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NASAL DRUG DELIVERY SYSTEM AN OVERVIEW

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ABSTRACT

Drug delivery through nasal route has attracted the interest of scientific community as it has been potentially explored as an alternative route for the administration of vaccines and bio molecules such as proteins, peptides and non-peptide drugs that are susceptible to enzymatic or acidic degradation and first-pass hepatic metabolism. Nasal route is beneficial for the drugs which are unstable on oral administration because they are significantly degraded in GIT or metabolized by first pass effect in liver. In addition it minimizes the lag time associated with oral drug delivery and offers noninvasiveness, self medication, patient comfort and patient compliance which are hurdled in intravenous drug therapy. In this article an overview of intranasal drug delivery with its various aspects like factors affecting nasal absorption, strategies to improve bioavailability are discussed.

KEYWORDS: Intranasal drug delivery, Bioavailability, Permeation enhancers.

INTRODUCTION

Historically, the use of the nasal route for drug delivery has received attention of mankind since ancient times. Nasal therapy, also called "NASAYA KARMA", has been recognized form of treatment in the Ayurvedic systems of Indian medicine. For the past few decades, the transdermal route has been selected for delivery of certain drugs. However, its use is limited due to low permeability of the skin to many drugs. Now a day, researchers have been on selected nasal mucosa as an alternate route to achieve faster and higher drug absorption.[1,2]

Nasal route is easily accessible, convenient, and a reliable with a porous endothelial membrane and a highly vascularized epithelium that provides a rapid absorption of compounds into the systemic circulation, avoiding the hepatic first pass elimination. In addition, intranasal drug delivery enables dose reduction, rapid attainment of therapeutic blood levels, quicker onset of pharmacological activity, and fewer side effects[3,4] In addition to that, nasal administration minimizes the lag time associated with oral drug delivery and offers noninvasiveness, self-administration, patient comfort, and patient compliance, which are the hurdles in intravenous drug therapy.[5] Intranasal delivery is non-invasive, essentially painless, does not require sterile preparation and it is easily and readily administered by the patient or a physician for e.g. in an emergency setting It is easily accessible and suitable for self-medication. The large surface area of the nasal mucosa affords a rapid onset of therapeutic effect, potential for direct-to central nervous system delivery, no first-pass metabolism, and non-invasiveness; all of which may maximize patien convenience, comfort, and compliance.[6,7] Drugs ranging from small chemicals to large macromolecules including peptide/protein therapeutics, hormones, and vaccines, are being delivered through the nasal cavity.[8,9] From extensive literature search, it can be considered that the nasal delivery is suitable for drugs with the following criteria:

- ineffective orally
- used chronically
- used in small doses
- rapid entry to the general circulation is desirable.[10,11]

ADVANTAGES OF NASAL DRUG DELIVERY SYSTEM[12-14,90]

- Availability of large nasal mucosal surface area for dose absorption.
- Non invasive and easy for administration.
- By pass the BBB.
- Nasal bioavailability of small drug molecules is good.
- Alternate to parenteral route especially for proteins and peptides.
- Side effects are reduced due to low dose.
- A self-administration is possible.
- Drug degradation that is observed in the gastrointestinal tract is absent.

LIMITATIONS OF NASAL DRUG DELIVERY SYSTEM[10-14]

- High molecular weight compounds cannot be delivered through this route (mass cut off ~1kDa).
- Smaller absorption surface compared with GIT.
- Volume that can be delivered into nasal cavity is restricted to 25-200 µl.
- Adversely affected by pathological conditions
- Nasal irritants drugs cannot be administered through this route
- Exact mechanism is not yet clearly.

PROFILE OF AN 'IDEAL' DRUG CANDIDATE FOR NASAL DELIVERY[15]

- Appropriate aqueous solubility to provide the desired dose in a 25–150 ml volume of formulation administration per nostril.
- 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.

ANATOMY AND PHYSIOLOGY OF NASAL CAVITY

Researchers became interested in the nasal route for the systemic delivery of medication due to a high degree of vascularization and permeability of the asal mucosa. 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.[16,17] The nasal passage which runs from the nasal vestibule to the nasopharynx has a depth of approximately 12- 14 cm. In this passage the nasal cellular apparatus is in close contact with mucus which protects the mucosa from the inspired air. There are 3 distinct functional zones in the nasal cavities, viz. vestibular, respiratory and olfactory regions.[18] The total surface area of both nasal cavities is about 150 cm2 and the total volume is about 15 ml. Approximately 1.5 cm from the nares (nostrils) is the narrowest portion of the entire airway, the internal ostium (or nasal valve) with a cross-sectional area of about 30 mm2 on each side. The nasal valve accounts for approximately 50% of the total resistance to respiratory airflow from the nostril to the alveoli.[19]

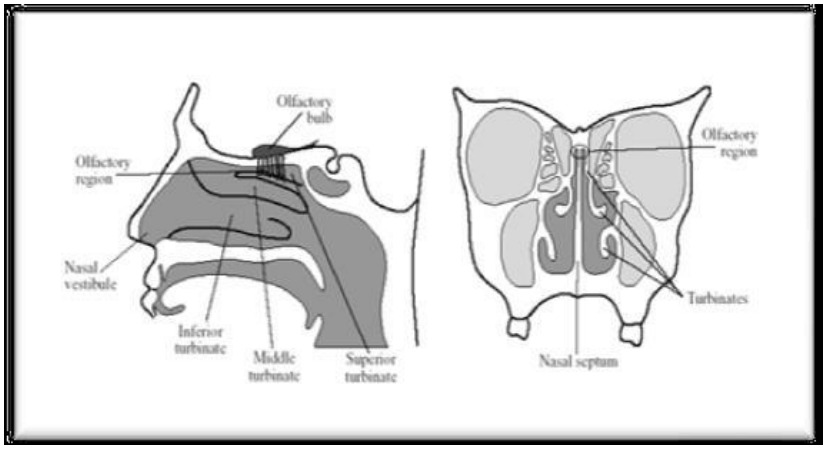

Fig 1: Anatomy of the nose (to the right is a cross-section of the nose).

The vestibular region

It is located at the opening of nasal passages and is mainly responsible for restricting entry of air borne particles.[4] In the nasal hairs (vibrissae) Epithelial cells are stratified, squamous and keratinized Sebaceous glands present. It is least permeable because of the presence of Keratinized cells.[18]

Atrium[18,20,21]

Transepithelial region Stratified squamous cells present anteriorly and pseudo stratified cells with microvilli present posteriorly. It is less permeable as it has small surface area and stratified cells are present anteriorly.

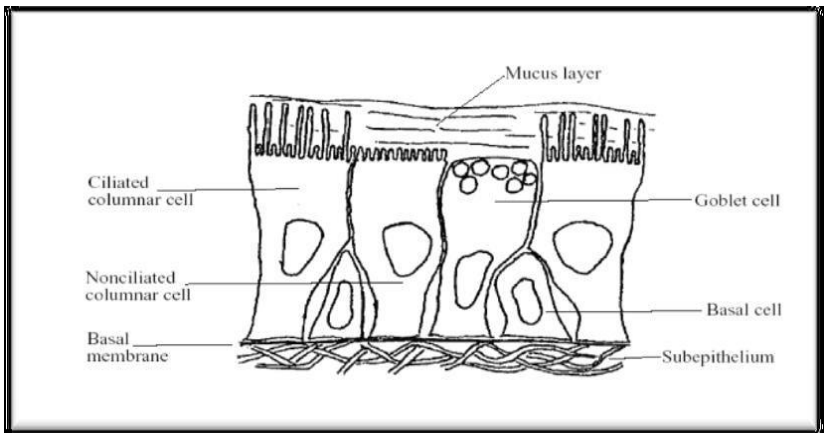

Fig 2: Respiratory epithelium of the nasal cavity, showing the four main types of cells

The olfactory region

The respiratory region

The respiratory region is the largest having the highest degree of vascularity. The respiratory region contains three nasal turbinates: superior, middle, and inferior which project from the

lateral wall of each of the nasal cavity.[22] Pseudostratified ciliated columnar cells with microvilli (300 per cell), large surface area. It receives maximum nasal secretions because of the presence of seromucus glands, nasolacrimal duct and goblet cells.It is richly supplied with blood for heating and humidification of inspired air, presence of paranasal sinuses. Most permeable region because of large surface area and rich vasculature.[18]

The olfactory region is situated between the nasal septum and the lateral walls of each of the two nasal cavities and just below the cribriform plate of the ethmoid bone separating the cranial cavity from nasal cavity.[23] Specialized ciliated olfactory nerve cells for smell perception. Receives ophthalmic and maxillary divisions of trigeminal nerve. Direct access to cerebrospinal fluid Direct access to cerebrospinal fluid.[18,20,21]

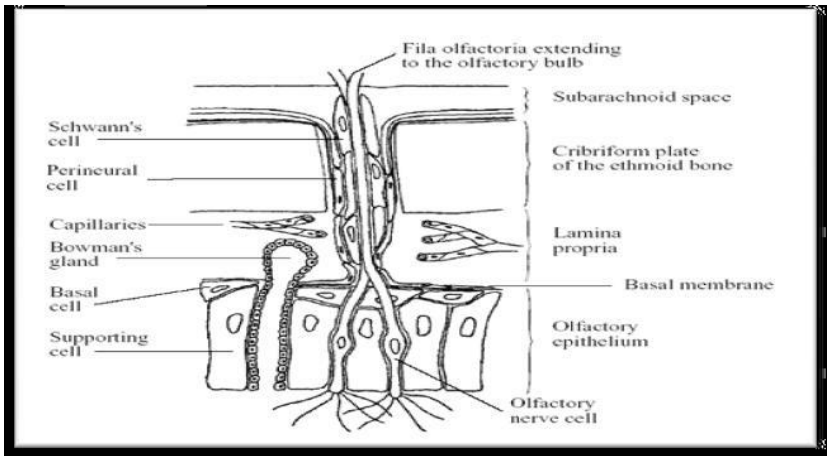

fig 3: Anatomical connections between the olfactory mucosa in the nose and the csf in the subarachnoid space outside the olfactory bulb.

Mucus membrane of nose and its composition[23]

viscous and dense, and an internal, fluid and serous. Overall, nasal mucus layer consists of 95% of water, 2.5-3% of mucin and 2% of electrolytes, proteins, lipids, bacterial products.

Epithelial cells[23]

basically there are two functions of these cells,

1. Provide a physical barrier to the invasion of infectious microorganisms and allergic particles;
2. Work in conjunction with mucus glands and cilia tsecrete and remove mucus and foreign particles from the nasal cavity.

Blood supply to nasal cavity[13,24]

Nasal vasculature is richly supplied with blood to fulfill the basic functions of the nasal cavity such as heating and humidification, olfaction, mucociliary clearance and immunological functions. Blood supply comes from branches of both the internal and external carotid artery

including branches of the facial artery and maxillary artery. The named arteries of the noseare,

- **Sphenopalatine artery**, a branch of maxillary artery.
- **Anterior ethmoidal artery**, a branch of ophthalmic artery.
- **Branches of the facial artery** supplying the vestibule of the nasal cavity.

MECHANISM OF DRUG ABSORPTION THROUGH NOSE

The first step in the absorption of drug from the nasal cavity is passage through the mucus. Small unchanged particles easily pass through this layer. However, large or charged particles may find it more difficult to cross. These include transcellular or simple diffusion across the membrane, paracellular transport *via* movement between cell and transcytosis by vesicle carriers.[25]

- The first mechanism involves an aqueous route of transport, which is also known as the paracellular route. This route is slow and passive. Poor bio-availability was observed for drugs with a molecular weight greater than 1000 Daltons.[26]
- The second mechanism involves transport through a lipoidal route that is also known as the transcellular process and is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. Drugs also cross cell membranes by an active transport route *via* carrier-mediated means or transport through the opening of tight junctions.[27]

DIFFERENT FACTORS AFFECTING NASAL DRUG ABSORPTION

Various factors affect bioavailability of nasally administered drugs as follows;

i Biological factors

• Structural features

• Biochemical changes

ii Physiological factors

• Blood supply and neuronal regulation Nasal secretions

• Mucociliary clearance and ciliary beat frequency
• Pathological conditions
• Environmental conditions.
• Membrane permeability.

iii Physicochemical properties of drugs

• Molecular weight
• Size
• Solubility
• Lipophilicity
• pka and Partition coefficient
• Chemical form of drug.
• Polymorphism.
• Chemical state.
• Physical state.

iv Physicochemical properties of formulation

• Physical form of formulation
• pH
• Osmolarity
• Volume of solution applied and drug concentration
• Viscosity.

I Biological factors

Structural features

There are five different sections of nasal cavity: nasal vestibule, atrium, respiratory area, olfactory region and the nasopharnyx. 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.[28]

Biochemical changes

Drugs nasally administered circumvent gastrointestinal and hepatic first-pass effect. However ,they may be significantly metabolized in lumen of nasal cavity or during the passage across the nasal epithelial barrier due to the presence of cytochrome P450 dependent monoxygenase, lactate dehydrogenase, oxidoreductase, hydrolases, acid phosphatase and esterase. It has been

reported that cytochrome P450 isoenzymes metabolized the drug such as cocaine, nicotine, alcohols, progesterone and decongestants.[29] Protease and peptidase were responsible for the presystemic degradation and subsequent lower permeation of various peptide drugs, such as calcitonin, insulin, LHRH and desmopressin.[30]

ii Physiological factors

Blood supply and neuronal regulation[31-33]

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

Nasal secretions[34]

Nasal secretions are produced by anterior serous and seromucus glands. Mucus production is approximately 1.5–2 l ml daily.

- **Viscosity of nasal secretion** The viscous surface layer will inhibit the ciliary beating
- **Solubility of drug in nasal secretions** For permeation of drug solublisation is necessary.
- **Diurnal variation** Nasal secretions are also affected by circadian rhythm.
- **pH of nasal cavity** variation in pH is observed between 5.5–6.5 in adults and 5.0–7.0 in infants.

Mucociliary clearance[35,36]

The function of mucociliary clearance system is to remove foreign substances and particles from the nasal cavity, consequently preventing them from reaching the lower airways. Nasally administered formulation can be cleared from the nasal cavity with a half-life of clearance of about 15 min with the result of limiting time available for absorption. The normal mucociliary transit time in humans has been reported to be 12-15 min.

Effect of pathological condition

Intranasal pathologies may affect the nasal mucociliary transport process and/or capacity for nasal absorption[37] Common cold, rhinitis and other pathological conditions cause changes in mucociliary clearance affecting nasal absorption of drug. Also hypo and hyper secretion of nasal mucosa influence the drug permeation.[38]

Environmental conditions

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

Membrane permeability[39,40]

Nasal membrane permeability is the most important factor, which affect the absorption of the drug through the nasal route. The water soluble drugs and particu-larly large molecular weight drugs like peptides and proteins are having the low membrane permeability. So the compounds like peptides and proteins are main-ly absorbed through the endocytotic transport process in low amounts.

iii Physicochemical properties of drug

Molecular weight [41]

A linear inverse correlation has been reported between the absorption of drugs and molecular weight upto 300 Da. Absorption decreases significantly if the molecular weight is greater than 1000 Da except with the use of absorption enhancers. Linear molecules have lower absorption than cyclic – shaped molecules.

Particle size[41]

It has been reported that particle sizes greater than 10μm are deposited in the nasal cavity. The lipophilic drugs have direct relationship between the MW and drug permeation whereas watersoluble compounds depict an inverse relationship.

Lipophilicity

Absorption of drug substance through biological membrane may be dependent on hydrophilic lipophilic balance of the compound. On increasing lipophilicity, the nasal absoption of the compound normally increases[44,45] Lipophilic compounds tend to readily cross biological membranes via the transcellular route since they are able to partition into the lipid (bilayer) of the cell membrane and diffuse into and traverse the cell in the cell cytoplasm[46] A number of lipophilic drugs such as naloxone, buprenorphine, testosterone and 17a-ethinyloestradiol, have been shown to be completely or almost completely absorbed nasally in animal models.[47,48]

pKa and the partition coefficient of drug[49,50]

The nasal membrane is predominantly lipophilic, hence, the rate and extent of absorption of adrug across a biological membrane is influenced by its lipophilicity. Normally, the permeation of the compound through nasal mucosa increases with increasing lipophilicity . Low molecular weight lipophilic drugs are absorbed quite efficiently across the nasal epithelium, whereas larger hydrophilic drugs, such as peptides and proteins, have substantially lower bioavailability because they are not easily transported across nasal membrane thereby enhancing mucociliary clearance.

Chemical state: prodrugs[15,51]

The chemical form in which a drug is presented at the nasal mucosa can be important in determining its absorption. If a drug does not have the desired absorption properties, several options can be considered to improve the drug's delivery. Prodrug technique has been employed to increase the lipophilicity.

Polymorphism [15]

Polymorphism is known to affect dissolution of drugs and their absorption through biological membranes. The effect of polymorphism on the nasal drug absorption has not been explored to date. However, in view of the information available on other biological membranes, this factor should be considered.

Chemical state of drug[15]

Absorption of the drug is determined by the chemical form of the drug in which it is presented to nasal mucosa. The prodrug approach provides many additional challenges which need to be overcome in the drug product developmental process.

Physical state of drug[15]

Particle size and morphology of drug are two main important properties for particulate nasal drug products. Generally, particles in the 5–10 micron range are deposited in the nostrils.

vi Physicochemical properties of formulation:

Physical form of formulation

Solution and suspension type of nasal drops are preferred over powders as powders cause irritation to nasal mucosa. Nasal gels and nasal in-situ gels are preferred over low viscosity nasal drops as the gels reduce mucociliary clearance, postnasal drip, anterior leakage and

localize drug in nasal mucosa to enhance nasal residence Leading to increased permeation of drug.

pH of the formulation

Both the pH of the nasal cavity and pKa of a particular drug need to be considered to optimize systemic absorption. Nasal irritation is minimized when products are delivered with a pH range of 4.5 to 6.5. The delivery volume is limited by the size of the nasal cavity. An upper limit of 25 mg/dose and a volume of 25 to 200 µL/ nostril have been suggested.

Osmolarity [25]

Drug absorption can be affected by tonicity of formulation. Shrinkage of epithelial cells has been observed in the presence of hypertonic solutions. Hypertonic saline solutions also inhibit or cease ciliary activity. Low pH has a similar effect as that of a hypertonic solution.

Drug concentration, dose and volume of administration[23]

There should be clear positive relationship between absorption and drug concentration upto a certain level. Such a relationship is not always observed. In general, higher nasal absorption or therapeutic effect was observed with increasing dose. If the dose is increased by increasing formulation volume, there may be a limit as to what extent nasal absorption can be increased. The nostrils can remain only a limited volume, beyond which a formulation will drain out of the nasal cavity. The ideal dose volume range is 0.05-0.15 ml with an upper limit of 0.20 ml.

Viscosity

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

THERAPEUTIC CONSIDERATIONS

1. Local delivery[60]

IN is a logical delivery choice for local (or topical) treatment. Prominent examples are decongestants for nasal cold symptoms, and antihistamines and corticosteroids for allergic rhinitis.

2. Systemic delivery[61]

Positive attributes of IN systemic delivery include a relatively large surface area for drug absorption, rapid drug onset, no first-pass metabolism, and non-invasiveness to maximize patient comfort and compliance. In administration provides an alternative route for systemic delivery of drugs more conventionally delivered by oral or (for poorly orally absorbed compounds such as peptides and proteins) injection routes.

3. Chronic versus acute therapeutic use[63]

When deciding on a delivery route, it is important to consider the dosing regimen for the drug. For an acute indication, the advantage of patient comfort and compliance afforded by IN dosing (as compared with injections) may not be a major factor. Even so, there are advantages to IN dosing in certain acute situations.

4. Vaccine delivery[64]

The nasal mucosa has received some attention as a vaccination route. Presentation of a suitable antigen with an appropriate adjuvant to the nasal-associated lymphoid tissue (NALT) has the potential to induce humoral and cellular immune responses. This approach may be a particularly effective approach to achieving rapid mass immunization, for instance in children and/or in developing countries and disaster areas.

5. Nose to brain delivery[65]

IN delivery of drugs targeting the central nervous system (CNS) is currently an area of great interest.

6. Nasal delivery of peptides and proteins[66]

 Nasal salmon calcitonin Marketed by Novartis Novel nasal formulations under development by other pharmaceutical companies

 Nasal desmopressin Marketed by Ferring and partners

 Nasal buserelin Marketed by Aventis

 Nasal nafarelin Marketed by Searle

 Nasal PTH, nasal leuprolide, nasal insulin, nasal interferon, etc. In clinical trials.

EXCIPIENTS USED IN NASAL FORMULATIONS

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

Gelling agents[67-69]

Retention of the nasal formulation in the nasal cavity can enhance therapeutic effect by virtue of enhancing rate and extent of drug absorption. A drug carrier, hydroxyl-propylcellulose was effective for improving the absorptionof low molecular weight drugs.

Buffer capacity

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 administered dose. This can affect the concentration of unionized drug available for absorption. Therefore, an adequate formulation buffer capacity may be required to maintain the pH.

Bioadhesive polymers[13]

Compound that is capable of interacting with biological material through interfacial forces and being retained on such material for prolonged periods of time is called as bioadhesive polymer. They are also called as mucoadhesive if biological material is mucus membrane,. On molecular level, process of 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).

Table1 : Bioadhesive polymer used in NDDS

Cellulose derivatives Soluble: hydroxypropyl methylcellulose, hydroxypropyl cellulose(HPC),methyl cellulose(MC), carboxymethyl cellulose(CMC) Insoluble: ethylcellulose, microcrystalline cellulose(MCC)	-Prolong the residence time of drug in nasal cavity -Sustain the release of drug due to high viscosity -Act as absorption enhancer - Effectively increase intranasal bioavailability
Polyacrylates -Carbomers -Polycarbophils	-Excellent mucoadhesive and gel forming capability -Capable of attaching to mucosal surfaces hence ensure intimate contact between the formulation and membrane surface
Starch -Maize starch -Degradable starch microspheres (DSM)	-Effectively improve absorption of both small hydrophobic and hydrophilic macromolecular drugs -Mostly used in mucoadhesive microparticulate nasa l delivery system
Chitosan	-Insoluble at neutral and alkaline Ph -It can form water soluble salts with inorganic and organic acids -Low cost, Biodegradable and Biocompatible

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 C8- C10 glyceride) can be used to enhance the solubility of drugs.

Preservatives

Most nasal formulations are aqueous based and need preservatives to prevent microbial growth. Parabens, benzalkonium chloride, phenyl ethyl alcohol, EDTA and benzyl alcohol are some of the commonly used preservatives in nasal formulations.

Antioxidants

Depending upon the stability profile of a given drug in the formulation chosen, it may be necessary to use antioxidants to prevent drug degradation. Commonly used antioxidants are sodium metabisulfite, sodium bisulfite, butylated hydroxy toluene and tocopherol.

Humectants[78]

Adequate intranasal moisture is essential for preventing dehydration. Therefore, humectants can be added especially in gel based nasal products to avoid nasal irritation and are not likely to affect drug absorption Some common humectants used includeglycerin, sorbitol and mannitol

Surfactants[79]

Surfactants such as bile salts are mostly used and several other promoters are also investigated subsequently. Non-ionic and anaionic surfactants including bile salts were found to enhance the nasal absorption of the drugs by multiple mechanisms such as alteration of the mucous layer, opening of the tight junctions between the epithelial cells, reversed micelle formation in the membrane, extraction of membrane components by co-micellisation and inhibitory effects on proteolytic enzymes.

Permeation enhancers[70-78]

Small and large hydrophilic drugs may be poorly permeable across nasal epithelium and may show an insufficient bioavailability. Their permeation can improve by administered in combination with absorption enhancers which induce reversible modifications on the structure of epithelial barrier.

Table 2: Mucosal penetration enhancers and mechanisms of action

Classification	Examples	Mechanism
Surfactants	**Anionic:** Sodium lauryl sulphate **Cationic:** Cetylpyridinium Chloride **Nonionic:** Poloxamer, Span, Tween	Perturbation of intercellular lipids, Protein domain integrity, Distrusts membrane,
Bile salts	Sodium glycodeoxycholate, Sodium glycocholate, Sodium taurodeoxycholate,	Distrusts membrane, Open tight junctions, Mucolytic activity
Cyclodextrins	α, β, γ Cyclodextrin, Methylated β–Cyclodextrins	Inclusion of membrane Compounds, Open Tight junctions
Fatty acids	Oleic acid ,Lauric acid, Caprylic acid, Phosphotidylcholine	Increase fluidity of phospholipid domains, Distrusts membrane
Cationic Compounds	Poly-L-arginine, L-lysine	Ionic interaction with negative charge on the mucosal surface
Chelators	EDTA, Citric Acid, Sodium citrate,	Interfere with Ca Polyacrylates
+ Ve Charged polymers	Chitosan, Trimethyl chitosan	Ionic interaction with negative charge on the mucosal surface

FORMULATIONS BASED ON NASAL DELIVERY SYSTEM [69,80]

Liquid dosage forms

Nasal drops

Nasal drops are one of the most simple and convenient delivery systems among all formulations. The main disadvantage of this system is the lack of dose precision.

Nasal sprays [82]

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 anywhere from 25 to 200 µL Solution and suspension sprays are preferred over powder sprays because powder results in mucosal irritation.

Nasal emulsions, microemulsions and nanoparticles [81]

Intranasal emulsions and nanoparticles have not been studied as extensively as other liquid nasal delivery systems. Nasal emulsions offer the advantages for local application mainly due to the viscosity. One of the major disadvantages is poor patient acceptability.

Semi-solid dosage forms: Semi-solid systems, for example gels, ointments and liquid systems containing polymers that gel at particular pH changes are usually employed for designing the nasal drug delivery systems.

Nasal gels[83]

Nasal gels are thickened solutions or suspensions, of high-viscosity. The advantages of a nasal gel include the reduction of post-nasal dripping due to its high viscosity, reduction of the 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 the mucosa for better absorption.

Solid dosage forms

Solid dosage forms are also becoming popular for intranasal drug delivery, although these formulations are more suitable for pulmonary drug delivery and similar applications, since it can cover the vasculature within the epithelium of nasal mucosa.

Nasal powders [26]

Powder dosage forms may be developed if solution and suspension dosage forms cannot be developed, mainly due to lack of drug stability. The advantages of a nasal powder dosage form are the absence of preservative and superior stability of the drug in 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. An additional advantage of this system is local application ofdrug.

Novel drug formulations

Several claims have been made in favour of developing nasal formulations containing liposomes, microspheres and nanoparticles for intranasal drug delivery. These systems can include, besides the drug, enzymatic inhibitors, nasal absorption enhancers or/and mucoadhesive polymers in order to improve the stability, membrane penetration and retention time in nasal cavity.

Liposomes[83]

Liposomes are non-toxic, biodegradable and biocompatible lipid carrier made up of animal lipid such as phospholipids and sphingolipid. They having advantage of carrying hydrophilic, lipophilic and amphoteric drug molecules entrapped inside or on its micellar surface. Mostly lipids are used in liposomal drug delivery are phospholipids which forms self sustained bilayer structure to form liposomes of various size such as small unilamellar vesicles to multilamellar vesicles. The basic mechanism by which liposomes achieve brain concentration

by crossing brain brain barrier is by coupling with brain drug transporter vector through absorptive mediated transcytosis.

Nanoparticles[84]

Nanoparticles are solid colloidal particles with diameters raging from 1-1000 nm. They consist of macromolecular materials and can be therapeutically used as adjuvant in vaccines or as drug carriers, in which the active substance is dissolved, entrapped, encapsulated, adsorbed or chemically attached.The smaller size is advantageous for the nanoparticles, but by the paracellular route smallest nanoparticles penetrate the mucosal membrane and in a limited quantity because the tight junctions are in the order of 3.9-8.4 A.

Microspheres[84]

for nasal drug delivery microsphere technology has been widely applied in formulation desining. Microspheres are usually based on mucoadhesive polymers (chitosan, alginate), which present advantages for intranasal drug delivery. Furthermore, microspheres may also protect the drug from enzymatic metabolism and sustain drug release, prolonging its effect.

Microemulsions[85]

Microemulsions are clear, stable, isotropic mixtures of oil, water and surfactant, frequently in combination with a co surfactant. They offer the advantage of spontaneous formation, ease of manufacturing and scale-up, thermodynamic stability, and improved drug solubilization and bioavailability.

EVALUATION OF NASAL DRUG FORMULATIONS

In vitro nasal permeation studies[69,86]

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 away that it just touches the diffusion medium in recipient chamber. At predetermind time intervals sample with drawn [0.5ml] from recipient chamber and store in to amber colored ampoules. For the estimation of drug suitable analytical method applied. . 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 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

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.

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 grouptreated 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 half-life (t1/2) can be calculated using the formula; t1/2 = 0.693/Kel.

MARKETED PREPARATION

Table 3: Nasal drug products (proteins and peptides) for systemic drug delivery in the market[2]

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

Table 4: Nasal drug products (non peptide) for systemic drug delivery in the market[2]

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

Table 5: Nasal drug product for vaccination available in the market[87-89]

Vaccine (Product name)	Dosage form	Status	Manufacturer
Human influenza vaccine (Nasalflu Berna)	Virosomes (Spray)	Marketed (withdrawn)	Berna Biotech
Equine influenza vaccine (Flu Avert)	Drops	Marketed	Heska
Feline Bordetella bronchiseptica vaccine (Nobivac Bp)	Suspension drops	Marketed	Intervet
Human Streptococcus A vaccine (StrepAvax)	Proteosomes (nanoparticulate)	Phase 2	ID Biomedical

CONCLUSION

Nasal drug delivery is a novel promising alternative to inject able route of administration. There is vast scope in nearest future that more drug candidates will come in global market in the form of nasal formulation for systemic treatment. Several factors influence the development of drug with a drug delivery system. For the treatment of major issues such as diabetes, osteopossrosis, fertility treatment novel nasal products are also expected to be marketed. The major challenge in the nasal product development is Bioavailability of the

nasal product. In the contradictory scenario a huge of amount of money is invested by the pharmaceutical companies in the development of nasal product, because of high growing demand of nasal products in the global pharmaceutical market. Hence for the avoidance of adverse effects and improve effectiveness of nasal product we should pay attention to basic research in nasal drug delivery.

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