Opt2Fill™Dispersible Tablet – A Novel Method for the Manufacture of pMDIs

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Summary

Manufacture of suspension-type pressurised metered dose inhalers (pMDI) requires judicious in-process homogenization and agitation to ensure homogeneity of suspended drug(s) and accurate and reproducible canister filling. In this study, the aerosol characteristics of pMDIs manufactured by the addition of propellant dispersible tablets (Opt2Fill™ tablet) to pMDI canisters prior to the addition of HFA134a/ethanol blend was assessed. The tablets contained a combination of salbutamol sulphate (SS) and beclometasone dipropionate (BDP), a dispersant (menthol) and lactose. Each tablet weighed approximately 90 mg and contained sufficient drug for 200 metered doses each containing 120 µg of SS and 50 µg of BDP. The aerosol particle size distributions (PSD) of the Opt2Fill™ products were compared with marketed formulations containing either SS or BDP, i.e. Airomir® and QVAR® 50. The PSD characteristics clearly demonstrated effective dispersion of the Opt2Fill™ tablets with fine particle fraction (FPF) properties similar to the comparators. The PSD of Opt2Fill™ products showed acceptable pMDI performance from a solid dosage form consisting of two drugs of differing physicochemical properties, i.e. one insoluble, one soluble. It is proposed that this technology can overcome some of the challenges commonly encountered during conventional single stage and two-stage pMDI filling processes. Dispensing the solid dosage form into the canister simplifies in-process checks and eliminates the requirements for homogenisation / recirculation of suspension systems and the need for large pressure vessels. Cleaning processes between products can also be greatly simplified. Batch sizes can be readily varied and scaled ensuring process continuity from pilot batches to large commercial batches.

Introduction

Suspension-type pMDI formulations require judicious in-process homogenisation and agitation controls during manufacture to ensure reproducible canister content uniformity. Both single-stage and two-stage pMDI filling processes have other associated challenges in addition to homogeneity issues. These may 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. The objective of this study was to evaluate the novel manufacturing method of adding the active pharmaceutical ingredients API(s) to the aerosol container in the form of a propellant dispersible tablet (Opt2Fill™ tablet), prior to addition of propellant [1], thereby circumnavigating the challenges described above. Opt2Fill™ tablet formulations contained API and optionally a dispersant e.g. menthol and an inert carrier / bulking agent e.g. lactose. The propellant dispersible tablets were formulated to produce a combination product containing a micronised suspended API (SS) and a non-micronised soluble API (BDP). Aerosol characterisation tests were conducted to compare the novel formulation with the performance of marketed reference products. Previous studies have shown that Opt2Fill™ powders can be used to effectively formulate suspension pMDI products [2].

Methods

Micronized SS (Jayco Chemical Industries Ltd, India) (d_{50} 1.94 µm) and unmicronized BDP (Farmabios SpA, Italy) and were blended together by low shear mixing (Turbula® Mixer, Wiley A, Bachofen AG, Switzerland) with commercial inhalation grade α-lactose monohydrate (Respitose SV010, DFE-Pharma, Germany) (d_{50} 112 µm) previously coated with 1% (w/w) menthol (Sigma-Aldrich, UK). The final powder blend contained approximately 12% (w/w) SS:Lactose and 5% (w/w), BDP:Lactose.

The powder blends were used to produce SS/BDP Opt2Fill™ tablets. Tablets were produced on a single punch tablet machine (RIVA Minipress MII, Argentina) using a 6 mm round flat bevelled edge punch operating with a compression force not exceeding 60 kN to produce tablets weighing approximately 90 mg for a formulation calculated to produce metered doses of 120 and 50 µg for SS and BDP respectively. In addition, uncompressed SS/BDP blended with 1% (w/w) menthol coated lactose powders (Opt2Fill™ powder) were produced.

Single Opt2Fill™ tablets or appropriate amounts of Opt2Fill™ powder were dispensed into either plain aluminium aerosol canisters (Presspart Manufacturing Ltd, UK) or polyethylene terephthalate (PET) vials (19 mL, Createchnic, Germany). Appropriate volumes of pre-mixed 5% (w/w) absolute ethanol in propellant HFA 134a were cold transferred to the containers, which were crimp sealed with Kemp KHFA 50 µL metering valves (VARI SpA, Italy). Containers were shaken and briefly sonicated, in order to ensure full dissolution of the BDP. Canisters were then stored for a minimum of two days quarantine at ambient temperature / humidity prior to testing. Using actuators with 0.25 mm orifice diameters aerosol PSD, was determined via the next generation impactor (NGI) at a flow rate of 30 L/min. The dose characteristics and PSD of the Opt2Fill™ tablet and Opt2Fill™ powder formulations were compared with two marketed reference products i.e. a suspension SS pMDI Airomir® (Teva, UK Ltd.) and a solution BDP pMDI QVAR® 50 (Teva, UK Ltd.). Analyses of SS and BDP were conducted by validated high-performance liquid chromatography (HPLC).

Briefly, following deposition from the pMDI, SS/BDP were quantitatively recovered from NGI components in 80% methanol:water. The actuator, induction port (IP) and collection cups were recovered with 25, 50 and 10 mL respectively. HPLC analysis was performed using a Waters Sphersiorb S5ODS2, column (4.5 x 250 mm, 5 µm), at a flow rate of 1.0 ml/min (75% methanol v/v), 100 µl injection volume, UV detection at 276 nm.

Results

The measured content uniformity of the Opt2Fill™ tablet and Opt2Fill™ powder formulations were consistent, with RSD values below 2 % (data not shown). Figure 1 shows an example of an Opt2Fill™ tablet prior to 5% ethanol/HFA 134 addition and following agitation and brief sonication.

Figure 1. Photographs of a SS/BDP Opt2Fill™ tablet prior to 5% ethanol/HFA134a addition and following dispersion.

The key aerosol characterisation results are presented in Table 1. i.e. fine particle fraction (FPF) (% < 5 µm), mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD). The data showed broad similarities in aerosol characteristics between the non-optimised experimental formulation and the appropriate marketed comparator products.

Table 1. Aerosol particle size distribution of SS and BDP from Opt2Fill™ Powder and Tablet formulations compared to Airomir® and QVAR 50®.

	Opt2Fill™ Powder	**Opt2Fill™ Tablet**	**Airomir®**	**QVAR 50®**
SS FPF (% < 5 µm)	43.02	48.47	48.80	
SS MMAD (µm)	3.23	3.49	2.00	
SS GSD	1.77	1.80	1.57	
BDP FPF (% < 5 µm)	70.70	68.90		72.96
BDP MMAD (µm)	1.11	1.50		0.72
BDP GSD	3.95	2.95		1.96

The aerosol particle size distribution from NGI analysis of the formulations for SS and BDP are shown in Figures 2 and 3 respectively. The distribution profiles were broadly similar for each test formulation and the appropriate reference product. Inspection of the SS profile shows there was a trend for reduced IP deposition for the test formulations compared to Airomir®, this trend was reversed on Stage 1, consequently overall the total combined fractions on IP and Stage 1, were similar. On Stages 3 to Filter the test formulations deposition tended to be shifted to the left, relative to Airomir®, indicating a larger particle size distribution within the 'respirable range'.

Inspection of the BDP profile shows there was similar IP deposition for the test formulations compared to QVAR®. Very little BDP was recovered from Stages 1 – Stage 4 for QVAR® with the majority of the drug recovered from Stage 5 – Filter. For the test formulations BDP was evenly distributed over Stages 3 to Filter.

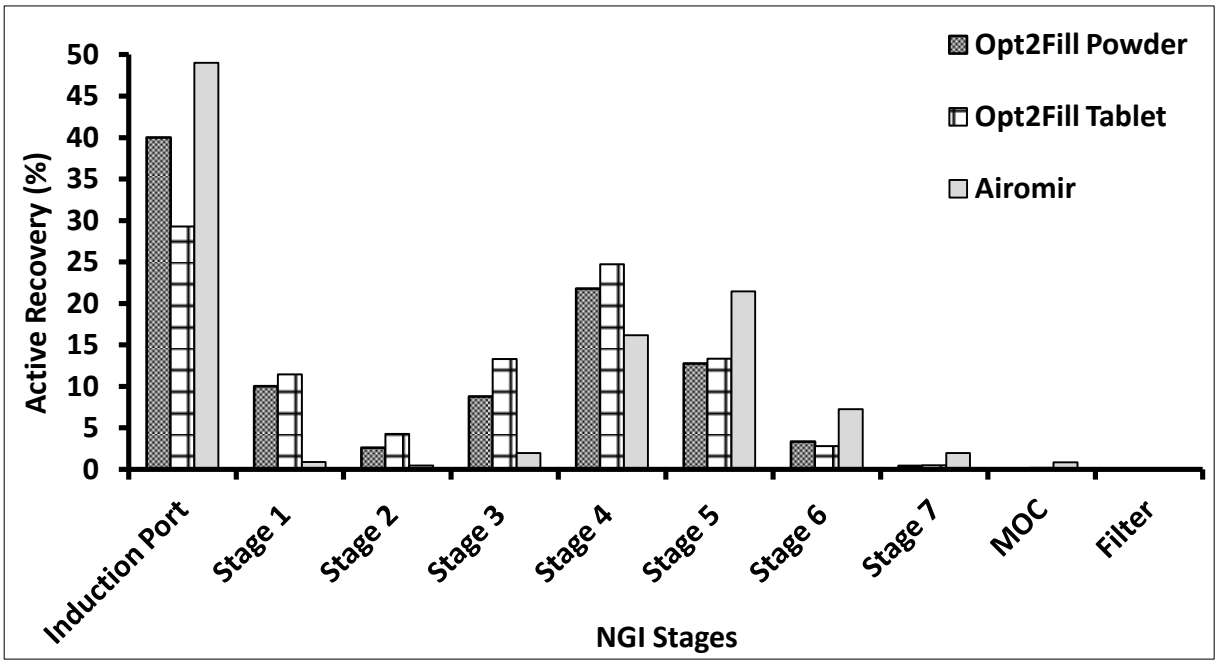

Figure 2. Aerosol particle size distribution of SS from Opt2Fill SS/BDP tablet and powder pMDI formulations compared to Airomir® using the NGI at 30 L/min.

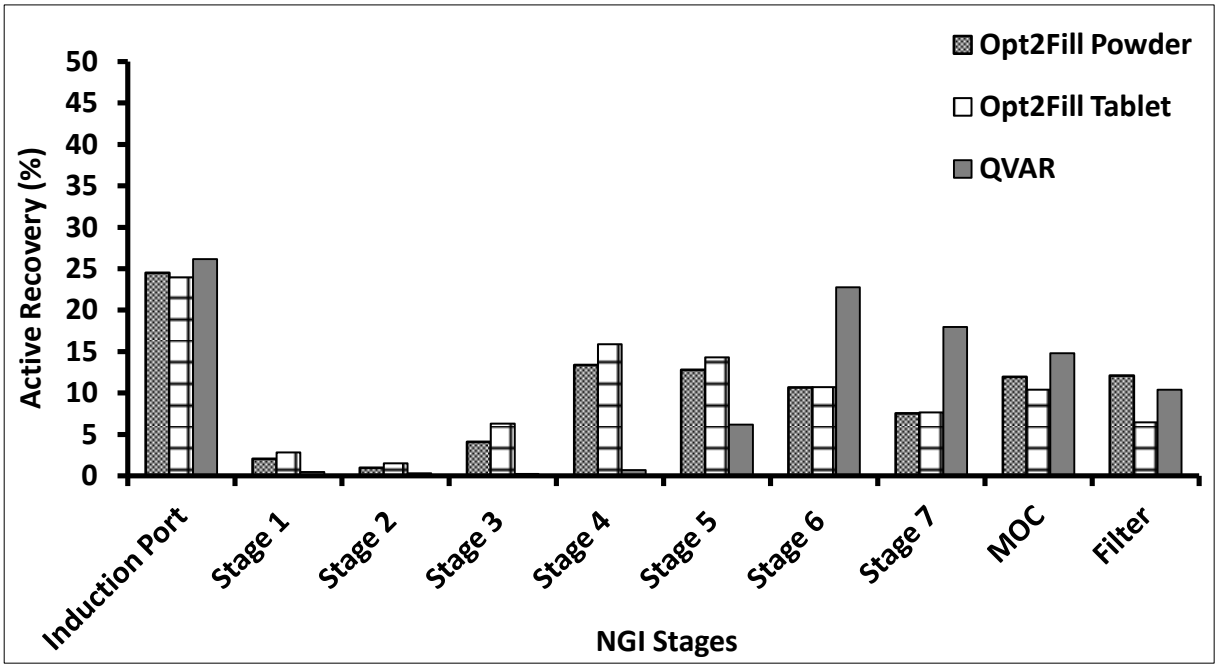

Figure 3. Aerosol particle size distribution of BDP from Opt2Fill SS/BDP tablet and powder pMDI formulations compared to QVAR® 50 determined using the NGI at 30 L/min.

Discussion and Conclusion

Previous studies have shown that Opt2Fill™ powders i.e. API(s) blended with inert carriers (without disintegrant) can be used to effectively formulate suspension pMDI products [2]. In this study we have demonstrated that Opt2Fill™ tablet technology can be used to prepare a pMDI combination formulation containing both a suspended and a soluble drug. The performance of this non-optimised formulation compared favourably with appropriate reference products.Differences in PSD for the suspended API (i.e. SS) could have resulted from disparities in the primary particle size of the micronised SS in Airomir® and Opt2Fill™. In the case of the solution API (i.e. BDP) it is possible that differences in the ethanol content and also hardware differences e.g. valve materials and actuator orifice diameter may have contributed to the contrasting PSD profiles. It is also likely that some propellant droplets contained both particulate SS and solubilised BDP and thus co-deposition of BDP and SS may have occurred thereby increasing the particle size characteristics of the solubilised BDP.

It was previously reported [3] that an Opt2Fill™ tablet formulation containing menthol coated lactose and salmeterol xinafoate/fluticasone propionate was efficiently dispersed in HFA 134a. The resultant pMDI formulation demonstrated aerosol particle size distribution results similar to those of the marketed comparator, Seretide™.

Experiments to date indicate that effective pMDI formulations may be manufactured by the novel approach of dispensing APIs in the form of propellant dispersible tablets. This technology offers manufacturing advantages compared to established single-stage and two-stage filling methods. It is anticipated that upon scale up the technology will provide a flexible approach to pMDI manufacturing using essentially standard equipment. Batches of bulk tablets complying with release specifications will be dispensed into canisters followed by valve crimping and check weighing. The final step i.e. propellant filling will only require standard pressure filling and check weighing equipment with no necessity for homogenization/mixing, pressure lines, or pressure vessels. Propellant filling may be conducted immediately after valve crimping or alternatively following a predetermined delay and could if desired be performed at a separate facility. Cleaning processes between products will be greatly simplified. Batch sizes can be readily varied and scaled ensuring process continuity from pilot batches to large commercial batches.

References

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