Coating Stages of Next Generation Impactor (NGI) When Testing Metered Dose Inhalers (MDIs) – A Comparative Study on US Commercial MDI Products

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INTRODUCTION

Determination of the aerodynamic particle size distribution (APSD) of orally inhaled drug products (OIDPs) is performed for quality control (QC) and many other purposes, such as formulation and product development, in-vitro bioequivalence (IVBE) assessment between a candidate generic and the originator product, or assessment of in-vivo/in-vitro correlation (IVIVC). Testing is typically performed using one of the pharmacopeial impactors. For dry powder inhalers (DPIs), it is standard to coat stages of the impactor with some sticky material (e.g., silicone) to reduce the risk for particle bounce (non-size related transfer of material to lower stages). For metered dose inhalers (MDIs), impactor stage coating is typically seen as not necessary.

During evaluation of APSD data collected as part of a U.S. Food and Drug Administration (FDA) Generic Drug User Fee Amendments- (GDUFA-) sponsored study on the effect of formulation factors on MDI performance [1,2,3], some method differences were observed when the same batches of three suspension-based MDI formulations of mometasone furoate (MF) differing in MF particle size, ethanol and oleic acid content, were tested by two different laboratories. Review of the testing methodology revealed that one laboratory coated the Next Generation Impactor (NGI) stages while the other did not. To explore the possible magnitude of this "coating effect", one of the laboratories re-tested all three MF MDI batches using the NGI with both coated and un-coated stages (3 canisters per batch; each canister tested 3 times with coated NGI stages and 3 times without coating). The results for fine particle dose less than 2 µm (FPD<2) are summarized in Table 1.

The results clearly showed a statistically significant reduction in FPD<2 upon coating (t-test: p = 0.0024, 0.0056, 0.0002 for N1, N2, and N4, respectively) indicating that particle bounce occurred for these MF MDI batches when stage coating was not used. It is also seen that the extent of this effect differs across the batches (N2 differed from N1 and N4), indicating that the composition of the formulation might influence the need for coating the cascade impactor stages. Based on these findings it was decided to perform a similar study for a wide range of MDI products currently available on the U.S. market.

Batch	MF MDI Formulations* API D50** (µm)	Ethanol (w/w%)	Oleic acid (w/w%)	FPD<2 Without coating (µg)	With coating (µg)	With coating (% of without)
N1	1.69	0.53	0.004	24	7.7	32
N2	1.10	2.15	0.015	23	16	70
N4	1.69	1.35	0.010	27	9.0	33

(*) Actual results, not targets. (**) D50 = median volumetric particle size

Table 1: *FPD<2 for three MF MDI formulations tested at 30 L/min, with or without coating.*

MATERIAL AND METHODS

Eleven U.S. commercial MDI products were purchased for this study. Table 2 presents these MDI products together with information about the batches and formulations studied.

One canister for each MDI product was tested in this study. NGI runs with and without coating (3 of each) were performed in alternating order at 30 L/min flow rate. An internal standard solution consisting of 40 g glycerol and 10 mL of a mix of 15 g Brij-35 in 100 mL 96% ethanol was used as coating material. In agreement with current practice, an uncoated USP inlet was used. For all 11 US commercial MDI products, 6 actuations were fired into the NGI. The API amounts on the NGI stages were analyzed by HPLC using an internal standard technique.

Product	API(s) (µg)	Strength	Batch number	Expiration date	Formulation propellant	HFA	Ethanol	Oleic acid	excipients Other
Symbicort	Budesonide (BUD)/ Formoterol (FFD)	80/4.5	2000536C	03/2020	Suspension	227			PEG & PVP
Advair	Fluticasone (FLU)/ Salmeterol (SAL)	45/21	VY4F	05/2020	Suspension	134a			
Flovent	Fluticasone (FLU)	44	KP8U	04/2020	Suspension	134a			
QVAR Redihaler	Beclomethasone Dipropionate (BDP)	40	AFH68A	01/2020	Solution	134a	X		
Alvesco	Ciclesonide (CIC)	80	423745	02/2020	Solution	134a	X		
Atrovent	Ipratropium (IPRA)	17	180447	07/2020	Solution	134a	X	X	Citric acid & water
Asmanex	Mometasone (MOM)	100	S001211	05/2020	Suspension	227	X	X	
Proair	Albuterol (ALB)	90	DAD92A	10/2020	Suspension	134a	X		
Ventolin	Albuterol (ALB)	90	AN3V	12/2019	Suspension	134a			
Proventil	Albuterol (ALB)	90	180340	03/2020	Suspension	134a	X	X	
Bevespi	Glycopyrrolate (GBP)/ Formoterol (FFD)	9/4.8	6030069A	04/2020	Suspension	134a			DSPC* & calcium chloride

(*) DSPC = 1,2-Distearoyl-sn-glycero-3-phosphocholine

Table 2: *Investigated US commercial MDI products and related information.*

A total of 6 (3 coated and 3 uncoated) NGI runs were collected for each MDI product. The sample size selected was based on the results from the pilot MF MDI study which showed a standard deviation of 18% in the FPD<2 with/without coating ratio. Therefore, with n=3 tests both with coated NGI stages and with uncoated NGI stages, there is 80% chance to detect a 15% difference between FPD<2 determined with coated and uncoated NGI stages. This was considered to provide sufficient power for the study.

For each MDI product and API, the mean FPD<2 and 90% confidence interval (CI) for the mean FPD<2 with/without coating ratio was calculated. The difference between coated and uncoated FPD<2 was assessed by a standard t-test. The possible effect by formulation factors on the FPD<2 with/without coating ratio was assessed by ANOVA. The effect by coating vs. aerodynamic particle size was assessed graphically.

RESULTS

The results for FPD<2 are summarized in Table 3 and the 90% confidence intervals are also shown in Figure 1. Table 3 indicates that the mean FPD<2 is lower with coating in 11 of the 14 cases. The difference between coating and non-coating is statistically significant at the 5% level for 6 cases; all with lower FPD<2 for coated stages. The lack of statistical significance despite several mean ratios being <100% indicates that a larger sample size could have been more appropriate. The obtained with/without coating ratio ranged from 61.7% (Asmanex) to 105.6% (Atrovent). It can be noted that the product with the most distinct coating effect (Asmanex) is very similar in composition to the MF MDI formulations of the pilot study which triggered this more comprehensive investigation.

While overall FPD<2 was reduced upon coating, results also indicated that the extent of this coating effect and consequently the importance of coating NGI stages differs across the investigated MDI products. To identify potential reasons for this observation, an ANOVA was performed to investigate the effect by four factors on the FPD<2 with/without coating ratio: formulation type (suspension or solution), HFA propellant (227 or 134a), ethanol (present or not), and oleic acid (present or not). The factors PVP/PEG, citric acid, water and DSPC were not included in the analysis as each of these excipients were present only in one product (see Table 2). The results of the ANOVA are shown in Table 4.

The results demonstrate significant effects on FPD<2 by formulation type (suspension- or solution-based) and propellant (Table 4). By comparing Tables 2 and 3, it is seen that results for solution-based MDIs are not affected by coating, and that the coating effect is much stronger for products containing HFA 227. The lack of effects for other factors should not be considered definitive as the present analysis is only assessing the effect by presence or lack thereof. In addition, the excipient concentrations (which is not provided in the labels of these MDI products) might also play a role. This is particularly the case for "sticky" excipients such as oleic acid and PVP/PEG. Another factor that might affect results is the emitted dose. The effect of this could unfortunately not be assessed in the present data. The possible effect by coating for vs. APSD is shown for each product in Figure 2.

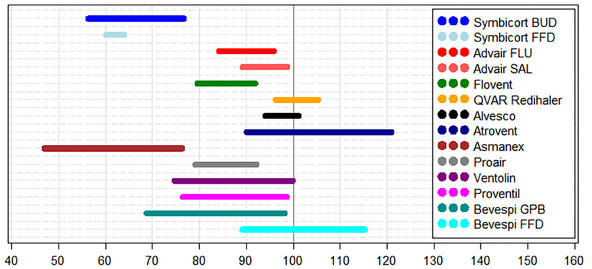

Figure 1: *90% CIs for the mean FPD<2 with/without coating ratio.*

Product	API	Mean without coating (% LC*)	Mean with coating (% LC)	p-value	With/without coating ratio (%)	90% CI for mean coating ratio
Symbicort	BUD	11.4	7.6	0.0108	66.6	56.3 - 76.8
	FFD	15.3	9.5	0.0003	62.1	60.2 - 64.1
Advair	FLU	21.0	18.9	0.0387	90.1	84.2 - 95.9
	SAL	23.8	22.4	0.0679	94.0	89.3 - 98.8
Flovent	FLU	24.2	20.7	0.0216	85.8	79.7 - 92.0
QVAR Red	BDP	54.5	54.9	0.6315	100.9	96.3 - 105.4
Alvesco	CIC	64.0	62.6	0.2045	97.7	94.1 - 101.3
Atrovent	IPRA	36.0	37.9	0.4021	105.6	90.1 - 121.0
Asmanex	MOM	10.2	6.2	0.0168	61.7	47.0 - 76.4
Proair	ALB	35.4	30.4	0.0238	85.7	79.2 - 92.3
Ventolin	ALB	25.2	22.0	0.1007	87.4	74.8 - 100.1
Proventil	ALB	30.1	26.3	0.0820	87.6	76.5 - 98.7
Bevespi	GBP	20.2	16.8	0.0825	83.5	68.8 - 98.3
	FFD	22.5	22.8	0.6647	102.3	89.1 - 115.4

(*) Label Claim.

Table 3: *Summary of results for FPD<2.*

Factor	Formulation	Propellant	Ethanol	Oleic acid
p-value	0.0099	<0.0001	0.4314	0.7466

Table 4: *Summary of ANOVA for coating effect on FPD<2*

Figure 2 clearly demonstrates that the effect by coating only impacts particles <4 µm, and that the size of the effect increases as particles become smaller. The key parameter fine particle dose <5 µm (FPD<5) will thus not be affected by coating. Additionally, Figure 2 illustrates that suspension-based MDI products would be better evaluated with coated stages to reduce bounce, and that those using HFA 227 are the most affected. The latter result is rather surprising and further investigation is needed to confirm or falsify this finding.

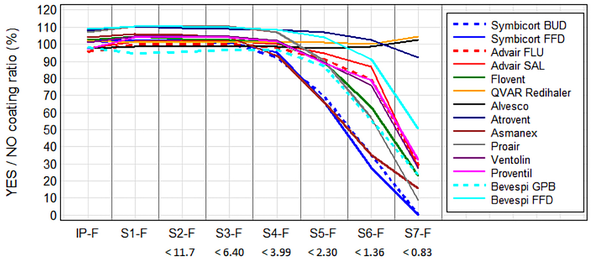

Figure 2: *Coating effect (%) vs. aerodynamic particle size.*

CONCLUSIONS

An investigation on the effect by coating NGI stages has been performed for 11 U.S. commercial MDIs. The results show that

- coating reduces bounce and FPD<2 is typically lower with coating,
- the effect by coating increases with decreasing particle size,
- solution products are not significantly affected,
- products using HFA 227 may benefit the most by coating, and
- no effect by the presence of ethanol or oleic acid in the formulation could be detected.

Based on the results, it is suggested that coating of NGI stages when testing suspension MDIs should be considered.

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