A REVIEW ON CHALLENGES IN DEVELOPING NASAL DRUG DELIVERY SYSTEMS

M. Akanksha Reddy\textsuperscript{1}, N. Sravanthi\textsuperscript{2}, M. Vidyra Rupa\textsuperscript{3}, Dr. T. Rama rao\textsuperscript{4}, T. Srilakshmi\textsuperscript{5}.

1,2,3- CMR College of pharmacy (kandlakoya), Hyderabad- 501401
4- professor- CMR College of pharmacy (kandlakoya), Hyderabad- 501401
5- assistant professor- CMR College of pharmacy (kandlakoya), Hyderabad- 501401

ABSTRACT:
The intranasal route has aroused increasing interest as means of systemic administration of vaccines, hormones, peptides, and certain other drugs. This is due to high vascularity, large surface area, the avoidance of first-pass metabolism. The drugs which are delivered through the nasal route have been shown to achieve a better systemic bioavailability, than by oral route. This review sets out to discuss anatomical, physiological attributes of the nasal cavity, factors affecting nasal absorption, challenges in developing nasal drug delivery, strategies to improve nasal absorption of drugs.

KEYWORDS: Nasal drug delivery, applications, factors influencing, challenges, strategies

INTRODUCTION
Nasal therapy also called Nasaya karma has been recognized form of treatment in ayurvedic system of Indian medicines. Nasal route is considered as a promising systemic delivery alternative to other conventional drug delivery routes. Nasal route provides a rapid absorption of compounds in to the systemic circulation by avoiding hepatic first pass effect. Nasal drug delivery is easily accessible, and reliable with a porous endothelial membrane and highly vascularized epithelium that provides rapid absorption of many drugs.\textsuperscript{(1,2)}

Intranasal therapy is a useful method for delivery of drugs that are active in low dose and show no minimal oral bioavailability such as proteins and peptides [Eg: luteinizing hormone, growth hormone, adrenocorticotropic hormone]. It is also considered for administration of vaccines [ Buserelin, Desmopressin]. It is also suitable for restricting and obstacles blood brain barrier, so that drug can be delivered in bio phase of CNS [ Central Nervous System]. Drugs have been administered nasally for both topical and systemic action. Topical administration includes the treatment of congestion, rhinitis, sinusitis and also different medications including corticoids, antihistamines and vasoconstrictors have been shown to produce considerable systemic effects. For Nasal drug delivery various systems such as Nasal drops [multiple or single dose formulation], Nasal sprays, Nasal pumps, gels, Pressurize MDI’S, Dry powder inhalers and thermo reversible mucoadhesive gels have been studied.\textsuperscript{(3)}

MERITS\textsuperscript{(4)}
• Degradation of drug in gastrointestinal tract is avoided.
• The bioavailability of larger drug molecules can be improved by means of absorption enhancers or other approaches.
• Nasal drug delivery system delivers drugs to systemic circulation which cannot be absorbed orally.
• Nasal bioavailability will be better for smaller drug molecules.
• When compared with parenteral medication, convenient route for patients on long term therapy

DEMERITS\textsuperscript{(5,6)}
• When compared to gastrointestinal tract, absorption surface area of nasal cavity is smaller compared to GIT.
• Some surfactants which are used as chemical enhancer may disrupt or even dissolve the membrane in high concentration.
• Possibility of nasal irritation.
• Because of improper technique of administration there is a lose of dosage form in the other parts of the respiratory tract.
• When the substances or constituents are added to the dosage form they cause irreversible damage to the cilia on the nasal mucosa.

ANATOMY AND PHYSIOLOGY OF NASAL CAVITY\textsuperscript{(7,8,9)}
The nasal cavity is divided into two halves by the nasal septum and extends posterior half to the naso-pharynx, while the most anterior part of the nasal cavity, the nasal vestibule opens to the face through the nostril. Nasal vestibule, respiratory region and the olfactory region are the three main regions in the nasal cavity. Breathing and olfaction are major functions of the nasal cavity.

The nose can be enlarged or can be extended up to the surface area of the lateral walls in the nasal cavity, includes a folded structure having very high surface area compared to its small volume. The superior, the inferior and the median are the three turbinate’s which are present in the folded structure. A narrow structures (or) passages of 1-3mm which are located in the main nasal airway are useful to nose to perform its main functions.
Vestibular region:
Most anterior part of nasal cavity. Nasal hairs are present in this area, called as vibrissae, which filter the inhaled particles. Nasal vestibule is covered by a stratified squamous keratinized epithelial cells with sebaceous gland.

Respiratory region:
The respiratory region have highest degree of vascularity which mainly helps in systemic absorption of drugs. The respiratory epithelium is composed of non-ciliated and ciliated columnar cells, basal cells and goblet cells. This cell facilitates in active transport processes in exchange of water and ions between cells and motility of cilia and also prevents drying of the mucosa by trapping moisture.

Atrium: It is area between nasal vestibule and respiratory region. Its anterior section is constituted by a stratified squamous epithelium and the posterior area by pseudostratified columnar cells in which microvilli are present.

Olfactory region:
This region is located at the roof of the nasal cavity and extends down the septum and lateral wall. The neuro-epithelium is one of the part of the CNS that is directly exposed to the external environment. The olfactory region also consists of pseudostratified columnar cells but contains specialized olfactory receptor cells important for smell perception.

Mucus membrane of nose and its composition:
Nasal mucus layer is of 5 μm thick and has two distinct layers, an external layer is viscous and dense, whereas internal layer consists of fluid and serous. The mucus secretion is composed of about 95% of water, 2.5-3% of mucin, 1% salts and 2% of electrolytes, proteins, lipids, enzymes, antibodies, sloughed epithelial cells.

MECHANISM OF DRUG ASORPTION THROUGH NASAL CAVITY: (10)  
In the nasal cavity the first step includes passage of absorbed drug through the mucus layer. It is difficult for large and charged drugs to cross the layer but small particles can easily pass through this layer. The structural changes in the mucus layer are possible due to environmental changes (i.e; pH, temperature etc.). Several mechanisms are involved in absorption of drug through the mucosa. Predominantly used mechanisms include trans-cellular or simple diffusion across the membrane, paracellular transport via movement between cell and transcytosis by vesicle carriers.

- First mechanism involves aqueous route also known as paracellular route of transport. It is a slow and passive process. In this route, poor bioavailability was observed for the drugs which have molecular weight more than 1000 Daltons. Intranasal absorption of water soluble compounds is related to molecular weight of drugs.

- The transcellular route, is the second mechanism which involves the drug transport is through lipoidal route and is responsible for transport of lipophilic drugs that shows a rate dependency on their lipophilicity. Drugs also cross by active transport route via transport through opening of tight junctions or via carrier mediated transport.
Factors influencing nasal absorption of drugs: (11)

Factors influencing absorption are related to nasal physiology, physicochemical characteristics of drugs and formulation aspects

- **Biological Factors**
  - Structural features
  - Biochemical changes
- **Physiological factors**
  - Blood supply and neuronal regulation
  - Nasal secretions
  - Mucociliary clearance and ciliary beat frequency
  - Pathological conditions
  - Environmental conditions.
  - Membrane permeability.
- **Physicochemical Properties of Drugs**
  - Molecular weight
  - Size
  - Solubility
  - Lipophilicity
  - pKa and Partition coefficient
  - Chemical form of drug.
  - Polymorphism.
  - Chemical state
  - Physical state.
- **Physicochemical Properties of Formulation**
  - Physical form of formulation
  - pH
  - Osmolarity
  - Volume of solution applied and drug concentration
  - Viscosity.

CHALLENGES IN NASAL DRUG DELIVERY SYSTEM

- **Mucociliary clearance (MCC):**
  Mucociliary clearance (MCC) is one of the functions of the upper respiratory tract to prevent allergens, bacteria, toxins, viruses etc. from reaching lungs. In nasal mucosa the absorption of drug is influenced by contact time between drug and epithelial tissue. When a substance is administered nasally, it is cleared from the nasal cavity within ~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. MCC is affected by drug and additives used in nasal formulations (acetylcholine, methacholine agonists stimulate ciliary activity while salmeterol, isoprenaline receptor agonists were found to reduce ciliary activity). Preservatives such as chlorobutol cause reversible inhibition of MCC. Drug permeation increases the contact time between drug and mucus membrane by reducing MCC, increase in MCC will decrease the drug permeation. (12)

- **Enzyme degradation:**
  Nasal mucosal lining and enzymes present in nasal cavity are one of the major barriers in the nasal absorption of drugs. The transnasal absorption of both lipophilic and hydrophilic drug is influenced by the existence of these enzymes. The proteins and peptides have low bioavailability across nasal cavity. Drugs may undergo enzymatic degradation during it passage through the nasal epithelial barriers and also in the lumen of nasal cavity. The various enzymes like aldehyde cytochrome P-450 dependent monoxygenase hormones are found to exist in nasal mucosa. Cytochrome P-450 dependent monoxygenase is used to catalyse the different xenobiotics metabolism. It metabolizes many drugs in nasal mucosa like nicotine, phenacetin nasal decongestant. Another class of enzymes which has the highest activity reported in the nasal epithelia are carboxylesterases. (13)

- **Lipophilicity:**
  The permeation of the drug normally increases through nasal mucosa with increase in lipophilicity. It appears that nasal mucosa is primarily lipophilic in nature and some are hydrophilic but lipid molecule plays an important role in barrier function of the membrane. Lipophilic drugs like naltrexone, buprenorphine, testosterone completely absorbed through intranasal route. Systemic bioavailability of many drugs is reduced due to excess hydrophilicity in such cases prodrug approach is useful. (14)

- **Molecular size:**
Molecular size influences absorption of drug through nasal route. Drug molecules having molecular weight greater than 1000 Dalton nasal absorption falls sharply. The rate of permeation is highly sensitive to molecular size of compounds with MW (≥300 Daltons) due to high permeability, fairly wide absorption area, porous and thin endothelial basement membrane of nasal epithelium.\(^{(14)}\)

- **Preservatives:**
  Most of the nasal formulations are aqueous based; to prevent microbial growth some preservatives such as (parabens, benzalkonium chloride, phenyl ethyl alcohol, EDTA and benzoyl alcohol) are included in nasal formulations. The preservatives which contains mercury has a fast and irreversible effect on ciliary movement.\(^{(15)}\)

- **Solubility and dissolution:**
  In Intranasal administration the allowable volume should be very low and therefore drugs with low aqueous solubility require higher doses that may be a problem for a drug to dissolve in fluid present in nasal cavity. If drug remains as particles it is cleared away and no absorption takes place. Drugs should have sufficient solubility in nasal secretion.\(^{(16)}\)

- **pH:**
  The drug permeation which affected by pH of the formulation and nasal surface Nasal formulation should be adjusted to appropriate pH to avoid irritation, to obtain efficient absorption and to prevent growth of pathogenic bacteria. The pH of the formulation 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.\(^{(17)}\)

- **Nasal blood flow:**
  Nasal mucosal membrane is supplied by rich vasculature. The drug absorption and blood flow depend upon the vasoconstriction and vasodilation of the blood vessels. Nasal blood flow is affected by several external and physiological factors such as ambient temperature, humidity, presence of drugs, trauma, inflammation as well as psychological factors such as emotion, fear, anxiety etc., Nasal blood flow is sensitive to both locally and systemically acting drugs.\(^{(18)}\)

- **Drug concentration, Dose and volume of administration:**
  The concentration of drug increases as the nasal drug absorption increases at the site of administration. As the primary mechanism of drug absorption this phenomenon is more prominent with the drugs that are absorbed by passive diffusion. Higher concentration and higher volume of drug administration, negatively impacts absorption of drug and in some cases leads to damage of nasal mucosa. Therefore, low doses are preferred (25-200µl).\(^{(19)}\)

- **Particle size:**
  Particles larger than 30 mm are removed as there is a large degree of air-mucosa contact time due to cilia air turbulence in the nasal airway which increases with a faster respiratory rate. It has been reported that particle greater than 10 μm is deposited in nasal cavity and less than 1 μm are exhaled.\(^{(20)}\)

**STRATEGIES:**

Many barriers are present in the nasal cavity. Some of the methods which are used for the improvement of nasal drug absorption are:

**NASAL ENZYME INHIBITORS:**
To minimize metabolism of drugs in nasal cavity various kinds of enzyme inhibitors are used, which minimize activity of enzymes present in nasal cavity. Enzyme inhibitors like peptidases and proteases are used to eliminate the nasal metabolism of the drug. The absorption enhancers (salts and fusidic acid derivatives) also shows enzyme inhibition activity to increase absorption and bioavailability of drugs. The other commonly used enzyme inhibitors are tripsin, aprotinin, bestatin inhibitors.\(^{(21)}\)

**PRODRUG APPROACH:**
Prodrug is an inactive chemical moiety which becomes active at the target site. These are mainly used to improve taste, odor, solubility and stability. This approach used to improve nasal bioavailability (proteins and peptides) to increase membrane permeability along with increased enzymatic stability. Absorption can be enhanced by peptides like angiotensin-II, bradykinine, vasopressin, calcitonin, when prepared into enamine derivatives.\(^{(22)}\)
IN SITU GEL:
In situ gel preparations get converted into gel after instillation into nasal cavity because of the influence of stimuli which includes pH, ionic concentration and temperature. By the influence of ciliate movement the thick gel like consistency makes the formulation difficult to drain. \(^{(23)}\)

ENHANCEMENT OF NASAL DRUG ABSORPTION: \(^{(24)}\)
The physicochemical properties of drug in formulation can be altered by adding enhancers

- **Structure modification**: The chemical modification of a drug molecule has been commonly used to modify the physicochemical properties of drug and could also be utilized to improve the nasal absorption of drug.
- **Salt or ester formation**: The drug may be converted to form a salt or an ester for better nasal permeability. For example, nasal absorption is improved significantly by salt formation with increased solubility in nasal fluid or an ester with enhanced uptake by nasal epithelium.
- **Surfactants**: When the surfactants incorporated into the nasal dosage forms they may modify the permeability of nasal membranes, which may facilitate the nasal absorption of drug. A number of surfactants have been reported to enhance the absorption of drugs through the nasal mucosa to a level sufficient to achieve their systemic effects. Mild surfactants at low concentrations may only alter membrane structure and permeability whereas certain surfactants at high concentrations may disrupt or even dissolve biological membranes. ex; -polyoxyethylene-9-lauryl ether (laureth-9) saponin.

PARTICULATE DRUG DELIVERY:
In the particulate drug delivery carriers are used for the encapsulating the drug which prevents exposure of drug to nasal environment and improves the retention capacity in nasal cavity. Examples of these drug delivery are microspheres, liposomes, nanoparticles and niosomes. \(^{(25)}\)

BIOADHESIVE POLYMERS:
Bioadhesive polymers are used to improve the nasal residence and absorption of the drug. The retention time of the drug is increased in the nasal cavity by adhesive force between formulation and nasal mucosa, which leads to reduction of mucociliary clearance of formulation. Bio-adhesive polymers such as methylcellulose, carboxy methyl cellulose and hydroxyl propyl cellulose or polyacrylic acid are used.

NASAL PERMEATION ENHANCERS:
The permeation enhancers have been investigated to improve the nasal absorption like fatty acids, bile salts, phospholipids, surfactants, cyclodextrins etc. \(^{(26)}\)

LIST OF AVAILABLE NASAL PRODUCTS ON MARKET: \(^{(27)}\)

<table>
<thead>
<tr>
<th>S.NO</th>
<th>PRODUCT</th>
<th>DRUG</th>
<th>INDICATION</th>
<th>MANUFACTURER</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Beconase Ò AQ nasal spray</td>
<td>Beclomethasone Dipropionate Monohydrate</td>
<td>Symptomatic treatment of seasonal and perennial allergic rhinitis</td>
<td>Allen and hanbury’s/ Glaxo wellcome Inc.</td>
</tr>
<tr>
<td>2</td>
<td>Rhinocort Ò nasal inhaler</td>
<td>Budesonide</td>
<td>Management of symptoms of seasonal and perennial allergic rhinitis and non allergic perennial rhinitis.</td>
<td>Astra USA, Inc.</td>
</tr>
<tr>
<td>3</td>
<td>Miacalcin Ò nasal spray</td>
<td>Calcitonin, salmon</td>
<td>Post-menopausal osteoporosis</td>
<td>Sandoz, pharmaceutical Corp.</td>
</tr>
<tr>
<td>4</td>
<td>Nasalide Ò nasal solution</td>
<td>Flunisolide</td>
<td>Symptomatic prevention and treatment of seasonal or perennial rhinitis</td>
<td>Roche Laboratories</td>
</tr>
</tbody>
</table>
Application of Nasal Drug Delivery Systems:

- **Delivery of Vaccines Through Nasal Route**
  Nasal mucosa is rich in specialized cells and organized lymphatic tissues involved in the first line defense against airborne microorganism. Nasal delivery of vaccines not only produce systemic immune response, but also local immune response in the nasal lining, and also provides additional barrier of protection. The majority of the invading pathogens enter the body through mucosal surfaces. Therefore, mucosal sites have a potential as first line of defense against entering pathogens. Pathogens are filtered from the inspired air by compaction and mucociliary clearance. But the nose with its nose associated lymphoid tissue (NALT) is also an inductive as well as an effective site of the immune system. In humans the NALT is known as the Waldeyer’s Ring. Nasal secretions are known to contain immunoglobulins (IgA, IgG, IgM, IgE), protective proteins such as complement as well as neutrophils and lymphocytes in the mucosa. Delivering the vaccine to the nasal cavity itself stimulates the production of local secretory IgG antibodies as well as IgA, providing an additional first line of defense, which helps to eliminate the pathogen before it becomes established. (28)

- **Local delivery**
  The drugs are administered through nasal route for the treatment of topical nasal disorders. examples are antihistamines and corticosteroids for rhino sinusitis, and nasal decongestants for cold symptoms. when administered through nasal route relatively low doses are prefered with less systemic toxicity. (29)

- **Systemic delivery**
  The intranasal administration of drugs is more effective way for systemic availability than that of oral and intravascular routes. Examples include analgesics (morphine), cardiovascular drugs as propranolol and carvedilol. (30)

**CONCLUSION:**
The nasal cavity has promising and efficient absorption of drugs into rich network of blood vessels directly into the systemic circulation by avoiding first pass metabolism. The challenges in nasal drug delivery systems such as enzyme degradation, mucociliary clearance, pH, molecular size, considered while preparation of formulation to ensure the maximum absorption by the nasal route. These strategies can help to develop formulations to increase bioavailability of drugs.

**REFERENCES:**
10. [https://doi.org/10.1007/s13346-020-00089-5](https://doi.org/10.1007/s13346-020-00089-5)
15. Snehalata S. Mali “Review article on nasal drug delivery system” ijert Volume 9, Issue 7 July 2021
27. Surbhi Verma “Review article on Nasal drug delivery system” ISSN: 2455-2631 © February 2021 IJSISR | Volume 6 Issue 2