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A RECENT REVIEW ON NASAL DRUG DELIVERY SYSTEM

Jayesh K. Kakad[*1], Prasad K. More[1], Sheetal B. Gondkar[2], Ravindranath B. Saudagar[3]

[*1] Department of Quality Assurance Technique, KCT'S R.G. Sapkal College of Pharmacy, Anjaneri, Nasik 422 213, Maharashtra, India

[2] Department of Pharmaceutics, KCT'S R.G. Sapkal College of Pharmacy, Anjaneri, Nasik 422 213, Maharashtra, India

[3] Department of Pharmaceutical Chemistry, KCT'S R.G. Sapkal College of Pharmacy, Anjaneri, Nasik 422 213, Maharashtra, India

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***Correspondence for Author**
Jayesh K. Kakad
Department of Quality Assurance Technique, KCT'S R.G. Sapkal College of Pharmacy, Anjaneri, Nasik 422 213, Maharashtra, India

ABSTRACT

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 is due to high vascularity, large surface area, the avoidance of hepatic first-pass metabolism, gut wall metabolism and/or destruction in gastrointestinal tract. Since nasal mucosa offer several benefits for target delivery, a wide variety of therapeutic compounds may be administered intranasally for topical, systemic and central nervous system action. In this review we have discussed advantages, disadvantages, mechanism of action and factor affecting the permeability of drugs or biomolecule through nasal mucosa of nasal drug delivery system in local delivery, systemic delivery of the Drug. The principles underlying the development of Nasal Formulations are reviewed here.

KEY WORDS: Nasal Drug Delivery, Nasal Absorption, Nasal Preparations, Nose.

INTRODUCTION

Oral route is the desirable and convenient method of drug administration as their ease of manufacture and administration. Failure of adequate absorption through the gastrointestinal tract led to research on alternate routes of drug delivery. [1]

Therapy through intranasal administration has been accepted form of treatment in the Ayurvedic system of Indian Medicine. In recent years many drugs have been shown to achieve better systemic bioavailability through nasal route by oral administration. [2]

In nasal mucosa high permeability, high vascularity and low enzymatic environment of nasal cavity are well suitable for systemic delivery of drug molecules. The non-invasiveness and self administrative nature of nasal also attract the formulation scientist to deliver protein and peptides compounds. [3]

NASAL ANATOMY AND PHYSIOLOGY

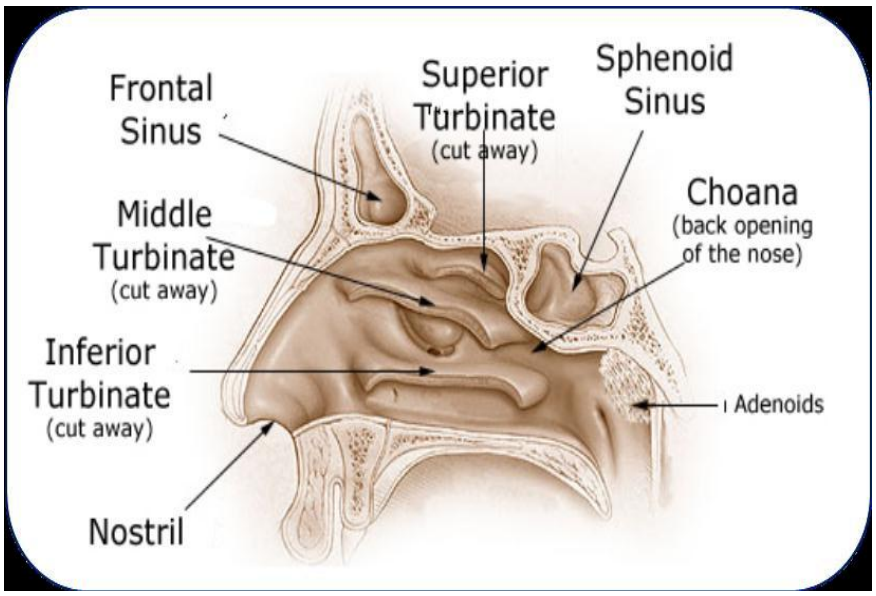

Fig. 1 Anatomy of Nasal Cavity [1]

In studying drug absorption from the nasal mucous membrane, it is necessary to have a clear understanding of anatomy and Physiology of the nose and how it relates to the characteristics of the delivery system used. The nasal passage which runs from the nasal vestibule to the nasopharynx has a depth of approximately 12-14 cm. In this passage the nasal cellular apparatus is in close contact with mucus which protects the mucosa from the inspired air. [1]
There are three separate functional zones in the nasal cavities, vestibular, respiratory and olfactory region.[2]

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

1) The Respiratory Region[2]

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

2) The Vestibular Region[2]

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

3) The Olfactory Region

It is of about $10cm^2$ in surface area and it plays a vital role in transportation of drugs to the brain and the CSF. Human olfactory region comprises if thick connective tissue lamina propria, upon which rests the olfactory epithelium. Lamina propria has axons, Bowens bundle and blood vessels whereas epithelium consist of three different cells i.e. basal cells, supporting cells and olfactory receptor cells etc. Neurons are interspersed between supporting cells. The olfactory receptor cells are bipolar neurons with a single dendrite and extending from the cell body to the free apical surface where it ends in an olfactory knob carrying non-motile cilia, which extend above the epithelium.[2]

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 secretions range from 5.5-6.5 in adults. Numerous enzymes for instance, Cytochrome P-450, Carboxylesterase and Glutathione S-tranferase are present in nasal cavity.

ADVANTAGES OF NASAL DRUG DELIVERY SYSTEM[4]

- Rapid absorption, higher bioavailability therefore lower dose.
- Fast onset of therapeutic action.
- Avoidance of liver first pass effect.
- Avoidance of metabolism by gastrointestinal tract.
- Reduction risk of overdose.
- Non-invasive therefore reduced risk of infectious disease transmission.
- Improved patient compliances.

LIMITATIONS OF NASAL DRUG DELIVERY SYSTEM[1]

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[5]

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.[5]

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.[1]
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.[1, 5]

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.
5. **Lipophilicity:** As lipophilicity goes on increasing it increases permeation through the nasal mucosa. Lipophilic compounds tend to readily cross biological membranes via the transcellular route since they are able to partition into the lipid (bilayer) of the cell membrane and diffuse into and transverse the cell in the cell cytoplasm. Drug like testosterone has been absorbed nasally already prove in animal models.
6. **Partition Coefficient and pKa:** As pH partition theory state that unionized species are absorbed well as compared with ionized hence it is same in the case of nasal absorption also.[1]

B) Factors Related to Formulation[8]

1. **pH:** The pH of the formulation, as well as that of nasal surface can affect a drug's permeation. To avoid nasal irritation, the pH of the nasal formulation should be adjusted to 4.5-6.5.
2. **Viscosity:** A higher viscosity of the formulation increases contact time between the drug and the nasal mucosa thereby increasing the time for permeation. At the same time highly viscous formulations interfere with the normal functions like ciliary beating or mucociliary clearance and thus alter the permeability of drugs.
3. **Osmolarity:** Optimum osmolarity should maintain as it causes shrinkage of the nasal epithelial mucosa and alters the permeation of drugs.
4. **Buffer Capacity:** Nasal formulations are generally administered in small volume ranging from 25-20 µL. Hence, nasal secretions may alter the pH of the administrated dose. This can affects the concentration of unionized drug available for absorption. Therefore, an adequate formulation buffer capacity may be required to maintain the pH.
5. **Drug Concentration, Dose and Dose Volume:** Drug concentration, dose and volume of administration are three interrelated parameters that impact the performance of the nasal delivery performance. Nasal absorption of L-Tyrosine was shown to increase with drug concentration in nasal perfusion experiments.[8]

C) Physiological Factors

1. **Effect of Deposition on Absorption:** Deposition of the formulation in the anterior of the nose provides a longer nasal residence time. The anterior portion of the nose is an area of

low permeability while posterior portion of the nose where the drug permeability is generally higher, provides shorter residence time.

2. **Nasal Blood Flow:** Nasal mucosal membrane is very rich in vascular and plays a vital role in the thermal regulation and humidification of the inhaled air therefore the drug absorption will depend upon the vasoconstriction and vasodilation of the blood vessels.[4]
3. **Effect of Enzymatic Activity:** Several enzymatic that are present in the nasal mucosa might affect the stability of drugs. For example, proteins and peptides are subjected to degradation by proteases and amino peptidase at the mucosal membrane. The level of amino peptidase present is much lower than that in the gastrointestinal tract. Peptides may also form complexes with immunoglobulin (IgS) in the nasal cavity leading to an increase in the molecular weight and a reduction of permeability.
4. **Effect of Mucociliary Clearance:** The absorption of drug is influenced by the residence (contact) time between the drug and the epithelial tissue. The mucociliary clearance is inversely related to the residence time and therefore inversely proportional to the absorption of drugs administered.
5. **Effect of Physical Condition:** Intranasal pathologies may affect the nasal mucociliary transport process and/or capacity for nasal absorption. There are times when the mucosa is crushing, bleeding, or dry. One may be suffering from rhinorhea, sinitis, or nasal infection. In people suffering from severe nasal allergies, an excessive nasal secretion can wash away the formulation before the drug has a chance of getting absorbed through the mucosa or before acting locally.[4]

APPROPRIATE DRUG CANDIDATE FOR NASAL DELIVERY[4]

1. Appropriate aqueous solubility to provide the desired dose in a 25-150µL volume of formulation administered per nostril.
2. Appropriate nasal absorption properties.
3. No nasal irritation from the drug should be there.
4. A suitable clinical rational for nasal dosage forms e.g. Rapid onset of action.
5. Low dose generally 25mg per dose.
6. No toxic metabolites.
7. No offensive odors associated with the drug.
8. Suitable stability characteristics.

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 Hydrocloride

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 has 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.

INTRANASAL DRUG DELIVERY SYSTEM[2]

Over the last years, due to the understanding of the positive attributes and appropriate characteristics of the nasal cavity, intranasal route has been increasingly considered for drug delivery when developing new chemical entities or improving the therapeutic profile of existing drugs. However, to assess the therapeutic viability of intranasal drug delivery several approaches should be considered, specially, to the nature of pathologic condition (acute or chronic) and intended effects of drug treatment (local, systemic or at CNS). Indeed, for acute disease conditions, the advantages afforded by intranasal drug delivery in terms of patient comfort and compliances may not be much relevant when compared with drug delivery by parenteral route. In contrast, this is particularly important to treat or control chronic medical conditions.

Intranasal Drug Delivery System[2]

1. Local Delivery
2. Systemic Delivery
3. Nasal Vaccines
4. CNS Delivery through Nasal Route

NOVEL INTRANASAL DRUG DELIVERY SYSTEM TO TARGET CNS[6]

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[6]

Nano-particles are colloidal systems with compact structure where the therapeutic agent is either entrapped within colloidal matrix or coated on the particle surface by conjugation or adsorption. Nano-particles can provide sustained and controlled drug release; they are mostly made up of 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, nano-micelles 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 nano-

particles 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 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[2]

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.[1]

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.[1]

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.[1]

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.[3]

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.[1]

MARKETED NASAL FORMULATIONS

1. **Nasal Drops**

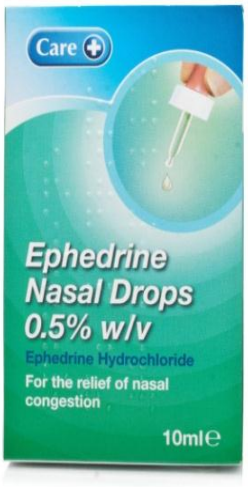

Fig. 2 Ephedrine Nasal Drops 0.5% w/v[13]

2. **Nasal Spray**

Fig. 3 Vicks Vapospray[14]

3. **Nasal Gel**

Fig. 4 Clevian (1% Piroxicam)[15]

4. **Nasal Inserts**

Fig. 5 Nasal Antisnoring Inserts[16]

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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