The effect of shaking on solution MDIs

The impact of dosing parameters on the delivered dose uniformity of a suspension MDI vs. a solution MDI

Shari Sellers, Julianne Berry, Jennifer Wylie, and Brent Donovan
Merck

As with most inhalation technologies, MDI performance depends strongly on the interaction of the formulation and the device, and understanding the role of dosing parameters and handling of the device during actuation is necessary for accurate and reproducible performance from an MDI [1]. The industry-wide transition from CFC- to HFA-based metered dose inhalers (MDIs), along with the application of Quality by Design (QbD) concepts to inhaler development, has increased interest in understanding the formulation variables that influence MDI delivery performance [2, 3] as measured by the delivered dose uniformity (DDU) test. The DDU test, mandated by the USP, determines the shot weight or total amount of formulation delivered from an MDI, as well as the recovery or total amount of active delivered per dose.

Researchers at Schering Plough, now Merck, undertook a study of factors that influence the delivered dose of suspension MDIs, including the vigorousness of shaking prior to actuation. Because the FDA requires manufacturers of suspension MDIs to conduct studies to determine the impact of shaking in order to justify patient use instructions, shaking holds particular interest for pharmaceutical developers. Theoretically, suspension MDIs require shaking in order to break up flocculates and to distribute the drug homogeneously during the filling of the inhaler's valve chamber. Failure to shake the device adequately could result in inconsistent dosing [4].

In order to provide a control for the shaking study, the researchers included a solution MDI, whose performance, theoretically, should be independent of shaking since drugs in solution are naturally homogenous. Surprisingly, however, both total shot weight and drug delivery for the solution MDI showed a strong dependence on the vigorousness of shaking prior to actuation, indicating that shaking plays a role in valve performance and suggesting that developers of MDIs may need to account for shaking and actuation factors regardless of the type of formulation.

The study design

The team performed manual studies with four different variables that could affect delivered dose uniformity: shaking vigor, wait time between end of shaking and firing, hold time after firing, and force to fire. Shaking, for a total of 5 seconds, was either "gentle," approximately 5 up/down strokes ranging 6", in a fluid motion with little to no jerking of the wrist at

continued on p. 13

the top or bottom of each stroke, or "vigorous," approximately 20 up/down strokes ranging 6", with more exaggerated jerking at the top and bottom of the stroke. Wait times were either 1 or 5 seconds, and hold times were either 0.5 or 2 seconds. The analyst used an oscilloscope attached to a suspension MDI can/actuator system to produce either a high force shake of ≥ 1.7 N or a low force shake of ≤ 1.4 N.

The DDU test involved shaking each MDI and then actuating it into a plastic separatory funnel connected to a vacuum. Weighing the MDI before and after firing allowed for determination of the total shot weight. The amount of API in the shot recovered from the separatory funnel was determined by high pressure liquid chromatography (HPLC).

First, one analyst performed DDU testing on 10 canisters of suspension MDI using a full factorial design, testing every possible combination of the factors. The team chose to use a small volume valve (25 µL) as a worst case for reproducibility that would highlight differences more dramatically than a larger valve. After analyzing the suspension MDI data, the same analyst repeated the tests at the most critical settings in the study using solution MDI samples. The solution MDIs used a different drug but the same HFA-227 and ethanol co-solvent, formulated in the same types of canisters, with the same valve components and actuator as the suspension samples.

The impact of shaking vigor

The study demonstrated that shaking vigor had the most significant impact on drug delivery of the four variables examined for the suspension MDI, with a vigorous shake producing higher results for both total shot weight and recovery, with lower variability, than did a gentle shake (Table 1a). Varying the actuation force also produced a significant difference in recovery, with a higher force giving slightly higher recovery values. Shorter wait times, shorter hold times, and higher actuation force resulted in reduced variability compared to longer wait and hold times and lower actuation force.

To the team's surprise, actuation after a vigorous shake also resulted in a significant increase in total shot weight and drug delivery for the solution MDI compared to actuation after a gentle shake (Table 1b). For the suspension MDI, a significant difference in recovery remained even after normalization of the data for the lower shot weights produced by gentle shaking, with normalized results of 95.1% of target recovery for vigorous shaking vs. 88.4% for gentle shaking. For the solution MDI, however, normalizing the data to account for the lower shot weights produced by gentle shaking eliminated the significance in differences in drug delivery, with normalized results of 94.6% for vigorous shaking vs. 94.3% for gentle shaking, indicating that the difference in recovery has to do with the amount of total formulation being delivered from the valve rather than the properties of the formulation.

Actuation with higher force produced higher recovery values for both MDI systems, while wait time and hold time produced a negligible impact on the magnitude of the recovery but appeared to play a role in the observed variability. For the solution MDI, wait time had a barely significant impact for shot weight, with the observed shot weight differences due to wait time that are insignificant in terms of real-world

Table 1

Means comparison results

	1a Suspension MDI		1b Solution MDI	
	% of target shot weight	% of target recovery	% of target shot weight	% of target tecovery
Gentle	94.5 ± 2.1	83.8 ± 10.3	97.1 ± 2.1	91.5 ± 3.9
Vigorous	100.5 ± 1.6	95.9 ± 8.4	102.2 ± 1.9	96.7 ± 4.0
1 sec wait	97.1 ± 3.8	90.4 ± 8.9	98.8 ± 3.1	94.8 ± 4.2
5 sec wait	98.0 ± 3.3	89.2 ± 13.0	100.4 ± 3.3	93.5 ± 5.2
0.5 sec hold	97.2 ± 3.5	91.0 ± 8.0	NT	NT
2 sec hold	97.8 ± 3.6	88.6 ± 13.5	NT	NT
Low force	97.8 ± 3.6	85.5 ± 12.7	99.7 ± 3.5	92.4 ± 5.5
High force	97.2 ± 3.5	94.1 ± 7.1	99.6 ± 3.1	95.8 ± 3.8

Note: Pairs of means that have been determined to be statistically different are highlighted. (Significance determined using $\propto = 0.05$)

practicality.

These findings indicate that shaking vigor has the greatest impact on both shot weight and recovery for both the suspension and solution MDIs among all of the factors tested in this case. Vigorous shaking and high force appear to be necessary not only to ensure homogeneity of a suspension formulation, but also to ensure proper and consistent functioning of the MDI valve, regardless of the formulation type.

Analysis indicates that vigorous shaking, short wait times, short hold times, and high force individually give the most reproducible recovery results for both the suspension and the solution MDIs. The increased variation observed for the suspension MDI vs. the solution MDI is expected due to the greater complexity and the propensity for the API to flocculate upon resting for the suspension formulation. The fact that a high actuation force reduced variability in the amount of API delivered also highlights the need to ensure application of enough pressure to the canister to obtain complete and reproducible emptying of the valve.

Currently, the USP chapter <601> requires that at least 18 of the 20 doses required for DDU testing must be within 80-120% of the label claim, and all must be within 75-125% of the label claim. For the suspension MDI, a gentle shake combined with a low actuation force resulted in a nearly 40% probability of failure to meet the 75% lower target for recovery and introduced a very small chance of failure for the solution MDI (Table 2). A combination of vigorous shaking and high actuation force virtually eliminated the chance of failure for either type of formulation.

This type of approach has proven very useful in defining the product performance in the specific design space of dosing variables and can be applied to other products/test methods as part of a QbD approach to method development. Based on the results of this study, developers of solution MDIs, not just suspensions, may want to consider performing a shake/fire study.

Table 2

Probability of failure

(a) Suspension MDI

Shake	Force to fire	% Probability of failure (single value < 75% LC)
Gentle	Low	38.9
Vigorous	Low	3.2
Gentle	High	0.35
Vigorous	High	0.0007

(b) Solution MDI

Shake	Force to fire	% Probability of failure (single value < 75% LC)
Gentle	Low	0.035
Vigorous	Low	0.0000
Gentle	High	0.0000
Vigorous	High	0.0000

References:

1. Warren, J., and Farr, S. J. Formulation of solution metered dose inhalers and comparison with aerosols emitted from conventional suspension systems. Int. J. Pharm. 124.

2. Bowles, Cahill, Haeberlin, et al., on behalf of European Pharmaceutical Aerosol Group, Application of quality by design to inhalation products, RDD Europe 2007.

3. Smyth, Hugh. The influence of formulation variables on the performance of alternative propellant-driven metered dose inhalers. Adv. Drug Delivery Reviews 55:7.

4. Everard, M. L., et al. Factors affecting total and "respirable" dose delivered by a salbutamol metered dose inhaler. Thorax 50.

The authors would like to acknowledge Monisha Dey and David Christopher of the Schering-Plough Research Institute for their guidance and statistical expertise in planning these experiments.

Shari Sellers is Scientist II, Julianne Berry is Fellow, Jennifer Wylie is Principal Scientist, and Brent Donovan is Associate Director at Merck, 556 Morris Avenue, Summit, NJ 07901. Tel.: +1 908 473-3329. Shari.Sellers@spcorp.com