

REVIEW ARTICLE ON NASAL DRUG DELIVERY SYSTEM

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Abstract: The use of the nasal route for the delivery of challenging drugs such as small polar molecules, vaccines, hormones, peptides and proteins has created much interest in nowadays. Due to the high permeability, high vasculature, low enzymatic environment of nasal cavity and avoidance of hepatic first pass metabolism are well suitable for systemic delivery of drug molecule via nose. The present review describes nasal delivery systems in recognizing to its potential and limits. The present review is an attempt to provide some information concerning nasal drug delivery system such as limitations, advantages, mechanism of drug absorption, anatomy of nasal cavity, factors affecting of nasal drug delivery, strategies to enhance nasal absorption, applications, novel drug formulations, and recent advancement of nasal delivery systems.

Keywords: Nasal Drug Delivery, Anatomy and physiology, Nasal Absorption, Nasal Preparations, Nose.

INTRODUCTION

In recent time, the nasal drug delivery received a great deal of attention for its convenient, promising, and reliable way of systemic administration for drugs, especially for those drugs which are ineffective orally and those which must be administered by injections. Over the last few decades, transmucosal nasal drug delivery as a non-invasive route has occupied an important place in the field of drug delivery technology. This route provides a large surface area, porous endothelial membrane, high total blood flow, bypassing the first-pass metabolism, and ready accessibility. Furthermore, nasal mucosa is permeable to more compounds than the gastrointestinal tract due to the absence of pancreatic, gastric enzymatic activities, and interference by gastrointestinal contents. The early recorded historical application of nasal drug delivery was restricted to topical applications of drugs intended for only local effects. However in recent times, its application grown to include a wide range of targeted areas in the body to produce local and systemic effects. Nasal drug delivery also finds a special place in the traditional system of medicine such as the Ayurvedic system of Indian medicine which is called as “Nasya karma” and is a well-recognized way of treatment [1-4].

CENTRAL NERVOUS SYSTEM (CNS) DELIVERY THROUGH NASAL ROUTE

The intranasal route has encouraging approach for the delivery of drugs to the brain. The delivery of drugs to CNS from the nasal route may occur through olfactory neuroepithelium.

Drug delivery through nasal route into CNS has been reported for Alzheimer’s disease, brain tumors, epilepsy, pain, and sleep disorders [5,6,7,8]

Table 1: Structural features of various regions and their impact on the permeability of nasal cavity

Region	Structural features	Permeability
Nasal vestibule	Nasal hairs (vibrissae) Epithelial cells are stratified, squamous, and keratinized Sebaceous glands present	Least permeable due to the presence of keratinized cells, very resistant to hydration and can withstand insults from noxious substances of the environment
Atrium	Transepithelial region Stratified squamous cells present anteriorly and pseudostratified cells with microvilli present posteriorly The narrowest region of the nasal cavity	Less permeable as it has small surface area and stratified cells are present anteriorly

Respiratory region (inferior turbinate middle turbinate superior turbinate)	Pseudostratified ciliated columnar cells with microvilli (300 per cell), large surface area Receives maximum nasal secretions due to the presence of seromucous glands, nasolacrimal duct, and goblet cells Richly supplied with blood for heating and humidification of inspired air, the presence of paranasal sinuses	Most permeable region due to large surface area and rich vasculature
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Olfactory region
Direct access to cerebrospinal fluid

Specialized ciliated olfactory nerve cells for smell perception

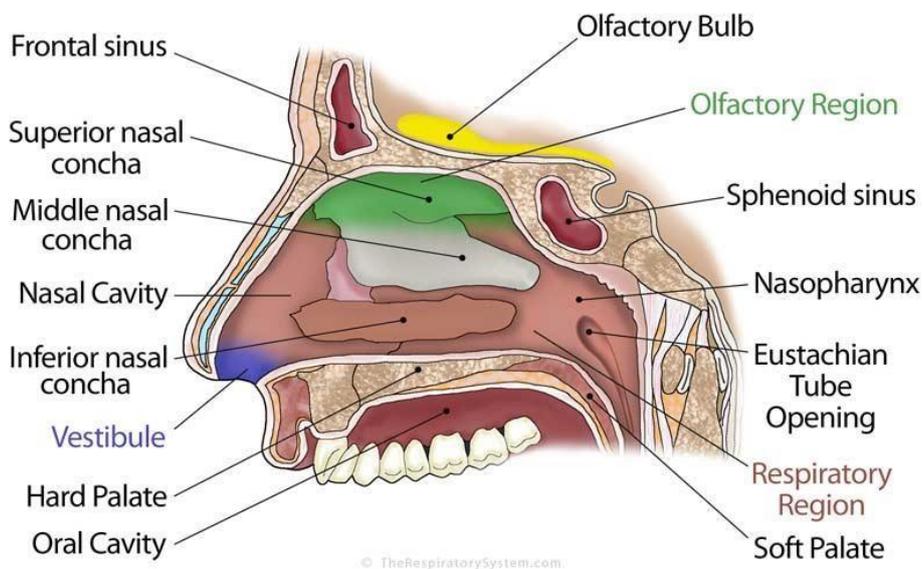
Nasopharynx

Receives ophthalmic and maxillary divisions of the trigeminal nerve
The upper part contains ciliated cells, and the lower part contains squamous epithelium

Receives nasal cavity drainage

NASAL ANATOMY AND PHYSIOLOGY

Nasal Cavity



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 150cm² 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 turbinates: the superior, the median and the inferior (Michael *et al.*, 2005).The main nasal airway having the narrow passages, usually it has 1-3mm wide and these narrows structures are useful to nose to carryout its main functions. 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, where as respiratory region, which has a typical airways epithelium covered with numerous microvilli, resulting in a large surface area available for drug absorption and transport (Sarkar MA, 1992). In this way the mucus layer is propelled in a direction from the anterior to-towards the posterior part of the nasal cavity. The goblet cells are present in the mucus membrane which covers the nasal turbinate and the atrium; it secretes the mu-cus as mucus granules which are swelling in the nasal fluid to contribute to the mucus layer.

ADVANTAGES OF NASAL DRUG DELIVERY SYSTEM

1. Rapid absorption, higher bioavailability therefore lower dose.
2. Fast onset of therapeutic action.
3. Avoidance of liver first pass effect.
4. Avoidance of metabolism by gastrointestinal tract.

5. Reduction risk of overdose.
6. Non-invasive therefore reduced risk of infectious disease transmission.
7. Improved patient compliances.

LIMITATIONS OF NASAL DRUG DELIVERY SYSTEM

1. There is a risk of local side effects and irreversible damage of the cilia of nasal mucosa, both from substances and from constituents added to the dosage form.
2. Certain surfactants used as chemical enhancer may disrupt and even dissolve membrane in high concentration.
3. There could be a mechanical loss of the dosage form into the other parts of the respiratory tract like lungs because of the improper technique of administration.

MECHANISM OF NASAL ABSORPTION

The initial step in the absorption of drug from the nasal cavity is passage through the mucus; large or charged particles may find it more difficult to cross. But small unchanged particles easily pass through this layer, the mechanisms for absorption through the nasal mucosa. These include paracellular transport via movement between cell and transcytosis by vesicle carriers, transcellular or simple diffusion across the membrane.[9]

1. The first mechanism includes aqueous route of transport, which is also called as the paracellular route. This is slow and passive route, inverse log-log relationship between intranasal absorption and the molecular weight of water soluble compounds. Poor bio-availability was observed for drugs with a molecular weight greater than 1000 Daltons.[10]
2. The second mechanism is transport a lipoidal route is known as transcellular process and is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. Drugs also cross membrane by an active transport route via carrier mediated means or transport through the opening of junctions. For example, Chitosan, a natural biopolymer opens tight junctions between epithelial cells to facilitate drug transport.[11, 12]

STRATEGIES TO IMPROVE NASAL ABSORPTION

Various strategies used to improve the bioavailability of the drug in the nasal mucosa which includes

1. To improve the nasal residence time
2. To enhance nasal absorption
3. To modify drug structure to change physicochemical properties.

APPLICATIONS

1. Delivery of non-peptide pharmaceuticals

Low molecular weight (below 1000 daltons) small non-peptide lipophilic drugs are well absorbed through the nasal mucosa even though absence of permeation en-hancer.

Delivery of Drugs to Brain through Nasal Cavity:

This delivery system is beneficial in conditions like Par-kinson's disease, Alzheimer's disease or pain because it requires rapid and/or specific targeting of drugs to the brain. The development of nasal delivery system to brain will increase the fraction of drug that reach the CNS after nasal delivery.

4. Delivery of Vaccines through Nasal Route:

Main reasons for exploiting the nasal route for vaccine deli-very are 1) the nasal mucosa is the first site of contacts with inhaled pathogens, 2) The nasal passages are rich in lymphoid tissue, 3) Creation of both mucosal and systemic immune responses, 4) Low cost, patient friendly, noninjectable, safe.

Nasal delivery of vaccines has been reported to not only produce systemic immune response, but also local immune response in the nasal lining, providing additional barrier of protection (Mestecky J *et al.*, 1997). Delivering the vaccine to the nasal cavity itself stimu-lates the production of local secretory IgA antibodies as well as IgG, providing an additional first line of de-fense, which helps to eliminate the pathogen before it becomes established (Durrani Z *et al* 1998).

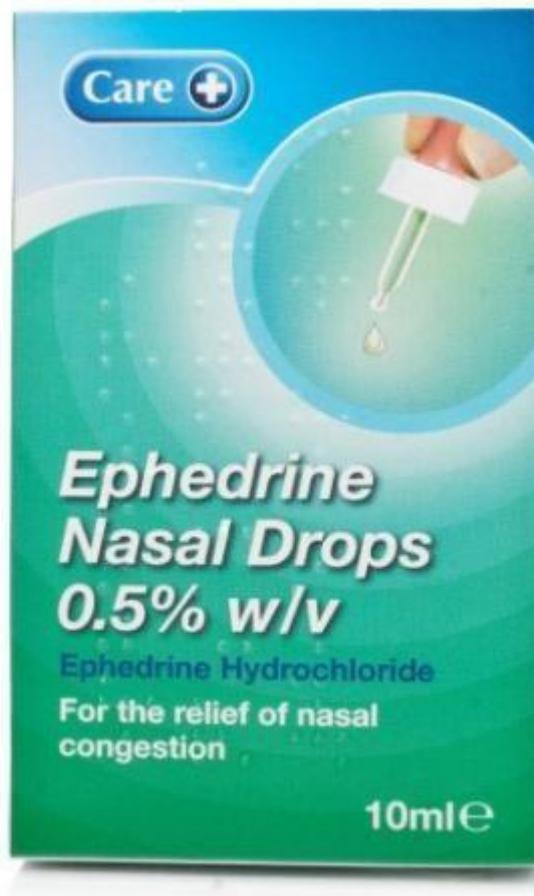
Table 1-Formulation and Active Agent that have been utilized in Nasal Drug Delivery[5, 9]

SR. NO.	FORMULATION	ACTIVE AGENT
1.	In-situ Nasal Gel	Midazolam, Insulin, Triptans, Diltiazem
2.	Nasal Inserts	Chlorpromazine, Albuterol
3.	Microspheres	Beta-Amyloid Fibril, Starch Microspheres, Dextran Gentamicin, Insulin, Desmopressin
4.	Microparticles	Serum albumin, Thiolated Chitosan Microparticles
5.	Dry Powder	Zolmitriptan
6	Nasal Gel	Oxytocin, Metoclopramide Hydrochloride

ADVANCEMENT IN THE NASAL DOSAGE FORMS

- Nasal Drops:** Nasal drops are one of the most simple and convenient system developed for nasal delivery. The main disadvantage of this system is the lack of the dose precision and therefore nasal drops may not be suitable for prescription products. It has been Reported that nasal Drops deposits human serum in the nostrils more efficiently than nasal spray.[1]
- Nasal Spray:** 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. These are preferred over powder sprays because powder results in mucosal irritation.[1]
- Nasal Powders:** This dosage form may be developed if solution and suspension dosage forms cannot be developed e.g. due to lack of drug stability. The advantages to the nasal powder dosage form are the absence of preservative and superior stability of 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. Local application of drug is another advantage of this system.[1]
- Nasal Gel:** The nasal gel showed growing interest due to reduction of post-nasal drip, high viscosity, reduction of taste impact due to reduced swallowing, reduction of anterior leakage of the formulation, reduction of irritation by using soothing/emollient excipients and target delivery to mucosa for better absorption.[3]
- Nasal Inserts:** Nasal inserts are novel, bioadhesive, solid dosage forms for prolonged systemic drug delivery via the nasal route. The principle of the dosage form is to the nasal fluid from the mucosa after administration and to form a gel in the nasal cavity to avoid foreign body sensation.[1]

1. Nasal Drops



Ephedrine Nasal Drops 0.5% w/v[14]

2. Nasal Spray



Vicks Vapospray[15]

3. Nasal Gel



Clevian (1% Piroxicam)[16]



Nasal Antisnoring Inserts

4. Nasal Inserts

EVALUATION OF NASAL FORMULATIONS

To improving the efficiency and effectiveness of active principles, formulations, and devices, another important objective of the pharmaceutical research is improving the link between *in vitro* test data and *in vivo* performance. In this way, the helpful dialogue among manufacturing, regulators, and academic investigators, which already started with workshops concerning bioequivalence, is continuing. These formal attitudes are most likely to reflect those involved in the development of oral or nasal inhalation orally inhaled and nasal drug products, and this reflex is often given special attention to their design and analytical control [17,18,19].

In vitro nasal permeation studies

Various methods are used to determine the drug diffusion through nasal mucosa from the formulation. The two most important ways to study the diffusion profile of the drug are discussed below.

In vitro diffusion studies

The nasal diffusion cell is fabricated in the glass. The water-jacketed recipient chamber has a total capacity of 60 ml and a flanged top of about 3 mm; the lid has three opening, each for sampling, thermometer, and a donor tube chamber. The 10 cm long donor chamber and a donor tube chamber has a total capacity of 60 ml and a flanged top of about 3 mm; the lid has three openings, each for sampling, thermometer, and a donor tube chamber. The 10 cm long donor chamber tube has an internal diameter of 1.13 cm. The nasal mucosa of sheep was separated from sublayer bony tissues and stoned in distilled water containing few drops at gentamicin injection. After the complete removal of blood from mucosal surface, is attached to the donor chamber tube. The donor chamber tube is placed such a way that it just touches the diffusion medium in recipient chamber. At predetermined intervals, samples (0.5 ml) from recipient chamber are with a draw and transferred to amber colored ampoules. The samples withdrawn are suitably replaced. The samples are estimated for drug content by a suitable analytical technique. Throughout the experiment, the temperature is maintained at 37°C [61,69-71], *in vitro*, one study showed that almost 95.2% drug was released from the formulation within 2 min [20].

In vivo nasal absorption studies*Animal models for nasal absorption studies*

The animal models employed for nasal absorption studies can be of two types, namely whole animal or *in vivo* model and isolated organ perfusion or *ex vivo* model.

In vivo models are rat model, rabbit model, monkey model, and dog model [21,22,23,24].

FACTORS INFLUENCING THE NASAL DRUG ABSORPTION**A) Factors Related to Drug[1, 6]**

- 1. Molecular Weight:** The permeation of drug less than 300 Dalton is not significantly influenced by the physicochemical properties of the drug.
- 2. Chemical Form:** Chemical form is the important parameter in drug absorption because conversion of the drug into a salt or ester form may alter its absorption.[1]
- 3. Polymorphism:** Polymorphism is known to affect the dissolution rate and solubility of drugs their absorption through biological membranes. So it is of prime importance that polymorphic stability and purity of drugs for nasal powders and/or suspensions should study.[7]
- 4. Solubility and Dissolution Rate:** For better absorption drug should get dissolve. If particles are present, it is somewhat difficult for absorption.

CONCLUSION

Nasal drug delivery system is a promising alternative route of administration for the several systemically acting drugs with poor bioavailability and it has advantages in terms of improved patient acceptability and compliance compared to parenteral administration of drugs. This delivery system is beneficial in conditions like Parkinson's disease, Alzheimer's disease or pain because it requires rapid and/or specific targeting of drugs to the brain and it is a suitable route to produce immune response against various diseases like anthrax, influenza etc., The delivery of drug molecules across the nasal mucosa opens a new hope for the both local and systemic delivery of medicaments. Nasal drug delivery is a promising alternative route of drug administration for local, systemic and central nervous system action. It has advantages in terms of reduces systemic exposure and hence side effects and avoiding first-pass metabolism. However, the intranasal route presents several limitations which must be overcome to develop a successful nasal medication. Physiological conditions, physicochemical properties of drug and formulation are most important factors that affect nasal absorption. In future, the extensive research is necessary to make this route of delivery more efficient and popular.

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