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The Comprehensive Review: Exploring Future Potential of Nasopulmonary Drug Delivery Systems for Nasal Route Drug Administration

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Abstract

This comprehensive review aims to explore the future potential of nasopulmonary drug delivery systems for the administration of drugs through the nasal route. Nasal drug delivery has gained significant attention due to its numerous advantages, including rapid absorption, avoidance of first-pass metabolism, and non-invasive administration. This review provides an overview of the nasal anatomy and physiology, highlighting the factors influencing drug absorption and bioavailability. Additionally, it discusses the various types of nasopulmonary drug delivery systems, such as nasal sprays, powders, and gels, along with their advantages and limitations. Furthermore, the review delves into the challenges associated with nasal drug delivery, including mucociliary clearance, nasal irritation, and formulation issues. The potential applications of nasopulmonary drug delivery systems in the treatment of various diseases, such as allergies, respiratory disorders, and systemic conditions, are also discussed. Finally, the review concludes with an outlook on the future prospects of nasopulmonary drug delivery systems, emphasising the need for further research and development to optimise their efficacy and safety.

Keywords: nasal pulmonary; nasal spray; nasal mucosa; gels; drops; nasal approaches; nasal route; nasal delivery.

1. INTRODUCTION: NASOPULMONARY DRUG DELIVERY SYSTEM (NPDDS)

In recent years, the nasopulmonary drug delivery system has emerged as a promising approach for the efficient delivery of drugs through the nasal route. This comprehensive review aims to explore the future prospects of this innovative drug delivery system, highlighting its potential applications and benefits.

Naso-pulmonary drug delivery systems (NPDDS) are non-invasive methods of administering drugs through the nose and into the lungs. These systems offer several advantages over traditional oral and injectable drug delivery methods, including rapid absorption as the large surface area and high vascularity of the nasal and pulmonary mucosa allow for rapid absorption of drugs into the bloodstream; avoidance of first-pass metabolism as drugs administered through the NPDDS bypass the liver, which means they are not subjected to first-pass metabolism, a process that can reduce the bioavailability of certain drugs; targeted delivery as the NPDDS can be used to target drugs directly to the lungs, which is particularly beneficial for the treatment of respiratory diseases; ease of administration as NPDDS are relatively easy to administer, making them a good option for patients who are unable or unwilling to take oral or injectable medications [1,2].

NPDDS are typically administered using nasal sprays, inhalers, or nebulizers. The type of device used depends on the drug being administered and the desired site of action. The several drugs that are commonly administered using NPDDS are asthma medications as inhaled corticosteroids, bronchodilators, and leukotriene inhibitors are all commonly used to treat asthma; nasal decongestants as nasal sprays containing decongestants can be used to relieve nasal congestion caused by allergies or the common cold; Migraine medications as Sumatriptan is a migraine medication that can be administered as a nasal spray; hormone replacement therapy as estrogen and testosterone can be administered as nasal sprays for hormone replacement therapy [3-5].

1.1. The Mechanism of Drug Delivery in Nasal Drug Delivery System

Drug absorption through the nasal route involves the passage of drugs across the nasal mucosa, a highly vascularized and permeable membrane lining the nasal cavity. The nasal mucosa offers a large surface area and direct access to the bloodstream, making it an attractive route for drug delivery. The mechanism of drug delivery in nasal drug delivery systems involves several key steps aimed at facilitating the efficient transport of drugs from the nasal cavity into systemic circulation or to target sites within the respiratory tract [6]. Upon administration, the drug formulation is typically delivered as a liquid spray or a powder into the nasal cavity. The drug then comes into contact with the nasal mucosa, which is rich in blood vessels and offers a large surface area for drug absorption. Various factors influence drug absorption in the nasal mucosa, including drug physicochemical properties, formulation characteristics, and the integrity of the nasal epithelium.

Once absorbed, drugs can enter systemic circulation directly through the highly vascularized nasal mucosa, bypassing first-pass metabolism in the liver. Alternatively, drugs may be transported via the olfactory or trigeminal nerves to reach the central nervous system or other target sites within the respiratory tract. Nasal drug delivery systems can also facilitate targeted delivery of drugs to specific regions within the nasal cavity or lungs, thereby enhancing therapeutic efficacy while minimizing systemic side effects [7-8]. The mechanism of drug delivery in nasal drug delivery systems thus involves a complex interplay of factors governing drug absorption, distribution, and targeting within the nasal and pulmonary regions, ultimately influencing drug bioavailability, pharmacokinetics, and therapeutic outcomes. The mechanism of transport process discussed in the given **Fig. 1** as below followings:

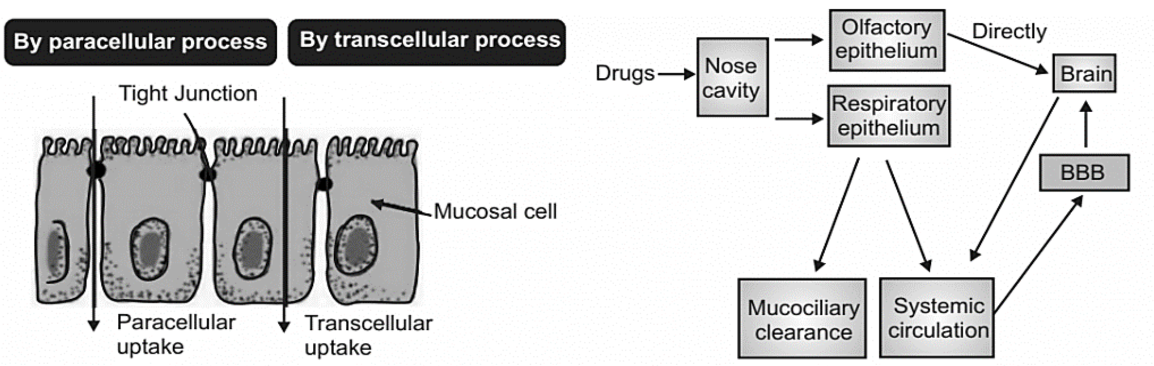

Figure 1: The mechanistic representation of nasal drug delivery system [7].

The drugs molecule can cross the nasal mucosa via two main pathways:

Transcellular Pathway: Lipophilic drugs, which can dissolve in the lipid bilayer of cell membranes, preferentially take this route. They pass directly through the epithelial cells lining the nasal mucosa.

Paracellular Pathway: Hydrophilic drugs, which cannot easily penetrate the cell membrane, primarily use this pathway. They pass through the spaces between the epithelial cells [9-10].

Table 1: The list of mechanism of Nasal Drug Delivery System

Mechanism	Description
Transcellular Pathway	Lipophilic drugs pass directly through the epithelial cell membranes.
Paracellular Pathway	Hydrophilic drugs pass through the spaces between epithelial cells.

The various marketed drug products widely used in the treatment of nasal delivery via different types of mechanism pathways discussed in the given **Table 2** as below followings:

Table 2: The list of marketed products depends on their mechanism of absorption [9-11]

Marketed Nasal Drug	Therapeutic Uses	Mechanism of Absorption
Oxymetazoline (Afrin)	Nasal decongestant	Transcellular and paracellular
Sumatriptan (Imitrex Nasal Spray), Desmopressin (DDAVP)	Treatment of Migraine, diabetes insipidus (DI) treatment	Transcellular
Azelastine (Astelin), Fluticasone propionate (Flonase), Beclomethasone dipropionate (Beconase), Budesonide (Rhinocort)	Allergy medication	Transcellular and paracellular
Nitroglycerin (NitroMist), Morphine (Rylomine), Midazolam (Nayzilam), Calcitonin (Miacalcin)	Treatment of angina, pain, seizure emergencies, osteoporosis	Transcellular

Factors Affecting Nasal Drug Absorption

Drug Properties: Lipophilicity, molecular weight, and solubility of the drug affect its ability to cross the nasal mucosa.

Nasal Mucosa: The thickness and permeability of the nasal mucosa can vary depending on age, health conditions, and environmental factors.

Formulation: The pH, viscosity, and osmolarity of the drug formulation can impact drug absorption and nasal tolerability [8-12].

1.2. Advantages Over Conventional Delivery Routes:

Nasal drug delivery systems offer several advantages over conventional delivery routes, contributing to their increasing popularity and utility in pharmaceutical formulations. Nasal drug delivery systems offer numerous advantages over conventional delivery routes. They provide a rapid onset of action, bypass first-pass metabolism, and offer non-invasive administration, improving patient compliance. Additionally, nasal delivery allows for targeted and localized drug delivery, reducing systemic side effects. With ease of administration and suitability for a variety of drugs, including peptides and proteins, nasal delivery systems represent a valuable alternative for achieving enhanced drug efficacy and therapeutic outcomes. These advantages include:

Rapid Onset of Action: Nasal drug delivery provides a rapid onset of action due to the rich vasculature and thin mucosal membrane in the nasal cavity, allowing for quicker absorption and therapeutic effect compared to oral administration.

Avoidance of First-Pass Metabolism: Drugs delivered via the nasal route bypass first-pass metabolism in the liver, leading to higher bioavailability and more consistent plasma concentrations compared to oral administration.

Non-Invasive Administration: Nasal drug delivery is non-invasive and typically well-tolerated, making it suitable for patients who may have difficulty swallowing pills or require frequent dosing.

Ease of Administration: Nasal drug delivery is simple and convenient, often requiring minimal patient effort and no specialized equipment for administration, which can improve patient compliance.

Localized Drug Delivery: Nasal drug delivery allows for targeted delivery of drugs to specific regions within the nasal cavity or lungs, minimizing systemic exposure and reducing the risk of systemic side effects [10-14].

The advantages of nasal drug delivery systems over conventional delivery routes make them a valuable option for delivering a wide range of drugs, particularly those requiring rapid onset of action, avoidance of first-pass metabolism, or targeted delivery to specific sites within the respiratory tract or systemic circulation.

1.3. The Theories of Nasopulmonary Drug Delivery System

Nasopulmonary drug delivery refers to the administration of drugs through the nasal route, targeting both the upper respiratory tract (nasal cavity) and lower respiratory tract (lungs). This approach offers several advantages such as rapid onset of action, avoidance of first-pass metabolism, and non-invasive delivery. There are 5 theory based on pulmonary drug delivery system. These 5 theories are considered for the pulmonary drug delivery route for delivery of the drug medicament:

Electronic Theory

Adsorption Theory

Wetting Theory

Diffusion Theory

Fracture Theory

The theories underlying nasopulmonary drug delivery systems encompass various principles aimed at optimizing drug deposition, absorption, and efficacy in both the nasal and pulmonary regions. One prominent theory involves the concept of mucociliary clearance, which governs the movement of mucus and particles across the respiratory epithelium. Nasal drug delivery systems must overcome this clearance mechanism to ensure sufficient drug retention and absorption in the nasal cavity, while pulmonary drug delivery systems must account for clearance mechanisms in the lungs to achieve optimal drug deposition and retention. Another theory revolves around particle size and aerodynamic behavior, emphasizing the importance of optimizing particle size distribution and aerodynamic properties to facilitate efficient drug delivery to both the nasal and pulmonary regions [13-16]. These theories are discussed in **Table 3** as mentioned below.

Table 3: The list and description of theory of pulmonary drug delivery system with its application and marketed drug[16]

Theory	Description	Applications	Marketed Drugs
Electronic Theory	Interaction between drug particles and lung surfactant based on electronic properties.	Predict dispersion and stability of inhaled drug particles in lung lining fluid.	TOBI Podhaler (tobramycin inhalation powder)
Adsorption Theory	Adhesion of drug particles to lung surface based on intermolecular forces.	Design drug formulations with optimal surface properties for enhanced lung retention.	Respimat (tiotropium bromide inhalation spray)
Wetting Theory	Spreading of drug particles on lung surface based on surface tension and contact angle.	Develop drug formulations that spread effectively on lung surface for improved drug absorption.	Spiriva HandiHaler (tiotropium bromide inhalation powder)
Diffusion Theory	Movement of drug molecules from lung surface into bloodstream based on concentration gradients.	Optimize drug release profiles and achieve sustained drug delivery to lungs.	Advair Diskus (fluticasone propionate/salmeterol inhalation powder)
Fracture Theory	Breakdown of drug particles into smaller fragments due to mechanical forces in lungs.	Develop drug formulations that withstand mechanical stress and maintain integrity for effective drug delivery.	Pulmicort Flexhaler (budesonide inhalation powder)

These are the 5 theories for the drug absorption and drug delivery to the particular disease treatment with their some marketed drug products in **Table 3** above mentioned. Additionally, theories related to drug solubility, permeability, and formulation characteristics play a crucial role in nasopulmonary drug delivery, guiding the design of formulations that can enhance drug solubility, permeation across mucosal barriers, and targeted delivery to specific regions within the respiratory tract [17].

2. NASAL ROUTE ADMINISTRATION: THE STRUCTURE & COMPOSITION OF NASAL CAVITY

"Nasal route administration" refers to the delivery of drugs or therapeutic agents through the nasal cavity for systemic or local effects. This route offers several advantages over traditional oral or injectable routes, including rapid onset of action, avoidance of first-pass metabolism in the liver, and non-invasiveness. The nasal cavity provides a large surface area with rich blood supply, allowing for efficient drug absorption directly into the systemic circulation. Additionally, the nasal mucosa contains various enzymes and transporters that can facilitate drug uptake and distribution. Nasal administration is particularly useful for drugs that are poorly absorbed orally, sensitive to enzymatic degradation in the gastrointestinal tract, or require rapid onset of action [18]. The various dosage forms such as solutions, suspensions, nasal sprays, powders, and gels can be formulated for nasal delivery, depending on the physicochemical properties of the drug and desired therapeutic outcomes.

The nasal cavity **Fig.2** is a complex anatomical structure located between the nostrils (nares) and the nasopharynx, serving various functions including respiration, olfaction (sense of smell), and filtration of airborne particles. Its structure and composition play a crucial role in nasal drug delivery. Here's an overview of the structure and composition of the nasal cavity:

Nasal Vestibule: This is the most anterior part of the nasal cavity, lined with skin containing hair follicles and sebaceous glands. The presence of hair helps in filtering larger particles from the inspired air.

Nasal Septum: The nasal cavity is divided into two halves by the nasal septum, composed of cartilage anteriorly and bone posteriorly. The septum is lined with a mucous membrane and contains blood vessels.

Nasal Turbinates (Conchae): There are three pairs of nasal turbinates (superior, middle, and inferior) on each side of the nasal cavity. These bony projections covered with vascular mucosa increase the surface area of the nasal cavity and help in humidifying, warming, and filtering inspired air.

Nasal Mucosa: The nasal cavity is lined with respiratory mucosa, which consists of pseudostratified ciliated columnar epithelium. This mucosa contains various cell types, including ciliated cells, goblet cells (mucus-producing), basal cells, and brush cells. The mucus layer traps and removes foreign particles and pathogens, while ciliary movement propels them toward the pharynx for swallowing or expectoration.

Blood Supply: The nasal cavity receives a rich blood supply from branches of the internal and external carotid arteries. The extensive vasculature in the nasal mucosa facilitates rapid absorption of drugs administered intranasally.

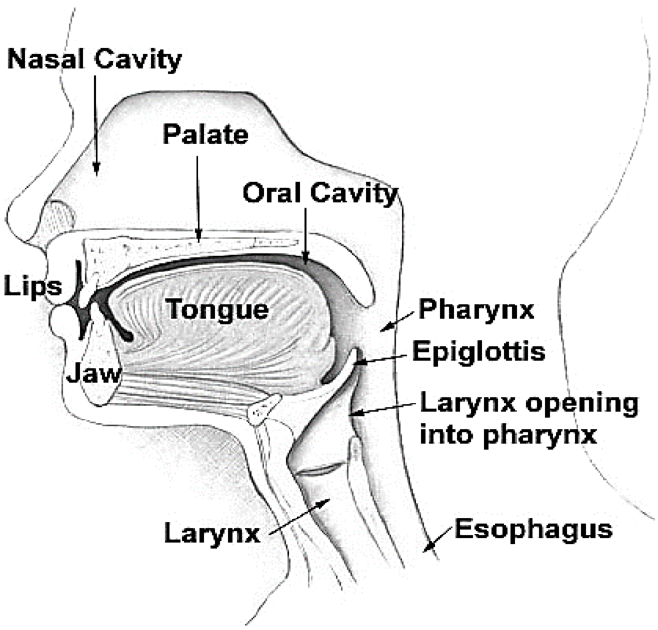

Figure 2: The structural representation of nasal cavity [19].

Nerves: The nasal cavity is innervated by branches of the trigeminal nerve (CN V), which is responsible for sensation (touch, pain, temperature) and reflexes such as sneezing and nasal congestion.

Olfactory Region: The superior aspect of the nasal cavity contains the olfactory region, where olfactory receptors responsible for the sense of smell are located. This region is lined with specialized olfactory epithelium containing olfactory sensory neurons.

Nasopharynx: The posterior part of the nasal cavity opens into the nasopharynx, connecting the nasal cavity to the throat (oropharynx). This region serves as a common pathway for air and food, as well as for drainage of the nasolacrimal ducts [17-20].

The structure and composition of the nasal cavity is essential for designing nasal drug delivery systems that can effectively bypass the nasal mucosal barrier and achieve targeted drug delivery to the desired sites within the respiratory system. Various factors such as nasal physiology, mucociliary clearance, and epithelial permeability influence the efficiency of nasal drug absorption and ultimately determine the pharmacokinetics and therapeutic efficacy of intranasally administered drugs.

2.1. *Factors Influencing Drug Absorption and Bioavailability:*

Nasal drug delivery offers several advantages, such as rapid onset of action, avoidance of first-pass metabolism, and non-invasive administration. The absorption and bioavailability of drugs delivered via the nasal route can be influenced by various factors mentioned in the given **Table 4** as below followings:

Table 4: The list of factors influencing drug absorption and BA [21]

Factors	Description
Physicochemical Properties of the Drug	Molecular weight, lipophilicity/hydrophilicity, solubility, and pH of the drug formulation.
Nasal Mucosal Factors	Surface area and permeability, mucociliary clearance, and nasal blood flow.
Formulation Factors	Excipients (e.g., absorption enhancers, viscosity modifiers), particle size, and formulation pH.
Device Design and Administration Technique	Spray pattern, nasal anatomy, and administration technique.
Patient-related Factors	Nasal pathology, individual variability, and compliance with dosing regimen.
Drug Interactions	Interactions with endogenous substances or other drugs.
Disease State	Conditions affecting nasal mucosa and systemic diseases affecting blood flow or mucosal integrity.
Metabolism and Clearance	Metabolism within the nasal mucosa, drug clearance mechanisms within the nasal cavity.

The each of these factors can significantly influence the effectiveness of nasal drug delivery systems by affecting the absorption and bioavailability of the drug.

2.2. Challenges and Limitations:

Nasal drug delivery presents a promising alternative for drug administration, yet it encounters several challenges and limitations. One significant limitation is the potential for nasal mucosal irritation caused by certain drugs or formulations, leading to discomfort and non-compliance among patients. Additionally, nasal congestion poses a challenge by reducing the available surface area for drug absorption and altering mucociliary clearance mechanisms, thus affecting drug delivery efficiency. Variable absorption rates among individuals further complicate nasal drug delivery, influenced by factors such as nasal anatomy, mucosal thickness, and blood flow. The rapid clearance of drugs from the nasal cavity by mucociliary action and swallowing limits the duration of drug action, while nasal discomfort, sneezing, or dryness may occur as side effects, affecting patient acceptability. Furthermore, the limited dosage volume that can be administered in a single dose due to the restricted space within the nasal cavity presents another constraint [20-22]. Nasal delivery devices must be used correctly for effective drug deposition and absorption, adding another layer of complexity. Nasal pathologies such as congestion or inflammation can impair drug absorption, while ensuring drug stability within nasal formulations is crucial to prevent degradation.

3. ADVANCEMENTS IN NASOPULMONARY DRUG DELIVERY SYSTEMS

3.1. Formulation Strategies for Enhanced Drug Delivery: The several types of dosage form for the drug delivery to particular disease treatment. Inhalers are medical devices used to deliver medication directly to the lungs, providing a targeted and effective treatment for various respiratory conditions, such as asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis [23]. They offer several advantages over oral or injectable medications, including rapid onset of action, reduced systemic side effects, and improved patient compliance. Inhalers come in different types, each with its own mechanism of action, advantages, and limitations. The three main types of inhalers are:

Types of Inhaler formulations: There are basically 3 types of inhalers as follows:

Metered Dose Inhalers (MDIs): MDIs **Fig. 3** deliver a pre-measured dose of drug in a propellant-driven spray. They are commonly used for asthma and chronic obstructive pulmonary disease (COPD) medications.

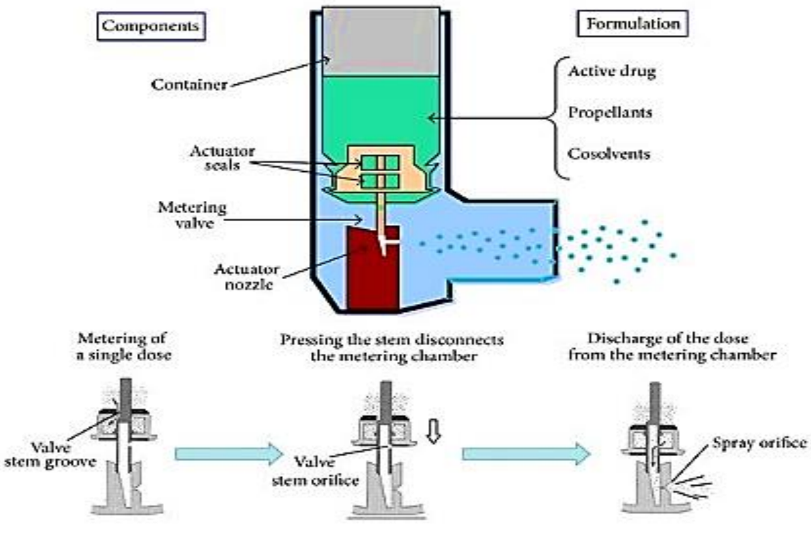

Figure 3: The compositional parts of meter dose inhalers [22].

Dry Powder Inhalers (DPIs): DPIs deliver a dry powder formulation that is dispersed by the patient's inspiratory effort. They are often used for drugs that are unstable in solution or sensitive to propellants.

Nebulizers: Nebulizers generate a fine mist of drug solution or suspension that is inhaled over a longer period. They are typically used for patients with severe respiratory conditions or those who cannot use MDIs or DPIs effectively [23-25].

The different types of formulation as per their dosage form and mode of action (MOA) discussed in the given **Table 5** as below mentioned:

Table 5: The types of inhalers with its Mechanism of action (MOA) and marketed products [23]

Inhaler Type	MOA	Marketed Examples
Metered Dose Inhalers (MDIs)	Delivers a pre-measured dose of medication in a propellant-driven spray.	ProAir HFA, Ventolin HFA, Flovent HFA
Dry Powder Inhalers (DPIs)	Delivers a dry powder formulation that is dispersed by the patient's inspiratory effort.	Advair Diskus, Breo Ellipta, Spiriva HandiHaler
Nebulizers	Generates a fine mist of medication that is inhaled over a longer period.	Pari Trek S Portable Nebulizer, Philips Respironics InnoSpire Essence Nebulizer, Omron MicroAIR Nebulizer

These are the some important marketed products with the different types of inhalers in the formulation as per the **Table 5** with discussed briefly.

3.2. *Novel Drug Delivery Devices and Technologies:*

The several novel drug delivery devices and technologies have been developed to enhance drug delivery to the nasal and pulmonary regions. The some of them as examples discussed below followings:

Nasal Sprays with Microfluidic Systems: Microfluidic systems integrated into nasal spray devices allow for precise control over droplet size and distribution, optimizing drug deposition and absorption in the nasal cavity.

Nasal Powder Inhalers: These devices deliver powdered formulations directly to the nasal mucosa, offering advantages such as improved stability of drugs and enhanced patient convenience compared to traditional liquid nasal sprays.

Nasal Drug Delivery Systems with Nanotechnology: Nanoparticle-based nasal drug delivery systems offer controlled release and targeted delivery of drugs to specific regions within the nasal cavity, improving bioavailability and therapeutic efficacy.

Nasal Inserts and Implants: These devices are placed inside the nasal cavity to provide sustained drug release over an extended period, offering a convenient and non-invasive alternative to frequent dosing.

Nasal Aerosol Devices with Vibrating Mesh Technology: Vibrating mesh technology generates fine aerosol particles with a narrow size distribution, improving drug deposition in the nasal cavity and enhancing drug absorption.

Nasal Pumps with Smart Inhaler Technology: Smart inhaler technology integrated into nasal pumps allows for real-time monitoring of drug delivery parameters such as dose, frequency, and patient adherence, facilitating personalized treatment regimens [26].

The different of others, the nasal spacer devices attached to nasal spray pumps help optimize drug delivery by controlling the spray pattern and reducing nasal deposition variability, ensuring consistent and efficient drug absorption. Nasal delivery systems with mucoadhesive formulations adhere to the nasal mucosa, prolonging contact time and enhancing drug absorption, thereby improving therapeutic outcomes. Pulmonary drug delivery devices with dry powder inhalers (DPIs), DPIs deliver drug formulations directly to the lungs in the form of dry powder, offering improved stability and ease of use compared to traditional nebulizers and nasal delivery systems with inhaled corticosteroids (ICS), ICS formulations delivered via nasal sprays or inhalers are used to treat respiratory conditions such as asthma and chronic obstructive pulmonary disease (COPD), providing localized anti-inflammatory effects with reduced systemic side effects [24-26]. These novel drug delivery devices and technologies hold great promise for improving the efficacy, safety, and patient adherence of nasal and pulmonary drug delivery systems, offering innovative solutions for the treatment of various respiratory and systemic diseases.

3.3. *Formulation approaches in Nasopulmonary drug delivery system:*

These are the most common formulation approaches in naso-pulmonary drug delivery system. These are listed as below follows:

- ***Nasal Gels***
- ***Nasal Drops***
- ***Nasal Sprays***
- ***Nasal Powders***
- ***Liposomes***
- ***Microspheres***

Formulation approaches in nasopulmonary drug delivery systems aim to optimize drug efficacy and patient compliance by addressing the unique challenges associated with delivering drugs to both the nasal and pulmonary regions. One approach involves designing multifunctional formulations that can efficiently target both sites of delivery. For instance, nanoparticle-based formulations can be engineered to encapsulate drugs and facilitate their transport across mucosal barriers in the nasal cavity while also enabling deposition and absorption in the lungs upon inhalation [27-29]. These approaches are discussed in **Table 6** in details as follows:

Table 6: The several formulation approaches in naso-pulmonary drug delivery system with its example, disadvantages and strategies to overcome the disadvantage[28]

Formulation Approach	Applications	Marketed Examples	Strategies to Overcome Disadvantage
Nasal Gels	Prolonged drug release and residence time in the nasal cavity	Mucinex Sinus-Max Full Force Nasal Gel	Use of biocompatible and less viscous gelling agents
Nasal Drops	Simple and convenient administration for small volumes	Otrivin Nasal Drops, Afrin Nasal Drops	Use of droppers with precise dosing mechanisms
Nasal Sprays	Widely used for various drugs due to ease of administration	Flonase Nasal Spray, Nasonex Nasal Spray	Use of mucoadhesive polymers or controlled-release formulations
Liposomes	Enhance drug absorption and bioavailability	None currently marketed for nasal delivery	Use of stable liposome formulations with controlled release properties
Microspheres	Controlled drug release and targeted delivery	None currently marketed for nasal delivery	Use of biocompatible and biodegradable microspheres with optimal particle size distribution

These are the some formulation approaches in the naso-pulmonary drug delivery system as per (**Table 6**) their marketed applications of products including their various applications.

3.4. *The evaluations of naso-pulmonary drug delivery system:*

The several types of evaluations conducted for the naso-pulmonary drug dosage forms. The evaluation of naso-pulmonary drug delivery systems involves a multifaceted approach to assess their efficacy, safety, and feasibility for clinical application. Firstly, the physicochemical properties of the drug formulation are scrutinized to ensure optimal aerosolization and deposition within the respiratory tract. Techniques such as cascade impaction are employed to characterize particle size distribution and aerodynamic behavior, which are critical determinants of deposition efficiency and lung penetration [28-31].

Secondly, preclinical studies are conducted to investigate the pharmacokinetics and pharmacodynamics of the delivered drug. Animal models are utilized to assess systemic absorption, tissue distribution, and drug clearance following nasal administration. Additionally, efficacy studies in relevant disease models provide insights into the therapeutic potential of the drug delivery system. The various evaluations shown as per the **Table 7** as below followings:

Table 7: The several list of evaluation of naso-pulmonary drug delivery system [29-31]

Parameter	Description	Procedure	Equation
Fine Particle Fraction (FPF)	Represents the percentage of particles with an aerodynamic diameter less than 5 micrometers, which are more likely to reach the lower airways.	Calculated from the APSD data.	**FPF = (Mass of particles < 5 µm) / (Total mass of particles) x 100%**
Emitted Dose (ED)	Represents the total amount of drug released from the device.	Measured using a dose collection chamber or gravimetric analysis.	**ED = (Mass of drug collected) / (Number of actuations)**
Delivered Dose (DD)	Represents the amount of drug that reaches the patient's lungs.	Measured using a breathing simulator or in vivo techniques.	**DD = (Mass of drug deposited in lungs) / (Number of actuations)**
Drug Content Uniformity (DCU)	Assesses the consistency of drug content in individual doses.	Measured using high-performance liquid chromatography (HPLC) or other analytical methods.	**DCU = (Standard deviation of drug content) / (Mean drug content) x 100%**
In vitro/In vivo Correlation (IVIVC)	Establishes a relationship between in vitro performance parameters (e.g., APSD, FPF) and in vivo pharmacokinetic parameters (e.g., drug concentration in plasma).	Statistical analysis is used to correlate in vitro and in vivo data.	**-**

These are the discussed evaluations of naso-pulmonary drug delivery vesicles in above **Table 7** as per the directions of the evaluations. Clinical trials play a pivotal role in validating the performance of naso-pulmonary drug delivery systems in human subjects. Pharmacokinetic assessments determine drug absorption, bioavailability, and pharmacokinetic parameters in vivo. Additionally, efficacy trials evaluate the therapeutic outcomes and disease management potential of the drug delivery system in patient populations. The safety monitoring ensures the identification and management of any adverse events or side effects associated with nasal administration [32,33].

Furthermore, patient-centered evaluations gauge the acceptability and usability of naso-pulmonary drug delivery systems from the end-user perspective. Patient-reported outcomes, preference surveys, and usability testing provide valuable insights into patient acceptance, satisfaction, and adherence to the delivery system.

4. POTENTIAL APPLICATIONS OF NASOPULMONARY DRUG DELIVERY SYSTEMS

Nasopulmonary drug delivery systems hold significant promise for a wide range of therapeutic applications due to their ability to efficiently target both the upper and lower respiratory tract. One potential application lies in the treatment of respiratory diseases such as asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis. Nasopulmonary drug delivery systems (NDDS) have a wide range of potential applications, including:

Local delivery to the nose and lungs: NDDS can be used to deliver drugs locally to the nose and lungs to treat a variety of respiratory conditions, such as asthma, COPD, allergies, and infections.

Systemic delivery: NDDS can also be used to deliver drugs systemically, meaning that the drugs are absorbed into the bloodstream and distributed throughout the body. This can be useful for delivering drugs that are poorly absorbed from the gut or that need to be delivered quickly.

Delivery to the brain: NDDS can also be used to deliver drugs directly to the brain. This can be useful for treating conditions such as Parkinson's disease, Alzheimer's disease, and brain tumors [31-33].

The several disease in which nasopulmonary plays an important role of their treatment via nasal route drug delivery.

4.1 Treatment of Respiratory Disorders:

Nasopulmonary drug delivery systems (NDDS) are a promising new approach for the treatment of respiratory disorders. NDDS allow drugs to be delivered directly to the nose and lungs, where they can be absorbed into the bloodstream or act locally.

NPDDS are currently being used to treat a variety of respiratory disorders, including:

Asthma: NDDS can be used to deliver a variety of asthma medications, such as bronchodilators, corticosteroids, and anti-inflammatory drugs. NDDS have been shown to be effective in reducing asthma symptoms and improving lung function.

Chronic obstructive pulmonary disease (COPD): NDDS can be used to deliver bronchodilators and other medications to treat COPD. NDDS have been shown to improve lung function and quality of life in patients with COPD.

Cystic fibrosis: NDDS can be used to deliver antibiotics and other medications to treat cystic fibrosis. NDDS have been shown to improve lung function and reduce the frequency of exacerbations in patients with cystic fibrosis.

Lung cancer: NDDS are being investigated for the delivery of chemotherapy drugs to treat lung cancer. NDDS have the potential to improve the efficacy of chemotherapy and reduce side effects [33].

In addition to the respiratory disorders listed above, NDDS are also being investigated for the treatment of other conditions, such as diabetes, pain, and neurological disorders. The several types of respiratory disorder treated via naso-pulmonary drug delivery discussed in the given **Table 8** as below followings:

Table 8: The list of nasal drug delivery example and their treated respiratory disorder

Nasal drug delivery example	Respiratory disorder
Flunase nasal spray	Allergic rhinitis (hay fever)
Nasal influenza vaccine	Influenza
Ipratropium bromide nasal spray	Asthma and chronic obstructive pulmonary disease (COPD)
Budesonide nasal spray	Asthma and allergic rhinitis
Beclomethasone dipropionate nasal spray	Allergic rhinitis and COPD

These are the some examples discussed in the given above description in **Table 8** as above.

4.2 Systemic Drug Delivery:

Systemic drug delivery in nasopulmonary drug delivery systems (NDDS) is the process of delivering drugs to the bloodstream through the nose and lungs. This can be achieved in two ways:

Direct absorption: Drugs can be directly absorbed into the bloodstream through the nasal and pulmonary mucosa. This is a relatively fast and efficient process, and it can be used to deliver a variety of drugs, including peptides, proteins, and small molecules.

Enhanced absorption: Absorption enhancers can be used to increase the permeability of the nasal and pulmonary mucosa, which can facilitate the absorption of larger molecules and drugs that are poorly absorbed passively.

Systemic drug delivery via NDDS has a number of advantages over traditional drug delivery methods, such as oral and parenteral administration. These advantages include:

Rapid onset of action: Drugs delivered via NDDS can be absorbed into the bloodstream very quickly, resulting in a rapid onset of action. This is important for the treatment of acute conditions, such as pain and allergic reactions.

High bioavailability: Drugs delivered via NDDS can achieve high bioavailability, meaning that a large proportion of the drug is absorbed into the bloodstream. This is important for drugs that are poorly absorbed from the gut, such as insulin.

Non-invasive administration: NDDS are non-invasive, meaning that they do not require needles or injections. This makes them more convenient and acceptable to patients.

Reduced side effects: NDDS can reduce side effects by delivering drugs directly to the bloodstream, bypassing the first-pass metabolism. This is important for drugs that have a high incidence of side effects, such as chemotherapy drugs.

Systemic drug delivery via NDDS is still under development, but it has the potential to revolutionize the way that drugs are delivered for a wide range of conditions. The some examples of drugs that are being investigated for systemic delivery via NDDS like, *Insulin, Pain relievers, Vaccines, Cancer drugs, Gene therapies, Peptide drugs and Protein drugs*. NDDS offer a promising new approach for the systemic delivery of a wide range of drugs [33-36].

4.3 *Vaccination and Immunotherapy:*

Nasopulmonary drug delivery systems (NDDS) are a promising new approach for the delivery of vaccines and immunotherapies. NDDS allow drugs to be delivered directly to the nose and lungs, where they can be absorbed into the bloodstream or act locally to stimulate the immune system.

NDDS offer a number of advantages over traditional vaccination methods, such as injectable vaccines. These advantages include:

Non-invasive administration: NDDS are non-invasive, meaning that they do not require needles or injections. This makes them more convenient and acceptable to patients, especially children and people with needle phobia.

Rapid onset of action: NDDS can deliver vaccines to the immune system very quickly, resulting in a rapid onset of immunity. This is important for vaccines against emerging infectious diseases, such as COVID-19.

Improved mucosal immunity: NDDS can deliver vaccines to the mucosal surfaces of the nose and lungs, where they can induce strong mucosal immunity. Mucosal immunity is important for protecting against respiratory infections.

Reduced side effects: NDDS can reduce side effects by delivering vaccines directly to the immune system, bypassing the first-pass metabolism. This is important for vaccines that have a high incidence of side effects, such as live attenuated vaccines [37].

NDDS are also being investigated for the delivery of immunotherapies, such as checkpoint inhibitors and cancer vaccines. The several vaccine and immunotherapy involves in the different treatment as below followings as per the **Table 9:**

Table 9: The list of vaccines and immunotherapies in the nasopulmonary drug delivery

Nasopulmonary DDS	Vaccines and immunotherapies
Nasal influenza vaccine	Influenza
COVID-19 nasal vaccine	COVID-19
Nasal allergy vaccine	Allergic rhinitis (hay fever)
Nasal cancer vaccine	Lung cancer and other cancers
Pulmonary checkpoint inhibitor	Lung cancer and other cancers

Immunotherapies are drugs that activate the body's own immune system to fight cancer and other diseases. NDDS have the potential to improve the efficacy and safety of immunotherapy delivery.

5. FUTURE PERSPECTIVES AND CHALLENGES

NDDS is a promising route of drug administration with a wide range of potential applications. The future of NDDS is bright, and we can expect to see significant advances in this field in the years to come. Some of the key trends that are likely to shape the future of NDDS include:

Increased use of nanotechnology: Nanomaterials offer several advantages for NDDS, including the ability to improve drug solubility, permeability, and targeting. We can expect to see increased use of nanomaterials in the development of new NDDS systems in the future.

Development of personalized NDDS systems: Personalized NDDS systems can be tailored to the individual needs of each patient. This can be achieved by taking into account factors such as the patient's age, sex, and disease condition. We can expect to see more personalized NDDS systems being developed in the future.

Use of NDDS for delivery of complex drugs: NDDS systems can be used to deliver complex drugs, such as proteins and vaccines that are difficult to deliver using traditional routes of administration. We can expect to see NDDS being used to deliver an increasingly wide range of complex drugs in the future [38].

These are the various some future prospective for the nasopulmonary drug delivery system.

5.1. Regulatory Considerations and Safety Profiles:

In the realm of nasopulmonary drug delivery systems, it is imperative to address regulatory considerations and ensure the safety profiles of such systems. This professional discourse aims to shed light on the importance of adhering to regulatory guidelines and maintaining a robust safety profile in the development and utilization of these systems.

Nasopulmonary drug delivery systems (NDDS) are regulated by the **US Food and Drug Administration (FDA)** as medical devices. The FDA requires that NDDS be safe and effective for their intended use. The safety profile of NDDS is generally good. However, there are some potential side effects, such as, Irritation of the nasal mucosa, Dryness of the nose, Sneezing, Headache, Nosebleed and Coughing. In rare cases, NDDS can cause more serious side effects, such as, Allergic reaction, increased intracranial pressure and Seizures [39].

Regulatory considerations and safety profiles play a pivotal role in the development and utilization of nasopulmonary drug delivery systems. Adhering to regulatory guidelines and conducting comprehensive safety assessments are essential to ensure the efficacy, quality, and safety of these systems. By prioritizing regulatory compliance and maintaining robust safety profiles, we can enhance patient care and contribute to advancements in the field of drug delivery.

5.2. Marketed Research products for the nasopulomary drug delivery system (NPDSS):

Marketed products are enlisted along with its application and mechanism of absorption is presented in **Table 10** as below followings:

Table 10: The list of marketed products available in nasopulmonary drug delivery system for enhancing the bioavailability (BA) in different disease targeting [36-41]

Disease	Product name	Drug
Asthma	Rhinocort Aqua, Pulmicort Respules, Azmacort	Budesonide
Allergic rhinitis	Flonase Sensimist, Nasonex, Veramyst	Fluticasone furoate, fluticasone propionate, mometasone furoate
Sinusitis	Xhance, Omnaris	Fluticasone propionate, ciclesonide
Chronic obstructive pulmonary disease (COPD)	Spiriva HandiHaler, Breo Ellipta, Symbicort	Tiotropium bromide, olodaterol/mometasone furoate, budesonide/formoterol
Diabetes	Afrezza	Insulin
Migraine	Sumavel DosePro, Zomig ZMT	Sumatriptan, zolmitriptan
Pain	Zomig ZMT, Narcan Nasal Spray	Zolmitriptan, naloxone

The nasopulmonary drug delivery system represents a promising avenue for improving therapeutic outcomes and patient compliance in various disease conditions. These are some products which are widely used in the treatment of several diseases with through the nasal route of drug delivery [38-43].

CONCLUSION

NDDS is a promising route of drug administration with a wide range of potential applications. The future of NDDS is bright, and we can expect to see significant advances in this field in the years to come. The nasopulmonary route offers numerous advantages, including rapid absorption, avoidance of first-pass metabolism, and non-invasive administration. Furthermore, the nasal cavity's large surface area and rich blood supply make it an ideal route for systemic drug delivery. However, challenges such as nasal mucociliary clearance and limited drug permeability need to be addressed to optimise the efficacy of this delivery system. With ongoing advancements in formulation technologies and nasal drug delivery devices, the nasopulmonary route holds great promise for the future of drug delivery. Further research and development efforts are warranted to fully exploit the potential of this route and translate it into clinical applications.

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Author contributions

All authors made equal contributions to this study. They all conducted a thorough literature search, collected and analyzed the data. Furthermore, all authors have given their approval for the final version of the manuscript to be submitted.

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