

Comparison of methods for evaluation of aerosol deposition in the model of human lungs

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Abstract. It seems to be very convenient to receive a medicine by inhalation instead of injection. Unfortunately transport of particles and targeted delivery of a drug in human respiratory airways is very complicated task. Therefore we carried out experiments and tested different methods for evaluation of particle deposition in a model of human lungs. The model included respiratory airways from oral cavity to 7th generation of branching. Particles were dispersed by TSI Small-scale Powder Disperser 3433 and delivered to the model. The model was disassembled into segments after the deposition of the particles and local deposition was measured. Two methods were used to analyse the samples, fluorescence spectroscopy and optical microscopy. The first method was based on measuring the intensity of luminescence, which represented the particle deposition. The second method used the optical microscope with phase-contrast objective. A dispersion of isopropanol and particles was filtrated using a vacuum filtration unit, a filter was placed on glass slide and made transparent. The particles on the filter were counted manually and the deposition was calculated afterwards. The results of the methods were compared and both methods proved to be useful.

1 Introduction

Inhaled aerosols are commonly used for treatment of lung diseases, such as asthma or chronic obstructive pulmonary disease. But there is also a possibility to use them for treatment of systemic diseases. The rich blood supply and large absorptive surface (over 100 m²) in the alveolar region are the main advantages of this approach. Depending on the size of the particles they can either reach the alveolar region of the lung or they can deposit on their way there. There are several deposition mechanisms: the most important are impaction, diffusion and sedimentation. Large particles deposit by impaction, because they are unable to follow the streamlines of the airflow. This phenomenon mainly occurs in the first 10 generations, because there are high velocities and turbulent airflows. Sedimentation and diffusion take place in smaller airways and alveolar regions, where the velocities are very low. Particles with diameter from 10 to 5 μm deposit mainly by impaction, from 5 to 0.5 μm by sedimentation and particles with smaller diameter than 0.5 μm deposit by diffusion.[1]

Few studies were devoted to deposition of porous particles. Porous particles with low mass density (>0.4 g/cm³) and large mean diameter (< 5 μm) have the ability to avoid lung clearance mechanisms [2]. These particles are able to penetrate to lower airways and

therefore escape the mucociliary escalator. In the lower airways they can withstand fast phagocytosis, which is done by macrophages. Thus they are ideal carriers for therapeutic drugs. They can carry the drug to the alveolar regions and release it for a very long time, i.e. extend the time of drug effect from hours to days [3].

We describe different methods of evaluation of particle deposition in this study. Deposition characteristics were calculated and compared to results of other authors. These methods will be important in next studies of aerosol transport and drug delivery.

2 Materials and Methods

2.1 Experimental setup

Two types of particles were chosen for this study and two different methods were carried out to evaluate the deposition of these particles in a model of human lungs. The model consists of human airways from oral cavity to seventh generation of branching (Figure 1.). The model comprises 32 segments, thus investigation of local deposition can be performed. Silicon oil (Dow Downing 550) was applied on the inner walls of the model to reduce bouncing of the particles. More information about the model is published in [4].

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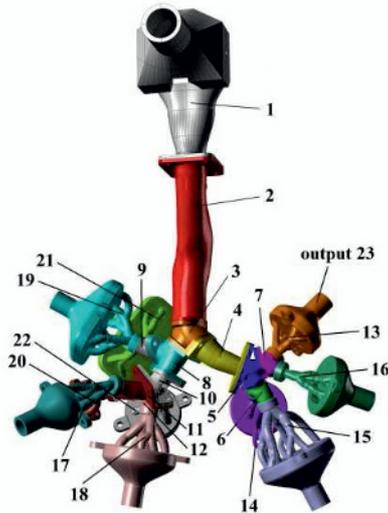


Fig. 1. Model of the human lungs

The particles were in a form of powder therefore Small scale powder disperser (SSPD), TSI 3433, was used as a generator. The SSPD is based on the principle of Venturi effect. With increasing air flow through the venturi aspirator the pressure is decreasing in the capillary tube, which sucks the rigid particles from the annular ring. Particles are deagglomerated in the venturi aspirator by shear forces. After the dispersion the particles go to the neutralizer, which creates the Boltzmann charge equilibrium, and then the particles continue to the model of the human lungs. Because the model does not include complete airways, some of the particles pass through and are collected on output filters (Millipore AAWP02500 Nitrocellulose membrane filters). The rest of the experimental setup (Figure 2.) consists of flow meters, which ascertain realistic distribution of the air flow, and a vacuum pump. The total flow rate through the model was 30 LPM and flow rate ratio between right and left lung was 70:30.

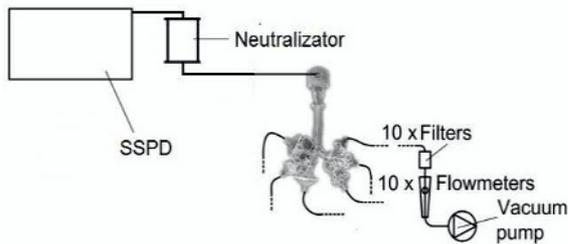


Fig. 2. Experimental setup

The SSPD was connected to an Aerodynamic particle sizer (APS), TSI 3321, before the experiment. APS measures aerodynamic diameter, which represents aerodynamic behaviour of the particles of different shapes.

2.2 Fluorometric method

This method is based on fluorescence technique. Amount of deposited aerosol can be determined from intensity of fluorescence of given sample. The main task was to find

proper particles with linear relationship between their concentration and intensity of fluorescence. Di(2-ethylhexyl) sebacate (DEHS) molecules were studied in previous experiments. The experiments indicated that fluorescence of DEHS itself can be detected. Thus DEHS was used in condensation monodisperse aerosol generator with sodium chloride nuclei and deposition in a model of human lungs was evaluated. It was found out that the fluorescence of DEHS can be measured, but it is not directly proportional to the amount of deposited aerosol [5]. Therefore fluorescence dye, fluorescein sodium salt, was tested. Several solutions with different concentration of fluorescein were prepared and their fluorescence intensity was measured. The results are depicted in Figure 3. A correlation between intensity of fluorescence and concentration of fluorescein in the sample was found and Pearson correlation coefficient was 0.967.

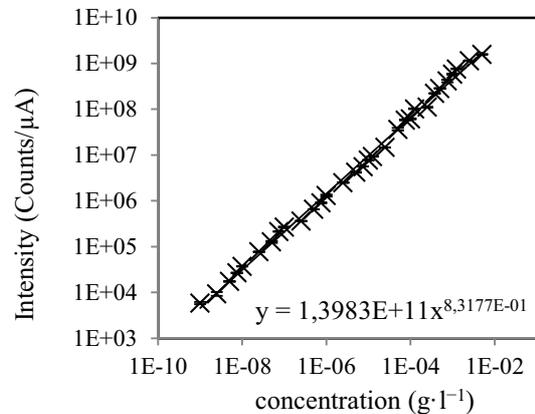


Fig. 3. Intensity of fluorescence and concentration of fluorescein

Fluorescein sodium particles were dispersed using SSPD and transported in to the model. Some of the particles deposited there and the rest of them passed through the model and deposited on output filters. The exposition of the model lasted 30 min and the model was disassembled afterwards. Each segment was sonicated in distilled water for 15 min, thus deposited fluorescein was dissolved in the water. The output filters were sonicated as well. Intensity of fluorescence of the resulted solutions was measured by fluorescent spectrometer Horiba Jobin Yvon and deposition parameters were calculated thereafter.

2.3 Optical method

In the next experiment semiporous nickel particles were used. These particles did not fluoresce, therefore fluorometric method was not possible to use. Optical method, which is usually used for analysis of fibers, was chosen. The exposition of the model to particles lasted 2 hours, but the output filters had to be replaced every 30 min, otherwise they would be overfilled and the optical analysis would be impossible.

After the deposition the model was disassembled and the lavage of the segments with isopropanol was performed. The resulted solution of isopropanol and

particles was filtrated using a vacuum filtration unit. The filters were dried in desiccator and made transparent using acetone vapours. The output filters were made transparent as well. After that microscope Nikon Eclipse E200 with phase-contrast objective was used to analyse the samples.

The microscope contained Walton-Beckett graticule, which ease counting of the particles. Because counting of the particles on the whole filter would be time consuming, only sixteen regions were randomly selected on every filter and deposited particles in these regions were counted. Total count of the particles on every filter was calculated proportionally to the surface of the filter and surface of the analysed regions. The particles are depicted in Figure 4. Deposition parameters were calculated from the total counts of the particles on filters.

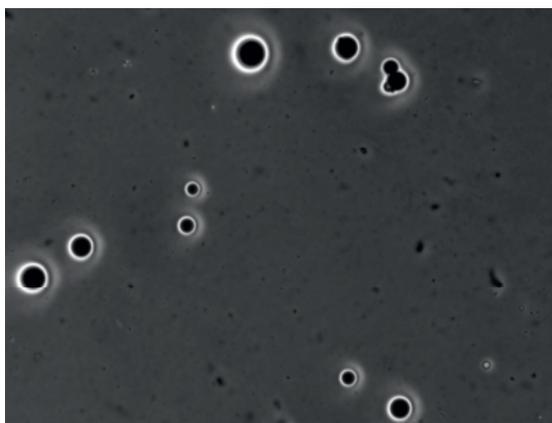


Fig. 4. Semiporous particles

3 Results and discussion

Particles were analysed by APS before the experiment. Count mean aerodynamic diameter is displayed in Table 1.

Table 1. Particle properties

Type	CMAD (μm)	Density (g cm^{-3})
Fluorescein sodium salt	1.29	1.6
M-18-Ni	10	0,69

Deposition parameters, in particular deposition fraction and deposition efficiency, were calculated after the analysis of the samples. Deposition fraction is the ratio of aerosol amount deposited in current segment and aerosol amount entering the model. Deposition efficiency is ratio of aerosol amount deposited in given segment and aerosol amount entering that segment. Hence deposition fraction represents proportional distribution of deposited aerosol, whereas deposition efficiency is better for intersegment comparison, because it includes the fact that different amount of aerosol is entering different segments.

Distribution of deposition fraction corresponds to the distribution of flow rates, which indicates that deposition of the particles is proportional to the flow rate. Total deposition fraction of the nickel particles in the model is 38 %, while only approximately 7% of fluorescent particles deposited in the model and the rest of them deposited on output filters. The fact, that deposition of

fluorescein particles was lower than that of the nickel particles, can be explained by lower aerodynamic diameter. Aerodynamic diameter of a particle can be thought of as the diameter of a water droplet having the same aerodynamic properties as the particle. For that reason the particles with higher aerodynamic diameter are more likely to deposit in bifurcating human airways. Deposition efficiency is displayed in Figure 5 with segment numberings depicted in Figure 1. Deposition efficiency is increasing with increasing segment number. This is probably caused by decreasing diameter of human airways. In addition, segments 13 to 22 encompass several bifurcations, which are common hot spots of deposition. Larger surface area of these segments can also contribute to higher deposition efficiency.

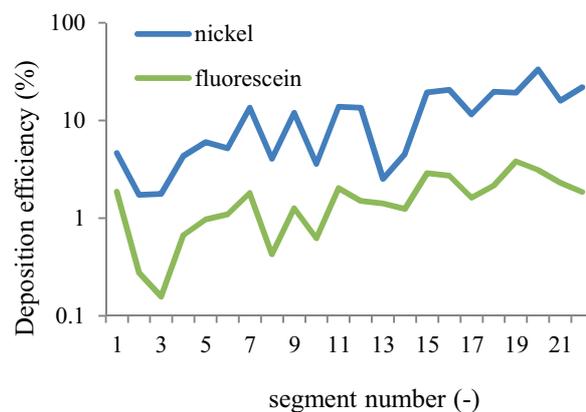


Fig. 5. Deposition efficiency

Because the segments have different surface area, deposition density was calculated. Deposition density is deposition fraction divided by surface of the segments. The results of deposition density are displayed in Figure 6. The highest deposition density was measured in segment 12. This fact can be explained by flow rate differences in individual branches. The segment 12 is situated in right lung and the particle route is very straight. Segments 13 and 14 are positioned in left lung and there is very low flow rate through them.

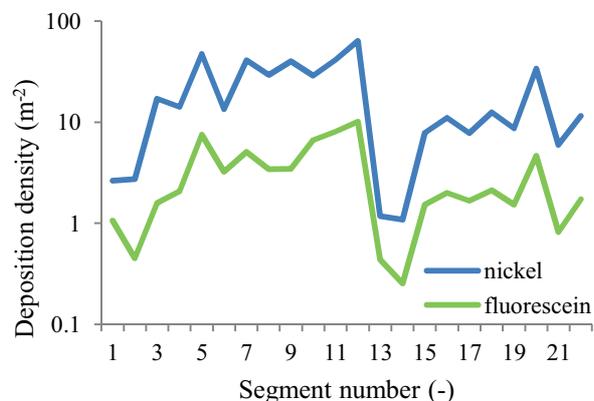


Fig. 6. Deposition density

Stokes number was calculated from the particle properties. Stokes number is dimensionless number, which represents behavior of the particle suspended in the fluid flow and is defined as a ratio of the stopping distance of a particle to a characteristic dimension of the

obstacle. When $Stk \ll 1$, particles follow the gas streamlines perfectly; when $Stk \gg 1$, particles continue moving in a straight line when a gas turns. Stokes number was counted using equation 1.[6]

$$Stk = \frac{S}{d_c} = \frac{\rho_0 \cdot d_a^2 \cdot U}{18 \cdot d_0 \cdot \eta} \quad (1)$$

Where ρ_0 is unit density, d_a is aerodynamic diameter, U is velocity, d_0 is characteristic dimension (airway diameter) and η represents dynamic viscosity of air. Both velocity and airway diameter were measured at the inlet of every segment.

Relationship between Stokes number and deposition efficiency is displayed in Figure 7. Data from previous studies of deposition in realistic geometry are presented for comparison. Positive relationship between deposition efficiency and Stokes number suggests that deposition by impaction is the dominant deposition mechanism in this case. Zhou and Cheng carried out experiments with deposition in realistic model, which included respiratory airways up to 4th generation of branching [7]. Deposition efficiency from our study is lower than that from Zhou and Cheng. The differences can be caused by dissimilarities in the model geometries, although both models have realistic geometry. In addition every experiment was carried out only once in this study, thus more experiments are needed to determine the standard deviation and precision of the methods.

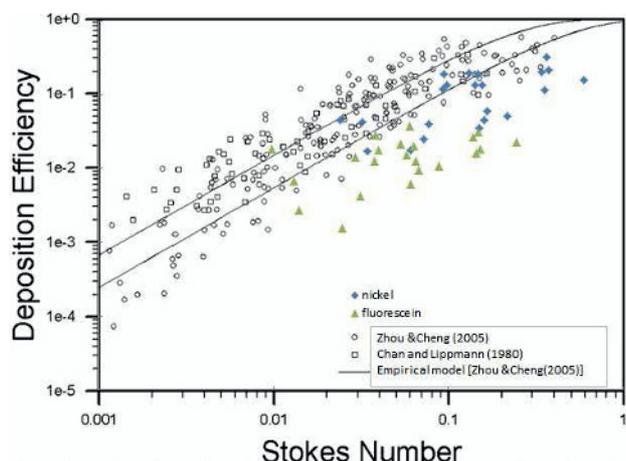


Fig. 7. Relationship between deposition efficiency and Stokes number

4 Summary

Different methods were applied on evaluation of deposition in the model of human lungs. Both methods proved to be useable, but choice of the right method depends on the used particles. The linear relationship between intensity of fluorescence and concentration is very important in fluorometric method otherwise calculated deposition can be biased. Adequate amount of particles on filters is necessary for optical analysis. If the filters are overfilled or the particles are too small, the optical counting is impossible. In addition if the quality

of the filters is high, the automatic analysis can be applied using camera attached to the microscope.

Deposition characteristics were calculated after the experiments. Deposition efficiency and deposition fraction were increasing with decreasing diameter of respiratory airways. Moreover segments with smaller airways have larger surface area, which can cause increase in deposition efficiency. Deposition density was introduced because of this fact. The highest deposition density is in segments with highest flow rates. Positive relationship between Stokes number and deposition efficiency has been found, which indicates that impaction mechanisms causes particles to deposit on the walls. In comparison with other studies, our deposition efficiency is lower. This can be explained by differences in model geometries and precision of methods of this study. More data is needed to ascertain repeatability.

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