Comparison of the Aerodynamic Performance of Pressurized Metered Dose Inhalers Manufactured by Respitab™ and Drum Dose Dry Filling

Chen Zheng[1], Aneta Obirek[1], Sylwia Fowler[1], Cuong Tran[2], Lucas Silva[2], Lena Dietz[3] & Irene Rossi[3]

[1]i2c Pharmaceutical Services, Cardiff Medicentre, Cardiff, CF14 4UK, UK

[2]Nanopharm Ltd. An Aptar Pharma Company, Franklin House, Grange Road, Cwmbran, NP44 3WY, UK

[3]Harro Höfliger, Helmholtzstraße 4, Allmersbach im Tal, 71573, Germany

Summary

In response to the environmental impact of traditional propellants in pressurized metered dose inhalers (pMDIs), this study evaluates two alternative manufacturing processes: Respitab™ tablet filling and drum dose dry filling with the new generation propellant HFA-152a. Conventional pMDI manufacturing pose safety and operational challenges, specifically with flammable propellants like HFA-152a. To address this, decoupled filling approaches have been developed, allowing safer and more flexible production.

The study compares the aerodynamic performance of Salbutamol Sulphate formulations produced using both processes. For drum dose dry filling, a lactose-based powder blend was filled into canisters using a semi-automated dosing system. Respitab™ samples involved dispensing a dispersible tablet into a canister before propellant filling. Both methods used identical canisters, valves, and propellant quantities.

Results showed that both methods achieved consistent fill weights with low variability (RSD < 2.5% for drum dosing). Drug delivery uniformity and aerodynamic particle size distribution were broadly comparable across both processes, with no statistically significant differences observed across specific stages between the two novel approaches and the reference product (Ventolin® Evohaler). Whereas some clear differences between the reference product and both or either process were noticed for other impactor stages.

The findings support the viability of both Respitab™ and drum dose dry filling as effective alternatives to traditional pMDI manufacturing, particularly for transitioning to environmentally sustainable propellants. These methods also offer potential for continuous manufacturing, enhancing scalability and supply reliability for essential medications. Future research will explore broader applications across different active pharmaceutical ingredients and formulation complexities.

Key Message

The study found that Respitab™ and drum dose dry filling methods deliver similar aerodynamic performance and offer alternative approaches to conventional pMDI manufacturing facilitating a safer, scalable process with new generation propellants.

Introduction

Following the Kigali Amendment, HFA-152a and HFO-1234ze have emerged as low-global warming potential alternative to HFA-134a, with HFA 152a reducing the carbon footprint of pressurized metered dose inhalers (pMDIs) by over 90% [1]. However, HFA-152a flammability is compelling manufacturers to implement additional safety measures making traditional manufacturing processes more challenging.

Conventional pMDI filling typically utilizes either a single-stage or two-stage process, with single-stage pressure filling the most common. In this method, the active pharmaceutical ingredient (API) is mixed with a solvent or propellant in a drug addition vessel, then transferred under pressure to a vessel containing pre-loaded propellant [2]. Complete mixing and circulation are essential for uniform drug dispersion [3]. The final formulation is then pressure-filled into the canister through the metering valve. Alternatively, two-stage filling involves preparation of a suspension or API concentrate in the propellant or in an excipient, e.g. ethanol, and dispensing into open canisters prior to crimping of the metering valve and final propellant filling up to target volume [2].

Both processes involve numerous in-process control steps and complex line cleaning must be performed as part of good manufacturing practices before every new batch start. These essential interventions during production and cleaning involving connection and disconnection of equipment lead to the increased chance of propellant escape and associated risk of an explosion, in the case of handling flammable propellant.

To address these challenges, approaches to decouple the filling of the individual ingredients have been developed by the industry [4]. A first example, reported by Johnson et al., utilises dry powder filling by implementing direct micronized / particle engineered powder filling technologies, traditionally used for commercial production of dry powder inhalers, into pMDI manufacturing. By step-by-step addition of each component into the canisters, challenges and issues due to the current pMDI manufacturing can be resolved allowing a smoother pMDI transition to new generation propellants [1].

In another approach, a novel propellant dispersible tablet (Respitab™) for pMDI manufacturing circumvents the challenges described above [4]. This staged filling process involves dispensing the tablet into the canister, crimping the metering valve and pressure filling with propellant.

In this study, both alternative filling approaches for the production of a next generation pMDI were assessed and compared for aerodynamic performance of a Salbutamol Sulphate suspension formulation.

Material and Methods

Salbutamol Sulphate was uniformly blended by low shear mixing (Turbula®, Willy A. Bachofen, CH) with an inhalation grade lactose (SV003; DFE Pharma, DE) in ratio 1:1.5 (w/w) and with 0.1% (w/w) of disintegrant (menthol; Sigma-Aldrich, UK). The formulation was analysed in triplicate for content uniformity using high-performance liquid chromatography (HPLC) method.

The powder blend was dispersed as loose compacts via a semi-automated drum dosing system (Drum Lab, Harro Höfliger, DE) into plain 19 mL (Presspart, UK) aluminium canisters with a target blend weight of 100 mg, sufficient for delivering 200 actuations of 100 µg of salbutamol (as salbutamol sulphate). Initially, a filling trial was performed in order to define drum size and the best parameters to achieve a reproducible target fill weight. Respitab™ samples were prepared by dispensing one 100 mg tablet, produced by a single punch tablet press (LFA Machines Oxford Ltd, UK) in each canister. All cans were then gassed with 12.2 g of HFA 152a Propellant (Koura, UK), and crimped with DF316P 50 µL valves (Aptar Pharma, FR).

Following the manufacturing process, the canisters were stored inverted in a 25°C/60% RH cabinet overnight and tested without quarantine period for the drum filled samples and after 14 days of quarantine for Respitab™ tablet filled samples. The drug delivered uniformity (DDU) through canister life was determined using a dose unit sampling apparatus (DUSA) operated at flow rate of 28.3 L/min. Whilst aerosol performance was assessed using a Next Generation Impactor (NGI; Copley Scientific, UK) at flow rate of 30 L/min. Aerodynamic Particle Size Distribution (APSD) was also measured for the reference product (Ventolin® Evohaler, batch 7G3S/JV6T, GSK, UK) at beginning of can life. Quantitative analysis of SS from DUSA and NGI components was performed using a validated HPLC method.

Results and Discussion

Initially, a filling trial was performed to define the drum size and filling parameters to reproducibly achieve the target fill weight (100 mg of blend). 30.000 mm^3 drum size with 6 consecutive dosing and -300 mbar as setpoint vacuum allowed to hit the target fill weight with a relative standard deviation (RSD) < 2.5% (Figure 1). The fill weight of the three canisters tested for performance evaluation was 101.35 ± 1.04 mg by drum filling.

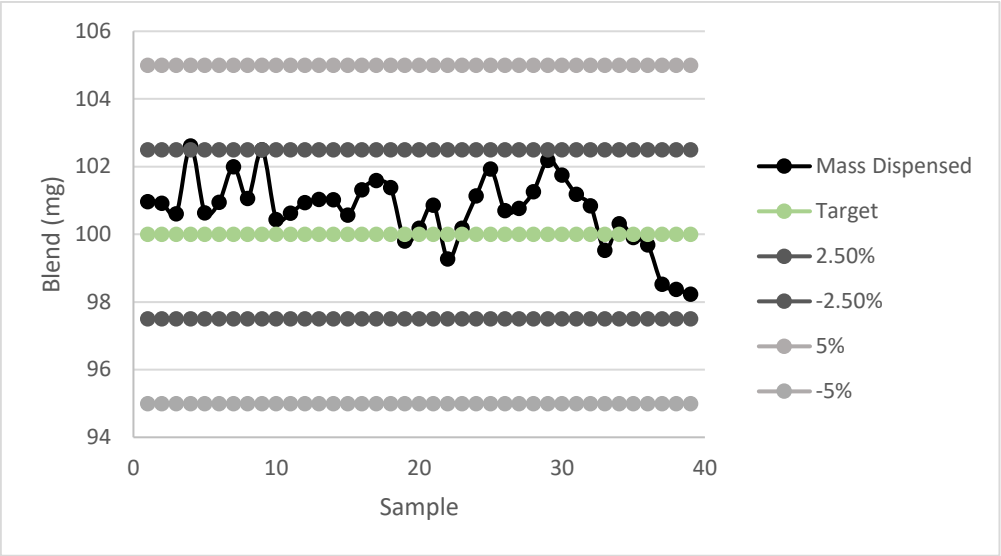

Figure 1 - Mass of blend dispensed into primary container by drum filling with defined parameters (n=40).

Both filling methods visually reported homogenous suspensions. DDU was tested through life and showed comparable performance between the drum dry filled canisters and tablet filled samples (Figure 2).

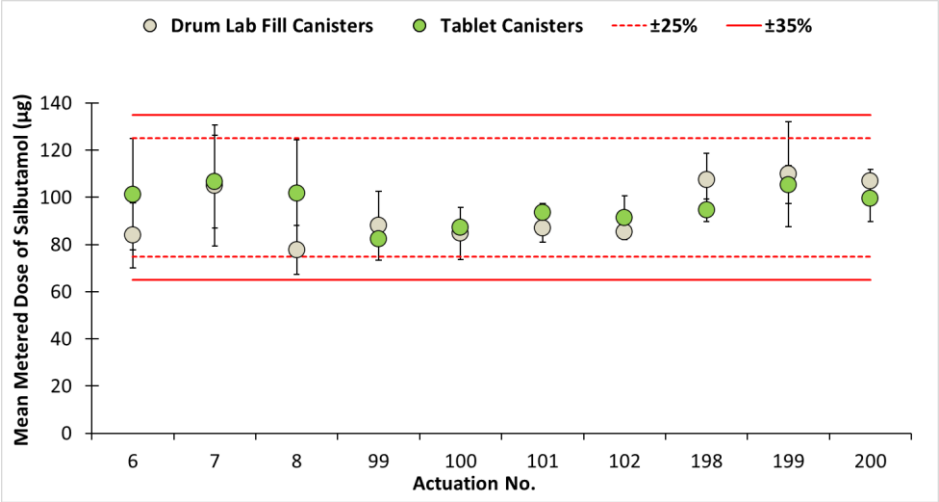

Figure 2 - DDU through life for drum dry filled canisters and tablet filled canisters (n=3 canisters, bars represent standard deviation).

The mean APSD, determined from through life performance average derived from beginning, middle, and end of each canister with the different filling procedures, was compared to the APSD of Ventolin® Evohaler collected at beginning of each canister life (Figure 3). The results demonstrated comparable salbutamol deposition across specific impactor stages (such as Stage 2, Stage 4 and MOC), with no statistically significant differences observed ($p > 0.05$, ANOVA followed by post hoc Tukey-Kramer HSD). Whereas some clear differences between the reference product and both or either process were noticed for other impactor stages, particularly induction port and Stage 1. While further optimisation of both the formulation and filling process is necessary to achieve a complete match with the reference product, the overall aerodynamic performance remains encouraging and supports the feasibility of both approaches for continued development.

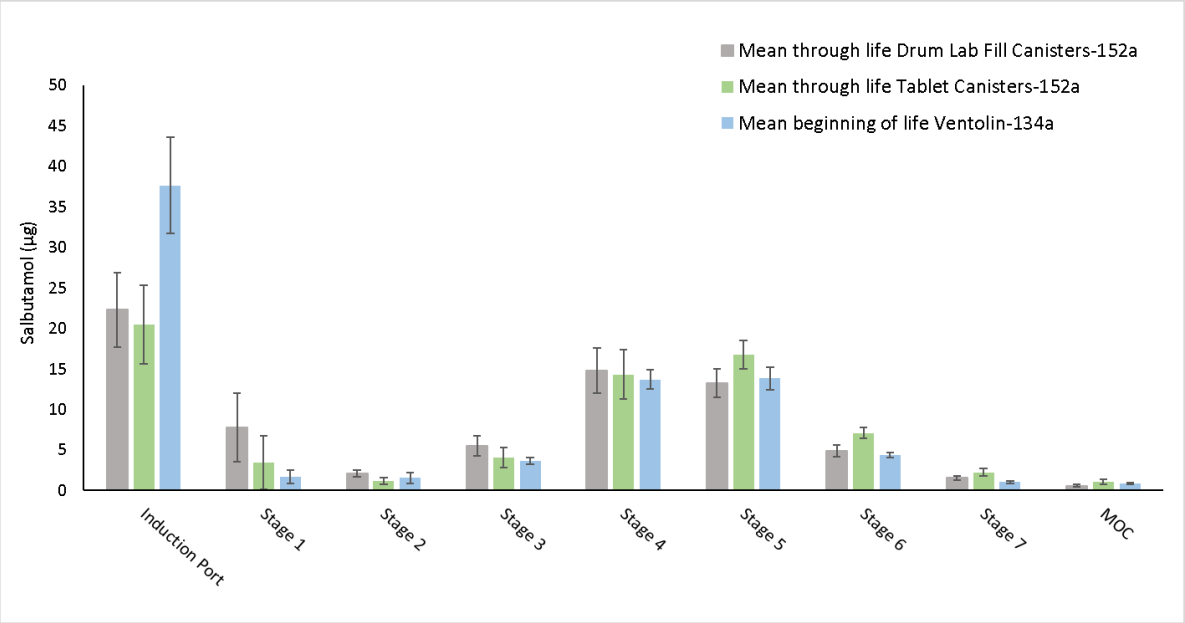

Figure 3 - APSD for drum dry filled canisters (n=12 determinations of 3 canisters through life, bars represent standard deviation), tablet filled canisters (n=9 determinations of 3 canisters through life, bars represent standard deviation) and Ventolin (n=5 determinations of 5 canisters at beginning of life, bars represent standard deviation).

Conclusions

The handling complexities associated with new generation propellants, particularly HFA 152a, have prompted the industry to explore alternative manufacturing approaches that enable the continued use of current facilities for production of greener pMDIs. Notably, these decoupled manufacturing approaches offer the additional advantage of facilitating continuous manufacturing, which can be fundamental for the supply of life saving medications such as Salbutamol pMDI.

In this study, two such alternative manufacturing methods were evaluated and demonstrated comparable in vitro performance with APSD profiles typical of suspension pMDIs filled by conventional processes. These approaches provide potential alternative flexible manufacturing approaches to pMDI production. Future research will focus on expanding the scope of these approaches to include a broader range of APIs and more complex formulations, with the aim of delineating the operational boundaries and scalability of these innovative manufacturing platforms.

References

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