The Influence of Temperature and Humidity Control in Laboratory Settings on the Aerodynamic Particle Size Distribution of Soft Mist Inhalers

Sunilkumar Patel – Amneal Pharmaceuticals, New Jersey, USA, and **Heli Chauhan** – MSP, a Division of TSI®, Minnesota, USA

Introduction

Soft mist inhalers (SMIs) are an emerging delivery platform due to their longer spray duration and slower rate of discharge, making it a preferred mode of delivery for patients with impaired breathing. Compared to metered dose inhaler and dry powder inhaler products, the fraction of fine particles in SMI is often higher (65–80%) [1]. Ease of use and propellent-free nature of formulation also contribute to its popularity.

The spray properties of SMIs are similar to nebulizers, both containing aqueous droplets. Rapid size changes of the aerosol particles due to evaporation is well-known for aqueous droplets [2]. Ambient conditions can significantly influence aerosol measurements. It is therefore important to minimize evaporation by testing at low temperatures and/ or high humidity, as recommended in compendial methods.

The current study's objective was to evaluate the impact of temperature and humidity control when testing aerodynamic particle size distribution (APSD) for SMI products under different standard laboratory conditions. We compared key APSD metrics across different testing conditions.

Materials and Methods

- APSD experiments were conducted using Next generation Impactor (NGI), manufactured by MSP Corp, Div of TSI, USA.
- Regular micro-orifice collector (MOC) cup was used for this set of data and no internal or external filters were used.
- Two commercially available lots of Spiriva Respimat® (Tiotropium Bromide Inhalation Spray), 1.25mcg/ actuation, were sourced and used for testing. 3 NGI runs per condition per lot were performed at 28.3L/min flow rate.
- A suitable High Performance Liquid Chromatography (HPLC) method for tiotropium bromide (1.562 mcg equivalent to labeled 1.25 mcg Tiotropium base) was used for chemical analysis following sample recovery from the NGI assembly.

Experimental setup

- The NGI setup consisted of the low-capacity pump (Model LCP5), flow meter (Model: DFM2000), NGI Leak Tester (MSP Corporation, USA), NGI induction port and the NGI body (MSP Corporation, USA).
- Before every actuation, the NGI cups were placed in the cup tray and inserted into the NGI body. No coating solution was used to coat the cups.
- NGI cooler (Copley Scientific, UK) was used to control temperature conditions
- Portable humidifier was used to control different humidity conditions

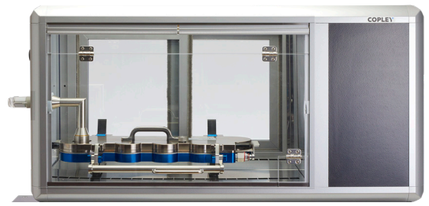


Figure 1: NGI setup within the NGI Cooler (Copley Scientific, UK) along with Spiriva Respimat device

Parameter	Experimental Condition					
	1	2	3	4	5	6
Humidity (%RH)	20	40	Ambient	Ambient	Ambient	Ambient
Temperature (C)	Ambient	Ambient	5	10	15	20

Table 1: Experimental conditions (two humidity conditions and four temperature conditions were evaluated)

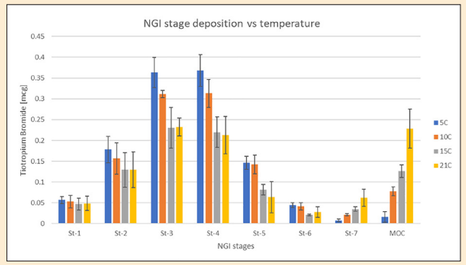
Key metrics evaluated

- Fine Particle Dose (active drug <5 microns particle size),
- Mass Median Aerodynamic Diameter (MMAD) (aerosol diameter at which 50% of the particles by mass are larger and 50% are smaller),
- Mass Balance (sum of drug mass collected from the mouthpiece adapter, induction port and impactor stages)
- Geometric Standard Deviation (GSD).

Results

- Figure 2 shows APSD data for the Respimat inhaler at 5C,10C, 15C and 20C. The %RH across all 4 conditions was consistent between 35-45%RH during the experiment.
- Data indicated statistically significant dependence on temperature along with decrease in mass balance with increase in testing temperature (t-test, p value 0.08).
- No significant changes in MMAD and FPD were seen across the different temperatures.

Figure 2: Impact of temperature on APSD deposition data (n=3 NGI per lot, 2 lots tested; prob>F<0.05 for stages 2 to MOC).



- Decrease in deposition until stage 6, along with an increase in the amount of drug on stages 7 and MOC was observed at lower humidity (20%).
- The temperature control at both humidity levels was 21C, which led to overall lower mass balance and higher variability in data. This indicates statistically significant impact of humidity on these metrics.

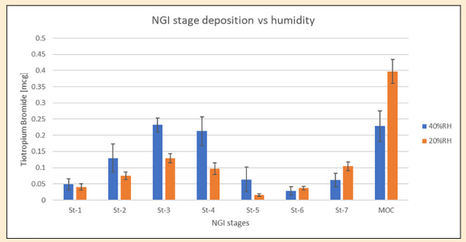


Figure 3: Impact of humidity on APSD mass deposition data: 20% vs 40% humidity at ambient temperature (N=3 per lot, 2 lots tested, Prob>F<0.05 for stage 7 and MOC).

Conclusion

- The results demonstrate the changes in deposition pattern for APSD results as a function of temperature and humidity.
- Although generally reported metrics such as MMAD and FPD do not change significantly, testing conditions can bias the amount of fine particles leading to inaccurate data.
- Controlling testing environment, especially temperature (5C± 3C) in lab setting is crucial for APSD determination in soft mist inhalers.

References

- Dalby R et al.: A review of the development of Respimat® Soft Mist Inhaler. International Journal of Pharmaceutics 2004, 283: 1–9.
- Dhapare S: Demonstrating bioequivalence with inhalation spray drug products. Presentation part of SBIA 2021.
- USP <1601> Products For Nebulization – Characterization Tests.

Contact

- Sunilkumar@amneal.com
- Heli.Chauhan@tsi.com

Learn More:

6453618246 2024 MSP, a Division of TSI®