

Fibrous particles as a drug form for inhalation therapy: in vitro and in silico study**Jana Kánská¹, František Prinz¹, Miloslav Bělka¹ & František Lízal¹**¹Faculty of Mechanical Engineering, Brno University of Technology, Technická 2896/2, Brno, 616 69, Czech Republic**Summary**

Inhalation of drugs in the form of fibres has been shown as a promising approach for targeted drug delivery. Due to their elongated shape, fibres carriers can penetrate deeply into the pulmonary system and reach the alveoli, enabling effective delivery of API. In this fundamental study, a model fibrous system was employed to investigate the deposition of fibrous microparticles in the female respiratory airways, providing insights that can later be applied to real drug delivery systems. The experimental part involved the deposition of glass fibres, which served as model particles, followed by numerical simulations to compare and validate the results. Both were conducted using a female lung model extending from the oral cavity to the 7th generation of the tracheobronchial tree. A realistic deep inhalation, simulating heavy female breathing (peak flow rate 135 L/min), was applied. The numerical simulations employed the Lattice Boltzmann method coupled with Euler-Lagrange Euler-Rotation approach used for the particle phase. Compared with previously published results for normal breathing, the present study demonstrated a higher deposition fraction in the specified airway replica. The investigation focused not only on particle deposition in specific regions of the replica, but also on how deposition varies with particle size, aiming to identify a suitable size range for targeted delivery to distinct lung regions. Fibres with a diameter of 1 µm have the greatest potential, with more than 58% reaching the region below the defined geometry in both experiment and simulation. Presented data can be used for further utilisation in inhalation therapy.

Key Message

Fibre-based drug delivery remains effective in targeting the deep lungs, even during heavy breathing. Among the tested sizes, fibres with a diameter of 1 µm showed the highest deposition efficiency in the deep lung regions.

Introduction

Inhalation therapy is suitable not only for the treatment of pulmonary diseases but also for systemic drug delivery. Conventional spherical therapeutic aerosols could achieve a delivery efficiency to the deeper regions of the lungs (bronchial regions, deep acinus) up to 30%, depending on the type of dry powder inhaler (DPI) used [1]. One promising approach to improve inhalation therapy and targeted drug delivery to the deep parts of the lungs is the use of fibrous aerosols as drug carriers. Due to their aerodynamic properties, these aerosols can reach the acinar regions of the lungs, as their main axis aligns with the airflow. At the same time, they demonstrate resistance to the immune defence mechanism of phagocytosis, which can ingest conventional spherical particles [2]. Recently, Pioch *et al.* [3] developed a potential nanostructured fibrous microcarrier, with negligible toxicity, suitable for inhalation delivery of active pharmaceutical ingredients (API). In addition to particle properties, patient-specific anatomical differences play a crucial role in aerosol deposition. Notably, differences between male and female airways are often overlooked in inhalation therapy design, despite their potential to affect delivery efficiency [4]. This study extends our previous study [5] on a female airway spanning from the mouth to the 7th generation of the tracheobronchial tree to higher flow rates. Deposition efficiency of polydisperse fibrous particles was investigated under transient flow conditions mimicking heavy breathing, as a higher flow rate is recommended for DPIs [6]. Supporting numerical simulations were conducted to evaluate the accuracy of the Euler-Lagrange Euler-Rotation (ELER) framework under turbulent flow conditions. This was not previously investigated, according to the best knowledge of the authors.

Experimental methods and materials

For the deposition experiment, glass fibres of variable dimensions (1.39 ± 0.76 µm in diameter and 16.5 ± 13.97 µm in length) were used to simulate realistic fibre particles exposure scenarios in female respiratory airways. These glass fibres were intended solely for fundamental research as a model particle and not as a drug carrier. In future studies, e.g., nanostructure microfibers developed by the Pioch *et al.* [3] could be employed as carriers for API in inflammatory lung diseases. Fibres were discharged from a hopper via a rotary feeder and introduced into a fluidised-bed-type disperser. The fluidized bed enabled the fibres to reach the inlet of the lung replica. The female lung model, extending from the oral cavity to the 7th generation of bronchial branching, was scaled from a previously developed male model [7] by scaling factor 0.88. The simple downscaling approach was chosen to enable better

comparison between the male and female models, both with our own results and with those of other research groups using the same male model, although it introduces certain limitations related to gender-specific anatomical features. The internal surfaces of the replica were coated with silicone oil to enhance fibre adhesion and simulate mucociliary capture. The deeper lung regions were represented by filters connected to ten output segments (see Figure 1). The breathing profile was controlled by a breathing simulator equipped with an individual piston for each pulmonary lobe, generating a lobe-specific flow pattern. The total maximum flow rate was 135 L/min, and the average flow rate was 72 L/min, as a higher flow rate is recommended for DPIs [6]. This supports the notion that adequate lung deposition can be achieved at flow rates of 120 L/min or above for DPIs and MDIs [4]. After exposure to the fibres, the airway replica was dismantled into individual segments. Each segment was placed into a beaker and immersed in isopropanol to ensure complete submersion. The beaker was then placed in an ultrasonic bath. This procedure produced an isopropanol-fibre suspension, which was filtered using a vacuum filtration unit with nitrocellulose membrane filters. The filters were dried and subsequently rendered transparent on microscope slides, whereas the outlet filters were cleared directly on the slides. Each sample was manually evaluated using phase contrast microscopy (Nikon Eclipse), with a 40x objective and a Ph2 aperture diaphragm. Fibre quantification was performed using a modified method based on the WHO, and for the diameter and length measurements were used the Walton-Beckett graticule on the microscope [8].

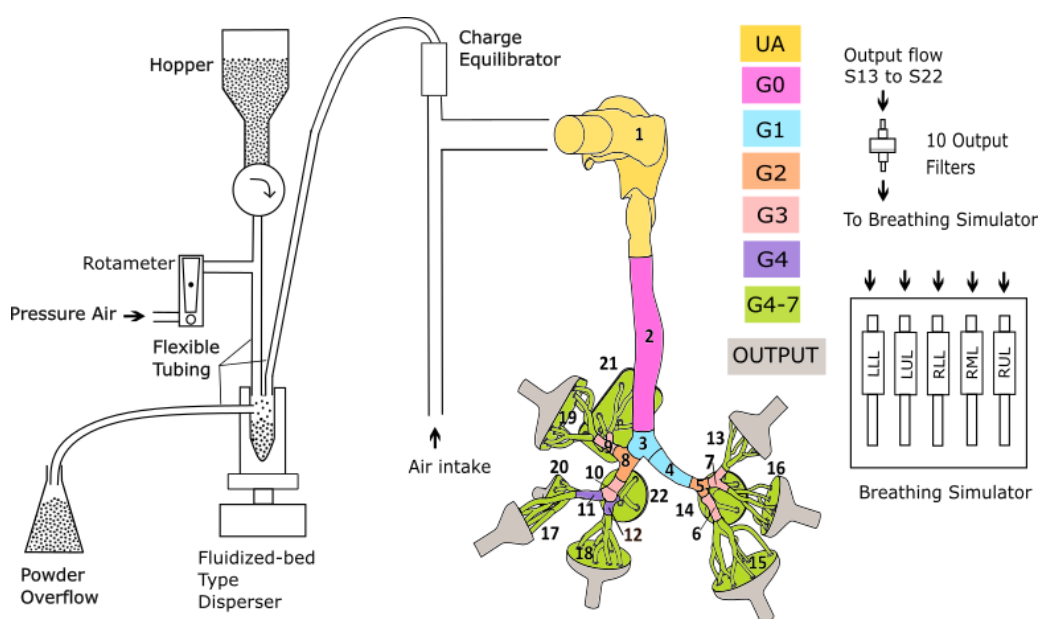


Figure 1 Schematic of fibre deposition measurement, UA – upper airways, GX – number of tracheobronchial generation

Numerical setup

Particle transport and deposition were simulated using the Computational Fluid and Particle Dynamics (CFPD). The fluid phase was simulated using the Lattice Boltzmann method. This method is a mesoscopic approach based on the Boltzmann equation and gains from the efficient algorithmization and scalability utilising a performant parallelisation [9]. After the discretizations the final equation called lattice Boltzmann equation is solved at each cell for each discrete velocity:

$$f_i(\vec{x} + \vec{c}_i \Delta t, t + \Delta t) = \left(1 - \frac{\Delta t}{\tau}\right) f_i(\vec{x}, t) + \frac{\Delta t}{\tau} f_i^{(eq)}(\vec{x}, t), \quad \forall i \in \langle 0, 18 \rangle.$$

f_i is the distribution function, $\vec{x}$ spatial coordinates, $\vec{c}_i$ is the discrete velocity, t time, Δt the time step and $f_i^{(eq)}$ the equilibrium distribution function and τ the relaxation parameter. Macroscopic quantities are computed using discrete velocity moments. The turbulent subgrid character of flow was modelled using LES Smagorinsky subgrid scale model. Time-dependent velocity profiles are prescribed in accordance with the distribution by Jahani et al [10], to obtain the same conditions as in the experiment.

The particle phase is simulated using the Euler–Lagrange Euler–Rotation approach. This method is an extension of the effective diameter method and takes the rotational movement into account. Particles are approximated by ellipsoids to enable an efficient computation of the rotation. In our previous work,

a higher accuracy compared to Tran-Cong and Haider-Levenspiel drag models was demonstrated [4]. The translatory motion is governed by the Newton's Second Law:

$$m_p \frac{d\vec{v}}{dt} = m_p \vec{g} + \vec{F}_D + \vec{F}_L,$$

m_p is the particle mass, $\vec{v}$ velocity of the particle, $\vec{g}$ the gravitational acceleration, $\vec{F}_D$ the drag force defined by Brenner and $\vec{F}_L$ the lift force defined by Cui *et al.* [11].

The rotational movement is computed using the Euler Rotational equation:

$$I_{x''} \frac{d\omega_{x''}}{dt} - \omega_{y''} \omega_{z''} (I_{y''} - I_{z''}) = T_{x''}; I_{y''} \frac{d\omega_{y''}}{dt} - \omega_{x''} \omega_{z''} (I_{z''} - I_{x''}) = T_{y''}; I_{z''} \frac{d\omega_{z''}}{dt} - \omega_{x''} \omega_{y''} (I_{x''} - I_{y''}) = T_{z''}$$

$I_{x'',y'',z''}$ are the components of the moment of inertia in the particle coordinate system, $\omega_{x'',y'',z''}$ the angular velocity components and $T_{x'',y'',z''}$ the hydrodynamic torque components. These equations are solved for each particle every time step until they deposited or reached the outlet. Every contact with the wall was considered deposition. Orientation-dependent deposition mechanism was enabled (*cf.* [4]). Particle size distribution was assigned according to the experiment with a random position in the mouth inlet.

Results

Deposition fraction in the replica (segments 1 – 22) is higher for both experimental and simulation results in comparison with published results for normal breathing conditions. In the case of the heavy activity regime, the experimental results showed a significantly lower deposition fraction in the upper airways than the simulation results (see Figure 2). Figure 3 provides a comparison of deposition fractions obtained from experimental measurements and numerical simulations, sorted by airway generation and fibre diameter. It shows that fibres could be suitable for deeper lung drug delivery, especially fibres with 1 μm diameter.

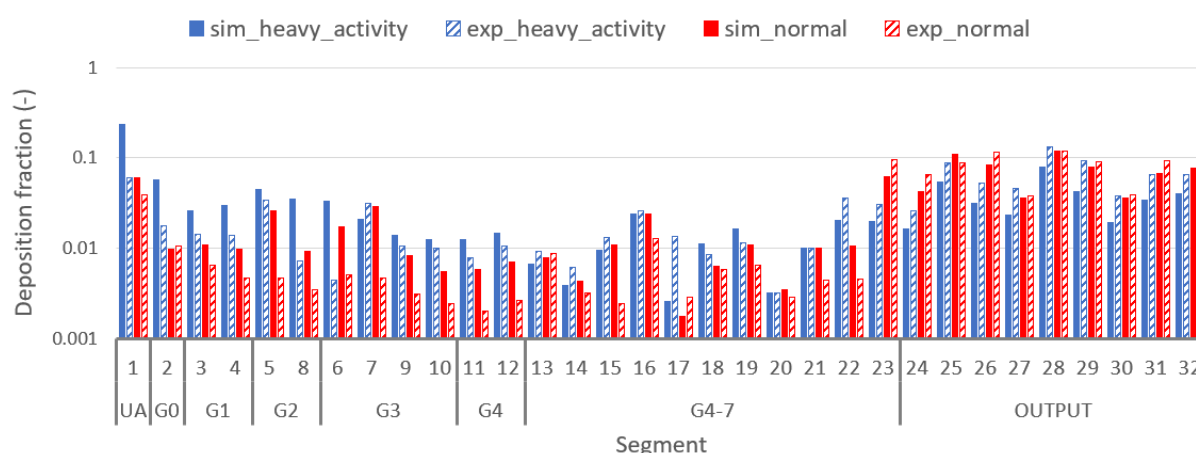


Figure 2 Comparison of deposition fractions obtained from experimental measurements (exp) and numerical simulations (sim) of heavy activity compared to normal breathing presented in [4].

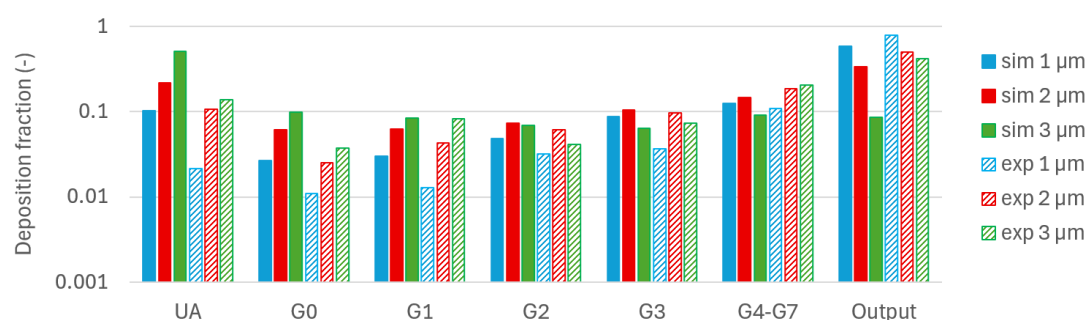


Figure 3 Comparison of deposition fractions obtained from experimental measurements (exp) and numerical simulation (sim) for heavy breathing, sorted by airway generation (see Fig. 1) and fibre diameter (1, 2 and 3 μm)

Discussion

The greatest differences between the simulation and experiment can be observed in the upper airways and first generations of branching. A possible source of discrepancies may be due to the turbulent

character of the flow. The highest flow velocities and the highest diameter of the geometry in the first segments result in the greatest Reynolds number across the whole geometry. The corresponding turbulent character (e.g. Dean vortices, laryngeal jet) and turbulent fluctuations may not be captured correctly by the simulation model and may influence the deposition. Consequently, the segments of the generations 3 – 7 show better agreement between the methods due to smaller dimensions. The deposition fraction of the filters (23–32) is lower in the simulations, caused by the deposition excess in the first segments. The experimental part was limited to a single run due to the high time demands of the procedure.

The size analysis indicated that fibres with small diameters (1 μm) have the potential to penetrate deeper into the lungs (in our case, beyond the 7th generation of bronchiolar branching). Overall, the simulation and experimental results show the same trend; however, the higher deposition observed in the upper airways in the simulations is reflected across all airway generations.

To quantitatively evaluate the accuracy of the ELER the mean absolute error to the experiment was evaluated and is 0.0199. For the normal activity this value was 0.0106 showing worse accuracy for heavy breathing [9]. The observed discrepancies may be attributed to particle force and torque formulations using creeping flow assumptions, which is not fully satisfied for higher flow rates and turbulent conditions. Non-creeping formulations for drag, lift and torque coefficients are available (e.g. [12]) and will be implemented in future work to evaluate the accuracy. Furthermore, with increasing fibre velocity, the assumptions that each particle touching the wall sticks may not be true in all cases.

Conclusion

Comparison between results for heavy breathing and normal breathing conditions showed that for potential drug delivery to the deeper lung is more suitable normal breathing. However, fibrous particles remain an effective choice for targeted drug delivery when used with inhalers that rely on deep inhalation. The size analysis indicated that fibres with a diameter of 1 μm are the most suitable for drug delivery to the deeper parts of the lungs. In the experiment, 78% of such fibres reached beyond the 7th generation of airway branching, compared to 58% in the simulation. In contrast, larger fibres represent a more appropriate option for the tracheal and upper bronchial regions. Although further work is needed to achieve closer agreement between simulations and experimental results, fibrous particles can be considered a promising option for targeted drug delivery to the deep regions of the lungs in females.

Acknowledgements. This work was supported by the Czech Science Foundation grant Nr. 25-16971S and University Specific Research project FCH/FSI-J-25-8785. We acknowledge the assistance of ChatGPT, an AI language model, in refining the text of this paper.

References

- [1] Tavernini, S., Farina, D. J., Martin, A. R., & Finlay, W. H., 2021. Using Filters to Estimate Regional Lung Deposition with Dry Powder Inhalers. *Pharmaceutical Research*, 38(9), 1601–1613.
- [2] Shachar-Berman, L., Ostrovski, Y., Koshiyama, K., Wada, S., Kassinos, S.C., Sznitman, J., 2019. Targeting inhaled fibers to the pulmonary acinus: Opportunities for augmented delivery from in silico simulations. *European Journal of Pharmaceutical Sciences* 137.
- [3] Ploch, T., Fischer, T., & Schneider, M., 2024. Aspherical, Nano-Structured Drug Delivery System with Tunable Release and Clearance for Pulmonary Applications. *Pharmaceutics*, 16(2).
- [4] Christou, S., Chatziathanasiou, T., Angeli, S., Koullapis, P., Stylianou, F., Sznitman, J., Guo, H.H., Kassinos, S.C., 2021. Anatomical variability in the upper tracheobronchial tree: Sex-based differences and implications for personalized inhalation therapies. *J Appl Physiol* 130, 678–707.
- [5] Prinz, F., Kánská, J., Elcner, J., Hájek, O., Kummerländer, A., Krause, M.J., Jícha, M., Lízal, F., 2025. Transport and deposition of inhaled fibers in a realistic female airway model: A combined experimental and numerical study. *Computers in Biology and Medicine* 194, 110473.
- [6] Haidl, P., Heindl, S., Siemon, K., Bernacka, M., & Cloes, R. M., 2016. Inhalation device requirements for patients' inhalation maneuvers. In *Respiratory Medicine* (Vol. 118, pp. 65–75). W.B. Saunders Ltd.
- [7] Lízal F, Elcner J, Hopke PK, Jedelsky J, Jícha M. Development of a realistic human airway model. *Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine*. 2011;226(3):197-207.
- [8] World Health Organization, 1997. Determination of airborne fibre number concentrations: a recommended method, by phase-contrast optical microscopy (membrane filter method).
- [9] Prinz, F., Pokorný, J., Elcner, J., Lízal, F., Mišík, O., Malý, M., Bělka, M., Hafen, N., Kummerländer, A., Krause, M.J., Jedelský, J., Jícha, M., 2024. Comprehensive experimental and numerical validation of Lattice Boltzmann fluid flow and particle simulations in a child respiratory tract. *Computers in Biology and Medicine* 170, 107994.
- [10] Jahani, N., Sanghun Choi, X., Choi, J., Iyer, K., Hoffman, E.A., Lin, C.-L., 2015. Assessment of regional ventilation and deformation using 4D-CT imaging for healthy human lungs during tidal breathing. *J Appl Physiol* 119, 1064–1074.
- [11] Cui, Y., Ravnik, J., Verhnjak, O., Hriberšek, M., Steinmann, P., 2019. A novel model for the lift force acting on a prolate spheroidal particle in arbitrary non-uniform flow. Part II. Lift force taking into account the non-streamwise flow shear. *International Journal of Multiphase Flow* 111, 232–240.
- [12] Ouchene, R., Khalij, M., Arcen, B., Tanière, A., 2016. A new set of correlations of drag, lift and torque coefficients for non-spherical particles and large Reynolds numbers. *Powder Technology* 303, 33–43.