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Pharmaceutical transition to non-CFC pressurized metered dose inhalers

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The production of ozone-depleting chlorofluorocarbons (CFCs) was discontinued on 1 January 1996 for all uses deemed non-essential under the Montreal Protocol. However, the use of CFCs as propellants in pressurized metered dose inhalers (pMDIs) was classed as essential, providing an exemption from the agreement. Following extensive research, the hydrofluoroalkanes (HFA) 134a and 227 were identified as the only suitable replacements for CFC propellants in pMDIs.

The drug delivery of pMDIs formulated with HFA 134a as a propellant and containing either salbutamol (100 μg per actuation) or fluticasone propionate (125 and 250 μg per actuation) have been assessed for dose uniformity and particle size distribution.

All of the HFA 134a pMDIs delivered doses throughout the life of the canisters that were reproducible and within specified regulatory requirements. Each of the products provided an emitted dose which was within ±25% of the mean value indicating accurate and consistent dosing (93, 112 and 221 μg per metered dose for the salbutamol 100 μg and fluticasone propionate 125 and 250 μg HFA 134a pMDIs, respectively). These findings were unaffected by changing the storage orientation of the pMDI or by using the device in a manner designed to simulate typical patient use. The particle size distributions of HFA 134a pMDI doses did not differ significantly from those of the corresponding CFC pMDIs. As a result of the similar pharmaceutical performance, it is unnecessary to change the label claim dose of active drug when making the transition from a CFC to an HFA 134a pMDI for salbutamol (Ventolin™) and fluticasone propionate (Flixotide™). A seamless transition to non-CFC pMDIs will help to maintain the confidence of patients and healthcare professionals in asthma therapy.

Key words: metered dose inhaler; hydrofluoroalkane 134a; HFA 134a; chlorofluorocarbons; CFC; Montreal Protocol; CFC transition.

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Introduction

Under the Montreal Protocol, the production of ozone-depleting chlorofluorocarbons (CFC) was discontinued on 1 January 1996 for all uses deemed non-essential (1). However, the pharmaceutical use of CFC propellants in pressurized metered dose inhalers (pMDIs) was given an exemption, thereby providing a time period to develop alternative propellants. Subsequent research led to the development of hydrofluoroalkanes (HFA), and 1,1,1,2 tetrafluoroethane (HFA 134a) was chosen as the replacement propellant for pMDIs containing salbutamol (Ventolin™) and fluticasone propionate (Flixotide™). HFA 134a does not deplete the ozone layer, and animal studies have shown that it has an exceptionally good toxicity profile, without geno- or fetotoxicity, and does not affect peri- or postnatal development (2,3).

When evaluating new HFA 134a pMDIs, it is important to compare the dose delivery and particle size distribution with that of existing CFC pMDIs. Considerable formulation changes were necessary when switching to HFA 134a. The incorporation of cosolvents such as ethanol proved necessary if those surfactants routinely used in the CFC pMDI were to be used, as the traditional surfactants are not sufficiently soluble in HFA 134a (4). Ethanol has been used as a cosolvent in either suspension or solution formulations. However, in the cases of Ventolin™ and Flixotide™, an alternative approach was adopted in which suspension formulations were developed in the absence of excipients other than the propellant.

In conjuction with these formulation changes, it was essential to maintain the particle size distribution close to that of the CFC pMDIs. Establishing the performance of new products in these terms is essential to demonstrate that

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new non-CFC pMDIs meet the regulatory requirements laid down by the Committee for Propriety Medicinal Products (CPMP) and other regulatory agencies around the world (5). In recognition of the need to validate the performance of the HFA pMDI products with the appropriate spacer devices, particle size data were generated for both salbutamol (Ventolin™) and fluticasone propionate (Flixotide™) with the Volumatic™ and Babyhaler™ spacer devices.

The present *in vitro* study was conducted to establish the accuracy and consistency of dosing throughout the life of the canister, and the particle size distribution of active ingredient (salbutamol or fluticasone propinate) released from a pMDI using HFA 134a as the propellant.

Methods

DOSE UNIFORMITY

HFA 134a pMDIs containing salbutamol 100 μg and flucticasone propionate 125 and 250 μg per actuation were tested to determine dosing reproducibility. This was achieved using a variety of test protocols designed to evaluate single actuation reproducibility, content uniformity and simulated patient use.

The test for single actuation reproducibility measures the consistency of drug content in single actuations discharged from the inhaler during a typical dosing regimen. Nine pMDIs for each of the three formulations were primed and two single actuations from each inhaler were collected separately. Each pMDI was shaken prior to priming and collection of each actuation. The inhalers were then stored such that three inhalers were placed in each of the valve-up, valve-down and valve-horizontal orientations. Throughout the following 3·5 days, the contents of two consecutive actuations were collected separately once in the morning and evening for the flucticasone propionate pMDI and the contents of two actuations were collected separately morning and evening for the salbutamol pMDI. Each inhaler was stored in the defined orientation between collections.

The test for content uniformity aims to assess the accuracy and uniformity of dosing. During the test, the delivered dose collected at the beginning of the products's use and again after delivery of the label claim number of actuations was measured for 10 pMDIs for each of the three formulations. For fluticasone propionate, the delivered dose comprised two actuations (namely actuations 1 and 2 and actuations 119 and 120), whereas for salbutamol, the delivered dose corresponded to actuation 1 at the beginning of use and actuation 200 at the end of use.

The simulated use test was designed to reflect patient use of the product. Two actuations were released four times daily and twice daily from the salbutamol and fluticasone propionate pMDIs, respectively, until the last of the label claim actuations had been released (i.e. 200 actuations for salbutamol and 120 actuations for fluticasone propionate). The mean content of drug per actuation was determined at multiple points between the first and final actuation. Five pMDIs were tested for each of the three formulations.

For all dose delivery analyses, the actuated doses were collected from the pMDI after shaking into a 500 ml separatory funnel fitted with a cotton wool plug compacted into its base, through which air was drawn at 20 l min^{-1}. After 1 min the airflow was disconnected and the funnel was rinsed several times with methanol. The amount of active ingredient in each actuation was determined using high-performance liquid chromatography (HPLC).

PARTICLE SIZE DISTRIBUTION

An Andersen cascade impactor (Andersen Samplers Inc, Atlanta, Georgia, U.S.A.) fitted with a small volume metal induction port (throat) was used to determine the particle size distribution of the active constituent (salbutamol or fluticasone propionate) in an actuated dose released from a HFA 134a or CFC pMDI.

The cascade impactor contains eight aluminium stages held together by spring clamps and airtight seals. The plates of the cascade impactor were not coated with silicone. The aerosol spray is introduced through an induction port (throat), and the aerosol particles are drawn through the impactor by a stream of air (28 l min^{-1}). Each aluminium stage contains a defined number of accurately drilled holes, which decrease in size from stage 0 to stage 7. Thus, particles of a defined size range are collected by each stage (Table 1).

The primed inhaler was shaken and the contents of a single actuation were released into the Andersen cascade impactor. This process was repeated until five actuations for salbutamol and 10 actuations for fluticasone propionate had been discharged into the impactor. Each stage of the impactor, including the collection plates and filter, was then washed separately with methanol and the washings collected. The amount of active ingredient on each stage was determined by HPLC and expressed as the amount of active constituent per metered dose.

TABLE 1. The relationship between particle size and particle penetration into the airways and stages of the Andersen cascade impactor (operated at 28 l min^{-1})

Stage	Particle size (μm)	Deposition in respiratory tract
0	9·00–10·00	
1	5·80–9·00	
2	4·70–5·80	Pharynx
3	3·30–4·70	Trachea and primary bronchi
4	2·10–3·30	Secondary bronchi
5	1·10–2·10	Terminal bronchi
6	0·65–1·10	Alveoli
7	0·43–0·65	Alveoli
Filter	<0·43	

For each pMDI, particle size distributions were assessed with the standard actuator only, then with the Volumatic™ spacer fitted. In addition, the salbutamol pMDI was tested with the Babyhaler™ spacer device.

Results

As for all inhaler device testing, a proportion of the metered dose delivered from the formulation adheres to the surfaces in contact with the product. In the case of pMDIs, a dose is

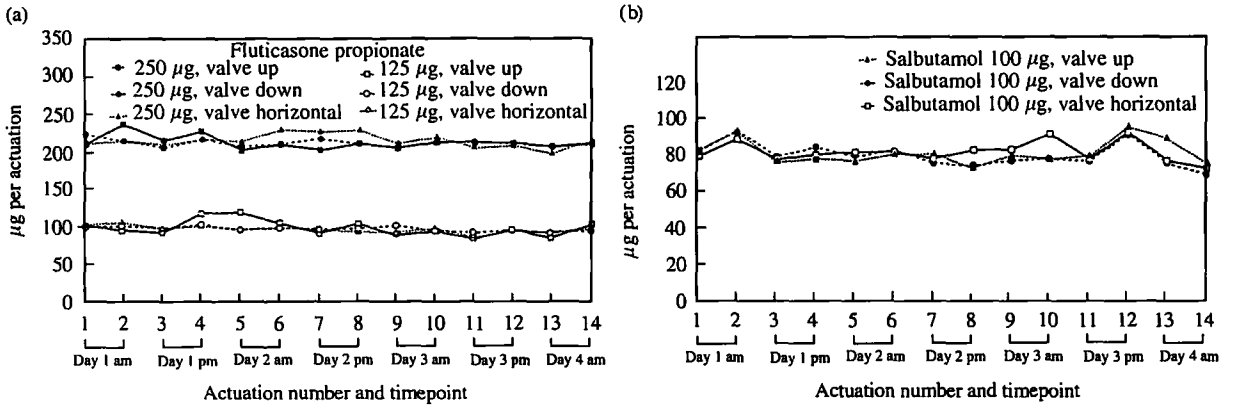

FIG. 1. Drug content delivered during single actuation reproducibility testing for (a) fluticasone propionate and (b) salbutamol hydrofluoroalkane (HFA) 134a pressurized metered dose inhalers (pMDIs) in three storage orientations.

TABLE 2. Content uniformity for the ex-actuator content of salbutamol 100 μg and fluticasone propionate 125 μg and 250 μg hydrofluoroalkane (HFA) 134a pressurized metered dose inhalers (pMDIs)

	Salbutamol (μg per metered dose)	Fluticasone propionate (μg per metered dose)				
Ex-actuator target	90 μg		110 μg		220 μg	
N	10		10		10	
pMDI number	1st actuation	200th actuation	1st and 2nd actuation (mean)	119th and 120th actuation (mean)	1st and 2nd actuation (mean)	119th and 120th actuation (mean)
1	84	102	118	113	217	233
2	86	99	108	109	212	233
3	93	97	101	110	212	225
4	91	87	126	110	218	224
5	83	104	115	111	223	212
6	87	97	105	112	214	226
7	89	96	106	113	217	223
8	91	102	123	112	211	232
9	78	105	120	102	211	227
10	83	86	111	111	216	225
Mean*	93		112		221	
±10% of label claim	81–99		99–121		198–242	
±25% of mean†	70–116		84–140		166–276	
±35% of mean†	60–126		73–151		144–298	

*Overall mean of 20 results.
†As defined by CPMP guidelines for content uniformity.

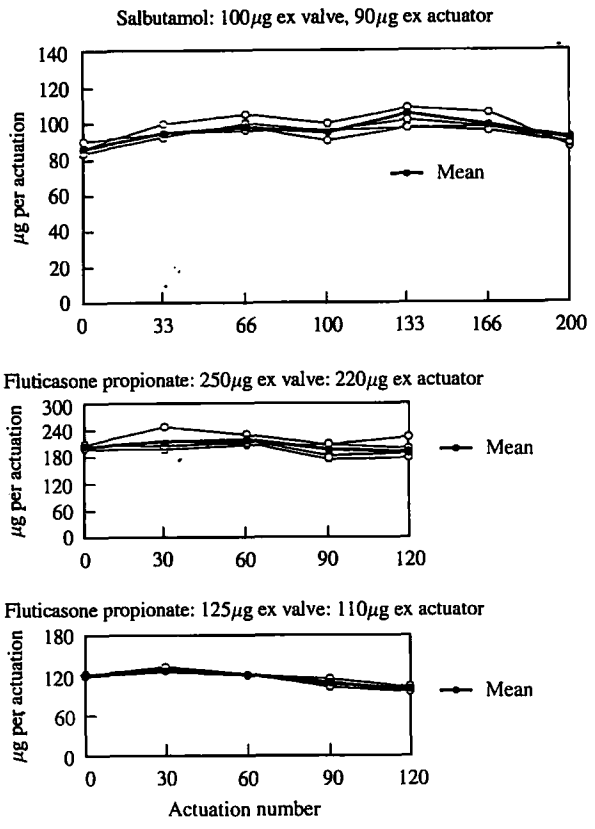

FIG. 2. Drug content delivered during simulated use testing for salbutamol and fluticasone propionate hydrofluoroalkane (HFA) 134a pressurized metered dose inhalers (pMDIs). The five lines on each graph represent the five MDIs used for each formulation

delivered by the valve (the ex-valve dose) and an amount of the dose is retained on the actuator. The dose reaching the patient is termed the ex-actuator dose. In practice, 100 μg of salbutamol released from the valve equates to 90 μg released from the actuator and 125 and 250 μg of flucticasone propionate released from the valve equates to 110 and 220 μg released from the actuator, respectively.

SINGLE ACTUATION REPRODUCIBILITY

The data for all three HFA 134a products showed consistent performance in all three orientations (Fig. 1). This demonstrates the durability of the performance of the HFA 134a pMDI under storage conditions likely to be encountered during patient use. All products tested remained close to the target value for the active ingredient per actuation throughout the test period.

CONTENT UNIFORMITY

Data on the content per actuation for 10 salbutamol and 10 fluticasone propionate HFA 134a pMDIs are presented in Table 2. Each of the products provided individual contents

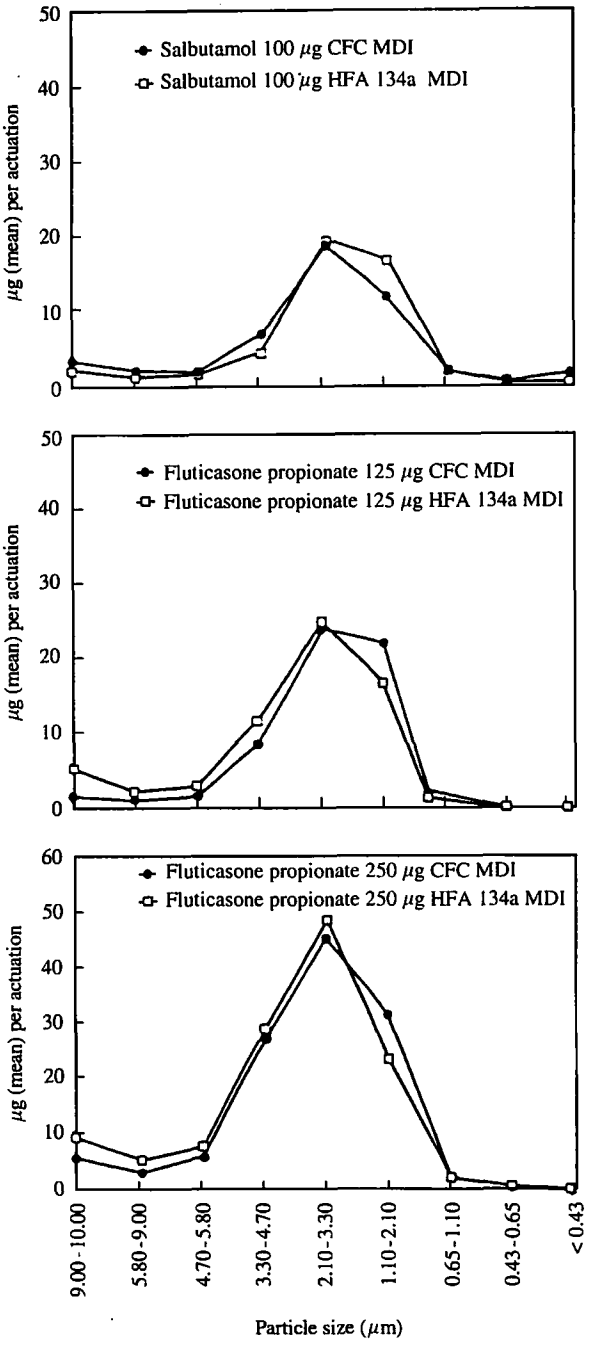

FIG. 3. Particle size distribution of salbutamol and fluticasone propionate hydrofluoroalkane (HFA) 134a and chlorofluorocarbon (CFC) metered dose inhalers. Particle size distribution was measured using an Andersen cascade impactor.

per actuation which were within ±25% of the mean value, indicating accurate and consistent dosing. For each product, the overall mean content per actuation was within ±10% of the target ex-actuator value. This complies with the first tier of testing for the CPMP specification (5).

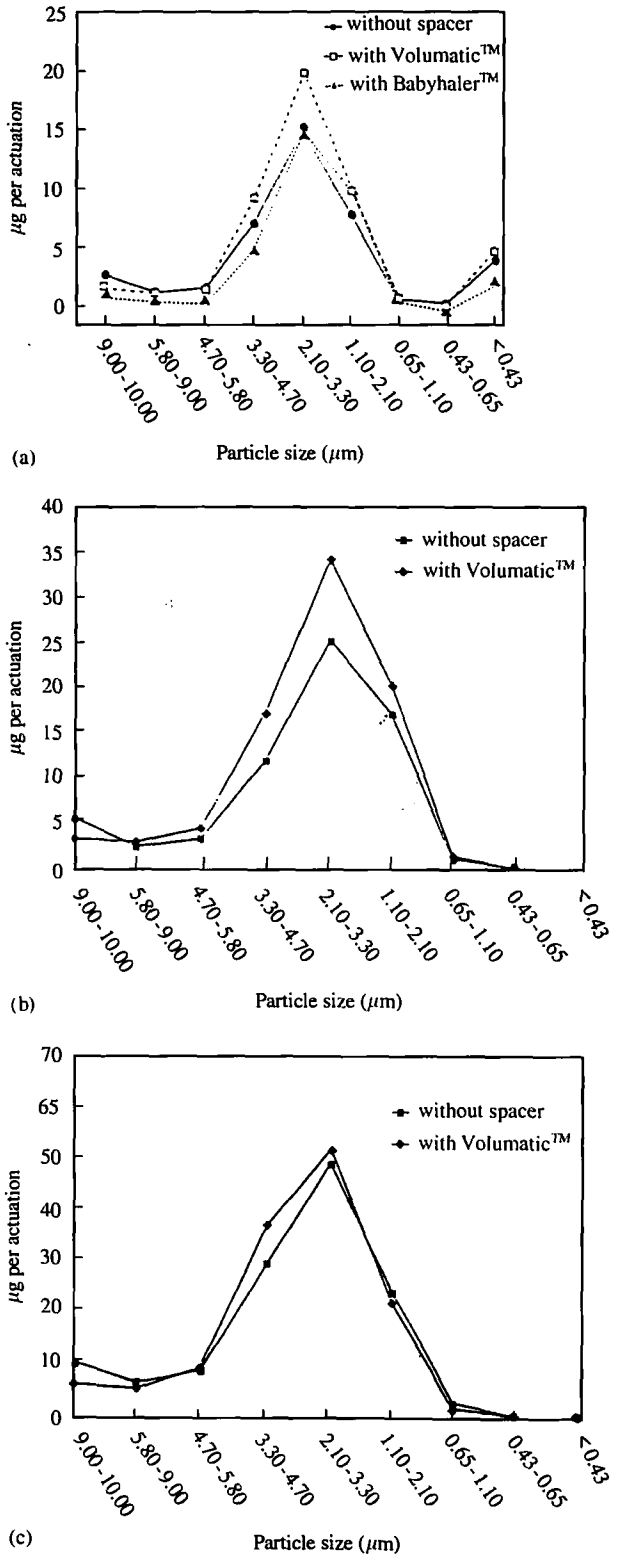

FIG. 4. Particle size distribution profiles for hydrofluoroalkane (HFA) 134a pressurized metered dose inhalers (pMDIs) with or without fitted spacer devices, containing (a) salbutamol 100 μg, (b) fluticasone propionate 125 μg and (c) fluticasone propionate 250 μg.

SIMULATED USE

For all three products (salbutamol 100 μg and fluticasone propionate 125 and 250 μg HFA 134a pMDIs), the delivered doses closely approximated to the target values throughout the label claim number of actuations (Fig. 2). This simulation of patient use provides valuable information about the consistency of the product performance. The data for all five canisters tested for each product were similar, indicating a high degree of inter-canister consistency over the label claim contents of the inhaler.

PARTICLE SIZE DISTRIBUTION

The particle size distributions for the corresponding HFA 134a and CFC salbutamol and fluticasone propionate pMDIs were similar (Fig. 3). Figure 4 demonstrates that use of the salbutamol HFA 134a pMDI in conjuction with the Volumatic™ and Babyhaler™ spacer devices had no significant effect on the particle size distribution profiles of salbutamol other than a significant reduction in throat deposition. The Volumatic™ spacer had a similar effect on the fluticasone propionate pMDIs. The mass median aerodynamic diameter (MMAD) for salbutamol with the HFA 134a pMDI was 2·4 μm, and 2·2 μm with the CFC pMDI. In the case of fluticasone propionate, MMAD values differed according to dose, but were comparable for the HFA 134a and CFC formulations (125 μg dose: 2·4 μm and 2·8 μm, respectively; 250 μg dose: 2·6 μm and 3·2 μm)

The active drug deposition in the throat and spacer after dose actuation with or without spacer devices, together with the fine particle mass, are presented in Table 3.

DISCUSSION

These data show that it has been possible to formulate non-CFC pMDIs for salbutamol and fluticasone propionate with a similar *in vitro* pharmaceutical performance to the CFC pMDIs. This development was particularly challenging because the physicochemical properties of HFA 134a necessitated modification of the formulation and the primary packaging components for both the salbutamol and fluticasone propionate pMDIs in order to achieve an equivalent pharmaceutical profile.

The simulated use results of this study demonstrate that the amount of salbutamol and fluticasone propionate released per metered dose of the HFA 134a pMDIs was consistent throughout the label claim number of actuations when the product was used according to a typical patient dosing regimen.

Due to their physicochemical properties, suspension aerosols can be sensitive to the effects of separation of the suspended particles within the valve on standing due to either creaming or sedimentation, and this can affect the dosing characteristics of the product (6). Careful evaluation of all suspension formulations is therefore required. Measurement of the single actuation content reproducibility demonstrated that the amount of active ingredient delivered in each actuation was unaffected by the storage

orientation of the inhaler over periods typical of those elapsing between patient use. The data showed that the content per actuation of HFA 134a pMDIs was consistently close to the target dose delivery values.

The particle size distribution of active ingredient from the HFA 134a and CFC pMDIs was determined using the Andersen cascade impactor. The size distribution of fine particles in the discharged aerosol can be expected to relate to the degree of drug penetration into the respiratory tract. Indeed, there is a correlation between particle penetration through the stages of the Andersen cascade impactor and *in vivo* penetration of particles into the airways (7–9). Thus, the fact that the HFA 134a pMDI particle size distribution results are similar to those from the corresponding CFC pMDIs suggests that the total lung deposition characteristics of these devices are similar.

The optimal particle size necessary for the bronchodilator salbutamol to achieve a demonstrable increase in lung function is 3 μm (10). In this study the mass median aerodynamic diameters of the salbutamol particles were 2·1 and 3·3 μm for the HFA 134a and CFC pMDIs, respectively. The similarity of both the delivered dose and fine particle fractions of salbutamol from HFA 134a and CFC pMDIs underpins the clinical equivalence of these devices. This clinical equivalence has been indicated by single-dose pharmacological and multiple-dose clinical studies (11–13).

A relationship between the site of pulmonary deposition of inhaled corticosteroids and their anti-inflammatory effect has not been demonstrated. However, a recent reformulation of the beclomethasone dipropionate inhaler (QVAR™) using ethanol resulted in an increase in the proportion of fine particles less than 1·1 μm. This necessitated a two-fold reduction in dosage with the new formulation compared with the CFC pMDI, under certain circumstances (14). The lung deposition data for QVAR™, in comparison, suggest a six-fold increase in the quantity of drug reaching the lung with QVAR™ (14). Thus there is a discrepancy between lung deposition and the resultant clinical efficacy, and the relationship between lung deposition and clinical efficacy and safety remains poorly understood.

The characteristics of the aerosol spray can be influenced by the formulation and packaging components. It has been reported that the plume temperature for salbutamol HFA products (Proventil™ HFA containing ethanol; Sultanol N™ or Ventolin™ CFC-free excipient-free) is warmer than that of some comparator CFC products (15). The excipient-free formulation in this study maintained the same impact force as the CFC formulation. This provides reassurance that patients will experience a similar sensation from the aerosol spray when taking a dose (15).

The addition of a spacer device had no effect on the particle size distribution of the HFA 134a pMDIs, although, as with the CFC pMDIs, there was a slight increase in fine particle mass. These data indicate that the new pMDIs can be used successfully in conjuction with spacer devices in the same way as currently available CFC pMDIs. The slight increase in fine particle mass, regardless of propellant, is likely to be due to the deceleration of the aerosol through the spacer and increased droplet evaporation within the spacer. However, these differences are unlikely to be of clinical significance given the inter-patient variability seen with inhaled drug delivery.

TABLE 3. Cascade impactor data for hydrofluoroalkane (HFA) 134a and chlorofluorocarbon (CFC) pMDIs used with or without spacer devices

	Ex-actuator dose (μg)	Throat deposition (μg)	Spacer deposition (μg)	Fine particle mass (sum of stages 3–5*; μg)
Salbutamol 100 μg (HFA 134a propellant)				
Standard actuator	82	39	—	34
Volumatic™ spacer	90	1·3	37	43
Babyhaler™ spacer	93	0·7	54	33
Fluticasone propionate 125 μg (HFA 134a propellant)				
Standard actuator	101	35	—	54
Volumatic™ spacer	113	1·1	28	72
Fluticasone propionate 125 μg (CFC propellant)				
Standard actuator	109	45	—	56
Volumatic™ spacer	109	0·4	34	67
Fluticasone propionate 250 μg (HFA 134a propellant)				
Standard actuator	206	79	—	102
Volumatic™ spacer	234	1·8	102	111
Fluticasone propionate 250 μg (CFC propellant)				
Standard actuator	223	98	—	106
Volumatic™ spacer	231	1·2	82	131

*Stages 2–6 for the salbutamol pMDI

In conclusion, the results of this study suggest that the replacement of CFC propellants with non-ozone depleting HFA 134a in pMDIs has now become feasible, without affecting the pharmaceutical characteristics of these devices.

Acknowledgements

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