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Nasal Drug Delivery System: A Review

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ABSTRACT

The use of the nasal route for the delivery of challenging drugs such as small polar molecules, vaccines, hormones, peptides and proteins has created much interest in nowadays. Due to the high permeability, high vasculature, low enzymatic environment of nasal cavity and avoidance of hepatic first pass metabolism are well suitable for Systemic delivery of drug molecule via nose Many drug delivery devices for nasal application of liquid, semisolid and solid formulation are investigated to deliver the drugs to the treat most crisis CNS diseases (i.e., Parkinson's dis-ease, Alzheimer's disease) because it requires rapid and/or specific targeting of drugs to the brain. It is well suitable for the delivery of biotechnological products like proteins, peptides, hormones, DNA plasmids for DNA vaccines to give enhanced bioavailability. This review sets out to discuss some factors affecting nasal absorption, bioavailability barriers, strategies to improve nasal absorption, new developments in nasal dosage form design and applications of nasal drug delivery system.

KEYWORDS: *Bioavailability, Patient Compliance, First pass effect, absorption Enhancers*

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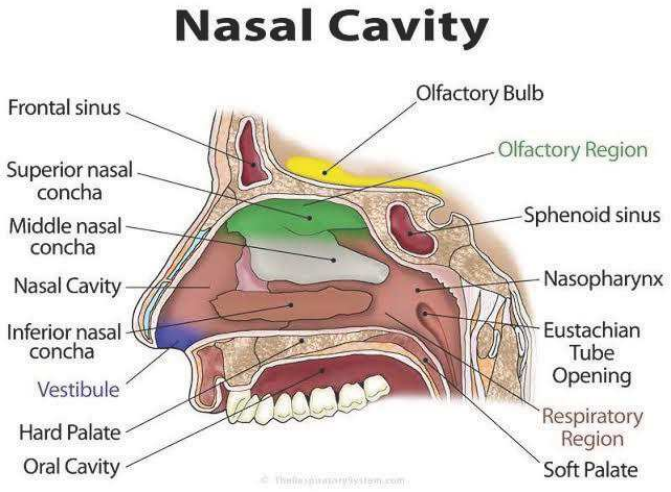
INTRODUCTION

Nasal mucosa has been considered as a potential ad-ministration route to achieve faster and higher level of drug absorption because it is permeable to more com-pounds 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 . In recent years many drugs have been shown to achieve better systemic bioavailability through nasal route than by oral administration. Nasal therapy, has been recognized form of treatment in the Ayurvedic systems of Indian medicine, it is also called "NASAYA KARMA" (Chien YW et al., 1989).

This review article provides a brief overview of the ad-vantages and limitations of nasal drug delivery system and anatomy of nasal cavity, mechanism of nasal ab-sorption, barriers to nasal absorption, strategies to improve nasal absorption, nasal drug delivery formulation issues and applications of nasal drug delivery systems.

Anatomy and physiology of Nasal Cavity:



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. The nasal cavity consists three main regions are nasal vestibule, olfactory region and

respiratory region. The surface area in the nose can be enlarges about 150cm2 by the lateral walls of the nasal cavity includes a folded structure, it is 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 (Michael et al., 2005).The main nasal airway having the narrow passages, usually it has 1-3mm wide and these narrows structures are useful to nose to carryout its main functions. The nasal cavity is covered with a mucous membrane which can be divided into two areas; nonolfactory and olfactory epithelium, in this non-olfactory area includes the nasal vestibule which is covered with skin-like stratified squamous epithelium cells, where as respiratory region, which has a typical airways epithelium covered with numerous microvilli, resulting in a large surface area available for drug absorption and transport (Sarkar MA, 1992).In this way the mucus layer is propelled in a direction from the anterior to-wards 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 the mucus as mucus granules which are swelling in the nasal fluid to contribute to the mucus layer. The mucus secretion is composed of about 95% water, 2 % mucin, 1% salts, 1% of other proteins such asal-bumin, immunoglobulin s, lysozyme and lactoferrin, and b 1% lipids (Kaliner M et al.,1984).The mucus secretion gives immune protection against inhaled bacteria and viruses. It also performs a number of physiological functions. (1) It covers the mucosa,and physically and enzymatically protects it. (2) The mucus has water-holding capacity. (3) It exhibits surface electrical activity. (4) It permits efficient heat transfer. (5) It acts as adhesive and transport s particulate matter towards the nasopharynx(Bernstein JM et al., 1997).

Advantages:

1. Drug degradation that is observed in gastrointestinal tract is absent.
2. Hepatic first pass metabolism is absent.
3. Rapid drug absorption and quick onset of action can be achieved.
4. Bioavailability of the large drug molecules can be improved by means of absorption enhancer or other approach.
5. Availability for the smaller a drug molecule is good.
6. Drugs that cannot be morally absorb can be reached to the systemic circulation by the nasl route.
7. Convenient for the patients those who are on long-term therapy when compared with parental medication.
8. Large nasal mucosal surface area for drug absorption.
9. Rapid drug absorption via highly vascularized mucosa.

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.

Mechanism of Action:

1. The first mechanism involves an aqueous route of transport, which is also known as 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 Drug absorption: 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 the drug
- Polymorphism
- Properties of the drug
- Molecular weight
- Particle size
- Solubility and dissolution rate

2. Nasal effect:
- Membrane permeability
- Environmental PH
- Cold, Rhinitis
- Mucociliary clearance.

3. Delivery Effects:
- Drugs distribution and deposition.
- Formulation effect on mucociliary clearance.
- 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

Safety and efficacy of absorption enhancers:

1. 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.

2. 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.

3. ciliary beat frequency:
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).

Excipients used in nasal formulation:
Commonly used excipients that are frequently added to nasl preparations can be listed below

1. **Bioadhesive polymers**: it can be defined as a compound that is capable of interacting with biological materials through interfacial forces and being retained on search material for prolonged period of time if the biological material is a mucous membrane the Bioadhesive material is term as a mucoadhesive on molecular level muco edition can be explained on the basis of attraction molecular interactions involving forces such as Van der Waals, electrostatic interactions, hydrogen bonding and hydrophobic interactions.

   The bioadhesive material of a polymer material is dependent on the nature of polymer the surrounding medium pH swelling and physiological factors such as mucin turnover disease state.

Examples of some bioadhesive polymers employed for nasal drug delivery systems:
A. Carbopol
B. Sodium carboxymethyl cellulose
C. Hydroxypropyl cellulose
D. Hydroxypropyl methyl cellulose
E. Hydroxyethyl cellulose
F. Methyl cellulose
G. Guar gum
H. Sodium alginate
I. Starch
J. Dextran
K. Chitosan.

2. **Gelling agent**: according to a study of pennington increasing solution viscosity may provide a means of prolonging the therapeutic effect of nasal preparation show that a drug carrier such as hydroxypropyl cellulose was effective for improving the absorption of the low molecular weight drugs but did not produce the same effect for high molecular weight peptides use of a combination of a carriers is often recommended from a safety point of view.

3. **Penetratration enhancer:** chemical penetration enhancers are widely used in a national Drug delivery classification of chemical penetretion includes the following

A. Solvents
B. Alkyl dimethyl sulfoxide
C. Pyrrolidones
D. 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 charge drug by forming iron pair
- Inhibiting proteolytic activity

4. **Buffers**: Nasal formulations are generally administered in small volumes ranging from 25 to 200 microliter with hundred microliter being the most common dose volume.

   Hans Nasir secretions may alter the pH of the administered dose. This can affect the concentration of an ionized drug available for absorption. For an adequate formulation buffer capacity may be required to maintain the pH in situ.

5. **Solubilizers**: aqueous solubility of a drug is always a limitation for nasal drug delivery in a solution. Convectional solvents for co solvent such as glycols small quantities of alcohol transcutol glycol monoethyl ether medium chain triglycerides and labrasol can be used to enhance the solubility of the drugs. Other options includes the use of surfactants or cyclodextrin such as HP beta cyclodextrin that serve as a biocompatible solubilizer and stabilizer in combination with the lipophilic Absorption enhancers.

6. **Preservatives**: most nasal formulations are equispaced and need preservatives to prevent microbial growth parabens benzalkonium chloride phenyl ethyl alcohol and benzyl alcohol are some of the commonly used preservatives in another formulations have shown that the Mercury containing preservatives have a fast and irreversible effect on the ciliary movement and should not be used in nasal system.

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.

8. **Humectants**: many allergic and chronic diseases are often connected with crossed and drying of mucous membrane. Certain preservatives antioxidants among other excipients are also likely to cause nasal irritation especially when used in higher quantity. Adequate internal moisture is essential for preventing the hydration. Therefore humic terms can be added especially in a gel based Nasal products. Human things avoid nasal irritation are not likely to infect drug absorption examples include glycerine sorbitol and mannitol.

9. **Surfactants**: incorporation of surfactant into nasal dosage form 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 the drug.
- **Salt or Easter formulation:** the drug could be converted to form of a salt or an Easter for better transnasal permeability. For example, nasal absorption could be improved significantly by forming a salt with increase solubility in measure fluid for an Easter with enhanced uptake by nasal epithelium.
- **Formulation design**: proper selection of Pharmaceutical excipients in the development of national formulation could enhance the formulation stability for the nasal bioavailability of the drug.
- **Surfactants**: incorporation of surfactant into nasal dosage form could modify the permeability of national membranes which may facilitate the national 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 surfactant has been reported to enhance the absorption of drugs through the nasal mucosa to a level sufficient achieve their systemic effect.

Research and development in nasal drug delivery:
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 posssible 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

Evaluation of Nasal Drugs:

A. vitro nasal permeation studies: Various aproaches 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: 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.

Throughout the experiment the temperature is Maintained at 37oC.

A) 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 **a**nd 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: 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: 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 wiith 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.

Ex vivo Nasal Perfusion Models:
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^® 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^® 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^®, and 3% for both Carbopol 971P^®/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^®, 12% for Carbopol971P^®/Apomorphine, and27 For Carboxymethylcellulose/ 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^® 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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