# The Influence of Formulation Variables on Mometasone Furoate pMDIs


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## INTRODUCTION

Pressurized metered dose inhalers (pMDI) are commonly used to deliver drugs locally to the lung. In addition to the active ingredient(s), pMDI formulations consist of propellant and frequently a cosolvent and/or a surfactant. The inclusion of these excipients can have an impact on the product performance of the pMDI. The purpose of this study is to use a design of experiments (DoE) approach to systematically evaluate the effect of formulations variables (primary particle size, concentrations of ethanol, (EtOH) and oleic acid (OA)) on HFA-227 mometasone furoate (MF) suspension pMDI performance, as determined by compendial and non-compendial aerosol characterization methods. The primary objective of the study is to develop mathematical models relating key product performance parameters to the different formulation variables, ultimately allowing for formulation selection with optimized properties.

## METHODS

Eight MF pMDI batches were prepared using a one-step pressure filling process (Table 1) with the following components: 17mL uncoated cans, 50µL metering valves, and actuators with orifice diameters of ~0.4 mm. Table 2 summarizes the methods used to evaluate the batches. Statistical analyses were performed using SAS v9.2.

**Table 1:** Prepared MF pMDI Batches

| Batch # | Target / Actual Micronized MF Primary Particle $X_{50}$ (µm) | Target / Assayed EtOH Conc. (% w/w) | Target / Assayed OA Conc. (% w/w) | Assayed MF Conc. (% w/w) |
|---|---|---|---|---|
| 1 | 1.1 / 1.07 | 0.45 / 0.422 | 0.001 / 0.00069 | 0.3392 |
| 2* | 2.0 / 1.98 | 0.45 / 0.426 | 0.025 / 0.01976 | 0.3094 |
| 3 | 2.0 / 1.98 | 0.90 / 0.870 | 0.001 / 0.00123 | 0.3313 |
| 4 | 1.1 / 1.07 | 0.90 / 0.898 | 0.025 / 0.02566 | 0.3240 |
| 5 | 2.0 / 1.98 | 1.80 / 1.79 | 0.001 / 0.00393 | 0.3104 |
| 6 | 1.1 / 1.07 | 1.80 / 1.77 | 0.025 / 0.02755 | 0.3285 |
| 7 | 1.1 / 1.07 | 3.60 / 3.52 | 0.001 / 0.00306 | 0.3380 |
| 8 | 2.0 / 1.98 | 3.60 / 3.59 | 0.025 / 0.03037 | 0.3287 |

*Results for Batch 2 are excluded from all data analyses due to sub-optimal performance, likely due to the relatively high concentration of OA that was not sufficiently solubilized by 0.45% EtOH.

**Table 2:** Evaluation of DoE pMDI Batches

| Test | Method | Replicates per Batch |
|---|---|---|
| MF concentration by total canister assay | High performance liquid chromatography with ultraviolet detection | n = 6 cans |
| EtOH and OA | Gas chromatography with flame ionization detection | n = 3 cans for each test |
| Aerodynamic particle size distribution | Next Generation Impactor (NGI) operated at 30 L/min using USP induction port at initial time point and after four weeks of storage at 40°C/75%RH | n = 4 cans, 1 collection per can per time point |
| Ex-throat dose ("lung dose") | Evaluated at 15, 30, 60, and 90 L/min using the medium anatomical throat model developed by the Oropharyngeal Consortium (OPC) [1]. Filter deposition was assayed downstream of the throat model | n = 2 collections for each flow rate |

## RESULTS

Figure 1 presents a summary of the NGI results for seven batches (i.e., all batches but Batch 2) evaluated at the initial time point and after four weeks of storage at 40°C/75%RH. The impact of micronized drug volumetric median diameter ($X_{50}$), EtOH and OA concentrations, and effect of storage condition ("month") on fine particle dose (FPD) were evaluated statistically. Summary of the analysis of variance (ANOVA) and evaluation of the size of effects using least square-means (LS-means) are presented in Table 3. Based on the statistical analyses, EtOH and $X_{50}$ had a greater effect on the FPD than OA and storage, which has been reported in prior articles [2,3]. The following model explains 95% of the variation observed in FPD:

$$FPD = 145 - 28.3\times X_{50} - 7.7\times EtOH - 376.5\times OA - 10.4\times month.$$

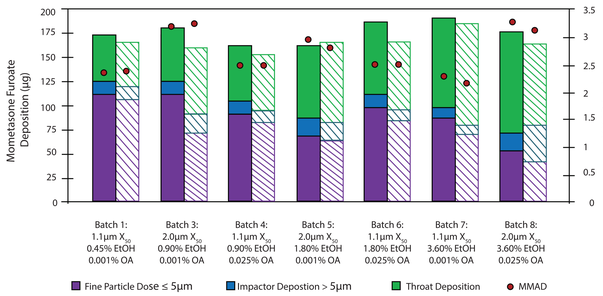


**Figure 1:** Comparison of NGI data for initial time point (left bar, solid fill) and after one month storage at 40°C/75%RH (right bar, hatched).

**Table 3:** Summary of ANOVA and Size of Effects for Fine Particle Dose

| Factor | ANOVA | Size of Effects | |
|---|---|---|---|
| | p-Values | Target Levels | LS-Means for FPD (µg) |
| $X_{50}$ (µm) | 0.0001 | 1.1 | 92.4 |
| | | 2.0 | 67.5 |
| EtOH (% w/w) | 0.0014 | 0.45 | 93.5 |
| | | 0.90 | 83.0 |
| | | 1.80 | 79.1 |
| | | 3.60 | 64.2 |
| OA (% w/w) | 0.0445 | 0.001 | 83.6 |
| | | 0.025 | 76.4 |
| Month | 0.0049 | 0 | 85.2 |
| | | 1 | 74.8 |

Figure 2 presents the correlation of ex-throat deposition for the OPC throat model to impactor mass (sum of stage 1 to MOC) as determined by NGI testing. The impactor mass for a given formulation is typically greater than the corresponding ex-throat deposition, with the difference between the impactor mass and ex-throat deposition decreasing with increasing flow rate. Statistical analyses shows that the ex-throat dose is significantly dependent on $X_{50}$ of the micronized drug, EtOH concentration, and flow rate (see Table 4). While flow rate is not a batch parameter, it was included in the statistical analyses with (1) the intent to extrapolate this model to subject/patient variability based on inhalation rate and/or (2) identify formulations that are not particularly sensitive to flow rate. Decreasing the $X_{50}$ of the micronized drug, decreasing the EtOH concentration, or increasing the flow rate increases the ex-throat drug deposition, as supported by published findings [4,5]. The following model explains 96% of the variation seen in ex-throat dose for the medium throat:

$$\text{Ex-Throat Dose} = 5.2 - 31.4\times\ln(X_{50}) - 10.0\times EtOH + 0.37\times OA + 18.6\times\ln(\text{flow rate}).$$

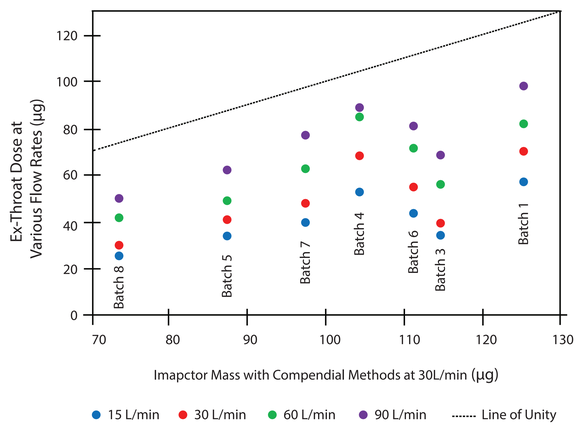


**Figure 2:** Correlation of ex-throat dose for medium OPC throat model at four flow rates to impactor mass as determined by compendial method using the NGI with USP induction port operated at 30 L/min. Data are only presented for initial time point.

**Table 4:** Summary of ANOVA and Size of Effects for Ex-Throat Dose (Medium Throat)

| Factor | ANOVA | Size of Effects | |
|---|---|---|---|
| | p-Values | Target Levels | LS-Means for Ex-Throat Dose (µg) |
| $X_{50}$ (µm) | <0.0001 | 1.1 | 67 |
| | | 2.0 | 47 |
| EtOH (% w/w) | <0.0001 | 0.45 | 66 |
| | | 0.90 | 62 |
| | | 1.80 | 55 |
| | | 3.60 | 47 |
| OA (% w/w) | 0.9574 | 0.001 | 57 |
| | | 0.025 | 57 |
| Flow Rate (L/min) | <0.0001 | 15 | 41 |
| | | 30 | 50 |
| | | 60 | 64 |
| | | 90 | 75 |

## CONCLUSIONS

Through evaluation of FPD and ex-throat dose data for HFA-227 MF suspension pMDIs with varying micronized drug $X_{50}$, and EtOH and OA concentrations, it was found that micronized drug $X_{50}$ and EtOH concentration significantly impact pMDI product performance, while OA concentration has a less significant effect. The mathematical models presented herein can be utilized as a tool to design similar formulations with desired in vitro product performance by determining suitable combination of formulation components.

## ACKNOWLEDGEMENTS


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