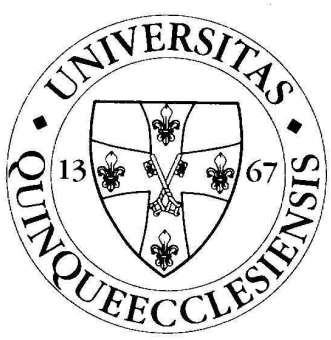


# DEVELOPMENT AND APPLICATION OF OPTICAL MEASUREMENT METHODS FOR THE INVESTIGATION OF THE DEPOSITION OF AEROSOLS IN HUMAN AIRWAYS

PhD Thesis

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## 1. Introduction

The most frequently used medications commonly applied during the therapy of human airway diseases are the inhalation medicines and systems that can introduce the active substances directly into the respiratory system. Determination of the deposition properties of aerosol medications is of particularly great importance during their development and approval, where the delivery of the proper dose to the targeted area and the overdose has to be controlled precisely.

There are three main research methods for the investigation of the deposition of aerosol particles in human airways: *in vivo*, *in silico* and *in vitro* methods. The main problem with the *in vivo* method – where measurements are performed on healthy persons and patients who are under treatment – is that the examinations require human contribution, what makes it intricate and raises ethical issues, while the required instrumentation is quite expensive and in many cases does not provide the necessary resolution. If the goal is to determine the effects of the variation of certain physical parameters, and the physiological effects can be neglected, then other methods seem to be more favourable.

The second, alternative method is the *in silico* examination, where computer simulations are used to determine the deposition efficiencies of the aerosols. In this case idealised or realistic flow conditions and airways geometries are used to model the particles' behaviour in the respiratory system and calculate the deposition patterns or efficiencies. Nowadays, this method is greatly supported by the rapid expansion of the computational capacities, although the mathematical description of the trajectories of particles in multiple bifurcated geometries and particles affected by different forces is still a challenge.

The last group consist of the *in vitro* methods where laboratory experiments are used for the investigations. The main advantage of this procedure versus the *in silico* method is that the input parameters are directly provided by the inhalation device. Furthermore, here more

freedom is given in the selection of measurement techniques compared to the *in vivo* method. The technological development brought important results in the physical model development, too. Computer tomography can be used to reconstruct digital airway geometries of patients having certain degree of obstruction in their lung. Rapid prototyping techniques (3D printing) can be utilized to produce realistic replicas of digital airway geometries that are suitable for flow and deposition measurements in the laboratory. The *in vitro* method is an efficient research tool, where high *in vitro* - *in vivo* correlation can be achieved if realistic flow conditions and geometries are used and sensitive measurement techniques are available in the laboratory.

## 2. Objectives

In my work I proposed to solve practical problems determined in cooperation with pulmonologists and experts in the field of computer simulations of aerosol deposition in airways. My main research area is to study the behaviour of aerosols in the human respiratory system, including the determination of the deposition efficiency and pattern, flow characteristics and hygroscopic properties of the inhaled particles. My approach was to perform the measurements with the developed experimental laboratory background under highly realistic conditions. Systematic studies of the different effects can be performed by varying the parameters (size distribution of inhaled particles, airway geometries, pulmonary waveforms, etc.) that mainly influence the deposition of the particles. For these studies I planned to design a highly flexible and controllable system.

According to the above objectives, I proposed to develop and apply new optical and spectroscopic methods, where my goals can be summarized as follows:

– Establishment of an experimental research laboratory background, which can be used for studying the deposition and transport properties of aerosol drugs, and determine their

individual properties. An important property of the instruments is that the main factors can be precisely varied to systematically evaluate the whole scale of their effects.

– Development of new measurement methods for the determination of the main physical properties of aerosol drugs which substantially influence their flow characteristics and deposition in the human airways.

– Application of the above laboratory background and measurement methods in idealized and realistic human airways replicas under realistic conditions.

The above goals were elaborated in cooperation with physicians and engineers, utilizing the institute's several decade experiences in the field of optical measurement techniques.

## *3. Applied methods*

I've designed and established a complex experimental laboratory background for the investigation of the delivery and deposition properties of inhaled particles in the human respiratory system. I've developed several measurement methods, tools and instruments.

I used an optical measurement procedure to determine the size distribution and the mass median aerodynamic diameter of commercial inhalation devices, and compared the results with reference data from the literature.

I've designed a temperature and humidity controlled measurement chamber to provide realistic atmospheric conditions (like in human airways) for the examinations and to study the effects of the humidity on the size distribution. I applied a new method for the data evaluation which is based on image processing and interferometry. For this method I've redesigned the catch plates of a cascade impactor so that they can hold interchangeable sampling plates. I've validated the developed method and compared my results with reference literature data that were obtained by HPLC based method. I've designed and developed an experimental setup for the investigation of the flow patterns in the human respiratory system. In order to increase

the *in vitro - in vivo* correlation I've designed a pulmonary waveform generator. I designed a laser Doppler anemometer with variable fringe distance and measurement volume, which I used to measure the velocity profile of aerosol particles in an idealised airway model, and then compared the results of the measurements with data obtained by computational fluid dynamics based simulations.

I attached silicon sample collector substrates on the inner wall of realistic human airway replicas produced by 3D printing of digital airway geometries reconstructed from computer tomography images in order to determine the spatial deposition distribution of inhaled aerosol drug particles. After inhalation I performed mapping Raman-spectroscopic measurements on the surfaces of the sample collector substrates. I've reconstructed the distribution map of the amount of the active substances on the surface by determining the characteristic Raman peak intensities throughout the surface. The selectivity of the Raman scattering allows to distinguishing between different active substances and enables to create specific distribution maps for them.

## *4. Theses*

4.1 I've developed a laser Doppler anemometer with variable fringe distance and measurement volume, the special fibre optic illumination and detection geometry of which makes it capable for the measurement of the flow velocity profiles in transparent airway models. Using this instrumentation I've validated a computational fluid dynamics based deposition model developed for the determination of flow characteristics and particle deposition in an idealised airway model consisting of straight cylindrical sections. I showed that for the same initial conditions, input parameters and geometries the results of the numerical computer simulations are in good agreement with the results of the *in vitro* measurements up to the 3$^{rd}$ generation of the airway. [T1-T3]

4.2 Using calculations and measurements based on laser Doppler anemometry and optical particle counting I've experimentally proved that an optical measurement method can be at least as effective as the aerodynamic measurement methods for the determination of the size distribution of the particles released from a pressurized metered dose inhaler. The results obtained for the size distribution and mass median aerodynamic diameter were in good agreement with the aerodynamic reference data. [T1, T3]

4.3 Using experimental measurements performed with a cascade impactor and a new optical measurement method utilizing image processing and interferometry, I've showed that the humidity and the temperature conditions typical for the human respiratory system have no significant effect on the physical properties of the inhaled particles. The size distributions obtained by the widely used cascade impactor showed good correlation with the time spent by the particles in the humid environment, but the mass median aerodynamic diameter did not increased significantly, the change was less than 7%. We have submitted a patent application on the optical measurement method utilizing image processing and interferometry. [T4, T5]

4.4 I've elaborated a new procedure for the determination of the amount and the distribution of deposited aerosol drug particles on the wall of lung models, utilizing mapping Raman-spectroscopy to determine the distribution of the substances on the sample collector substrates attached to the wall of the airway replicas. I've showed that the amount and the distribution of the active substance can be determined from the intensity distribution of the characteristic Raman peaks of the given substance. The advantage of this Raman spectroscopy based method is that it enables the chemical identification of the species and also the determination of the specific deposition of the components in case of combined medications. [T6, T7]

## 5. Publications related to the theses

[T1] A. Kerekes, A. Nagy , M. Veres, I. Rigó, Á. Farkas, A. Czitrovszky *In Vitro and In Silico (IVIS) flow characterization in an idealized human airway geometry using Laser Doppler Anemometry and computational fluid dynamics techniques.* Submitted for publication to the **Measurement** (Elsevier) journal

[T2] A. Kerekes, A. Nagy, A. Czitrovszky *Experimental flow and deposition studies with hollow bronchial airway models.* In: 17th ISAM Congress, Monterey, **Journal of Aerosol Medicine and Pulmonary Drug Delivery**. 22, No. 2: 175-176, (2009)

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***Patent application***

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