SHAPING THE PROPERTIES OF THE AEROSOL CLOUD OF NEBULIZING DRUGS. PART I. THEORETICAL BACKGROUND

Kształtowanie właściwości chmury aerozolowej leków nebulizacyjnych. Część I. Podstawy teoretyczne

Andrzej Emeryk[1], Anna Piela[2], Kamil Janeczek[3], Tomasz R. Sosnowski[4]

1. *Department of Paediatric Pulmonology and Rheumatology, University Children's Hospital in Lublin, Poland*
2. *Department of Paediatric Pulmonology and Rheumatology, Medical University of Lublin, Poland*
3. *Department of Allergology and Pediatrics, Medical University of Lublin, Poland*
4. *Faculty of Chemical and Process Engineering, Warsaw University of Technology, Poland*

Andrzej Emeryk – 0000-0003-1853-8696
Anna Piela – 0009-0006-4188-7703
Kamil Janeczek – 0000-0002-8163-873X
Tomasz Sosnowski – 0000-0002-6775-3766

Abstract

The paper presents basic data on various types of nebulizers and indications for nebulization. We discuss the most commonly assessed parameters of the aerosol cloud and factors influencing the efficacy of nebulization, emphasizing the relationship between the characteristics of the inhaled aerosol agents (budesonide, salbutamol) and both the site of their deposition in the respiratory tract and their clinical effect.

Streszczenie

W pracy przedstawiono podstawowe dane dotyczące różnego rodzaju nebulizatorów oraz wskazań do nebulizacji. Przypomniano najczęściej oceniane parametry chmury aerozolowej i omówiono czynniki wpływające na efektywność nebulizacji. Podkreślono związek między charakterystyką chmury aerozolowej inhalowanych leków (budezonid, salbutamol) a miejscem ich depozycji w drogach oddechowych i efektem klinicznym.

Keywords: budesonide; nebulization; jet nebulizer; MMAD; lung deposition

Słowa kluczowe: budezonid; nebulizacja; nebulizator pneumatyczny; MMAD; depozycja w drogach oddechowych

DOI 10.53301/lw/191758

Received: 06.06.2024

Accepted: 29.07.2024

Corresponding author:
Andrzej Emeryk
Department of Paediatric Pulmonology and Rheumatology, Medical University of Lublin
e-mail: emerykandrzej@gmail.com

Introduction

The aim of this study was to demonstrate the rationale behind and the possibility of influencing the physical properties of an aerosol cloud of selected nebulized agents to improve their targeted deposition in the airways, and thereby optimise clinical outcomes and safety. To this end, we reviewed the literature available in the PubMed database and studies done by nebulizer manufacturers on the background of our own research. The research comprised two parts: theoretical and practical.

Nebulization is a type of inhalation therapy using a device (nebulizer) that generates an aerosol by mechanically dispersing (atomising) a liquid drug (solution or suspension) [1, 2]. There are several classes of nebulisers, differing in their mechanism of liquid dispersion, with pneumatic nebulisers (PNs) and ultrasonic nebulisers (classic and ultrasonic mesh nebulizers [MNs]) representing the two main classes (fig. 1).

Nebulization is recommended for the treatment of laryngitis/tracheitis, asthma, obstructive bronchitis in children, bronchitis (both recurrent and chronic), chronic obstructive pulmonary disease, cystic fibrosis, bronchiectasis, primary ciliary dyskinesia, bronchiolitis, neonatal respiratory distress syndrome, bronchopulmonary dysplasia, pulmonary hypertension, pneumonia in immunocompromised patients, as well as in the prevention of ventilator-associated pneumonia [3, 4]. Glucocorticoids s (GCs) (budesonide, fluticasone propionate), short-acting beta$_2$-agonists (salbutamol, fenoterol), short-acting muscarinic receptor

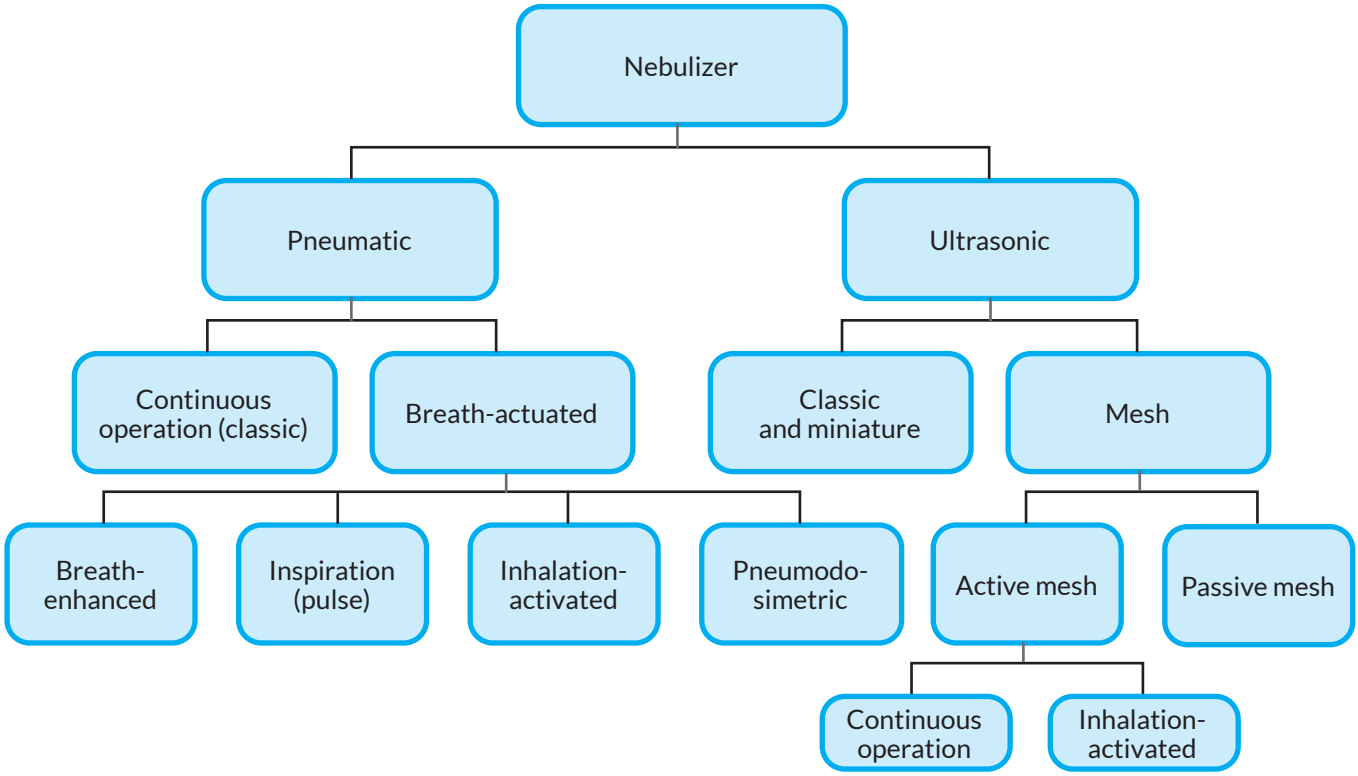

Figure 1. Types of nebulisers [1, 3]

agonist (ipratropium bromide), antibiotics (colistin, tobramycin, aztreonam, amphotericin B), saline solutions, mucoactive agents (e.g. ambroxol), dornase alfa, iloprost, surfactants, and opioids are the most commonly used nebulized agents in Poland. There is also a relatively large group of nebulized drugs not available in our country, such as epinephrine, terbutaline, formoterol, levofloxacin, pentamidine, insulin, and some antibiotics [5].

The properties of the drug itself (dose, formulation) and the inhaler, the characteristics of the patient (age, type of pathology), and the inhalation technique are the main factors determining the clinical efficacy and safety of inhalation therapy, including nebulization [6]. In clinical practice, the choice of drug and nebuliser should primarily depend on the type of pathology and the involved airway region, as this is where the inhaled substance will be delivered and deposited [7–9].

Aerosol cloud characteristics and assessment methods

The aerosol cloud leaving any inhaler (including a nebuliser) may be described by several parameters that provide important information about the characteristics (quality) of the therapeutic aerosol. The most commonly used parameters include [2, 3, 9]:

- mass median aerodynamic diameter (MMAD) – aerodynamic diameter of a particle (μm) or a nebulized droplet (when liquid is sprayed), corresponding to the median mass distribution. This parameter provides data on the average particle/droplet size in a given aerosol, or more precisely, in the inhaled portion of aerosol. The smaller the MMAD, the smaller the particles/droplets, and therefore the greater the likelihood that the drug will deposit in the lower airways;
- fine particle fraction (FPF) – the proportion of fine particles/droplets, i.e. with an aerodynamic diameter <5 μm. The higher the FPF value, the higher the amount of drug that reaches the lower airways, and the higher the fine particle dose (FPD);
- geometric standard deviation (GSD) – a measure (a dimensionless value) of the particle/droplet size distribution in a given aerosol with a lognormal distribution (typical for nebulized aerosols). Monodisperse aerosols, i.e. composed of particles of similar size (GSD <1.2), and polydisperse aerosols, which contain particles of different sizes (GSD >1.2) have been distinguished.

These parameters are conventionally assessed using an Andersen cascade impactor or a Next Generation impactor [10]. For nebulized aerosols, it is convenient and reasonable to use optical methods, including laser diffraction [11]. The method involves determining, among other things, Dv50 (μm), also known as volume median diameter (VMD), i.e. the median distribution relative to the volume of droplets in the total aerosol leaving the nebulizer [12, 13]. Other percentile values of aerosol droplet size distribution are also often determined, such as Dv10 (with 10% of droplets smaller than this value) and Dv90 (with 90% of droplets smaller than this value), as well as Span = Dv50/(Dv90–Dv10), which is a measure of the polydispersity of droplets in the cloud, yet more universal than GSD as it is also used for non-lognormal distributions [12]. It is worth highlighting a certain difference between MMAD and Dv50 (VMD). MMAD is estimated for aerosol that can enter the airways, as it is determined for aerosol deposited in the cascade impactor. Thus, it does not include the largest aerosol particles. In comparison, Dv50 informs about the total nebulized cloud (i.e. all-size droplets) [12]. There-

fore, Dv50 equals MMAD only if all nebulized droplets are smaller than approx. 10 µm [14, 15].

Airway aerosol deposition and clinical outcomes

The properties of aerosol cloud, FPF, MMAD and GSD in particular, are the most important factors determining the site, extent and mechanisms of drug deposition in the airways [16] (tab. 1).

Inhalation technique used by the patient is another important aspect [18]. If nebulized aerosol shows monodisperse characteristics (GSD <1.2), its site of deposition in a given airway region is more predictable, and the therapy becomes more targeted [19, 20]. Given the deposition mechanisms of aerosol particles in the airways, there is a range of particle sizes that will not be properly deposited in any part of the airways, but will be expelled in exhalation instead. Therefore, 0.3–0.7 µm particles/droplets may be considered therapeutically useless; however, these account for a negligible proportion of total nebulized aerosol [16].

In vitro and *in vivo* studies indicate a close correlation between the size of particles produced by different inhalers and the extent and site of pulmonary deposition of different drugs. Large particles (>5 µm) tend to deposit mainly in the upper and large airways, limiting the amount of aerosol that can be delivered to the peripheral lungs. Fine particles (2–5 µm) mainly deposit in the central and small airways, whereas ultrafine particles (<2 µm) tend to deposit in the alveolar region [18, 21–25].

Acute laryngitis in children or adults and acute bronchiolitis in children are good examples. In patients with laryngitis, GCs should deposit mainly in the larynx, which will be highly effective with an aerosol cloud with an average particle size of 8–10 µm and short, forceful inhalations during nebulization to increase inertial deposition of the aerosol in this region [26]. In the case of acute bronchiolitis, a common infection in children <3 years of age, GCs or short-acting beta$_2$-agonists with the lowest possible MMAD (<2.0 µm) should be used, with breathing rate as low as possible [27].

The relationship between aerosol cloud structure, inspiratory flow rate and clinical outcome was best documented by Usmani et al. for monodisperse salbutamol [28]. They demonstrated that asthmatic patients showed greater improvement in forced expiratory volume in 1 second (FEV_1) after slow inhalation of 6 µm salbutamol particles vs. rapid inhalation of 3.0 or 1.5 µm particles.

Different nebulisers, different aerosol clouds

Nebulisers produce aerosol clouds with highly variable parameters. This is due to the type and technical characteristics of the device (PNs vs. MNs) and the type and formulation of the drug (solution/suspension physicochemical properties) [29, 30]. It was already more than 10 years ago when Pirozynski et al. showed that 0.9% NaCl solution produced by the various PNs available at that time in our country had MMAD ranging from 1.8 to 4.5 µm [31]. Hatley et al. demonstrated that the parameters of the salbutamol aerosol cloud from 9 different nebulisers could differ by up to twofold, particularly among PNs [29] (tab. *2*).

The same phenomenon was demonstrated by Sosnowski et al. for budesonide aerosol generated by three different MNs [32]. The multiple factors determining the efficacy and safety of nebulization in children and adults are illustrated with an example of budesonide in figure 2.

Conclusions

Nebulization is a commonly used form of aerosol therapy for acute and chronic airway conditions in both children and adults. This paper presents the rationale behind and theoretical background for the possible impact on the physical properties of the aerosol cloud of selected nebulized agents to improve their targeted deposition in the airways. The clinical effect and safety of a nebulised drug depend on the type of nebuliser used, the properties and dose of the drug administered and the way the patient inhales the aerosol. Achieving an optimal clinical effect of nebulization therapy is only possible if all the above-mentioned considerations are properly taken into account.

Table 1. Particle size of medical aerosols and site of their deposition in the airways [17, 18]

Fraction	MMAD [µm]	Primary deposition site
Therapeutic aerosol	<10	larynx, trachea, bronchi, bronchioles
Fine particles	<5	bronchi, bronchioles, alveoli
Ultrafine particles	<1,5	bronchioles, alveoli
MMAD – Mass Median Aerodynamic Diameter (particle size of medical aerosols)		

Table 2. Characteristics of salbutamol aerosol cloud produced by different PNs and MNs [29]

Type od nebuliser	VMD (µm) min–max	FPD (% DN) min–max
Pneumatic nebulisers	3,27–7,35	30,1–73,1
Ultrasonic mesh nebulisers	4,44–5,04	50,3–59,9
FPD – fine particle dose; DN – nominal dose; VMD (volumetric median diameter volumetric) – diameter corresponding to the median droplet size distribution		

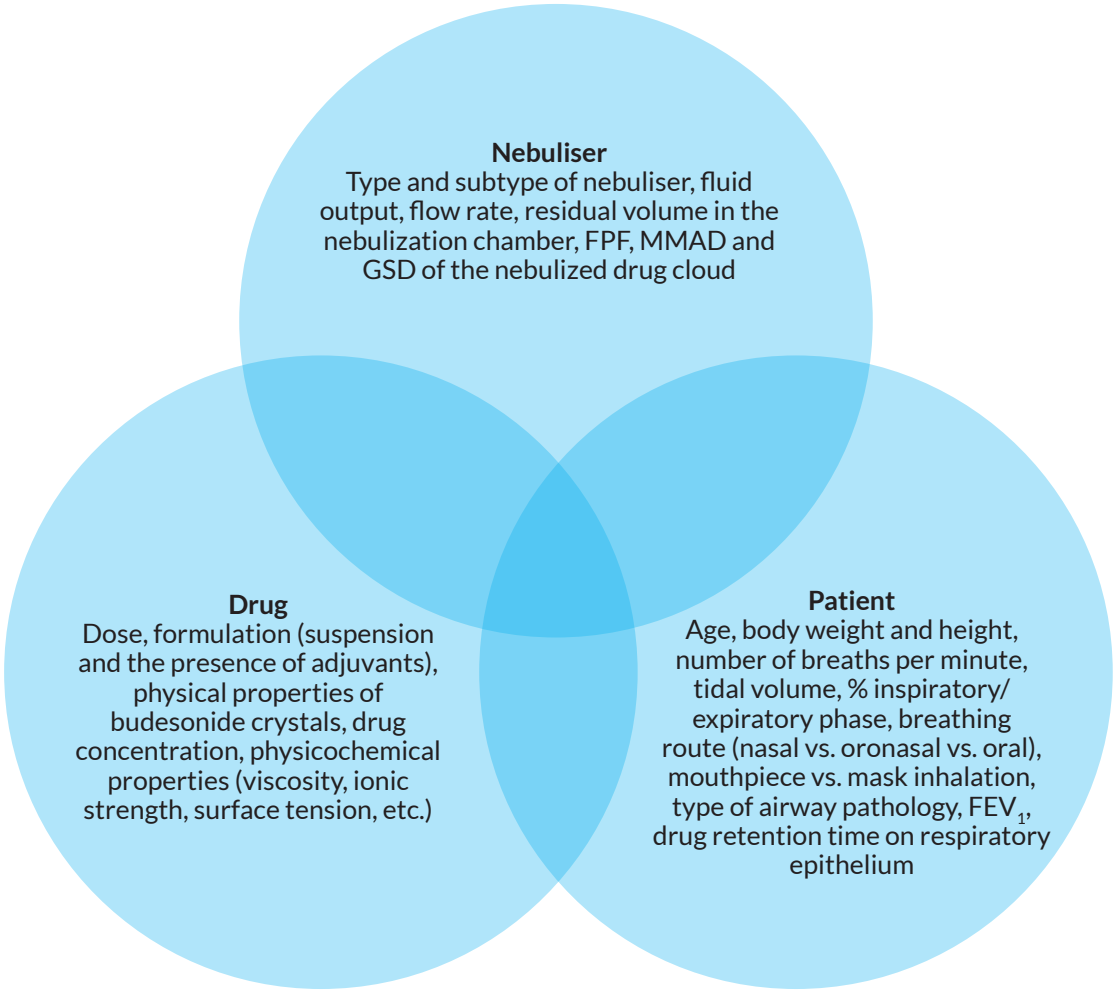

Figure 2. Factors influencing the clinical efficacy and safety of nebulised budesonide [30, 33-37]. FPF – fine particle/droplet fraction; MMAD – mass median aerodynamic diameter used for defining particle size distribution; GSD – geometric standard deviation

Acknowledgements

We would like to thank Boleslaw Samodulski and Mateo Zanelli for their assistance in the preparation of the paper.

References

1. Ari A. Jet, ultrasonic, and mesh nebulizers: an evaluation of nebulizers for better clinical outcomes. Eurasian J Pulm, 2014; 16: 1–7. doi: 10.5152/ejp.2014.00087
2. Emeryk A, Pirożyński M, Sosnowski T, Florkiewicz E. Leksykon nebulizacyjny. Wydanie I. Teva Polska 2017; 6–22
3. Emeryk A, Pirożyński M, Mazurek H. Polski przewodnik inhalacyjny. Wydanie II. Gdańsk: Via Medica, 2021; 1–36
4. Boe J, Dennis HJ, Driscoll BR, et al.; European Respiratory Society Task Force on the use of nebulizers. European Respiratory Society Guidelines on the use of nebulizers. Eur Respir J, 2001; 18: 228–242. doi: 10.1183/09031936.01.00220001
5. Anderson S, Atkins P, Bäckman P, et al. Inhaled medicines: past, present, and future. Pharmacol Rev, 2022; 74: 48–118. doi: 10.1124/pharmrev.120.000108
6. Borghardt JM, Kloft C, Sharma A. Inhaled therapy in respiratory disease: the complex interplay of pulmonary kinetic processes. Can Respir J, 2018: 2732017. doi: 10.1155/2018/2732017
7. Laube BL, Janssens HM, de Jongh HC, et al.; European Respiratory Society; International Society for Aerosols in Medicine. What the pulmonary specialist should know about the new inhalation therapies. Eur Respir J, 2011; 37: 1308–1331. doi: 10.1183/09031936.00166410
8. Schuepp KG, Jauernig J, Janssens HM, et al. In vitro determination of the optimal particle size for nebulized aerosol delivery to infants. J Aerosol Med, 2005; 18: 225–235. doi: 10.1089/jam.2005.18.225
9. Cheng YS. Mechanisms of pharmaceutical aerosol deposition in the respiratory tract. AAPS Pharm Sci Tech, 2014; 15: 630–640. doi: 10.1208/s12249-014-0092-0
10. Sosnowski TR. Metody pomiaru właściwości aerozolu leczniczego oraz badań jakościowych produktów inhalacyjnych. In: Sosnowski TR, ed. Aerozole wziewne i inhalatory. Wyd. 2. WIChiP PW, Warszawa 2012; 125–152
11. Kwong WTJ, Ho SL, Coates AL. Comparison of nebulized particle size distribution with Malvern diffraction analyzer versus Andersen cascade impactor and marple personal cascade impactor. J Aerosol Med, 2000; 13: 303–314. doi: 10.1089/jam.2000.13.303
12. Sosnowski TR. Critical assessment of the quantitative criteria used in the comparison of nebulizers. EC Pulmonol Respir Med, 2019; 8.9: 656–662
13. Virden A. Spraytec Laser Diffraction System: robust, reproducible droplet size data. ONdrug Delivery, 2023; 154: 48–50

14. Mitchell JP, Nagel MW, Doyle CC, et al. Relative precision of inhaler aerodynamic particle size distribution (APSD) metrics by full resolution and abbreviated Andresen cascade impactors (ACIs): part 1. AAPS Pharm Sci Tech, 2010; 11, 843–851. doi: 10.1208/s12249-010-9452-6
15. Roberts DL, Mitchell JP. Measurement of aerodynamic particle size distribution of orally inhaled products by cascade impactor: how to let the product specification drive the quality requirements of the cascade impactor. AAPS Pharm Sci Tech, 2019; 20: 57. doi: 10.1208/s12249-018-1276-9
16. Darquenne C. Aerosol deposition in health and disease. J Aerosol Med Pulm Drug Deliv, 2012; 25: 140–147. doi: 10.1089/jamp.2011.0916
17. Newman SP. Drug delivery to the lungs: challenges and opportunities. Ther Deliv, 2017; 8: 647–661. doi: 10.4155/tde-2017-0037
18. Darquenne C. Deposition mechanisms. J Aerosol Med Pulm Drug Deliv, 2020; 33: 181–185. doi: 10.1089/jamp.2020.29029.cd
19. Meyer T, Müllinger B, Sommerer K, et al. Pulmonary deposition of monodisperse aerosols in patients with chronic obstructive pulmonary disease. Exp Lung Res, 2003; 29: 475–484. doi: 10.1080/01902140303775
20. Brand P, Meyer T, Häussermann S, et al. Optimum peripheral drug deposition in patients with cystic fibrosis. J Aerosol Med, 2005; 18: 45–54. doi: 10.1089/jam.2005.18.45
21. Cripps A, Riebe M, Schulze M, Woodhouse R. Pharmaceutical transition to non-CFC pressurized metered dose inhalers. Respir Med, 2000; 94(Suppl B): S3–S9
22. Newman SP. How well do in vitro particle size measurements predict drug delivery in vivo. J Aerosol Med, 1998; 11(Suppl 1): S97–S104
23. Cabrera M, Le Pennec D, Le Guellec S, et al. Influence of mesh nebulizer characteristics on aerosol delivery in non-human primates. Eur J Pharm Sci, 2023; 191: 106606. doi: 10.1016/j.ejps.2023.106606
24. Carvalho TC, Peters JI, Williams RO 3rd. Influence of particle size on regional lung deposition – what evidence is there? J Pharm, 2011; 406: 1–10. doi: 10.1016/j.ijpharm.2010.12.040
25. Walenga RL, Longest PW. Current inhalers deliver very small doses to the lower tracheobronchial airways: assessment of healthy and constricted lungs. J Pharm Sci, 2016; 105: 147–159. doi: 10.1016/j.xphs.2015.11.027
26. Wang Y, Ma R, Sun S, et al. Modeling of inhaled corticosteroids delivery for topical croup treatment in pediatric upper airways. J Drug Deliv Sci Technol, 2023; 85: 104613. doi: 10.1016/j.jddst.2023.104613
27. Amirav I, Newhouse MT. Deposition of small particles in the developing lung. Paediatr Respir Rev, 2012; 13: 73–78. doi: 10.1016/j.prrv.2011.05.006
28. Usmani OS, Biddiscombe MF, Barnes PJ. Regional lung deposition and bronchodilator response as a function of beta$_2$-agonist particle size. Am J Respir Crit Care Med, 2005; 172: 1497–1504. doi: 10.1164/rccm.200410-1414OC
29. Hatley RHM, Byrne SM. Variability in delivered dose and respirable delivered dose from nebulizers: are current regulatory testing guidelines sufficient to produce meaningful information? Med Devices (Auckl), 2017; 10: 17–28. doi: 10.2147/MDER.S125104
30. Dobrowolska K, Emeryk A, Janeczek K, et al. Influence of physicochemical properties of budesonide micro-suspensions on their expected lung delivery using a vibrating mesh nebulizer. Pharmaceutics, 2023; 15: 752. doi: 10.3390/pharmaceutics15030752
31. Pirożyński M, Bodasiński J, Taff J. Zestawienie wybranych inhalatorów dostępnych w kraju. In: Pirożyński M, ed. Praktyczne aspekty nebulizacji. Alfa-Medica Press 2013; 33–36
32. Sosnowski TR, Odziomek M. Steroidy wziewne podawane z nebulizatorów siateczkowych – co powinniśmy wiedzieć? Terapia, 2019; nr spec. 3, 1–6.
33. Martin AR, Finlay WH. Nebulizers for drug delivery to the lungs. Expert Opin Drug Deliv, 2015; 12: 889–900. doi: 10.1517/17425247.2015.995087
34. O'Callaghan Ch, White JA, Kantar A. Nebulization of corticosteroids to asthmatic children: large variation in dose inhaled. Respirology, 2014; 19: 276–279. doi: 10.1111/resp.12208
35. Pirożyński M, Floriewicz E, Bodasiński J, et al. Calculation of the delivered dose in patients undergoing nebulized asthma therapy. Respir Drug Deliv Europe, 2017; 2: 269–272
36. Rubin BK. Nebulizer therapy for children: the device-patient interface. Respir Care, 2002; 47: 1314–1319
37. Terzano C, Petroianni A, Parola D, Ricci A. Compressor/nebulizers differences in the nebulization of corticosteroids. The CODE study (Corticosteroids and Devices Efficiency). Eur Rev Med Pharmacol Sci, 2007; 1: 225–237