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Review Article on Nasal Drug Delivery System

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ABSTRACT
Nasal drug delivery has received a great deal of attention as a convenient, reliable, and promising method for the systemic administration of drugs.
It is especially for those molecules which are ineffective orally and only effective if administered by injection. The nasal route of drug delivery has advantages over the other alternative systems of non-invasive drug administration. The present review describes nasal delivery systems in recognizing to its potential and limits. The present review is an attempt to provide some information concerning nasal drug delivery system such as limitations, advantages, mechanism of drug absorption, anatomy of nasal cavity, factors affecting of nasal drug delivery, strategies to enhance nasal absorption, strategies to extend duration of drug formulations within the nasal cavity, leading to improved nasal drug absorption, novel drug formulations, sorts of nasal drug delivery system with uses of nasal drug delivery in various diseases, and recent advancement of nasal delivery systems.
Keywords: Nasal drug delivery systems, Non-invasive drug administration, Anatomy and physiology, Recent advancement.

I. INTRODUCTION

In recent time, the nasal drug delivery received a great deal of attention for its convenient, promising, and reliable way of systemic administration for drugs, especially for those drugs which are ineffective orally and those which must be administered by injections. Over the last few decades, transmucosal nasal drug delivery as a non-invasive route has occupied an important place in the field of drug delivery technology. This route provides a large surface area, porous endothelial membrane, high total blood flow, bypassing the first-pass metabolism, and ready accessibility. Furthermore, nasal mucosa is permeable to more compounds than the gastrointestinal tract due to the absence of pancreatic, gastric enzymatic activities, and interference by gastrointestinal contents. The early recorded historical application of nasal drug delivery was restricted to topical applications of drugs intended for only local effects. However, in recent times, its application grown to include a wide range of targeted areas in the body to produce local and systemic effects. Nasal drug delivery also finds a special place in the traditional system of medicine such as the Ayurvedic system of Indian medicine which is called as "Nasya karma" and is a well-recognized way of treatment [1-4]

Anatomy and physiology of nasal cavity

In humans and other animal species the major functions of the nasal cavity are breathing and olfaction. However, it also affords an important protective activity once it filters, heat and humidify the inhaled air before reaching the lowest airways. Passage of the nasal cavity which runs from nasal vestibule to nasopharynx has a depth of approximately 12-14cm. The total surface area of the nasal cavity in human adult is about 150 cm2 and total volume is about 15 ml [5]. Each of two nasal cavities can be

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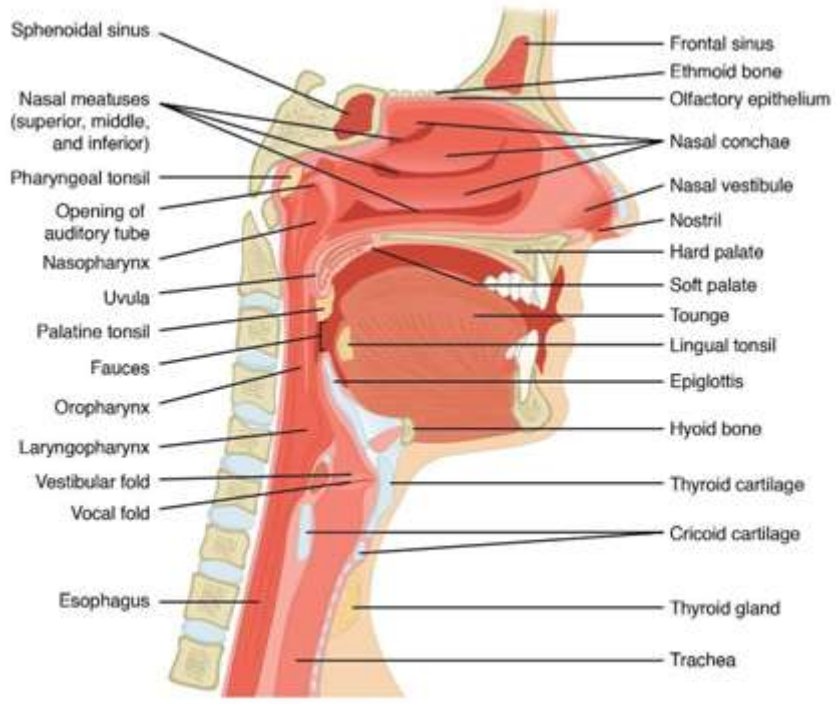

For example a prominent profile can cause gas to escape around the side of the nose. Sagittal section through subdivided into different regions: nasal vestibule, inferior turbinate, middle turbinate, superior turbinate, olfactory region, frontal sinus, sphenoidal sinus, and cribriform plate of ethmoid bone. The nasal cavity also contains the nasal associated lymphoid tissue (NALT), which is mainly situated in the nasopharynx. Nasal cavity is lined with mucus layer and hairs which are involved in those functions are trapping inhaled particles and pathogens. Moreover, mucociliary clearance, immunological activities and metabolism of endogenous substances are also essential functions of nasal structures [9]. 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, whereas respiratory region, which has a typical airways epithelium covered with numerous microvilli, resulting in a large surface area available for drug absorption and transport [10] . Nasal cavity is divided by middle septum into two symmetrical halves, each one opening at the face through nostrils and extending posterior to the nasopharynx. Both symmetrical halves consist of four areas (nasal vestibule, atrium, respiratory region and olfactory region) that are distinguished according to their anatomic and histological characteristics [9]

The nose extends from the nostrils to the nasopharynx. It is an organ designed to humidify and warm air as it travels to the nasopharynx and on to the lungs. Airway adjuncts such as a nasopharyngeal airway or a nasotracheal tube can be passed through the nose. It can also act as a conduit for a fiberoscope during nasal intubation. The shape and size of the nose can determine how easily an anaesthetic face mask fits. the nose the nose encases two nasal cavities, lined by mucous membranes. Each nasal cavity is divided by three turbinates. These are the superior, middle and inferior turbinates The sinuses drain through holes (or ostia) into the nose, between the middle and the inferior turbinate, a reason to keep your scope or tube away from this area and direct it along the floor of the nose. Another important opening includes the Auditory tube which connects the middle ear to the nasopharynx. It equalises the pressure in the middle ear with that outside the body.

Nerve Supply of the nose and pharynx

In broad terms the nasopharynx is supplied by the Trigeminal nerve, the oropharynx is supplied by the Glossopharyngeal nerve, and the

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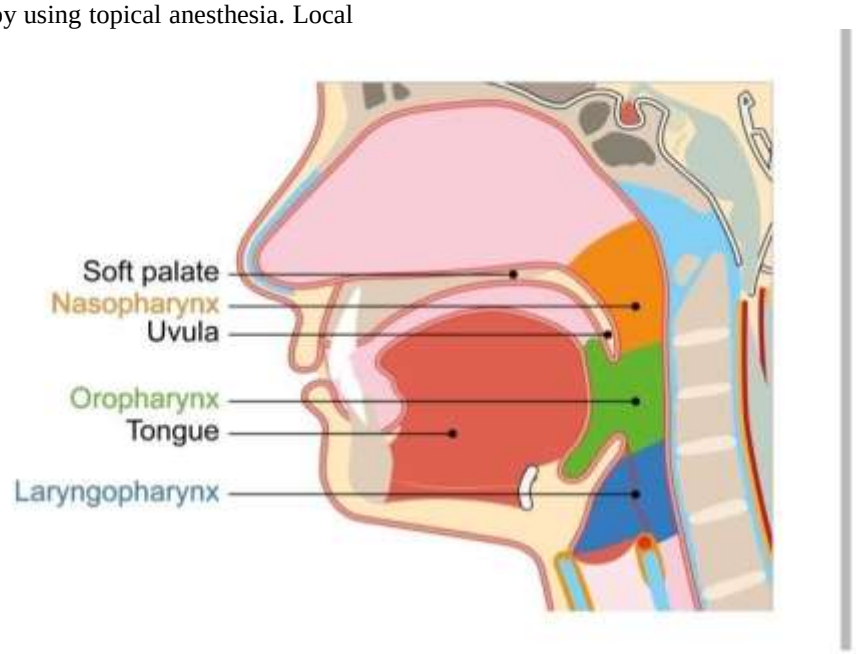
laryngopharynx is supplied by the Vagus nerve. Due to the complex innervation, the best way to numb the nose is by using topical anesthesia. Local anaesthetic is administered by spray or gel to facilitate passage of airway equipment.



CENTRAL NERVOUS SYSTEM (CNS) DELIVERY THROUGH NASAL ROUTE

The intranasal route has encouraging approach for the delivery of drugs to the brain. The delivery of drugs to CNS from the nasal route may occur through olfactory neuroepithelium. Drug delivery through nasal route into CNS has been reported for Alzheimer's disease, brain tumors, epilepsy, pain, and sleep disorders [5,6,7,8].

Table 1: Structural features of various regions and their impact on the permeability of nasal cavity

Region	Structural features	Permeability
Nasal vestibule	Nasal hairs (vibrissae) Epithelial cells are stratified, squamous, and keratinized Sebaceous glands present	Least permeable due to the presence of keratinized cells, very resistant to hydration and can withstand insults from noxious substances of the environment

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Atrium	Transepithelial region Stratified squamous cells present anteriorly and pseudostratified cells with microvilli present posteriorly The narrowest region of the nasal cavity	Less permeable as it has small surface area and stratified cells are present anteriorly
Respiratory region (inferior turbinate middle turbinate superior turbinate)	Pseudostratified ciliated columnar cells with microvilli (300 per cell), large surface area Receives maximum nasal secretions due to the presence of seromucous glands, nasolacrimal duct, and goblet cells Richly supplied with blood for heating and humidification of inspired air, the presence of paranasal sinuses	Most permeable region due to large surface area and rich vasculature

ADVANTAGE OF NASAL DRUG DELIVERY SYSTEM [11,12,13,14]

1.Reach directly into Systemic blood circulation and avoid first pass hepatic and intestinal

1. metabolism
2. Drug degradation is absent in GIT tract
3. Drug absorption is very fast and quick onset of action
4. Smaller size of drug molecules having higher bioavailability.
5. It provides good penetration of, especially Lipophilic, low molecular weight drugs
6. through the nasal mucosa.
7. Lipophilic drug easily penetrate in BBB
8. Absorption of drug is rapid via highly vascularized mucosa.
9. Availability of large nasal mucosal surface area for dose absorption.
10. Onset of action is rapid.
11. Non invasive and easy for administration.
12. Bypass the BBB.
13. Degradation of drug observed in GIT is avoided.
14. Hepatic first pass metabolism is absent.
15. Nasal bioavailability of small drug molecules is good.
16. Bioavailability of large drug molecules can be increased by means of absorption enhancers.
17. Unsuitable drug candidates for oral route can be successfully given via nasal route.
18. Alternate to parenteral route especially for proteins and peptides.
19. Convenient route for the patient on long term therapy.
20. Improved bioavailability.
21. Side effects are reduced due to low dose.
22. Patient convenience and compliance is improved.
23. A self-administration is possible.
24. Direct transport into systemic circulation and CNS is Possible.
25. Offers lower risk of overdose
26. Does not have any complex formulation Requirement.

DISADVANTAGE OF NASAL DRUG DELIVERY SYSTEM[15-17]

1. The nasal cavity provides a smaller absorption surface area when compared to gastrointestinal tract.
2. There is a possibility of irritation when compared to the oral delivery system since.
3. The substance and constituents added to the dosage form may cause local side effects and irreversible damage of the cilia on the nasal mucosa.
4. There could be a mechanical loss of the dosage form into the other parts of the respiratory tract like lungs due to the improper technique of administration.
5. Certain surfactants used as chemical enhancers may disrupt and even dissolve the membrane in high concentration.

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LIMITATIONS:[12] [18,15-17,19]

1. The histological toxicity of absorption and used in nasal drug delivery system is not yet
2. clearly established.
3. Relatively inconvenient to patients when compared to oral delivery systems since there is a
4. possibility of nasal irritation.
5. Nasal cavity provides smaller absorption surface area when compared to GIT.
6. There is a risk of both of irreversible damage of the cilia of the nasal mucosa and local side effects from both constituents and substances additional to the dosage form.
7. There can be a mechanical loss of the dosage form in other parts of the respiratory system, for example, lungs due to the inappropriate technique of administration.
8. Some of the surfactants used as a chemical catalyst and may cause or even dissolve the membrane at high concentrations

Different factors affecting nasal drug absorption [20, 12,]

Various factors affect bioavailability of nasally administered drugs as follows;

I Biological Factors [20]

1. Structural features
2. Biochemical changes

II Physiological factors

1. Blood supply and neuronal regulation
2. Nasal secretions
3. Mucociliary clearance and ciliary beat frequency
4. Pathological conditions
5. Environmental conditions.
6. Membrane permeability.

III Physicochemical Properties of Drugs [20]

1. Molecular weight
2. Size
3. Solubility
4. Lipophilicity
5. pka and Partition coefficient
6. Chemical form of drug.
7. Polymorphism.
8. Chemical state.
9. Physical state.

IV Physicochemical Properties of Formulation

1. Physical form of formulation
2. pH
3. Osmolarity
4. Volume of solution applied and drug concentration
5. Viscosity.

I Biological factors

1] **Structural features** There are five different sections of nasal cavity: nasal vestibule, atrium, respiratory area, olfactory region and the nasopharynx. These structures and the type of cells, density and number of cells present in that region influence the permeability. Absorption enhancers used in combination with drugs increase the permeation of compounds. [21]

2] **Biochemical changes** Enzymatic barrier to the delivery of drugs is nasal mucosa because of the presence of a large number of enzymes, which include oxidative and conjugative enzymes, peptidases and proteases. These enzymes are responsible for the degradation of drugs in the nasal mucosa and result in creation of a pseudo-first-pass effect. Metabolism of nasal decongestants, alcohols, nicotine and cocaine IS due to p450 dependent monooxygenase system. Protease and peptidase were responsible for the presystolic degradation and subsequent lower permeation of various peptide drugs, such as calcitonin, insulin, LHRH and desmopressin. To overcome these degradations various approaches have been used. These include the use of protease and peptidase inhibitors such as bacitracin, amastatin, and puromycin [22].

II Physiological factors

1. Blood supply and neuronal regulation

Nasal mucosa is highly permeable site. High blood supply due to parasympathetic stimulation gives congestion and low blood supply due to sympathetic stimulation gives relaxation, regulate the rise and fall in the amounts of drug permeated, respectively [27]. Based on the above observations, we can conclude that the increased permeability of a compound is due to parasympathetic stimulation.

2. Nasal secretions

Nasal secretions are produced by anterior serous and seromucus glands. Mucus production is approximately 1.5–2 l ml daily.The permeability of drug through the nasal mucosa is affected by:

- **Viscosity of nasal secretion**The viscous surface layer will inhibit the ciliary beating if the sol layer of mucus is too thin and

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mucociliary clearance is impaired if sol layer is too thick, because contact with cilia is lost. Permeation of the drug is affected due to impairment of mucociliary clearence by altering the time of contact of drug and mucosa.

- **Solubility of drug in nasal secretions**For permeation of drug solublisation is necessary. A drug needs to have appropriate physicochemical characteristics for dissolution in nasal secretions.
- **Diurnal variation**Nasal secretions are also affected by circadian rhythm. Permeation of drug is altered at night due to secretions and clearance rates are reduced. Chronokinetics dictate the pattern and rate of permeation in such cases.

pH of nasal cavityvariation in pH is observed between 5.5–6.5 in adults and 5.0–7.0 in infants. Permeation of drug is greater if the nasal pH is lower than pKa of drug because under such conditions the penetrant molecules exist as unionized species. Increase or decrease in the permeation of drug is observed because ionization is affected by change in pH of mucus, depending on the nature of the drug. pH of formulation should be between 4.5 to 6.5 for better absorption and should also have good buffering capacity[28].

3. Mucociliary clearance (MCC) and ciliary beating Whenever a substance is nasally administered, it is cleared from the nasal cavity in ~21 min by MCC because mucociliary clearance is the normal defense mechanism of the nasal cavity which clears substances adhering to nasal mucosa and cleared in GIT by draining into nasopharynx. Drug permeation is enhanced by increasing contact time between drug and mucus membrane because reduced MMC; whereas, increased MCC decreases drug permeation.

4. Pathological conditions:

Mucociliary disfunctioning, hypo or hypersecretions, irritation of the nasal mucosa occurs due to diseases such as the common cold, rhinitis, atrophic rhinitis and nasal polyposis, and drug permeation is affected by this.

5. Environmental conditions:

Moderate reduction in the rate of MCC occurs at the temperature of 24^{o}C, it has been predicted that a linear increase in ciliary beat frequency occurs with increase in temperature.

6. Membrane permeability:

Absorption of the drug through the nasal route is affected by membrane permeability which is most important factor. The large molecular weight drugs and water soluble drugs like peptides and proteins have low membrane permeability hence absorbed through endocytic transport in fewer amounts [29].

III Physicochemical properties of drug:

1. **Molecular weight and size:**Drug permeation is determined by molecular weight, molecular size, hydrophilicity and lipophilicity of the compound. For compounds 1 kDa, bioavailability can be directly predicted from knowledge of MW. In general, the bioavailability of these large molecules ranges from 0.5% to 5%. Physicochemical properties of the drug don't significantly affect permeation of drug LT 300 Da, which will mostly permeate through aqueous channels of the membrane. By contrast, for compounds with MW 300 Da rate of permeation is highly sensitive.
2. **Solubility**: Major factor in determining absorption of drug through biological membranes is drug solubility. As nasal secretions are more watery in nature, a drug should have appropriate aqueous solubility for increased dissolution. Lipophilic drugs have less solubility in the aqueous secretions. Water soluble drugs are absorbed by passive diffusion and lipophilic drugs via active transport depending on their solubility. [30]
3. **Lipophilicity**: The permeation of the compound normally increases through nasal mucosa with increase in lipophilicity. It appears that nasal mucosa is primarily lipophilic in nature and the lipid domain plays an important role in the barrier function of these membranes although they have some hydrophilic characteristics. Systemic bioavailability of many drugs is decreased due to excess hydrophilicity in such cases prodrug approach is beneficial.
4. **pKa and partition coefficient:** As per the pH partition theory, unionized species are absorbed better compared with ionized species and the same fact is true in the case of nasal absorption. There is constant relationship between pKa and nasal absorption of these drugs. With an increase in lipophilicity or the partition coefficient of the drugs its concentration in biological tissues increases. The absorption rate of aminopyrine increased with the increase in pH and was found to fit well to the theoretical profile Major factor

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governing nasal absorption is partition coefficient[31].

5. **Polymorphism**: Polymorphism is the important parameter in the nasal drug product development which is administered in particulate form. Polymorphism is known to affect dissolution of drugs and their absorption through biological membranes is affected by polymorphism. This factor should be carefully considered in the dosage form development for the nasal delivery. [16]
6. **Chemical state of drug:**Absorption of the drug is determined by the chemical form of the drug in which it is presented to nasal mucosa. Chemically alter a drug molecule by adding a bio-cleavable lipophilic moiety is the alternative for improving absorption of the drug which is not having desired absorption properties. The prodrug approach provides many additional challenges which need to be overcome in the drug product developmental process. The toxicity of the prodrug itself needs to be fully evaluated [16].
7. **Physical state of drug:**

Particle size and morphology of drug are two main important properties for particulate nasal drug products. These both parameters should be controlled to obtain suitable drug dissolution properties in the nostrils. Too fine particles below 5 microns should be avoided because it may get inhaled in lungs. Generally, particles in the 5–10 micron range are deposited in the nostrils. [16].

VI Physicochemical properties of formulation:

1. **Physical form of formulation**:

Physical form of the formulation is very important in nasal drug absorption. Liquid formulations are less effective than powder form in delivering insulin in rabbits. Less efficient systemic nasal drug delivery observed with more viscous formulation. Scientist found that somewhat more sustained effects of desmopressin are observed with addition of viscous agent but total bioavailability is not enhanced. Viscous formulations may help in minimizing nasal drip.

2. **pH**:extent of drug ionization IS determined by pH partition hypothesis hence it is related to formulation pH. Nasal formulation should be adjusted to appropriate pH to avoid irritation, to obtain efficient absorption and to prevent growth of pathogenic bacteria. Ideal formulation pH should be adjusted between 4.5 and 6.5. pH of the nasal surface is 7.39 and the pH of nasal secretions is 5.5–6.5 in adults and 5.0–6.7 in infants and children.
3. **Osmolarity:** Formulation tonicity substantially affect the nasal mucosa generally, an isotonic formulation is preferred. Some scientist studied the effects of formulation osmolarity, on the nasal absorption of secretin in rats. They found that all cells of the nasal mucosa were affected by the concentration of sodium chloride in the formulation and-the absorption reached a maximum at a 0.462 M sodium chloride concentration. At this concentration shrinkage of epithelial cells was observed. Hence tonicity is also having impact on drug absorption. [32]
4. **Volume of solution applied and drug concentration**: There is no constant relationship between volume of administration and extent of absorption. Clement studied the effect of three nasal spray concentrations of cetrizine on the clinical efficacy. The results showed that 16.7%, 30.8%, 42.9%, and 26.7% of days the patients experienced appeared to improve with the drug concentration up to only 0.125%. At the higher concentration, 0.250%, the efficacy declined.[33]
5. **Viscosity:**contact time between the drug and the nasal mucosa is increased by higher viscosity of formulation thereby increasing the time for permeation.

Formulation of nasal spray [24]

Nasal spray drug products contain therapeutically active ingredients (drug substances) dissolved or suspended in solutions or mixtures of excipients (e.g., preservatives, viscosity modifiers, emulsifiers, buffering agents) in no pressurized dispensers that deliver a spray containing a metered dose of the active ingredient. The dose can be metered by the spray pump. A nasal spray unit can be designed for unit dosing or can discharge up to several hundred metered sprays of formulation containing the drug substance. Nasal sprays are applied to the nasal cavity for local and/or systemic effects. Although similar in many features to other drug products, some aspects of nasal sprays may be unique (e.g., formulation, container closure system, manufacturing, stability, and drug product). Metering and spray producing (e.g., orifice, nozzle, jet) pump mechanisms and components are used for reproducible delivery of drug formulation and these can be constructed of many parts of different design that are precisely controlled in terms of dimensions and composition. Energy is required for

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dispersion of the formulation as a spray. This is typically accomplished by forcing the formulation through the nasal actuator and its orifice. The formulation and the contain closure system (container, closure, pump, and any protective packaging) collectively constitute the drug product. The design of the container closure system affects the dosing performance of the drug product.
Both solution and suspension formulations can be formulated into nasal sprays. Fig no 2:
Pictorial diagram of nasal spray.

1) Active Pharmaceutical Ingredient
An ideal nasal drug candidate should possess the following attributes:
•Appropriate aqueous solubility to provide the desired dose in a 25–150 ml volume of formulation

- Appropriate nasal absorption properties.
- No nasal irritation from the drug.
- A suitable clinical rationale for nasal dosage forms, e.g. rapid onset of action.
- Low dose. Generally, below 25 mg per dose.
- No toxic nasal metabolites.
- No offensive odors/aroma associated with the drug.
- Suitable stability characteristics.

2) Excipients used in nasal spray formulations
There are various types of excipients used in nasal formulations. Commonly used and frequently added excipients are as follows:

a) **Buffers:** Nasal secretions may alter the pH of the administrated dose which 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. Examples of buffer used in nasal spray sodium phosphate, Sodium citrate, citric acid.

b) **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 monomethyl ether), medium chain glycerides and Labrasol (saturated polyglycol zed C8- C10 glyceride) can be used to enhance the solubility of drugs. Other compounds can be used like, the use of surfactants or cyclodextrins such as HPsCyclodextrin that serve as a biocompatible solubilizer and stabilizer in combination with Lipophilic absorption enhancers. In these cases, their impact on nasal irritancy should be considered.

c) **Preservatives:** Most nasal formulations are aqueous based so needs preservatives toprevent microbial growth. Parabens, phenyl ethyl alcohol, benzalkonium chloride, EDTA and benzoyl alcohol are some of the commonly used preservatives in nasal formulations.

d) **Antioxidants:** A small quantity of antioxidants may be required to prevent drug Oxidation. Commonly used antioxidants are sodium bisulfite, butylated hydroxytoluene, Sodium metabisulfite and tocopherol. Usually, antioxidants do not affect drug absorption or cause nasal irritation.

e) **Humectants**: Because of allergic and chronic diseases there can be crusts and drying of mucous membrane. Certain preservatives/antioxidants are also likely to cause nasal irritation especially when used in higher quantities. Adequate intranasal moisture is essential for preventing dehydration.

ADVANCEMENT IN THE NASAL DOSAGE FORMS

1. **Nasal Drops:** Nasal drops are one of the most simple and convenient system developed for nasal delivery. The man 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 deposits human serum in the nostrils more efficiently than nasal spray.[1]
2. **Nasal Spray:** 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. These are preferred over powder sprays because powder results in mucosal irritation.[1]
3. **Nasal Powders:** 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, particle size, aerodynamic properties and nasal irritancy of the active drug and/or excipients. Local application of drug is another advantage of this system.[1]

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4. **Nasal Gel:** The nasal gel showed growing interest due to reduction of post-nasal drip, 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.[3]

5. **Nasal Inserts:** Nasal inserts are novel, bio adhesive, solid dosage forms for prolonged systemic drug delivery via the nasal route. The principle of the dosage form is to the nasal fluid from the mucosa after administration and to form a gel in the nasal cavity to avoid foreign body sensation.[1]

1.Nasal Drops

2.Nasal Spray

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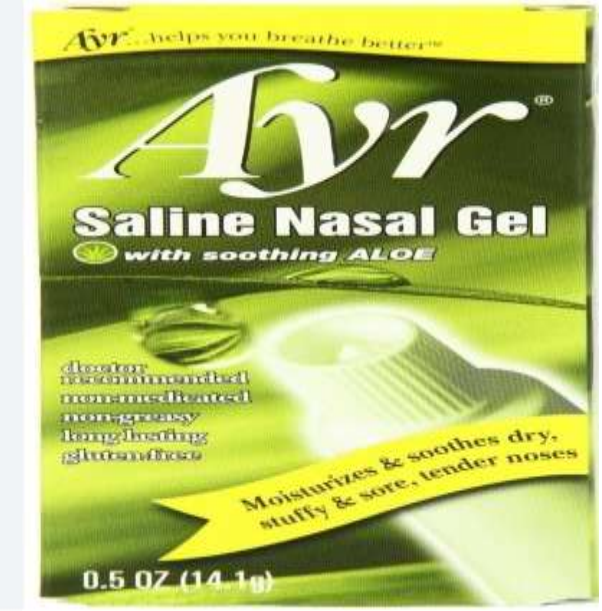
3.Nasal Gel



4.Nasal insert

Table 1-Formulation and Active Agent that have been utilized in Nasal Drug Delivery[5, 25]

SR. NO.	FORMULATION	ACTIVE AGENT
1.	In-situ Nasal Gel	Midazolam, Insulin, Triptans, Diltiazem
2.	Nasal Inserts	Chlorpromazine, Albuterol

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3.	Microspheres	Beta-Amyloid Fibril, Starch Microspheres, Dextran Gentamicin, Insulin, Desmopressin
4.	Microparticles	Serum albumin, Thiolated Chitosan Microparticles
5.	Dry Powder	Zolmitriptan
6.	Nasal Gel	Oxytocin, Metoclopramide Hydrocloride

Evaluation of nasal drug formulations [9, 26]

In vitro nasal permeation studies Various approaches used to determine the drug diffusion through nasal mucosa from the formulation. There are two different methods to study diffusion profile of drugs,

(A)In vitro diffusion studies

The nasal diffusion cell is fabricated in glass. The water-jacketed recipient chamber having 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 donor chamber is 10 cm long with internal diameter of 1.13 cm, 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. The nasal mucosa of sheep was separated from sub layer bony tissues and stoned in distilled water containing few drops at genatamycininjection. After the complete removal of blood from muscosal surface, it 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. Samples (0.5 ml) from recipient chamber are with draw at predetermined intervals, and transferred to amber colored ampoules. The samples withdrawn are suitably replaced. The samples are estimated for drug content by suitable analytical technique. The temperature is maintained at 37oC throughout the experiment.

(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. 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. Femoral vein is used to collect the blood samples. 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 permits pharmacokinetic studies as with large animals (like monkey) 2. It is relatively cheap, readily available and easily maintained in laboratory settings 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 adrug. Rabbits (approx. 3 kg) are either anaesthetized or maintained in the conscious state depending on the purpose of study. In the anaesthetized model, intramuscular injection of a combination of ketamine and xylazine is given to anasthetized rabbit. The rabbit's head is held in an upright position and nasal spray of drug solution is administered into each nostril. The body temperature of the rabbit is maintained at 37°C during experiment with the help of a heating pad. The blood samples are collected by an indwelling catheter in the marginal ear vein or artery.

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Ex vivo Nasal Perfusion Models

Surgical preparation is the same as that is for in vivo rat model. During the perfusion studies, to minimize the loss of drug solution a funnel is placed between the nose and reservoir. 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. 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. To avoid drainage of drug solution from the nasal cavity the nasopalatine tract (that connects nasal cavity to the mouth) is closed with an adhesive. The drug in isotonic buffer solution is recirculated using a peristaltic pump.

In-vivo bioavailability studies

In-vivo bioavailability study is conducted on healthy male rabbits. Study consists of three groups each containing six rabbits and fasted for 24 h. One group treated with conventional preparation, second group kept as control (i.e., not received any test substances) and third group of test formulation. Water is given ad libitum during fasting and throughout the experiment. For the collection of blood samples, the marginal ear vein of the rabbits used and sample of about 2 ml collected in heparinized centrifuge tubes at 0.5, 1, 2, 3, 4, 5, 6, 7 and 8 h after the drug administration. The blood samples are centrifuged at 3000 × g for 15 min to obtain the plasma and stored at -20°C until analysis. The extraction of drug from plasma can be carried out as reported previously and then analyze using the HPLC system.

Pharmacokinetic analysis

Pharmacokinetic parameters are derived from the plasma concentration vs. time plot. The area under the curve (AUC), the peak plasma concentration (Cmax) and the time to attain peak concentration (Tmax) can be obtained from these plots. The elimination rate constant (Kel) is determined from the semilogarithmic plot of plasma concentration vs. time. Elimination halflife (t1/2) can be calculated using the formula; t1/2 = 0.693/Kel.

Marketed Preparation [26, 27]

Table 2: Nasal drug products (proteins and peptides) for systemic drug delivery in the marke

Drug Substance (Product name)	Indication	Dosage form	Status	Manufacturer
Salmon calcitonin (Karil 200 I.E.)	Osteoporosis	Solution (spray)	Marketed	Novartis Pharma
Desmopressin (Minirin Nasenspray)	Antidiuretic hormone	Solution (spray)	Marketed	Ferring Arzneimitted
Buserelin (Profact nasal)	Buserelin	Solution (spray)	Marketed	Aventis Pharma
Nafarelin (Synarela)	Endometriosis	Solution (spray)	Marketed	Pharmacia
Oxytocin (Syntocinon)	Lactation induction	Solution (spray)	Marketed	Novartis Pharma
Protirelin (antepan* nasal) (Relefact* TRH nasal)	Thyroid diagnostics	Solution (spray)	Marketed	Aventis Pharma

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Table 3: Nasal Drug Products (Non Peptide) For Systemic Drug Delivery in the Market

Drug Substance (Product name)	Indication	Dosage form	Status	Manufacturer
Zolmitriptan (AscoTop* Nasal)	Migraine	Solution (spray)	Marketed	Astra Zeneca
Sumatriptan Imigran* Nasal	Migraine	Solution (spray)	Marketed	Glaxo SmithKline
Dihyfroergotamin (Migranal* Nasal Spray)	Migraine	Solution (spray)	Marketed	Novartis Pharma
Estradiol (Aerodiol*)	Hormone replacement	Solution (spray)	Marketed	Servier

II. CONCLUSION

The intranasal route is an reachable alternative route for drug administration. The development of drugs for directly target the brain in order to achieve a good therapeutic effect in CNS with reduced systemic side effects. It has advantages in terms of reduces systemic exposure and hence side effects and avoiding first-pass metabolism. Nasal spray drug products Contain active ingredients dissolved or suspended in Solutions or mixtures of excipients in nonpressurized dispenser that deliver a spray containing a metered Dose of the active ingredient. Vital characterization Test for nasal spray includes spray pattern, droplet size Distribution, spray .

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