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NASAL DRUG DELIVERY- AN OVERVIEW

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ABSTRACT: Over the past few decades the nasal route has gained widespread interest as a promising and an alternative route to oral and parenteral drug delivery. The nasal mucosa being highly vascularized and permeable provides a rapid onset of therapeutic action. It is a convenient, compliant and needleless mode of drug delivery suitable for the treatment of both acute and chronic diseases. In addition, nasal drug delivery circumvents the issues of poor and slow absorption, first pass hepatic metabolism, blood brain barrier. Intranasal administration can be used to deliver small polar molecules, hormones, vaccines, proteins and peptides. Despite the several potential advantages the nasal route has certain limitations. The present review outlines the various merits and demerits of intranasal administration, the relevant anatomy and physiology of the nasal cavity. The present article gives a detailed description of the factors affecting drug absorption and the different strategies that can be used to improve the drug absorption.

INTRODUCTION: Conventionally, the oral route of drug administration was preferred due to ease of ingestion, pain avoidance and versatility [1]. Many orally administered drugs show poor bioavailability which prompted to search for an alternative route of drug delivery. The use of nasal cavity as a route of drug delivery has been practiced since ancient times. Nasal route is an attractive alternative for local as well as systemic delivery of drugs especially when rapid absorption and effect are desired [2, 3]. This is due to the avoidance of presystemic elimination of gastrointestinal tract, bypass of the first pass effect, extensive blood supply and porous endothelial membrane [4, 5, 6].

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Traditionally, it has been widely used for the symptomatic relief and treatment of various topical nasal conditions. It has now emerged as a promising choice to both oral and parenteral route [7]. Intranasal drug administration can be used for the delivery of drugs ranging from small chemicals to large macromolecules such as peptide/protein therapeutics, hormones etc. [8]. Drugs can be effectively delivered directly to the CNS via the nasal route that circumvents the Blood Brain Barrier (BBB) [9]. Nasal route also attracts attention of many pharmaceutical companies specializing in vaccine delivery [10].

It can be considered for rapid mass immunization [4]. Various novel concepts have proved to be suitable candidates for the delivery of nasal vaccines such as synthetic biomimetic supramolecular biovectors (SMBVs) [11]. Hence it is a useful and reliable route for the treatment of not only nasal diseases but also

for a range of acute or chronic conditions that requires systemic drug availability [5].

Intranasal drug formulations are limited to the drugs which are active in low dose and possess sufficient aqueous solubility. Many drugs having lipophilic or large hydrophilic character show an insufficient nasal absorption. Different solubilizers and absorption enhancers can be used to increase the absorption efficiency of drugs such as the use of bio adhesive polymers (e.g. Microspheres of albumin, starch and DEAE-dextran) and cyclodextrins (e.g. Methylated β-cyclodextrins) [3, 12, 13]. Further a number of strategies can be applied in the design of the delivery devices to achieve effective and safe delivery of therapeutics through the nasal route.

An efficient nasal product can be designed by keeping three things in mind: the drug, the delivery carrier and the administration device [14].

Depending on the lipophilic nature of the drug, it can be absorbed both actively and passively. Active absorption takes place via transcellular pathway and passive absorption via paracellular pathway. The other means of drug permeation across the nasal mucosa are carrier mediated transport, transcytosis and transport through intercellular tight junctions [15]. The present review highlights the anatomy and physiology of the nasal cavity, merits and demerits of the nasal route for drug administration. It also gives a detailed description of the various factors affecting the permeability of the drug across the nasal cavity and different strategies to improve nasal absorption.

Anatomy and physiology of nasal cavity:

The nasal cavity lies dorsally to the vestibulumnasi which is lined with squamous epithelium [16]. The nasal cavity causes filtration, warming and humidification of the inhaled air before it reaches the lower airways and thus plays an important protective function [17]. The goblet cells continuously produce mucus which traps any inhaled particle while the propulsive force generated by ciliated cells transports the mucus towards the nasophyranx and gastrointestinal tract for elimination. This cleansing mechanism is called mucociliary clearance (MCC). The MCC is dependent on characteristics of the covering mucus which can be affected by various ailments and the function of the cilia. The MCC time is approximately 20 min and is subjected to great inter subject variability. The MCC has a direct influence on the drug absorption efficiency through the nasal mucosa [18]. The mucus moves at an approximate rate of 5 to 6 mm/min through the nose resulting in particulate clearance from the nose in 15 to 20 min. The total surface area of the human nasal cavity is about 180 cm^2 and a total volume of about 16 to 19 ml. Further, the nasal cavity is divided into two nasal cavities through the septum. The approximate volume and surface area of each cavity is 7.5 ml and 75 cm^2 respectively [19].

Anatomically, the nasal cavity can be divided into three functional regions [6]:

Vestibular region – It is situated just inside the nostrils and is covered with stratified, keratinised and squamous epithelium with sebaceous glands. It has an area of 10 to 20 cm^2 and is considered to be the least important of the three regions in respect of drug absorption. The vestibular area acts as a baffle system where the nasal hairs filter the inhaled particles [5, 20].

Respiratory region - It is the largest part of the nasal cavity, has an area of about 130 cm^2 and consists of three turbinates namely inferior, middle and superior which are responsible for humidification and temperature regulation of inhaled air. The nasal absorption of drugs is considered to take place mainly in the respiratory region because it is having the highest degree of vascularity [3, 5].

Olfactory region – It is located in the roof of the nasal cavity and on the upper part of the nasal septum. It has an area of about 10 - 20 $cm^2$and contains the receptors for the sense of smell. Human olfactory region consists of thick connective tissue lamina propria, upon which rests the olfactory epithelium. The cilia are non- motile in this region in contrast to the respiratory region because they lack the dyne in arms which contain the Mg^{+2} ATPase that generates the force for ciliary motility[20].

The nasal cavity also contains nasal associated lymphoid tissue (NALT). In humans, the NALT is normally associated Waldeyerring, contains specialized M- like cells which are specialized for the uptake and transcytosis of macromolecules and microorganisms. Lymphoid tissue present under the nasal mucosa contains B and T lymphocyte follicles, macrophages and dendritic cells which produce systemic immune response [21].

Merits and demerits of nasal drug delivery: [22, 23, 24, 25]

Nasal drug delivery has got attention in the pharmaceutical field due to anatomical, physiological and histological characteristics of the nasal cavity.

Merits:

- Easily accessible, non- invasive, painless
- Rapid and quick onset of action
- Avoids drug degradation due to gastrointestinal tract
- Bypass first pass metabolism
- Bypass the blood brain barrier
- Higher bioavailability and thus lower dose requirement
- Lower risk of overdose
- Self- medication
- Minimal side effects due to low dose
- No complex formulation requirement
- No sterility conditions to be maintained [26]
- Improved convenience and compliance
- Convenient for long term therapy

Demerits:

- Nasal irritation
- Mucociliary clearance
- Enzymatic barrier to permeability of drug
- Restricted delivery volume in nasal cavity
- Large interspecies variability
- High molecular weight compounds cannot be delivered
- Local side effects and irreversible damage of cilia
- Smaller absorption surface area
- Limited understanding of mechanisms and less developed models at this stage

Mechanism of intranasal absorption:

The initial step in the absorption of drugs from the nasal cavity involves passage through the mucus layer. Small, uncharged drugs easily pass through this layer whereas large and charged molecules may find it difficult to cross because the mucin protein present in the mucus binds to the solutes and thus interferes with the diffusion process. Any structural change in the mucus layer which may be the effect of environment has a direct influence on drug absorption [27]. Following mechanisms are involved in nasal absorption:

a) First mechanism: It involves drug absorption through the paracellular route which is an aqueous route of drug transport. There is an inverse log-log relationship between intranasal absorption and molecular weight of water soluble species. The drugs having greater than 1000 Dalton molecular weight shows poor bioavailability. The absorption through this route is slow and passive [28].

b) Second mechanism: It is also known as paracellular process. It involves drug transport through a lipoidal route and is mainly responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. Drugs are also absorbed by active transport via carrier mediated means or through the opening of tight junctions [28], like Chitosan (a natural biopolymer) opens tight junctions to facilitate drug transport between epithelial cells [29].

Factors affecting nasal drug absorption:

The different factors that affect the bioavailability of intranasally administered drugs can be categorized as follows:

1. **Biological factors:**
   a) Biochemical changes
   b) Structural features

2. **Physiological factors:**
   a) Mucociliary clearance
   b) Nasal secretions

c) pH of nasal cavity
d) Blood flow
e) Pathological conditions
f) Environmental effects

3. Physicochemical properties of drug:
a) Molecular weight
b) Size
c) Solubility
d) Lipophilicity
e) $pk_a$and partition coefficient
f) Stability

4. Physiochemical properties of formulation:
a) Dosage form
b) pH
c) Osmolarity
d) Viscosity

1. Biological factors:

a) Biochemical changes: In the nasal mucosa various enzymes are present which act as a barrier for the absorption of drugs. These include oxidative and conjugative enzymes, peptidases and proteases such as cytochrome P450 (CYP-450) -dependent monooxygenase, carboxyl esterase, and amino peptidase, which cause degradation of the administered drug [30].Various strategies can be employed in order to overcome these hurdles. One of which can be the use of enzymatic inhibitors, such as bacitracin, amastatin, boroleucin, and puromycin[31, 32].

b) Structural features: The anatomical features of the nasal cavity affect the drug permeability through the nasal mucosa. The respiratory region is most suitable for drug permeability as it is highly supplied with blood which provides a large surface area [8, 15]. The presence of microvilli on cells also greatly increases the surface area for absorption [3].

2. Physiological factors

a) Mucociliary clearance (MCC): It is known as self defence mechanism of the respiratory tract. It filters the foreign particles, which get attached to mucus layer by draining them into the nasophyranx and are cleared by the gastrointestinal tract [33]. So MCC alters the residence time of the drugs administered from the nasal cavity thereby altering the drug absorption [34]. In physiological conditions, 5 mm/min is the rate of mucus transportation and 15-20 min is the reported as the transit time in human nasal cavity. Thus, if there is decrease in the MCC, there will be increase in the residence time of the therapeutics in nasal mucosa. Which will results into increased permeation and vice versa [22]. The permeation of drug can be enhanced by increasing the time of contact between mucus membrane and drug by using mucoadhesive drug delivery system [4].

b) Nasal secretions: The nasal secretion vary from person to person and depend on the individual health condition. The viscosity and rate of nasal secretion greatly affects the bioavailability. The production of mucus is about 1.5-21 ml per day. As the rate of nasal secretion is increased, bioavailability of the drug is decreased [35]. The viscosity of the nasal secretion affects drug permeability through the nasal mucosa. The viscous surface layer will inhibit the ciliary beating if the sol layer of mucus is too thin and if the sol layer is too thick, mucociliary clearance is impaired which in turn affects the drug permeation by altering the contact time with the mucosa. A drug needs to be solubilized in the nasal secretions before it permeates. Thus, appropriate physicochemical characteristics of the drug are required for dissolution in nasal secretions[3, 36, 37].

c) pH of the nasal cavity: Drug permeation is usually greater at a nasal pH that is lower than the drug's pK_a because under these conditions the penetrant molecules exist as unionized species. Normally, the pH of the nasal cavity varies between 5.5-6.5 in adults and 5.5-7.0 in infants. Depending on the nature of the drug, a change in the pH of the mucus affects the ionizations which in turn,

can increase or decrease the drug permeation [38, 39].

d) Blood flow: Nasal mucous membrane is richly supplied with the blood. Nasal absorption of drugs is influenced by the blood flow rate as nasal congestion and relaxation regulate the rise and fall in amounts of the drug permeated, respectively. Thus, it may be concluded that parasympathetic stimulation results in increased permeability [3].

e) Pathological conditions: Any factor that can influence the efficacy and pace of mucociliary clearance, nasal secretions and irritation of the nasal mucosa may modify the drug absorption profile such as in common cold, rhinitis, atrophic rhinitis and nasal polyposis [8, 40].

f) Environmental effects: A linear increase in ciliary beat frequency occurs with the increase in temperature, whereas temperature in the range of 24^0C causes a moderate reduction in the rate of mucociliary clearance [8]. The environmental pH also affects the nasal drug absorption. The drug absorption is greater at the pH values where the drug is in the non-ionized form. This means that the non-ionized lipophilic form crosses the nasal epithelial barrier via transcellular route whereas the more lipophilic ionized form passes through the paracellular route [22].

1. Physicochemical properties of drug:

a) Molecular weight and size: Molecular weight (MW) and size also controls the drug permeation through the nasal cavity. Bioavailability usually ranges from 0.5% to 5% for compounds with MW around 1kDa like proteins and peptides [41]. A direct relationship exists between the MW and drug permeation in case of lipophilic agents whereas water soluble compounds show an inverse relationship. Further, it has been reported from various studies, that the rate of drug permeation is highly sensitive for molecules with MW>300 Da, while permeation for drugs having MW<300 Da is not much influenced by the physicochemical properties of the drug because most of them permeate through the aqueous channels of the membrane [42-45]. The particles having size greater than 10 micron can be administered through nasal administration because they could get deposited in the nasal cavity, whereas too fine particles having size below 5 microns should be avoided as they are inhaled directly into the lungs [46].

b) Solubility: Drug solubility is an important factor in determining absorption of drug through biological membranes. Due to the small size of nasal cavity, the allowable volume of drug solution is low for intranasal drug administration. Drugs with poor aqueous solubility and/or requiring high doses may create a problem. Therefore, a drug should have appropriate solubility in the nasal secretions for increased dissolution [47].

c) Lipophilicity: Being nasal mucosa primarily lipophilic in nature, the nature of the drug plays an important role in absorption. The lipid part plays a critical role in the barrier function of these membranes, although they have some hydrophilic characteristics. The permeation of the compound through the nasal mucosa normally increases with increase in the lipophilicity of the drug [48]. Various lipophilic drugs like naloxone, buprenorphine, testosterone and estradiol are almost completely absorbed, when administered through the nasal route [49, 50]. However, the drug permeation through the wall also reduces when lipophilicity is too high because drug does not dissolve sufficiently in the nasal secretions. So a balance between the two factors is necessary [51].

d) pK_a and partition coefficient: According to the pH partition theory, the unionized species are better absorbed when compared with the ionized species and the theory also

holds good fornasal absorption. It has been found that there is a constant relationship between pK_a and nasal absorption of the drugs [52]. A number of studies also indicated that with increase in the lipophilicity or the partition coefficient of the drugs, the drug concentration in the cerebrospinal fluid also increases [53]. The nasal absorption of weak electrolytes is highly dependent on their degree of ionization such as in the case of salicylic acid and aminopyrine [54].

e) **Stability:** The biological, physical and chemical stability of drugs play a crucial role in all processes of drug absorption, which should be maintained before the drug is finally available in the systemic circulation. The biological stability of nasally administered drugs may be affected/ reduced due to the metabolism by a number of enzymes present in the nasal cavity [7].

2. Physicochemical properties of formulation:

a) **Dosage form:** Nasal drops are the simplest and most convenient pharmaceutical dosage form but the dose is not reproducible and often results in overdose [55]. Moreover, rapid nasal drainage with these drops makes them unsuitable. Solution and suspension sprays are preferred than powder sprays because the later cause mucosal irritation [56]. Nowadays metered dose gel devices are used that delivers the drug more accurately and gels also localize the formulation in the nasal mucosa, which enhances the drug residence time in the nasal cavity and diminishes mucociliary clearance and thus potentially results in better absorption[15, 57].

b) **pH:** The pH of the nasal formulation should be adjusted to 4.5-6.5 to achieve efficient drug permeation. It maintains normal ciliary movement, the stability of the administered drug and avoids nasal irritation. Lysozymes (also known as suicidal bags) in nasal secretions is active at acidic pH for destroying certain bacteria, it gets inactivated under alkaline conditions and the mucosa becomes susceptible to microbial infection. Thus, pH should be maintained very cautiously [4, 20, 22].

c) **Osmolarity:** The tonicity of the formulation also affects the drug absorption. The hyper tonicity of the solution cause shrinkage of the nasal epithelium and also inhibits the ciliary activity. Hence, an isotonic solution is generally preferred for optimum results[5].

d) **Viscosity:** The higher viscosity of the formulation increases the time for drug permeation by increasing the residence time of the drug in the nasal mucosa. In addition, highly viscous formulations also interfere with the normal functions of the cilia like ciliary beating or mucociliary clearance and thus finally affect the drug permeability[15]. Some studies suggested that by administering highly viscous formulations the residence time can be increased but there could be diminished drug absorption due to decreased drug diffusion from the formulation. Further, it has also been reported that the viscosity of the solution provides a larger therapeutic period of the nasal formulations [58].

Strategies to improve intranasal absorption:

Bioavailability of nasally administered drugs is limited due to enzymatic degradation in the nasal cavity, poor membrane penetration, rapid MCC and low drug solubility [59]. The drug absorption can be improved by employing any one or combination of the following strategies:

1) Enzymatic inhibitors
2) Permeation enhancers
3) Prodrugs
4) Bioadhesive polymers
5) Co-solvents

1) Enzymatic inhibitors: Nasal mucosa is an active enzymatic barrier as it contains a variety of metabolizing enzymes. Various kinds of enzymatic inhibitors can be used to avoid degradation like the use of proteases and peptidases inhibitors mainly in the formulation

of protein and peptide molecules. For e. g. bestatine and comostate amylase are used as aminopeptidase inhibitors and leupeptine and aprotinin as trypsin inhibitors involved in calcitonin degradation [60]. Enzymatic degradation of leucine encephalin and human growth hormone can be avoided by the use of bacitracin, amastatin, boroleucin and puromycin [31, 32, 61-63]. The use of certain absorption enhancers also avoids enzymatic degradation such as bile salts and fusidic acid [64]. Disodium EDTA reduces enzymatic degradation of beta sheet breaker peptide used in the treatment of Alzheimer's disease [65].

2) **Permeation enhancers:** A range of permeation enhancers can be used for the enhancement of absorption of active medicament. Generally, the absorption enhancers may act via one of the following mechanisms:

- Solubilize or stabilize the drug
- Open tight junctions
- Decrease mucociliary clearance
- Inhibit enzyme activity
- Reduce mucus viscosity or elasticity

Certain drug molecules may be poorly permeable across nasal epithelium and may show an insufficient bioavailability. Though nasal permeation enhancers can improve the bioavailability and therapeutic efficacy of nasal products, but its toxicity should be considered while developing dosage form. One of the most common problems reported with permeation enhancers is the nasal irritation.

The ideal penetration enhancer should have the following characteristics:

- It should be inert pharmacologically.
- It should be non-allergic, non-toxic and non-irritant.
- It should be compatible with a wide variety of excipients.
- It should be potent.
- It should be inexpensive and readily available.
- It should be odorless, colorless and tasteless.
- The effect should be temporary and reversible.

Various types of penetration enhancers can be used such as surfactants, cyclodextrins, fatty acid salts, phospholipids, bile salts, chelating agents and glycols. Surfactants are the most effective permeation enhancer, but epithelial toxicity, ciliostatic activity, nasal irritation are the main drawbacks. Beta cyclodextrin is generally considered safe among cyclodextrins [4, 22, 40].

3) **Prodrugs:** Prodrugs may be defined as the compounds that undergo biotransformation at the target site in order to show the pharmacological effects. Prodrugs are used to improve the physicochemical properties such as solubility, enzymatic stability and lipophilicity. The prodrug approach by improving the membrane permeability and chemical stability is mainly used for improving the nasal bioavailability of proteins and peptides[66]. Lipophilic drugs easily pass through biomembranes but they have poor aqueous solubility. Their bioavailability can be improved by administering them as prodrugs with high hydrophilicity. Similarly, hydrophilic polar drugs may find it difficult to cross the biomembranes.

   Thus, their membrane permeation can be improved by giving them as prodrugs with higher lipophilic character. The absorption of peptides like angiotensin, bradykinin, caulein, carnosine, encephalin, vasopressin and calcitonin can be improved by preparing into enamine derivatives [4, 5, 22].

4) **Bioadhesivepolymer:** MCC reduces the time allowed for drug absorption and thus is one of the limiting factors for nasal drug delivery. The nasal absorption and residence time of the drug can be improved by using bioadhesive polymers. There are lots of methods for the improvement of therapeutic efficacy of both local as well as systemic drug delivery. Mucoadhesions are implies the attachment of the drug delivery system to the mucus that

involves an interaction between synthetic or natural polymer and mucin called mucoadhesive [67]. This process involves several steps. Mucoadhesive systems first absorb water from mucus layer and becomes wet leading to swelling.

5) The polymer then penetrates the mucus and localizes the formulation into the nasal cavity enhancing the drug concentration gradient across the epithelium of the body. Bioadhesive force of a polymer is depends on the nature of the polymer, the surrounding medium, swelling and physiological factors [62-72]. The mucoadhesive polymers mainly used in intranasal drug delivery are chitosan, alginate and cellulose and its derivatives such as carbapol 934P, polycarbophil, sodium alginate, carboxymethylcellulose etc.[4, 59]. The lectins also known as second generation mucoadhesive material are a new class of mucoadhesive material. These are non-immunogenic proteins or glycoproteins capable of specific recognition and reversible binding to carbohydrate moieties of complex glycoconjugates [73].

6) **Co-solvents:** The drug absorption of intranasally administered drugs can be enhanced by improving the drug solubility by employing co-solvents. Co-solvents mostly used in intranasal formulations include glycerol, ethanol, propyleneglycol and polyethylene glycol. This approach has an edge over other approaches since these are non- toxic, pharmaceutically acceptable and non- irritant to nasal mucosa [5].

Particle size plays vital role in enhancement of absorption of drugs. Liposome, nanoparticles and microspheres are different systems that can be used to maximize drug absorption by encapsulating an active drug in these carriers.

CONCLUSION: The nasal route is a lucrative and promising alternative of drug administration but the potential has not been fully realized. This delivery system can be used to treat both acute and chronic diseases since the drugs are absorbed into the systemic circulation through the nasal mucosa. Indeed, it offers several advantages such as the ease of administration, rapid onset of action due to high vasculature and permeability and avoidance of first pass metabolism.

It is one of the painless and non- invasive therapy suitable for the administration of a variety of therapeutics such as hormones, proteins, vaccines, small polar molecules and peptides. Through the nasal cavity, direct transport of drugs to the CNS has generated immense interest among the pharmaceutical companies in devising strategies to exploit this pathway for CNS drug delivery.

Physiological conditions, physiochemical properties of drug and formulation are the factors that determine nasal drug absorption. Mucociliary clearance which is the self- defense mechanism acts by propelling any foreign substance adhering to the nasal mucosa to the nasopharynx which is finally cleared through the GIT. Thus, Mucociliary clearance effects the residence time of the intranasally administered drug into the nasal cavity and has a direct influence on the absorption of drug. Any factor that increases the contact time of the drug with the mucosa enhances drug bioavailability. Different strategies have been applied to improve the intranasal absorption such as the use of mucoadhesive polymers, prodrugs, permeation enhancers, co-solvents and the use of enzymatic inhibitors.

The intranasal route suffers also from certain limitations. Inter and intra subject variability is the one of the most important factors hindering the quality of nasal products. Nasal irritation and toxicity faced on long term therapy are the other problems which can be overcome by the design of an efficient delivery system. Because of the widespread benefits of this route, novel nasal products will continue to reach the market. This route provides future potential for several drugs through the development of safe and efficacious formulations for simple and long term therapy. However, much more efforts are required to be done to make it more popular and efficient delivery system.

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