Transient Aerosol Measurements: Assessing the eFlow Nebulizer Aerosol Bolus

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Background and Objectives

The output of nebulizers is commonly assumed to be constant over the breathing cycle. Accordingly, time-averaged values such as aerosol output rate (AOR, measured during tidal breathing) and Mass Median Aerodynamic Diameter (MMAD, measured at constant flow) are used to characterize the systems (e.g. USP, ISO27427) and to estimate aerosol deposition in the lungs. However, recent measurements show that especially nebulizers with aerosol storage chambers yield a highly unsteady aerosol output rate (uAOR), the so-called “aerosol bolus” [1].

PARI’s eFlow nebulizer (Fig. 1) is such a nebulizer using an aerosol storage chamber, a continuously operated vibrating mesh, and inhalation and exhalation valves [2,3]:

Figure 1: Investigational PARI eFlow nebulizer during exhalation (left) and inhalation (right)

Exhalation:
Inhalation valve is closed, exhaled air escapes through exhalation valve. Aerosol is stored in aerosol storage chamber.

Inhalation:
Inhalation valve open: Stored aerosol leaves the device first followed by the continuously generated aerosol, leading to an unsteady aerosol output rate (uAOR) especially at the beginning of the inhalation phase. Excess aerosol is called “aerosol bolus”.

Only if the main parameters of the aerosol, such as AOR MMAD or fine particle fraction (FPF) are known as a function of time, correct predictions can be made on aerosol deposition using standard models such as respirable delivered dose (RDD), respirable delivered dose rate (RDDR) or in the use of in-silico models which are enjoying growing popularity.

Objective: Develop a measurement method to quantify the aerosol bolus in terms of aerosol output and droplet size and compare data of PARI eFlow nebulizer (using an aerosol storage chamber) to Philips InnoSpire Go (Fig. 2, without chamber).
Note: In this study mass median diameter (MMD) rather than MMAD was used as it can be measured during tidal breathing using a laser diffractor. However, MMD correlates well with MMAD for different aqueous drug formulations [4].

Figure 2: Philips InnoSpire Go

Table 1: Aerosol parameters of the two devices at constant flow conditions at 20 L/min

	PARI eFlow	Philips InnoSpire Go
gravimetrical Total Output Rate (TOR)	615 mg/min	580 mg/min
MMD (conditioned air)	2.84 µm	4.24 µm

Materials and Methods

uAOR
Addition of a fast-switching valve and a secondary filter to a standard setup for AO-measurements (Fig. 3):
- Using the fast-switching valve, aerosol can be repeatedly diverted from the measurement filter to a secondary filter at any time during the breathing cycle.
- The cumulated AO as a function of time can be determined by increasing the duration between start of inhalation and switching of the valve.
- The first derivative of cumulated AO is the uAOR which is used to quantify the bolus.
- Test solution: Isotonic saline +0.1 % tartrazine.
- Concentration of tartrazine assessed using ultraviolet-visible photometry.

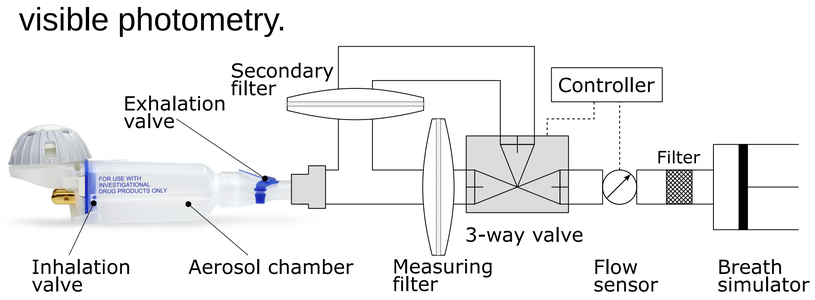

Figure 3: Experimental setup to measure cumulated AO as a function of time

uMMD
A connector piece was placed between a breath simulator and the nebulizer (Fig. 4):
- The connector piece contains two glass covered openings
- Laser diffractor can measure droplet size through windows (sampling rate 50 Hz)
- Constant cross-sectional area of the mouthpiece outlet through the entire connector piece to minimize flow disturbances
- 5 sets of 6 breath cycles were recorded and phase averaged, the glass windows were cleaned after each set to prevent contamination

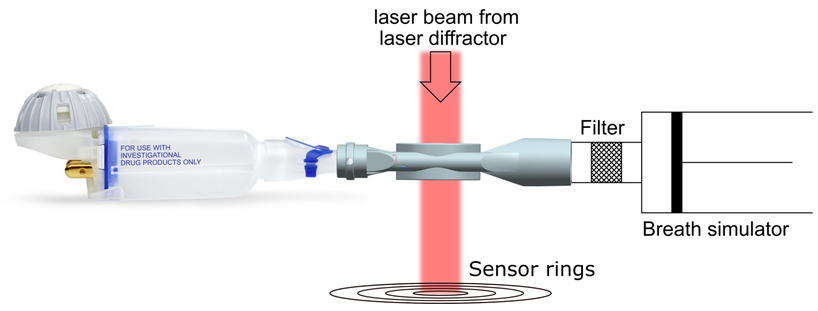

Figure 4: Measurement setup to determine MMD over a breathing cycle (uMMD)

Results

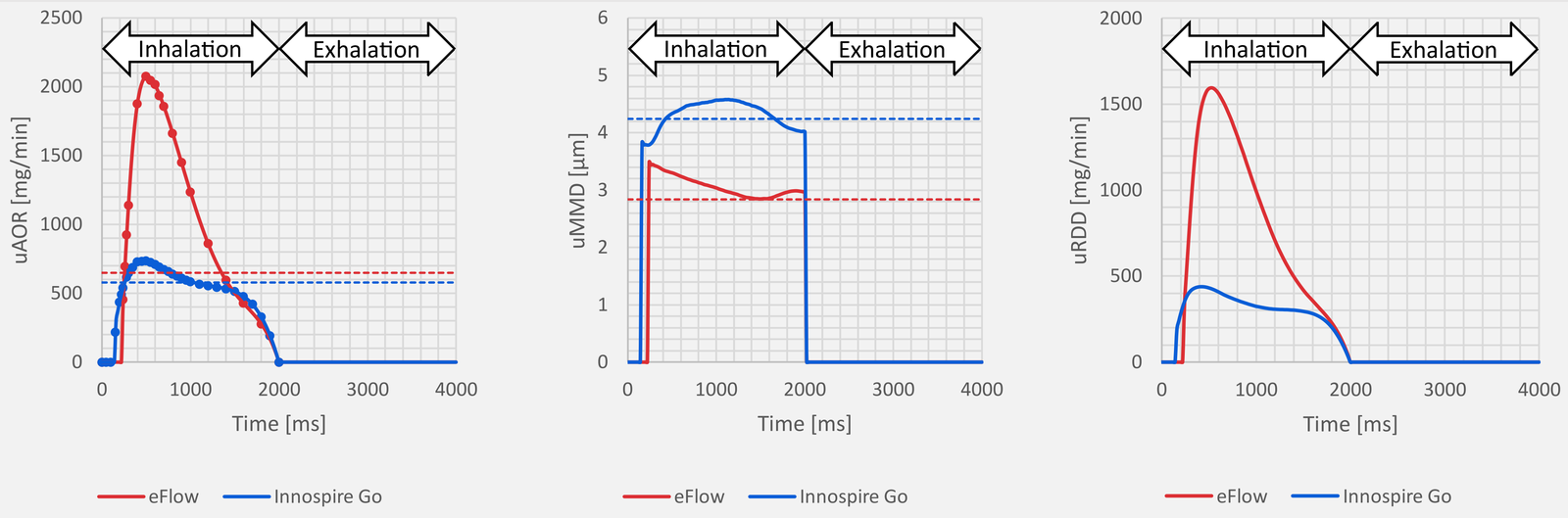

Figure 5: Comparison of the main aerosol parameters of the two nebulizers during a single breath: uAOR (left, each data point represents a measured time segment), uMMD (mid) and unsteady respirable delivered dose (uRDD, right). The dashed lines represent measurements at a constant flow rate of 20 L/min.

uAOR:
- Beginning of the inhalation phase: The aerosol bolus is transported from the aerosol chamber to the filter
- Both nebulizers show a sudden increase in uAOR in the first quarter of the cycle with the peak value of the eFlow being 2.8 times higher than the InnoSpire
- Due to the storage effect of the eFlow, uAOR is up to 320 % of what is currently produced by the vibrating mesh unit. For the InnoSpire the same parameter is only 128 %

→ AOR strongly varies over time, especially for systems using an aerosol storage chamber

uMMD:
The two nebulizers show an adverse behavior in terms of droplet size:
- eFlow: Most likely due to coalescence of droplets during storage, MMD is highest at the beginning of inhalation, reaching the values of the constant flow case just after the maximum flow rate. This behavior should have very limited impact on throat deposition
- InnoSpire: MMD is a function of flow rate; low values at low, and high values at high flow rates. Reason for this could be that at high flow rates large droplets follow the air stream that would otherwise impact in the device

→ MMD is a function of time for both systems

uRDD:
- Mainly due to high AOR, but also due to lower MMD (resp. higher FPF) results in higher uRDD for essentially the entire breathing cycle of the eFlow nebulizer, reaching peak values 2.5 times higher than for the InnoSpire
- Reduced exhalation losses and increased residence times for storage system as most aerosol is delivered early in the breathing cycle
- The area below the uRDD curve is comparable to RDD per breath and hence RDDR, but more precise because it considers the change in MMD

Summary and Key Findings

We developed methods to time resolved measure the aerosol output of nebulizers, showing the significant unsteadiness especially for nebulizers with storage chamber (eFlow) compared to systems without (InnoSpire):
- Using the eFlow, a large amount of aerosol is delivered at the beginning of inhalation, resulting in a uAOR peak of 320% of what is continuously produced. For the InnoSpire (no storage), values are much closer to constant AOR.
- During storage, MMD increases by up to 22 % most likely due to coalescence, which reduces the FPF especially at the beginning of inhalation (where flow rates are low). However, also without aerosol storage MMD shows a strong variation over the breathing cycle of 21 %.
- As a result of higher AOR and lower MMD, the RDD per breath (and hence RDDR) of the eFlow is 2.5x higher than for the Innospire Go. Due to differences in MMD we could not fully isolate the effect of the storage chamber, however we could clearly demonstrate the advantages of using such a system:
- A large amount of aerosol is delivered to the lungs right at the beginning of the inhalation, leading to reduced exhalation losses and higher peripheral deposition [5].
- More aerosol can be delivered during inhalation, leading to reduced treatment times [6].
- Higher drug efficiency as aerosol is stored during exhalation.
- Due to the strong unsteadiness, the development of the aerosol characteristics during one breathing cycle must be considered in order to correctly predict lung deposition in empiric models or deposition simulation.

References

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