The Effect of Ethanol Concentration on pMDI Evaporation Fraction

Linda Liao[1], Ameet Sule[2], Ben Okorodudu[1], Ian Flaherty[1], Heli Chauhan[1], Andrew Newman[2], Sunita Sule[2], Richard Turner[2]

[1]Proveris® Scientific Corporation, Hudson, Massachusetts, USA
[2]H&T Presspart, Blackburn, Lancashire, UK

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SUMMARY

1. The evaporation rate of inhalation aerosol was proposed as an alternative *in vitro* approach for bioequivalence (BE) study in a recent FDA guidance.[2]

2. A novel measurement method and data analysis process based on the well-established SprayVIEW® technique was applied to quantify the evaporation rate (as a measure of evaporation fraction) of three non-commercial samples.

3. Tested samples are three formulations with different ethanol concentration using identical devices: Presspart NMRM, round mouthpiece actuator with dose counter, 17 mL Presspart Plain Aluminum canister with Aptar 50 µL valve.

4. Among the samples that we studied (5%, 10%, and 15% ethanol concentration), the higher the ethanol concentration, the lower the evaporation fraction throughout all the distances (20 mm, 30 mm, 60 mm) away from the mouthpiece edge.

INTRODUCTION

For aerosol drug products, traditional *in vitro* methods often show little correlation with *in vivo* performance in clinical studies, which tend to be costly and time intensive. In 2012, US FDA started the Generic Drug User Fee Amendments (GDUFA) program, aiming to expedite the delivery of safe and effective generic drugs to the public and improve upon the predictability of the review process.[1] In the interim, numerous product-specific guidances were released for orally inhaled and nasal drug products (OINDPs). In May 2019, FDA released a product-specific guidance for beclomethasone dipropionate delivered by MDI that proposed approaches using new, alternative *in vitro* characterization studies that were more representative and/or predictive of the clinical effect in the deep lung. Measurement of the evaporation rate of the aerosol is among the recommended alternative approaches.

Due to the mechanism of aerosolization of pMDI products, aerodynamic properties—such as evaporation rate—impact drug delivery and lung deposition. However, it is extremely difficult to capture the variable bulk mass of aerosols without interrupting the spray, and limited studies regarding the evaporation rate have been reported.

In this study, we extended the basics of the well-established SprayVIEW technique (which produces calibrated, time-synchronized image sequences of the entire aerosol spray and duration) with a novel measurement method to quantify the evaporation fraction (as a measure of the evaporation rate) from non-commercial pMDI product samples across 3 different ethanol concentrations.

METHODS

Materials

The details regarding the test samples are listed below:

Formulations:	Placebo (5%, 10%, and 15% Ethanol) with HFA-134a (1,1,1,2-tetrafluoroethane)
Cans and Valve:	17 mL Presspart Plain Aluminum canister with Aptar 50 µL valve
Actuator type:	Presspart NMRM, round mouthpiece actuator with dose counter with orifice diameter (OD) 0.3 mm, and jet length (JL) 0.5 mm

For each ethanol concentration:

- 3 identical devices coupled with 3 canisters were measured.
- 3 replicate measurements were collected per device and canister combination (a total of 9 scenarios) for the evaluation fraction.
- All samples were stored and measured under ambient laboratory conditions.

METHODS

Data collection and instrument setup

Raw image sequences of the aerosol spray were obtained using a standard SprayVIEW Measurement System (Proveris Scientific Corporation, Hudson, MA). This non-impaction measurement system uses a laser-light sheet and high-speed digital camera to collect time-correlated calibrated images of the spray. The SprayVIEW Measurement System was configured with a Vereo® SFMDx Automated Actuator (Proveris Scientific Corporation, Hudson, MA) whose angle was adjusted to ensure horizontal spray from the pMDI products. Optimized method settings (camera and laser) were used for the devices while actuation parameters (velocity, hold time, and acceleration) were kept identical for all the pMDI samples across the study. A wait time of 1 minute was used between sprays for temperature equilibration of the pMDI canisters.

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METHODS

Data analysis and evaporation fraction determination

Step 1: As shown in Figure 1, during the data collection for spray pattern (SP), the camera records the entire cross-sectional intensity of the aerosol in the illumination plane. The intensity represents all the drug mass (formulation + propellant) passing through the illuminated cross-section from the beginning to end of the aerosol emission. With that dynamic image information, we calculated the cumulative intensity over time data after normalization and smoothing.

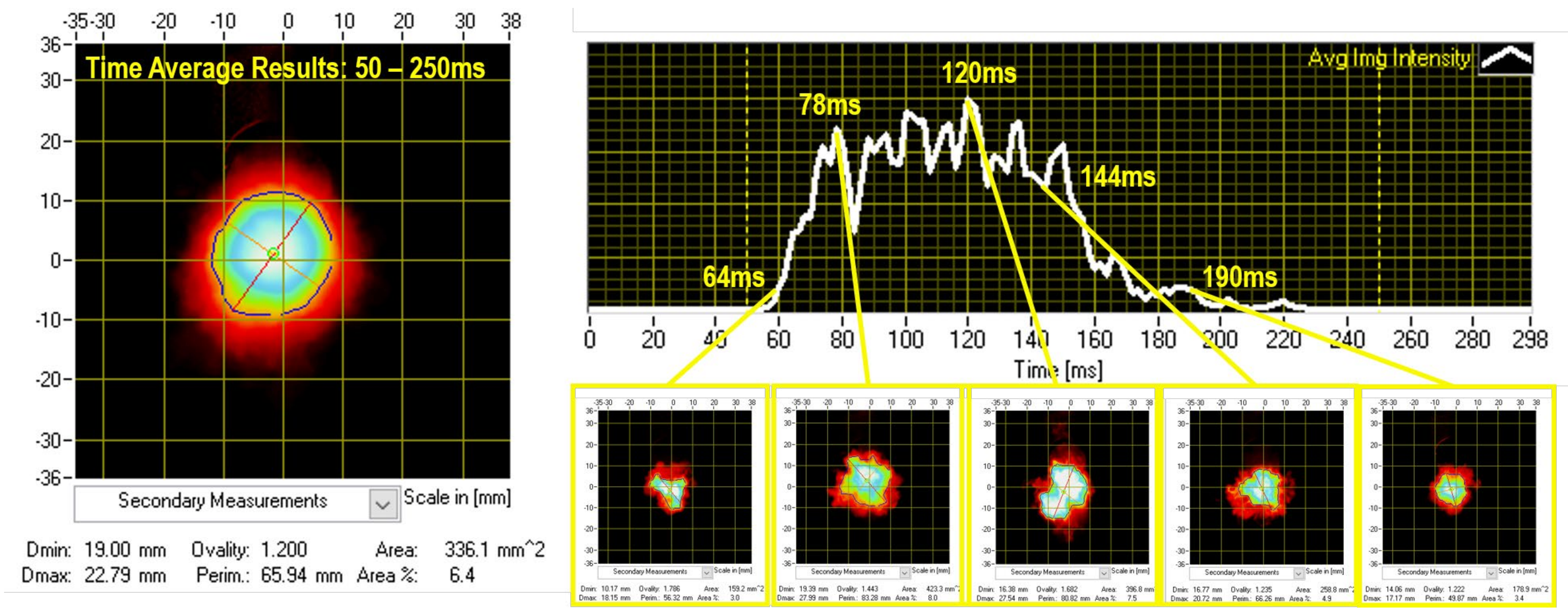

Figure 1. The intensity profile with the time-averaged spray pattern results and example spray patterns at single time points

METHODS

Data analysis and evaporation fraction determination

Step 2: As shown in Figure 2, the area under the curve (AUC) indicates the drug mass at a certain distance from the mouthpiece: the AUC decreases as the spray aerosol moves further away from the mouthpiece because of drug mass loss due to evaporation. We established a comparative baseline for computing the evaporation fraction by assuming that the AUC at 10 mm from mouthpiece represents the total drug mass (formulation + propellant) emitted from the device. The evaporation fraction (EF) at a specific distance (e.g., 20, 30, 60 mm) is based on the drug mass, calculated through AUC, in comparison with the baseline. Each SP measurement was taken at a single distance per spray.

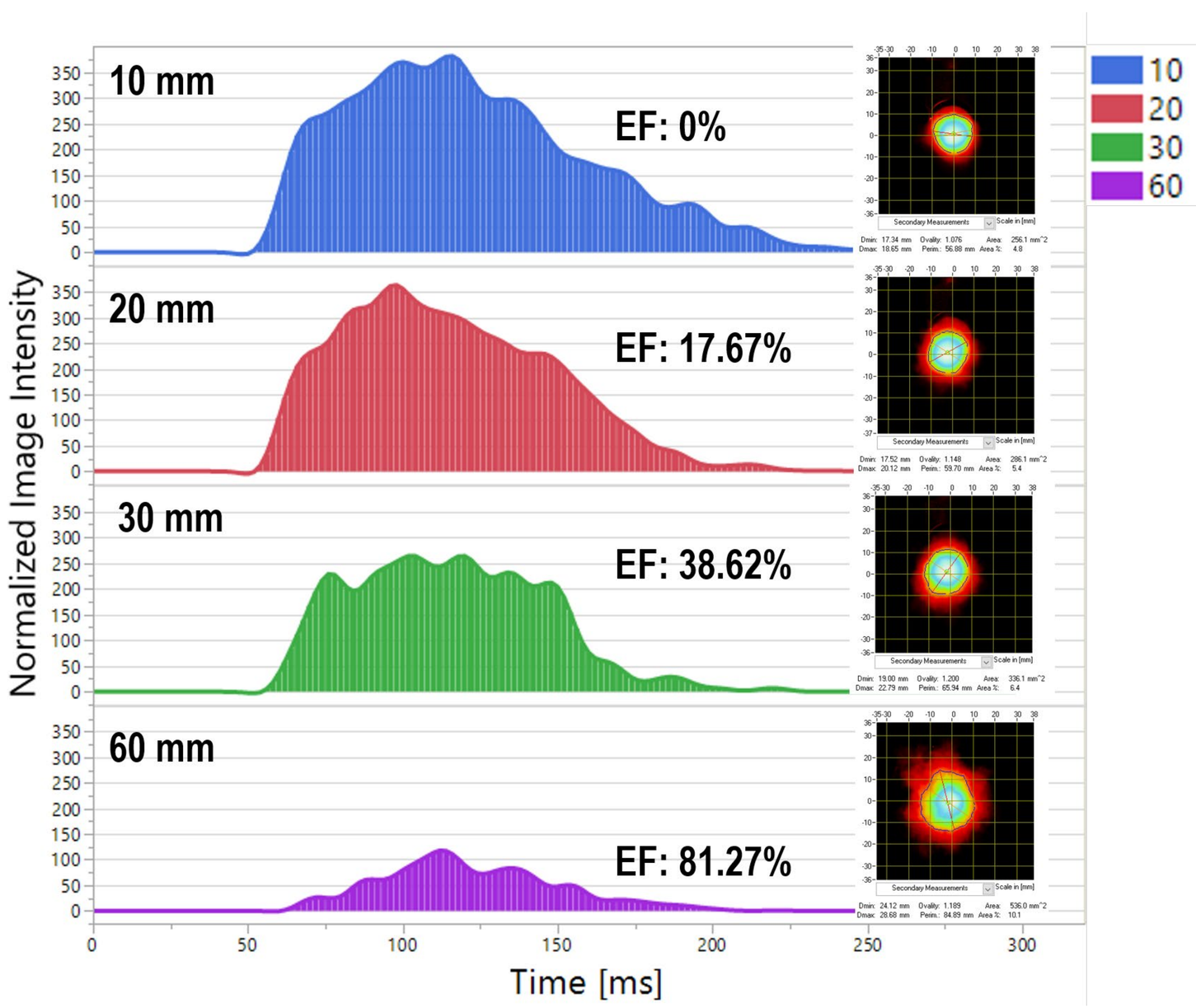

Figure 2. Normalized intensity vs. time graph at different distances, with the calculated evaporation fraction (EF) and the time-average spray pattern results

RESULTS

Figure 3 shows the evaporation fraction results at 3 distances (20, 30, and 60 mm) for the three ethanol concentrations: 5% ethanol concentration has the highest evaporation fraction at all the distances, and as the aerosol travels further away from the mouthpiece, the evaporation slows down. The evaporation fraction decreases as the ethanol concentration increases. It is found in other studies that the increase of the ethanol concentration leads to larger particle sizes,[3] which results in smaller surface area to volume ratio for evaporation.

We also observed that the 10% and 15% ethanol concentration have almost identical SP area results (less than 3.6% differences) and have larger SP area compared to the 5% ethanol concentration samples.

	Pattern Distance [mm]			
	10	20	30	60
	Evaporation Fraction	Evaporation Fraction	Evaporation Fraction	Evaporation Fraction
Ethanol Conc.	Mean	Mean	Mean	Mean
5%	-0.00%	22.58%	50.31%	87.88%
10%	0.00%	15.11%	37.61%	79.01%
15%	-0.00%	11.59%	31.29%	73.94%

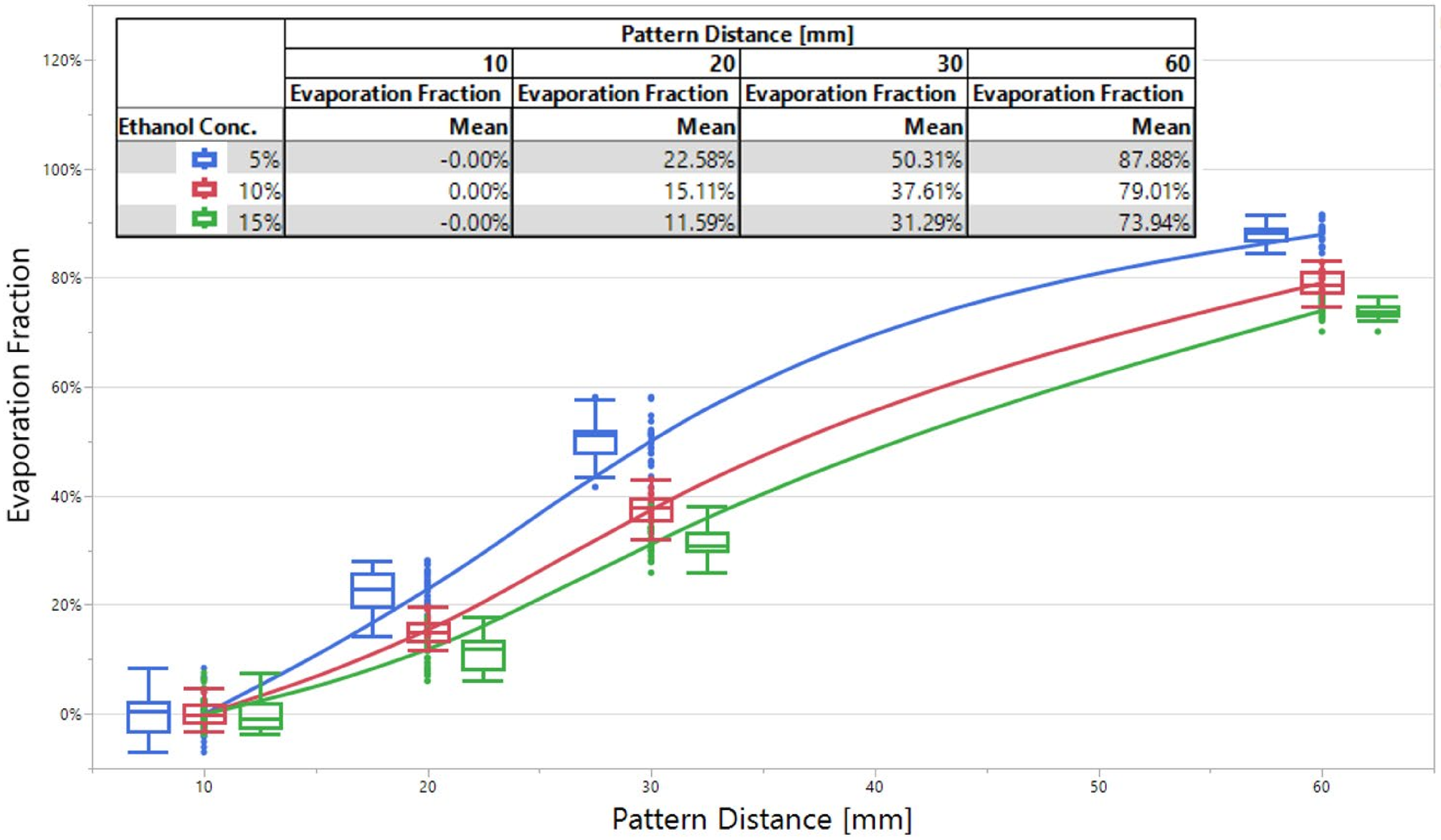

Figure 3. Evaporation fraction comparison of 3 ethanol concentrations at 3 distances

CONCLUSIONS

Among the samples that we studied, the 5% ethanol concentration has the highest evaporation fraction. The approach presented here is not based on a direct measurement of the drug mass, but instead uses a non-impaction laser imaging technology to obtain more insight into drug product evaporation. Our data indicates this approach is sensitive enough to distinguish differences in evaporation rates. This tool may be useful in performing *in vitro* bioequivalence comparisons between Test and Reference products.

Other factors, such as propellant properties, API properties, other excipients, as well as actuator device designs (sump, exit orifice, jet length, mouthpiece), may also influence the evaporation rate.

Please contact us if you have questions or comments:

Linda Liao
Senior Field Applications Scientist
Proveris Scientific
lliao@proveris.com

Ameet Sule
Director, Inhalation Product Development Centre
H&T Presspart
ameet.sule@presspart.com

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