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Evaluation of a Novel Fluorosurfactant for Beclomethasone Dipropionate Pressurized Inhaler with HFA 134a as the Choice Propellant.

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The in-vitro performance of a novel fluorosurfactant was evaluated for a formulation of beclomethasone dipropionate pressurised inhaler with propellant HFA 134a. The fluorosurfactant is a non-ionic polymeric fluorinated alkly ester.

Formulations were prepared by adding 0.05g of beclomethasone dipropionate and between 0.001-0.20g of the fluorosurfactant into polyethylene clear plastic canisters, followed by 10ml of the propellant. Particle size characteristization was then performed by the Malvern particle sizer. A Twin Stage Impinger, operated at 60ml min^{-1}, was used to study deposition characteristics. HPLC assay was used to determine the drug recovered from the impinger stages.

A significantly higher ($P<0.05$) particle fraction of 46.30%, calculated as the amount of drug collected from stage 2 expressed as a percentage of the total drug in the stage 1 and 2 of the TSI, was obtained from the batch with surfactant concentration of 0.1% w/v. This compared with 34.45% for a commercial chlorofluorocarbon beclomethasone inhaler product. However, the mass median diameters (MMD) in both cases, as determined by the Malvern sizer instrument were 3.50μm.

The fluorosurfactant performs well as a dispersing agent for HFA beclomethasone inhaler as evidenced by the higher particle fraction. Optimization of the formulation should be done with propellant HFA 134a and 227. A solution system should also be explored.

Key words: Metered dose inhaler, Hydrofluoroalkanes, Flurosurfactant, Beclomethasone, Asthma

INTRODUCTION

The pressurized inhaler is a widely used device for the treatment of airway obstructive diseases such as asthma. Corticosteroid drugs such as beclomethasone dipropionate (BDP) are used for the prophylactic management of moderate to severe asthma and are commonly delivered by a pressurized inhaler (PI)[Freedman 1956, Global initiative for asthma 1995, Pauwels *et al* 1995].

A PI formulation generally consists of the active ingredient dissolved or suspended in a propellant in a suitable canister. The efficiency of drug delivery from a PI formulation depends on production of particles that are within the respirable range. Aerosols with a mass median diameter (MMD) of 3-5μm are considered optimal for delivery to the upper airways and small bronchi whereas a lower MMD of 0.8-3.0μm is optimal for treatment of parenchymal disease. Above 5μm, oropharyngeal deposition prevents significant amounts of drug reaching the lungs while particles with MMD of 0.8μm are exhaled (Aerosol consensus committee 1991). In order to meet this requirement, suspension based formulations should be stable and well dispersed. This necessitates the addition of a suitable surfactant to disperse and stabilize drug particles [Moren 1985, Bower 1995, Zelko 1997].

The impending phase-out of chlorofluorocarbon (CFC) propellants, which have been the propellants of choice for long, has necessitated the

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search for alternative propellants and a need to reformulate products that previously used CFC propellants. However, the two hydrofluoroalkane (HFA) compounds, HFA 134a and 227 developed, have different properties from CFC propellants. Reformulation has been difficult in relation to surfactants, valves and elastomeric seals. Surfactants used for CFC propellant formulations are immiscible in HFA propellants and therefore unsuitable for HFA products [Tansey 1995].

Particle size is the most important parameter in assessing the effectiveness of an aerosol formulation. This is usually performed using techniques based on the principle of inertial impaction. The Twin Stage Impinger (TSI), used in this study, was the first technique to be adopted by the British Pharmacopoeia. It divides the aerosol cloud into two fractions, with an effective cut-off diameter (ECD) of 6.4μm [Hallworth & Westmoreland 1987]. Although the ECD above is relatively large and can inflate estimates of fine particle fraction (FPF), the TSI is still a useful and convenient tool for aerosol formulation characterization. In addition, the wet stages of the TSI reduce particle re-entrainment, as in dry impaction systems and the humid environment closely approach lung conditions.

This study investigated the performance of a fluorosurfactant for formulation of a CFC-free HFA BDP MDI using HFA 134a as the propellant. The fluorosurfactant is non-ionic and chemically described as a polymeric fluorinated alkyl ester with a general formula $C_xF_{2y+1}(CH_2)_y(OC_2H_4)_zOH(C_{xy}H_z)$, where x ranges from 4-7, y 1-2 and z 4 or 6.

MATERIALS AND METHODS

Materials

Beclomethasone (micronized) from Chiesi Farmaceutici s.p.a, Palermo, Italy; Trichloro-monofluoroethane (HFA 134a) from Astra AV, SE151, Sweden; Methanol (HPLC grade) from Rathburn Chemicals Ltd., Walkerburn, Scotland Fluorosurfactant from M HealthCare Plc., UK; Polyethylene (PET) clear plastic canisters from Fluorchem Ltd., Derbyshire, UK; Microfilters (pore size 0.2μm) from Whatman, UK; MDI valves, HFA compatible from Bespak Plc., UK; MDI actuator adapters from Allen and Hanburys, UK.

Methods

Particle Size Analysis of BDP Powder

The MMD of beclomethasone was determined by the Malvern Sizer Instrument (MSI) (Malvern Instruments Co., Worcestershire, UK). For analysis, a background solution was prepared by dispersing about 0.025mg of beclomethasone in 1ml of Tween 80 or 1g of the fluorosurfactant and diluting the resulting mixture to 100ml with distilled and de-ionized water. The dispersion was sonicated for 30 min. The solution obtained was filtered with a microfilter (pore size 0.2μm). Size characteristics were obtained by adding about 0.005g of BDP to the background solution above and sonicating the dispersion for a further 30min. The obtained dispersion was pipetted into the MSI cell and placed in the helium-neon laser beam of the MSI. Results (n=6) were obtained with the help of an IBM-compatible computer integrated with the MSI particle size characterization software.

Preparation of HFA MDI Samples (50μg per actuation)

Samples were prepared by adding 0.05g of BDP and the fluorosurfactant (0.01-2.0% w/v) into polyethylene clear plastic canisters. Prior to charging with the propellant, each canister and contents were briefly chilled in liquid nitrogen and the valve assembly loosely attached. About 2ml of the propellant was added and the canister gently swirled to expel any trapped air. The valve was then quickly crimped in place with a crimping machine (Pamasol, Essex, UK). Canisters were finally charged with 10ml of the propellant by means of a propellant-filling machine (Pamasol, Essex, UK). Samples prepared were shaken for 30 min to disperse the drug and surfactant, appropriately labeled and secured into actuator adapters.

Particle size analysis of HFA MDI samples

The MMD and size distribution of HFA MDI samples were also determined by the MSI. For

analysis, each sample was shaken for 30 sec and discharged twice to waste. The sample was again shaken for 30 sec and fired in the laser-neon laser beam of the MSI. For firing consistency, a special actuating device (in-house) consisting of a timer, transducer and a mechanic actuating element was used. Results (n=6) were obtained from measurements taken at time-delays between 10ms and 150ms with obscuration values above 0.160%.

Fine Particle Fraction (FPF) of HFA MDI and Commercial CFC MDI Samples

A Twin Stage Impinger (TSI), BP 1993, apparatus A) was used to determine the FPF of MDI samples. Airflow was adjusted to 60±l/min. The FPF, calculated as the amount of BDP that deposits on stage 2 of the TSI expressed as a percentage of the total drug in the impinger, was then determined using the BP 1993 protocol, with 7ml of the washing solution (30:70, methanol: water) in stage 1 and 30ml in stage 2.

The total drug output (TDO) from the MDIs and drug depositing on the actuator were also determined. The TDO was determined from an average of 10 discharges of the MDI fired into a 100ml beaker containing 25ml of the washing solution, while the amount on the actuator was determined from an average of 10 discharges fired to waste.

MDI samples were individually primed by shaking for 30s and discharging twice to waste. Subsequent firings were done after MDI had been shaken for a further 30s. All rinsings were individually transferred into 100ml volumetric flasks, made to volume with the washing solution, sealed with paraffin film paper and stored under refrigeration pending analysis.

Assay

HPLC assay was used to determine the content of BDP in the solutions collected. The chromatographic parameters were as follows:

System: Milton Ray, LDC Analytical, Column: Waers, Bondapak C_{18}, Flow rate:0.800ml/min, Pressure: 975 p.s.i, Temperature: ambient, Injection volume: 100µl, Detection:, UV, at 276nm, Mobile phase: Methano:water, (30:70v/v),sonicated and de-gassed with Neon/Nitrogen prior to use.

A five-point calibration curve (R^2=0.9995) was obtained with BDP working standards of concentration ranging from 0.05 mg% - 0.6 mg%.

RESULTS

The particle size distribution of BDP powder was found to be log-normal distributed with an MMD of 3.57µm (SD 0.20) and 3.50µm (SD 0.15) when Tween 80 and the fluorosurfactant respectively were used as the dispersants. The fluorosurfactant achieved a significantly ($P<0.05$) lower MMD than Tween 80.

Table 1 below shows the respective amounts of drug recovered from the different stages, the respirable fine particle fraction (FPF) and the mass median diameter for both HFA and CFC pressurized inhalers. Amount of drug that deposited on the actuator was on average higher for HFA formulations (mean 6.57%, SD 1.34) than CFC formulations (mean 4.69% SD 1.27). Furthermore, the amount depositing on the actuator for HFA formulations generally decreased with an increase in the surfactant The results for FPF, TDO, amount of drug that deposited on stage 1, stage 2 and the actuator as obtained from the TSI, as well as the results for the MMD of samples as determined from the MSI are shown in table 1.

All MDI were 50µg/actuation type. Results show drug recovered from a Twin stage impinger and mass median diameter (MMD) determined from a Malvern sizer. Deposition on actuator, stage 1 & 2 are expressed as a percentage of the total drug output (TDO) from inhalers, while the Fine particle fraction (FPF) is calculated from the fraction of the drug deposited on stage 2 as a percentage of the total amount of drug deposited on stage 1 and 2. Each value was an average of six determinations (±SD).

Table 1

FORMULATION		% DEPOSITION				
Code	Surfactant Conc.% w/v	Actuator	Stage 1	Stage 2	FPF	MMD
1	0.01	8.52 (3.07)	36.33 (0.87)	32.13 (5.89)	46.90	3.28 (0.78)
2	0.10	7.23 (1.90)	34.52 (2.07)	32.56 (2.68)	48.53	3.35 (0.46)
3	1.00	6.25 (2.12)	54.56 (3.49)	26.77 (3.61)	32.91	5.88 (1.40)
4	1.50	5.75 (1.19)	58.89 (3.07)	25.45 (1.08)	30.18	6.18 (1.18)
5	2.00	5.10 (0.74)	60.29 (6.69)	25.20 (0.83)	29.50	7.10 (0.73)
CFC		4.69 (1.27)	59..90 (2.76)	28.48 (2.76)	32.22	-

Table 1. *In vitro characteristics of HFA beclomethasone metered dose inhalers (MDIs) and CFC beclomethasone MDI.

Figure 1 is a bar chart plot showing a comparison of these results and those of commercial CFC samples investigated at the conditions as HFA samples.

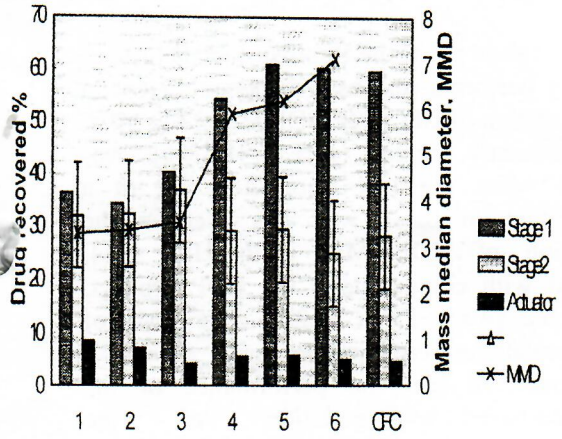

Fig. 1. Drug recovered from stage 1 and 2 of a Twin stage impinger and the actuator device for HFA BDP samples compared with a CFC BDP MDI (CFC) and the corresponding mass median diameter (MMD) in μm, as measured by a Malvern sizer. Error bars refer to standard deviation (SD) for n=6.

Figure 2a shows the relationship between the surfactant concentration and FPF.

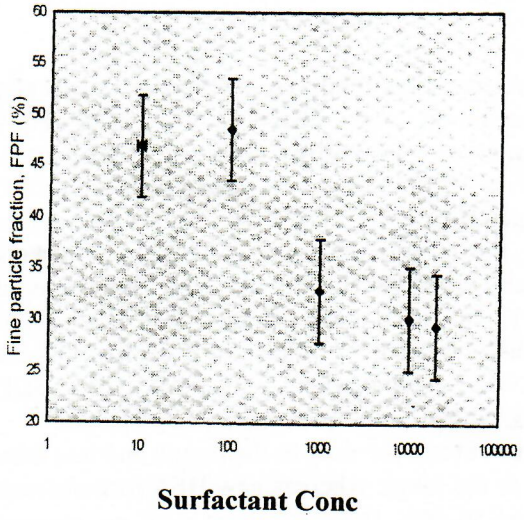

Fig 2a. The effect of surfactant concentration on the fine particle fraction (FPF) . The highest FPF is obtained at surfactant concentration of 0.1% w/v. Increase in surfactant concentration results into decrease of FPF achieved. Error bars (n=6) refer to standard deviation SD.

Figure 2b shows the relationship between surfactant concentration and MMD.

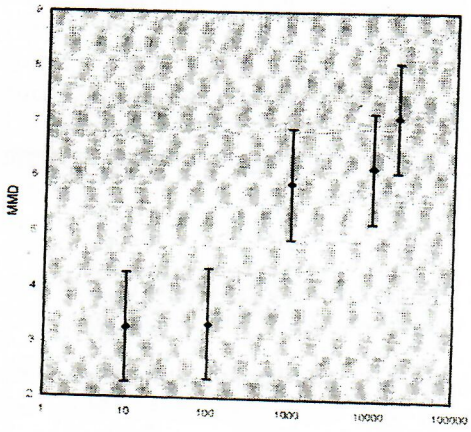

Fig 2b. The effect of surfactant concentration on the mass median diameter (MMD). The lowest MMD is obtained at surfactant concentration of 0.1% w/v. Increase in surfactant concentration results into increase of MMD achieved. Error bars (n=6) refer to standard deviation SD.

DISCUSSION

The results show that, except where the surfactant concentration was above 1.50% w/v, HFA formulations generally achieved significantly higher FPF (32.91-48.53%) compared with CFC products (32.22%). These results actually agree with those reported earlier by other workers (Leach *et al* 1998, Busse *et al* 1999, Harrison *et al* 1999) that have demonstrated that HFA BDP formulations achieve higher FPF compared with CFC BDP formulations. In vivo, CFC BDP MDIs, with an average particle size of 3.5μm, deliver 90% of the drug to the mouth and less than 10% to the lungs, whereas new HFA formulations deliver 50-60% (FPF <4.7μm) with an average particle size of 1.1μm of the drug to the lungs and 30% to the mouth (Leach *et al* 1998). This pattern is attributed to more physically stable formulations typical of new solution-based HFA BDP formulations. Consequently, compared to suspension-based CFC products, solution based HFA formulations deliver the drug in a more consistent manner. HFA formulations also have higher vapour pressures. (Williams *et al* 1998).

The high respirable fraction, however, results in more BDP depositing in the alveoli than the airways. This necessitates a 50% dose reduction for patients switching from a CFC-BDP to HFA BDP MDI. From a patient perspective, a 1:1 switch would be simpler and probably more preferable to a half dose switch. In addition, as deposition of BDP with new HFA BDP MDI is more in the alveoli than the airways, this may result in systemic absorption, with the drug bypassing the relevant site of action. This may be critical, since asthma is a disease of the airways rather than the alveoli.

This study shows that the fluorosurfactant performs well as a dispersing agent for HFA formulations. At a surfactant concentration of 0.1%w/v , the highest FPF of 48.53% with an MMD of 3.52μm is achieved. This is higher than the FPF achieved with CFC-BDP inhalers, but not sufficiently high to produce less desired alveolar deposition typical of HFA BDP products currently being marketed.

CONCLUSION

It has been shown that the fluorosurfactant used in this study performs well as a dispersing agent in the formulation of CFC-free BDP HFA134a MDI. A significantly higher FPF (48.53%) was achieved when the test fluorosurfactant at a concentration of 0.1% w/v was used in the formulation of BDP MDI with HFA 134, compared with commercial CFC BDP product, which achieved an FPF of 32.22%. The MMD of both formulations were however comparable.
We recommend that the performance of the suspension-based formulation of the fluorosurfactant be further optimized by varying the propellant composition using HFA 134a and 227. The feasibility of formulating a solution system with the test surfactant should also be explored.

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