REVIEW ARTICLE

SHAPING THE PROPERTIES OF THE AEROSOL CLOUD OF NEBULIZED DRUGS. PART II. PRACTICAL ASPECTS

Kształtowanie właściwości chmury aerozolowej leków nebulizacyjnych. Część II. Aspekty praktyczne

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Abstract

In clinical practice, the aerosol cloud of nebulized drugs can be shaped in several ways: by using nebulizers that vary significantly in the characteristics of the aerosol cloud they generate; modifying the nebulization chamber by replacing its internal dispersing elements; adjusting the operating conditions of the nebulizer chamber; adding a holding chamber; and by using different formulations of the same drug in the same nebulizer.

Streszczenie

Możliwości kształtowania chmury aerozolowej leków w praktyce klinicznej obejmują: zastosowanie urządzeń różniących się istotnie charakterystyką wytwarzanej chmury, modyfikację charakterystyki głowicy nebulizacyjnej poprzez zmianę jej wewnętrznych elementów rozpraszających ciecz, przełączenie głowicy na inne warunki wytwarzania aerozolu, dołączenie komory inhalacyjnej, a także zastosowanie różnych formulacji tego samego leku w tym samym nebulizatorze.

Keywords: nebulization; jet nebulizer; ultrasonic mesh nebulizer; aerosol cloud; airways deposition

Słowa kluczowe: nebulizacja; nebulizator pneumatyczny; nebulizator ultradźwiękowy siateczkowy; chmura aerozolowa; depozycja w drogach oddechowych

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How can the parameters of an aerosol cloud generated by a nebulizer be adjusted to meet the patient's needs?

In part I of the paper, we presented the clinical justification and theoretical framework for shaping the properties of aerosols generated by nebulization of drugs [1]. Adjusting aerosol cloud parameters to the patient's current needs is intended to enhance the efficacy and safety of inhalation therapy. The parameters of the aerosol cloud depend primarily on the technical properties of the device, specifically the nebulizer chamber and the compressor in jet nebulizers, or the chamber in mesh nebulizers, and, to a much lesser extent, on the formulation of the drug used. The definitions and abbreviations of the most commonly used aerosol cloud parameters are based on Pirożyński [2].

In practice, shaping the properties of the aerosol cloud is achieved by appropriately selecting the type of nebulizer and its operating parameters [3–5].

In the case of budesonide, it is possible to select a formulation that influences the properties of the aerosol cloud [6]. Our research, along with studies by other authors, has shown that adding a holding chamber to a mesh nebulizer significantly alters the parameters of the inhaled aerosol [7–9].

Currently available nebulization devices allow for adjustment of aerosol cloud parameters in various ways, both in jet and mesh nebulizers (Tab. 1).

Table 1. Methods for modulating aerosol cloud parameters in drug nebulization

	Method	Type of nebulizer	Examples and practical notes
1	The use of nebulizers that produce significantly different aerosol cloud properties from the same drug formulation	JN, MN	The solution is inconvenient, expensive and has little prospects
2a	Modifying the nebulizer chamber by replacing internal components of the liquid dispersion unit	JN	Pari Company System
2b	Changing the parameters of the nebulizer chamber by switching (setting) the nebulizer chamber to a different aerosol generation mode	JN	Many JN s, e.g. Omron, Diagnostic or Flaem Easy and convenient, currently most commonly used
3	Attaching the holding chamber	MN	For example Aerogen Solo + HC Ultra Aerogen or MN Intec Mesh + HC Intec Spiro Kids Only tested sets (MN + HC) should be used
4	Using different formulations of the same drug in the same nebulizer	MN, JN	Data are available only for some drugs, e.g. budesonide
JN – jet nebulizer; MN – mesh nebulizer; HC – holding chamber			

Exemplary solutions for modifying aerosol cloud parameters

Below we present examples of specific solutions currently available on the market.

Solution 1

Over 25 years ago, Finlay et al. compiled data on various types of nebulizers producing different salbutamol aerosol clouds, which gave rise to significant differences in pulmonary deposition [10]. According to this widely cited publication, *in vitro* studies demonstrated that regional pulmonary deposition of salbutamol (expressed as % of the nominal dose) varied significantly (5–8 times) in both jet and classical ultrasonic nebulizers (Tab. 2).

These observations were further expanded nearly 20 years later with regard to mesh nebulizers. Hatley et al., analysing several models of these devices, demonstrated nearly 2.5-fold differences in the volumetric median diameter (VMD) and fine particle fraction (FPF) of salbutamol aerosol clouds [11]. Similar results were reported by Sosnowski et al., who investigated inhaled corticosteroids [12]. These differences clearly translate into clinical outcomes, as demonstrated by the use of salbutamol in asthmatic patients with chronic obstructive pulmonary disease (COPD) [13–15]. The use of nebulizers with varying aerosol cloud characteristics may result in different patterns of drug deposition in the airways, leading to significant variations in clinical efficacy.

Solution 2a

Another method for modifying the aerosol cloud of nebulized drugs involves using nebulizer chambers with different aerosol generation modes for the same drug, within the same jet nebulizer and using the same compressor. This effect is achieved by replacing plastic nozzle inserts inside the nebulizer chamber, which are responsible for aerosol generation. This solution was introduced over 20 years ago by Pari in their LC Sprint jet nebulizers [16, 17]. It involves selecting appropriate inserts that alter the size of the generated droplets, which can be easily evaluated by comparing the mass median aerodynamic diameter (MMAD), mass median diameter (MMD), and fine particle fraction (FPF) of the aerosol cloud. The Pari LC Sprint nebulizer, which is available on the market, includes five nozzle inserts in different colours that enable generation of five distinct aerosol clouds, each designed to target different areas of the airways. The data presented in Table 3, Table 4, and Table 5 refer to studies conducted using a 0.9% NaCl solution (Tab. 3). A similar technology was also employed in Diagnostic Econstellation Plus jet nebulizers [17]. However, this device can generate only three types of aerosol clouds (Tab. 4).

Solution 2b

A similar solution involves a simple, quick adjustment of the nebulizer chamber characteristics in a jet nebulizer, achieved by turning the cover or pressing a button to alter the aerosol generation conditions and the properties of the generated cloud. This approach is becoming increasingly popular. The OMRON A3 nebulizer, which features three different operating positions of the same nebulizer chamber, resulting in varied aerosol cloud parameters and nebulization efficiencies, is a good example (Tab. 5).

The Flaem RF9 4 NEB jet nebulizer operates similarly, offering the user 4 modes of nebulization. Switching the

Table 2. Salbutamol deposition expressed as % of the nominal dose (ND) in different areas of the respiratory tract from different types of nebulizers (Finley, 1998 [10])

Airway region	Expected Salbutamol Deposition Range (%ND)	Maximum differences in deposition between the nebulizers tested
Extrapulmonary	1.8–9.5	5×
Entire lungs	3.1–23.4	7×
Tracheobronchial	1.6–10.6	6×
Alveolar	1.6–12.8	8×

Table 3. Aerosol cloud modulation in Pari LC Sprint NP

Insert colour	MMAD or MMD (µm)	FPF (% ED)	Main deposition site and type of nebulizer
Red	MMAD 2,8	80	Distal (peripheral) airways. Designed for infants and small children with bronchial obstruction and COPD patients. Nebulizers: Pari Boy Junior, Pari Boy Pro, Pari LC Sprint Baby, Pari LC Sprint Star
Yellow	MMAD 3,1	73	Small bronchi in infants and young children. Nebulizer: Pari LC Sprint Junior
Blue	MMAD 3,8	62	Central lungs in older children and adults. Nebulizers: Pari LC Sprint and Pari LC Sprint Tracheo
Transparent	MMD 7,3	65	Optimal deposition in the upper airways (larynx, trachea). Nebulizer: Pari LC Sprint Xlent
Orange	MMD 3,2	71	In combination with the pulsating system – effective deposition in the paranasal sinuses. Nebulizer: Pari LC Sprint Sinus
MMAD – mass median aerodynamic diameter; MMD – mass median diameter; FPF – fine particle fraction; ED – emitted dose; COPD – chronic obstructive pulmonary disease			

Table 4. Possibilities of shaping aerosol cloud parameters in Diagnostic E-Constellation Plus jet nebulizer

Parameters	Position 1	Position 2	Position 3
MMAD (µm)	8.0	5.4	4.0
FPF (% ED)	36	50	64
Efficiency (mL/min)	0.32	0.16	0.14
MMAD – mass median aerodynamic diameter; FPF – fine particle fraction; ED – emitted dose			

position modifies the function of the nebulizer chamber, leading to aerosol clouds with different MMAD values (Tab. 6) [18].

In the latest Flaem nebulizer, the Flaem RF7 Dual Speed Plus Koala, the chamber features a simple switch that allows users to change the mode of generating the aerosol cloud [19]. This device produces an aerosol (data for salbutamol) with likely the most optimal parameters (the lowest MMAD and the highest FPF) required for effective therapy of lower respiratory tract diseases (Tab. 7).

It is worth noting that the changes in MMAD and FPF, as shown in Table 5, Table 6, and Table 7, are accompanied by variations in the aerosol emission efficiency (expressed in mL/min), which impacts nebulization time (shorter for aerosols with larger droplets targeting the upper airways).

All the solutions described above lead to a rapid change in aerosol cloud parameters. In the future, these parameters may be adjusted smoothly and linearly, allowing for even more precise personalization of inhalation therapy to suit individual patient needs. This could be achieved,

Table 5. Possibilities of shaping aerosol cloud parameters in OMRON A3 jet nebulizer

Parameters	Position 1	Position 2	Position 3
MMAD (µm)	about 10.0	about 5.0	about 3.0
Efficiency (mL/min)	0.7	0.5	0.3
MMAD – mass median aerodynamic diameter			

Table 6. Aerosol cloud shaping with NP Flaem RF9 4 NEB

Parameters	Position 0	Position 1	Position 2	Position 3
MMAD (µm)	7.7	5.1	3.7	2.5
Efficiency (mL/min)	0.53	0.36	0.29	0.23
MMAD – mass median aerodynamic diameter				

Table 7. Salbutamol aerosol clouds generated from the Flaem RF7 Dual Speed Plus Koala nebulizer

Parameters	Salbutamol Position 1	Salbutamol Pozycja 2
Efficiency (mL/min)	0.20	0.42
MMAD (µm)	1.64	3.72
FPF (%ED)	95.8	63.5
FPF – fine particle fraction; ED – emitted dose		

among others, by adjusting the airflow rate generated by the compressor [20].

Solution 3

Adding a holding chamber to a mesh nebulizer not only increases aerosol availability by collecting aerosol generated during exhalation, but also modifies the characteristics of the inhaled aerosol cloud by reducing MMAD and increasing FPF due to the chamber's filtering effect. This leads to greater lung deposition, while reducing the oropharyngeal deposition, as well as minimizing aerosol escape into the environment [21–23]. Available data are limited to a small number of in vitro-tested mesh nebulizer and holding chamber combinations. Table 8 presents research findings for the Intec Mesh set used in conjunction with the Spiro Kids holding chamber [8].

The studies conducted using NaCl 0.9% showed (Tab. 8):
- a nearly 73% increase in the mass of the dose available for inhalation compared to a MN used without a holding chamber;
- reduction in Dv50 (median of the volumetric distribution) from 6.2 µm (MN alone) to 4.7 µm (MN + holding chamber);
- an increase in FPF from approximately 35% (MN alone) to about 55% (MN + holding chamber).

Solution 4

As recently demonstrated for nebulized budesonide, generic drug formulations may differ in aspects such as the number of budesonide crystals in suspension, as well as the type and concentration of excipients, which affects the physicochemical properties of the nebulized liquid and, consequently, the quality of the aerosol cloud [6]. Therefore, switching to a generic formulation with different characteristics may lead to variations in clinical efficacy. Previous studies have shown that the size of aerosol droplets can also be modified by changing the physicochemical properties of the liquid, including viscosity (or, more broadly, rheology), surface tension, and, in some cases, ionic strength [24, 25].

In the case of inhaled drugs, this effect can be achieved by incorporating suitable additives, such as biosurfactants or natural viscosity modifiers [26]. These substances offer a potential alternative to the synthetic adjuvants commonly used in inhaled medications, such as polysorbate 80 in nebulized corticosteroids.

In the future, new solutions are likely to emerge that will allow for more precise customization of the properties of aerosol clouds generated by jet nebulizers to better meet individual patient needs. We can anticipate the development of systems that will enable smooth, continuous modulation of aerosol generation rates across multiple operating modes, along with the dynamic adjustment of parameters such as MMAD and FPF. This will be made possible, among others, by adjusting the compressor airflow rate – optimal for the patient and the target deposition site [18].

In a mesh nebulizer, this shaping can be achieved by altering the diameter of the mesh holes and adjusting the mesh vibration frequency [27]. Currently, only models for *in vitro* studies are available, e.g. Micronice®.

Interchangeable nebulization chambers in mesh nebulizers could be another solution. Such attempts have been made by Aerogen/Nektar Therapeutics with Aeroneb Lab Control Module nebulizers. This device features two modules (chambers) that spray solutions, producing aerosol clouds with VMDs of 2.5–4.0 µm and 4.0–6.0 µm, but it has not yet been commercialized as a personal nebulizer [28].

Conclusions

Drug deposition in target airway sites is a key factor determining the efficacy and safety of inhalation therapy with any type of inhaler. The size and mechanisms of nebulized drug deposition are influenced by the patient's condition and inhalation technique, but primarily by the characteristics of the aerosol cloud, which depend on the nebulization method and drug formulation.

Several approaches are available in clinical practice to shape the aerosol cloud, such as selecting the appropriate nebulizer (jet or mesh), choosing the nebulization chamber operating mode (for jet nebulizers), using a holding chamber (with mesh nebulizers), and selecting the suitable drug formulation (for both jet and mesh nebulizers).

In the future, the development of nebulizers (primarily jet nebulizers) is expected to allow smooth modulation

Table 8. Results of measurements and calculations of emission and increased aerosol availability (average of 3 measurements ± standard deviation) for Intec Mesh MN with Spiro Kids type HC

Size	Value
Aerosol emission from a nebulizer: m_E [mg/min]	209.4 ± 31.7
Quantity deposited in IC, m_{KI} [mg/min]	66.6 ± 27.7
Aerosol available for inhalation: m_{INH} [mg/min]	144.5 ± 21.0
Gain [%] compared to the aerosol available without IC, $Z = \left(\frac{m_{INH}}{0{,}4m_E} - 1\right) \times 100\%$	+ 72.5%
HC – holding chamber	

of aerosol particle size (e.g., MMAD, FPF), tailored to the patient's age, type of respiratory pathology, optimal deposition site, drug type, and the functional status of the respiratory tract. This will enable precise calculation of the required therapeutic dose deposited in the target airway region. Such nebulization is expected to be highly clinically effective, safe, and potentially more cost-efficient due to reduced drug loss.

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