Characterization of Aerosol Nebulized by Aerogen Solo Mesh Nebulizer

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Abstract. Nebulizers are commonly used devices for inhalation treatment of various disorders. There are three main categories of medical nebulization technology: jet nebulizers, ultrasound nebulizer, and mesh nebulizer. The mesh nebulizers seem to be very promising since this technology should be able to produce aerosol with precisely determined particle size and is easy to use as well [1]. Aerosol generated from the mesh nebulizer Aerogen Solo was measured in this work. Particle size distribution with a mass median of aerodynamic diameter (MMAD) was determined by two different methods.

1 Introduction

An inhalation treatment has nowadays a wide range of use. Besides the therapy of pulmonary diseases, inhalers are beginning to be used also for the treatment of systemic diseases. However, the efficiency of drug delivery is quite a complex topic. Its efficacy depends on aerosol characteristics (particle size, particle velocity), inhaler technology, drug formulation, or inhalation technique [2–5].

There are three main categories of inhalers: pressurized metered-dose inhalers (pMDIs), dry powder inhalers (DPIs), or nebulizers. pMDIs are small pocket-size inhalers that contain the drug formulation and liquidized propellant inside the reservoir [2]. During the actuation, the precisely metered dose of the solution is emitted through the mouthpiece and dispersed. Such aerosol is emitted with high velocity, which results in a high fraction of drug deposited in upper airways. It is also difficult to coordinate the manual actuation and the patient's inspiration [2, 5, 6].

DPIs are devices that are used to disperse dried powder drug formulation during the inhalation. Conventionally, they are passive devices, it means the patient needs to make an inspiration effort to suck the powder from the inhaler.

Nebulizers are devices that atomize a liquid drug solution. In contrast with DPIs or pMDIs, nebulizers do not require difficult inhalation techniques so they are much easier to use. Their disadvantage is size and portability. However, nebulizers can be used for a wide range of applications since they can deliver a large range of drug formulations. There are three types of medical nebulizers: jet nebulizers, ultrasonic nebulizers, and mesh nebulizers. Jet nebulizers are the most common and cheapest nebulizers. The airstream is driven by the compressor through the nozzle. The liquid solution is sucked into

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the airstream due to the Venturi effect and liquid is dispersed because of the shear forces [7]. However, approximately only 5 % of the produced aerosol is respirable [5]. It is not very sensitive to variability in viscosity or the surface tension and can be used for plenty of nebulized drugs. However, it is not portable and because of the compressor, these devices are usually quite big and loud. The ultrasonic nebulizers use the piezoelectric horn to nebulize the liquid. In the version with a battery, it can be portable, but its usage is very limited because the piezoelectric elements increase the temperature of liquid so it is not appropriate for thermolabile drugs. The mesh nebulizers are the most promising devices for liquid drug nebulization. This type of device contains a mesh with small precise orifices. The piezo elements make the mesh vibrations and produce the droplets of aerosol with narrow particle size distribution [5, 7]. It means, it is possible to select the MMAD of aerosol by the size of mesh orifices and up to 100 % of the aerosol can be respirable [5]. The mesh nebulizers can be portable, it allows short treatment times because of high output rate and it is suitable for a wide range of medications due to low shear forces [5]. The mesh nebulizer drug delivery is discussed in the context of various therapy, for instance, it is suitable for liposomal system nebulization as well [8]. Moreover, it is recommended for aerosol therapy of very current SARS-Cov-2 aerosol treatment [9]. In comparison with the jet nebulizers, in the case of the mesh nebulizers, the nebulized fluid is isolated from the breathing circuit which prevents nebulization of the contaminated solution [10] in the case of infection.

The local deposition of the therapeutic aerosol within the airways is the critical factor that determines the efficacy of inhalation treatment. Particle size and aerosol velocity are two main attributes of aerosol that influence the local aerosol deposition.

Aerogen Solo is a mesh nebulizer produced by Aerogen Ltd. (Galway, Ireland). According to the current literature, this nebulizer seems to be very effective (as stated by Arzu et al., the aerosol delivery efficiency of Aerogen Solo is two to fourfold higher than in the case of the jet nebulizer [11]) and several authors mention the MMAD under 2 μm for aerosol generated by Aerogen Solo, determined by Andersen cascade impactor or the Next-generation impactor [12–14]. However, Gowda et al showed an issue with the continuity of nebulization and made some doubts about the reliability of the Aerogen Solo device [15]. The troubles with the continual nebulization seem to be caused by unceaned vibration mesh, so this work will focus on it as well. Since in the above-mentioned works, the parameters of aerosol generated by Aerogen Solo were measured only by impactors, other methods were used in this study.

Fig. 1. Aerogen solo nebulizer. [17]

2 Methods and Materials

The particle size distribution was measured by two different instruments – Aerodynamic Particle Sizer (APS, TSI) and Phase Doppler Anemometry. According to the manufacturer, Aerogen Solo nebulizer should be able to work properly for 7 days in mode of continual nebulization and subsequently needs to be cleaned by nebulization of a few droplets of normal saline. The measurement was performed for two cases: nebulization of distilled water through the uncleaned mesh and nebulization of normal saline (0.9 % NaCl solution) and distilled water, to focus on the effect of neglected cleaning.

2.1 Aerodynamic Particle Sizer (APS) measurement

APS (TSI, USA) is an instrument for aerosol particle size measurement. This device measures the particle time-of-flight between two lasers with a certain distance. The particle size is determined as the aerodynamic diameter. Since the density of normal saline is near the density of water, in both cases was density in aerodynamic diameter calculations set as 1 g/cm^3. The aerosol was dosed continually, right to the inlet of the device without the usage of any inlet hoses. In this form of dosing, the concentration limit was set as 5000 particles/cm^3. Before the measurement of Aerogen Solo, the ambient aerosol was measured and during the analyses of particle size distribution, it was subtracted from the measured aerodynamic particle size distribution. At least 10 samples of Aerogen Solo aerosol were measured.

2.2 Phase Doppler Anemometry (PDA) measurement

Particle size distribution was measured by PDA as well. The size and velocity of the aerosol droplets were probed using a two-component fiber-based commercial Phase Doppler Anemometry (PDA) by Dantec Dynamics A/S (Skovlunde, Denmark). Which consists of 60X81 transmitting optics fitted with 1.98x beam expander, 57X50 receiving optics, and multi-line Ar–Ion laser Spectra Stabilite 2017. The receiver collected refracted light with scattering angle 70° and was fitted with mask A. Both optics used lenses with a 310 mm focal length. The PDA acquires the axial and radial velocity components in the non-coincidence mode along with the simultaneous drop sizes. The aerosol was probed at axial distances of Z = 3, 25, 50, and 75 mm from the nebulizer outlet along two radially orthogonal axes. There were 11 radial measurement positions on each axis with either, 50.000 samples acquired or a 10-second acquisition duration. The BSA flow software v5.20 was used to control the data acquisition and the following setting was used for drop size measurement: Photomultiplier sensitivity 850 V, signal gain 10 dB, velocity center 3 m/s, velocity span 12 m/s. The maximum measurable particle diameter was 40 μm. Both fluids, water, and normal saline were measured.

2.3 Statistical analyses

In the case of APS, the relative mass particle size distribution in cumulative form was expressed from the absolute mass particle size distribution. From the relative cumulative form of particle size distribution, the MMAD and geometric standard deviation (GSD) were determined (similar method to cascade impactor analyses [16]).

PDA measurement data presents a count optical particle size distribution. The measured diameter is raised to the third to express the volumetric distribution, which, in the case of water density, represents the mass particle size distribution and size of this volumetric distribution use to be marked as *„D_v“*. Such particle size distribution is comparable with APS mass particle size distribution. Again, these data were transformed into the relative cumulative volumetric particle size distribution, and a volumetric median of the distribution (D_{v50}) was calculated.

3 Results

3.1 PDA results

According to the PDA data, the particle size was uniform within the whole plane section and there were no differences in the particle size in the measured locations. Table 1 shows the D_{v50} values averaged from all positions within the one plane section for the normal saline solution at different distances.

Table 1. D_{v50} averaged values measured in various distance from the nebulizer outlet.

Distance from the outlet [mm]	D_{v50} average [µm]
3	9.54 ± 0.65
25	9.37 ± 0.23
50	9.45 ± 0.19
75	9.54 ± 0.23

However, in the case of distilled water and uncleaned nebulizer mesh, the work of the Aerogen Solo was not reliable, since it used to stop the nebulization randomly and the nebulization was not continual. This resulted in a low number of detected particles in measuring volume especially in distance 50 mm and 75 mm from the outlet. Table 2 presents the values of D_{v50} averaged across the plane section in 3 mm and 25 mm distance from the nebulizer outlet. In more remote positions. The counts of detected particles were too low for the determination of the particle size distribution. The lower reliability of the uncleaned device filled with the water is visible on a higher deviation of D_{v50}.

Figure 2 shows the comparison of particle velocity in the middle of the stream for the case of normal saline and uncleaned mesh with distilled water linked to the distance from the outlet. As it is visible in Figure 2, the velocity of distilled water aerosol was significantly different from the case of the normal saline. The length of the stream is shorter and the velocities of the particles were lower in general.

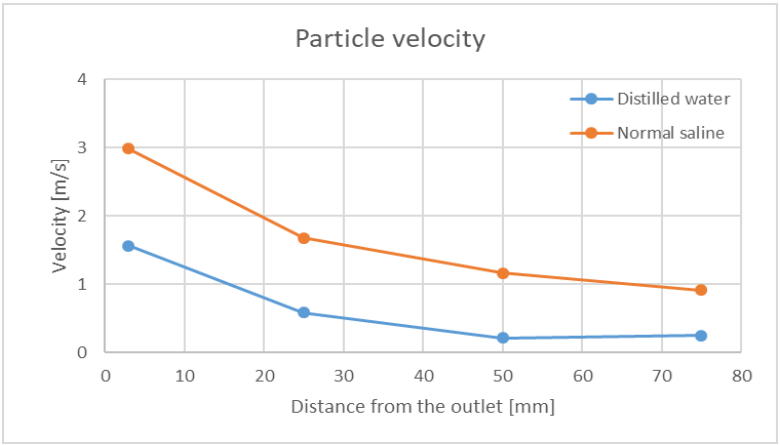

Fig. 2. The velocity of aerosols for both cases (normal saline and distilled water) depending on the distance from the outlet.

Table 2. Averaged D_{v50} in 3 mm and 25 mm distance from the nebulizer outlet.

Distance from the outlet [mm]	D_{v50} average [µm]
3	9.30 ± 1.37
25	10.69 0.75

3.2 APS results

Normal saline and distilled water were measured on APS as well. In both cases, MMAD and GSD were assessed (Table 3). The particle size distribution had a unimodal shape (Figure 3).

Table 3. MMAD and GSD of nebulized normal saline and distilled water measured by APS.

Normal saline		**Distilled H_2O**	
MMAD [µm]	GSD [µm]	MMAD [µm]	GSD [µm]
10.27	1.48	11.43	1.50

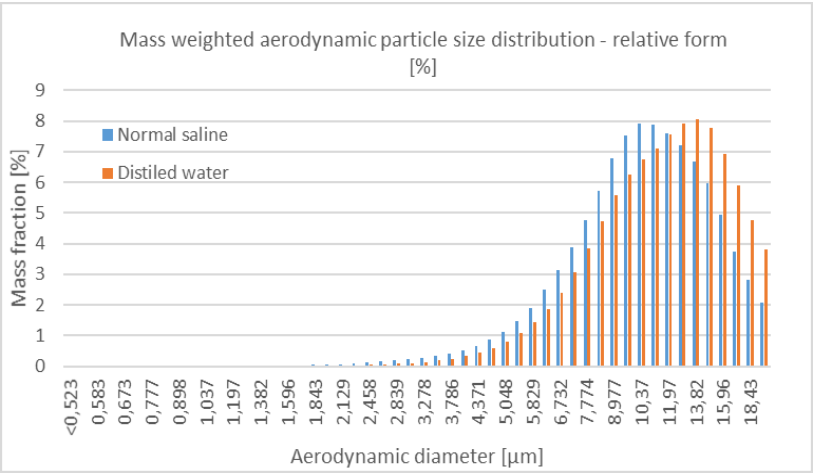

Fig. 3. The particle size distribution of normal saline solution and distilled water nebulized by Aerogen Solo measured on APS.

4 Discussion

Results from both measurements, APS and PDA, were very similar and the medians of mass (resp. volumetric) distributions were approximately 10 µm. This is a much higher value than the results reported from cascade impactors measurement [12–14]. However, data from PDA measurement are in good agreement with the APS data as can be seen in Figure 4. Mostly, the inhaler efficiency is assessed according to the so-called Fine Particle Fraction (FPF). It expresses the percentage of particles smaller than 5 µm since these particles should be respirable and able to penetrate into the lungs. It means they can be efficient for inhalation treatment. According to the measured data, the FPF of Aerogen

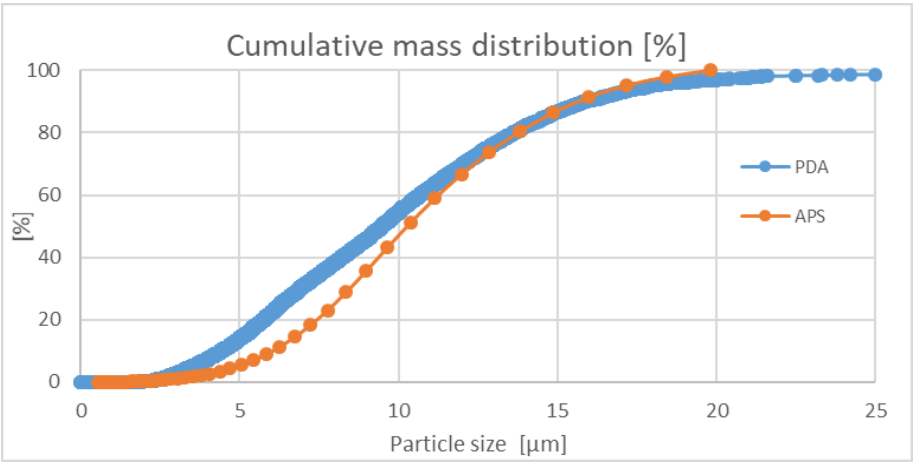

Fig. 4. The comparison of cumulative particle size distribution (volumetric, resp. mass) measured on PDA resp. APS.

nebulizer is very low. The particle size distribution did not change in the distance up to 7 cm from the nebulizer outlet.

The non-reliable behavior of Aerogen Solo with the distilled water was caused by the uncleaned mesh. After cleaning, the length of the stream was for some time similar as in the case of normal saline. However, Aerogen Solo is a device recommended for aerosol drug delivery for the mechanically ventilated patients as well and hence should be working even for 7 days continually. It means, in practice, it is really necessary to check the device function and clean the device frequently.

5 Conclusion

Aerosol nebulized by Aerogen Solo device was measured in two cases: 1. with unclean nebulizer mesh and distilled water and 2. with normal saline solution. Both cases were measured on APS and PDA. According to the PDA measurement, the behavior of the uncleaned nebulizer with distilled water was significantly different as in the case of normal saline nebulization. It means, the nebulizer used to stop working frequently, produced a lower amount of aerosol, and the velocity of emitted particles was lower. Particle size did not differ markedly.

Measured MMAD was much higher than expected and the particles were in all cases much larger than it is recommended for pharmaceutical aerosols. Since the literature presents significantly different values of the particle size distribution from the cascade impactor measurements, it is demanded to measure the aerosol from several Aerogen Solo devices to eliminate the case of a wrongly manufactured device and consider if cascade impactor measurement is sufficient.

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