ejpmr, 2021,8(9), 223-238

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

FORMULATION APPROACHES FOR NASAL DRUG DELIVERY SYSTEM - A REVIEW

Harshada Rokade[1*], Monika Ola[2], Somnath Tambade[3], Rajveer Bhaskar[4] and Shwetal Pawar[5]

[1]Department of Pharmaceutics, R.C. Patel Institute of Pharmaceutical Education and Research, Shirpur – 425 405, Maharashtra, India.

[2]Department of Pharmaceutics, R.C. Patel Institute of Pharmaceutical Education and Research, Shirpur – 425 405, Maharashtra, India.

[3]Department of Pharmaceutics, Government College of Pharmacy, Aurangabad – 431 005, Maharashtra, India.

[4]Department of Quality Assurance, R.C. Patel Institute of Pharmaceutical Education and Research, Shirpur – 425 405, Maharashtra, India.

[5]Department of Cosmetic Technology, R.C. Patel Institute of Pharmaceutical Education and Research, Shirpur – 425 405, Maharashtra, India.

***Corresponding Author: Harshada Rokade**

Department of Pharmaceutics, R.C. Patel Institute of Pharmaceutical Education and Research, Shirpur - 425 405, Maharashtra, India.

Article Received on 1/07/2021 **Article Revised on 20/07/2021** **Article Accepted on 08/08/2021**

ABSTRACT

Most oral drugs have low bioavailability and limited bioaccessibility to the brain with rapid biotransformation, unwanted side effects, and high costs all of which are distressing to patients. The intranasal route of drug administration promotes better bypass across the blood brain barrier and reduces systemic side effects by reducing the frequency of dose administration. Drugs administered via the nasal route generally have high bioavailability, higher brain exposure at a lower dose than the oral dose with fewer side effects. It presents some possibilities for improving drug penetration through the nasal barrier and summarizes some in vitro, ex vivo and in vivo technologies for testing drug release through the nasal epithelium in the brain. In this review article includes, physiology of nose and nasal to brain drug delivery approaches.

KEYWORDS: Nasal drug delivery systems, Vivo and Vitro technologies to test drug delivery through the nasal epithelium of the brain.

INTRODUCTION

Nowadays, many drugs have better systemic bioavailability via the nasal route than oral administration.[1] Over the past two decades, there has been a marked improvement in our understanding of the underlying etiology and treatment of central nervous system (CNS) disorders.[2] Intranasal drug delivery has long been explored for topical nasal conditions such as decongestion and rhinitis. The nasal mucosa serves as a favorable site for the installation of drugs due to its easy accessibility, large surface area and high blood flow with high perfusion area. Nasal administration of the drug avoids first-pass hepatic metabolism, resulting in faster onset of action at lower doses and fewer side effects.[3] According to the World Health Organization (WHO), brain disorders account for 35% of diseases in Europe.[4] More than 98% of small molecule drugs do not reach the brain through the bloodstream and about 100% of large molecule drugs do not reach the brain through the blood stream.[5]

The intranasal administration of drugs or biological products such as peptides, proteins, oligonucleotides, viral vectors, stem cells targeting the central nervous system (CNS) is still currently a field of research of great interest to overcome the limits imposed by BBB and BCSFB.[6] The intranasal route of administration is a non-invasive method for rapid administration of drugs directly from the nasal mucosa to the brain and spinal cord to treat central nervous system disorders while minimizing systemic exposure.[7] New drug delivery strategies to access the brain involve bypassing the blood-brain barrier (BBB), rather than crossing it. Nose-brain release has been shown to transport the drug directly to the brain via the olfactory and trigeminal nerve pathways.[8] This unique configuration offers a promising route for the direct delivery of drugs from the nasal cavity to the brain.[9] In the current scenario, the intranasal route to bypass BBB is explored, as this route provides a novel, practical, simple and non-invasive approach to bypassing the blood-brain barrier and reduces systemic exposure and therefore systemic adverse effects.[10] The drug after intranasal administration reaches the region of the olfactory epithelium of the nasal mucosa which acts as a gateway for substances entering the CNS due to the neural connection between the nasal mucosa and the brain.[11]

The nasal cavity offers several distinctive advantages for systemic administration such as.[12,13,14]

1. A large surface for the absorption of the drug.
2. Comfort and good patient compliance.
3. Rapid attainment of therapeutic levels of the drug in the blood.
4. High drug permeability, especially for hydrophobic and low molecular weight drugs.
5. Prevention of unfavourable environmental and gastrointestinal conditions.
6. Bypass of first pass hepatic metabolism.
7. Potential direct release of the drug in the brain along the olfactory nerves.
8. Site of direct contact of vaccines with lymphatic tissues.

The nasal route of drug administration can be used for both local and systemic administration For example; the administration of localized nasal medications is usually used to treat conditions related to the nasal cavity, such as congestion, rhinitis, sinusitis and associated allergic conditions.[15] A wide range of drugs, including corticosteroids, antihistamines, anticholinergic, and vasoconstrictors, can be given locally.[16] A wide variety of pharmaceutical dosage forms including solutions, gels, suspensions, emulsions, liposomes and microparticles can be used to achieve systemic pharmacological action.[17,18,19] Most of dosage forms are primarily designed to take advantage of the rapid onset of action when administered nasally. For example, morphine.[20] and ketamine.[21] can be administered intranasal to achieve rapid analgesic effects. In addition, vaccines can also be given using the nose as a potential route, such as those against influenza.[25]

This article provides an overview of the nose-brain pathway, focusing on the anatomy of the nasal cavity and the cellular and molecular mechanisms that play an important role in nasal drug delivery and drug penetration into the brain. After this introductory part, the situations for improving nasal drug administration have been summarized and a critical assessment of the nasal drug administration route has been provided based on the limitations and advantages of this technique. Finally, the various in vitro, ex vivo and in vivo models for the study of intranasal drug administration based on the most recent literature in the field will be presented.

Anatomy and Physiology of Nasal Cavity

The passage of the nasal cavity that goes from the nasal vestibule to the nasopharynx has a depth of about 12 to 14 cm. The total area of the nasal cavity in an adult human is about 150 cm2, and the total volume is about 15 ml.[20,22] The main functions of the nasal cavity are breathing and smell. However, it also exerts an important protective activity once it filters, heats and humidifies the inhaled air before reaching the lower respiratory tract. Each of the two nasal passages can be divided into several regions:[22,23]

Nasal vestibule
Lower cone
Medium cone
Upper turbine
Olfactory region
Frontal sinus
Sphenoid sinus

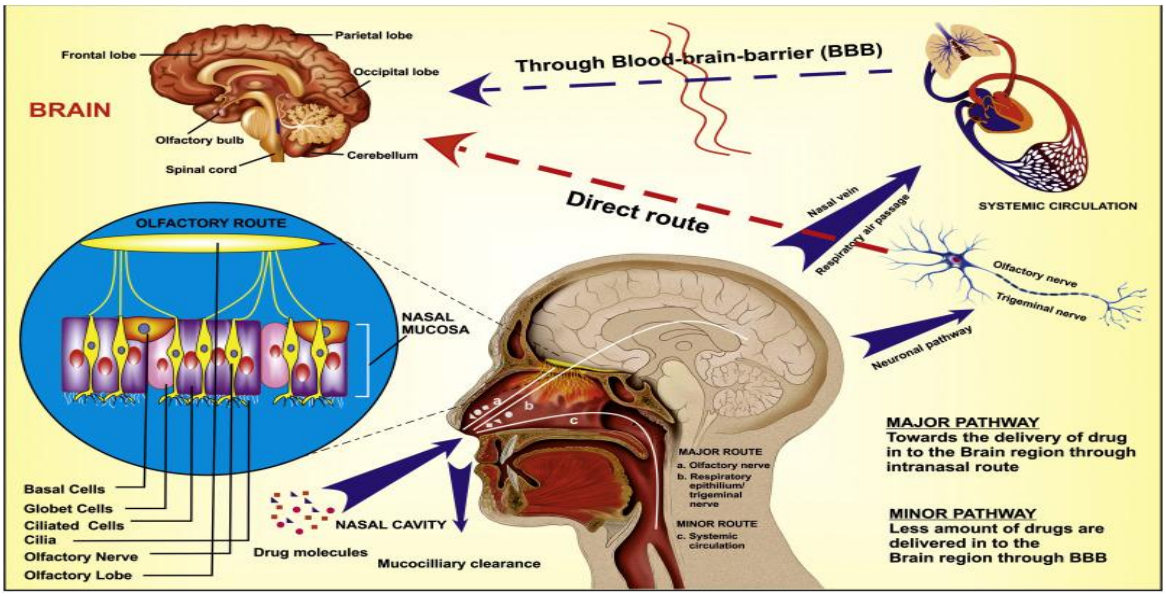

Figure 1: Nasal cavity showing the nasal vestibule A, atrium B, respiratory area C.

The nasal cavity is covered with a mucous membrane which can be divided into two zones; Non-olfactory and olfactory epithelium, in this non-olfactory area includes the nasal vestibule which is covered with stratified skin-like squamous epithelial cells, while the respiratory region, which has the typical airway epithelium covered with numerous microvilli, this which results in a large

surface area available for absorption and transport of the drug.[24,25]

Nasal vestibule: The nasal vestibule, located just inside the nostrils and occupying approximately 0.6 cm^2, is the most anterior part of the nasal cavity. In this region there are nasal hairs which filter inhaled particles. A stratified and keratinized squamous epithelium with sebaceous glands histologically covers this nasal section.[26]

Atrium: An atrium is a space between the nasal vestibule and the respiratory area. The anterior section is composed of superimposed scaly epithelium, while the posterior section is composed of pseudostified columnar cells with microvilli.[27,28]

Respiratory region: The respiratory area, also known as conca, is the largest part of the nasal cavity and is divided into upper, middle and lower vortexes that project from the side wall. The epithelium, basal membrane and appropriate aluminum foil form the nasal respiratory lining, which is considered the most important section for systemic drug distribution. Pseudostified columnary epithelial cells, global cells, basal cells and mucous membrane glands and serous cocoecone the nasal respiratory epithelium.[29,30]

Direct Nose-Brain Transport Path

The administration of intranasal drugs has been described as an effective alternative to bypass the blood-brain barrier. Because of the direct link between the nasal cavity and the central nervous system (CNS) bypassing the cephalo-brain barrier, this pathway can be managed as an alternative approach to treating neurological disorders in rodents, primates and humans.[31] In recent decades, it has been found that materials can be transported directly to cerebral interstitial fluid and cerebrospinal fluid if administered intranasally. By using intranasal administration, it is possible to overcome BBB barriers by exploiting the only place where the CNS is in direct contact with the epithelium olfactory environment.[32]

Nerve pathway of the olfactory mucosa: The pathway of administration of the naso-cerebral drug includes olfactory or trigeminal nervous systems that begin in the brain and end in the nasal cavity with the olfactory epithelium.[33] The location of the olfactory region is located on the roof of the nasal cavity and briefly extends along the septum and side wall. Neuro-epithelium is the only part of the CNS directly exposed to the outside environment. Similar to respiratory epithelium, olfactory epithelium is also pseudostified, but contains specialized olfactory receptor cells important for the perception of smell.[34]

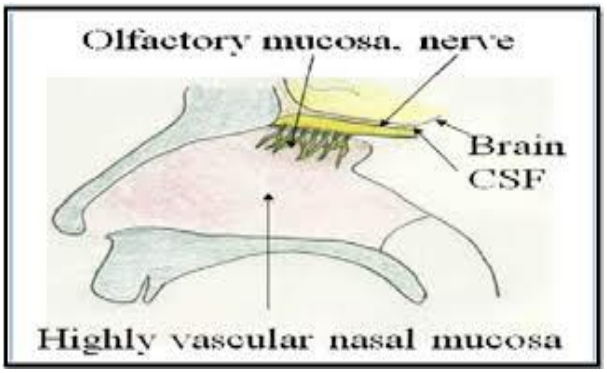

Figure 2: Potential Drug Transport Mechanism through Olfactory mucosa nerve.

Trigeminal nerve pathway: The trigeminal nerve is the largest cranial nerve and its main function is to transmit chemosensory and thermosensory information to the mucous membranes of the mouth, eyes and nose. Along with the mandibular branch, the three branches of the trigeminal nerve synapse at the trigeminal ganglion and enter the brainstem at Pons, before being then directed to the rest of the hindbrain and the forebrain.[35] The trigeminal nerve fiber endings are not directly exposed in the nasal cavity, it is assumed that the initial point of entry is probably branches (eg, ophthalmic and maxillary) of the trigeminal nerve, which innervates the dorsal nasal mucosa with the anterior part respectively of the nasal cavity and the lateral walls of the nasal mucosa.[36]

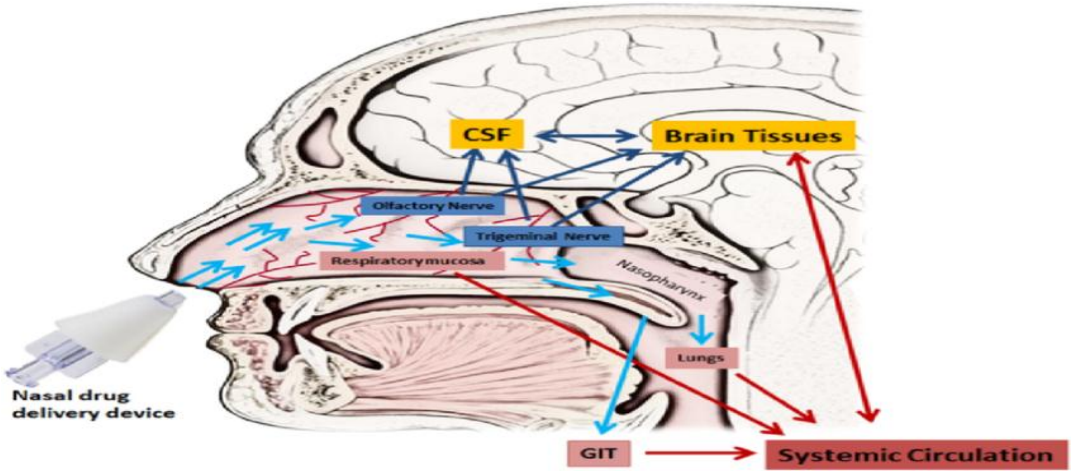

Figure 3: Potential Drug Transport Mechanism via Trigeminal nerve pathway.

As in the case of olfactory neurons discussed previously, trigeminal transport can occur both intracellularly and extracellularly, several studies have been published on axonal transport of various agents (e.g., insulin-like growth factor 1 (IGF-1), Lidocaine, Interferon-β-1b (IFNβ-1b), WGA-HRP, etc.) through the trigeminal nerves by intranasal administration.[**Error! Reference source not found.**]

The lymphatic pathway: The submucosal zone of the olfactory region (lamina propria) has numerous extracellular pathways for the transport of drugs. A drug can be transferred via extracellular pathways (eg, perineural, perivascular, or lymphatic ducts) associated with olfactory nerve bundles that extend from the lamina propria through the cribriform lamina into the olfactory bulb of the brain. Alternatively, a drug can be removed from the lamina propria by absorption into the olfactory blood vessels or the olfactory lymph vessels which drain into the deep cervical lymph nodes of the neck. Although the exact routes are not yet clear, it has been established that there is a link between the subarachnoid space, the nasal mucosa and the deep cervical lymph nodes.[37,38]

Systemic route: Absorption of the drug into the brain from the nasal cavity also occurs through the bloodstream due to the rich vascularization of the respiratory epithelium, the olfactory mucosal fraction of the drug has been absorbed into the systemic circulation.[**Error! Reference source not found.**] Small hydrophobic molecules readily enter the blood and cross the BBB compared to molecules of high molecular weight and hydrophilic. The active part was distributed through the systemic circulation and enters the nasal blood vessels and was quickly transferred into the bloodstream from the carotid artery to the brain and spinal cord, this process is called countercurrent exchange. [39,40]

Profile Of An Ideal Medicine For Nasal:[41,42,43]

An ideal nasal drug candidate should possess the following attributes:

- Appropriate aqueous solubility to provide the desired dose in a volume of 25 to 150 ml of administration of the formulation per nostril.
- Adequate nasal absorption properties.
- No nasal irritation due to the drug.
- Appropriate clinical justification for nasal dosage forms, eg rapid onset of action.
- Low dose, usually less than 25 mg per dose.
- No toxic nasal metabolites.
- No offensive aroma associated with the drug.
- Adequate stability characteristics.

Advantages of Nasal Drug Delivery System:[42,43]

- Drug degradation is absent.
- First-pass hepatic metabolism is absent.
- Rapid absorption of the drug.
- Fast action.
- The bioavailability of larger drug molecules can be improved using an absorption enhancer or another approach.
- Improved nasal bioavailability for smaller drug molecules.
- Drugs that cannot be absorbed orally can be released into the systemic circulation through the nasal drug delivery system.

Disadvantages[9,40,43,44]

- The nasal cavity offers a smaller absorption surface than the gastrointestinal tract.
- There is a possibility of irritation from the oral delivery system.
- The substance and ingredient added to the dosage form can cause local side effects and irreversible damage to the eyelashes on the nasal mucosa.
- There may be mechanical loss of the dosage form in other parts of the airways such as the lungs due to improper administration technique.
- Some surfactants used as chemical enhancers can break and even dissolve the membrane at high concentration.

Limitation[10,43,44]

- Absorption enhancers used to improve the nasal drug delivery system may have histological toxicity which is not yet clearly established.
- The absorption surface is smaller than in GIT.
- Once the drug has been administered, it cannot be withdrawn.
- Nasal irritation.

Mechanism of Drug Absorption[45,46,47,48]

Passing drugs through the mucous membrane is the first step in absorption from the nasal cavity. Small particles discharged easily pass through the mucus. However, charged particles and large particles may have a harder time passing. Several mechanisms have been proposed, but the following two mechanisms have mainly been considered.

The **first mechanism** includes the aqueous transport pathway, also called the paracellular pathway. This is the slow and passive way. Low bioavailability has been observed for drugs with a molecular weight greater than 1000 Daltons, as there is an inverse relationship between molecular weight and absorption.

The **second mechanism** involves the transport of drugs by a lipoid pathway (transcellular process). The transcellular pathway is responsible for the transport of lipophilic drugs which are dependent on their lipophilicity. Cell membranes can be crossed by drugs by an active transport pathway through vector-mediated transport through the opening of a narrow junction.[49]

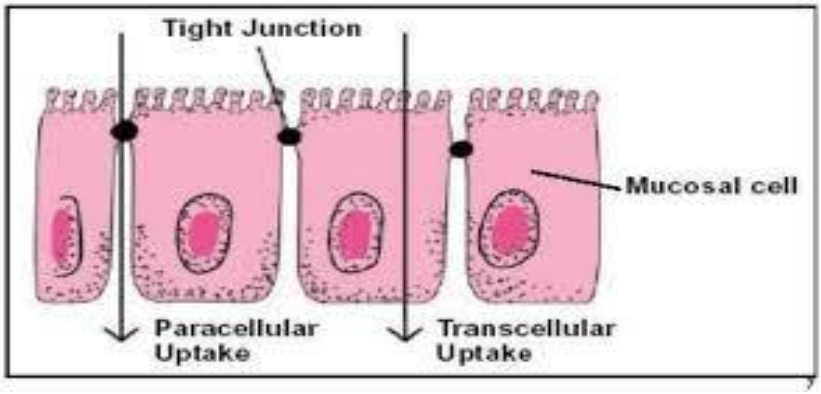

Figure 4: Mechanism of drug transport through epithelial cell.

Table 1: Nasal drug absorption enhancers and mechanisms.

Class of compound	Example	Possible action	Reference
Fatty acids	Dideconoylphosphatidylcholine, lysophosphatidylcholine	Membrane disruption	[50]
Surfactants	Sodium lauryl sulphate, saponin, polyoxyethylene-9-lauryl ether	Membrane disruption	[51]
Bile salts	Sodium deoxycholate, sodium glycocholate, sodium taurodihydrofusidate	Open tight junctions, enzyme inhibition, mucolytic activity	[52]
Cyclodextrines and derivatives	α-, β-, γ-cyclodextrin DMβ-, HPβ-cyclodextrin	Open tight junctions, membrane disruption	[53]
Enzyme inhibitors	Bestatin, amastatia	Enzyme inhibition	[54]
Bio-adhesive materials	Carbopol, starch microspheres, chitosan	Reduce nasal clearance, open tight junctions	[55]

Barriers For Nasal Absorption

Low bioavailability: Lipophilic drugs are generally well absorbed from the nasal cavity than polar drugs. The pharmacokinetic profiles of lipophilic drugs are often identical to those obtained after intravenous injection and a bioavailability close to 100%. A good example of this is the nasal administration of fentanyl where the tmax for intravenous and nasal administration is very rapid (7 min or less) and the bioavailability for the nasal anterior nasal cavity may decrease the clear administration was close to 80 %.[44,56]

Low membrane transport: Another important factor in poor membrane transport is rapid systemic elimination of the administered formulation from the nasal cavity due to the mechanism of mucociliary clearance. This is especially true for drugs that are not easily absorbed through the nasal membrane. It has been shown that for liquid and powder formulations, non-mucoadhesive, the clearance half-life is very rapid about 15-20 min.[57]

Enzymatic Degradation: Another contributing factor (but normally considered to be less important) to the poor transport of peptides and proteins especially across the nasal membrane is the possibility of enzymatic degradation of the molecule in the lumen of the nasal cavity or on passage through the nasal membrane. Epithelial barrier, these sites both contain exopeptidases such as mono- and aminopeptidases which can cleave peptides at their N and C terminals and terminal peptidases such as serine and cysteine, which can attack internal peptide bonds.[58]

Strategies To Improve Nasal Absorption:[1,3,6,36,**Error! Reference source not found.**.67]

There are many barriers in the nasal cavity that interfere with the absorption of different drugs. Certain drugs have been used successfully to improve nasal absorption of drugs.

Nasal enzyme inhibitors: Various enzyme inhibitors are used to reduce drug metabolism in the nasal cavity by inhibiting the activity of enzymes present in the nasal cavity, such as protease and peptidase, which are used as inhibitors for the formulation of peptides and protein molecules.

Structural modification: The modification of the structure of the drug can be carried out without modifying the pharmacological activity for the improvement of nasal absorption.

Permeation enhancer: Surfactants, fatty acids, phospholipids, cyclodextrins, bile salts and other permeation enhancers have been studied to improve nasal absorption.

Administration of particulate drugs: Carriers are used to encapsulate drugs and prevent them from being exposed to the nasal environment, while also increasing their retention capacity in the nasal cavity. Examples of carriers are microspheres, liposomes, nanoparticles and niosomes.

Prodrug approach: the prodrug is an inactive chemical moiety that becomes active at the target site. Taste, odor, solubility, and stability are the most common uses of prodrugs.

Bioadhesive Polymer: Bioadhesive polymers are used to improve nasal residence and drug absorption. They increase the retention time of the drug in the nasal cavity by creating an adhesive force between the formulation and the nasal mucosa, which reduces the mucociliary clearance of the formulation.

Gel in situ: these are the formulations which, once instilled into the nasal cavity, turn into a gel under the effect of stimuli such as temperature, pH and ionic concentration. The gel has a thick consistency which makes it difficult to drain the formulation due to the ciliated movement.

Excipients Used In Formulation

Excipients are used in nasal formulations in a variety of ways. Here are some of the most commonly used and most frequently added excipients.[47]

Bioadhesive Polymers: Bioadhesive polymer is a compound capable of interacting with biological material through interfacial forces and remaining on that material for long periods of time. If the biological material is the mucous membrane, they are also called mucoadhesives. The mucoadhesion process can be explained at the molecular level using attractive molecular interactions such as Van Deer Waals, electrostatic interactions, hydrogen bonds, and hydrophobic interactions. The nature of the polymer, the surrounding environment (pH), swelling, and physiological factors all influence the bioadhesive strength of a polymeric material.

Table 2: Bioadhesive polymers used in nasal drug delivery.

Polymer	Characteristics
Cellulose derivatives Soluble: hydroxypropyl methylcellulose,hydroxypropylcellulose(HPC),methyl cellulose(MC), **carboxymethyl cellulose(CMC) Insoluble**: ethylcellulose, microcrystalline cellulose(MCC)	-Prolong the residence time of drug in nasal cavity -Sustain the release of drug due to high viscosity -Act as absorption enhancer -Effectively increase intranasal bioavailability
Polyacrylates -Carbomers -Polycarbophils	-Excellent mucoadhesive and gel forming capability -Capable of attaching to mucosal surfaces hence ensure intimate contact between the formulation and membrane surface
Starch -Maize starch -Degradable starch microspheres (DSM)	-Effectively improve absorption of both small hydrophobic and hydrophilic macromolecular drugs -Mostly used in mucoadhesive microparticulate nasal delivery system
Chitosan	-Insoluble at neutral and alkaline pH -It can form water soluble salts with inorganic and organic acids -Low cost, Biodegradable and Biocompatible

Penetration Enhancer: In nasal drug administration, chemical penetration enhancers are commonly used.

1) solvents
2) Alkylmethylsulfoxides
3) Pyrrolidones
4) 1- Dodecyl azacycloheptan-2-one
5) Surfactants.

Buffers are a type of storage device. Nasal formulations are usually administered in small doses ranging from 25 to 200 ml, of which 100 ml are the most common. As a result, nasal secretions can affect the body's pH. The concentration of non-ionized drugs available for absorption can be influenced by the dose administered. Therefore, maintaining the pH in situ may require sufficient formulation buffer capacity.

Solubilizers: The drug having aqueous solubility is always a constraint for nasal administration of the drug in solution. Glycols, small amounts of alcohol, transcutol (diethylene glycol monoethyl ether), medium chain glycerides and Labrador (C8-C10 saturated polyglycolized glyceride) are examples of conventional solvents or co-solvents that can be used. to improve the solubility of drugs. They can be used as surfactants or cyclodextrins such as HP-s-cyclodextrin, which act as biocompatible solubilizers and stabilizers when they are associated with lipophilic absorption promoters. In these situations, their effect on nasal irritation should be taken into account.

Preservatives: Since most nasal formulations are aqueous in nature, preservatives are needed to prevent microbial growth. Preservatives such as parabens, phenyl alcohol, benzalkonium chloride, EDTA, and benzoyl alcohol are commonly used in nasal formulations.

Antioxidants: A small amount of antioxidants may be needed to prevent oxidation of the drug. Sodium bisulfite, butylated hydroxytoluene, sodium metabisulfite, and tocopherol are all common antioxidants. Antioxidants rarely interfere with absorption of the drug or cause nasal irritation. Antioxidants and preservatives should be evaluated for their chemical and physical interactions with drugs, excipients, manufacturing equipment, and packaging components as part of the formulation development process.

Humectants: drying of the mucous membrane can occur due to allergic and chronic diseases. Some preservatives and antioxidants can also irritate the nose, especially when used in large amounts. Prevention of dehydration requires adequate intranasal humidity. Therefore, humectants can be used in nasal products, especially gel based nasal products. Irritation of the nose is avoided and absorption of the drug is not affected by humectants. Common examples are glycerin, sorbitol, and mannitol.

Surfactants: Surfactants in nasal dosage form may alter the permeability of the nasal membranes, facilitating absorption of the drug through the nose. Surfactants are substances used to clean surfaces. Surfactants in nasal dosage forms can alter the permeability of the nasal membranes, making it easier for the drug to be absorbed through the nose.

Different Factors Affecting Nasal Drug Absorption:[48]

I Biological Factors
- Structural features
- Biochemical changes

II Physiological factors
- Blood supply and neuronal regulation
- Nasal secretions
- Mucociliary clearance and ciliary beat frequency
- Pathological conditions
- Environmental conditions.
- Membrane permeability.

III Physicochemical Properties of Drugs
- Molecular weight
- Size
- Solubility
- Lipophilicity
- Pka and Partition coefficient
- Chemical form of the drug.
- Polymorphism.
- Chemical state.
- Physical state.

IV Physicochemical Properties of Formulation
- Physical form of formulation
- PH
- Osmolarity
- Volume of solution applied and drug concentration
- Viscosity**.**

I Biological factors:[48]

Structural features: the nasal cavity is divided into five sections: nasal vestibule, atrium, respiratory zone, olfactory region and nasopharynx. Permeability is affected by these structures, as well as the cell type, density, and number of cells present in that region. The permeation of the compound increases when absorption enhancers are used with drugs.[49]

Biochemical changes: The presence of a large number of enzymes, including oxidative and conjugative enzymes, peptidases and proteases, creates an enzymatic barrier to the administration of the drug into the nasal mucosa. These enzymes are responsible for the breakdown of the drug in the nasal mucosa, which results in a pseudo first pass effect. The p450 dependent monooxygenase system is responsible for the metabolism of nasal decongestants, alcohols, nicotine and cocaine. Protease and peptidase have been found to be responsible for the systemic degradation of peptide drugs such as calcitonin, insulin, LHRH and desmopressin, as well as their consequent lower permeation. Various approaches have been used to overcome these degradations. Examples are protease and peptidase inhibitors such as bacitracin, amastatin, boroleucine and puromycin.[50]

II Physiological factors: Neuronal regulation and blood supply to the nasal mucosa are extremely permeable. High blood supply due to parasympathetic stimulation causes congestion, while low blood supply due to sympathetic stimulation causes relaxation, regulating the increase and decrease in the amount of drug permeation.[51] We can conclude that parasympathetic stimulation causes an increase in the permeability of a compound based on the above observations. The anterior serous and serous glands produce nasal secretions. Mucus production averages 1.5 to 2ml per day. The following factors affect the permeability of the drug through the nasal mucosa:

Viscosity of nasal secretion: If the soil layer of mucus is too thin, the viscous surface layer inhibits ciliary beat and mucociliary clearance is compromised if the soil layer is too thick because contact with the eyelashes is lost. Since mucociliary clearance is impaired, drug permeation is affected by altering the drug contact time with the mucosa.

Solubility of the drug in nasal secretions: Solubilization of the drug is necessary for permeation. To dissolve in nasal secretions, a drug must have the right physicochemical properties.

Daytime variation The runny nose is also affected by the 24 hour clock. Due to the secretions, the permeation of the drug is impaired overnight and the rates of

elimination are reduced. In these cases, chronokinetics determines the pattern and rate of permeation.

Nasal cavity pH: adults have a pH between 5.5 and 6.5, while infants have a pH between 5.0 and 7.0. Since the penetrating molecules exist as syndicated species when the nasal pH is lower than the pKa of the drug, the permeation of the drug is increased. Since ionization is affected by a change in the pH of the mucus, depending on the nature of the drug, an increase or decrease in the permeation of the drug is observed. For better absorption, the pH of the formulation should be between 4.5 and 6.5, with good buffering power.[52]

Mucociliary clearance (MCC) and ciliary beat: since mucociliary clearance is the normal defense mechanism of the nasal cavity, it removes substances that adhere to the nasal mucosa and removes them in the GIT by draining into the nasopharynx over 21 minutes each. once a substance is nasal Due to the reduction in MMC, the permeation of the drug increases by increasing the contact time between the drug and the mucous membrane; however, an increase in MCC reduces drug permeation.

Mucociliary dysfunction: Diseases such as colds, rhinitis, atrophic rhinitis and nasal polyposis cause hypo or hyper secretions, irritation of the nasal mucosa, and drug permeation is affected. Environmental conditions: at a temperature of 24 ° C, there is a moderate decrease in the level of MCC; however, a linear increase in eyelash beat speed is expected with increasing temperature.

Membrane permeability: The permeability of the membrane, which is the most important factor, influences the absorption of the drug through the nose. High molecular weight drugs and water soluble drugs such as peptides and proteins have low membrane permeability, so they are absorbed in smaller amounts via endocytic transport.[53]

Pathological conditions: Diseases such as colds, rhinitis, atrophic rhinitis and nasal polyposis cause mucociliary dysfunction, hypo or hyper secretions and irritation of the nasal mucosa, affecting the permeation of the drug.

Ambient conditions: A moderate reduction in the level of MCC occurs at a temperature of 24 ° C. However, a linear increase in the speed of eyelash fluttering is expected with increasing temperature.

III Physicochemical properties of the drug

Molecular Weight and Size: The molecular weight, molecular size, hydrophilicity, and lipophilicity of the compound determine the permeation of the drug. Bioavailability can be predicted directly from WM for compounds with a molecular weight of 1 kDa. The bioavailability of these large molecules generally varies between 0.5 and 5%. A drug less than 300 Da penetrates mainly through the aqueous channels of the membrane and its physicochemical properties have no effect on its permeation. On the contrary, the Da permeation rate is very sensitive for compounds of PM 300.

Solubility: The solubility of the drug is an important factor in determining the absorption of the drug across biological membranes. Since nasal secretions are more watery, aqueous solubility of the drug should be appropriate for greater dissolution. In aqueous secretions, lipophilic drugs have lower solubility and water-soluble drugs are absorbed by passive diffusion and lipophilic drugs are absorbed by active transport.[54]

Lipophilicity: those compounds with high lipophilicity which increase permeation through the nasal mucosa. Although the nasal mucosa exhibits some hydrophilic characteristics, it appears to be predominantly lipophilic and the lipid domain plays an important role in the barrier function of these membranes. The systemic bioavailability of many drugs is reduced due to excessive hydrophilicity in these cases, a prodrug approach is advantageous.

Pka and partition coefficient: unionized species are better absorbed than ionized species, according to the pH partition theory and the same is true for nasal absorption. The pKa of these drugs and their nasal absorption are inextricably linked. The concentration of drugs in biological tissues increases as the lipophilicity of the partition coefficient of the drugs increases. The rate of absorption of aminopyrine increases with increasing pH and has been found to correspond well to the theoretical profile. The partition coefficient is one of the main determinants of nasal absorption.[55]

Polymorphism: Polymorphism is an important parameter in the development of nasal pharmaceuticals administered in particulate form. Polymorphism has been shown to affect drug dissolution and absorption across biological membranes. This factor should be carefully considered when developing a nasal dosage form.

Chemical status of the drug: The chemical form of the drug in which it is presented to the nasal mucosa determines its capacity for absorption. Chemical alteration of a drug molecule by adding a bio-clearable lipophilic moiety is an option to improve drug absorption that does not meet expectations.[56]

Drug Physical State: Particle size and drug morphology are two of the most important properties of particulate nasal pharmaceuticals. To achieve proper drug dissolution properties in the nostrils, both parameters should be controlled. Particles smaller than 5 microns should be avoided as they can be inhaled and cause lung damage. In most cases, particles with a diameter of 5 to 10 microns are deposited in the nostrils.

VI Physico-chemical properties of the formulation

Formulation Form: Upon nasal absorption of the drug, the physical form of the formulation is critical. In rabbits, liquid formulations are less effective than powder formulations at delivering insulin. The more viscous formulation led to less efficient systemic nasal administration of the drug with the addition of viscous agents, scientists found that the effects of desmopressin were slightly more sustained, but the overall bioavailability did not improve. Runny nose can be reduced with viscous formulations.

PH: The pH partition assumption determines the extent of drug ionization, so it is related to the pH of the formulation. To avoid irritation, achieve efficient absorption, and prevent the growth of pathogenic bacteria, the nasal formulation should be adjusted to the appropriate pH. The pH level of the ideal formulation should be between 4.5 and 6.5. In adults, the pH of the nasal surface is 7.39 and the pH of nasal secretions is 5.5-6.5, while in infants and children the pH is 5.0-6, 7.

Osmolarity: The tonicity of the formulation has a significant impact on the nasal mucosa, therefore an isotonic formulation is preferable. The effects of the osmolarity of the formulation on the absorption of nasal secretion in rats have been studied by some scientists. They found that the concentration of sodium chloride in the formulation affected all cells in the nasal mucosa with an absorption peak at a sodium chloride concentration of 0.462 M. Epithelial cells shrink when exposed to this concentration. . Therefore, tonicity has an effect on the absorption of the drug.[57]

Volume of Solution Applied and Drug Concentration: Administration volume and degree of absorption are inconsistent. Clement has reviewed the clinical effectiveness of three different strengths of cetirizine nasal spray. The results showed that with drug concentrations up to 0.125%, 16.7%, 30.8%, 42.9%, and 26.7% of days, patients seemed to improve. Efficiency increased to 0.250% at the highest concentration.[58]

Viscosity: A higher viscosity of the formulation increases the contact time between the drug and the nasal mucosa, prolonging the permeation time.

Table 3: Drugs and Their Formulations Reported for Nose-to-Brain Delivery.

Drug	Formulation Description	Animal Model	Disease State Being Treated	Results	Reference
5-FU	Solution	Rats pre-dosed with acetazolamide	CNS malignancy	104% increased brain uptake compared to i.v.	[59]
Bromocriptine	Chitosan Nanoparticles (~160 nm)	Mice	Parkinson's Disease	Showed significant increase in dopamine levels	[60]
Buspirone	Chitosan/HP-β-CD solution	Rats	Depression	DTE-4.13 compared with 3.38 for in plain solution	[61]
Carbamazepie	Hypromellose/Carbopol Gel	Rats	Epilepsy	Significantly higher brain uptake compared to i.v	[62]
Curcumin	InSituGelling Micro emulsion	Rats	Brain tumor/ Alzheimer's Disease	DTE-6.5	[63]
Doxepin	Thermoreversible Gel	Mice	Depression	No difference in pharmacodynamic endpoint	[64]
GDF-5	Micro emulsion	Rat	Parkinson's Disease	Significantly higher midbrain concentrations compared to acidic solution	[65]
Olanzapine	Nanomicellar Carrier (~18-380 nm)	Rats	Schizophrenia/Bipolar Disorder	DTE- 520.26%	[66]
Tacrine	Solution of Propylene glycol and Normal Saline	Mice	Alzheimer's Disease	DTE-207.23%	[67]
Zidovudine prodrug	Solid Lipid Microparticles (16 and 7 µm)	Rats	CNS involved HIV infection	6-fold higher CSF uptake	[68]
Zolmitriptan	Micellar Nanocarrier (~23 nm)	Rats	Migraine	Significant increase in brain conc.as soon	[68]

				as 30min upto 120 min	

Type of Formulation:[69]

Solid preparation

Nasal powder

Liquid preparation

Micro emulsion

Nasal spray

Nasal drop

Semi-solid preparation

Nasal gel

Nasal suspension

Mucoadhesive microspheres

Solid dosage forms

Solid dosage forms are also becoming popular for intranasal drug delivery, although they are more suitable for pulmonary drug delivery and other applications because they can cover the vascular system in the epithelium of the nasal mucosa.

- **Nasal powders**

If it is not possible to develop solution and suspension dosage forms due to lack of drug stability, powder dosage forms may be developed. The absence of a preservative and the superior stability of the drug in the formulation are two advantages of a nasal powder dosage form. However, the suitability of the powder formulation is determined by the solubility of the active drug and / or excipients, particle size, aerodynamic properties, and nasal irritation.

Liquid dosage forms

- **Nasal drops**

Nasal drops are one of the simplest and most affordable delivery systems available. The main drawback of the system is the lack of dose accuracy.

- **Nasal sprays**

Nasal sprays can be prepared from solution and suspension formulations. A nasal spray can deliver an exact dose between 25 and 200 L thanks to the availability of metering pumps and actuators.

• Nasal emulsions, micro emulsions

Other liquid nasal delivery systems have been studied extensively, but not intranasal emulsions. The viscosity of nasal emulsions makes them ideal for topical application.

Semi-solid dosage forms

Nasal drug delivery systems are generally designed using semi-solid systems such as gels, ointments, and liquid systems containing polymers that gel at specific changes in pH.

• Nasal gels

Nasal gels are thickened solutions or suspensions with high viscosity. The advantages of a nasal gel include reduced post-nasal drip due to its high viscosity, reduced taste impact due to reduced swallowing, and reduced loss from the prior formulation. Solid dosage forms are also becoming popular for intranasal drug delivery, although they are more suitable for pulmonary drug delivery and other applications because they can cover the vascular system in the epithelium of the nasal mucosa.

New drug formulations

Several arguments have been made in favor of the development of formulations for intranasal administration of drugs containing liposomes, microspheres and nanoparticles, including enzyme inhibitors, nasal absorption stimulators and mucoadhesive polymers that improve stability, membrane penetration and retention time in the nasal cavity, allowing release. Drugs for better systemic absorption.

• Liposomes

Liposomes are phospholipid vesicles made up of lipid bilayers that surround one or more aqueous compartments and may contain drugs and other substances. Liposomal drug delivery systems have a number of advantages, including the ability to encapsulate small and large molecules with a wide range of hydrophilicity and pKa values. They have been found to increase membrane penetration of peptides such as insulin and calcitonin, thereby improving absorption from the nose. This has been attributed to an increased retention of peptides in the nasal cavity. The encapsulated peptides are protected from enzymatic degradation and rupture of the mucous membrane.

• Microspheres

Bead technology has been widely used in the development of formulations for nasal drug delivery. Mucoadhesive polymers (chitosan, alginate) are used to produce microspheres, which have advantages for intranasal administration of the drug. In addition, the microspheres can protect the drug from enzymatic metabolism and prolong its effect by promoting the release of the drug.

• Nanoparticles

Solid colloidal particles with diameters between 1 and 1000 nm are called nanoparticles, are made from macromolecular materials and can be used as a vaccine adjuvant or vehicle for drugs in which the active ingredient is dissolved, trapped, encapsulated, adsorbed or chemically bound. Due to their small size, nanoparticles can have several advantages, but only the smallest nanoparticles can penetrate the mucous membrane via the paracellular route and to a limited extent because tight junctions are in the range of 3.9-8.4 AT.

Evaluation:[70]

In situ method

Male Sprague-Dawley rats weighing 300 g are normally used. An injection of 50 mg / kg sodium pentobarbital is used to anesthetize the rats. The rat's trachea is cannulated with a polyethylene tube after making an incision in the neck. Another tube is inserted at the back of the nasal cavity through the esophagus and the infused solution has been introduced into the nasal cavity through this tube. To prevent the drug solution from flowing from the nasal cavity into the mouth, nasopalatine is sealed with an adhesive agent. Different pharmacological solutions, with a volume of between 3 and 20 ml, are placed in a bekar with a water jacket (20 ml) and maintained at 37 ° C in a circulating water bath. A polysial pump is used to circulate each solution through the nasal cavity of the rat at a rate of 2-3 ml / min. The infusion solution comes out through the nostrils, passes through the funnel and returns to the beaker. A magnetic stir bar is used to constantly mix the solution (Figure 5). A syringe is used to withdraw the sample solution. The degree of absorption is determined over the course of an hour by analyzing at regular intervals the amount of drug remaining in the infusion solution. The most important advantage is that standard analytical procedures can be used to screen different drugs quickly and easily. Additionally, if the experiment is conducted with different infusion volumes, the in situ data can be used to predict the rate of absorption in vivo.

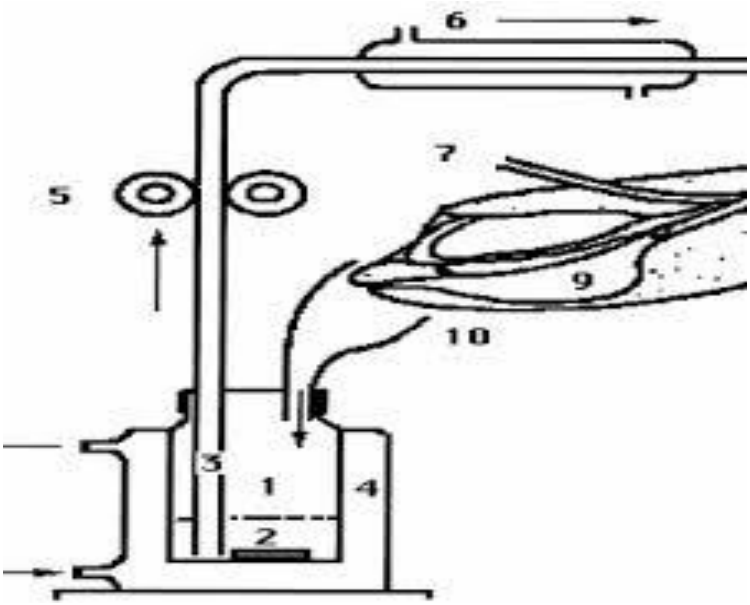

Figure 5: Experimental set-up for the in situ nasal perfusion experiment.
(1) Drug reservoir; (2) magnetic stirring bar; (3) Tygon tube cannulation; (4) water-jacketed beaker; (5) peristaltic pump; (6) water bath; (7) trachea cannulation; (8) esophagus; (9) nasal cavity; (10) funnel.

In-vivo method in situ

In this method, small volumes of the drug of 50 to 100 µl are administered into the nasal cavity. The concentration of the drug in the nasal cavity is determined using simple analytical procedures. In addition, the data generated can be used directly to predict absorption rates in vivo.

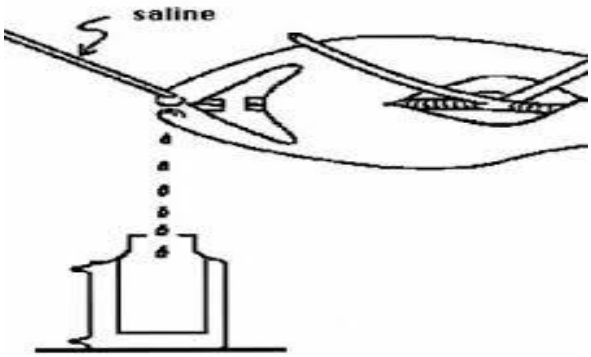

Figure 6: Experiment set-up for the in-vivo in-situ nasal absorption experiment.

The surgical procedure is similar to that described for in situ recirculation studies, except that a glass tube (3 cm long and 0.3 mm in diameter with a sealed end) is inserted through the esophagus into the cavity. Nasal posterior to keep the solution in the nostril. To remove all traces of blood, the nasal cavity is washed thoroughly with 10 ml of Ringer's buffer before administering the drug. A micropipette is used to place a 100 µl aliquot of solution containing the drug into one nostril. The nasal cavity is rinsed with 3.9 ml of circular buffer using a peristaltic pump at an appropriate time interval and the experiment is terminated.

The surgical procedure is performed on a rat that has been anesthetized (Figure 6). The data obtained are very reproducible and reliable because this method uses a closed and confined system. Additionally, this model can be used to predict drug uptake profiles in other species such as dogs and humans. The drug is injected directly into the nasal cavity and blood samples are taken and analyzed regularly. The drug is administered while the animal is under anesthesia in large animals such as dogs,

sheep and monkeys and care should be taken to minimize physical loss of the drug due to drainage.

Table 4: Commonly used animals in intranasal drug administration studies.

Animal	Strain	Tools for administration	Volume administered per nostril (µl)	Subject of the study	References
Dogs	Labrador Retriever	Mucosal atomizer device	2400	Analgesic treatment	[71]
Guinea pigs	Hartley	Pipette/syringe	10	Induction of rhinitis	[72]
Mice	CD-1 Bal/c	Micropipette	10	Insulin delivery to the brain	[73]
Monkey	Rhesus monkey	Modified nasal atomizer	50-200	Opioid administration	[74]
Rabbits	Japanese White	Nasal actuator	100	New-generation corticosteroid treatment	[75]
Rats	Wistar	Intranasal cannula	40	Minimal-stress model for intranasal administration in freely moving rats	[76]
Sheep's	Karaman Suffolk	Syringe	1000	Intranasal inoculation with prion to compare different scrapie strains	[77]

The Rapeutic Considerations

Topical (or topical) treatment: Decongestants for nasal cold symptoms and antihistamines and corticosteroids for allergic rhinitis are two prominent examples: histamine H1 antagonist, levocabastine, anticholinergic agent ipratropium bromide and steroidal anti-inflammatory agents such as budesonide mometasone furoate are examples. Nasal products commonly used in this field.

2. Systemic Administration: Systemic IN administration has several advantages, including large surface area for drug absorption, rapid onset of drug, absence of first-pass metabolism, and non-invasion for comfort and compliance patient's maximum. The pharmacokinetics of IN administration are discussed in more detail elsewhere. As discussed in the case studies below, administration of IN provides an alternative route for systemic administration of drugs which are most commonly administered orally or by injection (for orally absorbed compounds that are poorly absorbed such as peptides and proteins).[78]

3. Chronic versus Acute Therapeutic Use: It is essential to consider the dosage regimen of the drug when choosing a method of administration. Is the intended use short or long term? The benefit of patient comfort and compliance provided by the IN test may not be an important factor for an acute indication.[79]

4. Vaccine administration: The nasal mucosa has been studied as a potential route of vaccination. Presentation of an appropriate antigen to associated nasal lymphoid tissue (NALT) with an appropriate adjuvant has the potential to elicit both humoral and cellular immune responses disaster areas. Vaccination with IN can lead to the development of both local and systemic immunity. In addition, the IN vaccination route does not require the use of a sterile product or sterile dosing technique (a distinct advantage in developing regions of the world). FluMist®, a live influenza virus adapted to cold, is an example of an IN vaccine. During influenza season, this product is administered via a syringe sprayer in one or two doses. [80]

Main reasons for using the nasal route for vaccine administration

The nasal mucosa is the first site of contact with inhaled antigens.

The nasal passages are rich in lymphoid tissue (Nasal Associated Lymphoid Tissue-NALT

NALT is known as the walleye ring in humans

Adenoid or nasopharyngeal tonsils

Bilateral lymphoid bands

Bilateral tubular tonsils and facial or palatal tonsils

Bilateral lingual tonsils

Creation of mucosal (sIgA) and systemic (IgG) immune responses

Low cost, patient friendly, non-injectable, safe

5. Nasal administration of peptides and proteins: Salmon calcitonin in the nose Novartis is the company selling the drug. Other pharmaceutical companies are working on new nasal formulations. Ferring and its partners market nasal desmopressin. Aventis is the manufacturer of nasal buserelin. Searle sells nasal nafarelin. Nasal PTH, nasal leuprolide, basal insulin, nasal interferon, and other hormones can be found in the nose. Clinical trials are currently underway

CONCLUSION

The development of new forms such as the intranasal route, which has been shown to have equivalent efficacy to the intravenous route, is the result of increased research in the field of new drug delivery systems. The rapid onset is a key feature of the typical nose-brain pharmacokinetic profile in the latter case and may provide a distinct benefit in certain situations, such as pain management. Vaccine therapy is another application for intranasal dosing.IN administration can be used for high molecular weight drugs such as peptides and proteins, but the presence of permeation enhancing agents has a significant impact on systemic bioavailability. it is a better alternative route of administration for a variety of systemically acting drugs with low bioavailability. It also has advantages in terms of acceptability and patient compliance. Because it requires rapid and / or specific targeting of drugs to the brain, this delivery system is useful in conditions such as Parkinson's disease, Alzheimer's disease, seizures, epilepsy, cancer brain or pain and is a suitable pathway to produce a response against various diseases. such as anthrax, influenza and other diseases by administering vaccines through the nasal mucosa Intranasal products for erectile dysfunction, sleep induction, acute pain (migraine), panic attacks, nausea, heart attacks and Parkinson's disease, as well as because it is likely that in the near future, new nasal products will be available for the treatment of long-term conditions such as diabetes, growth retardation, osteoporosis, the treatment of fertility and endometriosis.

REFERENCES

1. Paun S.J, A. A. Bagada, M. K. Raval. Nasal Drug Delivery- As an Effective Tool for Brain Targeting-A Review. International Journal of Pharmaceutical and Applied Sciences, 2010; 43-52.
2. Falzarano MS, Passarelli C, Bassi E, Fabris M, Perrone D, Sabatelli P, et al. Biodistribution and molecular studies on orally administered nanoparticle-AON complexes encapsulated with alginate aiming at inducing dystrophin rescue in MDX mice. Biomed Res Int., 2013; 22-26
3. Türker S, E. Onur, Y. Özer, Nasal route and drug delivery systems, Pharm. World Sci., 2004; 26: 137–142
4. Andlin-Sobocki P, B. Jonsson, H.U. Wittchen, J. Olesen, Cost of disorders of € the brain in Europe, Eur. J. Neurol., 2005; 12: 22.
5. Pardridge W M, The Blood-brain barrier: bottleneck in brain drug development, NeuroRx., 2005; 2: 45.
6. L. Casettari, L. Illum, Chitosan in nasal delivery systems for therapeutic drugs, J. Control. Release, 2014; 190: 25.
7. S.V. Dhuria, L.R. Hanson, W.H. Frey II, Intranasal delivery to the central nervous system: mechanisms and experimental considerations, J. Pharm. Sci., 2010; 99: 34.
8. Bourganis V, Kammona O, Alexopoulos A, Kiparissides C. Recent advances in carrier mediated nose-to-brain delivery of pharmaceutics. European Journal of Pharmaceutics and Biopharmaceutics., 2018 Jul 1; 128: 337-62.
9. P.G. Djupesland, J.C. Messina, R.A. Mahmoud, The nasal approach to delivering treatment for brain diseases: an anatomic, physiologic, and delivery technology overview, Ther. Deliv., 2014; 5: 709–733.
10. Krishnamoorthy. R, Mitra. A.K, Prodrugs for nasal drug delivery. Adv Drug Deliv Rev., 1998; 29: 135–146.
11. Haque S, M, Sahn J.K, Ali J, Baboota S. Development and evaluation of brain targeted intranasal alginate nanoparticles for treatment of depression. J Psychiatr Res., 2014; 48.
12. Duquesnoy, C., Mamet, J.P., Sumner, D., & Fuseau, E, Comparative clinical pharmacokinetics of single doses of sumatriptan following subcutaneous, oral, rectal, and intranasal administration. European Journal of Pharmaceutical Sciences, 1998; 6: 99-104.
13. Eller, N., Kollenz, C.J., Bauer, P., & Hitzenberger, G., The duration of antidiuretic response of two desmopressin nasal sprays. International Journal of Clinical Pharmacology and Therapeutics, 1998; 36: 494-500.
14. Slot, W.B., Merkus, F.W.H.M., Deventer, S.J.H.V., & Tytgat, G.N.J., Normalization of plasma vitamin B12 concentration by intranasal hydroxocobalamin in vitamin B12- deficient patients. Gastroenterology, 1998; 113: 430-433.
15. Casettari, L & Illume. L, Chitosan in nasal delivery systems for therapeutic drugs, Journal of Controlled Release, 2014; 190: 189-20.
16. Kubli, H., & Vidgren, M. T., Nasal delivery systems and their effect on deposition and absorption. Advanced Drug Delivery Reviews, 1998; 29: 157-177.
17. Chaturvedi, M., Kumar. M., & Pathak. K., A review on the mucoadhesive polymer used in nasal drug delivery system. Journal of Advanced Pharmaceutical Technology and Research, 2011; 4: 215-222.
18. Aulton, M. E., Taylor, K., Aulton's Pharmaceutics: the design and manufacture of medicines, Edinburgh, Churchill Livingstone., 2013; 5: 13-18.
19. Mahdi, M. H., Conway, B. R., & Smith, A. M .Development of mucoadhesive sprayable gellan gum fluid gels. International Journal of Pharmaceutics, 2015; 488(1): 12-19.
20. Rhidian, R., & Greatorex, B., Chest pain in the recovery room, following topical intranasal cocaine solution use. British Medical Journal Case Reports, 2015; 21-27.
21. Andrade, C., Intranasal drug delivery in neuropsychiatry: Focus on intranasal ketamine for refractory depression. Journal of Clinical Psychiatry, 2015; 76(5): 628-631.

22. Gizurarson S. Anatomical and histological factors affecting intranasal drug and vaccine delivery. Current drug delivery, 2012 Nov 1; 9(6): 566-82.
23. Elad D, Wolf M, Keck T. Air-conditioning in the human nasal cavity. Respiratory physiology & neurobiology. 2008 Nov 30; 163(1-3): 121-7.
24. Ogle OE, Weinstock RJ, Friedman E. Surgical anatomy of the nasal cavity and paranasal sinuses. Oral and Maxillofacial Surgery Clinics., 2012 May 1; 24(2): 155-66.
25. Agrawal M, Saraf S, Saraf S, Antimisiaris SG, Chougule MB, Shoyele SA, Alexander A Nose-to-brain drug delivery: An update on clinical challenges and progress towards approval of anti-Alzheimer drugs. J Control Release, 2018; 281: 139-177.
26. Karpagavalli, M.L., Nasal drug delivery of a short acting hypnotic and antimigraine agent for the treatment of insomnia associated migraine. 2017
27. Sarkar M.A. Drug metabolism in the nasal mucosa. Pharm. Res., 1992; 9: 1–9.
28. Arora P., Sharma. Gary S. Permeability issues in nasal drug delivery. Drug Discov Today, 2002; 7: 967–975.
29. Dusemund F, Albrich W, Rüegger K, Bossart R, Regez K, Schild U, Conca A, Schuetz P, Sigrist T, Huber A, Reutlinger B. Optimized patient transfer using an innovative multidisciplinary assessment in the Kanton Aargau (OPTIMA I): an observational survey in lower respiratory tract infections. Critical Care. 2011 Feb; 15(1):1-90.
30. Markus F.W., Verhoef J.C., Schipper N.G., Martin E. Nasal mucociliary clearance as a factor in nasal drug delivery. Adv Drug Deliv Rev., 1998; 29: 13-38.
31. Charlton S., Jones N.S., Davis S.S., Illume L. Distribution and clearance of bioadhesive formulations from the olfactory region in man: Effect of polymer type and nasal delivery device. Eur J Pharma Sci., 2007; 30: 295- 302.
32. Graff L.C., Pollock G.M. Nasal drug administration: potential for targeted central nervous system delivery. J Pharma Sci., 2005; 94: 1187-1195.
33. Johnson N.J, Hanson L.R, Frey W.H. F, Trigeminal pathways deliver a low molecular weight drug from the nose to the brain and or facial structures, Mol. Pharm., 2010; 884–893.
34. Watelet JB, Strolin-Benedetti M, Whomsley R. Defence mechanisms of olfactory neuro-epithelium: Mucosa regeneration, metabolising enzymes and transporters. Actaoto-rhino-laryngological belgica., 2009 Jan 1; 8:21.
35. Frey, W. H. Delivery of 125I-NGF to the brain via the Olfactory Route. Drug Delivery, 1997.
36. Mistry a, Skolnik S, Illume L, Nanoparticles for direct nose-to-brain delivery of drugs, Int. J. Pharm., 2009; 146–157.
37. Illume, Potential for nose-to-brain delivery of drugs, in A. Tsuda, P. Gehr (Eds.), Nanoparticles Lung - Environ, CRC Press, Expo. Drug Deliv., 2014; 1–368.
38. Takeuchi T, Kitagawa H, Harada E. Evidence of lactoferrin transportation into blood circulation from intestine via lymphatic pathway in adult rats. Experimental physiology, 2004 May; 89(3): 263-70.
39. Lochhead. L.L, Thorne. R.G, Intranasal delivery of biologics to the central nervous system, Adv. Drug Deliv. Rev., 2012; 64: 614–628.
40. Fischer H, Gottschlich R, Seelig A. Blood-brain barrier permeation: molecular parameters governing passive diffusion. The Journal of membrane biology, 1998 Oct; 165(3): 201-11.
41. Allori AC, Mulliken JB. Evidence-based medicine: secondary correction of cleft lip nasal deformity. Plastic and reconstructive surgery, 2017 Jul 1; 140(1): 166e-76e.
42. Ito MM, Catanhêde LM, Katsuragawa TH, Silva Junior CF, Camargo LM, Mattos RD, Vilallobos-Salcedo JM. Correlation between presence of Leishmania RNA virus 1 and clinical characteristics of nasal mucosal leishmaniosis. Brazilian journal of otorhinolaryngology, 2015 Oct; 81(5): 533-40.
43. Pearson DC, Adamson PA. The ideal nasal profile: rhinoplasty patients vs. the general public. Archives of facial plastic surgery, 2004 Jul 1; 6(4): 257-62.
44. Kushwaha SK, Keshari RK, Rai AK. Advances in nasal trans-mucosal drug delivery. Journal of applied pharmaceutical science, 2011 Sep 1; 1(7): 21.
45. Illum L. Nasal drug delivery: new developments and strategies. Drug discovery today, 2002 Dec 1; 7(23): 1184-9.
46. Ghori MU, Mahdi MH, Smith AM, Conway BR. Nasal drug delivery systems: an overview. American Journal of Pharmacological Sciences, 2015; 3(5): 110-9.
47. Alagusundaram M, Chengaiah B, Gnanaprakash K, Ramkanth S, Chetty CM, Dhachinamoorthi D. Nasal drug delivery system-an overview. Int J Res Pharm Sci., 2010; 1(4): 454-65.
48. Dhakar RC, Maurya SD, Tilak VK, Gupta AK. A review on factors affecting the design of nasal drug delivery system. International journal of drug delivery, 2011 Apr 1; 3(2): 194.
49. Chaefer. M.L, Bottler B, Silver WL, Trigeminal collaterals in the nasal epithelium and olfactory bulb: a potential route for direct modulation of olfactory information by trigeminal stimuli. J Comp Neurol., 2002; 444: 221–226.
50. Sivilotti L, Nistri A, GABA receptor mechanisms in the central nervous system: Prog Neurobiol., 1991; 2(1): 35–92.
51. M. I., Agu, R. U., Verbeke, N., & Kinget, R. Nasal mucoadhesive drug delivery: background, applications, trends, and future perspectives. Advanced Drug Delivery Reviews, 2005; 57(11): 1640-1665.
52. Zhou.M, Donovan, M.D., Recovery of the nasal mucosa following Laureth-9 induced damage.

International Journal of Pharmaceutics, 1996; 130: 93-102.
53. Yamamoto A, Moria.T, Hashida. M, Sezaki. H, Effect of absorption promoters on nasal absorption of drugs with various molecular weights. International Journal of Pharmaceutics, 1993; 93: 91-99.
54. Marttin, E, Vehoef.J.C, Merkus.F.W, Efficacy, safety, and mechanism of cyclodextrins as absorption enhancers in nasal drug delivery of peptide and protein drugs. Journal of Drug Targeting, 1998; 17-36.
55. Touitou. E., & Barry. B. W. Enhancement in drug delivery. CRC Press.
56. Davis. S.S, & Illume. (2003). Absorption enhancers for nasal drug delivery. Clinical Pharmacokinetics, 2006; 42(13): 1107-1128.
57. Shingaki, T, The transnasal delivery of 5-fluorouracil to the rat brain is enhanced by acetazolamide (the inhibitor of the secretion of cerebrospinal fluid). Int. J. Pharm., 2009.
58. Alagusundaram M., Deepthi N., Ramkanth S., Angalaparameswari S., Mohamed Saleem T.S., Gnanaprakash K.. Thiruvengadarajan V. S, Madhusudhana Chetty C, Dry Powder Inhalers - An Overview, Int. J. Res. Pharm. Sci., 2010; 1: 34-42
59. Illume L. In: Mathiowitz E, Chickering DE, Lehr CM Ed, Bioadhesive formulations for nasal peptide delivery: Fundamentals, Novel Approaches, and Development. Marcel Dekker. New York., 1999; 507- 539.
60. Lee, V.H, Enzymatic barriers to peptide and protein absorption. Crit. Rev. The Drug Carrier Syst., 5: 69–97.
61. Ibrahim A., Alsarra A.Y., Hamed., Fars K.A., and Gamal M., Maghraby E. Vesicular Systems for Intranasal Drug Delivery, K.K. Jain (ed.), Drug Delivery to the Central Nervous System, Neuromethods
62. Chad S., Sangle S., and Barhate S. Advantageous nasal drug delivery system; a review.International journal of pharmaceutical science and research, 2011; 2(6): 1322-1336.
63. Arora P., Sharma. Gary S. Permeability issues in nasal drug delivery. Drug Discovery Today, 2002; 7: 967–975.
64. Machida M. Effects of surfactants and protease inhibitors on nasal absorption of recombinant human granulocyte colony-stimulating factor (rHGCSF) in rats. Biol. Pharm. Bull.
65. Watanabe H., and Tsuru H. Nippon Yakurigaku Zasshi, 1999; 113: 211–218.
66. Cornaz A.L. and Buri P. Nasal mucosa as an absorption barrier. Eur. J. Pharm. Bio pharm., 1994; 40: 261–270.
67. Gannu Praveen Kumar and Kiran S. Strategies and prospects of nasal drug delivery systems. Indian Journal of Pharmaceutical Science & Research, 2012; 2(1): 33-41.
68. Corbo .D.C. Characterization of the barrier properties of mucosal membranes. J. Pharm. Sci., 1990; 79: 202– 206.
69. Sakane T. The transport of a drug to the cerebrospinal fluid directly from the nasal cavity: the relation to the lipophilicity of the drug. Chem. Pharm. Bull., 1991; (Tokyo) 39: 2456–2458.
70. Ohwaki K., Ando H., Watanabe S., Miyake Y. Effects of Krenistsky, Amino acid ester prodrugs of acyclovir, Antiviral dose, pH, and osmolarity on nasal absorption of secretin in Chem. Chemother, 1992; 3: 157–164.
71. Behl C, R., Pimplaskar N.K., Sileno A.P., Demeireles J., Romeo VD. Effect of physicochemical properties and other factors on nasal drug delivery. Advanced drug delivery reviews, 1998; 89-116
72. Clement P., Roovers M.H., Francillon C., Dodion P. Dose-ranging, placebo-controlled study of cetirizine nasal spray in adults with perennial allergic rhinitis. Allergy, 1994; 49: 668–672.
73. Donovan M.D., Flynn G.L., Amidon G. L. Pharm. Res., 1990; 7: 863-868.
74. Malid.S, Optimised nanoformulation of bromocriptine for direct nose-to-brain delivery: biodistribution, pharmacokinetics and dopamine estimation by ultra-HPLC/mass spectrometry method. Expert Opin. Drug Delivery, 2014; 827–842.
75. Khan, M. S., Patil, K., Yeole, P. & Gaikwad, R. Brain targeting studies on buspirone hydrochloride after intranasal administration of mucoadhesive formulation in rats. J. Pharm. Pharmacology, 2009; 1-14
76. Barakat, N. S., Omar, S. A. & Ahmed, A. a. E. Carbamazepine uptake into rat brain following intra2 olfactory transport. J. Pharm. Pharmacology, 2006; 56-66.
77. Wang, S., Chen, P., Zhang, L., Yang, C. & Zhai, G. Formulation and evaluation of microemulsion6 based in situ ion-sensitive gelling systems for intranasal administration of curcumin. J. Drug Target., 1999; 831–840.
78. Naik, A. & Nair, H. Formulation and Evaluation of Thermo sensitive Biogels for Nose to Brain Delivery of Doxepin. BioMed Res. Int., 2014; 214-223.
79. Hanson, L. R. Intranasal delivery of growth differentiation factor to the central nervous system. Drug Deliv., 2012; 149–154.
80. Abdelbary, G. A. & Tadros, M. I. Brain targeting of olanzapine via intranasal delivery of core–shell difunctional block copolymer mixed nanomicellar carriers: In vitro characterization, ex vivo estimation of nasal toxicity and in vivo biodistribution studies. Int. J. Pharm., 2013; 300–310.
81. Jogani, V. V., Shah, P. J., Mishra, P., Mishra, A. K. & Misra, A. R. Nose-to-brain delivery of tacrine. J. Pharm. Pharmacol., 2007; 59: 1199–1205.

82. A. Brain Uptake of a Zidovudine Prodrug after Nasal Administration of Solid Lipid Microparticles. Mol. Pharm., 2007; 11: 1550–1561.
83. Jain, R., Nabar, S., Dandekar, P. & Patravale, V. Micellar Nanocarriers: Potential Nose-to-Brain Delivery of Zolmitriptan as Novel Migraine Therapy. Pharm. Res., 2010; 27: 655–664.
84. Zia H., Dondeti P., Needham T.E., Intranasal drug delivery, Clin. Res. Reg. Affairs, 1993; 10: 99–135.
85. Hughes B.L., Allen D.L., Dorato M.A., Wolff R.K., Effect of devices on nasal deposition and mucociliary clearance in rhesus monkeys, Aerosol Sci. Technol., 1993; 18: 241–249.
86. Micieli, F., Santangelo, B., Napoleone, G., Di Dona, F., Mennonna, G., Vesce, G., Intranasal fentanyl for acute severe pain episodes control in a dog. Vet. Anaesth. Analg., 2017; 44: 1400–1401.
87. Mizutani, N., Nabe, T., Takenaka, H., Kohno, S., Acquired nasal hyperresponsiveness aggravates antigen-induced rhinitis in the guinea pig. J. Pharmacol. Sci., 2003; 132-143.
88. Salameh, T.S., Bullock, K.M., Hujoel, I.A., Niehoff, M.L., Wolden-Hanson, T., Kim, J., Morley, J.E., Farr, S.A., Banks, W.A., Central nervous system delivery of intranasal insulin: mechanisms of uptake and effects on cognition. J. Alzheimer's Dis., 2015; 715–728.
89. Saccone, P.A., Lindsey, A.M., Koeppe, R.A., Zelenock, K.A., Shao, X., Sherman, P., Quesada, C.A., Woods, J.H., Scott, P.J.H., Intranasal opioid administration in Rhesus monkeys: PET imaging and antinociception. J. Pharmacol. Exp. Ther., 2016; 359; 366–373.
90. Stevens, J., Suidgeest, E., Van Der Graaf, P.H., Danhof, M., De Lange, E.C.M., A new minimal-stress freely-moving rat model for preclinical studies on intranasal administration of CNS drugs. Pharm. Res., 2009; 26: 1911–1917.
91. Moore, S.J., Smith, J.D., Greenlee, M.H.W., Nicholson, E.M., Richt, J.A., Greenlee, J.J., Comparison of two US sheep scrapie isolates supports identification as separate strains. Vet. Pathol., 2016; 53: 1187–1196.
92. Costantino, H.R., Sileno, A.P., Johnson, P.H., Pharmacokinetic attributes of intranasal delivery: case studies and new opportunities. On Drug Delivery, 2005; 3: 811.
93. Wolfe, T., Barton, E.,Zia H., Dondeti P., N, Nasal drug delivery in EMS: reducing needlestick risk. JEMS, 2003; 28: 5263.
94. Zuercher, A.W., Coffin, S.E., Thurnheer, M.C., Fundova, P., Cebra, J.J., Nasal-associated lymphoid tissue is a mucosal inductive site for virus-specific humoral and cellular immune responses. J. Immunol., 2002; 168: 179-618.