The Performance of Opt2Fill® Propellant Dispersible Tablet pMDI Formulations of Salbutamol Sulphate and Salbutamol Sulphate with Beclometasone Dipropionate in HFA 134a and HFA 152a.

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Summary

Opt2Fill® tablets are novel propellant dispersible tablets for the manufacture of pressurised metered dose inhalers (pMDIs). This study has investigated salbutamol sulphate (SS) formulated as Opt2Fill tablets using inhalation lactose and menthol as excipients. The SS Opt2Fill tablet pMDI formulations were evaluated in two propellants, HFA 134a and HFA 152a. A combination formulation of SS with beclometasone dipropionate (SS/BDP) in Opt2Fill tablets was also investigated using HFA 134a and HFA 152a which also contained ethanol to ensure that the BDP was in solution. HFA 152a has a global warming potential that is approximately 10-fold less than HFA 134a and thus, in the light of increasing environmental regulation of fluorine containing gases, is being considered as an alternative propellant. Next Generation Impactor data showed that high quality aerosols, with fine particle fractions (FPF's, %< 5.0 µm, emitted dose) for SS and BDP in excess of 60% can be generated from both SS and SS/BDP Opt2Fill tablet pMDI formulations using either HFA 134a or HFA 152a as propellant. The FPF's are significantly higher than the currently marketed SS products, Ventolin® and Airomir® and not inferior to the BDP marketed product, QVAR® 50. Differences in the physical properties of HFA 134a and 152a did not significantly influence aerosol performance in terms of FPF or mass median aerodynamic diameter (MMAD) for the Opt2Fill SS formulations. There were however some small but statistically significant differences in the FPF and MMAD of Opt2Fill SS/BDP formulations in HFA 134a and HFA 152a containing ethanol.

Introduction

This study was conducted to characterise pMDI formulations prepared using propellant dispersible (Opt2Fill®) tablets. This novel manufacturing approach is being investigated as an alternative to 'traditional' single-stage and two-stage pMDI filling processes and the associated challenges which include drug losses by adsorption onto filling lines and pressure vessels, sensitivity to product flow and pressure variations, and suspension concentration due to propellant losses into pressure vessel headspace. In addition, stability issues may arise during two-stage filling processes as a consequence of partial drug solubility in excipients such as ethanol. Many of these problems, i.e. drug losses and suspension homogeneity also apply to cold filling processes with additional issues related to possible condensation / moisture inclusion.

In this study aerosol assessments of Opt2Fill tablet pMDI formulations were performed following formulation in two different propellants, HFA 134a and HFA 152a. HFA 152a is being considered as a potential replacement for existing HFA propellants in the light of more stringent environmental regulation of fluorine-containing gases. HFA 152a has a boiling point of -24.7°C, and at 25°C, a density of 0.91 g/mL and vapour pressure of 4.99 barg compared with values for HFA 134a of - 26.9°C, (and at 25°C) 1.22 g/mL and 5.65 barg[1]. HFA 152a has a 10-fold lower global warming potential than the commonly used medicinal HFA propellants. Switching to the use of HFA 152a would reduce the pMDI product carbon footprint, making it comparable to a typical dry powder inhaler[1].

Opt2Fill dispersible tablet formulations contain active pharmaceutical ingredient(s) (API's) a dispersant e.g. menthol, and an inert carrier e.g. inhalation lactose. Some examples of proof of concept formulations in HFA 134a have been described previously[2, 3]. In this study Opt2Fill tablets were formulated to produce different types of pMDI formulation: a suspension pMDI of salbutamol sulphate (SS); and a combination pMDI of SS (in suspension) with beclomethasone (BDP) (in solution). The SS Opt2Fill tablets were formulated in HFA 134a and HFA 152a and comparisons are made. The SS/BDP Opt2Fill tablets were formulated in HFA 134a and HFA 152a both with ethanol as co-solvent for the BDP. Further comparisons are also made with marketed HFA 134a pMDI products containing a single API: Ventolin® and Airomir® for SS; and QVAR® for BDP.

Methods and Materials

Powder blends were prepared containing the APIs i.e. either micronised SS (Jayco Chemical Industries Ltd, India) (d_{50} 2.16 µm) or micronised SS with non-micronised BDP (Farmabios SpA, Italy) with the excipients; menthol (Sigma Aldrich, UK) and commercial inhalation grade α-lactose (Lac) monohydrate (Respitose SV003, DFE-Pharma, Germany). Blending was performed using low shear mixing (Turbula® Mixer, Wiley A, Bachofen AG, Switzerland). The ratio of SS:Lac was 1:1.5 in both the SS and SS/BDP tablets. The BDP:Lac ratio was 1:1.36 in the SS/BDP tablet. Menthol, a propellant soluble excipient, was incorporated into both tablet formulations such that the final concentration was 0.10% w/w in HFA 134a and 0.13% w/w in HFA 152a pMDIs.

Prior to tabletting the Opt2Fill powder blends were quantitatively sampled to determine the content uniformity for each of the APIs. Following satisfactory content uniformity tests, tablets were manufactured using a RIVA Minipress MII single punch tabletting machine (RIVA, Argentina) fitted with a 6 mm diameter round flat bevelled edge punch. The tablet machine was operated with a compression force not exceeding 60 kN, to produce tablets weighing approximately 90 mg (for SS tablets) or 100 mg (for SS/BDP tablets). Following production, samples of tablets were taken to determine the content of each API.

Single tablets were dispensed into plain aluminium canisters (19 mL, Presspart Manufacturing Ltd, UK). Additionally, tablets were added to clear polyethylene terephthalate (PET) vials in order to visualise disintegration/dispersion of the tablets. For the SS formulations, a metering valve (50 µL, Kemp KHFA, VARI, SpA Italy) was crimped and HFA 134a or HFA 152a was immediately added. For the SS/BDP formulations, ethanol was present at 5% w/w in HFA 134a and 4% w/w in HFA 152a. For these formulations, the required quantity of ethanol was carefully added to each container so as to minimise contact with the tablet. The metering valve (as above) was crimped and HFA 134a or HFA 152a was immediately added. Filled canisters were stored inverted, for at least two days quarantine at ambient temperature and humidity prior to testing.

Dispersion of the tablets was visually assessed by conducting hand shaking of the formulations prepared in clear PET vials to establish a standardised procedure. In brief, the procedure involved the inverted cans being shaken vertically through approx. 6 inches at a frequency of approximately 15 shakes in a five s period. This process was repeated twenty times. After completing the shaking procedure the cans were primed by firing 4 actuations to waste.

The Aerodynamic Particle Size Distribution (APSD) was determined by inertial impaction testing using the Next Generation Impactor (NGI) at a flow rate of 30 L/min. Five canisters of each formulation were tested using actuators with a 0.25 mm orifice diameter (VARI SpA, Italy). For each determination, five actuations were fired into the NGI and quantitatively recovered. The marketed reference products; Ventolin, Airomir and QVAR were also evaluated using three canisters with five actuations per determination.

Analyses of SS and BDP were conducted by validated high-performance liquid chromatography methods. For SS (from SS Opt2Fill, Ventolin and Airomir pMDIs) a Genesis C18, column (4.6 x 150 mm, 4 µm, Hichrom, UK), with a flow rate of 1.0 ml/min (40% methanol v/v), a 30 µl injection volume, with UV detection at 278 nm, was used. The retention time of SS was 6.0 min. For SS and/or BDP (from SS/BDP Opt2Fill and QVAR pMDIs) a Waters Sphersiorb S5ODS2, column (4.5 x 250 mm, 5 µm), with a flow rate of 1.0 ml/min (75% methanol v/v), a 100 µl injection volume, with UV detection at 276 nm, was a used. Retention times of SS and BDP were 5.7 and 9.1 min.

Results

The powder blends showed good content homogeneity for all formulations, with relative standard deviations (RSD's) between 0.8% and 1.1% (n=5). Following manufacture of Opt2Fill tablets, content uniformity of the API's was also high with RSD's between 0.4% and 1.5% (n=5).

Images of propellant filling into PET vials containing Opt2Fill tablets were digitally recorded and tablets were shown to rapidly disintegrate in both HFA 134a and HFA 152a, for both Opt2Fill SS and Opt2Fill SS/BDP pMDIs. An example, using an Opt2Fill SS tablet in HFA 134a is shown in Figure 1. The times indicated are relative to the start of propellant addition, whilst propellant filling took approximately 1 s. Further disintegration of tablet fragments were noted to occur during storage over two days at room temperature.

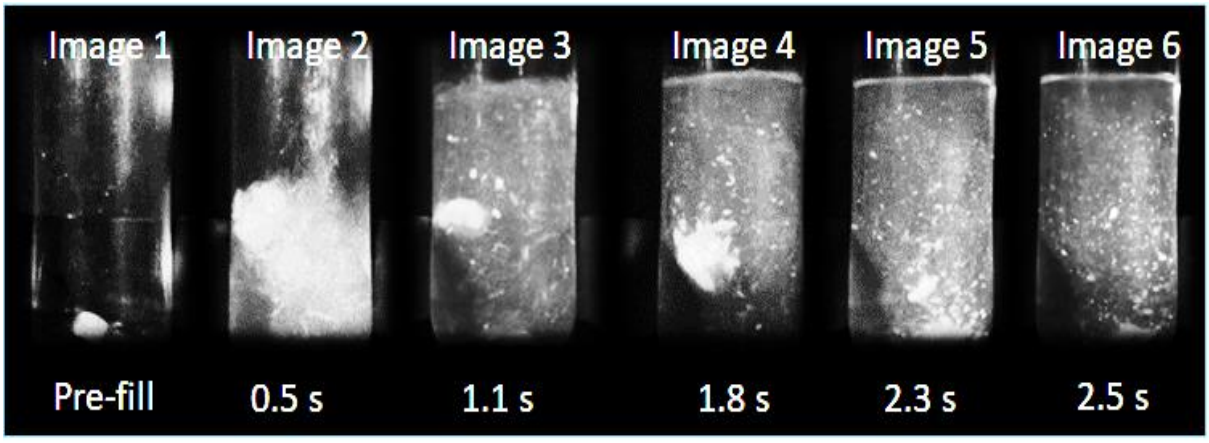

Figure 1. Images Taken During Propellant HFA 134a Filling of a PET Vial Containing an SS Opt2Fill Tablet.

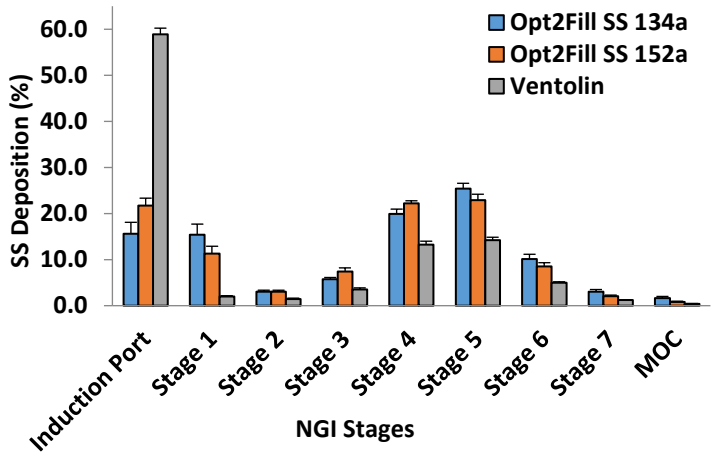

Figure 2. Aerodynamic Particle Size Distribution (%) of SS from Opt2Fill SS in HFA 134a and HFA 152a (Mean ± SD, n=5) and Ventolin (Mean ± SD, n=3).

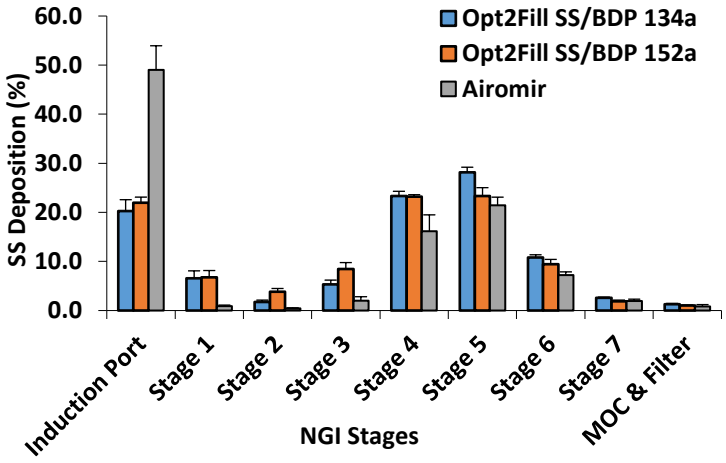

Figure 3. Aerodynamic Particle Size Distribution (%) of SS from an Opt2Fill SS/BDP in HFA 134a and HFA 152a (Mean ± SD, n=5) and Airomir (Mean ± SD, n=3).

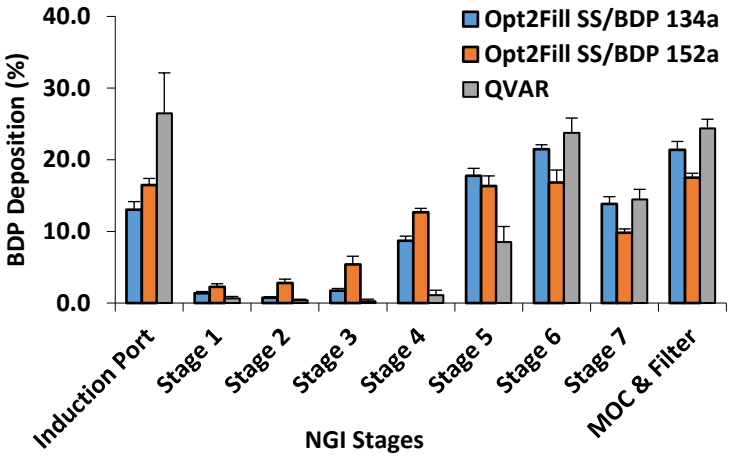

Figure 4. Aerodynamic Particle Size Distribution (%) of BDP from an Opt2Fill SS/BDP in HFA 134a and HFA 152a (Mean ± SD, n=5) and QVAR (Mean ± SD, n = 3).

Aerosol particle size distributions (APSD's) from NGI analysis of SS Opt2Fill and Ventolin pMDIs are shown in Figure 2. The deposition profiles from the Opt2Fill preparations were highly comparable between the HFA 134a and HFA 152a formulations with the largest amounts (i.e. approximately 45% of the emitted doses) of SS associated with deposition on Stages 4 and 5 of the NGI. In comparison with the marketed Ventolin formulation, it can be seen that the largest difference between the three formulations is deposition on the Induction Port. The Opt2Fill formulations showed significantly lower amounts of 16% (for Opt2Fill SS 134a) and 22% (for Opt2Fill SS 152a) compared with 59% for Ventolin. In contrast, the results for Stage 1 deposition show significantly smaller amounts for Ventolin. Combining the Induction Port, Stages 1 and 2, to provide estimates of the likely extra-thoracic deposition still highlights lower percentages for the Opt2Fill formulations, i.e. 34% (for Opt2Fill SS 134a) and 36% (for Opt2Fill SS 152a) compared with 62% for Ventolin.

APSD's from NGI analysis of SS from SS/BDP Opt2Fill and Airomir pMDIs are shown in Figure 3. The deposition profiles from the two Opt2Fill formulations were highly comparable but were observed to differ from the marketed Airomir formulation with respect to significantly lower Induction Port deposition. Within the impactor the drug recovery patterns were most similar to Airomir in the smaller particle size range, i.e. Stages 5 - Micro-Orifice Collector (MOC) & external filter.

Figure 4 shows the APSD profiles for BDP from HFA 134a and HFA 152a Opt2Fill formulations and the marketed BDP formulation (QVAR). As expected for BDP, which is in solution, a large fraction of the drug was recovered from the lower stages of the impactor, i.e. Stages 5 - 7 and the MOC & external filter for all formulations. The novel Opt2Fill formulations showed reduced Induction Port deposition compared to QVAR and greater deposition on Stages 1 – 5, whilst recovery from Stages 6 – MOC & external filter was similar for all three formulations.

The results of NGI evaluations are summarised in Table 1. FPF values for the Opt2Fill SS pMDIs were in excess of 60% and were not significantly different when formulated with either HFA 134a or HFA 152a. The FPF of Ventolin was however significantly lower achieving only around 60% of the performance seen with Opt2Fill SS pMDIs.

Table 1. Summary of Key Aerosol Parameters for SS and BDP from Opt2Fill pMDIs (Mean (SD); n=5) & Marketed Comparators Ventolin and QVAR (Mean (SD); n=3).

	Opt2Fill SS		Ventolin	Opt2Fill SS/BDP		Airomir
	HFA 134a	HFA 152a		HFA 134a	HFA 152a	
SS: FPF (% < 5 µm)	63.04 (3.25)	60.26 (1.56)	36.01(1.43)	68.88 (2.05)	63.35 (2.56)	48.80 (4.55)
SS: MMAD (µm)	2.45 (0.16)	2.58 (0.14)	2.28 (0.02)	2.19 (0.07)	2.47 (0.12)	2.00 (0.12)
SS: GSD	2.15 (0.37)	2.08 (0.05)	1.67 (0.02)	1.69 (0.02)	1.91 (0.13)	1.57 (0.01)
				Opt2Fill SS/BDP		QVAR
				HFA 134a	HFA 152a	
BDP: FPF (% < 5 µm)				84.08 (1.11)	76.05 (2.22)	72.36 (5.93)
BDP: MMAD (µm)				1.00 (0.04)	1.27 (0.05)	0.78 (0.05)
BDP: GSD				2.17 (0.05)	2.59 (0.21)	2.05 (0.30)

The FPF of SS in Opt2Fill SS/BDP pMDIs (containing EtOH) also exceeded of 60%; Opt2Fill SS/BDP134a was significantly greater than Opt2Fill SS/BDP 152a and both Opt2Fill formulations were significantly greater than Airomir. However, the Opt2Fill SS/BDP 152a achieved a FPF in excess of 90% of the Opt2Fill SS/BDP 134a, whilst the Airomir performance was only 71% of the Opt2Fill SS/BDP 134a. There were significant differences in some MMAD's for SS between the EtOH-containing and EtOH-free formulations, however the range of MMAD's was not large and this is reflected in the broadly similar NGI deposition profiles in Figures 2 and 3.

FPF values for BDP in the Opt2Fill SS/BDP and QVAR pMDIs were all in excess of 70%, with the Opt2Fill SS/BDP 152a was significantly different from the Opt2Fill SS/BDP 134a, but not from QVAR. The MMAD values for BDP in both Opt2Fill pMDIs were significantly higher than QVAR.

Discussion and Conclusion

This study clearly demonstrates proof of concept of the Opt2Fill dispersible tablet approach as a novel manufacturing method for pMDIs. The in vitro performance of the aerosols generated from the dispersible Opt2Fill tablets using both HFA 134a and HFA 152a propellants illustrates that high quality aerosols were generated and were not significantly different between the propellants. The Opt2Fill formulations were prepared using standard hardware components i.e. plain aluminium canisters and metering valves as well as excipients which are used in other inhalation formulations. The tablets were found to readily disintegrate during propellant filling with HFA 134a and also with HFA 152a. Complete dispersion, in both propellants, was achieved by a short quarantine period and subsequent hand shaking.

Propellants HFA 134a and 152a differ in terms of vapour pressure, density and solvency power, however aerosols generated from the suspension Opt2Fill SS performed highly efficiently in both systems. The inclusion of EtOH in the SS/BDP combination products also did not greatly influence SS aerosol performance. In contrast, the BDP MMAD values from Opt2Fill SS/BDP pMDIs were significantly greater than those of QVAR. This may be a consequence of some propellant droplets from the combination formulations containing both particulate SS and dissolved BDP and thus co-deposition of BDP and SS may have occurred thereby increasing the apparent particle size characteristics of the BDP. A shift in the BDP deposition pattern away from ultrafine particles of QVAR might be expected to result in reduced exhaled drug.

The Opt2Fill formulations reported here are non-optimised in terms of excipients (Lac, menthol and EtOH). Alterations of SS:Lac ratios and lactose particle size may be used to modify performance as reported previously for Opt2Fill powder formulations in HFA 134a[4].

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Acknowledgements

The authors thank the following companies for their generous provision of materials, as follows: Mexichem UK Ltd – HFA 134a and HFA 152a; VARI SpA – metering valves; H&T Presspart – canisters; DFE-Pharma – lactose monohydrate.