THE EFFECTS OF FORMULATION FACTORS ON THE AEROSOLIZATION PERFORMANCE OF METERED DOSE INHALERS

Denise S. Conti[1], Jay Holt[2,4], Poonam Sheth[2], Dennis Sandell[3], Anthony Hickey[2,5], Bhawana Saluja[1,6]

[1] Office of Generic Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD, USA; [2] Recipharm Laboratories, Inc., Morrisville, NC, USA; [3] S5 Consulting, Blentarp, Sweden; [4] Present: Aurobindo Pharma USA, Inc., Raleigh, NC, USA; [5] Present: RTI International, Research Triangle Park, NC, USA; [6] Present: Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD, USA.

Introduction

Metered dose inhalers (MDIs) are complex drug-device combination products widely used as portable delivery systems to treat pulmonary disorders, such as asthma and chronic obstructive pulmonary disease (COPD). A typical MDI consists of a canister containing the formulation, a metering valve, and an actuator-mouthpiece.[1] The formulation can be either a solution [active pharmaceutical ingredient (API) dissolved in the liquid propellant] or a suspension (API particles dispersed in the liquid propellant) along with inactive ingredients (e.g., co-solvents and surfactants).[2] Figure 1 presents the components of a typical MDI.

The product performance of MDIs depends on a multitude of factors including, but not limited to, the physicochemical properties of API, device geometry (e.g., valve metering chamber volume, actuator nozzle orifice diameter, actuator sump depth and actuator orifice jet length) and nature and amount of inactive ingredient(s).[3] Under the Quality by Design (QbD) paradigm, systematic investigations are necessary to understand how changes in critical quality attributes (CQAs) of formulation, device and manufacturing process influence the product performance.[4]

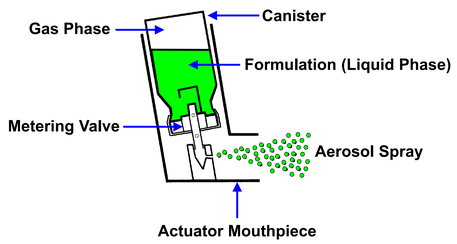


Figure 1. Schematic of a typical MDI.[3]

Although much is known about the effects of changes in device geometry on MDI product performance,[5,6] the effects of changes in formulation factors are not clearly defined. Therefore, the purpose of this work is to provide a better understanding of the effects of different levels of inactive ingredients and drug particle size distribution (PSD) on the aerosolization performance of MDI products. The systematic approach applied in this work can be utilized as a QbD tool to develop mathematical models and design spaces, allowing the manufacture of formulations with desired product performance parameters through a proper combination of formulation factors.

Methods

Selection of Commercial MDIs: Proventil® HFA 90 mcg base/inhalation (albuterol sulfate suspension), Qvar® 40 mcg/inhalation (beclomethasone dipropionate solution) and Dulera® 200 mcg/inhalation (mometasone furoate suspension, the formulation of interest). These MDIs represent two types of formulations (suspension and solution), two drug categories (bronchodilator and corticosteroid) and have inactive ingredients, in addition to propellant, at concentrations that could be varied around central targets.

Reverse Engineering and Characterization of Commercial MDIs: (1) total content per canister (drug, ethanol, oleic acid and moisture); **(2)** drug PSD (D_{50}, the median volumetric particle size, that is, a diameter such that 50% of particles are smaller) via static laser-light diffraction (Sympatec HELOS) using dry and wet dispersion techniques; **(3)** delivered dose uniformity (DDU); **(4)** aerodynamic particle size distribution (APSD) using Next Generation Impactor (NGI) with USP induction port and flow rate at 30 L/min.

Establishment of Model System MDIs: Similar to the commercial MDIs with respect to formulation composition and key aerosolization performance parameters.

MDI Batch Manufacturing Plan: The levels of inactive ingredients [ethanol (EtOH) and oleic acid (OA)] and drug PSD D_{50} were varied according to a reduced factorial statistical design of experiments (DoE) approach. The following ranges were studied:

MDI Formulation	*PSD D_{50} (μm)*	*EtOH (% w/w)*	*OA (% w/w)*
Albuterol Sulfate (AS) Suspension	*1.4 - 2.5*	*7 - 20*	*0.005 - 0.1*
Mometasone Furoate (MF) Suspension	*1.1 - 2.0*	*0.45 - 3.6*	*0.001 - 0.025*
Beclomethasone Dipropionate (BDP) Solution	*N/A*	*7- 9*	*0 - 2*

Manufacture of DoE MDIs: Micronized drug was prepared from the same mother batch by sizing down to the desired drug PSD D_{50} using jet mill process. Suspension MDIs were manufactured via one-step pressure filling. Solution MDIs were manufactured via two-step pressure filling. A total of 18 (AS), 8 (MF) and 9 (BDP) batches of DoE MDIs were manufactured. At least 20 canisters were filled per batch.

Aerosolization Performance Parameters of DoE MDIs: Delivered dose (DD) and fine particle dose less than 5 μm (FPD<5) at beginning (B) canister life stage.

Statistical Analysis and Simulation of Design Spaces: A formulation factor was considered to have a statistically significant effect on the aerosolization performance parameter if p value < 0.05. Multivariate mathematical models and design spaces were developed to predict MDI aerosolization performance parameters according to the different levels of formulation factors.

Results

Delivered Dose

DoE MDIs	Factors	DD
AS Suspension	Drug PSD D_{50}	0.4717
	Ethanol	0.0193
	Oleic Acid	0.2645
MF Suspension	Drug PSD D_{50}	0.2433
	Ethanol	0.0122
	Oleic Acid	0.2433
BDP Solution	Ethanol	0.8691
	Oleic Acid	0.0006

Table 1: ANOVA for DD of DoE MDIs (p < 0.05 yellowed).

The effects of ethanol and oleic acid were statistically significant.

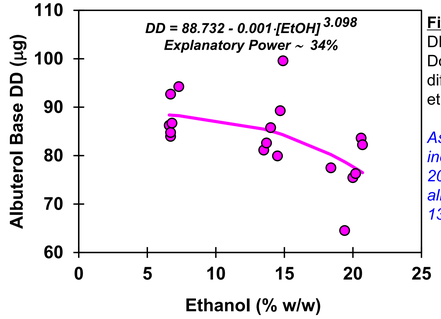


Figure 1: Changes in DD of AS suspension DoE MDIs according to different levels of ethanol.

As the level of ethanol increased from 7% to 20% w/w, the DD of albuterol decreased by 13%.

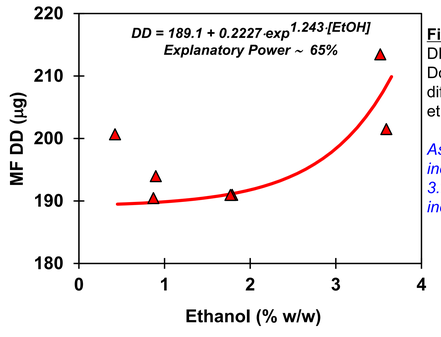


Figure 2: Changes in DD of MF suspension DoE MDIs according to different levels of ethanol.

As the level of ethanol increased from 1.8% to 3.6% w/w, the DD of MF increased by 9%.

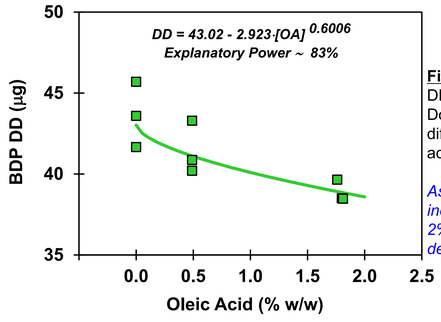


Figure 3: Changes in DD of BDP solution DoE MDIs according to different levels of oleic acid.

As the level of oleic acid increased from 0% to 2% w/w, the DD of BDP decreased by 11%.

Fine Particle Dose < 5 μm

DoE MDIs	Factors	FPD<5
AS Suspension	Drug PSD D_{50}	0.0006
	Ethanol	0.0000
	Oleic Acid	0.5790
MF Suspension	Drug PSD D_{50}	0.0001
	Ethanol	0.0014
	Oleic Acid	0.0445
BDP Solution	Ethanol	0.5973
	Oleic Acid	0.0121

Table 2: ANOVA for FPD<5 of DoE MDIs (p < 0.05 yellowed).

The effects of ethanol, oleic acid and drug PSD D_{50} were statistically significant.

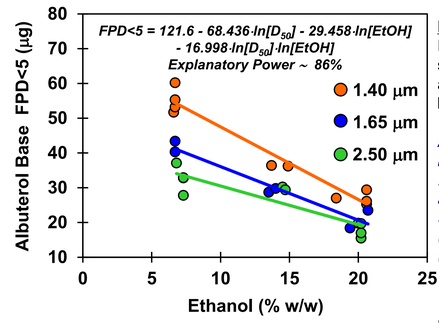


Figure 4: Changes in FPD<5 of AS suspension DoE MDIs according to different levels of ethanol.

As the level of ethanol increased from 7% to 20% w/w, the FPD<5 of albuterol decreased by 51% (1.40 μm), 50% (1.65 μm) and 45% (2.50 μm).

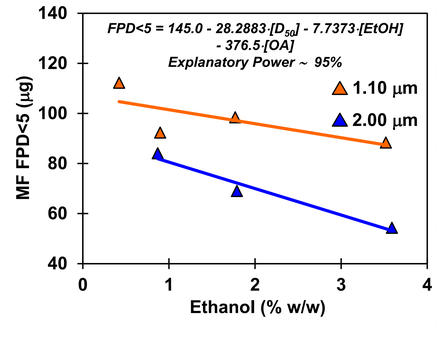


Figure 5: Changes in FPD<5 of MF suspension DoE MDIs according to different levels of ethanol.

As the level of ethanol increased from 0.45% to 3.6% w/w (1.1 μm) and from 0.90% to 3.6% (2.0 μm), the FPD<5 of MF decreased by 21% and 35%. As the level of oleic acid increased from 0.001% to 0.025% w/w, the FPD<5 of MF decreased by 5% (1.1 μm) and 29% (2.0 μm).

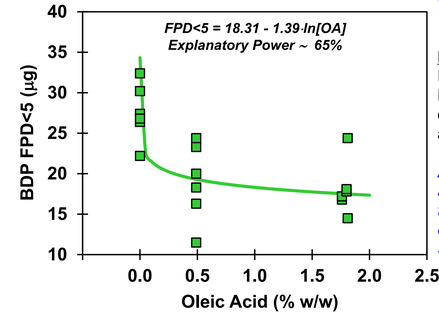


Figure 6: Changes in FPD<5 of BDP solution DoE MDIs according to different levels of oleic acid.

As the level of oleic acid increased from 0% to 2% w/w, the FPD<5 of BDP decreased by 34%.

Design Spaces

Figure 7: FPD<5 (specified to be 21-43 μg of albuterol base) according to different levels of ethanol (EtOH) and drug PSD D_{50} in AS suspension DoE MDIs.

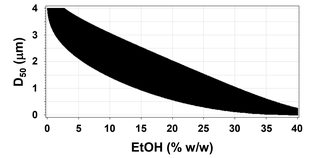
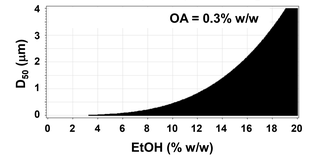


Figure 8: Coefficient of variation (CV) of DD (specified to be < 10%) according to different levels of ethanol (EtOH) and drug PSD D_{50} at a constant level of oleic acid (OA) in AS suspension DoE MDIs.



Conclusions

- The changes in drug PSD D_{50} had statistically significant effects on the FPD<5 of suspension MDI formulations studied, but not on DD.
- The changes in concentrations of ethanol and oleic acid showed, in some cases, statistically significant effects on DD and FPD<5 of suspension and solution MDI formulations studied. However, several cases without effects were also found, despite some large changes in concentrations of inactive ingredients studied. The possible effects of varying these must hence be studied on a case-by-case basis.
- The outcomes of this study allowed defining design spaces for DD and FPD<5 according to the different levels of formulation factors (ethanol and oleic acid concentrations, and drug PSD D_{50}). The systematic approach utilized in this work can contribute as a QbD tool to evaluate the extent to which the formulation factors govern the aerosolization performance of MDI products, helping to design MDI formulations with desired product performance parameters.

References

1. Stein, S.W., *et al.*, *AAPS PharmSciTech*, 2013. 15(2): p. 326-338.
2. Bell, J. and S. Newman, *Expert Opinion on Drug Delivery*, 2007. 4(3): p. 215-234.
3. S.P. Newman. *Respiratory* Care, 2005. 50(9): p.1177-1190.
4. Lionberger, R.A., *et al.*, *The AAPS Journal*, 2008. 10(2): p. 268-276.
5. Smyth, H., *et al.*, *Drug Development and Industrial Pharmacy*, 2006. 32(9): p. 1033-1041.
6. Smyth, H., *et al.*, *Pharmaceutical Research*, 2006. 23(7): p. 1591-1596.

Acknowledgements

- Funding for this work was made possible, in part, by the Food and Drug Administration through grant U01FD004943.
- Views expressed in this publication do not necessarily reflect the official policies of the Department of Health and Human Services, nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.