

Towards a More Realistic Method for Measuring Nebulized Aerosols: Measurement of Fine Particle Fraction During Simulated Adult Breathing with a Nephele Mixing Inlet and Laser Diffraction with Simultaneous Drug Dose Analysis

Lois Slator^{1,2}, Owen Currie¹, Markus Hijlkema¹ & Darragh Murnane²

¹Respironics Respiratory Drug Delivery (UK) Ltd, a business of Philips Electronics UK Limited, Chichester, West Sussex, UK

²School of Life and Medical Sciences, University of Hertfordshire, Hatfield, UK

Summary

The pursuit of more clinically relevant in vitro tests for nebulizers and other inhalation devices continues, as the desire to demonstrate bioequivalence using in vitro data and to refine the predictions of in vivo behaviour is still an ambition. Use of laser diffraction to determine particle size with simulated breathing showed only a minimal decrease in fine particle fraction. Simultaneous measurement of particle size by laser diffractometry and delivered dose by HPLC whilst using the Nephele mixing inlet to introduce a standard adult breathing pattern was assessed and compared to the same parameters recorded under continuous flow extraction. A small decrease in fine particle fraction was observed when a breathing profile was introduced, in line with the previous observations. A much larger percentage decrease in the delivered dose was recorded, even with the sampling time corrected for time spent inhaling. This results in a fine particle dose in the range reported by Svensson et al. in 2018. This outcome suggests that the observed decrease is mainly due to a reduction in drug being delivered to the test system and only slightly due to a change in the aerosol particle size distribution.

Key Message

The reduction in fine particle dose observed when using the Nephele mixing inlet compared to the pharmacopeial method is primarily due to a reduction in drug delivered, whilst the fine particle fraction of that drug is only slightly reduced.

Introduction

The pursuit of more clinically relevant in vitro tests for nebulizers and other inhalation devices continues, as the desire to demonstrate bioequivalence using in vitro data and to refine the predictions of in vivo behaviour is still a shared ambition in industry¹.

Use of the Nephele mixing inlet to introduce an adult breathing pattern to the droplet size measurement of nebulizers has previously been demonstrated with the cascade impactor where the fine particle dose collected using the Nephele mixing inlet was only 72% of the pharmacopeial method². Use of the same test setup on the Spraytec laser diffractometer indicated that there was no significant difference in the volume median diameter (VMD) calculated between the continuous flow method and the simulated breathing pattern method and therefore no significant difference in fine particle fraction³. This work aimed to investigate further the relative importance of the contributing factors to the difference in fine particle dose observed by Svensson et al.

Method

Five InnoSpire Go mesh nebulizers (Respironics Respiratory Drug Delivery (UK) Ltd, Chichester, UK) with a range of VMD were selected for the tests using a previously described method³.

Each device nebulised salbutamol sulphate solution (5mg/2.5ml) under the following conditions:

Continuous flow	Delivered dose was collected on a 200g electrostatic blended synthetic fibre filter at the outlet of the Spraytec inhalation cell with an extraction of 30 L/min for 30s, with simultaneous measurement of particle size by laser diffraction.
Simulated breathing	Delivered dose was collected on a 200g electrostatic blended synthetic fibre filter at the outlet of the Spraytec inhalation cell with an extraction of 30 L/min and a simulated adult breathing pattern ($V_t=500\text{mL}$, $I:E=1:1$, $f=15\text{bpm}$) for 60s, with simultaneous measurement of particle size by laser diffraction.

The sampling time during the simulated breathing method was doubled to 60 seconds compared with the corresponding duration for the continuous flow method to enable similar amount of drug to be delivered to the sampling area, as aerosol was only collected during the inspiratory phase of the breathing simulation. Average VMD and fine particle fraction < 5 μm for each device with the continuous flow and simulated breathing methods were recorded by laser diffractometry. The mass of drug deposited onto the filter for both methods was analysed and quantified by a validated HPLC method.

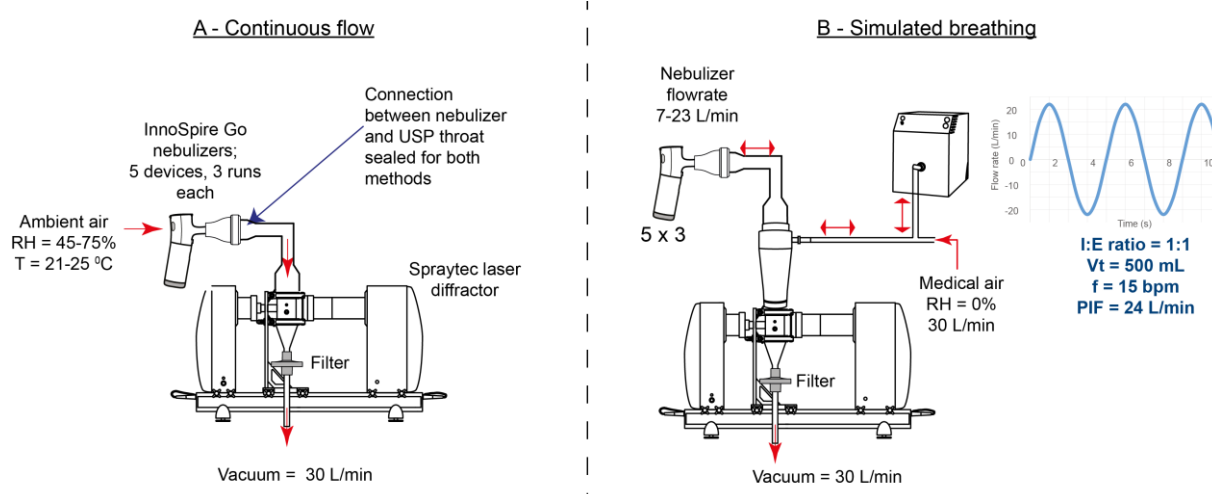


Figure 1. Schematic test setups for (A) continuous flow and (B) simulated breathing methods.

Results and Discussion

Table 1. Mean VMD (standard deviation;SD) and fine particle fraction < 5 μm (standard deviation; SD) of InnoSpire Go nebulizers tested under continuous flow and simulated breathing methods.

	VMD			Fine particle fraction < 5 μm		
	Continuous flow Mean (μm) (SD)	Simulated breathing Mean (μm) (SD)	Simulated breathing VMD as a % of continuous flow VMD	Continuous flow Mean (%) (SD)	Simulated breathing Mean (%) (SD)	Simulated breathing fine particle fraction as a % of continuous flow fine particle fraction
Device 1 (n=3)	4.07 (0.06)	4.21 (0.05)	103.5	63.93 (1.22)	60.69 (0.66)	95.0
Device 2 (n=3)	4.80 (0.01)	4.82 (0.06)	100.5	52.66 (0.19)	52.25 (0.74)	99.2
Device 3 (n=3)	3.90 (0.01)	3.97 (0.07)	103.2	67.29 (0.30)	65.17 (1.82)	96.9
Device 4 (n=3)	3.58 (0.01)	3.66 (0.04)	103.7	73.22 (0.76)	69.99 (1.33)	95.6
Device 5 (n=3)	3.91 (0.03)	4.03 (0.03)	102.7	66.69 (0.49)	63.56 (0.48)	95.3
All devices (n=5)	4.05 (0.02)	4.14 (0.01)	102.15 (1.13)	64.76 (7.57)	62.33 (6.57)	96.39 (1.74)

Spraytec-measured VMD increased by more than an order of magnitude in the range of 0.02-0.14 μm from continuous flow to simulated breathing. This increase was consistent with previous observations³. As the VMD and the fine particle fraction < 5 μm are inversely related, it is not surprising to find that the

fine particle fraction < 5 μm for simulated breathing decreased to 95.0-99.2% of that recorded for the continuous flow method, which was significant (paired $t(4)=4.44$, $p=0.011$).

The delivered dose for the simulated breathing method was found to have significantly decreased (paired $t(4)=4.80$, $p=0.009$) to 79.9-95.7% of the delivered dose recorded for the continuous flow method. Fine particle dose < 5 μm was estimated by multiplying the fine particle fraction < 5 μm and the delivered dose captured on the filter.

Table 2. Mean delivered dose (standard deviation; SD) and mean fine particle dose < 5 μm (standard deviation; SD) of InnoSpire Go nebulizers tested under continuous flow and simulated breathing methods.

	Delivered dose			Fine particle dose < 5 μm		
	Continuous flow Mean (μg) (SD)	Simulated breathing Mean (μg) (SD)	Simulated breathing delivered dose as a % of continuous flow delivered dose	Continuous flow Mean (μg) (SD)	Simulated breathing Mean (μg) (SD)	Simulated breathing fine particle dose as a % of continuous flow fine particle dose
Device 1 (n=3)	528.19 (29.33)	443.18 (54.36)	83.8	337.45 (13.93)	269.08 (34.83)	79.7
Device 2 (n=3)	654.13 (41.10)	523.35 (61.91)	79.9	344.40 (20.64)	273.73 (36.21)	79.4
Device 3 (n=3)	537.44 (44.09)	434.53 (57.91)	80.6	361.60 (29.07)	282.50 (30.07)	78.0
Device 4 (n=3)	470.86 (17.65)	397.30 (19.34)	84.4	344.86 (16.17)	277.96 (10.20)	80.7
Device 5 (n=3)	449.52 (34.71)	423.90 (96.91)	95.7	299.70 (21.33)	269.69 (63.56)	91.2
All devices (n=5)	528.03 (79.72)	444.45 (47.36)	84.89 (6.37)	337.60 (22.98)	274.59 (5.68)	81.79 (5.36)

There was a significant reduction in the estimated fine particle dose < 5 μm with the simulated breathing method to 78.0–91.2% of that observed with the continuous flow method (paired $t(4)= 7.40$, $p=0.002$) (Table 2). Figure 2 shows the mean percentage reduction in fine particle fraction < 5 μm , delivered dose (μg) and fine particle dose < 5 μm (μg) between the continuous flow method and the simulated breathing method. The outcome indicates that the reduction in amount of drug delivered was the greatest contributing factor to the reduction in fine particle dose < 5 μm , as previously reported ².

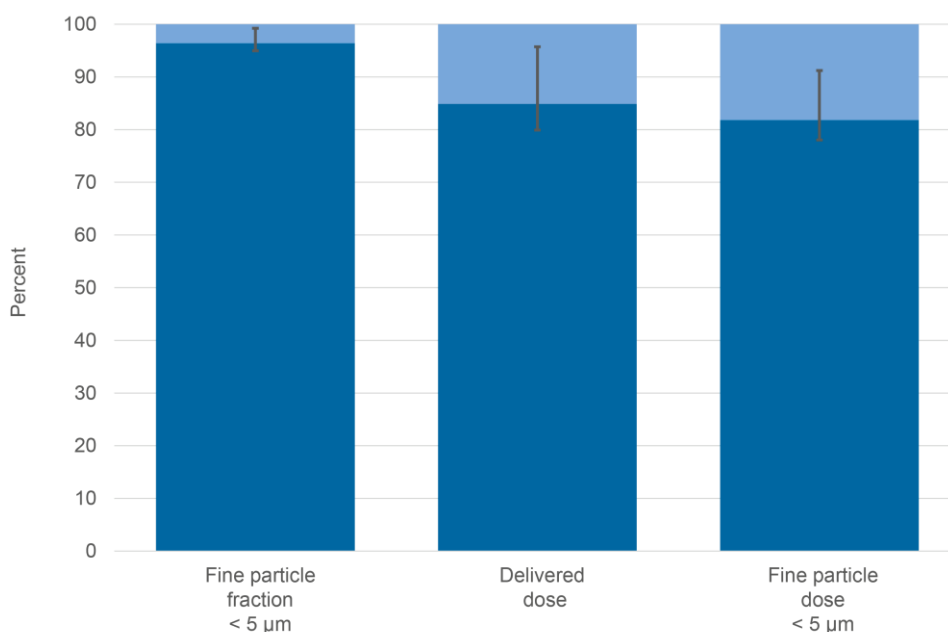


Figure 2. Mean fine particle fraction < 5 µm, mean delivered dose (µg) and mean fine particle dose < 5 µm (µg) for the simulated breathing method (■) as a percentage of the continuous flow method (■) (error bars show range of results)

Conclusions

The use of the Nephele mixing inlet to introduce an adult breathing pattern for the assessment of particle size distribution during simulated breathing resulted in only a small change to the aerosol size distribution and the fine particle fraction < 5 µm of the measured drug, but caused a much greater decrease in the amount of drug delivered, and therefore reduced the fine particle dose < 5 µm.

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