

**NASAL ROUTE: A NOVELISTIC APPROACH FOR TARGETED DRUG DELIVERY TO CNS**

Choudhary Rakhi *, Goswami Lakshmi

Division of pharmaceutical sciences, S.G.R.R.I.T.S, Patel Nagar, Dehradun-248001, Uttarakhand, India

E-mail: rakhichoudhary211@gmail.com

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ABSTRACT

Drug delivery through nasal route has attracted the interest of scientific community as it has been potentially explored as an alternative route for the administration of vaccines and biomolecules such as proteins, peptides and non-peptide drugs that are susceptible to enzymatic or acidic degradation and first-pass hepatic metabolism. The nasal mucosa is one of the most permeable and highly vascularised sites for drug administration ensuring rapid absorption and onset of therapeutic action. Intranasal administration is a non-invasive route for drug delivery, which is widely used for the local treatment of rhinitis or nasal polyposis. Since drugs can be absorbed into the systemic circulation through the nasal mucosa, this route may also be used in a range of acute or chronic conditions requiring considerable systemic exposure. In addition it minimizes the lag time associated with oral drug delivery and offers non-invasiveness, self medication, patient comfort and patient compliance which are hurdled in intravenous drug therapy. The objective of this review is to provide an anatomical, histological and physiological overview of nose, absorption enhancers, barriers related to nasal drug delivery, physicochemical, biological and formulation related factors affecting nasal drug delivery system and its advantages. It also highlights research approaches on brain targeting through nasal cavity.

Keywords: Non-invasiveness, Intranasal drug delivery, Barriers to intranasal delivery, Brain targeting.

INTRODUCTION

Historically, the use of the nasal route for drug delivery has received attention of mankind since ancient times. Nasal therapy, also called “nasaya karma”, has been recognized form of treatment in the Ayurvedic systems of Indian medicine.

Currently, Nasal drug delivery has been recognized as a very promising route for delivery of therapeutic compounds¹. Conventionally, the nasal route has been used for local delivery of drugs for treating nasal allergy, nasal congestion, or nasal infections. However systemic delivery through the nasal route has recently begun to explore possibilities for those requiring a rapid onset of action or necessitating avoidance of severe proteolysis involved in oral administration².

The use of the nasal pathway for the delivery of drugs is an emerging field in both pharmaceutical sciences and pharmaceutical industry. While the great majority of nasal formulations are designed and used for local delivery to treat nasal allergy, congestion or infections, other applications of nasal delivery have gained importance in recent years. Diseases of the Central Nervous System (CNS) such as schizophrenia, meningitis, migraine, Parkinson's disease and Alzheimer's disease require delivery of the drug to the brain for treatment³. Intranasal Therapy has been an accepted form of treatment in the Ayurvedic system of Indian Medicine. Nowadays many drugs have better systemic bioavailability through nasal route as compared to oral administration. Biotechnological advancement has lead to the development of a large number of protein and peptide drug for the treatment of several of diseases.

Anatomy and physiology of Nasal cavity

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.

There are 3 distinct functional zones in the nasal cavities, viz. vestibular, respiratory and olfactory regions:-

The vestibular area serves as a baffle system and its surface is covered by a common pseudo stratified epithelium where the long hairs may provide the function of filtering air borne particles.

Respiratory area has a surface lined by a pseudo stratified columnar epithelium and is normally covered by a dense layer of mucus that is constantly moving towards the posterior apertures of the nasal cavity by a powerful system of motile cilia⁴.

The olfactory segment is lined with a specialized type of pseudo stratified columnar epithelium, known as olfactory epithelium, which contains receptors for the sense of the smell. Olfactory mucosal cell types include: bipolar neurons, supporting cells, basal cells, and Bowman's glands. The axons of the bipolar neurons form the olfactory nerve (cranial nerve I). Bowman's glands are serous glands in the lamina propria, whose secretions trap and dissolve odoriferous substances. The total surface area of both nasal cavities is about 150 cm² and the total volume is about 15 ml as shown in figure I.

The olfactory neural cells or the axons are un-myelinated and interspaced between the supporting cells. They originate at the olfactory bulb in the CNS and terminate at the apical surface of the olfactory epithelium.

The olfactory knob (or vesicle) protrudes out from and above the apical surface of the olfactory epithelium. Approximately 10–23 cilia project from the basal bodies of the knob, each of length up to 200 μ m. The cilia contain chemical detectors that, once activated by odorants, initiate depolarisation of the olfactory axon by either direct ion-gated channels or cAMP operated ion-channels. The cilia entangle with the thick brush border of microvilli of the supporting cells at the air/mucus/tissue interface. The cilia are non-motile in the olfactory region (in contrast to respiratory tissue) since they lack the dynein arms which contain the Mg²⁺-ATPase that generates the force for ciliary motility.

The lamina propria of the olfactory epithelium, which is located beneath the epithelial layer(s), contains the blood supply, mucus secreting acinar glands (Bowman's glands),

nasal lymphatics, and a neuronal supply that consists of olfactory axon bundles, autonomic nerve fibres and the maxillary branch of the trigeminal nerve. Bowman's glands are under the control of the parasympathetic nervous system. These acinar-type glands produce nasal secretions in the lamina propria and secrete them through a narrow tube-like opening into the luminal space.

In the lamina propria the olfactory neurones taper together and are ensheathed by glial cells (or Schwann cells). These processes are called filia olfactoria. Filia olfactoria are unique features in the mammalian body in that around twenty axons are partitioned by the Schwann cell into fascicles. In this way a single Schwann cell may ensheath around a hundred or so axons. This feature allows 10–15 nm sized spaces between axons that act as ionic reservoirs for action potential propagation. Hence, perineuronal transport of molecules to the olfactory bulbs is limited by the size of these spaces. Mesaxons are pores in the filia olfactoria structure that allow passage of extracellular fluid into the neuronal bundle structure.

The average diameter, by electron microscopy, of olfactory axons in 2-month-old rabbits is ~200 nm, however, many of the axons have diameters of <100nm. Theoretically therefore transcellular transport of up to 200nm diameter particles is possible in these animals. Other species show similar olfactory axonal diameters, for example, the African Clawed frog, various bird species and humans have diameters of 198±93, 210–260 and 100–700 nm, respectively. The Schwann-sheathed axonal bundles then pass through the lamina propria and into the porous structure of the cribriform plate⁶ as shown in figure II.

Blood supply to nasal cavity

Nasal vasculature is richly supplied with blood to fulfil the basic functions of the nasal cavity such as heating and humidification, olfaction, mucociliary clearance and immunological functions⁶. Blood supply comes from branches of both the internal and external carotid artery, including branches of the facial artery and maxillary artery.

The named arteries of the nose are:

- **Sphenopalatine Artery**, a branch of maxillary artery.
- **Anterior Ethmoidal Artery**, a branch of ophthalmic artery.
- Branches of the **facial artery** supplying the vestibule of the nasal cavity.

Nose to brain delivery

The olfactory region is a small patch of tissue containing the smell receptor and is located at the very top of the nasal cavity near the inner end of the upper throat. The patch has a yellowish tinge, in contrast to its surrounding pink tissue, and consists of several million tiny endings of the olfactory nerve whose bundle passes through the cribriform plate and enters the farthest forward extension of the brain as shown in figure III. The olfactory epithelium is known to be a portal of entry for substance into the central nervous system and peripheral circulation. The transport of the drug across the nasal membrane and into the bloodstream may involve either passive diffusion of drug through the pores in the nasal mucosa or some from non passive transport.

Mechanism for drug permeation^{7,8}

The first step in the absorption of drug from the nasal cavity is passage through the mucus. Small, unchanged particles easily pass through this layer. However, large or charged

particles may find it more difficult to cross. Mucin, the principle protein in the mucus, has the potential to bind to solutes, hindering diffusion. Additionally, structural changes in the mucus layer are possible as a result of environmental changes (i.e. pH, temperature, etc.). Subsequent to a drug's passage through the mucus, there are several 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. Obstacles to drug absorption are potential metabolism before reaching the systemic circulation and limited residence time in the cavity. Several mechanisms have been proposed but the following two mechanisms have been considered predominantly.

The first mechanism involves an aqueous route of transport, which is also known as the paracellular route. This route is slow and passive. Poor bioavailability was observed 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.

Advantages of nasal drug delivery systems⁹

- Large nasal mucosal surface area for dose absorption
- Rapid drug absorption via highly vascularised mucosa
- Rapid onset of action
- Ease of administration, non invasive
- By pass the BBB
- Avoidance of the gastrointestinal tract and first pass metabolism
- Improved bioavailability
- Direct transport into systemic circulation and CNS is possible
- Lower dose/reduced side effects
- Improved convenience and compliance
- Self-administration

Limitations of nasal drug delivery systems⁹

- Volume that can be delivered into nasal cavity is restricted to 25-200µl.
- Not feasible for high molecular weight more than 1k Da.
- Adversely affected by pathological conditions.
- Drug permeability may alter due to ciliary movement.
- Drug permeability is limited due to enzymatic inhibition.
- Nasal irritants drugs cannot be administered through this route.
- Exact mechanism is not yet clearly known.

Factors affecting nasal drug absorption and approaches to overcome them

Some of the physicochemical, formulation and physiological factors are imperative and must be considered prior to designing intranasal delivery as shown in figure IV.

Physicochemical properties of drugs

Chemical form: The chemical form of a drug is important in determining absorption.

For example, conversion of the drug into a salt or ester form can also alter its absorption. Huang et al 1985 studied the effect of structural modification of drug on absorption¹⁰. It

was observed that in-situ nasal absorption of carboxylic acid esters of L-Tyrosine was significantly greater than that of L-Tyrosine.

Polymorphism: Polymorphism is known to affect the dissolution rate and solubility of drugs and thus their absorption through biological membranes.

Molecular Weight: A linear inverse correlation has been reported between the absorption of drugs and molecular weight up to 300 Da. Absorption decreases significantly if the molecular weight is greater than 1000 Da except with the use of absorption enhancers. Shape is also important. Linear

molecules have lower absorption than cyclic – shaped molecules.

Particle Size: It has been reported that particle sizes greater than 10 μ m are deposited in the nasal cavity.

Solubility & dissolution Rate: Drug solubility and dissolution rates are important factors in determining nasal absorption from powders and suspensions. The particles deposited in the nasal cavity need to be dissolved prior to absorption. If a drug remains as particles or is cleared away, no absorption occurs.

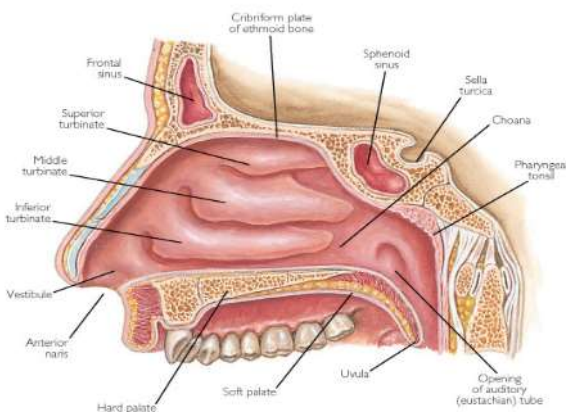


Figure I: Anatomy and physiology of nasal cavity

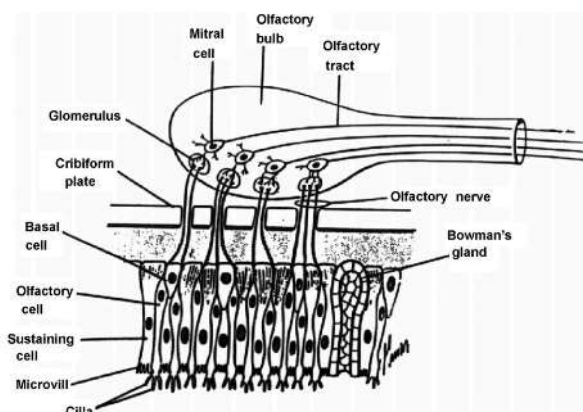


Figure II: Diagram of the olfactory area showing the olfactory epithelium, bulb and tract

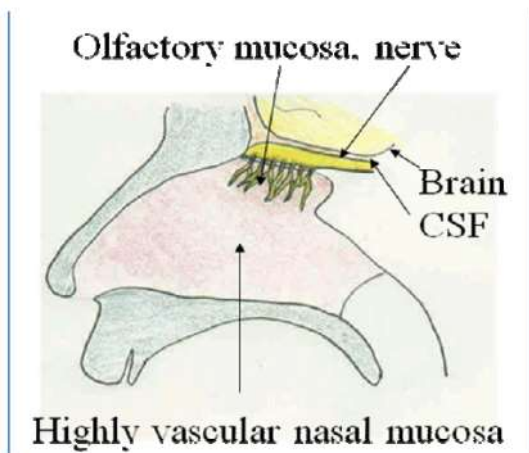


Figure III: Olfactory mucosa, a pathway for nose to brain delivery

Formulation factors

pH of the formulation: Both the pH of the nasal cavity and pKa of a particular drug need to be considered to optimize systemic absorption. Nasal irritation is minimized when products are delivered with a pH range of 4.5 to 6.5. Also, volume and concentration are important to consider. The delivery volume is limited by the size of the nasal cavity. An upper limit of 25 mg/dose and a volume of 25 to 200 μ L/nostril have been suggested.

- To avoid irritation of nasal mucosa;
- To allow the drug to be available in unionized form for absorption;
- To prevent growth of pathogenic bacteria in the nasal passage;
- To maintain functionality of excipients such as preservatives; and
- To sustain normal physiological ciliary movement.

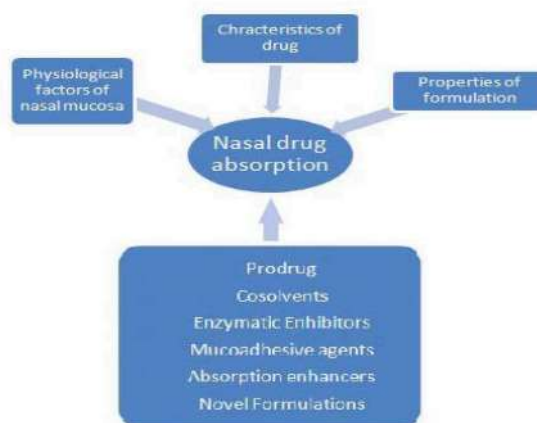


Figure IV: Factors affecting the characteristics of nasal drug delivery

Gelling / Viscosity building agents or gel-forming carriers: Pennington et al 1988 studied that increase in solution viscosity may provide a means of prolonging the therapeutic effect of nasal preparations¹¹.

Solubilizers: Aqueous solubility of drug is always a limitation for nasal drug delivery in solution. Conventional solvents or co-solvents such as glycols, small quantities of alcohol, Transcutol (diethylene glycol monoethyl ether), medium chain glycerides and Labrasol can be used to enhance the solubility of drugs.

Preservatives: Most nasal formulations are aqueous based and need preservatives to prevent microbial growth. Parabens, benzalkonium chloride, phenyl ethyl alcohol, EDTA and benzoyl alcohol are some of the commonly used preservatives in nasal formulations.

Antioxidants: Usually, antioxidants do not affect drug absorption or cause nasal irritation. Commonly used

antioxidants are sodium metabisulphite, sodium bisulphite, butylated hydroxyl toluene and tocopherol.

Humectants: Many allergic and chronic diseases are often connected with crusts and drying of mucous membrane. Therefore humectants can be added especially in gel-based nasal products. Humectants avoid nasal irritation and are not likely to affect drug absorption. Common examples include glycerin, sorbitol and mannitol.

Physiological factors

Effect of Deposition on Absorption: Deposition of the formulation in the anterior portion 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.

Nasal blood flow: Nasal mucosal membrane is very rich in vasculature and plays a vital role in the thermal regulation and humidification of the inhaled air. The blood flow and therefore the drug absorption will depend upon the vasoconstriction and vasodilatation of the blood vessels.

Effect of Enzymatic Activity: Several enzymes 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.

Effect of Mucociliary Clearance^{12,13}: The absorption of drugs 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.

Effect of Pathological Condition: Intranasal pathologies may affect the nasal mucociliary transport process and/or capacity for nasal absorption.

Nasal formulations¹⁴

Designing of nasal formulation depends upon the therapeutic need of the particular drug molecule, duration of action and duration of therapy. Both controlled release and conventional release drug delivery are possible through nasal route. Requirement of the pharmaceutical excipients depend upon the mode of drug delivery, i.e. local or systemic drug delivery.

Wide range of nasal formulations has been studied so far, and these include:

1. Nasal drops
2. Nasal powders
3. Nasal sprays (solution/suspension)
4. Nasal mucoadhesive particulate delivery (micro/nanoparticles, liposomes)

CONCLUSION

Targeted drug delivery system is the one which delivers the drug only to its site of action and not to the nontargeted organs or tissues. Drug delivery to the brain is a challenging task in the treatment of various diseases related to Central Nervous System (CNS) such as brain tumors, epilepsy, Parkinson's, Alzheimer's and Huntington's diseases owing to the blood-brain barrier (BBB). The delivery of the drug

through nasal route is a non invasive method of by passing the blood brain barrier (BBB) in order to deliver therapeutic agents to the brain. This method is generally useful for those drugs that do not cross the BBB to be delivered to the central nervous system in a few minutes along with both the olfactory and trigeminal neuronal pathway. This delivery system also have various clinical benefits like reduction in drug dosage and systemic exposure, due to which lesser side effects is seen. Drug related factor and Patho physiological condition of nose determine the nasal drug absorption. Some common approaches for enhancing the bioavailability of nasal drug are increasing the nasal residence time of drug, use of absorption or penetration enhancers and minimization of the mucociliary clearance. This route is believed to be an alternative route to oral and parenteral because of the successful administration of vaccines and biomolecules such as proteins, peptides and non-peptide drugs, that are susceptible to enzymatic or acidic degradation and first-pass hepatic metabolism .Moreover it also offers non-invasiveness, self medication, patient comfort for the delivery of the drug.

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