Effect of Coating of Andersen Cascade Impactor and Next Generation Impactor on the Aerodynamic Particle Size Distribution of Nine Commercial Metered Dose Inhalers

T1030-08-44

Abhinav R. Mohan[1]; Sneha Dhapare[1, 2]; Bryan Newman[1]; Mårten Svensson[3]; Peter Elfman[3]; Jackie Stuckel[3]; Dennis Sandell[4,#]; Lawrence Winner[5]; Jürgen Bulitta[5]; and Günther Hochhaus[6]

1 Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD, USA, 2 Current Affiliation: Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD, USA, 3 Emmace Consulting AB, Scheelevägen 22, SE-223 63 Lund, Sweden, 4 S5 Consulting, Ekvägen 8, SE-275 62 Blentarp, Sweden; # In Memoriam, October 29, 2020, 5 Department of Statistics, College of Liberal Arts and Sciences, University of Florida, Gainesville, FL, USA, 6 Department of Pharmaceutics, College of Pharmacy, University of Florida, Gainesville, FL, USA

CONTACT INFORMATION: abhinav.mohan@fda.hhs.gov

PURPOSE

The aerodynamic particle size distribution (APSD) measurements of metered dose inhalers (MDIs) are a key component for formulation and product development, quality control, and for the in vitro assessment of bioequivalence between a branded and generic product. Evaluation of the APSD parameters is performed using one of the two pharmacopeial impactors: Andersen Cascade Impactor (ACI) and Next Generation Impactor (NGI). Typically, coating of different stages of an impactor with a material such as brij/glycerol is considered for dry powder inhalers (DPIs) to reduce the risk for particle bounce but is not generally utilized for MDIs.

OBJECTIVE(S)

To investigate whether coating of the impactor stages should be considered for solution and suspension MDIs, this study assessed the effect of coating of ACI stages on the APSD measurements of 9 commercial MDI products and compared the effect of stage coating between an ACI and NGI.

METHOD(S)

Experimental

- **Number of products studied:** 9 solution and suspension MDI products
- **Experimental parameters:** ACI – 28.3 LPM; NGI – 30 liters per minute (LPM); ACI and NGI stages coated with a solution consisting of 40 g glycerol and 10 ml of a mixture comprised of 15 g Brij-35 in 100 ml of 96% ethanol**;** USP inlet not coated; 6 actuations fired into the impactor

Product	API(s)	Strength(s)	Formulation Type
ADVAIR® HFA	Fluticasone Propionate; Salmeterol Xinafoate	0.045 mg/inh; EQ 0.021 mg base/inh	Suspension
ALVESCO®	Ciclesonide	0.08 mg/inh	Solution
ASMANEX® HFA	Mometasone Furoate	0.05 mg/inh	Suspension
ATROVENT® HFA	Ipratropium Bromide	0.021 mg/inh	Solution
BEVESPI AEROSPHERE™	Formoterol Fumarate; Glycopyrrolate	0.0048 mg/inh; 0.0090 mg/inh	Suspension
FLOVENT® HFA	Fluticasone Propionate	0.044 mg/inh	Suspension
PROAIR® HFA	Albuterol Sulfate	EQ 0.09 mg base/inh	Suspension
PROVENTIL® HFA	Albuterol Sulfate	EQ 0.09 mg base/inh	Suspension
SYMBICORT®	Budesonide; Formoterol Fumarate	0.08 mg/inh; 0.0045 mg/inh	Suspension

Analytical

- **Parameters evaluated:** Fine particle dose (FPD); Fine particle fraction < 5 µm (FPF5) and FPF < 1 µm (FPF1); Mass median aerodynamic diameter (MMAD)
- **Statistical analysis:** ANOVA model built in RStudio using the MDI product, impactor type and coating, and their interaction as effect factors to distinguish effects of impactor type and coating

RESULT(S)

Coating effect vs. aerodynamic particle size

- Figure 1 shows the effect by coating vs. aerodynamic particle size for each product using an ACI
- There was no significant effect of coating from stage 1 to stage 4 of the ACI
- Coating effects were evident at the later stages of the ACI for particles < 2 µm, with the size of the effect increasing with decreasing size

Coating of the ACI vs. NGI

- Figure 2 shows the FPF1, and MMAD measurements from the ACI and NGI, as a ratio of coated to uncoated impactor. A coated/uncoated ratio greater than 1 indicates that the measurements increase with coating; while a coated/uncoated ratio less than 1 indicates that measurements decrease with coating
- Coating significantly decreased small fines (FPF1, $p<0.05$), and increased aerodynamic particle size (MMAD, $p<0.05$) as compared to when the stages were uncoated
- This was observed by 19 of 24 samples having a coated/uncoated ratio of less than 1 for FPF1 and 18 of 24 samples having a coated/uncoated ratio greater than 1 for MMAD
- More products showed a significantly higher MMAD as a result of coating for an NGI than the ACI
- This study using an ACI suggested that the effect of coating appeared to be unrelated to the formulation type

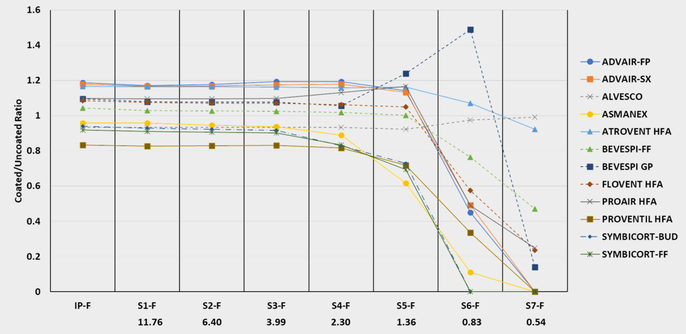

Figure 1: *Coating effect vs. aerodynamic particle size. Data: ratio of the mean of triplicate runs. FP: Fluticasone propionate; SX: Salmeterol xinafoate; FF: Formoterol fumarate; GP: Glycopyrrolate; BUD: Budesonide. The Andersen Cascade Impactor stage cutoff values (µm) are shown in the x-axis.*

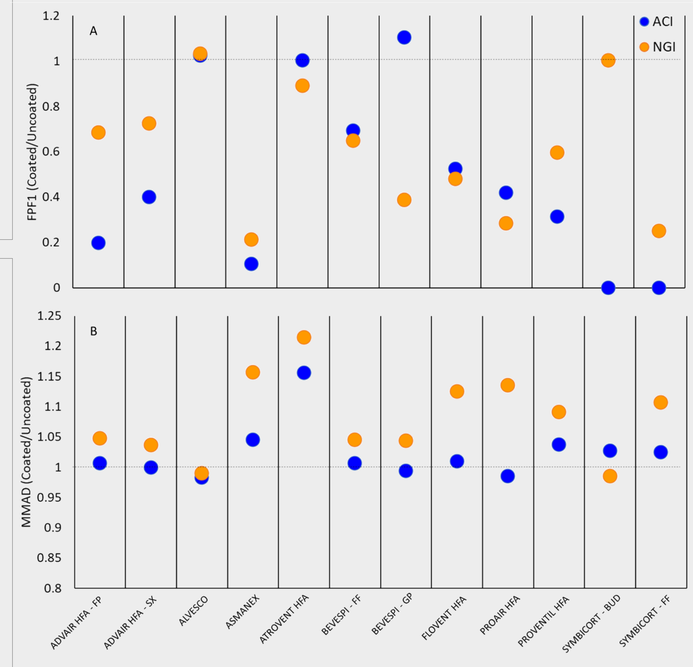

Figure 2: *Ratio of coated to uncoated* ***A)*** *FPF1, and* ***B)*** *MMAD of 9 commercial MDI products identified in Table 1. Data: ratio of the mean of triplicate runs. FP: Fluticasone propionate; SX: Salmeterol xinafoate; FF: Formoterol fumarate; GP: Glycopyrrolate; BUD: Budesonide. FPF5: fine particle fraction < 5 µm; FPF1: fine particle fraction < 1 µm; MMAD: mass median aerodynamic diameter. ACI: Andersen Cascade Impactor; NGI: Next Generation Impactor. Dotted line represents a coated to uncoated ratio of 1 indicating no change.*

CONCLUSION(S)

Impactor coating showed significant effects on FPF1 and MMAD, but not on FPF5 (data not shown), indicating that coating may influence smaller particulates and reduce the amount of respirable small fines while maintaining the respirable fraction (FPF5) relatively unchanged. The data suggest that coating may reduce the particle bounce in case of superfine particles for MDIs.

REFERENCE(S)

Sandell, D., Svensson, M., Conti, D., Sheth, P., Oguntimein, O., Bielski, E., Bulitta, J., Hochhaus, G. Coating Stages of Next Generation Impactor (NGI) When Testing Metered Dose Inhalers (MDIs) – A Comparative Study on US Commercial MDI Products. *Respiratory Drug Delivery 2020.* Volume 2. 2020: 463-468.

ACKNOWLEDGEMENT(S)

- Funding for this work was made possible, in part, by the U.S. Food and Drug Administration through Contract 75F40119C10154 and Grant U01FD004943
- Abhinav Mohan was supported by a fellowship program administered by the Oak Ridge Institute for Science and Education (ORISE) through an interagency agreement between the U.S. Department of Energy and the U.S. FDA
- The views expressed in this poster are from the authors only and 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