Novel Method for Droplet Size Distribution Measurements from Respimat Inhalers

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Introduction

- Respimat® Soft Mist™ Inhaler (Boehringer Ingelheim, Ingelheim am Rhein, Germany) is a type of orally inhaled drug product (OIDP) with unique attributes in comparison to metered dose inhalers.
- The device delivers a solution-based spray with a low velocity, high fine particle fraction, and long spray duration.[1]
- The Office of Generic Drugs (OGD) is currently investigating potential in vitro metrics for OIDPs that use the Respimat device to establish bioequivalence between the brand and generic drug products.
- There are several methods that may be used to quantify the high fine particle fraction in the spray as a comparator metric, but the relative value of each method has not been fully explored.
- The Andersen cascade impactor (ACI) is the most commonly used instrument for measuring aerosols emitted from inhalers. However, ACI studies are time-consuming as they require several hours to be spent on plate preparation and particle size analysis.
- The Aerodynamic Particle Sizer (APS) Spectrometer (TSI, Inc. Model 3321, St. Paul, Minnesota, USA) provides an alternative approach for measuring the aerodynamic particle size distribution (APSD) and is frequently used for pharmaceutical analysis of metered dose inhalers.
- APSD data produced by the APS are comparable to data collected using an ACI in terms of capabilities for measuring aerodynamic particle size and drug particle mass.[2] The use of the APS to quantify APSD for Respimat inhalers was evaluated for this study.

Materials and Methods

- The APS was used with the Impactor Inlet (Model 3306, TSI, Inc. St. Paul, Minnesota, USA), which included a United States Pharmacopeia (USP) induction port and provided a fixed 80:1 dilution ratio to the aerosol cloud that was then sent to the APS.
- An acrylic chamber was used to isolate the experimental apparatus from the laboratory environment. Schematics of the experimental setup are shown in Figure 1.
- The USP induction port had an inlet flow rate of 28.3 L/min provided by a mass flow controller (MFC) (Alicat Scientific, Inc., Tucson, AZ, USA) connected to the house vacuum source.
- Humidified air (relative humidity [R.H.] of 96 +/-2%), was introduced to the measurement chamber using a humidifier.
- The humidified air was consistent with the moist environment in the mouth and lungs; it also served to dilute the spray and prevent evaporation (drying) of the spray droplets prior to being measured by the APS.
- The temperature of the ambient laboratory environment 20°C was used for the experiments.
- Four inhalers (Spiriva Respimat [tiotropium bromide] inhalation metered spray - NDA 021936) were tested in this study with eight actuations collected from each inhaler.
- The USP induction port was also removed and replaced with a straight inlet tube to determine the effect of the USP induction port on APSD measurements; the inhalers were then retested.
- A microcontroller was used to synchronize the actuation of the inhaler with the data collection process of the APS.
- Data analysis was conducted using Microsoft EXCEL® (Microsoft Corporation, Redmond, WA, USA).
- A comprehensive search of literature data was conducted to obtain APSD data for Respimat inhalers collected using an ACI.

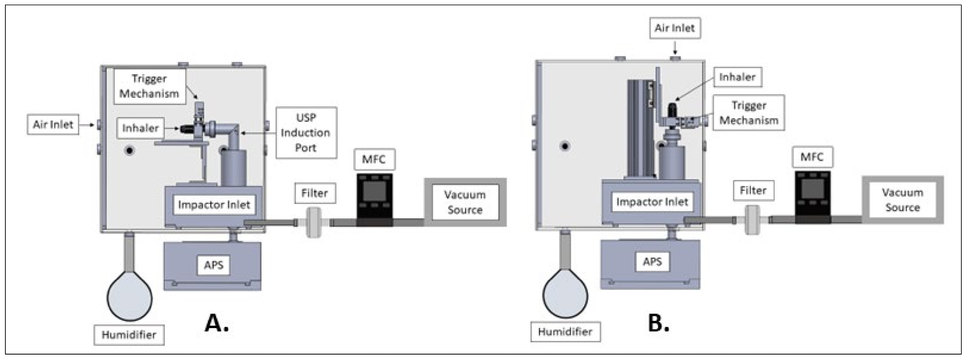

Figure 1. Experimental Setup. A) A USP induction port is used with the inhaler; B) A straight inlet tube is used with the inhaler.

Results

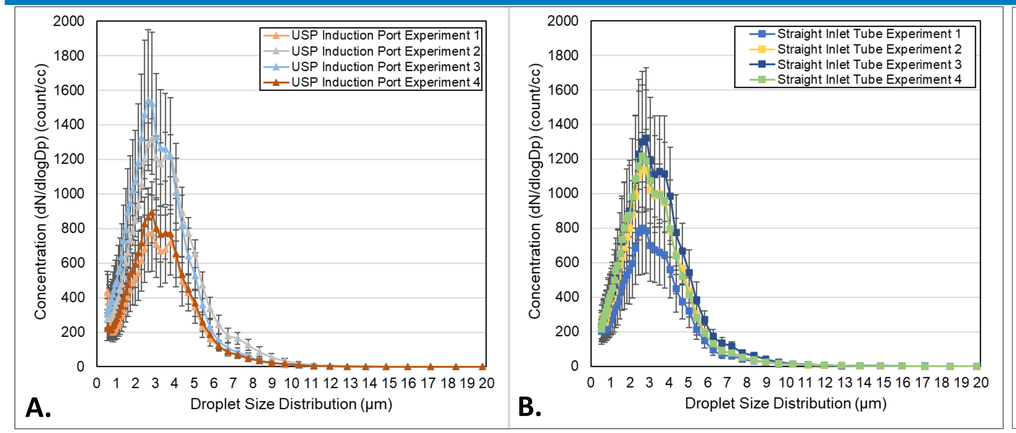

Figure 2. Normalized concentration (dN/dlogDp); A) 2 units (n=8 sprays per device) with USP induction port connected to the Impactor Inlet; B) 2 units (n=8 sprays per device) with straight inlet tube connected to the Impactor Inlet. The data are plotted as mean ± standard deviation (SD).

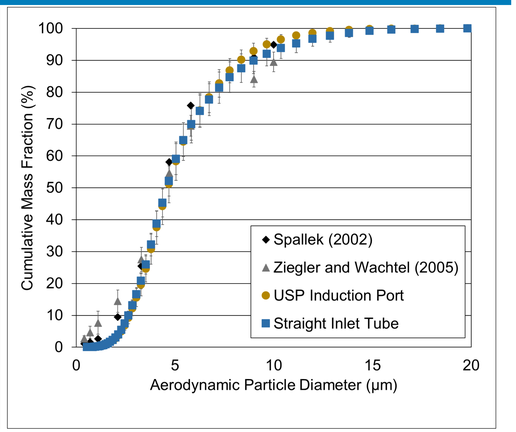

Figure 3. Cumulative mass fraction APS data for four units (n=8 sprays per device) compared to literature ACI data. The APS data are plotted as mean ± SD.

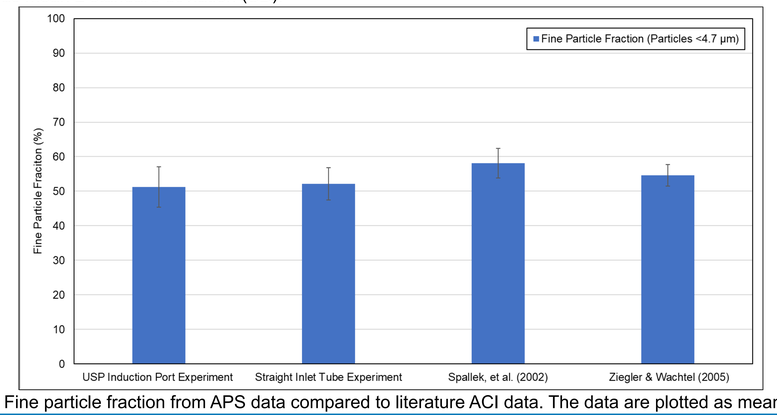

Figure 4. Fine particle fraction from APS data compared to literature ACI data. The data are plotted as mean ± SD.

- Data collected from the APS are plotted in **Figure 2** as normalized concentration versus bin size; the results did not show a distinct difference between using a USP induction port and using a straight inlet tube with the Impactor Inlet in the experimental apparatus.
- The data are plotted as cumulative mass fraction versus bin size in **Figure 3**, along with ACI data acquired from the literature.[3,4]
- The collected APS data were similar across the two experimental setups and the ACI data.
- The ACI data from Spallek, et al.[3] and Ziegler & Wachtel[4] provide a close match to the APS data.
- The fine particle fraction for particles <4.7 µm is compared between the APS data and the literature ACI data in **Figure 4.**

Conclusion

- The current work presents research on the use of an APS to evaluate APSD for inhalers that use the Respimat platform.
- The Impactor Inlet was used with the APS to dilute the aerosol cloud to avoid overwhelming the APS.
- The dilution effect from the Impactor Inlet decreased the normalized concentration (less total droplet counts), shifting the curve down; the amount of curve shift was still within the range for shot-to-shot variability of aerosol concentration.
- The high R.H. environment used for testing provided some dilution to the aerosol. However, this effect was small compared to the dilution effect from the Impactor Inlet.
- The results were similar between the USP induction port and the straight inlet tube and are comparable to ACI data collected from the literature.
- The results suggest that the APS may provide a fast and efficient method to measure the APSD from drug products that use the Respimat inhaler platform.

References

1. Dalby R. Int J Pharm. 2004;283(1-2):1-9.
2. Harris JA. AAPS PharmSciTech. 2006;7(1): E1-E8.
3. Spallek, M. Respiratory drug delivery VIII: biological, pharmaceutical, engineering, clinical and regulatory issues relating to optimized drug delivery by aerosol. 2002;2:375-378.
4. Ziegler J., Wachtel H. J. Aerosol Med. Vol. 18. No. 3. 2005. pp. 311-324.

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