Quantitative Studies to Inform PSG Development for Tiotropium Bromide Inhalation Spray, Metered

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Introduction

- The Respimat® Soft Mist™ inhaler (Boehringer Ingelheim, Ingelheim am Rhein, Germany) is classified as an inhalation metered spray product.[1,2]
- Marketed inhalation metered spray products have unique characteristics in comparison to metered dose inhalers (MDIs):
  - Aqueous drug solution droplets (resembling nebulized aerosol)
  - Long duration (e.g., 1.5 seconds; approximately 10 times that of an MDI)
  - Slow moving aerosol (spray velocity approximately 1/10th that of an MDI)[1,4]
- Spray velocity characterization provides a critical performance metric for emitted spray plume characterization; spray velocity may be indicative of regional particle deposition in the lungs.[3]
- Particle image velocimetry (PIV) and high-speed videography (HSV) were used for this study to collect spray velocity data on tiotropium bromide inhalation spray, metered (NDA 021936; Spiriva Respimat) to assist FDA in developing study design recommendations for an in vitro spray velocity bioequivalence study as part of product-specific guidance (PSG) development for generic inhalation metered spray products.[3]

Materials and Methods

- Data collection occurred on two tiotropium bromide inhalation metered spray inhalers which were each fired 3 times.
- An experimental setup was constructed with an acrylic chamber to contain the inhaler aerosol (Figure 1).
- The PIV laser was connected to a lens array to form a laser light sheet to illuminate a plane.
- The laser light sheet was in-line with the nozzle of the inhaler and the camera was positioned orthogonally.
- The PIV system and the inhaler firing were synchronized to resolve the plume.
- The camera recorded the plume using a sampling rate of 500 Hz.
- A condition of stable, quiescent air was applied to the measurement chamber to measure the spray velocity as it exits the inhaler.
- Data collection occurred at ambient conditions (20°C, 35% relative humidity).
- Plume front velocity or velocity at the front edge of the aerosol cloud was assessed from PIV or HSV recordings of the spray.
- The image data were analyzed using Spray Geometry® software (Ypsilanti, MI, USA) to track the movement of the front edge of the plume (Figure 2).
- The elapsed time and the distance traversed by the plume front were collected.
- The spray velocity was determined by calculating the slope of the distance versus time curve using a backward differencing scheme.
- Plume front velocity was determined at 6-, 8-, 10-, 12-, and 14 cm downstream of the nozzle.
- To determine the plume front velocity at each specific distance, linear interpolation was used.

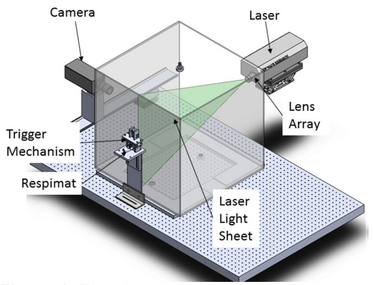

Figure 1. Experimental setup.

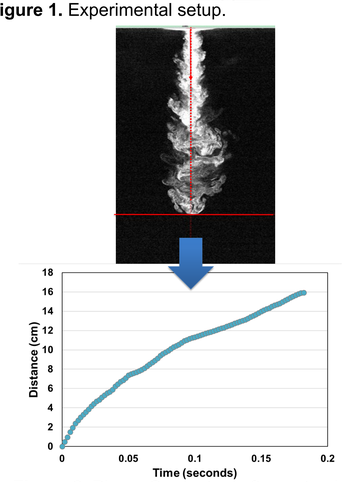

Figure 2. Plume Geometry software tracks the plume front displacement over time.

Results

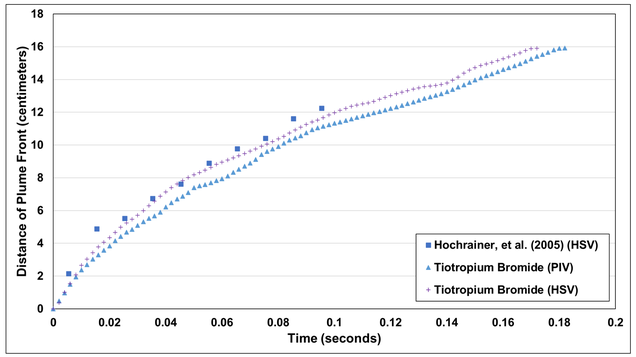

Figure 3. Plot of distance of plume front vs. time data. Data from Hochrainer, et al. (2005) were collected using a different active pharmaceutical ingredient (ipratropium bromide/fenoterol).[4]

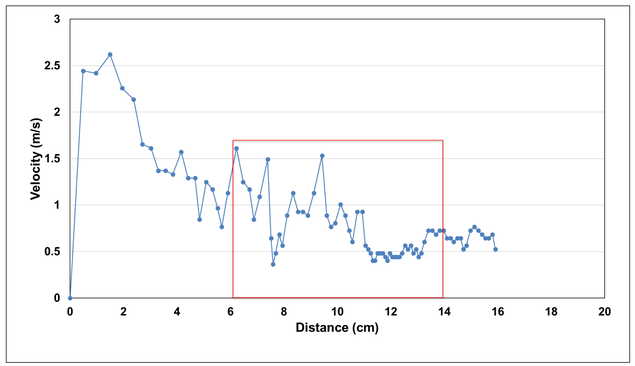

Figure 4. Plot of plume front velocity vs. distance.

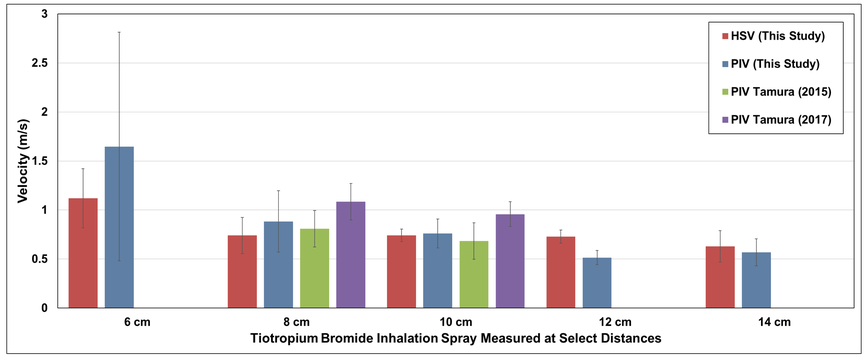

Figure 5. Plume front velocity measured at different locations in the spray plume. Data are presented as the mean value at each location. Error bars are standard deviation. HSV data (n=6 actuations), PIV data (n=6 actuations), Tamura (2015) (n=30 actuations), and Tamura (2017) (n=30 actuations).

- Tiotropium bromide inhalation metered spray distance vs. time curves were assessed from both PIV and HSV data and were found to be consistent with the work of Hochrainer, et al. for an inhalation spray using the Respimat inhaler (Figure 3).[3,4]
- Plume front velocity was extracted from the plume front displacement (distance) vs. time curves.
- Plume front velocity was plotted as a velocity vs. distance curve (Figure 4).
- The selected distances of 6-, 8-, 10-, 12-, and 14 cm were assessed on the velocity vs. distance curve to find the most appropriate distances for assessment of spray velocity.
- High variability was observed for plume front velocity measurements at distances of 0-6 cm from the nozzle (Figure 5).
- The 6 cm location showed very high variability in the plume front velocity measurement as is visible from the large error bars (Figure 5).
- The 14 cm location was difficult to measure the plume front velocity because of breakup of the plume front in some measurements (Figure 5).
- Data at the locations of 8-, 10-, and 12 cm provided reliable (less variable) measurements.
- Comparisons of the plume front velocity data at these locations were consistent with literature data collected by Tamura (2015, 2017) for 3 devices with 10 actuations per device.[5,6]

Conclusions

- Plume front velocity is best measured 8-12 cm from the nozzle of the Respimat inhaler due to the relatively low variability in the region.
- The regulatory impact of the study is that it provided valuable information for the study design recommendations for the spray velocity bioequivalence study that were used to support development of the PSG that is now posted.[7]
- The spray velocity test may use PIV, HSV, or other suitable methods to measure the spray velocity.
- The PIV data collected in this study will be used to validate computational fluid dynamics (CFD) simulations of the generated spray plume of the Respimat inhaler.

Disclaimer

Views expressed in this poster do not reflect the official policies of the Department of Health and Human Services; nor does mention of trade names, commercial practices or organizations imply endorsement by the U.S. Government.

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