How critical quality attributes and process variables drive the in-vitro performance of pMDIs: new technologies and methods

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Keywords

Pressurized metered dose inhaler ("pMDI"), design of experiments ("DoE"), shaking duration, spray pattern, dose content uniformity ("DCU"), aerodynamic particle size distribution ("APSD")

Background

Few published sources exist to help guide pMDI formulation and device development that incorporate an understanding of the complex relationships driving product performance. Current analytical methods are complicated and labor intensive, and provide little insight into commonly occurring defects in pMDIs or their performance during development and release testing. The three new measurement technologies and analysis techniques described in this poster rapidly promote a knowledge-driven understanding of the complex relationships between the critical quality attributes and process variables that drive pMDI in vitro performance. This paper will examine the following:

1. The importance of shaking;
2. The connection between DCU and spray pattern using predictive models; and
3. New technology for rapidly screening for actuator mold defects to aid in APSD testing.

Methods

1. Using commercially available albuterol sulfate pMDIs [1], a three variable, three level Box-Behnken design of experiments ("BB-DoE") approach [2] was employed to determine the effects of device shaking (duration, angle, and frequency) on spray pattern. Table 1 shows the derived control ranges in BB-DOE coded formats. The scenarios were implemented into Viota® software methods and executed using a SprayVIEW® measurement system SFpMDI with automated shaking actuator (Proveris Scientific, Marlborough, MA U.S.A.). Thirteen canisters from the same lot were used in these experiments and 10 replicates were collected from each sample for each scenario.
2. From the results, an optimal shaking regime was determined. Comparing the optimal shake and a "no shake" condition, three devices per condition were tested through each canister's 200 actuations; obtaining alternating spray pattern and DCU measurements for 10 actuations at the beginning, middle, and end of the canister's life, and firing down the intermediate shots.
3. Additionally, through precise alignment of the device and it's orifice, the center of gravity ("COG") coordinates of each collected spray pattern were used to rapidly screen various actuator molds for defects using a Proveris Scientific proprietary COG measurement tool and the SprayVIEW® system SFpMDI to measure spray pattern area.

Results

1. Using predictive modeling, the data indicates that shake duration was the driving shake parameter for product performance. Figure 1 shows the prediction profiler graph demonstrating that shake duration had significant influence on the pMDI product's spray pattern area. There was about a 20% change in spray pattern area when the device was shaken before each actuation for 5 seconds compared to 15 seconds. This result is significant because shake duration is not commonly defined in patient usage instructions for pMDIs.
2. The device's relative drug concentration and spray pattern area were compared in the shake vs. no shake test conditions. When the device was not shaken, drug concentration was highly variable at the canister's beginning of life and showed significant tail off by end of life ("EoL") with the emitted spray below the expected dose. The coupled spray pattern area results for the no shake condition mirrored the drug concentration results, with the same tail off effect by EoL. When the device was shaken using the parameters determined in the previous step, expected dose amounts were consistently measured. Both the drug concentration and spray area results remained stable through life with no tail off effect. The consolidated results from the shake vs. no shake study are shown in Figure 2.
3. Through proper alignment and setup, spray pattern was used to rapidly screen the tested actuator molds for defects. By setting the (0,0) grid coordinate to be coincident with the pMDI actuator orifice during the calibration process, the resulting area shown in Figure 3 exemplified the direction in which the spray was delivered from the mold. As seen in Figure 4, the expected drug deposit around the orifice was validated based on the results of the tested actuator mold in Figure 3.

Conclusions

1. The tested pMDI albuterol sulfate samples show that shake duration has a statistically significant effect on the device performance during through life testing.
2. Optimal shaking is critical to ensure the patient receives the desired emitted dose from the pMDI. The correlation between DCU and spray pattern allows product knowledge to be gained rapidly during the development process.
3. Proveris's COG rapid screening method can easily detect malfunctioning actuator molds leading to better root cause determination for poor performance and improved product performance – particularly during APSD testing using cascade impaction techniques.

References

[1] Draft Guidance on Albuterol Sulfate, Revised June 2013. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm346985.pdf.

[2] Guo C, Stine KJ, Kauffman JF, Doub WH: Assessment of the influence factors on *in vitro* testing of nasal sprays using Box-Behnken experimental design. Eur. J. Pharm Sci 2008, 35:417–426.

Table 1. BB-DoE control variable ranges for tested shake parameters.

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

Prediction Profiler: Effects of Shaking Parameters on Spray Pattern Area (mm2)

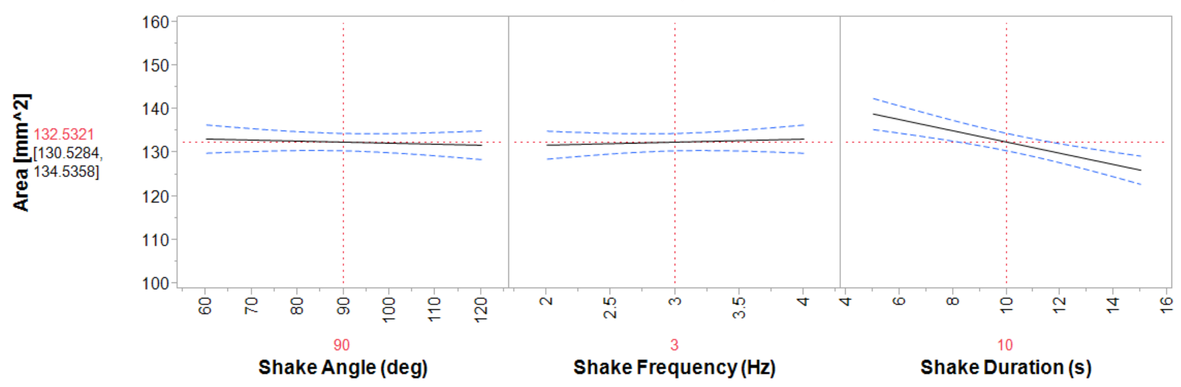

Figure 1. The graph demonstrates that shake duration is the driving parameter for product performance.

Shake vs. No Shake: Spray Pattern Area & Drug Concentration

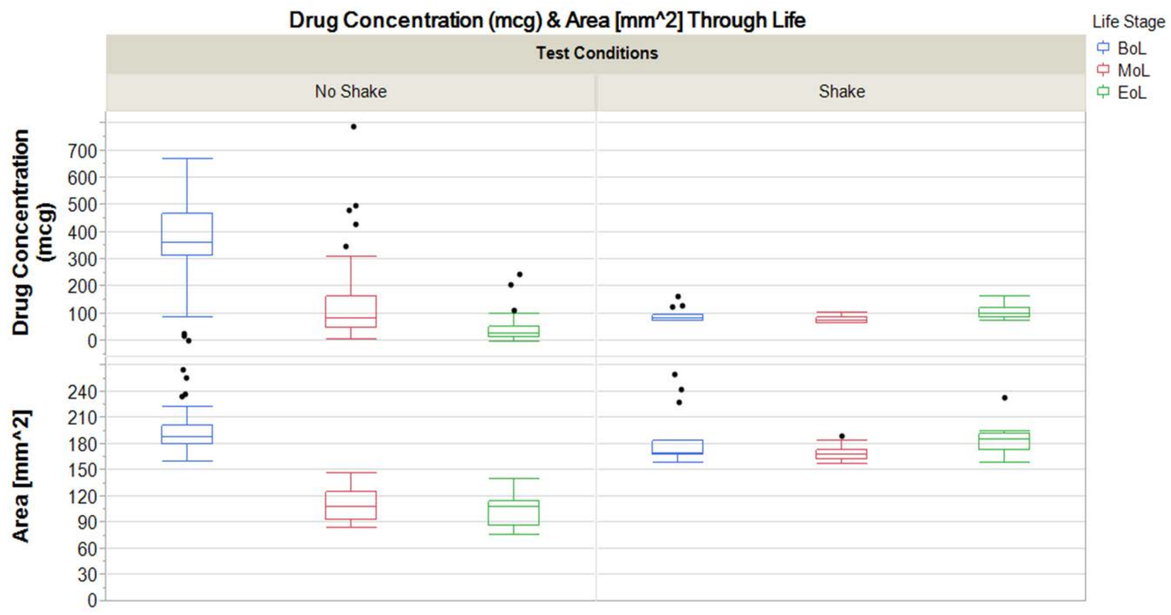

Figure 2. The graph demonstrates the importance of shaking a pMDI and the significant correlation between spray pattern area and drug concentration results.

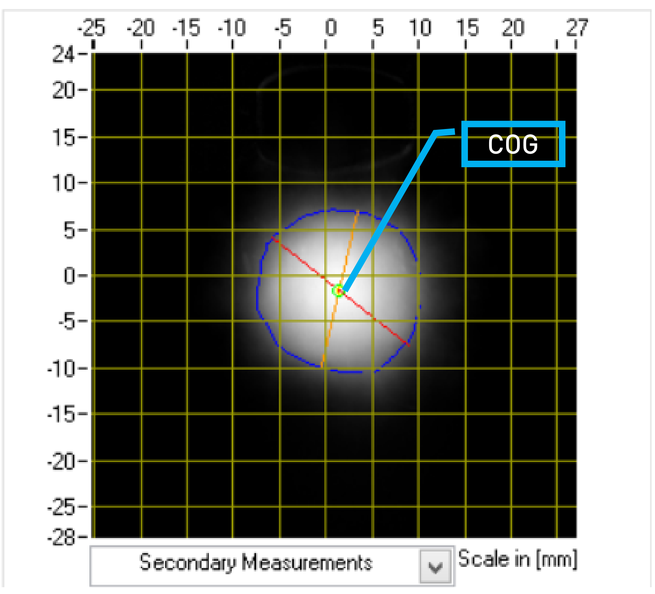

Figure 3. A spray pattern area measurement from Viota® software shows a slightly southeastward direction of the aerosol spray based on the location of the pattern's COG.

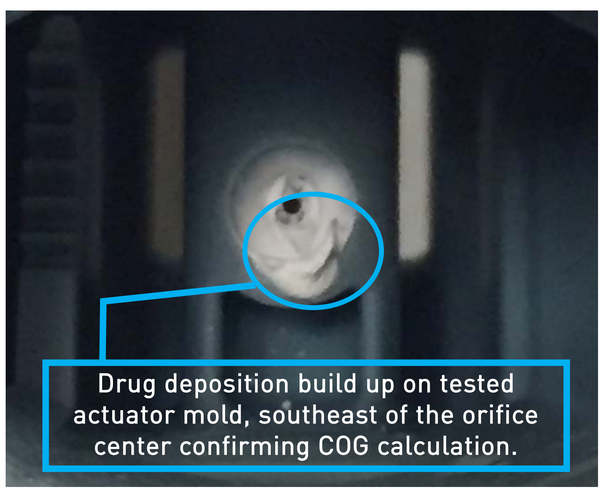

Figure 4. The data in Figure 3 indicates that a defective actuator mold produces a skewed spray angle position, which is manifested by drug deposition build up on the interior surfaces of the actuator mouthpiece from 70 actuations during the fire down process, as shown above.

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