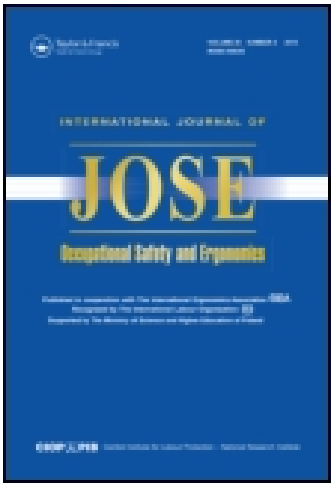

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Pulse Nebulization in Pneumatic Devices

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Aerosols of a physiological salt solution and aqueous solutions of salbutamol, sodium cromoglicate, and dornase alfa were generated in a pneumatic nebulizer and analyzed in a system with controlled humidity of air as a carrier gas. Mass distribution of aerosol particles and yield of generation for pulse nebulization were measured. Pulsation of generation was realized with an attachment maintained by a computer program. Opening times of the valve were in the range 50–800 ms. The results indicate the possibility of improving aerosol particle delivery to the lung using a pulse generation system.

inhalation nebulizer flow pulsation

1. INTRODUCTION

Recent epidemiological studies indicate health effects on the general population at air particulate mass concentrations that are considerably below existing air quality standards (Roth, Wyzga, & Hayter, 1986). These new data indicate that an increase in human mortality and morbidity is associated with levels of air particulate pollution. The synergetic effect of the reaction of deposited particles and inhaled harmful gases in the pulmonary region of human lungs can significantly change the mechanical properties of lung parenchyma.

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New observations, experimental results, and hypotheses underline the role of very fine insoluble particles with dimensions smaller and much smaller than 1 μm, mainly particles in the size range between 10 and 50 nm, which are now of interest to toxicologists (Heinrich, 1995). Although these particles have very low mass, there are extremely many of them and their sheer numbers mean that they present a large surface and interface when they reach the alveoli in the lung. Once in the alveoli, they may induce oxidant production, lung inflammation, and biological activity. Lung diseases caused by long-term exposure to particulate or gaseous pollutants at the workplace, like emphysema, asthma, or fibrosis, require efficient medical treatment.

Aerosolotherapy is one of the best methods of treating lung diseases. Modern methods of aerosolized particle detection allow precise measurement of particles smaller than 1 μm. Currently, experimental and theoretical analyses of deposition focus on particles of such dimensions.

A theoretical model concerning the efficiency of aerosolized particle deposition in peripheral bronchiole and alveoli (Gradoń & Podgórski, 1996) in healthy human has shown that for particles 0.1–0.5 μm big, local deposition efficiency in that area ranges around 30–50%. Taking into consideration how easily submicron particles penetrate the peripheral part of the respiratory system and the fact that the deposition of particles heavily depends on diffusion—a mechanism equally efficient in both inspiration and expiration phases—it may turn out that particle production from such a range of dimensions will be of great importance in aerosolotherapy. This has also been confirmed by the results of experimental tests.

Mason and Miller (1994), with the help of a gamma camera, measured the deposition efficiency of physiological salt's aerosol particles marked with technetium ^{99}Tc. Tests were carried out on 9 patients using two types of pneumatic nebulization means. In the first case, the average mass diameter of the generated particles was 1.45 μm; in the second case—modified by the use of a special uni-directional valve—the average mass diameter was 0.55 μm. The tests have shown that an average full mass deposition efficiency in the peripheral part of a lung counted in relation to the generated pharmaceutical's mass was about 8% in the first case, with 5% of particle penetration into the digestive system, whereas in the second case, deposition efficiency was about 19% and penetration into the digestive system was about 1%. Taking into consideration the conditions of the experiment (times of inhalation and

of measurement) and the analysis of retention curves (Gradoń & Podgórski, 1996), it turns out that for a spectrum of particles with an average diameter of 1.45 μm, their majority is deposited in the nasopharynx and the upper airways, where they are easily removed into the digestive system during mucociliary transport.

For a spectrum of particles with an average diameter of 0.55 μm, most particles are deposited in peripheral bronchiole and alveoli, where clearance efficiency is much smaller than in the bronchial tree. Hence such low penetration of this type of particles into the digestive system through clearance mechanisms in the airways of the respiratory system.

An extended model of deposition for pathological cases, taking into account the specific movement of the alveolar membrane (i.e., in asthma or emphysema) in respect to the flow pattern of inhaled air (Orlicki & Gradoń, 1996), has shown that in such cases the efficiency of submicron particle deposition is equally high. This is due to strong convection near the walls of the airways and enhancement of the deposition effect in the convective diffusion process. The aforementioned data point to the fact that submicron particles have a considerable influence on deposition and can be used in aerosolotherapy providing that such particles can be generated and their dimensions stabilized (Gradoń, 1997). As a fraction of submicron particles that have not been deposited is easily exhaled, there is a problem of their interaction with inhaled particles during the next inspiration phase of the breathing cycle. In order to avoid such a situation, it would be advisable to apply a pharmaceutical into the respiratory system during the inspiration phase divided into an active phase (generation of a pharmaceutical) and a passive phase (no generation of a pharmaceutical). This may improve the overall treatment effect, that is, increase the effective amount of the pharmaceutical delivered to the peripheral part of a lung. However, there are questions of how to control the pulse generation of the pharmaceutical and of whether the generated aerosol has an appropriate dispersion distribution.

To allow measurement of this type, an experimental model was built. A control attachment that provides a pulse method of opening a valve that stops the air flow from the compressor to the aerosol generator (nebulizer) is the main element of the model. The time and frequency of the opening may be maintained by a computer and synchronized by a breathing simulation signal. The objective of the presented investigation is to analyze the characteristics of a Sidestream nebulizer, that is, the efficiency and mass distribution of the particles generated with the

pulse method from a physiological salt solution, salbutamol, sodium cromoglicate, and dornase alfa aqueous solutions.

2. METHOD

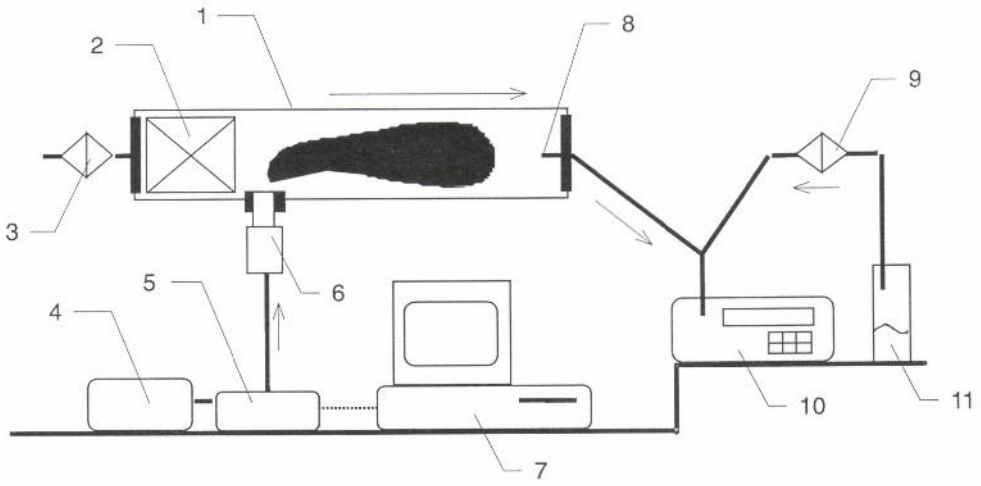

Figure 1. Experimental setup. *Notes.* 1—dilution chamber, 2—fibrous humidifier, 3—air filter, 4—air compressor, 5—PNEUMONEB® attachment (artmed Ltd., Poland), 6—Sidestream nebulizer, 7—computer, 8—sampling probe, 9—air filter, 10—A3 laser aerosol counter, 11—humidifier.

The studies were carried out in the experimental setup presented in Figure 1. Employment of the aerosol analyzer A3 (10; A3 GmbH, Germany) required—like the use of other laser meters—an appropriate dissolving of the generated aerosol. This was done with a cylindrical dilution chamber (1) fed with atmospheric air passing the absolute filter (3). To eliminate aerosol evaporation on its way to the analyzer, the air was humidified on flow through a fibrous humidifier (2) mounted in the inlet of the chamber. A Sidestream nebulizer (6) was supplied by a mechanical compressor (4; Medic-Aid Ltd., UK) through a controlling attachment PNEUMONEB® (5; artmed Ltd., Poland). It was maintained by computer software PNEUMO RS (artmed Ltd., Poland) from a personal computer (7). Sampling of the aerosol by the particle counter was done automatically through an isokinetic glass probe (8). Before the sample reached the counting means of the A3 device, it was additionally diluted with the air passing through the humidifier (11) and the absolute filter (9).

Parameters of the diluting air stream were periodically measured with a digital thermometer and a Tri Sense hygrometer (Cole Palmer, USA). The experiments were carried out at room temperature (25 ± 1 °C) and at the relative humidity of the diluting air ranging from 75 to 85%. The nebulizer efficiency in different programs controlled by the attachment was estimated on the basis of the liquid mass deficit at time intervals during the process of aerosol generation. The size distribution of the generated droplets was measured by the aerosol counter in the range 0.3–10 μm. Each measurement was preceded by 120 s of idle time needed for stabilization of the conditions in the mixing chamber and the probe line. Each type of measurement was independently repeated three to five times.

3. RESULTS

In the first stage of the measurements, 10 Sidestream nebulizers were tested to evaluate their efficiency (i.e., rate of aerosol production) in continuous generation and change in efficiency during nebulization. The aerosolized liquid was a physiological salt solution. Test results are shown in Table 1 and Figure 2. Some differences among 10 units of the same type of nebulizer can be observed, probably as a result of small differences in the construction of important elements of the nebulizer (e.g., the nozzle or the impact plane), which may originate in the manufacturing process. Apart from nebulizers marked A and D, all tested devices had generation rates between 0.12 and 0.15 g/min.

TABLE 1. Generation Rate of Sidestream Nebulizers Supplied with a Continuous Air Stream

Nebulizer's Working Symbol	Generation Rate (g/min)	Average Deviation
A	0.174	0.009
B	0.115	0.009
C	0.131	0.005
D	0.096	0.003
E	0.121	0.010
F	0.144	0.006
G	0.131	0.015
H	0.148	0.022
I	0.124	0.008
J	0.141	0.017
average	0.132	0.010

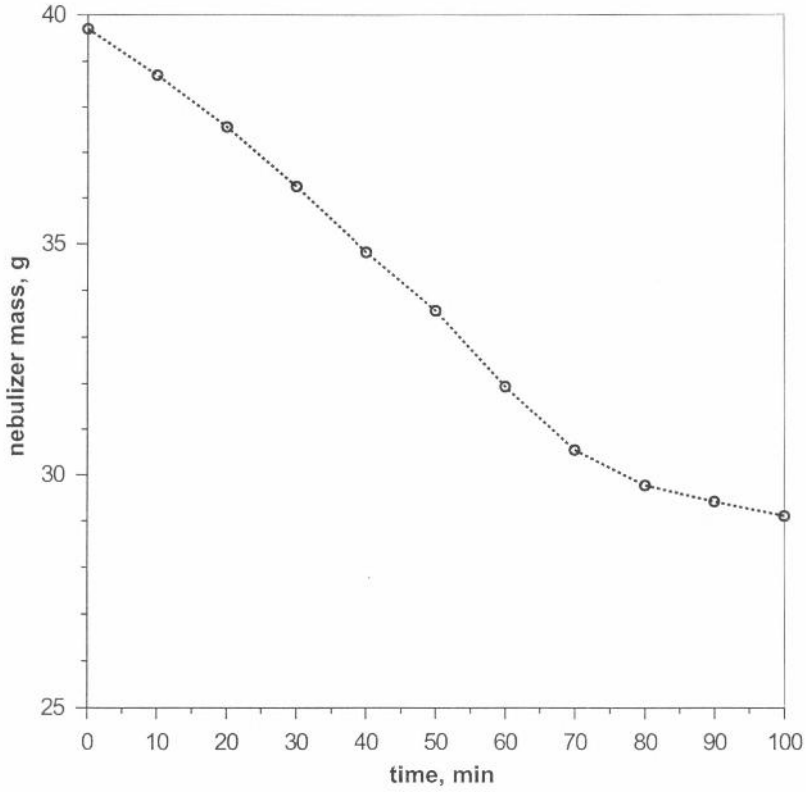

Figure 2. Typical mass change curve of a Sidestream nebulizer during continuous generation.

Figure 2 shows that mass loss during generation is constant (the nebulizer's efficiency remains unchanged) for about 1 hr of nebulization. Then, the generation rate decreases, which is a consequence of the fact that the nebulizer runs out of liquid (only single dripping droplets reach the nozzle).

During the second stage of testing, the influence of the nebulizer's pulse supply on the nebulization rate and the droplet size distribution were measured. One type of pulsation was used according to the following formula:

5 repetitions: 100 ms (O) / 300 ms (C), and a long break of 2000 ms (C),

where O stands for an open valve (air flow) and C stands for a closed valve (i.e., no air flow). In other words, 1 cycle of impulses took 4 s, during which the valve was opened 5 times for 100 ms at 300 ms

intervals. Pulse cycles were repeated 200 times, and then the generation efficiency was measured. The results are shown in Table 2 and in Figure 3.

TABLE 2. Generation of Continuous and Pulse Generation for Selected Substances

Pharmaceutical	Generation Rate (Continuous Generation, g/min)	Average Deviation	Generation Rate (Pulse Generation, g/min)	Average Deviation	Dose per 100 ms Impulse (g)
Salbutamol aq. 2.5 mg	0.284	0.004	0.0086	0.0003	0.00012
Sodium cromoglicate aq.	0.202	0.004	0.0113	0.0008	0.00015
Dornase alfa aq.	0.222	0.003	0.0098	0.0004	0.00013
NaCl aq. 0.9%	0.131	0.007	0.0068	0.0003	0.00009

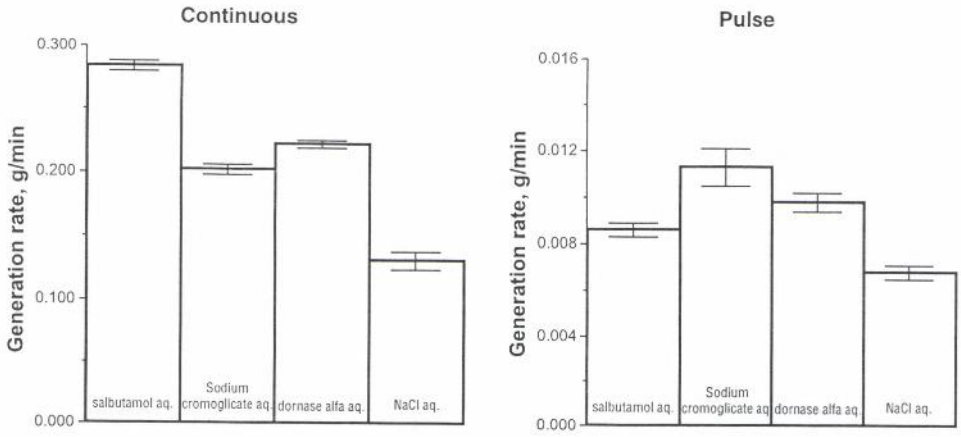

Figure 3. Comparison of nebulization efficiency (during 1 working min) with different substances at continuous and pulse supply.

Test results of droplet mass distribution obtained in both methods of aerosol generation are shown in Figures 4–7.

The last part of the project focused on a detailed test of the influence of the pulse supply method on droplet size distribution of a physiological salt solution aerosol. Supplying nebulizers with air was based upon the following formula:

$$n \text{ repetitions } \tau_o \text{ ms} / \tau_c \text{ ms, and a final interval } \tau_f \text{ ms,}$$

where τ_o stands for time of valve opening (air flow to nebulizer), and τ_c and τ_f denote times when the valve was closed. A complete series of

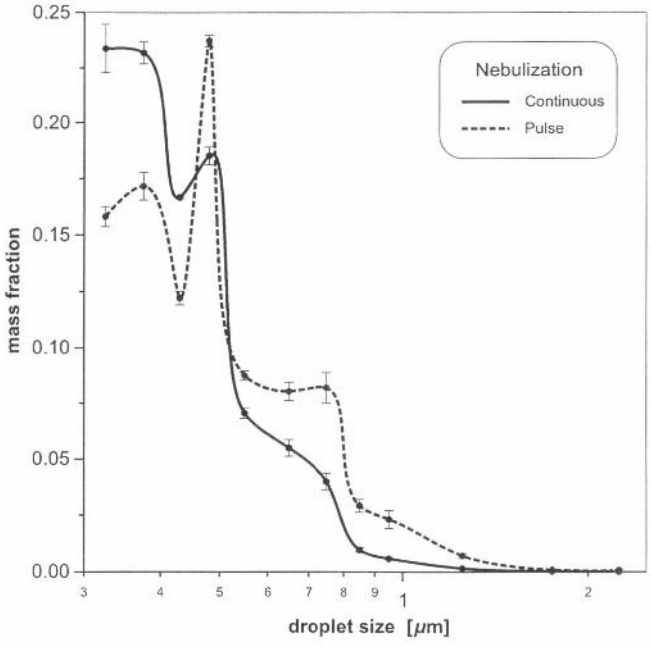

Figure 4. Comparison of droplet size distribution at continuous and pulse supply for physiological salt (NaCl aq. 0.9%).

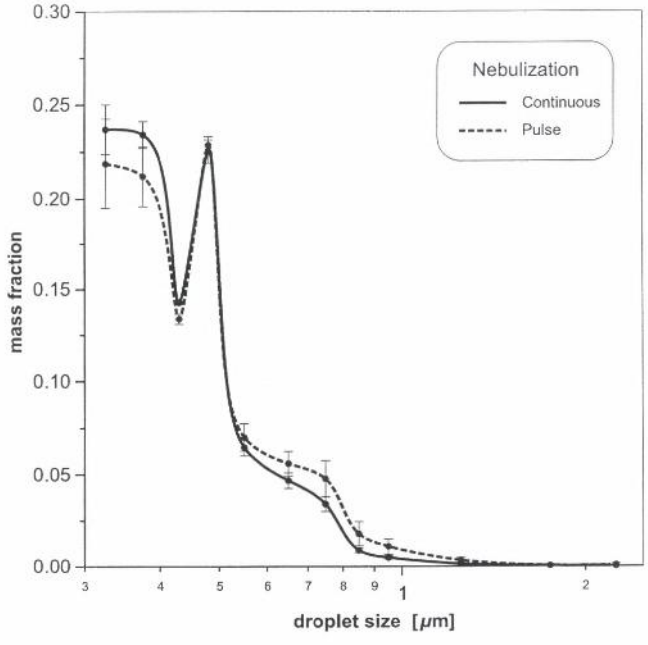

Figure 5. Comparison of droplet size distribution at continuous and pulse supply for salbutamol aq.

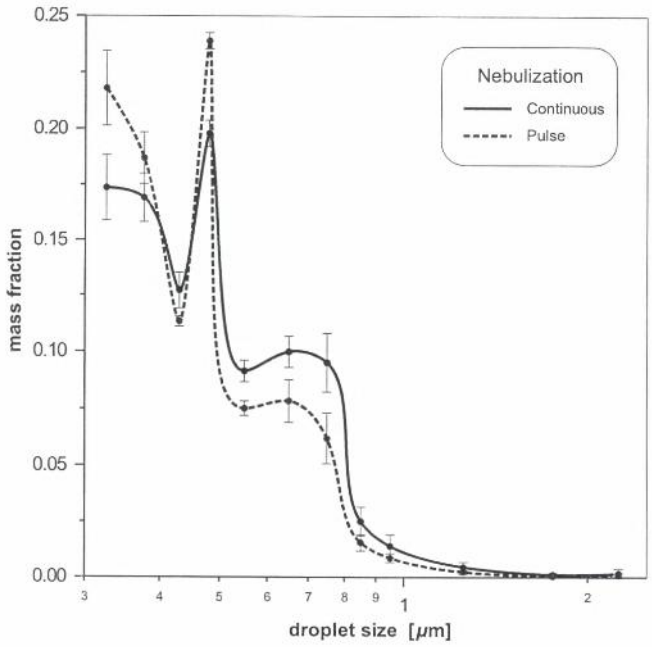

Figure 6. Comparison of droplet size distribution at continuous and pulse supply for sodium cromoglicate aq.

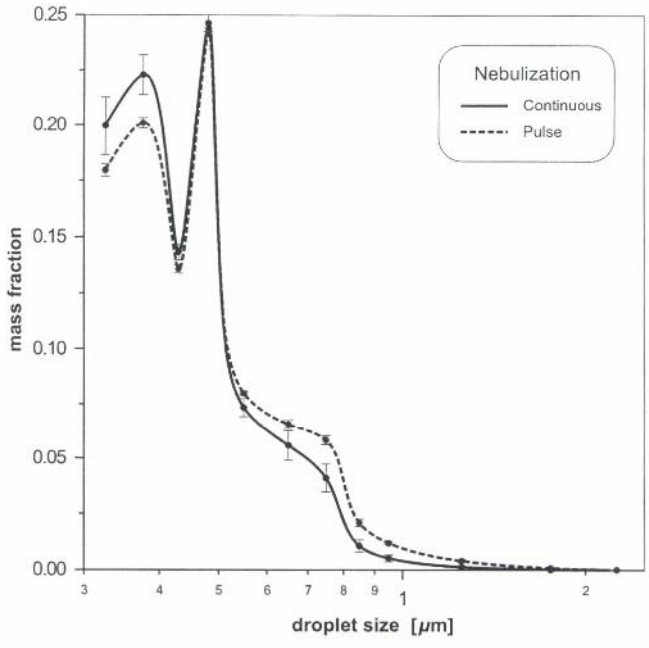

Figure 7. Comparison of droplet size distribution at continuous and pulse supply for dornase alfa aq.

impulses was emitted in time τ_{total} ms and was repeated 200 times. The tested variants of pulse generation are presented in Table 3.

TABLE 3. Variants of Aerosol (NaCl aq. 0.9%) Pulse Generation

Variant	n (ms)	τ_0 (ms)	τ_c (ms)	τ_f (ms)	τ_{total} (ms)
1	1	800	100	3200	4100
2	2	500	500	2500	4500
3	3	300	300	2500	4300
4	4	250	250	2250	4250
5	5	200	200	2200	4200
6	5	150	200	2450	4200
7	5	100	200	2700	4200
8	5	50	200	2950	4200

Notes. n—number of repetitions, τ_0—time of valve opening (air flow to nebulizer), τ_c, τ_f—times when valve was closed, τ_{total}—time in which a complete series of impulses was emitted.

The influence of pulse generation on droplet size distribution is presented in Table 4 and, collectively, in Figure 8.

TABLE 4. Mass Distribution of Physiological Salt Aerosol in Different Variants of Pulse Generation

Diameter	Variant							
(μm)	1	2	3	4	5	6	7	8
0.325	0.2511	0.2092	0.2151	0.2157	0.2348	0.2313	0.2303	0.3156
0.375	0.2539	0.2238	0.2280	0.2298	0.2457	0.2427	0.2414	0.2838
0.425	0.1821	0.1771	0.1803	0.1808	0.1834	0.1855	0.1793	0.1758
0.475	0.1865	0.2087	0.2049	0.2062	0.1963	0.1939	0.1993	0.1546
0.550	0.0611	0.0801	0.0791	0.0770	0.0699	0.0710	0.0707	0.0431
0.650	0.0406	0.0574	0.0517	0.0509	0.0421	0.0436	0.0461	0.0186
0.750	0.0207	0.0352	0.0328	0.0337	0.0225	0.0262	0.0261	0.0069
0.850	0.0022	0.0057	0.0058	0.0043	0.0038	0.0043	0.0048	0.0006
0.950	0.0009	0.0025	0.0019	0.0014	0.0012	0.0012	0.0015	0.0006
1.250	0.0002	0.0003	0.0004	0.0003	0.0003	0.0004	0.0001	0.0000
1.750	0.0001	0.0000	0.0000	0.0001	0.0001	0.0000	0.0004	0.0002
2.250	0.0002	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0003
2.750	0.0002	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000

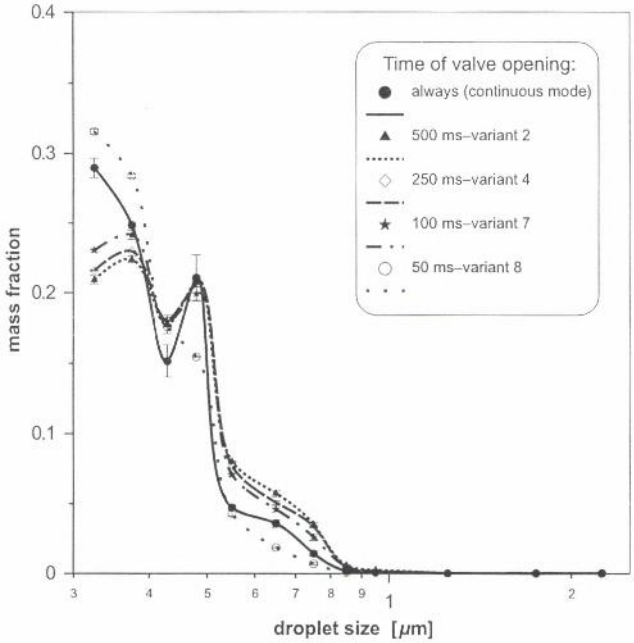

Figure 8. Comparison of mass distribution of a physiological salt solution (NaCl aq.) aerosol generated at different types of a nebulizer's pulse supply with compressed air with the help of PNEUMONEB®.

4. DISCUSSION OF RESULTS

The generation rate for substances (pharmaceuticals) generated in continuous nebulization changes from about 0.3 g/min (salbutamol) to about 0.15 g/min (NaCl solution). In this generation method, nebulization efficiency depends mainly on the nozzle construction and pressure. For the same type of generators, differences appear as a result of different liquid viscosity and especially surface tension of a liquid from which the aerosol is generated. A smaller efficiency difference is observed in pulse aerosol generation because the time of droplet formation in relation to the time of opening the valve generating the pressure impulse comes into play. Due to this effect, the generation rate is stabilized by the pulse method.

The dimension distribution in generated particles for both continuous and impulse methods is similar. For a valve opening exceeding 100 ms, the impulse method provides an additional advantage. In the pulse method, at opening times exceeding 100 ms, there is an increase in the mass percentage (15% on average) of particles of 0.5 μm and more. This

creates a higher mass fraction of the pharmaceutical delivered to pulmonary alveoli.

On the basis of a formerly prepared model of aerosol particle deposition and inhaled aerosol dispersion, it turns out that the pulse method of dosing a pharmaceutical may appear more efficient than the continuous method when using an appropriate strategy. Assuming that the valve opening time (an impulse duration) equals 100 ms, generation efficiency of salbutamol, for example, is 0.12 mg per impulse. Furthermore, if we assume that the time of one single inspiration is 2 s and this phase is divided into a 10-impulse sequence at 100 ms intervals during which a patient inhales clean air, then 1.2 mg of the pharmaceutical per inspiration will be delivered to lungs. Considering the amount of the pharmaceutical delivered per one inspiration, it is possible to program the number of inspirations in order to deliver the therapy required dose. The suggested method may considerably improve pharmaceutical deposition in lungs, not to mention better supervision of the pharmaceutical.

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