



# OVERVIEW ON RECENT ADVANCES IN NASAL DRUG DELIVERY DEVICES

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**Abstract:** Nasal drug delivery, an ancient practice rediscovered in modern pharmaceuticals, offers a promising avenue for achieving rapid and enhanced drug absorption. Nasal drug delivery devices have undergone significant advancements in recent years, revitalizing this age-old method as a promising avenue for achieving rapid and enhanced systemic drug absorption. The nasal mucosa offers a prime administration route due to its permeability to a wide range of compounds, overcoming the limitations posed by the gastrointestinal tract. Recent research has highlighted the superior systemic bioavailability of various drugs administered nasally compared to traditional oral routes, thereby improving patient compliance and therapeutic outcomes. The growing preference for nasal drug delivery among patients and healthcare providers is evident, supported by specific guidelines from the World Health Organization for the safe adoption of new nasal delivery devices with single-use systems. This review explores the latest advancements in nasal drug delivery devices, including Vibrating mech nebulizer, dry powder inhalers, and powder spray devices, highlighting their potential to revolutionize drug therapy outcomes and patient care.

**Index Terms** - Nasal drug delivery devices, bioavailability, nebulizer, inhalers

## I. INTRODUCTION

Nasal drug delivery – which has been practiced for thousands of years, has been given a new lease of life. Nasal mucosa has been considered as a potential administration route to achieve faster and higher level of drug absorption. Innately, the nose offers easy access to a large mucosal surface well suited for drug- and vaccine delivery.

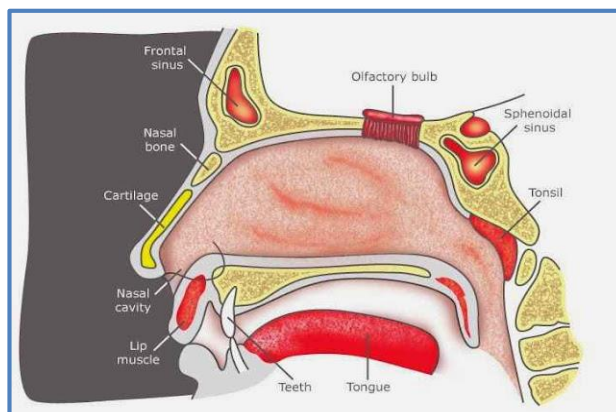
Nasal mucosa has been considered as a potential ad-ministration route to achieve faster and higher level of drug absorption because it is permeable to more com-pounds than the gastrointestinal tract due to lack of pancreatic and gastric enzymatic activity, neutral pH of the nasal mucus and less dilution by gastrointestinal contents. In recent years many drugs have been shown to achieve better systemic bioavailability through nasal route than by oral administration. The easy administration of these drugs plays a crucial role in improving the compliance to drug therapies among patients, which in turn drives patient outcomes.

Considering these factors, the preference for nasal drug delivery is increasing among patients as well as healthcare providers. The World Health Organization (WHO) has specific guidelines for manufacturers, which outlines all necessary requirements for the adoption of new nasal delivery devices with a single-use delivery system. In recent years, achieving a systemic drug action using the nose as the entry portal into the body has received more attention. A wide range of pharmaceutical dosage forms including solutions, gels, suspensions, emulsions, liposomes and microparticles can be used to achieve systemic drug actions. This Dosage form can be administered using various Nasal Drug Delivery Devices such as Squeezed bottle, Instillation and rhinyle catheter, Dry powder inhaler, Powder spray device etc.

## II. NASAL ANATOMY AND PHYSIOLOGY INFLUENCING DRUG DELIVERY REGULATION OF NASAL AIRFLOW

Nasal breathing is vital for most animals and for human neonates in the first weeks of life. The nose is the normal and preferred airway during sleep, rest, and mild exercise up to an air volume of 20–30 l/min. The nasal cavity is divided into two halves by the nasal septum and extends posterior to the nasopharynx, while the most anterior part of the nasal cavity, the nasal vestibule, opens to the face through the nostril.

The nasal cavity consists three main regions are nasal vestibule, olfactory region and respiratory region. The surface area in the nose can be enlarges about 150cm<sup>2</sup> by the lateral walls of the nasal cavity includes a folded structure, it is a very high surface area compared to its small volume. This folded structure consists of three turbinate's the superior, the median and the inferior. The main nasal airway having the narrow passages, usually it has 1-3mm wide and these narrows structures are useful to nose to carry out its main functions. The nasal cavity also contains the nasal associated lymphoid tissue (NALT), which is mainly situated in the nasopharynx.



Anatomy of the Nasal Airways and Paranasal Sinus

Nasal cavity is lined with mucus layer and hairs which are involved in those functions are trapping inhaled particles and pathogens. Moreover, mucociliary clearance, immunological activities and metabolism of endogenous substances are also essential functions of nasal structures.

The nasal cavity is covered with a mucous membrane which can be divided into two areas; nonolfactory and olfactory epithelium, in this non-olfactory area includes the nasal vestibule which is covered with skin-like stratified squamous epithelium cells, whereas respiratory region, which has a typical airways epithelium covered with numerous microvilli, resulting in a large surface area available for drug absorption and transport. Nasal cavity is divided by middle septum into two symmetrical halves, each one opening at the face through nostrils and extending posterior to the nasopharynx.

Both symmetrical halves consist of four areas (nasal cavity, atrium, respiratory region and olfactory region) that are distinguished according to their anatomic and histological characteristics.

- a) **Nasal Cavity:** Most anterior part of the nasal cavity is nasal vestibule, just inside the nostrils, and presents an area about 0.6 cm<sup>2</sup>. Nasal hairs are present in this area, also called vibrissae, which filter the inhaled particles. Histologically, this nasal portion is covered by a stratified squamous and keratinized epithelium with sebaceous glands.
- b) **Atrium:** Intermediate area between nasal vestibule and respiratory region is atrium. Its anterior section is constituted by a stratified squamous epithelium and the posterior area by pseudostratified columnar cells presenting microvilli.
- c) **Respiratory:** Largest part of the nasal cavity is respiratory region, also called conchae, is the cavity and it is divided in superior, middle and inferior turbinate's which are projected from the lateral wall. The nasal respiratory mucosa, considered the most important section for delivering drugs systemically, is constituted by the epithelium, basement membrane and lamina propria. The nasal respiratory epithelium consists of pseudostratified columnar epithelial cells, goblet cells, basal cells and mucous and serous glands. Many of the epithelial cells are covered on their apical surface with microvilli and the major part of them also has fine projections, called cilia.
- d) **Olfactory region:** Location of olfactory region is at the roof of the nasal cavity and extends a short way down the septum and lateral wall.

### III. MECHANISM OF DRUG ABSORPTION

The principal step in the absorption of a drug from the nasal cavity is the passage through the mucus. Fine particles easily pass through the mucus layer; however, large particles may find some difficulties. Mucus contains mucin, a protein with the potential to bind with solutes and thus affect the diffusion process. Structural changes can occur within the mucus layer as a result of environmental or physiological changes. After a drug's passage through the mucus, there are numerous mechanisms for absorption through the mucosa.

These include transcellular or simple diffusion across the membrane, paracellular transport via movement between cell and transcytosis by vesicle carriers. Several mechanisms have been proposed, but paracellular and transcellular routes dominate. Paracellular transport is slow and passive. There is an inverse correlation between intranasal absorption and the molecular weight of water-soluble compounds. Poor bioavailability was reported for drugs with a molecular weight greater than 1000 Daltons.

The second mechanism involves transport through a lipoidal route that is also known as the transcellular process and is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. Drugs also cross cell membranes by an active transport route via carrier-mediated means or transport through the opening of tight junctions. Obstacles to drug absorption are potential metabolism before reaching the systemic circulation and inadequate residence time in the nasal cavity.

### IV. NASAL DRUG DELIVERY SYSTEM DOSAGE FORMS

Formulations based on Nasal Delivery System

#### A. Liquid Dosage Forms

- a) Nasal Drops: Nasal drops are one of the most simple and convenient delivery systems among all formulations. The main disadvantage of this system is the lack of dose precision.
- b) Nasal Sprays: Both solution and suspension formulations can be formulated into nasal sprays. Due to the availability of metered dose pumps and actuators, a nasal spray can deliver an exact dose anywhere from 25 -200  $\mu$ l.
- c) Nasal Emulsions: Micro emulsions Intranasal emulsions have not been studied as extensively as other liquid nasal delivery systems. Nasal emulsions offer the advantages for local application mainly due to the viscosity. Semi-solid dosage forms Semi-solid systems, for example gels, ointments and liquid systems containing polymers that gel at particular pH changes are usually employed for designing the nasal drug delivery systems.
- d) Nasal Gels: Nasal gels are thickened solutions or suspensions, of high-viscosity. The advantages of a nasal gel include the reduction of post-nasal dripping due to its high viscosity, reduction of the taste impact due to reduced swallowing, reduction of anterior leakage of the formulation.

**B. Solid Dosage Forms:** Solid dosage forms are also becoming popular for intranasal drug delivery, although these formulations are more suitable for pulmonary drug delivery and similar applications, since it can cover the vasculature within the epithelium of nasal mucosa.

- a) Nasal Powders: Powder dosage forms may be developed if solution and suspension dosage forms cannot be developed, mainly due to lack of drug stability. The advantages of a nasal powder dosage form are the absence of preservative and superior stability of the drug in the formulation. However, the suitability of the powder formulation is dependent on the solubility, particle size, aerodynamic properties and nasal irritancy of the active drug and/or excipients.

#### C. Novel Drug Formulations

Several claims have been made in favor of developing nasal formulations containing liposomes, microspheres and nanoparticles for intranasal drug delivery. These systems can include, besides the drug, enzymatic inhibitors, nasal absorption enhancers or/and mucoadhesive polymers in order to improve the stability, membrane penetration and retention time in nasal cavity.

- a) Liposomes: Liposomes are phospholipids vesicles composed by lipid bilayers enclosing one or more aqueous compartments and wherein drugs and other substances can be included. Liposomal drug delivery systems present various advantages such as the effective encapsulation of small and large molecules with a wide range of hydrophilicity and pKa values. In fact, they have been found to enhance nasal absorption of peptides such as insulin and calcitonin by increasing their membrane penetration. This has been attributed to the increasing nasal retention of peptides. Protection of the entrapped peptides from enzymatic degradation and mucosal membrane disruption.

- b) **Microspheres:** Microsphere technology has been widely applied in designing formulations for nasal drug delivery. Microspheres are usually based on mucoadhesive polymers (chitosan, alginate), which present advantages for intranasal drug delivery. Furthermore, microspheres may also protect the drug from enzymatic metabolism and sustain drug release, prolonging its effect.
- c) **Nanoparticles:** Nanoparticles are solid colloidal particles with diameters ranging from 1-1000 nm. They consist of macromolecular materials and can be therapeutically used as adjuvant in vaccines or as drug carriers, in which the active substance is dissolved, entrapped, encapsulated, adsorbed or chemically attached. Nanoparticles may offer several advantages due to their small size, but only the smallest nanoparticles penetrate the mucosal membrane by paracellular route and in a limited quantity because the tight junctions are in the order of 3.9-8.4 Å.

## V. NASAL DRUG DELIVERY DEVICES:

### Liquid Devices

- 1) **Drops Delivered with Pipette:** Drops and vapor delivery are probably the oldest forms of nasal delivery. Dripping breast milk has been used to treat nasal congestion in infants, vapours of menthol or similar substances were used to wake people that have fainted, and both drops and vapours still exist on the market. Drops were originally administered by sucking liquid into a glass dropper, inserting the dropper into the nostril with an extended neck before squeezing the rubber top to emit the drops. For multi-use purposes, drops largely have been replaced by metered-dose spray pumps, but inexpensive single-dose pipettes produced by “blow-fill-seal” technique are still common for OTC products like decongestants and saline. An advantage is that preservatives are not required. However, although drops work well for



some, their popularity is limited by the need for head-down body positions and/or extreme neck extension required for the desired gravity-driven deposition of drops. Compliance is often poor as patients with rhinosinusitis often experience increased headache and discomfort in head-down position.

- 2) **Squeeze Bottles:** Squeeze bottles are mainly used to deliver some over-the counter (OTC) products like topical decongestants. By squeezing a partly air-filled plastic bottle, the drug is atomized when delivered from a jet outlet. The dose and particle size vary with the force applied, and when the pressure is released, nasal secretion and microorganisms may be sucked into the bottle. Squeeze bottles are not recommended for children. The bottles are made up of polyethylene. A nozzle with adapted size and shape allows easy application of lines, beads, dots of different sizes and shapes, and it may be easily refilled when it is empty. A fine nozzle allows an accurate application in recessed parts where no other tool could access.



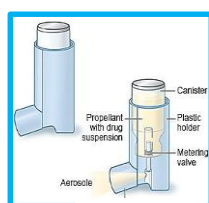
3) **Metered-Dose Spray Pump:** Metered spray pumps have, since they were introduced some four decades ago, dominated the nasal drug delivery market. The pumps typically deliver 100  $\mu\text{l}$  (25– 200  $\mu\text{l}$ ) per spray, and they offer high reproducibility of the emitted dose and plume geometry in in vitro tests. Traditional spray pumps replace the emitted liquid with air, and preservatives are therefore required to prevent contamination. These systems use a collapsible bag, a movable piston, or a compressed gas to compensate for the emitted liquid volume. These preservative-free pump systems become more complex and expensive, and since human studies suggest that preservatives are safe and well tolerated, the need for preservative-free systems seems lower than previously anticipated. More recently, pumps have been



Metered-dose  
spray pumps

designed with side-actuation and introduced for delivery of fluticasone furoate for the indication of seasonal and perennial allergic rhinitis. The pump was designed with a shorter tip to avoid contact with the sensitive mucosal surfaces. New designs to reduce the need for priming and re-priming, and pumps incorporating pressure point features to improve the dose.

4) **Nasal Pressurized Metered-Dose Inhalers (pMDIs):** While first introduced in the 1950s, pressurized metered dose inhalers (pMDIs) remain as a first line treatment of pulmonary conditions. Most drugs intended for local nasal action are delivered by spray pumps, but some have also been delivered as nasal aerosols produced by pMDIs. The particles from a pMDI are released at a high speed and the expansion of a compressed gas, which causes an uncomfortable “cold Freon effect”. Like spray pumps, nasal pMDIs produce a localized deposition on the anterior non-ciliated epithelium of the nasal vestibule and in the anterior parts of the narrow nasal valve, but due to quick evaporation of the spray delivered with a pMDI, noticeable “drip out” may be less of an issue. The use of pressurized metered-dose inhalers (pMDIs) with or without a spacer represents an alternative not evaluated so far in conjunction with NHF. pMDI has the advantages of being economic and portable, it should be seen important by manufacturers, physicians and regulatory authorities to mandate the use of spacers with the device and the addition of an accurate dose counter to help patients track the number of doses and improve patient satisfaction



pMDIs

5) **Simple Membrane Nebulizer:** Nebulizers use compressed gasses (air, oxygen, and nitrogen) or ultrasonic or mechanical power to break up medical solutions and suspensions into small aerosol droplets that can be directly inhaled into the mouth or nose. The smaller particles and slow speed of the nebulized aerosol are advocated to increase penetration to the target sites in the middle and superior meatuses and the paranasal sinuses. Indeed, nasal inhalation from a nebulizer has been shown to improve deposition to the upper narrow part of the nose when compared to a metered-dose spray pump, but with 33 % and 56 % of the delivered dose deposited in the lungs in the subjects assessed. Recent evidence shows that nebulizers are no more effective than metered dose inhalers (MDIs) with spacers. An MDI with a spacer may offer advantages to children who have acute asthma. Those findings refer specifically to the treatment of asthma and not to the efficacy of nebulisers generally, as for COPD for example. For COPD, especially when assessing exacerbations or lung attacks, there is no evidence to indicate that MDI (with a spacer) delivered medicine is more effective than administration of the same medicine with a nebulizer.



6) **Vibrating Mech Nebulizer:** a new nasal mesh nebulizer system designed to minimize lung inhalation with the same mean particle size ( $5.6 \pm 0.5 \mu\text{m}$ ). The new system consists of two integrated components: the nebulizer compressor administering a constant airflow rate transporting the aerosol into one nostril via a nozzle and a pump simultaneously aspirating from a second nozzle in the other nostril at the same airflow rate while the subject is instructed to avoid nasal breathing. The new nasal mesh nebulizer produced more deposition in terms of volume of liquid (27 % vs. 9 %, i.e., 0.81 vs. 0.27 ml) in the nasal cavity. The much higher fraction found in the nasal cavity in this study is probably a result of the shorter nebulizing time and smaller delivered volume in the study testing the PARI pulsating nebulizer.

7) **Atomizer:** A medical atomizer includes a liquid storage container, a nozzle and an adjustable valve. The liquid storage container includes an air inlet, a fixed cover plate installed at the periphery of the air inlet, and a high-pressure jet installed at the bottom of the liquid storage container. The nozzle is installed in the liquid storage container and covered onto the high-pressure jet. In general, a conventional atomizer structure comprises a cup shaped body, a nozzle, a cap, a high-pressure jet installed in the cup shaped body, a spray outlet formed on the cap or body, and a liquid medicine stored in the cup shaped body. By injecting high pressure air into the cup shaped body, the air passes through the high-pressure jet into the cup shaped body, and then the air is mixed and atomized with the liquid medicine around the top opening of nozzle, and finally the aerosol medicine is passed through the spray outlet and provided for an inhale by a patient.



atomizer spry

The atomizer may be used with different air pressure sources. If a different air pressure source is used, the nebulization rate of the medicine is also different. Different patients (such as adults and children) require different dosages (or different nebulization rates). In addition, the viscosities of different medicines are different, so that the efficiency for the atomizer to atomize different medicines varies. The conventional atomizer is unable to adjust the nebulization rate for different applications and results in low medication efficiency and high medical fees.

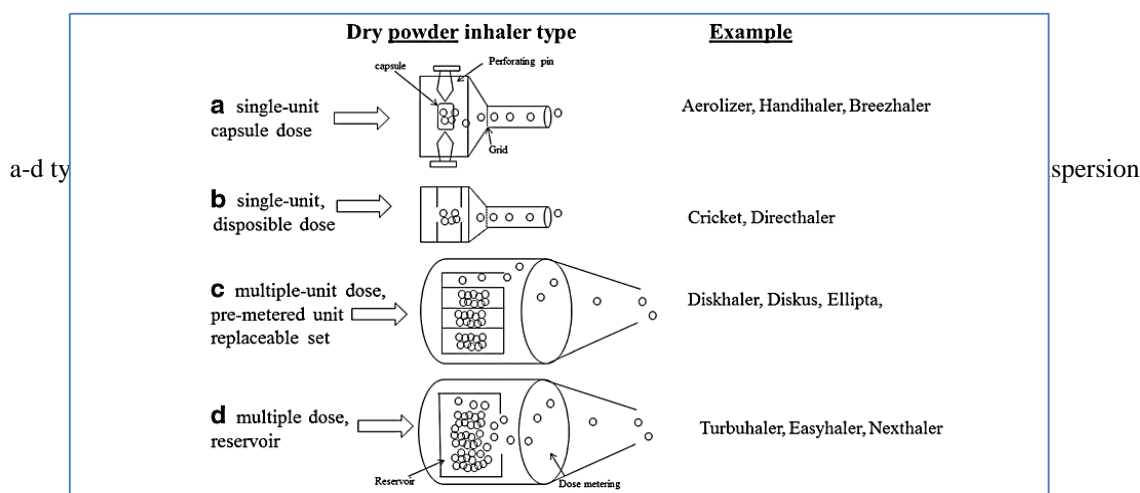
### Powder Devices

Powder medication formulations can offer advantages, including greater stability than liquid formulations and potential that preservatives may not be required. Powders tend to stick to the moist surface of the nasal mucosa before being dissolved and cleared. The use of bio adhesive excipients or agents that slow ciliary action may decrease clearance rates and improve absorption. A number of factors like moisture sensitivity, solubility, particle size, particle shape, and flow characteristics will impact deposition and absorption. The function of nasal powder devices is usually based on one of three principles:

- 1) Powder sprayers with a compressible compartment to provide a pressure that when released creates a plume of powder particles fairly similar to that of a liquid spray
- 2) Breath-actuated inhalers where the subject uses his own breath to inhale the powder into the nostril from a blister or capsule; and
- 3) Nasal insufflators describe devices consisting of a mouthpiece and a nosepiece that are fluidly connected.

**1) Dry Powder Inhaler (Capsule Based):** Dry powder inhalers (DPIs) are the devices most commonly used for drug delivery in the treatment of asthma and COPD. DPIs are actuated and driven by a patient's inspiratory flow, they do not require propellants to generate the aerosol, nor coordination of inhaler actuation with inhalation. However, a forceful and deep inhalation through the DPI is needed to de-aggregate the powder formulation into respirable particles as efficiently as possible in order to ensure that drug is delivered to the lungs. Although most patients are capable of generating enough flow to operate a DPI efficiently. The need to inhale forcefully, and therefore generate a sufficient inspiratory flow, remains a problem for young children and patients with severe airflow limitation. For this reason, DPIs are not recommended for use in children under the age of 5 years.

The main types of DPI systems are shown in Figure. The single-unit dose inhaler requires the patient to load a single hard gelatine capsule containing the powder formulation into the device before each use (Fig. a). This is a very common type of DPI device currently available. Figure shows a device containing a pre-metered amount of a single dose that is discarded after use. eg, cricket, directhaler. Multiunit devices deliver individual doses from pre-metered replaceable blisters, disks, dimples or tubes (Fig. c). Multiple-dose reservoir inhalers (Fig. d) contain a bulk amount of drug powder in the device with a built-in



mechanism to meter a single dose and individual doses are delivered with each actuation. The multi-unit inhalers (Fig. 10c) are likely to ensure greater dosage control and chemical stability of the formulation than multiple dose types (Fig. d) eg. Turbuhaler, easyhaler, nexthaler.

**2) Breath Powered Bi-Directional Delivery (OptiNose):** This novel concept exploits natural functional aspects of the upper airways to offer a delivery method that may overcome many of the inherent limitations of traditional nasal devices. Importantly, the breath-powered Bi-Directional™ technology can be adapted to any type of dispersion technology for both liquids and powders. Breath-powered Bi-Directional™ devices consist of a mouthpiece and a sealing nosepiece with an optimized frusto-conical shape and comfortable surface that mechanically expands the first part of the nasal valve. The user slides a sealing nosepiece into one nostril until it forms a seal with the flexible soft tissue of the nostril opening, at which point, it mechanically expands the narrow slit-shaped part of the nasal triangular valve.

The user then exhales through an attached mouthpiece. When exhaling into the mouthpiece against the resistance of the device, the soft palate (or velum) is automatically elevated by the positive oropharyngeal pressure, isolating the nasal cavity from the rest of the respiratory system. Owing to the sealing nosepiece, the dynamic pressure that is transferred from the mouth through the device to the nose further expands the slit-like nasal passages. Importantly, the positive pressure in the entry nostril will, due to the sealing nosepiece, balance the oropharyngeal pressure across the closed velum to prevent the velum from being “over-elevated,” thus securing an open flow path between the two nasal passages behind the nasal septum and in front of the elevated velum. The Bi-Directional™ devices currently in phase 3 clinical trials are a multi-dose liquid device incorporating a standard spray pump and a capsule-based powder multi-use device with disposable drug chamber and nosepiece, but other configurations are possible.



## 6. CONCLUSION:

The nose is attractive for delivery of many drugs and vaccines, but the potential has not been fully realized. Inherent challenges related to the nasal anatomy, physiology, and aerodynamics that may severely limit the potential and clinical efficiency are not widely understood.

The small and dynamic dimensions of the nasal cavity and the anterior anatomy are among the most important hurdles for more efficient nasal drug delivery. Despite important improvements in the technical device attributes that can offer more reproducible and reliable in vitro performance, this has to a limited extent translated into improved clinical performance.

While in vitro performance testing is undoubtedly of value for product quality assessment, predictive value for in vivo clinical performance is highly questionable. Human in vivo deposition and clearance studies can be very important, providing valuable information particularly if recent advances allowing regional quantification and tissue attenuation correction are employed. Still, delivery by trained assistants in controlled environments may not adequately reflect the device performance in the clinical setting. Even the most advanced nebulizer technologies introduced have shown poor delivery efficiency, with undesirable localized delivery in the non-ciliated anterior nasal region and along the floor of the nose and problems with inhalation exposure of the lungs.

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