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Review Article

Critical Assessment of the Quantitative Criteria Used in the Comparison of Nebulizers

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Abstract

Inhalation of aerosols from nebulizers remains an important method of drug delivery in treating diseases of the respiratory system. To be effective, aerosol droplets generated in nebulizers must hold certain size distribution which allow them to pass the oropharynx and be distributed in the bronchial tree. The assessment of droplet size distribution can be made by several experimental techniques and various quantitative parameters are used to characterize the operation of nebulizing devices. In this paper the physical meaning and usefulness of standard and non-standard quantitative parameters (i.e., MMAD, *Dv50*, FPF, *GSD, Span*) are discussed and followed by conclusions regarding their application to compare different nebulizers in the most reliable way.

Keywords: *Nebulizers; MMAD; Dv50; FPF; GSD; Span*

Symbols and Abbreviations

d_a: Aerodynamic diameter of a droplet/particle; *d*: Geometric diameter of a droplet/particle; *m*: Mass; *v*: Velocity; *Dv10*: 10^{th} percentile of the cumulative droplet/particle size distribution by volume (mass); *Dv50*: Median diameter of the cumulative droplet/particle size distribution by volume (mass); *Dv90*: 90^{th} percentile of the cumulative droplet/particle size distribution by volume (mass); DPI: Dry Powder Inhaler; FPF: Fine Particle Fraction; FPF_{IMP}: Fine particle fraction based on the aerosol mass collected inside the impactor; *GSD*: Geometric Standard Deviation; LDAS: Laser Diffraction Aerosol Spectrometer; LPM: Liters Per Minute; MMAD: Mass Median Aerodynamic Diameter; NGI: Next Generation Impactor; pMDI: Pressurized Metered Dose Inhaler; *Span*: The measure of width of droplet/particle size distribution

Introduction

Inhalation allows to deliver drugs directly to the surface of the respiratory system which makes this treatment effective and almost free of side effects [1,2]. Nebulization of medicines which are available in a liquid form as solutions, suspensions or emulsions, is a convenient method of drug dispersion (atomization) to fine droplets that may be effectively carried with inhaled air to the bronchial tree. This air/droplets system - or more general: air/particles system - is called aerosol.

To be effective, aerosol droplets generated in nebulizers must present a certain size distribution which allow them to pass the oropharynx and be distributed in the bronchial airways. To assess the quality of inhalation aerosol, the reliable measurement of droplet size distribution is needed, and it can be made by several techniques. Some of them are done according to Pharmaceopial recommendations

[3] which were originally developed for any type of aerosols (e.g. powders, sprays). However, fast and reproducible modern methods have been also proposed after demonstration of their reliability and applicability to characterize medical aerosols generated in nebulizers [4].

In this paper the physical meaning and usefulness of standard and non-standard numerical parameters derived from droplet size distribution measurements done with different techniques are discussed. This analysis leads to conclusions regarding the application of these quantitative criteria in reliable comparison of different nebulizers and various drugs atomized in these devices.

Nebulized aerosols - The basic facts

Inhalation aerosols which are generated by nebulizers of various design and operation principle (jet, ultrasonic, mesh), are composed of tiny micrometer-size liquid droplets dispersed in the air. It is known that the effective drug penetration beyond the oral cavity, i.e. to the bronchial tree and alveoli requires aerosol droplets (or particles) smaller than 5 μm regarding the aerodynamic diameter. The aerodynamic diameter, d_a, is the apparent diameter of a particle with a real (geometric) diameter d, assuming that it would have density of water:

$$d_a = d\sqrt{\frac{\rho_{particle}}{\rho_{water}}} \qquad (1)$$

For nebulized drugs which are diluted aqueous solutions or microsuspensions, d_a is practically equal to d.

The inhalation maneuver is another important factor governing aerosol penetration and deposition in the respiratory system. This is because inertia and sedimentation are the main deposition mechanisms for the majority of aerosol droplets, which are characterized by a few-micrometer size. Inertial deposition is proportional to droplet momentum, i.e. $v \times m$, where m - denotes droplet mass, and v - droplet velocity, resulting from the airflow rate. Since nebulization is typically associated with the tidal breathing (i.e. breathing at rest), the flow rate of aerosol is low comparing to the flows typically achieved with other inhalers (e.g., DPIs). It may be claimed that at these moderate air velocities of tidal breathing, even droplets larger than 5 μm may penetrate beyand the oro-pharyngeal region and reach some distal locations in the bronchial tree [5].

Clouds (mists) that leave nebulizers contain droplets of various sizes, forming poly-disperse aerosol, distribution of which is shown - as an example - in figure 1. The presented size distribution is log-normal, being typical for aerosols generated in nebulizers. It may be noticed that the aerosol contains both droplets smaller than 1 μm and larger than 10 μm, while the largest fraction is represented by droplets in the 2 - 6 μm range. The result illustrated in figure 1 was obtained by a fast and convenient laser diffraction aerosol spectrometry (LDAS) using Spraytec device (Malvern Instruments, UK). Assuming that concentration of the drug is identical in droplets of any diameter (which is obvious e.g., for atomized solutions), LDAS results directly inform about the mass of aerosolized drug which can be delivered to the respiratory system.

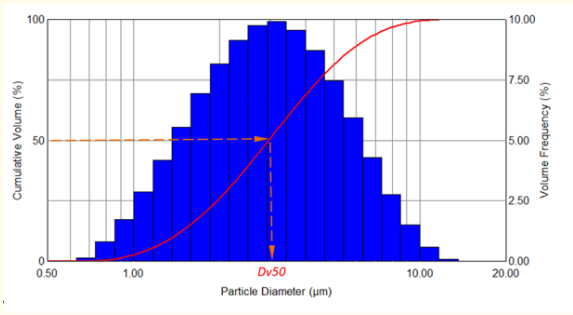

Figure 1: *An example of droplet aerosol size distribution in an aerosol released from a nebulizer measured with the laser diffraction method.*

Quantitative criteria in the characterization of nebulized aerosols

To facilitate and speed-up the assessment of droplet sizes in the cloud in the view of their potential usefulness in inhalation therapy, some numerical parameters derived directly from particle (droplet) size distribution are used instead of analyzing the whole distribution. These basic parameters are:

1. Median diameter of the size distribution, *Dv50,*
2. Geometrical standard deviation, *GSD*,
3. *Span*
4. Mass percentage of fine particles, *FPF (= fine particle fraction)*
5. Mass median aerodynamic diameter, MMAD.

The value of *Dv50* informs about the droplet size in micrometers (μm) which corresponds to the half of the total mass of droplets forming the aerosol cloud emitted from a nebulizer. In other words, *Dv50* divides the measured distribution into two halves: of smaller and larger droplets, both representing the equal mass. In case of typical log-normal distribution shown in figure 1, *Dv50* is equal to the mode of the distribution, i.e. the diameter which corresponds to the maximum in the histogram.

GSD characterizes the spread of the droplet size distribution around the mean value (i.e. around the *Dv50* value of the log-normal distribution). *GSD* is a correct value only for log-normal droplet size distribution however it is not applicable for other distributions. In those cases, it is convenient to characterize the width of the distribution by the criterion of *Span*, defined as:

$$Span = \frac{Dv90 - Dv10}{Dv50} \qquad (2)$$

Dv10 and *Dv90* in the nominator of eq. (2) denote the 10th and 90th percentiles of the cumulative droplet size distribution, respectively.

Another important parameter used to assess the aerosol quality is *FPF* which denotes a mass fraction of particles smaller than 5 μm, expressed as % of the aerosol mass [3].

MMAD (mass median aerodynamic diameter) value is often used in the assessment of inhalers, including nebulizers. However, the meaning of this parameter is unique, and - in spite of its name - it is rarely equivalent to the real median (*Dv50*). This is because MMAD is measured in a very distinct way. Historically, MMAD was introduced as a quality parameter for the comparison of aerosols generated from different batches of the same inhalation product (the combination of inhaler and drug), i.e. when the overall characteristics of the aerosol cloud is almost unchanging. By a principle, according to the recommendations of the Pharmacopoeia [3], MMAD is measured using a cascade impactor, in which particles or droplets larger than a certain size (forming, so called, "ballistic" fraction) are neglected as not relevant in therapeutic action of inhaled medicines [6]. This limiting size is ~9 μm when measured in the Andersen impactor at the standard flow rate of 28.3 liters per minute (LPM) or ~8 μm in the Next Generation Impactor (NGI) at 60 LPM (Figure 2). Accordingly, MMAD value is usually lower than *Dv50* determined for a full spectrum of aerosol droplets which are present in the cloud. Both criteria are equivalent i.e. *Dv50* = MMAD, only in the special case when all droplets are smaller than the upper limiting size (8 - 9 μm). This problem remains important also for aerosols produced with other inhalers. Even if the majority of aerosol particles are big (for instance, larger than 10 μm), MMAD may be low (less than 10 μm), because it is calculated based only on particles collected on the impactor stages, i.e. in the limited size range. Therefore, the substitution of *Dv50* by MMAD or interchangeable use of both parameters often leads to ambiguity of the assessment of the size of aerosol droplets generated in nebulizers. In fact, the use of MMAD for that purpose should be considered inappropriate (although it is commonly done) since it does not inform about the full spectrum of drug droplets released from a given nebulizer. For this reason, MMAD should not be used as parameter of comparison between different nebulizing devices.

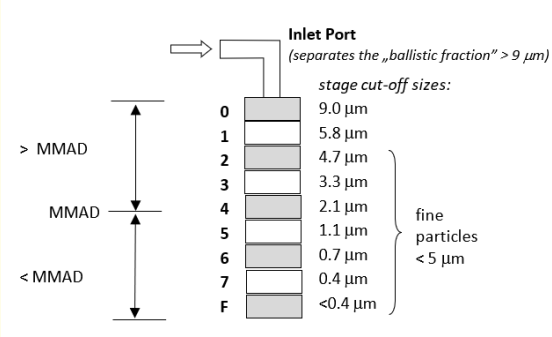

Figure 2: *Scheme of Andersen cascade impactors which shows that MMAD is determined only considering particles/droplets smaller than 9 µm, i.e. neglecting larger droplets (ballistic fraction) which are deposited in the inlet port (modified after [7]).*

The discussed earlier LDAS method is free from the mentioned shortcomings of droplet size determination. It has been also shown to be fully equivalent to impactors when non-ballistic droplets are considered [4]. However, in the general case LDAS gives a more complete information, so parameters like *Dv50* and *GSD* (or *Span*) determined with this method seem to be more appropriate and recommended in comparing different nebulizers and nebulizer-drug combinations.

MMAD can be misleading in assessing nebulizer performance - The case study

If one needs to compare MMAD values obtained with the impactor to *Dv50* measured with LDAS, then *Dv50* determined from the latter technique should be recalculated, i.e. reduced to a more narrow range of droplet sizes. The general principle of such conversion is shown in figure 3. As seen in this example, the greater the amount of aerosol particles larger than 9 µm (particles to the right of the black vertical arrow in the upper panel of figure 3), the more particles are neglected during the determination of MMAD based on the impactor data. These data also confirm the earlier statement that the MMAD value is typically smaller than *Dv50.*

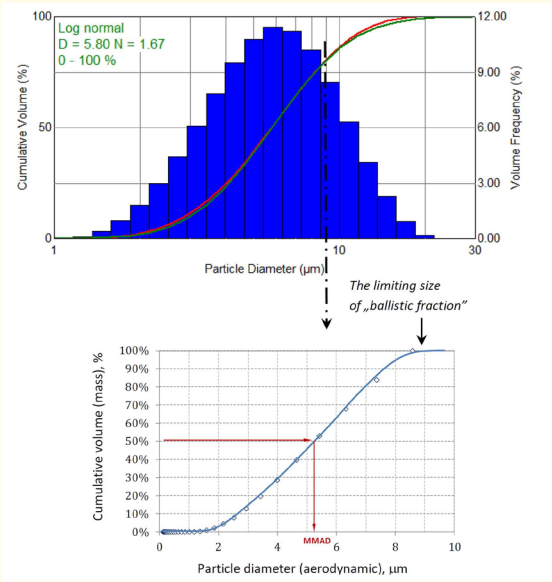

Figure 3: *The general rule of determining MMAD based on distributions of droplets obtained by LDAS. The graph shows that the MMAD can be less than Dv50.*

Presented considerations also indicate the possibility of finding the similar MMAD values for aerosols containing droplets with dissimilar size distributions and characterized by different values of *Dv50*. Simply, diverse size distributions may become quite similar to each other after setting the limit of the upper size of analyzed droplets to 9 μm. Again, this confirms the previous statement that MMAD should be considered an useful parameter only for assessing the repeatability of different batches of the same aerosol product, however it may be misleading during comparison of different products (e.g. two different nebulizing devices, or two different drugs sprayed in the same nebulizer).

The FPF value as an indicator of the amount of drug that can penetrate into the lower respiratory tract should be determined for the complete size range of aerosol droplets released from the device [3] and such data are easily obtained from LDAS analysis with the measuring range up to several hundred micrometers. The FPF can also be correctly determined from impactor measurements, providing that the mass of particles deposited in the inlet port is included into the total mass balance of emitted aerosol (Figure 2). It is possible, however, to include only particles captured inside the impactor (stages: 0, 1, 2..., F - i.e. smaller than 9 μm, Figure 2) in further calculations of the mass fraction of fine particles. In such case, this particle fraction (let us call it here as: FPF_{IMP}) has obviously a value which is larger than FPF determined in the accordance with the Pharmacopoeia guidelines (i.e. for the entire spectrum of particle sizes).

To illustrate the relationships between all discussed quantitative parameters, table 1 lists *Dv50*, *GSD* and FPF values experimentally determined by the diffraction method for steroid drug (budesonide) atomized in various nebulizers, and after conversion of these data into MMAD values according to the method depicted in figure 3, and FPF_{IMP} values calculated taking into account only droplets smaller than 9 μm.

Item	Nebulizer name	Dv50 [μm]	FPF [%]	MMAD [μm]	FPF_{IMP} [%]	GSD [-]
1	Pariboy SX (pneumatic)	5.1	53.4	4.2	67.5	1.78
2	Esperanza Breeze (pneumatic)	5.6	48.1	4.8	61.1	1.46
3	Intec Twister Mesh (vibrating mesh)	6.6	38.1	5.3	48.2	1.62
4	Intec Chamber Mesh (vibrating mesh)	5.1	44.3	4.2	56.0	1.80

Table 1: *Comparison of operating aerosol parameters obtained in clouds emitted from selected nebulizers with steroid drugs (budesonide).*

Data in table 1 show that MMAD is approximately 1 μm smaller than *Dv50*. Similarly, FPF determined from the mass of all droplets present in the aerosol cloud is less by about 10 - 20% than FPF_{IMP} determined taking into account only droplets smaller than 9 μm. Such relationships is analogus for both the pneumatic and vibrating mesh nebulizers. This shows that the same aerosol can be described by significantly different values of parameters used to characterize its quality and that these values depend on the measuring method/approach. At the same time - as mentioned earlier - aerosol clouds with different particle size distribution (e.g. produced in nebulizer No. 1: FPF = 53.4%, and in nebulizer No. 4: FPF = 44.3%) can have the same MMAD value (in both cases, MMAD = 4.2 μm).

The importance of droplet size in steroid nebulization

Steroids (e.g. budesonide) form aqueous suspensions which contain water-insoluble micronised solid particles. To be delivered as aerosol generated in the nebulizer, these microparticles must be contained inside droplets that are present in the cloud. If these droplets are too small, they probably do not contain steroid particles which means that they carry only pure solvent from the nebulizer whereas the drug is retained in the nebulizing vessel (Figure 4).

Therefore, data which show that a nebulizer is capable of producing drops with a low MMAD (for instance, less than 3 μm) may suggest that this nebulizer may be not suitable for the delivery of steroid drugs. This conclusion holds independently on the atomizing principle

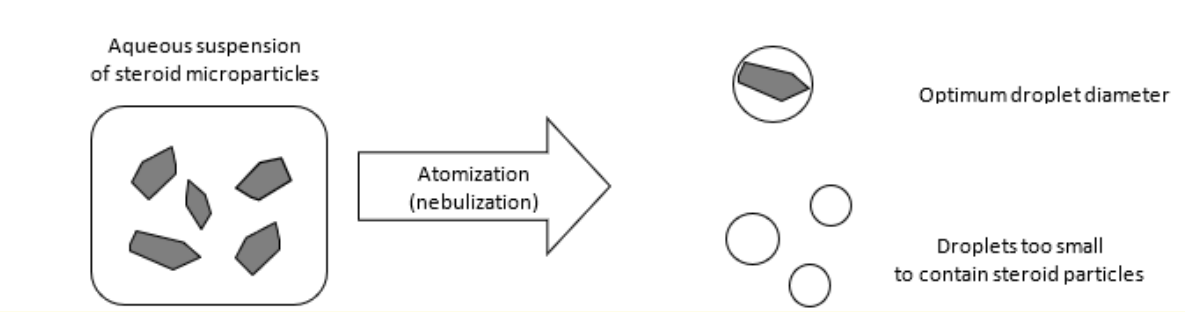

Figure 4: *Schematic picture showing the role of the required droplet diameter in relation to the insoluble drug particle (e.g. steroid).*

used in the nebulizers. Accordingly to the presented discussion, size of droplets shown in table 1 should be considered correct in case of steroid nebulization despite the apparently large *Dv50* values (5.0 - 6.5 μm) and, consequently, moderate FPF values (40 - 50%). As already mentioned, slightly larger droplets observed in the presented example should be still considered beneficial regarding aerosol penetration to the lungs, because the inhalation done with nebulizers takes place with a slow inspiration of tidal breathing, which significantly reduces inertial separation of droplets in the mouth and throat as compared to more intense flows applied with other inhalers (e.g. DPIs, pMDIs).

Final Remarks

It has been demonstrated that different quantitative criteria used to assess aerosol quality has to be used with caution in characterizing nebulizers operation, and their meaning has to be adequately recognized. In general the MMAD (mass median aerosol diameter) value is not the best parameter in such comparisons since it neglects droplets larger than approximately 9 μm as a consequence of the procedure adapted to determine this parameter (i.e. measurements using Pharmacopeial cascade impactors). It should be noted that deposition of nebulized drug in different parts of the respiratory system depends both on droplet size and inhalation maneuver, and is related not only to beneficial, but also to unwanted effects. Therefore, neglecting large droplets means also a disregarding possible side effects localized mainly in the mouth and throat region. However, there are indications where larger droplets may be required to better target the aerosol in certain health conditions (e.g. in croup symptoms [8]). The slightly increased droplet size may be also beneficial in inhalation delivery of medicines which form suspensions (e.g. steroids) to allow solid particles of the drug be carried to the lower respiratory tract during slow inhalation of the mist formed in nebulizers.

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