Nasal Drug Delivery: Advantages, Limitations and Future Perspectives – A systemic overview

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ABSTRACT

Intranasal drug route administration has its efficacy and potentiality over other alternative drug routes, not only considered by modern scientists, researchers, clinicians but also various traditional systems of medicine viz. Ayurveda, Unani, Persian has its use from ancient time. It provides most promising route for those drugs showing low bioavailability, used orally. Being highly vascularized, permeable, having adequate surface area (150 cm^2) and volume capacity 15 ml, nasal cavity provides a rapid absorption and onset of action. Intra-nasal route leaves hepatic first-pass metabolism. It is non-invasive, painless, no sterile preparation, handy and suitable for self –medication. The present article depicts the benefits and potentiality of nasal drug delivery comparing to others routes. The goal of this review is to provide an overview on the anatomical consideration of nasal cavity, mechanism of absorption, its advantages, limitations, factors affecting this route and the future perspectives of intra-nasal route.

Keywords: nasal drug delivery, shamoom, bioavailability, trans-cellular process, neuro-cranium

INTRODUCTION

Since the civilization of human beings, healthcare system remains progressive. Physicians from ancient time to the modern age had been using different forms of drug delivery system to the patients. In the complementary or traditional systems of medicine viz. Ayurveda, intra-nasal drug delivery was a promising route rather than oral for treatment which is known as Nasya Karma. [1,6] In the traditional Persian Medicine, its pharmaceutical literatures described over 100 dosage forms and among them nasal application as a drug

route administration has been mentioned.[7-8] For the local pharmacological effects of the drugs nasal application as an alternate route remained in use for many years.[9]

The nasal drug delivery was also considered in other traditional systems of medicine viz. Unani and Persia.[10, 11]Early Persian practitioners were aware of the systemic effect of nasally applied medicaments. Predictable with this conviction, eleven sorts of nasal methodologies incorporating powder, fluid and vaporous structures have been recorded in related compositions. Among them, powdered structures were partitioned to nasal insufflation (Nofookh) and errhine or sternutator medication (Otoos). Then again, arrangements or fluids contained nasal drop (Qotoor) and nasal snuffing drop (Saoot) just as fluid snuff plan (Noshoogh). At last the last detailed nasal measurement structures found as vaporous arrangements were as fumigations (Bakhoor), restorative fume washes or bubbled fluid concentrates (Enkebab) and inward breath structures (Lakhlakheh) just as fragrance specialists (Ghalieh).Interestingly, smelling a herb for a period of time was also considered as a pharmacological approach (*Shomoom*).[12, 13, 14]

For opting a preferred route than other conventional routes, nasal drug delivery performs better results for those drugs like proteins and peptides, which are active in low doses and show no minimal oral bioavailability.[15] At the end of the intra-nasal route, the concentration time profiles we achieve are just equivalent to the results of intra-venous route, which leads to rapid onset of pharmacological activity.[16]Proteins and peptides when used via intra-nasal route, low degree of absorption, the fast movement away from the absorption site in the nose which on account of the mucocilliary mechanism.[17]

In recent years, for systemic drug delivery, it has been emphasized on nasal drug delivery.[18] For the administration of vaccines intra-nasal route has also been considered.[19, 20] Some peptides viz. calcitonin, insulin, desmopresin, buserelin, Luteinizing hormone, growth hormone and adreno-corticotrophic hormone have been given via intra-nasal getting better results. In relation to this many steroids viz. cortico-steroids, progesterone, estradiol and testosterone have been successfully used.[21, 22] In addition to nasal drug delivery, many forms viz. nasal spray, nasal pump, gels, suspensions and powders have been documented.[23]

The anatomical, physiological and histological features of nasal cavity give rise to quick onset and rapid systemic drug absorption.[24] The use of nasal drug delivery leaves the gastrointestinal and hepatic metabolism and causes to increase the bioavailability of drug.[25, 26]

Beside this it also provides many benefits in the form of non-invasiveness, painless and convenient drug delivery.[27, 28] In the present review article, emphasis in focused on the advantages, limitations of nasal drug delivery, anatomy of nasal cavity, physiology of nasal absorption, factors influencing nasal absorption as well as future perspectives of nasal drug delivery.

ANATOMY OF NASAL CAVITY

The two main segments neurocranium and viscerocranium forms the human skull. The brain and its associated structures are protected and surrounded by neurocranium while viscerocranium consisting several bones forms the facial skeleton including face, eyes, mouth and nasal cavity.[29, 30]

The nasal septum divides the nasal cavity onto two halves and it extends from anterior nares to posterior choanae. There are three main regions in the nasal cavity viz. vestibule, olfactory region and respiratory region. Anatomically, nasal cavity is the space between the base of skull and the roof of the mouth; superiorly it is supported by the ethmoid bones, laterally by the ethmoid, maxillary, inferior nasal conchae.[34]

Vestibule- It is the anterior most part of the nasal cavity, just inside the nares, having an area about 0.6 cm^2.[31]

Atrium- It is the area between vestibule and respiratory region, its anterior part is composed of by stratified squamous epithelium while posterior part has pseudostratified columnar cells presenting microvilli.[32, 33]

Respiratory region- It is the largest part of the nasal cavity, having three turbinates: superior, middle and inferior.[34] It is lined by the nasal respiratory epithelium, consists of pseudostratified columnar epithelial cells, globet cells, basal cells, mucous and serous glands.[35]

Olfactory region- It is located at the roof of nasal cavity extending a little way down the medial wall and lateral wall. Neuroepithelium of this area, the lone piece of focal sensory system is straightforwardly presented to the outer climate. It consists of pseudostratified but also has specialized olfactory receptors for smell perceptions.[32,33]In the adult human, nasal cavity has total surface area about 150 cm^2 and the total volume about 15 ml.[36,37,38,39,40,41]

Physiologically, nasal cavity has two functions, breathing and olfaction. The high degree of vascularization and permeability of nasal mucosa has attracted the researchers towards nasal drug delivery.[42] The nasopharynx contains nasal associated lymphoid tissue. Nasal cavity is lined with mucus layer and hairs which are involved in these functions are trapping inhaled particles and pathogens. Moreover, mucocilliary clearance, immunoglobulin activities and metabolism of endogenous substances are also essential functions of nasal structures.[34, 43,44,45,46]

The mucous secretion is composed of 95% water, 20% mucin, 1% salts, 1% of other proteins such as albumin, immunoglobulins, lysozomes and lactoferrin and b 1% lipids.47 The mucous secretion gives immune protection against inhaled bacteria and viruses. It also performs a number of physiological functions. (a) It covers the mucosa, physically and enzymatically protects it. (b) The mucous has water holding capacity. (c) It exhibits surface electrical activity. (d) It permits efficient heat transfer. (e) It acts as adhesive and transports particulate matter towards the nasopharynx.[48]

PHYSIOLOGY OF NASAL ABSORPTION

For nasal absorption of drug, it must pass through the mucous layer; the mucous, large/charged particles are unable to cross it while small charged particles easily pass through this layer. Mucin, the principle protein of mucous having the tendency to bind solutes, produces hindering diffusion. Additionally, structural changes in the mucous layer are possible due to environmental changes.[49]Earlier many mechanisms were established for absorption through nasal mucosa, but two mechanisms are mainly used, para-cellular and trans-cellular transport.

1. The first mechanism comprises aqueous route of transport, known as para-cellular route, it is slow and passive. There is an inverse log-log correlation between intra-nasal absorption and the molecular weight of water soluble compounds. The drug having molecular weight greater than 1000 Daltons shows poor bio-availability.[50,51]
2. The second mechanism comprises transport through lipid route, known as trans-cellular process, responsible for the transport of lipophilic drugs that show a rate dependency on their lipophillicity. Drug also cross cell membranes by an active transport route via carrier mediated means or transport through the opening of tight junctions.50 For example, Chitosan, a natural polymer from shellfish, open tight junctions between epithelial cells to facilitate drug transport.[52]

FACTORS INFLUENCING NASAL DRUG ABSORPTION

A few variables influence the foundational bioavailability of medications which are controlled through the nasal course. The components can be influencing to the physiochemical properties of the medications, the anatomical and physiological properties of the nasal cavity and the sort and qualities of chose nasal medications delivery support. These factors play key role for most of the drugs in order to reach therapeutically effective blood levels after nasal administration.

1) Physiochemical properties of drug.
2) Molecular size.
3) Lipophilic-hydrophilic balance.
4) Enzymatic degradation in nasal cavity.

2) Nasal Effect

1) Membrane permeability.
2) Environmental pH
3) Mucociliary clearance
4) Cold, Rhinitis.

3) Delivery Effect

1) Formulation (Concentration, pH, osmolarity)
2) Delivery effects
3) Drugs distribution and deposition.
4) Viscosity

1) Physiochemical properties of drug

Molecular size

The sub-atomic size of the medication impact assimilation of the medication through the nasal course. The lipophilic medications have direct connection between the MW and medication saturation though water dissolvable mixtures portray a backwards relationship. The rate of permeation is highly sensitive to molecular size for compounds with MW ≥ 300 Daltons.[53]

Lipophilic-hydrophilic balance

The hydrophilic and lipophilic nature of the drug also affects the process of absorption. By expanding lipophilicity, the penetration of the compound ordinarily in-wrinkles through nasal mucosa. Although the nasal mucosa was found to have some hydrophilic character, apparently these mucosae are essentially lipophilic in nature and the lipid space assumes a significant part in the hindrance capacity of these layers.[54, 55]

Enzymatic degradation in nasal cavity

If there should arise an occurrence of peptides and proteins are having low bioavailability across the nasal hole, so these medications may have possibility to go through enzymatic corruption of the medication particle in the lumen of the nasal cavity or during section through the epithelial obstruction.[56]

2) Nasal effect factors

Membrane permeability

Nasal stratum permeability is the main factor, which influence the ingestion of the medication through the nasal course. The water dissolvable medications and especially huge atomic weight drugs like peptides and proteins are having the low membrane penetrability. So the compounds like peptides and proteins are mainly absorbed through the endocytotic transport process in low amounts.[57]

Environmental pH

The biological pH assumes a significant part in the productivity of nasal medication retention. Little water-dissolvable mixtures, for example, benzoic acid, salicylic acid, and alkaloid acid show that their nasal assimilation in rodent happened furthest degree at those pH esteems where these compounds are in the non-ionized form.[58]

Mucociliary clearance

Mucociliary flexibility is a one of the elements of the upper respiratory plot is to forestall toxic substances (allergens, microscopic organisms, infections, poisons and so forth) from arriving at the lungs. At the point when such materials hold fast to, or disintegrate in, the bodily fluid coating of the nasal cavity, they are shipped towards the nasopharynx for possible release into the gastrointestinal tract.[59]

Cold, Rhinitis

Rhinitis is a most every now and again related regular illness, it impact the bioavailability of the medication. It is mainly classified into allergic rhinitis and common, the symptoms are hyper secretion, itching and sneezing mainly caused by the viruses, bacteria or irritants.

3) Delivery effect factors

Elements that influence the conveyance of medication across nasal mucosa, for example, surfactants, portion pH, osmolarity, consistency, molecule size and nasal freedom, drug design can be utilized to bit of freedom to improve absorption.

Formulation (Concentration, pH, Osmolarity)

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. Notwithstanding escaping disturbance, it brings about getting effective medication saturation and forestalls the development of microorganisms. Concentration inclination assumes vital part in the ingestion/pervasion interaction of medication through the nasal layer because of nasal mucosal harm. Models for this are nasal ingestion of L-Tyrosine was appeared to increment with drug focus in nasal perfusion tests. Another is assimilation of salicylic corrosive was found to decay with concentration. This decline is likely due to nasal mucosa damage by the permanent.[61]

The osmolarity of the dose structure influences the nasal assimilation of the medication; it was concentrated in the rodents by utilizing model medication. The sodium chloride convergence of the detailing influences the nasal retention. 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.[62]

Drugs distribution and deposition

The medication dispersion in the nasal pit is one of the significant components, which influence the proficiency of nasal assimilation. The method of medication organization could impact the dissemination of medication in nasal hole, which thusly will decide the retention proficiency of a medication. The assimilation and bioavailability of the nasal measurement frames mostly relies upon the site of air. The anterior portion of the nose gives a drawn out nasal inhabited time for temperament of formulation, it enhances the absorption of the drug. And the posterior chamber of nasal cavity will use for the deposition of dosage form; it is eliminated by the mucociliary clearance process and hence shows low bioavailability.[63]

Viscosity

A higher thickness of the formulation increases contact time between the drug and the nasal mucosa thereby increasing the time for infiltration. Simultaneously, highly sticky formulations hinder with the normal functions like ciliary beating or mucociliary clearance and thus modify the penetrability of medications.

ADVANTAGES OF NASAL DRUG DELIVERY[64, 66, 67,68,69,70]

Drugs that are orally not absorbed can be delivered to volume that can be delivered into nasal cavity are restricted to 25–200 μL

1. High-molecular-weight compounds cannot be delivered through this route (mass cut off ~1 kDa).
2. Adversely affected by pathological conditions
3. Huge interspecies inconstancy is seen in this track.
4. Normal defense mechanisms such as mucociliary clearance and ciliary beating affect the permeability of the drug.
5. The enzymatic blockade to the penetrability of medications.
6. Irritation of nasal mucosa by drugs.
7. Limited understanding of mechanisms and less developed models at this stage.
8. Enhanced patient compliances.
9. Decrease risk of overdose
10. Fast onset of therapeutic action.

DISADVANTAGES OF NASAL DRUG DELIVERY[64, 65, 66]

1. The nasal cavity provides a smaller absorption surface area when compared to gastrointestinal tract.
2. There is a opportunity of exasperation when compared to the oral delivery system since.
3. The substance and constituents added to the dosage form may cause local side effects and irreversible damage of the cilia on the nasal mucosa.
4. There could be a mechanical loss of the dosage form into the other parts of the respiratory tract like lungs due to the improper technique of administration.
5. Certain surfactants utilized as synthetic enhancers may disturb and even break up the film in high absorption.

LIMITATIONS OF NASAL DRUG DELIVERY[64, 66, 67, 68]

1. There is a risk of both of irreversible damage of the cilia of the nasal mucosa and local side effects from both constituents and substances additional to the dosage form.
2. There can be a mechanical loss of the dosage form in other parts of the respiratory system, for example, lungs due to the inappropriate technique of administration.
3. A portion of the surfactants utilized as a substance impetus and may cause or even break up the layer at high concentrations.

FUTURE PERSPECTIVES

In the recent years, nasal drug delivery has gained the promising status along other various drugs administration routes. Its potential benefits will open the doors for future need, the treatment of acute and chronic diseases. As previously discussed that nasal cavity provides a maximum surface area for drug absorption, allowing small charged particles to cross easily, it will help in developing vaccines as well as development of such drugs directly targeting the brain for obtaining the therapeutic effects in central nervous system to relieve disorders i.e. Alzheimer's, Parkinoson's, Multiple sclerosis. Development in nanotechnology has appeared to connect the hindrance of natural and actual sciences by applying nanostructures and nanophases, particularly in nanomedicine and nano based drug delivery system.[71, 72, 73] Nanomaterials, having the size from 1-100 nm, influences the frontiers of nanomedicine.[74, 75, 76]

The contemporary needs to be focused are to rectify solubility/stability, biological half-life and bio-availability augmentation of inadequate absorbed drugs. To make the nasal drug delivery well-turned scientists and researchers should aim on: (a) how to increase efficacy and reduced side-effects of drugs by developing new delivery techniques. (b) to develop improved and integrated nasal formulations. (c) to develop new nasal devices for delivering macromolecules, using bio-technology and high technology.

CONCLUSION

Despite that nasal drug delivery has several limitations which must be overcome to develop a successful nasal drug. For regulating the nasal drug absorption, various important factors viz. physiological conditions, physiochemical properties of drugs and nasal formulations play a key role. So, there is potentiality of more drugs, which will come among the people in form of nasal formulations with improved effectiveness and less side-effects.

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CONFLICT OF INTEREST

Authors report none.

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