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CUTTING EDGE FOR NASAL SPRAYS - REVOLUTIONIZING DRUG DELIVERY OF NEW DRUGS APPROVED BY FDA

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ABSTRACT

The advent of novel nasal spray formulations represents a transformative approach in drug delivery, particularly for new drugs approved by the FDA. This paper explores the cutting-edge technologies and methodologies employed in the development of nasal sprays, emphasizing their advantages over traditional delivery systems. By enhancing bioavailability, minimizing first-pass metabolism, and improving patient compliance, these innovative sprays are set to revolutionize therapeutic strategies across various medical conditions. We will discuss recent advancements in formulation science, including the use of nanotechnology, mucoadhesive agents, and targeted delivery systems. Additionally, the regulatory landscape and clinical implications of FDA- approved nasal sprays will be examined, highlighting their role in improving treatment outcomes and patient experiences. This comprehensive overview aims to underscore the potential of nasal spray technology as a pivotal player in modern pharmacotherapy.

KEYWORDS: FDA, targeted drug delivery, Nasal sprays, Bioavailability, Nanotechnology, pharmacotherapy.

INTRODUCTION

Recently, nasal drug delivery has garnered significant attention because of its convenient, promising, and reliable method of systemic drug administration. Drugs that are ineffective when taken orally or require injection are especially beneficial. This delivery route offers a large surface area, porous endothelial membrane, and high total blood flow, bypasses first-pass metabolism, and allows easy accessibility. Furthermore, the nasal mucosa is more permeable to a wider range of compounds than the gastrointestinal tract is because it lacks pancreatic and gastric enzymatic activities and is not interfered with by gastrointestinal contents.[1]

Advantageous nasal drug delivery system: a review the early recorded historical application of nasal drug delivery was originally limited to topical applications of drugs intended for only local effects. However, in recent times, its application has expanded to include a wide range of targeted areas in the body to produce both local and systemic effects. Nasal drug delivery also holds a special place in traditional systems of medicine, such as Ayurvedics. In Indian medicine, nasal administration, known as "Nasya karma," is a recognized form of treatment.[2]

The nose plays a crucial role in drug absorption, allowing faster and higher drug levels in the body and even enabling self-administration. A wide range of drugs, from small molecules to large molecules such as peptides, proteins, hormones, and vaccines, can be delivered through the nasal cavity. Notably, lipophilic drugs are generally well absorbed through the nasal cavity, often showing pharmacokinetic profiles similar to those from intravenous injection, with bioavailability's approaching 100% in many cases.[3]

The intranasal route shows promise for delivering drugs to the brain. Drugs can be delivered to the central nervous system (CNS) via the olfactory neuroepithelium via the nasal route. This delivery method has been reported for conditions such as Alzheimer's disease, brain tumors, epilepsy, pain, and sleep disorders.

The high permeability, abundant blood supply, and low enzyme levels in the nasal cavity make it ideal for delivering drug molecules into the bloodstream. The noninvasive and self-administrative nature of nasal delivery also makes it appealing for the formulation of protein and peptide compounds. Many nasal products are used to treat conditions such as allergic rhinitis, migraines, colds, and pain. Nasal formulations include gels, sprays, powders, etc., making the nasal route a promising alternative for drug delivery compared with other systems.[4]

Anatomy and Physiology of Nose

The human nasal cavity has a total volume of approximately 16 to 19 ml and a total surface area of approximately 180 cm^2. It is divided into two nasal cavities via the septum. Some of the regions are described as follows:

1. **Respiratory region**: The respiratory region is the region with the highest degree of vascularity and is mainly responsible for systemic drug absorption.[5]
2. **The Vestibular region** is located at the opening of nasal passages and is responsible for filtering out airborne particles. It is considered to be the least important of the three regions for drug absorption.[5]
3. **The Olfactory region** is approximately 10 cm2 in surface area and plays a vital role in the transportation of drugs to the brain and CSF. The human olfactory region comprises thick connective tissue lamina propria, upon which the olfactory epithelium rests. The lamina propria has axons, bowel bundles, and blood vessels, whereas the epithelium consists of three different types of cells, i.e., basal cells, supporting cells, and olfactory receptor cells. Neurons are interspersed between supporting cells. The olfactory receptor cells are bipolar neurons with a single dendrite and extend from the cell body to the free apical surface, where it ends in an olfactory knob carrying nonmotile cilia, which extend above the epithelium. The epithelium of the nasal passage is covered by a mucus layer, which entraps particles. The mucus layer is cleared from the nasal cavity by cilia and is renewed every 10 to 15 minutes, and the pH of the mucosal secretions ranges from 5.5 to 6.5 in adults. Numerous enzymes, such as cytochrome P-450, carboxylesterases, and glutathione S-transferase, are present in the nasal cavity.[6,7,8,9,10,5,11]

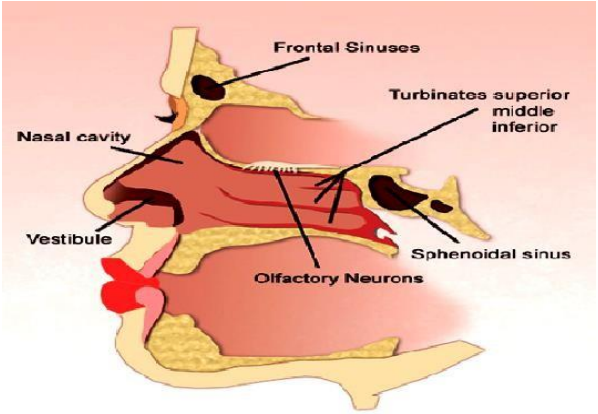

Fig. 1: Anatomy of nose.[3]

Mechanisms for absorption

Through the nasal mucosa, substances can be transported via movement between cells (paracellular transport) and simple diffusion across the membrane (transcellular).[12,13,14]

1. The first mechanism includes the aqueous route of transport, which is also called the paracellular route. This is a slow and passive route. Poor bioavailability was observed for drugs with a molecular weight greater than 1000 Daltons because an inverse relationship exists between the molecular weight and absorption.[15]
2. The transcellular process is the second mechanism of transport through a lipoidal route and is responsible for the transport of lipophilic drugs that are dependent on their lipophilicity. Drugs also cross cell membranes via an active transport route via carrier-mediated means or transport through the opening of tight junctions. For example, chitosan, a natural biopolymer, opens tight junctions between epithelial cells to facilitate drug transport (Figure 3: Drug transport pathways across the epithelium). (A), paracellular transport (B), transcytosis (C), carrier-mediated transport (D), and intercellular tight junctions (E).[15,16,17,18,19,20]

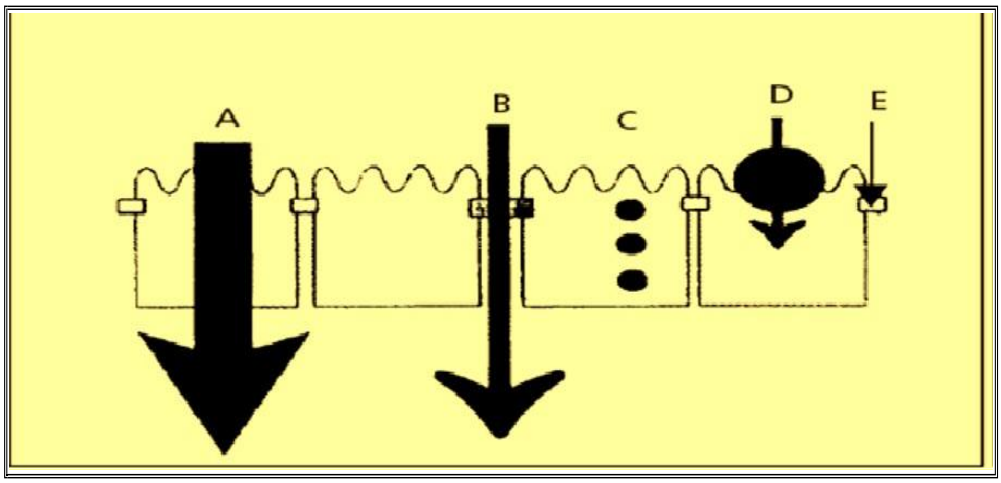

Fig 2: Mechanism of drug absorption in the nasal cavity.[3]

Advantages of nasal drug delivery

- Self-administration is possible.
- Drug degradation that is observed in the gastrointestinal tract is absent.
- Hepatic first-pass metabolism is avoided.

- Rapid drug absorption and quick onset of action can be achieved.
- The nasal bioavailability of smaller drug molecules is good.
- Bypass the BBB.
- Alternate to parenteral routes, especially for proteins and peptides.
- Convenient route for long-term therapy.
- Offers a lower risk of overdose
- Does not have any complex formulation requirements.[21,22,23]

Limitations or disadvantages

- Drugs cannot be withdrawn once they are administered.
- The delivery volume in the nasal cavity is restricted to 25–200 μL.
- High-molecular-weight compounds cannot be delivered through this route (mass cutoff of ~1 kDa). • Adversely affected by pathological conditions.
- Large interspecies variability is observed via this route.
- Normal defense mechanisms such as mucociliary clearance and ciliary beating can impact the permeability of drugs.
- Irritation of the nasal mucosa by drugs such as budesonide and azilactine.
- There is a limited understanding of the mechanisms and less developed models at this stage.
- The occurrence of systemic toxicity due to absorption enhancers has not yet been established.
- Compared with that of the GIT sample, the absorption surface is smaller.
- The possibility of nasal irritation is hence more inconvenient than the oral route is.
- Enzymatic barrier to the permeability of the drug.[21,22,23]

Methods for Nasal Drug Delivery

- The mucus layer in the nasal cavity acts as a barrier for the absorption of liquids. When drugs are administered through the nose, the mucus helps carry drug molecules to other mucous membranes by prolonging their stay at the absorption site. Additionally, the mucus facilitates deeper penetration of drug molecules and wider distribution of particles. Different nasal delivery techniques are discussed, some of which are associated with mucus adhesion systems, whereas others are associated with mucus permeation systems.[24]
- Hydrogels have porous and hydrated molecular networks that are similar to those in natural tissue microenvironments. They are often used as matrix systems to control the release of large molecules. When combined with nanoparticles, they can create new systems that significantly improve the absorption of medications.[25]
- Nasal administration of medication shows promise but has challenges, especially those related to toxicity. The high hydration capacity of HA allows it to adhere to the nasal mucosa, increasing its permeability for drug delivery. Stable micelles with precise drug release control have been developed. Lipid-based nanoparticles are widely used because of their high bioavailability. Liposomes enable direct drug delivery to the brain, bypassing the blood–brain barrier and enhancing drug effectiveness.[26]
- An increase in drug solubility in the nasal mucosa can be achieved via nanosuspensions and nano emulsions. These formulations have improved drug delivery via nasal administration, including better mucosal adherence and brain delivery. However, its limited bioavailability may be a concern because of its low water solubility.[27]

- Compared with solutions, dry powder nasal preparations have better stability and higher drug concentrations, leading to increased drug absorption by the nasal mucosa. Freeze-dried budesonide powder is more suitable for nasal administration than is a water-based suspension because of its faster release in the nasal mucosa. Microparticles, ranging from 1 to 1000 μm, consist of soluble excipients or polymers encapsulated with drug-active substances for sustained drug release. Compared with gold and other semiconductor quantum dots, carbon quantum dots are less toxic and more biocompatible. Researchers have developed carbon quantum dots from sodium alginate for gene delivery, showing effective plasmid DNA aggregation. Additionally, graphene quantum dots have been found to enhance the intracellular absorption of formulated drugs. While carbon nanotubes have potential for medical applications, especially in drug delivery, some issues need to be addressed before they can be used in clinical trials. A study revealed the harmful effects of carbon nanotubes on normal human nasal epithelial cells after 12 days of exposure, which affected cell function and oxidative stress.
- Both the mucus adhesion system and the mucus penetration system have potential for mucosal administration. Combining these two systems into one drug delivery system with both adhesion and penetration characteristics is expected to be a future trend.[8,22,28,29]

Devices for nasal drug delivery systems

1. **Nasal drops:** One of the easiest and most practical nasal administration modalities is nasal drops. Because self-administration is simple, it is growing in popularity. The primary reason for the absence of dosage control in this approach is the drawback of accuracy.[27,30]

Fig 3: Nasal drops.

Nasal sprays: Nasal sprays can be made from suspensions or solution formulations. Since the metered dose is readily available via actuators and pumps, a nasal spray can be used as a precise dosage. These are favored above the powder. The powder is sprayed since it causes mucosal irritation.[31]

Fig. 4: Nasal sprays.

2. Nasal inserts: Nasal inserts are innovative, solid, bio adhesive dosage forms for extended systemic administration of medications through the nasal route. The basic idea of the dosage form is to ingest nasal mucosal fluid upon administration and to create a gel in the nose cavity to prevent foreign physical perception.[32]

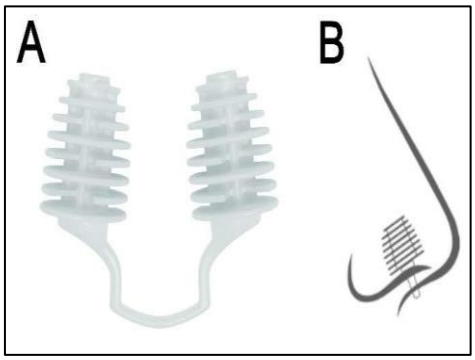

Fig 5: Nasal inserts.

Pressurized MDIS: With the help of a metered-dose inhaler (MDI), a patient can inhale a brief aerosolized medicine burst that contains a predetermined amount of medication. This is the most widely used method for treating respiratory conditions such as asthma and chronic obstructive pulmonary disease (COPD). When asthma and COPD are treated, the drug used in a metered-dose inhaler is typically a bronchodilator, a corticosteroid, or a combination of the two. Mast cell stabilizers such as cromoglicate or nedocromil are additional, less often utilized drugs that are nonetheless given by MDI (Hickey AJ., 2004). The benefits of MDIs include their small size and portability, availability across a broad dosage range per actuation, dose accuracy and consistency, content protection, and speedy readiness for use.[33,34]

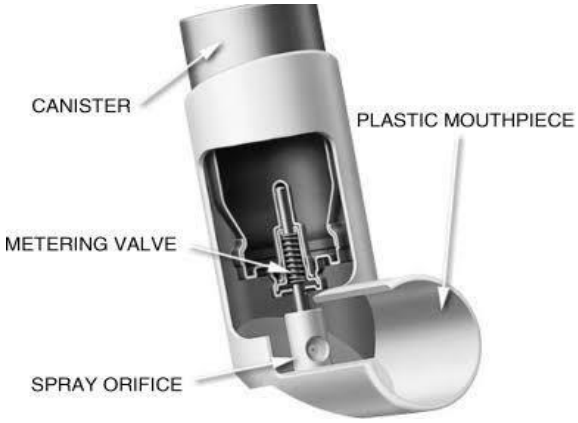

Fig. 6: Pressurized MDI'S.

3. Nasal powders: These formulas are created when there is a stability issue. However, the appropriateness of powder formation is influenced by the degree of soluble particle size, aerodynamic characteristics, and nasal irritability of the medicine in use.[8,35,36]

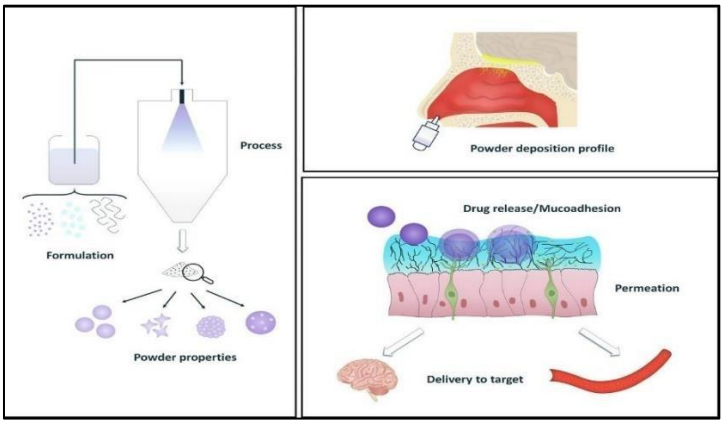

Fig. 7: Nasal powders.

Newly approved medications designed for nasal administration

Table 1: Newly approved nasal drugs by the FDA.

S. No.	Name	Approved date	Uses	Site of action
1.	Neffy (epinephrine nasal spray)	Aug 9, 2024	Type 1 allergic reasons, including anaphylaxis	Single-dose nasal spray administered into one nostril
2.	Xhance (fluticasone propionate)	Mar 15, 2024	Chronic rhinosinusitis and nasal polyps in adults	Acts as a stent in the nasal valve & creates positive pressure that expands narrow passages.
3.	Naloxone (nascan)	March, 2023	Used as opioid antagonist.	Opioid antagonist that competitively inhibits sedative, analgesic, and cardiopulmonary depressant effects of opioids.
4.	Nasonex (mometarone furoate)	Mar 17, 2022	Treats symptoms of allergies like sneezing and running nose.	The pressive mechanism of corticosteroid action on allergic rhinitis is not known
5.	Ryattris nasal spray	Jan 14, 2022	To relieve seasonal allergy symptoms of the nose.	Blocking certain natural substances called histamines that are responsible for allergic symptoms.
6.	Astepro allergy (Azelastin)	Jun 17, 2021	Treat seasonal & perennial allergic rhinitis	Exhibits histamine H1 receptor antagonist activity.
7.	Diazepam nasal spray (valtoco)	Jan 10, 2020	Emergencies to stop cluster seizures in adults & children 6 years of age.	Suppress or stop seizure activity by arguing a substance in the brain called GABA (gamma- aminobutyric acid)
8.	Sparavato	Mar 5, 2019	Used along with an antidepressant	Blocking N- Methyl-D aspartate (NMDA) receptors in the brain.
9.	Dupilumab (Dupixent)	Mar 28, 2017	Treats some types of skin conditions, such as eczema.	Blocking interleukin 4 & interleukin 13 proteins in the immune system.
10.	Isopropamide phenylpropanolamine hydrochloride.	Jan 31, 2018	Treats pain & other symptoms of gastrointestinal conditions	Anticholinergic blocks acetylcholine binding to its reporter in nerve cells, inhibiting parasympathetic nerve impulses.
11.	Desmopressin	2018	Central diabetes insipidus & bed wetting	Act as a selective agonist of V2 receptors in the renal collecting duct to increase water reabsorption and

				reduce urine production.
12.	Desmopressin acetate nasal spray (NOCTIVIA)	Mar 3, 2017	Treat central cranial diabetes insipidus	Act as a selective agonist of V2 receptors in the renal collecting duct to increase water reabsorption and reduce urine production.
13.	Mometasone furate sinus implant (sinuva)	Dec 8, 2017	To treat nasal polyps & relieve nasal congestion	Corticosteroid reduces inflammation by diffusing across all membranes & activating pathways that reduce inflammation.
14.	Nucala (mepolizumab)	Nov 4, 2015	Treatment of chronic rhinosinusitis with nasal polyps (CRSWNP)	Binding to interleukin, a protein that is responsible for eosinophil production.
15.	Ciclesonide	Jan 10, 2008	To help prevent the symptoms of asthma.	Reduces inflammatory reaction by limiting the capillary dilatation and permeability of the vascular structures.

Future aspects of nasal drugs

1. **Enhanced delivery systems**

- **Advanced Devices:** Development of more precise and user-friendly delivery devices that optimize spray patterns and minimize drug waste.
- **Nanotechnology:** Use of nanoparticles to improve drug penetration and targeting within the nasal mucosa.[43]

2. **Targeted therapies**

- **Brain Targeting:** Nasal drugs that can bypass the blood–brain barrier to treat neurological conditions, such as Alzheimer's disease or Parkinson's disease.
- **Local Treatment:** Medications specifically designed to address localized infections or conditions within the nasal passages and upper respiratory tract.[44]

3. **Improved Formulations**

- **Extended-Release:** Formulations that provide a controlled release of medication over a longer period, reducing the need for frequent dosing.
- **Combination therapies:** Nasal formulations that combine multiple drugs or therapeutic agents to treat complex conditions more effectively.[45]

4. **Bioavailability**

- **Enhanced Absorption:** Techniques to improve the absorption of drugs through the nasal mucosa, such as using permeation enhancers or optimizing drug properties.
- **Reduced Degradation:** Strategies to protect drugs from degradation within the nasal cavity, ensuring that more active ingredients reach the systemic circulation.[38,45,46]

5. **Personalized Medicine**

- **Genomic Tailoring:** Development of nasal drugs that are customized on the basis of an individual's genetic profile to increase efficacy and minimize adverse effects.
- **Patient-specific Formulations:** Formulations that are tailored to specific patient needs and responses, potentially via advanced diagnostics.[47]

6. Nasal vaccines

- **Needle-free Vaccination:** Nasal vaccines offer an alternative to injections, potentially increasing accessibility and compliance.
- **Broad-Spectrum Immunity:** Research into nasal vaccines that can protect against a range of pathogens or variants of diseases.[48,49,8]

7. Regulatory and Safety Advances

- **Regulatory Innovations:** Evolving regulatory frameworks to accommodate new nasal drug technologies and ensure their safety and efficacy.[50,51]
- **Safety monitoring:** Enhanced methods for monitoring and assessing the safety of nasal drugs, including post market surveillance and real-world evidence.[52,53]

8. Patient Compliance and Convenience

- **Ease of** use: Nasal drug products that are more user friendly and convenient should be designed to improve patient adherence to treatment regimens.
- **Reduced Side Effects:** Formulations aimed at minimizing side effects and improving the overall patient experience.

Together, these factors represent a broad and evolving landscape in nasal drug development, promising more effective, personalized, and convenient treatment options in the future.

CONCLUSION

Newly approved nasal drugs represent a significant improvement in treatment options. They offer enhanced efficacy through advanced delivery systems and improved formulations, making them more effective and easier for patients to use. Innovations such as targeted therapies and nasal vaccines have broadened their application, addressing a wider range of conditions. Personalized approaches promise tailored treatments, while ongoing safety advancements ensure broader accessibility. Overall, these new nasal drugs improve both therapeutic outcomes and patient convenience.

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