ABSTRACT

Nebulization, as a method of dispersing liquid into small droplets creating a mist, is one of the important processes used in aerosol therapy, i.e. inhalation administration of drugs into the lungs. The medicine used in this process are aqueous solutions or suspensions containing - apart from the pharmacologically active substance itself - also substances stabilizing the formulation (e.g. synthetic surfactants). The effectiveness of inhalation treatment depends on the deposition area of mist droplets in the respiratory system, which is influenced primarily by the size distribution of drops emitted via nebulizers, which depends on the mechanism of atomization and the nebulizer design, as well as on the physicochemical properties of the sprayed medicinal formulation. Despite many studies, there is still no in-depth analysis of the atomization processes in nebulizers of various designs (jet, mesh), including the relationship between the composition of drugs and the properties of the resulting aerosol, which results in the treatment effectiveness. Chemical engineering with its research tools of analysis of dispersed systems and description of phenomena occurring near interfacial surfaces (flow, mass transport) can significantly contribute to expanding knowledge about drug nebulization, which should result in an increase in the effectiveness of aerosol therapy.

The aim of the work is to characterize the atomization process of selected liquids in typical medical nebulizers, including, in particular, the analysis of the spraying process depending on the liquid composition, as well as the calculation of the expected deposition of drops in the respiratory system. These studies were extended to include measurements of the interaction of the tested (i.e. inhaled) substances with a model pulmonary surfactant, allowing for the determination of the safety of their use in relation to the surface of the alveoli. The research showed that by influencing the properties of atomized liquids (in particular: thanks to the use of biocompatible substances of natural origin), it is possible to obtain an inhalation aerosol characterized by increased deposition in specific areas of the respiratory system, which should translate into an increase in the therapeutic effect and a simultaneous reduction in side effects of aerosol therapy.

As basic properties of the liquid that may affect the size of the droplets, and thus the processes of aerosol transport in the respiratory system and deposition, were indicated: rheological properties, surface tension and conductivity, and their importance was analyzed in detail in this work. The research included selected inhalation drugs, synthetic additives and newly proposed natural compounds that could potentially excipients in inhalation drugs.

Studies assessing the impact of the deposited aerosol on the lung surfactant focused on analyzing changes in the viscoelastic properties of the model liquid-gas interface. It was paid attention to the relationship between these properties and the mass exchange processes in the lungs, including gas exchange and the so-called hydrodynamic clearance of the lungs, which are related to the Marangoni effects occurring on the surface of the alveoli. Measurements of the effects of selected inhalation drugs and excipients were carried out in dynamic conditions (simulation of the surface condition in the lungs) using two models of lung surfactant: lipid (single- and two-component) and multi-component lipid-protein. In the case of the lipid model, measurements were performed using a Langmuir-Wilhelmy balance equipped with Brewster's angle microscopy (BAM). Measurements using a multi-component model carried out using the pulsating drop method made it possible to determine the dilatational rheological properties of the liquid-gas interface and to determine the surface tension hysteresis during oscillations. Thanks to the introduction of appropriate quantitative parameters (criteria) describing the tested dynamic system, it was possible to determine the impact of excipients added to drugs on the course of the hysteresis loop, and thus on the safety of their use in inhalations.

To sum up, in this work the following assumptions were verified:

1) The characteristics of the aerosol produced in the nebulizers are influenced by the principle of operation and device design, the physicochemical properties of the sprayed liquid and the conditions of the process. Thus, by appropriately selecting the atomization parameters carried out in nebulizers, it is possible to change the quality of the aerosol and thus influence the efficiency of deposition of inhaled aerosol droplets in individual areas of the respiratory system.

2) In order to improve aerosol and deposition parameters, biocompatible compounds of natural origin can be used and their safety can be assessed experimentally in *in vitro* conditions by measuring their physicochemical interactions with the components of fluids present in the respiratory system.

One of the most important results is the finding of a clear dependence of the size distribution of aerosol droplets released from nebulizers on the type of atomizing device (operating principle and individual design features) and the physicochemical properties of the sprayed liquid. The method of implementing the liquid atomization process is the dominant element in shaping the properties of the aerosol cloud, including the droplet size range. However, in a specific nebulizer, the physicochemical parameters of the liquid (mainly

viscosity and surface tension) have a visible impact on the mass efficiency of aerosol emission, the size of droplets, their polydispersity and the fraction of fine droplets (FPF).

Based on studies on the interaction between a model lung surfactant and the components of the inhaled aerosol, it was found that the proposed additives of natural origin do not negatively affect the biophysicochemical function of the surfactant. In order to analyze the results more efficiently, it was shown how the criteria for assessing the shape of surface tension hysteresis can be linked to parameters describing the viscoelastic features of the surface area modifying the area of the alveoli.

In the course of this work, which is at the border of scientific disciplines, knowledge and research tools from the field of chemical engineering were used, confirming the possibility of its application to solve practically important issues in the field of medicine and pharmacy. The proposed measurement methods and method of analysis of measurement data, allowing for testing at the physicochemical level of the impact of active substances and additives of inhalation drugs on the process of aerosol formation and its impact on the respiratory system, can be used to further carry out measurements on other substances with similar potential.

Keywords: liquid atomization; medicinal aerosol; nebulizer; pulmonary surfactant; interfacial surface; inhalation drugs