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A Review On-Naso Pulmonary Drug Delivery System

Onkar Kalwale
Dr. Vedprakash Patil Pharmacy College, Aurangabad

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ABSTRACT
The intranasal route has become one of the most explored areas in the field of pharmaceutical research for the delivery of small polar molecules, vaccines, hormones, peptides, and proteins. Due to its high membrane permeability, high vasculature, low enzymatic environment, and avoidance of hepatic first-pass metabolism, this route has been chosen for the systemic distribution of medicines. The enormous surface area of the nasal mucosa promotes non-invasiveness, direct medication transport to the central nervous system (CNS), and rapid commencement of therapeutic impact. The intranasal route can enhance patient convenience, comfort, and compliance because it is practically painless and simple for doctors or patients to administer. This page seeks to provide information about the nasal cavity, its benefits and drawbacks, factors affecting nasal drug absorption, methods to enhance drug absorption, dosage forms, and delivery systems for pharmaceuticals, and some of their applications.

KEYWORDS: Naso-Pulmonary drug delivery, mucociliary clearance, first-pass metabolism, proteins, peptides.

I. INTRODUCTION

Due to its ease of manufacture and administration, the oral route is the preferred and practical mode of drug delivery. Research on alternative drug delivery methods began as a result of inadequate gastrointestinal absorption. [1]In ancient times the Indian Ayurvedic system of medicines used a nasal route for the administration of drugs and the process is called "Nasya". Nowadays, oral and parenteral medication delivery methods are seen as less effective and less dependable than intranasal drug delivery. Without a doubt, intranasal medication administration has been utilized extensively for a long time for the symptomatic alleviation, prevention, or treatment of topical nasal diseases. [2, 3]

To overcome the problems associated with the oral and parenteral route, the alternative route of drug administration such as transdermal, rectal, buccal, and nasal are being investigated. All these routes bypass hepatic first-pass metabolism and offer alternative routes for the systemic delivery of drugs.

Currently, migraine, osteoporosis, smoking cessation, nocturnal enuresis, and vitamin B12 insufficiency are all being treated with nasal administration systems. Cancer treatment, epilepsy treatment, antiemetics, rheumatoid arthritis treatment, and insulin-dependent diabetes treatment are additional therapeutic areas that are being researched or may benefit from nasal delivery [4, 5,6].

NASAL ANATOMY AND PHYSIOLOGY

The nasal channel that connects the nasal vestibule to the nasopharynx is around 12–14 cm deep. The mucus that shields the mucosa from the inspired air is in close contact with the nasal cellular machinery in this channel. [1] The vestibular, respiratory, and olfactory regions are three distinct functional zones located in the nasal cavities. [7]

The human nasal cavity has a total surface area of about 180 cm2 and a roughly 16–19 ml volume. The septum divides it into two nasal chambers. The following are descriptions of a few of the regions:

1) The Respiratory Region

The respiratory region is the largest having the highest degree of vascularity and is mainly responsible for systemic drug absorption.

2) The Vestibular Region

It is located at the opening of the nasal passage and is responsible for filtering out airborne particles. It is considered to be the least important of the three regions with regard to drug absorption.

3) The Olfactory Region

It is about 10cm2 in surface area and it plays a vital role in the transportation of drugs to the brain and the CSF. The human olfactory region comprises thick connective tissue lamina propria, upon which the olfactory epithelium rests. Lamina propria has axons, Bowen's bundle, and blood vessels whereas epithelium consist of three different cells i.e. basal cells, supporting cells, olfactory receptor cells, etc. Neurons are interspersed between supporting cells. The

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olfactory receptor cells are bipolar neurons with a single dendrite extending from the cell body to the free apical surface where it ends in an olfactory knob carrying nonmotile cilia, which extend above the epithelium.[8] 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 10-15 minutes the pH of the mucosal secretion'sranges from 5.5-6.5 in adults. Numerous enzymes, for instance, Cytochrome P-450, Carboxylesterase, and Glutathione S-transferase are present in the nasal cavity.

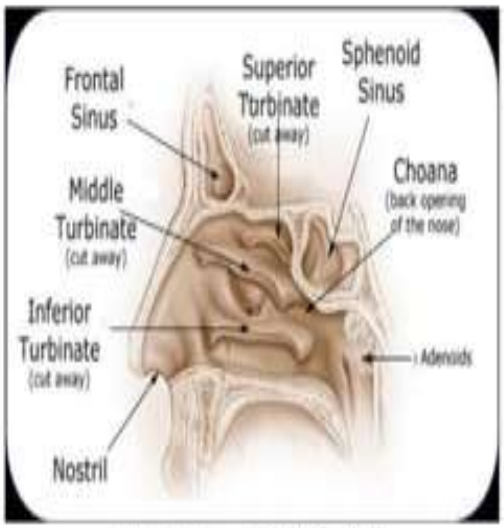
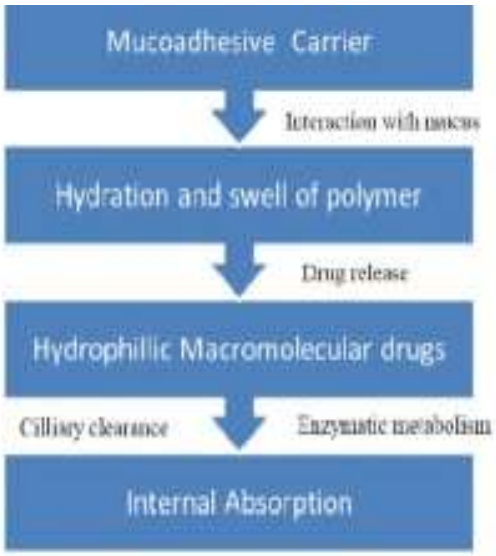


Fig. 1 Anatomy of Nasal Cavity [1]



ADVANTAGES OF NASAL DRUG DELIVERY SYSTEM [9]

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 the gastrointestinal tract.
5. Reduction of risk of overdose.
6. Non-invasive therefore reducing risk of infectious disease transmission.
7. Improved patient compliance

LIMITATIONS OF NASAL DRUG DELIVERY SYSTEM [1]

1. Both chemicals and ingredients added to the dose form carry a risk of local side effects and irreversible damage to the cilia of the nasal mucosa.
2. When present in high concentrations, certain surfactants utilized as chemical enhancers can disrupt and even dissolve membranes.
3. Due to incorrect delivery methods, the dosage form could mechanically leak into other respiratory tract organs, such as the lungs.

CHARACTERISTICS OF AN IDEAL DRUG CANDIDATE FOR NASAL DELIVERY[10,11]

1. The drug's particle size should range from 5 to 10 micrometers. Particles smaller than 5 m are immediately inhaled into the lungs, while those larger than 10 m are deposited in the nasal cavity.
2. The drug's molecular weight should be less than 1000 Da.
3. Drug molecules with cyclic shapes are more absorbable than those with linear shapes.
4. The medication shouldn't irritate the nasal mucosa and shouldn't smell or taste bad.
5. The drug's dosage shouldn't exceed 25 mg per dose.
6. It shouldn't cause any hazardous nasal metabolites and should have adequate stability qualities.
7. The clinical justification for the nasal dosage form should be appropriate.

FACTORS AFFECTING NASAL DRUG ABSORPTION[12,13]

The systemic bioavailability of the drug through the nasal route is affected by several factors e.g. physiochemical properties of the drug, the anatomical and physiological properties of thenasal cavity, the type and characteristics of

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selected nasal drug delivery system, andpathophysiological conditions.

1) Physiochemical properties of drug
a. Molecular size and molecular weight
b. Lipophilic- hydrophilic balance
c. Enzymatic degradation in the nasal cavity
d. Polymorphism
e. Solubility and dissolution rate

2) Nasal mucosal-related factors
a. Blood supply and membrane permeability
b. Mucociliary clearance and ciliary beatings
c. Pathological conditions
d. Nasal secretions

3) Formulation-related factors
a. Physical form
b. pH
c. osmolarity
d. viscosity
e. volume of solution applied and drug concentration

Formulation Development Research In Nasal Drug Delivery [1]

Most of the over-the-counter nasal preparations are formulated as solution, to treat the nasal symptoms of allergic rhinitis and common cold. A simple drug solution is adequate for this purpose as it produces better dispersion over greater surface area. The nasal residence time of such formulation is short (3-20 min) and exhibit high inter individual variability. This route provides fast peak levels in circulation. Large number of drugs has been evaluated for systemic bioavailability after transnasal administration in experimental animal models. Transnasal administration of drugs in diverse dosage forms such as sprays, powders, and microspheres have been attempted for improved residence and bioavailability. The nasal delivery is receiving attention for management of postoperative pain; mucosal administration requires only a 1.1-1.5-time higher dose of fentanyl than intravenous dose. The nasal delivery of vaccines is a very attractive route of administration in terms of efficacy.

Novel Intranasal Drug Delivery System To Target Cns [14]

a) Microemulsion

The microemulsion system is a promising approach for intranasal delivery. Microemulsions are clear, stable, isotropic mixture of oil, water and surfactant, frequently in combination with a co-surfactant. These systems are currently of interest to the pharmaceutical scientist because of their considerable potential to act as drug delivery vehicles by incorporating a wide range of drug molecules. They offer the advantage of spontaneous formation, ease of manufacturing and scale-up, thermodynamic stability and improved drug solubilization and bioavailability. Preparing a pharmaceutically acceptable dosage form demands a clear understanding of the micro-emulsion structure, phase behavior, factors leading to its thermodynamic stability, factors influencing drug release from the formulation, requirements of ideal microemulsion excipients, and the potential uses and limitations of the microemulsion system.

b) Nano-particles [14]

polymer, lipid or combination of both. Nano-systems employed for the development of nano drug delivery system in the treatment of CNS disorder include polymeric nano-particles, nano-spheres, nano-suspension, nano-emulsions, nano-gels, nanomicelles and nano-liposomes, carbon nano-tubes, nano-fibres and nano-robots, solid lipid nano-particles (SLN), nan-structured lipid carriers (NLC) and lipid drug conjugates (LDC). The correct mechanism of barrier opening by nano-particles is not exactly known. But the delivered nano-particles enter into the brain by crossing the BBB by various endocytotic mechanisms. The polymeric nano-particles made from albumin or poly (butylcyanoacrylate) is reported to enter into the brain by their small size mediated endocytosis. These nanoparticles travel intact and release the drug in brain microenvironment directly which is finally biodegraded due to endocytotic uptake because of very small size by BBB.

c) Microsphere

Microsphere technology is one of the specialized systems becoming popular for designing nasal products, as it provides prolonged contact with nasal mucosa and thus enhances absorption and bioavailability. In the presence of microsphere, the nasal mucosa is dehydrated due to moisture uptake by the microspheres. This result in reversible shrinkage of the cells, providing a temporary physical separation of the tight (intercellular) junctions that increases the absorption of the drugs. Microspheres used in nasal drug delivery are water insoluble but absorb water into matrix resulting swelling of the spheres to form a gel. The materials used in formulation of microspheres are starch, dextran, albumin and hyaluronic acid. Starch and dextran microspheres

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administered repeatedly. Bioavailability of protein and peptides has been improved in different animal by microsphere formulation. Some low molecular weight drugs also successfully delivered in microsphere formulation. Microspheres have been reported to be present up to 3-5 hours in the nasal cavity depending upon the bioadhesive material used for formulation. The ideal microsphere particle size requirement for nasal delivery should range from 10-50µm as smaller particles than this will enter the lungs.

d) Nasal In-situ Gels [15]

In-situ gel formulations are drug delivery systems that are in solution form before administration in the body, but after administration it undergoes gelation to form gel. This can be achieved by using deferent polymers such as Chitosan, PVA, Poloxamers, Carbopol.

ADVANCEMENT IN THE NASAL DOSAGE FORMS

1. Nasal Drops: Nasal drops are one of the most simple and convenient system developed for nasal delivery. The man 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.

2. 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.

3. 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.4. 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.

5. 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.

MARKETED FORMULATIN.

(1) XLEAR (2)VAPO SPRAY (3)FLO SALINE PLUS

II. CONCLUSION

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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