Understanding the importance and effects of shaking on pMDI performance

Alyssa Newcomb[1], Dino J. Farina[1]

[1] Proveris Scientific Corporation, 290 Donald Lynch Boulevard, Suite 100, Marlborough, MA U.S.A.

Summary

This paper explores how a design of experiments ("DoE") approach was employed to provide a foundational understanding of the effects of shaking on dose content uniformity ("DCU") and spray pattern performance of commercially available albuterol pressurized metered dose inhaler ("pMDI") products. The pMDIs tested were suspension formulations with different excipients that are all known to be sensitive to shaking based on their respective usage instructions for patients (i.e. the instructions only include language such as "…shake well before each use…"). The DoE focused on controlling and systematically varying the duration, angle, and frequency of shaking immediately prior to automated actuation and measuring the resultant DCU and spray pattern performance of the emitted aerosols. DCU was selected as an obvious output for in vitro performance based on accepted regulatory guidance documents. Specific optical spray pattern measurements were included in the DoE to see if such measurements could be correlated to the shaking conditions, and if so, how these measurements could be used to build an alternative model for efficient, high resolution, in vitro performance prediction for through life testing of pMDIs. The results indicate that the pMDIs tested have statistically significant differences in their performance sensitivities to shaking and that these differences should be explained to patients for optimal benefit.

Introduction

The drive for an approved generic albuterol based pMDI has significantly increased in recent years due to the cost barrier, patent expiration of reference products, and recently released draft FDA guidance documents. Product usage instructions for all the current FDA approved albuterol pMDIs only include non-descript language for shaking the pMDI such as "… shake well before each use…" with no indication for the patient regarding shaking duration, frequency, orientation, shake-to-fire interval, or what the effects might be if the patient doesn't shake the product before use. From a formulation perspective, shaking is critical for suspension pMDIs because the active drug particles in the formulation tend to rapidly sink or rise to the liquid surface due to differences in density from the propellants. Excipients, such as ethanol and oleic acid, are often added to suspension pMDI formulations to provide a more stable suspension of the active drug into the propellant [1].

Another factor that was used in selecting the particular albuterol pMDIs in this study is that patients are rarely prescribed just one inhaled medication. And since all of these products contain the same active ingredient, albuterol, a doctor/therapist could likely prescribe any of these products to a patient for the same indication thinking that the products are equivalent, when they may not be due to their different excipients (among other physical differences) – and the effect of these differences may influence the performance of the product from a patient perspective. The implications of this type of patient confusion has been well documented in the respiratory literature [2].

Lastly, the in-vitro spray test methods required to show bioequivalence of pMDI products from a regulatory perspective, particularly DCU and aerodynamic particle size distribution ("APSD") through-life testing, are time intensive, complicated, and error-prone. Hence, a faster, more efficient, and less labor intensive performance indicating metric, such as optical spray pattern, would help relieve the testing/characterization burden for pMDI product development and help support the generation of more valuable DCU and APSD measurements.

Methodology

Three different reference products containing albuterol sulfate were tested through life following a 3 variable, 3 level Box-Behnken DOE ("BB-DoE") approach. Table 1 below shows the derived control ranges employed to determine the effects of shaking (duration, angle, and frequency) on spray pattern in BB-DoE coded formats. The ranges for the shaking parameters shown in Table 1 were derived from separate human ergonometric studies conducted by Proveris Scientific analysts using the pMDI products. Three canisters per product were tested using 13 variable shaking combinations that were inputted into Viota® software methods and executed using a SprayVIEW® measurement system SFpMDI (Proveris Scientific, Marlborough, MA U.S.A.).

Table 1: BB-DoE control variable ranges for tested shake parameters. These ranges were derived from separate human ergonometric studies conducted by Proveris Scientific analysts using the same pMDI products.

Control Variable	BB-DoE Values		
	-	0	+
Shake Frequency (Hz)	2.0	3.0	4.0
Shake Angle (degrees)	60	90	120
Shake Duration (s)	5	10	15

Using the same shaking regime for each product, an experiment alternating actuations for spray pattern and DCU collection was designed and is being executed at the time of publication to see if optical spray pattern and DCU are statistically correlated. This study will involve collecting ten (10) actuations each at the beginning, middle, and end of life on three (3) cans for each product. Additionally, a DCU through-life experiment was conducted for the product with no excipients using a "shake vs. no shake" comparison where the "shake" parameters were derived from the optical spray pattern DoE results. In these studies, each DCU sample was collected following the protocol outlined in the United States Pharmacopeia using an alternative dose uniformity sampling apparatus and quantified using a spectrophotometric method (ThermoFisher GENESYS 10S UV-Vis Spectrophotometer).

Discussion and Results

The consolidated results from the multi-dimensional spray pattern DoE are shown in Figure 1 below as a "sensitivity plot" of the spray pattern area plotted against the shaking parameters for each pMDI product (indicated by the number of excipients where Product A had no excipients, Product B had 1 excipient, and Product C had 2 excipients). Table 1 below summarizes the sensitivity analysis in simple "yes" or "no" terms based on statistical p-value analysis.

The results clearly indicate that the products produce vastly different sized spray patterns under identical test conditions with Product A producing the smallest patterns (mean value of about 132 mm^2) and Product C producing the largest (mean value of about 350 mm^2). The results also indicate that Product A has acute sensitivity to shake duration (about a 20% change in spray pattern area when the device was shaken before each actuation for 5 seconds compared to 15 seconds), while Product B has some sensitivity to shake angle. This result is significant since shake duration is not indicated in the any of the product's respective patient usage instructions. Product C seems immune to shaking within the tested range. However, this product did exhibit substantially more shot-shot variation than the others and this variation may be masking the product's true sensitivity.

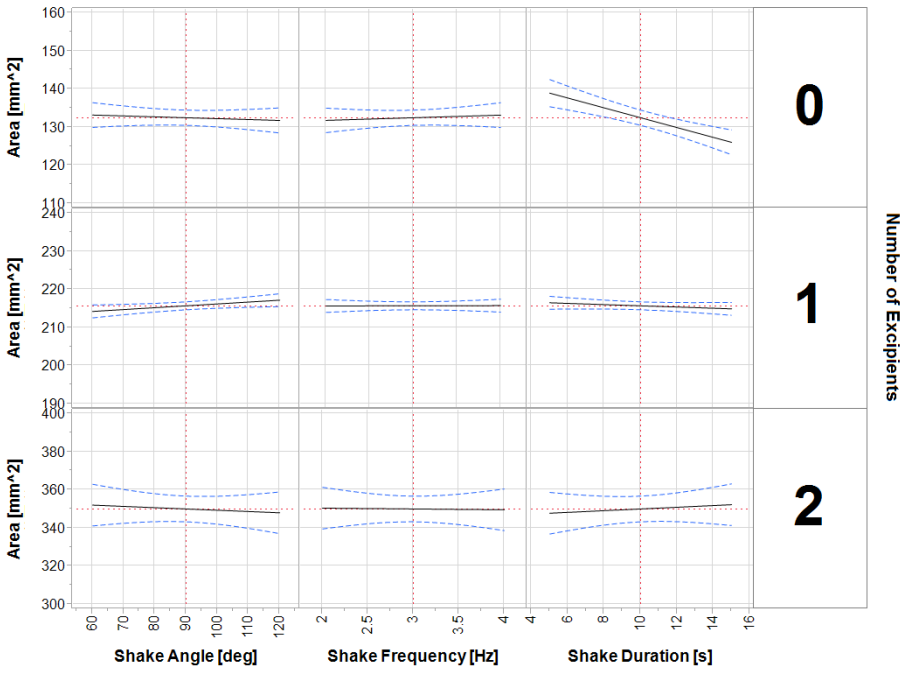

Figure 1: Consolidated optical spray pattern sensitivity profiles for the three (3) tested pMDI products (identified by the number of excipients) as a function of shaking. Auto-scaled y-axes were used to accommodate the different spray pattern area ranges for the products.

Table 2. Simplified optical spray pattern area sensitivity results. A "Yes" entry indicates a statistically significant sensitivity was found (i.e. the p-value of the statistics was less than 0.05) while a "No" entry indicates no statistically significant sensitivity was found.

Number of Excipients	Shake Angle	Shake Frequency	Shake Duration
0	No	No	Yes
1	Yes	No	No
2	No	No	No

Results from DCU through-life testing of Product A (no excipients) are shown in Figure 2 and Figure 3 where "no shake" indicates that the product samples were not shaken at any point during the experiments; and "shake" indicates that the product samples were shaken with the following parameters: (10 second duration, 60 degree angle, and 4 Hz frequency) prior to automated actuation. In all cases the product samples were allowed to rest for 3 minutes (180 seconds) between consecutive automated actuations.

The results show a startling effect of not shaking the product on DCU performance: the emitted dose during beginning of life is considerably variable and nearly three times the target value (108 mcg) before it starts to taper off at the middle and end of life stages. However, since so much excess drug was emitted during BoL, the EoL performance shows only about 25% of the target dose is being delivered as shown in Figure 3. In contrast, the "shake" data indicates very consistent and very near target DCU performance from the product at all life stages.

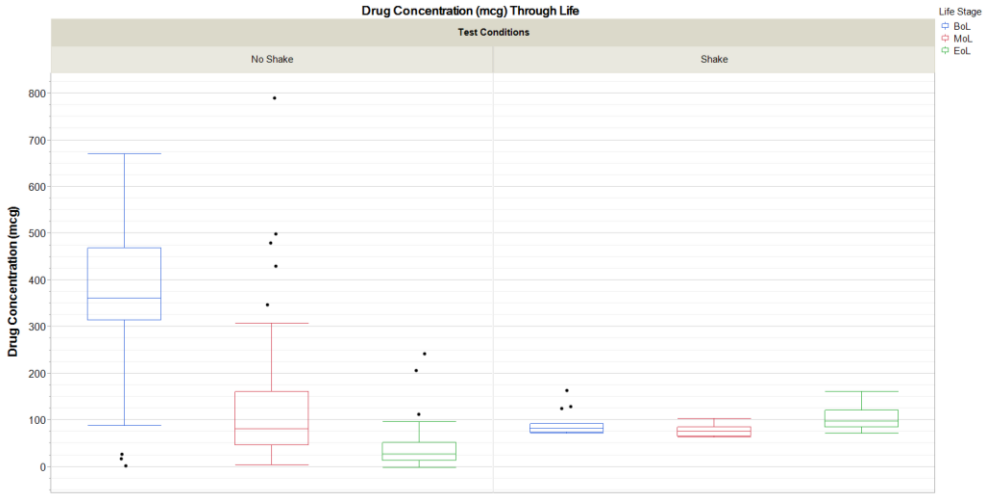

Figure 2: The effects of shaking vs. not shaking on through-life DCU performance for Product A (no excipients).

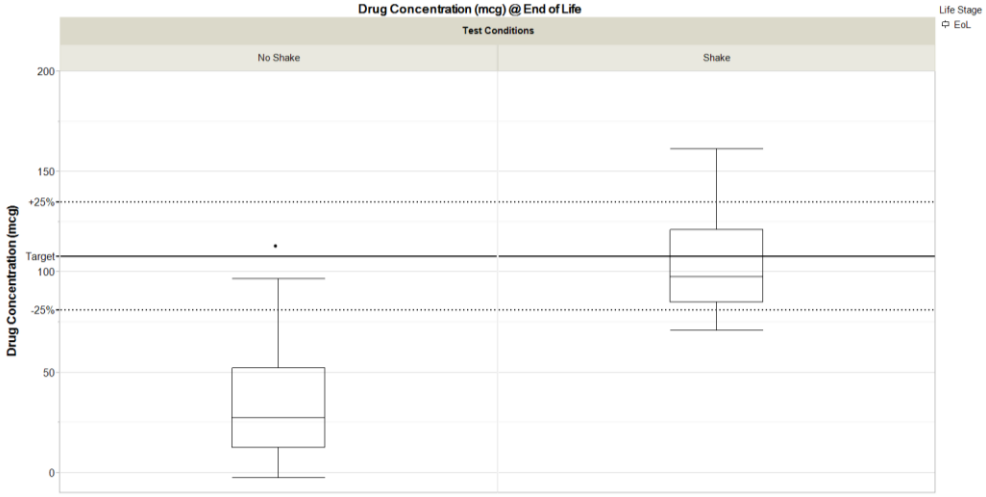

Figure 3. Detailed view of end of life DCU performance for Product A (no excipients) with and without shaking.

Conclusion

The DCU and optical spray pattern performance of three different commercially available albuterol pMDI products were shown to have markedly different sensitivities to shaking. The product with no added excipients produced the smallest optical spray patterns and was sensitive to shake duration – a parameter not included in any of the product's patient usage instructions. Additionally, the effects of not shaking the product without excipients were profound – nearly 3 times the target DCU was measured at the beginning of life which resulted in only about 25% of the target dose being delivered at the end of life. Current patient instructions for the respective products do not include specified guidelines on shaking (particularly shake duration) or the effects of not shaking the product, which were shown here to be rather profound with respect to DCU on one product. However by providing more defined instructions on how to shake and the importance of shaking, patient confusion could be reduced and more effective patient usage could occur.

References

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[2] Fink J, Rubin B: *Problems with Inhaler Use: A Call for Improved Clinician and Patient Education*. Respiratory Care Journal, September 2005; Vol. 50 No. 10: pp 1360-1365.