Nebulizer particle size distribution measured by various methods

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Abstract. Pari LC Sprint Star nebulizer is an inhaler device dedicated to delivering the liquid drug formulation into peripheral lung regions. The particle size is one of the critical parameters which determine the location of aerosol deposition within the human lungs. In this study, the particle size distribution of aerosol was measured by two different methods: Andersen Cascade Impactor (ACI) and Aerodynamic Particle Sizer (APS). Mass Median of Aerodynamic Distribution (MMAD), and Geometric Standard Deviation (GSD) were evaluated. MMAD gained by APS was approx. 7 μm, MMAD acquired by ACI was approx. 2.5 μm. According to the results, these two measuring methods are not very consistent, and the comparison of the particle size acquired by the different methods is not appropriate.

1. Introduction

Inhalation treatment became usable for an incredible range of diseases in the last decade. Most of the inhalers are dedicated to asthma or COPD (Chronic obstructive pulmonary disease), but there are also applications for the therapy of various other diseases like diabetes, cystic fibrosis, or bacterial lung infections [1–3]. Nebulizers are very attractive devices for inhalation drug delivery. In contrast with pMDIs (pressurized Metered Dose Inhalers) or DPIs (Dry Powder Inhalers), with nebulizers patients do not need to make a deep forced inhalation during the usage. The therapeutic aerosol from the nebulizers is inhaled during normal tidal breathing. This makes it much more comfortable and easier for patients and usable for weaker subjects like old patients or patients in a late stage of the disease.

There are four main categories of nebulizers: air-jet nebulizers, vibrating mesh nebulizers, ultrasonic nebulizers, and soft mist inhalers. Air-jet (AJN) nebulizers are probably the most common. The nebulization process works on the principle of the Venturi effect. Airstream is forced through a small jet placed in a tiny tube, therefore there is a small space between the outer wall of the jet and the inner wall of the tube. The bottom side of the tube is submerged in the liquid drug solution. When the air stream is passing through the jet orifice, it creates a vacuum in the space between jet and tube which sucks the liquid solution into the airstream. The solution is subsequently atomized into the aerosol due to shear forces caused by the airstream [4]. A baffle placed in front of the orifice makes the largest aerosol particles stay in the device and returns them back for the next nebulization [4]. Such devices are used very frequently, although, they need a compressed air supply and electricity connection.

The second group of nebulizers is vibrating mesh nebulizers (VMN). Such devices contain a small plate with a large number of small orifices (approx. 1 μm). This mesh vibrates in high frequencies. In contact with a liquid drug solution, small droplets of liquid are torn off by mesh orifices and emitted out of the device in form of an aerosol [4, 5]. Such aerosol particles have usually a narrow particle size distribution and particle size is affected by orifices size. This enables the determination of the aerosol particle size distribution (PSD) by manufacturing, which can be very helpful [5]. VMNs are usually quite small devices, which can be supplied by batteries as well. However, the biggest disadvantage of VMNs is probably their price. They are usually much more expensive in comparison with other nebulizer types.

The third category of nebulizers is ultrasonic nebulizers (USN). A piezoelectric element is placed at the bottom of the reservoir. This makes high-frequency vibrations and waves on the liquid level, which leads to liquid atomization [5]. However, these vibrations warm up the solution and for this reason, such nebulizers cannot be used for thermolabile drug solutions [4].

Soft Mist Inhalers (SMI) represent the last category. These devices are a combination of pressurized metered dose inhalers (pMDI) and nebulizers. Respimat SMI is the most popular and frequent member of this group. The liquid drug is stored in a reservoir in Respimat. Before the actuation, a dose of liquid is filled into the metering chamber. During the actuation, the drug solution is forced

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through the twin nozzle, which makes a collision of two liquid streams, which leads to atomization [6]. Such aerosol is much slower than in the case of common pMDA and the time of atomization period is longer, which makes such a device suitable for patients who are not able to follow the proper inhalation technique as well [6].

The efficacy of drug delivery is affected by several factors. Particle size distribution and breathing pattern are probably the most significant. There are some commonly used abbreviations for particle size distribution and local lung deposition in pharmaceutical literature. Orally inhaled products are usually designed to have MMAD (Mass median aerodynamic diameter) under 5 µm. It is believed, that particles larger than 6 µm deposit preferentially in the oropharyngeal region, particles between 2 – 6 µm deposit in the central airways, and particles under 2 µm in the peripheral airways and alveoli[7]. Although, this is not completely true (explained in sources [8, 9][1]), the critical influence of particle size on lung deposition is obvious. Therefore, this study discusses the suitability and comparability of various methods for the measurement of aerosol PSD.

Lung deposition of aerosol particles is caused by the superposition of five deposition mechanisms: inertial impaction, interception, sedimentation, Brownian diffusion, and electrostatic precipitation. Each mechanism dominates in different conditions. Inertial impaction is significant for larger particles and occurs in the case of particles larger than 1 µm. Its rate grows with the particle mass and its velocity, in other words, it grows with Stokes number [9]. Interception is usually caused by the specific shape of particles and occurs in the case of prolonged particles like fibers [9]. The effect of sedimentation is significant only in the case of very low air velocities [9]. Brownian diffusion begins to be a significant cause of aerosol deposition for particles smaller than 0.3 µm when their movement starts to be affected by the collisions with ambient gas particles [9]. Electrostatic precipitation is caused by electrostatic charges of aerosol particles and walls [9]. According to the abovementioned, pharmaceutical aerosols are usually designed to have PSD between 2 – 6 µm, which is the reason why inertial impaction is considered to be the dominant deposition mechanism for pharmaceutical aerosols.

Methods for PSD measurements of inhaler aerosols are normalized by Ph. Eur. [10, 11]. Since inertial impaction is the main deposition mechanism for them, these methods separate the particle size fractions according to their inertial behavior. Ph. Eur. describes four such devices: Glass Impinger (GI), Multi-stage liquid impinger (MLI), Andersen Cascade Impactor (ACI), and Next Generation Impactor (NGI). These devices have one big advantage. They enable an assessment of an Aerodynamic Particle Size Distribution (APSD) directly for active pharmaceutical ingredients (API) since the measurements are evaluated by chemical analyses like HPLC (High-Performance Liquid Chromatography). However, such measurements are very time-consuming, and their uncertainty is very high. The list of variabilities and uncertainties of measurement on ACI is discussed in [12]. In the case of nebulizer measurements, an obstacle with the evaporation of droplets was found out, which should be solved by impactor cooling [13, 14]. Several studies showed significantly large particles while measured on a cooled impactor than at room temperature [13, 14].

However, there are some other methods for APSD measurements, which evaluate the sizes according to the particle aerodynamic and inertial behavior. These are time-of-flight measuring devices like an Aerodynamic Particle Sizer (APS, TSI Inc., USA) or previously Aerosizer (TSI Inc., USA). Such devices measure the same type of particle size as the impactors, the aerodynamic diameter. Moreover, this technique can be more precise and significantly less time-consuming than normalized methods, and even when it does not bring information directly about API, it can be suitable for some other applications. But are these devices comparable with ACI measurements and are they suitable for inhaler aerosol testing?

This study discusses the comparison of measurements of aerosol produced by nebulizers performed by different measuring methods.

2. Methods

Air-Jet nebulizer Pari LC Sprint Star was operating with a nebulization flowrate of 4.5 LPM. The atomized solution was distilled water with 100 µg/ml concentration (sodium salt) to enable the evaluation of ACI measurement. The vacuum pump Busch R5 PA0008C, control valve, and flowmeter TSI 4040 (TSI Inc., Minnesota, USA)

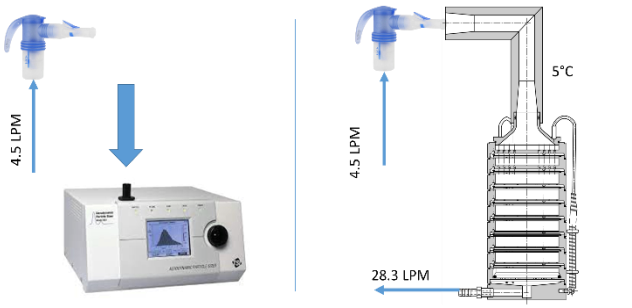

Fig. 1. Schema of the measurement rig: APS measurement (left), ACI measurement (right).

[1] Extra fine particles with MMAD < 0.3 µm use to deposit well in all regions of airways and lung deposition of particles > 6 µm can be effective as well, while it depends intensively on breathing pattern [8, 9].

Before the APS measurement, three samples of ambient air aerosol were measured. These were subtracted from the samples of nebulized aerosol. Aerosol was nebulized into the ambient environment above the APS sampler. 10 samples of aerosol were measured in this way.

Subsequently, aerosol from the same device was measured on ACI, as well. As is mentioned above, in this case, the nebulized liquid was dyed with fluorescein. ACI has been cooled in the refrigerator for at least 90 minutes at a temperature of approx. 5° C as is recommended in Ph. Eur. [11]. Dosing of aerosol into the impactor was performed within 5 minutes after taking ACI out of the refrigerator. ACI contained the kit for the flowrate 28.3 LPM which is the lowest flowrate ACI can be operated with. The nebulizer Pari LC Sprint Star was operating with a nebulization flowrate of 4.5 LPM and was connected to the ACI induction port through the modeled adapter. Before the measurements, the flow rates on the ACI inlet and outlet were checked to be the same and it was verified the ACI is leakage-free.

Dyed aerosol was dosed into the ACI continually for the time of 1 minute. Subsequently, ACI was disconnected and dismantled. Each segment of ACI was washed properly in a certain volume of distilled water to extract the deposited aerosol.

For analyses of deposited aerosol mass, a fluorimeter Quamtus™ Fluorometer (Promega Corp., USA) was employed. The calibration for the dye and solvent was performed. Concentrations of dye within the samples were determined and the mass of dye deposited in each segment was calculated.

Normalized mass aerodynamic particle size distribution was calculated from the obtained data. The deposited mass fraction was calculated as deposited mass at a certain impactor stage divided by the total deposited mass. Such results were also expressed by cumulative APSD. MMAD was gained by linear interpolation from the cumulative APSD and GSD was calculated by equation 1. according to the source [15]. The MMAD and GSD of APS results were evaluated similarly.

$$GSD = \frac{MMAD}{D_{16}} \quad [\mu m] \qquad (1)$$

In ACI measurements it is appropriate to evaluate the Emitted Dose (ED) and Fine Particle Fraction (FPF; a fraction of the particles smaller than 5 µm as a percentage of emitted dose) as well. However, in the case of a nebulizer, it would be problematic to evaluate ED due to the principle of its operation. This is the reason why this study compares only APSD data, like MMAD and GSD.

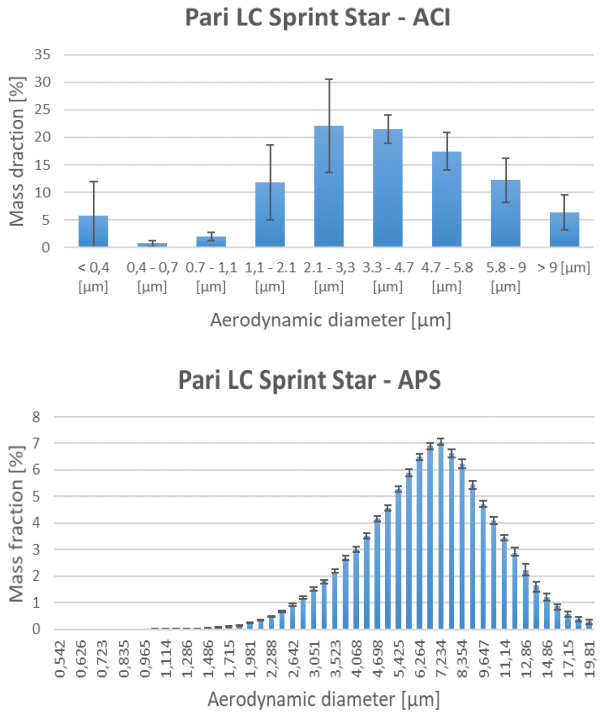

Fig. 2. Upper distribution - APSD of aerosol generated by PARI LC Sprint measured by APS; Lower distribution - APSD of aerosol generated by Pari LC Sprint Star measured by ACI.

3. Results and discussion

Table 1. APSD parameters measured by two different methods.

	ACI	APS
MMAD [µm]	2.53±0.56	6.89±0.27
GSD [µm]	2.76±0.89	1.60±0.17

According to the measured values, APS results show significantly larger particles than the results of ACI measurements. Parameters of APSD are shown in table 1.

Particle size distributions measured by both methods are shown in figure 1. From both, *table 1* and *figure 1* it is evident that the results measured by these two techniques differ significantly. However, data measured by ACI are in quite good agreement with the results of the same nebulizer measured on NGI reported in the study (MMAD approx.. 2.7 µm) [14]. A similar difference between ACI and other methods has been found in the literature as well. In the study [16], the aerosol generated by NE-U22V MicroAir (Omron Healthcare Inc. USA) was measured by ACI, NGI, and APS. Such results have shown significantly higher MMAD, approx. 6.9 µm, measured by APS than MMAD measured by ACI, respectively NGI (approx.. 4.1 µm, resp. 4.5 µm). However such differences

can be found also in comparison of ACI with other techniques. McDermott et al [17] measured particle size distribution of vibrating mesh nebulizer Aerogen Solo by Phase Doppler Anemometry. The median of volumetric PSD (D_{v50}) of nebulized albuterol was 5.7 µm on average. The MMAD of albuterol aerosol nebulized by the very same VMN Aerogen Solo measured by cooled ACI in a different study [18], was 4.0 µm. Moreover, several studies [19–21] show MMAD of aerosol generated by Aerogen solo under 2 µm, but the aerosol was in these works dosed through the nasal cannula, which could hypothetically affect the APSD. On the other hand, measurements by Misik et al [22] showed good agreement between MMAD measured by APS and D_{v50} measured by PDA for Aerogen Solo nebulizer.

According to the abovementioned, it is probable, that in the case of aqueous aerosols, the ACI and APS (and maybe also other) measuring techniques are not very consistent and comparable, while ACI results tend to show smaller particle size. This should be investigated more. APS result can depends on the way of sampling. This should be tested and optimized in future steps.

4. Conclusion

The APSD of aerosol generated by AJN Pari LC Sprint Star was measured by two techniques: APS and cooled ACI. Our results confirmed the issue reported in [16] and APS showed MMAD approx. 6.9 µm while ACI is only 2.5 µm. Considering such results, it is obvious that methods are not very comparable. However, there has not been a very good explanation for this difference and more comparative measurements need to be done.

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