Challenges in Drug Delivery Through Intranasal Route: A CFD Perspective

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Abstract. The paper discusses the various challenges encountered during drug delivery through intranasal routes. It also investigates how the computational fluid dynamics (CFD) is effectively utilized by the researchers in mitigating these challenges and to develop a efficient intranasal drug delivery device.

Keywords: Nasal drug delivery · Nose-mouth-throat (NMT) model · Human respiratory tract (HRT) · Computational fluid dynamics (CFD) · Discrete phase model (DPM)

1 Introduction

Oral and intramuscular drug administration is a common method of drug delivery, although it has a number of drawbacks when compared to the nasal route. Intranasal drug delivery is secure, simpler to use, and can trigger both local and systemic immune function [1]. Most inhaled vaccines delivered as a nasal spray are needle-free, low-cost, do not require refrigeration for storage or shipment, and are self-administered, eliminating the need for healthcare workers and infrastructure facilities [2]. Recently, the scientific community has witnessed a plethora of researches considering various aspects related to COVID-19 viruses and its treatments [3, 4]. Among them, nasal vaccinations are seen as the most promising method for treating COVID-19 that can replace intramuscular vaccination [5].

Intranasal drug delivery devices are also used to treat a variety of brain diseases, such as drug addiction, Alzheimer's disease, eating disorders, depression, anxiety, seizures, Parkinson's disease, and stroke, by delivering drugs directly in the brain through the olfactory tract [6]. It is also used to treat different lung diseases like pulmonary fibrosis, lung cancer, hypertension, asthma, and chronic obstructive pulmonary disease (COPD) [7]. Despite the availability of many devices for drug delivery through the nasal route, there is a lack of efficient equipment for the same. Computational fluid dynamics (CFD) is considered an important tool for the design and development of efficient drug delivery devices including nasal inhalers. The design of nasal inhalers can be efficiently optimized demonstrating the basic feature of drug deposition in the nasal airways and human respiratory tract (HRT) in the lungs with the help of CFD simulation [8]. The paper therefore, discusses the use of CFD in design and development of an effective intranasal drug delivery.

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2 Nasal and Lung Anatomy

The nose, which is the principal entrance into the respiratory tract, allows air to enter the body for breathing [9]. The nasal anatomy and human airways are very important for the study. The internal structure of the nasal cavity is typically complex and has several functions viz. moistening and warming of the inhaled air [10, 11]. The vestibular, turbinate, and olfactory areas are the three primary regions of the nose. Human airways, on the other hand, consists of pharynx, larynx, trachea, and bronchi and is shown in Fig. 1. The pharynx is located behind the nasal cavity and oral cavity called the throat. The air coming from the oral and nasal cavity meets at the same time in the pharynx. The trachea is the windpipe located between the cricoid cartilage ring that is fastened and beginning the bronchial tree. A bronchus is the air passage connected with the trachea with left and right bronchi after bifurcation.

The human lungs have 23 bifurcated junctions [12]. The basic unit of a respiration mechanism where the exchange of the air occurs is known as the alveolar region. The surface of the alveoli bubbles work as a gas exchange membrane. This is the section where the drug particles are deposited and dissolved with blood directly for different types of medications.

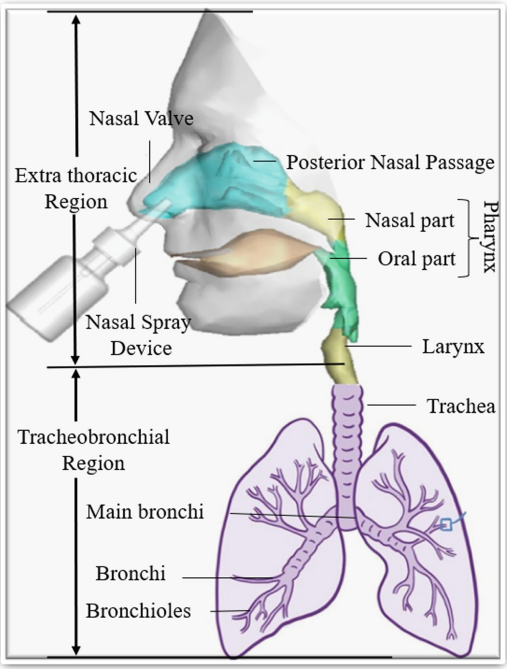

Fig. 1. Deposition of drug particles in the human airways using a nasal inhaler

3 Physiology Influencing Drug Delivery

3.1 Regulation of Nasal Airflow

Almost all living beings breathe through the nose. On an average, 20–30 L/min of air is required during sleep, while exercising or resting and is fulfilled by the nasal route [13]. As the intensity of the workout increases, the excess requirement of air is fulfilled through the oral pathway. Every day, more than 12,000 L of air passes through the nasal route of an adult person. The effectiveness of the nose is achieved through its complicated construction and aerodynamics. Surprisingly, while inspiration, comparatively small air channels in the nasal cavity contribute 50–75% of overall airway resistance [14].

3.2 Nasal Valve and Aerodynamics

The expansion of the human nasal valve (Fig. 1) ranges from the nostril opening to the head of the inferior turbinate, usually 2–3 cm from anterior to the posterior sides. The nasal valve is triangular in shape and it is also called the primary flow-limiting segment [15]. During respiration, this small triangular-shaped slit functions like a dynamic valve, enabling it to change the direction as well as the rate of airflow [16]. Under normal breathing conditions, the airflow velocity is 18 m/s, while in sniffing it reaches to 32 m/s i.e. equivalent to the air speed generated during a hurricane [16]. Flow in the nasal cavity is mainly laminar during rest (flow rate up to 15 L/min). When the flow rate of air increases to 25 L/min downstream of the nasal valve, the flow becomes completely turbulent [16]. As the rate of expiratory flow increases after inhalation, Bernoulli forces gradually cause the valve to narrow. Positive respiratory airway pressure is maintained by valves that act as a brake during exhalation, helping to keep the pharynx and lower airway open and extending the respiratory phase.

The alveoli have more time to exchange gas and retain fluid and heat from the warm, saturated respiratory air because of this braking [17]. In the case of nasal drug delivery, the small dimension of the nasal valve and its triangular shape cause the nose to become narrower during breathing, and hence is posed as a significant barrier to achieve an efficient nasal drug delivery.

4 Targeted Nasal Delivery

A targeted drug delivery system is a smart process of drug delivery at the right place where the drug is required [18]. For the improvement of regeneration procedure, and a controlled medication is required to achieve the targeted drug delivery. Figure 2 shows the factors associated to achieve successful targeted drug delivery system.

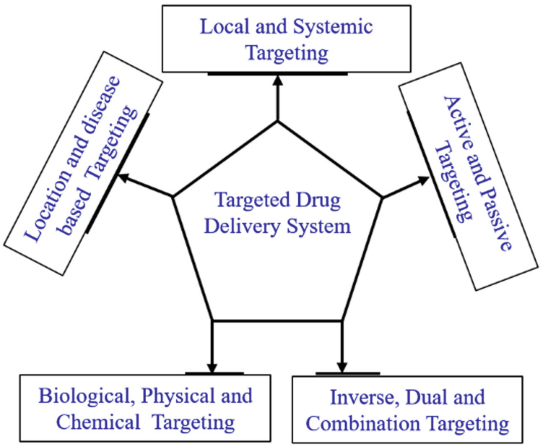

Fig. 2. Different types of targeted drug delivery system

5 Nasal Drug Delivery Devices

Vidgren and Kublik [19] conducted comprehensive study on different types of nasal inhalers available in the market, based on the mechanism of particle delivery and deposition, including the newly designed nasal inhaler embedded with latest technology. Nowadays, liquid formulated nasal inhalers totally dominates in the nasal drug delivery market but powdered formulated nasal devices are also in the existence and many inhalers are in various developmental stages. The following sub-sections furnish brief description and critical analysis of the nasal inhalers both in liquid and powder formulation.

5.1 Devices for Liquid Formulations

The liquid formulated devices contain aqueous solutions and deliver the drug into the nasal cavity in the form of suspensions and emulsions. Devices prepared on the basis of liquid contain aqueous solutions and deliver the drug in the form of suspensions and emulsions into the nasal cavity [19]. Preservatives are often used in conventional spray systems for the maintenance of microbial stability.

5.2 Squeeze Bottles

The application of the squeeze bottles is to dispense the over-the-counter (OTC) medications such as topical decongestants. Atomization of drug particles occurs when drug particles are delivered from a jet outlet by squeezing a plastic bottle partially filled with air. Particle size and the delivered dose depend on the magnitude of the applied force, and after releasing the pressure, the sucking phenomenon of nasal secretion etc. This is however strictly prohibited for the children [20].

5.3 Metered-Dose Spray Pumps

Despite its introduction over four decades ago, metered-dose spray pumps still dominate the nasal medication delivery market. The liquid volume in the metered-dose spray pumps is compensated by using a collapsible bag or compressed gas, for the medicinal drug particles. This device is used for a patient who is lying on a bed with his head down. The contamination of the drug is prevented with the help of the valve with is actuated within the device which makes the device expensive, so researchers suggest preservatives [21]. Recently, side-actuated spray pumps are designed for drug delivery that overcomes the problem of an existing device.

5.4 Single- and Dual-Dose Spray Devices

The dose conformity of meter-dose spray pumps may require priming and overfilling to ensure labelled dosage amounts. Despite their suitability for daily administration over a long period of time, they're not as well suited to medications with a smaller therapeutic window, due to the priming procedure and inability to precisely control the dose. Single-dose or dual-dose spray devices are preferred for expensive or sporadic drugs or vaccines where control of formulation and dosage is of particular importance.

5.5 Nasal Pressurized Metered-Dose Inhalers (pMDI)

The pMDI is an old technology for aerosol generation and drug inhalation. In 1950, Riker Laboratories first introduced the concept of drug inhalation through the use of pressurized container containing drugs, atomized by passing through a nozzle. The effective transfer and deposition of drugs take place only when it is deposited into the small-sized pulmonary tracks of the lungs. β_2 adrenoceptors which absorb the bronchodilator drugs are present preferably in the alveolar region of the lungs so it is necessary to produce particles for the device to be efficient. Since the invention of the pMDIs, the chlorofluorocarbon (CFC) used as a propellant with the drug particles which deplete the ozone layer creates a harmful effect in the environment. In 1987, the Montreal Protocol banned the use of CFCs as propellants in PMDI, and HFAs have been used in place of CFCs since that time [22]. The CFC propelled pMDIs were completely removed from the US market since 2003.

6 Powder Devices

DPI was introduced in the market in 1980, at that time the process of invention and modification is going on. When the device was launched, this device was used to treat various types of lung and oral infections through oral inhalation. The powdered nasal inhaler came into the market to overcome the specific drawbacks of liquid nasal inhalers [23]. Basically, there are three principles involved in the working of the nasal powder inhaler. The first is the method of dispensing the powdered drug, the second is to act the powder with the help of the breath, and the third is the nasal inflators that are attached to both the mouth and the nasal passages. Based on a literature survey, some nasal-based powder inhalers, are critically discussed in the following sub-sections.

6.1 Nasal Powder Inhalers

The use of the additive for the formulation of dry powder inhalers (DPI) improves the deposition and dispersion of the drug particles into the lungs. Powdered inhalers have many advantages such as chemically stable, having no requirement of preservation, and also being free from propellants [24].

6.2 Nasal Powder Sprayer

The principle of the spray powder inhaler depends on the compression of air in the closed container of the inhaler equipment. The air in the chamber is compressed with the applied force and the capsule valve is activated and the powder is dispersed. Single and multiple-dose capsules are used for the medications.

6.3 Nasal Powder Insufflators

The structure of this device looks like a two-bifurcated drinking straw. The first one is used for the inhalation for the medication to the lung and the second one for the nasal medication. Drug delivery into the nasal cavity for dispersion of powder with exhalation by the patient by means of a blowing action with a small tumbler part.

6.4 Bi-directional Breath Powered

Researchers have tried to address the problem of conventional devices for dispersion and deposition of drug particles from the nasal cavity. The mechanism of this device relies on the bidirectional flow of liquid as well as a powder [25]. This is an efficient breath-actuated device as compared to several nasal delivery devices. But further development and innovation of nasal drug delivery devices are required by optimizing various parameters such as flow rate, size of drug particles, angle of release, and profile with targeted drug delivery.

7 Computational Methodology

The computational methodology includes the different governing equations, turbulence modeling, particle transport model, and solver setting. The computational analysis of nasal powder inhalers can be performed by solving the Reynolds Averaged Navier-Stokes (RANS) equation. The RANS equations are as follows:

$$\rho \frac{D\overline{u}_i}{Dt} = \rho g_i - \frac{\partial \overline{P}}{\partial x_i} + \frac{\partial \overline{\tau}_{ij}}{\partial x_j} + \frac{\partial \overline{\tau}'_{ij}}{\partial x_j}$$

Here ρ is the fluid density, $\overline{u}$ is the mean flow velocity, g is the gravitational acceleration, $\overline{P}$ is the mean pressure, is the Newtonian shear stress $\bar{\tau}_{ij} = -\rho\overline{\acute{u}_i\acute{u}_j}$ is the Reynolds stress. This equation along with the continuity equation are discretized using various numerical schemes available in the finite volume method to solve the equations on a

computational grid generated [26]. Appropriate use of boundary conditions like compliant walls [27], inhalation pattern [28] are necessary to get the realistic results in any biological flows.

Turbulence can be modelled by incorporating $k-\omega$ SST turbulence model with low Re number correction. This model provides good accuracy for low-speed interior flows subjected to boundary layer separation and swirl-dominated flows. Literature review showed that most of the CFD analysis of nasal inhalers utilized this turbulence as it predicts the physics of the flow accurately, the near-wall node was kept at a y^+ less than 10. This can be done by adapting the meshing which resulted in localized refinement of meshing in certain regions, and ensured, that y^+ criteria are met and all the residuals are less than 10^{-5} [29].

The volume fraction of drug particles in the flow is verysmall, and therefore,CFD simulations can be performed using discrete phase model (DPM) for tracking of a particle of drug particle and

$$\frac{\partial u_p}{\partial t} = F_D(u - u_p) + \frac{g(\rho_p - \rho)}{\rho_p}$$

Here, F_D represents the drag force, u, ρ, and μ has represented the velocity, density, and dynamic viscosity of the air. u_p, ρ_p and μ_p represent the velocity, density, and dynamic viscosity of the drug particle, respectively. Several researchers have performed DPM simulation to study the drug deposition in the HRT via oral [30, 31] and nasal [31] passages.

8 CFD Findings

Kleven et al. [8] used CT-scan nose model and generated a triangular computational grid for the CFD study. They optimized the nasal drug delivery device and observed that the CFD technique helped to improve the efficiency of the nasal inhaler and also reduced the need for costly laboratory for experimentation.

Longest et al. [33] constructed a nose-mouth-throat (NMT) model from the CT-scan image data. They used at the tetrahedral meshing on the surface of the NMT model and adopted pentahedral meshes near the wall. The low Reynolds number (LRN) k-ω turbulence model was used for the study while increasing the inlet temperature of aerosol delivery from 21 °C to 35 °C followed by enhanced condensational growth (ECG) conditions. They reported that the ECG method could improve lung deposition of nasally administered aerosols under conditions consistent with non-invasive ventilation.

Inthavong et al. [34] constructed a nasal cavity and sixth-generation lung airway model based on CT-scan data, and observed the deposition of the nanoparticle in the human airways with the help of two CFD methods- Eulerian and Lagrangian approaches. The transportation of nanoparticle size ranging from 1 to 10 nm was used for the simulation under laminar condition by using the Eulerian approach. A Lagrangian approach was also used to predict individual particle motion which is based on force equilibrium that includes various types of forces such as inertia, lift, thermophoretic and Brownian motion. The authors confirmed deposition of large amounts of nanoparticles in the nasal cavity.

Longest et al. [35] also constructed a realistic model of the entire airway from the nose-mouth-throat (NMT) region to the upper trachea-bronchial region with the chambers as realistic as the human airway. They performed an in-vitro experiment to predict the performance of the inhaler and to validate these results with the computational results. Finally, realistic boundary conditions cannot be created in an in-vitro model, it is only explored with help of CFD model. The authors evaluated nasal-to-lung drug delivery with the excipient enhanced growth (EEG) formulation via inline DPI along the respiratory tract.

Calmet et al. [36] constructed a CT-scan model that consists ofnose, mouth and lung airways up to third-generation. CFD simulation was performed using realistic geometry of NMT to lung airways with computationally précised mesh and identified the probable location of human airway infection. They adopted different sized unstructured mesh and the finite element for the simulation. The authors investigated unsteady flow dynamics in human airways by introducing large-scale computational modeling along with large eddy simulation (LES) during rapid inhalation.

Inthavong et al. [37] constructed a CT-scan model from nasal cavity to nasopharynx. They obtained the consistent flow pattern by varying geometrical parameters of the models and at the nasal valve portion. In another study, Inthavong et al. [34] constructed a CT-scan nasal cavity model and described the importance of the y^+ parameter at the near-wall boundary layer in a laminar flow (Poiseuille flow). The researchers advocated the use of appropriate grid sizes at the right location (such as near the wall area) to produce efficient results even with the limited computational resources and concluded that the airflow velocity magnitude curve was found to be sensitive to mesh size near the boundary.

Bass et al. [38] constructed an infant nose and throat model with the inhaler with the help of CT-scan data and polyhedral and tetrahedral mesh generated for the analysis and calculated y^+ value. They used the LRN k-ω turbulence model for the deposition of the particle in the lung for transitional and turbulent flows. The in-vitro experimental data was compared with the computationally simulated data of nose-to-lung administration and proposed a guideline for a computationally efficient model for the infants. The researchers worked to develop a highly efficient nose-to-lung aerosol drug delivery device for the infants.

Recently, Dutta et al. [39] constructed an adult NMT model connected with a third-generation human airways with a nasal inhaler. They adopted the polyhedral mesh, used LRN k-ω turbulence modelfor transitional and turbulent flows. A combination of appropriate aerosol synchronization and small particle size allowed for efficiently distribution of aerosol from nose-to-lung that was not affected by inhalation flow rate.

9 Conclusions

Based the availability of the literature, it is found that most of the researchers worked on the distribution and deposition pattern of drug particles into the nasal cavity and in the human respiratory tract (HRT). They constructed the nasal cavity and HRT model by using CT-scan data. Bass et al. [38] and Dutta et al. [39] used complete pulmonary model connecting NMT to the HRT to predict the deposition and distribution of the drug

taken from nasal route. Some researchers reported that with the help of CFD laced with optimization techniques, the efficiency of nasal inhalers can be improved [40]. But only a few articles are available that worked on the design modification of inhalers. From the above findings, it is concluded that the efficiency of the nasal inhalers can be improved with the help of the design modification in the nasal inhaler.

Two distinct types of air motions are envisaged from the CFD studies of all nasal inhalers reported in the literature. The first category is dominated by swirling motion of airflow while the second category is predominantly with axial flow having less swirl motion. For the drug to penetrate deep into the lungs it is desired that the airflow at the nasal inlet to have swirl as it is able to deliver a significant amount of drug. As seen from the literature, the inhalers with less swirl was more efficient than those with swirl airflow. For best performance, that high amount of drug penetrates deeper into the lungs with no significant losses in the device.

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Authors' Contributions. AT: Wrote the manuscript, figures, tables.
ARP: Conceived the idea.
AJ: Review, Editing.

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