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Modulation of aerosol clouds produced by pressurised inhalation aerosols

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Abstract

The inclusion of non-volatile components such as glycerol or polyethylene glycol in hydrofluoralkane (HFA) solution formulations for pressurised metered dose inhalers (pMDIs), greatly increases the particle size of the aerosol. Cloud characteristics can be further modulated by permuting this factor with the choice of propellant and the dimensions of the actuator, to give a chosen fine particle dose and particle diameter. This principle has been used to design solutions which closely match the performance of chlorofluorocarbon based suspension formulations containing beclomethasone dipropionate, budesonide and ipratropium bromide as assessed for pharmaceutical equivalence using the Andersen Cascade impactor.

Keywords: Aerosol; Pressurized metered dose inhaler; Particle size distribution; Hydrofluoroalkane; HFAs

1. Introduction

The problems created by the replacement of chlorofluorocarbons (CFCs) with hydrofluoralkanes (HFAs) in pressurised metered dose inhalers are well known. The most serious derive from the changed solubility of drugs and excipients in the new propellants. Solubility of some drugs precludes presentation as suspensions and, where suspensions are possible, conventional stabilisers cannot be used alone because of their inadequate solubility. The use of co-solvents to overcome these problems may create further complexity.

Such problems may be solved by accepting the physicochemical nature of drug and propellant and then devising stable solution or suspension formulations. The disadvantage of this approach is that existing CFC formulae may not have been optimised, consequently generating coarse clouds which have non-ideal deposition patterns in the lung. Their HFA replacements may not be pharmaceutically or clinically equivalent and adjustment of dose and regimen may be necessary,

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creating problems for clinician, pharmacist and patient. An alternative is a seamless transition from the old to the new formula which demands the same deposition of the drug in the lung. For any product, this can be inferred from the amount of drug and its particle size distribution in the aerosol cloud.

Where it is possible, matching CFC and HFA formulations using suspension technology could be potentially advantageous because the particle size of the cloud is dominated by the particle size of the suspended drug, defined by the milling or precipitation process. Cloud characteristics can then be further refined by the level of stabiliser, the vapour pressure of the propellant, the metered volume and the dimensions of valve and actuator. For example, Polli et al. (1969) showed that a decrease in the ratio of CFC propellant 12 to propellant 11, and an increase in actuator aperture diameter all increased the particle size of the cloud, In a similar permutation, Moren (1978) showed that droplet deposition is improved by a combination of high vapour pressure and low metered volume. These modulations of cloud characteristics were found to be reflected in in vivo deposition patterns by Newman et al. (1982).

When, as commonly occurs, solution formulations are unavoidable, the volumetric contribution of suspended drug particles is absent and much finer clouds, largely defined by the drug concentration in the solution, are generated. A co-solvent, such as ethanol is often present in these solutions to ensure satisfactory drug solubility is maintained. The finer clouds from such formulations give more extensive deposition in the lung periphery than their CFC counterparts, (June, 1997; Leach et al., 1998).

However, a seamless transition can be achieved if clouds are constructed which closely match those given by existing suspension formulations. In the novel procedure described below this is achieved by the inclusion of a non-volatile excipient, such as glycerol or polyethylene glycol. Such formulations can be further refined by manipulation of the geometry of the inhaler device as described below.

2. Experimental

2.1. Materials

Beclomethasone dipropionate, (BDP), budesonide, ipratropium bromide, (IPBr), ethanol, glycerol and polyethylene glycol 400 (PEG 400) used to prepare HFA solution formulations were all pharmacopoeial (Ph. Eur.) quality. HFA 134a (Zephex MDI, I.C.I) and HFA 227 (Solkane 227 pharma, Solvay) were inhalation grade. Commercial CFC formulations were obtained from a local pharmaceutical wholesaler as follows:

Becotide 50™ (Allen & Hanbury, BDP 50 μg per shot), BNs 10279317, 10289757, 10241497; Pulmicort 200 ™ (Astra, budesonide 200 μg per shot), BNs YH697, ZC712; Atrovent 40 ™ (Boehringer–Ingelheim, IPBr 40 μg per shot), BN 701621

HPLC solvents and 1-butane sulphonic acid sodium salt were HPLC grade. All other analytical reagents were AR grade. Water was either fresh or obtained from a Milli-Q model R105/16 RO system.

2.2. HPLC methods

2.2.1. Equipment

Spectrasystem P1000 pump, AS1000 autosampler fitted with 100 μl Rheodyne loop valve, UV1000 variable wavelength deductor, (all Thermoseparation Products).

2.2.2. Chromatography conditions and external standards

Chromatography conditions are shown in Table 1. External standard solutions for BDP (0.1–10.0 μg ml^{-1}) and budesonide (0.1–5.0 μg ml^{-1}) analysis were prepared in the relevant HPLC mobile phase. External standards for IPBr (0.1–5.0 μg ml^{-1}) were prepared in 4×10^{-4} M aqueous sulphuric acid. The drug content of the Andersen cascade impactor samples was calculated from the product of the mean response factors of bracketing external standards and the sample solution volume. All HPLC procedures were validated for linearity and reproducibility.

Table 1
HPLC chromatography conditions

	BDP	Budesonide	IPBr
Column	Hypersil MOS 5 μm; 100×4.6 mm (Hewlett Packard)	Supelcosil LC-C18-DB 50×4.6 mm (Supelco)	C8 Apex EC 5 μm; 150×4.6mm (Jones Chromatography)
Mobile phase	Me CN:water (60:40)	Ethanol:water (43:57)	Me CN:Aq ion pair (16:84)[a]
Flow rate	1.0 ml min^{-1}	2.0 ml min^{-1}	2.0 ml min^{-1}
Detection	238 nm	244 nm	210 nm
Temperature	30°C	30°C	30°C
Run time	6 min	3 min	9 min
Retention time	~3.6 min	~1.3 min	~5.0 min

[a] Aqueous ion pair reagent; 1-butane sulphonic acid sodium salt 0.909 g, water 1000 ml, triethylamine 4.55 ml, orthophosphoric acid to pH 3.6.

2.3. Solubility studies

Solubility studies to establish likely formulations of solution aerosols containing BDP, budesonide or IPBr were conducted in mixtures of the chosen HFA, ethanol and small amounts of water. Formulations were prepared in plastic coated glass containers (St. Gobain/Desjonqueres UK) sealed with BK 357 continuous valves (Bespak, UK) and stored at 4°C for 50 days or over. Formulations were assessed visually and the resultant phase diagram created. An example is given in Fig. 1 which displays the regions in which combinations of HFA 134a, ethanol and water will dissolve 0.037% w/w ipratropium bromide to give a single phase. Water was added to establish the tolerance of the formulations to small amounts which arise from components or by absorption during processing. Final water content was determined by Karl Fischer analysis (Metrohm 684 KF Coulometer).

2.4. Preparation of HFA solution pMDIs

Drug concentrates were prepared in ethanol and appropriate volumes transferred to tared cut edge aluminium cans (Presspart) using Gilson pipettes. The cans were then re-weighed before adding the non-volatile excipient. Using Pamasol 2016 laboratory scale, crimping and filling equipment the cans were sealed with BK 357 valves incorporating a 50-μl metering chamber (Bespak, UK) and filled to weight with HFA propellant. Final compositions were calculated as percent w/w. For drug delivery evaluations, cans were fitted with Bespak type BK 630 standard actuators with orifice diameters of 0.25, 0.30, 0.33 or 0.42 mm.

2.5. pMDI pack pressure determination

This was determined by coupling a pressure gauge (DH Industries Model No. P700) to the

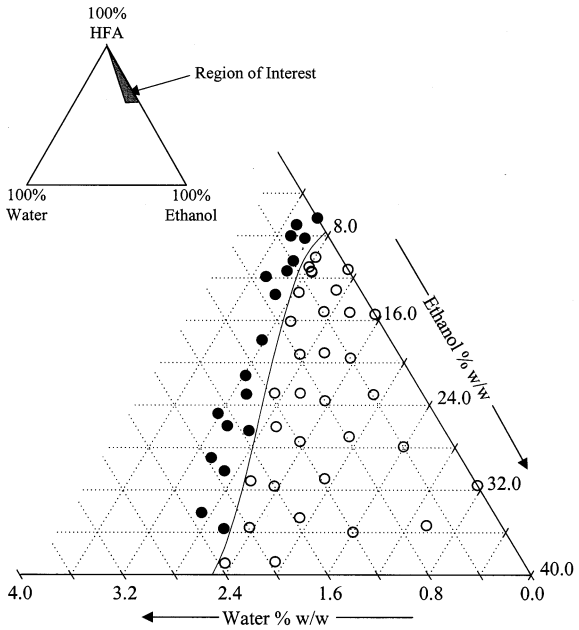

Fig. 1. Solubility phase diagram for IPBr (0.037% w/w) at 4°C: ○ Single phase solution; ● 2 or 3 phase dispersion. Ordinate: Increasing ethanol content (% w/w).

Table 2
Effect of non-volatile components on BDP HFA 134a solution pMDI characteristics: mean ± SD ($n \geq 3$)[a]

Formulation (% w/w)					
BDP	0.085[b]	0.424[c]	0.424[c]	0.424[c]	0.424[c]
Ethanol	14.0	15.0	15.0	15.0	15.0
Glycerol	–	–	1.0	1.6	–
PEG 400	–	–	–	–	6.1
HFA 134a	85.9	84.6	83.6	83.0	78.5
Delivered dose (μg)	43.2 ± 1.9	222.1 ± 5.1	227.9 ± 3.6	230.7, 232.6	223.4, 228.0
Fine particle dose (μg)	14.7 ± 0.7	65.9 ± 4.2	51.8 ± 1.6	45.7, 46.7	27.5, 28.6
MMAD (μm)	1.1 ± 0.1	1.8 ± 0.2	2.9 ± 0.3	3.1, 3.1	4.4, 4.1
GSD	2.2 ± 0.1	2.2 ± 0.1	2.3 ± 0.2	2.3, 2.3	2.5, 2.5
Replicates	6	6	4	2	2

[a] Actuator orifice 0.33 mm.
[b] Metered dose; 50 μg.
[c] Metered dose; 250 μg.

stem of a continuous valve fitted to an aluminium can containing the relevant formulation, according to the method of Herzka and Pickthall (1961).

2.6. Drug delivery determination

CFC suspensions were shaken thoroughly between each shot. pMDI valves were primed by discharging five shots to waste. For BDP and budesonide formulations, ten shots were discharged into an Andersen Cascade Impactor (ACI) fitted with a metal throat (Apparatus 2 Ph. Eur. Supp 1999) at a flow rate of 28.3 l min^{-1}) (± 5%), i.e. under the conditions specified in the pharmacopoeia. For IPBr preparations, 25 shots were collected to compensate for its low extinction co-efficient. The pump was switched on for 5 s prior to pMDI discharge. There was a pause of 60 s or longer after each individual discharge. Drug was recovered by rinsing the ACI Stage plate and corresponding lower compartment into 50 ml volumetric flasks with HPLC mobile phase and adjusting to volume with the same. Drug on the throat and actuator was similarly recovered. Deposition on the filter was obtained by ultrasonication in mobile phase, filtration through a PTFE 0.2 μm filter (Merck 402/0805/42) to remove glass fibres and adjustment to 25 ml. Drug content of the flasks was determined by HPLC.

Mean delivered dose was calculated from the cumulative deposition in the ACI (Throat and Stages). Mean fine particle dose was obtained from the deposition on Stages 3 to filter corresponding to particles less than or equal to 4.7 μm. Mass median aerodynamic diameter (MMAD) and its associated geometric standard deviation (GSD) were obtained from probit transformation of cumulative percent undersize-log (ACI effective cut-off particle size diameter) and linear regression analysis of the resultant data, (Ph. Eur. Supp 1999). Mass balance was confirmed by analysis of ten shots individually collected into a validated dose unit sampling apparatus (DUSA), at 28.3 l min^{-1} ± 5%. In all cases mean delivered doses from each ACI determination were well within 80–120% of that from the DUSA determination thus meeting the validity requirement of the USP 23 chapter < 601 > .

3. Results

3.1. Effect of non-volatile components

The effect of non-volatile components on cloud characteristics of BDP formulations is given in Table 2. In the absence of non-volatile additives, very fine clouds are generated and the MMADs are determined by the concentration of the drug

in the HFA propellant/ethanol mixture. For BDP this increases from 1.1 to 1.8 μm as the drug concentration is increased from 0.085 to 0.424% w/w, corresponding to metered doses of 50 and 250 μg, respectively. These values are very much smaller than those observed with marketed CFC suspension formulations which have typical values of 3.5–4.5 μm. However, values within the latter range are observed when small amounts of glycerol or PEG 400 are added. This effect is presented graphically in Fig. 2 with the experimental MMAD shown as a function of the total non-volatile component, i.e. drug plus non-volatile additive. The additional non-volatile components depress the fine particle dose to a degree which depends on the amount added. Corresponding data for budesonide and IPBr shown in Tables 3 and 4, exhibit the same qualitative behaviour.

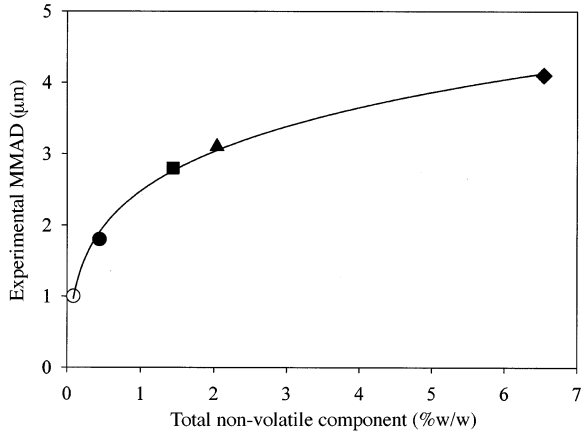

Fig. 2. Effect of total non-volatile component on MMAD (μm) of BDP pMDI solution formulations in HFA 134a. Open symbols, 0.085% w/w BDP; closed symbols 0.424% w/w BDP.

Table 3
Effect of non-volatile components on budesonide HFA 134a solution pMDI characteristics: mean ± SD, $n \geq 3$[a]

Formulation (% w/w)			
Budesonide	0.085[b]	0.085[b]	0.085[b]
Ethanol	15.0	15.0	15.0
Glycerol	–	1.3	1.6
HFA 134a	84.9	83.6	83.3
Delivered dose (μg)	42.1, 40.2	43.6 ± 1.3	46.4, 46.4
Fine particle dose (μg)	10.6, 10.6	7.9 ± 0.4	8.8, 8.4
MMAD (μm)	1.4, 1.4	3.2 ± 0.1	4.5, 3.8
GSD	3.0, 2.9	2.3 ± 0.1	2.4, 2.3
Replicates	2	4	2

[a] Actuator orifice 0.42 mm.
[b] Metered dose; 50 μg.

3.2. Effect of actuator orifice diameter

The effect of actuator orifice diameter on aerosol performance was studied with BDP (0.424 w/w) and budesonide (0.339% w/w) formulations containing 15.0% ethanol and 1.3% glycerol in HFA 134a. The results are shown in Table 5. Reduction in the size of the aperture markedly increases fine particle dose. This is associated with a very much smaller decrease in MMAD.

3.3. The effect of propellant

HFA 134a and HFA 227 differ significantly in vapour pressure; 570 and 390 kPa at 20°C, respectively. Addition of cosolvent and non-volatile additive lowers the propellant vapour and pack pressures, although those for HFA 134a systems remain higher than for equivalent HFA 227 systems. Drug delivery data for selected formulations of BDP. budesonide and IPBr in the two propellants are given in Table 6. As an example, the BDP/ethanol/glycerol combination shows that the higher pack pressure HFA 134a formulation (550 kPa at 20°C) gives a cloud with an MMAD of 2.8 μm compared to 3.5 μm when HFA 227 is used (pack pressure at 20°C = 350 kPa). Similar effects are obtained with formulations containing budesonide and IPBr. In all cases, higher pressure leads to more efficient atomisation and finer sprays. However, unlike the effect of actuator orifice, there is little associated change in fine particle dose.

4. Discussion

A dominating effect on the control of particle size of clouds generated from solution aerosols is exerted by the total content of non-volatile com-

Table 4
Effect of non-volatile components on IPBr HFA 134a solution pMDI characteristics: mean ± SD, ($n \geq 3$)[a]

Formulation(% w/w)					
IPBr	0.037[b]	0.037[b]	0.037[b]	0.075[c]	0.075[c]
Ethanol	13.0	13.0	13.0	13.0	13.0
Glycerol	–	0.5	1.0	1.1	1.3
HFA 134a	86.9	86.4	85.9	85.8	85.6
Delivered dose (μg)	16.6 ± 0.6	18.7 ± 1.0	18.8 ± 0.7	35.4, 36.5	35.5, 35.0
Fine particle dose (μg)	4.0 ± 0.2	6.7 ± 0.8	5.2 ± 0.3	9.3, 10.3	8.3, 9.1
MMAD (μn)	1.2 ± nil	1.9 ± 0.1	2.5 ± 0.1	2.6, 2.9	2.7, 2.9
GSD	1.9 ± 0.1	2.1 ± 0.1	2.1 ± 0.1	2.5, 2.4	2.5, 2.3
Replicates	3	6	6	2	2

[a] Actuator orifice 0.33 mm.
[b] Metered dose; 20 μg.
[c] Metered dose; 40 μg.

Table 5
Effect of actuator orifice diameter on BDP and budesonide HFA solution pMDI characteristics: mean (± SD)

Formulation	% w/w	Diameter (mm)	Delivered dose (μg)	Fine particle dose (μg)	MMAD (μm)	GSD	Replicates
BDP	0.424[a]	0.25	220.8 ± 6.0	93.5 ± 7.1	2.6 ± 0.1	2.0 ± 0.1	3
Ethanol	15.0	0.30	231.4 ± 16.0	55.3 ± 1.8	2.7 ± 0.2	2.2 ± 0.1	16
Glycerol	1.3	0.33	228.7 ± 5.3	50.9 ± 1.4	2.9 ± 0.2	2.2 ± 0.1	12
HFA 134a	93.3	0.42	216.2 ± 11.3	34.9 ± 1.9	2.9 ± 0.3	2.3 ± 0.2	3
Budesonide	0.339[b]	0.25	176.4 ± 3.7	84.7 ± 0.5	2.8 ± 0.1	1.9 ± 0.1	3
Ethanol	15.0	0.30	167.5 ± 1.7	49.3 ± 2.0	2.8 ± 0.2	2.0 ± 0.1	3
Glycerol	1.3	0.33	168.6 ± 5.5	45.3 ± 1.1	3.0 ± 0.3	2.0 ± 0.1	3
HFA 134a	84.4	0.42	168.8 ± 1.7	30.5 ± 1.2	3.4 ± 0.2	2.1 ± 0.1	3

[a] Metered dose; 250 μg.
[b] Metered dose; 200 μg.

ponents. Supplementing the contribution of the drug by addition of non-volatile excipients is a powerful means of modulation and changes in cloud size may be explained simply in terms of the volumetric contribution of these components. Assuming that the cloud particles approximate to spherical geometry, the size, d, is related to its volume, V, by Eq. (1):

$$d = (6V/\pi)^{0.33} \quad (1)$$

If atomisation patterns are unchanged, the particle size may be increased from a baseline value of d_0 to d_1 by increasing the volume of the non-volatile components from V_0 to V_1 (Eq. (2)).

$$d_1 = d_0(V_1/V_0)^{0.33} \quad (2)$$

For a given combination of drug, excipients and propellant, assuming density changes are small as the percent composition varies and spray patterns are unchanged, volume may be replaced by MMAD, giving Eq. (3):

$$\mathrm{MMAD}_1 = \mathrm{MMAD}_0(m_1/m_0)^{0.33} \quad (3)$$

where m_0 is the mass of drug in the baseline reference formulation (i.e. drug, cosolvent and HFA but without non-volatile additive) and m_1 is the mass of drug plus non-volatile components. In Fig. 3, predicted MMAD values derived from Eq. (3) are related to the experimental data in Table 2, using the BDP/ethanol formula containing 0.085% drug as the reference solution. Theory and experiment are in close agreement. The lower

Table 6
Effect of HFA propellant on the characteristics of solution pMDIs containing BDP, budesonide and IPBr: mean ± SD, ($n \geq 3$)

Formulation	(% w/w)	Actuator diameter (mm)	Propellant	Delivered dose (μg)	Fine particle dose (μg)	MMAD (μg)	GSD	Replicates
BDP	0.085[a]		HFA 134a	44.0 ± 1.2	13.9 ± 0.6	2.8 ± 0.2	2.1 ± 0.1	3
Ethanol	13.0	0.30						
Glycerol	1.3		HFA 227	46.2 ± 0.2	13.1 ± 1.0	3.5 ± 0.3	2.2 ± 0.1	3
HFA	85.6							
Budesonide	0.085[b]		HFA 134a	46.3 ± 1.3	7.9 ± 0.4	3.1 ± 0.1	2.2 ± 0.1	4
Ethanol	15.0	0.42						
Glycerol	1.3		HFA 227	45.2 ± 1.1	6.5 ± 0.5	4.9 ± 0.2	2.3 ± 0.1	4
HFA	83.6							
IPBr	0.037[c]		HFA 134a	18.8 ± 1.6	6.8 ± 1.1	2.4 ± 0.3	2.1 ± 0.8	8
Ethanol	13.0	0.30						
Glycerol	1.0		HFA 227	20.6, 20.9	6.6, 7.4	3.5, 3.3	2.2, 2.1	2
HFA	85.9							

[a] Metered dose; 50 μg.
[b] Metered dose; 50 μg.
[c] Metered dose; 20 μg.

values of fine particle dose arise naturally from the coarsening of the cloud. A higher portion of the delivered dose impacts in the right-angled throat of the apparatus or on the upper stages of the impactor.

Although the effect of actuator orifice diameter and propellant on cloud character is less pronounced, useful modulating effects are observed. The atomisation of liquid during the discharge of a solution formulation metered dose inhaler is simpler than for a suspension, but basic mechanisms are poorly understood. Clark (1991) favours aerodynamic shear thinning rather than flash atomisation as the mechanism of dispersion. Fig. 4 illustrates his analysis of discharge from valve through aperture to the atmosphere, shown part way through the process, at a point where flow into and out of the expansion chamber are equal and the pressure is at a maximum. It is clear that vapour pressure controls the generation of the two phases in the expansion chamber and the orifice diameter will influence rate of efflux. He concluded that the amount of fine particles in the spray would be inversely proportional to the orifice diameter and proportional to the square root of the pressure. In the studies reported here, the effect of actuator orifice diameter (Table 5), is largely to effect change in the fine particle dose because, as the diameter increases, the proportion of the delivered dose depositing in the throat increases. However, the MMAD of the material that enters the ACI does not show the expected increase associated with a general coarsening of the cloud. This may be explained if a larger amount of material expelled through the wider

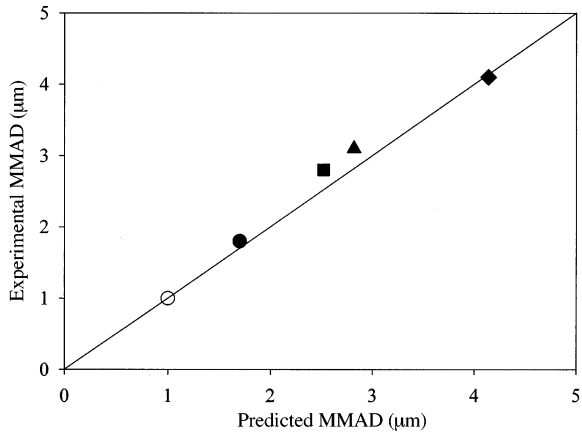

Fig. 3. Relationship between experimental and predicted MMAD values using Eq. (3) for BDP pMDI solution formulations in HFA 134a. Open symbols, 0.085% w/w BDP (base line value); closed symbols 0.424%w/w BDP; (——) theoretical slope (1.00).

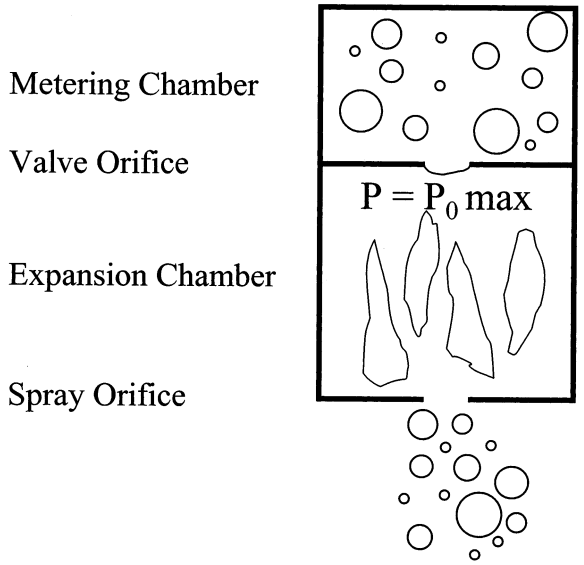

Fig. 4. Schematic for metered discharge from a solution pMDI (following Clark, 1991).

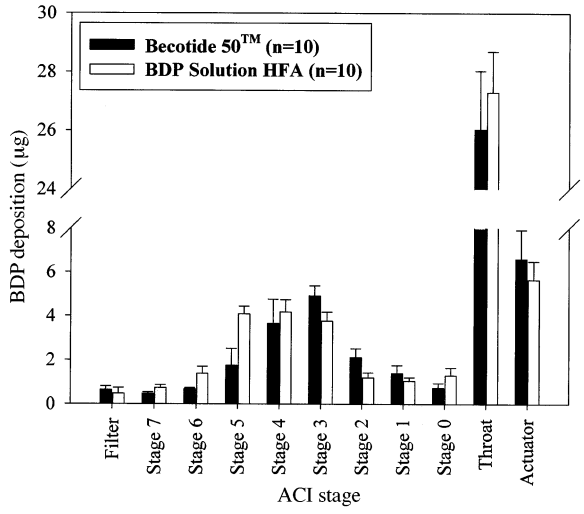

Fig. 5. Comparative ACI stage deposition from Becotide 50™ CFC suspension pMDI and BDP HFA 134a solution pMDI (metered dose 50 μg).

orifice is captured in the throat because of the high velocity of efflux. This ballistic effect would be less pronounced with small orifices. In both cases, the residual cloud entering the impactor is not greatly different in size. For the formulator matching a CFC product, the effect permits the variation of MMAD and fine particle dose in a largely independent manner.

With an actuator orifice chosen to minimise ballistic effects, the opposite effect can be secured by varying the internal pressure of the formulation. In this case, the fine particle dose can be sustained whilst the MMAD is modified. As shown in Table 6, use of the higher pressure HFA 134a propellant will promote greater shear thinning with the generation of a finer cloud. However, although coarser clouds are generated by the lower pressure resulting from the use of HFA 227, both clouds negotiate the entry conditions of the ACI with similar losses so that the fine particle dose is maintained.

If all the factors discussed above, non volatile components, actuator orifice diameter and choice of propellant are permuted, it becomes possible to create clouds with solution formulations which closely match the corresponding CFC suspension formulation currently in use. Matches of ACI distribution data for commercial formulations with HFA solutions are shown for BDP (Becotide 50™), budesonide (Pulmicort 200™), IPBr (Atrovent 40™) in Figs. 5–7, respectively. The solution formulations show close correspondence in deposition on the plates of the impactor to their com-

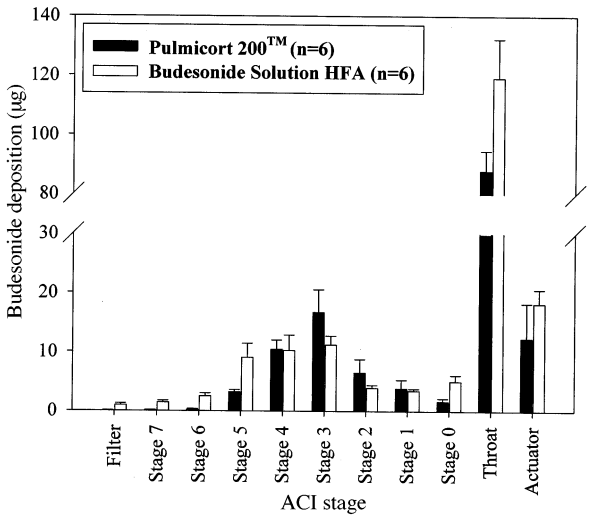

Fig. 6. Comparative ACI stage deposition from Pulmicort 200™ CFC suspension pMDI and budesonide HFA 134a solution pMDI (metered dose 200 μg).

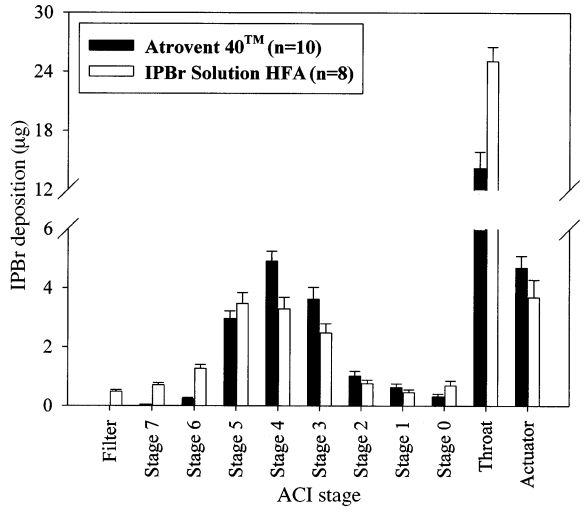

Fig. 7. Comparative ACI stage deposition from Atrovent 40™ CFC suspension pMDI and IPBr HFA 134a solution pMDI (metered dose 40 μg).

mercial counterparts. Assuming that the impactor and entry port configuration used reflects the balance between oro-pharyngeal deposition and delivery to the lung, such replacement formulations are likely to have similar patterns of in vivo deposition and to be bioequivalent. Substitution should therefore be possible without change of dose or clinical response thus giving a seamless transition from CFC to HFA based products.

References

Clark, A.R. 1991. Metered atomisation for respiratory drug delivery. Ph.D. Thesis Loughborough University of Technology, UK.

Herzka, A., Pickthall, J., 1961. Pressurised Packaging (Aerosols). Butterworth, London, pp. 167–169.

June, D., 1997. Achieving the change: challenges and successes in the formulation of CFC-free MDIs. Eur. Respir. Rev. 7, 32–34.

Leach, CL., Davidson, P., Boudreau, R., 1998. Improved targeting of the airways with CFC-free HFA-beclomethasone metered dose inhaler compared with CFC-beclomethasone. Respir. Med. 92(Suppl. A).

Moren, F., 1978. Drug deposition of pressurised inhalation aerosols II. Influence of vapour pressure and metered volume. Int. J. Pharm. 1, 213–218.

Newman, S.P., Moren, F., Pavia, D., Corrado, O., Clarke, S.W., 1982. The effects of changes in metered volume and propellant vapour pressure on the deposition of pressurised inhalation aerosols. Int. J. Pharm. 11, 337–344.

Polli, G.P., Grim, W.G., Bacher, F.A., Yunker, M.M., 1969. Influence of formulation on aerosol particle size. J. Pharm. Sci. 58, 484–486.