A design of experiment applied to pMDI manufacture in order to explore the impact of the critical process parameters on product performance

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Summary

Salmeterol Xinofoate (SX) is a long-action β_2 adrenoceptor agonist used in asthma and COPD treatment as a bronchodilator. The aim of this work was to evaluate the effect of specific Critical Process Parameters (CPPs) on the aerodynamic performance of an SX pMDI using a Design of Experiment (DoE). The CPPs chosen were the homogenisation time, the mixer speed and the vessel temperature. The Critical Quality Attributes (CQAs) identified as affecting the product performance were the fine particle dose, emitted dose and the total drug content (TDC).

In this study, the formulation used was kept constant at 99.95% (w/w) HFA134a and 0.05% (w/w) SX. The mixing time and the recirculation time prior to product filling were also kept constant both at 30 min. A full factorial design was generated using Minitab (Minitab17 Statistical Software, 2010) to evaluate the CPPs effects.
The aerodynamic assessment of the batches was assessed by Andersen Cascade Impactor (ACI) at 28.3L/min (n=10 shots per ACI). Data such as ACI and TDC for each batch were determined using an appropriate HPLC method in triplicate.

In summary, the use of a DoE increased the process and product understanding. For all of the three CQAs, the highest values (TDC higher than 5.8mg/can, ED higher than 20µg, FPD higher than 9.5µg) are reached when the CPPs have their highest levels (homogenisation time 36min, mixer speed 200rpm and vessel temperature 12ºC) but this batch has also an high variability, so further investigations are proposed to confirm the relationship.

Introduction

The pressurized metered dose inhalers (pMDIs) are a milestone in inhalation therapy since their introduction on the market more than 50 years ago. They are commonly used for the treatment of lung disease such as asthma and COPD. In pMDIs the drug can be dissolved or suspended in a propellant with or without other excipients (i.e. ethanol used as co-solvent). Recently, the use of the chlorofluorocarbons as propellants has been abandoned due to their role in ozone layer depletion. They were replaced by hydrofluoroalkanes (HFA). Because of the chemical differences between the chlorofluorocarbons and hydrofluoroalkanes, some pMDIs were required to be reformulated in order to achieve stable inhalation products. [1]
Salmeterol Xinofoate (SX), a long-action β_2 adrenoceptor agonist used in asthma and COPD treatment as a bronchodilator, has been reformulated as excipient-free particle suspension in HFA 134a. [2]

The aim of this work was to evaluate the effect of specific Critical Process Parameters (CPPs) on the aerodynamic performance of a SX pMDI using a Design of Experiment (DoE) according the Quality by Design approach. [3,4]. There is not a wide selection of scientific literature available on DoE applied on inhalation products and more specifically to the manufacture of SX pMDIs. The use of a DoE for this study enabled a better understanding of the process and product.

The CPPs identified for evaluation as part of this study were chosen based on knowledge gained from previous small scale (5L) manufacturing of the product and also from manufacturing of similar suspension pMDIs at 100L scale. The CPPs chosen were the homogenisation time (min), the mixer speed (rpm) and the vessel temperature (ºC). The temperature was chosen to investigate the SX behaviour in suspension (to assess flocculation or settling out) at higher (12ºC) and lower temperatures (6ºC). Mixer speed (100-200rpm) was chosen in order to check its effect on homogeneity of the suspension. A higher speed may be required in order to keep the drug suspended sufficiently but this may cause local heating of the suspension around the mixer motor and also a higher vessel pressure. A lower mixer speed would minimise vessel heating and pressurising effects although this may lead to a less homogenous product. Finally, the homogenisation time (0-36min) was chosen as a CPP to evaluate its effect on the homogeneity of the batch. The large amount of energy supplied by the homogenisation process will de-agglomerate the API particles and this could affect the particle size distribution of the product.
The Critical Quality Attributes (CQAs) identified were the Fine Particle Dose (FPD), the Emitted Dose (ED) and the Total Drug Content (TDC).

Materials and Methods

The manufacturing process was performed in a pilot scale 100L stainless steel vessel with a magnetic stirrer. The HFA 134a (batch Q12102) was purchased from Mexichem Fluor. A filling machine Pamasol P2079 and a vacuum crimping machine Pamasol P2002 were used to fill and crimp the canister respectively. The components used were Presspart FCP coated 14ml canisters, Aptar DF316 POM/PBT/EPDM 63µl valves and Presspart NM120 actuators. The SX raw material used was a European Pharmacopoeia (EP) grade material of a specific particle size. Before the finished product manufacture, the SX particle size was determined by laser light scattering (Mastersizer, Malvern, UK). Approximately 10 mg of powder were dispersed in isooctane with phospholipon 50 at 0.05 (w/w) and sonicated for 30s.The test has been performed in triplicate.
For this study, the formulation used was 99.95% (w/w) HFA 134a and 0.05% (w/w) SX. The mixing time (min) and the recirculation time (min) prior to product filling were kept constant both at 30 min. A full factorial design was generated using Minitab (Minitab 17 Statistical Software, 2010) to evaluate the CPPs effects. In Table 1 the full factorial design matrix is shown.

Table 1. Full Factorial Design Matrix

Batch	Vessel Temperature (ºC)	Homogenisation Time (min)	Mixer Speed (rpm)
4E990	6	0	100
4E994	6	36	100
4F997	12	36	100
4G020	12	36	200
4G022	12	0	100
4G023	6	0	200
4G025	12	0	200
4G027	6	36	200

During filling and crimping standard checks were performed to monitor both the processes.
TDC data for each batch manufactured were determined using an appropriate HPLC method in triplicate.
The aerodynamic assessment of the batches was assessed by Andersen Cascade Impactor (ACI) at 28.3 L/min (n=10 shots per ACI) in triplicate. For all *in vitro* impaction measurements, the SX mass deposited in each stage was determined by HPLC. All solvents used were of analytical grade.

Results and Discussions

The particle size distribution of the micronized powder used for the preparation of each QbD batch were 1.28 ± 0.45µm as $D_{v,10}$, 2.98 ± 0.47µm as $D_{v,50}$ and 5.86 ± 0.62µm $D_{v,90}$. The particle size distribution is suitable for the preparation of a pMDI suspension in order to obtain a pulmonary deposition.
Briefly during crimping the crimp depth and the crimp diameter were monitored and they were respectively 5.7 mm and 17.7 mm. The fill weight for each batch was keep constant (11.7g) during the manufacturing process. The process capability of the filling activity was evaluated using Minitab. The Process Capability Index (C_{pk}) for each individual batch were all above 1.4. Combining the fill weights from each batch and analysing as a campaign, the C_{pk} is 3.5. These values confirm that the filling process is in control.
All product testing was performed at Pharmaserve NW. In summary, although the mean TDC values for each data set were mostly consistent, statistical analysis shows that the batches manufactured with higher energy input (homogenised, higher mixer speed and high temperature), tend to have higher TDC values. It may be possible that the extra energy used during the production of those batches gives less opportunity for the drug to adhere to system surfaces as it is agitated more than during production of low energy input batches. A plot of the mean TDC values is shown in Figure 1a. The data sets of 4E990 and 4G020 have the lowest and highest mean values, respectively. They also correspond to the batches with the lowest and highest energy input during manufacturing. Pareto analysis of the TDC data (Figure 1b) shows that temperature (A) and mixer speed (B) is the combination with the most statistically significant effect on the TDC values. This combination has a negative effect on the TDC (blue bar). Mixer speed (B), a combination of vessel temperature, mixer speed and homogenisation (ABC), and homogenisation (C) on its own are identified as the other parameters that are statistically significant. All of them (orange bars) have a positive effect on the TDC. A multiple regression analysis (R^2= 38%) of the TDC data collected was performed in Minitab. This was performed using a target TDC value of 5.98 mg/can. In order to obtain the target value, the model identified the optimal CPP values of mixer speed as 149 rpm, vessel temperature as 10 ºC and homogenisation switched on. The positive effect of the three CPPs is shown also in the main effects plot (Figure 1c). The main effect plot shows the Critical Quality Attribute (TDC in this case) increasing or decreasing in function of the CPP. The homogenisation time has been plot as N and Y to indicate the absence (0 min) or the presence (36 min) of this CPP during the manufacturing process. According to Figure 2c, TDC increases with upper values for each CPP. This effect is higher for the mixer speed than for the other two parameters.

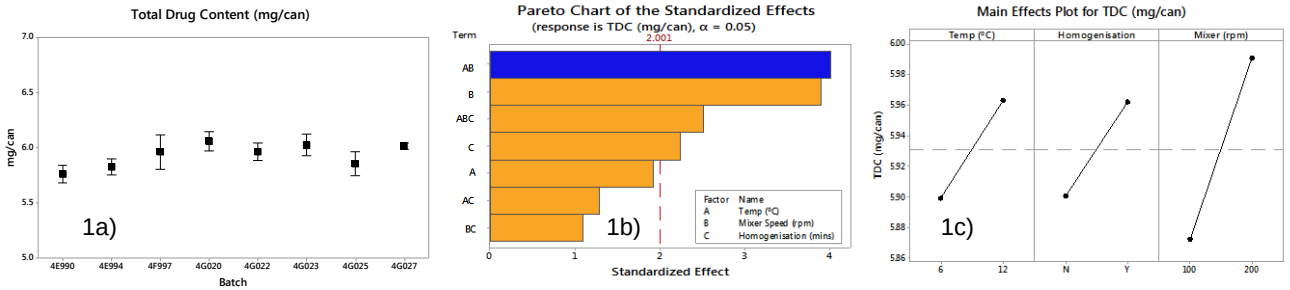

Figure 1. Total Drug Content (TDC) graphs: 1a) TDC mean values; 1b) TDC Pareto Chart (blue bar: negative effect, orange bars: positive effect), 1c) Main Effects Plot for TDC

The ACI data generated for each batch is generally consistent. A multiple regression analysis was performed on the data and optimal CPP values identified. Figure 2a shows the Emitted Dose (ED) mean values obtained from each batch. Other than batch 4G020, the mean values are close to the target of 21 µg and have quite low variability within each batch. Values for batch 4G020 show a high variability but the statistical analysis does not highlight any of them as outliers from the data set. Further data points could be generated to better understand the spread data. In Figure 2b the Pareto chart of ED data is shown. Although all of the CPPs and their interactions have a positive effect on the ED, only the vessel temperature (A) has a significant effect on the CQA. In Figure 2c the effect of each CPP on the ED of the batches is shown. As for the previous CQA, increasing each parameter it is possible to increase the ED. In this case, the increase of the CQA is higher for the temperature than for the other two parameters.

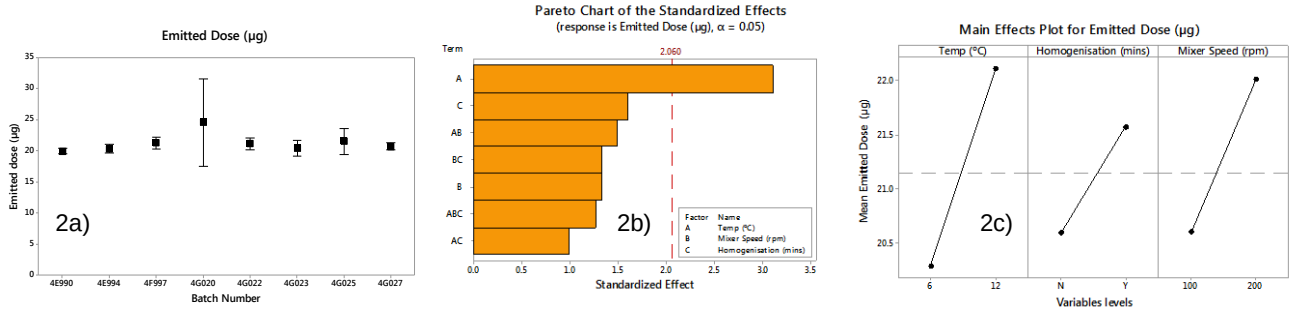

Figure 2. Emitted Dose (ED) graphs: 2a) ED mean values; 2b) ED Pareto Chart (blue bar: negative effect, orange bars: positive effect), 2c) Main Effects Plot for ED

The Fine Particle Dose (FPD) of particles smaller than 5µm is shown in Figure 3. In Figure 3a the mean values of each batch were plotted. As seen for the ED, the batch 4G020 shows a high variability (11.86 ± 2.06 µg) but the statistical analysis does not highlight any of them as outliers from the data set. This batch is obtained with the highest values chosen for each CPP. Further investigations are needed to understand the reason of this variability. The FPD mean values of the other batches are between 10.2 µg (batch 4F997) and 9.1 µg (4G023). In Figure 3b the Pareto chart of FPD is shown. Although all of the CPPs and their interactions have a positive effect on this CQA, only the vessel temperature (A) and its interaction with the homogenisation time (AC) has a significant effect on the CQA. As for the other CQAs, increasing all the CPPs it is possible to obtain higher values of FPD as shown in the Main effects plot (Figure 3c). The mean MMAD of each batch is between 2.3 µm (batch 4G020) and 2.7 (batch 4G025). In general, the ACI data was consistent across the tests and in agreement with the particle size of the SX particles used for the manufacture. No particle aggregation seemed happened during the production. Otherwise, batch 4G020 has more variability than all other batches. Further investigations are needed to understand the reason for this variability.

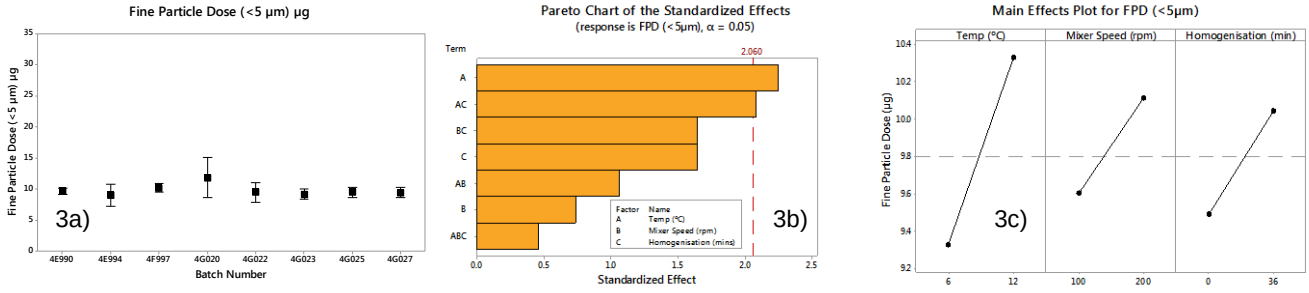

Figure 3. Fine Particle Dose (FPD) graphs: 3a) FPD mean values; 3b) FPD Pareto Chart (blue bar: negative effect, orange bars: positive effect), 3c) Main Effects Plot for FPD

CONCLUSIONS

In general, the best product performances are reached when the CPPs have their highest levels. All the CPPs analysed are shown to be critical for the quality of the SX pMDI in terms of the selected CQAs. In some cases a high variability has been detected, and this aspect requires a deeper investigation. The design space will be enlarged in order to investigate in more detail, the influence of each of the CPPs. In particular for the homogenisation time, more levels will be evaluated to confirm if higher energy input can affect FPD of SX. Further investigations will be added in order to evaluate in more detail, the design space and the robustness of the model (i.e. center points will be added to this DoE).

References

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