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EXPERIMENTAL STUDY OF AEROSOL DEPOSITION IN A REALISTIC LUNG MODEL

EXPERIMENTÁLNÍ STUDIUM DEPOZICE AEROSOLU V REALISTICKÉM MODELU PLIC

Abstract

The inhalation route for administration of medicaments is becoming more and more popular in recent years. The reason is non-invasiveness of the method and instantaneous absorption of drugs to the blood circulation. It is necessary to deliver exact amount of drug to the specific segment because of occurrence of diverse diseases in different segments of lungs. The aim of our work is to contribute to better understanding of transport and deposition of aerosolized drugs in lungs and hence to more effective treatment of respiratory diseases due to the targeted drug delivery. We provided measurements of aerosol deposition in segmented realistic model of lungs without a mouth cavity. Monodisperse particles marked with fluorescein were supplied to the model. The model was then disassembled to segments and each segment was rinsed with isopropanol, whereby fluorescent samples were created. Each sample was analysed by fluorometer and an amount of aerosol deposited in the segment was calculated. Experiences obtained by this study were used for creation of a new model with the mouth cavity. This model will be used for future studies with porous and fiber aerosols.

Abstrakt

V současné době získává podávání léků inhalační formou stále větší popularitu. Důvod spočívá v neinvazivnosti metody a v okamžité absorpci léku do krevního oběhu. Je ovšem nutné dopravit přesné množství léčiva do požadované oblasti plic, jednak z toho důvodu, že různá onemocnění si vyžadují dodávku léku do různých částí plic, a dále z důvodu snížení zbytečného zatížení dalších oblastí plic vedlejšími účinky léku. Cílem naší práce je proto přispět k lepšímu porozumění mechanismům transportu a depozice aerosolizovaného léčiva v plicích a tudíž k efektivnější léčbě nemocí dýchacího ústrojí. Provedli jsme měření depozice aerosolu v segmentovém modelu plic bez ústní dutiny. Použité monodisperzní částice byly značkovány fluoresceinem. Model byl po vystavení aerosolu rozebrán na jednotlivé segmenty, z nichž každý byl vypláchnut isopropanolem v ultrazvukové vaně, čímž vznikly fluorescenční vzorky. Každý vzorek byl analyzován pomocí fluorometru a bylo vypočteno množství usazeného aerosolu v každém

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segmentu. Zkušenosti získané během měření byly pak využity při tvorbě nového modelu, který již obsahuje ústní dutinu. Tento model bude použit pro měření porézních a vláknitých aerosolů

1 INTRODUCTION

The term aerosol denotes a system of solid or liquid particles that are dispersed in a gaseous medium in which they are able to float over a sufficiently long period of time compared to the time of observation, and have a large surface to volume ratio [5]. The size of aerosol particles is in the range of 1 nm to 100 μm.

There are three main methods for investigation of transport and deposition of aerosol in lungs. The first method is measurement in vivo - that is, conducting experiments on human volunteers or on animals (mostly rats, hamsters, guinea pigs and rabbits). This is the only virtually realistic method. However, its disadvantages are: strict legislation, expensiveness, inability or difficulty of optical inspection, and (when human volunteers used) the need to obtain their informed consent. The results also show considerable variations due to the inter-and intra-subject variability [2]

The second method is in vitro measurement – i.e. outside of the human body, on physical models. Advantages over in vivo methods are: cost, easier handling, the possibility to visualize the flow field and better repeatability. It is possible to repeat the experiment on exactly the same geometry and to change any input parameter. Such models, however, contain some simplifications compared to real conditions [2].

The third option is the approach in silico - numerical modelling. These methods are being developed since 1990s. There is no need to make any difficult measurement, it is possible to arbitrarily set the boundary conditions and it is easy to obtain data on aerosol transport and deposition. So far, however, is not in current computer technology capabilities to model a realistic geometry of the whole lung, so the models often contain a considerable simplifications compared to the real situation and even to in vitro measurements. The results are strongly dependent on initial setup and boundary conditions, on the geometry of the model and on the numerical method used [2].

2 EXPERIMENTAL SETUP

2.1 Model without the mouth cavity

With regard to the available equipment of the Department of Thermodynamics and Environmental Engineering, and considering the current state of the art, we preferred the choice of in vitro method. This paper will focus mainly on in vitro measurements of aerosol deposition. Based on the literature review, it was decided to study the deposition in a realistic model. Its geometry was created by combining a geometry published by Schmidt et al. [3], which contains airways from the trachea to 17th generation of branching, with geometry of upper airways obtained by the CT at the St. Anna University Hospital in Brno. Obtaining full geometry using CT failed due to poor quality of images caused by movements generated by heartbeat. Only upper airways were applicable. Schmidt's model was obtained in the form of data containing the coordinates of nodes, links between them and branch diameters. The data were processed by "marching cube" algorithm into a vector model with polygonal net and the resulting model geometry was smoothed in the Rhinoceros (McNeel) software and stored in a stereolitographic format (STL). The data processing was made by doc. Přemysl Kršek at Institute of Computer Graphics and Multimedia FIT BUT. Only the part of the model from larynx to the 7th generation of branching was used for physical model fabrication. However, this geometry does not contain mouth cavity. According to findings of Choi et al. [1] who made Large Eddy Simulation (LES) of airflow variability in different geometries, it is necessary to incorporate at least the glottis to the model, if the results are to be reliable. The reason why at least the glottis should be incorporated is the requirement of correct development of the so called laryngeal jet which essentially affects the deposition. Ideally there should be the mouth cavity to truly simulate the airflow. In the first phase of our work only the glottis was incorporated and we performed deposition tests on the model without the mouth cavity (see fig. 1). In the second phase we acquired the data of the mouth

cavity and created a new realistic model which will be used for more accurate deposition measurements (see fig. 4).

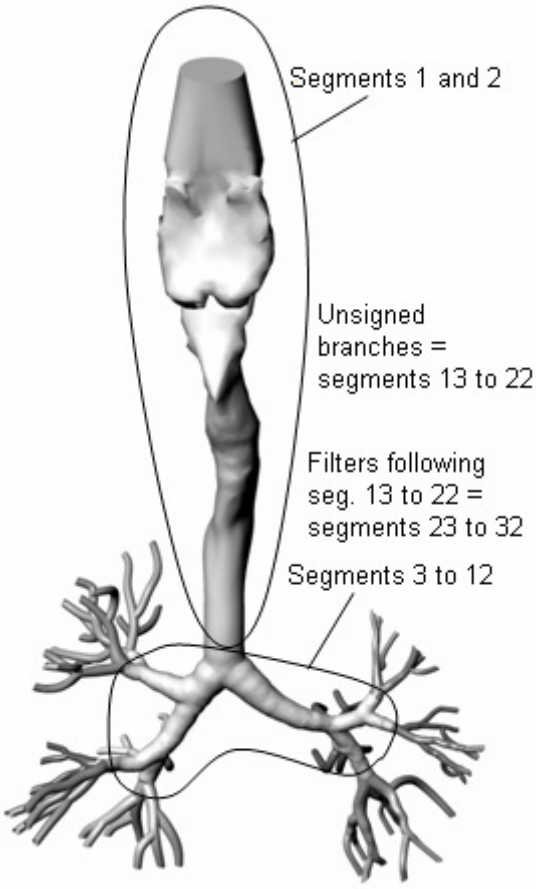

Fig. 1 The airway geometry of a model without a mouth cavity

The deposition efficiency (i.e. the fraction of particles entering the airway segment that have deposited in this segment) and the deposition fraction (i.e. the fraction of inhaled particles that have deposited in a respiratory region) had to be analyzed. To satisfy this demand it was necessary to divide the model to segments in which the quantity of deposited aerosol had to be evaluated. It was preferable to directly fabricate segments of the model by a suitable type of rapid prototyping method for deposition measurements. Two different rapid prototyping methods were used and hence two different approaches were employed. First the envelope over the airway geometry from larynx to 4th generation of branching was created with a thickness of 1-5 mm, then the geometry was divided to segments and each segment was provided by flanges to assemble the segments by screws. This part of the model was fabricated by stereolithography method using the Viper machine from the 3D Systems Company. Thickness of one layer of the material 11 122 XC Watershed was 0.1 mm, what is the default setting. The machine allows printing of layers with thickness up to 0.02 mm. The segments from 4th to 7th generation were made up of two parts. The upper part contains the airway branching and the bottom part provides the down lead of airflow from the segment to one output. The segments have been produced on the Eden 250 machine (Objet Geometries Company) from FullCure material by Polyjet technology. The complete model of the lungs from larynx to the 7th generation of branching was created by joining of all segments together.

2.2 Experimental stand

The measurement of aerosol deposition was provided by fluorometry based method. Solid fluorescent aerosol made from fluorescein sodium salt was generated with a vibrating orifice aerosol generator (VOAG) TSI 3450. Particle size, monodisperzity and concentration of aerosol were measured by Aerodynamic Particle Sizer (APS) TSI 3321. Aerosol was then led to the model. Airflow through the branches was measured by rotameters. Stationary flow was generated by the vacuum pump Gast 72R645-V114-D303X. When sufficient quantity of aerosol deposited, the model was disassembled into segments and each of them was washed in an ultrasonic bath with exact amount of isopropylalcohol. So the fluorescent samples, whose concentration is proportional to the intensity of fluorescence, were created. The measurement of fluorescence intensity was provided by Turner Quantech ™ Digital Filter Fluorometer FM 109 535, Barnstead International.

2.3 Experiments with solid particles

Measurement of deposition was performed for the stationary airflow of 15 and 60 lpm for three particle sizes. Segments were numbered and the quantity of aerosol in each of them was evaluated, also deposition fraction and deposition efficiency was calculated. Deposition fraction chart (i.e. ratio of the quantity deposited in the aerosol segment to the total amount of matter brought into the model) is shown in fig. 2.

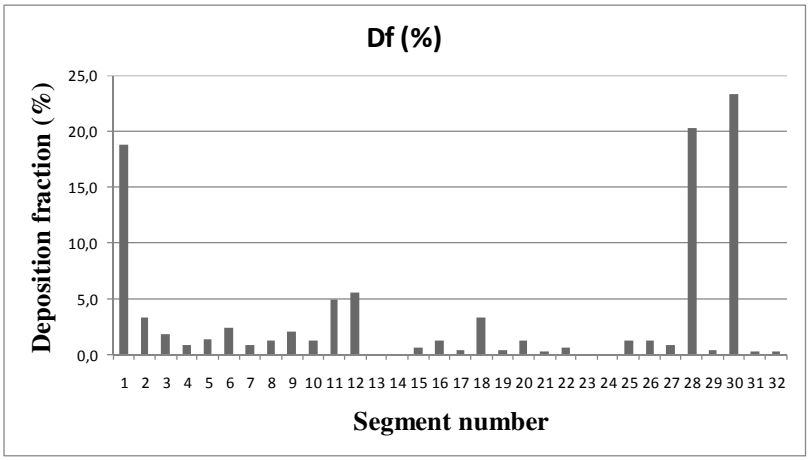

Fig. 2 Deposition fraction for 60 lpm and particles 6 µm

Measurement showed that the fluorometric method is suitable for lung deposition investigation. It is essential to precisely calibrate the fluorometer and to ensure a perfect tightness of the model. Generally, it is proved that the segments with higher airflow embody higher deposition. It also depends on the geometry of the segment. To determine the dependence on the Stokes number it is necessary to carry out another series of experiments.

However, some problems appeared while using this method. The first was with securing of tightness of the model. This was solved with a Teflon tape and a heat shrinkable insulation and also some recommendation for upgrade of the model geometry in future were made regarding this problem. The second trouble was with possible rebouncing of solid fluorescein particles on solid surface of the model. This rebounce is not present in real human lung, because a wet surface of airways does not allow particles to bounce. To avoid this problem it is possible to apply silicon oil on the surface of the model or to use liquid particles. We decided to use liquid particles. Therefore we changed the experimental setup to produce the liquid fluorescent particles.

2.4 Experiments with liquid particles

The Vibrating Orifice Aerosol Generator was replaced by Condensation Monodisperse Aerosol Generator (CMAG TSI 3475). The principle of the generator is based on controlled heterogeneous condensation (see fig. 3). Vapour of suitable material (in this case di-2-ethyl hexyl sebacate, DEHS) condense in a controlled manner on small particles (usually sodium chloride), which serves as a condensation nuclei (TSI). It is possible to obtain a relatively high concentration (106 Particles.cm-3) of monodisperse particles. Generator could generate particles of aerodynamic diameter between 0.1 µm to 8 µm.

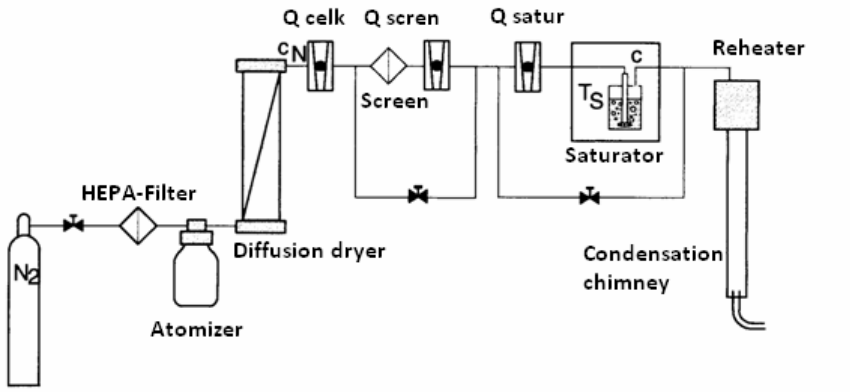

Fig. 3 Principle of condensation aerosol generator [4]

Water solution of fluorescein sodium salt was used as a condensation nuclei source instead of water solution of sodium chloride. Average diameter of nuclei was about 100 nm. DEHS condensed on these nuclei and size of final aerosol was 3 μm. It means that total quantity of fluorescent content is considerably lower then while using completely fluorescent (solid) particles. Therefore more sensitive spectrometer (Aminco-Bowman Luminescence Spectrometer) had to be used. Results of the first experiment confirmed that this method could be used and it solves the problem with rebounce of particles.

2.5 Model with the mouth cavity

The mouth cavity was acquired from Lovelace Respiratory Research Institute, Albuquerque, USA. It was 3-D scanned, transformed to STL format and joined with model geometry from trachea to 7th generation of branching (see fig. 4). As a next step the same procedure as during the first model creation will be done. The envelope around the geometry will be created and divided into segments that will be provided with flanges. The model will be than fabricated by rapid prototyping.

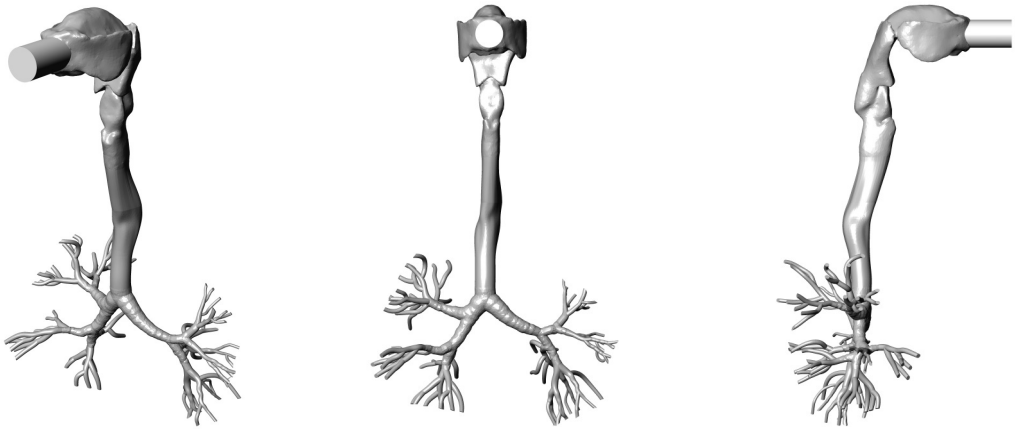

Fig. 4 Airway geometry of the model with the mouth cavity

3 CONCLUSIONS

Deposition measurements were done in realistic model of human lungs without a mouth cavity. Fluorescent method was used at first with solid particles. However, problems with rebouncing of particles led to use of liquid particles with fluorescent content. First experiment confirmed applicability of the method. To achieve more realistic flow field in the model the mouth cavity was added to the model geometry. The new geometry will be fabricated and used for future investigation of aerosol deposition.

Acknowledgement

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