



**Experimental and Numerical Investigation of Drug Delivery and Aerosol
Deposition in the Mouth-Throat Airway using a
Pressurized Metered Dose Inhaler (pMDI)**

By

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**To my family, whose unwavering support, endless encouragement,
and unconditional love have been my greatest source of strength.**

This journey would not have been possible without you.

The moving finger writes, and, having writ, moves on.

Khayyam

Author's Declaration

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Abstract

Experimental and Numerical Investigation of Drug Delivery and Aerosol Deposition in the Mouth-Throat Airway Using a Pressurized Metered Dose Inhaler (pMDI)

Inhalation therapy is a widely used and effective method for treating respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD). Among the various inhalation devices, pressurized metered-dose inhalers (pMDIs) are the most commonly utilized due to their portability and rapid onset of action. However, despite their popularity, challenges remain in ensuring efficient and targeted drug delivery to the lungs. Factors such as airflow dynamics, inhalation profiles, device actuation, and anatomical variations can significantly impact drug deposition, particularly in the mouth-throat (MT) region, where substantial particle loss is often observed.

This study aimed to improve the performance of inhalation therapy devices by leveraging insights gained from experimental *in vitro* studies and computational fluid dynamics (CFD) simulations. The thesis combines experimental measurements with CFD simulations (including USP-IP, COPD, and CF inhalation, pediatric geometry, and mucus modeling) to investigate the transport and deposition behavior of pharmaceutical aerosols delivered by pMDI devices.

The experimental studies utilized an eight-stage Next Generation Impactor (NGI) setup paired with an industrial induction port (IP) and three-dimensional (3D)-printed mouth-throat geometries to quantify the deposition fraction on each stage, allowing for the plotting of particle size distribution. To facilitate this research, the geometry of the mouth-throat region was constructed using 3D printing technology with Ultimaker S3 and S5 printers, employing tough polylactic acid (PLA) for precise and durable models. High-performance liquid chromatography (HPLC) was used at the inhaler, MT geometry, and collection cup of each stage of the NGI to accurately measure the deposition of the active pharmaceutical ingredient (API). Additionally, CFD models were developed using the Eulerian-Lagrangian framework, which included the Discrete Phase Model (DPM) and turbulence models such as low Reynolds number (LRN) $k-\omega$ and Large Eddy Simulation (LES) to simulate particle and airflow dynamics under realistic physiological conditions. These models were validated against experimental data to ensure their accuracy and reliability.

The initial project examined how airflow rate and spray cone angle affect aerosol deposition in an adult model of the mouth and throat. It was found that recirculation zones at the 90° bend in the oropharynx caused larger particles to be selectively retained. As airflow rates increased, the aerodynamic size of the particles decreased, leading to better delivery to the distal airways. However, larger cone angles resulted in more deposition in the mouth, while an 8° cone angle was identified as optimal for minimizing particle loss in the upper airway. These findings emphasized the importance of understanding the relationship between device parameters and inhalation dynamics to enhance drug delivery efficiency.

The second part of the study examined the effects of constant and COPD-specific breathing profiles under varying humidity levels, focusing on how these factors influence particle transport and deposition. At low flow rates (30 *L/min*), there was a 39% increase in the deposition of large particles on the airway walls. In contrast, high humidity levels (99%) allowed more large particles (>5 μm) to pass through the airway, thereby reducing deposition in the mouth and throat. The COPD breathing profiles caused a slowdown in the development of the aerosol plume, leading to an increase in the deposition of large particles. Interestingly, regions of high turbulence, when combined with humidity, resulted in a 4% reduction in the deposition of large particles. This finding indicates complex interactions between environmental conditions and inhalation profiles.

The third study expanded the research to a pediatric mechanical ventilation model that simulates a cystic fibrosis (CF) breathing profile. A 3D-printed airway derived from a CT scan was integrated into an NGI to validate CFD simulations. The study focused on the mucus boundary conditions using the Eulerian Wall Film (EWF) model and introduced a shear-thinning, non-Newtonian mucus layer. The results indicated that transient airflow broadened the particle size distribution, and the shear-thinning mucus disrupted the secondary flow, causing a more than 60% increase in the minimum particle size exiting the trachea. Additionally, a synchronized actuation ($t = 0\text{ s}$) has the highest deposition efficiency at 45.6%. Flow rate emerged as the most influential factor affecting deposition patterns, as supported by a Morris sensitivity analysis.

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Chapter 1 – Introduction

1.1 Introduction

Respiratory illnesses, such as asthma and chronic obstructive pulmonary disease (COPD), are prevalent around the world. Inhalation-based therapies have emerged as a promising, non-invasive approach for directly delivering therapeutic agents to the site of action. This approach enhances treatment effectiveness while minimizing adverse systemic effects [1]. Recent advancements in medicine and nanoscience have led to the development of inhalable nanomedicines, which aim to improve effectiveness, increase patient adherence, and enhance the quality of life for individuals suffering from chronic pulmonary diseases and tuberculosis [2–4].

Inhalation therapy devices are designed to address various patient conditions and needs, including the accuracy of inhalation coordination and the type of medication used. As a result, the efficiency of drug absorption and deposition in the lungs depends on both the patient and the inhaler utilized [4]. Several factors influence this process, including the characteristics of the drug-aerosol, such as particle size distribution and velocity, the type of delivery device, the mode of inhalation, the complexity of the airways, and the patient's age [5–8].

Three common types of inhalers are used in inhalation therapy: nebulizers, dry powder inhalers (DPIs), and pressurized metered-dose inhalers (pMDIs). The pMDI consists of a pressurized canister that contains a propellant, a surfactant, and a suspension or solution of the therapeutic agent. The high pressure inside the canister keeps the drug components in a liquid state [9]. It is essential to optimize where the drug-aerosol is deposited within the lower respiratory tract to ensure targeted delivery and minimize unwanted systemic side effects. If the drug is deposited in the mouth-throat area, it can lead to medication loss, which reduces its therapeutic effectiveness, increases variability among patients, and may heighten the risk of side effects [10, 11].

The effectiveness of drug delivery to the lungs is typically assessed by comparing the amount of aerosolized medication that reaches the targeted lung areas to the total dose emitted from the inhaler device [12–14]. This measure is significantly essential for patients with COPD, where inflammation and excessive mucus can narrow the airway, further restricting the flow of air

and drug aerosols [15]. A higher lung deposition efficiency indicates that a greater percentage of the medication successfully reaches the lungs, overcoming these airway obstacles.

The primary objective of this study was to investigate the factors that directly influence the size distribution of drug aerosols and their deposition efficiency in the mouth-throat region when using a pMDI. This investigation was carried out using both experimental and numerical methods. The development of effective and economically viable CFD techniques aims to provide practical solutions for improving drug delivery efficiency in inhalation therapy devices, such as pMDIs. The simulated results contributed to a better understanding of pMDI performance under both *in vitro* and realistic conditions. Ultimately, these findings aim to offer new strategies for the pharmaceutical industry to analyze the key factors that can enhance pulmonary drug delivery efficiency and minimize unwanted side effects.

1.2 Thesis Structure

This thesis is organized into eight chapters as follows:

Chapter 1 serves as the introduction and provides a summary of the study. It offers an overview of the topic and discusses strategies for optimizing inhalation therapy. The chapter also examines the factors affecting drug delivery efficiency across various inhalers (i.e. pMDIs, DPIs, and Nebulizers). Additionally, it concludes with a detailed outline of the thesis structure.

Chapter 2 provides a comprehensive review of the scientific literature on drug delivery to the lungs through inhalers, with a particular emphasis on pMDIs. The review covers several important areas, including (i) the efficiency of various inhaler devices, taking into account their different designs and mechanisms; (ii) both *in vitro* and *in vivo* inhalation profiles, along with hydrodynamic studies within the human respiratory tract [19–21]; (iii) the impact of mucus on drug delivery in the respiratory tract [22–24]; and (iv) key studies that utilize CFD to model drug aerosols [22, 25–27]. By examining these vital topics, the chapter identifies research gaps and sets the objectives of this study, ultimately aiming to enhance drug delivery in the respiratory tract.

Chapter 3 outlines the research methodology, encompassing theoretical concepts, the *in vitro* setup, and the techniques employed, including the Next-generation Impactor (NGI) and High-performance Liquid Chromatography (HPLC). It examines various mouth-throat geometries, referencing standards established by the United States Pharmacopeia (USP) and discussing the use

of 3D printing to create more complex and realistic geometries. The chapter also describes the process of submitting simulation tasks to computing clusters to leverage high-performance computing resources. Additionally, it addresses the integration of experimental data with computational models to enhance the accuracy and relevance of the simulations, thereby improving their reliability [28–30].

In *Chapter 4*, the application of CFD is discussed alongside the governing equations of continuity, momentum, energy, and species. The Navier-Stokes equations are presented as the fundamental principles governing these processes. This chapter also explains how turbulence models—such as Reynolds-Averaged Navier-Stokes (RANS) with the $k-\omega$ model and Large Eddy Simulation (LES)—are used to capture complex airflow behavior. Additionally, it introduces the Discrete Phase Model (DPM) for simulating the motion of particles in aerosols and employs statistical distributions, such as the Rosin-Rammler distribution, to represent the size distribution of polydisperse particles. Emphasis is placed on the significance of these models in obtaining accurate and reliable results for particle deposition analysis [31–35].

In *Chapter 5*, we analyze the performance of pMDIs using CFD modeling, which is validated with in vitro data. The chapter focuses on aerosol deposition efficiency at the USP induction port, flow patterns within the device, and the cone angle of the pMDI nozzle. We investigate five constant inhalation flow rates and their corresponding plume cone angles for the pMDI. Our observations revealed that recirculation at the 90° bend in the mouth-throat airway selectively retained larger particles, and we found a correlation between fluid flow patterns and the behavior of drug deposition. Increasing the airflow rates by up to three times led to a 20% reduction in aerodynamic particle diameters. Furthermore, we noted that as the cone angle increased, mouth deposition also increased, with an 8° cone angle proving to be optimal for minimizing mouth-throat deposition. This study was published in the journal “*Processes*”.

In *Chapter 6*, we incorporated the inhaler into our model and examined the hydrodynamic aspects of the flow patterns while introducing COPD breathing profiles into the system. To enhance the realism of our model, we applied a relative humidity of over 50% RH. Our approach utilized both experimental methods, employing an eight-stage NGI setup, and numerical methods, including CFD with the LRN $k-\omega$ turbulence model, along with a DPM. These methods were used to determine particle size distribution, deposition, and delivery within the mouth-throat airways.

Under COPD breathing conditions, the development of the inhaler spray was slower, resulting in a greater deposition of larger particles on the walls of the mouth-throat airways. Notably, relative humidity had a significant impact on particle deposition fractions. At higher humidity levels (99%), an excessive number of large particles passed through the airway outlet, leading to a decrease in deposition within the mouth-throat area. This study was accepted for publication in the journal “*Experimental and Computational Multiphase Flow*” in 2025.

Chapter 7 explores the effects of the mucus layer in the pediatric mouth-throat airway on particle deposition efficiency. The chapter discusses and validates three different methods for numerically modeling mucus using *in vitro* data. This validation involved creating a 3D print of a CT scan of the mouth-throat airway of a 5-year-old boy. The findings indicated that the Eulerian wall film (EWF) model predicts secondary flow more accurately than the shell-conduction model and its associated thickness. The mucus is modeled as a shear-thinning fluid, similar to the mucus found in patients with cystic fibrosis (CF), and it is compared to the simplified low-viscosity material commonly referenced in the literature. Furthermore, a comprehensive statistical analysis is conducted to evaluate the sensitivity of various responses—including deposition efficiency, pressure drop, and wall shear stress—to changes in each input parameter (flow rate, viscosity, and delay time). The analysis identifies that flow rate has the most significant impact on both deposition efficiency and pressure drop.

In conclusion, *Chapter 8* summarizes the thesis and provides recommendations for future research in this field.

1.3 Nomenclatures

Abbreviation

3D	3-dimensional
CFD	computational fluid dynamics
COPD	chronic obstructive pulmonary disease
DPI	dry powder inhaler
DPM	discrete phase model
HPLC	high-performance liquid chromatography
LES	large eddy simulation

MP	mouthpiece
NGI	next generation impactor
pMDI	pressurized metered dose inhaler
RANS	Reynold averaged Navier-Stokes
USP	United States Pharmacopeia

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Chapter 2 – Literature Review

2.1 Literature Review

Inhalation is the primary route for administering drugs used to treat chronic obstructive pulmonary disease (COPD) and asthma. This method enables rapid drug delivery while ensuring both efficacy and safety. By targeting the site of action directly, inhaled administration allows for the use of lower drug doses, which reduces the risk of systemic side effects compared to oral therapy. There are four main types of inhaler devices used for medication delivery: pressurized metered-dose inhalers (pMDIs), dry powder inhalers (DPIs), soft mist inhalers (SMIs), and nebulizers. Each device type has its own unique advantages and limitations, which can influence its suitability for individual patients with COPD [1]. These devices are illustrated in **Fig 2.1**, which shows (a) a nebulizer, (b) a DPI, (c) an SMI, and (d) a pMDI [2].

Nebulizers (as shown in **Fig 2.1(a)**) are devices that convert liquid solutions or suspensions into aerosols, enabling inhalation into the lower respiratory tract. There are three main types of nebulizers: pneumatic jet nebulizers, ultrasonic nebulizers, and mesh nebulizers. The mesh nebulizer, such as the MicroAir® NE-U22 from Omron (Chicago, IL, USA), is highly efficient and leaves minimal residual volume (0.1–0.5 *mL*) in the device after treatment. Mesh nebulizers operate using one of two basic mechanisms: active vibrating and passive mesh. Active vibrating mesh nebulizers have plates with thousands of funnel-shaped holes that are vibrated by a piezo-ceramic element located around the aperture plate. In contrast, passive mesh nebulizers use an ultrasonic horn to push fluid through a mesh screen [3]. However, nebulizers are less portable and often require power sources or regular maintenance, making them less convenient than other inhaler devices.

DPIs (**Fig 2.1(b)**) have become increasingly popular over the past decade as a method for delivering medications in the form of dry powder formulations. These can either consist of pure active pharmaceutical ingredients or be combined with inert excipients, such as lactose, to improve flowability and ensure consistent dosing [4]. The patient's inhalation, typically ranging from 30 to 60 *L/min* depending on the specific device, provides the necessary energy to break down the drug particles and disperse them as an aerosol. However, certain characteristics of DPIs limit their suitability for some patient groups. The powder-based formulation makes DPIs sensitive to

humidity, which can negatively affect their performance. Additionally, high-resistance DPIs can be challenging for young children, particularly when their respiratory effort is compromised due to illness [5]. Humidity from exhaled breath can also reduce the efficiency of the inhaler, as moisture may cause drug particles to stick to the inhaler's opening, impairing aerosolization and delivery. Unlike pMDIs, DPIs do not require precise coordination between device activation and patient inhalation [6].

(a)



(b)



(c)



(d)



Fig 2.1. Inhaler devices for drug delivery: (a) Nebulizer; (b) DPI; (c) SMI; and (d) pMDI [2].

The Soft Mist Inhaler (SMI- Spiriva Respimat) refers to **Fig 2.1(c)**, manufactured by Boehringer Ingelheim, Ingelheim, Germany. The medication is a slow-moving aerosol that enhances both deposition in the lungs and the consistency of the dosage [7]. The aerosolized spray disperses at a slow speed of 0.8 m/s from a distance of 10 cm , lasts for 1.5 s , and has a high fine-particle fraction,

with 66% of the particles measuring less than $5.8\ \mu\text{m}$. To operate the device, the patient must twist the base of the inhaler 180° . This action dispenses a specific dose of medication and compresses the spring within the base, providing the necessary energy to deliver the medication [8]. Each actuation releases $2.5\ \mu\text{g}$ of tiotropium bromide monohydrate, the active ingredient in the Spiriva Respimat inhaler [9].

When selecting an inhalation device, healthcare professionals consider several key factors. These include the patient's inspiratory flow capacity, the coordination between inhalation and device actuation, cognitive and motor skills, as well as the patient's or caregiver's preferences and any financial constraints. Effective treatment relies heavily on the correct use of inhaler devices. Misusing these devices can hinder medication delivery, which may result in increased exacerbations, higher healthcare costs, and a greater risk of premature mortality [10]. To address these issues, pMDIs have been developed, and their details will be discussed in the following sections.

2.1.1 Pressurized Metered Dose Inhalers (pMDIs)

pMDI devices deliver a short burst of aerosolized medication that is inhaled into the lungs. Since their introduction in the latter half of the last century, pMDIs have gained widespread recognition. Millions of patients worldwide currently rely on them [11]. Due to their effectiveness and ease of use, pMDIs are considered the most widely prescribed aerosol delivery system [12]. A typical pMDI (**Fig 2.2**) consists of three components: the canister, the actuator, and the metering valve [13]. The canister is usually a pressurized metal container made from aluminum, which contains the medication and propellant. It is housed in a plastic sleeve with a mouthpiece. The propellants used in pMDIs are typically chlorofluorocarbons (CFCs) or hydrofluoroalkanes (HFAs). CFCs are known to deplete the ozone layer and have been linked to increased health risks, such as cataracts, leading to their prohibition under the Montreal Protocol [14].

In specific pMDI designs, aerosol dose delivery is achieved by pressing the inverted canister into the actuator, ensuring precise and consistent doses. Many manufacturers have enhanced their formulations by adding ethanol to improve the solubility of surfactants in the propellant. For instance, Schering-Plough developed a salbutamol formulation using HFA-134a, incorporating ethanol for better solubility. Another formulation of salbutamol in HFA-134a demonstrated a significantly smaller particle size (mean diameter of approximately $1\ \mu\text{m}$ compared to $4\ \mu\text{m}$ in

older CFC formulations) at a reduced spray velocity, resulting in over 50% greater lung deposition. This also allows for precise quantification of the dose and eliminates the need to shake the inhaler before use. As a result of these advancements, newer inhalers offer more consistent dosing and improved lung deposition. However, changes in excipients, elastomers, and propellants can lead to variations in taste and sensation compared to older inhalers. Furthermore, HFA-based pMDIs produce sprays with lower impact force and a smaller, warmer plume, providing patients with a gentler and more comfortable inhalation experience [15].

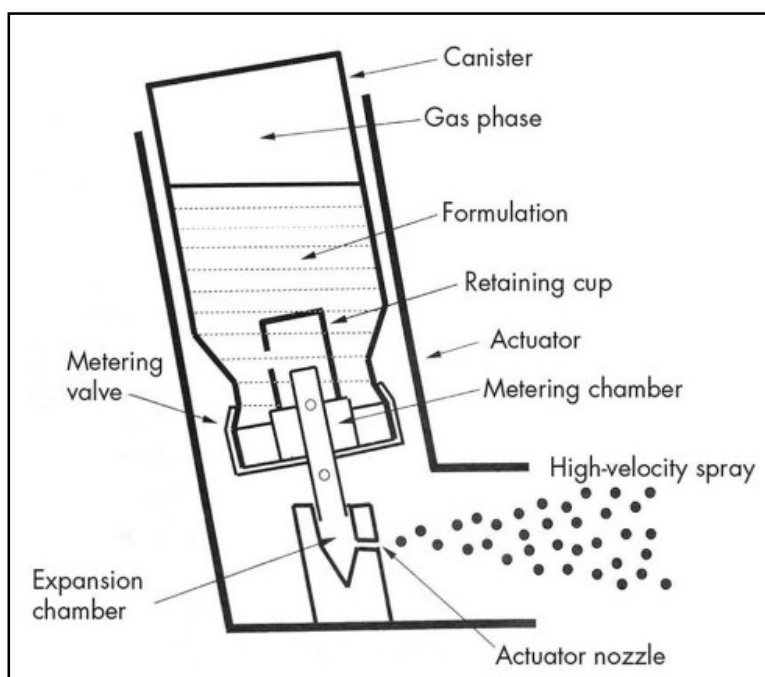


Fig 2.2. Standard components of a pMDI [16].

The canister pressure is a significant factor in designing MDIs, as it influences the distribution of atomized droplets and the shape of the plume. The higher-pressure level results in higher spray velocity and, consequently, faster droplet evaporation rate [17]. The smaller actuator orifice produces a finer spray and generates a slower-moving aerosol cloud over a longer emission period. The spray droplet velocity varies depending on its position in the spray plume [18]. Droplets at the center of the spray cone have the maximum velocity, decreasing with the distance from the spray cone centerline and from the injection nozzle [19].

The metering valve isolates a precise drug formulation and propellant dose, preparing it for each actuation. As illustrated in **Fig 2.3**, the metering valve connects the canister to the spray nozzle

through a system of one-way inlet and outlet valves. At rest, the inlet valve remains open, allowing the formulation to flow freely into the metering chamber until it is filled completely (Stage 1). Upon actuation, movement of the valve stem closes the inlet valve, isolating the dose within the chamber (Stage 2). Next, the outlet valve opens, releasing the formulation through the spray nozzle (Stage 3). When actuation is complete, the valve stem returns to its initial position, driven by the valve stem spring, causing the outlet valve to close and the inlet valve to reopen (Stages 4 and 5). This allows the metering chamber to refill, preparing the inhaler for the subsequent dose (Stage 6) [20].

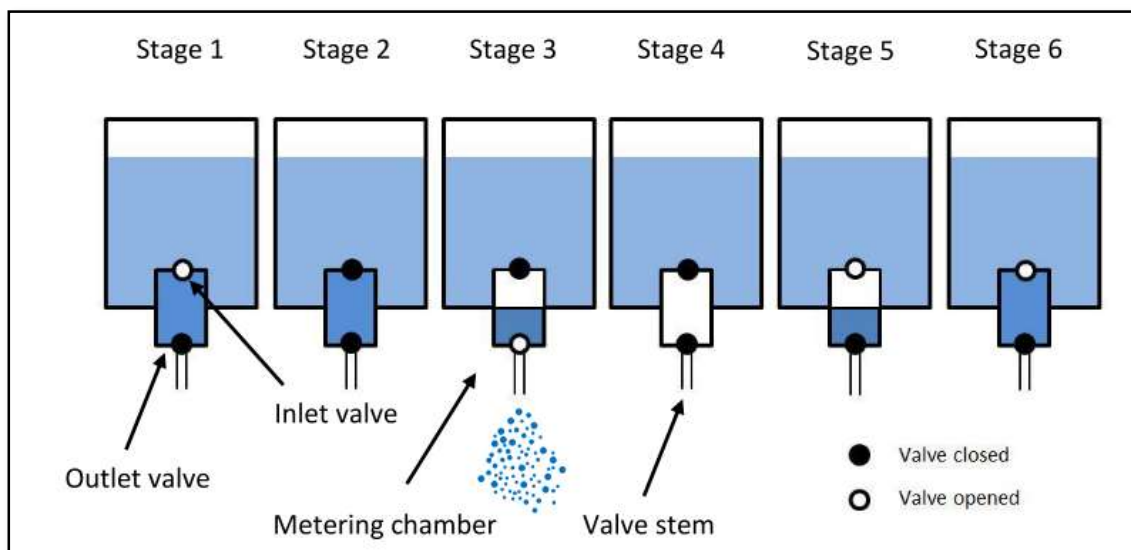


Fig 2.3. Schematic stages of actuation [21].

pMDIs can produce fine particles through an atomization mechanism during actuation. The initial particle characteristics were derived from the atomization properties of Ventolin-HFA (albuterol sulfate), a common medication used to treat COPD. The histograms displaying particle size distributions measured at 0 mm from the origin for Ventolin-HFA are shown in **Fig 2.4**. These size distribution data served as the basis for curve fitting using three probability distribution functions. As illustrated in **Fig 2.4**, the Rosin–Rammler distribution (solid line) provided the best fit for the measured data compared to the other two probability distribution functions (PDFs). In contrast, the log-normal PDF demonstrated poor fitting performance [22].

The results indicated a particle size distribution obtained through laser diffraction measurements at 0 mm from the nozzle of a commercial pMDI device, with mean diameters typically ranging

from 2 to 6 μm . Several factors can influence the measured particle size distributions, including the distance from the inhaler nozzle, the design of the atomizer, the type of propellant, the drug formulation, the actuation pressure, and the patient's inhalation technique [23].

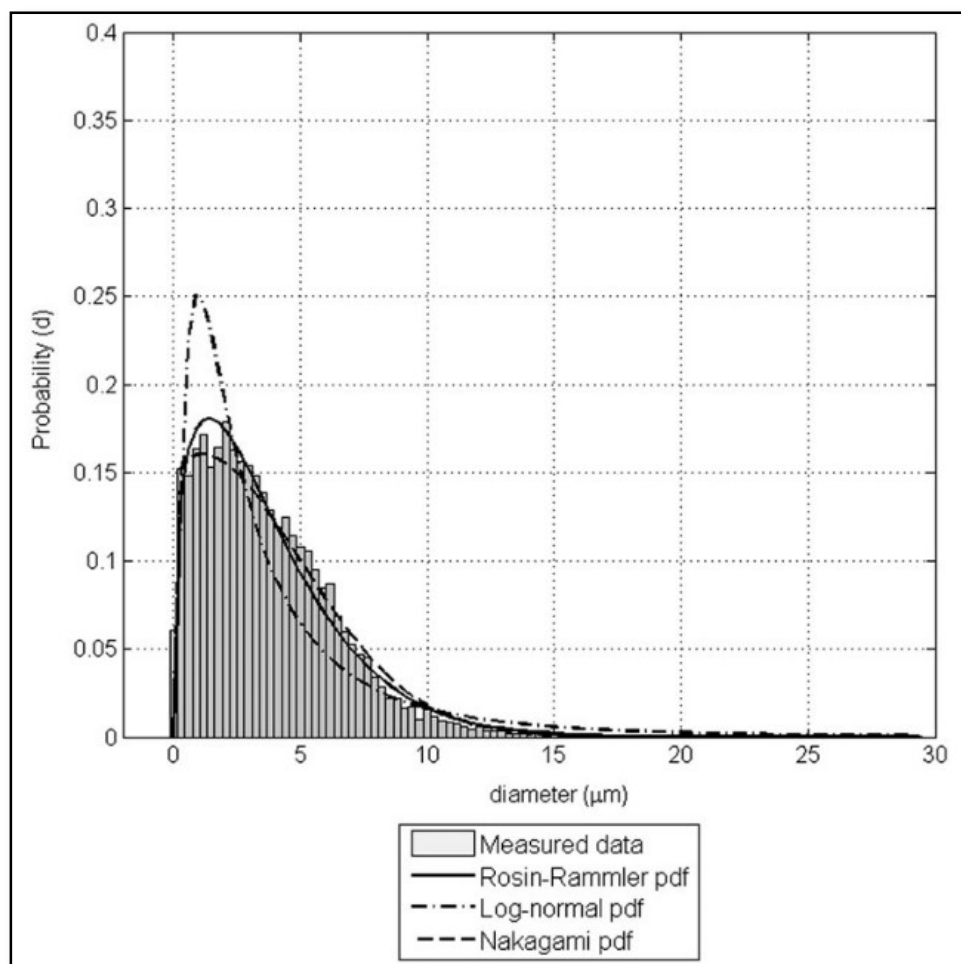


Fig 2.4. Histogram of the experimental data of particle diameter for Ventolin HFA with curve fitting of probability distribution functions (at 0 mm) [22].

2.1.2 Experimental, Numerical, and Clinical Studies of the pMDI

As highlighted in the introduction and literature review, drug deposition plays a crucial role in the effectiveness of pulmonary drug delivery. When aerosol particles from a pMDI are inhaled into the human respiratory tract, their deposition in various regions is influenced by several factors, including airway geometry, breathing patterns, aerosol characteristics, particle size, and particle density. Case studies conducted by Newman demonstrated that the clinical effects of asthma treatments are directly correlated with the dose that is deposited in the lungs [24, 25].

The aerodynamic size of particles is a critical factor in determining the regional deposition of aerosolized particles within the respiratory tract, as it influences how aerosols distribute following inhalation [26]. The aerodynamic size of particles is a critical factor in determining how aerosolized particles are distributed within the respiratory tract after inhalation. The aerodynamic diameter of a particle is defined as the diameter of an idealized spherical particle with a unit density ($\rho = 1.00 \text{ g/cm}^3$) that settles at the same velocity as the actual particle. Particles larger than $6 \mu\text{m}$ primarily deposit in the mouth, throat, and airway bifurcations of the upper respiratory tract, a phenomenon known as oropharyngeal deposition. In contrast, particles sized between 2 and $5 \mu\text{m}$ tend to penetrate deeper into the respiratory tract and deposit more effectively within the lungs. Particles smaller than $0.1 \mu\text{m}$ can either settle due to random Brownian motion or remain suspended in the airflow because of their low inertia, which allows them to be exhaled later. Consequently, the ideal particle size range for effective deposition in the lungs is approximately 2-5 μm [27, 28].

The primary mechanisms contributing to particle deposition within the respiratory tract are inertial impaction, gravitational sedimentation, Brownian diffusion (commonly in the Alveoli region), and, to a lesser extent, interception and electrostatic precipitation [25, 29]. The contribution of these deposition mechanisms is a function of particle size and flow rate in each region of the respiratory tract.

The human respiratory tract is a complex anatomical system. Aerosol deposition within the lungs has been investigated through various approaches, including *in vivo* studies involving human volunteers [30–32], *in-vitro* studies using physical airway replicas [33–35], and theoretical studies using mathematical models [36]. These studies typically categorize the respiratory tract into three main regions: the extrathoracic, thoracic, and pulmonary regions, as illustrated in **Fig 2.5**. The extrathoracic region, also referred to as the head airway, encompasses the nasal, oral, pharyngeal, and laryngeal structures. This region serves as the entry point to the respiratory system and acts as an initial defense mechanism against inhaled hazards. The tracheobronchial (TB) region, often referred to as the conducting airways, comprises the trachea and the subsequent 16 generations of branching airways.

During breathing, airflow changes direction multiple times through the nasal and oral passages, pharynx, larynx, and at airway bifurcations. Larger particles (greater than $0.5 \mu\text{m}$) tend to deposit in these regions through a process called inertial impaction, where their inertia prevents them from

closely following the airflow streamlines. Oropharyngeal deposition due to impaction accounts for a significant portion of the emitted dose from pMDIs and DPIs [29]. In small airways and alveolar regions, sedimentation is the predominant deposition mechanism for inhaled particles. Conversely, smaller particles can be deposited throughout all areas of the respiratory tract by diffusion; diffusion is particularly crucial for nanoparticles. Interception deposition also plays an essential role for elongated particles, such as fibrous aerosols, when the length of the particle is comparable to the dimensions of the pulmonary airways. Additionally, pharmaceutical aerosols may carry electrostatic charges during their generation and transport, especially in the case of DPI and pMDI devices [37, 38].

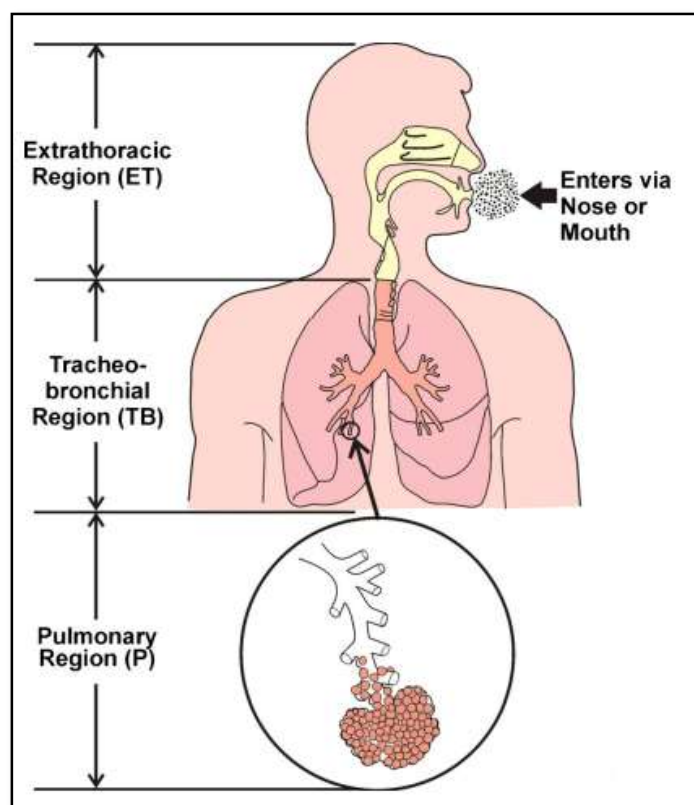


Fig 2.5. A schematic diagram of the human respiratory tract [29].

Inertial impaction is the primary mechanism by which particles deposit in the respiratory tract. Inertia refers to a particle's tendency to resist changes in its motion. This process occurs at the points where the respiratory tract branches, known as bifurcations, where the direction of airflow changes. As a result, particles in the airstream tend to continue their original path instead of following the new direction of the airflow. The Stokes (St) number (Eq. (2.1)) is a dimensionless

quantity used to predict the deposition of particles caused by impaction as they travel through the airways.

$$St = \frac{\rho_d d_p^2 u}{18\mu R} \quad (2.1)$$

Here, ρ_d represents the droplet density, d_p is the particle diameter, u is the air velocity, μ is the air viscosity, and R is the airway radius. The St number indicates that the likelihood of a particle depositing due to inertial impaction is directly proportional to the particle density, the square of the particle diameter, and the air velocity, while being inversely proportional to the airway radius. Inertial impaction is a velocity-dependent mechanism, which causes most particles larger than $5 \mu m$, particularly those greater than $10 \mu m$, to deposit in the upper respiratory tract and large conducting airways [39].

The second mechanism of particle deposition is gravitational sedimentation (Eq. (2.2)), which refers to the process by which particles settle under the influence of gravity. The terminal settling velocity (u_t) of particles falling due to gravity is described by Stokes' law.

$$u_t = \frac{(\rho_d - \rho)d_d^2 g}{18\mu R} \quad (2.2)$$

Here, ρ represents the air density, and g is the gravitational constant. According to Eq. (2.2), the gravitational sedimentation of a respirable particle depends on its size and density. This is a time-dependent process, with deposition increasing as the residence time of a particle in the airways and alveoli lengthens, such as during slow, steady breathing or breath-holding. Gravitational sedimentation is a key mechanism for particle deposition in the size range of $0.5\text{--}2 \mu m$, particularly in the small airways and alveoli [40].

Interception occurs when the distal end of a particle encounters the airway wall, even though its center of mass remains within the gas-phase streamlines. While this mechanism has little impact on spherical particles, it becomes significant for depositing elongated particles with small aerodynamic diameters. Finally, during aerosolization, particles can become electrostatically charged. Deposition of charged particles through electrostatic precipitation may occur either by inducing an opposing charge on the airway surfaces, leading to electrostatic attraction, or through repulsion between similarly charged particles, which directs them towards the airway walls [41].

Having reviewed the aerosol deposition mechanisms, the remainder of this section focuses on examining the parameters that influence pulmonary drug delivery from inhalers, particularly pMDIs. One of the early studies regarding the detailed, temporal, and spatial characterization of the pMDI spray was done by Dunbar et al. [42], using Phase-Doppler particle analysis. This study led to information on the spray structure, primary atomization, and localized data for validating a theoretical spray model [42, 43]. It was proposed that the primary atomization mechanism of pMDI is internal flash evaporation based on the results obtained from the flow visualization and the work conducted on internal flashing flows. Spatial analysis of the two propellant formulations (Chlorofluorocarbons (CFC), and hydrofluoroalkane (HFA 134a)) revealed that the formulation containing drug and surfactant produced a spray consisting of a central core of faster-moving particles. It is also observed that the friendly propellant (HFA 134a) produced smaller mean-diameter drops than the CFC propellant.

Newman et al. [44] highlighted the crucial role of the actuator nozzle in the formation of aerosols. As the dose exits the nozzle, aerodynamic forces stretch and fragment liquid ligaments within the propellant vapor, producing a dispersion of liquid droplets [44]. The evaporation of the propellant cools the droplets, often making the spray feel cold on the back of the throat. However, as discussed below, this effect is less pronounced with HFA pMDIs. The Montreal Protocol, adopted in 1987, mandated the complete phase-out of CFCs. In 2005, the U.S. Food and Drug Administration (FDA) ruled that the sale of CFC-based albuterol pMDIs would be prohibited in the United States after 2008. While HFAs are greenhouse gases, their environmental impact is significantly lower than that of CFCs, and the contribution from medical use is considered negligible [45]. Consequently, formulation, valve, and actuator designs were modified to accommodate the HFA propellant.

Fig 2.6 compares the plume characteristics of HFA- and CFC-based pMDIs. The left panel shows the cloud leading-edge travel distance over time, indicating that the HFA plume (dashed line) travels faster and farther than the CFC plume (solid line) within the first 100 milliseconds. This reflects the higher initial spray velocity and finer aerosol dispersion of HFA formulations [15]. The right panel visually confirms these differences: the HFA-based inhaler emits a narrower, more concentrated spray with a slower thermal dissipation profile, while the CFC plume appears broader and more forceful, potentially increasing oropharyngeal deposition [46]. Compared to CFC-based

systems, HFA formulations produce aerosols at a warmer temperature and with lower impaction force at the back of the throat, reducing local side effects. Additionally, products like Proventil HFA maintain consistent dosing when stored in various orientations, are less affected by cold temperatures, and show reduced dose variability toward the end of the canister's life.

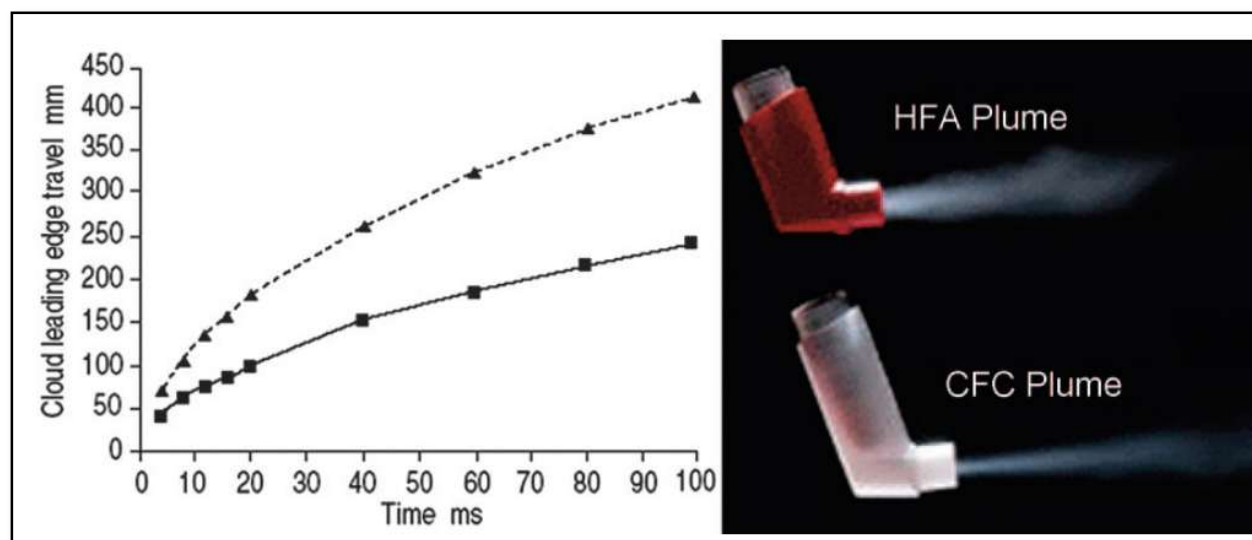


Fig 2.6. Left: Distance traveled by the leading edge of the aerosol cloud from pMDI with HFA 134a, and CFC. Right: HFA 134a, and CFC plumes [46].

These characteristics are partly due to differences in propellant chemistry, actuator design, and excipient formulation, which also influence taste and mouthfeel. To replicate the spray plume behavior of salbutamol delivered via HFA-134a pMDI, Oliveira et al. developed a CFD model validated against high-speed imaging. The particle size distribution was fitted with a log-normal curve, and axial droplet velocity was extracted from frame-by-frame analysis of the high-speed footage [47]. The particle distribution from the experiment was fitted with a Log-Normal distribution, and the mean velocity of the droplet along the axial distance from the nozzle was calculated using high-speed images, as shown in **Fig 2.7** [47]. The initial plume velocity was considered 10 *m/s*, and the plume was considered as a solid cone with an actuation time of 0.11 *s*. Observing the air temperature revealed that it ranges from 289.89 to 293.15 K, with the highest variation occurring at the spray plume formation zone. A sudden drop of 3.3 K occurs at the nozzle exit due to the injection of droplets with an initial temperature of 215.15 K [48]. This temperature drop occurs due to the energy required to evaporate the propellant.

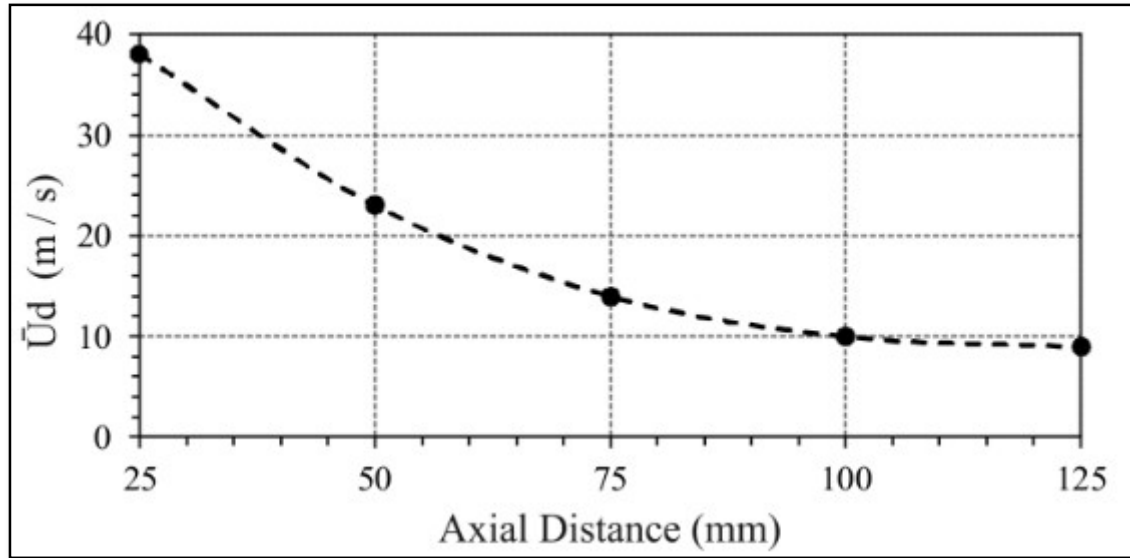


Fig 2.7. Droplet mean velocity along the axial distance from the nozzle of a pMDI in the open air [47].

As shown in **Fig 2.8**, the particle velocity magnitude in the spray plume ranges from approximately 100 m/s to 0.01 m/s. The particles located downstream of the actuator mouthpiece decelerate rapidly until they reach the same velocity as the air. Larger particles travel further into the still air than the small ones. The influence of the gravitational acceleration is noticeable for higher particles when the slip velocity equals zero.

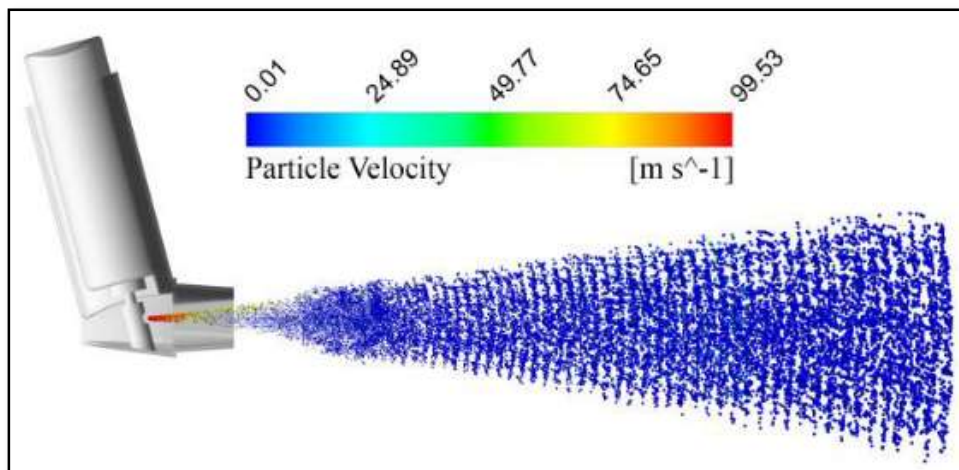


Fig 2.8. Representation of the particle stream velocity at the end of the injection (0.11 s) [21].

Cheng et al. [49] conducted a study for actuated monodisperse particle deposition in confined geometries (USP-IP, realistic mouth-throat geometry). They investigated the realistic mouth-inlet diameter, as well as internal airway dimensions, and their influence on oropharyngeal deposition

based on experimental data. The aerosol deposition increased with the decreasing mouth inlet diameter. Several mathematical expressions were tried to correlate the deposition efficiency with the impaction parameter ($d_{ae}^2 Q$), and independent from the Reynolds number. Particularly applicable for flow rates ranging from 15 to 60 L/min . Other studies have reported small effects of Reynolds number within the range of 30 to 90 L/min as a flow rate [49-51]. **Fig 2.9** shows the deposition efficiency as a function of the impaction parameter, indicating that for the identical replica, the deposition efficiency increases with the impaction parameter. Data for Replica A indicated that, at the same flow rate, deposition increased with a decreasing mouth inlet diameter for the same oropharyngeal replica, consistent with the results obtained by Lin et al. [50]. It again confirms that impaction is the primary deposition mechanism for micro-meter-sized particles.

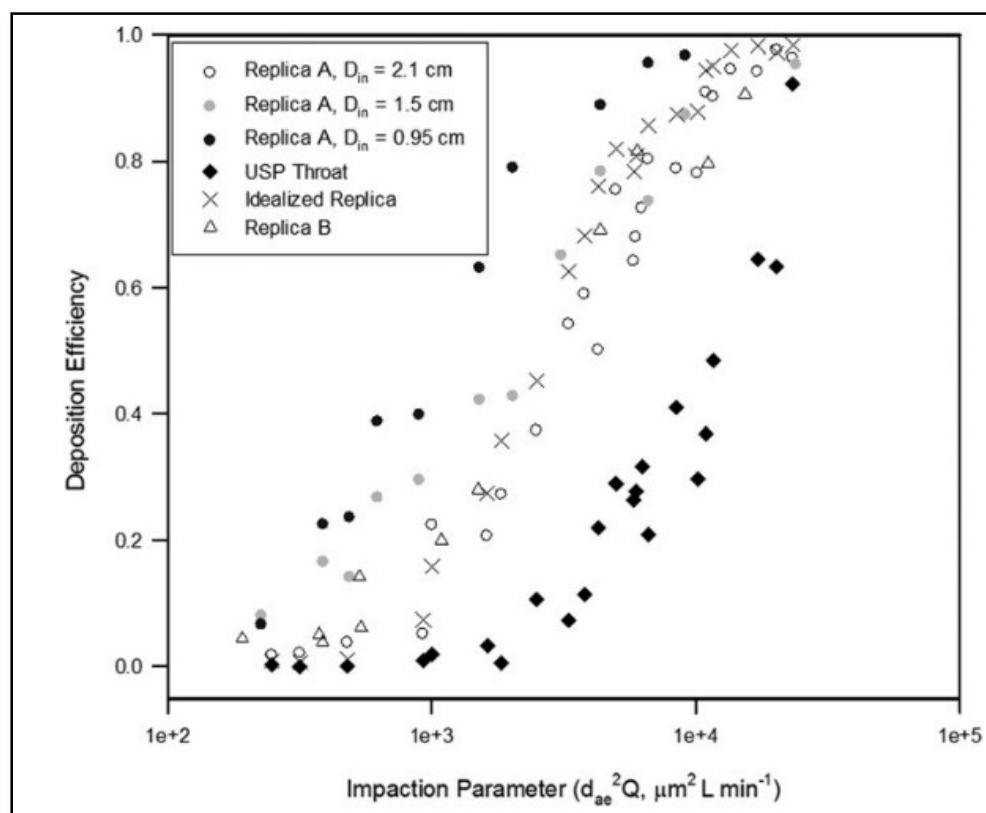


Fig 2.9. Deposition efficiency as a function of the impaction parameter for all the replicas and USP-IP [49].

In aerosol drug delivery, the size of the mouthpiece affects the oropharyngeal deposition. A higher oropharyngeal deposition is expected in a drug-delivery device with small mouthpiece diameters (<1.7 cm), resulting in a smaller amount of the drug being delivered to the lungs [51]. They could

derive a good correlation between deposition efficiency and the Stokes number for a set of four oral airway replicas and the USP-IP, with a wide range of diameters, D_{inlet} and D_{min} , and inlet velocities. The minimum diameter of oropharyngeal replicas is the glottis opening in the larynx region.

Therefore, it is essential to consider the realistic human respiratory tract when investigating particle deposition. Ahookhosh et al. [52] conducted a computational study with the primary objectives of investigating the flow structure within a pMDI and analyzing the transport and deposition of micron-sized particles in a model of human tracheobronchial airways. Their study also examined how these processes depend on inhalation airflow rate and key parameters of the pMDI. The upper airway geometry, which includes the extrathoracic region, trachea, and bronchial airways up to the fourth generation in some branches, was constructed based on computed tomography (CT) images of an adult healthy female [52]. The CFD simulation was employed using the $k-\omega$ model with low-Reynolds number (LRN) corrections to accomplish the objectives. The mesh structure was first generated using the octree method to create an appropriate surface mesh, and then produced with a Delaunay triangulation-based method to create a high-quality volume mesh. Finally, five layers of prism mesh were placed near the airway walls to capture the turbulent boundary layer profile. The height of the first layer was specified based on one of the widely used y^+ correlations, the average Reynolds number, and the average diameter of the Trachea.

The deposition results of the present study were verified against the in vitro deposition data from their previous investigation on pulmonary drug delivery, which utilized a hollow replica of the same airway geometry used for CFD modeling. It was found that the flow structure inside the pMDI and extrathoracic region strongly depends on the inhalation flow rate and geometry of the inhaler. In addition, **Fig 2.10** shows that regional aerosol deposition patterns were investigated at four inhalation flow rates between 30 and 120 L/min , as well as at for 60 L/min , yielding the highest deposition fractions of 24.4% and 3.1% for the extrathoracic region, and the trachea, respectively.

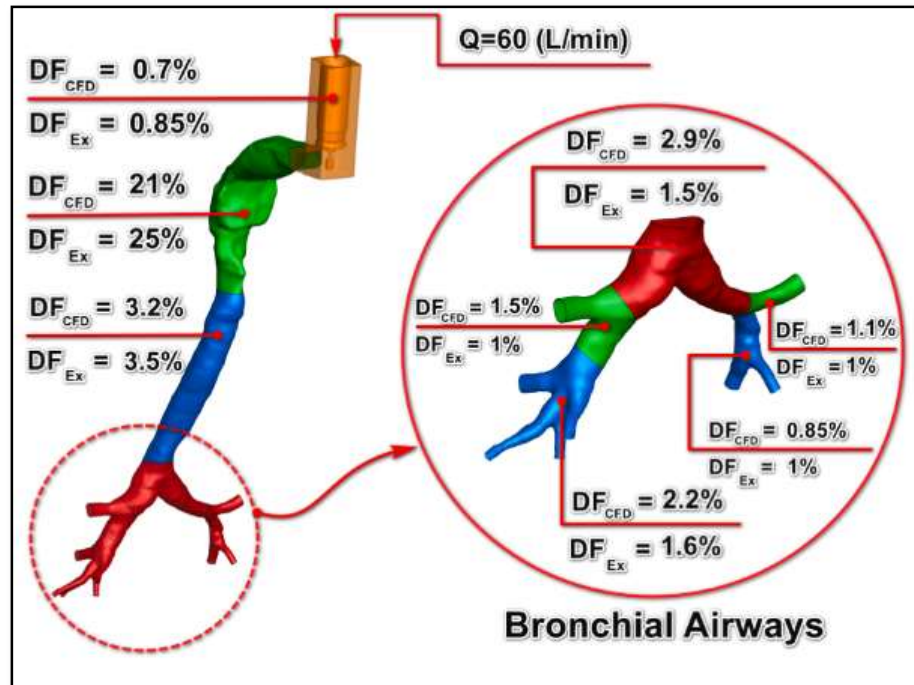


Fig 2.10. Regional deposition fractions for the CFD model, and experiment data [52].

As shown in **Fig 2.11(a)**, the particle deposition was more prominent in the right branches of the bronchial airways (right lung) than in the left branches (left lung) for all of the considered cases. Flow rates affect regional deposition by influencing the airflow stream and recirculation areas of the complex geometry. Thus, the generated inspiratory flow depends on the patient's inspiratory effort, as shown in **Fig 2.11(b)**. The inspiratory effort produced by patients, inhaling through a device, generates negative pressure in the mouth. The mouth pressure versus time curve was defined as an inhalation profile [53,54].

Talaat et al. [54] considered the transient inhalation profile, aiming to develop/validate a computational model for MDI-releasing delivery and evaluate the device actuation effects on dose distribution using the newly developed model. **Fig 2.12** shows the transient inhalation flow rate with 60 L/min as the peak inhalation rate. The MDI was actuated at different times to assess the effect of the actuation timing on the regional deposition. An integrated MDI–mouth–lung (G9) geometry was developed. An albuterol MDI with the chlorofluorocarbon propellant was simulated, featuring a polydisperse aerosol size distribution measured by laser light scatter and aerosol discharge velocity derived from measurements taken using a phase Doppler anemometry.

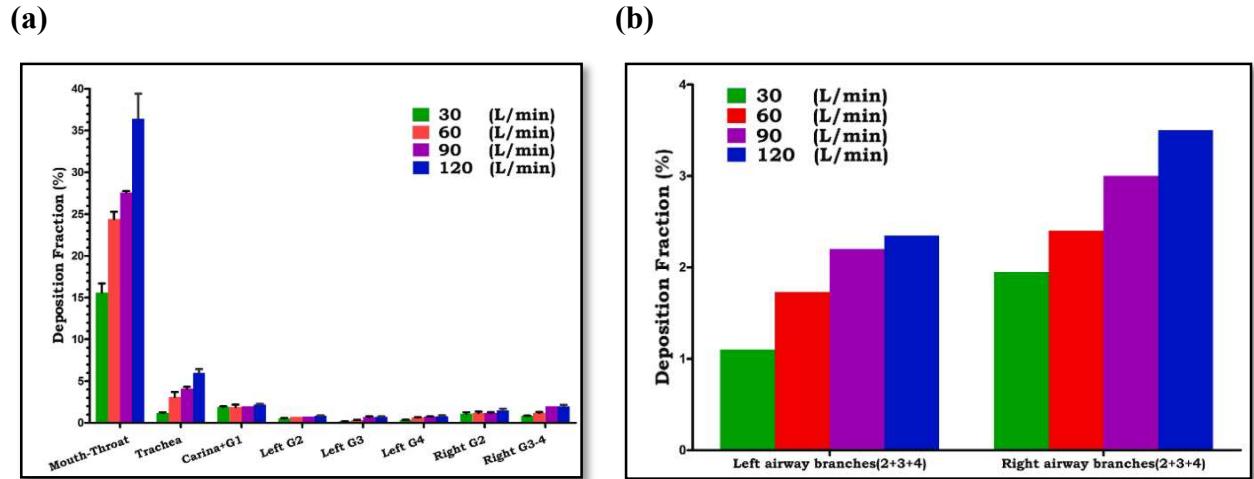


Fig 2.11. (a) Bar chart of regional deposition fraction at four constant inhalation flow rates; and **(b)** Bar chart of total deposition fractions in the left and right airway branches (generations 2-4) [52].

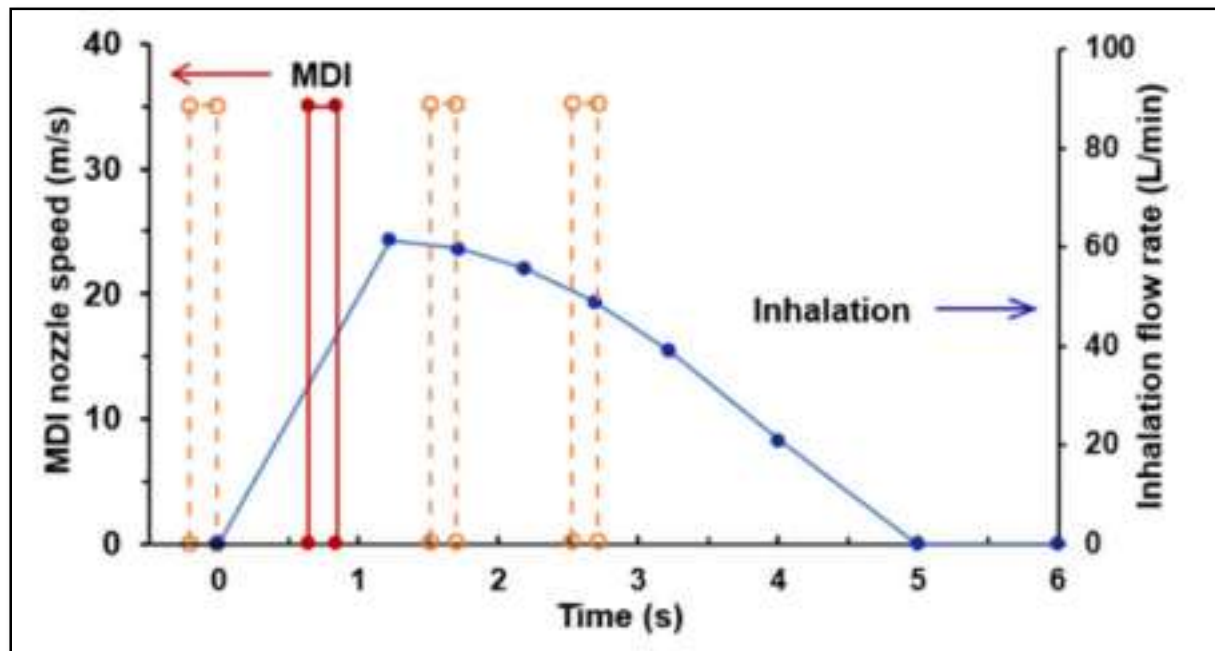


Fig 2.12. Deep, slow inhalation and MDI administration waveforms [54].

The highly transient, multiscale airflow and droplet dynamics were simulated by using large eddy simulation (LES) and Lagrangian tracking with a sufficiently fine computational mesh. LES emerges as a favorable middle ground, directly resolving the larger turbulent structures while modeling the smaller scales using a subgrid-scale model. This approach allows for a more accurate representation of significant flow features and is less computationally demanding than direct

numerical simulation (DNS). LES provides a detailed understanding of large-scale turbulence dynamics, making it particularly useful for applications requiring insight into transient behavior and complex interactions within the flow. Thus, many researchers regard LES as a suitable and reliable method for simulating airflow within this complex geometry [54, 55].

Moreover, high-speed camera imaging of the MDI plume formation was conducted and compared with LES predictions [54]. The aerosol discharge velocity at the MDI orifice was reversely determined to be 40 *m/s* based on the phase Doppler anemometry measurements at two different locations from the mouthpiece. The LES-predicted instantaneous vortex structures and corresponding spray clouds resembled each other. There are three phases of the MDI plume evolution (discharging, dispersion, and dispensing), each with distinct features regardless of the actuation time. Good agreement was achieved between the predicted and measured doses in both the device, mouth–throat, and lung [54]. The LES-predicted MDI nozzle flows also compared favorably with the MDI plume images recorded using the Phantom VEO high-speed camera (refer to **Fig 2.13(a)**).

Droplet dynamics in the third phase (200 *ms* and beyond) are shown in **Fig 2.13(b)**, respectively, for the case with MDI firing into quiescent airspace. Without an inhalation flow, the plume moved straight forward without apparent dispersion as opposed to the prompt dispersion in the control case. The large droplets (red color) quickly reduced their speeds; from 200 *ms*, the inhalation started, and droplet dispersion became intensified. At the same time, droplets were transported by the inspiratory flow and advanced to the pharynx at 300 *ms* and the lower trachea at 400 *ms*.

Chrystyn et al. [56] conducted an *in-vitro* study examining the COPD inhalation profile for DPI. The main strength of their study was the use of a methodology (lung simulator), which showed that patient inhalation profiles could be used *in-vitro* to characterize the dose that the patient would receive during real-life use of the inhaler. Including a range of throat anatomies and inhalation profiles from real COPD patients represents further strengths [56]. Allen et al. [57] confirm that the inhalation profile for pediatric upper airway is different from that of adults, as well as the complexity of geometry, which is the lower tracheal Reynolds number due to the smaller characteristic dimensions. They started a nonlinear relation between the pressure drop (dependent on the geometry complexity) and flow rate, like $\Delta P = 0.868 * Q^2$.

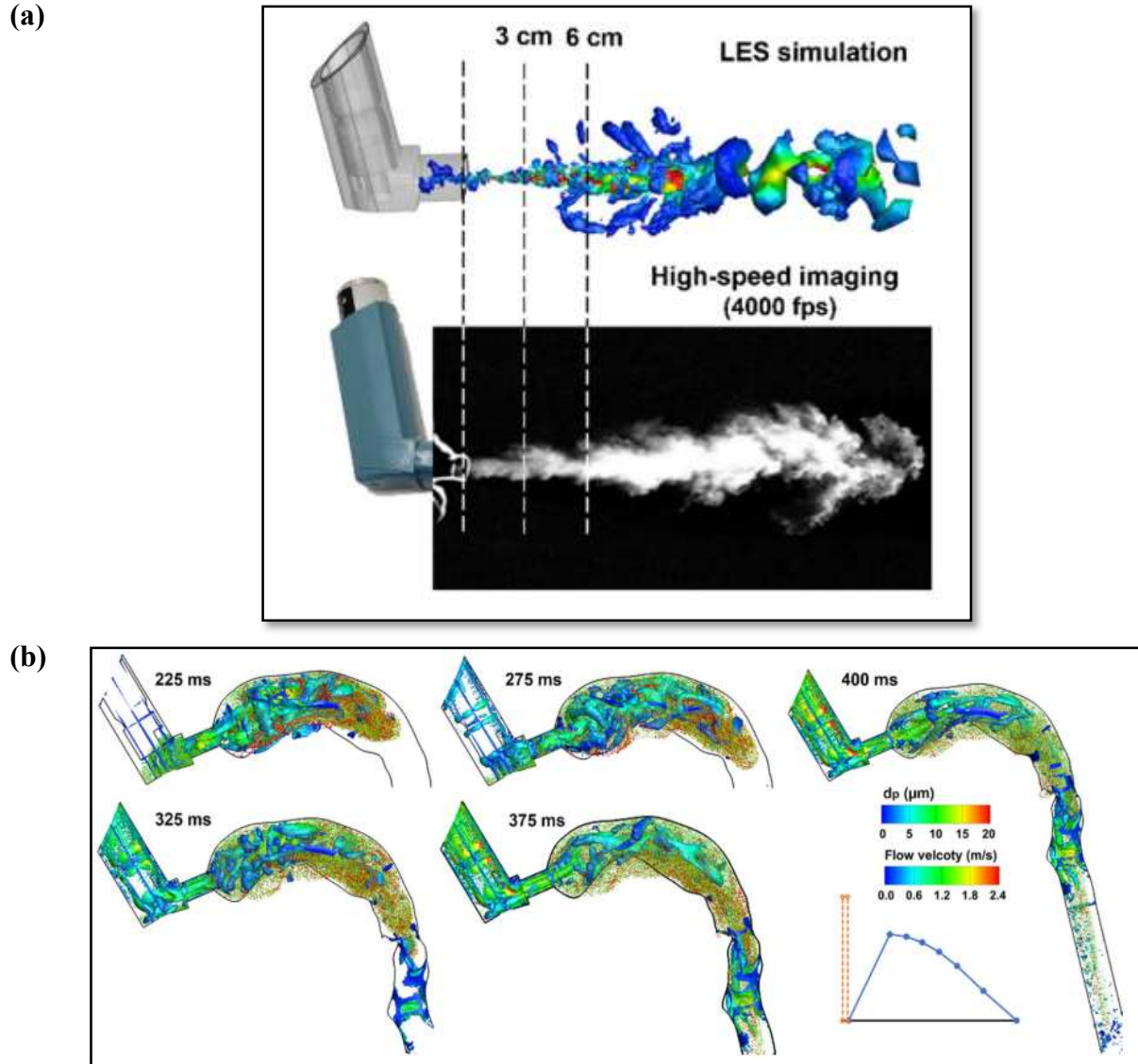


Fig 2.13. (a) Comparison between CFD-predicted and experimentally recorded MDI plumes recorded; and (b) Droplet dynamics between 200-400 *ms* [54].

Zhou et al. [58] conducted a study on the effect of inhaler position with realistic pediatric geometry, as shown in **Fig 2.14**. The oral cavity is the key region with the largest deposition fraction (DF) and deposition efficiency (DE). The DF and DE of the oral cavity are negatively correlated with the L_m (i.e., the distance from the center of the inhaler outlet to the tongue surface) when the mass median aerodynamic diameter of 150 μg indacaterol was utilized as the input parameter. This highlights the essential role of relative position parameters in the particle deposition in the mouth-throat (MT).

Numerous studies have examined the effects of parameters such as particle size, inhalation flow rate, and breathing mode on particle transport and deposition within the human upper airway. However, discussions on other important factors, including inlet airflow temperature and the presence of a mucus layer, which can alter flow patterns due to heat transfer, are relatively limited in the existing literature. Very few studies have examined the impact of the mucus layer and airway tissue on airflow dynamics and thermal characteristics within human upper airway models. Chen et al. [59] employ the transition SST turbulence model to simulate flow and temperature fields in a simplified mouth-throat geometry incorporating a mucus layer. Their findings indicated that aerosol transport and deposition are significantly affected by heat transfer resulting from the presence of the mucus layer and airway [59]. Further, they extended their investigation into a realistic human airway model incorporating a mucus layer and uniform inlet air temperature, reporting that neglecting boundary heat transfer calculations resulted in variations of approximately 10% in aerosol deposition fractions [60]. Commonly, the mucus layer is simplified to a solid material with properties similar to those of water, as defined in the works of Jahed et al. and Narayanan et al. [61, 62]. The mucociliary layer in the respiratory tract acts as the first line of defense against pathogens and chemical pollutants in inhaled air [62]. The mucus layer traps the inhaled particles, which are then removed from the lungs by the rhythmic beating of the cilia. Mucus is a viscoelastic gel that resists deformation at low shear rates and exhibits strong shear-thinning behavior under high shear [63]. From the perspective of CFD simulations, it is difficult to use classical models, such as the volume of fluid or Eulerian–Eulerian multiphase methods. Recently, a new formulation, the Eulerian wall film (EWF) model, has been developed for thin films adhered to walls. The EWF model allows for the prediction of the evolution of thin fluid films on the surface of walls. The EWF model allows for the prediction of the evolution of thin fluid films on the surface of walls [64]. Although it is a relatively recent development, it has been successfully applied in predicting condensation, evaporation, and the movement of fuel films subjected to shear forces from the gas phase in gas turbines [65]. This method allows the computationally inexpensive calculation of the main interactions between a flow and a liquid film sliding on a wall [66, 67].

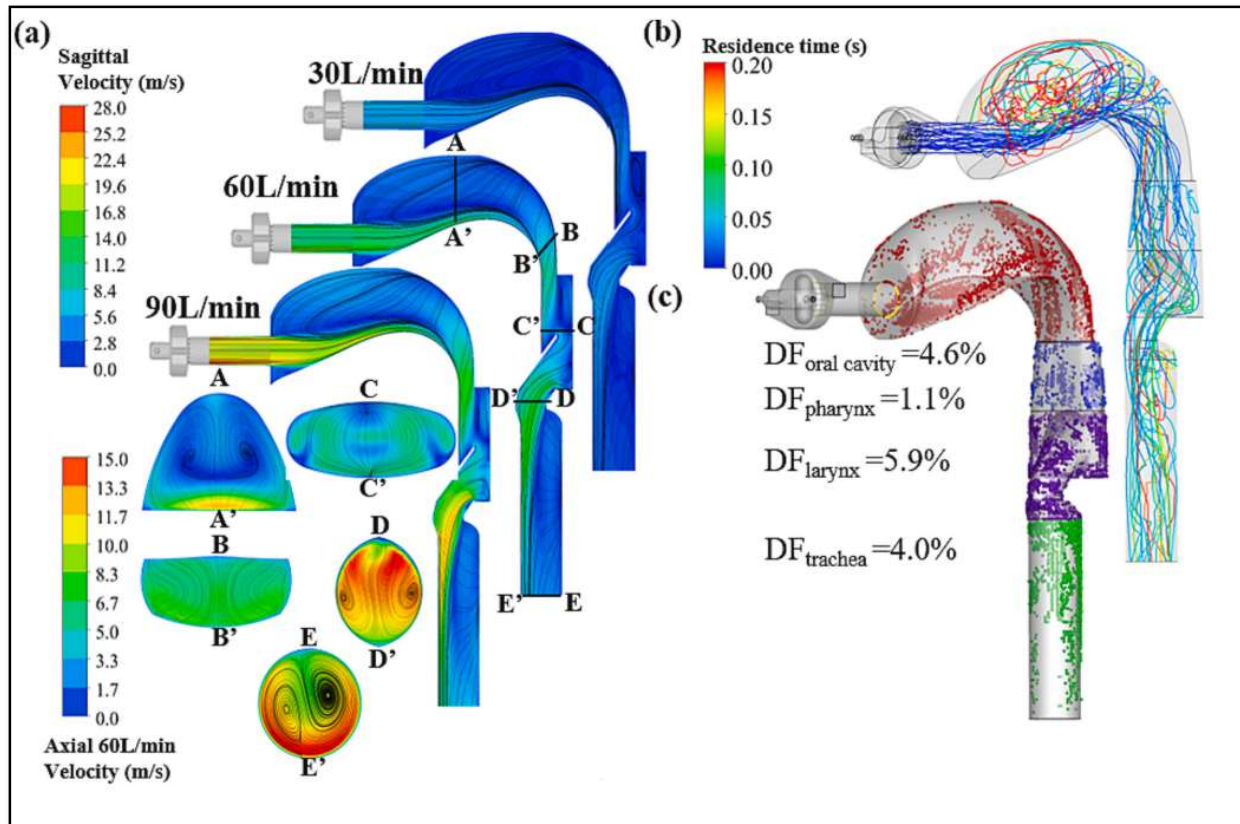


Fig 2.14. (a) Velocity contours and airflow streamline at sagittal and axial cross sections at different flow rates; (b) Particle trajectory against residence time; and (c) Deposition distribution for particles [58].

2.2 Research Gaps

A thorough review of the literature has identified research gaps in pMDI studies as follows:

- **Device Geometry and Design:** While pMDIs are widely used for pulmonary drug delivery, limited experimental and computational studies assess the impact of actuator and nozzle design, particularly under suboptimal or improper patient usage scenarios.
- **In-vitro Testing Limitations:** Many in-vitro setups fail to replicate real-world inhalation conditions such as mucus, inhalation profile, and surface tension of MT, leading to discrepancies in validating CFD models and aerosol dispersion predictions.
- **CFD Model Validation:** Existing CFD studies on aerosol behavior often lack robust validation through in-vitro experiments, which is crucial for accurate predictions of flow behavior and particle size distributions.

- **Environmental Effects:** The influence of temperature and humidity on pMDI aerosol characteristics and deposition efficiency within the respiratory tract remains underexplored.
- **Physiological Factors in Aerosol Delivery:** Factors such as inhalation profiles, mucus layer, airway movement, nasal inhalation, and tongue dynamics during medication delivery, especially with SMI devices, have received little attention in both experimental and numerical studies.
- **Numerical Simulation Challenges:** Current numerical methods often lack accuracy in simulating aerosol behavior. Mesh modifications are necessary to improve resolution while balancing computational efficiency. More advanced numerical techniques are needed to enhance accuracy without significantly increasing computational costs.
- **Patient-Specific Variability:** There is a lack of research on how patient-specific factors, such as inhalation coordination errors, mucus presence, airway motion, and tongue placement, affect aerosol deposition efficiency.
- **pMDI Formulation Optimization:** The role of excipients, surfactants, and additives in enhancing aerosol formation, plume stability, and lung deposition under variable inhalation conditions remains under-investigated.
- **Pediatric Airway Considerations:** Most studies focus on adult airway geometries, neglecting key anatomical differences in pediatric respiratory systems. Further research is needed to optimize pMDIs for pediatric patients.

2.3 Research Objectives

The primary goal of this research is to enhance the efficiency of pulmonary drug delivery using pMDI devices through a combined approach of experimental investigations and numerical simulations. Experimental validation is crucial to ensuring the accuracy and reliability of the computational models.

A key aspect of this study involves developing a three-dimensional (3D)-printed mouth-throat geometry that replicates realistic anatomical features, enabling precise and localized measurements of aerosol deposition. These anatomically accurate geometries were integrated with the NGI for detailed experimental analyses. The NGI was employed to assess particle deposition and size

distribution, collecting aerosolized particles across multiple stages based on their aerodynamic diameters. To mitigate evaporation risks, an NGI cooling box was used to maintain lower temperatures, preventing the loss of volatile aerosol components—an effect typically not accounted for in numerical models. Additionally, high-performance liquid chromatography (HPLC) was used to quantify the Active Pharmaceutical Ingredient (API) deposited at each NGI stage and collection cup, further ensuring the reliability of simulation predictions.

This research is structured around three key objectives, each addressing critical factors in optimizing pulmonary drug delivery. The ultimate goal is to accurately predict aerosol deposition, improving our understanding of pMDI drug behavior within a realistic mouth-throat model. This will lead to more effective pulmonary drug delivery and a reduction in potential adverse effects. The specific objectives are outlined below:

Objective 1: Effective Use of pMDI: Essential for Minimizing Drug Loss in the Mouth

The primary objective of this study is to model drug aerosol dynamics, size distribution, and deposition of a pMDI using the $k-\omega$ SST turbulence model combined with the Discrete Phase Model (DPM) to track aerosol trajectories within the USP-IP geometry. This phase focuses on developing a predictive model that accurately characterizes the pMDI aerosol plume at the onset of actuation and within the mouth, where significant drug loss occurs.

Key aspects of this objective include:

- Investigating the effects of constant inhalation flow rates on particle deposition within the induction port and the distribution of actuated particles from the inhaler.
- Examining the impact of cone angle and initial plume velocity on the median particle diameter.
- Comparing aerosol droplet behavior across various conditions to assess its influence on flow patterns, aerosol deposition, and size distribution.

This modeling effort aims to enhance our understanding of aerosol transport mechanisms, ultimately improving drug delivery efficiency and reducing drug losses within the upper airway.

Objective 2: Impact of COPD Breathing Profile and Relative Humidity on pMDI Aerosol Drug Delivery

The second objective of this study is to investigate the effects of a realistic COPD inhalation profile

on airflow hydrodynamics, aerosol deposition, and particle size distribution inside a USP-IP geometry using a pMDI. To account for the influence of relative humidity (%RH) within a realistic mouth-throat model, different %RH levels were applied in combination with various constant flow rates. Since humidity significantly affects hygroscopic particle growth and alters airflow patterns, the Shear Stress Transport (SST) $k-\omega$ turbulence model was employed to enhance simulation accuracy.

Key aspects of this objective include:

- Examining the effects of relative humidity on aerosol deposition by testing different %RH levels alongside varying flow rates.
- Analyzing turbulent kinetic energy and vortex structures to understand their role in particle transport and deposition.
- Validating the numerical model using experimental data under dry conditions (50% RH airflow), followed by simulations at higher flow rates and increased humidity levels.
- Investigating recirculation regions and their influence on aerosol behavior under different inhalation and humidity conditions.

This study aims to improve our understanding of how COPD-specific inhalation patterns and humidity variations impact drug delivery, ultimately contributing to the optimization of pMDI performance for patients with obstructive lung diseases.

Objective 3: Pediatric Airflow Patterns and pMDI Drug Delivery: Effects of Presence of Mucus with Cystic Fibrosis (CF) Inhalation Profile

The third objective of this study is to investigate the effects of a mucus layer on droplet deposition, size distribution, and airflow patterns within a realistic pediatric mouth-throat geometry using a pressurized metered-dose inhaler (pMDI).

Key aspects of this objective include:

- Evaluating the influence of mucus viscosity (Newtonian vs. shear-thinning behavior) on aerosol deposition efficiency and droplet size distribution.

- Analyzing the effects of different inhalation profiles, including constant flow and COPD-like (CF) inhalation profiles, on airflow dynamics and deposition patterns.
- Utilizing Large Eddy Simulation (LES) to study the interplay between airflow dynamics, secondary flow rates, and particle deposition.
- Developing a correlation among deposition efficiency, wall shear stress, and mucus viscosity, providing insight into how these factors impact drug transport in pediatric airways.
- Conducting a sensitivity analysis using the Morris method to determine the relative importance of different variables affecting deposition efficiency.
- Comparing aerosol deposition in pediatric vs. adult mouth-throat geometries to highlight critical differences in drug delivery performance between age groups.

This study aims to improve our understanding of mucus-airflow interactions in pediatric airways, ultimately leading to better inhaler design and optimized drug delivery strategies for young patients.

2.4 Nomenclatures

Abbreviation

COPD	chronic obstructive pulmonary disease
CF	cystic fibrosis
CFC	chlorofluorocarbons
CFD	computational fluid dynamics
DF/DE	deposition fraction/efficiency
DNS	direct numerical solution
DPI	dry powder inhaler
DPM	discrete phase model
EWF	Eulerian wall film
HFA	hydrofluoroalkanes
LES	large eddy simulation
LRN	low Reynolds number
MP	mouthpiece

pMDI	pressurized metered dose inhaler
SMI	soft mist inhaler
St	Stokes number
USP	United States Pharmacopeia

Greek Letters

ρ	air density, [kg/m ³]
ρ_d	droplet density, [kg/m ³]
μ	viscosity of air molecules, [kg/m.s]

Notations

u	velocity of air, [m/s]
u_t	settling velocity, [m/s]
g	gravitational acceleration, [m/s ²]
D_{in}, D_{out}	USP-IP diameters for inlet and outlet boundary, [m]
d_p	particle diameter, [m]
d_{ae}	aerodynamic diameter, [m]
Q	air flow rate, [L/min]
Δp	pressure drop, [Pa]

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Chapter 3 – Experimental Methodology

3.1 Experimental Setup

3.1.1 Next Generation Impactor (NGI)

The regional deposition of particles in the lung is strongly dependent on their aerodynamic diameter. The lung essentially acts as an aerosol classifier, with larger particles predominantly depositing in the upper respiratory tract, particularly at airway bifurcations. In comparison, smaller particles penetrate and deposit deeper within the lungs [1]. Due to three primary advantages, impactors are the preferred instruments for assessing the in vitro delivery efficiency of inhaled medications. First, impactors provide a drug-specific particle size distribution using targeted drug assays, thereby avoiding interference from non-drug constituents. Second, impactors measure the size distribution of the entire delivered dose rather than analyzing potentially unrepresentative subsamples. Lastly, impactors classify aerosol particles according to aerodynamic diameter, aligning closely with particle deposition mechanisms in the respiratory tract [1, 2]. The cascade impactor is, therefore, a logical choice for evaluating aerosols emitted from metered-dose inhalers (MDIs). However, it is crucial to recognize that cascade impactors do not accurately simulate actual lung conditions due to several inherent limitations, including the geometry of the impaction sites, the hardness and coatings of the collection surfaces, and their operation under a constant flow rate.

Additionally, the stages of a cascade impactor do not correspond directly to specific deposition sites within the respiratory tract. The Andersen cascade impactor was initially developed in 1958 with six stages to sample airborne viable particles onto agar gel contained in Petri dishes [3]. In 1971, an improved eight-stage version, known as the Andersen impactor, was introduced by Riker Laboratories [4] (see **Fig. 3.1(a)**).

The Next Generation Impactor (NGI) was used in our experiments (refer to **Fig 3.1(b)**). Unlike the Andersen Cascade Impactor (ACI), the NGI is arranged horizontally rather than stacked vertically. Using collection cups as impaction surfaces simplifies handling and allows for easier design modifications [5]. The NGI has been found to be operable across a broad range of flow rates.

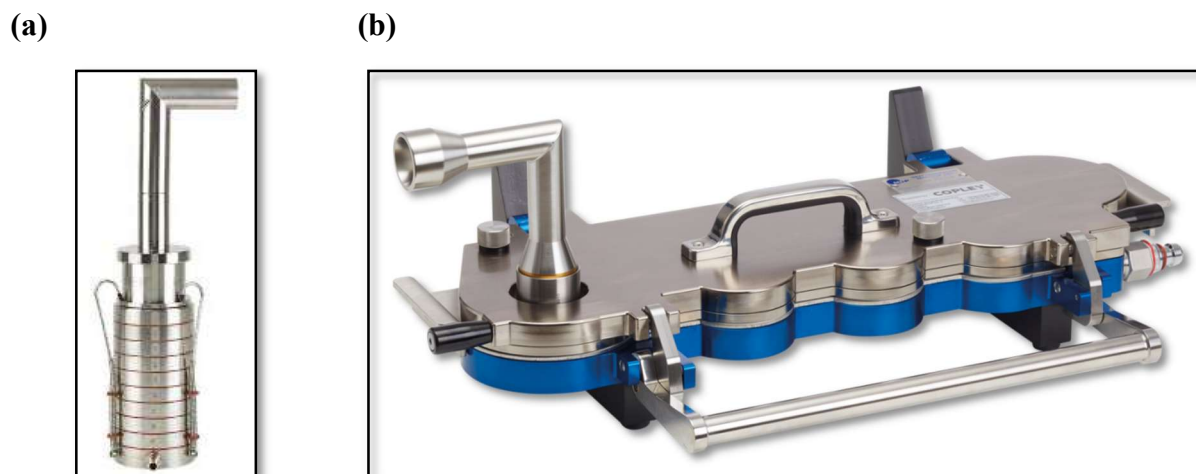


Fig 3.1. (a) Anderson cascade impactor; and (b) Next-generation impactor (NGI) (Copley Instruments Ltd, UK) [6].

Fig 3.2 is a schematic diagram of NGI stages, nozzles, and inter stages to clarify the NGI planar mechanism [6]. NGI is a planar impactor comprising seven stages, each consisting of removable collection cups, also called impaction surfaces. These cups are arranged horizontally and terminate in a micro-orifice collector (MOC), as shown in **Fig 3.2(a)** [6]. The NGI assembly comprises a base supporting a frame that houses the collection cups and a lid that secures the seal body, which contains eight nozzle sections. The lid also incorporates inter-stage passageways and is fastened to the seal body using two screws with torque limitations.

Each nozzle section corresponds to one of the seven stages or the final stage of the multi-orifice cascade impactor (MOC). Each section is designed with a specific number and size of holes to achieve precise particle separation, except for the first stage, which has a slightly different configuration. O-rings surrounding each nozzle ensure a tight seal, preventing leakage during aerosol testing. The collection cups have a distinctive tear-shaped design, with larger ends positioned directly beneath the nozzle openings where particle impaction occurs. Airflow moves across each collection surface from this impaction area toward the smaller end, where it is drawn upward through a cavity in the lid and directed to the subsequent stage. A unique external design for the particle collection cups enables them to be arranged in a single plane, allowing for the removal of the entire unit from the impactor. This feature facilitates the automation of the NGI, which was a primary design requirement.

As shown in **Fig 3.2(b)**, the nozzle plate and impaction plate are shown with the relevant dimensions labeled. Conventional theory for single-nozzle impactors has demonstrated that two dimensionless parameters are important in defining the flow field through such a nozzle, and the flow fields are essential in determining the sharpness of the cut of the stage [5]. These parameters are the ratio of the nozzle-to-plate distance to the nozzle diameter and the Reynolds number, Re , defined as [1]:

$$Re = \frac{4\rho Q}{n\pi\mu D} \quad (3.1)$$

where ρ is the air density, Q is the volumetric airflow rate, D is the nozzle diameter, μ is the dynamic viscosity of air, and n is the number of nozzle holes per stage. Thus, for a specific flow rate, n and W can be selected to keep Re in the desired range. In this process, particles in the airstream continue along their original path rather than aligning with the altered airflow. Stokes (St) number (Eq. (3.2)) is a dimensionless quantity used to predict deposition caused by impaction for a particle traveling through an airway.

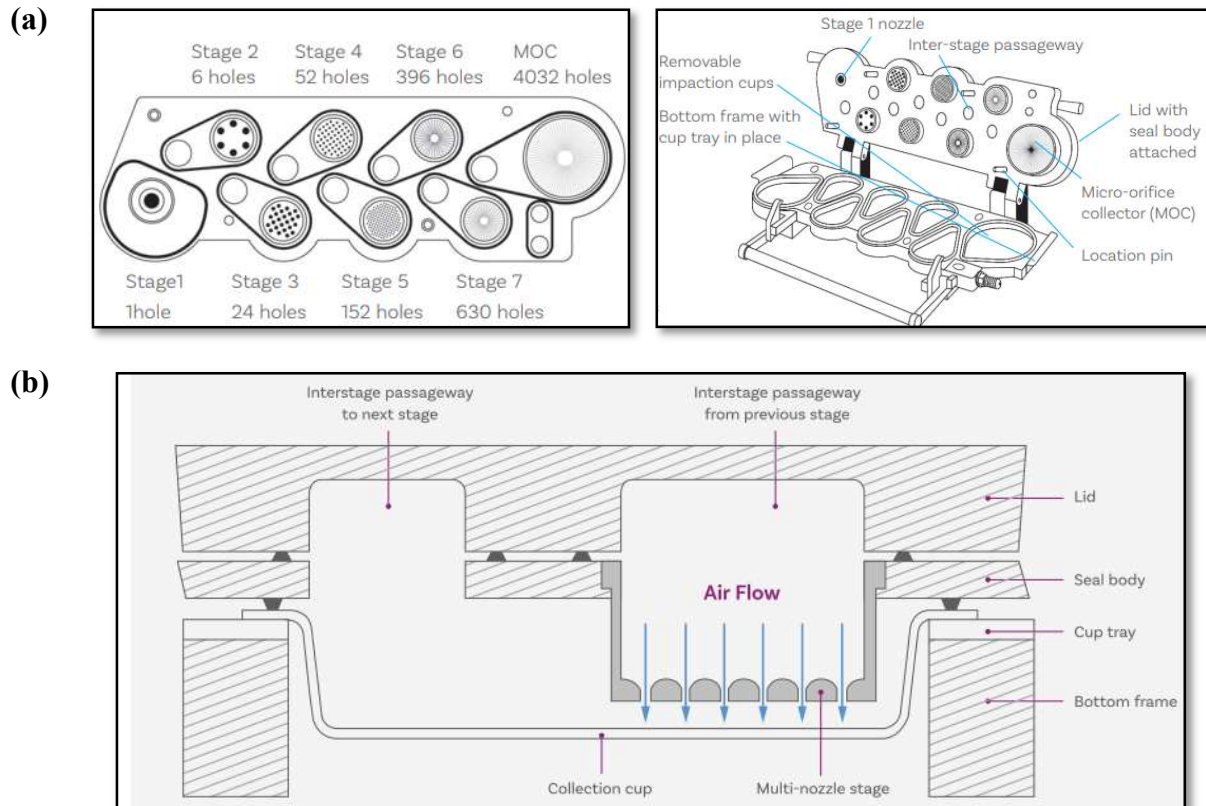


Fig 3.2. (a) Schematic of NGI in an open configuration with all the stages; and **(b)** NGI inter-stage [6].

Stokes number is important in determining the cut size of the impactor stage, which is defined in Eq. (3.2) [1]:

$$St = \frac{4\rho_p Q C_p d_p^2}{9n\pi\mu D^3} \quad (3.2)$$

where ρ_p is the particle density, C_p is the slip correction factor, and d_p is the physical particle diameter.

Additional equipment necessary for the NGI experimental setup (shown in **Fig 3.3**) includes a vacuum pump, which draws air through the system at the specified volumetric flow rate to achieve sonic flow. A mouthpiece adapter (MP) connects the inhaler to the induction port (IP) or mouth-throat (MT) airway, ensuring a proper seal to prevent drug or air leakage. Additionally, an NGI cooling box may be included to enhance the accuracy of measurements involving formulations containing volatile components, such as propellants or solvents. The cooling box maintains a controlled, reduced temperature to minimize the evaporation of these volatile substances, thereby providing more precise and reliable particle measurements. A critical flow controller generates a standardized breath profile (constant flow rate), depending on the available respiratory volume, ensuring consistent and reproducible pMDI testing. Ultimately, a flowmeter is crucial for accurately measuring and monitoring airflow rates during testing.

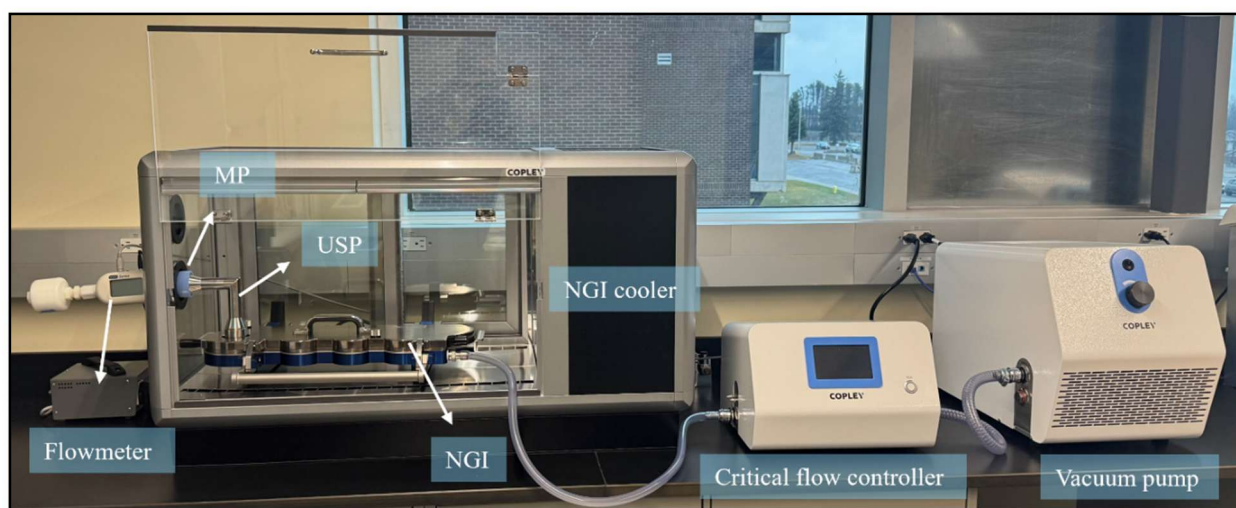


Fig 3.3. The experimental setup for the evaluation of drug deposition.

The NGI operates at flow rates ranging from 15 to 100 *L/min*, with cut sizes spanning a particle size range nominally from 0.25 to 11 *mm* in aerodynamic diameter [6]. The NGI is designed so that

the spacing of the stages varies between four and five cut points per decade of particle size, depending on the flow rate chosen for the measurement. The NGI is sealed by locking the lid onto the bottom frame using a past-center cam lock handle mechanism at the front of the device. The cut-off diameters for the relevant stages at volumetric flow rates of 15, 30, and 60 *L/min* are provided in **Table 3.1**.

Table 3.1. NGI cut-off sizes at different flow rates [6].

Stage	15 <i>L/min</i>	30 <i>L/min</i>	60 <i>L/min</i>
Stage 1	14.10	11.72	8.06
Stage 2	8.61	6.40	4.46
Stage 3	5.39	3.99	2.82
Stage 4	3.30	2.30	1.66
Stage 5	2.08	1.36	0.94
Stage 6	1.36	0.83	0.55
Stage 7	0.98	0.54	0.34
Stage 8	0.70	0.36	0.14

3.1.2 High-Performance Liquid Chromatography (HPLC)

High-performance liquid chromatography (HPLC) is employed to separate, identify, and quantify compounds within a liquid mixture. During an HPLC analysis, a small volume of sample solution is injected into an HPLC column packed with fine particles (usually 3 to 5 microns in diameter), known as the stationary phase. Individual components of the sample mixture pass through the column under high pressure provided by an HPLC pump, using a liquid mobile phase. Typical mobile phase flow rates for routine analyses in quality control and quality assurance laboratories range from 1 to 2 *mL/min*.

The selectivity properties of the HPLC column depend on chemical and physical interactions between the analyte molecules and the stationary-phase particles. A diverse array of column

materials and packing chemistries is available, catering to a broad range of applications. The chemical interactions between the analytes and the stationary phase result in differential retention times, enabling the separation of individual sample components, which are subsequently detected and quantified as they exit the column [7].

(a)



(b)

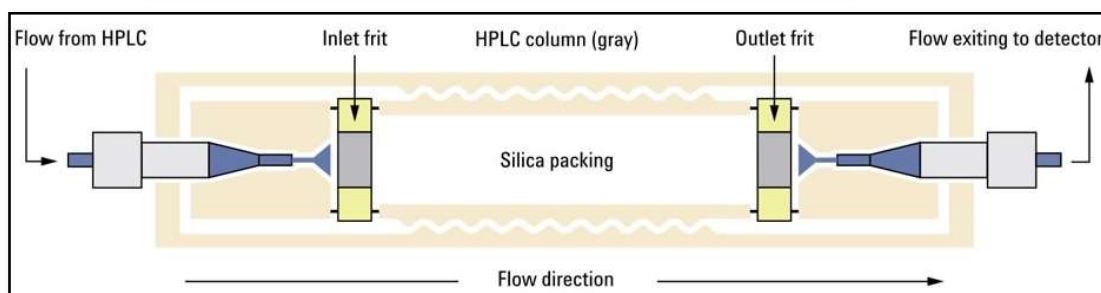


Fig 3.4. (a) High-performance liquid chromatography; and **(b)** Anatomy of an HPLC column [8].

Molecules exhibiting similar chromatographic polarities attract each other, whereas molecules with different polarities experience weaker interactions or may even repel each other. In normal-phase (NP) chromatography, nonpolar compounds elute first, while polar substances have longer retention times. Conversely, reversed-phase chromatography, which is widely used in HPLC analyses, elutes the polar compounds first, and the more nonpolar substances are retained longer in the column. Liquid chromatography techniques can be either analytical or preparative. Both

modes employ high pressures (commonly ranging from 600 to 1300 *bar*) to drive the mobile phase through the packed stationary-phase column to achieve effective compound separation. A standard HPLC system consists of a pump, an injector, a column compartment that houses the HPLC column, and a detector. The pump facilitates the controlled flow of mobile phase solvents through the system at specified flow rates (typically between 0.4 and 2 *mL/min*) at pressures ranging from 200 to 1300 *bar*.

Additionally, HPLC pumps enable the mixing of solvents. A solvent gradient can be created by gradually adjusting the ratio between two solvents (commonly designated as solvent A and solvent B), enhancing the elution strength and optimizing separation [8, 9]. Typical HPLC columns are cylindrical stainless-steel structures filled with silica particles that often have chemically modified surfaces. Column dimensions influence the column's sensitivity, efficiency, and analyte-loading capacity. Upon sample injection, analytes interact differently with the stationary-phase materials, resulting in variations in retention time and leading to effective compound separation.

3.1.3 Mouth-Throat Geometries

3.1.3.1 United States Pharmacopeia (USP) Induction Port (IP)

When new medical devices are being introduced, they are often tested to the standards of the United States Pharmacopeia (USP), which is recognized in more than 130 countries [10]. One such test of inhaler devices involves the use of a USP-IP in conjunction with a cascade impactor. The USP throat is a 90° bend metal pipe with a uniform cross-section, slight contractions at the inlet, and a small diffuser at the outlet (see **Fig 3.5**). A deposition analysis can be performed by simultaneously applying suction to this system and releasing particles into the air stream upstream to the USP-IP. In the USP-IP, large particles will deposit first because they are unable to follow the airflow around the bend of the induction port. This discharge of particles is meant to resemble the airflow in the oropharynx. Using this setup, the levels of deposition in the airway can be mapped to provide an estimation of the drugs available to reach the lungs and eventually enter the bloodstream.



Fig 3.5. USP-IP [6].

The USP throat's ability to resemble the oropharynx regarding deposition efficiency has been studied by Zang et al. [11], who found that the USP-IP was inadequate in mimicking the deposition characteristics of the upper airway. This was mainly because the USP-IP failed to simulate the airflow's acceleration, deceleration and rotation, which are brought about by the existing variation in the cross-sectional area of the mouth-throat region. A comparison of the experimental deposition values in the USP-IP with the *in-vivo* results obtained by Stalhofen et al. [12] showed the particle deposition in the USP-IP to be unrealistically low. Zang et al. [11] also analyzed a highly idealized mouth-throat model with a non-uniform cross-sectional area and a bend contraction to simulate the oral cavity. They found the idealized throat geometry to follow the average curve of total deposition efficiency obtained *in vivo* by Stalhofen et al. [12]. They suggested using their geometry as a substitute for the inadequate USP-IP.

3.1.3.2 Three-Dimensional (3D) Printing

To create the pediatric mouth-throat geometry and standard induction port, I utilized the Ultimaker S3 and Ultimaker S5 3D printers, as shown in **Fig 3.6(a)**. These printers are well-regarded for their precision, reliability, and versatility in producing high-quality prototypes, making them ideal for complex geometries required in aerosol deposition studies. As shown in **Fig 3.6(b)**, a 3-D print of pediatric mouth-throat geometry was developed from a CT scan provided by Bickmann et al. [13]. The precision of the printing nozzle in 3D printers is suitable for accurately reproducing small-scale geometries, such as those required in pediatric respiratory models. The Ultimaker S3 and S5 are equipped with advanced features, including a precise print head, a heated

bed, and a robust extruder system, which enable the creation of detailed and accurate models with smooth finishes. These features enable consistent printing with various materials, ensuring that the models printed for my research maintain high fidelity to the intended designs.

The Ultimaker S3 and S5 (Ultimaker S3, Lakehead University and Ultimaker S5, Confederation College) offer excellent compatibility with various materials. In this case, tough polylactic acid (PLA) was selected for its combination of ease of use, mechanical strength, and printability. Tough PLA is an enhanced version of standard PLA, offering improved durability, impact resistance, and layer adhesion. Compared to standard PLA, which can be brittle, tough PLA offers greater toughness, making it less prone to cracking or breaking during handling or experimental testing. This added strength is particularly important for creating anatomical models that can withstand mechanical stress, such as during airflow simulations and repeated handling.

(a)



(b)



Fig 3.6. (a) Ultimaker S3, S5 (Left to right, Lakehead University, Confederation College); and (b) Pediatric MT.

In addition to its superior strength, tough PLA is easy to post-process. One of the major advantages of this material is its ability to be easily polished and smoothed after printing. Unlike other 3D printing materials, such as acrylonitrile butadiene styrene or Nylon, which require more intensive post-processing (such as high-temperature curing or solvent treatments), Tough PLA can be easily sanded and polished to achieve a smooth surface finish. This property is especially beneficial when

working with precise geometries, as it ensures the printed models maintain their accuracy for computational fluid dynamics (CFD) simulations without introducing surface imperfections that could affect experimental results [14].

Key parameters in the 3D printing process, such as print resolution, layer height, and print speed, were carefully optimized [15]. The resolution, typically set at 0.1 to 0.2 *mm*, was chosen to capture the fine anatomical details of the pediatric MT region. The print speed was adjusted to strike a balance between precision and efficiency, ensuring the models were produced in a timely manner without compromising quality. Temperature settings for the heated bed and extruder were also fine-tuned to prevent warping and ensure good layer adhesion, further enhancing the accuracy of the printed geometries. The combination of the Ultimaker S3 and S5 printers, along with tough PLA, allowed for the efficient and accurate production of the mouth-throat geometries used in my research. These 3D printed models provided a strong, durable, and highly detailed foundation for studying aerosol deposition and airflow patterns in the pediatric respiratory tract.

3.2 Nomenclatures

Abbreviations

ACI	Andersen cascade impactor
CFD	computational fluid dynamics
3D	3-dimensional
HPLC	high-performance liquid chromatography
IP	induction port
MOC	micro-orifice collector
MP	mouthpiece
MT	mouth-throat
NGI	next generation impactor
PLA	poly lactic acid
pMDI	pressurized metered dose inhaler
USP	United States Pharmacopeia

Greek letters

μ	viscosity of air molecules, [kg/m.s]
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ρ	air density, [kg/m ³]
ρ_p	particle density, [kg/m ³]

Notations

Re	Reynolds number, [-]
Q	volumetric flow rate, [L/min]
D	nozzle diameter, [m]
n	number of nozzle holes per stage, [-]
C_p	slip correction factor, [-]
d_p	physical particle diameter, [m]

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Chapter 4 – CFD Model Development

Over the past few decades, computational fluid dynamics (CFD) has become a vital tool for analyzing fluid flow and particle transport across various fields, including chemical and environmental engineering, as well as human respiratory systems. Rooted in the fundamental equations of fluid dynamics, which encapsulate the conservation laws of physics [1, 2], CFD provides a computational framework that surpasses traditional experimental methods in both detail and cost-effectiveness. This approach allows researchers to investigate complex fluid interactions that are often difficult or impractical to measure experimentally. Key insights gained through CFD include flow turbulence characteristics and their evolution, velocity profiles [3], breathing dynamics [4], the interaction between discrete particles and a continuous phase [5], and the combined effects of inertia and gravity on particle transport [6].

In cases where experimental data are scarce, a validated CFD model can serve as a powerful tool for exploring additional aspects of the system, reducing the need for further physical experimentation and lowering associated costs. Furthermore, CFD allows for the safe analysis of volatile or complex substances, such as artificial mucus, before committing to time-intensive experimental setups. This predictive capability helps optimize experimental design, reducing resource consumption and minimizing potential risks associated with handling hazardous or intricate fluid systems. Another significant advantage is the flexibility to modify and test complex human respiratory tract geometries with ease, without the constraints of physical fabrication.

To accurately model complex fluid dynamics, CFD simulations rely on key assumptions to simplify mathematical formulations. These include treating fluids as continuous media, assuming incompressible and steady-state conditions, and selecting either laminar or turbulent flow based on the Reynolds number. The Navier-Stokes equations, fundamental to fluid dynamics, are adapted and simplified to suit various physical scenarios. While these assumptions facilitate computational efficiency, their validity depends on the specific context and required accuracy, emphasizing the need for careful evaluation when interpreting CFD results.

4.1 The Navier-Stokes Equations

By solving the Navier-Stokes (NS) equations for gas-aerosol multiphase flows, CFD models enable the detailed quantification of gas flow and aerosol dynamics, providing insights into total and regional aerosol deposition patterns within the respiratory system [7]. The fundamental principles of fluid flow are governed by the conservation of mass and momentum [8, 9]. The mass conservation principle is mathematically expressed through the continuity equation, ensuring that mass is neither created nor destroyed within a fluid system. Similarly, momentum conservation follows Newton's second law of motion, which describes the relationship between force and the rate of change of momentum. For viscous fluids, these governing equations take the form of the Navier-Stokes equations, which account for the effects of viscosity, pressure, and external forces, providing a comprehensive framework for modeling fluid motion [9, 10].

These equations are fundamental for characterizing both transient (time-dependent) and steady-state flow phenomena. The continuity equation, also known as the conservation of mass equation, is derived by applying the principle of mass balance to a differential volume element ($\Delta x \Delta y \Delta z$) through which the fluid flows. Mathematically, it is expressed as [10]:

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho u_i) = 0 \quad (4.1)$$

$$\frac{\partial \rho}{\partial t} = - \left(\frac{\partial}{\partial x} \rho u_x + \frac{\partial}{\partial y} \rho u_y + \frac{\partial}{\partial z} \rho u_z \right) \quad (4.2)$$

where ρ is the fluid density and u_i is the fluid velocity components along different coordinate directions, and t is the time. The continuity equation describes how the density of a fluid changes over time at a specific point in space. It can be expressed using vector notation as follows in Eq. (4.2). In this context, the rate at which the density changes over time, represented by $\frac{\partial \rho}{\partial t}$, is associated with the mass flux vector ρu .

4.2 The Reynolds Averaged Navier-Stokes (RANS) Equations

4.2.1 k- ω Turbulence Model

The k- ω turbulence model with low-Reynolds number (LRN) corrections has been successfully validated for predicting average velocity profiles, pressure drop, and shear stresses in

multi-regime flow fields within human airways [11]. This model is particularly effective in capturing near-wall turbulence effects, making it suitable for applications involving complex respiratory flows.

The Reynolds-Averaged Navier-Stokes (RANS) equations, which describe the conservation of mass and momentum in incompressible laminar and turbulent fluid flows, are expressed as Eq.

(4.3) and Eq. (4.4) [10]:

$$\frac{\partial \bar{u}_i}{\partial x_j} = 0 \quad (4.3)$$

$$\frac{\partial \bar{u}_i}{\partial t} + \bar{u}_j \frac{\partial \bar{u}_i}{\partial x_j} = -\frac{1}{\rho} \frac{\partial \bar{P}}{\partial x_i} + \frac{\partial}{\partial x_j} \left[(v + v_T) \left(\frac{\partial \bar{u}_i}{\partial x_j} + \frac{\partial \bar{u}_j}{\partial x_i} \right) \right] + F_i \quad (4.4)$$

where $\bar{u}_i$ is the mean air velocity component in three Cartesian coordinate directions, i.e., $i = 1, 2$ and 3 , $\bar{P}$ is the pressure, v is the air kinematic viscosity, and v_T is the kinematic turbulent (eddy) viscosity, F_i represents body forces acting on the flow, including the gravitational force. The turbulent kinematic viscosity, v_T , is given by Eq. (4.5):

$$v_T = c_\mu f_\mu \frac{k}{\omega} \quad (4.5)$$

where c_μ is a constant with a commonly accepted value of 0.09, and f_μ is a function of $Re_T = \frac{k}{v\omega}$, as defined in the following equation:

$$f_\mu = \exp \left[-\frac{3.4}{(1 + \frac{Re_T}{50})^2} \right] \quad (4.6)$$

In the k - ω turbulence model, two parameters are defined to represent the turbulent characteristics of the flow field: the turbulence kinetic energy, k , and ω is the turbulent dissipation rate [12]. These parameters describe the kinetic energy associated with turbulent velocity fluctuations and the rate of viscous dissipation due to turbulent shear stresses, respectively. The equations governing the transport of these turbulence parameters are given in the following equations.

$$\frac{\partial k}{\partial t} + \bar{u}_j \frac{\partial k}{\partial x_j} = T_{ij} \frac{\partial \bar{u}_i}{\partial x_j} - \beta^* k \omega + \frac{\partial}{\partial x_j} \left[(v + \sigma_k v_T) \frac{\partial k}{\partial x_j} \right] \quad (4.7)$$

$$\frac{\partial \omega}{\partial t} + \bar{u}_j \frac{\partial \omega}{\partial x_j} = \alpha \frac{\omega}{k} T_{ij} \frac{\partial \bar{u}_i}{\partial x_j} - \beta \omega^2 + \frac{\partial}{\partial x_j} \left[(v + \sigma_\omega v_T) \frac{\partial \omega}{\partial x_j} \right] \quad (4.8)$$

In this context, T_{ij} represents the Reynolds stress tensor, while β^* , σ_k , α , and β are constants assigned the commonly accepted values of 1.0, 0.5, 0.555, 0.8333, and 0.5, respectively. The initial boundary conditions for the parameters k and ω are typically established using empirical correlations; two examples of which are provided in the following equations.

$$k = 1.5(I \times u_{in}) \quad (4.9)$$

$$\omega = \frac{k^{1.5}}{0.6D} \quad (4.10)$$

where I , u_{in} , and D denote the upstream turbulence intensity, the average velocity magnitude at the specified boundary, and the hydraulic radius of the boundary, respectively.

4.2.2 Large Eddy Simulation (LES)

Large Eddy Simulation (LES) is an advanced alternative to RANS turbulence models, introducing a distinct approach. It employs filtered forms of the exact Navier-Stokes equations as its foundational framework, decomposing the velocity field into resolved and subgrid-scale components. This technique directly captures the larger, energy-containing eddies while relying on an algebraic model to approximate the smaller, dissipative eddies within the computational grid [13, 14]. The core concept is that boundary conditions have a significant influence on larger eddies, making it challenging to develop a universally applicable model for them. Conversely, smaller subgrid eddies exhibit more isotropic behaviour, allowing for the creation of a generalized model that effectively represents their effects. The filtered Navier-Stokes equations resulting from this method are expressed as follows [15, 16]:

$$\frac{\partial \rho}{\partial t} + \frac{\partial(\rho \bar{u}_i)}{\partial x_i} = 0 \quad (4.11)$$

$$\begin{aligned} & \frac{\partial(\rho \bar{u}_i)}{\partial t} + \frac{\partial(\rho \bar{u}_i \bar{u}_j)}{\partial x_j} \\ &= - \left(\frac{\partial \bar{p}}{\partial x_j} \right) + \frac{\partial}{\partial x_j} \{ [(\mu + \mu_s) \left(\frac{\partial \bar{u}_i}{\partial x_j} + \frac{\partial \bar{u}_j}{\partial x_i} \right)] - \frac{2}{3} \mu \frac{\partial \bar{u}_i}{\partial x_i} \delta_{ij} \} + F_i \end{aligned} \quad (4.12)$$

where the terms $\bar{u}_i$ is time-averaged air velocity, ρ is mixture density, $\bar{p}$ is time-averaged pressure, F_i is body force, including the gravitational force and momentum of particles, μ is the mixture dynamic viscosity, and μ_s is dynamic viscosity at subgrid scales as modeled [17, 18]:

$$\mu_s = (C_s \bar{\Delta})^2 (2\bar{S}_{ij} \bar{S}_{ij})^{1/2} \quad (4.13)$$

$$\bar{S}_{ij} = -\frac{1}{2} \left[\frac{\partial \bar{u}_i}{\partial x_j} + \frac{\partial \bar{u}_j}{\partial x_i} \right] \quad (4.14)$$

In Eq. (4.13), the term C_s represents the Smagorinsky coefficient constant with a default value of 0.1 in ANSYS. This coefficient is determined dynamically using the procedure proposed by Lilly [17] based on the Germano identity, to optimize accuracy across a wide range of flow conditions. The term $\bar{\Delta}$ denotes the local grid-scale and is defined as $\bar{\Delta} = V^{1/3}$, where V represents the volume of the computational cell, making it dependent on the grid resolution. Additionally, the resolved large-scale strain rate tensor is represented as $\bar{S}_{ij}$.

4.3 Discrete Phase Model (DPM)

An aerosol consisting of particles of uniform size is known as a monodisperse aerosol, whereas one containing particles of different sizes is termed a polydisperse aerosol. Aerosols are typically polydisperse in natural environments, while monodisperse aerosols are specifically produced under controlled laboratory conditions. The particle sizes in a polydisperse aerosol can vary across multiple orders of magnitude, necessitating statistical approaches to effectively characterize their size distribution. The Lagrangian Discrete Phase Model (DPM) method was used to capture the trajectories of particles [16]. It was assumed that the particles were spherical, inert, and occupied a low volume fraction, representing a dilute phase within the flow domain. To define particle motion, Newton's second law of motion was applied as follows:

$$m_p \frac{dV_p}{dt} = F_D + m_p \frac{g(\rho_p - \rho)}{\rho_p} \quad (4.15)$$

where V_p is the particle velocity, ρ_p is the particle density, and g is the gravitational acceleration. In this study, only the drag force (F_D) was considered, while other forces, such as Saffman's lift force, pressure gradient force, and virtual mass force, were neglected due to the particles having a significantly greater density than air [19]. The drag force is calculated as follows:

$$F_D = \frac{3}{4} \frac{\mu_g C_D Re_p}{\rho_p d_p^2} (u - V_p) \quad (4.16)$$

At minimal Reynolds numbers ($Re_N \sim 0.1$), the flow is known as Stokes flow and under these conditions: $C_D = 24/Re_N$. Solutions obtained using this condition are given by Zenz and Othmer

[20]. At very high Reynolds numbers ($R_N \sim 10^3$), the value of C_D becomes approximately constant at about 0.4. Still, in the intermediate range of R_N , which is the range of practical interest, C_D varies with R_N in a complicated manner. Many empirical formulae have been suggested, but these are suitable only in certain regions. In the present study, C_D is mainly calculated at the correct Reynolds number and is always within 1–2% of the experimental value. To achieve accuracy, the experimental drag curve (refer to **Fig 4.1**) is divided into several regions, and the curve in each region is approximated by Eq. (4.17).

$$C_D = a_1 + \frac{a_2}{Re_p} + \frac{a_3}{Re_p^2} \quad (4.17)$$

$$Re_p = \frac{\rho_p d_p |u - V_p|}{\mu_g} \quad (4.18)$$

where C_D is the drag coefficient of spherical particles, defined by the drag law of Morsi and Alexander [21]. The constants a_1, a_2 , and a_3 were obtained over a range of different Reynolds numbers. Re_p , d_p , μ_g , and u represent the particle Reynolds number, particle diameter, air dynamic viscosity, and airflow velocity, respectively.

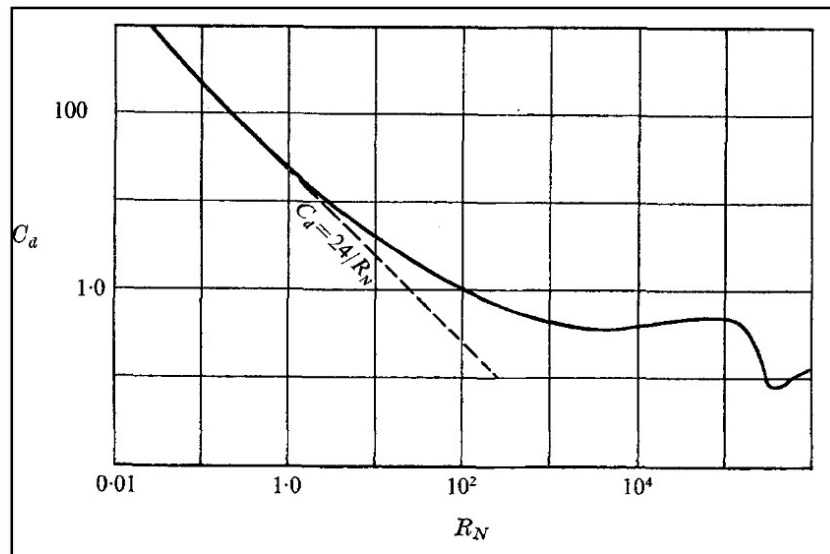


Fig 4.1. Drag coefficient for spherical particles vs Reynolds number [21].

An aerosol of the same size is called a monodisperse aerosol; otherwise, it is referred to as a polydisperse aerosol. Ambient aerosols are inherently polydisperse, while monodisperse aerosols can be precisely generated under controlled laboratory conditions. In a polydisperse aerosol,

particle sizes can span multiple orders of magnitude, necessitating the use of statistical methods to accurately characterize their size distribution. Aerosol sampling devices primarily measure the bulk properties of aerosols within a predefined particle size range. To determine aerosol size distribution parameters, the measured property in each size range must be normalized by the corresponding number of particles in that category [22]. To characterize aerosol size distribution, the measured property within each size range must be normalized based on the number of particles in that range. This allows the aerosol property to be expressed as the fraction of particles per unit size interval, providing a more precise representation of the distribution. The Probability Density Function (PDF) and Cumulative Distribution Function (CDF) are essential mathematical tools for describing aerosol dispersion, offering insights into both the relative frequency of particle sizes and their cumulative distribution across the range.

The Rosin-Rammler distribution is widely used in mineral processing to characterize particle size distributions. It assumes an exponential relationship between the droplet diameter d_p and the mass fraction of particles exceeding that diameter. The probability density function for this distribution is given by [23]:

$$F(d_p; \lambda, n') = 1 - \exp \left[-\left(\frac{d_p}{\lambda}\right)^{n'} \right] \quad (4.19)$$

Here, $n' > 0$ and $\lambda > 0$ are referred to as the shape and scale parameters of the distribution, respectively. The shape parameter n' determines the steepness of the cumulative curve, while λ represents a particle diameter such that 36.8% of the particles are larger than this value. A higher n' corresponds to a narrower distribution. By rearranging Eq. (4.19), the Rosin-Rammler distribution can be expressed in a linearized form:

$$\ln \left[\ln \left(\frac{1}{1 - F(d_p)} \right) \right] = n' \ln d_p - n' \ln \lambda \quad (4.20)$$

Eq. (4.20) demonstrates that a linear relationship emerges when $\ln \left[\ln \left(\frac{1}{1 - F(d_p)} \right) \right]$ is plotted against $\ln \lambda$. From the slope and intercept of this straight line, the shape parameter n and the scale parameter λ can be calculated. Examples of experimental data validating the Rosin-Rammler distribution are illustrated in **Fig 4.2**.

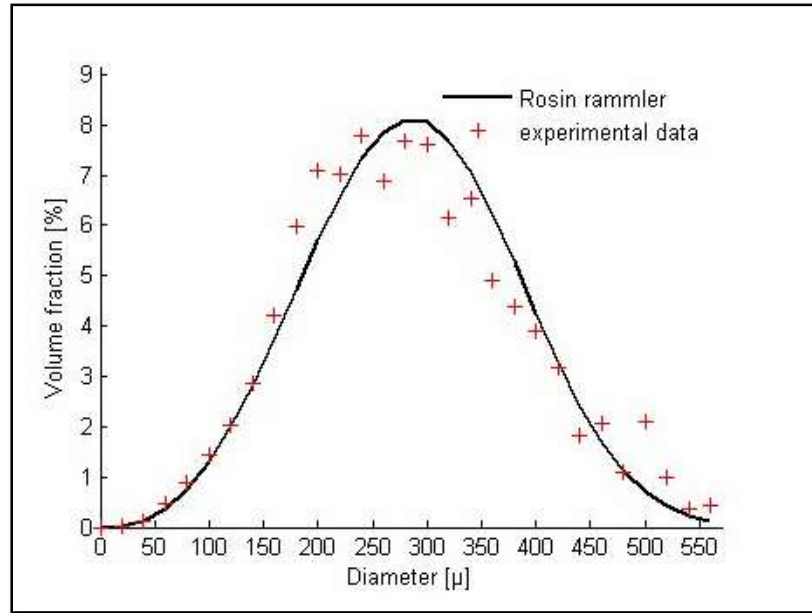


Fig 4.2. Rosin Rammler distribution fitted on experimental data [24].

4.4 Mucus Layer Modeling

The mucus layer in the respiratory tract is often overlooked in numerical studies for inhalation therapy, with wall boundary conditions typically assumed to be adiabatic, implying no heat transfer nor mass transfer. However, studies have shown that including the mucus layer at wall boundaries reveals a temperature difference between the inhaled air, the mucus, and the airway walls [16, 25]. **Fig 4.3**, adapted from Paz et al. [27], illustrates the structure of the mucus layer in the respiratory tract. The mucus is formed by two different layers: the serous layer (low viscosity-sol layer) and the mucus layer (high viscosity gel layer) [26].

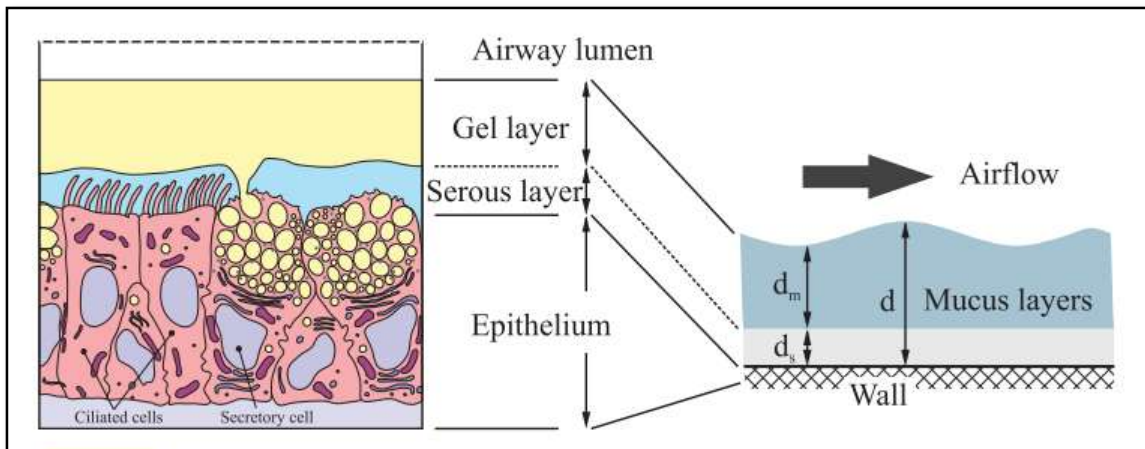


Fig 4.3. Airway epithelium and mucus layer detail [27].

4.4.1 Eulerian Wall Film (EWF)

In this study, the mucus layer was modeled using three different approaches. The first two methods focused on thickness and shell conduction, accounting only for heat transfer between the airway wall and the airflow. The third approach employed the Eulerian Wall Film (EWF) model, which was developed to simulate the flow of a thin liquid film while accounting for mass transfer. In all three models, the mucus layer extends from the airway wall into the fluid domain.

The EWF model simplifies the mucus structure to a single equivalent layer by excluding the serous layer. The continuity equation for a two-dimensional film within a 3D domain is given in Eq. (4.21) [28]:

$$\partial(\rho_f y_f) \partial t + \nabla_s \cdot (\rho_f y_f \vec{v}_f) = \dot{m}_s \quad (4.21)$$

where ρ_f is the film density, y_f is the film thickness, ∇_s is the surface gradient operator, $\vec{v}_f$ the mean film velocity, and $\dot{m}_s$ is the mass source per unit wall area resulting from droplet collection and film separation. The conservation of film momentum is given as follows:

$$\frac{\partial(\rho_f y_f \vec{v}_f)}{\partial t} + \nabla_s \cdot (\rho_f y_f \vec{v}_f \vec{v}_f) = -y_f \nabla_s P_f + \rho_f y_f \vec{g}_t + \frac{3}{2} \vec{\tau}_{fs} - \frac{3\mu_f}{y_f} \vec{v}_f + \dot{\vec{q}}_s \quad (4.22)$$

where P_f represents the film pressure, $\vec{g}_t$ indicates the gravity component that is normal to the surface, $\vec{\tau}_{fs}$ denotes the viscous shear force at the mucus-air interface, μ_f is the viscosity of the film (Eq. (4.26)), and $\dot{\vec{q}}_s$ refers to the momentum source term associated with droplet interactions.

The terms on the left side of Eq. (4.22) represent the transient effects and convection effects, respectively. On the right side, the first term includes the effects of gas-flow pressure (as described in Eq. (4.23)), the component of gravitational force that is normal to the wall surface (as seen in Eq. (4.24)), and surface tension (explained in Eq. (4.25)). The second term addresses the gravitational effect in a direction parallel to that of a liquid film. The third and fourth terms indicate the net viscous shear force at the gas-film and film-wall interfaces. The final term represents the collection or separation of droplets. These terms and interactions are critical for capturing the dynamics of the mucus layer in response to airflow and particle deposition [18, 28].

The pressure term is calculated using the following equations:

$$P_f = P_{gas} - P_z + P_\sigma \quad (4.23)$$

$$P_z = -\rho z(\vec{n} \cdot \vec{g}) \quad (4.24)$$

$$P_\sigma = -\sigma \nabla_s \cdot (\nabla_s y_f) \quad (4.25)$$

where P_{gas} represents the gas pressure, P_z is the component of gravity acting perpendicular to the wall, P_σ denotes the surface tension term, $\vec{n}$ is the normal vector, $\vec{g}$ indicates the gravity vector, and σ refers to the surface tension. These film equations (Eqs. (4.21) – (4.25)) were solved on the surface of the airway using the local coordinates of the wall. The thin film assumption is often made using the EWF model, as the film thickness is small compared to the curvature radius of the surface [29].

Healthy mucus consists of 95-99% water and typically behaves like a Newtonian fluid, with a viscosity similar to that of water [30]. However, previous studies have shown that mucus can also exhibit non-Newtonian, shear-thinning behavior [27, 31, 32]. The impact of modeling mucus as a non-Newtonian fluid on the predictions of particle deposition and flow patterns remains unclear in inhalation therapy, as many studies have neglected its influence on drug delivery and deposition [33]. In this study, we examined both Newtonian (Nmu) and non-Newtonian shear-thinning (non-Nmu) fluids in mucus layer modeling and compared the differences in the results. We used a mucus viscosity of $0.89 \text{ mPa}\cdot\text{s}$ for the Nmu layer, which is comparable to the viscosity of water at 25° , representing a low-viscosity Newtonian fluid [34]. Additionally, we employed the non-Newtonian power-law model [35] to capture the shear-thinning behavior of the mucus [32] :

$$\mu_f = K\dot{\gamma}^{n-1} \quad (4.26)$$

where μ_f represents the apparent viscosity of the film, $\dot{\gamma}$ is the shear rate, K is the consistency index, which was set to $2.52 \text{ mPa}\cdot\text{s}$, and n , the power-law index, set to 0.15 for the mucus film rheological properties in our model, as described by Ren et al. [36].

The conservation of film energy is given as follows [37]:

$$\frac{\partial(\rho_f y_f T_f)}{\partial t} + \nabla_s \cdot (\rho_f y_f T_{film} \vec{v}_f) = \frac{1}{Cc_p} \left[\frac{2k}{2y_f} (T_s + T_w - T_m) + \dot{m}_{vap} L \right] \quad (4.27)$$

where T_{film} is the average film temperature, T_s and T_m are the film surface and film half-thickness temperature, respectively. The $\dot{m}_{vap}$ is the mass vaporization or condensation rate, k is the thermal conductivity, and L is the latent heat associated with the phase change.

4.5 CFD Solver Setting

The Navier-Stokes equations for incompressible fluids are reformulated into their integral form to align with control volume-based CFD solvers. This study conducted simulations using ANSYS Fluent v20.2 (ANSYS Inc., Canonsburg, PA). The computational domain was discretized into control volumes, and the governing equations (Eqs. (4.3), (4.4), (4.11), and (4.12)) were integrated over each control volume within the mesh to generate a system of algebraic equations for dependent variables such as velocity, pressure, and temperature. These equations were then solved iteratively.

A segregated solver was employed in ANSYS Fluent, solving the governing equations sequentially and independently. The study utilized two turbulence modeling approaches: RANS $k-\omega$ and LES. For LES, unresolved subgrid scales were modeled using the kinetic energy transport model, and the bounded central differencing scheme was applied to the momentum equations. Gradients were computed using the least squares cell method, while pressure, subgrid kinetic energy, energy, and H_2O transport were discretized using the second-order upwind scheme. The bounded second-order implicit scheme, combined with warped-face gradient correction, was implemented for transient formulations. Pressure-velocity coupling was handled using the Semi-Implicit Method for the Pressure-Linked Equations Consistent (SIMPLEC) algorithm.

For the Shear Stress Transport (SST) $k-\omega$ model, the QUICK (Quadratic Upstream Interpolation for Convective Kinematics) scheme was employed to discretize the nonlinear convection terms in the Navier-Stokes equations. The SIMPLE (Semi-Implicit Method for Pressure-Linked Equations) algorithm was used for pressure-velocity coupling. The momentum equations were solved using a bounded central differencing scheme, while convective terms were interpolated from cell centers to nodes using a second-order upwind scheme. To enhance gradient accuracy, a warped-face gradient correction was incorporated. Additionally, algebraic multigrid controls were fine-tuned to ensure smooth convergence and prevent solution divergence.

4.6 Nomenclatures

Abbreviations

COPD	chronic obstructive pulmonary disease
3D	3- dimensional

APSD	aerodynamic particle size distribution
CF	cystic fibrosis
CFD	computational fluid dynamics
DPM	discrete phase model
LES	large eddy simulation
MMAD	mass median aerodynamic diameter
MT	mouth- throat
NGI	next generation impaction
Nmu	Newtonian mucus
non-Nmu	non-Newtonian mucus
NS	Navier-Stokes
pMDI	pressurized metered-dose inhaler
RANS	Reynolds-averaged Navier-Stokes
RMSE	root mean square error
SIMPLE	semi-implicit method for pressure-linked equations
TKE	turbulent kinetic energy

Notations

d_p	particle diameter, [μm]
y_f	film height, [mm]
$\bar{u}_i$	time-average velocity, [m/s]
u_i	fluid velocity, [m/s]
k_s	thermal conductivity, [W/m.k]
C_D	constant drag coefficient, [-]
C_s	Smagorinsky constant, [-]
V_p	particle velocity, [m/s]
$\vec{v}_f$	mean film velocity, [m/s]
V_T	tidal volume, [L]
m_p	particle mass, [kg]
Re_p	particle Reynolds number, [-]
k	turbulence kinetic energy, [m^2/s^2]

T_{ij}	Reynolds stress tensor, [Pa]
t	time, [s]
g	gravitational acceleration, [m/s ²]
$\vec{g}, \vec{g}_t$	gravity vector, component normal to surface, [m/s ²]
$\vec{n}$	normal vector, [-]
h	enthalpy, [J/kg]
h_f	fluid heat transfer coefficient, [W/m]
q_{rad}	radiation heat flux, [W/m ²]
T_B, T_w, T_f	temperature of boundary, wall, and fluid, [K]
T_{film}, T_s, T_m	temperature of average film, surface, film half depth, [K]
$\dot{m}_{vap}$	mass evaporation/condensation rate, [-]
$\vec{q}_s$	momentum sourced term, [-]
$\dot{m}_s$	mass source per unit wall area, [-]
t_B	total time for one breath, [s]
c_p	specific heat transfer, [J/kg.K]
p	static pressure, [Pa]
p_{gas}	gas pressure, [Pa]
p_f	film pressure, [Pa]
E	thermal energy, [J]
L	latent heat, [J/kg]
U	velocity of fluid in shell, [m/s]
V_p	particle velocity, [m/s]
Q_{In}	inhalation flow rate, [L/min]
f	breathing frequency, [1/min]
F_i	body force, [N]
F_D	drag force, [N]
$\overline{S}_{ij}$	rate-of-strain tensor, [1/s]
a_1, a_2, a_3	constant of drag coefficient, [-]
n	power-law index, [-]
K	consistency index, [-]

EE	elementary effect, [-]
r_s	Spearman correlation coefficient. [-]
I	turbulence intensity, [-]
D	hydraulic radius, [m]
V	volume of the computational cell, [m ³]
R_N	Reynold number, [-]
R_p	particle Reynold number, [-]
n'	shape parameter, [-]
<i>Greek letters</i>	
$\vec{\tau}_{fs}$	viscous shear force, [N]
∇_s	surface gradient operator, [-]
μ^*	mean absolute effect, [-]
ν	kinematic viscosity, [m ² /s]
ν_T	turbulent viscosity, [m ² /s]
ω	turbulent dissipation rate, [s ⁻¹]
μ_f	film viscosity, [N.s/m ²]
ρ_f	film density, [kg/m ³]
$\vec{v}_f$	mean film velocity, [m/s]
ρ_p	particle density, [kg/m ³]
τ_p	effective shear stress, [Pa]
γ	shear rate, [1/s]
μ, μ_s, μ_g	dynamic viscosity of mixture, subgrid-scale, and gas, [N.s/m ²]
ρ	air density, [kg/m ³]
σ	surface tension, [N/m]
ΔP	pressure drop, [Pa]
$\beta^*, \beta, \alpha, \sigma_k$	constants, [-]
σ_k and σ_ω	constant coefficient of the shear stress transport turbulence model, [-]
δ_{ij}	Kronecker delta, [-]
$\bar{\Delta}$	local grid scale, [m]
λ	scale parameter, [m]

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Chapter 5- A CFD Investigation on the Aerosol Drug Delivery in the Mouth-Throat Airway using Pressurized Metered-Dose Inhaler Devices

5.1 Abstract

Inhalation therapy using a pressurized metered-dose inhaler (pMDI) is one of the most commonly used and effective treatment methods for patients with chronic obstructive pulmonary disease (COPD) and asthma. This study aimed to develop a computational fluid dynamics (CFD) model to characterize aerosol flow issued from a pMDI into a simulated mouth-throat geometry. The effects of air flow rate and cone angle were analyzed in detail. The behavior of the multiphase flow initiated at the inhaler actuation nozzle and extended through the mouth-throat airway was simulated using the Eulerian-Lagrangian discrete phase model, with the $k-\omega$ model applied to model turbulence. We validated our model against published experimental measurements. The recirculation we observed at the 90° bend inside the mouth-throat airway resulted in the selective retention of larger-diameter particles, and the fluid flow patterns were correlated with drug deposition behaviour. Enhancing mass flow rates up to three times reduced the aerodynamic particle diameters by 20%. We also observed that mouth deposition increased as the cone angle increased; an 8° cone angle was found to be the optimal angle for minimizing mouth-throat deposition.

5.2 Introduction

Pulmonary drug delivery is of paramount importance to the pharmaceutical industry because it allows the delivery of low-bioavailability drugs to a large surface area of the lungs. The pressurized metered dose inhaler (pMDI) has been the primary choice for the therapeutic management of asthma since the late 1950s [1]. Despite recent improvements in respiratory drug delivery treatment, less than 30% of a dose reaches a patient's lungs [2]. The rest is either deposited in the valve stem, nozzle, valved holding chamber (if present) or within the mouth-throat airways [3], all of which are possible obstructions to airflow. Studies show that patients experience difficulty coordinating the timing between actuating the inhaler and inhaling due to a lack of

understanding of the device's technology and mechanics [4, 5]. Both drug formulation (in suspension or solution base) and proper device design are essential for the effective treatment of respiratory conditions. Since drug deposition has been found to be unevenly distributed within the lungs [6, 7], drug delivery must be better targeted to generate and deliver fine aerosols into the lungs [8].

Pharmaceutical aerosol movement is via multiphase flow, consisting of a continuous phase (inhaled air) and a discrete drug phase (particles or droplets containing an active therapeutic agent). The pharmaceutical aerosol size, or respirable size, ranges from nano to micrometres. An aerosol size of less than $7\ \mu\text{m}$ is ideal for preventing inertial impacts along its path to the lungs, and sizes ranging from 2 to $3\ \mu\text{m}$ are required to reach the peripheral lung for effective treatment [8, 9]. Some of the important factors that affect aerosol deposition include the inhaler's properties, such as the nozzle's shape [9–12], as well as the aerosol particle distribution, which is influenced by factors such as slow rate, spray actuation time, airflow obstruction, cone angle, and spray plume cloud [8, 13–17].

Experimental lung-drug delivery setups are expensive and limited by the complex geometry of the respiratory tract, measurement inaccuracies due to the spatial and temporal resolutions of imaging techniques such as laser diffraction, and the risk of exposing patients to radiation in *in-vivo* experiments [4, 18]. These limitations can be overcome through numerical computation, which would enable the study of the drug particle's delivery with high accuracy. Since the 1990s, the pharmaceutical industry has concentrated on drug delivery studies involving numerical modelling strategies using CFD for in-depth analysis [15, 19]. CFD simulations can address physical factors (such as velocity) related to both particles and airflow, with illustrations of contours, flow patterns, and particle track plots. Vinchurkar et al. [20] demonstrated the utility of a CFD model in evaluating the performance of the Andersen Cascade Impactor (ACI) in terms of particle size distribution and deposition efficiency. The authors demonstrated the benefits and accuracy of the CFD approach through particle size measurements, finding the results to vary within a 10% error of the experiments [20].

The mouth-throat airway's geometry and inhalation flow rate affect flow structure, subsequently affecting an aerosol's lung deposition. Zhang et al. [13] conducted a CFD study to propose a modified idealized induction port (IP) featuring a 90° curved bend. They observed that drug

delivery to the lung was enhanced with less flow circulation near the curved bend. When they applied the near-wall corrections to the turbulent kinetic energy in their simulations, the deposition of particles in the proposed idealized mouth-throat geometry showed good agreement with in vitro results. These corrections were necessary to account for complex flow characteristics (secondary flow regions and circulated areas) in the proposed mouth-throat airway [13]. A CFD analysis by Oliveira et al. [1] showed that stable air flow at the spacer's outlet reduced the recirculation area and provided better drug deposition. In another CFD study, Oliveira et al. [21] explored the characterization of the pMDI aerosol plume. They characterized the spray plume as a transient jet and found that drug aerosolization was completed in the first 0.1 s of the spray duration [21]. The impact of flow rate on spray plume behaviour and particle deposition was then investigated in their study. Buchamann et al. [22] also studied the effect of airflow rate on the development of the aerosol plume. They observed an axisymmetric plume pattern at zero flow rate and a downward-flected plume due to uneven shear [22].

To specifically study the impact of flow rate on particle deposition, Cheng et al. [23] designed an experiment based on three different flow rates (15, 30, and 60 *L/min*) on different replicas of United States Pharmacopeia (USP) IP geometries. They demonstrated that high-diameter particles (5-26 μm) sedimented as the flow rate increased and established a correlation for deposition efficiency using the Stokes number, which was calculated based on the outflow velocity and minimum particle diameter [23]. Bass and Longest [24] used a CFD study to investigate the dependence of particle deposition in the mouth-throat pathway on airflow and turbulence within the system. At higher flow rates and consequently high Reynolds numbers, the deposition fraction of fine particles ($< 4 \mu\text{m}$) was found to be most sensitive to turbulence; therefore, the air stream carried fine particles, but larger particles ($> 5 \mu\text{m}$) were deposited in the mouth-throat pathway [24]. This study also highlighted the importance of aerosol plumes in IP with a constant cone angle (particle entrance angle). Koullapis et al. [25] presented a benchmark case for validating computational tools intended for upper zone deposition. Particle deposition increased with particle size for all three flow rates tested (15, 30, and 60 *L/min*), and particles smaller than 5 μm were unaffected by the flow rates. The dominant deposition mechanism in the mouth-throat airway was found to be inertial impaction [25].

Through an in-vitro study, Duke et al. [26] demonstrated that approximately 20% of the total cumulative dose was delivered to the lung within the first 0.1 s of the spray. They noticed a rapid drop in drug mass fraction in the upper airway due to the drug deposition in that area. They concluded that the leading particles at the edge of the aerosol plume encounter a drag force against still air and thus experience fewer particle-particle interactions compared to the particles that follow [26].

Ganderton et al. [27] experimentally studied the importance of nozzle diameters. They observed a significant increase in fine particle dose when the actuator nozzle diameter was decreased from 0.42 to 0.22 mm [27]. Several other studies have confirmed that a small nozzle diameter leads to smaller drug particles [18, 28–30], considering the impact of varying cone angles from 0° to 40°, along with different flow rates and mouthpiece diameters, on inhaler efficiency. They showed that MDI efficiency increased to around 10% when the cone angle increased from 0° to 20°. They also showed that the flow rate and mouthpiece diameters do not impact the particle penetration efficiency through the upper airway. Buchmann et al. [22] designed an experiment to accurately characterize the spray plume. They investigated the impact of the air co-flow on the spray tip penetration, tip velocity, and cone angle. They reported that the air co-flow has minimal effect on the tip penetration and spray velocity despite impacting the width and angle of the spray plume [22].

Gavtash et al. [31] used a high-speed camera to capture the spray near the orifice. They showed that the spray velocity (affected by the flow regime and nozzle diameter) is one of the primary sources of particle fragmentation. They also showed the impact of the cone angle as a time-dependent spray characteristic on the particle size distribution [31]. Versteeg et al. [32] confirmed that cone angles change over time in the aerosol plume by analyzing the spray images near the nozzle. Cone angles are greater in the near-orifice region rather than in the far-orifice region because of the flash evaporation of superheated propellant in the near-orifice region [32]. By including the upper airway geometry, Yousefi et al. [33] found that the larger spray cone angle at the lower flow rates (i.e., 15 L/min) caused higher particle deposition in the pharynx zone [33]. Chen et al. [34] examined different nozzle designs (i.e., cone, curved cone, flat, and curved flat). They found that the curved-cone nozzle shape produced a narrower plume since this nozzle design

generated extra pressure on the initial plume after actuation. However, they found that different drug formulations also affected the shape of the aerosol plume [34].

All the above-mentioned studies discussed major parameters affecting particle deposition and spray plumes; however, they failed to adequately analyze the effects of flow rate and cone angle on particle deposition and spray plumes. Our study leveraged the exceptional capabilities of CFD to investigate the impact of flow rate and actuation cone angle on particle size distribution, mouth-throat airways deposition, and mass median aerodynamic diameter size, specifically concerning pMDI drug deposition in the mouth-throat airways. The aerosol plume hydrodynamics were also studied by observing the flow pattern and changes in turbulent kinetic energy over the actuation time. Our study has been validated with the experimental data of Lewis et al. [35].

5.3 CFD Model Development

The 3D model geometry and meshing were performed, respectively, using the Geometry and Mesh modules in ANSYS® Workbench (ANSYS® release 2019 R1 v193) [36].

5.3.1 Geometry and Material

Fig 5.1 shows the schematic of the mouth-throat airway, presented through side and cross-sectional views, along with dimensions and mesh. The mouth-throat airway had a 90° bend with the inner and outer diameters of 19 and 31.5 mm, respectively. The injection nozzle was positioned at the center of the outer circle (**Fig 5.1(a)**). The mesh mainly consisted of hexahedral elements.

A maximum skewness < 0.95 and a minimum orthogonal quality > 0.18 were set as the criteria for acceptable mesh quality [37]. This work did not model the mechanistic details of aerosol generation within the pMDI canister, from actuation to the nozzle. The effect of flow rate and cone angle (**Table 5.1**) was determined using beclomethasone dipropionate (BDP) particles with a density of 1300 kg/m^3 and viscosity of $1.75 \times 10^{-5} \text{ kg/m.s}$. The factory-adjusted constant flow rate of 28.3 L/min [35, 38] was adopted to analyze a realistic device and understand the effects of small changes in flow rates.

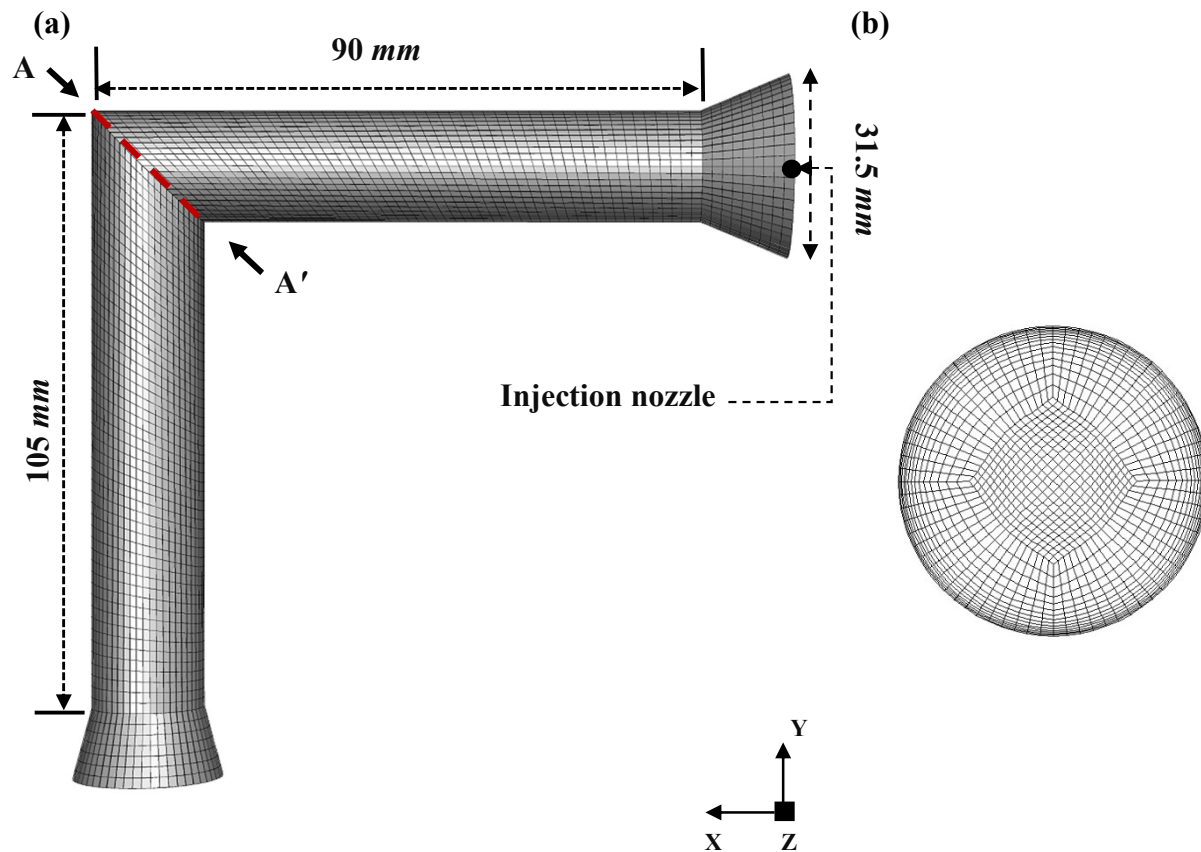


Fig 5.1. Schematic of the mouth-throat airway with mesh: **(a)** Side view; and **(b)** Cross-sectional area.

Table 5.1. Values of spray cone angle and flow rate.

Flow rate (L/min)	18.0	28.3	45.0	60.0	80.0	-
spray cone angle ($^{\circ}$)	2	4	8	10	17	20

5.3.2 Mesh Independency Study

Grid convergence was tested for various element sizes and refinements, as shown in **Table 5.2**. Meshes of ~114k, 222k, 414k, and 812k cells were applied for our mesh independence study. The tangential air velocity profiles were compared along the most turbulent area with circulation flows, line AA' (**Fig 5.1**), in the mouth-throat airway geometry at a flow rate of 28.3 L/min . We checked the velocity profiles at two different times, 0.08 s and 0.12 s, to observe the profiles before and after actuation (0.1 s). Comparing the obtained values for air velocity profiles at two different

times (**Fig 5.2(a), (b)**), the profiles revealed 0.293 and 0.351 root mean square error (RMSE) [39] on velocities proceeding from 114k cells to 222k cells. Therefore, we increased the cell numbers to obtain a finer mesh. The profiles showed approximately 0.135 and 0.152 RMSE in the velocity magnitudes between 222k and 412k cells at 0.08 s and 0.12 s, respectively. By decreasing the cell size to 0.82 mm, we reached 812k cells. As the data showed, the profiles for both times had RMSEs of 0.097 and 0.059 between the 412k and 812k, respectively. Continuing our study with 812k mesh was not feasible due to the computational cost. Since the velocity profile obtained with 812k cells was similar to that with 412k cells, we adopted a mesh with 414,589 cells for our studies.

Table 5.2. the number of

Parameter	Cell size, mm	Number of cells
Mesh A	2.00	114,825
Mesh B	1.98	222,150
Mesh C	1.68	414,589
Mesh D	0.82	812,448

Cell size and cells.

(b)

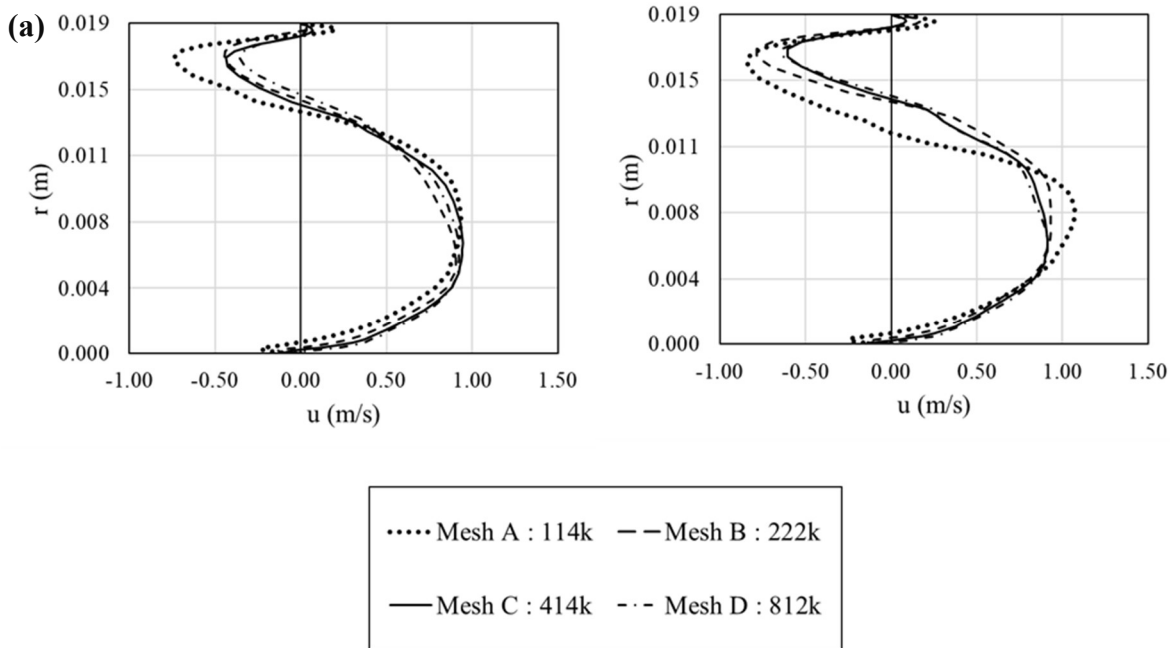


Fig 5.2. Mesh independence study on the tangential air velocity (u) at: **(a)** 0.08 s; and **(b)** 0.12 s.

5.3.3 Governing Equations

Our system consisted of a dilute multiphase flow; therefore, the Eulerian-Lagrangian approach in Ansys/Fluent (ANSYS® release 2019 R1, v193) was employed [40, 41]. The Lagrangian transport model tracks individual particles within the flow field. The primary advantage of this method is that a variety of forces, such as inertia, diffusivity, electrostatic effects, and near-wall terms, can be considered directly [42]. The fluid phase (air) is assumed to be a continuum phase. A fundamental assumption made in the discrete phase model is that the dispersed phase occupies a low volume fraction. A two-way turbulent dispersion on the particle was performed using the “discrete random walk” or “eddy interaction model”. The effect of turbulence on particle dispersion is then approximated through an eddy interaction model that implements the turbulence terms to recreate eddy structures and predict the chaotic motion of particles as a random walk [43]. In other words, it assumes that a particle interacts with a succession of random, discrete turbulent eddies, where a lifetime length and velocity scale define eddy. This method is achieved by assuming that the mass and momentum equations are solved separately for dispersed (droplets/particles) and continuous (gas) phases. In this approach, all phases, including the particulate phases, are modelled as continuous fluids, and consequently, mass, momentum, and energy conservation laws are applied to all phases in this model [44].

For gas phase modeling, the Reynolds-averaged Navier-Stokes equations governing the conservation of mass and momentum in incompressible laminar and turbulent fluid flows were represented as [45]:

$$\frac{\partial \bar{u}_i}{\partial \bar{u}_j} = 0 \quad (5.1)$$

$$\frac{\partial \bar{u}_i}{\partial t} + \bar{u}_j \frac{\partial \bar{u}_i}{\partial x_j} = -\frac{1}{\rho} \frac{\partial p}{\partial x_i} + \frac{\partial}{\partial x_i} \left([(\nu + \nu_T) \left(\frac{\partial \bar{u}_i}{\partial x} + \frac{\partial \bar{u}_j}{\partial \bar{u}_i} \right)] \right) \quad (5.2)$$

where, $\bar{u}_i$ is the time-averaged velocity in the direction referred to by index i ($i = 1, 2$, and 3 for a 3-D field), p is the time-averaged static pressure, ρ is the fluid-specific mass, ν is the kinematic viscosity, and ν_T is the turbulent viscosity. The turbulent viscosity ν_T is given in Eq. (5.3) and f_μ is expressed in Eq. (5.4) [46]:

$$v_T = c_\mu f_\mu \frac{k}{\omega} \quad (5.3)$$

$$f_\mu = \exp \left[-\frac{3.4}{\left(1 + \frac{R_T}{50}\right)^2} \right] \quad (5.4)$$

where $c_\mu=0.09$, and f_μ is a function of $R_T=(k/\nu\omega)$, in which k is turbulence kinetic energy and ω is turbulent dissipation rate.

Based on the flow Reynolds number ($300 < Re < 10^4$), for an inhalation flow rate and geometrical irregularities, laminar to transitional and even fully turbulent flow was expected [9]. The k - ω turbulence model was employed in this work instead of the k - ϵ model based on the ability to accurately predict pressure drop, velocity profiles, and shear stresses for transitional and turbulent flows, especially near the wall, which is significantly important for particle deposition [47,48]. The two parameters used to account for the turbulent nature of the flow field were turbulence kinetic energy, k , and turbulent dissipation rate, ω . The governing transport equations were as follows:

$$\frac{\partial k}{\partial t} + \bar{u}_j \frac{\partial k}{\partial x_j} = \tau_{ij} \frac{\partial u_i}{\partial x_j} - \beta^* k \omega + \frac{\partial}{\partial x_j} \left((\nu + \sigma_k \nu_T) \left(\frac{\partial k}{\partial x_j} \right) \right) \quad (5.5)$$

$$\frac{\partial \omega}{\partial t} + \bar{u}_j \frac{\partial \omega}{\partial x_j} = \alpha \frac{\omega}{k} \tau_{ij} \frac{\partial u_i}{\partial x_j} - \beta \omega^2 + \frac{\partial}{\partial x_j} \left((\nu + \sigma_\omega \nu_T) \left(\frac{\partial \omega}{\partial x_j} \right) \right) \quad (5.6)$$

where τ_{ij} is the Reynolds stress tensor, and $\beta^*=1.0$, $\sigma_k=0.5$, $\alpha=0.555$, $\beta=0.8333$, and $\sigma_\omega=0.5$ are constants [49].

Two-way coupling was assumed between the particle and the airflow. The interaction between particles was neglected since the particle flow is dilute, with a particle fraction of less than 0.1% [33].

In order to understand aerosol motion, we analyzed the behavior of its components. The motion depended on two types of forces: gravitational and resistance from the continuous phase against the particle's motion. The mass flow rate ($\dot{m}$) of a gas moving around a spherical particle is obtained as:

$$\dot{m} = \rho_g \frac{\pi}{4} d_p^2 V_p \quad (5.7)$$

where d_p is the particle diameter, V_p is particle velocity, and ρ_g is the gas density. The rate of change of momentum is equal to the force required to move a spherical obstacle in the gas, and hence, the resistant force due to drag force based on Newton's law can be expressed as follows [50]:

$$F_D = K \frac{\pi}{4} \rho_g d_p^2 V_p^2 \quad (5.8)$$

where K is the coefficient of proportionality and is independent of velocity for a certain shape, the general form of the above equation is:

$$F_D = C_D \rho_g \frac{\pi}{8} d_p^2 V_p^2 \quad (5.9)$$

where the constant drag coefficient, $C_D = 0.44$ is chosen for the Reynolds number, $Re > 1000$, since the particle diameter and velocity are unknown at most times, and the particle Reynolds number can not be calculated before solving the problem. The Stokes zone is the zone where the drag coefficient changes linearly with the Reynolds number. Clift et al. [50] obtained a correlation for the drag coefficient as follows:

$$C_D = \frac{24}{Re} (1 + 0.15 Re^{0.687}) \quad (5.10)$$

To account for the influence of the shape of non-spherical particles, a correction factor known as the dynamic shape factor, X , was applied to Stokes' law [51]. An essential assumption of the Stokes law is that the gas at the particle surface has zero velocity relative to the particle. This assumption holds well when the particle has a diameter much larger than the mean free path of gas molecules. The mean free path is the average distance a gas molecule travels between two successive collisions. The correction factor is defined as the ratio of the resistive force of the irregular particle to that of a spherical particle with the same volume and velocity as described in Eq. (5.11) [52]:

$$X = \frac{F_D}{3\pi\eta V_p d_p} \quad (5.11)$$

where X is the dynamic shape factor, F_D is the drag force, V_p is the particle velocity with respect to the fluid, d_p is the particle diameter, and η is the viscosity of the gas. In the mouth-throat airway, the primary force acting on micron particles is drag, while gravitational force is negligible [53]. Additionally, in the upper and large airways, the gravitational force on micron particles is negligible compared to the particle drag force [26].

Particle sizes in a polydisperse aerosol can range over two or more orders of magnitude. Therefore, the description requires a particle size distribution format. Accordingly, a Rosin-Rammler distribution was assumed for the drug in the size range from 1 μm to 10 μm . The Rosin-Rammler distribution is defined using Eq. (5.12) shown below [54]:

$$Q = \exp\left(-\frac{d_p}{\bar{d}}\right)^q \quad (5.12)$$

The Rosin-Rammler distribution function assumes that an exponential relationship exists between the droplet diameter, d_p , and the mean diameter, $\bar{d}$. Q is the fraction of total mass contained in particles of diameter greater than d_p , and q is the spread parameter, which is an index measure of the polydispersity of the spray. The corresponding parameters for spray properties and particle distribution model are shown in **Table 5.3**.

Table 5.3. Spray and particle distribution parameters.

Distribution model	Rosin-Rammler
Minimum diameter (μm)	0.45
Maximum diameter (μm)	9
Mean diameter (μm)	1.828
Spread parameter (-)	1.3676
Initial velocity (m/s)	100
Spray cone angle ($^\circ$)	17

Since the experimental article [35] did not provide the parameters for the MDI spray, we utilized measured data from Oliveira et al. [1] to establish the spray conditions. They reported the cone angle of the HFA-pMDI to be 17° . Additionally, the parameters of the discrete phase model, including the spread parameter and mean diameter, were tested across various configurations and were fitted to the Rosin-Rammler correlation. Consequently, the parameters presented in **Table 5.3** were identified as the most suitable for use in the simulation.

5.3.4 Boundary Conditions

The spray was modeled as a stream of BDP particles. As mentioned previously, the initial particle diameter ranged from 0.45 μm to 9 μm , as the cumulative mass curve based on diameter

was reported within this range. It included both the fine particle size and the upper limit of desirable particle size in the mouth-throat airway [35].

A pressure inlet was chosen at the inlet surface. The outlet was modelled as a velocity-inlet since coaxial airflow is generated through suction via a vacuum pump attached downstream of the pMDI configuration. This maintained a constant volumetric flow rate at the outlet. The air volume fraction inside the system at $t = 0$ s was 1.0. Gravity was considered to be acting in the negative y-direction (**Fig 5.1**). Both the coaxial airflow and the injection were initiated simultaneously at $t = 0$ s (in accordance with the experiment), and the injection time (corresponding to the duration of actuation) was specified as 0.1 s.

5.3.5 Numerical Controls and Computational Power

The convergence of the simulation was evaluated by monitoring the drop in continuity residuals to below 10^{-4} , while the other residuals were required to fall below 10^{-5} . The velocity and pressure were linked using the Phase Coupled SIMPLE method [48]. The second-order upwind scheme was adopted for the turbulent dissipation rate to limit numerical diffusion errors [37]. The supercomputing facility, having Intel (R) Xeon (R) Gold 6148 CPU @ 2.40GHz with 16 cores available at Lakehead University and parallel processing on 2 Intel (R) Xeon (R) CPU E5-2630 v4@2.20 GHz Processors were used to run the simulations.

5.4 Results and Discussion

5.4.1 CFD Model Validation

We validated our CFD model with the experiments conducted by Lewis et al. [35] on drug deposition in the mouth-throat airway. The validation was performed for a flow rate of 28.3 L/min. The curves of cumulative mass in terms of percentage and mass units per aerodynamic particle diameter were compared at the outlet surface and plotted in **Fig 5.3**. Pharmaceutical companies typically use the aerodynamic diameter to characterize particles in inhalable drugs. The aerodynamic diameter is defined as the diameter of the spherical particle with standard density (ρ_0) (1000 kg/m^3) and the same settling velocity as the irregular particle with a diameter, d_p , and density, ρ_p . It can be calculated using Eq. (5.13) below:

$$d_a = d_p \left(\frac{\rho_p}{\rho_0} \right)^{1/2} \quad (5.13)$$

where d_a is the aerodynamic diameter of an irregular particle [55].

Cumulative mass % RMSE were 0.0899 [based on **Fig 5.3(a)**] and 0.0789 [**Fig 5.3(b)**]; the total mass observed in the reference experiment (34.5 μg) and that obtained from this CFD study (34.32 μg) varied by a relative error of about 0.5%. This shows that our CFD results agreed well with the experimental results. The deviation between the experimental work and our simulation results may be explained in a couple of ways. In our CFD simulation, the airway surface was treated as smooth, whereas in the experiments, some microroughness would exist on the surface. This would affect the interaction between the near-wall fluid and particles. The other reason is that the Reynolds-averaged Navier-Stokes (RANS) turbulence models can never be perfect, especially in complex geometries that contain recirculation, pressure drop, and flow separation. However, these adopted turbulence models, especially the k- ϵ model, generally perform well in the literature [1, 24, 37].

5.4.2 Impact of Flow Rate

Table 5.4 shows the effect of five different flow rates on particle deposition and particle diameter. Our data showed that particle deposition decreased when the flow rate increased from 18.0 to 60.0 L/min , and then decreased slightly at 80.0 L/min . The experimental data for particle deposition at 28.3 reported the same pattern of deposition decrease with an increase in flow rate. However, due to ACI limitations for flow rates exceeding 28.3 L/min , Lewis et al. [35] had to actuate multiple times to achieve robust detection for each ACI stage. Therefore, the amount of particle dose that entered their experimental mouth-throat airway was different from our model for flow rates higher than 28.3 L/min . However, our goal was to study the impact of flow rate, which requires a constant drug dose during one actuation.

The mass median aerodynamic diameter (MMAD) is the diameter at which 50% of the particles of an aerosol by mass are larger, and 50% are smaller. Thus, the MMAD divides the aerosol size distribution in half. The MMAD of an inhaled aerosol is important since it is directly related to particle size distribution. The inhaled aerosol particle size distribution must contain the proper fraction of fine particles to be delivered effectively to the lungs or the patient's health [56]. As seen in **Table 5.4**, MMAD decreased as the flow rate increased up to 60.0 L/min .

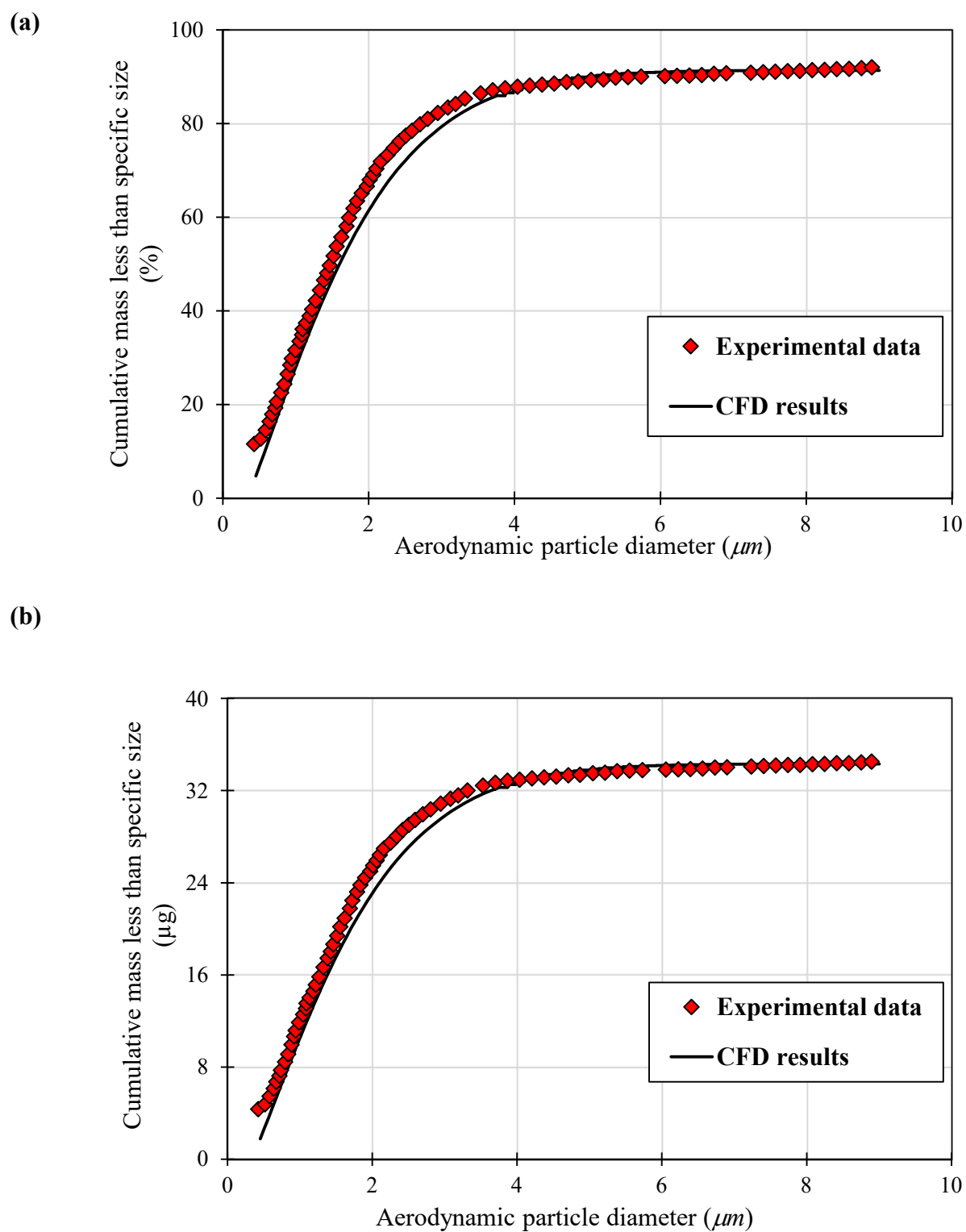


Fig 5.3. Model validation using cumulative mass based on: (a) Percentage; and (b) Microgram per aerodynamic particle diameter.

The increased flow rate caused more particles to break inside the mouth-throat airway, thereby creating smaller diameter particles and resulting in a narrower particle size distribution [35]. However, any further increase in the flow rate to 80.0 *L/min* did not significantly affect MMAD, as reported by Lewis et al. [35].

Table 5.4. Particle deposition efficiency and MMAD at different flow rates.

Flow rates (<i>L/min</i>)	18.0	28.3	45.0	60.0	80.0
Particle deposition in IP (%)	12.4	9.5	8.1	7.5	7.1
MMAD (μm)	1.8 ± 0.1	1.6 ± 0.1	1.5 ± 0.1	1.4 ± 0.1	1.4 ± 0.1

Fig 5.4 shows the cumulative mass versus drug aerodynamic diameter for five different flow rates. This figure shows that as the flow rate increased, the mass of fine drug particles reaching the outlet slightly increased. We also observed that as the flow rate increased, the particle size distribution shifted towards finer sizes. Li et al. [57] observed more fine particles at higher flow rates due to both high particle velocity and turbulent kinetic energy at the mouth-throat airway. The same pattern was observed in the Lewis et al. [35] study when the flow rate increased up to 84.9 *L/min*. This is important since, generally, particles in the size range of 1 to 5 μm have the highest chance of reaching deep inside the lung [58]. Feddah et al. [59] conducted an in-vitro experiment to compare the performance of DPI and MDI inhalers through the induction port. Their results showed that increasing the flow rate from 30.0 to 60.0 *L/min* resulted in a finer particle size distribution [59]. Also, there was no significant difference when the flow rate increased up to 90.0 *L/min*. Yousefi et al. [33] designed a model for an oral-pharynx cavity that was a replica of an experimental work of Cheng et al. [60]. In their study, they reported that the flow rates did not affect lung deposition efficiency.

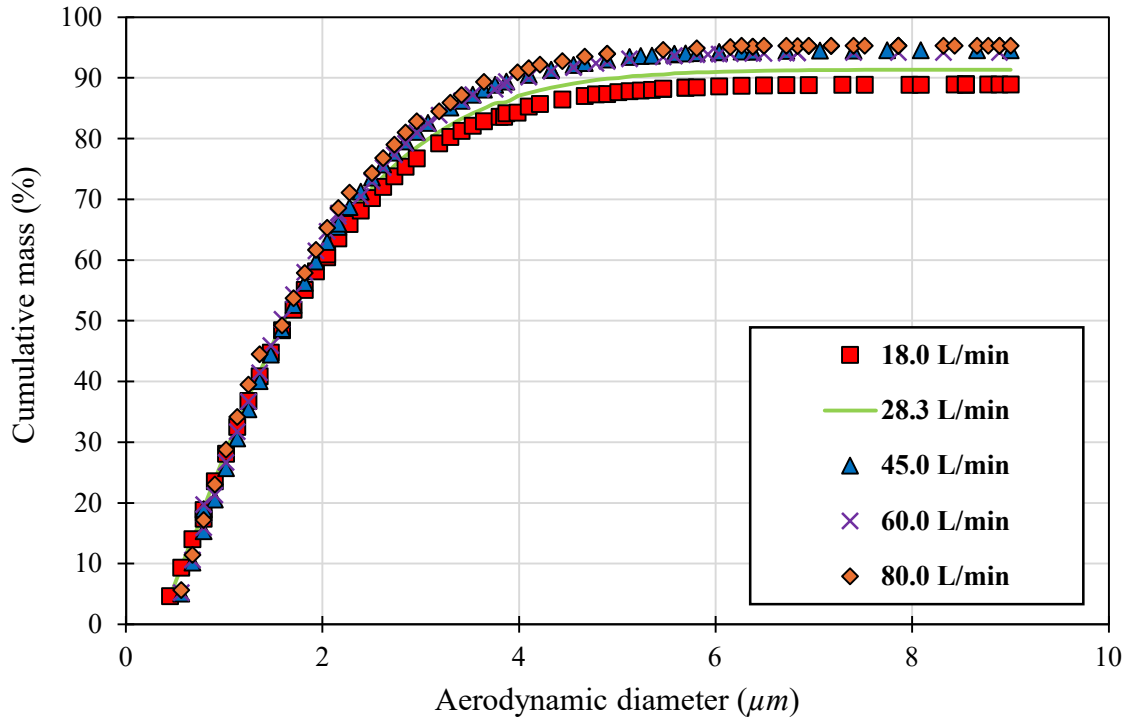


Fig 5.4. Cumulative mass percentage per aerodynamic particle diameter at different flow rates.

Fig 5.5 shows the simulated particle deposition on the mouth and throat surfaces (walls) in terms of mass as a histogram. We can see that nearly no significant changes occurred in particle deposition at the mouth as the flow rate increased. However, the deposition fraction in the throat decreased as the flow rate increased. Longest et al. [61] performed a CFD study on particle deposition of MDI through two different mouth-throat airway geometries. They reported the particle deposition on the throat wall was slightly lower than the mouth wall at 30.0 *L/min* [61]. The impact of flow rate on the mouth and throat particle deposition can be explained more accurately by analyzing the hydrodynamics of the particles and airflow through the mouth-throat airway at different flow rates.

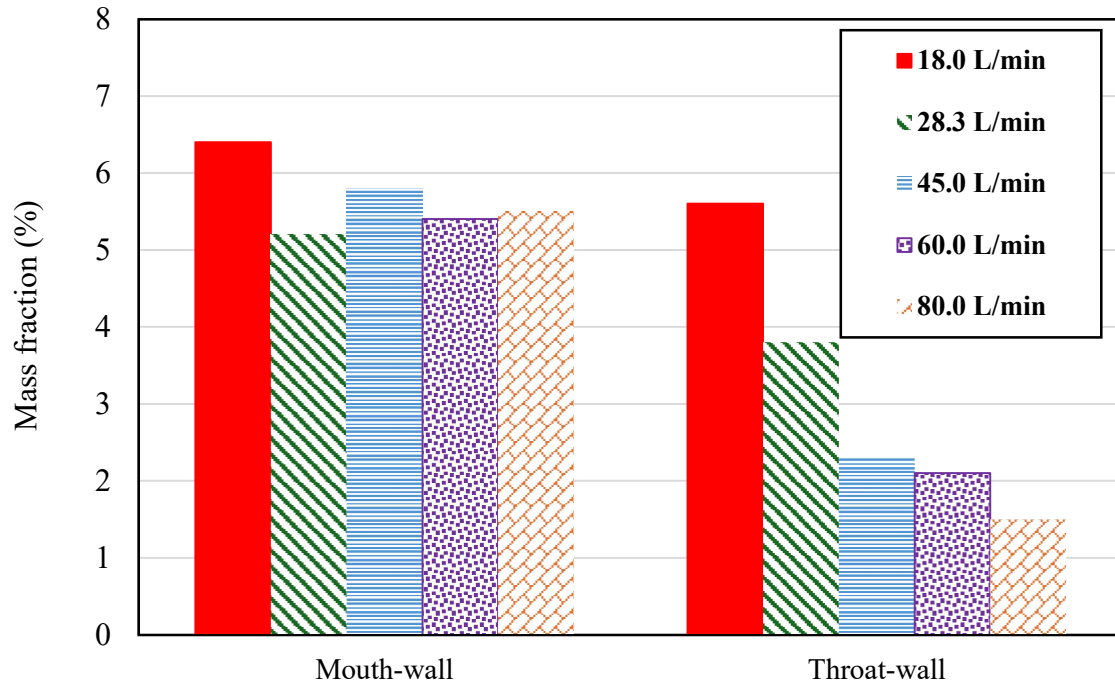


Fig 5.5. Particle deposition on the various solid surfaces with the spray cone angle of 17° at different flow rates.

Fig 5.6 shows the impact of flow rates on the turbulent kinetic energy through the mouth-throat airway at 0.08 s. The recirculation flows at the 90° bend are noticeable in all plots. However, this figure shows that increasing the air flow rate can also cause a more powerful recirculation flow at the 90° bend, which can trap more fine particles in this zone. This figure also shows that an enhancement in the flow rate creates higher fluctuation energy, mainly in the throat zone. Since turbulent kinetic energy is attributed to velocity fluctuations, its higher values confirm that particles that lost their initial momentum at the end of the injection (i.e., at 0.1 s) travelled with the airflow to pass through the throat. Therefore, the throat's particle deposition decreased as flow rates increased (refer to **Fig 5.5**). Tang et al. [62] investigated the impact of different induction ports on the deagglomeration of particles with a constant flow rate of 100 L/min. They noticed the high intensity in the turbulent kinetic energy below the 90° bend [62].

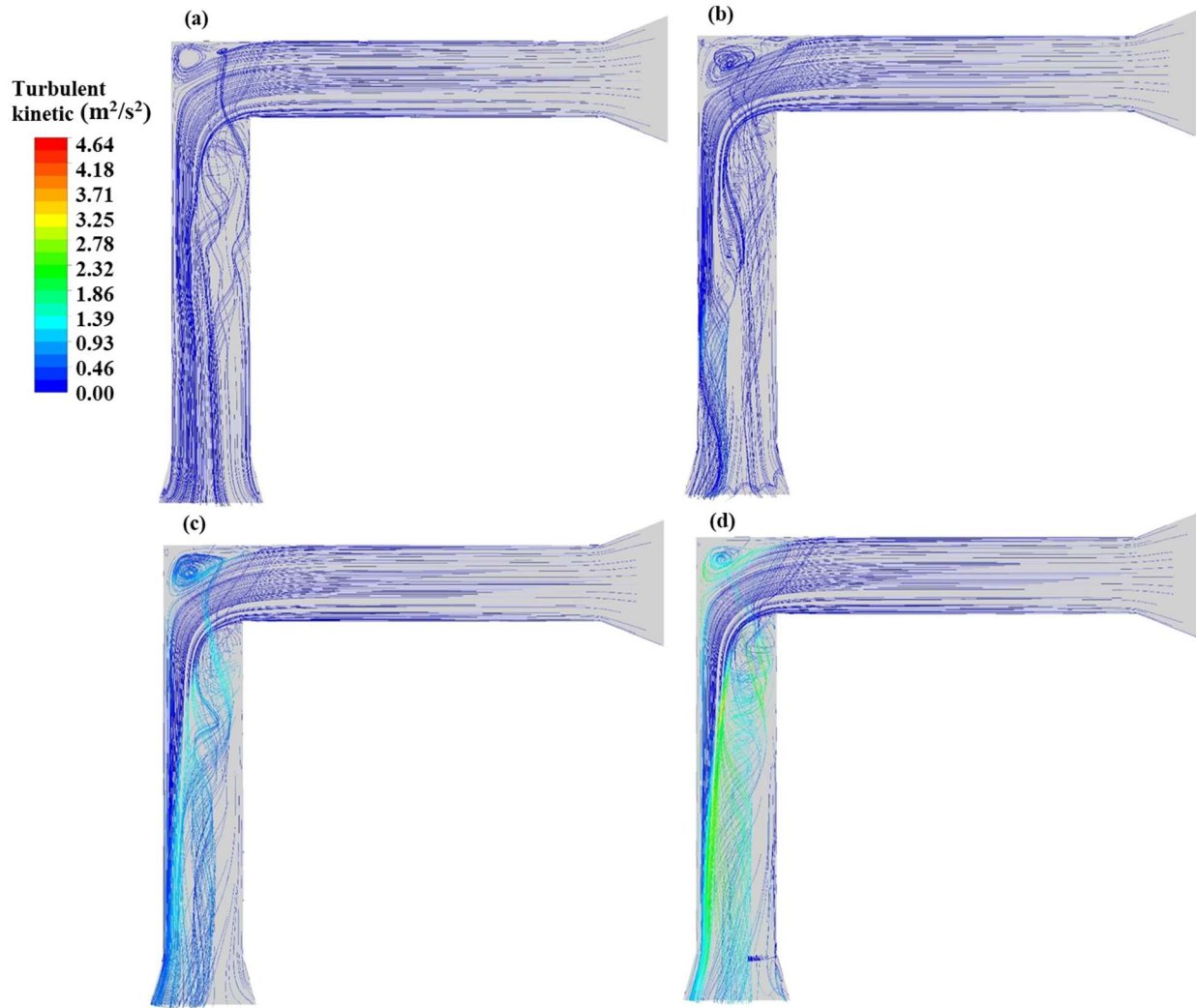


Fig 5.6. Turbulent kinetic energy path-line plots at 0.08 *s* for different flow rates: **(a)** 18.0 *L/min*; **(b)** 28.3 *L/min*; **(c)** 60.0 *L/min*; and **(d)** 80.0 *L/min*.

Air velocity profiles at different flow rates in the mouth-throat airway geometries at 0.08 *s* are displayed using velocity vector plots in **Fig 5.7**. At the flow rate of 28.3 *L/min* [**Fig 5.7(a)**], the velocity profiles had a higher value in the centerline with a small circulation streamline at the corner of the 90° bend. As flow rates increased to 80.0 *L/min* [**Fig 5.7(b)**], the velocity profiles became more uniform in the mouth zone, with higher velocity profiles at the back of the throat. This flow pattern has also been observed by Longest et al. [61]. They observed the intense air velocity profiles skewed toward the outer wall of the throat geometry with a flow rate of 30.00 *L/min*. This behaviour was justified because of the significant recirculation zone at the 90° bend.

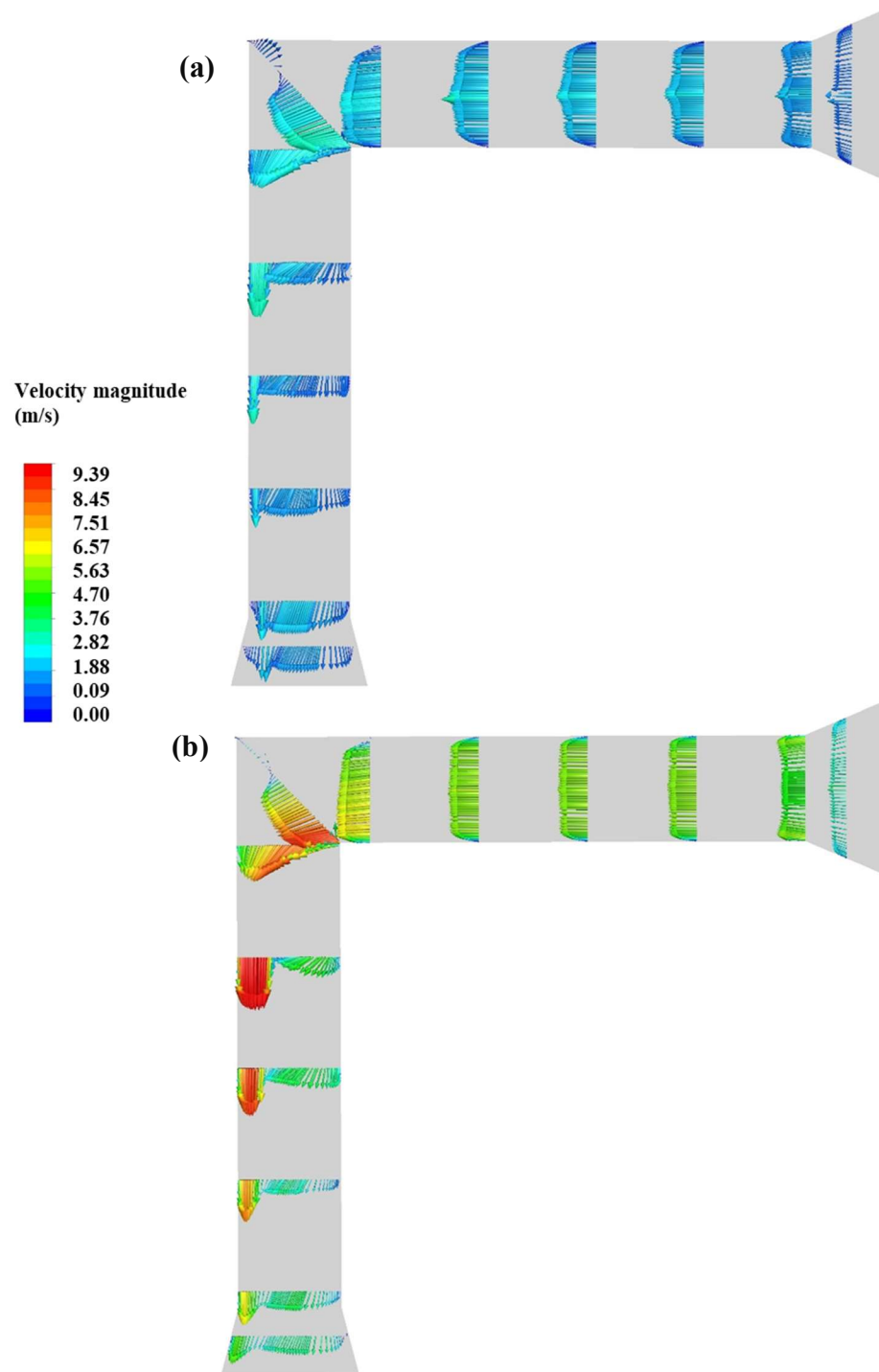


Fig 5.7. Air velocity vector plots at 0.08 s for different flow rates: **(a)** 28.3 *L/min*; and **(b)** 80.0 *L/min*.

Fig 5.8 shows the air streamlining at a flow rate of 80.0 *L/min* at the 90° bend. We can see two main flow streams at the 90° bend. Part of the airflow recirculated, passed through the 90° bend,

and entered the throat area. The recirculation flow redirects the particles to the mouth zone, which is undesirable. Gjellerup et al. [63] investigated the flow hydrodynamics inside two different airway geometries via *in-vitro* and CFD studies. They also observed the recirculation area at the 90° bend at a flow rate of 30.0 *L/min*. They observed that the recirculation flow could push fluid against the main flow stream direction toward the inlet in a very thin region close to the mouth wall [63].

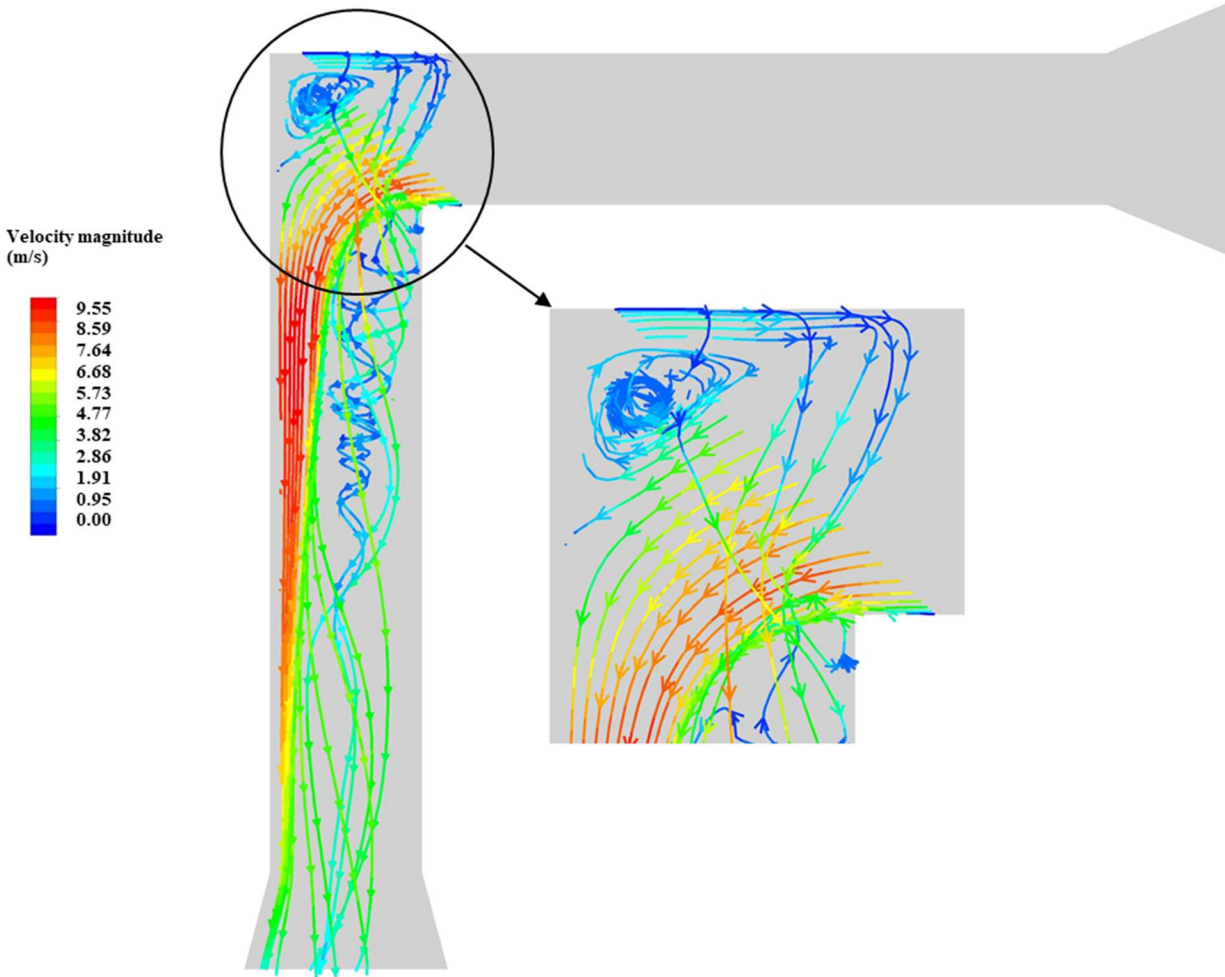


Fig 5.8. Air streamlines inside the mouth-throat airway geometry at 0.08 *s* for the flow rate of 80.0 *L/min*

Fig 5.9 displays the diameters of fine particles (less than 5 μm) for different flow rates at 0.2 *s* (e.g., post-actuation). As can be seen in **Fig. 5.9(a)**, since the 28.3 *L/min* flow rate was insufficient to keep the fine particles together in the centerline, the majority of the fine particles are visible in the mouth-throat airway due to the low flow rate and greater deposition on the mouth-throat wall.

In fact, after particles reach their stopping distance, they need the continuous phase (i.e., air) to travel through the mouth-throat airway to the outlet. As the flow rate increased up to 80.0 L/min [Fig 5.9(b)], a small number of fine particles were still in the mouth-throat airway; most of the particles were either deposited or passed the mouth-throat airway at the time frame of 0.2 s .

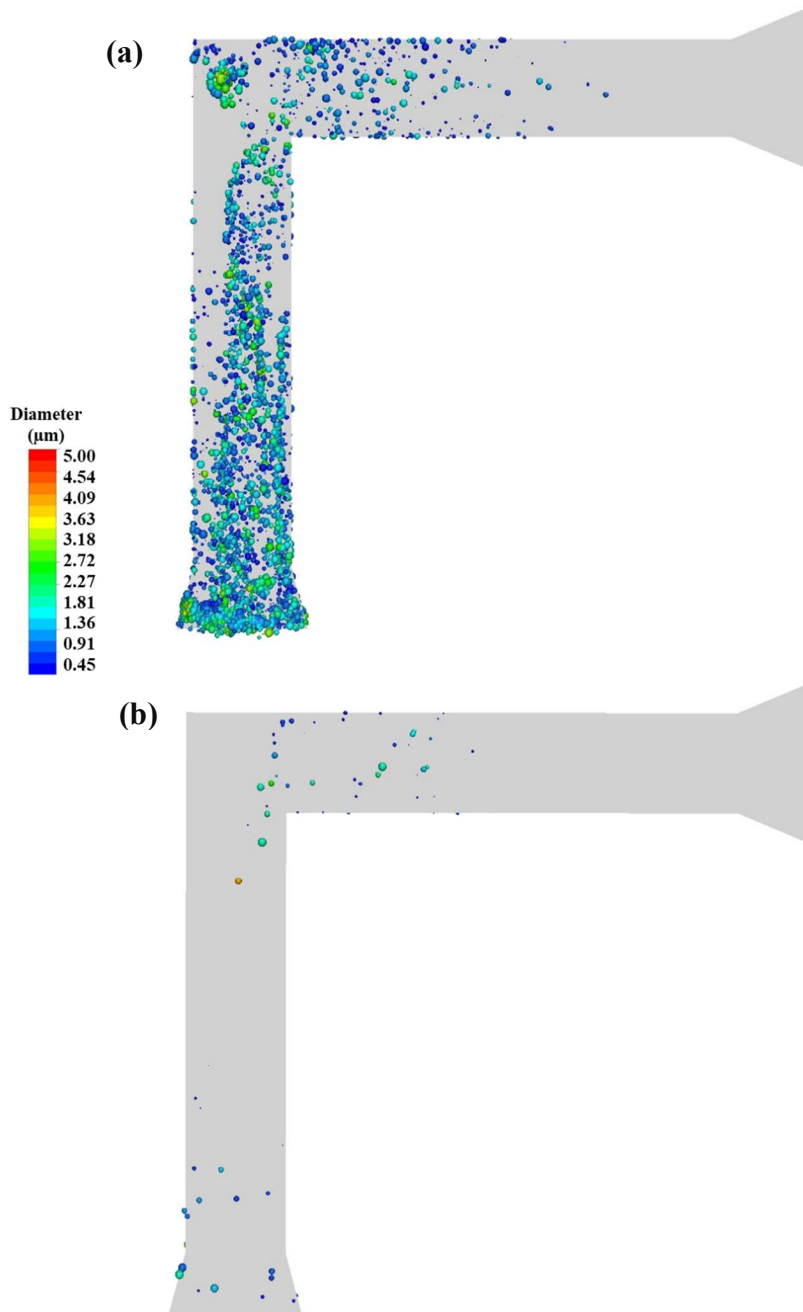


Fig 5.9. Particle diameter tracking at 0.2 s for different flow rates: **(a)** 28.3 L/min ; and **(b)** 80.0 L/min , (spheres with proportional size scaled 200 times more than the real diameter).

We expected not to see fine particles in the mouth area at 0.2 s; however, due to the intense recirculation flow in the 90° bend, as previously shown in **Fig 5.8**, some submicron particles appear to have been pushed back to the mouth zone. Yousefi et al. [33] concluded that smaller particles show more scattered deposition patterns due to a lack of sufficient drag force at lower flow rates. Therefore, fine particles at 15.0 *L/min* flow rate compared to 30 *L/min* may separate from the main air stream and slowly deposit on the airway wall over time. Meanwhile, at higher flow rates, such as 60.0 *L/min*, the inertial force of particles increases, resulting in deposition on the mouth-throat wall in a shorter period of time [33].

5.4.3 Impact of Cone Angle

Fig. 5.10 illustrates the effect of spray cone angles, ranging from 2° to 22°, at a constant flow rate of 28.3 *L/min* on drug particle deposition. The particle mass fraction deposited on the mouth wall at a cone angle of 2° was the lowest, with 0.14% deposition; however, for the same cone angle, the deposition on the throat wall was the highest. Our results show that the particle mass fraction gradually increased from 0.14% to 7.56% and from 77.35 % to 79.79% as the spray cone angle increased from 2° to 22° for the mouth wall and throat wall, respectively. Ahookhosh et al. [7] also modeled a real-life upper respiratory tract geometry and reported 29% mass fraction deposition with a spray cone angle of 20° [7]. We found 20.2% mass fraction deposition for a 22° spray cone angle. This difference may be due to the consideration of a higher spray velocity (60.0 *L/min*) compared to our study (28.3 *L/min*), as well as the 2° difference between the two cone angles studied (i.e., 20° and 22°). **Fig 5.10** also shows that at both minimum and maximum cone angles, 2° and 22°, respectively, the particle mass fraction exiting the mouth-throat airway's outlet was approximately the same. Therefore, the cone angle particularly affects particle depositions on the mouth and throat walls. Our results showed that the 8° spray cone angle was the best choice among the investigated spray cone angles, as it effectively controlled particle depositions on both the mouth and throat walls.

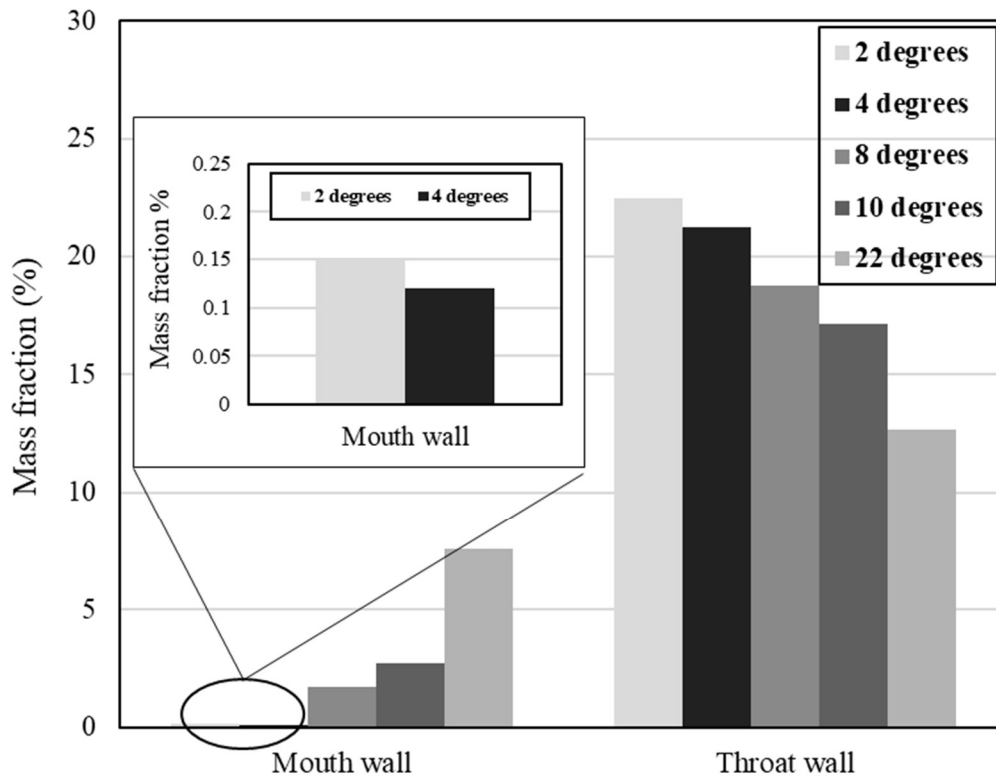


Fig 5.10. Particle deposition on the various solid surfaces at a flow rate of 28.3 *L/min* with different cone angles

Fig 5.11 shows the particle diameter tracking for the aerosol plume after 0.01 *s* of actuation at a constant flow rate of 28.3 *L/min* as the cone angles varied from 2° to 22°. Smaller cone angles produced larger diameter particles (i.e., > 5 μm) mainly on the centerline in the mouth area and specifically at the 90° bend, which is inappropriate for patients. At the larger cone angles, wider aerosol plumes were formed near the nozzle, thereby covering a larger area in the mouth. At the highest cone angles [as shown in **Fig 5.11(e) & (f)**], the aerosol plume almost covered the entire mouth zone space from the beginning of actuation; consequently, the highest mouth deposition occurred with these cone angles. For medium-sized cone angles, i.e., 8° and 17°--especially 8°--an aerosol plume was created with smaller particle diameters and covered the mouth zone at an acceptable distance from the nozzle. Yousefi et al. [33] investigated the effect of spray cone angle (0°-10°) on wall deposition. They observed that increasing the spray cone angle in their investigative range helped deliver more particles to the lungs. They also confirmed that very high spray cone angles cause lower efficiency [33].

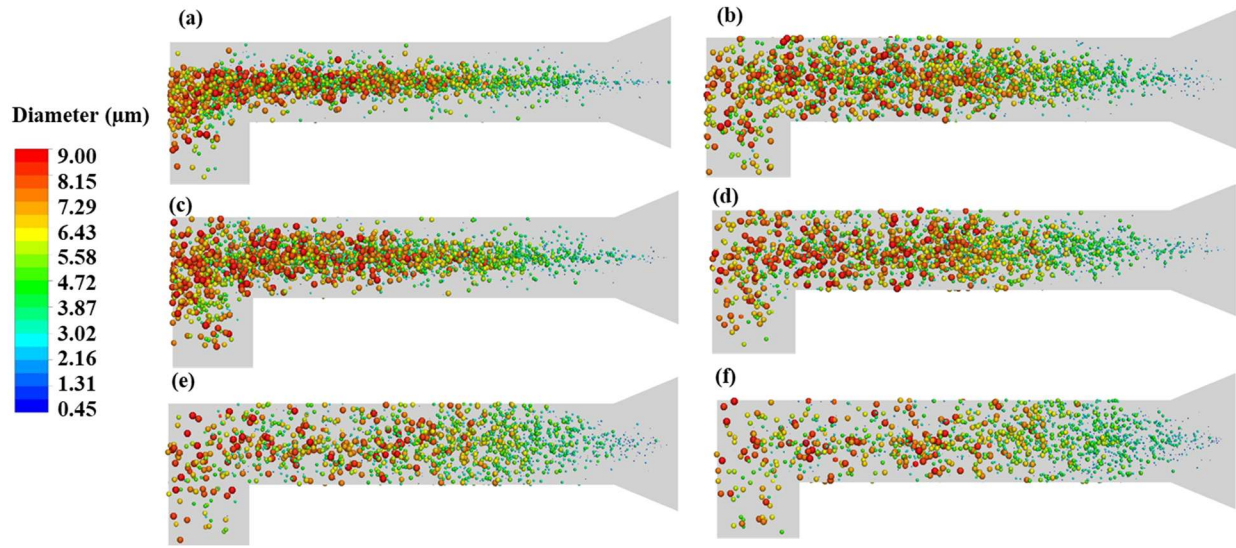


Fig 5.11. Particle tracking based on diameter (μm) at 0.01 s at the flow rate of 28.3 L/min for different cone angles: (a) 2°; (b) 4°; (c) 8°; (d) 10°; (e) 17°; and (f) 22°. Spheres with proportional size scaled 200 times more than the real diameter.

Fig 5.12 shows the particle residence time at 0.08 s after actuation for two different flow rates. At the flow rate of 60.0 L/min , particles in the throat area, especially the lower part of the mouth-throat airway, had a shorter residence time compared to the 28.3 L/min . At the lower flow rate, more fine particles were trapped at the 90° bend due to Brownian motion. Some particles were still in the mouth area (higher residence time). Meanwhile, by increasing the flow rate to 60.0 L/min , more particles either passed the bend and reached the lower part of the throat area (i.e., left the mouth-throat airway) or deposited in the airways. Oliveira et al. [1] discussed their CFD study of particle residence time during actuation in open air. Their results showed a similar pattern with finer particles located near the nozzle [1]. Additionally, particles with high particle residence times still remained near the orifice and were expected to move forward as time passed.

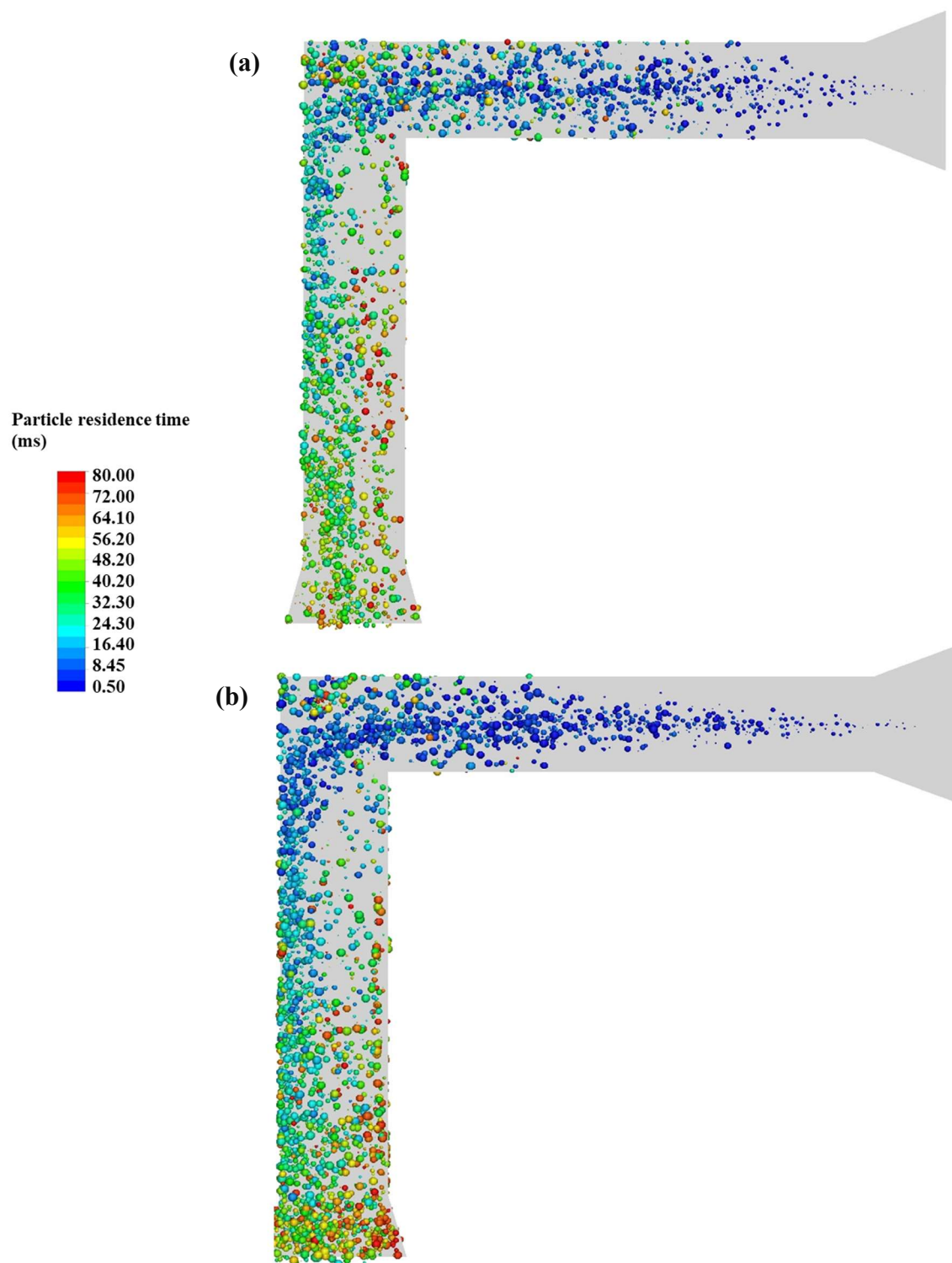


Fig 5.12. Particle residence time (s) for spray cone angle of 8° at the flow rates of: **(a)** 28.3 *L/min*; and **(b)** 60.0 *L/min*. Spheres with proportional size scaled 200 times more than the real diameter.

5.5 Conclusions

We conducted a CFD study to investigate the impact of flow rates and cone angles on the spray plume and drug particle deposition in a simulated mouth-throat airway. Our CFD model was first validated with the experimental results of Lewis et al. [35]. As the flow rate increased, larger particles (with aerodynamic particle diameters of $5\ \mu\text{m}$ to $9\ \mu\text{m}$) deagglomerated, and finer particles were produced. As the flow rate increased, mouth particle deposition remained almost constant. In contrast, the throat particle deposition decreased gradually since the lower airflow rates didn't create sufficient drag force to deliver the particles through the mouth-throat airway. Once particles lost their initial momentum, they were more dependent on the airflow to pass the throat after actuation. Increasing the cone angle from 2° to 22° at the constant flow rate mainly impacted mouth particle deposition. Particle deposition showed a greater dependency on the cone angle rather than the flow rate. As the cone angle changed to 8° or 10° , throat deposition decreased, and the spray plume exhibited a proper particle size distribution. However, higher cone angles (greater than 8°) directed particles toward the boundaries of the inhaler nozzle and mouth cavity, thereby increasing mouth particle deposition and reducing the efficiency of the pMDI in mouth-throat drug delivery.

5.6 Nomenclature

Abbreviations

COPD	chronic obstructive pulmonary disease
pMDI	pressurized metered-dose inhaler
CFD	computational fluid dynamics
APSD	aerodynamic particle size distribution
IP	induction port
USP	United States Pharmacopeia
TKE	turbulent kinetic energy
3D	3- dimensional
BDP	Beclomethasone Dipropionate particles
RMSE	root mean square error
SIMPLE	semi-implicit method for pressure-linked equations
MMAD	mass median aerodynamic diameter

Notations

d_p	particle diameter, [μm]
$\bar{d}$	mean diameter, [μm]
k	turbulent kinetic energy, [m^2/s^2]
C_D	constant drag coefficient, [-]
V_p	particle velocity, [m/s]
Re	Reynolds number, [-]
q	spread parameter, [-]
Q	fraction of total mass, [-]
$X,$	dynamic shape factor, [-]
K	coefficient of proportionality, [-]
d_a	aerodynamic diameter, [μm]
$\bar{u}_i$	time-averaged velocity, [m/s]
p	static pressure, [Pa]

Greek letters

ρ_0	standard density, [kg/m^3]
ρ	fluid specific mass, [kg]
ρ_p	particle density, [kg/m^3]
ν	kinematic viscosity, [m^2/s]
ν_T	turbulent viscosity, [m^2/s]
η	viscosity of gas, [m^2/s]
ρ_g	gas density, [kg/m^3]
ω	turbulent dissipation rate, [s^{-1}]
$\beta^*, \sigma_k, \alpha, \beta, \sigma_\omega$	constant coefficient of the SST model, [-]
$\dot{m}$	mass flow rate, [kg/s]

5.7 References

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Chapter 6- Impact of COPD Breathing Profile and Airflow Relative Humidity on Drug Delivery in Mouth-throat Airway through pMDIs: In-vitro & CFD Studies

6.1 Abstract

We investigated important factors influencing medication delivery through pressurized metered-dose inhalers (pMDIs), including constant flow rates *versus* COPD (chronic obstructive pulmonary disease) breathing profiles and relative humidity. Our approach involved both experimental methods, using an eight-stage NGI (next-generation impactor) setup, and numerical CFD modelling methods, including low Reynolds number (LRN) $k-\omega$ turbulence and discrete phase model (DPM), to determine particle size distribution, deposition, and delivery in the mouth-throat airways.

Low flow rates of 30 *L/min* resulted in a 39% increase in the mass fractions of large particles (12-15 μm) deposited on the airway walls compared to those observed at high rates of 60 *L/min*. We identified two key flow recirculation regions in the upper airway, near the bend between the mouth and throat, that affected the particle deposition fraction. The amount of drug particles deposited in the mouth-throat airway was affected by humidity levels. Higher humidity levels (99%) caused an excessive number of large particles ($>10\ \mu\text{m}$) to pass through the airway outlet, resulting in decreased mouth-throat deposition.

Under COPD breathing conditions, we observed that the development of the inhaler spray was slower, resulting in a higher deposition of large particles on the walls of the mouth and throat airways. Interestingly, we observed a decrease of approximately 4% in the mass fraction of large particles deposited on the airway wall in areas with the highest turbulence, particularly in the presence of relative humidity.

6.2 Introduction

Inhalation therapy is crucial for treating respiratory diseases. Over 300 million people worldwide suffer from these ailments [1, 2]. Hundreds of case management and treatment processes involve medications and medical devices. Using inhaled aerosols enables targeted

treatment of the lungs by achieving high drug concentrations in the airways while minimizing systemic adverse effects [3, 4]. Pressurized metered-dose inhalers (pMDIs) are commonly used to deliver bronchodilators for the treatment of asthma [1, 5].

Although pMDIs are portable, easy to use, and cost-effective, their drug delivery efficiency is low [6]. According to Liu et al. [5], only 10-20% of the administered drug doses reach the lungs. Correct actuation coordination with inhalation and appropriate drug particle size distribution are common challenges that lead to low efficiency for this device [7, 8]. To ensure effective inhalation therapy, it is crucial to understand the distribution of particles in the respiratory tract. This is because inhaled aerosols from different types of inhalers have varying particle sizes. The optimal range of mean particle diameters for successful deposition in the deep lung is between 0.5 and 5 μm , as suggested by past research [9, 10]. It is essential to note that polydispersity is a common challenge in this field of study [11].

Particle size strongly affects the probability and location of deposition of inhaled aerosol particles in the respiratory tract [12]. The size of aerosol particles emitted by a pMDI depends on several factors, such as the pressure of the propellant mixture, ambient temperature, valve design, and actuator orifice [13, 14]. The size of aerosol particles has been analyzed and measured using various techniques. Some of these techniques include laser light scattering [15], aerodynamic particle sizer [16, 17], phase Doppler anemometry [18, 19], and cascade impactor [20, 21]. However, classifying particles based on their cut-off size by multi-stage cascade impaction is the only methodology capable of determining the physiological importance of the aerodynamic particle size distribution (APSD) while also capturing enough material for quantitative determination [22, 23]. For instance, the next-generation impactor (NGI), an industry-standard aerosol particle size classifier, successfully determines the *in-vitro* performance of inhalable drug particles [20, 24, 25].

Understanding particle transport in the human respiratory tract requires knowledge of fluid dynamics and numerical methods. Additionally, there is a strong correlation between the local deposition and mean flow velocity [26]. Computational fluid dynamics (CFD) applications have proven useful in investigating inhaler performance in the design of drug delivery technology [27–29]. The pMDI actuation involves turbulent flow, multiple phases, and heat and mass transfer between the droplets and the environment [19, 30–32]. Several forces contribute to aerosol

deposition, including gravitational, drag, buoyancy, and Magnus force [33, 34]. The main reason for aerosol deposition in the human respiratory tract is inertial impaction [35]. Several parameters can influence particle impaction, including respiratory tract geometry [36–38], particle size [5, 39], airflow rate [40], and relative humidity [41, 42]. Additionally, plume characterization [43] and the type of inhalation device affect particle deposition in the respiratory tract [44].

On the other hand, it is well known that hygroscopic aerosols increase in size due to water vapour condensation in the warm and humid respiratory airways [41, 45, 46]. Kim et al. [47] investigated the aerodynamic particle size distribution using an MDI device in dry and humid air (90% relative humidity) environments with a six-stage cascade impactor. They found that the mass median aerodynamic diameter (MMAD) increased from 1% to 26% in humid air compared to dry air. At high relative humidity (99.5%), the increase in nano-aerosol size did not improve lung deposition, as most of the particles were exhaled [47].

Ivey et al. [48] conducted a study to investigate the impact of air humidity on the morphology and solid phase of particles produced by the pMDI solution type. They found that a specific level of relative humidity is required for each formulation to create porous particles [48]. This critical relative humidity is dependent on the quantity of ethanol in the drug formulation, whereas the effect of the propellant on relative humidity is insignificant. Davidson et al. [49] conducted experiments on different micron-sized particles of pMDI's drugs, including salbutamol sulfate, salmeterol xinafoate, and fluticasone propionate. The experiments were conducted over a range of relative humidity values within a chamber with conditions similar to those of the respiratory tract. The study found that salbutamol sulfate was significantly hygroscopic, whereas salmeterol xinafoate showed some hygroscopic interactions. Fluticasone propionate, on the other hand, was observed to be non-hygroscopic [49].

In many computational studies, realistic inhalation conditions have not been considered, particularly for asthma patients, such as those recovering from an exacerbation, where the patient's inhalation is often faster and shorter. Islam et al. [50] investigated the impact of particle size on drug deposition in different breathing conditions. Their findings suggest that larger particles are deposited in higher concentrations in the upper airways during fast breathing conditions [50]. In a study by Williams et al. [51], the deposition of inhaled particles (10 and 4 μm) in the airways of three patients was compared using CFD analysis. They compared the drug deposition in the

breathing flow rates of healthy and COPD (chronic obstructive pulmonary disease) patients and found that healthy patients had 35% more drugs in the lower to upper lobes [51].

Fig 6.1 illustrates the different inhalation flow rates used in both *in-vivo* and *in-vitro* studies documented in the literature. This figure illustrates that Farkas et al. [52] employed a realistic inhalation flow curve for a patient inhaling relatively consistently and with low power [52]. The study found that particles with shorter residence times in the lungs are less likely to penetrate deeper airways, thereby affecting particle deposition. Zhu et al. [53] conducted *in-vitro* experiments to evaluate extrathoracic airflow velocity in patients with obstructive sleep apnea-hypopnea syndrome. During their discussion, they analyzed the airflow patterns across various segments of the airway geometry while considering a typical male's transient breathing flow rate [53]. Colasanti et al. [54] also conducted an *in-vivo* study focusing on the flow and time domain characteristics of resting tidal breathing patterns in obstructive airway disease [54]. Linear regression was used to examine interrelationships between body size, age, and tidal breathing in healthy and severe COPD patients. In their study, Abadelah et al. [55] described the breathing patterns of 16 patients; one of the patients' breathing pattern profiles is displayed in **Fig 6.1**. Their *in-vitro* study utilized a breathing simulator and an Anderson cascade impactor to investigate the drug deposition of dry powder inhalers. They demonstrated that different breathing conditions could impact changes in the MMAD [55]. Studies have shown that as the peak of inhalation flow increases, the MMAD gradually decreases.

Most research on respiratory flow has been conducted in simplified, smooth, multi-generation airways with a constant flow rate, due to limitations in research methodology. However, to predict lung deposition accurately, it is necessary to test a range of inhalation profiles since patients inhale at various volumetric flow rates through the device. Additionally, there is a lack of detailed information in the literature regarding the effects of high relative humidity on the delivery of respiratory medication.

This study aimed to understand how airflow patterns, drug particle size, and deposition are affected by constant and COPD breathing flow rates in both dry and humid conditions. We conducted experiments and employed modeling techniques to analyze the drug particles released from a pMDI device through the mouth-throat airway. Our *in-vitro* study, using the NGI, examined particle deposition and size distribution at constant flow rates of 30 and 60 *L/min*. We validated

our model using *in-vitro* data at these constant air flow rates. Additionally, we utilized the flow rate profile of COPD patients obtained from Colasanti et al. [54] to investigate particle deposition under more realistic conditions. We also investigated the impact of relative humidity on airflow patterns, recirculation areas, particle size, and deposition in the mouth-throat airway.

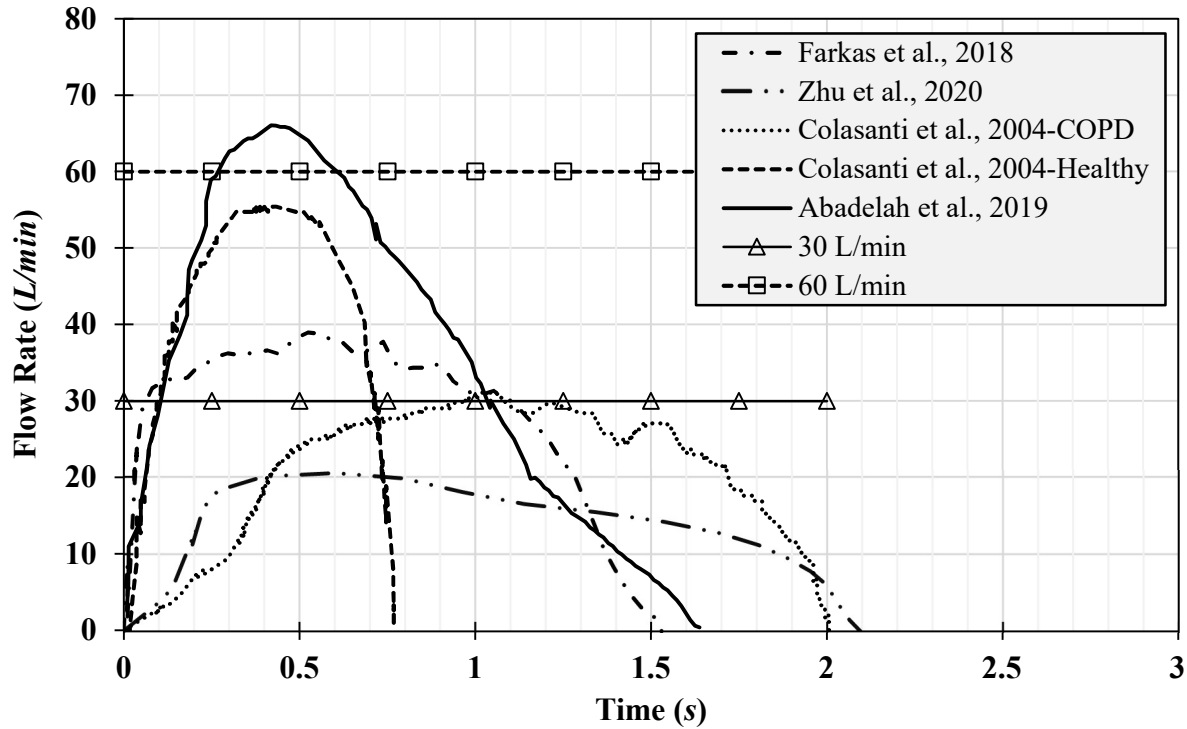


Fig 6.1. Time-varying inhalation flow rate profiles for adults.

6.3 Experimental Materials, Setup, and Sample Preparation

For this study, a pMDI device was utilized as a model inhaler. The medication used was Ventolin or Salbutamol sulfate (Ventolin- HFA (hydrofluoroalkane) MDI, Sigma Aldrich, US). Ventolin is a commonly used medication for treating and preventing bronchospasm in patients with reversible obstructive airway disease [56]. In all experiments, we used high-pressure liquid chromatography (HPLC) grade methanol (Fisher Scientific, US) and deionized water. Drug and propellant properties are presented in **Table 6.1**. HFA134a is a standard propellant for pMDI inhalers.

Fig 6.2 shows the experimental setup (Copley Scientific, UK) used in this study, which includes a pMDI device, a United States Pharmacopeia-Induction Port (USP-IP), an NGI, a flow controller (TPK 2000), and a vacuum pump (HCP5). Despite being a basic approximation of the mouth-

throat geometry, USP-IP (**Fig 6.2(a)**) is advantageous due to its ability to maintain consistency in testing methods. This is crucial for regulatory compliance and ensures accurate results for experimental study and comparison. It is also currently employed in the pharmaceutical industry as a standard airway geometry together with an impactor to estimate the oropharyngeal deposition fraction [37]. In addition, NGI has been successfully applied in various experimental studies, including those by Byehta et al., Cheng et al., and Gavtash et al. [57–59]. It is a modern impactor that is well-suited for efficient laboratory use and can even be automated for analysis [60]. The NGI, as shown in **Fig 6.2(f)**, has been designed with eight stages featuring sharp cut-off curves for efficient particle size distribution [25].

Table 6.1. Ventolin HFA pMDI and propellant properties.

pMDI Properties	Nozzle diameter (<i>mm</i>)	0.5 (Talaat et al., 2022)
	Spray angle (°)	10 (Oliveira et al., 2012)
	Spray velocity (<i>m/s</i>)	100 (Oliveira et al., 2012)
	Drug	Salbutamol Sulfate
	Propellant	HFA134a
Propellant Properties	Formula	CH ₂ FCF ₃
	Density (<i>kg/m³</i>)	1,311
	Viscosity (<i>kg/ms</i>)	3.8×10^{-4}
	Surface tension (<i>N/m</i>)	0.015
	Boiling point (°C)	-26.0
	Specific heat (<i>kJ/kgK</i>)	0.79

The NGI generated coaxial airflow via suction from a vacuum pump (**Fig 6.2(e)**). The vacuum pump was adjusted to generate the desired constant flow rates (i.e., 30 or 60 *L/min*). The NGI was preserved in a cooler (**Fig 6.2(c)**), providing a temperature-controlled testing environment. The constant temperature of 25°C was maintained to control evaporation. This is because the evaporation of the solvent can reduce aerosol size, potentially resulting in artificially low particle sizes and compromising the integrity of aerosol particle size distribution data [23]. The

concentration of samples trapped in each part, including the actuator block, USP-IP, and NGI cups, was first recovered using a rinsing solution (methanol- HPLC grade) and then determined through an HPLC (XSelect CSH (Charged Surface Hybrid) Prep C18 5 μm OBD 19x150 mm column, 40 °C, 1525 Binary HPLC pump, 2489 ultraviolet (UV)/Visible detector) (Waters, US).

The wavelength of the UV channel was 276.00 nm for salbutamol sulfate. Before injecting the samples into the HPLC, all samples were filtered through a Whatman nitrocellulose membrane filter with a pore size of 0.45 μm . The mobile phase was a mixture of methanol (Solvent A) and water with 0.1% formic acid (Solvent B). Gradient elution was 6:4 (A/B) to 8.5:1.5 (A/B) over 4.5 min using a flow rate of 0.8 mL/min and 100 μL injection volume. The HPLC method was validated for the concentration range of 0.25–20 ppm . HPLC data were analyzed using Inhalytix® software (Copley, UK) to calculate particle size and deposition. Each experiment was carried out three times at each constant flow rate.

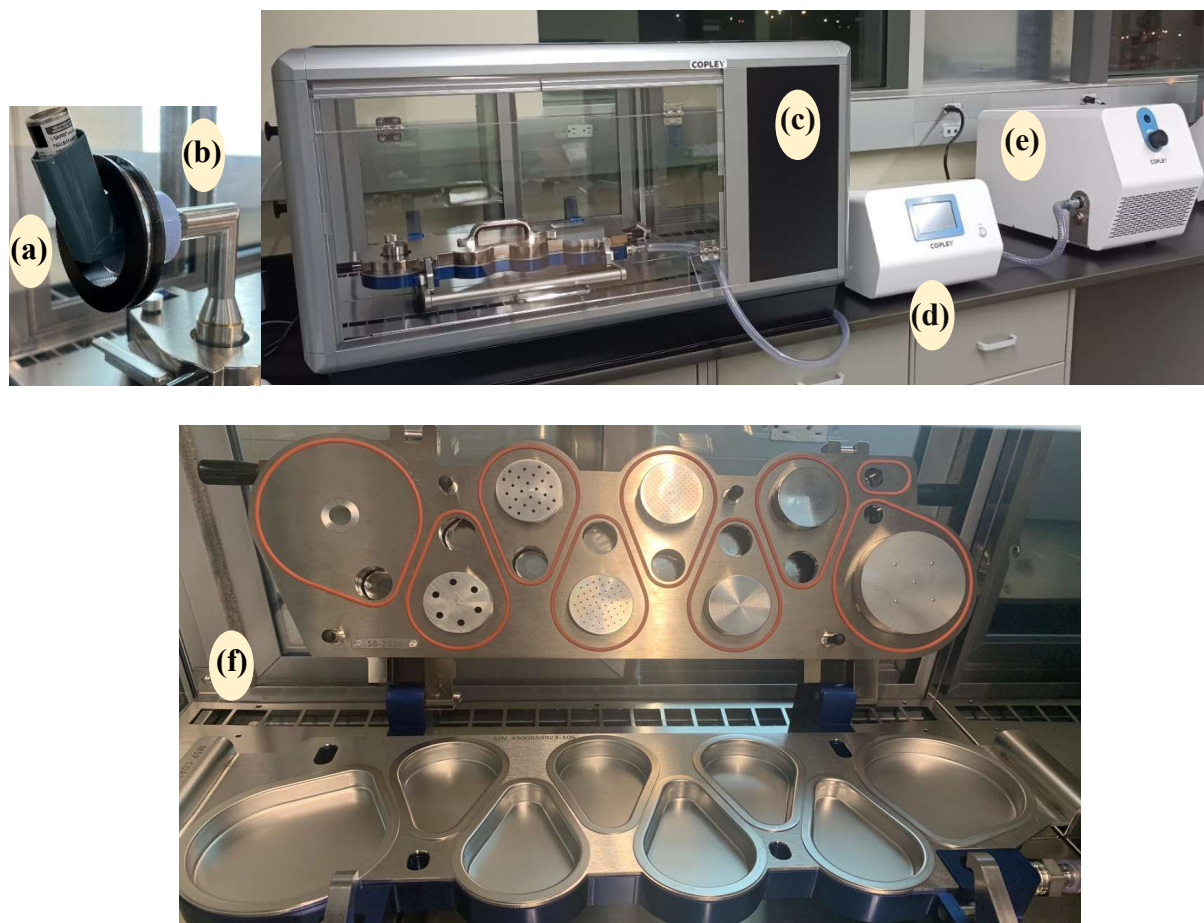


Fig 6.2. NGI experimental setup including (a) Ventolin HFA; (b) USP-IP; (c) Cooler; (d) Flow controller; (e) Vacuum pump; and (f) NGI eight stages (cups).

6.4 CFD Model Development

Transport characteristics associated with performance endpoints, such as MMAD, cannot often be resolved or explained by experiments. In contrast, the numerical approach explains the effect of design variables on transport properties and aerosol drug deposition in the inhaler and airway. This section presents the development of the numerical model for the study.

6.4.1 Geometry and Mesh

The model's geometry was based on the standard dimensions of the experimental setup, shown in **Fig 6.3(a)**. Based on Ventolin MDI, the inhaler's design was first created using SolidWorks® 2020, then attached to the USP-IP in ANSYS Design Modeler 2020 R2. As shown in **Fig 6.3(b)**, our computational model was divided into three distinct zones, each represented by a different color.

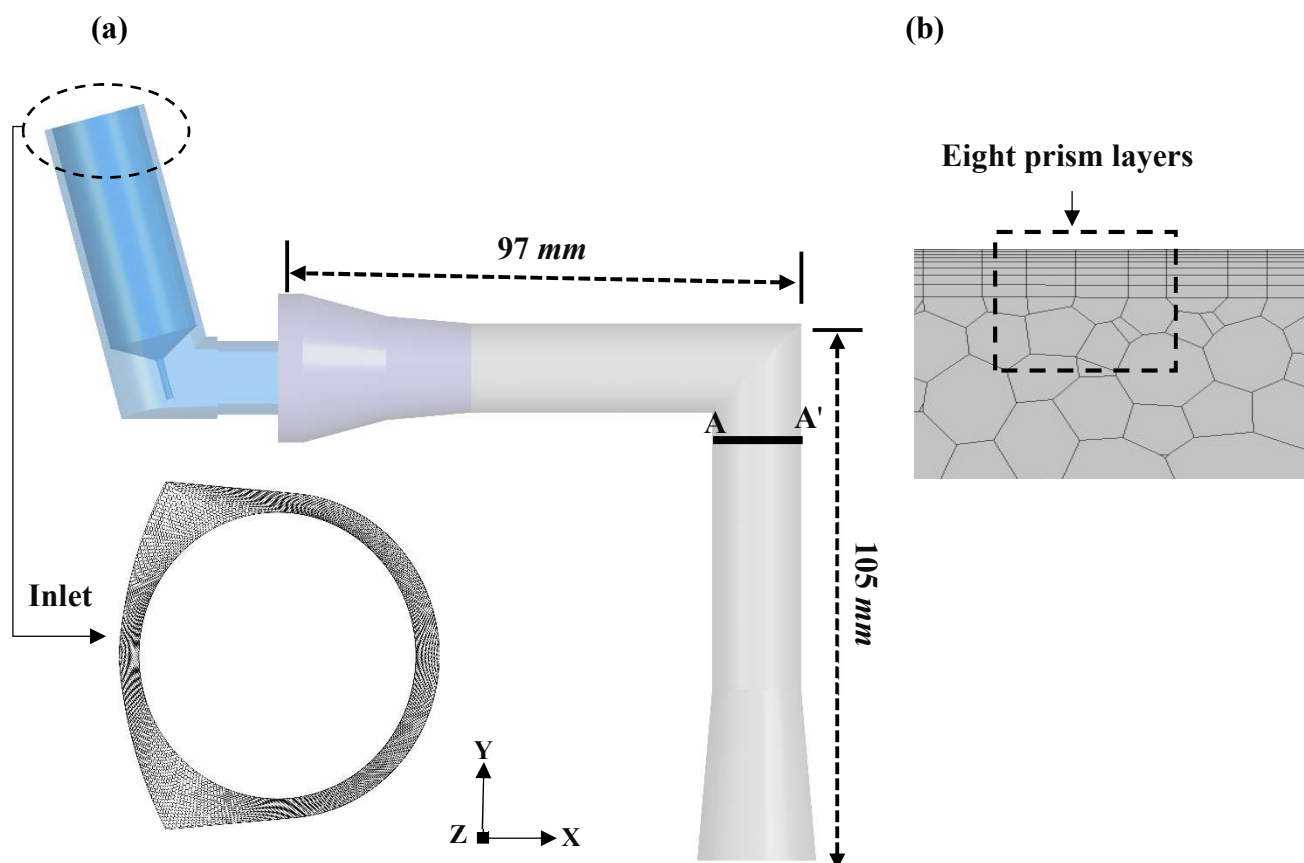


Fig 6.3. (a) Computational geometry of the inhaler and IP; and **(b)** Surface mesh from polyhedral style.

The polyhedral mesh was generated using the mesh generation tool in Fluent 2020 R2 (ANSYS Inc., Canonsburg, PA). Eight layers of prism mesh were employed to capture the turbulent boundary layer profile near the walls of USP-IP, as shown in **Fig 6.3(b)**. The sensitivity of turbulent flow to mesh resolution was evaluated by examining the wall y^+ values. To achieve the target y^+ value, we estimated the height of the near-wall cell layer using Blasius' equation for turbulent flow in a circular pipe [61]. This equation provides an approximation for skin friction, which is related to wall shear stress. We used the calculated shear stress in the standard y^+ formula to determine the distance from the centroid of the near-wall cell to the wall boundary [62].

The y^+ value for the first near-wall computational cell ranged from 0.25 to 0.75 across various walls, which aligns with the recommended target of less than 1 [62, 63]. After completing the meshing process, we smoothed the cell nodes using FLUENT meshing to ensure that all cells achieved an orthogonal quality greater than 0.25. This approach resulted in a high-quality discretization of the domain.

As part of our mesh independence study, we evaluated four meshes with approximately 0.5 million, 1 million, 2 million, and 4 million polyhedral cells. **Table 6.2** presents the average air velocity for the four meshes at a constant flow rate of 60 *L/min*. The average air velocity was checked at 0.07 *s*, which showed fluctuations before actuation was completed at 0.1 *s*. The average air velocity was measured in the (USP-IP) on the AA' plane (refer to **Fig 6.3**) and the XY plane at $Z=0$ (USP-IP cross-section). The latter created a 2D surface with a large recirculation area where grid refinement was essential. After comparing the results, we used a 2-million mesh with an acceptable maximum skewness of 0.860 for our study. We found that increasing the mesh to 4 million did not significantly affect the average velocity throughout the surface of IP and different cross sections. Furthermore, we examined the fraction of particles that passed through the USP-IP for all meshes.

Table 6.2. Grid independence test results for 60 *L/min* flow rate in dry air conditions.

Number of Elements	Maximum Skewness	Average Velocity at Plane AA' (m/s)	Average Velocity at Plane XY at $Z=0$ (m/s)
533,936	0.951	5.118	5.610
1,167,087	0.883	4.961	4.817
2,049,849	0.860	4.986	4.761
4,281,209	0.895	4.932	4.718

6.4.2 Governing Equations

Our CFD model simulated a 3D, incompressible, and Newtonian airflow that is generally inhaled during lung reconstruction. The Eulerian approach was applied for the simulation of the fluid phase. The continuity and momentum equations governed the airflow, as shown in Eqs. (6.1) and (6.2) [64]:

$$\frac{\partial \bar{u}_i}{\partial x_i} = 0 \quad (6.1)$$

$$\rho \frac{\partial \bar{u}_i}{\partial t} + \rho \bar{u}_j \frac{\partial \bar{u}_i}{\partial x_j} = -\frac{\partial p}{\partial x_i} + \frac{\partial}{\partial x_j} \left[(\mu + \mu_t) \left(\frac{\partial \bar{u}_i}{\partial x_j} + \frac{\partial \bar{u}_j}{\partial x_i} \right) \right] + \rho g_i \quad (6.2)$$

where $\bar{u}_i$ is the time-averaged air velocity in different directions of Cartesian coordinate, i.e., $i = 1, 2, \text{ and } 3$, p is the time-averaged pressure, ρ is the fluid density, g_i is the gravitational body force, μ is the dynamic viscosity, and μ_t is the turbulent (eddy) viscosity.

Among the various turbulence models available, such as large eddy simulation (LES) and low Reynolds number (LRN) methods, the LES model has become popular due to its ability to capture detailed turbulent characteristics. However, its high computational cost can be a drawback, especially for simpler geometries where such detailed information may not be necessary for broader predictions [65, 66]. Consequently, the LRN-k- ω turbulence model (Eqs. (6.3) and (6.4)) was selected for this study to effectively model the flow conditions and airflow profile. This model has been well-tested and reported in the literature and reasonably estimates aerosol transport and deposition in upper airway models. Moreover, the k- ω model offers better accuracy than the k- ϵ model for near-wall and separated flows by resolving the viscous sublayer without wall functions. While the k- ϵ model works well for free shear flows and allows coarser meshes, the k- ω model performs better under adverse pressure gradients, making it more suitable for complex wall-bounded flows. [39, 67, 68].

$$\frac{\partial}{\partial t}(\rho k) + \frac{\partial}{\partial x_i}(\rho k u_i) = \frac{\partial}{\partial x_i} \left[\left(\mu + \frac{\mu_t}{\sigma_k} \right) \frac{\partial k}{\partial x_j} \right] + G_k - Y_k \quad (6.3)$$

$$\frac{\partial}{\partial t}(\rho \omega) + \frac{\partial}{\partial x_i}(\rho \omega u_i) = \frac{\partial}{\partial x_j} \left[\left(\mu + \frac{\mu_t}{\sigma_\omega} \right) \frac{\partial \omega}{\partial x_j} \right] + G_\omega - Y_\omega \quad (6.4)$$

where G_k is the generation of turbulent kinetic energy that arises due to mean velocity gradients and G_ω is the generation of ω . Y_k and Y_ω represent the dissipation of k and ω due to turbulence.

The discrete phase model (DPM) and the Lagrangian approach have been employed to govern the equations of particles. Based on the sum of different forces (such as drag, buoyancy, gravity, Saffman, and Brownian) on each particle, this approach tracks the trajectories of individual particles. Newton's second law of motion gives the force balance equation as Eq. (6.5) [69]:

$$\sum \vec{F} = m_p \frac{\partial \vec{V}_i}{\partial t} \quad (6.5)$$

where F is the force term, m_p is the particle mass, $\vec{V}_i$ is particle velocity, and t denotes time. For this model, a Lagrangian particle tracking model was employed to determine the trajectories of each particle [67]:

$$\frac{d\vec{V}_i}{dt} = \vec{f}_d + g_i(1 - \alpha) + \vec{f}_{i,Brownian} \quad (6.6)$$

Brownian motion in relation to drag and gravitational forces negligible [70], where α is the ratio of mixture to droplet density (ρ/ρ_p), f_d is the drag force, which is the most important force on the particle and is expressed as follows [71]:

$$\vec{f}_d = \frac{f}{\tau_p} (\vec{u}_i - \vec{V}_i) \quad (6.7)$$

$$\tau_p = \frac{4\rho_p d_p C_c}{3\rho C_D v_{rel}^2} \quad (6.8)$$

$$C_D = a_1 + \frac{a_2}{Re} + \frac{a_3}{Re^2} \quad (6.9)$$

where f is a drag factor, τ_p is particle relaxation time, ρ_p is the particle's density, u_i is the fluid velocity, g_i is gravity. C_D and C_c are particle drag coefficient and slip correction factor, respectively. The ρ is the fluid density, and v_{rel} is the relative velocity between the particle and fluid. The a_i coefficients are constant for smooth spherical considered in the current study.

We also included interconnected relations governing the transport of heat and mass (water vapor) to evaluate temperature and relative humidity fields in the mouth-throat model. Eq. (6.10) is governed by the convection-diffusive equation, including turbulent dispersion [68, 72]:

$$\frac{\partial Y_v}{\partial t} + \frac{\partial u_j Y_v}{\partial x_j} = \frac{\partial}{\partial x_j} \left[\left(D_v + \frac{\mu_T}{Sc_T} \right) \left(\frac{\partial Y_v}{\partial x_j} \right) \right] + S_v \quad (6.10)$$

where Y_v is the mass fraction of water vapor, D_v is the binary diffusion coefficient of water vapor

in the air, μ_t is the turbulent viscosity, and the turbulent Schmidt number (Sc_T) was taken as 0.9 based on the range of Reynolds numbers in our simulation [67]. S_v is the water source term for increasing (decreasing) water vapor mass fraction in the continuous phase from evaporating (or condensing) droplets. Although inspired air is dry (25°C) at the onset of inhalation, it becomes saturated with humidity in the upper airways. In the mouth-throat region, the relative humidity can reach nearly 100% due to the presence of mucus. This local humidity significantly affects particles by promoting hygroscopic growth, which alters their size and behavior. Incorporating spatial variations in humidity ensures a more physiologically accurate representation of airflow conditions and particle deposition.

6.4.3 Boundary Conditions

The spray was modeled as a stream of salbutamol sulfate particles. The initial injection velocity of the particles was 100 m/s, causing choked flow conditions at the nozzle [34]. The airflow temperature was 25°C, which is consistent with the experiments. We modeled the constant flow rates (30 and 60 L/min) and the COPD breathing pattern at the inlet and used a pressure outlet on the outlet surface. In order to investigate the effect of COPD breathing patterns on the particle deposition in the upper airway model, a user-defined function (UDF) was employed to simulate the cyclic inspiratory flows based on Colasanti et al.'s study [54]. The boundary conditions for the turbulent inlet were defined in terms of turbulent kinetic energy (k) and specific dissipation rate (ω), with both values set to unity. The model applied “trap” conditions for walls, which assumes that once spray particles make contact with a wall, they are trapped there. For higher volume fractions, the influence of the particles on the fluid flow, which is often referred to as two-way coupling, needs to be accounted for.

At time $t = 0$ s, the system's air volume fraction was 1.0. According to **Fig 6.3**, the direction of gravity was downwards along the negative y -axis. At $t = 0$ s, both the co-airflow and injection started together. Each actuation lasted 0.1 s. As part of our study, we investigated the effects of relative humidity by considering four humidity conditions: 0%, 50%, 90%, and 99%.

6.4.4 Numerical Controls and Computational Power

The simulation convergence was assessed by monitoring the continuity residuals to be below 10^{-3} and other residuals to be below 10^{-5} . The semi-implicit method for pressure-linked

equations (SIMPLE method) was used to link velocity and pressure [73]. In addition, the second-order upwind was also adopted for the turbulent dissipation rate to limit the numerical diffusion errors [74]. We utilized the supercomputing facility at Lakehead University, which has 80 available cores and features an Intel® Xe®(R) Gold 6148 CPUs @ 2.40GHz. In addition, parallel processing was performed on 2 Intel Xeon Silver 4214 CPUs @ 2.20GHz and 2.19GHz (2 processors). Each computational task comprised 2,049,849 elements and took around 72 hours to complete.

6.5 Results and Discussion

In this section, we will begin by presenting the analysis results of NGI for Salbutamol particles. We will then compare our findings with existing literature and examine the impact of humidity and airflow patterns on drug delivery. Finally, we will compare constant flow rates with the breathing patterns of COPD patients in the presence of varying relative humidity levels.

6.5.1 NGI Analysis Data

The NGI, designed by Copley Scientific in the UK, has different particle cut-off diameters for each stage, depending on the inlet air flow rate. **Table 6.4** reports the particle mass deposition of Salbutamol through the mouthpiece, USP-IP, and cut-off sizes of each NGI stage for constant inspiratory flow rates of 30 and 60 *L/min*. The NGI's novel features an aerodynamic design principle that is well suited to the needs of the inhaler testing community, as Marple et al. explained [25].

As presented in **Table 6.3**, the cut-off diameters decreased from stage 1 to 8, in alignment with changes in flow rate. The metered dose refers to the mass of particles collected from the mouthpiece, USP-IP, and NGI stages when it is actuated. On the other hand, the delivered dose refers to the mass of particles that pass through the IP and are collected in the NGI stages. The delivered dose was then utilized to plot the particle size distribution and calculate the MMAD for each flow rate. This table demonstrates that drug deposition on the USP-IP wall decreases by 39% at 60 *L/min* compared to 30 *L/min*. Hence, more particles passed through the IP at a higher breathing flow rate of 60 *L/min*. We can observe a higher mass of fine particles in stages 2 to 5, ranging from 0.94 to 4.46 μm at a flow rate of 60 *L/min*. Generally, the mass of stages 2-5 plays a crucial role in increasing the likelihood of drug delivery to the lungs [67]. According to the literature, particles with a diameter less than 0.55 μm (from stages 6 to 8) are typically exhaled out

of a patient's respiratory tract due to their small size [75].

Using Copley's software (Inhalytix®), **Table 6.4** reports the delivered dose characteristics in terms of MMAD, fine particle fraction (FPF), and geometric standard deviation (GSD) for the constant inspiratory flow rates of 30 and 60 *L/min*. The FPF is the mass fraction of fine particles in the emitted dose, while the GSD represents the deviation of a set of numbers from their geometric mean. Hypothetically, particles with an aerodynamic diameter of less than 5 μm have a higher chance of passing the throat after inhalation [56].

Table 6.3. Salbutamol deposition and cut-off sizes for NGI stages.

Flow Rate (<i>L/min</i>)	30		60	
	Cut-off Diameter (μm)	Deposition (μg)	Cut-off Diameter (μm)	Deposition (μg)
Mouthpiece	-	19.68	-	10.58
USP- IP	-	51.25	-	31.12
Stage 1	11.72	6.27	8.06	5.81
Stage 2	6.40	0.76	4.46	8.73
Stage 3	3.99	3.05	2.82	12.41
Stage 4	2.30	13.60	1.66	14.27
Stage 5	1.36	2.68	0.94	6.53
Stage 6	0.83	0.48	0.55	0.59
Stage 7	0.54	1.21	0.34	0.06
Stage 8	< 0.54	0.25	< 0.34	0.27
Metered Dose	-	99.23 $\pm$ 1	-	90.27 $\pm$ 3
Delivered Dose	-	28.3	-	48.67

Table 6.4 shows that as the flow rate increased, the MMAD decreased, resulting in finer particles produced, as indicated by the FPF at 60 *L/min*, which were 7% higher than at 30 *L/min*. The GSD values at 60 *L/min* confirm that the particle size distribution was narrower for finer particles compared to 30 *L/min*. The higher flow rates of 60 *L/min* diluted the propellant concentration around the plume, thereby increasing the evaporation rate. As the volatile propellant evaporated more quickly, the size of the droplets reduced rapidly. On the other hand, droplets that took longer to evaporate were larger and more likely to deposit in the turbulent regions of the mouthpiece and

USP-IP. This is because turbulent regions have a greater affinity for collecting larger particles, as found by Stein and Myrdal [21] and Lewis et al. [76].

Table 6.4. The particle size distribution characteristics.

Flow Rate (L/min)	Delivered Dose (μg)	MMAD (μm)	FPF (%)	GSD (-)
30	28.3 ± 1.2	3.98 ± 0.25	30.17	2.07
60	48.67 ± 2.4	3.11 ± 0.18	37.96	1.94

6.5.2 CFD Model Validation

Fig 6.4 compares CFD results to the NGI data for two constant flow rates: **(a)** 30 L/min and **(b)** 60 L/min. This figure presents the cumulative deposition efficiency of particles with an aerodynamic diameter ranging from 0.45 to 10 μm that pass through USP-IP's outlet. The CFD results for particle diameters were categorized into the same cut-off sizes as those of NGI's cups, and the model's results generally agreed with the experimental data. The root-mean-square (RMS) error value between the simulation and experiment data was determined using Eq. (6.11) [77]:

$$RMS\ error = \sqrt{\frac{\sum_{i=1}^n (y_{CFD} - y_{exp})^2}{n}} \quad (6.11)$$

where y_{CFD} represents the simulated value, y_{exp} represents the experimental data, and n is the total number of data points.

RMS error for 30 L/min and 60 L/min flow rates are 14.08% and 9.71%, respectively, indicating acceptable agreement between model and experiment. Each experiment was repeated three times with maximum standard deviation (SD) error bars of 5.00% and 4.52% for 30 and 60 L/min, respectively. Additionally, the current data was compared with data from Cheng et al. [59], who used the same method of particle collection from NGI's cups.

6.5.3. Impact of Constant Flow Rates

Fig 6.5 presents the distribution of the particles deposited on the USP-IP wall at two constant flow rates of 30 and 60 L/min. It shows that particles in the 12-15 μm range have the highest percentage deposited on the wall for both flow rates. We can also see that much larger particles were deposited on the USP-IP wall at higher breathing flow rates. However, the mass

fraction of deposited particles was 5% less for the higher flow rate of 60 *L/min*. This result is also reported in Table 6.4, showing a 39% decrease in mass as the flow rate increased.

Additionally, the figure confirms the results shown in Fig 6.4, which demonstrated that the deposition efficiency was higher at a breathing flow rate of 60 *L/min* compared to 30 *L/min*. Longest et al. [68] characterized the MDI aerosol in real respiratory tract geometry with different flow rates. Their results also showed that at a higher flow rate of 80 *L/min*, the drug deposition fraction in the mouth-throat was 7.3% lower than at a flow rate of 40 *L/min*. They also observed that finer particles were generated at the high flow rate of 80 *L/min*, resulting in a 2.4% increase in deposition in the trachea [68].

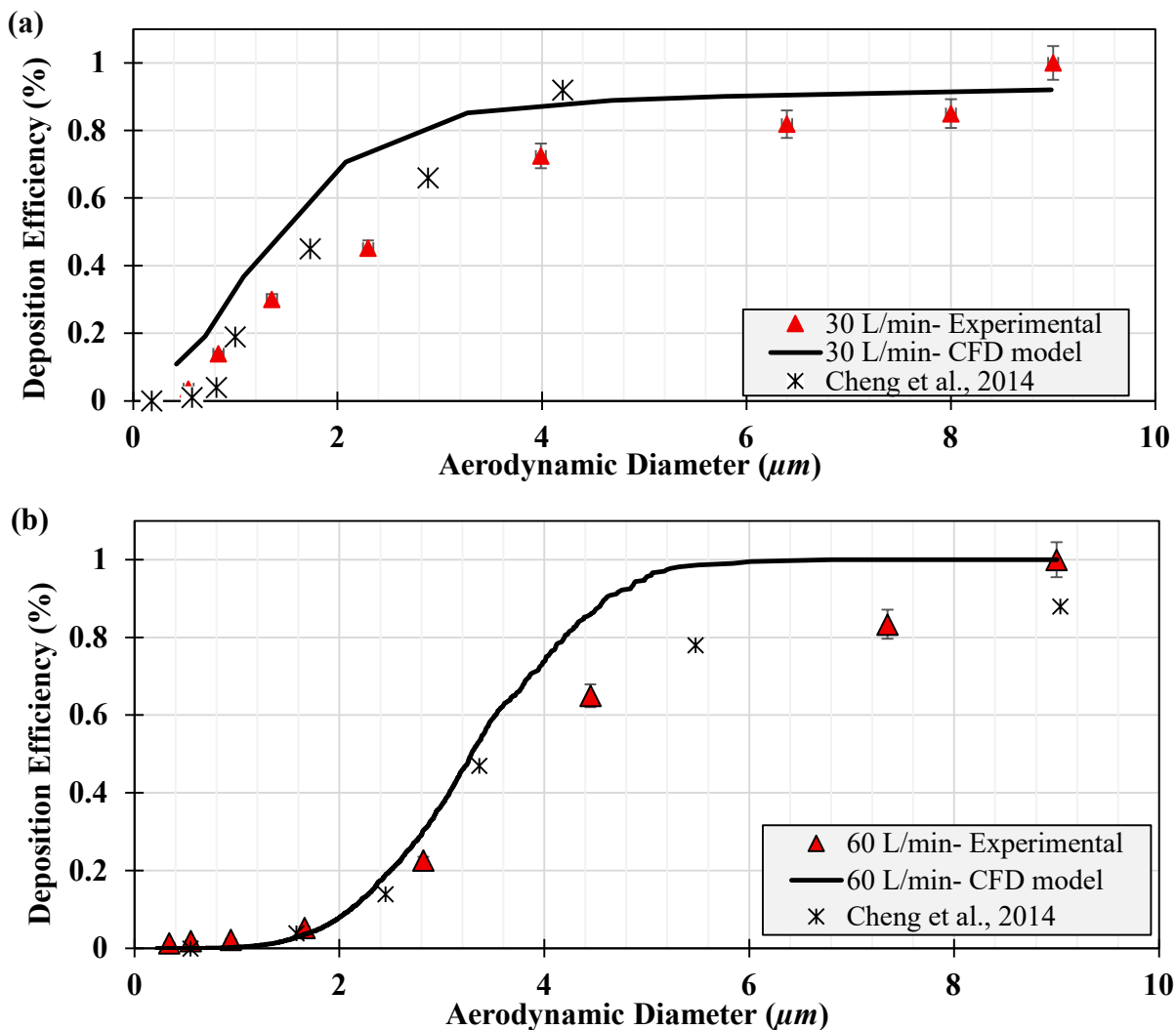


Fig 6.4. Particle deposition efficiency vs. aerodynamic diameter from the CFD model and experiment for (a) 30 *L/min*, (b) 60 *L/min* at dry conditions.

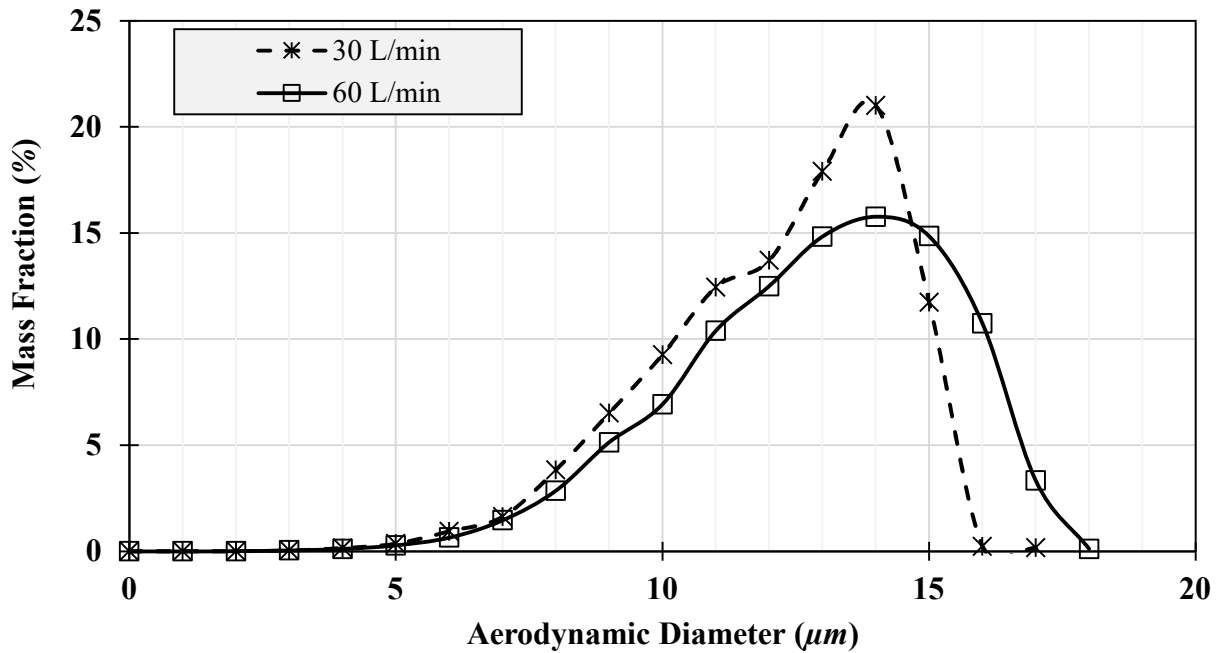


Fig 6.5. CFD results of mass fraction of deposited particle distribution on the USP-IP wall at two constant flow rates (30 and 60 *L/min*) at dry airflow conditions.

Fig 6.6 displays the velocity magnitude streamlines and contours on the cross-section plane of XY ($Z = 0$) at 60 *L/min* through the USP-IP geometry at different times (0.01, 0.05, 0.09, and 0.19 *s*). As highlighted in the figure, we noticed two major recirculation zones near the 90° bend. One circulation appeared near the upper wall of USP-IP ((a'') upper recirculation area), and the second circulation area was in the convex of the bend's inner side ((b'') lower recirculation area), which led to a higher velocity magnitude as the flow passed the bend. Throughout all time steps, a canal formed in the bend, depositing particles on the back wall of the throat. The circulation areas delayed inertia, allowing the air to closely follow the airway's contour without abrupt changes in direction. Drug particles were then deposited on the airway wall due to secondary-flow impaction caused by airflow streamlines near the wall.

We observed that the recirculation areas varied in size and number during actuation time in the USP-IP geometry. The presence of particles at the bend affected the recirculation areas. One central recirculation area can be observed at the beginning of the actuation before particles occupy the bend entirely (at 0.02 *s*), as shown in **Fig 6.6(a)**. At 0.05 *s*, multiple recirculation areas appeared and spread downward, as demonstrated in **Fig 6.6(b)**. In **Fig 6.6(c)**, at 0.09 *s*, the recirculation area expanded, with several minor recirculation areas due to the high presence of particles at the

bend. By 0.19 s , as depicted in **Fig 6.6(d)**, the majority of particles passed through the bend with the lowest degree of interaction with the co-airflow. As a result, the upper recirculation area has become smaller. Over time, the upper recirculation area shifted to the corner of the wall of the 90° bend. Although the lower recirculation area exhibited a similar pattern, the upper circulation area had a greater impact on the airflow canal in the middle of the IP.

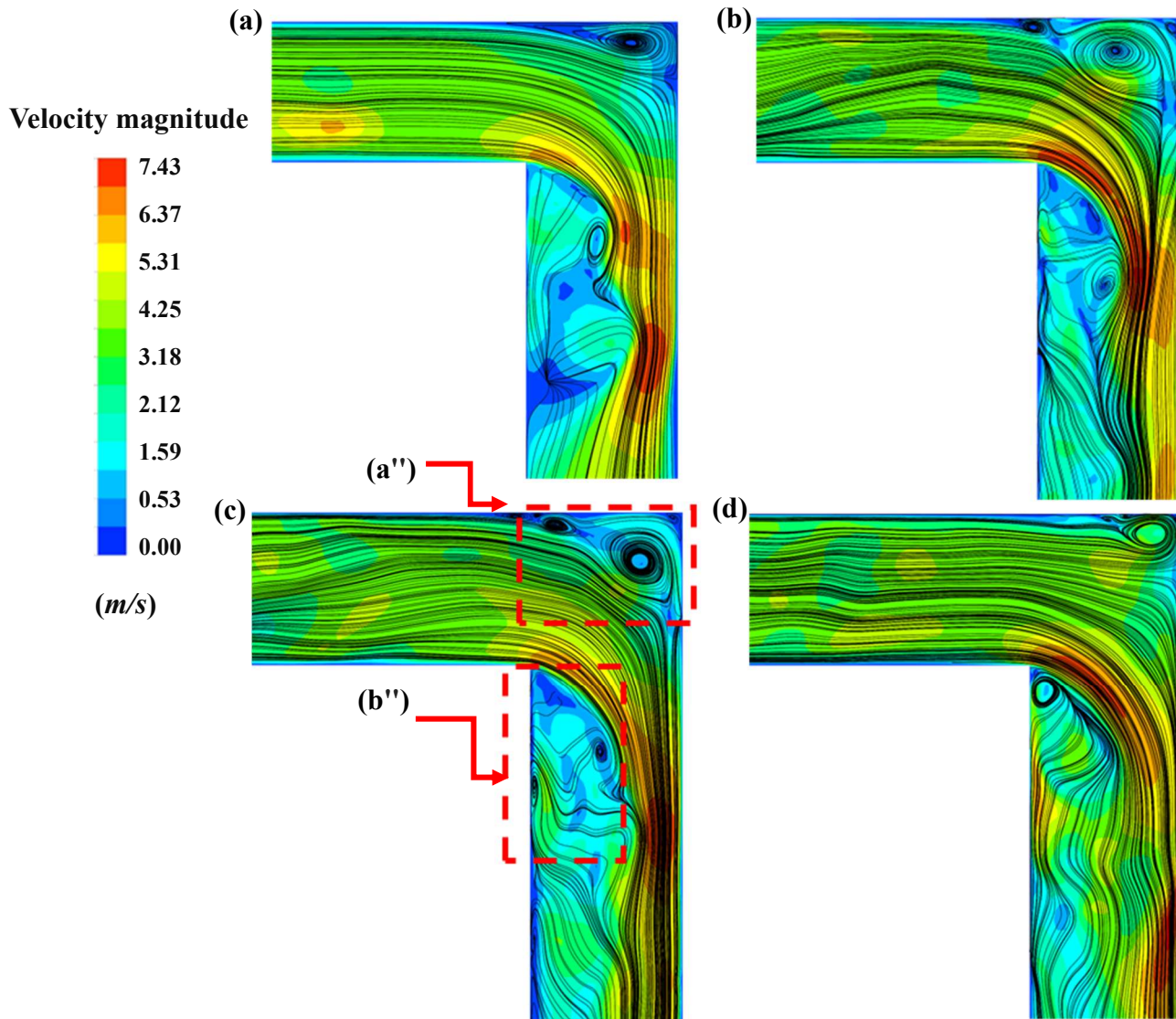


Fig 6.6. Velocity magnitude streamlines and contour at plane XY cross-section ($Z = 0$) for the USP-IP for 60 L/min constant dry airflow in different time steps: **(a)** 0.02 s ; **(b)** 0.05 s ; **(c)** 0.09 s ; and **(d)** 0.19 s , the actuation duration: 0.1 s .

6.5.4 Impact of Relative Humidity

Our experimental study was conducted in a dry airflow, which simplifies the humidity levels in the respiratory tract, as is typical in this field. However, through our CFD modeling, we investigated the effect of relative humidity on particle deposition fraction, particle distribution, and airflow pattern. Three different levels of relative humidity have been considered: 50%, 90%, and 99%. **Fig 6.7** displays the size distribution of escaped particles from the USP-IP outlet for two constant flow rates (30 and 60 *L/min*) under varying relative humidity levels. The particle diameter range that passed the USP-IP increased from 14 to 16 μm at a flow rate of 60 *L/min*, indicating that larger particles were able to pass through the mouth-throat airway due to the increased flow rate.

Fig 6.7 shows that the distribution of particles that escaped the USP-IP was not affected by the increase in relative humidity at either flow rate. However, at 99% relative humidity, the deposition on the IP wall decreased by 5% and 11% for flow rates of 30 and 60 *L/min*, respectively, compared to dry conditions. In humid conditions, small particles tend to grow larger due to hygroscopic growth. As a result, these larger particles were expected to deposit on the USP-IP wall, as Shemirani et al. [78] reported. They conducted experiments to evaluate how temperature and humidity affect the deposition patterns of solution and suspension pMDI formulations in the mouth-throat and lungs [78]. They used the Alberta Idealized Throat set in a controlled environment and found that increasing the relative humidity up to 80% caused a higher amount of particles to deposit on the mouth-throat and fewer to reach the lungs for both types of formulations. They also noticed differences in the behavior of solution and suspension formulations in response to environmental conditions. In our study, we examined higher relative humidity levels (90% and 99%) compared to the study conducted by Shemirani et al. [78]. These high humidity levels affected the deposition of particles on the walls, resulting in a difference compared to their data. After further analysis, we found that relative humidity also influenced the airflow pattern in the USP-IP, as shown in **Fig 6.8**.

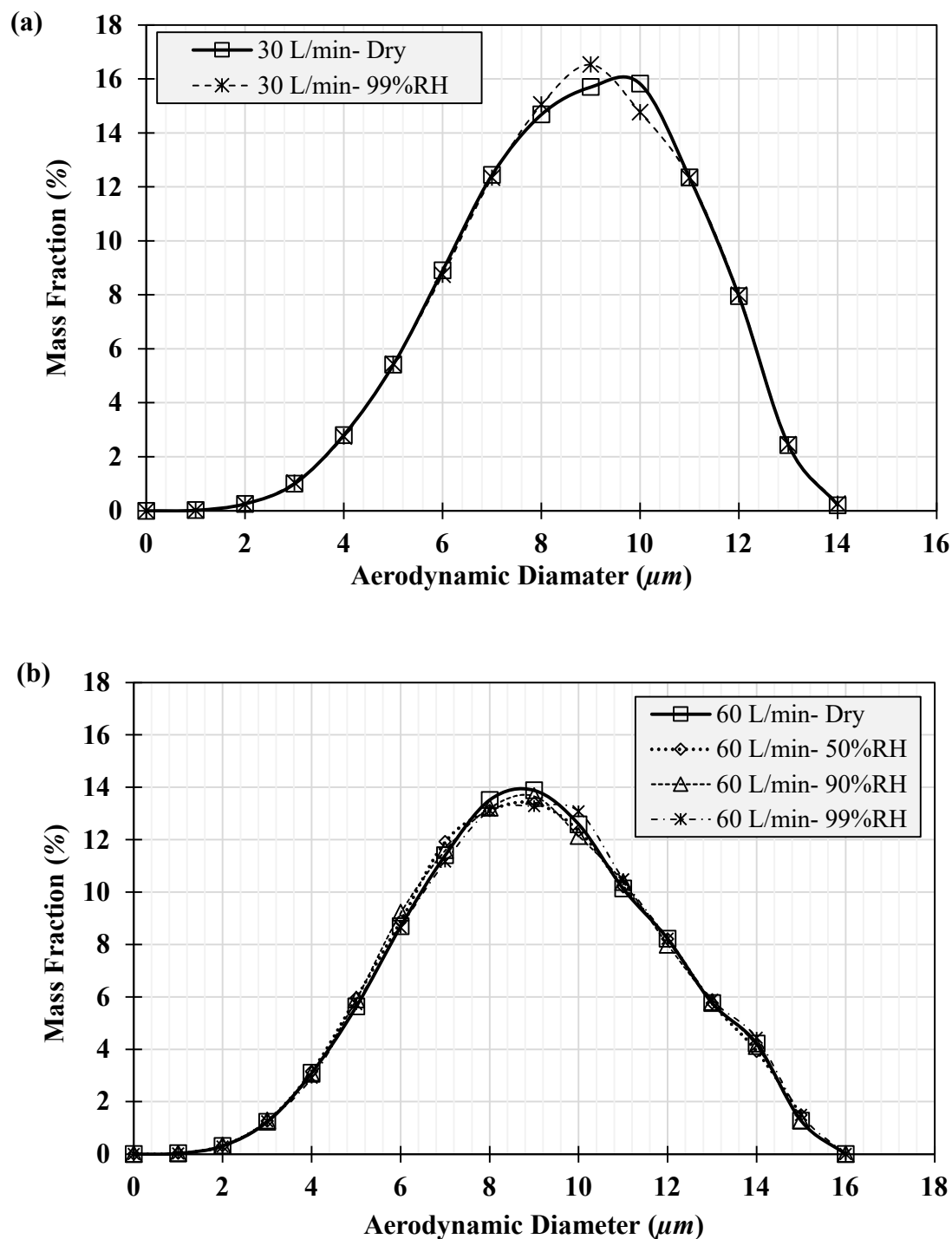


Fig 6.7. Outlet particle size distribution for constant flow rates of **(a)** 30 L/min; and **(b)** 60 L/min with different relative humidity levels; RH: relative humidity, CFD results.

At 0.09 s, **Fig 6.8** illustrates the velocity magnitude streamlines of the top of the IP for dry air and various relative humidity levels (50%, 90%, and 99%) at a constant airflow rate of 60 L/min. **Fig 6.8(a)** displays several slow, large, and small recirculations, resulting in increased particle deposition on the wall due to the longer particle residence time in the dry airflow. However, as the relative humidity increased to 50% (shown in **Fig 6.8(b)**), the recirculation areas merged and lifted near the wall with higher velocity magnitude streamlines. For the higher relative humidity (i.e., 90%) presented in **Fig 6.8(c)**, another small recirculation region was created between the original two. As the relative humidity increased to 99%, as shown in **Fig 6.8(d)**, the small recirculation area that was observed at 90% relative humidity became more defined and distinct from the other main areas.

When comparing **Figs 6.8(a)** and **8(d)**, we can observe that the velocity magnitude in the center of the main recirculation is three times higher for 99% relative humidity compared to dry conditions. This is because moisture in the airflow affects the density of the surrounding air. An increase in the percentage of relative humidity leads to lower air density. Less dense air tends to move more easily, which can cause greater turbulence in the flow domain [79, 80]. This phenomenon affects the flow pattern of vortices by providing nucleation sites for higher velocity, as noted by Feng et al. [81]. Turbulence forces larger particles to overcome their inertia and pass through the bend. As a result, the deposition of USP-IP particles is influenced by the recirculation area and its location. As the relative humidity increased to 99%, the deposition at the bend decreased by 23%. In conclusion, the reduction in relative humidity resulted in an increase in particle deposition due to alterations in the recirculation region, while an increase in relative humidity led to a decrease in particle deposition. The particle size distribution remained constant, as demonstrated in **Fig 6.7**.

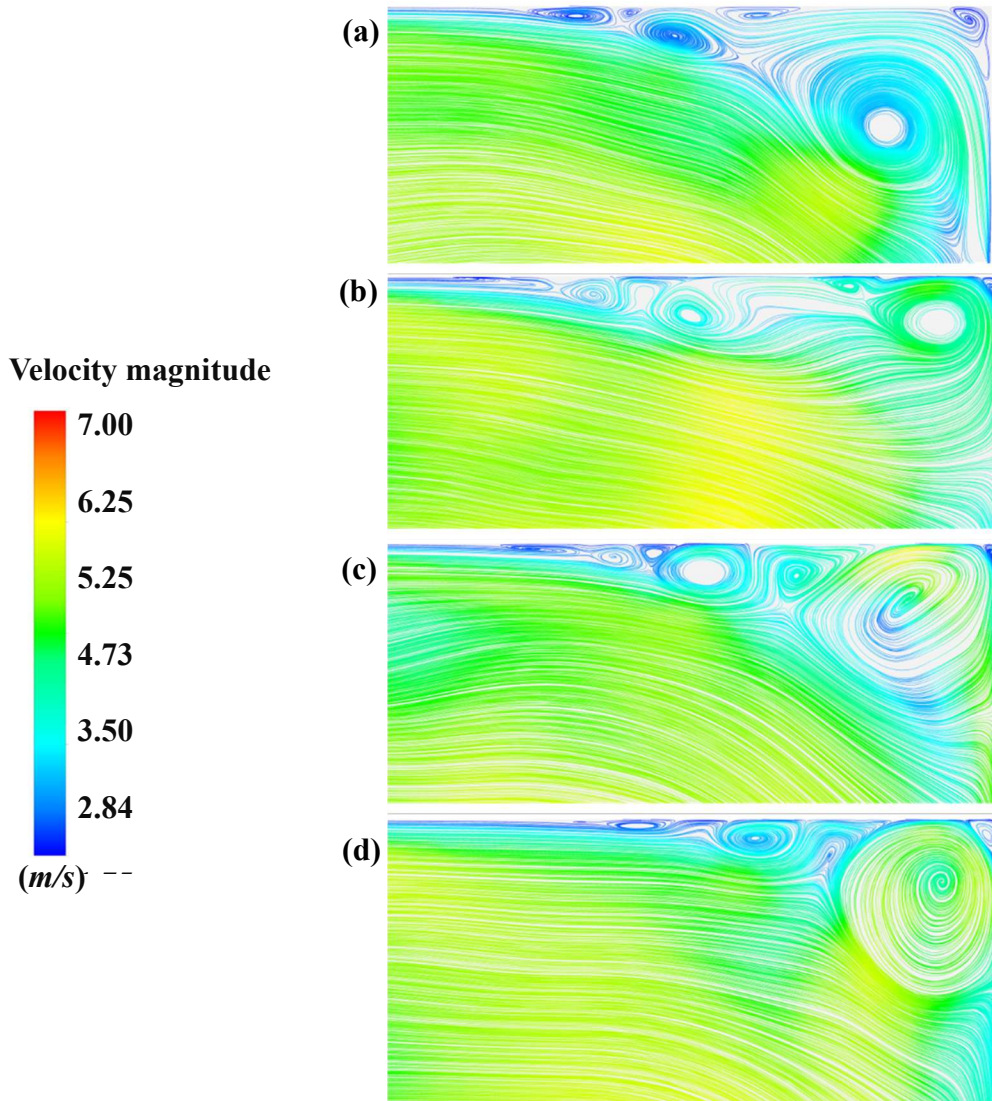
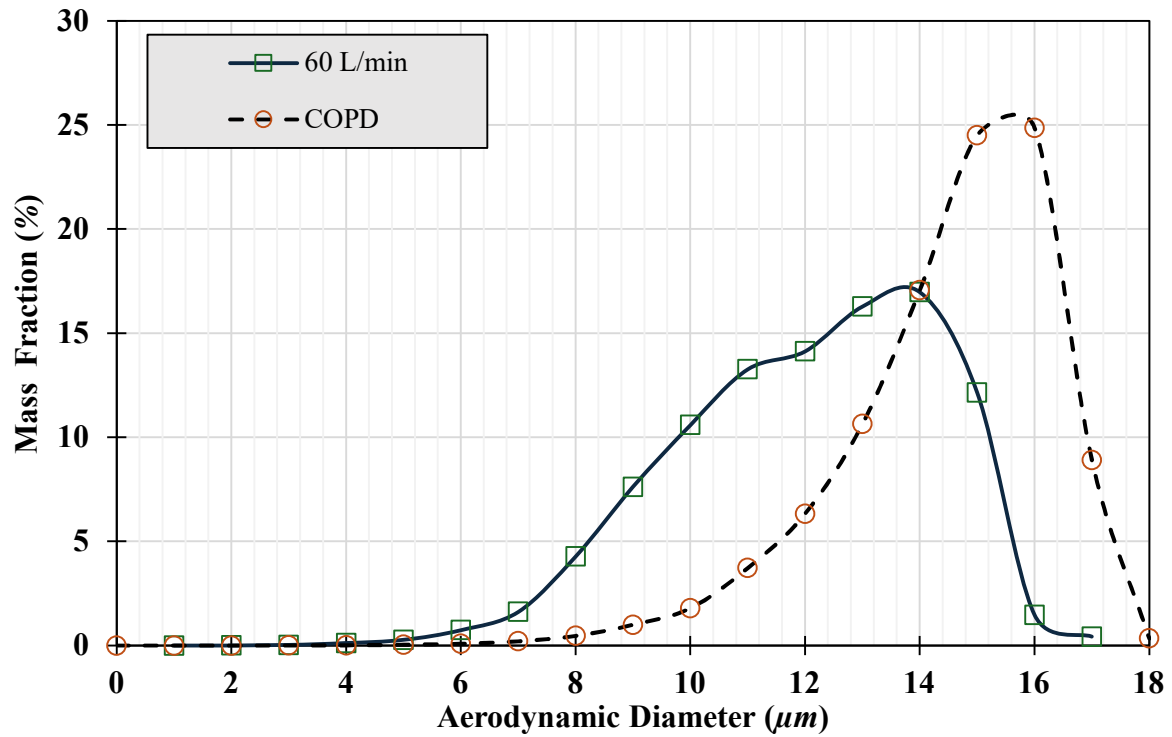


Fig 6.8. Velocity magnitude streamlines focusing on the upper recirculation area at different humidity conditions: (a) Dry air; (b) 50% RH; (c) 90% RH; and (d) 99% RH (with constant 60 L/min at 0.09 s); RH: relative humidity.

6.5.5 Impact of COPD Breathing Pattern

The impact of COPD inhalation on the distribution of particle size deposited in the mouth-throat airway is illustrated in **Fig 6.9**. The COPD sinusoidal breathing profile features an inhalation time of 0.6 seconds with a peak flow rate of 48 L/min . This figure indicates that, when compared to an inhalation rate of 60 L/min , the size distribution of particles deposited on the IP wall was shifted to larger particles during COPD inhalation, resulting in higher particle deposition in the USP-IP. Furthermore, the breathing pattern affected the proportion of deposited particles in the

middle-size range. In the case of COPD, the particle distribution was narrower, with most particles concentrated in the size range of approximately 14 to 16 μm and fewer fine particles observed.



Williams et al. [51] also studied the differences in drug deposition between healthy and impaired breathing using image-based models of both healthy and diseased patients. Their study found that the drug ratio in the lower lobes to the upper lobes was 35% higher during normal inhalation. Although the upper airway deposition of smaller particles was similar in all patients, differences were observed in the size, location, and intensity of local deposition hotspots. A study conducted by Farkas et al. [52] analyzed the impact of delayed time on different breathing patterns, including constant breathing and COPD. For their study, the COPD breathing pattern was simplified into a step-shaped profile. Despite this simplification, they found that particle deposition in the lungs decreased significantly over time. This result aligns with our research, which observed a 10.7% decrease in the escaped particle fraction from the USP-IP for the COPD inhalation case.

Fig 6.10 illustrates the behavior of fine particles, ranging from 0.45 to 10 μm , and their velocity magnitude at 0.07 s under a constant flow rate of 30 and 60 L/min and COPD profile in a dry airflow condition. At a flow rate of 30 L/min , as depicted in **Fig 6.10(a)**, most fine particles

followed the bend of the canal and passed it uniformly. Meanwhile, at a higher flow rate of 60 L/min , as shown in **Fig 6.10(b)**, the finer particles (less than $3\text{ }\mu\text{m}$) got trapped in the recirculation areas. On the other hand, larger particles (greater than $5\text{ }\mu\text{m}$) were affected by the upper and lower recirculation areas and travelled through the canal toward the back wall of the throat. As fewer particles uniformly travelled through the canal, unlike the 30 L/min (**Fig 6.10(a)**), the chance of particle deposition on the back of the throat is lower. We also observed particles with a size ranging from 1 to $5\text{ }\mu\text{m}$ passing through the bend. **Fig 6.10(c)** shows that the COPD breathing pattern generated a less developed aerosol plume because of its low velocity. As a result, most of the fine particles remained near the nozzle and had a greater range of particle size compared to the constant flow rates. Thus, the COPD inhalation flow rate influenced the size distribution of the IP deposited particles, as presented in **Fig 6.9**, in which particle deposition on larger particles is higher than 60 L/min . At this point, we need to analyze how the inhalation impacts the flow rate pattern within the IP.

Figs 6.11(a) and (b) display the x-velocity along the centerline near the upper recirculation region at 0.05 s with a constant flow rate of 60 L/min and COPD inhalation at the XY Plane at $Z=0$, respectively. As per **Fig 6.11**, at the highest pressure (11.52 Pa), the velocity reached its lowest value compared to the surrounding area. This point is called the stagnation point, at which, in the 2D plane, the x- and y-velocities are zero, and the slopes of the streamlines are indefinite. This point was found to be a key vortex generator for the selected plane. At the stagnation point, the kinetic energy is converted into the pressure term [82], resulting in the highest pressure value at the lowest velocity magnitude, as shown in **Fig. 6.11(c)**. This figure shows that the airflow pressure associated with COPD inhalation increases gradually near the recirculation area, unlike the 60 L/min , which has a maximum peak.

Fig 6.11(b) also identified the stagnation point for the COPD inhalation profile at 92 mm from the inhaler nozzle, which is further from the bend than the constant flow rate of 60 L/min . Due to the low inhalation velocity for COPD patients, recirculation areas developed after 0.9 s . Therefore, the range of x-velocity was lower (i.e., from -0.15 to 0.15 m/s), which affects the system's pressure energy changes.

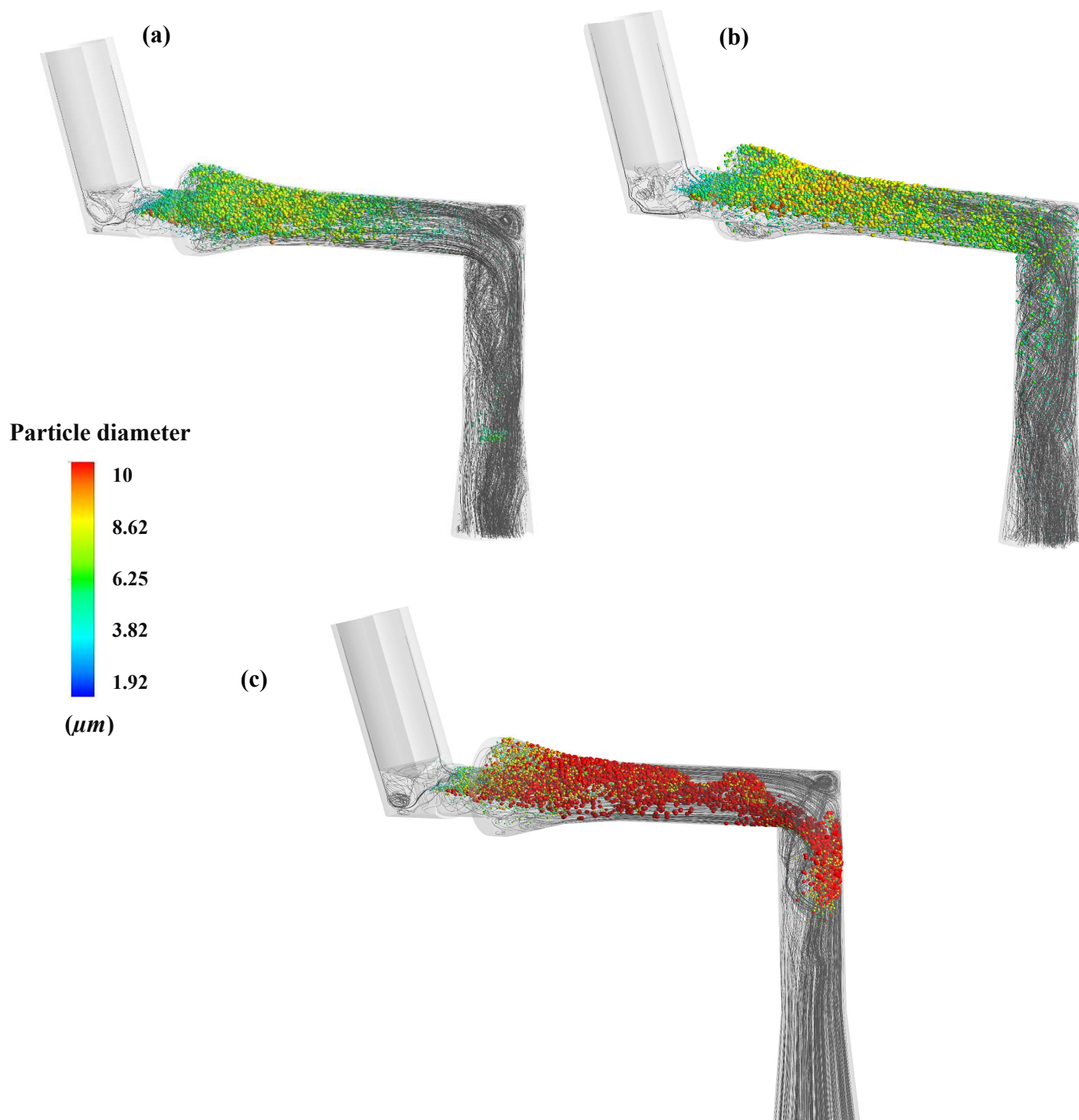


Fig 6.10. Particle tracking at (a) 30 L/min ; (b) 60 L/min ; and (c) COPD inhalation profile at 0.07 s USP-IP at dry airflow conditions.

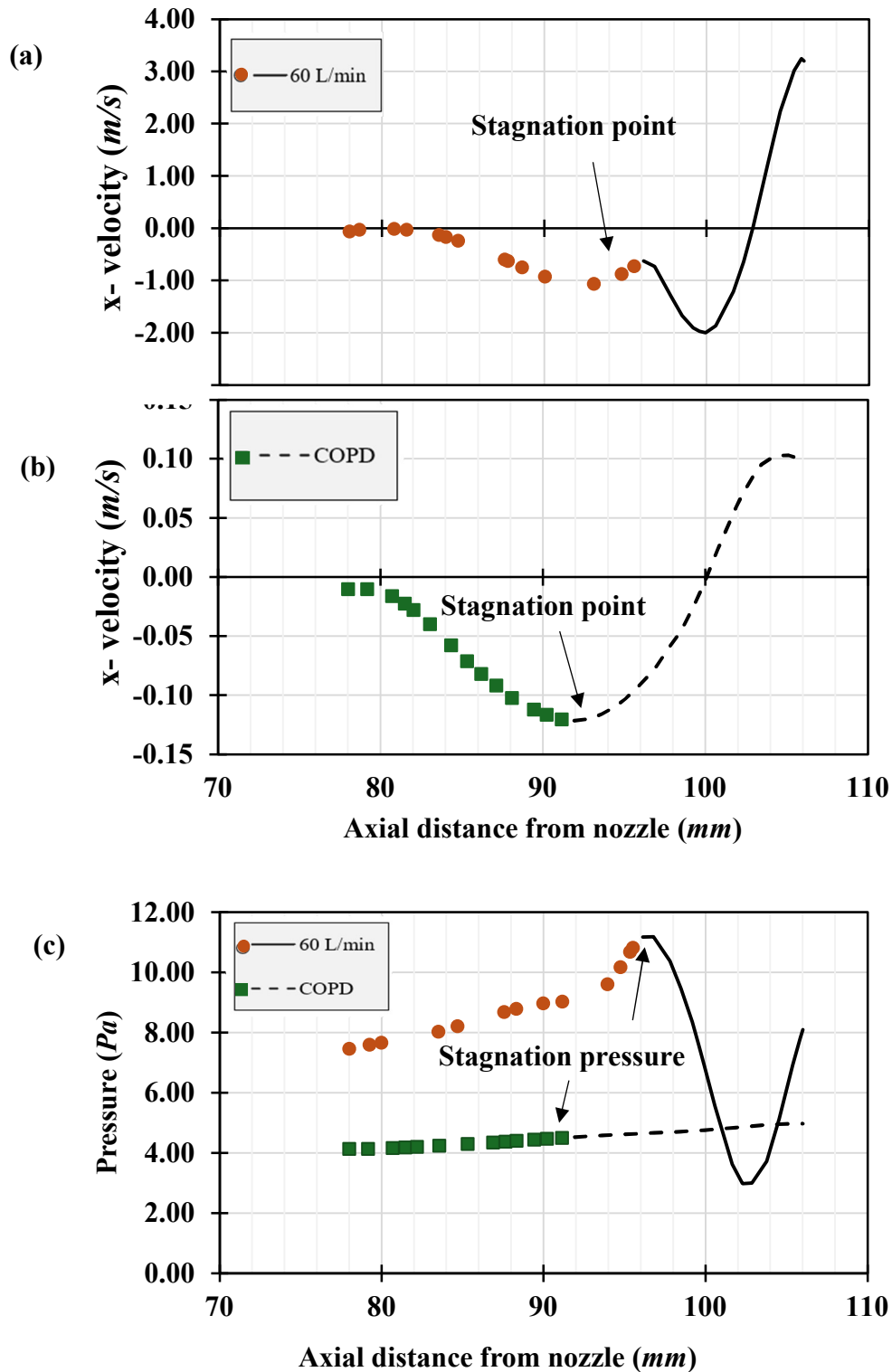


Fig 6.11. (a) X-velocity for constant 60 L/min ; (b) X-velocity for constant COPD breathing profile; and (c) Static pressure profiles for constant 60 L/min , and COPD breathing profile at 0.05 s along the centerline of USP-IP at dry airflow condition, CFD results.

6.5.6 Impact of both Relative Humidity and COPD Breathing Pattern

Fig 6.12 displays the size distribution of particles deposited on the USP-IP wall during COPD inhalation under dry airflow and 99% relative humidity conditions. The figure indicates that the presence of humidity reduced the mass of particles that got deposited on the wall. However, there were no significant changes in the particle size distribution due to the change in relative humidity. As previously explained in **Fig 6.8**, an increase in relative humidity affects the nuclear site of recirculation by increasing velocity. This allowed larger particles to overcome the drag force and pass through the USP-IP. As a result, the mass of larger particles between 8-14 μm decreased in humid conditions.

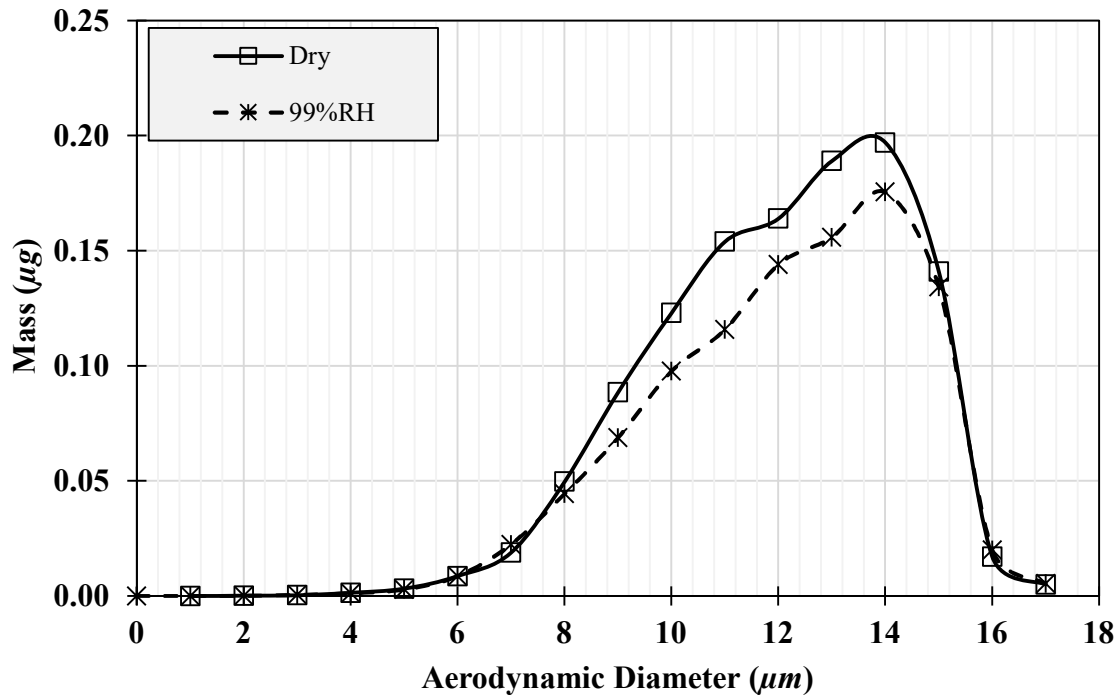


Fig 6.12. Deposited particle size distribution on USP-IP wall for COPD profile in dry airflow condition, and 99% RH (relative humidity), CFD results.

Fig 6.13 shows a comparison of particle deposition efficiency (DE) in the three main zones of the inhaler-USP-IP, which was calculated using Eq. (6.12). Deposition efficiency is a commonly used parameter for reporting the amount of inhaled particles deposited in the respiratory tract [68].

$$DE = \frac{\text{mass of drug particles deposited in each section}}{\text{mass of drug particles entered USP – IP}} \quad (6.12)$$

This figure indicates that the inhaler wall had the highest particle deposition (>20%) due to the low-velocity breathing profile in COPD patients, regardless of dry or humid conditions. This is despite the fact that the initial velocity of actuation has a greater effect on the momentum of the actuated particles than the breathing strength. Additionally, due to high turbulence near the nozzle and inhaler, most particles were deposited at the initial stage.

In the second zone, the plume was more developed with less turbulence. Particles followed the air streamline until they reached the bend with recirculation areas. The presence of recirculation areas in the third zone resulted in a higher deposition rate compared to the second zone. In their study, Hindle and Longest [67] explored the impact of relative humidity and temperature on the growth of nano-sized particles in the real mouth, throat and upper trachea. Their study found that, while the diameter of the drug particles increased in high humidity (consistent with our findings), the deposition fraction in the mouth-throat remained unchanged [67]. However, in the trachea, it increased by 2.7% during inhalation of supersaturated water vapour, leading to an increase in drug delivery to the lungs. In their research, the inlet particles were mono-disperse. In our study, we went a step further by applying the actual particle size distribution of the pMDI, which had a significant impact on the deposited particles on USP-IP.

To compare the effect of relative humidity, the deposition fraction decreased by 4.76% and 2.28% in the inhaler wall and bend zone, respectively, when exposed to 99% relative humidity for the COPD inhalation profile. The airflow pattern in turbulent areas, such as near the nozzle and the bend, was affected by relative humidity, resulting in lower wall deposition.

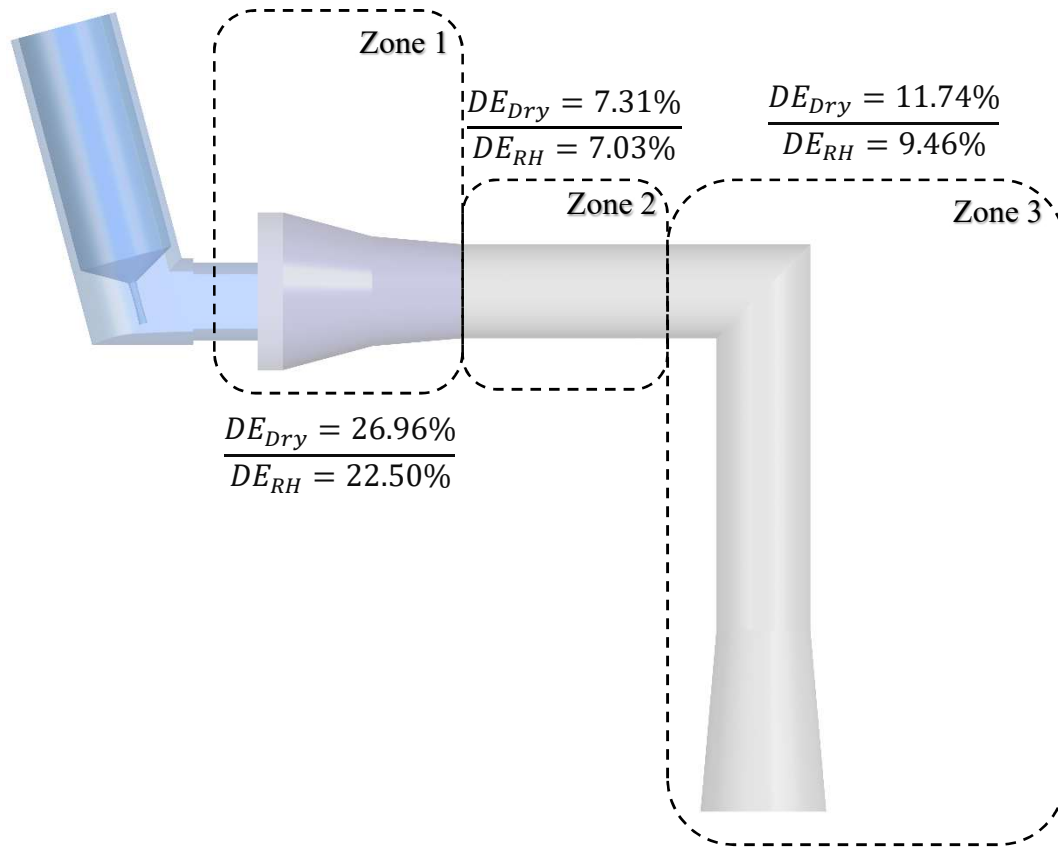


Fig 6.13. Comparison of deposition efficiency (DE) in three inhaler-USP-IP zones for COPD breathing profile under dry and 99% relative humidity (RH) conditions.

Fig 6.14 shows upper and lower recirculation widths during actuation under different conditions, including 30 and 60 L/min , COPD profile, dry airflow, and 99% relative humidity. The radius of the recirculation area (r) is measured as the maximum radial distance from the recirculation boundary to the stagnation point. The inner radius of the USP-IP is defined as r^* , and it is 9.5 mm. Moreover, t is the time the recirculation area is measured and t^* is the time particles pass the bend, which is 0.2 s.

As particles entered the mouth-throat bend at $t/t^* = 0.45$, vortices gained swirling strength and further decayed over time, as shown in **Fig 6.8**. The vortices caused turbulence in the system. **Fig 6.14(a)** shows the development of circulation zones at constant flow rates. These zones gradually expanded and then decreased slightly until the actuation was complete. Among all the cases studied, the one with a dry air flow rate of 60 L/min exhibited the most unstable behavior in the upper recirculation area, occurring at 0.35 (t/t^*). This instability resulted in the maximum size in

the upper recirculation area, which periodically decreased until it reached the same size as at the beginning of the actuation.

Initially, the upper recirculation area was insignificant for the COPD inhalation profile. However, at $t/t^* = 0.25$, the recirculation area started to form for the COPD inhalation profile. As time passed, the recirculation area for the COPD profile remained consistent and reached its maximum at $t/t^* = 0.65$. The vortices transported downstream of the bend contributed to the generation of turbulence, thereby compensating for the loss of turbulence in the bend region. As discussed in **Fig 6.8**, recirculation areas were more stable in the presence of relative humidity, with higher velocities in the center, resulting in less deposition on the walls. We also observed that the unstable upper recirculation areas in dry airflow were more affected by particles over time compared to those at 99% relative humidity.

Fig 6.14(b) shows the lower recirculation area that changed less compared to **Fig 6.14(a)** for all conditions during actuation time. After passing the bend at $t/t^* = 0.45$, particles did not affect the lower recirculation area of COPD, unlike in cases with constant flow rates. Due to the low air velocity in COPD, the recirculation areas had low particle interaction. This caused more particles to be trapped in these areas.

Under humid conditions, recirculation areas remained more stable compared to dry conditions, which show longer-lasting vortices. In the COPD slow inhalation profile, recirculation areas had smaller average sizes, resulting in less impact on particles. Additionally, the low-velocity air stream in COPD had less influence on the particles, causing them to take longer to reach the bend. As a result, the COPD airflow pattern resulted in higher deposition due to the particles' drag force, which could not be overcome compared to the constant 60 L/min. Sharma et al. [81] studied the interactions between cold spray and swirl airflow for various air swirler geometries. They changed the number of vanes, vane angle, vane curvature, and air velocity for the swirling airflow. They found that the recirculation area was independent of inlet air velocity; however, in our study, the presence of drug particles inside the recirculation areas caused significant instability in their sizes and locations [81].

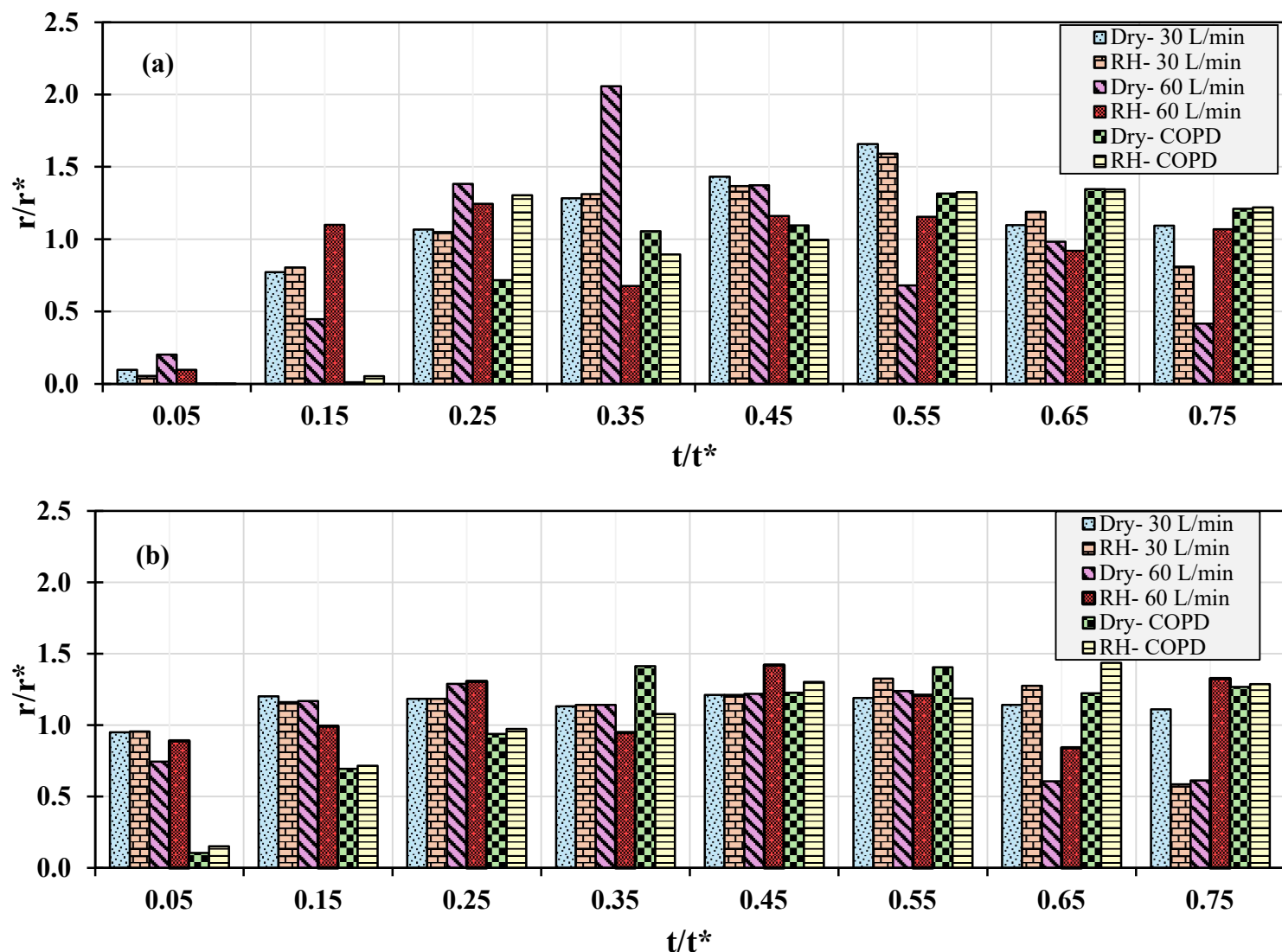


Fig 6.14. Normalized recirculation radius profile versus normalized time for **(a)** Upper recirculation area; and **(b)** Lower recirculation area with different flow rates and humidity conditions; RH: relative humidity, CFD results.

6.6. Conclusions

This study examined drug particle delivery through inhaler-USP-IP under two real-life conditions: breathing patterns and relative humidity. We employed an eight-stage NGI setup and an HPLC system to determine the particle size distribution at two constant flow rates, without considering the effect of relative humidity. Through the Lagrangian-Eulerian approach, we also developed CFD models to consider the interaction of drug particles and breathing flow rates.

Our experimental data showed that a flow rate of 60 *L/min* versus 30 *L/min* caused MMAD to decrease by 21% and produced more fine particles that passed through the USP-IP and collected in the NGI cups. We also noticed a reduction in particle deposition on the inhaler's walls as the flow rate increased.

Our numerical CFD model, validated against experimental data, identified two significant recirculation areas within the mouth and throat airways: the upper and inner bottom parts of the USP-IP bend. As the flow rate increased from 30 to 60 *L/min*, the deposited particle size distribution had a lower mass fraction of larger particles (12-15 μm). At a flow rate of 60 *L/min*, the upper recirculation was significantly impacted by the drug particles at the bend. As more particles got trapped in the bend, the size of the recirculation area increased, and then decreased as the actuation completed.

Our investigation into the effect of different percentages of relative humidity on constant flow rates revealed that the particle size distribution of particles that escaped from USP-IP was unaffected. However, under 99% relative humidity (as opposed to dry conditions), the deposition fraction decreased by 6% and 11% for flow rates of 30 *L/min* and 60 *L/min*, respectively. We discovered that relative humidity increased the stability of the recirculation area during actuation and boosted the velocity of the nuclear site of the recirculation area. This phenomenon allowed larger particles to pass through the mouth-throat bend more easily.

Under COPD breathing profiles, recirculation areas developed slower, yet more consistently, than for constant flow rates. After analyzing the slight changes in pressure and velocity under COPD breathing conditions, we noticed that the recirculation zones were small and had low velocity. This resulted in less-developed aerosol plumes and higher deposition of larger particles on the airway walls compared to those seen under constant flow breathing patterns. Interestingly, relative humidity had a lesser effect on the distribution of deposited particles under COPD breathing conditions, resulting in a lower mass fraction of larger particles being deposited on airway walls.

To effectively assess the efficiency of inhalers and drug delivery, it is essential to consider the actual inhalation flow rates of patients, rather than relying on constant flow rates. During our research, we identified a lack of information available on the study of particle deposition in COPD breathing patterns in the presence of relative humidity with polydisperse actuated particles. Our study is an important step towards comprehending the complexities of drug delivery in COPD

patients and will contribute to the development of more effective treatments in the future. Our findings underscore the importance of maintaining optimal humidity levels in indoor environments to promote healthy respiratory function. For our future studies, we plan to use realistic airway geometry instead of the USP-IP model and incorporate a mucus layer in the airway model to more accurately replicate biological airway conditions.

6.7. Nomenclature

Abbreviations

2D	2-dimensional
3D	3- dimensional
APSD	aerodynamic particle size distribution
BDP	beclomethasone dipropionate particles
CFD	computational fluid dynamics
HPLC	high-performance liquid chromatography
COPD	chronic obstructive pulmonary disease
DE	deposition efficiency
FPD	fine particle dose
FPF	fine particle fraction
GSD	geometric standard deviation
HFA	hydrofluoroalkane
IP	induction port
MDI	metered-dose inhaler
MMAD	mass median aerodynamic diameter
pMDI	pressurized metered-dose inhaler
RMSE	root mean square error
SIMPLE	semi-implicit method for pressure-linked equations
TKE	turbulent kinetic energy
USP	United States Pharmacopeia
DPM	discrete phase model
LRN	low Reynolds number
LES	large eddy simulation

RH	relative humidity
UK	United Kingdom
US	United States
UV	ultraviolet
UDF	user-defined function
CPU	central processing unit
RMS	root-mean-square
SD	standard deviation

Notations

C_D	constant drag coefficient, [-]
C_c	slip correction coefficient, [-]
n	number of sets of data, [-]
d_p	particle diameter, [μm]
k	turbulent kinetic energy, [m^2/s^2]
m_p	particle mass, [kg]
a_i	constant, [-]
p	static pressure, [Pa]
Re	Reynolds number, [-]
$\bar{u}_i$	time-averaged velocity, [m/s]
u_i	fluid velocity, [m/s]
V_i	particle velocity, [m/s]
F	force term, [N]
F_D	drag force, [N]
f	drag factor, [-]
g_i	gravity, [m/s^2]
Y_k , and Y_ω	dissipation of k and ω , [-]
k_B	Boltzmann constant, [-]
v_{rel}	relative velocity, [m/s]
G_ω	generation of ω , [-]
G_k	generation of turbulent kinetic energy, [-]

D_v	binary diffusion coefficient of water, [-]
Y_v	mass fraction of water vapor, [-]
S_v	water source term, [-]
Sc_T	Schmidt number, [-]
γ_{CFD}	simulated value of deposition efficiency, [%]
γ_{exp}	experimented value of deposition efficiency, [%]
r^*	inner radius of USP-IP, [mm]
t^*	time that actuated particles pass the USP-IP completely, [s]
T	absolute temperature, [°C]

Greek letters

ρ	fluid density, [kg/m ³]
α	ratio of mixture to particle density, [-]
ρ_p	particle density, [kg/m ³]
μ	dynamic viscosity, [kg/ms]
ζ_i	zero mean variant, [-]
μ_t	turbulent (eddy) viscosity, [kg/ms]
Δt	time step, [s]
ω	turbulent dissipation rate, [1/s]
σ_k and σ_ω	constant coefficient of the shear stress transport turbulence model, [-]
$\widetilde{D}_p$	diffusion coefficient of particle, [-]
τ_p	relaxation time, [s]

6.8 References

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Chapter 7- Multiscale Study of pMDI Aerosol Delivery in Pediatric Airways: Effects of Inhalation Flow, Mucosal Properties, and Actuation Timing

7.1 Abstract

Effective drug delivery to the lungs of pediatric patients using pressurized metered-dose inhalers (pMDIs) requires a deep understanding of airflow and particle transport within the airways. This study examines airflow patterns and aerosol deposition in a pediatric mouth-throat (MT) model, considering a cystic fibrosis (CF) inhalation profile and the presence of a mucus layer.

A CT-derived pediatric MT model was developed using 3D printing and integrated into a next-generation impactor (NGI) to evaluate drug deposition at a flow rate of 15 *L/min*. This process validated the computational fluid dynamics (CFD) model. Three different boundary conditions were used to represent the mucus layer, with the Eulerian Wall Film (EWF) approach demonstrating the highest accuracy. The study also explored the effects of a non-Newtonian shear-thinning mucus layer. Large Eddy Simulation (LES) was employed to analyze airflow dynamics, while the Discrete Phase Model (DPM) was utilized to simulate the transport and deposition of particles.

Synchronized actuation achieved the highest delivery efficiency at 46% due to smooth aerosol entrainment during the buildup of the CF inhalation profile. This transient CF profile also resulted in a broader particle size distribution, ranging from 0.78 to 20 μm , compared to constant flow rates of 7.5 and 15 *L/min*. Higher flow rates increased wall shear stress, which enhanced shear-driven transport. Morris's sensitivity analysis identified flow rate as the dominant factor, demonstrating a strong correlation with deposition efficiency ($r_s = 0.87$). Furthermore, shear-thinning mucus reduced secondary flows, induced asymmetric swirling, and increased the minimum particle size exiting the trachea by 60.2%, rising from 0.491 to 0.789 μm compared to Newtonian mucus.

7.2 Introduction

The 2017 global report on chronic respiratory diseases (CRDs) estimates that 545 million people, 7.4% of the worldwide population, live with chronic respiratory conditions [1,2]. According to the report, lung diseases in children under 5, including both acute infections and chronic conditions, pose a significant health threat. Among these, asthma is the most common chronic illness, affecting approximately 14% of children worldwide, with its prevalence steadily rising. Addressing these challenges is crucial to safeguarding the health and future of the youngest generation.

One effective treatment for respiratory conditions is the use of inhaler devices, particularly pressurized metered-dose inhalers (pMDIs). Over the past decade, pMDI technology has advanced with the development of add-on tools, such as Clip-Tone and Flo-Tone CR, which provide audio-visual feedback to help patients refine their inhalation techniques [3]. Additionally, advancements in nanoscience-based metered-dose formulations have helped reduce the side effects of pMDI [4,5]. Studies suggest that incorporating key factors—such as realistic, non-constant inhalation profiles [6,7], airway conditions [8], mouth-throat (MT) geometry complexity [9,10], environmental factors like temperature and relative humidity [11], and the presence of a mucus layer [12]—can enhance the accuracy of pMDI studies. However, the effectiveness of pMDI remains limited; despite these advancements, lung deposition rates range between 10% and 20% [13].

Most studies on aerosol behavior assume a constant flow rate during inhalation due to limitations of in vitro experiments [14–16]. While these constant flow models reasonably estimate aerosol behavior [10,17,18], recent studies have increasingly focused on non-constant inhalation profiles in drug delivery modeling. Kim and Garcia [19] investigated cyclic flow in bifurcating tubes at varying frequencies, reporting wall deposition efficiencies that were 80–200% higher than those under constant flow. Zhang et al. [20] extended this work to a fourth-generation airway branch, using simulations to analyze airflow patterns and their impact on secondary flow and deposition. Broeders et al. [21] examined inhalation profiles in asthma and COPD patients, highlighting the effectiveness of pMDIs as highly dependent on breath coordination. Williams et al. [22] studied expiratory airflow patterns in children and adults with cystic fibrosis (CF), categorizing profiles

based on age and disease severity. They identified a convex flow profile in children under 11 years old, differing from adult patterns.

To optimize pMDI inhalation timing, it is crucial to consider forced inhalation volume, peak inspiratory flow rate, and actuation timing (early versus delayed), as these factors significantly influence drug deposition in the inhaler, oropharynx, and lungs [23–25]. Farkas et al. [23] investigated the impact of delayed actuation during inhalation and found that a 2-second delay at a constant flow rate resulted in a 20% reduction in lung deposition. In a follow-up study, Farkas et al. [26] reported that the patients with severe COPD received only 17% of the prescribed lung dose, compared to 28% in mild and 23% in moderate COPD cases. This indicates that patients requiring higher medication doses may receive lower lung deposition, even when using the same inhaler dose [26].

The structure of the airway plays a crucial role in the delivery and deposition of drug particles in the respiratory system [25, 27, 28]. Talaat et al. [25] found that airway deformation from pulmonary diseases, especially moderate to severe contraction, significantly alters inhalation airflow. They also noted that higher airway resistance and wall shear stress during exhalation impact breathing dynamics and drug delivery. Additionally, children's airway structures differ significantly from those of adults and change as they grow. At birth, a child's larynx differs in shape and position compared to an adult's. Allen et al. [29] found that the airway model of a 5-year-old exhibited higher turbulent kinetic energy than the adult model at the same tracheal Reynolds number. They also found that airway resistance is proportional to the square of the volumetric flow rate, indicating that turbulent flow predominates in children's airways.

Golshahi et al. [30] conducted both *in-vivo* and *in-vitro* studies to quantify the deposition of micrometre-sized aerosols in realistic oropharyngeal airway replicas of children aged 6 to 14 years. They fabricated these replicas using pediatric oropharyngeal airway images obtained from CT scans. The dimensions of the replicas were used to establish a non-dimensional correlation involving Stokes and Reynolds numbers, which helped reduce variability in deposition results. Their proposed correlation are useful for predicting the deposition of micrometre-sized particles in the oropharyngeal airways of children during inhalation at moderate to high constant flow rates, similar to those observed when using pharmaceutical aerosol inhalers [30].

Liu et al. [31] analyzed particle deposition in the upper respiratory tract of a 3-year-old child at three activity levels, using inhalation flow rates based on breathing frequency and tidal volume. They found similar mouth cavity deposition rates in children and adults, but higher deposition in the larynx (2.5%), pharynx (5.3%), trachea (3.8%), and bronchi (3.2%) in children [31]. Kolewe et al. [32] examined the differences in airflow and particle deposition between children and adults, highlighting that the cricoid ring and epiglottis mature around the age of six. They found that glottal jet positioning increased deposition in the upper airway due to higher pressure [32]. Recently, Yang et al. [33] investigated how variations in tongue position affect respiratory airflow and aerosol deposition. Their study revealed a skewed deposition toward the lower oral regions and identified particle size and tongue positioning particularly central placement as key factors influencing drug delivery efficiency, as confirmed through sensitivity analysis.

The mucus layer serves as the main barrier for inhaled drugs in the upper airway, but its importance is often underestimated in assessing viral load [34, 35]. In patients with COPD and CF, impaired mucus swelling affects its rheological properties, which in turn significantly influences transport mechanisms. Our understanding of defective mucus is primarily based on observational studies, which have yielded varying reported properties [36]. For example, the viscosity of sputum in CF patients can range from 0.01 $Pa \cdot s$ (approximately ten times that of water) to 60 $Pa \cdot s$ (greater than that of honey).

The respiratory mucus layer consists of two distinct layers. The upper gel layer consists of 97% water and 3% mucin, salts, lipids, and immunoglobulins, with a thickness ranging from 0.5 to 5 μm . Beneath this layer is the periciliary fluid layer, which is 7–10 μm thick and has a viscosity similar to that of water, aiding in mucociliary clearance [37–39]. Kim and Eldridge [40] developed viscoelastic materials to model mucus in airway-like tubes. They observed that increased mucus viscosity resulted in pressure drops ranging from 0.14 to 2.5 cmH_2O , which impacted aerosol deposition. Hasan et al. [41] studied artificial mucus in a trachea model connected to a cough machine, revealing that mucus viscoelasticity affects the droplet size distribution (with peaks at approximately 0.4 μm and 10 μm) during coughing. Specifically, Newtonian mucus exhibited a bimodal distribution, whereas viscoelastic mucus showed a unimodal distribution. Elastic solid mucus reverted to a bimodal pattern with a peak around 0.7 μm [41]. Elastic solid mucus returned to a bimodal pattern, with a stronger peak at about 0.7 μm . Cingolani et al. [42] utilized bio-relevant

in vitro models to investigate mucus at the air-epithelial interface, demonstrating that mucus significantly influences the permeation and transport of salbutamol sulphate, thereby affecting drug absorption at the air-epithelial interface.

The mucus layer complicates experimental studies, leading researchers to use computational fluid dynamics (CFD) to understand its effects. Several studies have investigated the fluid dynamics of mucus, noting that, despite being thin compared to the airway diameter, it significantly influences airflow interactions [35, 43, 44]. For instance, Chen et al. [45] developed a model of the oral airway that treated mucus as a distinct phase, finding that evaporation lowered the mucus temperature by up to 1.11°C. Similarly, Narayanan et al. [46] employed Large Eddy Simulation (LES) to model the unsteady wavy structures and recirculation zones within a mucus-lined airway. They discovered that increased inlet air temperatures enhanced particle deposition efficiency by boosting particle kinetic energy and interactions with the mucus layer [46].

Our literature review identified key gaps in pediatric drug delivery research using pMDIs. Previous studies have not collectively addressed several key factors, including the realistic pediatric airway anatomy, inhalation variability, mucus layer effects, and synchronization between inhaler actuation and inhalation. This study analyzed the deposition of polydisperse particles (from pMDIs) in a pediatric airway [47]. We numerically compared three mucus layer modeling approaches: (1) wall thickness representation, (2) shell conduction model, and (3) Eulerian wall film (EWF) model. Using the third method, we examined Newtonian (Nmu) and non-Newtonian shear-thinning (non-Nmu) mucus. We evaluated three airflow rates—7.5 L/min, 15 L/min, and a variable CF profile—and tested both early (-0.050 s) and delayed (0.5 s and 0.7 s) actuation relative to the onset of inhalation.

We utilized three-dimensional (3D) printing (Ultimaker S5, Confederation College) to replicate Bickmann's pediatric MT geometry for *in-vitro* experiments. Actuated particles were collected using a next-generation impactor (NGI) at a constant flow rate of 15 L/min and analyzed with high-performance liquid chromatography (HPLC). We validated our CFD model by comparing the simulated particle size distributions with *in-vitro* data and findings from previous studies. This research provides a detailed analysis of flow patterns, particle size distribution, and deposition behavior under specified conditions.

7.3 Experimental Methodology

Fig 7.1 shows the 3D-printed pediatric airway geometry connected to a pMDI on the left and the Next Generation Impactor (NGI) setup on the right (Copley Scientific, UK). The NGI system comprises an impactor, a flow controller (TPK 2000), and a vacuum pump (HCP5), as previously described in studies by our research group [48, 49]. The impactor features eight distinct stages (S1–S8), each capturing specific particle size ranges at 15 L/min: S1 ($>14.10\ \mu\text{m}$), S2 ($8.61\text{--}14.10\ \mu\text{m}$), S3 ($5.39\text{--}8.61\ \mu\text{m}$), S4 ($3.30\text{--}5.39\ \mu\text{m}$), S5 ($2.08\text{--}3.30\ \mu\text{m}$), S6 ($1.36\text{--}2.08\ \mu\text{m}$), S7 ($0.98\text{--}1.36\ \mu\text{m}$), and S8 ($<0.98\ \mu\text{m}$). The vacuum pump was calibrated to maintain a steady airflow of 15 L/min at $25\ ^\circ\text{C} \pm 1\ ^\circ\text{C}$.

We developed a pediatric airway model of a 5-year-old male, based on Bickman et al. [47], for both experimental and CFD studies. This model was created in the Pharmaceutical Physics Laboratory at Boehringer Ingelheim Pharma GmbH & Co. KG and was presented in the Respiratory Drug Delivery (RDD). To construct the model, we imported the airway geometry as a stereolithography (STL) file into SOLIDWORKS® CAD software, where external portions of the original airway model were removed prior to 3D printing. The final geometry was printed using polylactic acid (PLA) with a 1.2 mm wall thickness, utilizing fused deposition modelling (FDM) on an UltiMaker S5 printer. The printed model was segmented into three sections —mouth, pharynx, and trachea—as shown in **Fig 7.1**, allowing for more effective particle deposition studies. We applied cotton soaked in acetonitrile to smooth the inner walls, which refined raised areas from the 3D printing process while preserving the internal volume. Mechanical pressure was also used to eliminate surface roughness without altering the model's shape, as PLA is minimally soluble in acetonitrile. Finally, the model was rinsed with distilled water to ensure that any residual material was removed, as PLA is not water-soluble.

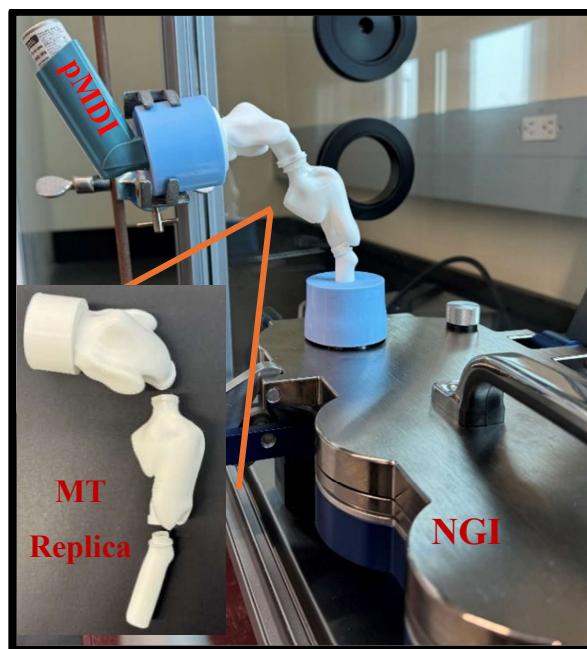


Fig 7.1. Experiment set up: Salbutamol HFA pMDI, MT replica, and NGI.

We used a 200-metered-dose Salbutamol Sulphate inhaler, delivering $100 \mu\text{g}$ per actuation, specifically the bioequivalent Ventolin® pMDI (SANIS Health, Canada). The inhaler was connected to the 3D-printed pediatric mouth-throat (MT) airway for deposition analysis. Samples were collected from four locations using a rinsing solution: the inhaler mouthpiece connector, the MT airway geometry (including all three segments), and the NGI cups. Subsequently, we performed an assay using HPLC) with the following specifications: an XSelect CSH Prep C18, $5 \mu\text{m}$ OBD, $19 \times 150 \text{ mm}$ column, which operated at 40°C . This setup was connected to a 1525 Binary HPLC pump and a 2489 UV/Visible detector (Waters, US). Using HPLC, we determined the particle concentration in each section. For all experiments, we used a rinsing solution consisting of water and 0.1% formic acid (Fisher Scientific, US).

The UV wavelength for salbutamol sulfate was measured at 276.00 nm . Samples were filtered using a Whatman® nitrocellulose membrane filter ($0.45 \mu\text{m}$) before HPLC injection. The mobile phase consisted of acetonitrile (Solvent A) and water with 0.1% formic acid (Solvent B) in a 6.5:3.5 ratio over 6 min , at a flow rate of 0.75 mL/min and an injection volume of $100 \mu\text{L}$. The HPLC technique was validated for concentrations from 0.2 to 20 ppm , showing a strong linear correlation ($R^2 = 0.98$). The limit of quantification was 1.9 ppm . Each experiment was repeated three times at a flow rate of 15 L/min to ensure reproducibility.

7.4 CFD Model Development

7.4.1 Geometry and Mesh Generation

Fig 7.2 shows the geometry and mesh of the pediatric mouth-throat (MT) model [47], divided into three sections—mouth, pharynx, and trachea—to align with the experimental setup. Five transverse planes were considered across the geometry to represent critical areas, which are discussed later. The pMDI nozzle, or cone injection point, was located at the center of the mouth's inlet surface [14]. The pMDI geometry was excluded from the model to reduce computational costs. Ahookhosh et al. [14] investigated tracheobronchial deposition with and without the pMDI geometry. They found a maximum deposition fraction error of only 1.1% between models with and without the pMDI at a flow rate of 60 *L/min*. On the other hand, our study focuses on mucus layer properties, inhalation flow rates, and inhalation-actuation synchronization, making the exclusion of the pMDI geometry a reasonable simplification that maintains accurate drug deposition analysis while enhancing computational efficiency.

We employed the LES turbulence model to accurately predict flow properties and particle transport in the airway, which requires a high-resolution mesh [43]. Polyhedral meshes were generated in the fluid zone using ANSYS Workbench 2020R2 (ANSYS, Inc.); and prism layers with a smooth transition ratio of 0.15 and a thickness of five layers were applied near the walls to effectively capture steep velocity gradients [25,48]. A mesh independence study was conducted using four different mesh resolutions: Mesh A (1,490,832 elements), Mesh B (3,169,201 elements), Mesh C (5,110,884 elements), and Mesh D (7,496,014 elements), each tested under a constant airflow of 15 *L/min*.

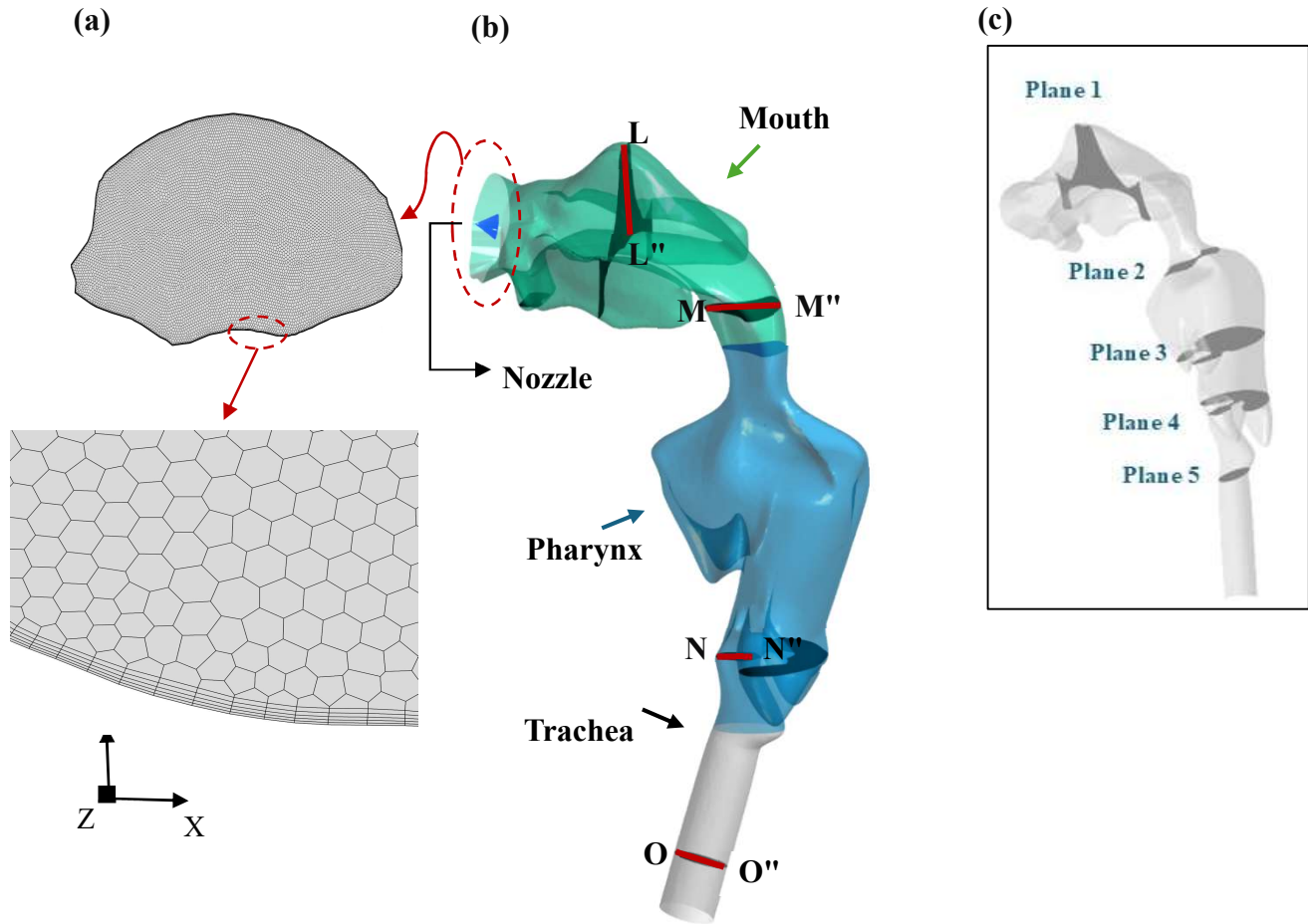
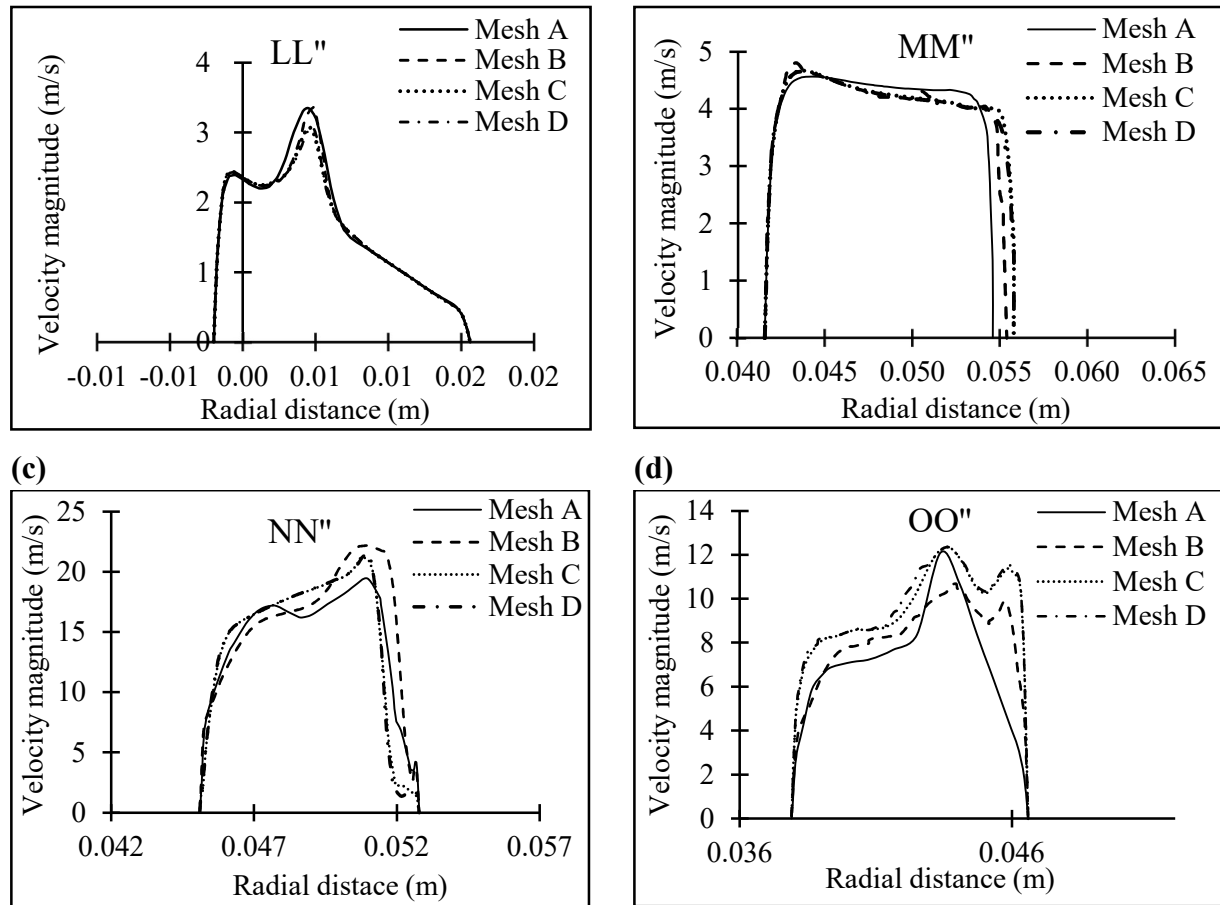


Fig 7.2. Geometry of the pediatric MT model used for CFD analysis. The figure includes (a) Reference lines LL'', MM'', NN'', and OO'' defined for mesh independence analysis; (b) A representative section of the polyhedral mesh used for the computational domain; and (c) Five selected transverse planes (Plane 1 to Plane 5) distributed along the airway geometry to assess flow and particle transport characteristics.

Fig 7.3 presents the velocity magnitude distribution across four regions: the mouth (LL''), the bend at the mouth (MM''), the pharynx (NN''), and the trachea (OO''). Notable variations in velocity magnitude were primarily observed in the pharynx and trachea (**Figs 7.3(c) and (d)**), likely due to increased turbulence in these regions compared to the mouth area (**Figs 7.3(a) and (b)**). The root mean square error (RMSE%) between Mesh C and Mesh D across all regions was less than 5%, indicating that further refinement had a negligible impact on the results [50]. Consequently, Mesh C, with 5,110,884 elements, was selected for the CFD model. Following a time step independence test, a final time step of 0.1 *ms* was chosen for the simulations.

(a) (b)



Mesh	RMSE%			
	LL''	MM''	NN''	OO''
Mesh A & B	11.03	23.67	20.57	35.56
Mesh B & C	6.26	17.15	16.56	15.18
Mesh C & D	2.64	4.16	3.31	2.84

Fig 7.3. Comparison of velocity magnitude through the radial direction of each cross-section of: (a) Mouth (LL''); (b) Mouth (MM''); (c) Pharynx (NN''); and (d) Trachea (OO'') for different mesh sizes. This comparison is made at 0.05 s with a flow rate of 15 L/min, excluding the mucus layer.

7.4.2 Governing Equations

- Continuous Phase

We employed the LES model to analyze airflow patterns in the pediatric MT airway, notably the transition from laminar to turbulent flow. Compared to the Reynolds-Averaged Navier-Stokes (RANS) approach, LES provided more accurate results, capturing transient flow structures more effectively, despite its higher computational cost [46, 51, 52]. This method allowed for a more realistic representation of inhalation dynamics. The three-dimensional governing equations for incompressible flow are presented as follows [53]:

$$\frac{\partial \rho}{\partial t} + \frac{\partial(\rho \bar{u}_i)}{\partial x_i} = 0 \quad (7.1)$$

$$\frac{\partial(\rho \bar{u}_i)}{\partial t} + \frac{\partial(\rho \bar{u}_i \bar{u}_j)}{\partial x_j} = - \left(\frac{\partial \bar{p}}{\partial x_j} \right) + \frac{\partial}{\partial x_j} \{ [(\mu + \mu_s) \left(\frac{\partial \bar{u}_i}{\partial x_j} + \frac{\partial \bar{u}_j}{\partial x_i} \right)] - \frac{2}{3} \mu \frac{\partial \bar{u}_i}{\partial x_i} \delta_{ij} \} + F_i \quad (7.2)$$

where the terms $\bar{u}_i$ is Favre-filtered air velocity, ρ is mixture density, $\bar{p}$ is time-averaged pressure, F_i is body force, including the gravitational force and momentum of particles, μ is the mixture dynamic viscosity, δ_{ij} is the Kronecker delta, used for isotropic stress components, and μ_s is dynamic viscosity at subgrid scales as modeled as follows [54, 55]:

$$\mu_s = (C_s \bar{\Delta})^2 (2 \bar{S}_{ij} \bar{S}_{ij})^{1/2} \quad (7.3)$$

$$\bar{S}_{ij} = -\frac{1}{2} \left[\frac{\partial \bar{u}_i}{\partial x_j} + \frac{\partial \bar{u}_j}{\partial x_i} \right] \quad (7.4)$$

In Eq. (7.3), the term C_s represents the Smagorinsky coefficient constant with a default value of 0.1 in ANSYS. This coefficient is determined dynamically using the procedure proposed by Lilly [54] based on the Germano identity, to optimize accuracy across a wide range of flow conditions. The term $\bar{\Delta}$ denotes the local grid-scale and is defined as $\bar{\Delta} = V^{1/3}$, where V represents the volume of the computational cell, making it dependent on the grid resolution. Additionally, the resolved large-scale strain rate tensor is represented as $\bar{S}_{ij}$.

- **Particle Transport (DPM)**

The Lagrangian DPM particle tracking method was used to capture the trajectories of particles [46]. It was assumed that the particles were spherical, inert, and occupied a low volume fraction, representing a dilute phase within the flow domain. To define particle motion, Newton's second law of motion was applied, as follows:

$$m_p \frac{dV_p}{dt} = F_D + m_p \frac{g(\rho_p - \rho)}{\rho_p} \quad (7.5)$$

where V_p is the particle velocity, ρ_p is the particle density, and g is the gravitational acceleration. In this study, only the drag force (F_D) was considered, while other forces, such as Saffman's lift force, pressure gradient force, and virtual mass force, were neglected due to the particles having a significantly greater density than air [56]. The drag force is calculated as follows:

$$F_D = \frac{3}{4} \frac{\mu_g C_D Re_p}{\rho_p d_p^2} (u - V_p) \quad (7.6)$$

$$C_D = a_1 + \frac{a_2}{Re_p} + \frac{a_3}{Re_p^2} \quad (7.7)$$

$$Re_p = \frac{\rho_p d_p |u - V_p|}{\mu_g} \quad (7.8)$$

where C_D is the drag coefficient for spherical particles, defined by the drag law of Morsi and Alexander [57]. The constants a_1, a_2 , and a_3 were obtained over different ranges of particle Reynolds numbers [57]. Re_p , d_p , μ_g , and u represent the particle Reynolds number, particle diameter, air dynamic viscosity, and airflow velocity, respectively.

The temperature of a droplet is estimated based on both convective and latent heat transfer between the droplet and the surrounding air (continuous phase), as described by Eq. (7.9) [58]:

$$\frac{m_p c_p dT_p}{dt} = h_c A_p (T - T_p) + \frac{dm_p}{dt} (h_{fg}) \quad (7.9)$$

where c_p is the specific heat capacity of the particle (1,418.37 J/kg.K), A_p is the particle surface area, respectively, h_c is the convective heat transfer coefficient, and h_{fg} is the latent heat [58].

The convective heat transfer coefficient, h_c , is calculated using Eq. (7.10) [58]:

$$Nu = h_c d_p / k = (\ln(1 + B_T) / B_T) (2 + 0.6 Re_p^{1/2} Pr^{1/3}) \quad (7.10)$$

Here, Nu is the Nusselt number, Re is the particle Reynolds number, Pr is the Prandtl number, and B_T is the Spalding heat transfer number, defined as follows [55]:

$$B_T = c_p (T - T_p) / h_{fg} - (\dot{q}_p / \dot{m}_p) \quad (7.11)$$

where $\dot{q}_p$ is the heat transfer rate to the particle, and $\dot{m}_p$ is the particle evaporation rate.

- **Mucus Layer Modeling**

The mucus layer in the respiratory tract is often overlooked in numerical studies, with wall boundary conditions typically assumed to be adiabatic, implying no heat transfer. However, studies have shown that including the mucus layer at wall boundaries reveals a temperature difference between the inhaled air, the mucus, and the airway walls [45,46]. Additionally, studies by Chen et al. [45] and Narayanan et al. [46] have shown that the transport velocity of mucus is much slower

than that of air and particles, which is why mucus movement over the tissue layer is often disregarded. **Fig 7.4**, adapted from Paz et al. [59], illustrates the structure of the mucus layer in the respiratory tract. This figure presents three schematics that represent the modeling methods used to characterize the airway mucus layer in three different ways: (1) as a wall thickness (**Fig 7.4(a)**), (2) as a shell with conductive heat transfer (**Fig 7.4(b)**), and (3) as an Eulerian wall film (EWF) representing the mucus layer (**Fig 7.4(c)**). In all three methods, the mucus layer extends from the airway wall into the fluid domain.

The first two modeling approaches treated the mucus layer as a uniform layer with a thickness of $30\ \mu m$ ($y = 30\ \mu m$). They assumed it to be a solid-like material, as suggested by Chen et al. [45] and Narayanan et al. [46]. In the first method, the heat flux was directed normal to the shell, taking into account the wall thickness. The second method used the shell conduction approach, which considered the heat flux along the shell surface. Unlike these first two methods, which focused solely on thermal boundary conditions and disregarded mass transfer, the third method incorporated both heat and mass transfer. While methods (1) and (2) primarily focused on thermal boundary conditions, Method (1) utilized the following equations [60]:

$$q = h_f(T_w - T_f) + q_{rad} \quad (7.12)$$

$$h_f = k_s \left(\frac{\partial T}{\partial n} \right)_{wall} \quad (7.13)$$

where q is the heat flux, h_f is the fluid-side local heat transfer coefficient, T_w is the wall surface temperature, T_f is the fluid temperature, and q_{rad} represents the radiative heat flux, which is zero in this study. Fourier's law describes the heat transfer between fluids and solid walls [61]. ANSYS utilizes the discrete form of this equation, as shown in Eq. (7.13), where k_s represents the thermal conductivity of the solid wall, and n denotes the local coordinate normal to the wall.

In Method (1), the boundary temperature of the wall changes when it interacts with the fluid. The heat flux emitted from each cell remains constant because heat transfers in only one direction and does not transfer between cells. This means that the heat transfer does not influence the overall heat flux of the wall. However, the wall surface temperature (T_w) is lower than the boundary temperature (T_B) as the wall thickness increases.

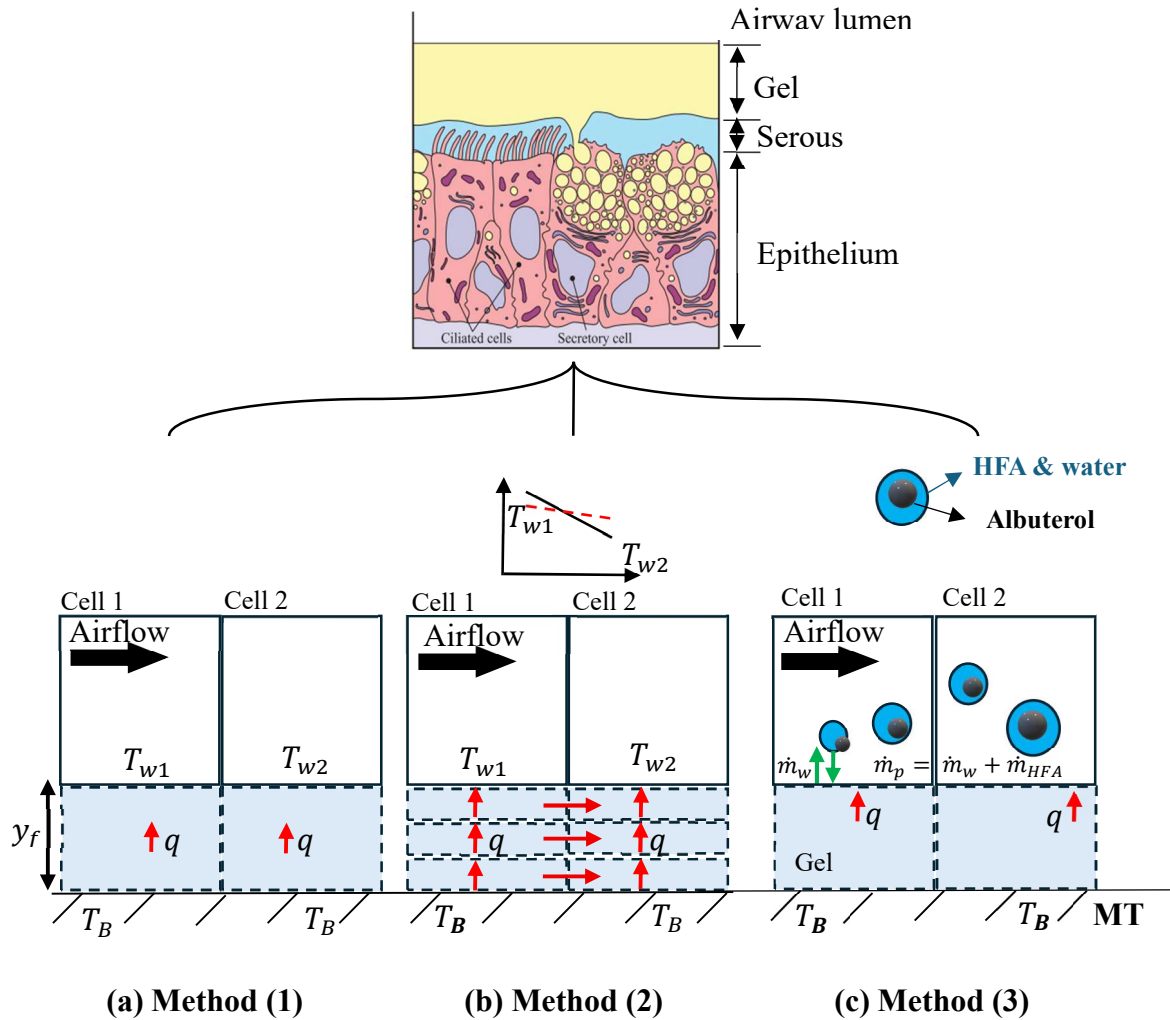


Fig 7.4. Mucus layer representation (adapted from Paz et al. [59]) and schematic illustrations of heat and mass transfer between airway wall and inhaled air under three modeling approaches: **(a)** Method (1) – wall thickness approach; **(b)** Method (2) – shell conduction model; and **(c)** Method (3) – Eulerian wall film (EWF) incorporating mass transfer of polydisperse drug particles across the mucus layer.

In Method (2), illustrated in **Fig 7.4(b)**, heat conduction in the wall is analyzed not only in the vertical direction (the standard approach for solving the energy equation) but also in the horizontal direction between adjacent cells. The shell-conduction method yields non-uniform thermal conductivity within the shell's cells, resulting in an improved temperature distribution throughout the wall. As a result, the wall temperatures in each cell, such as T_{w1} and T_{w2} differ from one another. For instance, if the initial wall temperature in one cell, T_{w1} , is higher than in another cell, T_{w2} , as shown in **Fig 7.4(b)**, this temperature difference gradually decreases as heat flows from

the hotter cell to the cooler one. This approach offers a more accurate representation of the actual distribution of surface temperatures.

In Method (2), the heat transfer between the airflow and the mucus layer is calculated using the energy equations solved within the fluid cells. These equations are designed to accurately capture the thermal interactions between the fluid (air) and the mucus layer, ensuring that the heat flux across the interface is modeled correctly. The energy equation within the fluid cells is given by:

$$\frac{\partial(\rho E)}{\partial t} + \nabla \cdot (U(\rho E + p)) = \nabla \cdot (k \nabla T) + S + \nabla \cdot (\tau \cdot U) + \rho g \cdot U \quad (7.14)$$

$$E = \underbrace{h - \frac{p}{\rho}}_{\text{Internal}} + \underbrace{\frac{1}{2}(|U|)^2}_{\text{Kinetic}} \quad (7.15)$$

$$h = c_p T \quad (7.16)$$

Eq. (7.14) represents the general governing equation form of shell conduction, and since the velocity within the shell is zero, the kinetic energy parameter is zero. Therefore, only internal energy is considered. In this context, c_p represents the specific heat transfer, k is the thermal conductivity, h denotes enthalpy, T stands for temperature, τ is the effective shear stress, and S is the heat source term [55].

In Method (3), we modeled the mucus layer using the EWF approach. This method simplifies the mucus structure to a single equivalent layer by excluding the serous layer, as shown in **Fig 7.4(c)**. The continuity equation for a two-dimensional film within a 3D domain is given in Eq. (7.17) [62]:

$$\frac{\partial(\rho_f y_f)}{\partial t} + \nabla_s \cdot (\rho_f y_f \vec{v}_f) = \dot{m}_s \quad (7.17)$$

where ρ_f is the film density, y_f is the film thickness, ∇_s is the surface gradient operator, $\vec{v}_f$ the mean film velocity, and $\dot{m}_s$ is the mass source per unit wall area resulting from droplet collection and film separation. The conservation of film momentum is given as follows:

$$\frac{\partial(\rho_f y_f \vec{v}_f)}{\partial t} + \nabla_s \cdot (\rho_f y_f \vec{v}_f \vec{v}_f) = -y_f \nabla_s P_f + \rho_f y_f \vec{g}_t + \frac{3}{2} \vec{\tau}_{fs} - \frac{3\mu_f}{y_f} \vec{v}_f + \vec{q}_s \quad (7.18)$$

where P_f represents the film pressure, $\vec{g}_t$ indicates the gravity component that is normal to the surface, $\vec{\tau}_{fs}$ denotes the viscous shear force at the mucus-air interface, μ_f is the viscosity of the film (Eq. (7.22)), and $\vec{q}_s$ refers to the momentum source term connected to the droplet interactions.

The terms on the left side of Eq. (7.18) represent the transient effects and convection effects, respectively. On the right side, the first term includes the effects of gas-flow pressure (as described in Eq. (7.22)), the component of gravitational force that is normal to the wall surface (as seen in Eq. (7.20)), and surface tension (explained in Eq. (7.21)). The second term addresses the gravitational effect in a direction parallel to that of a liquid film. The third and fourth terms indicate the net viscous shear force at the gas-film and film-wall interfaces. The final term represents the collection or separation of droplets. These terms and interactions are critical for capturing the dynamics of the mucus layer in response to airflow and particle deposition [55,62].

The pressure term is calculated using the following equations:

$$P_f = P_{gas} - P_z + P_\sigma \quad (7.19)$$

$$P_z = -\rho z(\vec{n} \cdot \vec{g}) \quad (7.20)$$

$$P_\sigma = -\sigma \nabla_s \cdot (\nabla_s y_f) \quad (7.21)$$

where P_{gas} represents the gas pressure, P_z is the component of gravity acting perpendicular to the wall, P_σ denotes the surface tension term, $\vec{n}$ is the normal vector, $\vec{g}$ indicates the gravity vector, and σ refers to the surface tension. These film equations (Eqs. (7.17)–(7.21)) were solved on the airway surface using local wall coordinates. The small film thickness justifies the thin-film assumption applied in the EWF model, considering its scale relative to the local surface curvature.

The primary assumption in Method (3) is that mucus forms a thin layer characterized mainly by its viscosity. Healthy mucus consists of 95-99% water and typically behaves like a Newtonian fluid, with a viscosity similar to that of water [34]. However, previous studies have shown that mucus can also exhibit non-Newtonian, shear-thinning behavior [63–66]. The impact of modeling mucus as a non-Newtonian fluid on particle deposition and flow patterns remains unclear, as it is often overlooked in studies of drug delivery [44, 67]. In this study, we analyzed both Newtonian and non-Newtonian shear-thinning fluids in mucus layer modeling and compared the differences in the results. We used a mucus viscosity of $0.89 \text{ mPa}\cdot\text{s}$ for the Newtonian layer, which is similar to the viscosity of water at 25°C , representing a low-viscosity Newtonian fluid [46, 68]. Furthermore, we utilized the non-Newtonian power-law model [69] to represent the shear-thinning behavior of mucus [65]:

$$\mu_f = K\dot{\gamma}^{n-1} \quad (7.22)$$

where μ_f represents the apparent viscosity of the film, $\dot{\gamma}$ is the shear rate, K is the consistency index, which was set to $2.52 \text{ mPa}\cdot\text{s}$, and n , the power-law index, set to 0.15 for the mucus film rheological properties in our model, as described by Ren et al. [70].

The conservation of film energy is given as follows [71]:

$$\frac{\partial(\rho_f y_f T_f)}{\partial t} + \nabla_s \cdot (\rho_f y_f T_{film} \vec{v}_f) = \frac{1}{Cc_p} \left[\frac{2k}{2y_f} (T_s + T_w - T_m) + \dot{m}_{vap} L \right] \quad (7.23)$$

where T_{film} is the average film temperature, T_s and T_m are the film surface and film half-thickness temperature, respectively. The $\dot{m}_{vap}$ is the mass vaporization or condensation rate, k is the thermal conductivity, and L is the latent heat associated with the phase change.

7.4.3 Boundary Conditions and Simulations

The spray of salbutamol sulfate particles was modeled as streams emitted from a pMDI at an initial velocity of 100 m/s [16]. To replicate the experimental conditions, the airflow temperature was set to 25°C , and a constant relative humidity of 50% was assumed for all validation cases, representing dry air. For the remainder of the study, an initial relative humidity of 99% was used to simulate the presence of mucus, especially near the trachea [48]. **Table 7.1** summarizes the model conditions, including mucus modeling methods, properties, inhalation flow conditions, and the timing of actuation and inhalation. The model was validated using *in-vitro* experiments with the NGI device, and deposition analysis was performed using HPLC at a constant airflow rate of 15 L/min . However, since the typical pediatric flow rate is lower than the NGI's minimum of 15 L/min , we also simulated a constant airflow of 7.5 L/min to better represent pediatric breathing conditions. Furthermore, we incorporated a CF inhalation profile, as outlined in **Table 7.1**. To simulate the CF inhalation profile, a user-defined function (UDF) was developed, as described in Eq. (7.24) [72]:

$$Q_{In}(t) = \frac{V_T \pi}{t_B} \sin\left(\frac{2\pi t}{t_B}\right) \quad (7.24)$$

where Q_{In} is the inhalation flow rate, V_T is the tidal volume (130 mL), and t_B is the duration of one complete breath cycle (2.5 s), with an inhalation flow peak (IFP) of 13.5 L/min [73]. In the

present study, due to the small size of the mouth–throat geometry and the short residence time of inhaled particles, the inhalation profile was simulated only up to 1.25 *s*. [73].

For optimal lung deposition, pMDIs should ideally be actuated simultaneously with the patient's inhalation at $t = 0$ *s*. However, achieving perfect synchronization can be a challenging task. To explore this issue further, our study examined three non-synchronized actuation conditions relative to the CF inhalation profile, as detailed in **Table 7.1**: -0.05 *s* (early actuation), +0.5 *s* (delayed actuation before the IFP), and +0.7 *s* (delayed actuation after the IFP). These timing variations, which are often unavoidable in real-world use, were selected arbitrarily for analysis. In methods (1) and (2), the wall boundary was treated as a trap, capturing particles upon contact. In method (3), mucus was modeled as an EWF, transforming the boundary into a wall film. This approach enabled the use of boundary layer formulations to calculate the vapour mass fraction at the air–liquid interface during evaporation.

Table 7.1. Simulation conditions.

Parameters		Values
Inlet flow rate		7.5 <i>L/min</i>
		15 <i>L/min</i>
		CF inhalation profile: Eq. (7.24)
Mucus modeling	Method (1): Wall thickness (total thickness)	-
	Method (2): Shell with conductive heat transfer (shell conduction)	-
	Method (3): Eulerian wall film (EWF model)	Newtonian: $\mu_f = 0.89$ <i>mPa.s</i> Non-Newtonian: Eq. (7.21)
Actuation timing relative to inhalation onset		-0.05 <i>s</i> (early)
		0 <i>s</i> (synchronized)
		+0.5 <i>s</i> (delayed before the IFP)
		+0.7 <i>s</i> (delayed after the IFP)

7.5 Results and Discussion

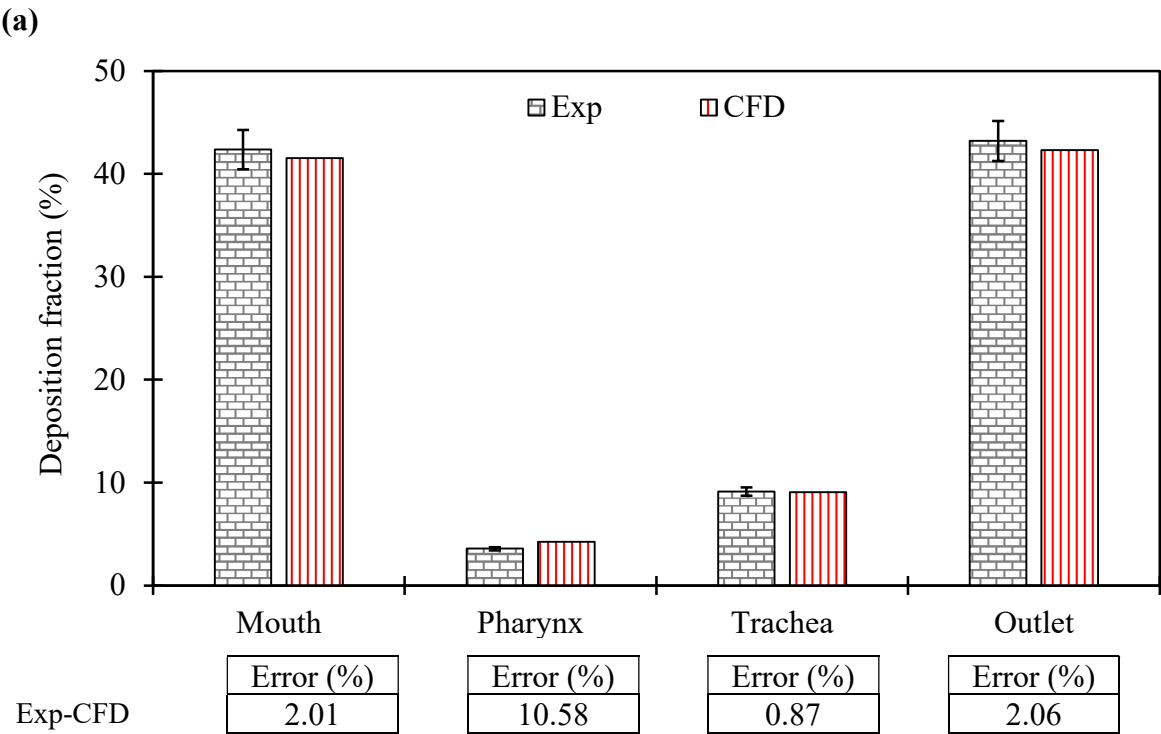
7.5.1 CFD Models (mucus models) Validation and Comparison

Fig 7.5(a) illustrates the deposition fractions across various sections of the airways, including the mouth, pharynx, trachea, and outlet. Experimental data collected under conditions without mucus were utilized to validate the CFD results for the no-mucus scenario. To evaluate

the impact of a 30 μm mucus layer, three modeling approaches were compared: (1) total thickness, (2) shell conduction, and (3) the EWF model. Mass fractions were determined based on the delivered dose per puff, averaging $104.5 \pm 3.25 \mu\text{g}$. The parameters for the CFD model were aligned with the experimental setup described in **Section 7.3**, including a flow rate of 15 L/min , airway geometry, and temperature and humidity conditions (25°C, 50% relative humidity). The results reveal a maximum discrepancy of 10.58% in the pharynx due to its complex geometry. In other regions, such as the trachea and outlet, errors were maintained below 3%, further confirming the accuracy of the turbulence model in comparison with the experimental data.

Fig. 7.5(b) illustrates the deposition fraction in the MT region based on the impaction parameter. It compares our CFD results with *in-vivo* studies [74], *in-vitro* studies [75], and other CFD studies [76,77]. The impaction parameter is determined by squaring the aerodynamic diameter and multiplying it by the volumetric flow rate, providing a comprehensive measure of flow rate and particle size (Jahed et al., 2024). As expected, higher impaction parameters—which correspond to larger particles or increased flow rates—result in higher deposition fractions in the MT region.

Golshahi et al. [75] presented *in-vitro* deposition data for nine pediatric upper-airway models, specifically for children aged 6 to 14 years. Our CFD-predicted deposition fractions follow a similar sigmoidal curve and align closely with their measurements. Since our model represents a smaller airway based on a 5-year-old child, the deposition fractions we obtained are slightly higher than the average for Golshahi's older child group. Our CFD model tended to underestimate deposition when compared to Zhou et al. [76], who utilized a DPI that generated a broader particle size distribution, reaching up to 30 μm . The most significant discrepancies between our model and theirs were observed for particles in the 5–10 μm size range, with impaction parameters ranging from 375 to 1500. Additionally, our findings align with those of Yang et al. [77], as both studies employed pediatric geometries and corticosteroid aerosols. They also noted that variations in anatomical structure and inspiratory flow rate contribute to greater deposition compared to Zhou et al. [76].



(b)

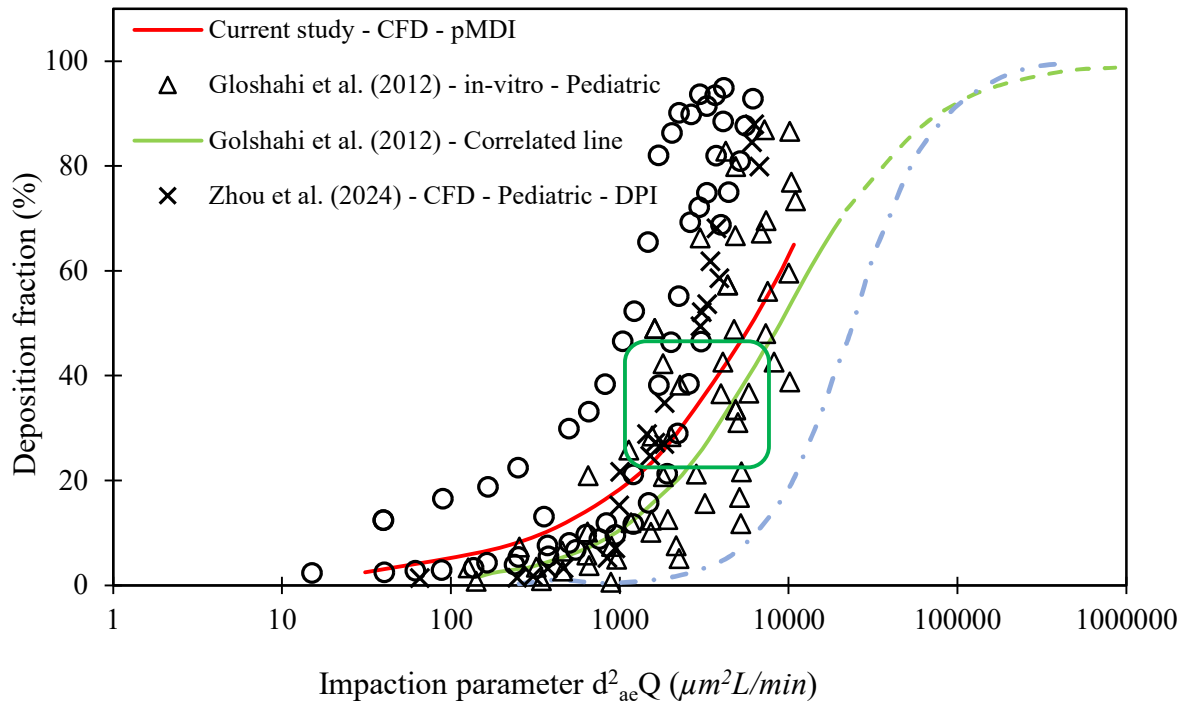


Fig 7.5. (a) Comparison of particle deposition fraction (%) across various sections of the MT region obtained from experimental measurements and CFD simulation; and **(b)** Comparison of MT deposition fraction (%) as a function of the impaction parameter at a flow rate of 15 *L/min* and 50% relative humidity with other studies.

When we compare pediatric results, including our own, with the adult data reported by Stahlhofen et al. [74] (see **Fig. 7.5(b)**), it becomes evident that the pediatric oral airway retains a significantly higher proportion of inhaled particles, particularly the larger ones. As a result, fewer particles reach the lungs in children. In contrast, the larger airway volume in adults leads to reduced deposition in the mouth and throat, which explains the lower mass deposition (MD) observed by Stahlhofen et al. compared to the predictions made for pediatrics. As outlined in Section 7.4.2, to evaluate the impact of a 30 μm mucus layer, three modeling approaches were compared: (1) total thickness, (2) shell conduction, and (3) the EWF model. The presence of a mucus layer is a natural characteristic of the human airway, so incorporating it into the simulation improves physiological realism and enhances the accuracy of predictions for inhalation therapy [64]. In the EWF model, the mucus is treated as a Newtonian fluid.

Fig 7.6 compares temperature contours from Plane 3 with a no-mucus layer against three wall models that include a mucus layer, all at a constant flow rate of 15 *L/min*, measured at 0.09 *s*. The air inlet temperature was consistently set at 25 °C across all scenarios. It is worth noting that, for

validation against dry-wall experiments, the wall temperature was maintained at 25 °C. For all other simulations, the wall temperature was elevated to 37 °C to reflect physiological conditions. In the dry, no-slip boundary case (i.e., without a mucus layer), the air stream essentially remains at the inlet temperature, exhibiting minimal heat transfer with the walls, except where it interacts with the injected particles. Methods (1) and (2) show similar temperature distributions, primarily influenced by conduction between the mucus layer and the airflow, with slight variations in the center due to differing heat flux directions. In Method (2), heat is transferred from the wall to the airflow, resulting in a more uniform temperature distribution and a higher temperature in the central region.

In contrast, the EWF model (Method 3) accounts for both conduction and phase change (evaporation/condensation). The inclusion of latent heat, as defined in Eq. (7.23), results in a higher temperature in the smaller area compared to Method (2). Additionally, since the EWF represents a thin liquid film, we applied the properties of water (representing Newtonian mucus) within this layer. Consequently, the temperature increase in the smaller area is more significant than in the first two models, which were based solely on solid definitions. This demonstrates the importance of selecting an appropriate wall model when predicting mucosal heat exchange in airway simulations.

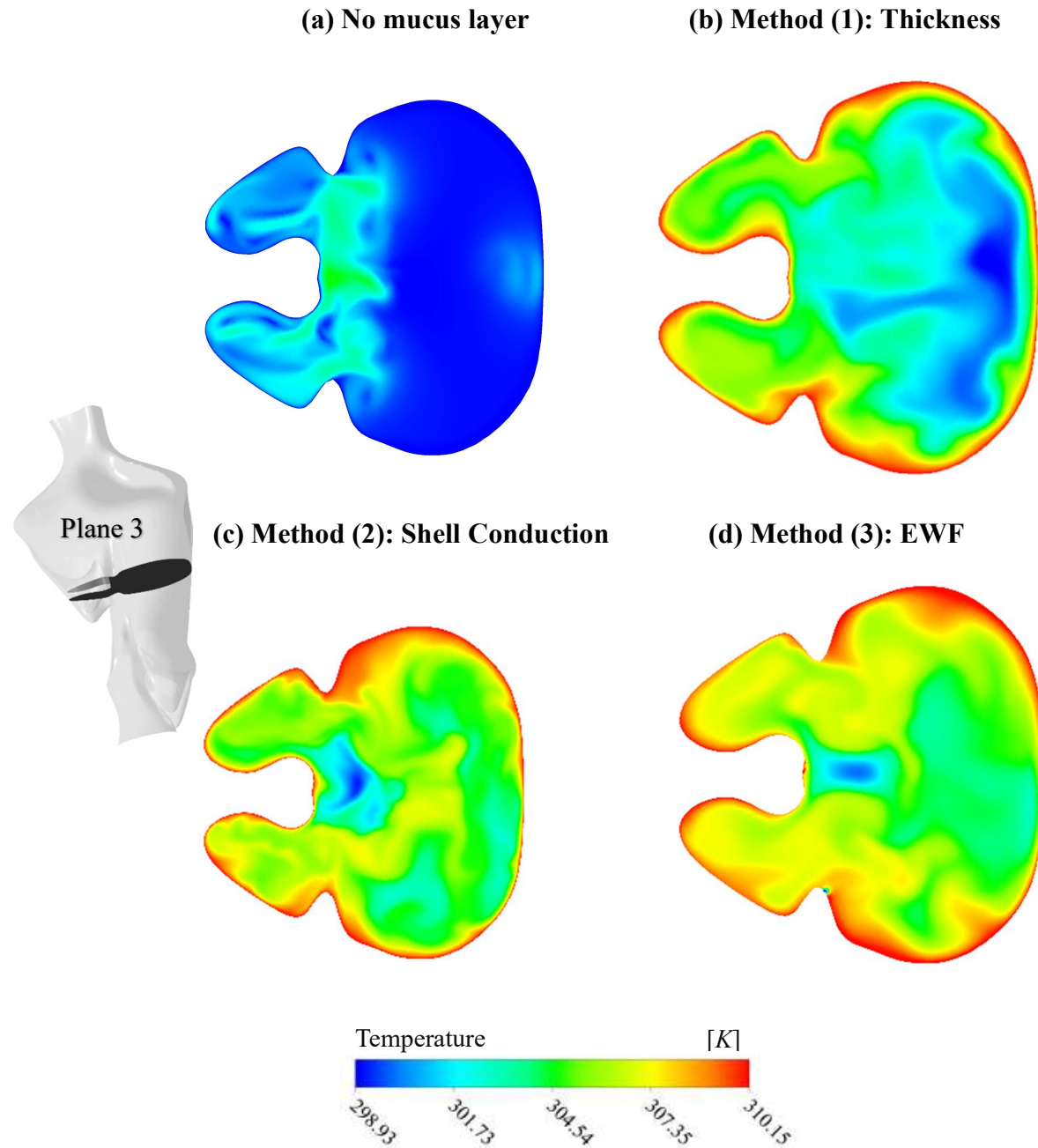


Fig 7.6. Temperature contours on Plane 3 at 0.09 s under a constant inhalation flow rate of 15 L/min, comparing (a) the no-mucus case; (b) Method 1: total thickness; (c) Method 2: shell conduction; and (d) Method 3: the EWF model.

Since we do not have an experimental setup that includes a mucus layer, we relied on literature-based validation to support our implementation of the EWF model for simulating heat and mass transfer under physiological conditions. Ferron et al. [78,79] predicted that during inhalation, ambient air enters the mouth at room temperature and a relative humidity of approximately 50–

60%. As this air travels through the upper airway, passing the larynx and reaching the tracheobronchial region, it rapidly warms to near core body temperature (about 37 °C), and the relative humidity increases to over 90%. Ultimately, it reaches full saturation (around 100% RH) in the lower airways, as illustrated in **Fig. 7.7(a)** and **(b)**. They further demonstrated that higher inhalation flow rates enhance convective transport and flow instabilities, which accelerate the rise in temperature and the equilibration of humidity along the airway.

Both our CFD-EWF simulations and the in vitro data from Ferron et al. [78] show a rise in mean RH from approximately 50-55% at the mouth to over 90% by the larynx. This indicates an initial rapid increase in the oral cavity, followed by a more gradual approach to saturation. As illustrated in **Fig. 7(a)**, our simulation curve is slightly above that of Ferron et al. [78], which reflects the combined effects of the Newtonian Eulerian wall film and the cold pMDI spray on RH. The Newtonian layer, modeled as water, contributes to higher humidity near the wall, resulting in RH levels exceeding 90%. Furthermore, the introduction of a cold plume (at -54 °C) enhances vapor condensation and increases local RH throughout the area.

Fig. 7.7(b) illustrates the typical increase in airway temperature as it transitions from ambient conditions to core body temperature. The steepest temperature gradient is observed in the larynx region, followed by a nearly linear increase. According to Ferron's profile, the temperature rises from approximately 296 K at the mouth to 304 K at the trachea. In contrast, our CFD model indicates a temperature increase from 298 K (corresponding to a 25 °C inlet) to about 306 K in the same region. The close alignment in slope and trend between the two curves indicates that both methods effectively capture the primary mechanisms of heat transfer—specifically, diffusive heating near the boundary and convective warming of the airflow core. The slightly higher absolute temperatures observed in our results can be attributed to three consistent factors: a warmer inlet temperature (25 °C compared to approximately 20 °C), the increased mixing effects resulting from the more compact and curved pediatric geometry, and the influence of the wall film.

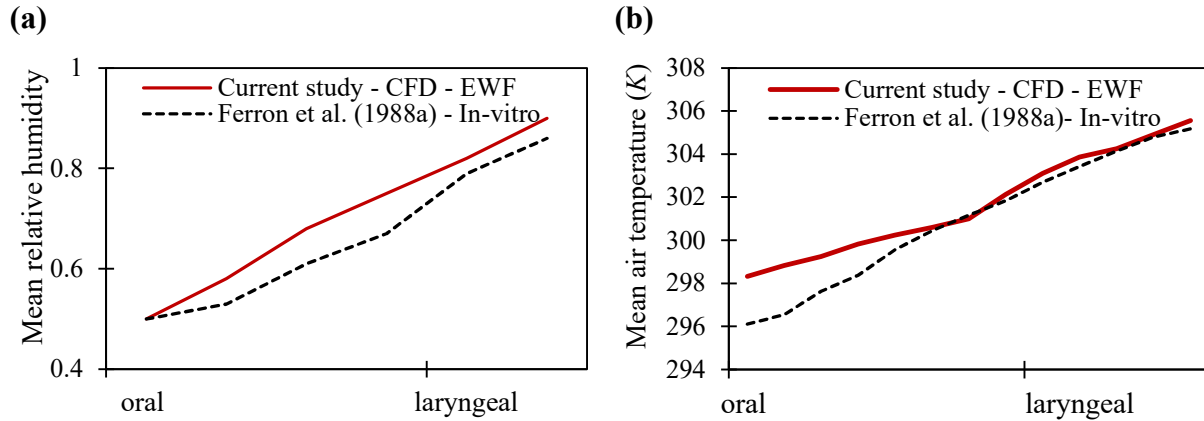


Fig. 7.7 (a) Mean relative humidity; and **(b)** Mean temperature of inhaled air across an airway cross-section during mouth breathing in the upper human respiratory tract.

Results from the present study are compared with predictions by Ferron et al. [78], demonstrating the progressive humidification and thermal conditioning of inspired air. As previously mentioned, direct experimental validation of the EWF implementation was not feasible in this study due to the inherent challenges in uniformly replicating a mucus coating along airway surfaces. Consequently, the current simulations should be considered a preliminary numerical investigation into the role of mucus-mediated heat and mass transfer during inhalation. To ensure numerical accuracy and reliability, mesh refinement and time-step convergence tests were conducted, with predicted temperature and humidity profiles remaining within physiologically relevant ranges. Based on these findings, the EWF model has been adopted for the next phase of our study, which will investigate the influence of flow rate, mucus film properties, and actuation delay on aerosol transport and deposition dynamics.

7.5.2 Effect of Airflow Conditions: 7.5 *L/min*, 15 *L/min*, and the Inhalation Profile

Fig. 7.8 presents the distribution of escaped particles (i.e., particles that passed through the MT outlet) under different airflow conditions: 7.5 *L/min*, 15 *L/min*, and the CF inhalation profile with an average flow rate of 6 *L/min* (refer to **Table 7.1**). These models include the EWF mucus layer, which incorporates the non-Newtonian properties as described in Eq. (7.22). This figure illustrates that higher flow rates result in a greater fraction of particles escaping from the MT region. Under the 15 *L/min* condition, fine particles (1–3 μm) exhibit the highest peak fraction, indicating that stronger inertial forces and shorter residence times reduce deposition, allowing more particles to exit. Additionally, larger particles can also escape due to the increased velocity

within the airway. Conversely, the 7.5 L/min condition yields a lower outlet fraction, particularly for smaller particles, suggesting increased deposition due to weaker airflow velocity and longer residence times [15]. The inhalation profile reveals a trend similar to that of the 7.5 L/min condition, particularly for larger particles ($>5\ \mu\text{m}$), but exhibits a broader distribution. The transient nature of inhalation delays the complete establishment of the airflow regime, causing even finer particles to deposit on the MT walls. During this phase, impaction predominates, resulting in increased deposition before the flow stabilizes.

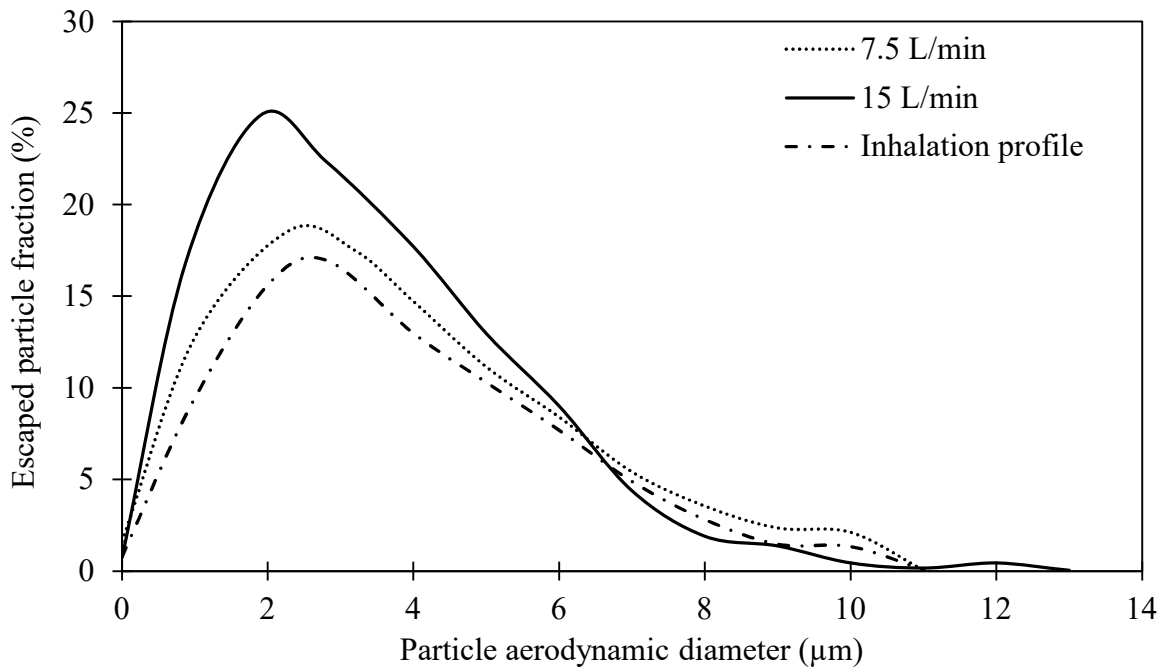


Fig 7.8. Escaped particle fraction at three different flow rate conditions—7.5 L/min, 15 L/min (constant flow rates), and an inhalation profile—simulated using the EWF model (Method (3)), incorporating a mucus layer with non-Newtonian viscosity.

Fig 7.9(a) displays violin plots that illustrate the particle deposition distribution in the MT region and the mass density of evaporated particles under three different inhalation conditions, emphasizing the influence of flow rate on deposition efficiency. Violin plots are particularly useful for showing the complete distribution of parameters derived from simulations, as they combine summary statistics with a kernel density estimate. This method offers a comprehensive overview of the entire data range and can reveal multiple peaks that traditional box plots might miss. Each plot features a solid central line that represents the median, with dashed lines indicating the 25th and 75th percentiles. The width of each plot reflects data density; narrower spacing between the

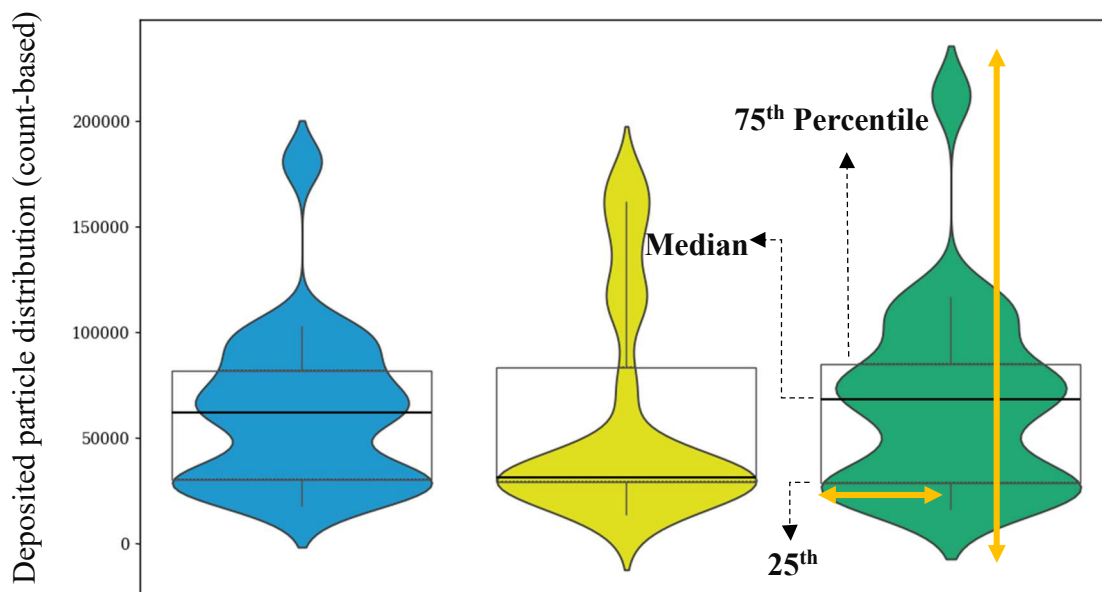
percentile lines signifies lower variability. **Fig. 7.9(a)** shows that the inhalation profile has the broadest distribution and the highest deposition, as indicated by its extended upper tail and larger interquartile range. This suggests that the transient nature of airflow enhances MT deposition, particularly for larger particles. The wide distribution at the median illustrates greater variability in deposition, likely caused by fluctuating airflow that periodically increases particle impaction. At an airflow rate of 7.5 L/min , deposition remains high but exhibits a more symmetric and moderate distribution, reflecting a steady interaction with the constant flow.

In contrast, at 15 L/min , deposition is at its lowest, with a compressed interquartile range. This suggests that higher airflow velocities reduce particle interactions with the MT region, resulting in decreased deposition. These trends align with findings from Chen et al. [80], who conducted a CFD study on aerosol deposition of inhaled multicomponent droplet-vapor mixtures under varying flow rates, relative humidity levels, and wet and dry airways. Their results showed that wall deposition increased at lower flow rates due to longer particle residence times [80]. Moreover, the CF inhalation profile, despite having a lower average flow rate (6 L/min), produced a broader and more skewed particle deposition distribution compared to the constant flow rates of 7.5 and 15 L/min . This wider interquartile range and extended upper tail in the CF case indicate greater variability in particle-wall interactions. The phenomenon can be explained by the parabolic nature of the CF inhalation profile, which includes an early acceleration phase followed by a decelerating tail. The initial high velocity promotes inertial impaction in the upper airway, while the later low-flow phase allows for prolonged particle residence, increasing the chances of secondary deposition through settling and diffusion. This highlights how unsteady inhalation profiles can increase spatial dispersion of deposited particles, especially in pediatric airways.

The evaporated mass distribution illustrated in **Fig. 7.9(b)** reflects how different airflow conditions interact with the MT mucus film. Median evaporated mass remains relatively stable across all cases, indicating that overall evaporation is not significantly affected by flow rate. Both 7.5 L/min and 15 L/min show consistent evaporation, though the 15 L/min case exhibits a shorter tail and tighter upper region, suggesting reduced particle residence time and less variability. In contrast, the 7.5 L/min case shows a more elongated tail, indicating a broader but still stable evaporation range. The CF inhalation profile shows a skewed distribution with a longer tail and a 50% larger interquartile range compared to constant flows, pointing to greater variability. This is due to the parabolic nature of the CF inhalation profile, where alternating high and low airflow leads to

fluctuations in evaporation rates. A small bump at the beginning of the tail suggests localized increases in evaporation, likely caused by longer particle residence during the low-flow phase post-actuation.

(a)



(b)

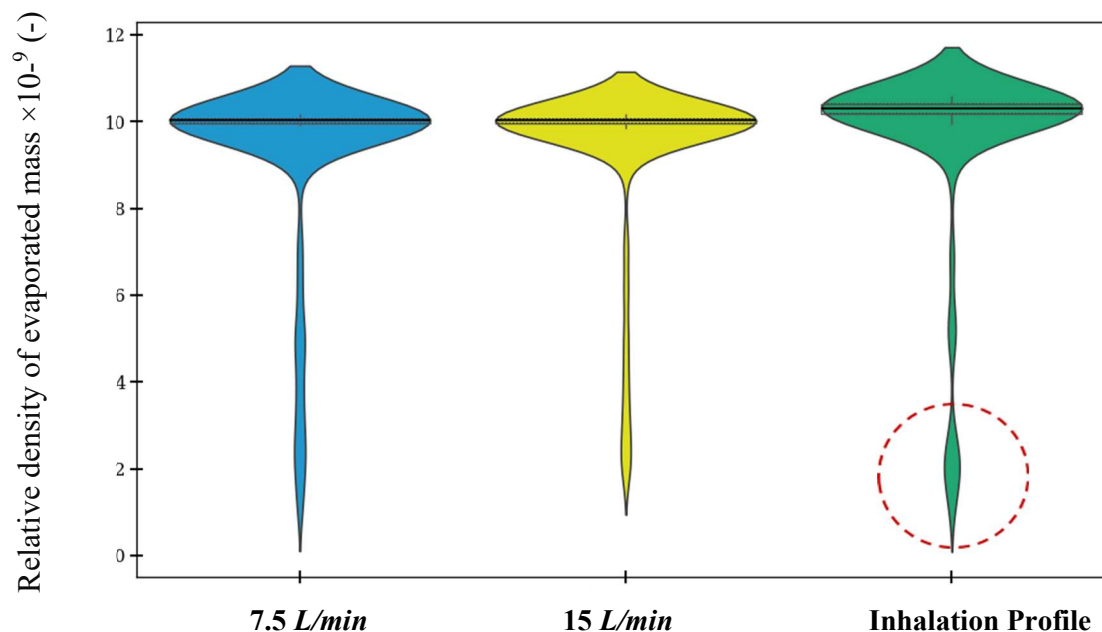
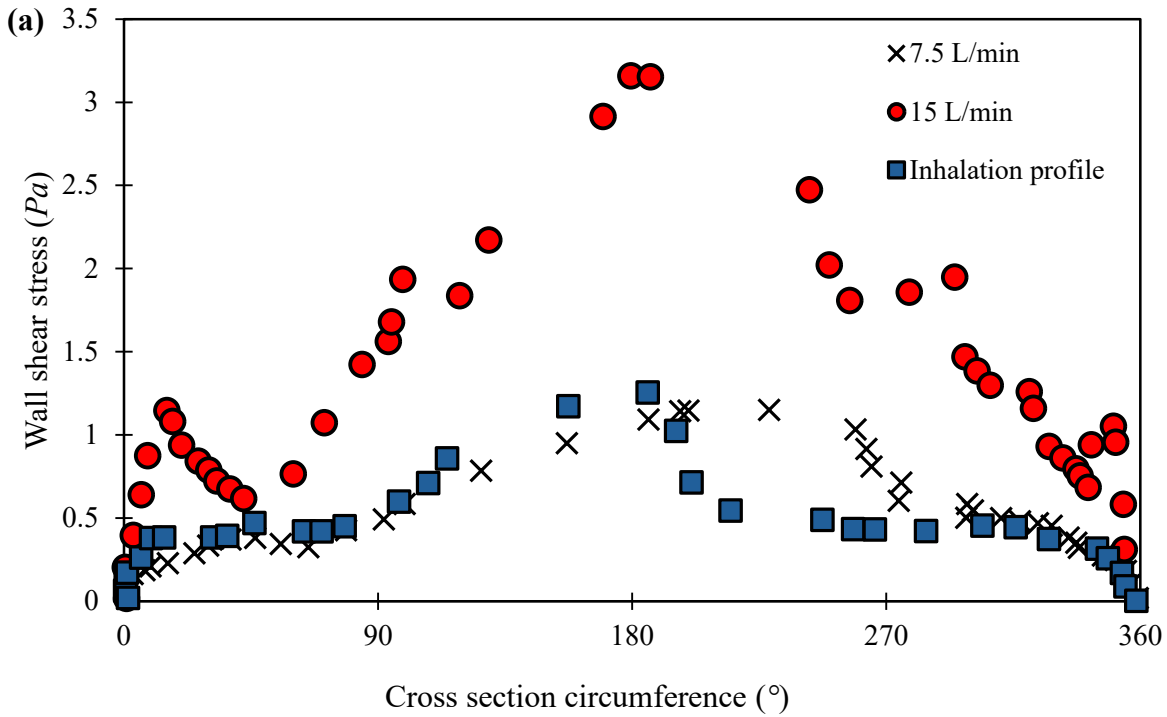


Fig 7.9. (a) Particle deposition distribution on the MT wall; and (b) Relative density of evaporated drug particle mass, over time under different inhalation conditions (7.5 L/min, 15 L/min, and CF inhalation profile).

Fig 7.10 shows the spatial distribution of wall shear stress around the tracheal circumference at the transverse plane (Plane 5) under three airflow conditions: 7.5 *L/min*, 15 *L/min*, and the inhalation profile with a mean flow rate of 6 *L/min*, all with a non-Newtonian mucus wall film (EWF). Note that the circumferential direction of the cross-section is counterclockwise. The figure also displays secondary flow contours and streamlines recorded 0.11 *s* after actuation. In **Fig. 7.10(a)**, wall shear stress varies significantly with flow conditions. The 15 *L/min* case has the highest shear stress due to greater velocity gradients and asymmetrical distribution, indicating secondary flow effects.

In contrast, the 7.5 *L/min* and inhalation profile cases show lower shear stress, with the 7.5 *L/min* condition being more symmetrical. **Fig. 7.10(b)** illustrates secondary airflow velocity contours and streamlines for Plane A, highlighting recirculation zones and swirling motion. At 7.5 *L/min*, distinct recirculation regions appear, while at 15 *L/min*, increased velocity enhances swirling near the airway walls. Under the inhalation profile, the transient flow centralizes recirculation zones, with moderate swirling persisting due to the complex geometry of the pediatric airway. These findings align with Green [81], who modeled peak expiratory flow in the trachea and bronchial passages and examined the correlation between wall shear stress distribution and flow rate. The observed decrease in wall shear stress within the recirculation regions—indicated by the dashed lines—supports Green's conclusions, especially at a flow rate of 15 *L/min*, where stronger interactions between mucus and air result in a significant decline. Furthermore, there is a localized drop in wall shear stress at 270° in the inhalation profile, which suggests the presence of a near-wall recirculation zone, as highlighted by the yellow dashed line in **Fig. 7.10(b-iii)**.



(b)

(i) 7.5 L/min

(ii) 15 L/min

(iii) Inhalation profile

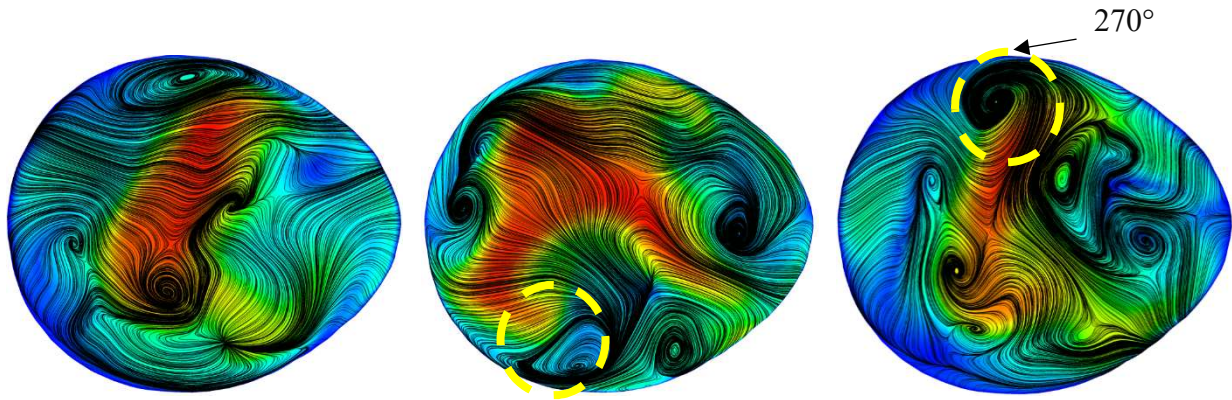


Fig 7.10. (a) Wall shear stress profiles on transverse Plane 5 at 0.011 s under three inhalation conditions; and (b) Airflow velocity contours with streamlines for input airflow of (i) 7.5 L/min, (ii) 15 L/min, and (iii) inhalation profile. Simulations were performed using the EWF model (Method (3)), incorporating non-Newtonian mucus viscosity.

Fig 7.11 illustrates the relationship between pressure drop (Δp) and flow rate in a pediatric airway model under three different conditions: with a Newtonian mucus layer (EWF model), without mucus (no-slip wall), and in comparison to experimental data from Allen et al. [29], who examined dry pediatric airways under a no-slip boundary condition. According to Allen et al. [29], airflow

in a dry airway exhibits turbulence, leading to a pressure drop that scales approximately with the square of the flow rate, described by the equation: $\Delta p = 0.868841 Q^2$, consistent with findings of West [82]. In our simulations, utilizing a different pediatric CT-scan geometry and a no-slip condition (without mucus), we observe a similar near-quadratic trend represented by the equation $\Delta p = 0.624 Q^{1.981}$. This finding reaffirms the expected relationship between pressure drop and flow rate. Although both studies examine pediatric airway geometries, subtle anatomical differences—especially in pharyngeal curvature and wall smoothness—can significantly influence flow resistance by affecting flow separation and the strength of secondary vortices. At low flow rates (less than 5 L/min), inertial losses are minimal, causing the pressure drop versus flow rate (Δp – Q) curves from both studies to align closely. However, at higher flow rates, the sharper bends and rougher surfaces in Allen's airway geometry result in increased flow resistance, which leads to a greater pressure drop. Additionally, our model incorporates pMDI injection, which adds downstream momentum and reduces the pressure gradient necessary to maintain the same flow. This contributes to a lower Δp compared to the results from Allen et al. (2004) at higher flow rates. To investigate the impact of wall boundary layer conditions, the pressure drop–flow rate relationship was also examined for the case with a Newtonian mucus layer [29]. The resulting fit, $\Delta p = 0.857 Q^{2.042}$ indicates a near-quadratic dependence, confirming that inertial effects dominate over viscous forces at higher flow rates.

At low flow rates ($Q < 6$ L/min), the pressure drop in the mucus-layer condition closely aligns with the no-mucus case, as both exhibit minimal resistance dominated by viscous effects. However, at higher flow rates ($Q > 10$ L/min), the pressure drop associated with the Newtonian mucus layer surpasses that of the no-mucus case. This increase can be attributed to the added wall shear resistance introduced by the constant-viscosity mucus, which interacts more actively with the core airflow. Unlike dry, rigid walls, the mucus–air interface facilitates momentum exchange, enhancing near-wall drag and energy dissipation. Functionally, the mucus behaves as a viscous sublayer, modifying the near-wall velocity gradient and increasing interfacial shear. Although the film thickness is only 30 μm , its influence is magnified in pediatric airway geometries due to their relatively small diameters and high surface-area-to-volume ratios.

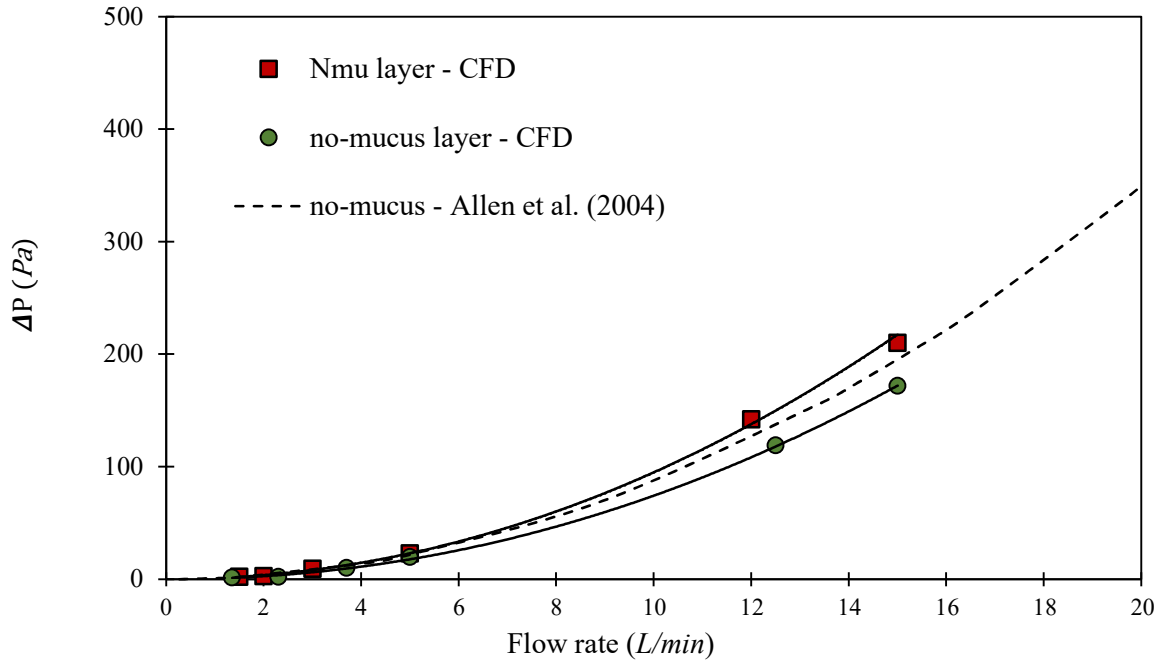
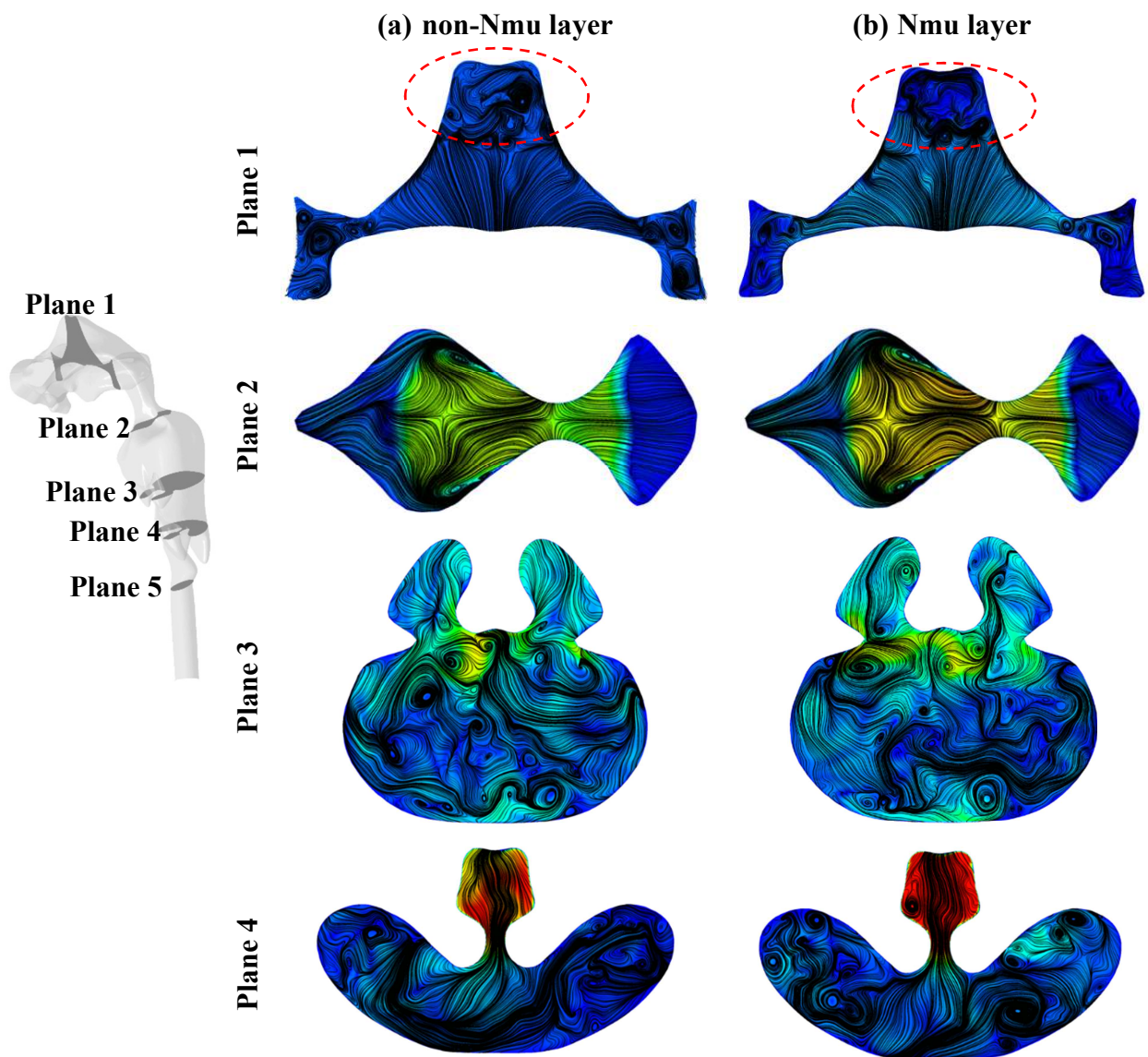


Fig 7.11. Pressure drop (Δp) versus flow rate (Q) in a pediatric mouth–throat (MT) airway model under three conditions: with a Newtonian mucus layer (Nmu) using the EWF model, without a mucus layer (no-slip wall), and experimental data from Allen et al. (2004) for a dry pediatric airway model (no mucus layer).

7.5.3 Effect of Mucus Rheological Property: Newtonian and non-Newtonian

Fig 7.12 illustrates the velocity streamlines and contour plots of secondary airflow across five cross-sections (planes) of the pediatric airway under the inhalation profile, comparing two scenarios: (a) a non-Newtonian mucus layer and (b) a Newtonian mucus layer. In **Fig. 7.12(a)**, the non-Newtonian layer exhibits a more irregular secondary airflow pattern, characterized by multiple recirculation zones and asymmetrical behavior resulting from variations in viscosity at different shear rates. Additionally, the velocity magnitudes are lower, especially at the center of the cross-sections. In contrast, **Fig. 7.12(b)** shows that the Newtonian layer creates smoother, more symmetrical streamlines with a uniform velocity distribution and even wall shear stress. The impact of mucus viscosity on airflow is evident, particularly in Plane 1, where both conditions show low velocity. However, the non-Newtonian layer complicates secondary flow near the walls. In high-shear areas of Planes 4 and 5, the shear thinning of the mucus layer reduces viscosity, facilitating increased airflow and generating complex secondary flow patterns.

Rajendran and Banerjee [65] conducted a CFD study on bifurcating lung airways to examine the effects of Newtonian layers under a constant coughing-induced flow rate of 70 L/min . Their analysis revealed that in Newtonian mucus layers, secondary flow vectors were more symmetrical, particularly in the trachea. In contrast, non-Newtonian layers exhibited more complex and irregular flow patterns, especially in the branching regions.



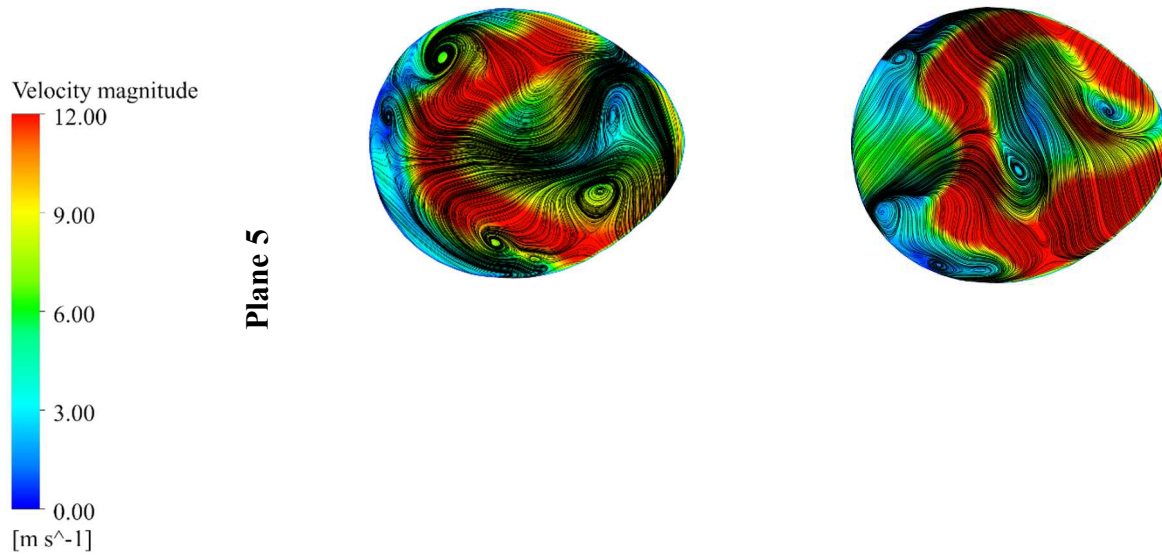


Fig 7.12. Secondary airflow velocity contours with streamlines at 0.08 s across five cross-sectional planes of the pediatric airway under the inhalation profile, using the EWF model for: **(a)** A non-Newtonian mucus (non-Nmu) layer; and **(b)** A Newtonian mucus (Nmu) layer.

Fig. 7.13 illustrates the distribution of wall shear stress along the circumference of Plane 5 under varying mucus viscosities, using the CF inhalation profile at 0.08 s. This figure also presents a wall shear stress contour of the pharynx and trachea regions with a non-Newtonian layer. The location and angular coordinates of Plane 5 ($Y = -89.58 \text{ mm}$) are marked in the figure.

In **Fig. 7.13(a)**, the Newtonian layer shows consistently higher wall shear stress values than the non-Newtonian layer. This is due to the constant viscosity of the Newtonian layer, which establishes a linear relationship between shear stress and velocity gradient. In contrast, the non-Newtonian layer adjusts its viscosity based on local shear conditions, resulting in a varied wall shear stress profile with lower peak values. This behavior corresponds with the secondary flow patterns observed in Plane 5, as shown in **Fig. 7.12(a)**. Both fluids reach their peak wall shear stress at 180° below the glottis curvature, with the Newtonian layer being only 7.2% higher than the non-Newtonian layer. The wall shear stress contour further emphasizes regions in the lower pharynx and near the glottis, where wall shear stress is particularly affected, as shown in **Fig. 7.13(b)**.

The inhalation profile, with a mean flow rate of 6 L/min , produces a low-velocity airflow and minimal variations in wall shear stress. As shown in **Fig. 7.13(a)**, the maximum difference in shear stress between 200° and 280° arises from secondary flow intensity and velocity magnitude variations. In the non-Newtonian mucus layer, weaker vortices and lower velocity gradients reduce

wall shear stress. In contrast, the water case exhibits stronger swirling and near-wall velocities, nearly three times higher, which increases shear stress. The Newtonian layer model enhances secondary flow, promoting momentum transfer and higher shear forces, while turbulence is dampened in the non-Newtonian case. Additionally, the thickness of the mucus layer is crucial in determining air-mucus interactions. In our study, the mucus layer is relatively thin, measuring only $30\ \mu\text{m}$ [59], which may contribute to the observed variations in shear stress.

A CFD study by Kulkarni and Kleinstreuer [34] examined the effects of high inhalation flow temperatures on the mucus layer in a realistic adult airway, assuming that the mucus properties were similar to those of water at a constant flow rate. Their findings revealed significant mucus evaporation in the same region as Plane 5, resulting in a notable reduction in mucus thickness. Although their study primarily focused on the temperature of the air inlet, it underscored the strong interaction between airflow and mucus, as well as the curvature of the mucosal tissue near the glottis, as key factors contributing to higher shear stress in this area.

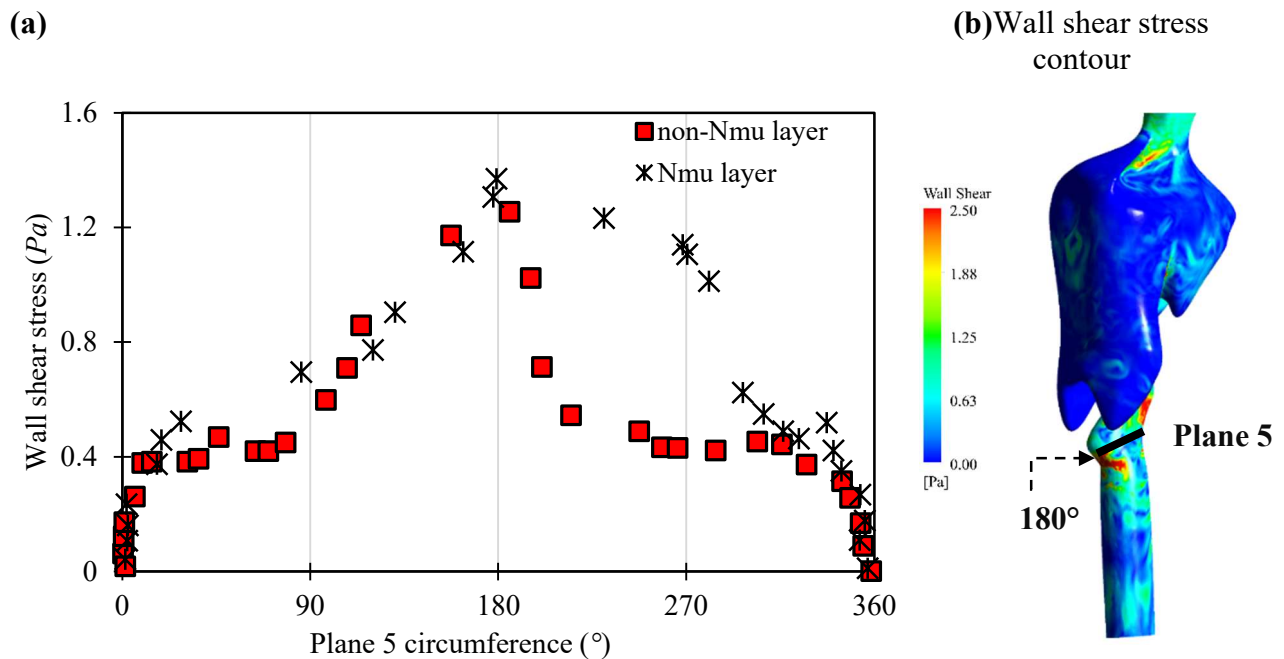


Fig 7.13. (a) Wall shear stress distribution on cross-sectional Plane 5 at $0.08\ s$ under the CF inhalation profile; and (b) Wall shear stress contour across the pharynx and trachea regions, incorporating the non-Newtonian mucus (non-Nmu) layer using the EWF model.

Fig. 7.14 illustrates how the presence of a mucus layer influences particle deposition on the MT wall, comparing wall conditions with Newtonian and non-Newtonian mucus layers under the CF inhalation profile. The count-based particle deposition fractions were calculated for both conditions, which highlight the detailing of deposition in each area of the MT geometry.

The particle deposition along the mouth wall is quite similar in both scenarios. This is primarily due to the high initial velocity of the emitted particles, which minimizes the effect of mucus on the deposition process. However, the lower inhalation power at the beginning of breathing leads to particle deposition on the mouth (palate wall) following the direction of the inhalation plume. As a result, particle deposition in the mouth appears to be largely independent of the presence of the mucus layer, with most particles being larger than $9\ \mu\text{m}$. Significant differences, however, are observed at the pharynx and trachea. In these areas, a higher deposition efficiency is achieved under Newtonian conditions, with a percentage deposition efficiency ($\%DE_{\text{Nmu}}$) of 49%. The presence of the Newtonian mucus layer as a wall film locally reduces particle deposition due to the stable secondary flow generated by the airway's curvature in this complex geometry. Additionally, the Newtonian mucus layer exhibits both a higher and more stable secondary flow velocity compared to the non-Newtonian mucus layer in the trachea (as shown in **Fig. 7.12**), resulting in a slightly greater number of particles passing through the outlet.

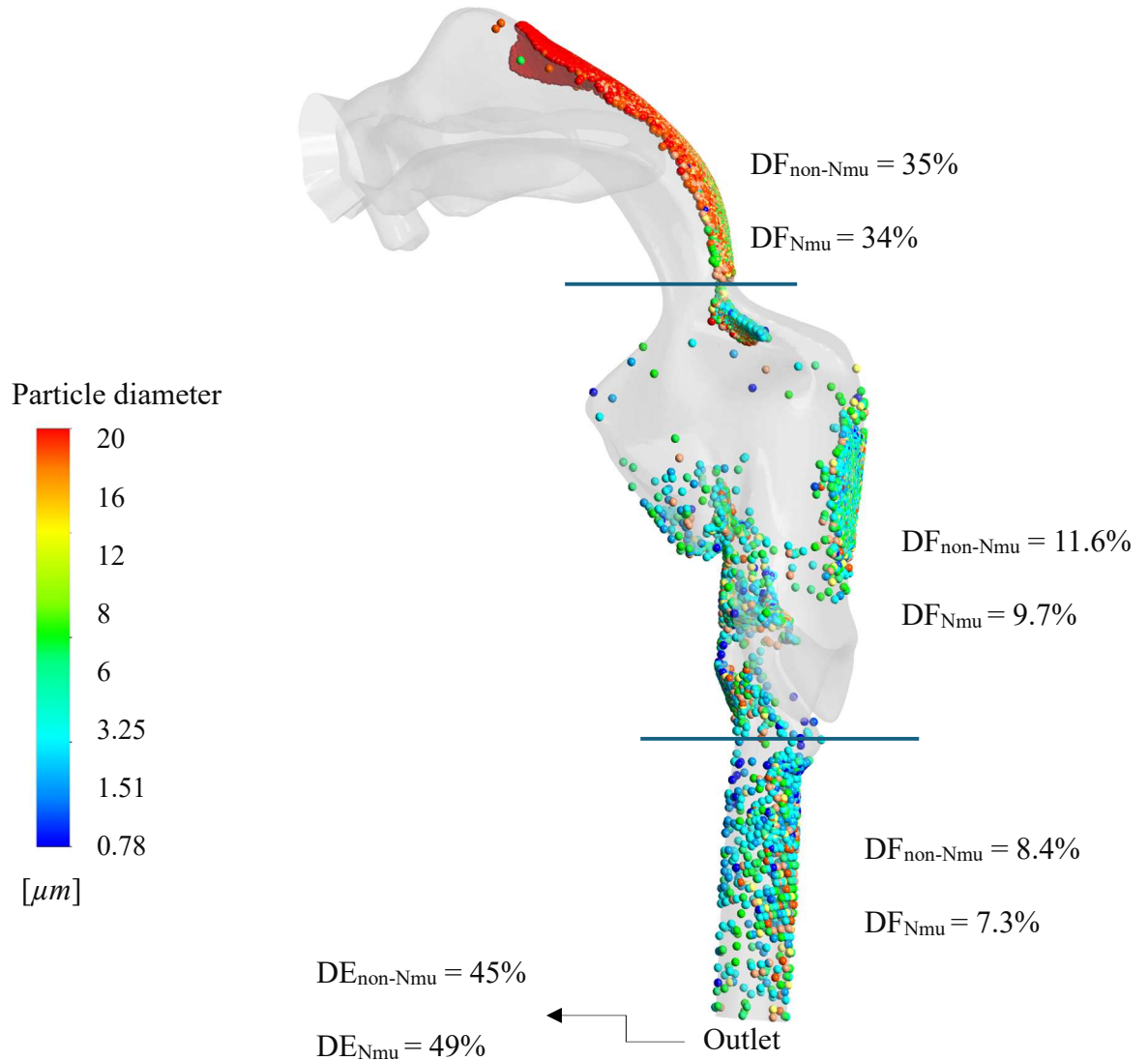


Fig 7.14. Comparison of deposition fraction (DF) across different regions of the pediatric MT airway and outlet deposition efficiency (DE) between Newtonian (Nmu) and non-Newtonian (non-Nmu) mucus conditions. Particle deposition patterns for the non-Nmu case are also shown. All results are based on the inhalation profile condition using the EWF model.

Fig. 7.15 shows the escaped particle fraction distribution at the MT outlet across a range of aerodynamic diameters under different mucus layer conditions. The experimental data and the validated CFD results for the no-mucus condition at 15 L/min show good agreement, with both escaped particle fraction peaking around 3 μm and covering a wide size range. When a Newtonian mucus layer is modeled under the CF inhalation profile, the escaped particle fraction increases overall but becomes concentrated in a narrower diameter range, with the peak shifting slightly leftward and a minimum escaped diameter of 0.491 μm . In contrast, the non-Newtonian (shear-

thinning) mucus case shows reduced escape fractions and a broader distribution skewed toward larger particles, with a minimum diameter of $0.789 \mu\text{m}$. This behavior is attributed to enhanced particle–wall interactions under the shear-thinning mucus, which generates more asymmetric secondary flows and promotes wall deposition. As a result, fewer particles especially smaller ones pass through the MT outlet. Overall, the presence and rheology of the mucus layer influence deposition dynamics: Newtonian mucus permits more particle escape with limited size variability, while non-Newtonian mucus promotes broader deposition and reduces overall transmission to the lungs.

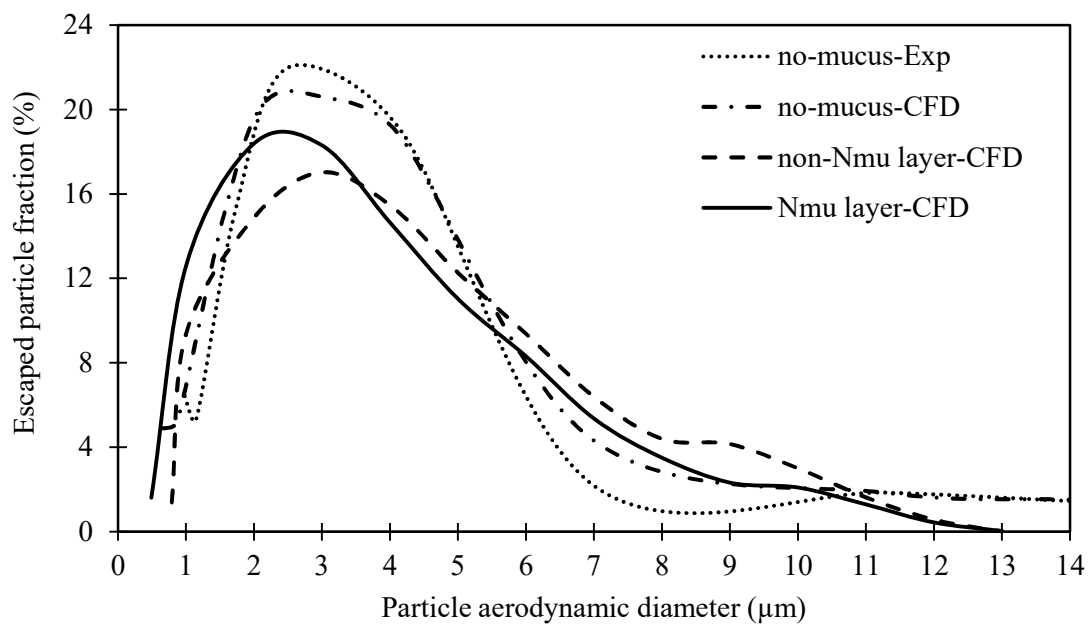


Fig 7.15. Escaped particle fraction distribution comparing experimental and CFD results for the no-mucus case at a constant flow rate of 15 L/min , and CFD results with the EWF mucus layer under the CF inhalation profile.

7.5.4 Effect of Actuation Timing with Respect to Inhalation Profile

Many patients struggle to synchronize their inhalation with the actuation of inhaler devices. The actuation timings selected in this study — -0.05 s (early), $+0.5 \text{ s}$ (delayed before the IFP), and $+0.7 \text{ s}$ (delayed after the IFP)—reflect the inherent challenge of achieving perfect inhalation-actuation synchronization, which is often hard for patients to achieve.

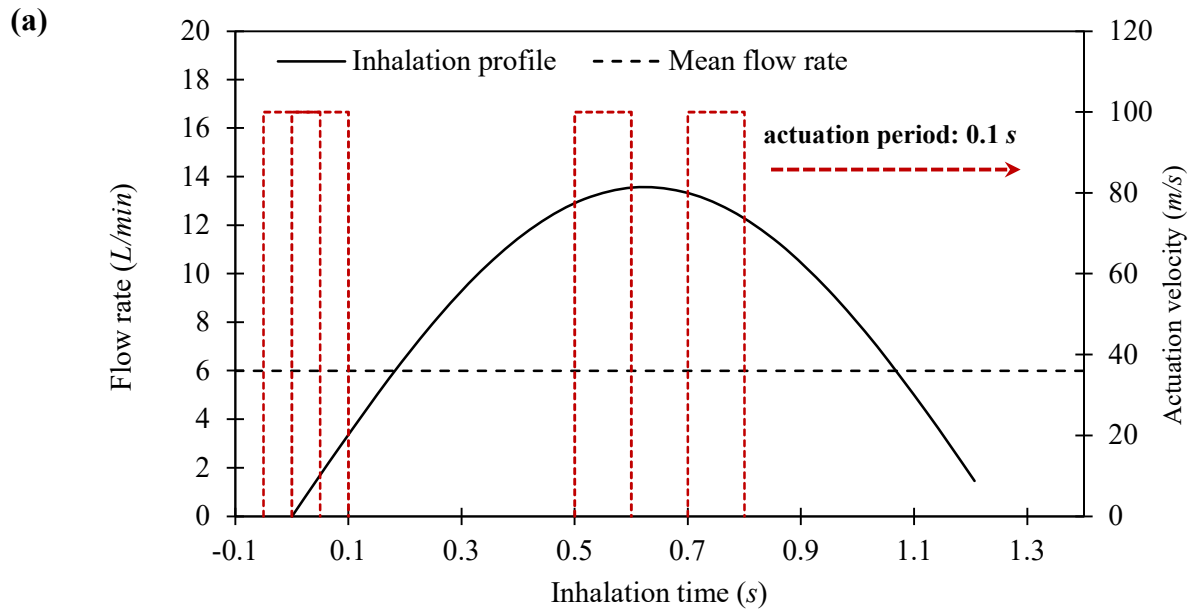
Fig. 7.16 illustrates the impact of device actuation timing relative to the inhalation profile on particle deposition in different areas of the respiratory tract. When the device is actuated slightly

early (e.g., at -0.05 s), particle motion is primarily governed by their initial momentum, as the inhalation airflow has not yet been fully established. As a result, some particles deposit in the mouth, which serves as the first barrier in their pathway. Liu et al. [31] conducted an *in-vitro* study investigating the effect of delayed actuation and inhalation on a valve-holding chamber (VHC) using a pMDI. Their findings showed that early actuation led to higher deposition within the VHC, which aligns with the results of this study, particularly regarding deposition on the mouth wall. When actuation occurs before inhalation begins, the high velocity of aerosolized particles increases the likelihood of their deposition on the airway walls, as there is no established airflow regime to guide them past the mouth region. In contrast, synchronized actuation (at $t = 0\text{ s}$) leads to a lower mouth wall deposition of 35%, which is 5% lower than the early actuation at $t = -0.05\text{ s}$.

The complexity of secondary flow influences the behavior of actuated particles. As a result, the timing of actuation in relation to the inhalation profile leads to different responses in particle deposition compared to a constant inhalation flow rate. As discussed in **Fig. 7.8**, a higher constant flow rate generates stronger inertial forces, which help more particles overcome impaction at the bends of the upper airway and reach the outlet. Changes in flow rate during the inhalation profile—whether they are increasing or decreasing—result in a time-dependent and transient airflow pattern. When actuation is delayed by 0.5 s , the inhalation flow rate starts at 12 L/min and is on the rise towards its peak. By 0.7 s , the flow rate enters the descending phase, decreasing from 12 L/min (as shown in **Fig. 7.16(a)**). This misalignment between the direction of actuation velocity and the ambient airflow, occurring at higher flow rates, results in sharper trajectory shifts and increased particle deposition. In contrast, under synchronized conditions (where actuation occurs at $t = 0\text{ s}$), particles follow a nearly ballistic path with minimal initial resistance, gradually becoming entrained in the accelerating flow. This process reduces impaction and increases the likelihood of particle escape through the outlet.

Studies have indicated that The oropharyngeal airway's skewed axial velocity profile and abrupt laryngeal contraction generate strong spatial gradients in particle inertia, driving inertial impaction [84,85] along curved streamlines at the back of the oral cavity and through the constriction [9]. This effect intensifies at higher flow rates, particularly for micron-sized particles [85,86]. In adult airways with fully developed airflow, higher flow rates enhance particle momentum, enabling particles to adhere to the streamlines as they approach the outlet [83] whereas in the narrower pediatric geometry, these inertial forces produce distinct deposition patterns. Overall, the interplay

between plume momentum and particle inertia dictates deposition efficiency, and synchronized, gentle inhalation by better entraining particles in the accelerating flow can minimize upper-airway impaction and improve deep-lung delivery. Talaat et al. [25] investigated the timing of MDI actuation in the adult airway using an inhalation profile with a peak flow rate of 60 L/min . They compared the actuation times of 1.5 s and 2.5 s. The study found that delaying the actuation had minimal impact on deposition in the pharyngeal and laryngeal regions, which areas correspond to the trachea in our research. However, consistent with our findings, delayed actuation resulted in increased deposition in the mouth.



(b)

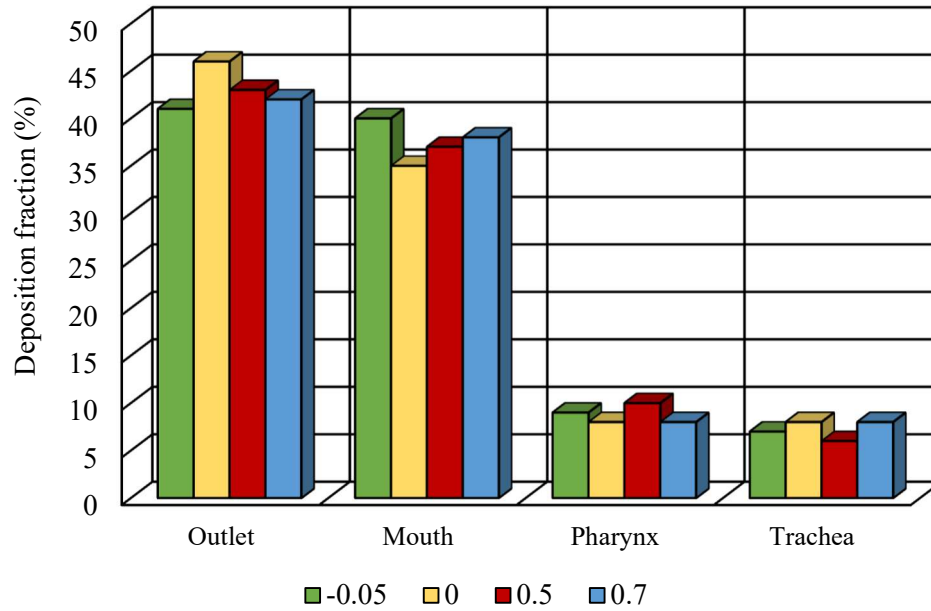


Fig 7.16. (a) CF inhalation profile showing device actuation timings relative to inhalation profile at -0.05 s , 0 s , 0.5 s , and 0.7 s ; and **(b)** Deposition fraction (%) as a function of device actuation timing across four regions: outlet, mouth, pharynx, and trachea.

7.5.5 Sensitivity Analysis

In this study, we identified wall shear stress as a key indicator of the influence of mucus and pressure drop as a measure of breathing resistance in the airways. We selected three output parameters for our sensitivity analysis based on our findings: deposition efficiency, wall shear stress, and pressure drop.

Among various sensitivity analysis techniques, the Morris method [87] is widely recognized for its computational efficiency and ability to capture global and local sensitivity effects. This method proves particularly advantageous in high-dimensional problems, where traditional variance-based approaches, such as Sobol analysis [88], can be computationally expensive, specifically for respiratory simulations. The Morris method employs a screening-based approach to estimate the influence of input parameters using elementary effects (EE), which quantify the impact of small perturbations in each input variable on the model outputs. The elementary effect of a given input parameter is calculated as follows:

$$EE_i(x) = [y(x_1, x_2, \dots, x_{i-1}, x_i + \Delta, x_{i+1}, \dots, x_k) - y(x)]/\Delta \quad (7.25)$$

where Δ represents the magnitude of a step, which is determined as a multiple of $1/(p-1)$, where p signifies the number of levels or values for sampling variables; this concept is known as the resolution of sampling [89]. The mean of the absolute elementary effects (μ^*) reflects the overall sensitivity of a parameter, while the standard deviation indicates the presence of interactions or nonlinear effects. A higher μ^* value signifies a more influential parameter, whereas a larger standard deviation suggests significant interactions or nonlinearity.

$$\mu^* = \frac{1}{N} \sum_{i=1}^N |EE_i| \quad (7.26)$$

where N represents the number of sampled trajectories.

Table 7.2 displays the mean absolute effects (μ^*) of three key input variables—mucus viscosity, inhalation flow rate, and device actuation timing—on three outputs: lung deposition efficiency, wall shear stress, and pressure drop. Among these variables, the inhalation flow rate has the most significant impact on deposition efficiency, with a μ^* of 18.75 and a considerable standard deviation of 19.09, indicating strong nonlinear interactions. Mucus viscosity also notably influences deposition efficiency, but its lower standard deviation suggests a more consistent effect with minimal interactions. In contrast, the timing of the device (pMDI) actuation exhibits moderate sensitivity, as indicated by its relatively high standard deviation of 12.72, which suggests interactions with other parameters and responses. Given the complexity of the pediatric airway and the short inhalation profile, the impact of actuation timing on deposition efficiency is likely to be limited.

Table 2 further indicates that mucus viscosity, flow rate, and actuation timing have very low μ^* values for wall shear stress, suggesting minimal individual and interactive effects. This is consistent with expectations, as wall-adjacent flow during inhalation therapy is generally insensitive to these parameters. In contrast, the flow rate ($\mu^* = 78.45$) primarily influences the pressure drop, demonstrating strong nonlinear interactions. Mucus viscosity has a slightly greater impact on pressure drop than actuation timing, likely due to its effect on airway resistance during particle actuation.

Table 7.2. Mean absolute effect and standard deviation for three input variables and three responses.

Output variables (responses)	Input variables	Mean absolute effect (μ^*)	Standard deviation
Deposition efficiency	Air flowrate	18.75	19.09
	Mucus viscosity	13.50	3.18
	Actuation timing	9.00	12.72
Wall shear stress	Air flowrate	0.05538	0.7832
	Mucus viscosity	0.00929	0.0131
	Actuation timing	0.00412	0.0003
Pressure drops	Air flowrate	78.45	110.94
	Mucus viscosity	8.72	11.14
	Actuation timing	4.54	6.42

To further explore the relationships among key parameters, a Spearman correlation analysis was conducted, as illustrated in **Fig. 7.17**. This analysis complements the sensitivity analysis by quantifying the monotonic associations between mucus viscosity, inhalation flow rate, actuation timing, and lung deposition efficiency, which is the primary indicator of inhalation therapy effectiveness. The heatmap in **Fig. 7.17** displays the Spearman correlation coefficient (r_s), where $r_s = 1$ signifies a perfect positive correlation. According to this classification, correlations were categorized as strong ($r_s > 0.7$), moderate ($0.3 \leq r_s \leq 0.7$), or weak ($r_s < 0.3$).

A strong positive correlation ($r_s = 0.87$) was observed between flow rate and deposition efficiency, reinforcing the results of Morris sensitivity analysis and indicating that higher flow rates promote more effective particle deposition. Actuation timing showed a moderate negative correlation ($r_s = -0.47$), suggesting that increased delay between actuation and inhalation reduces deposition efficiency, likely due to premature dispersion or particle loss before optimal inhalation. Mucus viscosity exhibited a mild positive correlation with deposition efficiency ($r_s = 0.32$), implying a modest impact that may stem from altered secondary flow structures and localized shear effects, as seen in **Fig. 12**.

Additionally, a weak correlation between viscosity and flow rate ($r_s = 0.24$) suggests limited interdependence, while no correlation was found between viscosity and actuation timing ($r_s = 0.00$), indicating these variables operate independently within the tested range. Overall, the results

highlight flow rate and actuation timing as the dominant factors affecting deposition, with mucus viscosity playing a secondary but still relevant role. Optimizing inhalation dynamics and synchronizing actuation can therefore enhance aerosol drug delivery, particularly in the presence of mucus.

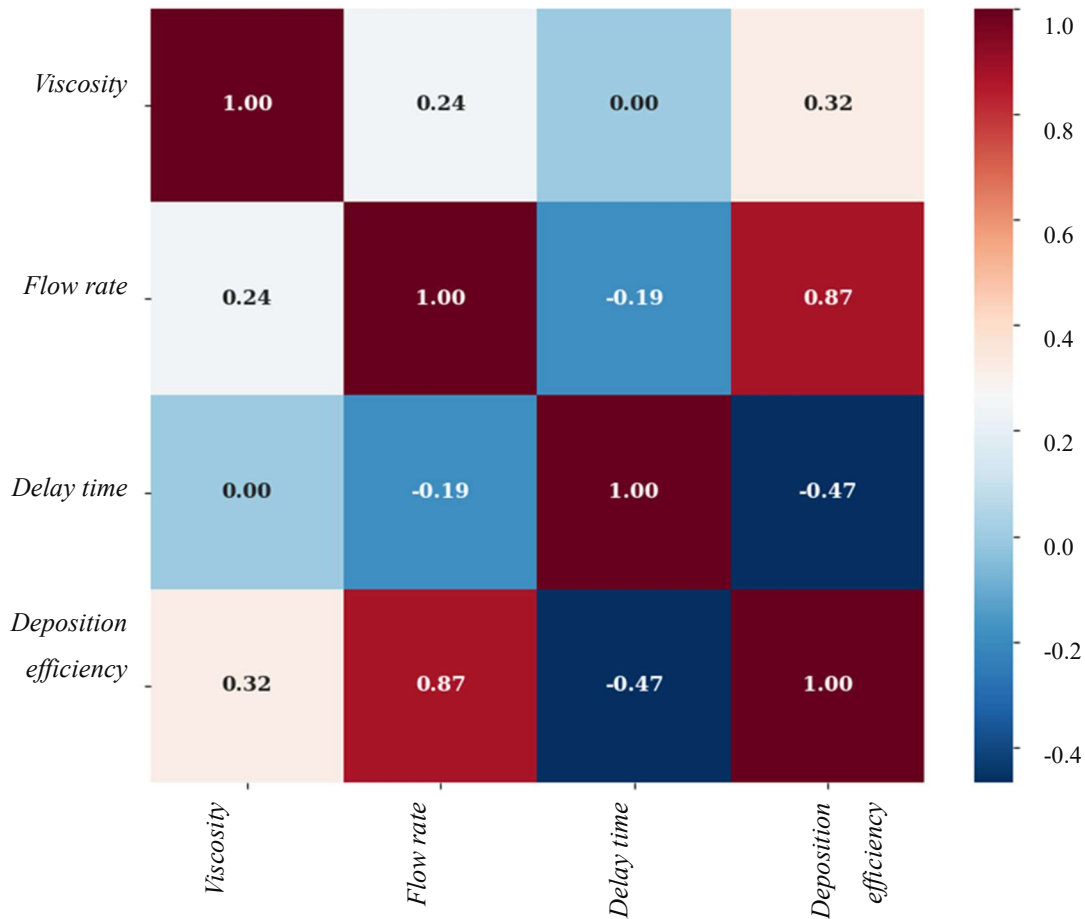


Fig 7.17. Spearman correlation heatmap illustrating the relationships between input variables—mucus viscosity, airflow rate, and actuation timing—and the primary response variable: outlet deposition efficiency.

7.6 Conclusions

This study investigates the effects of CF inhalation profile, mucus viscosity, and actuation timing on particle transport and deposition from a pMDI in a pediatric mouth–throat model. Three flow conditions (7.5 L/min, 15 L/min, and CF inhalation), two mucus types (Newtonian and non-Newtonian), and three actuation timings (early, synchronized, delayed) were evaluated. LES-DPM was employed to capture transient airflow and particle deposition dynamics accurately. To realistically model the mucus layer, three wall boundary conditions were evaluated: method (1)

for total thickness, method (2) for shell conduction, and method (3) for the EWF, applied to a 30 μm mucus layer. Results showed that the EWF model accurately represented the mucus-air interface by incorporating heat and mass transfer, capturing local vortex structures and swirling intensity. In contrast, methods (1) and (2) overpredicted wall deposition due to oversimplified wall interactions. Additionally, a 3D-printed replica of a CT-scanned pediatric airway was printed and integrated into an NGI setup, which operated at a flow rate of 15 L/min and 50% relative humidity. The concentrations of particles on the MT walls and NGI stages were quantified using HPLC. These data were used to validate the CFD model under experimentally replicated conditions.

At a flow rate of 15 L/min , a wider range of particle sizes was observed passing through the MT outlet compared to 7.5 L/min , particularly among the finer particles. However, under the CF inhalation profile, which caused a delay in flow stabilization, finer particles were more likely to deposit in the MT region. For example, 17% of 2.8 μm particles exited the airway under the CF profile, whereas 25% of 2 μm particles exited at a flow rate of 15 L/min . For particles larger than 10 μm , deposition patterns were consistent across both flow rates. Additionally, a secondary flow analysis indicated that stronger recirculation and vortex formation occurred at 15 L/min , whereas the CF profile resulted in lower secondary flow intensities. Correspondingly, the maximum wall shear stress was 3.2 Pa at 15 L/min compared to 1.22 Pa under the CF profile. However, secondary flow remained asymmetrical in both scenarios.

Breathing resistance (ΔP) showed a sub-quadratic relationship with flow rate, confirming inertial dominance at higher flow rates. Unlike the no-mucus condition, the presence of a Newtonian mucus layer consistently increased pressure drop, with the difference becoming more pronounced above 10 L/min . This effect is attributed to the constant viscosity of the mucus, which increases wall shear and energy dissipation. While particle deposition near the mouth remained largely unaffected, downstream behavior was influenced by the mucus layer, which stabilized secondary flows and promoted particle escape. The velocity field appeared smoother under the Newtonian condition, with only a modest 7.2% increase in peak wall shear stress compared to the mucus-free case.

Actuation timing significantly impacts deposition efficiency. Early actuation reduces outlet delivery by approximately 5%, while delayed actuation (0.5 and 0.7 s) leads to even greater reductions due to inertial impaction. The highest delivery efficiency, around 46%, occurs with

synchronized actuation ($t = 0$ s), which aligns with the peak acceleration of the flow. A Morris sensitivity analysis and Spearman correlation (r_s) were used to quantify the impact of three parameters—flow rate, mucus viscosity, and actuation timing—on deposition efficiency, wall shear stress, and pressure drop. Flow rate emerged as the dominant factor ($\mu^* = 18.75$, $r_s = 0.87$), significantly enhancing deposition as the rate increased. Actuation timing exhibited a moderate adverse effect ($r_s = -0.47$), while mucus viscosity had a weaker influence ($r_s = 0.32$). However, mucus viscosity is still relevant for altering secondary flow and wall interactions. In conclusion, deposition efficiency in pediatric airways is mainly driven by inhalation flow rate, while actuation timing and mucus rheology remain important secondary factors. Aligning actuation with peak inhalation and accounting for mucus properties can significantly improve aerosol drug delivery

7.7 Nomenclature

Abbreviations

COPD	chronic obstructive pulmonary disease
3D	3- dimensional
APSD	aerodynamic particle size distribution
CF	cystic fibrosis
CFD	computational fluid dynamics
DPM	discrete phase model
LES	large eddy simulation
MMAD	mass median aerodynamic diameter
MT	mouth- throat
NGI	next generation impaction
Nmu	Newtonian mucus
non-Nmu	non-Newtonian mucus
pMDI	pressurized metered-dose inhaler
RANS	Reynolds-averaged Navier-Stokes
RMSE	root mean square error
SIMPLE	semi-implicit method for pressure-linked equations
TKE	turbulent kinetic energy
IFP	inhalation flow peak

VHC valve-holding chamber

Notations

d_p	particle diameter, [μm]
A_p	particle surface area, [m^2]
d_{ae}	particle aerodynamic diameter, [μm]
y_f	film height, [mm]
$\bar{u}_i$	Favre-filtered velocity, [m/s]
k_s	thermal conductivity, [W/m.k]
C_D	constant drag coefficient, [-]
C_s	Smagorinsky constant, [-]
V_p	particle velocity, [m/s]
$\vec{v}_f$	mean film velocity, [m/s]
V_T	tidal volume, [L]
m_p	particle mass, [kg]
Re_p	particle Reynolds number, [-]
Pr	Prandtl number, [-]
Nu	Nusselt number, [-]
t	time, [s]
g	gravitational acceleration, [m/s^2]
$\vec{g}, \vec{g}_t$	gravity vector, component normal to the surface, [m/s^2]
$\vec{n}$	normal vector, [-]
h	enthalpy, [J/kg]
h_c	convective heat transfer coefficient, [W/m]
h_f	fluid heat transfer coefficient, [W/m]
h_{fg}	latent heat, [J/kg]
q_{rad}	radiation heat flux, [W/m^2]
T_B, T_w, T_f	temperature of boundary, wall, and fluid, [K]
T_{film}, T_s, T_m	temperature of film, surface, film half depth, [K]
$\dot{m}_{vap}$	mass evaporation/condensation rate, [-]

$\vec{q}_s$	momentum sourced term, [-]
m_s	mass source per unit wall area, [-]
t_B	total time for one breath, [s]
c_p	specific heat transfer, [J/kg.K]
p	static pressure, [Pa]
p_{gas}	gas pressure, [Pa]
p_f	film pressure, [Pa]
E	thermal energy, [J]
L	latent heat, [J/kg]
U	velocity of fluid in the shell, [m/s]
Q_{In}	inhalation flow rate, [L/min]
f	breathing frequency, [1/min]
F_i	body force, [N]
F_D	drag force, [N]
$\overline{S_{ij}}$	rate-of-strain tensor, [1/s]
a_1, a_2, a_3	constant of drag coefficient, [-]
n	power-law index, [-]
K	consistency index, [-]
EE	elementary effect, [-]
r_s	Spearman correlation coefficient. [-]
$\dot{q}_p$	heat transfer rate, [-]
$\dot{m}_p$	particle evaporation rate, [-]
B_T	Spalding heat transfer number, [-]

Greek letters

$\vec{\tau}_{fs}$	viscous shear force, [N]
∇_s	surface gradient operator, [-]
μ^*	mean absolute effect, [-]
μ_f	film viscosity, [Ns/m ²]
ρ_f	film density, [kg/m ³]
ρ_p	particle density, [kg/m ³]

τ_p	effective shear stress, [Pa]
γ	shear rate, [1/s]
μ, μ_s, μ_g	dynamic viscosity of mixture, subgrid-scale, and gas, [Ns/m ²]
ρ	air density, [kg/m ³]
σ	surface tension, [N/m]
δ_{ij}	Kronecker delta, [-]
ΔP	pressure drop, [Pa]

7.8 References

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Chapter 8- Concluding Remarks and Future Recommendations

Over the past five decades, human activities have released various harmful gases into the atmosphere, significantly contributing to the rise in lung diseases. Unlike injected medications, which do not directly target the lungs, inhaled drugs delivered as aerosol particles offer several advantages: they minimize systemic side effects, allow for direct absorption into the respiratory system, and provide rapid therapeutic relief. Pressurized metered-dose inhalers (pMDIs) have been developed for this purpose and remain the most commonly used inhalation devices. However, their overall effectiveness is still a topic of ongoing debate. This study explores the key factors that influence drug delivery efficiency, including device orientation and angle, inhalation patterns, and anatomical variations in the human airway. This chapter outlines the primary research methods used and summarizes the major findings of the investigation.

8.1. Effective Use of pMDI: Impact of the Varied Flow Rates and Cone Angles

This study employed computational fluid dynamics (CFD) to investigate the impact of varying flow rates and spray cone angles on aerosol dispersion and the deposition of drug particles within a simplified mouth-throat airway model. The CFD model was validated against published experimental data, providing confidence in the simulation results. The findings revealed that higher flow rates enhanced the deagglomeration of larger particles (5–9 μm), resulting in a finer aerosol distribution. While increased flow rates had little effect on mouth deposition, they significantly decreased throat deposition by creating enough drag forces to propel particles deeper into the airway after their initial momentum diminished. Moreover, the spray cone angle significantly influences deposition patterns, even more so than the flow rate. Moderate cone angles, particularly in the range of 8° to 10°, were found to optimize the distribution of drug particles. This is achieved by minimizing throat deposition and promoting uniform dispersion. In contrast, larger cone angles result in increased deposition on the surfaces of the mouth cavity and the inhaler nozzle, which ultimately decreases the efficiency of drug delivery to the lower airways. These findings are crucial for refining the design of pMDIs and optimizing inhalation strategies to achieve more effective therapeutic outcomes.

Future Recommendations

This study primarily focused on simplified mouth geometries; however, its findings establish a solid foundation for future research and practical applications. Future studies should aim to incorporate more anatomically accurate and patient-specific airway geometries, especially for pediatric and geriatric populations, to better represent variations in drug delivery. Additionally, exploring a wider range of actuation timings and synchronization with inhalation cycles could enhance delivery efficiency. Furthermore, combining CFD with advanced imaging techniques or in vivo measurements could provide deeper insights into the dynamic interactions within the airway.

8.2. The Impact of Relative Humidity and COPD Inhalation Profile on pMDI Drug Delivery

This study examined the effect of realistic breathing conditions and relative humidity on drug aerosol delivery through inhalers, utilizing both experimental and computational methods. Experimental data obtained from an eight-stage Next Generation Impactor (NGI) and a High-Performance Liquid Chromatography (HPLC) system revealed that increasing the flow rate from 30 to 60 *L/min* resulted in a 21% reduction in the mass median aerodynamic diameter (MMAD). This change led to the generation of more fine particles that bypassed the inhaler and reached the downstream collection stages. Additionally, particle deposition on the inhaler's inner surfaces decreased as the flow rates increased. CFD simulations, validated by experimental results, identified key recirculation zones within the mouth-throat region that significantly influenced particle retention and deposition. These effects were particularly notable in response to variations in flow rate and actuation.

The study also found that high humidity levels (99%) decreased drug deposition in the mouth-throat region by stabilizing airflow and enhancing the transport of larger particles. Under chronic obstructive pulmonary disease (COPD) breathing profiles, recirculation zones develop more gradually and with less intensity. This led to weaker aerosol plumes and greater deposition of larger particles compared to conditions with constant flow. These findings underscore the importance of considering actual patient breathing patterns and environmental humidity when evaluating inhaler performance and developing more effective drug delivery strategies.

Future Recommendations

Future research should focus on replacing simplified geometries, like the USP-IP model, with patient-specific or anatomically realistic airway models. This approach would better capture the complex interactions between airflow, anatomy, and drug particles. Additionally, incorporating a mucus layer with realistic properties would enhance the biological accuracy of simulations and provide deeper insight into deposition behavior under various disease conditions. Further studies should investigate the combined effects of actuation timing, particle polydispersity, and humidity on drug delivery performance across different patient profiles, particularly those with obstructive airway diseases. Expanding the range of breathing profiles to include pediatric, geriatric, and effort-dependent patterns would aid in developing more tailored and effective inhalation therapies.

8.3. Pediatric Airflow Patterns and pMDI Drug Delivery: Effects of Mucus Viscosity with Cystic Fibrosis Inhalation Profiles

This study investigated the interaction between inhalation flow rate, mucus viscosity, and actuation timing on aerosol transport and deposition from a pMDI in a pediatric mouth-throat (MT) geometry. Using a combination of numerical simulations and experimental methods, the research employed a validated Large Eddy Simulation-Discrete Phase Model (LES-DPM) for simulations. Deposition data were collected experimentally using a CT-based 3D-printed pediatric airway model integrated with an NGI. Among the three mucus modeling approaches tested—thickness-based, shell conduction, and Eulerian Wall Film (EWF)—the EWF method provided the most realistic representation of the air-mucus interface by enabling both heat and mass transfer. Additionally, it captured the formation of complex recirculation zones and local velocity gradients along the wall, which significantly affected deposition patterns. The flow rate was determined to be the primary factor influencing particle transport. At higher flow rates (15 L/min), a greater number of fine particles exited the airway without being deposited.

Additionally, transient inhalation profiles resulted in wider particle size distributions and increased impaction due to delayed flow stabilization. Larger particles (greater than 10 μm) exhibited consistent deposition behavior across various flow conditions. Further analysis of secondary flow patterns revealed more intense and asymmetrical recirculation zones at higher flow rates, resulting in increased wall shear stress. The presence of non-Newtonian shear-thinning mucus affected airflow dynamics by decreasing viscosity at higher shear rates. This resulted in a reduction in

airway resistance of up to 55% at a flow rate of 15 *L/min* compared to airways without mucus. Although mucus viscosity had a minimal effect on particle deposition in the mouth due to the initial velocity of the particles, it had a significant impact on deeper regions such as the pharynx and trachea. Deposition efficiency is strongly influenced by actuation timing, with synchronized actuation ($t = 0$ s) yielding the highest delivery (approximately 46%), while early or delayed actuation reduces efficiency due to particle loss from inertial impaction. Sensitivity and correlation analyses identified flow rate as the most influential factor ($\mu^* = 18.75$, $r_s = 0.87$), followed by actuation timing ($r_s = -0.47$) and mucus viscosity ($r_s = 0.32$). Although mucus viscosity has a weaker effect on deposition, it still plays a role in modifying secondary flows and wall interactions. Overall, flow rate is the primary driver of deposition, with actuation timing and mucus properties contributing to finer-scale variations. These findings emphasize the importance of patient-specific inhalation profiles and airway conditions in optimizing aerosol drug delivery for pediatric populations.

Future Recommendations

Future research should focus on refining airway modeling by incorporating patient-specific geometries from pediatric populations across various age groups and disease states, particularly those with cystic fibrosis and asthma. Expanding the investigation to include a broader range of mucus rheological properties, such as multi-layered and viscoelastic characteristics, would enhance physiological realism. Additionally, integrating real-time breathing data and simulating patient-specific inhaler use—particularly regarding actuation–inhalation synchronization errors—could improve the application of computational models in clinical practice. Advanced experimental methods, such as phase Doppler anemometry and high-speed imaging, could validate the airflow structures and droplet behavior observed in CFD. Lastly, coupling machine learning techniques with simulation data may help develop predictive tools for optimizing personalized inhaler therapies, especially for vulnerable pediatric patients and those with respiratory challenges.

8.4. Nomenclature

Abbreviation

COPD	chronic obstructive pulmonary disease
CFD	computational fluid dynamics
DPM	discrete phase model
HPLC	high-performance liquid chromatography
LES	large eddy simulation
MT	mouth-throat
NGI	next generation impactor
pMDI	pressurized metered dose inhaler
MMAD	mass median aerodynamic diameter
EWf	Eulerian-wall film