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ADVANTAGEOUS NASAL DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

The convenience of administration and improved patient compliance are important in the design of nasal drug delivery system which remains the preferred route of drug delivery in spite of various disadvantages. Therapy through intranasal administration has been an accepted form of treatment in the Ayurvedic system of Indian Medicine. Advances in biotechnology have made available a large number of protein and peptide drug for the treatment of a variety of diseases. These drugs are unsuitable for oral administration because they are significantly degraded in the gastrointestinal tract or considerably metabolized by first pass effect in the liver. Even the parenteral route is inconvenient for long term therapy. Of many alternate routes tried, intranasal drug delivery is found much promising for administration of these drugs. In this article, an overview on the design and development of intranasal drug delivery system is presented. Advantages of NDDS are Drug degradation that is observed in the gastrointestinal tract is absent, hepatic first pass metabolism is absent, Rapid drug absorption and quick onset of action can be achieved, bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approach, the nasal bioavailability for smaller drug molecules is good, Drugs that are orally not absorbed can be delivered to the systemic circulation by nasal drug delivery, Studies so far carried out indicate that the nasal route is an alternate to parenteral route, especially, for protein and peptide drugs, convenient for the patients, especially for those on long term therapy, when compared with parenteral medication, Large nasal mucosal surface area for dose absorption, rapid drug absorption via highly-vascularized mucosa, ease of administration, non-invasive, lower dose/reduced side effects.

INTRODUCTION: Therapy through intranasal administration has been an accepted form of treatment in the Ayurvedic system of Indian Medicine. In recent years many drugs have been shown to achieve better systemic bioavailability through nasal route than by oral administration [1]. Advances in biotechnology have made available a large number of protein and peptide drug for the treatment of a variety of diseases. These drugs are unsuitable for oral administration because they are significantly degraded in the gastrointestinal tract or considerably metabolized by first pass effect in the liver. Even the parenteral route is inconvenient for long term therapy. Of many alternate routes tried, intranasal drug delivery is found much promising for administration of these drugs [2]. In this article, an overview on the design and development of intranasal drug delivery system is presented.

The nasal cavity is divided into two symmetrical halves by the nasal septum, a central partition of bone and cartilage; each side opens at the face via the nostrils and connects with the mouth at the nasopharynx. The nasal vestibule, the respiratory region and the olfactory region are the three main regions of the nasal cavity. The lateral walls of the nasal cavity include a folded structure which enlarges the surface area in the nose to about 150cm^2.

This folded structure includes three turbinates: the superior, the median and the inferior. In the main nasal airway, the passages are narrow, normally only 1-3mm wide, and this narrows structure enables the nose to carry out its main functions. During inspiration, the air comes into close contact with the nasal mucosa and particles such as dust and bacteria are trapped in the mucous. Additionally, the inhaled air is warmed and moistened as it passes over the mucosa; and the high blood supply in the nasal epithelium.

The submucosal zone of the nasal mucosa directly to the systemic circulation, hus avoiding firs pass metabolism. Another, perhaps more familiar, major function of the nose is olfactory region is located on the roof of the nasal cavity [3].

The nasal cavity is covered with a mucous membrane which can be divided into non-olfactory and olfactory epithelium areas. The non-olfactory area includes the nasal vestibule, which is lined with skin-like cells, and respiratory region, which has a typical airways epithelium (**Fig. 1**).

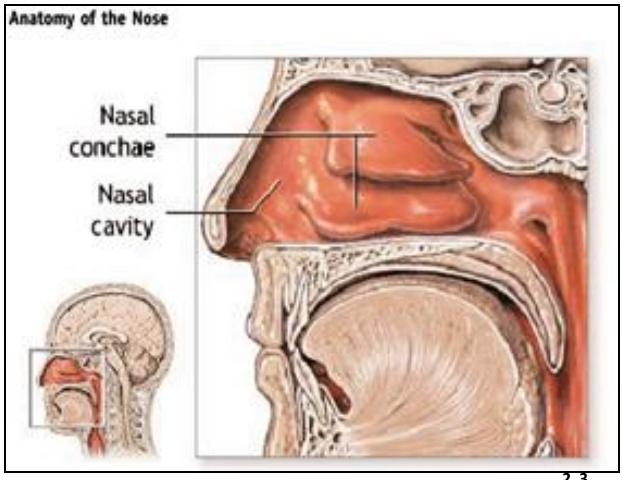

FIG. 1: ANATOMY & PHYSIOLOGY OF THE NOSE [2, 3]

The Respiratory Region: The nasal respiratory epithelium is generally described as a pseudo-stratified ciliated columnar epithelium. This region is considered to be the major site for drug absorption into the systemic circulation. The four main types of cells seen in the respiratory epithelium are ciliated columnar cells, non-ciliated columnar cells, goblet cells and basal cells. Although rare, neurosecretory cells may be seen but, like basal cells, these cells do not protrude into the airway lumen.

The proportions of the different cell types vary in different regions of the nasal cavity. In the lower turbinate area, about 15-20% of the total numbers of cells are ciliated and 60-70% is non-ciliated epithelial cells. The numbers of ciliated cells increase towards the nasopharynx with a corresponding decrease in non-ciliated cells. The high number of nonciliated cells indicates their importance for absorption across the nasal epithelium. Both columnar cell types have numerous (about 300-400 per cell) microvilli. The large number of microvilli increases the surface area and this is one of the main reasons for the relatively high absorptive capacity of the nasal cavity.

The role of the ciliated cells is to transport mucus towards the pharynx. Basal cells, which vary greatly in both number and shape, never reach the airway lumen. These cells are poorly differentiated and act as stem cells to replace other epithelial cells. About 5-15% of the mucosal cells in the turbinates are goblet cells, which contain numerous secretory granules filled with mucin. In conjunction with the nasal glands; the goblet cells produce secretions, which form the mucus layer.

The Olfactory Region: In human, the olfactory region is located on the roof of the nasal cavities, just below the cribriform plate of the ethmoid bone, which separates the nasal cavities from the cranial Cavity. The olfactory tissue is often yellow in color, in contrast to the surrounding pink tissue. Humans have relatively simple noses, since the primary function is breathing, while other mammals have more complex noses better adapted for the function of olfaction (**fig. 2**).

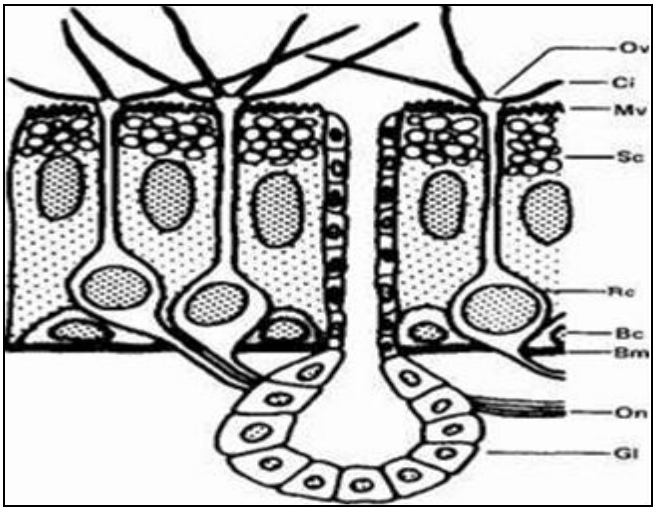

FIG. 2: SCHEMATIC DIGRAM OF OLFACTORY EPITHELIUM

Ov- olfactory vesicle, Ci- olfactory cilia, Mv- microvili, Sc- supporting cell(secretory cells inside the granule are indicated), Rc- olfactory (receptor) cell, Bc- bsal cell, Bm- basal membrane, On- olfactory nerve, Gi- olfactory gland

Nasal Blood Flow: The blood vessels in the nasal mucosa are of importance in the functions of the nose for thermal regulation and humidification of the inhaled air and for controlling the lumen of nasal passage.

The nasal mucosa is highly vascular. The surface of epithelium is supplied with a dense network of erectile cavernous tissue, which is particularly well developed over the turbinate and septum. The vascular bed provides a rich surface for rug absorption. Constriction of the blood vessel would decrease blood flow and blood content in nasal mucosa, whereas vasodilatation would yield opposite response. The penetration of drug through the sinus mucosa is partly influenced by the blood flow in the region under normal and pathological conditions.

The arterial supply to the nose is derived from both the external and the internal carotid arteries. The terminal branch of the maxillary artery, which is the branch of the external carotid, supply blood to the sphenopalatine artery, which in turn supplies blood to the lateral and medial walls of chamber. On the other hand the artery and the posterior ethmoid branches from the ophthalmic artery. These vessels supply the anterior portion of the nose. The porosity of the endothelial basement membrane seems to facilitate the exposure of the contractile elements in the blood wall to agents carried by the blood. The nasal vascular bed is so designed the rapid exchange can be done for fluid and dissolved substances between the blood vessels and the nasal tissues. The capillary floe in the nasal mucosa was reported to about 0.5 ml/g/min, whereas anteriovenous shunt flow was found to be 60% of the total blood flow in the cat. Sympathetic stimulation was reported to produce a greater reduction in shunt flow than in capillary flow.

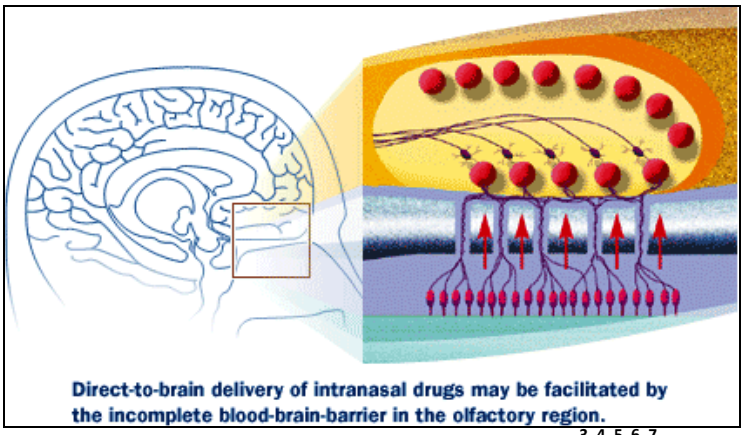

FIG. 3: NOSE TO BRAIN TRANSPORT DELIVERY [3, 4, 5, 6, 7]

In addition to its application to systemic delivery, as the olfactory nerve cells are in direct contact with both the environment and the CNS anatomically, a great deal of interest has recently been focused on the exploitation of the intranasal route for the delivery of drugs to the brain via the olfactory mucosa. Small molecular drugs, such as cocaine and benzoylecgonine [3, 4], local anesthetics [5], dihydroergotamine [6] and dopamine [7], have been shown to reach the CNS via the olfactory pathway in animals. Mathison [8] and Illum [9] have reviewed the transport of a lot of substances from the nasal cavity to the CNS (**Fig. 3 & table 1**).

TABLE 1: RESONSE OF THE NASAL AIRWAY TO SOME VASOACTIVE AGENTS

Increased Potency	Decreased Potency
Alpha agonists	Beta agonists
Nor epinephrine	Isoproterelol
Epinephrine	Nylidrin
Methoxamine	Alpha agonists
Phenylephrine	Phenoxybenzamine
Serotonin	Phentolamine
Dopamine	Acetylcholine
Prostaglandins	Histamine
Cocaine	Papaverine
Antihistamines	Aminophylline
Tyramine	Reserpine
vasopressin	

For long, the blood-brain barrier (BBB) has impeded the development of many potentially interesting CNS drug candidates due to their poor distribution into the CNS. Owing to the unique connection of nose and the CNS, the intranasal route can deliver therapeutic agents to the brain bypassing the BBB.[10] Via intranasal delivery, many abandoned potent CNS drug candidates are promising to become successful CNS therapeutic drugs. Recently, several nasal formulations, such as ergotamine (Novartis), sumatriptan (GlaxoSmithKline), and zolmitriptan (AstraZeneca) have been marketed to treat migraine.

TABLE 2: POTENTIAL PATHWAYS FOR SOME SUBSTANCES FOR THERE ABSORPTION

Substances	Possible pathways
Egg albumin	Nasal mucosa→ lymphatic stream
Serum albumin	Nasal mucosa→ lymphatic stream
Dopamine	Nasal mucous membrane → CSF and serum(detected within 15 min after administration
Potassium ferrocyanide dye	Nasal mucous membrane → olfactory receptor nerve cells→ lymphatic meshwork → retropharyngeal lymph nodes
Estradiol	Nasal membrane → CSF(within 1 min)
Progesterone	Nasal membrane → olfactory dendrites→ nervous system→ supporting cells in the olfactory mucosa→ submucosal blood vascular system→ CSF nasal membrane →CSF (within 1min)
Lead carbonate	Dissolved in nasal mucus and then absorbed as a true solution
Chloride salt(CsCl, SrCl, BaCl, CeCl), thorium B	Nasal membrane→ blood circulation Nasal septal mucosa→ anterior scala CSF CNS
Penicillines	Nasal membrane→ blood stream

Advantages of Nasal Drug Delivery System [1, 4]:

1. Drug degradation that is observed in the gastrointestinal tract is absent.
2. Hepatic first – pass metabolism is absent.
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. Studies so far carried out indicate that the 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. Large nasal mucosal surface area for dose absorption
10. Rapid drug absorption via highly-vascularized mucosa
11. Rapid onset of action
12. Ease of administration, non-invasive
13. Avoidance of the gastrointestinal tract and first-pass metabolism
14. Improved bioavailability
15. Lower dose/reduced side effects
16. Minimal aftertaste
17. Improved convenience and compliance
18. Self-administration
19. New patent coverage for drug formulations about to expire

Although traditional nasal drug delivery methods offer significant advantages over injection or oral administration, they face challenges that limit efficacy and applications.

LIMITATIONS:

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.

Nasal Drug Absorption [2, 4]:

Mechanism of Drug Absorption: Several mechanisms have been proposed for absorption of drug through nasal route, but following are highlighted here.

1. The first mechanism involves an aqueous route of transport, which is also known as the paracellular route. This route is slow and passive. There is an inverse log-log correlation between intranasal absorption and the molecular weight of water-soluble compounds. Poor bioavailability was observed for drug with a molecular weight greater than 1000 Daltons.
2. The second mechanism involves transport through a lipoidal route is also known as the transcellular process and is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity
3. Drug also cross cell membranes by an active transport route via carrier-mediated means or transport through the opening of tight junctions. For examples, chitosan, a natural biopolymer from shellfish, opens tight junctions between epithelial cells to facilitate drug transport.

Factors affecting Nasal Drug Absorption [1, 2, 4]: Many factors affect the systemic bioavailability of nasally administered drugs. The factors can be attributed to the physicochemical properties of the drugs and the characteristics of other ingredient of delivery system has been discussed in relevant section i.e. dosage forms and type and characteristics of selected nasal drugs delivery system. These play significant role for most of the drugs in order to reach therapeutically effective blood levels after nasal administration. The factors influencing nasal drug absorption are as follows.

1. Physicochemical properties of drug

- Chemical form of drug.
- Polymorphism
- Molecular weight
- Particle size
- Solubility & dissolution rate.

2. Nasal effect

- Membrane permeability
- Environmental pH
- Mucociliary clearance
- Cold, rhinitis

3. Delivery effect

- Formulation (Concentration, p^H, osmolarity)
- Delivery effects
- Drugs distribution and deposition.
- Formulation effect on mucociliary clearance.
- Toxic effect on ciliary function and epithelial membranes

Pharmacokinetics of Nasal Absorption:

Factors reported to affect the pharmacokinetic parameters following intranasal administration are:-

1. Physiology-related factors, such as

   a) speed of mucus flow
   b) presence of infection
   c) atmospheric conditions

2. Dosage form related factors such as

   a) concentration of active drug
   b) physicochemical properties of active drug
   c) density/ viscosity properties of formulations
   d) pH/toxicity of dosage form
   e) pharmaceutical excipients used

3. Administration related factors such as

   a) size of droplet
   b) size of deposition
   c) mechanical loss into the oesophagus
   d) mechanical loss into other regions in the nose
   e) mechanical loss anteriorly from nose

Strategies for improving availability in Nasal administration: Various strategies used to improve 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**: Mucocilliary clearance acts to remove the foreign bodies and substances from nasal mucosa as quickly as possible. One way of 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. **To Enhance the 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 are as follows;

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:

- Solvents
- Alkyl methyl sulphoxides
- Pyrrolidones
- Dodecyl azacycloheptan-2-one
- Surfactants

Mechanism of Penetration Enhancers:

- Increasing cell membrane permeability Opening tight junction and formation of intracellular aqueous channels
- Increasing lipophilicity of the charged drug by forming ion pair
- Inhibiting proteolytic activity

3. **To modify drug structure to change physicochemical properties**: Modification of drug structure without altering pharmacological activity is one of the lucrative 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.

Absorption Enhancers in Nasal Drug Delivery [4, 6]: Unlike the most small drug molecules, some drugs and peptides do not cross the nasal membrane efficiently. As a result the nasal bioavailability in simple solution formulation is very low. The low nasal absorption can be attributed to poor membrane permeability due to molecular size, lack of lipophilicity or enzymatic degradation. Enzyme inhibitors can be added to nasal formulation to prevent enzymatic degradation. The nasal mucosa is almost impermeable to molecular size greater than 1000 Dalton. To overcome these problems of poor membrane permeability most frequent used approach is the use of absorption enhancers. They act by one or combination of the following mechanisms:

1. Alteration of properties of mucosa layer.
2. Opening tight junctions between epithelial cells.
3. Reversed micelle formation between membranes.
4. Increasing the membrane fluidity by,

a) Extraction or leaching of membrane components
b) Creating disorders in the phospholipids domain in the membrane

Various types of penetration enhancers have been evaluated for organic drugs including surfactants, bile salts, chelators, fatty acid salts, phospholipids, glycyrrhetenic acid derivatives, cyclodextrins and glycols. Polyoxyethylene-9-lauryl ether (BL-9) in saline solution improves the nasal absorption of hydralazine in both in-situ and in vivo nasal absorption studies in rats. Polysorbate 80 (1 %) in saline solution was observed to promote the nasal absorption of atropine and hyoscine from nasal solution.

The absorption was rapid, complete and uniform with addition of sodium lauryl sulphate. A nasal formulation of meclizine (50 mg/ml) prepared in propylene glycol and 10 % glycerol results in 50 % of nasal drug absorption, which is equivalent to I.V.therapy. The nasal absorption of gentamycin (60 mg/ml in saline solution) in humans has observed to increase by incorporation of 1 % sodium glycocholate and peak serum levels were achieved in 30-60 min.

Most peptides and proteins show insufficient nasal bioavailability. Number of approaches has been described to improve their systemic bioavailability. Insulin is poorly absorbed from nasal mucosa. Many compounds of different chemical structure have been investigated to promote transnasal insulin absorption. The STDHF enhanced the effects of absorption enhancers on intranasal insulin delivery in rats, rabbits and sheep. Among medium chain fatty acids, sodium caprylate (1%) exhibit the strongest promoting effect. The fatty acids show higher hemolytic activity than glycocholate. The compound carbenoxolone, glycerrhetenic acid salt has structures similar to triterpenes and show promoting effect similar to bile acids and saponins.

Safety and Efficacy of Absorption Enhancers [14]: While it is important to establish the efficacy of absorption enhancers, it is equally imperative to prove their safety by measuring their effect on the mucociliary transport rate, nasal morphology and ciliary beat frequency.

(a) Mucociliary transport rate: It is measured using a frog palate model to test potential toxicity of absorption enhancers L-α-lysophosphatidylcholine, sodium deoxycholate and taurocholate, laureth-s and sodium taurodihydrofusidate irreversibly halted the mucus transport rate.

(b) Nasal morphology: This was studied by differing the contact times with the nasal epithelium using scanning electron microscope to detect gross structural and cellular changes, ciliary identity as well as prevalence or extra-cellular debris. Morphological damage caused by enhancers in the increasing order is: GC<<STDHF<<LAURETH-9<DC=TDC.

(c) Ciliary beat frequency: The chicken embryo tracheal tissue and human adenoid tissue were used to measure the in vitro reduction of the ciliary beat frequency caused by various enhancers ranging from laureth-9=DC =GC=TDC (fast and irreversible ciliostasis, brought about by preservatives like BAK and Mercury compounds).

Breakthroughs of Nasal Drug Delivery System [6, 19]:

1. **Insulin administered through nasal route:** Diabetes mellitus is a chronic disease that usually requires multiple insulin injections to achieve adequate glycaemic control. This represents a major cause of reduced compliance to treatment. Consequently, other routes for insulin administration have been explored. During recent years, much progress in the development of inhaled insulin has been made. Inhaled insulin has favorable properties, such as rapid onset of action, improved bioavailability and good tolerability, thereby providing satisfaction and ease of administration.

   However, long-term safety of inhaled insulin needs to be assessed, and the cost would be higher than inject able insulin. Nasal, oral and transdermal insulin are undergoing early phases of pharmacological development. The purpose of this review is to describe the latest developments in the area of non-invasive routes for insulin delivery. A large number of patients with diabetes worldwide require daily dose of insulin. Insulin therapy, using the vial and syringe method is

complicated and time consuming. To find an alternative way to deliver insulin will elude the researchers to replace inject able insulin by more comfortable, noninvasive and less strenuous delivery method, which can provide in pharmacokinetically consistent manner. The present article reviews the various alternatives for insulin delivery.

2. **Insulin gel administered through nasal route:** The objective of the present study was to formulate insulin gel for intranasal administration and to evaluate with respect in-vitro release study and hypoglycaemic activity in animal model and healthy human volunteers. The insulin gel was formulated using the combination of carbopol and hydroxypropylmethylcellulose as gelling agent. The in-vivo efficacy of insulin gel administered intranasally was assessed by measuring the blood glucose levels at specified time intervals in rats and humans.

   The use of bioadhesive nasal gel containing insulin not only promoted the prolonged contact between the drug absorptive sites in the nasal cavity but also facilitated direct absorption of medicament through nasal mucosa. Absorption of the drug through the nasal mucosa high in the first 0.5 to 1.5 hrs of the study with a sharp decline in blood sugar and rise in insulin values corresponding to that decline in blood sugar. This study further demonstrates that administration of insulin intranasally in gel form is a pleasant and painless alternative to inject able insulin.

3. **Cancer pain management through nasal route:** Cancer pain management necessitates the use of opioids when pain is moderate or severe. Opioids need to be versatile and effective. Newer formulations may improve patient compliance and may be more conductive to the management of transient flares of pain; they also may be tailored to treat certain special populations and may be particularly effective in certain clinical situations.

   For e.g. Newer opioids have been developed for transdermal, nasal and nebulized administration, providing a needle-less means of controlling pain in those unable to take oral medications. However, newer opioid formulations are not a substitute for good pain management strategies and will not control pain unless provided in adequate doses and schedules. Newer opioid formulations have niche roles in clinical practice, and pain palliative specialists need to be aware of new developments in opioids and delivery systems.

4. **Antibiotics and mucolytics are delivered to the nasal cavity:** Decongestants, antibiotics and mucolytics are delivered to the nasal cavity, their intended site of action. Due to its accessibility, relatively large surface area 160 cm^2 and rich vascular supply of the nasal mucosa, the nasal route of administration is attractive for many drugs for systemic absorption, including proteins and peptides. Due to rich blood supply, drugs absorbed via the nasal route have a rapid onset of action, which can be exploited for therapeutic gain. The nasal delivery is also recommended in order to avoid degradation in the gastro intestinal fluid, metabolization in the gastrointestinal tract or biotransformation by the first pass effect. The ease of administration via the nasal route may also lead to increased patient compliance. Nasal devices such as metered doses nasal sprays have been developed that are simple for patient to use. Patient with swallowing difficulty and\or children can be treated with less difficulty with nasal drug delivery system.

   Nasal drug delivery can:

- Promote rapid onset of action.
- Avoid gastrointestinal tract or first pass metabolism
- Enhance patient compliance

5. **Microsphere as nasal drug delivery system:** All types of microspheres that have been used as nasal drug delivery system are water insoluble but absorb water into the sphere matrix, resulting in swelling of the spheres and the formulation of a gel. The building materials in the microspheres have been starch, dextran, albumin and hyaluronic acid, and the bioavailability of several peptides and proteins has been improved in different animal

models. Also, some low molecular weight drugs have been successfully delivered in microsphere preparations. The residence time in the cavity is considerably increased for microspheres compared to solutions. However, this is not the only factor to increase the absorption of large hydrophilic drugs. Microsphere also exerts a direct effect on the mucosa, resulting in the opening of tight junctions between the epithelial cells. Starch and dextran microspheres have been administered repeatedly and can be classified as safe dosage forms.

6. **Utility of insoluble powder formulation for nasal systemic drug delivery:** Insoluble powder formulations improve nasal bioavailability predominantly by retarding drug elimination from the absorption site and appear to be effective for nasal systemic drug delivery.

7. **Nasal drug and vaccine delivery technology:** OptiNose is a drug company with breakthrough technology to transform the static nasal drug delivery market.

Potential application for the OptiNose nasal drug delivery concept: The Company's technology has significant market potential in several major disease areas. The OptiNose devices can deliver drug to the upper posterior segment of the nose where it can access the entrances to the sinuses to treat rhinitis and sinusitis.

Excipients used in Nasal Formulation: Commonly used excipients that are frequently added to nasal preparations are can be listed as below:

1. Bioadhesive polymers: It can be defined as a compound that is capable of interacting with biological material through interfacial firces and being retained on such material for prolonged periods of time. If the biological material is a mucus membrane, the bioadhesive material is termed as a mucoadhesive. On molecular level, mucoadhesion can be explained on the basis of attractive molecular interactions involving forces such as Van Der Waals, Electrostatic interactions, Hydrogen Bonding, and Hydrophobic interactions.

The bioadhesive force of a polymer material is dependent on the nature of the polymer, the surrounding medium (pH), swelling and physiological factors (mucin turnover, disease state).

Examples of some bioadhesive polymers employed for nasal drug delivery systems

a) Carbopol(car boxy polyethylene)
b) Sodium carboxy methyl cellulose (SCMC)
c) Hydroxypropyl cellulose(HPC)
d) Hydroxypropylmethyl cellulose(HPMC)
e) Hydroxyl ethyl cellulose(HEC)
f) Methyl cellulose(MC)
g) Sodium hyaluronate
h) Guar gum
i) Sodium alginate
j) Polycarbophil
k) Starch
l) Dextran
m) Chitosan

2. Gelling agent: According to a study by Pennington *et al.*[13], increasing solution viscosity may provide a means of prolonging the therapeutic effect of nasal preparations. Suzuki *et al.* [14] showed that a drug carrier such as hydroxypropyl cellulose was effective for improving the absorption of low molecular weight drugs but did not produce the same effect for high molecular weight peptides. Use of a combination of carriers is often recommended from a safety (nasal irritancy) point of view.

3. Penetration enhancer: Chemical penetration enhancers are widely used in the nasal drug delivery. Classification of chemical penetration enhancer includes, following

1) Solvents
2) Alkyl methyl sulphoxides
3) Pyrrolidones
4) 1- Dodecyl azacycloheptan-2-one
5) Surfactants

Mechanism of penetration enhancers is as follows,

- Increasing cell membrane permeability
- Opening tight junction and formation of intracellular aqueous channels

- Increasing lipophilicity of the charged drug by forming ion pair
- Inhibiting proteolytic activity.

4. Buffers: Nasal formulations are generally administered in small volumes ranging from 25 to 200 µL with 100 µL being the most common dose volume. Hence, nasal secretions may alter the pH of the administrated dose. This can affect the concentration of un-ionized drug available for absorption. Therefore, an adequate formulation buffer capacity may be required to maintain the pH in-situ.

5. **Solubilizers:** Aqueous solubility of drug is always a limitation for nasal drug delivery in solution. Conventional solvents or co-solvents such as glycols, small quantities of alcohol, Transcutol (diethylene glycol monoethyl ether), medium chain glycerides and Labrasol (saturated polyglycolyzed C_8- C_{10} glyceride) can be used to enhance the solubility of drugs. Other options include the use of surfactants or cyclodextrins such as HP–ß-Cyclodextrin that serve as a biocompatible solubilizer and stabilizer in combination with lipophilic absorption enhancers. In such cases, their impact on nasal irritancy should be considered.

6. Preservatives: Most nasal formulations are aqueous based and need preservatives to prevent microbial growth. Parabens, benzalkonium chloride, phenyl ethyl alcohol, EDTA and benzoyl alcohol are some of the commonly used preservatives in nasal formulations. Van De Donk *et al.*[15] have shown that mercury-containing preservatives have a fast and irreversible effect on ciliary movement and should not be used in nasal systems.

7. Antioxidants: A small quantity of antioxidants may be required to prevent drug oxidation. Commonly used antioxidants are sodium metabisulfite, sodium bisulfite, butylated hydroxytoluene and tocopherol. Usually, antioxidants do not affect drug absorption or cause nasal irritation. Chemical/physical interaction of antioxidants and preservatives with drugs, excipients, manufacturing equipment and packaging components should be considered as part of the formulation development program.

8. Humectants: Many allergic and chronic diseases are often connected with crusts and drying of mucous membrane. Certain preservatives/ antioxidants among other excipients are also likely to cause nasal irritation especially when used in higher quantities. Adequate intranasal moisture is essential for preventing dehydration. Therefore, humectants can be added especially in gel-based nasal products. Humectants avoid nasal irritation and are not likely to affect drug absorption. Common examples include glycerin, sorbitol and mannitol.

9. Surfactants: Incorporation of surfactant into nasal dosage forms could modify the permeability of nasal membranes, which may facilitate the nasal absorption of drug.

Enhancement of nasal absorption: Several methods have been used to facilitate the nasal absorption of drugs:

- **Structure modification**: The chemical modification of a drug molecule has been commonly used to modify the physicochemical properties of drug and could also be utilized to improve the nasal absorption of drug.

- **Salt or ester formation:** The drug could be converted to form a salt or an ester for better transnasal permeability. For example, nasal absorption could be improved significantly by forming a salt with increased solubility in nasal fluid or an ester with enhanced uptake by nasal epithelium

- **Formulation design**: Proper selection of pharmaceutical excipients in the development of nasal formulation could enhance the formulation stability and/or the nasal bioavailability of drug.

- **Surfactants**: Incorporation of surfactant into nasal dosage forms could modify the permeability of nasal membranes, which may facilitate the nasal absorption of drug. Survey of the literature indicates that surfactants have been extensively evaluated for the possibility of enhancing the nasal absorption of drugs, including peptide and protein drugs. A number of surfactants have been reported to enhance the

absorption of drugs through the nasal mucosa to a level sufficientto achive their systemic effect s.mild surfactantsat low concentrations may only alter membrane structure and permeabilitywhereas certain surfactants at high concentrations may disrupt and even dissolve biological membranes **(table 3)**.

TABLE 3: SOME SURFACTANTS USED TO INCREASE ABSORPTION OF FOLLOWING DRUGS [1, 4, 6]

Surfactant	Drug whose absorption is enhanced
1% sodium taurcholate	Scarlet fever toxin
1%sodium glycocholate	Gentamycin
Polyoxyethylene-9-lauryl ether(BL-9,0.5%) and sodium glycocholate	Hydralazine
Sodium glycocholate, polyacrylic acid gel(carbopol gel, 0 .1%w/v)	Rapid reduction of calcium level
Polysorbate 80(1%)	Progesterone, testosterone
Sodium lauryl sulfate	Atropine hyoscine
Sodium glycocholate (pH 7.6)	Crystalline porcine insulin administered intranasally – relatively prompt increase in the plasma levels of immunoreactive insulin(IRI)
1%sodium deoxycholate	Aerosol soray of insulin with surfactant resulted in a peak serum insulin concentration
Lysozyme, HCO-60, BYCO-E	Negligible absorption of insulin
Carbopol934(CP)	With powder form of insulin-enhancement of absorption

Research and development in nasal drug delivery [15]: Most of the over the counter nasal preparation are formulated as solution, to treat the nasal symptoms of allergic rhinitis and common cold. A simple drug solution is adequate for this purpose as it produces better dispersion over greater surface area. The nasal residence time of such formulation is short (3-20 min) and exhibit high inter individual variability. This route provides fast peak levels in circulation [15].

Large number of drugs has been evaluated for systemic bioavailability after transnasal administration in experimental animal models. Transnasal administration of drugs in diverse dosage forms such as sprays, powders, and microspheres has been attempted for improved residence and bioavailability.

The nasal delivery is receiving attention for management of postoperative pain; mucosal administration requires only a 1.1-1.5 time higher dose of fentanyl than i.v. dose. The nasal delivery of vaccines is a very attractive route of administration in terms of efficacy.

Various Dosage Forms used: There are several delivery systems which have been used for the delivery of drugs through the nasal cavity. The selection of delivery system depends upon the drug being used, proposed indication, patient population and last but not least, marketing preferences. Some of these delivery systems and their important features are summarized below:

- Nasal drops
- Nasal sprays
- Nasal gels
- Nasal powders

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. Technetium -99m- labeled human serum albumin was administered into the human nose by nasal spray or nasal drops. The results showed that about 40%of the dose cleared rapidly with average halftimes ranging from 6 to 9.

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.

Various nasal spray systems: A current trend is to develop preservative free formulations. In a traditional formulation basically the preservative takes care of a possible contamination issue. An unpreserved formulation has to rely on the integrity of the primary packaging.

This means in detail that the responsibility is shifted towards the manufacturer and supplier of the dispersing system. A typical example of a nasal spray system designed to administer sterile formulation.

A spring loaded mechanical scaling system, which is located directly behind the small orifice in the nasal actuator, prevents through its fast opening and closing profile a possible contamination from entering the primary packaging. When dispensing out of an airtight container a vaccum will built up. In the pump system, integrated microbiological filter holds back any contamination and allows the ventilation of the package.

Nasal gels: Nasal gels are high-viscosity thickened solutions or suspensions. Until the recent development of precise dosing device, there was not much interest in this system. The advantages of a nasal gel includes the reduction of post-nasal drip due to high viscosity, reduction of taste impact due to reduced swallowing, reduction of of anterior leakage of the formulation, reduction of irritation by using soothing/emollient excipients and target to mucosa for better absorption.

Entsol nasal gel: Entsol nasal gel is a drug free hypertonic saline gel with aloe and vitamin E. It provides soothing, moisturizing relief to dry, stuffy, irritated nasal passages. Entsol nasal gel also helps relieve nasal congestion by reducing edema and swelling, fast and effectively. It is ideal for people using CPAP machines for sleep apnea since the constant flow of air teds to dry out nasal passages. It is also very useful in dry climates of low humidity such as indoors during the winter, some of the dry western states and for individuals with nasal allergies or sinusitis.

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. But nasal mucosa irritancy and metered dose delivery are some of the challenges for formulation scientists and device manufacturers (**table 4**).

1. For fast, simple and safe reconstitution.
2. Cost-effective compared with traditional systems.
3. Universal use: hospital, home and extended care settings.

TABLE 4: DELIVERY MEANS AND DEVICES FOR INTRA NASAL ADMINISTRATION OF DRUG

Drugs	Delivery devices
ACTH	Insufflator, Nebulizer(De Vilbis No.40)
Adrenal corticosteroids	Nasal spray, Nasal drop, Nasal gel, Insufflators, Submucosal injection into the anterior tip of inferior turbinate, Metered dose aerosol.
Antihistamines	Nasal spray, Nasal drop.
Atropine	Nasal drop,Nasal spray, nasal aerosol.
cocaine	Nasal spray ,Nasal drops, Cotton pledget Gauge pack tail, Insufflator, Rubbing with cocaine mud
gentamycin	Nasal spray
glucagon	Nasal drop
insulin	Metered pump sprayer, Metered dose aerosolized spray, Fixed volume aerosol spray, Nasal spray, Nasal drops, Cotton pledget.
dopamin	Nasal spray
ipratropium	Nasal spray
LHRH	Nasal spray
Nicotine	Tobacco snuff, Injected into dog's frontal sinus.
Nitroglycerin	Metered dose spray
methacholine	Nasal aerosol, Nose drops.
Meclizine HCL	Nose drops
Isosorbide dinitrate	Nasal spray (IsoMack spray)
Naloxone	Micropipette
Lypressin	Nasal spray
Penicillin	Nebulizer(De Vilbiss No.40) Aerosol with intermittent negative pressure in the nasal passage and nasal accessory sinuses Aerosol with a balance calibrated suction and pressure
Penagastrin	Insufflators, snuff
Phenylephrine	Nasal drop
Propranolol	Micropipette
Prostaglandins	Nasal drop
Scarlet fever toxin	Nasal spray
Testosterone	Micropipette
Vaccines	Inhalation aerosol, Nasal spray, Nasal drop, Nasal aerosol spray, Nebulizer, aerosol
Vitamin B12	Nasal drop insufflators

Evaluation of Nasal Drugs [1, 6, 16, 17]:

(A) ***In vitro* nasal permeation studies:** Various approaches used to determine the drug diffusion through nasal mucosa from the formulation. The two important methodologies to study the diffusion profile of the drug are discussed here,

- ***In vitro* diffusion studies[16, 17]:** 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. The nasal mucosa of sheep was separated from sub layer bony tissues and stoned in distilled water containing few drops at genatamycin injection.

  After the complete removal of blood from muscosal surface, is attached to donor chamber tube. The donor chamber tube is placed such a way that it just touches the diffusion medium in recipient chamber. At predetermined intervals, samples (0.5 ml) from recipient chamber are with draw and transferred to amber colored ampoules. The samples withdrawn are suitably replaced. The samples are estimated for drug content by suitable analytical technique. Through out the experiment the temperature is maintained at 37^{o}C.

(B) *In Vivo* Nasal Absorption studies[1-6]:

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. These models are discussed in detail below:

Rat Model: The surgical preparation of rat for *in vivo* nasal absorption study is carried out as follows: The rat is anaesthetized by intraperitoneal injection of sodium pentobarbital. 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. 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. 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.

Rabbit Model [18]: The rabbit offers several advantages as an animal model for nasal absorption studies:

1. It is relatively cheap, readily available and easily maintained in laboratory settings
2. It permits pharmacokinetic studies as with large animals (like monkey)
3. The blood volume is large enough (approx. 300ml)
4. To allow frequent blood sampling (l-2ml)

Thus 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. In the anaesthetized model, the rabbit is anaesthetized by an intramuscular injection of a combination of ketamine and xylazine. The rabbit's head is held in an upright position and the drug solution is administered by nasal spray into each nostril. During the experiment the body temperature of the rabbit is maintained at 37°C with the help of a heating pad. The blood samples are collected by an indwelling catheter in the marginal ear vein or artery.

Dog Model [19]: The dog is either anaesthetized or retained hi the conscious condition depending on the drug characteristics and the purpose of experiment. The dog is anaesthetized by intravenous injection of sodium thiopental and the anesthesia is maintained with sodium Phenobarbital. A positive pressure pump through a cuffed endotracheal tube gives the ventilation. The body temperature is maintained at 37-38°C by a heating pad. The blood sampling is carried out from the jugular vein.

Sheep Model [20]: The sheep, rabbit and dog models are more practical and suitable for investigating nasal drug delivery from sophisticated formulations. They permit better evaluation of the parameters there involved. The *in vivo* sheep model for nasal delivery is essentially parallel to that for the dog model. Male in-house bred sheep are employed since they are free from nasal infections.

Monkey Model [20]: Monkeys (approx. 8 kg) are anaesthetized, tranquillized or maintained in the conscious state as per the experimental purpose. The monkey is tranquillized by intramuscular injection of ketamine hydrochloride or anaesthetized by intravenous injection of sodium Phenobarbital. The head of the monkey is held in an upright position and the drug solution is administered into each nostril. Following the administration, the monkey is placed in a supine position in a metabolism chair for 5-10 min. throughout the course of study the monkey breaths normally through the nostrils. The blood samples are collected through an indwelling catheter in the vein.

***Ex vivo* Nasal Perfusion Models [21]:** Surgical preparation is the same as that is for *in vivo* rat model. During the perfusion studies, a funnel is placed between the nose and reservoir to minimize the loss of drug solution. The drug solution is placed in a reservoir maintained at 37°C and is circulated through the nasal cavity of the rat with a peristaltic pump. The perfusion solution passes out from the nostrils (through the funnel) and runs again into the reservoir. The drug solution in the reservoir is continuously stirred. The amount of drug absorbed is estimated by measuring the residual drug concentration in the perfusing solution. The drug activity due to stability problems may be lost during the course of experiment. This is especially true for peptide and protein drugs that may undergo proteolysis and aggregation.

Rabbit can also be used as the animal model for *ex vivo* nasal perfusion studies. The rabbit is anaesthetized with parenteral uretliane-acepromazine. A midline incision is made in the neck and the trachea is cannulated with a polyethylene neonatal endotracheal tube. The oesophagus is isolated and ligated. The distal end of the oesophagus is closed with suture and flexible tygon tubing is inserted into the proximal end and advanced to the posterior part of the nasal cavity. The nasopalatine tract (that connects nasal cavity to the mouth) is closed with an adhesive to avoid drainage of drug solution from the nasal cavity. The drug in isotonic buffer solution is recirculated using a peristaltic pump.

Scintigraphic evaluation in rabbits of nasal drug delivery systems based on carbopol 971p^(R) and carboxymethylcellulose: The residence time of apomorphine mucoadhesive preparations incorporating ^9^9^mTc labeled colloidal albumin in rabbit nasal cavity was evaluated by gamma scintigraphy. This technique was used to compare the nasal clearance of preparations based either on Carbopol 971P^(R) or lactose (control), each with and without apomorphine, or carboxymethylcellulose with apomorphine.

The planar 1-min images showed an excipient-dependent progressive migration of radioactivity with time from the nasal cavity to the stomach and intestine. Thirty minutes post insufflation, the percentages of the formulations cleared from the nasal cavity were 47% for lactose, 26% for lactose/apomorphine, 10% for Carbopol 971P^(R), and 3% for both Carbopol 971P^(R)/apomorphine and carboxymethylcellulose/apomorphine.

Three hours post insufflation, the percentages of the formulations cleared from the nasal cavity were 70% for lactose, 58% for lactose/apomorphine, 24% for Carbopol 971P^(R), 12% for Carbopol971P^(R)/ apomorphine, and 27% for carboxy methylcellulose/apomorphine. Apomorphine inhibited nasal mucociliary clearance since migration of the radioactivity administered with apomorphine containing preparations was in all cases slower than that of the corresponding powder without apomorphine.

The peak plasma concentration of apomorphine was attained while all the formulations were still within the nasal cavity. The use of mucoadhesive polymers such as Carbopol 971P^(R) or carboxymethylcellulose in nasal dosage forms increases their residence time within the nasal cavity and provides the opportunity for sustained nasal drug delivery.

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