NASAL DRUG DELIVERY SYSTEM: A REVIEW

Prajakta Chavan1*, Shashikant Dhole1, Mayuri Yadav1

1P. E. S’s Modern College of Pharmacy (for ladies) Moshi, Pune, Maharashtra, India.

ABSTRACT
Nasal drug administration has been used as an alternative route for the systemic availability of drugs restricted to intravenous administration. This is due to the large surface area, porous endothelial membrane, high total blood flow, the avoidance of first-pass metabolism, and ready accessibility. The nasal administration of drugs, including numerous compound, peptide and protein drugs, for systemic medication has been widely investigated in recent years. Drugs are cleared rapidly from the nasal cavity after intranasal administration, resulting in rapid systemic drug absorption. Certain drugs are delivered to the nasal cavity because their intended site of action. These are administrated as nasal drops or sprays for a local effect. Such drugs in clinical use include decongestants, antibiotics and mucolytics.

KEYWORDS: Nasal drug delivery system, bioavailability, nasal cavity, nasal absorption, nasal route.

INTRODUCTION [1,2]
Nasal mucosa has been considered as a potential administration route to achieve faster and higher level of drug absorption because it is permeable to more compounds than the gastrointestinal tract due to lack of pancreatic and gastric enzymatic activity, neutral pH of the nasal mucus and less dilution by gastrointestinal contents. Nasal therapy is the recognized form of treatment in the Ayurvedic systems of Indian medicine, and also called as nasaya karma.

It is a useful delivery method for drugs that are active in low doses and show no minimal oral bioavailability such as proteins and peptides. One of the reasons for low degree of absorption of peptides and proteins via the nasal route is rapid movement away from the absorption site...
in the nasal cavity due to the mucociliary clearance mechanism. The nasal route circumvents hepatic first pass elimination associated with the oral delivery. It is easily accessible and suitable for self-medication. Drug candidates ranging from small metal ions to large macromolecular proteins have been tested in various animal models. It has been documented that nasal administration of certain hormones and steroids results in more complete absorption. This indicates the potential value of the nasal route for administration of systemic medications as well as utilization of this route for local effects.

Topical administration includes the treatment of congestion, rhinitis, sinusitis and related allergic or chronic conditions and has resulted in a variety of different medications including corticoids, antihistamines, anticholinergic and vasoconstrictors. To deliver therapeutics into the nasal cavities, i.e., nasal drops as multiple or single dose formulation, aqueous nasal sprays, nasal gel pump, pressurized MDIs and dry powder inhalers.

Intranasal delivery is currently being employed in treatments for migraine, smoking cessation, acute pain relief, osteoporosis, nocturnal enuresis and vitamin B12 deficiency. Other include cancer therapy, epilepsy, anti-emetics, rheumatoid arthritis and insulin-dependent diabetes.

**Advantages** [1,2]

1) Drug degradation that is observed in the gastrointestinal tract is absent.
2) Hepatic first pass metabolism is avoided.
3) Rapid drug absorption and quick onset of action can be achieved.
4) The bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approach.
5) The nasal bioavailability for smaller drug molecules is good.
6) Drugs that are orally not absorbed can be delivered to the systemic circulation by nasal drug delivery.
7) Nasal route is an alternate to parenteral route, especially, for protein and peptide drugs.
8) Convenient for the patients, especially for those on long term therapy, when compared with parenteral medication.
9) Drugs possessing poor stability in g.i.t. fluids are given by nasal route.
10) Polar compounds exhibiting poor oral absorption may be particularly suited for this route of delivery system.
Disadvantages\textsuperscript{[1,2]}
1) The histological toxicity of absorption enhancers used in nasal drug delivery system is not yet clearly established.
2) Relatively inconvenient to patients when compared to oral delivery systems since there is a possibility of nasal irritation.
3) Nasal cavity provides smaller absorption surface area when compared to GIT.
4) There is a risk of local side effects and irreversible damage of the cilia on the nasal mucosa, both from the substance and from constituents added to the dosage form.
5) Certain surfactants used as chemical enhancers may disrupt and even dissolve the membrane in high concentration.
6) There could be a mechanical loss of the dosage form into the other parts of the respiratory tract like lungs because of the improper technique of administration.

Limitation\textsuperscript{[2,3]}
1) The histological toxicity of absorption enhancers used in nasal drug delivery system is not yet clearly established.
2) Relatively inconvenient to patients when compared to oral delivery systems since there is a possibility of nasal irritation.
3) Nasal cavity provides smaller absorption surface area when compared to GIT.

Anatomy & Physiology of Nasal Cavity\textsuperscript{[1]}
1) The nasal cavity is divided into two halves by the nasal septum and extends posterior to the nasopharynx, while the most anterior part of the nasal cavity, the nasal vestibule, opens to the face through the nostril.
2) The nasal cavity consists of three main regions. They are nasal vestibule, olfactory region and respiratory region.
3) The surface area in the nose is enlarged about 150cm\textsuperscript{2} by the lateral walls of the nasal cavity which includes a folded structure. It has a very high surface area compared to its small volume. This folded structure consists of three turbinate’s - the superior, the median and the inferior.
4) The main nasal airway having the narrow passages usually has 1-3mm wide and these narrows structures are useful to nose to carry out its main functions. The nasal cavity is covered with a mucous membrane which can be divided into two areas i.e.; non-olfactory and olfactory epithelium. In non-olfactory area includes the nasal vestibule which is
covered with skin-like stratified squamous epithelium cells where as in respiratory region, it has typical airways in the epithelium covered with numerous microvilli, resulting in a large surface area available for drug absorption and transport.

5) In this way the mucus layer is propelled in a direction from the anterior towards the posterior part of the nasal cavity. The goblet cells are present in the mucus membrane which covers the nasal turbinate and the atrium. It secretes mucus as mucus granules which swell in the nasal fluid to contribute to the mucus layer.

6) The mucus secretion is composed of about 95% water, 2 % mucin, 1% salts, 1% of proteins such as albumin, immunoglobulins, lysozyme and lactoferrin, and 1% lipids. The mucus secretion gives immune protection against inhaled bacteria and viruses. It also performs a number of physiological functions. It covers the mucosa, and physically and enzymatically protects it. The mucus has water-holding capacity. It exhibits surface electrical activity. It permits efficient heat transfer. It acts as adhesive and transports particulate matter towards the nasopharynx.

**Parts of Nasal Cavity**[^1]

![Fig. 1: Parts of Nasal Cavity](image)

Fig. 1: (a) nasal vestibule, (b) palate, (c) inferior turbinate, (d) middle turbinate, (e) superior turbinate (olfactory mucosa), (f) nasopharynx
Cell Types of the Nasal Epithelium Showing Ciliated Cell $^{[1,2]}$

Fig. 2: (a), non-ciliated cell (b), goblet cells (c), gel mucus layer (d), sol layer (e), basal cell (f) and basement membrane (g)

Mechanism of Nasal Absorption $^{[2,3]}$

The absorbed drugs from the nasal cavity must pass through the mucus layer. It is the first step in absorption. Small, unchanged drugs easily pass through this layer but large, charged drugs are difficult to cross it. The principle protein of the mucus is mucin which has the tendency to bind to the solutes, hindering diffusion. Additionally, structural changes in the mucus layer are possible as a result of environmental changes. The two mechanisms that include there

First mechanism: It involves an aqueous route of transport, which is also known as the paracellular route but slow and passive. There is an inverse log-log correlation between intranasal absorption and the molecular weight of water soluble compounds. The molecular weight greater than 1000 Daltons show poor bioavailability.

Second mechanism: It involves transport through a lipoidal route known as the transcellular process. It is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. Drugs can also cross cell membranes by an active transport route via carrier-mediated means or transport through the opening of tight junctions. For example
chitosan, a natural biopolymer from shell fish opens tight junctions between epithelial cells to facilitate drug transport 9.

**Factors influencing nasal drug absorption** $^{2,3,8}$
 They include physiochemical properties of the drugs, anatomical and physiological properties of the nasal cavity and the type and characteristics of selected nasal drugs delivery system.

**A) Physiochemical properties of drug.**
1. Molecular size.
2. Lipophilic-hydrophilic balance.
3. Enzymatic degradation in nasal cavity.

**B) Nasal Effect**
1. Membrane permeability.
2. Environmental $p^H$
3. Mucociliary clearance
4. Cold, rhinitis.

**C) Delivery Effect**
1. Formulation (Concentration, $p^H$, osmolarity)
2. Delivery effects
3. Drugs distribution and deposition.
4. Formulation effect on mucociliary clearance.
5. Toxic effect on ciliary function and epithelial membranes

**A) Physiochemical Properties of Drug**

**Molecular size:** The molecular size of the drug influence absorption through the nasal route. The lipophilic drugs have direct relationship between the molecular weight and drug permeation whereas water soluble compounds depict an inverse relationship. The rate of permeation is highly sensitive to molecular size for compounds with MW $\geq$ 300 Daltons.

**Lipophilic-hydrophilic balance:** The hydrophilic and lipophilic nature of the drug also affects the process of absorption. By increasing lipophilicity, the permeation of the compound normally increases through nasal mucosa. Although the nasal mucosa is found to have some hydrophilic character, it appears that these mucosae are primarily lipophilic in nature and the lipid domain plays an important role in the barrier function of these membranes. Lipophilic drugs like naloxone, buprenorphine, testosterone and 17a-ethinyl- oestradiol are almost completely absorbed when administered intranasal route 12, 13.
Enzymatic degradation in nasal cavity: In case of peptides and proteins having low bioavailability across the nasal cavity, these may have possibility to undergo enzymatic degradation in the lumen of the nasal cavity or during passage through the epithelial barrier. These both sites have exopeptidases (mono-aminopeptidases, di-aminopeptidases) which have the capability to cleave peptides at their N and C termini and endopeptidases (such as serine and cysteine) which can attack internal peptide bonds.

Nasal Effect Factors
Membrane permeability
The water soluble drugs and particularly large molecular weight drugs like peptides and proteins have low membrane permeability. So the compounds like peptides and proteins are mainly absorbed through the endocytotic transport process in low amounts. Water-soluble high molecular weight drugs cross the nasal mucosa mainly by passive diffusion through the aqueous pores (i.e. tight junctions).

Environmental PH
The nonionised lipophilic form diffuses through the nasal epithelial barrier via transcellular route, whereas the more lipophilic ionized form passes through the aqueous paracellular route.

Mucociliary Clearance (mcc)
Mucociliary clearance is one of the functions of the upper respiratory tract to prevent noxious substances (allergens, bacteria, viruses, toxins etc.) from reaching the lungs.
When such materials adhere to or dissolve in the mucus lining of the nasal cavity, they are transported towards the nasopharynx for eventual discharge into the gastrointestinal tract. Clearance of this mucus and the adsorbed/dissolved substances into the GIT is called the MCC. The mucus transport rate is 6 mm/min. It is of utmost importance that the MCC is not impaired in order to prevent lower respiratory tract infections.

Rhinitis
It is mainly classified into allergic rhinitis and common. The symptoms are hyper secretion, itching and sneezing mainly caused by the viruses, bacteria or irritants.
It is caused by chronic or acute inflammation of the mucous membrane of the nose. These conditions affect the absorption of drug through the mucus membrane due the inflammation.
Delivery Effect Factors

Formulation (concentration, pH, osmolarity)
The pH of a nasal formulation is important for the following reasons:
- To avoid irritation of nasal mucosa;
- To allow the drug to be available in unionized form for absorption;
- To prevent growth of pathogenic bacteria in the nasal passage;
- To maintain functionality of excipients such as preservatives; and
- To sustain normal physiological ciliary movement.

Lysozyme is found in nasal secretions, which is responsible for destroying certain bacteria at acidic pH. Under alkaline conditions, lysozyme is inactivated and the tissue is susceptible to microbial infection. It is therefore advisable to keep the formulation at a pH of 4.5 to 6.5 keeping in mind the physiochemical properties of the drug as drugs are absorbed in the unionized form.

Drugs distribution and deposition
The absorption and bioavailability of the nasal dosage forms mainly depend on the site of disposition. The anterior portion of the nose provides a prolonged nasal residential time for disposition of formulation and this enhances the absorption of the drug.

The posterior chamber of nasal cavity will use for the deposition of dosage form. It is eliminated by the mucociliary clearance process and hence shows low bioavailability. The site of disposition and distribution of the dosage forms mainly depend on delivery device, mode of administration, physicochemical properties of drug molecule.

Viscosity
A higher viscosity of the formulation increases contact time between the drug and the nasal mucosa thereby increasing the time for permeation. At the same time, highly viscous formulations interfere with the normal functions like ciliary beating or mucociliary clearance and thus alter the permeability of drugs.

Strategies to Improve Nasal Absorption \[^{2,3,8}\]
Various strategies used to improve the availability of the drug in the nasal mucosa, include
1) To improve the nasal residence time
2) To enhance nasal absorption
3) To modify drug structure to change physicochemical properties

1) To improve the nasal residence time

Mucociliary clearance acts to remove the foreign bodies and substances from nasal mucosa as quickly as possible. For delaying clearance is to apply the drug to the anterior part of the nasal cavity, an effect that is largely determined by the type of dosage form used. The preparation could also be formulated with polymers such as methylcellulose, hydroxy propyl methyl cellulose or polyacrylic acid, in which incorporation of polymer increases viscosity of the formulation and also acts as a bio adhesive with mucus. Increase in residence time does not necessarily lead to increase the absorption; this concept can be illustrated by considering insulin solution with similar viscosity containing carbopol and CMC. Here carbopol enhance the absorption whereas CMC solution doesn’t enhance the absorption of insulin. If we increase the viscosity, slow diffusion of drug from matrix causes retention in absorption with CMC. Incase of carbopol causes enhancement of absorption due to opening the intracellular junctions. One more lucrative way to increase the nasal resistance time is using biodegradable microspheres as a carrier for drug delivery. Biodegradable microspheres swell in presence of water thereby increasing the viscosity. This phenomenon leads to increase the nasal residential time.

2) Enhancing nasal absorption

The mechanism of action of absorption enhancer is increasing the rate at which drug passes through the nasal mucosa. Many enhancers act by altering the structure of epithelial cells in some way, but they should accomplish this while causing no damage or permanent change to nasal mucosa.

General requirement of an ideal penetration enhancer-

1. It should lead to an effective increase in the absorption of the drug
2. It should not cause permanent damage or alteration to the tissue
3. It should be non irritant and nontoxic.
4. It should be effective in small quantity
5. The enhancing effect should occur when absorption is required
6. The effect should be temporary and reversible
7. It should be compatible with other excipients.
Classification of penetration enhancer
Chemical penetration enhancers are widely used in the nasal drug delivery. Classification of chemical penetration enhancer includes, following
a) Solvents
b) Alkyl methyl sulphoxides
c) Pyrrolidones
d) 1- Dodeyl azacycloheptan-2-oneSurfactants.

Mechanism of penetration enhancers is as follows
a) Increasing cell membrane permeability
b) Opening tight junction and formation of intracellular aqueous channels
c) Increasing lipophilicity of the charged drug by forming ion pair
d) Inhibiting proteolytic activity.

I. Modifying Drug Structure
Modification of drug structure without altering pharmacological activity is one of the best ways to improve the nasal absorption. Here modification of physiochemical properties such as molecular size, molecular weight, Pka and solubility, are favorable for nasal drug absorption.

Table 1-Nasal Drug Delivery System Dosage Forms\textsuperscript{[1,4,5]}

<table>
<thead>
<tr>
<th>DOSAGE FORM</th>
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<tbody>
<tr>
<td>LIQUID FORMULATION</td>
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<tr>
<td>POWDER FORMULATION</td>
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<tr>
<td>NASAL DROP</td>
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<tr>
<td>NASAL GEL</td>
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<tr>
<td>NASAL SPRAY</td>
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**Liquid Nasal Formulations**\textsuperscript{[2,4,5]}
They are mainly based on aqueous state formulations. Their humidifying effect is convenient and useful. Microbiological stability, irritation and allergic rhinitis are the major drawbacks.
preservatives impair mucociliary function and the reduced chemical stability of the dissolved drug substance and the short residence time of the formulation in the nasal cavity.

1) **Instillation and Rhinyle Catheter**

Catheters are used to deliver the drops to a specified region of nasal cavity easily. The formulation is placed in the tube. One end is positioned in the nose, and the solution is delivered into the nasal cavity by blowing through the other end by mouth.

2) **Compressed Air Nebulizers**

Nebulizer is a device used to administer medication in the form of a mist, inhaled into the lungs. These pharmaceuticals are inhaled instead of ingestion. It is in order to target their effect to the respiratory tract, which speeds onset of action of the medicine and reduces side effects, compared to other alternative intake routes. This device is not suitable for the systemic delivery of drug by patient himself.
3) Squeezed Bottle

Squeezed nasal bottles are mainly used as delivery devices for decongestants. They include a smooth plastic bottle with a simple jet outlet. While pressing the plastic bottle the air inside the container is pressed out of the small nozzle, thereby atomizing a certain volume. By releasing the pressure again air is drawn inside the bottle. This procedure often results in contamination of the liquid by microorganisms and nasal secretion sucked inside. Dose accuracy and deposition of liquids delivered via squeezed nasal bottles are strongly dependent on the mode of administration.

4) Metered-Dose Pump Sprays

Most of the pharmaceutical nasal preparations in the market containing solutions, emulsions or suspensions are delivered by metered-dose pump sprays. Nasal sprays, or nasal mists, are used for the nasal delivery of a drug or drugs, either locally to generally alleviate cold or allergy symptoms such as nasal congestion or systemically. Although delivery methods vary, most nasal sprays function by instilling a fine mist into the nostril by the action of a hand-operated pump mechanism. The three main types available for local effect are antihistamines, corticosteroids, and topical decongestants. Metered- dose pump sprays include the container,
the pump with the valve and the actuator. The dose accuracy of metered-dose pump sprays is dependent on the surface tension and viscosity of the formulation. For solutions with higher viscosity, special pump and valve combinations are available in the market.

POWDER DOSAGE FORMS

Dry powders are less frequently used in nasal drug delivery. Major advantages of this dosage form are the lack of preservatives and the improved stability of the formulation.

Types

1) Insufflators

Insufflators are the devices to deliver the drug substance for inhalation. It can be constructed by using a straw or tube which contains the drug substance and sometimes it contains syringe also. The achieved particle size of these systems is often increased compared to the particle size of the powder particles due to insufficient disaggregation of the particles.

2) Dry Powder Inhaler \[^{5,6}\]
Dry powder inhalers (DPIs) are devices through which a dry powder formulation of an active drug is delivered for local or systemic effect via the pulmonary route. These are commonly used to treat respiratory diseases such as asthma, bronchitis, emphysema and COPD & diabetes mellitus.

Nasal Gels

Nasal gels are high-viscosity thickened solutions or suspensions. The advantages of a nasal gel include reduction of post-nasal drip due to high viscosity, reduction of taste impact due to reduced swallowing, reduction of anterior leakage of the formulation, reduction of irritation by using soothing/emollient excipients and target delivery to mucosa for better absorption.

Nasal Drops

Nasal drops are one of the most simple and convenient systems developed for nasal delivery. The main disadvantage of this system is the lack of the dose precision and therefore nasal drops may not be suitable for prescription products. It has been reported that nasal drops deposit human serum albumin in the nostrils more efficiently than nasal sprays.

Nasal Sprays
Both solution and suspension formulations can be formulated into nasal sprays. Due to the availability of metered dose pumps and actuators, a nasal spray can deliver an exact dose from 25 to 200 μm. The particles size and morphology (for suspensions) of the drug and viscosity of the formulation determine the choice of pump and actuator assembly.

**Nasal Powder**

This dosage form may be developed if solution and suspension dosage forms cannot be developed e.g., due to lack of drug stability. The advantages to the nasal powder dosage form are the absence of preservative and superior stability of the formulation. However, the suitability of the powder formulation is dependent on the solubility, particles size, aerodynamic properties and nasal irritancy of the active drug and /or excipients. Local application of drug is another advantage of this system.

**Nasal Drug Delivery: Bioavailability Considerations** \(^{[7,8]}\)

As discussed earlier, the drug delivery via the nasal route encounters a number of barriers like the physiological barriers, physicochemical barriers and the formulation factors. These factors have already been discussed and the concern of the formulator is to optimize the dosage form in such a manner that these barriers are restricted to a minimum and the bioavailability of the drug delivery system is enhanced. The major factors that limit the bioavailability are the enzymatic degradation, low drug permeability and the poor physicochemical properties of the drug. A number of methods have reported in literature to improve the drug bioavailability when administered through the nasal route particularly for the systemic delivery. These are;

a) Use of Prodrug

b) Use of enzymatic inhibitors

c) Use of absorption enhancers

d) Use of novel drug delivery systems.

**Use of Prodrug**

The nasal formulations are administered in the form of powders or solutions, in order for the drug to cross the bio-membrane and undergo dissolution it must possess an optimum lipophillic and hydrophilic character, L-dopa, a poorly water soluble drug has been prepared into various prodrugs like benzyl esters, pentyl ester, cyclohexyl ester, butyl ester to increase its water solubility. \(^{[58]}\) Similarly the permeability of acyclovir was enhanced by conversion into L-aspartate prodrug. The drugs solubility can also be increased by the use of cosolvent.
recently the enamine derivatives of the peptide drugs like angiotensin II, calcitonin, vasopressin, carnosine which had an increased absorption.

**Use of Enzymatic Inhibitors**
Nasal mucosa acts as an enzymatic barrier during nasal drug delivery. Various approaches have been used to prevent enzymatic degradation, including the use of proteases and peptidases inhibitors. Bestatine and comostate amylase are used as aminoptidases inhibitors and leupeptine and aprotinin as trypsin inhibitors involved in the degradation of calcitonin. Recently bacitracin, amastatin, boroleucin and puromycin have been used to avoid enzymatic degradation of many drugs.

**Use of Absorption Enhancers**
A number of drugs although permeable across the nasal mucosa, but still show low bioavailability. The bioavailability can be increased by the use of absorption enhancers. The absorption enhancers most commonly used are surfactants, bile salts, fatty acids and polymeric enhancers. The absorption Enhancers act by changing the permeability of epithelial cell layer by modifying the phospholipidic bilayer and increasing membrane fluidity hence opening tight junctions. The polymeric enhancers used are chitosan and cyclodextrins.

**Use of Novel Drug Delivery Systems**
The novel drug delivery systems used for the nasal drug delivery are the liposomes, microspheres and nanoparticles. The use of mucoadhesive drug delivery systems has also been proposed in recent times. Liposomes have been found to enhance nasal absorption of peptides such as insulin and calcitonin by increasing their membrane penetration due to the increased retention. Microspheres have been widely applied in formulations for nasal drug delivery. Microspheres are usually based on mucoadhesive polymers. Microspheres may also protect the drug from enzymatic metabolism and sustain drug release. Recently gelatin microspheres loaded with insulin were prepared for nasal drug delivery.

**Application of Nasal Drug Delivery System**

**Delivery of Non-Peptide Pharmaceuticals**
Low molecular weight (below 1000 daltons) small non-peptide lipophilic drugs are well absorbed through the nasal mucosa even in the absence of permeation enhancer. Drugs with extensive pre-systemic metabolism, such as progesterone, estradiol, propranolol,
nitroglycerin, sodium chromoglycate can be rapidly absorbed through the nasal mucosa with a systemic bioavailability of approximately 100%.

**Delivery of Peptide-Based Pharmaceuticals**

Peptides & proteins have generally a low oral bioavailability because of their physicochemical instability and susceptibility to hepato-gastrointestinal first pass elimination. Examples are insulin, calcitonin, pituitary hormones etc. So, with the use of absorption enhancers like surfactants, glycosides, cyclodextrin and glycols will increase the bioavailability. Nasal route is proving to be the best route for such biotechnological products.

**Delivery of Drugs to Brain Through Nasal Cavity**

This delivery system is beneficial in conditions like Parkinson’s disease, Alzheimer’s disease or pain because it requires rapid and/or specific targeting of drugs to the brain. It increase the fraction of drug that reaches the CNS after nasal delivery. The olfactory region located at the upper remote parts of the nasal passages offers the potential for certain compounds to circumvent the blood-brain barrier and enter into the brain.

**Delivery of Vaccines Through Nasal Route**

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, which helps to eliminate the pathogen before it becomes established.

**Delivery of Diagnostic Drugs**

Used in delivery of diagnostic agents for the diagnosis of various diseases and disorders in the body. Because the intranasal route is more suitable for systemic release of medicament into blood circulation.

**EVALUATION OF NASAL FORMULATIONS [2,8]**

(a) *In vitro* nasal permeation studies various approaches used to determine the drug diffusion through nasal mucosa from the formulation.

**In Vitro Diffusion Studies**

The nasal diffusion cell is fabricated in glass. The water-jacketed recipient chamber has total capacity of 60 ml and a flanged top of about 3mm; the lid has 3 opening, each for sampling, thermometer, and a donor tube chamber. The 10 cm long donor chamber, and a donor tube chamber has total capacity of 60 ml and a flanged top of about 3mm; the lid has 3
openings, each for sampling, thermometer, and a donor tube chamber the 10 cm long donor chamber tube has internal diameter of 1.13 cm.

**Procedure**

1. The nasal mucosa of sheep was separated from sub layer bony tissues.
2. Stoned in distilled water containing few drops at gentamycin injection.
3. After the complete removal of blood from mucosal surface, is attached to donor chamber tube.
4. The donor chamber tube is placed such a way that it just touches the diffusion medium in recipient chamber.
5. At predetermined intervals, samples (0.5 ml) from recipient chamber are withdrawn and transferred to amber colored ampoules.
6. The samples withdrawn is suitably replaced. The samples are estimated for drug content by suitable analytical technique. Temperature is maintained at 37 °C.

**(b) In Vivo Nasal Absorption Studies**

**Animal Models for Nasal Absorption Studies**

The animal models employed for nasal absorption studies can be of two types, viz., whole animal or *in vivo* model and an isolated organ perfusion or *ex vivo* model.

**1) Rat Model**

**Procedure**

1. The rat is anaesthetized by intraperitoneal injection of sodium pentobarbital.
2. An incision is made in the neck and the trachea is cannulated with a polyethylene tube. Another tube is inserted through the oesophagus towards the posterior region of the nasal cavity.
3. The passage of the nasopalatine tract is sealed so that the drug solution is not drained from the nasal cavity through the mouth. The drug solution is delivered to the nasal cavity through the nostril or through the cannulation tubing.
4. The blood samples are collected from the femoral vein. As all the probable outlets of drainage are blocked, the drug can be only absorbed and transported into the systemic circulation by penetration and/or diffusion through nasal mucosa.

**2) Rabbit Model**

1. It is relatively cheap, readily available and easily maintained in laboratory settings.
2. It permits pharmacokinetic studies as with large animals. The blood volume is large enough (approx. 300ml).

3. To allow frequent blood sampling (1-2ml).

4. It permits full characterization of the absorption and determination of the pharmacokinetic profile of a drug. Rabbits (approx. 3 kg) are either anaesthetized or maintained in the conscious state depending on the purpose of study.

5. In the anaesthetized model, the rabbit is anaesthetized by an intramuscular injection of a combination of ketamine and xylazine.

6. The rabbit's head is held in an upright position and the drug solution is administered by nasal spray into each nostril.

7. During the experiment the body temperature of the rabbit is maintained at 37°C with the help of a heating pad.

8. The blood samples are collected by an indwelling catheter in the marginal ear vein or artery.

Some Currently Marketed Formulation

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<thead>
<tr>
<th>SR.NO</th>
<th>PRODUCT</th>
<th>ACTIVE INGREDIENT</th>
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<tbody>
<tr>
<td>1.</td>
<td>Otrivine adult nasal drop</td>
<td>Xylometazoline hydrochloride 0.1%w/v</td>
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<tr>
<td>2.</td>
<td>Dymista nasal spray, suspension</td>
<td>Azelastine hydrochloride, fluticasonepropionate</td>
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<tr>
<td>3.</td>
<td>Imitrex nasal spray</td>
<td>Sumatriptan</td>
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<tr>
<td>4.</td>
<td>Stimate nasal spray</td>
<td>Desmopressin acetate</td>
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<td>5.</td>
<td>Micalcic nasal spray</td>
<td>Calcitonin</td>
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<tr>
<td>6.</td>
<td>Vibrocil gel</td>
<td>Phenylephrine, dimethindene maleate</td>
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<tr>
<td>7.</td>
<td>Astelin nasal spray</td>
<td>Azelastine hydrochloride</td>
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CONCLUSION

Nasal drug delivery system is a promising alternative route of administration for the several systemically acting drugs with poor bioavailability and improved patient acceptability and compliance compared to parenteral administration of drugs. This delivery system is beneficial in conditions like Parkinson’s disease, Alzheimer’s disease or pain because it requires rapid and/or specific targeting of drugs to the brain and it is a suitable route to produce immune response against various diseases like anthrax, influenza etc., by delivering the vaccines through the nasal mucosa. In the near future, let us hope that intranasal products most probably comprise for crisis treatments, such as erectile dysfunction, sleep induction, acute pain (migraine), panic attacks, nausea, heart attacks and Parkinson’s disease and novel nasal
products for treatment of long-term illnesses, such as diabetes, growth deficiency, osteoporosis, fertility treatment and endometriosis, will also be marketed.

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REFERENCE