Rapid Screening Particle Size Analysis of Soft Mist Aerosolization Devices

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Introduction

- Soft mist inhalers (SMI) generate a metered dose of a liquid formulation with an extra-fine droplet size distribution.[1,2]
- The USA Food and Drug Administration (FDA) recommends that Aerodynamic Particle Size Distribution (APSD) must be carried out by impaction methods with a requirement to minimise spray evaporation. This can be achieved by either cooling the impactor to 5°C or working at high relative humidity (RH), as close to 100% as possible.[3]
- Laser diffraction (LD) methods can be used for APSD measurements on SMIs, but no specification given regarding minimisation of evaporation.[3]
- A previous study on nebulisers showed that both RH and temperature have an impact on droplet size measured by LD.[4] Evaporation of soft mist aerosols has already been demonstrated and preconditioned inlet air is required to reduce evaporation.[5]
- Impact of beam steering due to carrier air humidity and/or droplet evaporation on sizing accuracy has not been reported for SMIs yet.

Aim: The aim of this study was to develop a standardized approach for the characterisation of droplet size distribution using high frequency laser diffraction for SMI devices.

Methods

Experiments were conducted on three tiotropium inhalation solution soft mist inhalers (UK PL 14598/0084). Every inhalers was primed according to the patient instructions leaflet.

Particle size was measured by laser diffraction thanks to the Malvern Spraytec equipped with an inhalation cell positioned horizontally. Beam steering corrections were manually implemented during a post-processing stage by removing some of the detectors as advised by Malvern. Spray duration was also measured by multiplying the number of records by the acquisition sampling frequency.

Humidified air was provided by a climate-controlled chamber and delivered through the SMI air inlets and through the entire inhalation cell. Humidity levels were manually monitored by a handheld temperature and humidity probe prior to testing.

Experiments were carried out at four different conditions: 30 L/min – Ambient RH; 30 L/min – 98% RH; 90 L/min – Ambient RH; 90 L/min – 98% RH. All measurements were replicated for a total of five data points per testing condition.

Results & Discussion

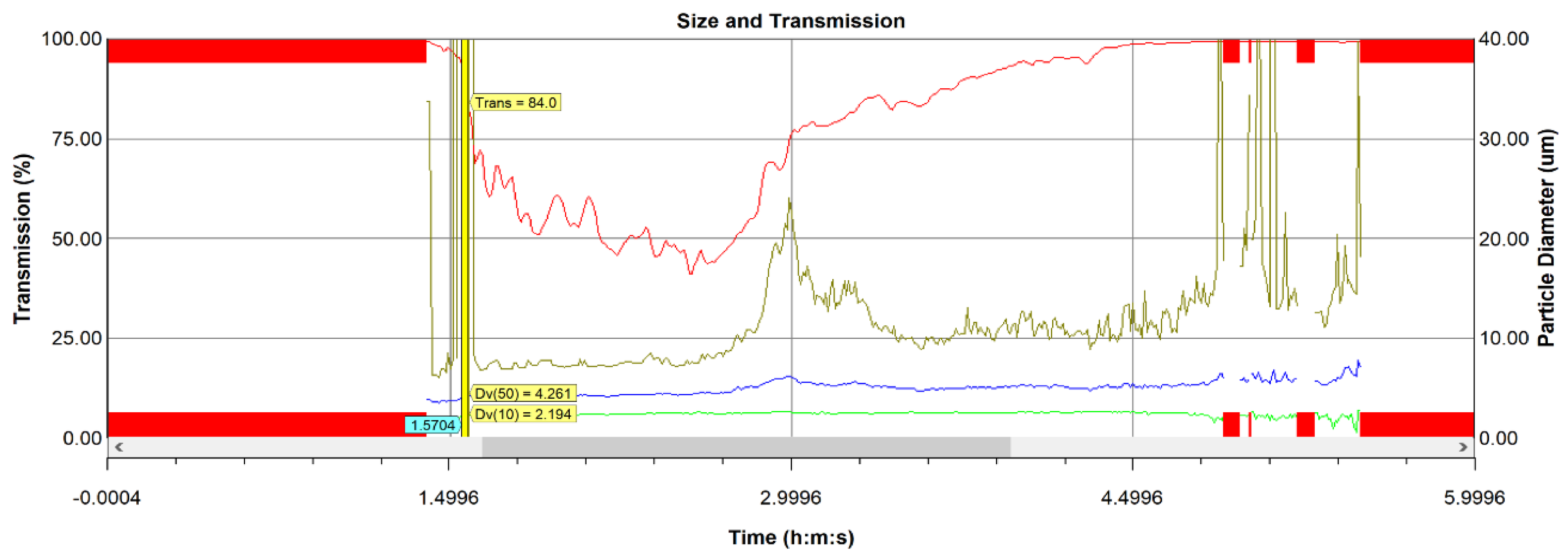

Figure 1 – Time trace of the transmission (top curve) without beam steering correction as well as the Dv(10), Dv(50) and Dv(90) (respectively 1st, 2nd and 3rd curve from the bottom) measured across the whole spray duration for a SMI device tested at 30 L/min and 98% RH.

Series of high peaks visible when laser transmission was above 98%, especially occurring for the Dv90 curve during the spray formation and extinction phases. As signal intensity is low, these peaks were suspected to be due noise.

Another post-processing step was decided: application of a cut-off filter at 98% transmission.

Laser transmission dropped to about 50% when testing at 98% RH compared to about 75% when at ambient RH. This would suggest a greater optical density at high RH due to minimization of evaporation.

Spray duration increased as RH increased, observed by a longer spray extinction phase.

No spray was being detected by the Spraytec when testing at 90 L/min and ambient RH.

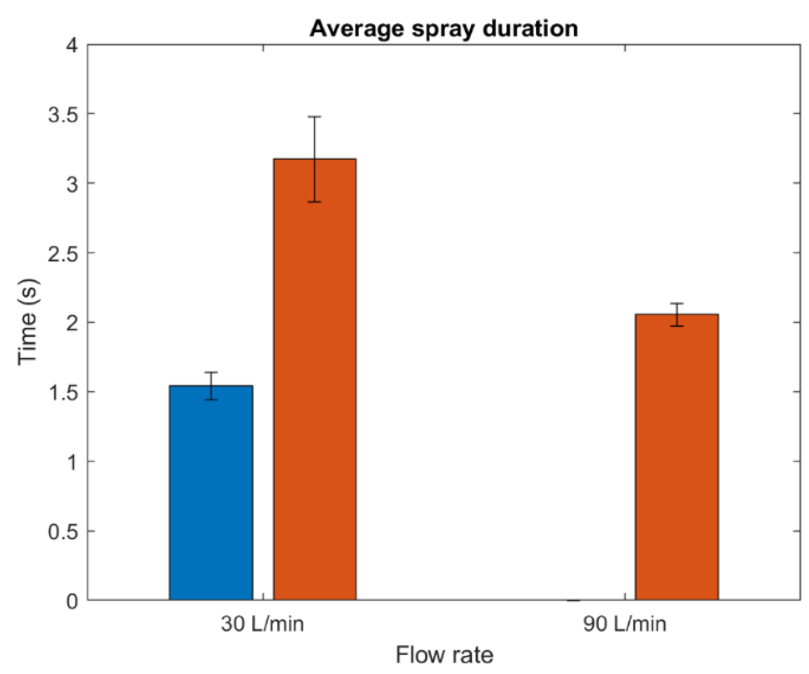

Figure 2 – Average spray duration of the SMI device at 30 and 90 L/min (error bars show standard deviation). Blue: ambient RH – Orange: 98% RH. No spray was detected at 90 L/min and ambient relative humidity

Table 1 – Comparative table of PSD measurements of the SMI device at 30 L/min with and without a detection threshold set at 98% of the transmission

		Dv10 (µm)		Dv50 (µm)		Dv90 (µm)	
Beam steering corrections		No	Yes	No	Yes	No	Yes
Without threshold	Ambient RH	2.28 ± 0.05	2.28 ± 0.05	4.50 ± 0.06	4.45 ± 0.08	8.80 ± 0.09	8.51 ± 0.15
	98% RH	2.31 ± 0.02	2.29 ± 0.02	4.57 ± 0.06	4.48 ± 0.06	9.12 ± 0.14	8.48 ± 0.17
With threshold	Ambient RH	2.28 ± 0.05	2.28 ± 0.06	4.43 ± 0.08	4.39 ± 0.12	8.47 ± 0.12	8.22 ± 0.19
	98% RH	2.31 ± 0.02	2.29 ± 0.02	4.56 ± 0.06	4.48 ± 0.06	9.08 ± 0.16	8.46 ± 0.18

Statistical analysis using paired or unpaired t-tests ($p < 0.05$):

- Dv10, Dv50 and Dv90 without beam steering correction significantly greater than Dv10, Dv50 and Dv90 after beam steering corrections for the tests at 98% RH without cut-off threshold. Also valid at ambient RH for the Dv90 only.
- Dv90 at 98% RH statistically greater than Dv90 at Ambient RH prior to beam steering corrections and no detection threshold. There is no statistical difference when applying the beam steering corrections.
- Similar observations to the two points above when focusing on the data after application of the detection threshold.
- Dv90 value at ambient RH prior to beam steering correction is greater before application of cut-off filter rather than after application of the filter. No difference at 98% RH. This could imply that the high peaks visible prior to thresholding might also be due to beam steering on top of noise.
- No statistical difference found at 98% RH about the impact of the 98% threshold filter compared to full spray. This might be due to the avoidance of the evaporation of the spray at high RH. This could also be thanks to the instrument background subtraction already correcting the impact of the humid air, unlike at ambient conditions.

Conclusion & Future work

This method, elaborated during this study, minimises spray evaporation thanks to high humidity air, corrects beam steering effects and poor scattering signal due to low laser beam obscuration within the inhalation cell. This work has developed a standardized laser diffraction sizing method for use with soft mist aerosolization devices, which is suitable for assessing the impact of formulation and device design on the aerosolization performance.

Future work will include a combined investigation of impaction and laser diffraction methods under conditions that minimise spray evaporation in soft mist devices.

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