Development of Inhaler Add-Ons for the Enhancement of Aerosol Drug Deposition in the Lungs

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Summary

The internal structure of dry powder inhalers (DPIs) is designed to facilitate the detachment of active pharmaceutical ingredients from their carriers through collisions, turbulence, and shear forces. However, this often results in disturbed airflow at the device's outlet, contributing to increased drug deposition in the upper airways and reduced lung deposition. This study aimed to design and assess DPI add-ons that, when attached to inhalers, manipulate the airflow to reduce upper airway deposition and enhance drug delivery to the lungs. To achieve this, various add-on geometries were developed to reduce turbulence and promote more uniform flow characteristics. Computational fluid and particle dynamics (CFPD) techniques were applied to optimize the shape and size of the add-ons. The selected configurations were integrated into an experimental setup to evaluate their impact on the filtration efficiency of an upper airway model, in combination with four commercial DPI systems: Breezhaler® delivering Ultibro® Breezhaler®, Turbuhaler® delivering Symbicort® Turbuhaler®, Ellipta® delivering Trelegy® Ellipta®, and NEXThaler® delivering Foster® NEXThaler®. The results demonstrated that the add-ons could enhance the amount of drug reaching the lungs by 6%–260% compared to baseline configurations without add-ons, depending on the specific drug formulation, inhaler type, and inspiratory flow rate. These findings suggest that such add-ons could contribute to more effective inhalation therapies by improving lung delivery and can be customized not only to match a patient's inhaler device but also to accommodate individual breathing profiles.

Key Message

Appropriately designed inhaler add-on geometries have been shown to reduce deposition of dry powder inhaler (DPI) drugs in the upper airways by decreasing turbulence and promoting a more uniform airflow profile entering the mouth. Lower extrathoracic deposition leads to higher lung doses and potentially more effective therapy.

Introduction

Lung deposition of aerosolized drugs is often suboptimal. One contributing factor is that a significant portion of the drug settles in the upper airways, preventing it from reaching the lungs. In the case of dry powder inhalers (DPIs), the active pharmaceutical ingredient (API) must detach from its carrier. To facilitate this, DPI devices are designed with internal geometries that promote non-uniform, often turbulent airflow. However, such disturbed airflow can also lead to increased deposition in the upper respiratory tract. This study aimed to design and evaluate DPI add-on components that manipulate inhaled airflow to reduce upper airway deposition and enhance pulmonary drug delivery.

Methods

Add-on design
The Breezhaler®, Turbuhaler®, Ellipta®, and NEXThaler® DPIs were the primary focus of our research, with add-ons specifically developed for each device. The geometry of these add-ons was designed not only in accordance with fluid dynamics principles, but also with attention to usability, practicality, and ergonomic considerations. From a fluid and particle dynamics standpoint, several competing effects must be balanced, making the selection of optimal shapes and dimensions a process of careful optimization. For example, while a diverging geometry may slow down airflow, a large cone angle can lead to excessive drug deposition due to recirculation near the walls [1]. On the other hand, a narrow opening angle necessitates a longer add-on with a larger surface area, which may also increase deposition. Internal partitioning within the add-on can help direct and stabilize the airflow, but at the cost of introducing additional surfaces where particles may deposit. Consequently, a variety of initial forms and sizes were considered, then narrowed down and further optimized based on computational fluid and particle dynamics (CFPD) simulations. The final set of designs was validated using both CFPD and experimental techniques.

CFPD simulations
Since the airflow at the mouthpiece of each device is strongly influenced by its unique internal architecture, it was essential to first replicate the airflow patterns specific to each inhaler. To achieve

this, the internal airspaces of the inhalers were reconstructed using CAD (computer-aided design) software, based on high-resolution surface data acquired with a 3D scanner (eviXscan 3D Heavy Duty Optima, Evatronix, Poland). The airflow field in the four internal geometries was simulated by the use of ANSYS FLUENT CFD (computational fluid dynamics) code (version 2025 R1). Airflow simulations inside the inhalers were performed for 30, 45, 60, 90 and 90 L/min flow rates. The driving force of the flow was the pressure drop through the inhaler corresponding to the above flow rates that we measured using a Copley pump (HCP6) in conjunction with a critical flow controller (TPK 100i) and a flow meter (DFM 2000). The flow profile at the exit of the inhaler was used as the inlet profile of the add-on or the upper airways (mouth). The upper airways were modelled as the hydraulic equivalent of a physical replica [2]. An Euler–Lagrange modelling approach was employed, wherein the air was treated as a continuous phase, while the drug particles were modelled as discrete entities. A one-way coupling between the phases was assumed: the airstream influenced the particle trajectories, but the particles had no effect on the airflow field. Airflow characteristics – including velocity, pressure, turbulence intensity, and dissipation rate – were computed across approximately 3.5 million control volumes (numerical cells). Drug particle transport was simulated in geometries both with and without the inhaler add-ons, and the corresponding filtration efficiencies were compared.

Experimental measurements

The efficiency of the 3D-printed add-ons connected to the four inhalers was further evaluated through experimental measurements of particle concentration and size distribution at both the inhaler mouthpiece and the outlet of the upper airway model, with and without the add-ons attached. The amount of drug deposited in the upper airways – or in the combined system of the upper airways and the add-on – was determined by calculating the size-fractionated difference in particle concentrations between these two locations. A schematic representation of the experimental setup can be seen in Figure 1. The main components of the setup were as follows. A high-volume pump was operated by a three-phase high-performance electric motor, enabling wide-range airflow to be controlled through the tubes connected to the system. The motor's rotation speed was regulated by a Mitsubishi S 300-type controller. Air and drug particles were drawn through a system consisting of the inhaler, an add-on piece (used in certain measurements), and a hollow upper airway model internally coated with silicon oil. This system was connected to an isokinetic sampler and a Grimm 1.108-type optical particle counter. The setup was further supplemented by a diluter, a flow meter, and a final filter designed to capture the drug particles exiting the system. The measurements were completed at 30, 60 and 90 L/min flow rates.

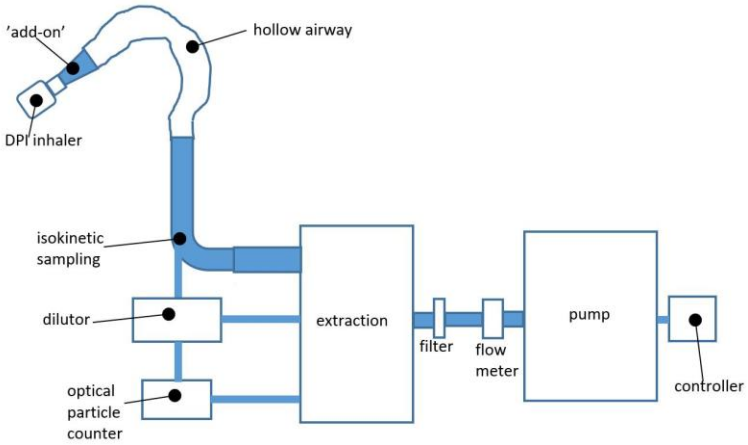

Figure 1 Schematic representation of the experimental setup for aerosol deposition measurements

Results and Discussions

Numerical simulations of airflow within the four inhalers revealed complex flow structures at the mouthpieces, characterized by highly perturbed turbulent behaviour. According to our findings, the outlet flow was least disturbed in the case of the Breezhaler®, while the Turbuhaler® exhibited the most complex and turbulent patterns – particularly at higher flow rates (>60 L/min). As an illustrative example, Figure 2 shows the velocity vectors at a flow rate of 30 L/min for the Ellipta®, captured at the inlet gaps, mouthpiece outlet, and in a cut-plane depicted in the 3D image.

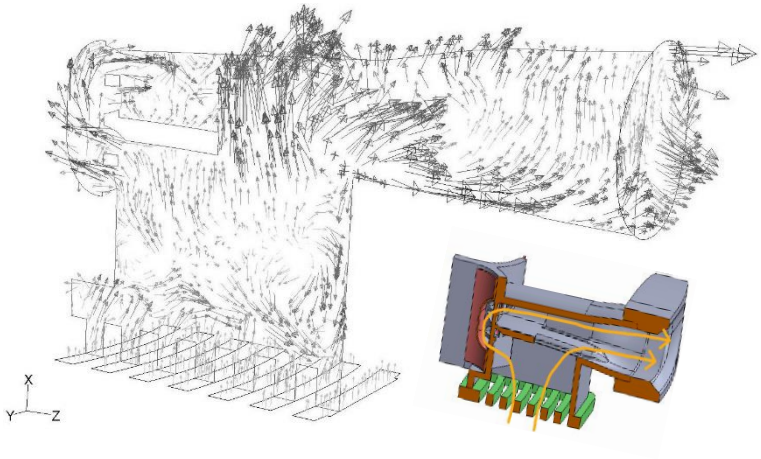

Figure 2 Velocity vectors inside Ellipta® inhaler

The add-ons were designed to simplify the complex airflow fields generated by the inhalers. Based on results from computational fluid and particle dynamics (CFPD) simulations, two geometric categories were selected for further analysis: (1) a hollow conical tube – tested with no internal partitions as well as configurations featuring 3, 4, or 6 inner divisions; and (2) a 'cup-shaped' design, evaluated both without and with 4 internal divisions. The two main types of add-ons and all the subtypes included in the experimental measurements are depicted in Figure 3.

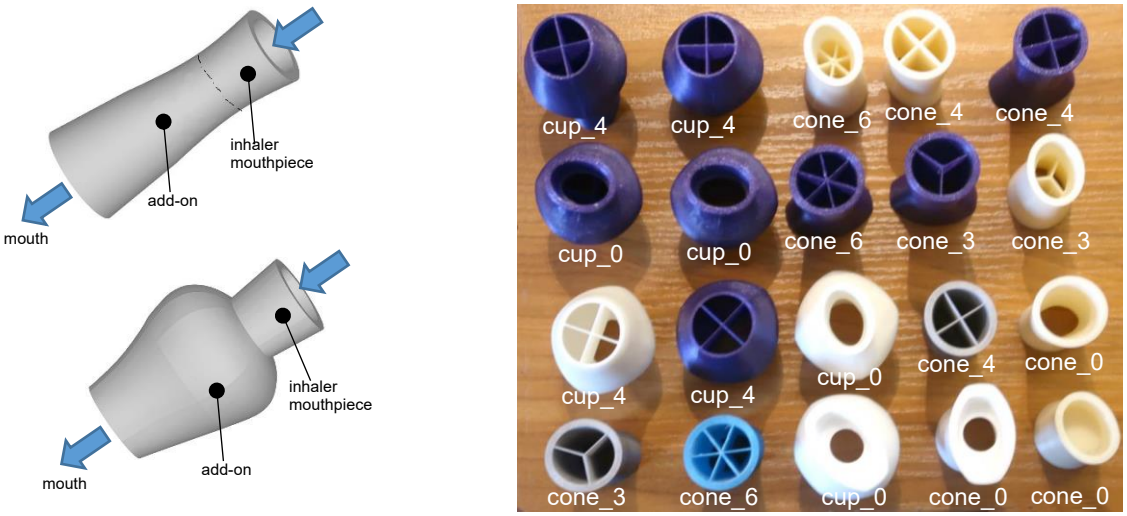

Figure 3 CAD images of the add-ons (left panel), and photo of the optimized add-on shapes selected for the experimental deposition measurements (right panel). The names refer to the shape of the add-ons ('cone' or 'cup') and the number of divisions (0, 3, 4 or 6)

The experimental measurements were performed with Ultibro® Breezhaler®, Symbicort® Turbuhaler®, Trelegy® Ellipta® and Foster® NEXThaler® drugs. A total number of 360 measurements (6 add-on types × 4 drugs × 3 flow rates × 5 repetitions) were performed. Table 1 presents the results in terms of relative increase of drug mass exiting the trachea (entering the lungs) as a result of the add-ons compared to the add-on-free case for each inhaler/drug and each add-on at 30, 60 and 90 L/min inhalation flow rates. Each percentage expresses the mean value of the five measurement repetitions.

In addition, the highest value of the relative increase of the mass of drug entering the lungs due to the add-on compared to the no add-on case, and the name of the corresponding add-on is shown in Figure 4 for each inhaler/drug at 30, 60 and 90 L/min flow rates.

Table 1 Changes of the drug mass reaching the lungs due to different add-ons relative to the case without any add-on. All the values are expressed in percent

Add-on	Drug	30 L/min	60 L/min	90 L/min	Drug	30 L/min	60 L/min	90 L/min
cone_0	Ultibro® Breezhaler®	3.4	-11.2	4.0	Symbicort® Turbuhaler®	-25.6	29.1	22.7
cone_3		6.1	-16.4	27.7		-20.0	33.5	-45.6
cone_4		1.6	-9.5	12.7		-10.2	110.2	4.2
cone_6		3.9	-6.1	30.8		-38.6	10.5	-52.2
cup_0		0.1	5.6	5.8		-19.3	160.1	68.1
cup_4		1.2	-6.9	-13.0		-17.7	41.5	44.6
cone_0	Foster® NEXThaler®	22.9	-13.4	-33.9	Trelegy® Ellipta®	23.6	10.1	13.9
cone_3		29.0	-6.6	12.5		21.6	7.6	15.3
cone_4		26.8	-15.6	-14.3		17.4	8.4	18.3
cone_6		36.1	-18.2	0.3		11.2	-2.1	15.9
cup_0		44.9	-4.7	-11.9		21.7	37.9	35.3
cup_4		48.6	6.8	-12.5		38.1	21.3	25.9

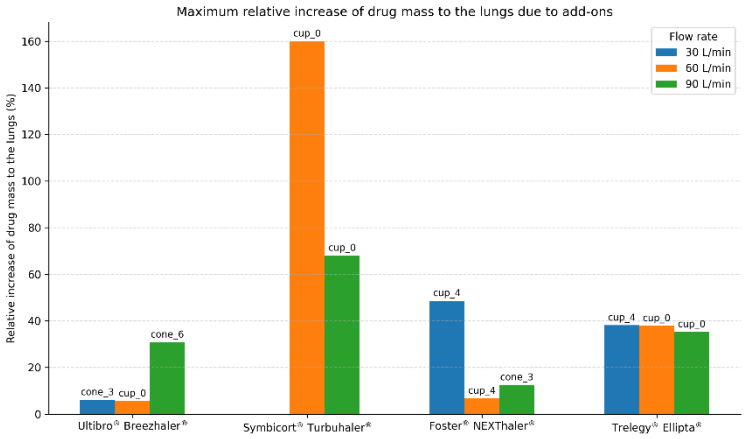

Figure 4 Maximum values of the relative increase of drug mass reaching the lungs due to add-ons for Ultibro® Breezhaler®, Symbicort® Turbuhaler®, Foster® NEXThaler® and Trelegy® Ellipta® dry powder aerosol drugs at 30, 60 and 90 L/min inhalation flow rates. The add-on providing the maximum value of the relative change is marked above the bars

Figure 4 demonstrates that the most effective design and the maximum improvement in pulmonary delivery depended on both the inhaler device and the specific medication. The smallest relative increase in the mass of drug reaching the lungs was observed with the Breezhaler® (up to 30%), while the largest gains were achieved with the Turbuhaler® (up to 160%). In most cases. the optimal add-on and the extent of improvement also depended on the inspiratory flow rate. For instance, with the Foster® NEXThaler® greater enhancement was seen at lower flow rates (30–35 L/min), whereas with the Symbicort® Turbuhaler® higher flow rates (60 L/min. 90 L/min) yielded more significant increases in drug delivery to the lungs as a result of the presence of add-ons. In general, the 'cup-shaped' add-ons proved to be more efficient than the conical ones, although exceptions were noted. The conical add-on was particularly effective in reducing flow velocity, while the cup-shaped version demonstrated superior turbulence-dampening properties. Among the conical designs those with internal divisions performed better than those without, but the ideal number of divisions was drug/inhaler dependent. As for the cup-shaped add-on. the divided version was generally more effective at lower suction (flow) rate, while the undivided version performed better under higher flow conditions.

It is clear from the results in Table 4 that not all the add-ons are advantageous for a given inhaler and flow rate. However, there is at least one add-on in almost all circumstances which provides higher drug doses reaching the lungs. Although, all of the add-ons make the flow more uniform and less turbulent leading to lower upper airway deposition, the deposition in the add-on can be higher than the resulting

gain in some cases (see the negative values in Table 1). The deposition in the add-ons was not measured in this work, but complementary CFD calculations were performed to reveal the characteristics of the deposition within the add-ons. From this perspective, an important question was the dependence of deposition on the internal surface area of the add-ons. With the increase of the number of divisions the flow uniformity becomes more accentuated causing less extrathoracic deposition, but the inner surface area increases leading to higher deposition in the add-on, and there is always an ideal number of divisions (which can be zero, as well) characteristic of a given inhaler/formulation and flow rate. The results of CFD simulations pointed out that not only the total surface area of the add-on is important, but also the thickness of the division walls, as the particles predominantly deposit on these side surfaces by impaction. Therefore, the internal division walls should be as thin as possible. In the present case, the wall thickness was 0.2 mm, which was the minimum 3D printable value. Based on the results of the CFD calculations, the efficiency of the add-ons could be increased by the further decrease of the wall thickness. This remains an important issue also in the case of large scale production, which is different from rapid prototyping.

In conclusion, the present results may support the development of more effective therapies in the future through enhanced pulmonary drug delivery. Based on the present findings, the add-ons can be customized not only for the patient's specific inhaler device but also for their individual breathing capacity. Therefore, the choice of add-ons should be knowledge-based and always tailored to the inhaler and drug pair and the special breathing characteristics of the patients. Further studies are needed to incorporate more inhalers and drugs, but also different add-on shapes and sizes. Last but not least, the add-ons should be tailored to the special shape of the mouthpiece of each inhaler, ensuring stable attachment to the inhaler and safe use for the patients.

Acknowledgement

Project no. 00057 has been implemented with the support provided by the Ministry of Culture and Innovation of Hungary from the National Research. Development and Innovation Fund. financed under the 2021–1.1.4-GYORSÍTÓSÁV-2022 funding scheme.

References

[1] Johnston J P: Diffuser design and performance analysis by a unified integral method. ASME J Fluids Eng 1998; 120: pp 6–18.

[2] Cheng Y S. Zhou Y. Chen B T: Particle deposition in a cast of human oral airways. Aerosol Sci Technol 1999; 31: pp 286–300.