

# MASS AND VOLUME BALANCES OF NEBULIZATION PROCESSES FOR THE DETERMINATION OF THE EXPECTED DOSE OF LIQUID MEDICINES DELIVERED BY INHALATION

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The work presents the application of mass/volume balances of liquid drug converted into the aerosol during atomization in medical nebulizers. The amount of liquid that can be delivered to the respiratory system during inhalation is reduced compared to the nominal dose not only because of drug losses both in the device (the residual volume, *RV*) and outside the nebulizer (in the mouthpiece, mask, or tubings), but also to the limitations of the patient (periodic flow with limited capacity). The paper should help to understand the complexity of aerosol therapy widely used in asthma, COPD and other pulmonary diseases.

**Keywords:** jet nebulizer, mesh nebulizer, residual volume of drug, inhaled dose, delivered dose, mass balance

## 1. INTRODUCTION

Nebulizers are medical devices for inhalation therapy that are widely used by patients in all age groups for the treatment of lung diseases and pulmonary rehabilitation. Nebulizers atomize drugs which are in form of liquid solution or suspension to fine droplets, preferably smaller than 5  $\mu\text{m}$  in diameter, allowing them to be transported to the lower airways of the human respiratory system (Sosnowski, 2020). Regarding the principle of operation, these devices belong to two main classes: pneumatic (jet) and ultrasonic nebulizers, whereas the latter can be classified into (i) classical and (ii) vibrating mesh nebulizers (VMNs) (Ari, 2014; Elphick et al., 2015). The clinical efficiency of nebulization depends on the characteristics of the aerosol cloud and on the parameters related to the patient, such as the health status and inhalation technique (Pirożyński and Sosnowski, 2016). It is known that only a fraction of a liquid drug loaded to the nebulizing vessel consisting the nominal (or declared) dose can be effectively aerosolized, inhaled and deposited in

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the respiratory system. Due to the properties of formulation-nebulizer system and patient-related factors (Fig. 1), the delivered drug fraction is typically in the range of 5–40%.

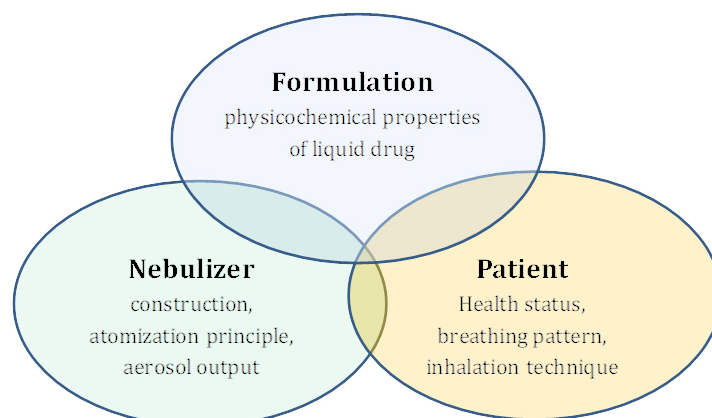


Fig. 1. Three factors determining the efficiency of aerosol delivery to the respiratory system via inhalation of nebulized drugs

In this paper, we theoretically analyze the main reasons, the range, and the significance of drug losses during nebulization taking into account the major internal and external factors of using nebulizers with various construction and working principles.

## 2. THEORETICAL ANALYSIS – MASS BALANCE OF THE NEBULIZING SYSTEM

The mode of operation of the most commonly used continuous pneumatic or mesh nebulizers (i.e. of the devices without breath-actuation or adaptation to the breathing pattern) results in aerosol emission that is schematically illustrated in Fig. 2. Aerosol continuously emitted from the nebulizer flows to the lungs during inhalation (Fig. 2a) and is released outside during the breath-hold and exhalation phase (Fig. 2b). Some nebulizers are designed in a way that allows to spare the aerosol. These technical solutions include, among others, the nebulization chambers, i.e. the closed vessels in which aerosol is kept until it can be inhaled by a patient in the consecutive breath. In this way, not only the drug losses are avoided, but also the aerosol emission outside the nebulizer-patient system is reduced, which prevents the contamination of the patient's surrounding (Fink et al., 2020; Emeryk et al., 2020; Dobrowolska and Sosnowski, 2020). Regardless of technical solutions used, one of the most important factors in the therapy using nebulizers is the maximization of the aerosol dose delivered to the respiratory system.

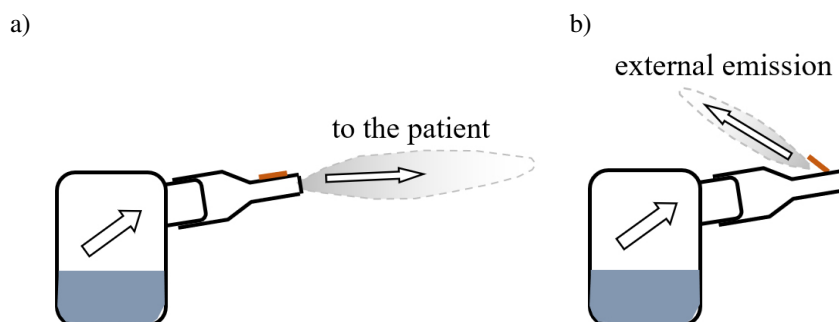


Fig. 2. Aerosol emission during operation of the continuous nebulizer when the aerosol is delivered through the valved mouthpiece: a) inhalation phase; b) breath-hold and exhalation phase

An important factor in the analysis of nebulizer operation is the residual volume ( $RV$ ), i.e., the volume of liquid that cannot be emitted from the atomization system during nebulization. The inability of converting the whole volume of liquid to the aerosol in a given nebulizer results mainly from the design of the device.  $RV$  is relatively high for pneumatic nebulizers (more than  $1\text{ cm}^3$ ) and much lower for mesh nebulizers ( $0.1\text{--}0.3\text{ cm}^3$ ). According to the therapeutic recommendations, nebulization is usually terminated when the nebulizer starts to produce the aerosol non-constantly. This moment indicates that the drug can no longer be properly delivered to the patient's respiratory tract.  $RV$  is determined by weighing the nebulizer (e.g., MacLoughlin et al., 2009; Chang et al., 2019). Subtracting the mass of the empty nebulizer  $M_N$  from the obtained value at the end of nebulization  $M_{RV}$ , the mass of the liquid remaining in the nebulizer is obtained, which, after considering the liquid density  $\rho$ , results in the value of  $RV$  [ $\text{cm}^3$ ]:

$$RV = \frac{M_{RV} - M_N}{\rho} \quad (1)$$

In most cases,  $\rho$  can be taken as equal to the density of the solvent (i.e., physiological saline or distilled water), since nebulized drugs are generally very dilute solutions or suspensions of the active pharmaceutical ingredient (API). For example, it can be shown that for budesonide at a concentration of  $1\text{ mg/cm}^3$  in physiological saline solution, the density of which is  $1000\text{ g/dm}^3$  (at  $20^\circ\text{C}$ ), the total density of the suspension will be (neglecting the volume of the steroid particles):

$$\rho = \frac{1\text{ g} + 1000\text{ g}}{1\text{ dm}^3} = 1001\text{ g/dm}^3 \quad (2)$$

resulting in only 0.1% relative difference to the density of the solvent. Therefore, the determination of the  $RV$  value (which is typically less than  $1.5\text{ cm}^3$ ), considering the density of the solvent instead of the density of the whole drug leads to a negligible inaccuracy, in the range of single microliters.

From the definition and the method of determination of  $RV$ , it follows that the residual volume includes not only the drug remaining at the bottom of the nebulization vessel but also the drug deposited on the inner impaction baffles and the walls. If a nebulizer is used with a mouthpiece and both parts are weighed together to determine the  $RV$  values, then the residual volume will also include the medicament captured in the mouthpiece. In a situation, when the nebulizer is operated without a mouthpiece (e.g., combined with a mask or attached to the ventilator circuit), the  $RV$  will only apply to the nebulization vessel since it is technically impossible to determine this parameter by weighing the entire aerosol delivery system. This important conclusion suggests the possibility of the misinterpretation of  $RV$  when the method of its determination is not clearly specified (for instance, by the manufacturers of nebulizers).

Knowing the mass of the empty (dry) nebulizer,  $M_N$ , and the mass of the nebulizer at the beginning of nebulization, i.e. just after filling it with the liquid drug,  $M_P$ , one can also express the initial mass of the liquid contained in the nebulizer,  $M_0$ , and the mass of the emitted aerosol,  $M_E$ :

$$M_0 = M_P - M_N \quad (3)$$

$$M_E = M_0 - M_{RV} = M_P - M_N - M_{RV} \quad (4)$$

Due to the constant value of  $\rho$ , in further considerations we can operate with either the liquid mass [g] or volume [ $\text{cm}^3$ ], keeping in mind that they are always interrelated:

$$V_i = \frac{M_i}{\rho} \quad (5)$$

( $i$  stands for any subscript).

The elimination of liquid droplets from the aerosol may also occur after the cloud exits the nebulizing vessel – in mouthpiece, external connectors or nebulization chamber (Fig. 3). This process can be described by a volumetric balance:

$$V_E = V_K + V_{DI} \quad (6)$$

Let us note that  $V_{DI}$  is notably lower than the drug volume introduced to the nebulizer,  $V_0$ . From Eqs. (3)–(6) we get:

$$V_{DI} = V_0 - RV - V_K \quad (7)$$

which shows that both the  $RV$  and the aerosol deposition in the parts through which the aerosol flows to the patient, significantly reduce the amount of drug that can be inhaled. For example, if the starting volume of the drug is  $V_0 = 3 \text{ cm}^3$ , then – with  $RV = 1 \text{ cm}^3$  and the  $V_K$  (external losses) e.g.,  $0.5 \text{ cm}^3$ , the patient receives  $V_{DI} = 1.5 \text{ cm}^3$ , i.e. only 50% of the drug that was prescribed, i.e. loaded to the nebulizer.

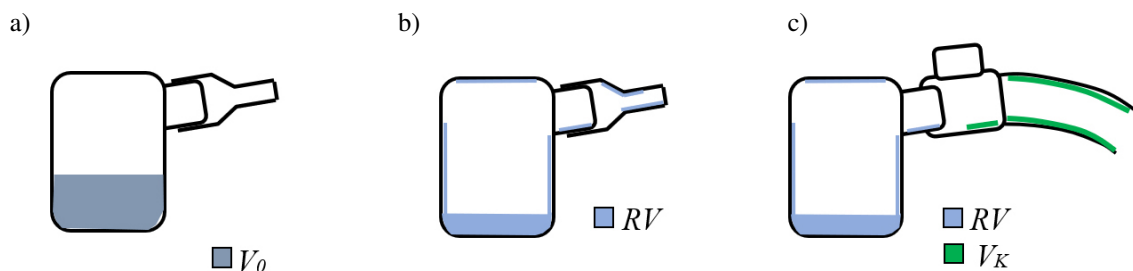


Fig. 3. Schematic illustration of the volumes of nebulized liquid: a) at the start of nebulization; b) after completion of nebulization – with a mouthpiece ( $V_K = 0$ ); c) after completion of nebulization – in a system with external aerosol delivery tubing. The volume available to the patient  $V_{DI}$  can be calculated from the relationship (Eq. (7))

### 3. ESTIMATION OF THE DELIVERED DOSE

The volume of drug available for inhalation calculated from Eq. (7) ( $V_{DI}$ ) is not equal to the volume of liquid deposited in the respiratory system, which is due to two factors:

- 1) aerosol deposition in the respiratory system is never complete (a part of the aerosol is exhaled);
- 2) the aerosol is drawn by the patient only during inhalation, while during exhalation the aerosol is pushed outside the nebulizing system (see Fig. 2b) or, alternatively, it may be retained either inside the nebulizer or in the nebulization chamber.

If the aerosol that is exhaled or generated during the expiration is emitted to the environment, the fraction of inspiration time ( $t_{INH}$ ) in the whole inhalation-exhalation cycle ( $t_C$ ) becomes decisive for droplets deposition in the respiratory system. In this case, the volume of the deposited drug,  $V_{DEP}$ , can be estimated from the relationship:

$$V_{DEP} = V_{DI} \frac{t_{INH}}{t_C} \quad (8)$$

where  $\eta$  is the average value of total deposition efficiency in the respiratory system. One can also calculate regional deposition volumes (in the upper or lower respiratory tract) using the same equation after inserting the known deposition efficiencies for each region. Deposition efficiency depends mostly on the size of the aerosol droplets, but it is also influenced by several individual features of a patient, such as lung volume, breathing dynamics, airway patency. More detailed considerations on the relationship between these parameters can be found in the literature (Pirożyński et al., 2015). The values of the deposition efficiency in the individual regions of the respiratory system of aerosol droplets with a known size distribution can be estimated, e.g., from the Multi-Path Particle Dosimetry – MPPD model (Sosnowski and Kramek-Romanowska, 2016).

In a situation where the aerosol does not leave the nebulization system during the expiration phase (e.g., is held inside thanks to one-way valve), it can be assumed that the entire drug volume that is generated,  $V_{DI}$ , will be inhaled and deposited:

$$V_{DEP} = V_{DI} \quad (9)$$

However, it may be expected that simultaneously  $V_K$  may be slightly increased (therefore  $V_{DI}$  decreased according to Eq. (7)) in such mode of nebulizer operation due to the longer residence time and higher aerosol concentration inside the generation system that cause droplet coalescence (growth) and their higher separation on the walls. This will reduce  $V_{DEP}$ . The droplets captured inside the nebulization vessel will drain and then become re-nebulized. Therefore  $RV$  does not increase, but the nebulization time does. For nebulizers with the mouthpiece (Fig. 2b)  $V_K$  equals 0; still a slightly higher  $RV$  value is expected due to droplets' accumulation in the mouthpiece without the possibility of draining to the vessel.

Figure 4 shows a few examples of the calculated volume of deposited liquid  $V_{DEP}$  a function of  $RV$  for three values of the average deposition efficiency 0.4, 0.5 and 0.6 (depending the size of generated droplets, i.e. on the type of nebulizer and properties of liquid) in two types of inhalers: (i) conventional, i.e. without holding-up of the produced aerosol, and (ii) with one-way valve that allows to collect the aerosol inside the vessel during breath-hold and expiration. The initial fluid volume was assumed to be  $V_0 = 5 \text{ cm}^3$  and  $V_K = 0.1V_0$ . The tidal breathing was assumed ( $t_{INH}/t_C = 0.4$ ). The relationships in Fig. 4 based on Eqs. (7)–(9) show a significant advantage of valved nebulizers with a small residual volume (the minimum value considered here equals  $0.1 \text{ cm}^3$ ). If they produce aerosol with large proportion of fine droplets resulting in high deposition efficiency ( $\eta = 0.6$ ), they can deliver above 55% of drug loaded to the nebulizer ( $2.76$  of  $5 \text{ cm}^3$ ). Higher  $RV$  value ( $1.5 \text{ cm}^3$ ) leads to a gradual decrease in the amount of drug delivered to about 38.5%. The same nebulizers working in analogous conditions, but without a valve limiting aerosol emission during exhalation, will deliver to the lungs, respectively,  $\sim 22\%$  ( $1.1 \text{ cm}^3$ ) and  $\sim 15.5\%$  ( $0.77 \text{ cm}^3$ ) of the drug initially present into the nebulizer. Thus, when comparing nebulizers with different  $RV$  which generate droplets of variable sizes, it can be concluded that the delivered volume of liquid medicine can vary within wide limits, from approximately 10% to approximately 50–60% of the nominal dose.

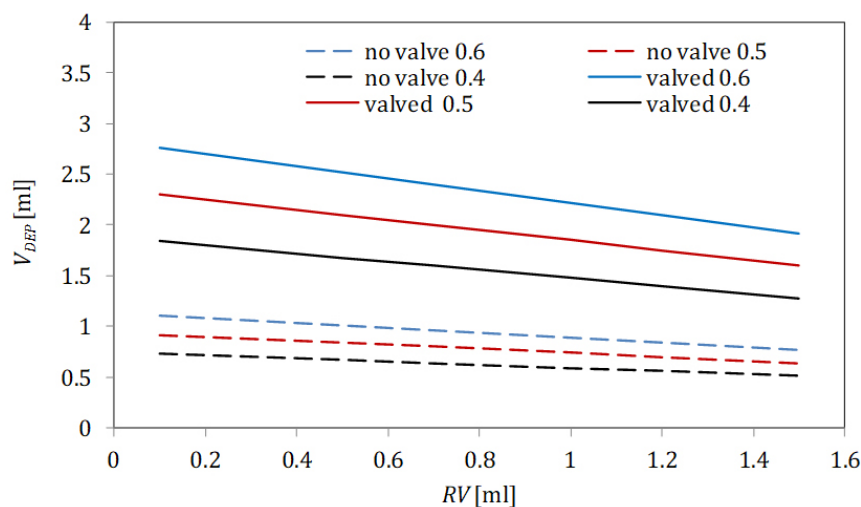


Fig. 4. The volume of liquid drug deposited in the lungs as a function of the nebulizer design ( $RV$  and the presence of the one-way valve) and aerosol properties (i.e., deposition efficiency – shown as the fraction in the legend – being a function of droplet size distribution)

For nebulizers without the valve, the effect of  $RV$  on the delivered dose is smaller than for valved devices. The data also show that it is practically impossible to deliver to the lungs more than approximately 60% of the nominal dose of the drug. To get close to this number, it is required using a nebulizer with a minimum  $RV$  (e.g., a mesh device) equipped with one-way valve, which can generate aerosol droplets having the deposition efficiency above 65%. It is difficult to obtain this value of  $\eta$  considering the physics of particle deposition in the respiratory system (except the deposition in the upper airways which is not of interest in the most common aerosol therapy of the lower respiratory tract).

The presented discussion shows that the theoretical determination of the emitted aerosol dose, delivered dose and aerosol losses is not simple but it is rather unambiguous due to the fact that some numerical parameters of nebulization process are interrelated and often cannot be determined *a priori* for a given patient-nebulizer-drug combination, shown earlier in Fig. 1. For a more precise analysis of the therapeutic dose, we should focus on the mass (or volume) of the active pharmaceutical ingredient, API, instead of the total mass (or volume) of droplets deposited in the lungs. Knowing the volume of deposited liquid  $V_{DEP}$  (Eq. (8) or (9)), it can be converted into the delivered dose  $DD$  of API using the relationship:

$$DD = cV_{DEP} \quad (10)$$

where  $c$  is the nominal concentration of the API in the nebulized liquid solution or suspension. Sometimes, such an estimate may be imprecise, because it is known that the API is gradually concentrated due to the evaporation of the solvent during nebulization, e.g., in pneumatic devices (Niven, 1996). In this case the droplets delivered at the end of nebulization have a higher API concentration than the nominal value declared on the drug packaging. There is another issue for nebulized suspensions. If some API microparticles are larger than aerosol droplets generated in a nebulizer, the inhaled aerosol may contain no medicine (Sosnowski, 2019; Sosnowski and Odziomek, 2019).

#### 4. PROBLEM OF AEROSOL OUTPUT RATE VS. INHALATION CAPACITY

The above discussion considered the volume of the liquid present as the continuous liquid phase (drug solution/suspension) or droplets present in the aerosol phase. In nebulization processes, however, we should consider also the volume of the entire aerosol cloud, i.e. the volume of air carrying the droplets. This volume is measured in a completely different scale. For liquid drugs we talk about milliliters, whereas for the aerosol we deal with at least three orders of magnitude greater volumes (liters). Pneumatic nebulizers are supplied with air delivered from compressors at a pressure of a few bars, with the volumetric flow rate of 10-30 liters per minute. It has important consequences for the patient ability to inhale the aerosol produced from a nebulizer. With too small inspiratory volume (typically the tidal volume  $TV$  is used during inhalation with nebulizers), the patient will not inhale the entire emitted cloud and this will result in the aerosol release outside the system, similarly to the situation schematically shown in Fig. 2b. Additionally, the variable flow of inhalation – from zero through the peak (maximum) inspiratory flow rate,  $PIFR$ , and back to zero – is superimposed on the constant aerosol output from the nebulizer, which makes the balancing of aerosol losses and the delivered dose even more complicated (Fig. 5).

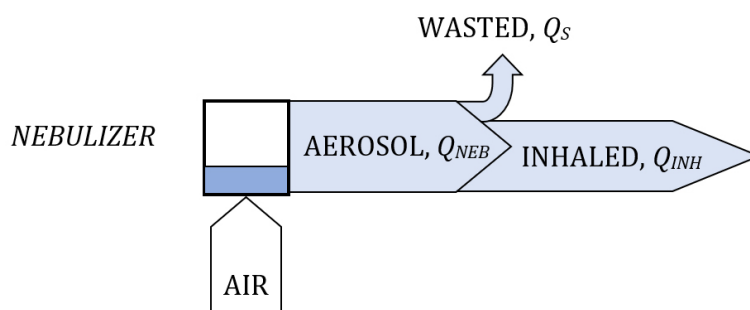


Fig. 5. Simplified Sankey-type graphs of aerosol inhalation using pneumatic nebulizer. Note that the system is semi-continuous for the liquid drug (drug content in the nebulizer decreases in time)

The equations describing the total volume of inhalable liquid drug (Eq. (9)) or the mass of delivered API (Eq. (10)) can therefore be used to provide an estimate only when the volume of the aerosol emitted from

the nebulizer is lower than the inhalation volume. In the opposite situation, the liquid losses  $V_S$  i.e. the total volume of droplets emitted outside the system as the aerosol during the whole nebulization time  $t_{NEB}$  can be expressed as:

$$V_S = Q_S t_{NEB} = (Q_{NEB} - Q_{INH}) t_{NEB} \tag{11}$$

where  $Q_{NEB}$  is the volumetric aerosol output rate of the nebulizer and  $Q_{INH}$  – the time-average inhalation airflow rate (inhalation capacity) of a patient. The inhalation capacity  $Q_{INH}$  can be calculated as the product of the volume of single inhalation (tidal volume:  $TV$ ) and the breathing frequency (known as breathing rate,  $BR$ ).

Accordingly, one obtains:

$$V_S = (Q_{NEB} - TV \cdot BR) t_{NEB} \tag{12}$$

and such a value of liquid losses  $V_S$  should be additionally included in the volume balance of the liquid (Eq. (7)). This allows to obtain the numerical expression valid when the aerosol emission from the nebulizer exceeds the possibility of the patient intake during inhalation:

$$V_{DI} = V_0 - RV - V_K - V_S \tag{13}$$

Eq. (13) shows that the discussed liquid drug losses additionally reduce the aerosol available for drug delivery to the patient’s respiratory system during nebulization treatment. Using this relationship to calculate the deposited API dose (Eqs. (9) and (10)) allows to better evaluate the impact of all essential factors of drug delivery using nebulizers, which are listed in Table 1.

Table 1. The key factors influencing the inhaled and delivered dose from nebulizers

Factor	Parameters that are influenced
Drug Dilution Before The Treatment	$c$
Nebulizer Design	$V_0, RV$ and $Q_{NEB}, t_{NEB}$
Interface Used For Aerosol Delivery	$V_K$
Aerosol droplet size distribution	$\eta$
Breathing maneuver	$Q_{INH}, t_{INH}$ and $t_C$

## 5. CONCLUSIONS

This work was focused on the application of the balances of selected extensive quantities (volumes or masses of the liquid drug, API dose, aerosol flow rates) for the quantitative analysis of the atomization process and drug delivery to the lungs during the use of medical nebulizers. The essential design parameters of medical nebulizers, the aerosol properties and patient-dependent factors were demonstrated to be of significance for the estimation of the amount (dose) of the API that can be effectively delivered to the target. The paper shows that the quantitative methods that are the typical tools in process engineering can be useful in acquiring the information needed for the assessment of the real outcome inhalation therapy offered by nebulization.

## SYMBOLS

- $BR$  breathing rate (frequency), 1/min
- $DD$  delivered (deposited) dose of the API, g

$M_0$	mass of the drug introduced to the nebulizer, g
$M_E$	emitted mass of drug (as aerosol droplets), g
$M_N$	mass of the empty (dry) nebulizer, g
$M_P$	mass of the nebulizer with the drug at the start of nebulization, g
$M_{RV}$	mass of the nebulizer with the remaining drug when at the termination of nebulization (corresponding to $RV$ ), g
$PIFR$	peak inspiratory flow, $\text{dm}^3/\text{min}$
$Q_{INH}$	volumetric flow rate of inhalation (average), $\text{cm}^3/\text{s}$
$Q_{NEB}$	volumetric flow rate of nebulization, $\text{cm}^3/\text{s}$
$Q_S$	volumetric flow rate of wasted aerosol, $\text{cm}^3/\text{s}$
$RV$	residual volume of the nebulizer (volume of the remaining drug at the termination of nebulization), $\text{cm}^3$
$t_C$	duration of a whole breath (respiratory cycle), s
$t_{INH}$	duration of inspiration in a single breath, s
$t_{NEB}$	time of nebulization, s
$TV$	tidal volume (volume of air inhaled/exhaled during normal breathing), $\text{dm}^3$
$V_0$	volume of the drug in the nebulizing vessel at the start of nebulization, $\text{cm}^3$
$V_{DEP}$	volume of the drug (as droplets) deposited in the respiratory system, $\text{cm}^3$
$V_{DI}$	volume of the drug (as aerosol droplets) available for inhalation by a patient, $\text{cm}^3$
$V_E$	emitted mass of drug (as aerosol droplets), $\text{cm}^3$
$V_K$	volume of the drug deposited (as droplets) in the mouthpiece or tubing outside the nebulizing vessel, $\text{cm}^3$
$V_S$	volume of the drug (as aerosol) emitted outside the nebulization system, $\text{cm}^3$
$x_{AER}$	volume fraction of liquid in the aerosol, –

#### Greek symbols

$\eta$	deposition efficiency of inhaled aerosol, –
$\rho$	liquid density, $\text{g}/\text{dm}^3$

#### Abbreviations

API	active pharmaceutical ingredient
MPPD	multi-path particle dosimetry model
VMN	vibrating mesh nebulizer

### ACKNOWLEDGMENTS

Work was supported by NCN project no. 2018/29/B/ST8/00273.

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*Received 27 June 2021*

*Received in revised form 04 August 2021*

*Accepted 05 August 2021*