Stressed and Accelerated Storage of Pressurized Metered Dose Inhalers with Various Valve Types to Explore the Impact on Aerosol Performance Characteristics and Product Quality Attributes

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INTRODUCTION

Selection of container closure system for metered dose inhalers (pMDI) is a critical factor in developing and manufacturing a successful pMDI. The metering valve plays a fundamental role in ensuring delivered dose uniformity and protecting the structural integrity of pMDIs. The elastomer seal secures the valve on to the canister, which then hermetically isolates the system to ensure the pressure of the propellant is maintained. However, the crimp around the valve and canister is a source for water ingression into the drug product [1]. In early development, selecting the right valve configuration is crucial to streamline the development program thereafter, but to do this, the associated stability studies can be large when many variants and month-long timelines are involved.

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines [2] reports the testing of finished products under long term conditions (25 °C/60% relative humidity (RH) or 30 °C/65% RH) for a minimum of 12 months, and accelerated storage conditions (40 °C/75% RH) for a minimum of six months. However, in many cases, especially in the early development stages, where a Quality by Design (Design of Experiment (DoE)) orientated process is applied, it may be useful and insightful to

accelerate the stability time, to screen different product variants in order to choose the optimum combination of formulation, valve and canister for pMDIs.

In this study, 12 different valve configurations prepared containing a Fluticasone Propionate/Salmeterol Xinafoate 50/25 μg formulation were evaluated. The DoE study focused on demonstrating how two weeks of storage at an extreme stress condition (50 °C/75% RH) may be used to give indications of stability issues or preferential configurations, for a product. The shorter study means that more variants can be explored and optimum pMDI configuration selected initially and more quickly.

METHODS

Following a DoE approach, 12 valve configurations were manufactured for this study. The DoE preparation and testing regimen was focused on studying different gasket elastomers and valve production processes for valve subassembly components. These different valves were then used to manufacture a final product containing 50/25 μg of micronized Fluticasone Propionate (FP) and Salmeterol Xinafoate (SX) respectively. Filling with hydrofluoroalkane 134a was carried out on a single high pressure shot filler line and valves were vacuum crimped to the canisters (Pharmaserve North West Ltd, UK).

Total drug content (TDC) was assessed together with related substances (RS) by high performance liquid chromatography (HPLC), at time zero, after two weeks at 50 °C/75% RH and at three months at 40 °C/75% RH. The United States Pharmacopeia monograph 43 [3] method was transferred for this analysis. Aerodynamic particle size distribution (APSD) measurements were performed in triplicate at each stability time-points, employing an Andersen Cascade Impactor (ACI), connected to a critical flow controller and a vacuum pump set at 28.3 $L \cdot min^{-1}$ (Copley Scientific, UK). Drug Delivered (DD) was measured with dosage unit sampling apparatus (DUSA, Copley Scientific, UK) for pMDIs at 28.3 $L \cdot min^{-1}$. The amount of each drug collected was quantified by HPLC and data statistically analysed using Microsoft Excel, JMP (SAS Institute) and R software (pairwise t-test, $p \leq 0.05$).

Finally, water content analysis was carried out employing Karl Fisher (KF, Mettler Toledo, USA).

RESULTS AND DISCUSSION

The canisters reported between 80–120% of the total expected canister content after three months at 40 °C/75% and two weeks at 50 °C. Moreover, the same unknown impurity was identified for almost all valve configurations at a similar concentration, at the two storage conditions (0.67% for two weeks 50 °C/75% RH vs 0.84% for three months 40 °C/75% RH) None of the related substances listed in US Pharmacopeia monograph 43 [3] were detected for the product at both stability conditions.

The ED performance (Figure 1) trend after three months at 40 °C/75% RH followed a similar distribution in terms of the valve performance, especially for FP, compared to the one obtained after two weeks of storage at 50 °C/75% RH for most of the valve configurations. In both cases, the highest levels of aerosol performance was reported by the same valve (#11): 43 vs 42 μg of FP and 22 vs 21 μg of SX base emitted at 50 °C/75% RH and 40 °C/75% RH, respectively.

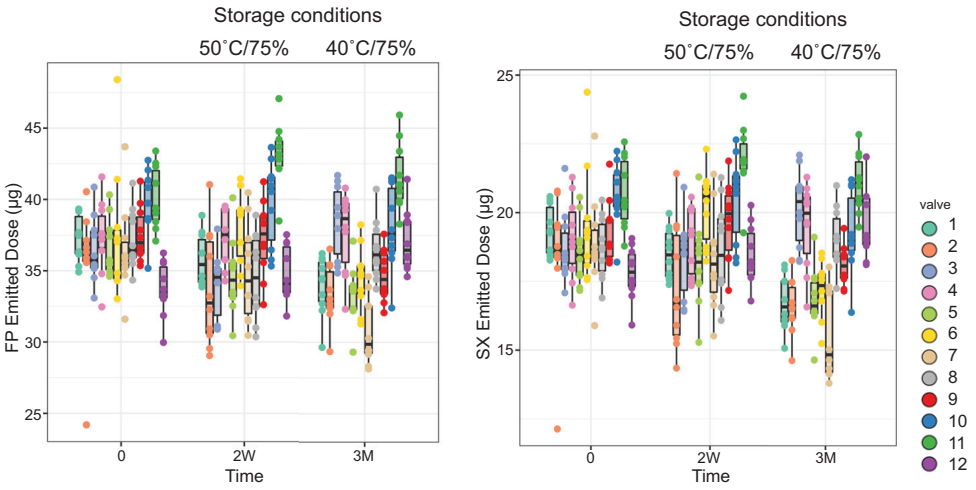

Figure 1. **Emitted dose for and FP and SX base obtained with the two storage conditions employed at two weeks (2W) and three months (3M) for the valve one to 12 (n=10).**

Most of the valve configurations reported a statistically significant different FPM for both storage conditions, if compared to their aerosol performance at time zero (Figure 2). The trend of FPM values showed by most of the valve types after two weeks at 50˚C/75% RH, was similar to the one reported at the three months time-point, under classical ICH accelerated storage conditions. Particularly, for both drugs, the highest values were reported by valves #1, 10 and 11, whereas the lowest values by valve #3. The only differences in terms of FPM observed between the two storage conditions, namely lower FPM after three months at 40˚C/75% RH, were related to the valves which showed the highest increase of water content (#5, 7 and 9) between the values collected after two weeks and three months.

For these valves a longer storage time at 75% RH resulted in the highest moisture content in the formulations [4], eliciting in the lowest aerodynamic performance, with higher deposition of both drugs in the throat and lower levels of drug content detected in stages 3, 4 and 5 of the ACI.

Moreover, as already shown by other formulation types comprising FP and Salmeterol, in this study, co-deposition of the two active pharmaceutical ingredients was observed in the stages of the ACI [5]. This co-association of FP and SX particles was reported for all the time-points analysed (Figure 2), identifying a comparable trend of aerodynamic performance for both drugs in the different valves employed.

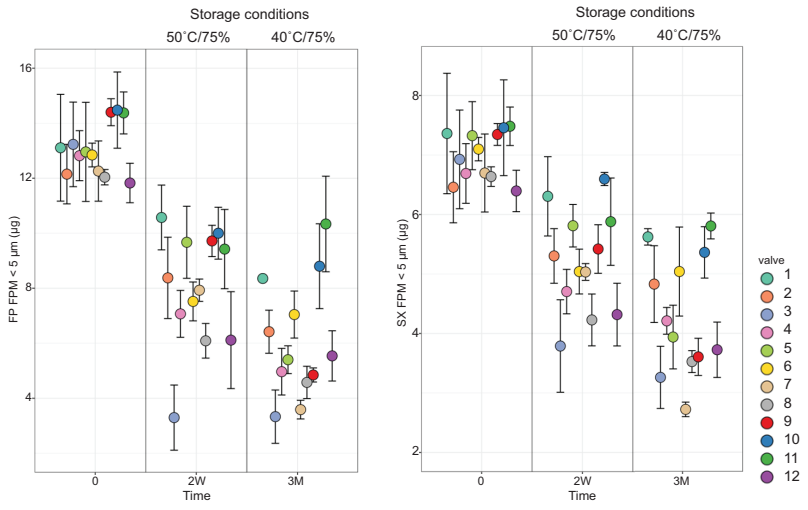

Figure 2. **Fine particle mass for FP and SX base obtained with the two storage conditions employed at two weeks (2W) and three months (3M) for the valve one to 12 (mean values and bars represent standard deviation, n=3).**

CONCLUSIONS

The results collected during this shortened stability study showed how extreme storage conditions (50 °C/75% RH) can be employed in order to predict product performance under 'stressed conditions', shorten the time for accelerated stability study from three months to two weeks.

The use of this extreme storage condition in early development DoE studies would allow scientists to evaluate several valve/formulation combinations in a shortened timeframe and to select the best performing formulation and pMDI valve combinations more rapidly, either increasing the amount of variants to be tested early on, or increasing the speed/decreasing costs associated with a development program.

REFERENCES

1. Stein WS *et al.*: Advances in metered dose inhaler technology: Hardware development. *AAPS PharmSciTech* 2014, 15(2): 326–338.

2. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (2003) Q1 A (R2). Stability testing of new drug substances and products. CPMP/ICH/2736/99, 2003.

3. USP 43–NF 38. Fluticasone Propionate and Salmeterol Inhalation Aerosol. USP Convention, Rockville, MD: 2005, 42(1).

4. Williams G: Moisture transport into chlorofluorocarbon-free metered dose inhalers. *J Allergy Clin Immunol* 1999, 104(6): S227–S229.

5. Theophilus A *et al.*: Co-deposition of salmeterol and fluticasone propionate by a combination inhaler. *Int J Pharm* 2006, 313: 14–22.