METHODOLOGY FOR MEASUREMENT OF EVAPORATION FRACTION AND EVAPORATION RATE, A COMPARISON OF HFA-134a AND HFA-152a FORMULATIONS

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INTRODUCTION

In 2019, the US FDA's Draft Guidance on Beclomethasone Dipropionate[1] indicated its support of novel bioequivalence (BE) approaches in submission of an abbreviated new drug application (ANDA) which includes evaporation rates. In addition, the pharmaceutical industry is at a critical point regarding reformulation efforts for pressurized metered dose inhalers (pMDI), as a response to the Kigali Amendment to the Montreal Protocol. In previous work,[2] we provided a basic exploration of evaporation fraction. Here, we further explore a methodology to compare evaporation fractions (EF) and evaporation rates (ER) on an alternative low Global Warming Potential (GWP) propellant HFA-152a to the currently used HFA-134a propellant in support of the FDA recommendations.

MATERIALS AND METHODS

Salbutamol sulfate formulations of pMDI were manufactured using a development grade of HFA-152a and Zephex® grade HFA-134a. To maintain consistency, all propellant formulations were filled in plain, uncoated aluminum cans (H&T Presspart, UK) on the benchtop and were manually crimped with 63 µL valves (Aptar Pharma, France). All pMDI canisters were quarantined for a minimum of 14 days, valve down, prior to testing for EF and ER.

EF/ER THEORY

EF is defined as the relative amount of aerosol that has evaporated at a specific spray pattern (SP) distance downstream of the actuator mouthpiece, expressed in units of %. ER is defined as the rate of change of EF calculated by a curve fit of EF as a function of SP distance and expressed in units of % per mm. The Proveris methodology for determining EF/ER uses a "control volume"[3] approach, based on conservation of mass principles as shown in Figure 1. When a pMDI is actuated and the metering valve opens, the volume of formulation that is expelled will flash evaporate. Control volume is the area where the process of interest is occurring.

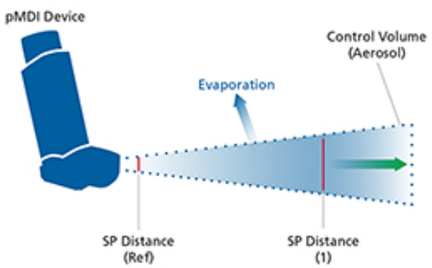

Figure 1, The "control volume" approach for determining Ef/ER.

Applying the theory of mass conservation, the initial (reference) mass term can be determined from a SP measurement made as close as possible to the mouthpiece edge (e.g., 10 mm in this work). SP measured at a greater downstream distance represents the aerosol mass leaving the control volume at the selected distance. The difference in these SP-based aerosol mass measurements represents the net amount of aerosol mass that has evaporated from the control volume. Aerosol mass is determined by the SP intensity.

Since the SP area under the curve represents the Aerosol Mass of the SP, EF is calculated as shown in the equation below, where x is the downstream distance and AUC is the area under the curve.

$$EF(x) = \frac{AUC(Ref) - AUC(x)}{AUC(Ref)} \times 100\%$$

For a specific distance, AUC is calculated from an integration of the intensity data divided by area % of the corresponding SP.

Once the EF is known, the ER can be calculated using the EF(x) and calculating the rate of change based on the SP distance. ER is calculated as the equation:

$$ER(x) = \frac{d}{dx} EF(x)$$

SPRAY PATTERN

SP measurements were performed using a SprayVIEW® (Proveris Scientific Corporation, USA) system with a Vereo® (Proveris Scientific Corporation, USA) SFMDx actuator with a custom device holder. Automated actuation parameters were determined[3] for both the HFA-134a and HFA-152a pMDIs. Since both formulations are suspensions, optimized automated mixing was performed on each sample.

SP methods were developed to utilize optimized camera and laser settings for measurements at distances of 10, 30, 50, 60, and 80 mm from the inhaler mouthpiece edge, all with the same field of view (FOV). SP measurements were performed in triplicate on a single HFA-134a formulation canister as a reference, and in triplicate for three HFA-152a formulation canisters as a test.

RESULTS AND DISCUSSION

AUC, EF, and ER Results:

Figure 2 shows normalized intensity by measured SP distance for both formulations. Drug mass (actuated formulation mass) is indicated by AUC at a specific distance from the mouthpiece. AUC decreases when moving from 10 mm (reference) to 80 mm spray distance due to evaporation of propellant, resulting in loss of drug mass for both HFA-134a and HFA-152a formulations.

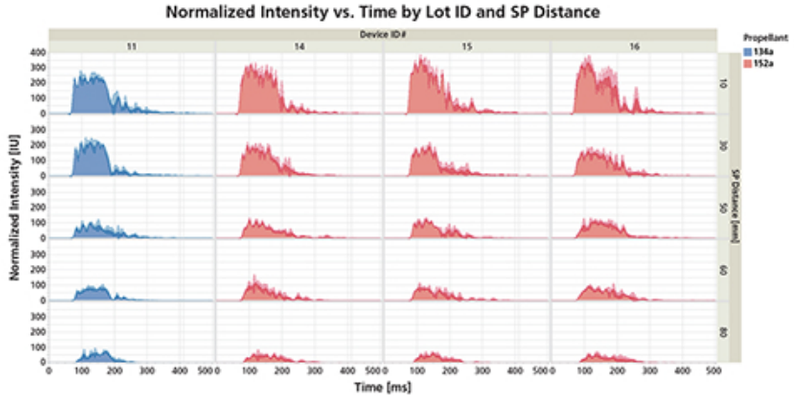

Figure 2: Normalized Intensity by SP Distance for HFA-134a and HFA-152a.

AUC results were further processed into EF and ER using the methodology described earlier. Figure 3 and Table 1 show EF results at 30, 50, 60, and 80 mm distance for HFA-134a and HFA-152a formulations. For data indicated at 30 mm, HFA-152a formulation has a higher mean EF than the HFA-134a formulation. Given the proximity to the mouthpiece edge, it was expected to have larger variability at 30 mm than at further downstream distances for both formulations. This finding may need to be confirmed with additional testing of samples. EF is highest at 80 mm for both formulations. However, EF looks similar for both formulations at 50, 60, and 80 mm.

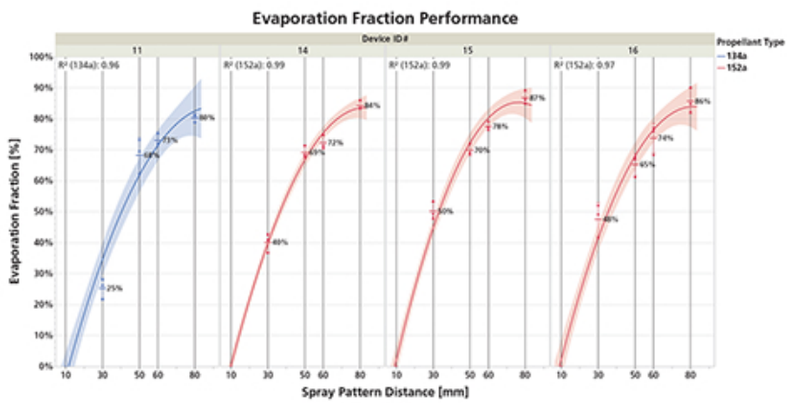

Figure 3: Evaporation Fraction of HFA-134a compared to HFA-152a.

RESULTS AND DISCUSSION (CONT)

Table 1: Evaporation Fraction for HFA-134a and HFA-152a

Evaporation Fraction	Propellant Type							
	HFA-134a		HFA-152a					
	Device ID 11		Device ID 14		Device ID 15		Device ID 16	
SP Distance (mm)	Mean (%)	CV (%)	Mean (%)	CV (%)	Mean (%)	CV (%)	Mean (%)	CV (%)
10	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
30	25.34	13.0	40.10	7.6	50.26	5.6	47.61	11.3
50	68.29	8.3	69.22	2.8	69.96	2.7	65.33	5.5
60	73.14	2.8	72.35	3.1	77.61	1.8	73.85	6.5
80	80.43	1.7	84.40	1.7	86.86	2.5	85.80	4.7

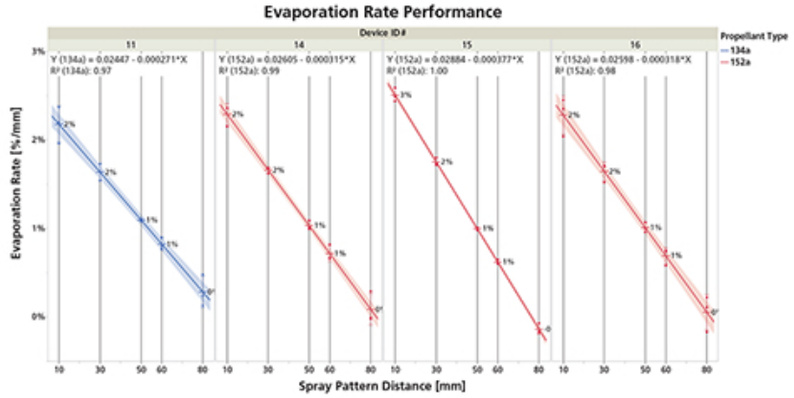

Figure 4: Evaporation Rate of HFA-134a compared to HFA-152a. ER data looks similar for both formulations measured from EF as a function of distance in %/mm.

CONCLUSION

This work showed a methodology for determination and comparison of ER and EF for formulations manufactured with low GWP propellant (HFA-152a) and HFA-134a. This approach utilized the measurement of ER using existing SprayVIEW technology. These limited datasets showed EF and ER look similar for both product formulations. In addition to pMDI formulation properties, evaporation rates may be influenced by device design. This tool could be useful during the development of new products in understanding evaporation behaviors of low GWP formulations and in performing *in vitro* bioequivalence comparison between Test and Reference products.

REFERENCES

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