[22]

Infants, young children, the elderly, and patients in acute
distress may not be able to use a pMDI effectively, even
after proper instruction. This is largely associated with the
need to coordinate actuation with inspiration or the inabil-
ity to use the mouthpiece of the actuator. Other technolo-
gy-dependent issues can also limit a patient's ability to use
a pMDI. The "cold FREON" effect occurs if the cold aerosol
plume (which may be 30° C below room temperature)
causes the patient to stop inhaling when the plume reaches
the back of the mouth.

Problems with home use of pMDI devices include poor
technique of use and poor storage.[5] The pMDI should
always be stored with the cap on, both to prevent foreign
objects from entering the boot and to reduce humidity and
microbial contamination. Pressurized pMDIs should al-
ways be discarded when empty, to avoid administering
propellant without medication. Although it has been sug-
gested that pMDIs can be tested for drug remaining by
floating the canister in water, this technique can be diffi-

cult to perform and interpret, and runs the risk of contam-
inating the device. Infiltration of water into the canister
can compromise pMDI performance. Consequently, many
manufacturers actively discourage the use of the "float
test." It is more accurate and reliable for the patient, par-
ent, or care provider to note when the medication was
started, the number of doses taken each day, and the num-
ber of doses in the canister, and to calculate a discard date.
For example, if there are 200 actuations in a canister (and
this information is always indicated on the canister label)
and 4 puffs are taken per day, the canister should be dis-
carded 50 days (7 weeks) after the start date. This discard
date should be written on the canister label on the day the
new canister is started. For rescue medication, patients
should be encouraged to track the number of actuations
used.

Pressurized Metered-Dose Inhaler Accessory Devices

A variety of pMDI accessory devices have been developed
to overcome the limitations of pMDI administration (hand-
breath coordination problems, cold FREON effect, and high
oropharyngeal deposition). Accessory devices include flow-
triggered pMDIs, spacers, and valved holding chambers.

Flow-Triggered Pressurized Metered-Dose Inhaler

The Autohaler is a flow-triggered pMDI designed to
reduce the need for hand-breath coordination by firing in
response to the patient's inspiratory effort.[23] To use the
Autohaler, the patient cocks a lever on the top of the unit
that spring-loads the canister against a vane mechanism.
When the patient's inspiratory flow exceeds 30 L/min, the
vane moves, allowing the canister to be pressed into the
actuator, firing the pMDI. In the United States this device
is only available with the β agonist pirbuterol, but other
formulations are in development. The flow required to

Table 3.   Optimal Technique for Using a pMDI with a Valved
            Holding Chamber

Warm pMDI to hand or body temperature.
Assemble apparatus and make sure there are no objects in device that
    could be aspirated or obstruct outflow.
Shake canister vigorously and hold canister vertically.
Place holding chamber in mouth (or place mask completely over nose
    and mouth), encouraging patient to breathe through mouth.
Breathe normally and actuate at the beginning of inspiration. Small
    children and infants should continue to breathe through the device
    for 5 or 6 breaths. Larger breaths with breath-holding may be
    encouraged in those patients who can cooperate.
Allow 30 seconds between actuations.

pMDI = pressurized metered-dose inhaler.
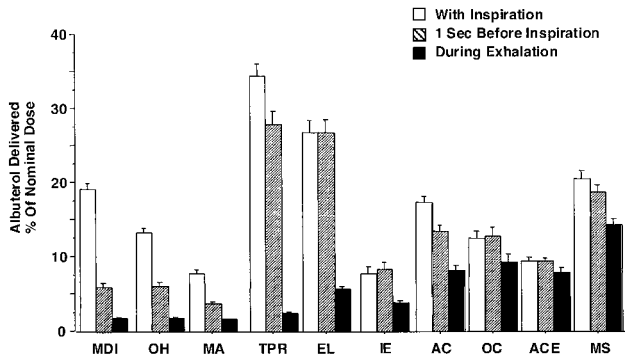(Adapted from data in Reference 5.)

Fig. 3. The percent of albuterol delivered from a pressurized metered-dose inhaler (pMDI) actuation synchronized with inspiration, compared to actuation of an albuterol pMDI (open bars) one second before inspiration (diagonally hatched bars) and during exhalation (solid bars) for the pMDI alone, and with 9 types of accessory devices. The pMDI alone and pMDI with low-volume spacers (OH, MA) suffered similar loss of dose in both conditions. Larger spacers (TPR, EL) protected against loss of dose in the case of actuation one second before inspiration, but provided no dose protection in the case of actuation during exhalation. Bag (IE) and valved holding chambers (AC, OC, ACE, MS) both provided protection from loss of dose in both conditions. OH=OptiHaler. MA=Mist Assist. TPR=toilet paper roll. EL=Ellipse. IE=InspirEase. AC=AeroChamber. OC=OptiChamber. ACE=Aerosol Cloud Enhancer. MS=MediSpacer. (Adapted from data in Reference 24.)
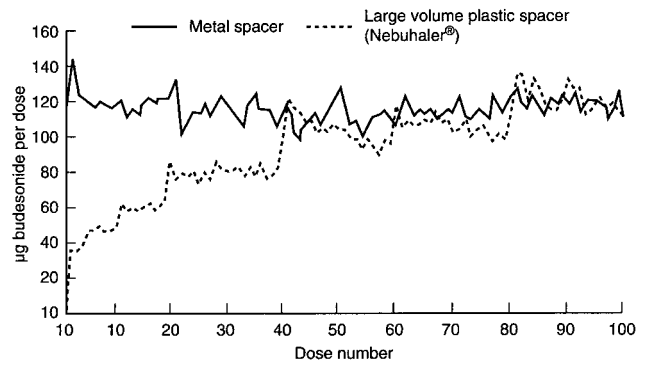

Fig. 4. The amount of budesonide delivered with each dose (actuation) of a pressurized metered-dose inhaler with a large-volume non-electrostatically-charged metal spacer (solid line) is relatively stable compared to the low initial dose available using an electrostatically charged plastic spacer (dashed line). The delivered dose with the plastic spacer increased dramatically over the first 40 doses, and then matched delivery with the metal spacer. (From Reference 32, with permission.)

actuate the device may be too great for some small children to generate, especially during acute exacerbations.

Spacers and Valved Holding Chambers

Spacers and valved holding chambers are accessory devices that, when properly designed, reduce oropharyngeal deposition of drug, ameliorate the bad taste of some medications, eliminate the cold FREON effect, and, in the case of valved holding chambers, reduce drug loss associated with poor hand-breath coordination. Table 3 outlines recommended steps for self-administering a bronchodilator using a pMDI with a valved holding chamber.

Clinicians should be careful to distinguish spacers from valved holding chambers. A spacer device is a simple open-ended tube or bag that, with sufficiently large volume, provides space for the pMDI plume to expand by allowing the CFC propellant to evaporate. To perform this function, a spacer device must have an internal volume of over 100 mL, and provide a distance of 10–13 cm between the pMDI nozzle and the first wall or baffle in the plume's path. Smaller low-volume spacers can reduce respiratory dose by 60% and offer no protection against poor coordination between actuation and breathing pattern. Spacers with internal volumes greater than 100 mL generally provide some protection against loss of dose from early firing of the pMDI, although exhaling immediately following the

actuation clears most of the aerosol from the device, wasting the dose.

The valved holding chamber (usually 140–750 mL) allows the plume to expand, and incorporates a one-way valve that permits the aerosol to be drawn from the chamber during inhalation only, diverting exhaled gas to the atmosphere and not disturbing remaining aerosol suspended in the chamber. Thus, the valved holding chamber combines the benefits of a spacer with the advantage of protecting the patient from loss of dose due to poor hand-breath coordination.

Fink et al[24] performed in vitro testing of drug delivered from a pMDI alone and from a pMDI in combination with a variety of spacers and holding chambers, when actuation of the pMDI was (1) synchronized with the beginning of inspiration, (2) one second before inspiration, or (3) during exhalation. Figure 3 shows the mean proportion of drug available to the lower respiratory tract with pMDI and a variety of small-volume spacers, large-volume spacers, bag holding chambers, and valved holding chambers. The pMDI alone and small-volume spacers offered little protection against drug loss with actuation 1 second before inhalation or with actuation during exhalation. The large-volume spacers offered good dose protection with actuation 1 second before inhalation, but not with actuation during exhalation.[24] The valved holding chambers provided good protection with actuation 1 second before inhalation, and 70% of baseline dose when the pMDI was actuated during exhalation.

A patient with a small tidal volume may use multiple breaths to empty the aerosol from the chamber,[3–6] except when there is an exceptionally large dead space. A valved holding chamber can also incorporate a mask to allow effective pMDI administration in a patient who is unable
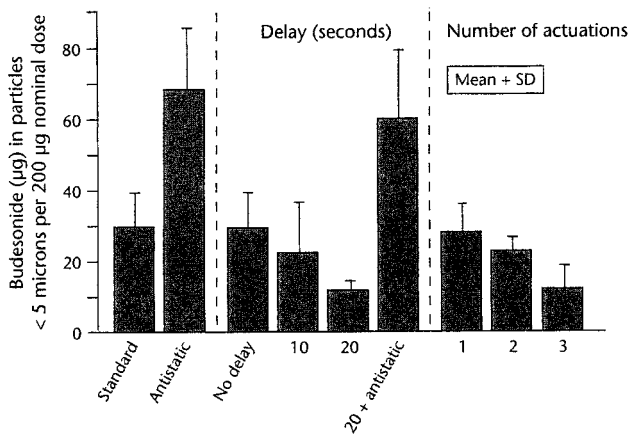
Fig. 5. Respirable dose of budesonide available with a standard spacer and with an antistatic spacer, with no delay in actuation (left), delays of 10 seconds and 20 seconds (center), and with multiple actuations from the pMDI into the standard plastic spacer (right). (From Reference 35, with permission.)
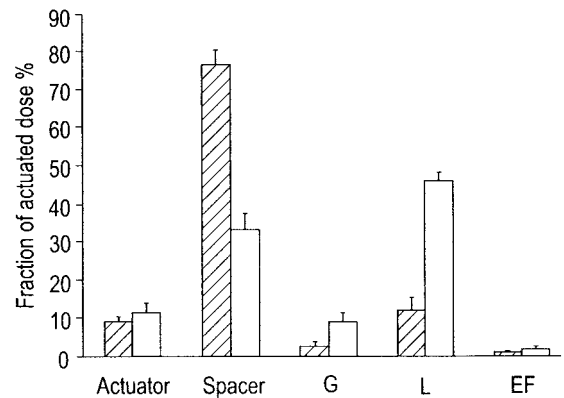

Fig. 6. Relative deposition of salbutamol, expressed as a percentage of total actuated dose, in the actuator, spacer, gastrointestinal tract (mouth, throat, esophagus, and stomach [G]), lung (L), and expiratory filter (EF) after inhalation through electrostatically charged (diagonally hatched bars) and non-electrostatically-charged, detergent-coated Volumatic spacer (clear bars) in 8 healthy adults. Values are means and standard deviations. (From Reference 36, with permission.)

to use a mouthpiece because of size, age, coordination, or mental status.[5] For use with infants, it is critical that these masks have minimal dead space, be comfortable to the child's face, and that the chamber have a valve that opens or closes with the low inspiratory flow generated by an infant.

The use of a valved holding chamber should be encouraged, especially for infants and small children, and for any child with steroid administration. A valved holding chamber reduces the need to coordinate the breath with actuation, reduces oral deposition (and, therefore, bad taste), decreases cold FREON effect, and decreases MMAD, which increases respirable particle mass, improves lower respiratory tract deposition, and significantly improves therapeutic effect.[5] These devices reduce the pharyngeal deposition of aerosol 10–15-fold, compared to administration without a holding chamber. This decreases the swallowed amount, which is an important consideration with steroid administration.[25,26]

The high percentage of oropharyngeal drug deposition with steroid pMDIs can increase the risk of oral yeast infections (thrush). Rinsing the mouth after steroid use can reduce this problem, but most pMDI steroid aerosol impaction occurs deeper in the pharynx, which is not easily rinsed. For this reason, steroid pMDIs should always be used in combination with a valved holding chamber.

Wheezy Infants

Valved holding chambers make pMDIs as or more reliable than SVNs for aerosol administration.[27] Closa et al studied 34 acutely asthmatic infants, ages 1–24 months. Each subject received 2 doses of terbutaline, 20 minutes apart, as either 2 mg/dose in 2.8 mL of 0.9% saline via

nebulizer or 0.5 mg/dose (5 puffs) via pMDI with valved holding chamber.[28] They found no difference in the rate of improvement or clinical score, and concluded that both devices were equally effective. Similarly, Williams et al studied 60 children, ages ≤ 6 years, suffering acute asthma exacerbations. The subjects were randomized to receive albuterol via nebulizer or via pMDI with valved holding chamber, for 3 treatments over 1 hour.[29] All patients showed improvement over baseline, with no difference between treatment groups.

To determine whether a single brief demonstration of the proper use of a valved holding chamber in the emergency department would result in improved outcomes, Cun-

Table 4. CFC and HFA MDIs in CFC, HFA, and Generic Actuators

Canister	Boot	MMAD ± GSD	Total Mass (g/m³)
CFC	CFC	2.51 ± 2.8	3.5
CFC	HFA	1.32 ± 3.1*	1.7*
HFA	HFA	2.16 ± 2.3	4.4
HFA	CFC	4.59 ± 4.2*	1.2*
CFC	GA	2.12 ± 1.9	2.1
HFA	GA	3.52 ± 3.1*	1.1*

Values represent mean ± standard error.
CFC = chlorofluorocarbon
HFA = hydrofluoroalkane
MDI = metered-dose inhaler
MMAD = mass median aerodynamic diameter
GSD = geometric standard deviation
GA = generic actuator
*p < 0.001 compared to standard MDI/boot actuator.
(Adapted from data in Fink JB, Dhand R, Grychowski J, Fahey PJ, Tobin MJ. Reconciling in vitro and in vivo measurements of aerosol delivery from a metered-dose inhaler during mechanical ventilation and defining efficiency-enhancing factors. Am J Respir Crit Care Med. 1999;159[1]:63–68.)
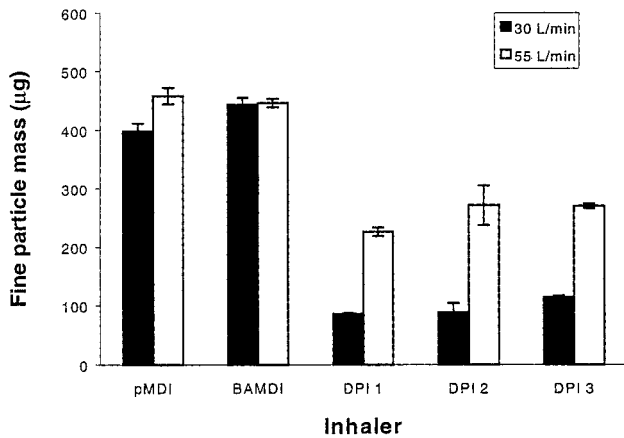
Fig. 7. The fine particle mass delivered from a 1,000 μg dose (± SD) as a function of flow. pMDI = pressurized metered-dose inhaler. BAMDI = breath-actuated pMDI (Autohaler). DPI = dry powder inhaler. DPI 1 = Rotahaler. DPI 2 = Turbuhaler. DPI 3 = Diskhaler. (From Reference 50, with permission.)
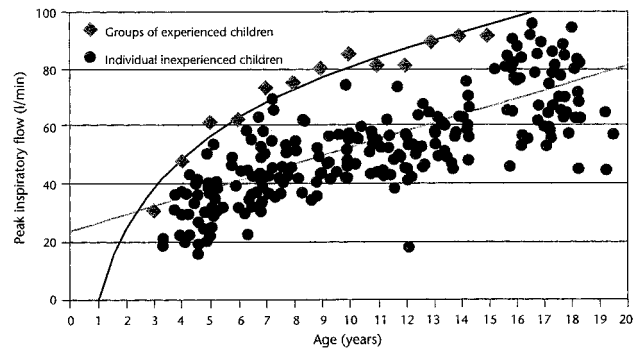

Fig. 8. Peak inspiratory flows in individual inexperienced children (filled circles) and groups of experienced children (gray diamonds). (From Reference 52, with permission.)

ningham and Crain enrolled 84 children in the emergency department to receive the inhaled medication with or without a valved holding chamber. The valved holding chamber group reported significantly faster resolution of wheezing, fewer days of cough, and fewer missed days of school (p < 0.01).[30]

The belief that an SVN is better than a pMDI if the patient is not able to inhale with optimal technique is not supported by research. In fact, if the patient cannot perform an optimal maneuver using a pMDI, he or she is unable to perform an optimal maneuver using an SVN. Although optimal technique is always preferred, it is often difficult to attain with an infant, small child, or severely dyspneic patient. In such cases, an alternative may be to increase the pMDI or nebulizer dose to achieve the desired outcome.

Care and Cleaning

Particles containing drug settle and deposit within the spacer or holding chamber, causing a whitish build-up on the inner chamber walls and valves. This residual drug poses no risk to the patient, but has been associated with increased variability in dose available to the patient.[31] Rau et al studied available dose from a pMDI formulation of beclomethasone for 3 spacers/holding chambers over 6 months when the devices were washed regularly, and without washing, which resulted in greater variability with all devices, but a significant increase in available dose was noted with one of the devices.[31] This effect appears to be associated with the static charge of plastic spacers. After washing a chamber or spacer with tap water, it is less effective for the next 10–40 puffs, until the static charge in the chamber (which attracts small particles) is once

again reduced (Fig. 4).[32] Use of regular dish soap to wash the chamber reduces or eliminates this static charge, increasing the amount of drug available to the patient.

The effect of static charge on aerosol has been shown to have a substantial impact on the respirable dose from a pMDI available to the patient. Static charge has been shown to decrease drug availability in the case of pMDI multiple actuations.[32–35] The use of multiple actuations into a holding chamber prior to inhalation was widely recommended in the past, but studies by O'Callaghan et al[33–35] found that that technique leads to a reduction in the proportion of respirable particles within the device, with the net effect that little or no additional drug may be available to the patient, compared to a single actuation.

Because of the inherently nonconducting surface of plastic spacers, electrostatic charge inevitably accumulates on these devices and affects charge output.[33–35] Plastic spacers initially have a strong electrostatic charge that causes particle deposition inside the spacer. The static charge can be eliminated by constructing the device of metal, or on a polycarbonate spacer by coating with an antistatic paint, washing with a deionizing soap, and repeated dosing without cleaning between use. In 1995, Barry and O'Callaghan[33] found that a greater dose of budesonide from a pMDI was available from an antistatic holding chamber than from a standard holding chamber, with standard use, with delays of up to 20 seconds between actuation and inhalation, and with multiple actuations (Fig. 5).

Pierart et al compared the influence of 4 household detergents, studying the influence of dilution and the subsequent duration of antistatic effects.[36] They found that detergents reduced the surface electrostatic charge in the spacer, increasing respirable mass of albuterol by ≥ 37%, compared to a water-rinsed/drip-dried spacer, in vitro. Results lasted for 4 weeks, independent of dilution. Lung deposition of radiolabeled albuterol was 45.6% in healthy subjects with the detergent-coated spacer, compared to 11.5% through a static device. The increased lung deposition with the non-electrostatically-charged device appears

Table 5. Salbutamol CFC and HFA pMDI Formulations

	Ventolin	Airomir
Propellants	CFC-12 CFC-11	HFA-134a
Surfactant	Oleic acid	Oleic acid
Cosolvent		Ethanol
Drug	Salbutamol	Salbutamol sulfate

CFC = chlorofluorocarbon
HFA = hydrofluoroalkane
pMDI = pressurized metered-dose inhaler
(Adapted from Reference 4.)

to coincide with the reduced amount of drug remaining in the spacer (Fig. 6). The authors recommended that plastic spacers be soaked in a dilute solution of household detergent and then allowed to drip dry without water rinsing once a month.

Accessory devices either use the manufacturer-designed boot that comes with the pMDI or incorporate a "universal canister adapter" to fire the pMDI canister. Different formulations of pMDI drugs operate at different pressures and use different sizes of actuator orifice that are specifically designed exclusively for that pMDI formulation. Output characteristics of a pMDI change when using an adapter with a different size orifice (Table 4). Therefore spacers or holding chambers with universal canister adapters should be avoided and those that use the manufacturers boot with the pMDI should be used.

Dry Powder Inhalers

DPIs create aerosols by drawing air through a dose of dry powder medication.[37] The powder contains either micronized drug particles (< 5 μm MMAD) with larger lactose or glucose particles (diameter $> 30\mu$m), or micronized drug particles bound into loose aggregates.[38] Micronized particles adhere strongly to each other and to most surfaces. Addition of the larger particles of the carrier decreases cohesive forces in the micronized drug powder, so that separation into individual respirable particles (deaggregation) occurs more readily. Thus, the carrier particles aid the flow of the drug powder from the device. These carriers also act as "fillers" by adding bulk to the powder when the unit dose of a drug is very small. Usually, the drug particles are loosely bound to the carrier,[39] and they are stripped from the carrier by the energy from the inhalation. The release of respirable particles of the drug requires inspiration at relatively high flow (30–120 L/min).[39,40] A high inspiratory flow results in pharyngeal impaction of the larger carrier particles that compose the bulk of the aerosol. The oropharyngeal impaction and taste of carrier particles gives the patient the sensation of having inhaled a dose.

The internal geometry of the DPI device influences the resistance to inspiration and the inspiratory flow required to deaggregate and aerosolize the medication. Devices with higher resistance require a higher inspiratory flow to produce a dose. Inhalation through a high-resistance DPI may provide better drug delivery to the lower respiratory tract
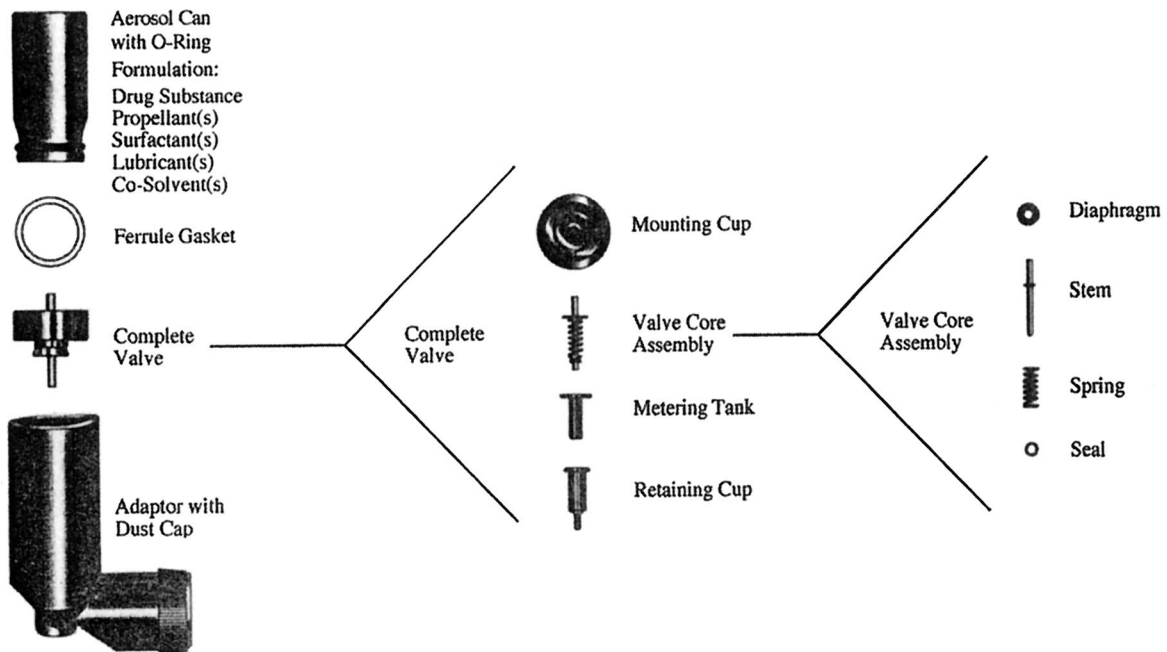

Fig. 9. Chlorofluorocarbon-free pressurized metered-dose inhaler assembly. (From Reference 1, with permission.)
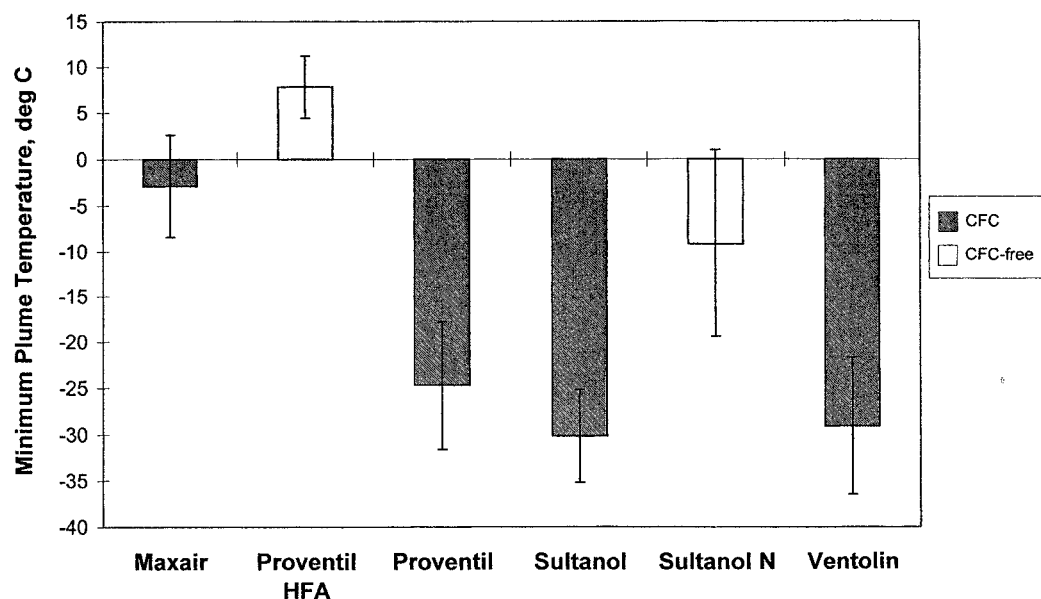
Fig. 10. The plume temperature of chlorofluorocarbon-propelled and chlorofluorocarbon-free albuterol pressurized metered-dose inhalers. Plume temperatures as low as –30° C have been associated with the cold-FREON effect. Only Proventil propelled by hydrofluoroalkane has a plume temperature greater than 5° C. (From Reference 1, with permission.)

than a pMDI[41,42] if the patient can reliably generate the required flow. High-resistance DPIs have not been shown to provide better lung deposition or bronchodilation than low-resistance DPIs.[43] DPIs with multiple components require correct assembly of the apparatus and/or priming of the device to ensure aerosolization of the dry powder.[44]

DPIs produce aerosols in which most of the drug particles are in the respirable range, with distribution of particle sizes differing significantly among various DPIs.[37] High ambient humidity produces clumping of the powder, which creates larger particles that are not as effectively aerosolized.[45] Humid air is less efficient than dry air at deaggregating particles of dry powder, so high ambient humidity increases the size of drug particles in the aerosol and may reduce drug delivery to the lung. Newer DPI devices contain individual doses more protected from humidity. Humidity can accumulate if the DPI is stored with the cap off, or from condensation if the device is brought from a very cold environment into a warmer area.

Inspiratory Flow

Since the energy from the patient's inspiratory flow disperses the drug powder, the magnitude and duration of the patient's inspiratory effort influences aerosol generation from a DPI.[46] Failure to perform inhalation at a sufficiently fast inspiratory flow reduces the dose of the drug emitted from a DPI[47] and increases the distribution of particle sizes within the aerosol, with a variety of devices. For example, the Diskus DPI delivers approximately 90%

of the labeled dose at inspiratory flows of 30–90 L/min, whereas the dose delivered by the high-resistance Turbuhaler DPI is significantly lower at 30 L/min than at 90 L/min. Also, the variability between doses at different inspiratory flows is higher with the Turbuhaler.[48–51] Figure 7 shows the effect of two inspiratory flows (30 L/min and 55 L/min) when using a pMDI, breath-actuated pMDI, Rotahaler, Turbuhaler, and Diskhaler.[50] The peak inspiratory flow of children is limited, and associated with age, making it unlikely that a child less than 6 years old could reliably empty a DPI that requires a flow > 50 L/min (Fig. 8).[52]

Active DPI delivery devices are under investigation. These use either a small motor and impeller or compressed gas propulsion to disperse the powder. Aerosol production and airway deposition with these devices is less influenced by the patient's inspiratory flow than existing DPIs, which rely solely on patient effort for aerosol production.

Breath coordination is also important when using DPIs. Exhalation into a DPI may blow the powder out of the device and reduce drug delivery. Moreover, the humidity in the exhaled air reduces subsequent aerosol generation from the DPI, so patients must be instructed not to exhale into a DPI.

DPIs are breath-actuated, which reduces the problem of coordinating inspiration with actuation. The technique of using DPIs differs in important respects from the technique for a pMDI. Although DPIs are easier to use than pMDIs, up to 25% of patients may use DPIs improperly.[53] DPIs are critically dependent on inspiratory air flow to
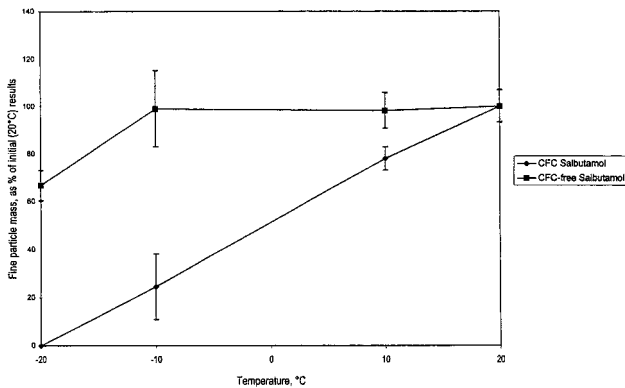
Fig. 11. Delivered fine particle mass versus temperature for chlorofluorocarbon-propelled albuterol and hydrofluoroalkane (HFA)-134a-propelled pressurized metered-dose inhalers (pMDIs). Compared to performance at 20° C, the chlorofluorocarbon-propelled pMDI delivers ≤ 74% at 10° C and < 23% at –10° C, whereas the HFA-propelled pMDI is unchanged down to –10° C. (From Reference 1, with permission.)

generate the aerosol, so they should be used with caution (if at all) in very young or ill children, weak patients, the elderly, or patients with altered mental status. Patients may need repeated instruction before they can master the technique of using a DPI, and periodic reassessment is necessary to ensure that patients continue to use optimal technique.[54] Clinicians must also learn the correct technique of using DPIs in order to train their patients in the use of these devices.

Although DPIs are widely used in Europe, where in some countries the use of CFC-propelled pMDIs was banned without exception, their acceptance in the United States has been less enthusiastic among both physicians and patients. Although DPIs and pMDIs have comparable clinical efficacy, projected DPI production and sales world-

wide appear not to be more than 20% of the current pMDI market (personal communication, Glaxo Wellcome, 1999).

Why Dry Powder Inhalers Will Not Replace Metered-Dose Inhalers

Although DPIs are effective, they are more expensive to produce than pMDIs, making their use less likely in third-world markets. In the United States there continues to be a limited number of drugs available in DPI form, and no one device type is available with a full range of respiratory drugs.

More important is the degree to which drug delivery from many commercially available DPI systems is reduced in the presence of humidity. The high inspiratory flows required for optimal delivery have raised concerns about DPI effectiveness for patients with severe airway obstruction and children under age 6. In response to these concerns, the United States Food and Drug Administration is waiting for more pMDI replacements before lifting the current exemption for CFC-propelled pMDIs, delaying the target date for a complete ban on CFC use, established by the Montreal protocol.

Montreal Protocol

In 1987, the United Nations, with 144 signatory nations, called for a phase-out of CFCs and other environmentally-harmful gases. By 1996, the production of most CFCs had ceased in developed countries.[1,4] Exemption was made for CFC use in pMDIs for essential users. Phased exemption gave industry time to find alternative propellants. An International Pharmaceutical Aerosol Consortium for Toxicology was formed to find suitable alternatives.[2] This led to identification of HFA-134a, the first non-ozone-deplet-
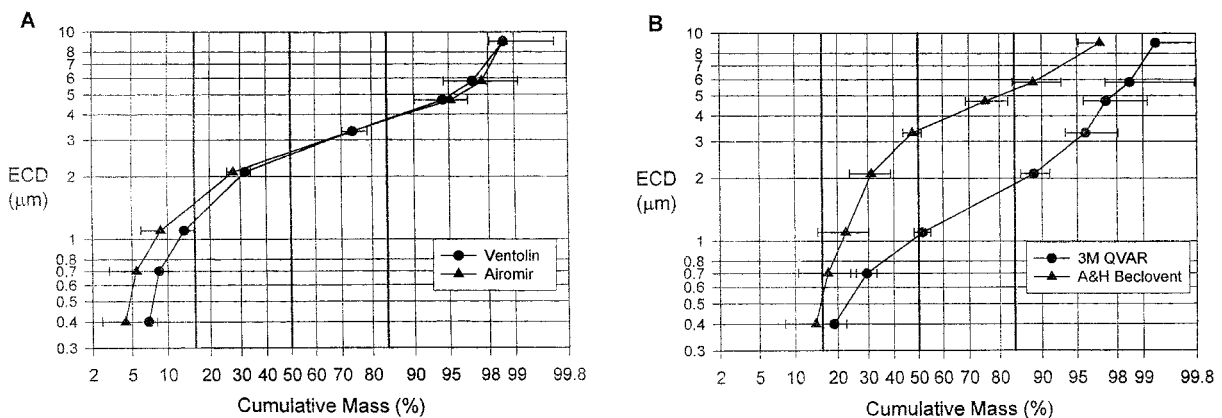
Fig. 12. Particle-size distributions from hydrofluoroalkane (HFA)-propelled pressurized metered-dose inhaler (pMDI) and from chlorofluorocarbon (CFC)-propelled pMDI. (A) Airomir (HFA) and Ventolin (CFC). (B) QVAR (HFA) and Beclovent (CFC). Measurements were made with an Anderson Cascade Impactor operated at 28.3 L/min. Cumulative mass (percent) refers to aerosolized drug that was deposited in an Anderson Cascade Impactor only. ECD = effective cut-off diameter. (From Reference 4, with permission.)

Table 6. Deposition of CFC- and HFA-Propelled BDP via pMDI

	Subjects (n)	Deposition* (nominal dose %)			
		Lungs	Oropharynx	Abdomen	Exhaled
CFC-BDP	Volunteers (9)	4 ± 3†	85 ± 20	9 ± 17	1 ± 1
HFA-BDP	Volunteers (3)	51 ± 12	29 ± 15	1 ± 2	18 ± 3
HFA-BDP	Asthmatics (16)	56 ± 9	31 ± 9	3 ± 4	9 ± 4

pMDI = pressurized metered-dose inhaler.
CFC = chlorofluorocarbon. BDP = beclomethasone dipropionate. HFA = hydrofluoroalkane.
*Deposition values are not corrected for tissue attenuation.
†Values represent means ± standard deviations.
(Adapted from Reference 55.)

ing pMDI propellant. Extensive toxicology and safety testing was conducted, which concluded that HFA-134a is at least as safe as CFC.

The first focus with the new propellant was on matching the performance characteristics of the CFC-propelled pMDI,[1] including drug concentration, metered volume, valve size, and pressure, to assure similar dose, similar particle size distribution, correct amount of fine particles < 4.7 μm, and dose reproducibility through the life of the pMDI. To achieve this, the pMDI valve, actuator, and formulation required modification.

Most widely-used CFC-propelled pMDIs are being reformulated as HFA-propelled pMDIs.[55] For the first time in 40 years, some manufacturers reevaluated performance of CFC-propelled pMDIs, addressing problems of inconsistent dosing, cold FREON effect, force of spray, and sensitivity of the pMDI to ambient temperature.

Airomir salbutamol sulfate (marketed in the United States as Proventil HFA) was the first HFA-propelled pMDI released with a new propellant and drug formulation (Table 5). This required substantial reengineering of key components, including the metering valve, elastome seals, smaller valve volume (25 μL), smaller actuator orifice, and wider mouthpiece orifice (Fig. 9).[1,56] The spray temperature is above freezing (14° C vs –2° C) (Fig. 10)[57] and the jetting force of the spray is reduced from 6.2 millinewtons to 2.4 millinewtons with the HFA device.[58] This reduced force and temperature drop at the plume was accompanied by less effect of temperature on performance (Fig. 11), providing more consistent and reliable performance than its CFC-propelled pMDI predecessor during winter, when canisters are cold.[55] While less temperature-dependent than the CFC formulations, deposition from the HFA-propelled pMDI is similarly reduced by humidity.

The CFC-propelled albuterol plume looks and sounds different than the HFA-propelled pMDI plume, because of lower jetting velocity.[4] Reformulation and hardware improvement improved canister performance with no reduction in dose per actuation when the inhaler is not used for hours or weeks, independent of orientation. The dose is consistent throughout the life of the canister, with less tail-off of drug when the canister is almost empty.[1] The particle size distributions of Airomir and Ventolin are similar (Fig. 12), with MMADs of 2.69 μm and 2.62 μm, respectively, but the respirable mass (< 5.8 μm) was 65.5% versus 41.4% (p < 0.05). However, the emitted dose of the HFA-propelled formulation is less.[4] With Airomir, the fine particle dose was higher with and comparable among several types and sizes of spacer.[59,60]

The transition to the HFA-propelled pMDI (eg, beclomethasone diproprionate and QVAR) has resulted in different formulations with different characteristics than the CFC-propelled formulations. Lack of a compatible surfactant required beclomethasone diproprionate to be dissolved in ethanol to make it soluble in HFA-34a, producing a solution rather than a suspension, as in CFC formulations.[55] Similar to the HFA-propelled albuterol pMDI, the plume force and temperature drop is less and storage stability better than the CFC-propelled Beclovent. While the emitted dose is similar (40.6 μg vs 45 μg), the particle distribution is substantially different—an MMAD of 1.07 μm versus 3.36 μm for the CFC-propelled formulation (see Fig. 12). These differences equate to better lung deposition and less oropharyngeal and abdominal deposi-

Table 7. Deposition of HFA-134a-Propelled Steroid from pMDI With and Without Spacer

HFA pMDI	Subjects, (n)	% Deposition	
		Lung	Oropharyx
BDP alone	normals (8)	51	29
BDP + Aerochamber		53	5
BDP + Volumatic		45	2
Flunisolide alone	normals (8)	23	60
Flunisolide + AeroHaler		41	15

pMDI = pressurized metered-dose inhaler
HFA = hydrofluoroalkane. pMDI = pressurized metered-dose inhaler.
BDP = beclomethasone dipropionate.
(Adapted from Reference 4.)

tion with the HFA-propelled formulation (Table 6). Lung deposition for HFA-propelled flunisolide was better and oropharyngeal deposition less with use of a valved holding chamber (Table 7).

Summary

Since 1956, the pMDI has become the most commonly prescribed and used aerosol device in the world. While concerns about global warming have led to a worldwide ban of CFCs, new HFA-propelled pMDIs are in development, requiring an evolutionary transition in the technology. The phase-out of CFC-propelled pMDIs has stimulated the development of more efficient DPIs, but issues such as cost of device production, inspiratory flow requirement, and the effects of ambient humidity on drug delivery may limit DPI acceptance, and industry projections suggest that the DPI will not completely replace the pMDI. Holding chambers may perform differently with HFA-propelled pMDIs, but HFA-propelled pMDIs generally appear to cause less oropharyngeal deposition and to improve lung delivery while continuing to provide protection from poor hand-breath coordination. The initial offerings of the emerging HFA-propelled pMDI technology appear to be resulting in an improved pMDI.

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