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INTRANASAL DRUG DELIVERY SYSTEM "AN OVERVIEW"

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INTRODUCTION

Smelling tobacco and hellucinogens have been used by inhalations for centuries by different culture worldwide. Intranasal administration offers a variety of attractive options for local and systemic delivery of diverse therapeutic agents. The nasal cavity is easily accessible, rich vascular plexus permits topically administered drugs to rapidly achieve effective blood levels while avoiding intravenous catheters. Due to the high vascularity and permeability of nasal mucosa, nasal delivery is considered for both topical and systemic action and an alternative route for the administration of drugs and biomolecules that are susceptible to enzymatic or acidic degradation and first-pass hepatic metabolism.[1]

Brain and central nervous system disorders like schizophrenia, meningitis, migraine, Parkinson's disease and Alzheimer's disease remains the world's leading cause of disability though tremendous advances occurring in brain research. The major problem in drug delivery to brain is the presence of the BBB. The major challenge in CNS drug delivery is the blood-brain barrier (BBB), which limits the access of most drugs to the brain. It is well established that the BBB is a membranous barrier that segregates the brain from the circulating blood.[2-5]

Nasal route has been explored as the conventional route, for the local delivery of drugs for treatment of local diseases like nasal allergy, nasal infections, rhinitis and nasal congestion. Most of the therapeutic agents have been abandoned because sufficient amount of drug levels in the brain have not been achieved by the drugs via the systemic circulation. Rapid onset of action due to rapid absorption because of direct transport into systemic circulation has led to increasing investigations of the nasal route focusing especially on nasal application for systemic drug delivery.[6]

1. Mechanism of Drug Absorption[7-9]

Passage of drug through the mucus is the first step in the absorption from the nasal cavity. Uncharged as well as small particles easily pass through mucus. However, charged as well as large particles may find it more difficult to cross. Several mechanisms have been proposed but the following two mechanisms have been considered predominantly.

1. The first mechanism of drug absorption involves an aqueous route of transport (Paracellular route). Paracellular route is slow and passive. In above route there is an inverse log-log correlation between the molecular weight of water-soluble compounds and intranasal absorption. Drugs with a molecular weight greater than 1000 Daltons shows poor bioavailability.
2. The second mechanism includes transport of drug through a lipoidal route (transcellular process). Transcellular route is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. Cell membranes may be crossed by drugs by an active transport route *via* carrier mediated means or transport through the opening of tight junctions.

Example: Chitosan opens tight junctions between epithelial cells and hence facilitate drug transport.

From extensive literature search, it can be considered that the nasal delivery is suitable for drugs with the following criteria:

- Drugs which are ineffective orally
- Drugs being used chronically
- Potent medicines
- Rapid entry to the circulation is the main concern
- Appropriate aqueous solubility to provide the desired dose
- No nasal irritation from the drug.
- Rapid onset of action.
- No toxic nasal metabolites.
- Suitable stability characteristics.
- Appropriate nasal absorption properties.
- No offensive odors/aroma associated with the drug.
- Suitable stability characteristics.

Advantages of administering medications via the nasal mucosa

1. The rich vascular plexus of the nasal cavity provides a direct route into the blood stream for medications that easily cross mucous membranes.
2. This direct absorption into the blood stream avoids gastrointestinal destruction and hepatic first pass metabolism (destruction of drugs by liver enzymes) allowing more drug to be cost-effectively, rapidly, and predictably bioavailable than if it were administered orally.
3. For many IN medications the rates of absorption and plasma concentrations are comparable to intravenous administration, and are typically better than subcutaneous or intramuscular routes.
4. Ease, convenience and safety: IN drug administration is essentially painless, and does not require sterile technique, intravenous catheters or other invasive devices, and it is immediately and readily available for all patients.
5. Because the nasal mucosa is nearby the brain, cerebrospinal fluid (CSF) drug concentrations can exceed plasma concentrations. IN administration may rapidly achieve therapeutic brain and spinal cord (CNS) drug concentrations.
6. Over and above the listed advantages following are the other concerns to be taken in to consideration;

- Painless
- Ease of use
- No shot needed
- Avoids first pass metabolism - improving bioavailability over oral and rectal doses
- Nose-brain pathway allows direct delivery to the cerebral spinal fluid
- Compliance not an issue - easy and fast to deliver to any patient
- rapid absorption, higher bioavailability, therefore, lower doses;
- fast onset of therapeutic action;
- avoidance of metabolism by the gastrointestinal tract;
- avoidance of irritation of the gastrointestinal membrane;
- reduced risk of overdose;
- non-invasive, therefore, reduced risk of infectious disease transmission;
- ease of convenience and self-medication;
- improved patient compliance;
- an be a beneficial adjunct product to an existing product;

Drawback of nasal drug delivery

- Limited medications that can be delivered in this fashion
- Many medications are not adequately concentrated to achieve ideal dosing volumes
- Mucosal health impacts absorption
- Mucociliary clearance reduces the residence time of drug
- Not applicable to all drugs
- Insufficient absorption due to lack of adequate aqueous solubility
- Require high volume of dose (25-200 ml) depending on aqueous solubility of drug
- Few drugs can cause nasal irritation
- Few drugs may undergo metabolic degradation in the nasal cavity
- Less suitable for chronically administered drugs
- Drugs requiring sustained blood levels should not be considered for nasal delivery as there is no conventional way of formulating sustained release type nasal dosage forms

2. Nasal Cavity: Anatomy, Physiology and Histology[10-17]

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 is lined with mucus layer and hairs which are involved in those functions, 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.[25-28] 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. The human nasal cavity has a total volume of 15-20 mL and a total surface area of approximately 150 cm^2. It is divided by middle (or nasal) 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.

2.1. Nasal vestibule: Nasal vestibule is the most anterior part of the nasal cavity, just inside the nostrils, and presents an area about 0.6 cm^2. Here, there are nasal hairs, also called vibrissae, which filter the inhaled particles. Histologically, this nasal portion is covered by a stratified squamous and keratinized epithelium with sebaceous glands. These nasal vestibular characteristics are desirable to afford high resistance against toxic environmental substances but, at the same time, the absorption of substances including drugs becomes very difficult in this region.

2.2. 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.

2.3. Respiratory region: The nasal respiratory region, also called conchae, is the largest part of the nasal cavity and it is divided in superior, middle and inferior turbinates which are projected from the lateral wall. 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 surface area, while cilia are essential to transport the mucus toward the nasopharynx. Under physiological conditions, nasal epithelium is covered with a thin mucus layer produced by secretory glands and globet cells. These ones secrete granules filled with mucin, a glycoprotein that determines the viscosity of the mucus. The nasal mucus layer is only 5 µm thick and it is organized in two distinct layers: an external, viscous and dense, and an internal, fluid and serous. Overall, nasal mucus layer consists of 95% of water, 2.5-3% of mucin, and 2% of electrolytes, proteins, lipids, enzymes, antibodies, sloughed epithelial cells and bacterial products. Nasal mucus is indispensable for several physiological functions, such as humidification and warming of the inhaled air, and also offers physical and enzymatic protection of the nasal epithelium against several foreign compounds, including drugs. The protective action results of the adhesive characteristics of mucus to attract inhaled particles or pathogens, which are removed towards the nasopharynx by nasal MCC. The presence of mucin in the nasal mucus layer is crucial because it may trap large molecular weight drugs, such as peptides and proteins. The basal cells that exist in the epithelium are progenitors of other cell-types and lye on a thickened layer of collagen called basement membrane. Beneath of it, there is the lamina propria which is richly supplied with blood vessels, including many very permeable fenestrated capillaries, nerves, glands and immune cells. The last ones produce immunoglobulin A antibodies that confer immunological protection against bacteria and virus.

2.4. Olfactory region: The olfactory region is located in the roof of the nasal cavity and extends a short way down the septum and lateral wall. Its neuroepithelium is the only part of the CNS that is directly exposed to the external environment.

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.

Mucus membrane of nose and its composition

The nasal mucus layer is only 5 µm thick and it is organized in two distinct layers: an external, viscous and dense, and an internal, fluid and serous. Overall, nasal mucus layer consists of 95% of water, 2.5-3% of mucin and 2% of electrolytes, proteins, lipids, enzymes, antibodies, sloughed epithelial cells and bacterial products.

Epithelial cells basically there are two functions of these cells

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

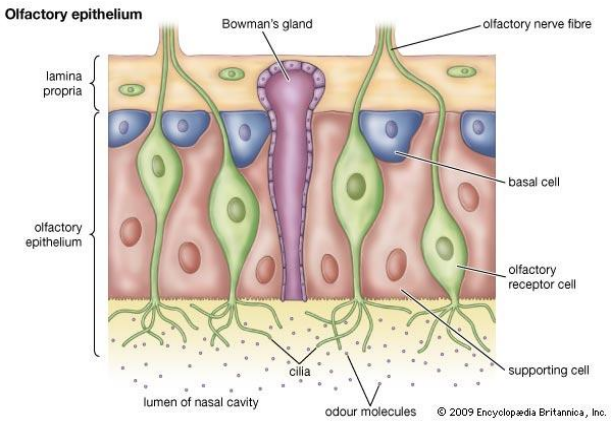

Figure 2: Cell type of the nasal epithelium.

Blood supply to nasal cavity Vasculature of the nasal cavity is richly supplied with blood to fulfill the basic functions such as heating and humidification, olfaction, mucociliary clearance and immunological functions. The nasal vascular bed is so designed that rapid exchange of fluid and dissolved Excipients between blood vessels and nasal tissue can be done easily. The capillary flow in the nasal mucosa was reported to be 0.5 ml/g/min.

Mechanism of Drug Absorption[18-22]

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Example: Chitosan opens tight junctions between epithelial cells and hence facilitate drug transport.

Barriers to Nasal Absorption[23-28]

Low bioavailability

Polar drugs possess bioavailability which is generally low, i.e., not above 1% for peptides such as calcitonin and insulin and 10% for low molecular weight drugs.31 Low membrane permeability is the most imperative factor limiting the nasal absorption of polar drugs and in particular large molecular weight polar drugs such as peptides and proteins.

Drugs traverse the epithelial cell membrane either by the transcellular route, by receptor mediated or vesicular transport mechanisms, or by the paracellular route. Polar drugs with molecular weights below 1000 Da will by and large cross the membrane by means of the transcellular route.32 Larger peptides and proteins have been shown to be able to pass the nasal membrane using an endocytic transport process but only in small amounts.

Mucociliary clearance

Mucociliary clearance results in the speedy removal of the drug from the site of deposition mostly of the peptide drugs. The prompt clearance of the administered formulation from the nasal cavity due to the mucociliary clearance mechanism is an added factor of consequence for low membrane transport. This is principally the case when the drug is not absorbed rapidly enough across the nasal mucosa. It has been shown that for both liquid and powder formulations, which are not bioadhesive, the half-life for clearance is of the order of 15-30 min. The use of bioadhesive excipients in the formulations is an approach to overcome the rapid mucociliary clearance. Mucociliary clearance can also be reduced by depositing the formulation in the anterior, less ciliated part of the nasal cavity thus leading to improved absorption.

Enzymatic Degradation

Numerous compounds are acknowledged to be metabolized by the nasal P 450-dependent monooxygenase system, e.g. nasal decongestant, essences, anesthetics, alcohols, nicotine, and cocaine. Together with the P450 monooxygenase system, quite a few other enzymes exist in the nasal secretions, e.g. lactate dehydrogenase, oxidoreductases, hydrolases, acid phosphatase and esterases. Additionally to cytochrome P450 enzymes, some oxidative Phase 1 enzymes and conjugative Phase 2 enzymatic activity are also present in the nasal epithelium. The Phase 1 enzymes incorporate flavin-monooxygenases and aldehyde dehydrogenases, epoxide hydrolases, carboxylesterases and carbonic anhydrases. The conjugative Phase 2 enzymes comprise of glucuronyl and sulphate transferases, and glutathione transferase. A further contributing, but often less considered aspect to the low bioavailability of peptides and proteins across the nasal mucosa is the likelihood of an enzymatic degradation of the molecule in the lumen of the nasal cavity or at some point in passage through the epithelial barrier. These sites both contain exopeptidases such as mono and diaminopeptidases that can slice peptides at their N and C termini and endopeptidases such as serine and cysteine, which can cleave internal peptide bonds. Utilizing enzyme inhibitors and/or saturation of enzymes may be techniques to surmount this barrier.

Summarizing, the nasal cavity offers unique advantages as an administration site for drug delivery. However, challenges like low permeability for polar and high molecular weight drugs, rapid clearance of the delivery system from the cavity and probable enzymatic degradation of the drug in the nasal cavity should be offset. These challenges can be surmounted by diverse approaches, such as use of absorption enhancers and bioadhesive systems.

Factors Influencing Nasal Drug Absorption

I. Biological Factors

1. Structural features

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

2. Biochemical changes

Enzymatic barrier to the delivery of drugs is nasal mucosa because of the presence of a large number of enzymes, which include oxidative and conjugative enzymes, peptidases and proteases. These enzymes are responsible for the degradation of drugs in the nasal mucosa and result in creation of a pseudo-first-pass effect. Metabolism of nasal decongestants, alcohols, nicotine and cocaine IS due to p450 dependent monoxygenase system.

Protease and peptidase were responsible for the presystemic degradation and subsequent lower permeation of various peptide drugs, such as calcitonin, insulin, LHRH and desmopressin. To overcome these degradations various approaches have been used. These include the use of protease and peptidase inhibitors such as bacitracin, amastatin, boroleucin and puromycin.

II. Physiological factors

1. Blood supply and neuronal regulation

Nasal mucosa is highly permeable site. High blood supply due to parasympathetic stimulation gives congestion and low blood supply due to sympathetic stimulation gives relaxation, regulate the rise and fall in the amounts of drug permeated, respectively.

Based on the above observations, we can conclude that the increased permeability of a compound is due to parasympathetic stimulation.

2. Nasal secretions

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

- Viscosity of nasal secretion. The viscous surface layer will inhibit the ciliary beating if the sol layer of mucus is too thin and mucociliary clearance is impaired if sol layer is too thick, because contact with cilia is lost. Permeation of the drug is affected due to impairment of mucociliary clearence by altering the time of contact of drug and mucosa.
- Solubility of drug in nasal secretions. For permeation of drug solublisation is necessary. A drug needs to have appropriate physicochemical characteristics for dissolution in nasal secretions.
- Diurnal variation Nasal secretions are also affected by circadian rhythm. Permeation of drug is altered at night due to secretions and clearance rates are reduced. Chronokinetics dictate the pattern and rate of permeation in such cases.
- pH of nasal cavity variation in pH is observed between 5.5–6.5 in adults and 5.0–7.0 in infants. Permeation of drug is greater if the nasal pH is lower than pKa of drug because under such conditions the penetrant molecules exist as unionized species. Increase or decrease in the permeation of drug is observed because ionization is affected by change in pH of mucus, depending on the nature of the drug. pH of formulation should be between 4.5 to 6.5 for better absorption and should also have good buffering capacity.[28]

3. Mucociliary clearance (MCC) and ciliary beating

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

4. Pathological conditions

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

5. Environmental conditions

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

6. Membrane permeability

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

III. Physicochemical Properties of Drugs[29-35]

1. Molecular weight, lipophilicity and pKa

Lipophilic drugs such as propranolol, progesterone and fentanyl are well absorbed from the nasal cavity, exihibiting pharmacokinetic profiles similar to those obtained after intravenous administration.

These drugs are absorbed quickly and efficiently across the nasal membrane via transcellular mechanisms. This observation is true for lipophilic compounds having molecular weight lower than 1 kDa.

The extent of nasal absorption of lipophilic drugs bigger than 1 kDa is significantly reduced. On the other hand, the rate and degree of nasal absorption of polar drugs is low and highly dependent of the molecular weight. Drug absorption is expected to be diminished with decrease lipophilicity because the nasal membrane is lipophilic.

Thus we can say that polar drugs may not easily transport across nasal membrane. Whenever lipophilicity is too high, the drug permeation through the wall may be reduced because drug does not dissolve easily in the aqueous environment of nasal cavity.

2. Stability[3,7,40]

Biological, chemical and physical drug stability studies are a major consideration in all process during the development of new drug formulations. The biological stability of nasally administered drugs may reduce due to the metabolism of drugs by defensive enzymatic mechanisms by nasal cavity. To overcome this difficulty a variety of strategies may be followed, mainly through the use of prodrugs and enzymatic inhibitors.

3. Solubility[4,25,35,37]

For drug absorption, drug dissolution is a pre-requisite because molecularly disperse form of a drug may cross the biomembranes.

Therefore the drug must be dissolved in the nasal cavity fluid before absorption. Drug allowed enough contact with the nasal mucosa which may show slow absorption. Drugs with poorly soluble in water may require high doses hence can cause a problem. The problem can be overcome by enhancing drug solubility using various techniques.

IV. Physicochemical Properties of Formulation[35-40]

1. Viscosity[35]

Formulation with higher viscosity has a better contact time thus increases the absorption. At the same time, high viscosity enhanced the permeability of drugs. This has been observed during nasal delivery of insulin, acyclovir and metoprolol. Zaki et al. observed that the residence time enhanced as viscosity increased but drug absorption diminished.

2. Ph[18,25,37]

The pKa of drug and pH at the absorption site plays important role in absorption of drug through nasal route. Thus the stability can achieve by proper selection of pH of formulation. However, the pH of formulation should be near on human nasal mucosa (5.0-6.5) to prevent the sneezing.

3. Pharmaceutical form[3,4]

Nasal drops are the simplest and the most convenient nasal pharmaceutical dosage form, but the exact amount of drug delivered is not easily quantified and often results in overdose. Moreover, rapid nasal drainage can occur when using this dosage form. Instead of powder sprays solution and suspension sprays are preferred because powder spray may cause nasal mucosa irritation. Nowadays nasal gel has been developed for accurate drug delivery. This increases the nasal absorption by enhancing the drug residence time and diminishing MCC.

4. Pharmaceutical excipients[3,4]

In nasal formulations pharmaceutical excipients are selected accordingly to their functions. The most commonly used Excipients are Solubilizers, buffer components, antioxidants, preservatives, humectants, and gelling/viscosifying agents.

CONCLUSION

There are multiple options to deliver medications to patients. The patients individual needs and issues, as well as the medication that one wishes to administer will determine the most appropriate option(s) for providing that medication. In selected cases, IN delivery has many advantages over other options.

Almost all molecules absorbed through the gut enter the blood through the "portal" circulation and are transported to the liver on their way into the main blood pool of the body. The liver is full of enzymes that breakdown these molecules (metabolize) and plays an important role in removing toxins from the body. In the case of medications that are taken by mouth, it is common for most of the medication to be destroyed by the liver and never make it into the main blood pool of the body. This destruction by the liver is called "hepatic first pass metabolism". Drugs that are delivered by other routes (IV, IM, SQ, nasal) do not enter the portal circulation and are not subjected to first pass metabolism.

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