Accelerated Stability Studies with pMDIs of Respitab HFA-152a Propellant Dispersible Salbutamol Tablets

Rachael Kay, Aneta Obirek, Wiktoria Wegrzyn and Cuong Tran
i2c Pharmaceutical Services, Cardiff, CF14 4UJ, UK.

Introduction

Transition to next-generation low global warming potential propellants for production of pressurised metered dose inhalers (pMDIs) presents on-going challenges for those involved in the manufacture of pMDIs to ensure safe working with propellants classified as flammable.

Respitab®, with drug in tablet form dispensed directly into canisters and crimped, avoids the need for pressurised mixing vessels and manipulation of large volumes of propellant in staffed working environments.

The objective of this study was to assess the stability of a propellant-dispersible salbutamol tablet formulation prepared in HFA-152a, stored under accelerated stability conditions of 40°C/75% relative humidity (RH) and evaluated at regular intervals for dose content uniformity (DCU) and aerodynamic particle size distribution (APSD) through canister-life.

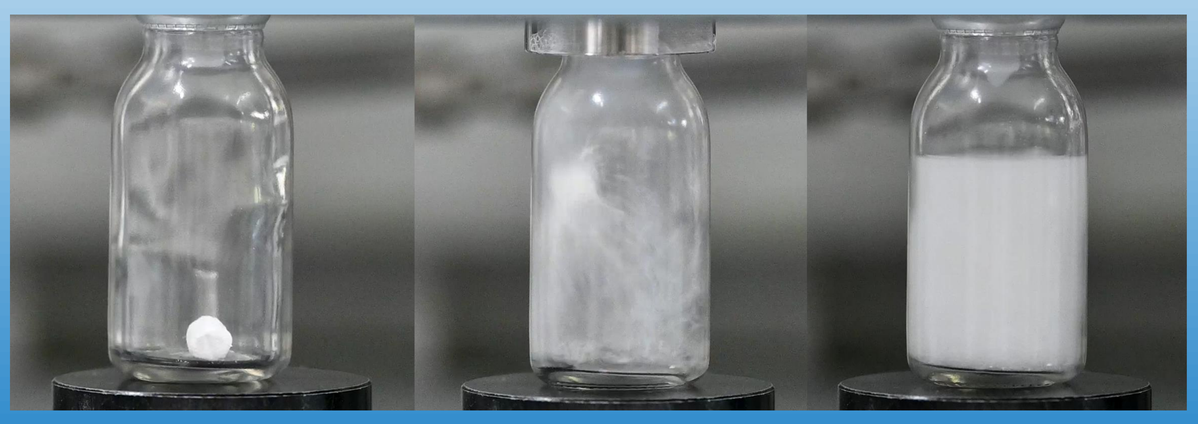


Figure 1. Dispersion of a salbutamol Respitab Tablet during pressure filling of HFA 152a (plastic coated glass bottle for visual assessment only)

Methods

A powder blend was prepared containing micronized salbutamol (as salbutamol sulphate) (Jayco Industries, India), menthol (Sigma-Aldrich, UK), and inhalation grade lactose (DFE Pharma, Netherlands). Blending was performed using a low shear mixer (Turbula®, Willy A. Bachofen, Switzerland). Prior to tableting, quantitative analysis was performed to determine content uniformity of salbutamol. A single punch tablet press (LFA Machines Oxford Ltd, UK) was used to produce tablets of approx.100 mg which provided 200 doses of 100 µg per actuation.

Tablets were dispensed into plain aluminium canisters (19 ml, H&T Presspart, UK), crimped with 50 µL metering valves (Aptar Pharma, France) and HFA-152a (Koura UK) was pressured filled through the valves. Following manufacture, canisters were stored inverted at 25°C / 60% RH for a two-week quarantine period.

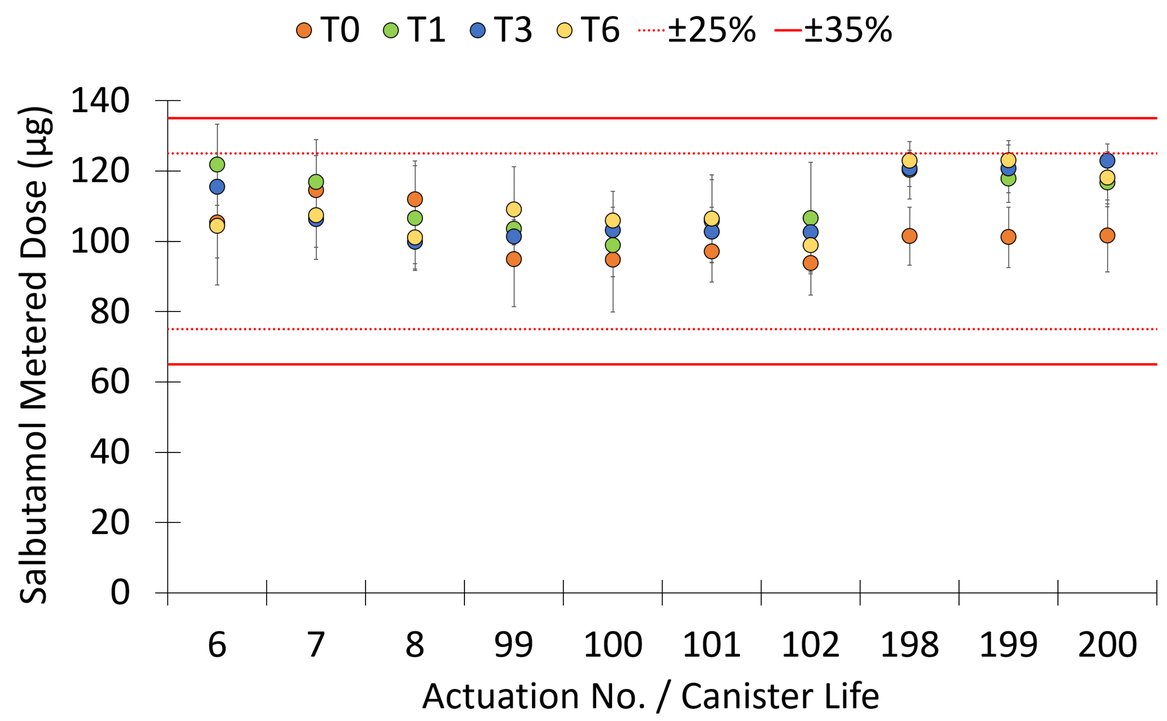
Standard tests to assess key quality aspects of pharmaceutical characteristics (DCU and APSD) were performed over a period of 6 months (release, 1, 3 and 6) at accelerated stability storage conditions, stored inverted with no foil overwrap.

Results & Discussion

Quality control checks showed salbutamol to be uniform in the powder blend prior to tableting with a relative standard deviation value of 1.70% (n=5).

Through canister life DCU data at release (T0) and after storage at 40°C/75% RH for 1 (T1), 3 (T3) and 6 (T6) months are presented in **Figure 2**.

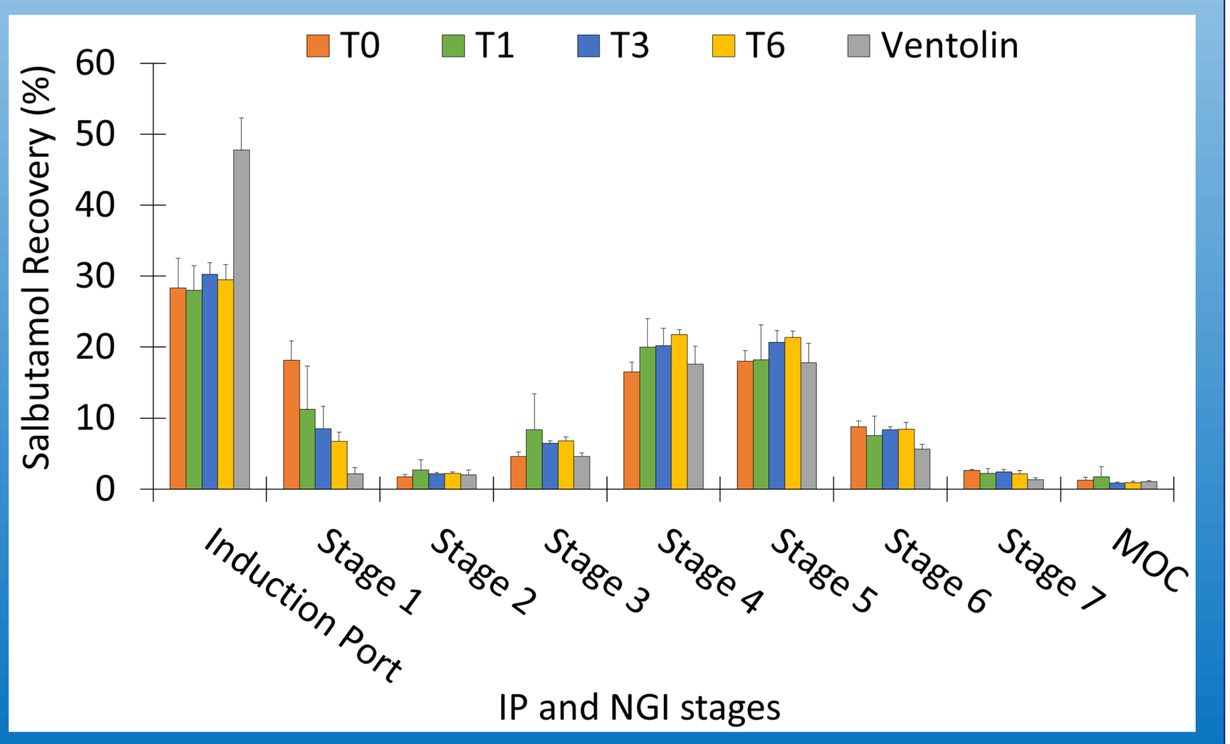
Figure 2. Through can life DCU (µg) of salbutamol in HFA-152a following accelerated stability storage) at release, 1, 3 and 6 months (mean ± SD, n=10).



DCU of salbutamol was within Pharmacopoeial limits, highlighting Respitab's dispersion and suspension stability.

Comparison of beginning of can life salbutamol APSD from Respitab with Ventolin is similar for Stages 2 – MOC, as shown in Figure 3. Fine particle fraction (% < 5 µm) was 46% for Ventolin compared with an average 59% from the pooled Respitab data. Changes in Stage 1 deposition over storage time were observed in beginning of can life data from Respitab but this was not a trend seen in the larger dataset pooled from through can life samples.

Figure 3. Beginning of can life APSD (%) of salbutamol in HFA-152a following accelerated stability storage at release, 1, 3 and 6 months with off the shelf Ventolin (no storage) (mean ± SD, n=5).



Conclusions

Salbutamol formulated as a Respitab propellant dispersible tablet was homogeneously suspended in HFA-152a, DCU was consistent through can-life and aerosol performance remained efficient throughout the six-month accelerated stability period with standard hardware.

References

[1] Zephex® 152a Safety Data sheet. https://www.zephex.com/wp-content/uploads/2021/04/Zephex-152a_UK_GHS04.pdf. Accessed 23 Nov 22.
[2] Solstice® Propellant Flammability Assessment. http://www.crcind.com/crc/HFO-1234ze.pdf. Accessed 23 Nov 22.

The authors thank Aptar Pharma for funding these studies, Koura UK for the supply of HFA-152a and DFE Pharma for lactose.