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# RECENT ADVANCES IN INTRANASAL DRUG DELIVERY SYSTEMS

**Chinmaya Keshari Sahoo*[1], Dibyalochan Mohanty[2], R.Soundharya[3], Kole Bhavana[3], G.Akshay Kumar[3]**

*[1]Research Scholar, Osmania University College of Technology, Osmania University, Hyderabad, Telangana – 500007, India.
[2]Assistant Professor, Department of Pharmaceutics, School of Pharmacy, Anurag Group of Institutions, Ghatkesar, R.R Dist, Telengana - 500088, India.
[3]UG Scholar, School of Pharmacy, Anurag Group of Institutions, Ghatkesar, R.R Dist, Telengana - 500088, India.

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**ABSTRACT**

Intranasal drug delivery provides as a non-invasive route for drugs. The nasal mucosa offers numerous benefits as a target tissue for drug delivery, a wide variety of therapeutic compounds may be administered intra nasally for topical, systemic and central nervous system. Nasal route is more suitable for those drugs which cannot be administered orally due to gastric degradation or hepatic first pass metabolism of the drug. Intranasal drug delivery is found much promising route for administration of peptides and protein drugs, vaccines. This present review has focused on mechanism, factors affecting nasal drug absorption, applications etc.

## INTRODUCTION

Intranasal drug delivery [1] provides rapid drug absorption compared to subcutaneous injection or oral administration, the avoidance of hepatic first pass effect, greater patient convenience and compliance, and the elimination of needle stick injuries and bio hazardous waste disposal problems associated with the use of syringes. In addition, consumer demographic trends point to an increasing popularity of self-administration of drugs for personal management and the control of chronic diseases. Topical nasal applications such as therapies for nasal congestion and allergic rhinitis still account for the major share of intranasal drug delivery. However, nasal administration of drugs intended for systemic absorption in the treatment of chronic diseases such as diabetes, osteoporosis, obesity, certain types of convulsive disorders, migraine headaches, together with symptomatic relief of pain, nausea, and anxiety is rapidly growing. Nowadays many drugs have better systemic bioavailability through nasal route as compared to oral administration. Oral administration of these drugs is not possible because they are significantly degraded in the gastrointestinal tract or considerably metabolized by first pass effect in the liver. Intranasal drug delivery offers a promising alternative route for administration of such drugs. Nasal drug delivery system is also suitable for restricting and obstacles blood brain barrier so that drug can be delivered in the biophase of CNS. It is also considered for the administration of vaccines. The interest in intranasal route for therapeutic purposes arises from the anatomical, physiological and histological characteristics [2,3] of the nasal cavity, which provides rapid systemic drug absorption and quick onset of action.Many low-molecular-weight, non-polar drugs (<300Da) in solution form are able to infiltrate the nasal epithelium with effortlessness. The effectiveness of a

Corresponding Author

**Chinmaya Sahoo**
Email: - sahoo.chinmaya83@gmail.com

particular delivery system is also affected by its formulation as a spray,liquid, powder, gel, microsphere, liposome or nanoparticle. Intranasal drug delivery is now recognized to be a useful and reliable alternative to oral and parenteral routes. In general, among the primary targets for intranasal administration arepharmacologically active compounds with poor stability in gastrointestinal fluids, poor intestinal absorption and/or extensive hepatic first-pass elimination, such as peptides, proteins and polar drugs [4,5].

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**Advantages of nasal drug delivery system [6,7]**

1. Drug degradation is absent.
2. Hepatic first pass metabolism is absent.
3. It provides rapid drug absorption and quick onset of action.
4. The bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approach.
5. There is better nasal bioavailability for smaller drug molecules.
6. Drugs which cannot be absorbed orally may be delivered to the systemic circulation through nasal drug delivery system.
7. It is the convenient route when compared with parenteral route for long term therapy

**Limitations [8,9]**

1. Volume that can be delivered into nasal cavity is restricted to 25–200 µl.
2. High molecular weight compounds cannot be delivered through this route (mass cut off ~1 kDa)
3.It is adversely affected by pathological conditions
4. Large interspecies variability is observed in this route
5. Normal defence mechanisms like mucociliary clearance and ciliary beating affects the permeability of drug
6. Enzymatic barrier affects permeability of drugs
7. Irritation of nasal mucosa occurs by drugs
8.There is limited absorption mechanism.
9. Absorption surface area is less when compared to GIT.
10. Once the drug administered can not be removed.
11. The absorption enhancers used to improve nasal drug delivery system may have histological toxicity.

**MECHANISM OF DRUG ABSORPTION [10,11]**

Passage of drug through the mucus is the first step in the absorption from the nasal cavity. Uncharged as well as small particles easily pass through mucus. However, charged as well as large particles may find it more difficult to cross. Several mechanisms have been proposed but the following two mechanisms have been considered predominantly.

**Mechanism of drug absorption by paracellular route**

It involves an aqueous route of transport of drugs. Paracellular route is slow and passive. In above route there is an inverse log-log correlation between the molecular weight of water-soluble compounds and intranasal absorption. Drugs with a molecular weight greater than 1000 Daltons shows poor bioavailability.

**Mechanism of drug absorption by transcellular route**

It includes transport of drug through a lipoidal route (transcellular process). Transcellular route is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. Cell membranes may be crossed by drugs by an active transport route *via* carrier mediated means or transport through the opening of tight junctions. Example: Chitosan opens tight junctions between epithelial cells and hence facilitate drug transport.

**NASAL ANATOMY AND PHYSIOLOGY OF NOSE**

In humans and other animal species the major functions of the nasal cavity are breathing and olfaction. However, it affords an important protective activity once it filters, heat and humidify the inhaled air before reaching the lowest airways. Nasal cavity is lined with mucus layer and hairs which are involved in those functions, trapping inhaled particles and pathogens. Moreover, resonance of produced sounds, mucociliary clearance MMC, immunological activities and metabolism of endogenous substances are also essential functions of nasal structures [12]. Anatomically, human nasal cavity fills the space between the base of the skull and the roof of the mouth; above, it is supported by the ethmoid bones and, laterally, by the ethmoid, maxillary and inferior conchae bones.The human nasal cavity has a total volume of 15-20 mL and a total surface area of approximately 150 $cm^2$. It is divided by middle (or nasal) septum into two symmetrical halves, each one opening at the face through nostrils and extending posterior to the nasopharynx. Both symmetrical halves consist of four areas (nasal vestibule, atrium, respiratory region and olfactory region) that are distinguished according to their anatomic and histological characteristics.

**Nasal vestibule**

Nasal vestibule is the most anterior part of the nasal cavity, just inside the nostrils, and presents an area about 0.6 $cm^2$. Here, there are nasal hairs, also called vibrissae, which filter the inhaled particles. Histologically, this nasal portion is covered by a stratified squamous and keratinized epithelium with sebaceous glands. These nasal vestibular characteristics are desirable to afford high resistance against toxic environmental substances but, at

the same time,the absorption of substances including drugs becomes very difficult in this region.

**Atrium**

Atrium is the intermediate area between nasal vestibule and respiratory region. Its anterior section is constituted by a stratified squamous epithelium and the posterior area by pseudostratified columnar cells presenting microvilli.

**Respiratory region [13,14]**

The nasal respiratory region, also called conchae, is the largest part of the nasal cavity and it is divided in superior, middle and inferior turbinates which are projected from the lateral wall. These specialized structures are responsible for humidification and temperature regulation of inhaled air. Between them there are spaces, called meatus, which are passageways where airflow is created to assure a close contact of the inhaled air with the respiratory mucosal surface. The inferior and middle meatus receive nasolacrimal ducts and paranasal sinuses which are air-filled pockets located inside the bones of the face and around the nasal cavity. The nasal respiratory mucosa, considered the most important section for delivering drugs systemically, is constituted by the epithelium, basement membrane and lamina propria. The nasal respiratory epithelium consists of pseudostratified columnar epithelial cells, globet cells, basal cells and mucous and serous glands. Many of the epithelial cells are covered on their apical surface with microvilli and the major part of them also has fine projections, called cilia. Actually, microvilli are important to enhance the respiratory surface area, while cilia are essential to transport the mucus toward the nasopharynx.

Under physiological conditions, nasal epithelium is covered with a thin mucus layer produced by secretory glands and globet cells. These ones secrete granules filled with mucin, a glycoprotein that determines the viscosity of the mucus. The nasal mucus layer is only 5 μm thick and it is organized in two distinct layers: an external, viscous and dense, and an internal, fluid and serous. Overall, nasal mucus layer consists of 95% of water, 2.5-3% of mucin, and 2% of electrolytes, proteins, lipids, enzymes, antibodies, sloughed epithelial cells and bacterial products. Nasal mucus is indispensable for several physiological functions, such as humidification and warming of the inhaled air, and also offers physical and enzymatic protectionof the nasal epithelium against several foreign compounds, including drugs. The protective action results of the adhesive characteristics of mucus to attract inhaled particles or pathogens, which are removed towards the nasopharynx by nasal MCC. The presence of mucin in the nasal mucus layer is crucial because it may trap large molecular weight drugs, such as peptides and proteins. The basal cells that exist in the epithelium are progenitors of other cell-types and lye on a thickened layer of collagen called basement membrane. Beneath of it, there is the lamina propria which is richly supplied with blood vessels, including many very permeable fenestrated capillaries, nerves, glands and immune cells. The last ones produce immunoglobulin A antibodies that confer immunological protection against bacteria and virus [15].

**Olfactory region**

The olfactory region is located in the roof of the nasal cavity and extends a short way down the septum and lateral wall. Its neuroepithelium is the only part of the CNS that is directly exposed to the external environment. Similarly to the respiratory epithelium, the olfactory one is also pseudostratified but contains specialized olfactory receptor cells important for smell perception . In this area there are also small serous glands (glands of Bowman) producers of secretions acting as a solvent for odorous substances.

**FACTORS INFLUENCING NASAL DRUG ABSORPTION**

The following factors affect drug absorption

**1. Nasal physiological factors**

**Blood flow**

Rich supply of blood and a large surface area make the nasal mucosa an optimal location for drug absorption. Nasal absorption of drugs is influenced by blood flow rate, as it increases the amount of drug that passes through the membrane and hence reaching the general circulation. Several studies were made to evaluate this influence. For example, Kao et al [16] stated that nasal absorption of dopamine was relatively slow and incomplete probably due to its own vasoconstrictor effect. From above observations, it was concluded that vasoconstriction decreases nasal drug absorption by diminishing the blood flow.

**Mucociliary clearance [17-19]**

MMC also referred to as mucociliary apparatus or mucociliar clearance (MCC) is the self-clearing mechanism of the bronchi. Nasal mucus layer plays an important role in the defence of respiratory tract because it prevents the lungs from foreign substances, pathogens and particles carried by inhaled air. These agents adhere to the mucus layer and, all together, they are transported to the nasopharynx and, eventually, to the gastrointestinal tract. This elimination is designated MCC and it influences also significantly the nasal drug absorption. The MCC system has been described as a conveyer belt wherein cilia provide the driving force whereas mucus acts as a sticky fluid that collects and disposes foreign particles. The efficiency of MCC thereby depends on the length, density and beat frequency of cilia as so as the amount and viscoelastic properties of mucus. Briefly, all factors that increase mucus production, decrease mucus viscosity or increase

ciliary beat frequency may increase the MCC. In physiological conditions, mucus is transported at a rate of 5 mm/min and its transit time in human nasal cavity is reported to be 15-20 min. Values out of these references are abnormal and suggestive of impaired MCC .Thus, if MCC decreases, residence time of the drug product in nasal mucosa increase and therefore, enhances its permeation. The opposite effect is observed when MCC increases. In the last case, a premature discharge of nasally administered drugs from nasal cavity toward the nasopharynx occurs, decreasing the amount of drug absorbed. The clearance of a drug product from the nasal cavity is also influenced by the site of deposition. A drug deposited in a posterior area of the nose is cleared more rapidly from the nasal cavity than a drug deposited anteriorly. This is because MCC is slower in the anterior part of the nose than in the more ciliated posterior part . On the other hand, the site of drug deposition in the nose is highly dependent on the dosage form. Nasal sprays deposit drugs more anteriorly than nasal drops, resulting in a slower clearance for drugs administered from spray formulations .Polar drugs are the most affected by MCC,since they are highly soluble in mucus and their passage across the membrane is very slow. Thus, all factors that influence the efficacy and pace of MCC may modify the drug absorption profile. For instance, environmental factors have a relevant influence in MCC. Temperature and sulphur dioxide seem to cause a significant reduction in MCC, but this the mechanism is not well known. Cigarette smoking also decreases MCC as it enhances the viscosity of the mucus and/or diminishes the number of cilia. In addition, several pathological conditions exist in which MCC does not work properly. Furthermore some components of drug formulations may also alter the MCC system, such as preservatives and nasal absorption enhancers. Finally, it is interesting to stand out the inter-individual variability observed in MCC and the influence of the menstrual cycle and circadian rhythm. Actually, during the periovulatory period MCC is increased and it is reduced at night.

**Enzymatic degradation [20-22]**

Drugs nasally administered circumvent gastrointestinal and hepatic first-pass effect.However, they may be significantly metabolized in lumen of nasal cavity or during the passage across the nasal epithelial barrier due to the presence of a broad range of metabolic enzymes in nasal tissues. Carboxyl esterases, aldehyde dehydrogenases, epoxide hydrolases and gluthatione S-transferases have been found in nasal epithelial cells and are responsible for the degradation of drugs in nasal mucosa. Cytochrome P450 isoenzymes are also present here and they have been reported as metabolizers of drugs such as cocaine, nicotine, alcohols, progesterone and decongestants.Similarly, proteolytic enzymes (aminopeptidases and proteases) were found and they are believed to be the major barrier against the absorption of peptide drugs, such as calcitonin, insulin and desmopressin. Thus, xenobioticmetabolizing enzymes existent in the nasal mucosa may affect the pharmacokinetic and pharmacodynamic profile of nasally applied drugs. In this context, although the nasal first-pass metabolism is usually weaker than hepatic and intestinal ones it cannot be ignored.

**Transporters and efflux systems [23-25]**

The absorption of drugs into systemic circulation and CNS through nasal route is of great interest. Multidrug resistance transporters have been identified which may be involved in the transportation of hydrophobic and amphiphilic drugs. The apical area of ciliated epithelial cells and sub mucosal vessels of the human olfactory region contain P-gp is an efflux transporter which plays an important role in avoiding the influx of drugs from nasal membrane.

**2. Physicochemical properties of drugs [26-32]**

**Molecular weight**

A linear inverse correlation has been reported between the absorption of drugs and molecular weight up to 300 Daltons. Absorption decreases significantly if the molecular weight is greater than 1,000 Daltons except with the use of absorption enhancers Based on the reports by Fisher et al.48 and Yamamto et al. it can be concluded that the permeation of drugs less than 300 Da is not significantly influenced by the physicochemical properties of the drug like molecular weight, size, formulation pH, pKa of molecule,, which will mostly permeate through aqueous channels of the biological membrane.

**pKa**

According to the pH partition theory, unionized form of drug are well absorbed compared with ionized form of drug and the same theory is applicable in the case of nasal drug absorption. Jiang et al. conducted a study to determine the quantitative relationship between the physicochemical properties of drugs and their nasal absorption, using diltiazem hydrochloride and paracetamol as model drugs. The results showed that a quantitative relationship existed between the partition coefficient and the nasal absorption constant

**Lipophilicity**

Absorption of drug substance through biological membrane may be dependent on hydrophilic lipophilic balance of the compound. On increasing lipophilicity, the nasal absorption of the compound normally increases. Although In one study it was found that lipophilic compounds alprenolol and propranolol were well absorbed from the nasal mucosa, in comparision to the hydrophilic drug metoprolol. 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 traverse the cell in the cell cytoplasm.Nasal absorption of steroids was directly correlated with lipophillicity of drug molecules and was found to be independent of pH. A number of lipophilic drugs such as naloxone, buprenorphine, testosterone and 17a-ethinyloestradiol, have been shown to be completely or almost completely absorbed nasally in animal models.

**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 alter its absorption. Huang et al. reported that in-situ nasal absorption of carboxylic acid esters of L-tyrosine was significantly greater than that of unmodified L-tyrosine.

**Particle size**

It has been reported that particles greater than 10 μm in size are deposited in the nasal cavity. Particles that are 2 to10 μm can be retained in the lungs, and particles of less than 1 μm are exhaled.

**Solubility and dissolution rate**

For drug absorption, drug dissolution is a pre-requisite because molecularly disperse form of a drug may cross the biomembranes. Therefore the drug must be dissolved in the nasal cavity fluid before absorption. Drug allowed enough contact with the nasal mucosa which may show slow absorption. Drugs with poorly soluble in water may require high doses hence can cause a problem. The problem can be overcome by enhancing drug solubility using various techniques.

Drug solubility and dissolution rates are important biopharmaceutical factors in determining nasal absorption from powders and suspensions. The particles deposited in the nasal cavity need to dissolve prior to absorption. Solubility of a drug or dosage form is the first prerequisite for absorption and bioavailibility of dosage form. The fluid available for dissolution of drug particles in nasal cavity or mucosa is very less when compared to the gastrointestinal fluid in oral drug delivery. Saturation solubility of drug in a given nasal physiological pH is very important parameter, which determines the rate and extent absorption of nasal dosage form.

**Stability [33]**

Biological, chemical and physical drug stability studies are a major consideration in all process during the development of new drug formulations. The biological stability of nasally administered drugs may reduce due to the metabolism of drugs by defensive enzymatic mechanisms by nasal cavity. To overcome this difficulty a variety of strategies may be followed, mainly through the use of prodrugs and enzymatic inhibitors.

**3. Effect of drug formulation [34,35]**

**Viscosity**

Formulation with higher viscosity has a better contact time thus increases the absorption. At the same time, high viscosity enhanced the permeability of drugs.As formulation viscosity increases, the contact time between drug and nasal mucosa enhances and, thereby, the potential of drug absorption increases. At the same time, high viscosity of formulations interferes with normal ciliary beating and/or MCC and, thus, increases the permeability of drugs. This has been observed during nasal delivery of insulin, acyclovir and metoprolol. However, sometimes, enhancing formulation viscosity does not enhance the drug absorption. For example, Zaki et al. performed a study to evaluate the influence of formulation viscosity on the retention time of metoclopramide hydrochloride in nasal cavity and on its absorption. Interestingly, they observed that although the residence time enhanced as viscosity increased the drug absorption diminished. This observation has been attributed to a decrease in the drug diffusion from the formulation. On the other hand, it has also been reported that the viscosity of the solution may provide a larger therapeutic period of nasal formulations.

**pH**

The extent of nasal absorption depends on the pKa of drug and pH at the absorption site,contributing for that also the pH of formulation.At this point, it should be stated that the pH of formulation must be selected attending to drug stability and if possible should be assured the greatest quantity of non-ionized drug species.However, the pH of formulation can induce nasal mucosa irritation and, hence, it should be similar to that found on human nasal mucosa (5.0-6.5). Besides, the pH often prevents the bacteria growth. In order to evaluate the effect of pH solution on the integrity of nasal mucosa, Pujara et al. dissolved drugs in phosphate buffer at different pH values in the range of 2-12. The study was performed in rats whose nasal pH is 7 and the results demonstrated that when pH ranged from 3-10minimal quantities of proteins and enzymes were released from cells, demonstrating no cellular damages. On the contrary, if pH values were below 3 or above 10 damages were observed intracellularly and at membrane level. The pH of a nasal formulation is important for the following reasons such as

- 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
- To sustain normal physiological ciliary movement

**Pharmaceutical form**

Nasal drops are the simplest and the most convenient nasal pharmaceutical form, but the exact amount of drug delivered is not easily quantified and often results in overdose .Moreover, rapid nasal drainage can occur when using this dosage form. Solution and suspension sprays are preferred over powder sprays because the last one easily prompted the development of nasal mucosa irritation. Recently, gel devices have been developed for a more accurate drug delivery. They reduce postnasal drip and anterior leakage, fixing the drug formulation in nasal mucosa. This enhances the drug residence time and diminishes MCC, thereby, potentially increases the nasal absorption. Over the last years, specialized systems such as lipid emulsions, microspheres, liposomes and films have also been developed to improve nasal drug delivery.

**Pharmaceutical excipients**

In nasal formulations, a wide variety of pharmaceutical excipients can be found and they are selected accordingly to their functions. Solubilizers, buffer components, antioxidants, preservatives, humectants, gelling/viscosifying agents, and flavoring or taste masking agents are some of the most usual excipients. Although they are responsible for several nasal irritations, antioxidants, preservatives, humectants and flavoring or taste masking agents are not expected to alter nasal drug absorption.

**Osmolarity**

Drug absorption can be affected by tonicity of the formulation. Ohwaki et al. studied the effect of osmolarity on the absorption of secretin in rats and found that absorption reached a maximum at a sodium chloride concentration of 0.462 M, because shrinkage of the nasal epithelial mucosa was observed at in the presence of hypertonic solutions. Hypertonic saline solutions are also known to inhibit or cease ciliary activity. Low pH has a similar effect on cells as hypertonic solutions.

**Gelling agents**

Retention of the nasal formulation in the nasal cavity can enhance therapeutic effect by virtue of enhancing rate and extent of drug absorption. According to a study by pennington et al, increasing the viscosity may provide a means of prolonging the effect of nasal formulation. Suzuki, et al. showed that a drug carrier, hydroxyl-propylcellulose was effective for improving the absorption of low molecular weight drugs but did not produce the same effect for high molecular weight peptides.

**Solubilizers**

The aqueous solubility of a 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 (saturated polyglycolyzed C8-C10 glyceride) can be used to enhance the solubility of drugs. Other options include the use of surfactants or cyclodextrins such as hydroxypropyl-beta-cyclodextrin that serve as biocompatible solubilizers and stabilizers in combination with lipophilic absorption enhancers. In such cases, impact of the solubilizers on nasal irritancy should be considered.

**Drug concentration, required dose, and dose volume**

Drug concentration, dose and volume of administration are three interrelated parameters that impact the performance of the nasal delivery system. Ex vivo experiments in rats demonstrated the effect of drug concentration on nasal drug absorption. Nasal absorption of I-tyrosyl-L-tyrosine was found to increase with increasing concentration of drug. However few experiments showed different effects of drug concentration on the absorption of drugs, for example the absorption of aminopyrine from rat nasal mucosa was constant as a function of its concentration. Interestingly, nasal absorption of salicylic acid was decreased with increasing concentration of administered drug and low absorption of high concentration of salicylic acid was lined with its nasal epithelial toxicity and nasal membrane resistance.

**APPLICATION OF NASAL DRUG DELIVERY SYSTEM**

**Local delivery [36-38]**

For the natural treatment of topical nasal disorders the drug is administered through nasal route. Among the most common examples are antihistamines and corticosteroids for rhinosinusitis, and nasal decongestants for cold symptoms. In fact, relatively low doses are effective when administered through nasal route with less systemic toxic effects.

**Systemic delivery [39-44]**

The intranasal administration of drugs is an effective way for systemic availability of drugs as compared to oral and intravascular routes. Actually, it seems to present fast and extended drug absorption, and it has been supported by many studies planned to compare intranasal drug delivery against oral and parenteral administration. Examples include analgesics (morphine), cardiovascular drugs as propranolol and carvedilol, hormones such as levonorgestrel, progesterone and insulin, anti-inflammatory agents as indomethacin and ketorolac, and antiviral drugs (acyclovir). Some examples which are available in the market include zolmitriptan and sumatriptan for the treatment of migraine and cluster headaches.

**Delivery of Vaccines [45-49]**

Nasal delivery of vaccines has been reported to not only produce systemic immune response, but also local immune response in the nasal lining, providing additional barrier of protection. The majority of the invading pathogens enter the body *via* mucosal surfaces. Therefore, mucosal sites have a potential as first line of defense against entering pathogens. Pathogens are filtered from the inspired air by compaction and mucociliary clearance. Nasal secretions are known to contain immunoglobulins (IgA, IgG, IgM, IgE), protective proteins such as complement as well as neutrophils and lymphocytes in the mucosa. Delivering the vaccine to the nasal cavity itself stimulates the production of local secretory IgA antibodies as well as IgG, providing an additional first line of defense system.Main reasons for exploiting the nasal route for vaccine delivery The nasal passages are rich in lymphoid tissue. Creation of both mucosal and systemic immune responses. Low cost, patient compliance, non-injectable and safe. The feasibility of the nasal route for administering vaccines against plague, diphtheria tetanus, influenza, cholera, and HIV has already been tested for inducing both mucosal and systemic immune response against the carried antigen. Nasal influenza vaccination may prove to be a good alternative to parenteral injection because of the enhancement of the mucosal immune response and the ease of vaccine administration. This study investigated the use of chitosan, a bioadhesive polymer, as a nasal delivery system with inactivated, subunit influenza vaccine.

**Nose to brain drug delivery system [50-51]**

The blood-brain barrier (BBB) limits substrate penetration based on several characteristics, including lipophilicity, molecular size and specificity for a variety of ATP-dependent transport systems. At the beginning of the previous century the direct connection between the brain and the open air was discovered: the olfactory neurons. Injection of dyes in the ventricles of rabbits and monkeys showed that the cerebrospinal fluid (CSF) is drained via the olfactory neurons into the olfactory neurons, originating from the olfactory bulb, connect the brain with the nasal cavity by penetrating the cribriform plate, which brings the neurons into the nasal mucosa. This coined the idea that this transport route could also exist in the opposite direction, which would imply direct access from the nasal cavity to the brain, thus circumventing the BBB. This opened up a new perspective in the research field of drug targeting to the CNS, lymphatic vessels and the nasal mucosa. A growing numbers of recent reports have demonstrated the effectiveness of intranasal administration of neuroprotective agents in decreasing ischemic brain injury. For example, Ying et al. recently reported that intranasal administration of NAD+ profoundly decreased in comparison to the formulation without cyclodextrin addition. It has been observed that increasing the time of contact with the nasal mucosa can increase the nasal brain injury in a rat model of transient focal ischemia.Similarly, Wei et al. showed that intranasal administration of the PARG inhibitor Gallo tannin decreased ischemic brain injury in rats. Such agents are believed to provide neuroprotection by diminishing or abolishing activation of poly (ADP-ribose) polymerase-1 (PARP-1), which plays a significant role in ischemic brain damage. NAD+ was observed to reduce infarct formation by up to 86% even when administered at 2 hours after ischemic onset. Chen et al. investigated the potential of delivering nerve growth factor to the brain along the olfactory neural pathway for the treatment of Alzheimer's disease and found that the nerve growth factor reached the brain within an hour achieving the highest concentration in the olfactory bulb and less in other brain regions.Kao et al. studied the nasal transport of various esters, such as butyl and methyl, of the carboxyl group of L-dopa in the rat model and found significantly higher levels of L-dopa in the CSF and the olfactory bulb than did equimolar doses given intravenously.

**Delivery of peptide and non-peptide drugs [52-53]**

Most peptides and proteins, being hydrophilic polar molecules of relatively high molecular weight, are poorly absorbed across biological membranes with bio-availability obtained in the region of 1–2% concentrations when administered as simple solutions. This low uptake may be adequate for the development of some commercial products like desmopressin and calcitonin because they have a wide therapeutic index. But for certain a peptide drug such as insulin which does not have the luxury of wide therapeutic index it is essential to develop the novel formulation strategies. In order to produce a product with a good bioavailability that can provide sufficient reliability in dosing and overcome these problems much research has been carried out in the areas of absorption enhancers and bioadhesive agents. Absorption enhancers are used to increase the bioavailability, and these enhancers are basically surfactants, glycosides, cyclodextrin and glycols. Recent studies have shown that the high bioavailability achieved with absorption enhancers for the delivery of polar compounds across mucosal membranes can be associated with tissue damage. Hence care should be taken that the absorption enhancer used should not only increase the bioavailability but should also be harmless to the nasal mucosa. The classical example of a polypeptide compound with low nasal bioavailability is calcitonin. Its molecular weight is approximately 3,500 daltons andcontains 32 amino acid in length. when calcitonin was given intranasally to rats and rabbits using a number of different cyclodextrins, its absorption when measured as decrease in serum calcium concentration, was found to be significant

absorption of insulin. When a surfactant such as saponin, sodium glycolate or BL-9 was added to the preparation, the absorption of insulin from the nasal mucosa was enhanced

independent of pH. Nasal absorption is also promoted by medium chain fatty acid salt glycyrrhetinic acid derivatives in rat sodium-tauro-24, 25-dihydrofusidate in sheep. Proteins like luteinizing hormone releasing hormone, growth hormone and adreno-corticotrophic hormone have been administered intranasaly. Unlike high molecular weight peptides, the small non-peptide lipophilic drugs (MW below 1000) are better absorbed through the nasal mucosa even in the absence of absorption enhancers. The underlying epithelium of the nasal membrane is highly vascularized and the nasal cavity has a large surface area readily accessible for drug absorption because of the presence of nasal turbinates. As a consequence, low molecular weight lipophilic drugs, such as propanolol, progesterone are well absorbed across the nasal cavity and resulting in a faster onset of action. Intranasal route has also been tried with limited success for drugs such as steroids (corticosteroids, estradiol, testosterone, and so on), anti-hypertensives (nifedipine, nitroglycerine, propranolol, hydralazine,), analgesics (buprenorphine, morphine), antibiotics and antivirals.

**Table 1. Nasal formulations available for local drug delivery**

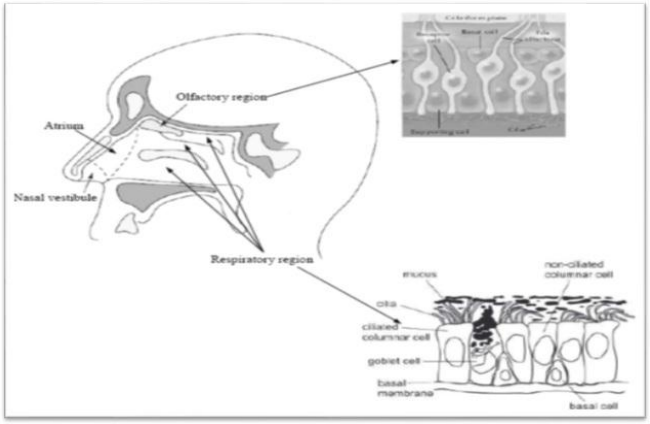
| Drug | Brand | Company | Indications |
|---|---|---|---|
| Azelastine | Astelin | Meda Pharmaceuticals | Treatment of rhino sinusitis |
| Beclometasone | Beconase | GlaxoSmithKline | Treatment of rhino sinusitis |
| Budesonide | Rhinocort | AstraZeneca | Treatment of rhino sinusitis |
| Levocabastine | Livostin | JansenCilag | Treatment of rhino sinusitis |
| Mometasone | Nasonex | Schering-Ploough | Treatment of rhino sinusitis |
| Olapatadine | Patanase | Alcon Laboratories | Treatment of rhino sinusitis |
| Mupirocin | Bactroban | GlaxoSmithKline | Eradication of nasal staphylococci |

**Table 2. Nasal formulations available for systemic drug delivery**

| Drug | Brand | Company | Indications |
|---|---|---|---|
| Estradiol | Aerodiol | Servier Laboratories | Hormone replacement therapy |
| Nicotine | Nicotrol NS | Pfizer | Smoking cessation |
| Oxytocin | Syntocinon | Novartis | Labour induction |
| Salmon Calcitonin | Miacalcin | Novartis | Postmenopausal osteoporosis |
| Buserelin | Suprefact | Sanofi Aventis | Prostate cancer |
| Zolmitriptan | Zomig nasal | AstraZeneca | Migraine |
| Cyanocobalamin | Nascobal | Strativa Pharmaceuticals | Vitamin $B_{12}$ deficiency |
| Desmopressin | Desmospray | Ferring Pharmaceuticals | Dehydration in diabetes insipidus |

**Fig.1. Currently marketed aqueous pump sprays**


**Fig.2. Anatomy and histology of nasal cavity**




## CONCLUSION

The intranasal route is an accessible alternative route for drug administration which provides future potential for several drugs through the development of safe and efficacious formulations for simple, painless and long-term therapy. It is expected that novel nasal products will continue to reach the market due to the widespread benefits of this route. Nasal product will include drugs for acute and long term diseases and also vaccines with better local or systemic protection against infections. From this route drugs can be directly target to the brain in order to

attain a good therapeutic effect in CNS with reduced systemic side effects. It is well known that intranasal route has several limitations which must be overcome to develop a successful nasal formulation. Drug related factor and pathophysiological condition of nose determine the nasal drug absorption. Some common approaches, like increasing the nasal residence time of drug, use of absorption or penetration enhancers and minimization of the mucociliary clearance, enhances the bioavailability of nasally administered drug. 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 noninvasiveness, self-medication, patient comfort and patient compliance which are hurdled in intravenous drug therapy**.**

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