Novel Method for Aerodynamic Particle Size Distribution Measurements from Respimat Inhalers

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Introduction

- The Respimat® inhaler (Boehringer Ingelheim, Ingelheim am Rhein, Germany) is a unique type of orally inhaled drug product (OIDP) with the following distinct characteristics:
  - **Aqueous drug solution droplets** (resembling nebulized aerosol)
  - **Longer spray duration** (i.e., 1.5 seconds; approximately 10 times that of a metered dose inhaler [MDI])
  - **Slow moving** (velocity is approximately 1/10th that of an MDI)
  - **High fine particle fraction** (FPF) in the aerosol (Dalby, et al. 2004)
- The Office of Generic Drugs (OGD) at the U.S. Food and Drug Administration (FDA) is evaluating new in vitro study designs for OIDPs that use the Respimat platform
  - Determine whether in vitro study designs are able to serve as sensitive discriminatory methods for detecting performance differences between a reference listed drug and a generic product.

Dalby R, Spallek M, Voshaar T. A review of the development of Respimat Soft Mist Inhaler. *Int J Pharm* 2004, 283: 1-9.

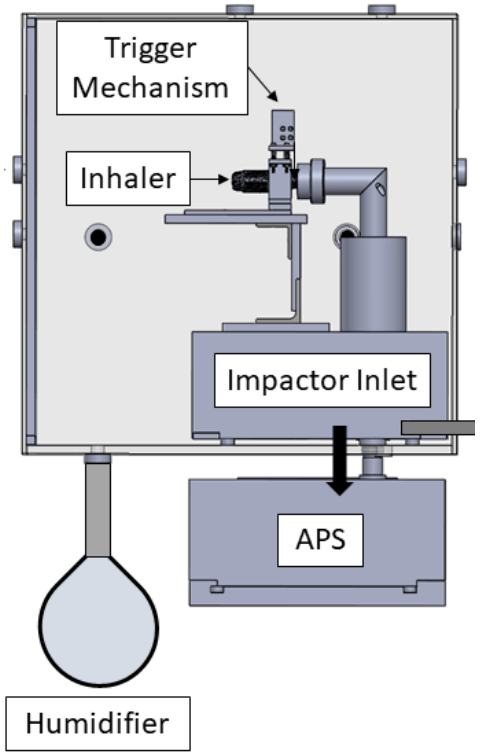
Introduction

- The high FPF characteristic of the Respimat inhaler may be used as a performance metric.
- FPF is defined as the fraction of drug mass likely to reach the airways of the lungs. Here, FPF represents particles <4.7 µm.
- Several methods may be used to quantify FPF.
- The Andersen cascade impactor (ACI) is one of the most commonly used instruments for measuring aerosols emitted from inhalers.
  - ACI studies are time-consuming and need several hours to be spent on collection plate preparation and chemical analysis following particle collection.
- The Aerodynamic Particle Sizer (APS™) Spectrometer (TSI, Inc. Model 3321, St. Paul, MN, USA) provides an alternative approach for measuring the aerodynamic particle size distribution (APSD) with potential for improved efficiency.
  - The APS is frequently used for pharmaceutical analysis of metered dose inhalers.
  - The APS measures aerodynamic particle size and drug particle mass, which is similar to what the ACI measures. (Harris et al. 2006)
- The application of the APS to quantify APSD for the Respimat inhaler was evaluated in the current study.

Harris JA, Stein, S.W., and Myrdal, P.B. Evaluation of the TSI aerosol impactor 3306/3321 system using a redesigned impactor stage with solution and suspension metered-dose inhalers. *AAPS PharmSciTech* 2006, 7: E138-45.

Methods

- An acrylic chamber was used to isolate the experimental apparatus from the laboratory environment.
- The Impactor Inlet (Model 3306, TSI, Inc. St. Paul, Minnesota, USA) was used in concert with the APS.
  - United States Pharmacopeia (USP) induction port
  - Fixed 80:1 dilution ratio
  - Regulated inlet flow rate of 28.3 L/min
- Humidified air was used to dilute the aerosol plume and prevent evaporation (drying) of the spray droplets as the droplets traveled through the Impactor Inlet.
  - Environmental conditions: relative humidity (RH) of 96 +/-2% 20^{o}C +/- 2^{o}C).
  - High RH is consistent with the moist environment inside of the mouth, upper respiratory tract, and lungs.
- The inhaler was actuated using a microcontroller to synchronize the actuation of the inhaler with the data collection process of the APS.

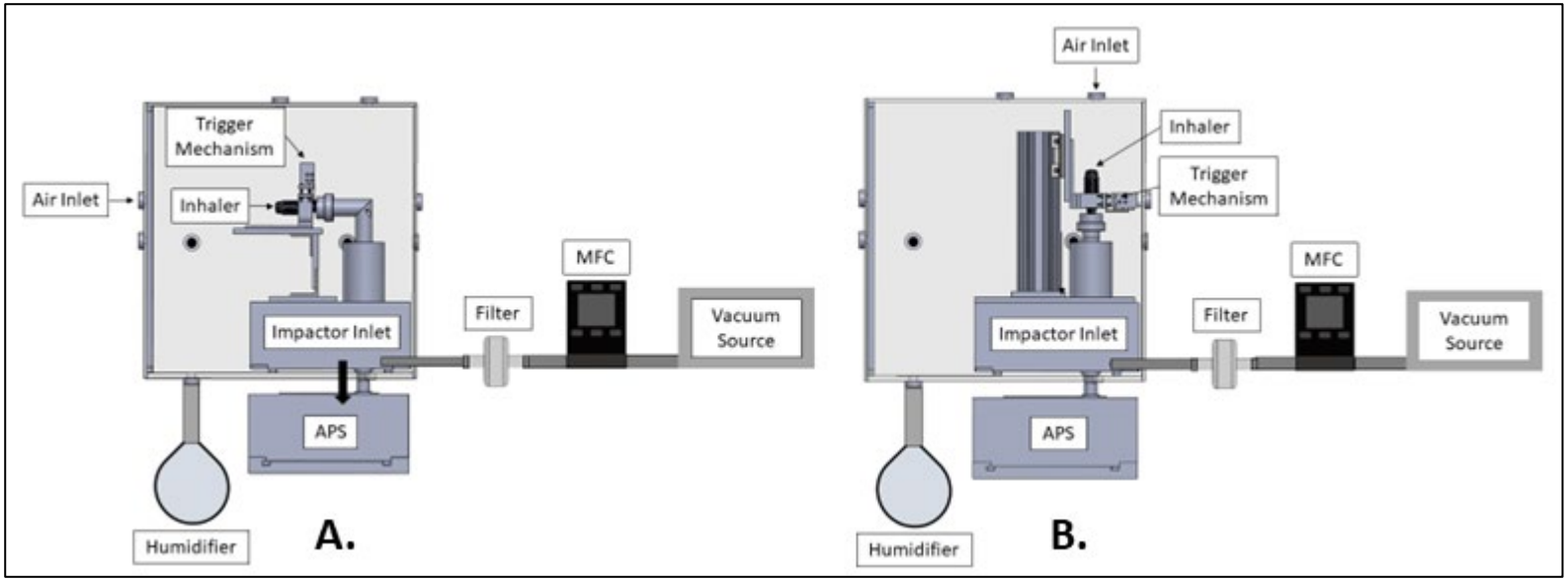


Methods

- The number of actuations was determined using a bootstrap sampling method to conduct a comparison of the mean normalized concentration results for successive numbers of replicates (n=3, n=4, …, n=11) using the earth mover's distance method. (Hu et al. 2006)
- Four inhalers containing tiotropium bromide were tested with eight actuations collected from each inhaler.
- Experiments were performed with the USP induction port, which was removed and replaced with a straight inlet tube; the inhalers were then retested.
- The experiments with the straight inlet tube were to determine the effect of the USP induction port on APSD measurements.

Hu M, Jiang X, Absar M, Choi S, Kozak D, Shen M, Weng YT, Zhao L, Lionberger R. Equivalence testing of complex particle size distribution profiles based on earth mover's distance. *AAPS J* 2018, 20: 62.

Methods

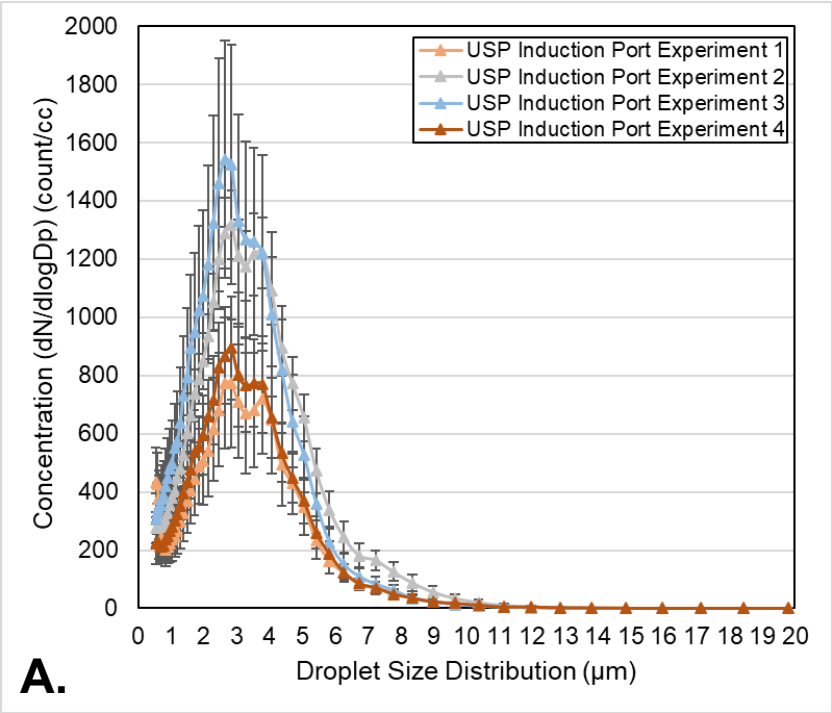


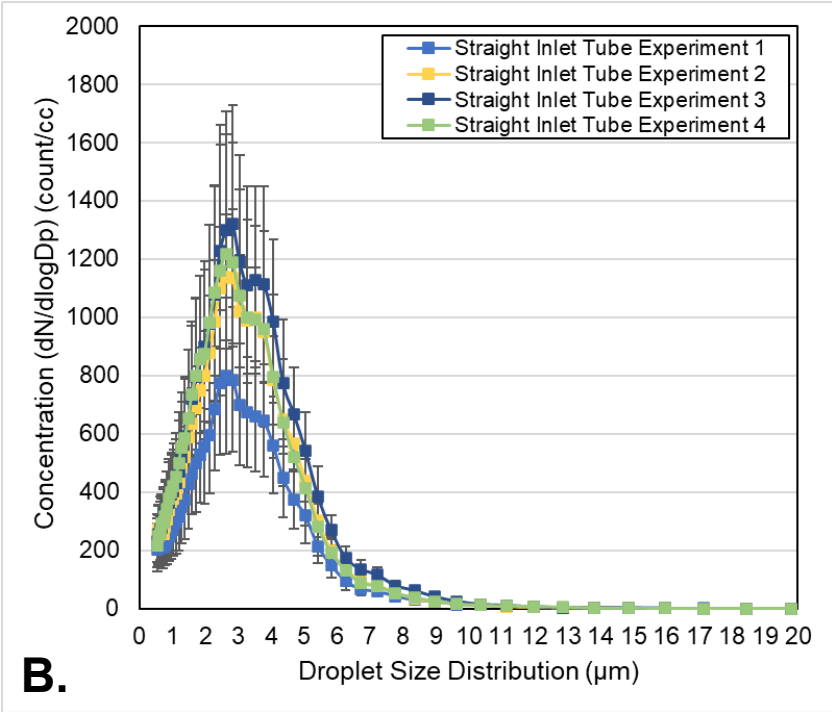
Experimental Setup. A) A USP induction port used with the inhaler; B) A straight inlet tube used with the inhaler.

Results

- Data collected from the APS were plotted 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 were plotted as cumulative mass fraction versus bin size along with ACI data acquired from the literature.
- The fine particle fraction for particles <4.7 μm was compared between the APS data and the literature ACI data.

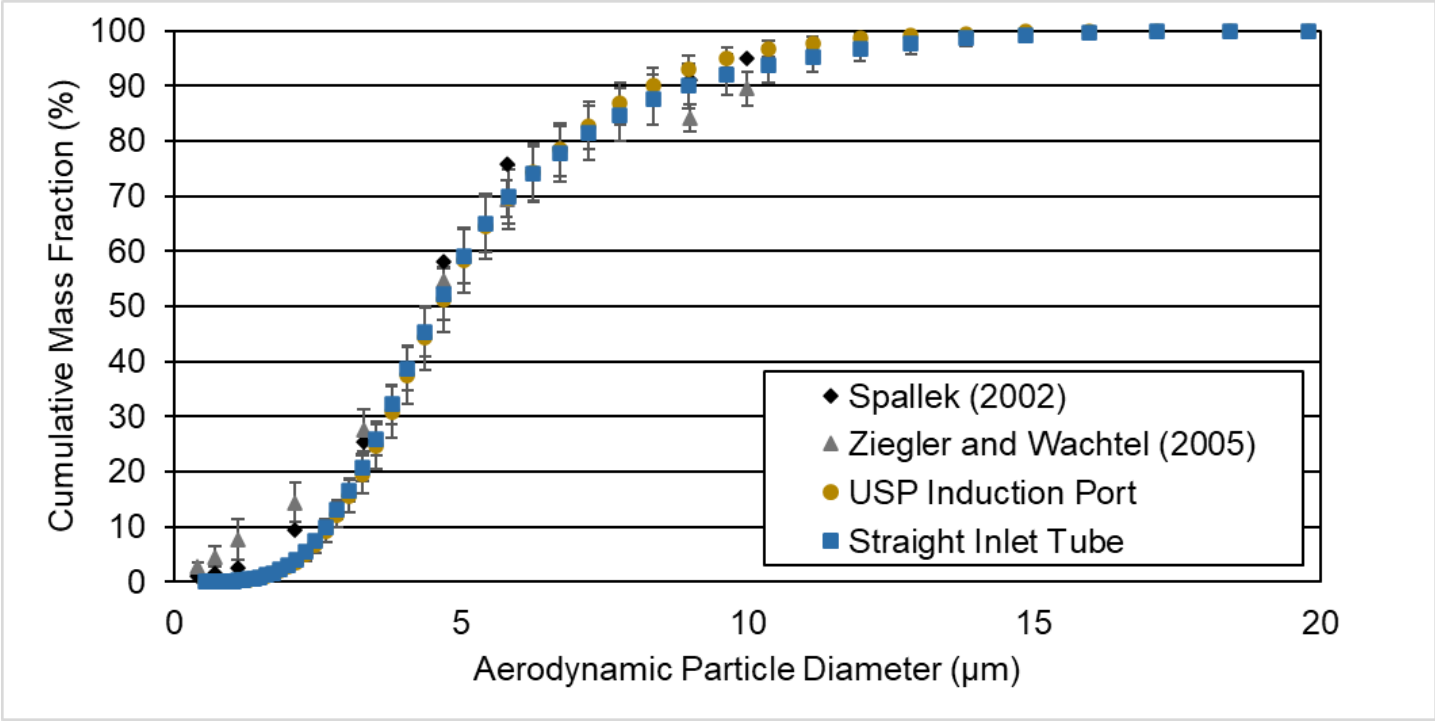
Results





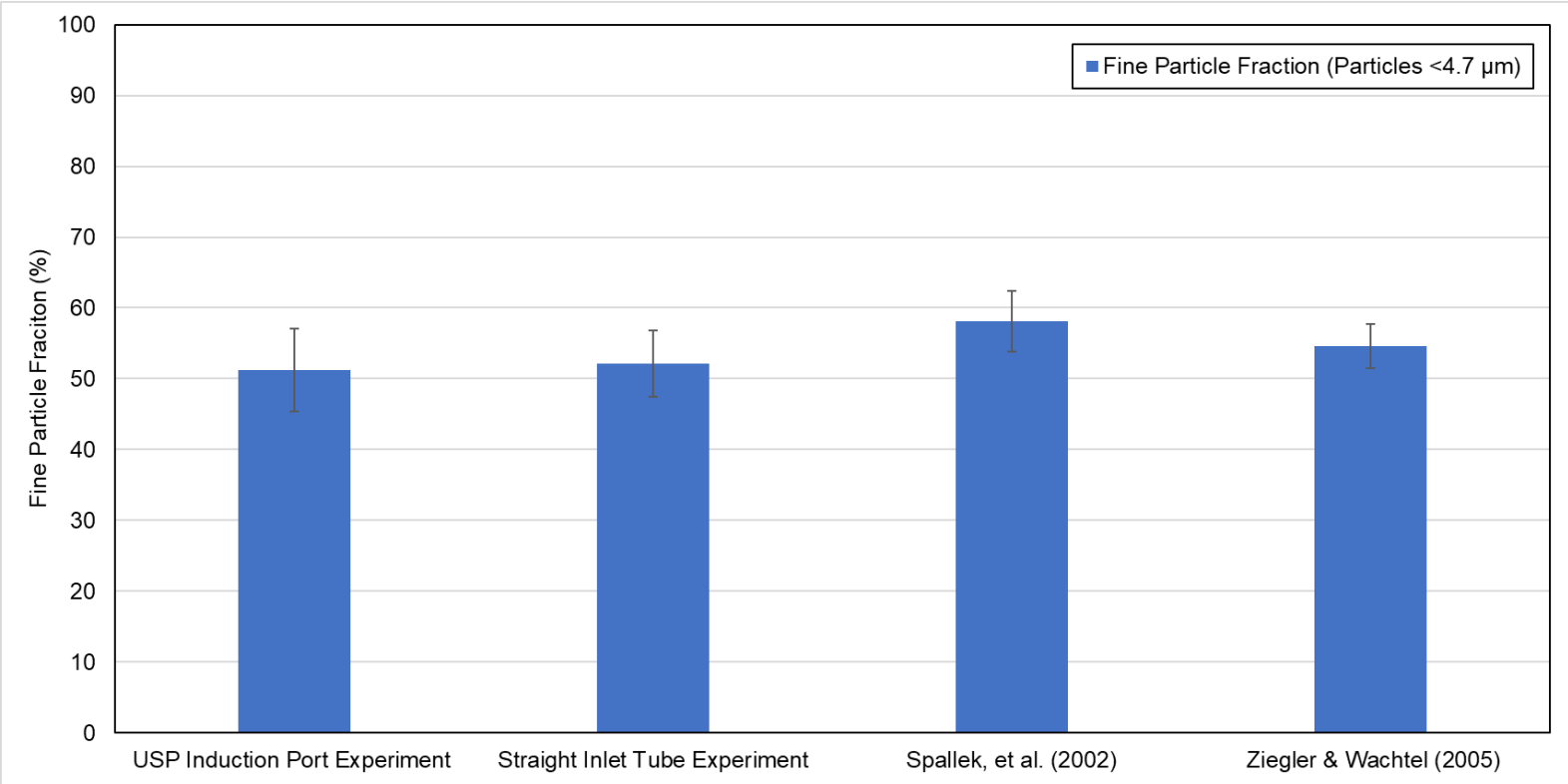
Normalized concentration (dN/dlogDp); A) 2 units (n=8 sprays per device) with USP induction port connected to the connected to the Impactor Inlet; B) 2 units (n=8 sprays per device) with straight inlet tube Inlet. The data are plotted as mean ± standard deviation (SD).

Results



Spallek MW, Hochrainer, D., Wachtel, H. Optimizing nozzles for soft mist inhalers. In *Respiratory Drug Delivery 2002*. RDD Online; Richmond, VA: 2002, 8: 375-8.
Ziegler J, Wachtel H. Comparison of cascade impaction and laser diffraction for particle size distribution measurements. *J Aerosol Med* 2005, 18: 311-24.

Results



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Results

1. The Impactor Inlet was used with the APS to provide a dilution to the aerosol cloud to avoid overwhelming the APS.
2. 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.
3. The high RH environment that was used for testing provided some dilution to the aerosol. However, this effect was small compared to the dilution effect from the Impactor Inlet.

Conclusions

1. The current work presents research on the use of an APS to evaluate APSD for inhalers that use the Respimat platform.
2. The results were similar between the USP induction port and the straight inlet tube and are comparable to ACI data collected from the literature.
3. 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.

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