A REVIEW ON NASAL DRUG DELIVERY SYSTEM FOR BRAIN TARGETING WITH RECENT ADVANCEMENT
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KEYWORDS:
Nasal drug delivery,
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ABSTRACT
Delivery of drugs through nasal route has been potentially explored as an alternative route for administration of vaccines and biomolecules such as proteins, peptides and non peptide drugs, hence it has attracted the interest of scientific community. Due to the high permeability, high vasculature, low enzymatic environment of nasal cavity, avoidance of hepatic first pass metabolism, rapid onset of action, no gastrointestinal degradation or lung toxicity are well suitable for systemic delivery of drug molecule via nose and also improves bioavailability. The nasal mucosa when compared to other mucous membranes is easily accessible and alternative to parenteral therapy which is useful for long term therapy. That is why over the last few decades transmucosal nasal drug delivery as a non-invasive route has occupied an important place in the field of drug delivery technology. Nasal route is widely used for the local treatment may also be used for systemic therapy as drug directly goes in systemic circulation. The Delivery from nose to central nervous system occurs within minutes along with both the olfactory and trigeminal neural pathways. It is thought that olfactory route of drug transport, by pass the Blood-Brain Barrier (BBB) and allows the direct transport of drug from the nose to the brain. We have, herein, outlined the relevant aspects of nasal anatomy, physiology, histology and the biological, physicochemical and pharmaceutical factors that must be considered during the process of discovery and development of nasal drugs as well as in their incorporation into appropriate nasal pharmaceutical formulations.
INTRODUCTION:
Intranasal Therapy has been an accepted form of treatment in the Ayurvedic system of Indian Medicine. Nowadays many drugs have better systemic bioavailability through nasal route as compared to oral administration. Biotechnological advancement has lead to the development of a large number of protein and peptide drug for the treatment of several of diseases. Oral administration of these drugs is not possible because they are significantly degraded in the gastrointestinal tract or considerably metabolized by first pass effect in the liver. Intranasal drug delivery offers a promising alternative route for administration of such drugs. Nasal route has also been considered for the administration of the vaccines [1,2]. However, although the oral route remains the most popular for systemic drug administration, low oral bioavailability of some compounds has prompted the search of more effective routes for their systemic delivery [3]. Intranasal drug delivery is now recognized to be a useful and reliable alternative to oral and parenteral routes. Undoubtedly the intranasal administration of medicines for the symptomatic relief and prevention or treatment of topical nasal conditions has been widely used for a long period of time. However, recently the nasal mucosa has seriously emerged as a therapeutically viable route for the systemic drug delivery. In general, among the primary targets for intranasal administration are pharmacologically active compounds with poor stability in gastrointestinal fluids, poor intestinal absorption and/or extensive hepatic first-pass elimination, such as peptides, proteins and polar drugs [4]. Despite tremendous advances occurring in brain research, brain and central nervous system disorders like schizophrenia, meningitis, migraine, Parkinson disease and Alzheimer disease remains the world’s leading cause of disability and account for more hospitalizations cases and prolonged care than accounted for almost all other diseases combined. The major problem in drug delivery to brain is the presence of the BBB [5]. The nasal delivery seems to be a favorable way to circumvent the obstacles for blood-brain barrier (BBB) allowing the direct drug delivery in the biophase of central nervous system (CNS) active compounds [6]. It was reported that lipophilic drugs are generally well absorbed from the nasal cavity with pharmacokinetic profiles which are often identical to those obtained after an intravenous injection with a bioavailability approaching 100% [7]. While the permeation of hydrophobic drugs can improve by by being administered in combination with absorption enhancers [8]. The nasal drug delivery system comprises of targeting a drug through nasal epithelium. This mode of drug delivery has gained recent interest due to the tremendous absorptive potential of the nasal mucosa owing to its high permeability because of high perfusion rate. This route can be selectively exploited for delivery of small molecules, peptides and proteins that are not easily administered by routes other
than i.v. where immediate response is desired. In the nasal cavity, the respiratory region has the highest degree of vascularity. The olfactory region is located in the top of the nasal cavity and it is the only site of the body where the CNS is in contact with the external environment [9,10]. For nasal drug delivery various systems such as: nasal spray, nasal pumps, gels, microemulsion, suspensions, powders and thermo reversible mucoadhesive gels have been studied [11]. In the last few years, the nasal route has received a great deal of attention as a convenient and reliable method for the systemic administration of drugs, especially those which are ineffective orally and must be administered by injection [12].

**Advantages of Nasal Drug Delivery System:**

- Absorption of drug is rapid via highly vascularised mucosa.
- Bypass the BBB.
- Unsuitable drug candidates for oral route can be successfully given via nasal route.
- Non invasive and easy for administration.
- Direct transport into systemic circulation and CNS is Possible.
- Degradation of drug observed in GIT is avoided.
- Side effects are reduced due to low dose.
- Patient convenience and compliance is improved.
- Hepatic first pass metabolism is prevented.
- Convenient route for the patient on long term therapy.
- Onset of action is rapid.
- A self-administration is possible [13,14].

**Disadvantages of Nasal Drug delivery Systems:**

- Absorption surface area is less when compared to GIT.
- Nasal irritation.
- Once the drug administered can not be removed.
- High molecular weight compounds cannot be delivered through this route.
- Adversely affected by pathological conditions.
- High cost of development.
- Enzymatic barrier.
- The nasal cavity delivery volume is restricted to 25–200 μL.
- More than 1kDa compounds cannot be delivering by this route.
- Risk of irreversible damage of the cilia and local side effect [15,16].
Ideal Characteristics of Nasal Drug Delivery System:

- The nasal route provides appropriate aqueous solubility approx 25–150 ml volume of formulation administration per nostril.
- Dose quantity is low (<25mg)
- Toxic nasal metabolites are avoided.
- Suitable nasal absorption properties.
- Rapid onset of action.
- Appropriate stability characteristics.
- Nasal irritation not produces by the drug [17,18].

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 nasal mucosa [19]. 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. Nasal cavity contains lining with mucus layer and hairs which are involved in functions like trapping inhaled particles and pathogens. Moreover, resonance of produced sounds, mucociliary clearance MMC, immunological activities and metabolism of endogenous substances are also essential functions of nasal structures. Passage of the nasal cavity which runs from nasal vestibule to nasopharynx has a depth of approximately 12-14cm. The total surface area of the nasal cavity in human adult is about 150 cm² and total volume is about 15 ml [9,20]. Anatomic and histological characteristics of the different areas of nasal cavity are such that allow these functions to be performed optimally. Thus anatomically, human nasal cavity fills the space between the base of the skull and the roof of the mouth; above it is supported by the ethmoid bones and laterally by the ethmoid, maxillary and inferior conchae bones [21]. The nasal cavity is covered with a mucous membrane which can be divided into two areas; nonolfactory and olfactory epithelium, in this non-olfactory area includes the nasal vestibule which is covered with skin-like stratified squamous epithelium cells, where as respiratory region which has a typical airways epithelium covered with numerous microvilli, resulting in a large surface area available for drug absorption and transport. In this way the mucus layer is propelled in a direction from the anterior towards the posterior part of the nasal cavity. The goblet cells are present in the mucus membrane which covers the nasal turbinate and the atrium; it secretes the mucus as mucus granules which are swelling in the nasal fluid to contribute to the mucus layer [22]. Nasal cavity is divided by middle
septum into two symmetrical halves, each one opening at the face through nostrils and extending posterior to the nasopharynx. Both symmetrical halves consist of four areas (nasal vestibule, atrium, respiratory region and olfactory region) that are distinguished according to their anatomic and histological characteristics [23].

**Nasal Vestibule:** It is located at the opening of nasal passages and is mainly responsible for restricting entry of air borne particles. It is considered to be less important of the three regions with regard to drug absorption [12].

**Atrium:** Atrium is the intermediate 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 presenting microvilli [24,25].

**Respiratory Region:** Largest part of the nasal cavity is respiratory region, also called conchae, is the cavity and it is divided in superior, middle and inferior turbinates which are projected from the lateral wall [8]. These specialized structures are responsible for humidification and temperature regulation of inhaled air. Between them there are spaces, called meatus. Which are passageways where airflow is created to assure a close contact of the inhaled air with the respiratory mucosal surface. The inferior and middle meatus receive nasolacrimal ducts and paranasal sinuses which are air-filled pockets located inside the bones of the face and around the nasal cavity. The nasal respiratory mucosa, considered the most important section for delivering drugs systemically, is constituted by the epithelium, basement membrane and lamina propria. The nasal respiratory epithelium consists of pseudostratified columnar epithelial cells, globet cells, basal cells and mucous and serous glands. Many of the epithelial cells are covered on their apical surface with microvilli and the major part of them also has fine projections, called cilia. Actually microvilli are important to enhance the respiratory suface area, where cilia are essential to transport the mucous towards the nasopharynx [26,27,28].

**Olfactory Region:** The olfactory region is situated between the nasal septum and the lateral walls of each of the two nasal cavities and just below the cribiform plate of the ethmoid bone separating the cranial cavity from nasal cavity. The olfactory epithelium is a pseudostratified epithelium, comprising olfactory sensory neurons and two types of cells; basal cells that are able to differentiate neuronal receptor cells and sustentacular cells (supporting cell) that provide mechanical support by ensheathing neuronal receptor cells and maintain the normal extracellular potassium level for neuronal activity [29]. Similarly to the respiratory epithelium, the olfactory one is also pseudostratified but contains specialized olfactory receptor cells important for smell perception. In this area there are also small serous glands (glands of Bowman) producers of secretions acting as a
solvent for odorous substances [24,30]. It is about 10 cm² in surface area, and it plays a vital role in drug delivery because it bypasses the BBB, delivering therapeutic drugs to CNS [31]. There are different mechanisms by which the drugs cross the olfactory membrane to reach CNS. The first mechanism involves direct transfer of the drug to primary neurons of the olfactory epithelium. The second mechanism depends on the drug permeation across the olfactory sustentacular epithelial cells, either by transcellular or paracellular mechanisms followed by uptake into CNS. The last one employs pinocytosis by olfactory neurons. The drug can cross olfactory lobe by one or combination of pathways [32].

Figure 1. Anatomy and histology of human nasal cavity.
Table 1. Human nasal epithelium characteristics [4,24,33,34].

<table>
<thead>
<tr>
<th>Nasal Sections</th>
<th>Epithelial Characteristics</th>
<th>Surface Area</th>
<th>Vascularization</th>
<th>Permeability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vestibule</td>
<td>• Stratified squamous and keratinized epithelial cells with nasal hairs / Support and protection</td>
<td>≈ 0.6 cm²</td>
<td>Low</td>
<td>Poor</td>
</tr>
</tbody>
</table>
| Atrium         | • Stratified squamous cells/ Support  
• Pseudostratified Cells/ Support | Not Found | Low | Reduced |
| Respiratory Region | • Columnar non ciliated cells/ Support  
• Columnar ciliated cells/ Support and mucilary clearance  
• Goblet cells/ Mucus secretions  
• Basal cells/ Progenitors of others cell types | ≈ 130 cm² | Very high | Good |
| Olfactory Region | • Sustentacular cells/ Support and synthetic  
• Olfactory receptor cell/ Olfaction preception  
• Basal cells/ Progenitors of other cell types | ≈ 15 cm² | High | Direct access to CNS |
MECHANISM OF DRUG ABSORPTION FROM NOSE:
The absorbed drug from the nasal cavity passes through the mucus layer. It is the first step in absorption. Small, unchanged drugs easily pass through this layer but large, charged drugs find difficulty to cross it. The principle protein of the mucus is mucin. It has the tendency to bind to the solutes and hinders diffusion of drug molecules. Structural changes in the mucus layer are possible as a result of environmental changes like change in pH, temperature. Many absorption mechanisms were proposed earlier but only two mechanisms have been predominantly used, such as [8].

First mechanism- It includes aqueous route of transport, which is also called as the paracellular route. This is slow and passive route. Poor bioavailability was observed for drugs with a molecular weight greater than 1000 Daltons, because inverse relationship exists between molecular weight and absorption [24].

Second mechanism- It involves transport through a lipoidal route and it is also known as the transcellular process. It is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. Drug also cross cell membranes by an active transport route via carrier-mediated means or transport through the opening of tight junctions [35]. For example, Chitosan, a natural biopolymer opens tight junctions between epithelial cells to facilitate drug transport.

**Figure 2:** Drug transport pathways across the epithelium (A), Paracellular transport (B), Transcytosis (C), Carrier mediated transport (D), and Intracellular tight junction (E)

PATHWAYS FOR REACHING THE DRUG TO BRAIN AFTER INTRANASAL ADMINISTRATION:
Intranasal drug delivery appears to be a rapidly developing field. However, the exact mechanisms that can lead to efficient drug delivery to the brain following intranasal administration are not completely elucidated. An accumulating amount of evidence demonstrates that drug can reach the brain following intranasal administration via several direct and indirect pathways. The drug that is deposited in the nasal cavity can escape enzymatic degradation and the normal rapid clearance by
the mucociliary system, undergo uptake to the cells of the olfactory or the trigeminal nerve pathways, or be absorbed into the systemic circulation.

The olfactory pathway consists of the olfactory epithelium, olfactory tract, anterior olfactory nucleus, piriform cortex, amygdala, and hypothalamus. It has been suggested that drugs can reach the CNS via extracellular or intracellular transport along olfactory nerves, and that this pathway can be the major route for brain delivery of certain drugs following intranasal administration.

Branches of the trigeminal nerve innervate the respiratory and olfactory epithelia of the nasal cavity. Thus, the trigeminal pathway, which is often overlooked by the researchers, can be an important direct pathway of drug delivery to the brain [36,37,38,39]. Three branches of the trigeminal nerve (ophthalmic division, maxillary division, and mandibular division) merge at the trigeminal ganglion, enter the CNS in the pons, and terminate in the spinal trigeminal nuclei in the brainstem. Therefore, cross-talk between the trigeminal and olfactory routes of brain drug delivery is possible.

In addition to these direct pathways, drug can enter the brain indirectly, via blood vasculature and/or lymphatic system. The nasal mucosa is highly vascularized, and the blood vessels (lined with continuous and fenestrated endothelium) allow passage of drugs (in free or maybe even in particle-encapsulated form), following nasal drug administration in nano-drug delivery systems.

The drug that has been absorbed into the systemic circulation has to cross the BBB in order to reach the CNS. It is possible that the BBB is breached (temporarily or for prolonged periods of time, in small or big regions of the brain) in certain pathological conditions [40,41]. Therefore, efficiency of this indirect pathway of drug delivery to the brain following intranasal administration can differ in individual patients, or depending on the applied disease model in preclinical in vivo studies [42].

Figure no 3: Pathways for reaching the drug to brain after intranasal administration
FACTORS INFLUENCING NASAL DRUG ABSORPTION:
The following factors which effect the drug absorption are:

1. **Physiochemical properties of drug:**  
   
   A) **Drug molecular weight:** The permeation of drugs having molecular weight less than 300 Da is not significantly influenced by the physicochemical properties of the drug as they will mostly permeate through aqueous channels of the membrane. On the other hand, the rate of permeation is highly sensitive to molecular weight for compounds more than 300 Da. The bioavailability of intranasally administered peptides and proteins including insulin may be low because of high molecular weight and hydrophilicity [43,44].  
   
   B) **Polymorphism:** Polymorphism is known to affect the dissolution rate and solubility of drugs and thus their absorption through biological membranes. It is therefore advisable to study the polymorphic stability and purity of drugs for nasal powders and/or suspensions [45].  
   
   C) **Chemical state of drug:** Absorption of the drug is determined by the chemical form of the drug in which it is presented to nasal mucosa. Chemically alter a drug molecule by adding a bio-cleavable lipophilic moiety is the alternative for improving absorption of the drug which is not having desired absorption properties. The prodrug approach provides many additional challenges which need to be overcome in the drug product developmental process. The toxicity of the prodrug itself needs to be fully evaluated [17].  
   
   D) **Drug solubility and dissolution rate:** Like other routes of administration, the nasal absorption can take place only after the drug’s dissolution. The dissolution rate is important in determining nasal absorption of powder and suspensions dosage forms. Rapid dissolution is very crucial for the drug particles after nasal administration otherwise the particles will be subjected to rapid clearance from the airway with subsequent reduction of the bioavailability [17].  
   
   E) **Lipophilic-hydrophilic balance:** The HLB nature of the drugs affects the absorption process. By increasing lipophilicity, the permeation of the compound normally increases through nasal mucosa. Although the nasal mucosa was found to have some hydrophilic character, it appears that these mucosae are primarily lipophilic in nature and the lipid domain plays an important role in the barrier function of these membranes. Lipophilic drugs like naloxone, buprenorphine, testosterone and 17a-ethinyl-oestradiol are almost completely absorbed when administered intranasal route [46,47].  
   
   F) **Particle size:** It has been reported that particle sizes greater than 10μm are deposited in the nasal cavity. Too fine particles i.e, below 5 μm should be avoided for nasal administration as there are chances of inhalation directly into the lungs [8].
G) **Partition coefficient and pKa:** Jiang et al. conducted a study to find out the quantitative relationship between the physicochemical properties of drugs and their nasal absorption, using diltiazem hydrochloride and paracetamol as model drug. The result showed that a quantitative relationship exist between the partition coefficient and nasal absorption constant. As per the pH partition theory, unionized species are absorbed better compared with ionized species and it holds true in the case of nasal absorption. The extent of absorption is pH dependent, being higher at a pH lower than the pKa and decreases beyond the pKa. In general, the authors found that nasal absorption increases with the lipophilicity of permeant. Various studies indicate that the drug concentration in the cerebrospinal fluid (CSF) rise with an increase in lipophilicity or partition coefficient of the drugs [17].

2. **Physiochemical properties of formulation:**

A) **pH:** The pH of the formulation and nasal surface, can affect a drug’s permeation. To avoid nasal irritation, the pH of the nasal formulation should be adjusted to 4.5–6.5 because lysozyme is found in nasal secretions, which is responsible for destroying certain bacteria at acidic pH. Under alkaline conditions, lysozyme is inactivated and the tissue is susceptible to microbial infection. In addition to avoiding irritation, it results in obtaining efficient drug permeation and prevents the growth of bacteria [48].

B) **Viscosity:** As formulation viscosity increases, the contact time between drug and nasal mucosa enhances and, thereby, the potential of drug absorption increases. At the same time, high viscosity of formulations interferes with normal ciliary beating and/or MCC and, thus, increases the permeability of drugs. This has been observed during nasal delivery of insulin. However, sometimes, enhancing formulation viscosity does not enhance the drug absorption. For example, Zaki et al. performed a study to evaluate the influence of formulation viscosity on the retention time of metoclopramide hydrochloride in nasal cavity and on its absorption. Interestingly, they observed that although the residence time enhanced as viscosity increased the drug absorption diminished [49,50].

C) **Osmolarity:** The osmolarity of the dosage form affects the nasal absorption of the drug; it was studied in the rats by using model drug. The sodium chloride concentration of the formulation affects the nasal absorption. The maximum absorption was achieved by 0.462 M sodium chloride concentration; the higher concentration not only causes increased bioavailability but also leads to the toxicity to the nasal epithelium [51].

D) **Pharmaceutical form:** Nasal drug absorption depends on the physical form of the formulation. A powder form was found to be more effective than liquid formulations in delivering insulin in
rabbits. Resta et al. who compared the powder reported a similar finding and solution dosage forms of sodium cromoglycate in humans suffering with allergic rhinitis. Their data show that both powder and solution forms were effective for treatment and suggested that the powder form was somewhat better than solution because powder is readily washed out with the nasal secretions [17]. Solution and suspension sprays are preferred over powder sprays because the last one easily prompted the development of nasal mucosa irritation. Recently, gel devices have been developed for a more accurate drug delivery. They reduce postnasal drip and anterior leakage, fixing the drug formulation in nasal mucosa. This enhances the drug residence time and diminishes MCC, thereby potentially increases the nasal absorption [52].

3. Physiological factors:

A) Membrane permeability: Nasal membrane permeability is the most important factor, which affect the absorption of the drug through the nasal route. The water soluble drugs and particularly large molecular weight drugs like peptides and proteins are having the low membrane permeability. So the compounds like peptides and proteins are mainly absorbed through the endocytotic transport process in low amounts Water-soluble high molecular weight drugs cross the nasal mucosa mainly by passive diffusion through the aqueous pores (i.e. tight junctions) [53].

B) Blood flow: Nasal mucosa is richly supplied with blood and presents a large surface area making it an optimal local for drug absorption. The blood flow rate influences significantly the systemic nasal absorption of drugs, so that as it enhances more drug passes through the membrane, reaching the general circulation. Indeed, bearing in mind that most of drug absorption takes place by diffusion, the blood flow is essential to maintain the gradient of concentration from the site of absorption to blood. Hence, it is well known that vasodilatation and vasoconstriction may determine the blood flow and, consequently, the rate and extent of drug to be absorbed. Several studies were made to evaluate this influence. For example, Huang et al. showed that phenylephrine, a vasoconstrictor agent, inhibited the absorption of acetylsalicylic acid in nasal cavity. More recently, Kao et al. stated that nasal absorption of dopamine was relatively slow and incomplete probably due to its own vasoconstrictor effect. Based on these observations, it was concluded that vasoconstriction decrease nasal drug absorption by diminishing the blood flow [54,55].

C) Mucociliary clearance: 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 [56]. The absorption of drugs is influenced by the residence (contact) time between the drug and the epithelial tissue. The mucociliary clearance is inversely related to the residence time and therefore inversely proportional to the absorption of drugs administered. The normal mucociliary transit time in humans has been reported to be 12-15 min [25,35].

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

- Viscosity of nasal secretion
- Solubility of drug in nasal secretions
- pH of nasal cavity

E) **Enzymatic degradation:** Internasally administration of drugs avoids gastrointestinal and hepatic first-pass effect. Drugs may be metabolized in lumen of nasal cavity due to the presence of a broad range of metabolic enzymes in nasal tissues. Some examples of enzyme which may play role in enzymatic degradation of drugs are carboxyl esterase, aldehyde dehydrogenases, epoxide hydrolases, glutathione S-transferases and Cytochrome P450 isoenzymes have been found in nasal epithelial cells. The proteolytic enzymes (amino peptidases and proteases) were also found and they play an important role in degradation of calcitonin, insulin and desmopressin. The pharmacokinetic and pharmacodynamic profile of drugs administered through nasal route may be affected by xenobiotic metabolizing enzymes [22,57,58,59].

F) **Pathological conditions:** Diseases such as the common cold, rhinitis, atropic rhinitis and nasal polyposis are usually associated with mucociliary dysfunctioning, hypo or hyper secretions and irritation of the nasal mucosa, which can influence drug permeation [60].

4. **Biological factors:**

A) **Biochemical factors:** Enzymatic barrier in nasal mucosa is directly influenced the drug absorption in nasal cavity. Various enzymes are responsible for the degradation of drug in the nasal mucosa. Enzymes such as peptidases and proteases present in the lumen of the nasal cavity or in the epithelial barrier limit the absorption of drugs such as calcitonin, insulin, leutinising hormone – releasing hormone (LHRH) and desmopressin [60,61].

B) **Structural features:** There are five different sections of nasal cavity: nasal vestibule, atrium, respiratory area, olfactory region and the nasopharynx. These structures and the type of cells, density and number of cells present in that region influence the permeability. Absorption enhancers used in combination with drugs increase the permeation of compounds [62].
Figure 4: Factors Affecting Nasal Drug Absorption and Practical Strategies to Overcome them
Table 2: Common problems associated to low nasal bioavailability of drugs, challenges and possible solutions.

<table>
<thead>
<tr>
<th>Problem</th>
<th>Challenge</th>
<th>Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor physicochemical properties of drug and/or</td>
<td>1. Improve physicochemical properties of drug and/or formulation.</td>
<td>• Prodrugs</td>
</tr>
<tr>
<td>formulation</td>
<td></td>
<td>• Cosolvents</td>
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<td></td>
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<td>• Cyclodextrins</td>
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<tr>
<td></td>
<td></td>
<td>• Pharmaceutical excipients</td>
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<tr>
<td></td>
<td></td>
<td>• Novel drug formulations</td>
</tr>
<tr>
<td>Enzymatic degradation</td>
<td>1. Reduce drug affinity to nasal enzymes.</td>
<td>• Prodrugs</td>
</tr>
<tr>
<td></td>
<td>2. Inhibit nasal enzymes.</td>
<td>• Enzymatic inhibitors</td>
</tr>
<tr>
<td></td>
<td>3. Protect drugs from nasal enzymes.</td>
<td>• Prodrugs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cosolvents</td>
</tr>
<tr>
<td>Low permeability through nasal membrane</td>
<td>1. Increase drug permeability and dissolution.</td>
<td>• Prodrugs</td>
</tr>
<tr>
<td></td>
<td>2. Modify nasal membrane.</td>
<td>• Cosolvents</td>
</tr>
<tr>
<td></td>
<td>3. Enhance drug residence time in nasal cavity.</td>
<td>• Absorption enhancers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Mucoadhesive systems</td>
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<td></td>
<td></td>
<td>• Jelling/Viscosifying agents</td>
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STRATEGIES TO INCREASE NASAL DRUG ABSORPTION:
Various strategies used to improve the absorption of the drug in the nasal mucosa which includes:

**Prodrug:** Prodrug approach is mainly meant for optimizing favorable physicochemical properties such as solubility, taste, odor, stability, etc. Prodrug is usually referred as promoiety, it is to cover the undesired functional groups with another functional groups or prodrugs are pharmacologically inactive compounds that result from chemical modifications of biologically active species. The chemical change is designed to improve some deficient physicochemical property, like membrane permeability and water solubility. After administration, the prodrug, by virtue of its improved characteristics, is brought closer to the receptor site and is maintained there for longer periods of time. Here it gets converted to the active form. Once in the CNS, hydrolysis of the modifying group will release the active compound and is ready to show therapeutic activity. This prodrug approach is mainly for improving the nasal bioavailability especially for the proteins and peptides to enhance the membrane permeability along with increased enzymatic stability. The term ‘pro drug’ was coined by Albert in 1951 [63,64,65].

**Absorption Enhancers:** Along with the common excipients added to maintain drug solubility, stability and ideal formulation characteristics, the formulation may require nasal absorption enhancers when the drug is a polar or a macromolecule which may show an insufficient bioavailability [60]. Their permeation can improve by administered in combination with absorption enhancers which induce reversible modifications on the structure of epithelial barrier [66].
mechanism of action of absorption enhancers is not well known but, generally, they change the permeability of epithelial cell layer by modifying the phospholipidic bilayer, increasing membrane fluidity or opening tight junctions between epithelial cells and, thus, increasing paracellular transport [67]. Eg- Chitosan, Cyclodextrins, Laureth-9, PLGA etc.

**Enzymatic Inhibitors:** Nasal metabolism of drugs can be eliminated by using the enzyme inhibitors. Mainly for the formulation of proteins and peptide molecule development enzyme inhibitors like peptidases and proteases are used [68]. Enzymatic inhibition can also be achieved using certain absorption enhancers (bile salts and fusidic acid) [69]. For example, bestatine and comostate amylase are used as aminoptidases inhibitors and leupeptine and aprotinin as trypsine inhibitors probably involved in the degradation of calcitonin, others are bacitracin, amastatin, boroleucin and puromycin [70].

**Structural modification:** Modification of drug structure without altering pharmacological activity is one of the lucrative ways to improve the nasal absorption. The chemical modification of drug molecule has been commonly used to modify the physicochemical properties of a drug such as molecular size, molecular weight, Pka and solubility are favorable to improve the nasal absorption of drug. Example, chemical modification of salmon calcitonin to ecatonin (C-N bond replaces the S-S bond) showed better bioavailability than salmon calcitonin [71].

**Co-Solvents:** An alternative approach to the use of prodrugs in order to increase drug solubility is the use of co-solvents. Co-solvents most used in intranasal formulations include glycerol, ethanol, propylene glycol and polyethylene glycol and may be of the most importance since they are nontoxic, pharmaceutically acceptable and nonirritant to nasal mucosa [69].

**Particulate drug delivery:** Carriers are used for the encapsulation of drug which prevent exposure of a drug to nasal environment and improve the retention capacity in nasal cavity. Some examples of carriers may include microspheres, liposomes, nanoparticles and niosomes [72]. Microspheres are mainly increase the absorption and bioavailability by adhering to the nasal mucosa and increase the nasal residence time of drug [73].

**FORMULATION BASED ON NASAL DRUG DELIVERY SYSTEM:**

**Liquid dosage forms:**

**Nasal sprays:** Both solution and suspension formulations can be formulated into nasal sprays. Due to the availability of metered dose pumps and actuators, a nasal spray can deliver an exact dose from 25 to 200 μm. The particles size and morphology(for suspensions)of the drug and viscosity of the formulation determine the choice of pump and actuator assembly [74].
Nasal emulsion and microemulsion: It is also a liquid dosage form. The main advantages to formulate this formulation are local application mainly due to the viscosity. The degradation of drug is less in emulsion form [18].

Nasal drops: Nasal drops are one of the most simple and convenient systems developed for nasal delivery. The main disadvantage of this system is the lack of the dose precision and therefore nasal drops may not be suitable for prescription products [8].

Solid dosage forms:

Nasal powder: This dosage form may be developed if solution and suspension dosage forms cannot be developed e.g., due to lack of drug stability. The advantages to the nasal powder dosage form are enzymatic metabolism and sustain drug release, prolonging its effect [75].

Semi-solid dosage forms:

Nasal gels: Nasal gels are high-viscosity thickened solutions or suspensions. Until the recent development of precise dosing devices, there was not much interest in this system. The advantages of a nasal gel include the reduction of post-nasal drip due to high viscosity, reduction of taste impact due to reduced swallowing, reduction of anterior leakage of the formulation, reduction of irritation by using soothing/emollient excipients and target delivery to mucosa for better absorption [76].

Novel drug formulations:

Nanoparticles: Recently, much attention has been given to nanotechnology in many areas. Nanoparticle systems are being investigated to improve drug delivery and intranasal drug administration. 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 [77].

Liposomes: Liposomes are phospholipids vesicles composed by lipid bilayers enclosing one or more aqueous compartments and wherein drugs and other substances can be included. Liposomal drug delivery systems present various advantages such as the effective encapsulation of small and large molecules with a wide range of hydrophilicity and pKa values [78].

Microspheres: 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. Microsphere technology has been widely applied in designing formulations for nasal drug delivery [75,79].
<table>
<thead>
<tr>
<th>DRUG</th>
<th>DELIVERY SYSTEM</th>
<th>PURPOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pentazocine [80]</td>
<td>Microspheres</td>
<td>Avoiding first pass metabolism</td>
</tr>
<tr>
<td>Metoclopramide HCl [82]</td>
<td>Microspheres</td>
<td>Permeation Enhancement</td>
</tr>
<tr>
<td>Domperidone [83]</td>
<td>Microspheres</td>
<td>Selective brain targeting</td>
</tr>
<tr>
<td>Clobazam [84]</td>
<td>Microemulsion</td>
<td>Brain targeting</td>
</tr>
<tr>
<td>Zolmitriptan [85]</td>
<td>Microemulsion</td>
<td>Enhanced bioavailability</td>
</tr>
<tr>
<td>Nimodipine [86]</td>
<td>Microemulsion</td>
<td>Enhanced solubility and brain targeting</td>
</tr>
<tr>
<td>Tetanus toxoid [87]</td>
<td>Liposomes</td>
<td>Improved immune response</td>
</tr>
<tr>
<td>Insulin [88]</td>
<td>Liposomes</td>
<td>Increased insulin permeability</td>
</tr>
<tr>
<td>Insulin, calcitonin [89]</td>
<td>Polyacrylic acid gel</td>
<td>Enhanced absorption</td>
</tr>
<tr>
<td>Insulin [90]</td>
<td>Powder</td>
<td>Improved bioavailability</td>
</tr>
</tbody>
</table>
APPLICATION OF NASAL DRUG DELIVERY SYSTEM:

Local Delivery: Prominent examples for locally acting intranasally administered drugs are decongestants for nasal cold symptom relief, antihistamines and corticosteroids for allergic rhinitis [69].

CNS delivery through nasal route: Intranasal route has promising approaches for delivery of drugs to the brain. The delivery of drugs to the CNS from the nasal route may occur via olfactory neuroepithelium. The transport via trigeminal nerve system from the nasal cavity to CNS has also been described. Drug delivery through nasal route into CNS has been reported for Alzheimer’s disease, brain tumors, epilepsy, pain and sleep disorders [91].

Vaccines delivery through nasal route: Nasal delivery of vaccines has been reported to not only produce systemic immune response, but also local immune response in the nasal lining, providing additional barrier of protection. Delivering the vaccine to the nasal cavity itself stimulates the production of local secretory IgA antibodies as well as IgG, providing an additional first line of defense system [92].

Systemic delivery: The intranasal administration is an effective way to systemically delivery of drugs as an alternative to oral and intravascular routes. Actually, it seems to present fast and extended drug absorption [93].

Delivery of diagnostic drugs: Nasal drug delivery system also play very important role in the delivery of diagnostic agents for the diagnosis of various diseases and disorders in the body. Because the intranasal route better for systemic release of medicament into blood circulation, so can get quick results with less toxicity. Phenolsulfonphthalein is a diagnostic agent used to diagnose the kidney function of the patients [2].

Table 4: Marketed Formulations [4,44,69].

<table>
<thead>
<tr>
<th>Drug Substance (Product name)</th>
<th>Indication</th>
<th>Dosage form</th>
<th>Status</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmon calcitonin (Karil 200 I.E.)</td>
<td>Osteoporosis</td>
<td>Solution (spray)</td>
<td>Marketed</td>
<td>Novartis Pharma</td>
</tr>
<tr>
<td>Desmopressin (Minirin Nasenspray)</td>
<td>Antidiuretic hormone</td>
<td>Solution (spray)</td>
<td>Marketed</td>
<td>Ferring Arzneimitted</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Indication</td>
<td>Formulation</td>
<td>Status</td>
<td>Manufacturer</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------------------------------</td>
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</tr>
<tr>
<td>Buserelin (Profact nasal)</td>
<td>Prostate cancer</td>
<td>Solution (spray)</td>
<td>Marketed</td>
<td>Aventis Pharma</td>
</tr>
<tr>
<td>Nafarelin (Synarel)</td>
<td>Endometriosis</td>
<td>Solution (spray)</td>
<td>Marketed</td>
<td>Pharmacia</td>
</tr>
<tr>
<td>Oxytocin (Syntocinon)</td>
<td>Lactation induction</td>
<td>Solution (spray)</td>
<td>Marketed</td>
<td>Novartis Pharma</td>
</tr>
<tr>
<td>Protirelin (antepan* nasal)</td>
<td>Thyroid diagnostics</td>
<td>Solution (spray)</td>
<td>Marketed</td>
<td>Sanofi-synthelabo Aventis Pharma</td>
</tr>
</tbody>
</table>

REFERENCES:


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