IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

NASAL ROUTES OF DRUG DELIVERY: A CREATIVE APPROACH

[1]Jeevan R. Rajguru, [2]Priti B. Shinde, [3]Sanket P. Shinde, [4]Komal A. Humbe,

[5]Priyanka P. Pawar

[1,4]DEPARTMENT OF PHARMACEUTICS, DELIGHT INSTITUTE OF PHARMACY, PUNE MH

[2]DEPARTMENT OF PHARMACEUTICS, DELIGHT COLLEGE OF PHARMACY, PUNE MH

[3-5]DEPARTMENT OF QAT, DELIGHT COLLEGE OF PHARMACY, PUNE MH

ABSTRACT:

An alternate approach for the systemic availability of medications restricted to intravenous administration is nasal drug administration. Large surface area, porous endothelium membrane, high total blood flow, lack of first-pass metabolism, and easy accessibility are the causes of this. A useful long-term therapeutic option to parenteral medication is the nasal route. Because the nasal mucosa is so porous and highly vascularized, it absorbs substances quickly and acts quickly. Since the medication enters the bloodstream immediately through the nasal route, it is a non-invasive, often utilised local therapeutic method that can also be utilised for systemic therapy. Small chemicals are better absorbed through the nasal route than large molecules, which can be enhanced by absorption promoters. This article discusses techniques to increase bioavailability and provides an overview of intranasal drug administration, including factors affecting nasal absorption.

KEYWORDS: Nasal Drug Delivery, Systemic Circulation, Bioavailability, Permeation Enhancers

I. INTRODUCTION

The nasal mucosa is recognized as a potential route for drug administration to achieve quicker and more efficient drug absorption. Unlike the gastrointestinal mucosa, the nasal mucosa allows permeability to a wider range of compounds because of the absence of pancreatic and gastric enzymatic activity, the neutral pH of nasal mucus, and reduced dilution by gastrointestinal contents. Nasal drug delivery has been practiced for millennia. The nasal route is particularly effective for drugs with high potency (active in low doses) and minimal oral bioavailability, such as proteins and peptides. However, peptides and proteins face challenges in nasal absorption as they quickly move away from the absorption site in the nasal cavity due to the mucociliary clearance mechanism.

The ideal properties NDD:

- It should exhibit appropriate aqueous solubility to provide the desired dose in a 25-150ml volume of formulation administration per nostril.
- It should exhibit appropriate nasal absorption properties.
- It should not produce nasal irritation.
- It should exhibit appropriate clinical rationale for nasal dosage forms, e.g., rapid onset of action.
- It should be potent, i.e., should be effective below 25mg per dose.
- It should not produce toxic nasal metabolites.
- It should not exhibit offensive odour/smell.
- It should exhibit appropriate stability characteristics.

Advantages NDD:

- Drug absorption through this route is rapid due to highly vascularised mucosa.
- A large nasal mucosal surface area is available for drug absorption.
- Its onset of action is rapid.
- It is a non-invasive technique and the drugs can be easily administered.
- It bypasses the blood-brain barrier.
- It does not undergo degradation in GIT.
- It does not undergo hepatic first pass metabolism.
- It shows improved bioavailability.
- Small drug molecules exhibit good nasal bioavailability.
- Bioavailability of large drug molecules can be increased by adding absorption enhancers in the formulation.

Disadvantages NDD:

- The drug delivery volume in nasal cavity is restricted to 25-200l.
- Drugs with high molecular weight (mass cut off ~1 kDa) cannot be delivered through this route.
- This route is adversely affected by pathological conditions.
- Large interspecies variability is observed in this route.
- Drug permeability is affected by normal defence mechanisms, like mucociliary clearance and ciliary beating.
- Some drugs, like Budesonide and Azilactine, irritate the nasal mucosa.
- Systemic toxicity occurs due to the absorption enhancers added in the formulation.
- The absorption surface is smaller than that of the GIT.

II. ANATOMY AND PHYSIOLOGY OF NOSE:

The nose is the primary entrance to the respiratory tract, allowing air to enter into the body for respiration. The nasal cavity is 120-140 mm deep, runs from the nasal vestibule to the nasopharynx and is divided into two by a cartilaginous wall called nasal septum. The nose has a surface area of around 160 cm2 and a total volume of ~16-19 ml. The nose serves as the mean of bringing warm humidified air into the lungs. It is the primary organ for filtering out particles in the inspired air, and it also serves to provide a first-line immunologic defence as it brings the inspired air into contact with the mucous-coated membrane. The nose has three main regions: vestibular, turbinate and olfactory regions (Figure 1). The vestibular region is the anterior part of the nose and it is the narrowest part of the nasal cavity. The vibrissae cover most of this area which renders it capable of filtering out particles with an aerodynamic particle size larger than 10 cm that may be inhaled with air. In the vestibular region, the surface lining changes from skin, at the first part of the passage, to a stratified squamous epithelium. The turbinate region is a large vascular part of the nose and can be divided into superior, middle and inferior regions (Figure 1). It is lined with a pseudostratified columnar epithelium. It is composed of mucus secreting, ciliated, non-ciliated and basal cells (Figure 2). The ciliated and non-ciliated cells are covered with non-motile microvilli, which are responsible for increasing the surface area, thus, this is the region where the drug absorption is optimal. Ciliated cells are covered with approximately 100 motile cilia which are responsible for mucus transport so mucociliary clearance prevails. Once drug (as particles or in solution) find their way to the mucociliary area, they will be cleared from nasal cavity and then have limited access to the absorption site.

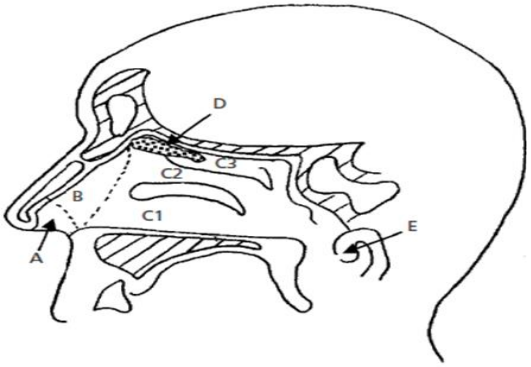


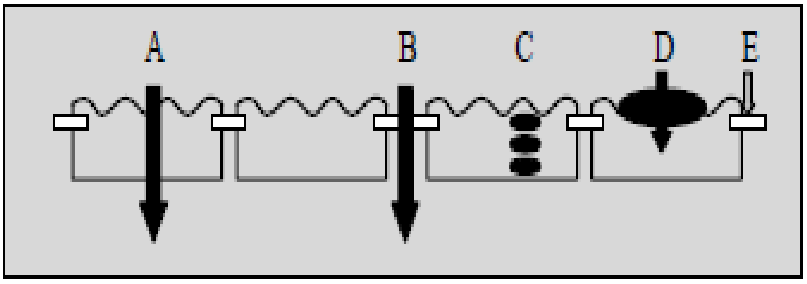
Figure 1: Sagittal section of the nasal cavity showing the nasal vestibule (A), atrium (B), respiratory area: inferior turbinate (C1), middle turbinate (C2) and the superior turbinate (C3), the olfactory region (D) and nasopharynx (E). Reproduced with permission from reference.

III. MECHANISM OF DRUG ABSORPTION FROM NOSE:

When a substance is absorbed from the nasal cavity, it initially traverses the mucus layer. While larger or charged particles encounter difficulty in this passage, smaller or uncharged particles can readily traverse the mucus layer. The absorption through nasal mucosa employs mechanisms such as paracellular transport (movement between cells) and transcellular or simple diffusion (movement across the cell membrane):

- The initial mechanism entails a slow and passive aqueous transport route, also known as the paracellular route. Substances with a molecular weight exceeding 1000 Daltons exhibit limited bioavailability through this route, as there is an inverse relationship between molecular weight and absorption.
- The second mechanism involves a transcellular process, specifically transport through a lipoidal route. Lipophilic drugs, whose transport rate depends on their lipophilicity, utilize this process. Additionally, substances can traverse cell membranes through an active transport route facilitated by carrier-mediated transport, opening tight junctions. For instance, the natural biopolymer chitosan facilitates drug transport by opening tight junctions between epithelial cells.

Figure 2: Drug Transport Pathways across the Epithelium**.**



(A) Paracellular Transport, (B) Transcytosis, (C) Carrier-Mediated Transport, and (D) Intercellular Tight Junction

IV. FACTORS INFLUENCING NASAL DRUG ABSORPTION:

The systemic bioavailability of drugs administered through the nasal route is influenced by various factors, all of which contribute significantly to achieving therapeutic blood levels upon nasal administration. These factors encompass the physiochemical properties of the drugs, anatomical and physiological characteristics of the nasal cavity, and the specific attributes of the chosen nasal drug delivery system.

a) Physiochemical Properties of Drug:

i) Molecular Size:

Drug absorption via the nasal route is subject to the molecular size of the drug. The absorption pattern is directly proportional for lipophilic drugs concerning their molecular weight, while it is inversely proportional for water-soluble drugs. Notably, the permeation rate is particularly sensitive to drugs with a molecular weight of ≥300 Daltons.

ii) Lipophilic-Hydrophilic Balance:

The hydrophilic and lipophilic nature of a drug also affects its absorption. An increase in the lipophilicity of a drug enhances its permeation through the nasal mucosa. Despite the generally hydrophilic nature of nasal mucosa, it is primarily lipophilic, with the lipid domain playing a crucial role in its barrier function.

iii) Enzymatic Degradation in Nasal Cavity:

Peptides and proteins, owing to their low bioavailability across the nasal cavity, may undergo enzymatic degradation either in the nasal cavity lumen or while traversing the epithelial barrier.

b) Nasal Effect Factors:

i) Nasal Membrane Permeability:
The permeability of the nasal membrane significantly influences drug absorption through the nasal route. Water-soluble drugs and large molecular weight drugs, such as peptides and proteins, exhibit low membrane permeability, resulting in limited absorption through endocytotic transport mechanisms.

ii) Environmental pH:
The efficiency of drug absorption through the nasal route is also impacted by the environmental pH. Studies have shown that in rats, optimal nasal absorption of small water-soluble drugs occurs when these compounds are in their non-ionized form at specific pH values.

iii) Mucociliary Clearance:
Mucociliary clearance, a protective function of the upper respiratory tract, prevents the entry of harmful substances into the lungs. Materials adhering to or dissolving in the nasal cavity's mucus lining are transported towards the nasopharynx and subsequently discharged into the gastrointestinal tract.

iv) Cold, Rhinitis:

Rhinitis commonly affects drug bioavailability. It is primarily categorized into allergic rhinitis, with symptoms such as hypersecretion, itching, and sneezing caused by viruses, bacteria, or irritants.

c) Delivery Effect Factors:

The delivery of drugs across the nasal mucosa is influenced by surfactants, dose pH, osmolarity, viscosity, particle size, nasal clearance, and drug structure. These factors contribute to the enhancement of drug absorption:

i) Formulation (pH, Concentration, and Osmolarity):

Drug permeation can be impacted by the pH of the formulation and nasal surface. The pH of nasal formulations should range between 4.5 and 6.5 to prevent nasal irritation, as lysozyme in nasal secretions destroys certain bacteria under acidic conditions. Conversely, under alkaline conditions, lysozyme is inactivated, rendering the tissue vulnerable to microbial infection. In addition to preventing irritation, maintaining this pH range promotes efficient drug permeation and inhibits bacterial growth. Concentration gradient plays a significant role in the absorption or permeation of drugs through the nasal membrane due to nasal mucosal damage.

ii) Drug Distribution and Deposition:

The efficiency of nasal absorption is influenced by the distribution of the drug in the nasal cavity. Drug distribution in the nasal cavity is also affected by the mode of drug administration, ultimately determining the absorption efficiency of the drug. The absorption and bioavailability of nasal dosage forms depend on the disposition site.

iii) Viscosity:

A formulation with high viscosity prolongs the contact time between the drug and the nasal mucosa, thereby increasing the permeation time. High-viscosity formulations also disrupt normal functions, such as ciliary beating or mucociliary clearance, and alter drug permeability.

V. BARRIERS TO NASAL ABSORPTION:

Nasal drug delivery system is a profitable route for the formulation scientists due to its easy and simple formulation strategies. Therapeutic efficacy and toxicity of the drugs administered intranasally are influenced by the barriers to the absorption of drugs through nasal cavity:

a) Low Bioavailability:

Absorption of lipophilic drugs from the nasal cavity is much more than that of polar drugs. Pharmacokinetic profiles of lipophilic drugs are similar to those obtained after an intravenous injection and bioavailability approaching 100%. For example, both intravenous and nasal administration of Fentanyl reaches its tmax very rapidly (7 minutes or less) and its bioavailability for anterior chamber of nasal cavity can decrease clear administration was near 80%.

Table 1: Enlists the strategies for improving nasal bioavailability of drugs:

Nasal enzyme inhibitors	e.g., bestatin, amastatin, boroleucine, fusidic acids, and bile salts.
Nasal permeation enhancers	e.g., cyclodextrins, surfactants, saponins, fusidic acids, and phospholipids
Prodrug approach	e.g., cyclic prodrug, esters, and derivatisation of C and N termini
Nasal mucoadhesives in nasal drug delivery	e.g., carbopol, polycarbophil, cellulose derivatives, lecithin, and chitosan.
Particulate drug delivery	e.g.microspheres, nanoparticles, and liposomes.

b) Low Membrane Transport:
This crucial factor involves the swift removal of administered formulations (drugs that are not readily absorbed across the nasal membrane) from the nasal cavity due to the mucociliary clearance mechanism. Research indicates that the half-life of clearance for non-mucoadhesive liquid and powder formulations is approximately 15-20 minutes.

c) Enzymatic Degradation:
This factor plays a contributory yet less significant role in the transport of peptides and proteins across the nasal membrane due to the potential enzymatic degradation of the molecule either within the nasal cavity lumen or while traversing the epithelial barrier. These sites harbor exopeptidases (e.g., mono- and diaminopeptidases) capable of cleaving peptides at their N- and C-termini and endopeptidases (e.g., serine and cysteine) capable of attacking internal peptide bonds.

VI. STRATEGIES TO ENHANCE NASAL ABSORPTION:

Approaches aimed at improving the bioavailability of drugs in the nasal mucosa encompass:
a) Prolonging nasal residence time,
b) Augmenting nasal absorption, and
c) Modifying drug structure to alter physicochemical properties.
A single approach or a combination of the aforementioned strategies is employed to enhance the absorption and bioavailability of nasal formulations.
The following methods have been adopted to facilitate nasal absorption of drugs:

a) Nasal Enzyme Inhibitors:
These are employed to hinder nasal metabolism of drugs. Development of enzyme inhibitors, such as peptidases and proteases, is used for protein and peptide formulations. Absorption enhancers, including salts and fusidic acid derivatives, exhibit enzyme inhibition activity to elevate the absorption and bioavailability of drugs. Examples of commonly used enzyme inhibitors include trypsin, aprotinin, borovaline, amastatin, bestatin, and boroleucin.

b) Permeation Enhancers:
These are utilized to amplify the absorption of the active drug. Absorption enhancers operate through one of the following mechanisms:
i) Inhibition of enzyme activity,
ii) Reduction of mucus viscosity or elasticity,
iii) Diminution of mucociliary clearance,
iv) Opening of tight junctions, and
v) Solubilization or stabilization of the drug.
The action mechanism of absorption enhancers involves accelerating the rate at which the drug passes through the nasal mucosa. Many enhancers modify the structure of epithelial cells in a way that causes neither damage nor permanent alteration to the nasal mucosa.

An ideal permeation enhancer should possess specific attributes to ensure optimal performance:

i) It must effectively enhance drug absorption.

ii) It should avoid causing any harm or permanent alterations to tissues.

iii) Non-irritation and non-toxicity are essential characteristics.

iv) Effectiveness in small quantities is a key requirement.

v) The enhancer should exert its effect when absorption is necessary.

vi) Temporary and reversible effects are preferred.

vii) Compatibility with other excipients is crucial.

Various permeation enhancers evaluated for organic drugs include surfactants, bile salts, chelators, fatty acid salts, phospholipids, glycyrrhetinic acid derivatives, cyclodextrins, and glycols.

c) Prodrug Approach:

This strategy aims to optimize physicochemical properties (e.g., solubility, taste, odor, stability) by using a promoiety to mask undesired functional groups. This approach enhances nasal bioavailability for proteins and peptides, improving membrane permeability and enzymatic stability. Enamine derivatives, employed in the prodrug approach, enhance the absorption of peptides like angiotensin II, bradykinin, cauline, carnosine, enkephalin, vasopressin, and calcitonin.

d) Structural Modification:

Nasal absorption can be enhanced through chemical modification of drug structures without altering their pharmacological activity. Modifying molecular size, weight, pKa, and solubility improves nasal absorption. For example, converting salmon calcitonin to elcatonin (replacing the S-S bond with a C-N bond) enhances bioavailability.

e) Particulate Drug Delivery:

Particle design significantly influences absorption enhancement. Microspheres, nanoparticles, and liposomes serve as carriers, altering properties to maximize therapeutic efficacy. Mucoadhesive systems, designed for increased retention time and sustained release, enhance absorption. Microspheres prepared with polymers like dextran, chitosan, and biodegradable starch improve drug bioavailability. Cationic liposomes demonstrate better permeation capacity than anionic liposomes, facilitating the delivery of water-soluble drugs to the nasal mucosa.

f) Bioadhesive Polymer:

The use of bioadhesive polymers enhances nasal residence time and drug absorption by creating adhesive forces between the formulation and nasal mucosa. This minimizes mucociliary clearance, ensuring prolonged drug retention in the nasal cavity.

VII. NASAL DRUG DELIVERY SYSTEM DOSAGE FORMS:

The choice of the dosage form is influenced by the specific drug employed, the intended indication, the target patient population, and, importantly, marketing preferences. Four fundamental formulations warrant consideration, namely, solution, suspension, emulsion, and dry powder systems.

a) Nasal Drops and Sprays:

Among all formulations, nasal drops represent a straightforward and convenient delivery system. However, their main drawback lies in the imprecision of administered dosages and the potential risk of contamination during use. Typically dispensed through a pipette or a squeezy bottle, nasal drops are commonly recommended for treating local conditions. Nevertheless, challenges arise, including microbial growth, mucociliary dysfunction, and non-specific loss either through the nose or down the back of the throat.

In contrast, nasal spray systems comprise a chamber, a piston, and an operating actuator. Nasal sprays offer a more accurate alternative to drops, providing precise doses (25 - 200 µl) per spray. Numerous studies have demonstrated the ability of nasal sprays to deliver consistent doses with reproducible plume geometry. The

formulation's properties, such as thixotropy, surface tension, and viscosity, have the potential to influence droplet size and dose accuracy. Additionally, factors like applied force, orifice size, and pump design can impact droplet size, consequently affecting the nasal deposition of sprays.

b) Nasal gels:

A nasal gel comprises a pliable, solid or semi-solid substance formed by the combination of two or more constituents, with one being a substantial quantity of liquid. The semi-solid nature of gels is characterized by two dynamic mechanical properties: elastic modulus G and viscous modulus G. The rheological features of gels are contingent upon the polymer category, concentration, and the physical state of the gel. They may span from fluidic solutions (such as hypromellose, methylcellulose, xanthan gum, and chitosan) to extremely rigid, brittle gels (for instance, gellan gum, pectin, and alginate). Bioadhesive polymers exhibit promising potential for nasal formulations, effectively regulating the pace and extent of drug release, thereby reducing the frequency of drug administration and enhancing patient adherence. Furthermore, the prolonged duration of contact at the absorption site can enhance drug bioavailability by retarding mucociliary movement.

c) Nasal Suspensions and Emulsions:

Nasal drug delivery systems rarely utilize or explore suspensions. Drawing a parallel to existing aqueous ophthalmic suspensions of soft corticosteroids, such as loteprednol etabonate (e.g., Alrex®, Bausch and Lomb Pharmaceuticals), a nasal aqueous suspension of the same drug has been patented by Senju Pharmaceuticals Inc., Osaka, Japan. This suspension contains microcrystalline sodium carboxymethylcellulose for stabilization and retention in the nasal cavity, aiming at the local treatment of allergic rhinitis. Additionally, Ando et al. (1998) investigated a nasal suspension for insulin delivery. In this study, soybean-derived steryl glycoside and sterol mixtures (1%) served as absorption enhancers, resulting in pharmacological bioavailabilities of 6.7% and 11.3%. It is noteworthy that, for oral drug delivery, emulsions have been reported by several authors to outperform suspensions in enhancing the bioavailability of poorly soluble drugs. This trend aligns with nasal formulations, where absorption enhancement is attributed to the solubilization of the drug and lipophilic absorption enhancers in the composition. Similarly, emulsions have been employed to formulate other low solubility compounds, such as diazepam and testosterone, to increase their solubility.

d) Nasal Micellar and Liposomal Formulations:

Various adjuvants can influence drug absorption. They are frequently necessary to achieve therapeutic plasma levels, especially when delivering hydrophilic macromolecular drugs like peptides and proteins through the nasal route. Bile salts, among other surfactants, are commonly employed as enhancers, often in the form of micellar solutions. Tengamnuay and Mitra explored the use of micelles composed of sodium glycocholate, and a combination of these micelles with fatty acid (linoleic acid) as absorption enhancers for the model dipeptide (D-Arg2)-kyotorphin and for insulin in rats. The synergistic effect of mixed micelles was found to be superior compared to using a single enhancer. In rats, the administration of nasal insulin with mixed micelles of sodium glycocholate and linoleic acid reduced blood glucose levels to 47% of those observed after an identical nasal dosage of unenhanced insulin. Pure sodium glycocholate resulted in a reduction to 55%. Unlike the membrane-solubilizing effect of pure bile salts, the proposed mechanism for mixed micelles involves an impact on the nasal paracellular pathway. In this context, bile salts were believed to act as solubilizing agents for fatty acids, thereby enhancing their availability at the nasal mucosa.

e) Nasal Powders:

Particulate nasal dosage forms are typically prepared by combining the drug substance and excipients, utilizing methods such as spray-drying or freeze-drying of the drug. The initial exploration of dry-powder formulations incorporating bioadhesive polymers for nasal delivery of peptides and proteins was conducted by Nagai et al. in 1984. They mixed water-insoluble cellulose derivatives and Carbopol® 934P with insulin, and the resulting powder mixture was administered nasally. Upon contact with water, the powder swelled and formed a gel, leading to prolonged residence time in the nasal cavity. The glucose reduction achieved was one-third of that observed with an intravenous injection of the same insulin dose. Subsequent research extensively investigated powder formulations for nasal drug delivery, including formulations for a somatostatin analogue using cross-linked dextran and microcrystalline cellulose, glucagon using microcrystalline cellulose, and leuprolide and calcitonin using microcrystalline cellulose in combination with hydroxypropyl cellulose. Additionally, a bioadhesive powder containing beclomethasone dipropionate and hydroxypropyl cellulose as the carrier exhibited significantly enhanced nasal residence time compared to the administration of a solution as drops. In a study by Ugwoke et al. in 2000, nasal retention time was compared for apomorphine freeze-dried with lactose,

Carbopol® 971P, or sodium carboxymethylcellulose. Three hours post-insufflation, 58%, 12%, and 27% of the formulation, respectively, had been cleared from the nasal cavity. In all cases, the administered powder reduced nasal mucociliary clearance. The difference in nasal residence time resulted in a sustained plasma peak level of 52 minutes for the Carbopol® formulation compared to 11 minutes for the lactose powder, while maintaining similar bioavailabilities. Callens and Remon in 2000 demonstrated nasal insulin delivery using freeze-dried powders of waxy maize starch and Carbopol® 974P, achieving an absolute bioavailability of 14.4%

f) Nasal Microparticles:

The utilization of microparticles as a strategy to extend the residence time in the nasal cavity was first introduced in 1987. This approach involved the use of microspheres composed of albumin, starch, and DEAE-dextran (diethyl aminoethyl-dextran) that absorbed water, forming a gel-like layer slowly cleared from the nasal cavity. Three hours post-administration, 50% of the delivered albumin and starch microspheres, and 60% of the dextran microspheres, were still present at the deposition site. The prolonged contact time was suggested to enhance drug absorption efficiency. In a specific case, the relative intranasal bioavailability (compared to subcutaneous) of human growth hormone in sheep increased from 0.1% for the solution to 2.7% for the degradable starch microsphere formulation. The addition of the absorption enhancer lysophosphatidylcholine further improved growth hormone absorption, reaching a relative bioavailability of 14.4%. Research by Björk and Edman (1990) demonstrated comparable plasma glucose reduction after nasal insulin administration for degradable starch microspheres (cross-linked with epichlorohydrin) and insoluble starch powder (molecular weight 25 kDa). However, soluble starch powder (molecular weight 11 kDa) resulted in significantly lower glucose reduction. This led to the conclusion that critical parameters for the absorption-promoting effect of microspheres include water absorption and aqueous insolubility. Scanning electron microscopy revealed no observable alteration of the nasal mucosa after 8 weeks of twice-daily administration of starch microspheres, except for slight hyperplasia in the septum wall. Despite strong retention in the nasal cavity, DEAE-dextran microspheres were not successful in promoting nasal insulin absorption in rats. The insulin was tightly bound to the DEAE-groups, preventing release by a solution with an ionic strength corresponding to physiological conditions. Dextran microparticles without ion exchange groups induced a 25% decrease in blood glucose level about 40 min after administration compared to initial levels. In a subsequent study, dextran microspheres with different distributions of encapsulated insulin were compared. When insulin was situated on the microsphere surface, a 52% reduction in plasma glucose was induced 30 min after administration in rats. However, microspheres incorporating insulin in the spherical matrix achieved a maximum plasma glucose level reduction of 30% after 60 min. The observed differences may be attributed to the limited amount of fluid in the nasal cavity, requiring microspheres to be completely swollen to release the entire incorporated insulin amount.

VIII. CURRENT FORMULATIONS FOR NASAL DRUG DELIVERY:

Table 2: Current formulations for nasal drug delivery

Indication	**Active pharmaceutical ingredient**	**Formulation**
Analgesia	Diamorphine hydrochloride Fentanyl citrate	Powder and diluent for reconstitution aqueous spray Nasal spray, solution
Acute treatment of migraine	Sumatriptan Zolmitriptan	Nasal spray, solution Nasal spray, solution
Nasal congestion (associated with sinusitis, common cold, rhinitis and other UTIs) Symptomatic relief of rhinorrhoea	Xylometazoline hydrochloride Oxymetazoline hydrochloride Azelastine Hydrochloride Ephedrine Ipatropium bromide	Nasal spray, solution, nasal drops Nasal spray, solution Nasal spray, solution Nasal drops Nasal spray, solution
Prophylaxis and treatment of perennial and seasonal allergic rhinitis	Budesonide, beclometasone dipropionate (and monohydrate (micronized), Mometasone furoate Triamcinolone acetonide Fluticasone propionate	Nasal spray suspension Nasal spray suspension Nasal spray suspension Nasal spray suspension Nasal spray suspension

	Fluticasone furoate Fluticasone with azelastine HCl Sodium cromoglicate	Nasal spray suspension Nasal spray suspension, spray solution
Prostatic carcinoma (hormone -dependent)	Buserelin acetate	Nasal spray, solution
Nasal congestion	Levomenthol	Nasal ointment
Nasal infection	Neomycin sulfate and Chlorhexidine dihydrochoride	Nasal cream
Nicotine withdrawal symptoms	Nicotine	Nasal Spray Solution
Vaccinations	Influenza vaccine	Nasal spray suspension

IX. APPLICATIONS

The Nasopulmonary drug delivery system demonstrates diverse applications:

a) Delivery of Non-Peptide Pharmaceuticals:

Small, non-peptide lipophilic drugs with low molecular weight (<1000 Daltons) exhibit efficient absorption through the nasal mucosa, even in the absence of permeation enhancers. The highly vascularized epithelial nasal membrane, coupled with the extensive surface area provided by nasal turbinates, facilitates rapid drug absorption. Compounds prone to pre-systemic metabolism, such as progesterone, estradiol, propranolol, nitroglycerine, sodium cromoglycate, etc., can be absorbed rapidly through the nasal mucosa, achieving a systemic bioavailability of approximately 100%. Compared to oral administration, intranasally administered drugs often demonstrate quicker and more efficient absorption, leading to rapid uptake.

Below are examples of non-peptide drugs under investigation for nasal delivery, displaying favorable bioavailability:

i) Adrenal corticosteroids.

ii) Sex Hormones: 17G-estradiol, progesterone, norethindrone, and testosterone.

iii) Vitamins: Vitamin B.

iv) Cardiovascular Drugs: Hydralazine, angiotensin-II antagonist, nitroglycerine, isosorbide dinitrate, propranolol, and clofilium tosylate.

v) Autonomic Nervous System: Sympathomimetics: Ephedrine, epinephrine, phenylephrine, xylometazoline, dopamine, and dobutamine. Parasympathomimetics: Nicotine and methacholine. Parasympatholytics: Scopolamine, atropine, and ipratropium. Prostaglandins

vi) Central Nervous System Stimulants: Cocaine and lidocaine.

vii) Narcotics and Antagonists: Buprenorphine and naloxone.

viii) Histamine and Antihistamines: Disodium cromoglycate and meclizine.

ix) Antimigraine Drugs: Dierogotamine and ergotamine tartrate.

x) Antibiotics: Penicillin, cephalosporins, and gentamycin.

xi) Antivirals: Phenyl-p-guanidine benzoate and enviroxime.

xii) Inorganic Compounds: Inorganic salts, colloidal gold, colloidal carbon, and colloidal silver.

b) Peptide-Based Pharmaceuticals Delivery:

The low oral bioavailability of peptides and proteins arises from their physicochemical instability and susceptibility to hepato-gastrointestinal first-pass elimination. Hydrophilic polar molecules with high molecular weight, such as insulin, calcitonin, and pituitary hormones, are poorly absorbed across biological membranes, resulting in only 1-2% bioavailability when administered as simple solutions. To enhance bioavailability, absorption enhancers like surfactants, glycosides, cyclodextrin, and glycols can be employed.

c) Drug Delivery to the Brain via Nasal Cavity:

The nasal delivery system proves beneficial in conditions like Parkinson's disease, Alzheimer's disease, or pain, where rapid and/or specific drug targeting to the brain is required. This approach increases the fraction of the drug reaching the central nervous system (CNS) post-nasal delivery. The olfactory region in the upper nasal passages enables certain compounds to traverse the blood-brain barrier and enter the brain. Recent research indicates that intranasal administration of neurotrophic factors (NGF, IGF-I, FGF, and ADNF) enhances drug bioavailability in the CNS. Human studies have demonstrated direct delivery of proteins (AVP, CCK analog, MSH/ACTH, and insulin) to the brain from the nasal cavity.

d) Vaccine Delivery through the Nasal Route:

Mucosal sites serve as the first line of defense against entering microorganisms. The nasal mucosa filters pathogens from inspired air through compaction and mucociliary clearance. The nose, housing Nose-Associated Lymphoid Tissue (NALT), acts as an effective immune system site, known as Waldeyer's Ring in humans. Nasal secretions predominantly contain immunoglobulins (IgA, IgG, IgM, and IgE), protective proteins, neutrophils, and lymphocytes in the mucosa**.**

Nasal route is considered an ideal option for vaccine delivery due to several factors:

i) Nasal mucosa serves as the primary point of contact with inhaled pathogens.

ii) Nasal passages contain abundant lymphoid tissue.

iii) It facilitates the development of both mucosal and systemic immune responses.

iv) Nasal delivery is cost-effective, patient-friendly, non-injectable, and safe.

v) Low cost, patient friendly, non-injectable, and safe:

Recent research highlights the efficacy of nasal vaccines in treating anthrax and influenza. These vaccines are formulated using recombinant Bacillus anthracis Protective Antigen (rPA) and chitosan, respectively. Conditions such as measles, pertussis, meningitis, and influenza, which enter the body through nasal mucosal surfaces, can be effectively addressed with nasal vaccines. Administering vaccines nasally, whether based on attenuated live cells or adjuvanted with an immunostimulator or delivery system, can induce both mucosal and systemic immune responses.

e) Delivery of Diagnostic Drugs:

Nasal drug delivery plays a crucial role in administering diagnostic agents for various diseases. The intranasal route ensures optimal systemic release of the medicament, minimizing toxicity. Examples include phenol sulphonaphthalein for diagnosing kidney function, secretin for identifying pancreatic disorders in diabetic patients, and pentagastrin for determining the secretory function of gastric acid.

X. CONCLUSION:

The nasal drug delivery system emerges as a promising alternative route for administering systemically acting drugs characterized by poor bioavailability. It offers notable advantages, including enhanced patient acceptability and compliance in comparison to the parenteral administration of drugs. This delivery method proves particularly beneficial in conditions like Parkinson’s disease, Alzheimer’s disease, or pain, where rapid and/or specific drug targeting to the brain is necessary. Additionally, it serves as a suitable avenue for generating immune responses against various diseases such as anthrax and influenza by delivering vaccines through the nasal mucosa. Looking ahead, we anticipate that intranasal products will primarily address crisis treatments such as erectile dysfunction, sleep induction, acute pain (migraine), panic attacks, nausea, heart attacks, and Parkinson’s disease. Furthermore, novel nasal products targeting long-term illnesses, including diabetes, growth deficiency, osteoporosis, fertility treatment, and endometriosis, are expected to enter the market. The effective application of these attributes hinges on meticulous design considerations for both the drug formulation and delivery device, coupled with a comprehensive understanding of their mutual impact.

XI. ACKNOWLEDGMENT:

The Authors Thankful To Mr. Nasir Shaikh And Adv. Mr. Johed N. Shaikh, AAEMF'S Koregaon Bhima, Pune For His Kind Co-Operation And Also Thankful To Dr. Sampat D. Navale Principal, AAEMF'S DIOP, Pune/ Dr. Rukhsana M. Pinjari Principal, AAEMF'S DCOP,., and also thankful Dr. Mrunal K. Shirsat For Providing Necessary Information To Carry Out The Review Work.

REFERENCES:

[1] Andrade, C., (2015). Intranasal drug delivery in neuropsychiatry: Focus on intranasal ketamine for refractory depression. Journal of Clinical Psychiatry 76(5): 628-631.

[2] Aulton, M. E., Taylor, K., (2013). Aulton's Pharmaceutics: the design and manufacture of medicines, Edinburgh, Churchill Livingstone.

[3] Casettari, L & Illum. L (2014), Chitosan in nasal delivery systems for therapeutic drugs, Journal of Controlled Release. 190, 189-200.

[4] Chandler, S.G., Illum, L., Thomas, N.W., 1994. Nasal absorption in rats. III. Effect on lysophospholipids on insulin

[5] Chaturvedi, M., Kumar. M.,(2011). A review on mucoadhesive polymer used in nasal drug delivery system. Journal of Advanced Pharmaceutical Technology and Research, 4, 215-222.

[6] Chien, Y.W., & Chang, S.F., (1987). Intranasal drug delivery for systemic medications. Critical Reviews In Therapeutic Drug Carrier Systems. 4 (2), 67-194.

[7] Chien, Y.W., Su, K.S.E., & Chang, S.F., (1989), Anatomy and physiology of the nose, in Y. W. Chen, K. S. E. Su, and S.-F. Chang, eds., Nasal systemic drug delivery: Drugs and the Pharmaceutical Sciences, v. 39: New York, Marcel Dekker Inc, p. 1-19.

[8] Duquesnoy, C., Mamet, J.P., Sumner, D., & Fuseau, E., (1998). Comparative clinical pharmacokinetics of single doses of sumatriptan following subcutaneous, oral, rectal and intranasal administration. European Journal of Pharmaceutical Sciences 6, 99-104.

[9] Electronic Medicines Compendium (2015) [Database on the Internet]. Datapharm Communications Ltd. http://emc.medicines.org.uk.

[10] Eller, N., Kollenz, C.J. The duration of antidiuretic response of two desmopressin nasal sprays. International Journal of Clinical Pharmacology and Therapeutics. 36 (9), 494-500.

[11] Harris, A.S., (1993). Review: Clinical opportunities provided by the nasal administration of peptides. Journal of Drug Targeting 1, 101-116.

[12] Hermann, N., (2015). Effectiveness of live attenuated influenza vaccines and trivalent inactivated influenza vaccines against confirmed influenza in children and adolescents in Saxony-Anhalt, 2012/13. Gesundheitswesen 77(7): 499-501

[13] Knoester, P.D., Jonker, Pharmacokinetics and pharmacodynamics of midazolam administered as a concentrated intranasal spray. A study in healthy volunteers. British Journal of Clinical Pharmacology. 53, 501-507.

[14] Kublik, H., & Vidgren, M. T., (1998). Nasal delivery systems and their effect on deposition and absorption. Advanced Drug Delivery Reviews, 29, 157-177.

[15] Mahdi, M. H., Conway, B. R.,. (2015). Development of mucoadhesive sprayable gellan gum fluid gels. International Journal of Pharmaceutics, 488(1), 12-19.

[16] Merkus, F. W. H. M., Schipper,. (1993). Absorption enhancers in nasal drug delivery: efficacy and safety. Journal of Controlled Release, 24(1), 201-208.

[17] Mundlia, J., & Mukesh, K. (2015). Nasal drug delivery: An overview. International Journal of Pharmaceutical Sciences and Research 6, 951-956.

[18] Natsume, H., Iwata, 1996. Screening of absorption enchancers for nasal peptide and protein delivery. Proceed. Internat. Symp. Control Release Bioactive Materials. 23, 481-482.

[19] Ozsoy, Y., Tuncel, T., Can, A., Akev, N., Gerceker, A. (2000). In vivo studies on nasal preparations of ciprofloxacin hydrochloride. Pharmazie, 55, 607-609

[20] Prajapati, S. T., Pathak, S.P., C. N., (2015). Nanoemulsion based intranasal delivery of risperidone for nose to brain targeting. Bulletin of Pharmaceutical Research 5, 6- 13.

[21] Rathbone, M. J., Hadgraft, J., & Roberts, M. S. (Eds.). (2002). Modified-release drug delivery technology. CRC Press.

[22] Rhidian, R., & Greatorex, B.,. Chest pain in the recovery room, following topical intranasal cocaine solution use. British Medical Journal Case Reports doi: 10.1136/bcr-2015- 20969

[23] Slot, W.B., Merkus, Deventer, (1997). Normalization of plasma vitamin B12 concentration by intranasal hydroxocobalamin in vitamin B12- deficient patients. Gastroenterology. 113, 430-433.

[24] Singh, L., & Khan, A. D., Nasal drug delivery: a promising way for brain targeting. The Pharma Research 13.2, 1-12.

[25] S.G., Illum, L., Thomas, N.W., 1991. Nasal absorption in rats. II. Effect of enhancers on insulin absorption and nasal histology. International Journal Pharmaceutics. 76, 61-70

[26] Ugwoke, M. I., Agu, R. U., Verbeke, N., & Kinget, R. (2005). Nasal mucoadhesive drug delivery: background, applications, trends and future perspectives. Advanced Drug Delivery Reviews, 57(11), 1640-1665.

[27] Ugwoke, M. I., Verbeke, N., & Kinget, R. (2001). The biopharmaceutical aspects of nasal mucoadhesive drug delivery. Journal of Pharmacy and Pharmacology, 53(1), 3-22.

[28] Zhou, M., Donovan, M.D., 1996. Recovery of the nasal mucosa following laureth-9 induced damage. International Journal of Pharmaceutics.130, 93-102.

[29] Z. Ghori, Muhammad U., Mahdi, Mohammed H., Smith, Alan M. and Conway, Barbara R. (2015) Nasal Drug Delivery Systems: An Overview. American Journal of Pharmacological Sciences, 3 (5).pp. 110-119. ISSN 2327-6711