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Nasal Route: A Suitable Choice For Delivering Drug Having Low Bioavailability

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ABSTRACT
The nasal route for drug administration is becoming an effective alternative for drugs with low bioavailability. Unlike oral and intravenous methods, which can suffer from issues like first-pass metabolism, poor gastrointestinal absorption, and rapid clearance, nasal delivery enables drugs to be absorbed directly into the bloodstream. This method avoids the digestive system and liver, thus improving the bioavailability of medications that are otherwise poorly absorbed or heavily metabolized. Nasal formulations use the nasal cavity's rich blood supply and large surface area for efficient drug absorption. They come in various forms: solutions for quick absorption, suspensions for poorly soluble drugs, powders that need a delivery device and gels that provide prolonged contact with the nasal mucosa. The nasal route offers several advantages, including bypassing the digestive system and liver, rapid absorption, noninvasiveness, ease of use, and targeted treatment for nasal conditions. Overall, it presents a practical and effective option for certain medications.

KEYWORDS = Intravenous, Bioavailability, Rapid, Mucosa, Absorptions, Nasal Drug Delivery.

1 . Introduction:

The nasal mucosa is a promising route for drug administration, offering faster and more effective absorption compared to the gastrointestinal tract. This is attributed to its ability to absorb a wider range of compounds, absence of pancreatic and gastric enzymes, neutral pH, and reduced dilution by digestive fluids [1]. Nasal therapy, or "NASAYA KARMA," has been a traditional practice in Ayurvedic medicine [2]. Intranasal delivery is especially useful for drugs with low oral bioavailability, such as proteins and peptides [3]. However, the rapid removal of drugs from the nasal cavity due to mucociliary clearance can limit absorption [4]. Various nasal drug delivery systems, including sprays, pumps, gels, microemulsions, suspensions, powders, and thermoreversible mucoadhesive gels, have been developed to enhance this route of administration [5]. It has been reported that lipophilic drugs are typically well absorbed through the nasal cavity, often achieving pharmacokinetic profiles similar to those seen with intravenous injections, with bioavailability approaching 100% [6]. Conversely, the absorption of hydrophilic drugs can be improved using absorption enhancers [7].

Advantages: [8,9]

- Drug degradation that typically occurs in the gastrointestinal tract is not a concern here.
- The metabolism of drugs in the liver during their first pass is bypassed.
- Quick absorption and rapid onset of action can be achieved.
- The bioavailability of larger drug molecules can be enhanced through absorption enhancers or other methods.
- Drugs that are not absorbed when taken orally can be introduced into the systemic circulation through nasal delivery.
- Current research suggests that the nasal route can be a viable alternative to injections, particularly for protein and peptide medications.
- Drugs that are unstable in gastrointestinal fluids can be administered via the nasal route.
- Polar compounds that typically have poor absorption may be well-suited for this delivery method.

Limitation: [10,11]

- The histological effects of absorption enhancers used in nasal drug delivery systems are still not well-defined.
- Nasal delivery systems may be less convenient for patients compared to oral methods due to the potential for nasal irritation.

- The nasal cavity offers a smaller surface area for absorption compared to the gastrointestinal tract. There is a potential risk of local side effects and permanent damage to the cilia in the nasal mucosa due to both the active substance and any additives in the formulation.
- Additionally, some surfactants used as chemical enhancers may, at high concentrations, damage or even dissolve the nasal membrane.
- Furthermore, if the dosage form is not administered correctly, there is a chance it could be inadvertently inhaled into other parts of the respiratory system, such as the lungs.

2 . Anatomy and physiology of Nasal Cavity:

Numerous studies have examined the anatomical and physiological characteristics of the nasal membrane, particularly its vascular features, in relation to drug delivery [12-19]. The nose is divided into two cavities by the septum, each with a volume of about 7.5 mL and a surface area of approximately 75 cm^2[20,21,22]. It has three main functional regions: the vestibular, respiratory, and olfactory regions, with the respiratory region being the most crucial for systemic drug delivery[22]. This region's epithelium includes basal cells, mucus-secreting goblet cells, ciliated columnar cells, and non-ciliated columnar cells .[22,23] The cilia on these cells move in a wave-like manner, helping to transport particles to the pharynx for swallowing[22,24]. Additionally, the epithelium is covered with nearly 300 microvilli, which greatly increase the surface area for absorption[22]. Beneath the epithelium lies the lamina propria, containing blood vessels, nerves, serous glands, and mucus-secreting glands[23]. This layer also contains a dense network of capillaries where drug absorption occurs. The nasal epithelium is coated with a mucus layer that is refreshed every 10 to 15 minutes[25]. The pH of nasal mucosal secretions ranges from 5.5 to 6.5 in adults and from 5.0 to 6.7 in children[26]. The mucus layer traps particles, which are then moved out of the nasal cavity by cilia. This mucus travels through the nose at a rate of about 5 to 6 mm per minute, clearing particles from the nasal cavity roughly every 20 minutes[21]. The nasal cavity also contains various enzymes[27,28]. In humans, cytochrome P450 enzyme isoforms, including CYP1A, CYP2A, and CYP2E, have been identified[22]. Additionally, carboxylesterases and glutathione S-transferases are among the other enzymes present in the human nose[29,30,31]

3 . Transport mechanism of Drug Absorption:

The primary step in a drug's absorption from the nasal cavity involves its passage through the mucus layer. While fine particles can easily move through this mucus, larger particles might face challenges[32]. Mucus, which contains the protein mucin, can bind with solutes and influence the diffusion process. The mucus layer can undergo structural changes due to environmental or physiological factors[33]. Once the drug has moved past the mucus, it can be absorbed through the mucosa via several mechanisms, including simple diffusion across the membrane (transcellular route), movement between cells (paracellular transport), or vesicle-mediated transcytosis. Of these, paracellular and transcellular routes are the most prominent[34].

Paracellular transport is a slow and passive process, and there is a negative correlation between the intranasal absorption of water-soluble compounds and their molecular weight. Drugs with a molecular weight over 1000 Daltons tend to have poor bioavailability[32].

Another mechanism involves the lipoidal **or transcellular route**, which facilitates the absorption of lipophilic drugs, with the rate of absorption being dependent on their lipophilicity. Additionally, drugs can be absorbed through cell membranes via active transport mechanisms, such as carrier-mediated transport, or by traversing through the openings in tight junctions[34]. Challenges to effective drug absorption include potential metabolism before the drug reaches systemic circulation and insufficient residence time in the nasal cavity.

3.1:Drug Absorption enhancement:

Most drugs with high solubility in water exhibit low effectiveness. permeability through nasal epithelial cells and could potentially be evident limited absorption of nutrients. In order to improve their penetration. permeation enhancers are commonly used to improve bioavailability working[35]. Permeation enhancers have the ability to increase permeation. modifications that can be undone on the epithelial structure obstacle. The precise way in which drugs work is not fully understood. insufficient understanding exists regarding absorption and permeation enhancement. It is commonly acknowledged that these substances alter the changing the permeability of epithelial cell layer through modification double layer of phospholipids[36].

4: Nasal Drug Delivery System:

4.1: Nasal Drops and Spray:

Nasal drops are one of the simplest and most convenient delivery systems among all formulations. Nasal drops can be administered via squeezy container or pipette. Generally speaking, these formulations are advised for the treatment of local problems; nevertheless, there are certain drawbacks, such as microbial growth, mucociliary dysfunction, and nonspecific loss from the nose or back of the neck.[37,38]The components of a nasal spray system include an operational actuator, a piston, and a chamber. Nasal sprays produce precise dosages (25–200 μl) each

spray and are somewhat more accurate than drops[38].Other elements that may influence the droplet size and, in turn, the nasal deposition of sprays include the pump's design, the applied force, and the size of the orifice[37,39].

4.2:Nasal gel:

A gel is a soft, solid or semi-solid-like material consisting of two or more components, one of which is a liquid, present in substantial quantity.The type, concentration, and physical state of the polymer all affect the rheological characteristics of gels. They can be as rigid and brittle as gellan gum, pectin, and alginate, or as fluid as hypromellose, methylcellulose, xanthan gum, and chitosan. With their ability to regulate the rate and amount of drug release, bioadhesive polymers have demonstrated considerable promise for nasal formulations. This has led to reduced medication administration frequency and increased patient compliance .[40,41]

4.3: Nasal suspensions and Emulsions:

An investigation of a nasal suspension for insulin delivery was conducted (1998)[42]. As absorption enhancers, stearyl glycoside and sterol combinations generated from soybeans were utilised in this case, and pharmacological bio-availabilities of 6.7% and 11.3% were attained. Nonetheless, emulsions have been shown by multiple authors[43-46] to be more effective than suspensions in increasing the bioavailability of poorly soluble medicines when it comes to oral drug administration, and this pattern also holds true for nasal formulations.For particles ranging from 1 to 500 nm, formulation as a nanosuspension facilitated passage through the blood-brain barrier (BBB). Furthermore, researchers have recently reported administering nano-emulsions by nasal route for brain targeting[47-49].

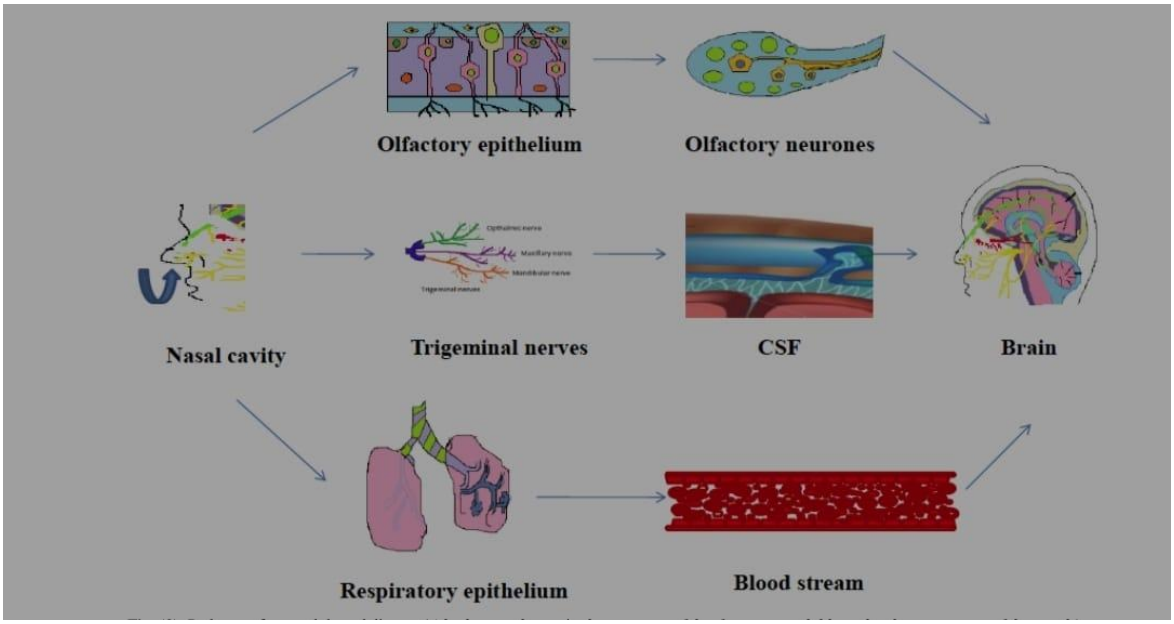

Fig 1: Pathways for nasal drug delivery

5: Pathways for nasal drug delivery:

The precise mechanism for delivering drugs to the brain via the intranasal route remains unclear. However, there is substantial evidence suggesting that the olfactory and trigeminal nerve pathways play a crucial role, as these nerves provide a direct route from the nose to the brain.[50] The olfactory and trigeminal nerves both originate in the brain and extend to the olfactory neuroepithelium in the nasal cavity. These nerve pathways are among the most superficially accessible parts of the central nervous system, making them considered as the most direct and non-invasive routes for delivering drugs to the brain.[51]

5.1: Olfactory pathway:

Transporting drugs through the olfactory mucosa is a well-researched method for targeting brain tissue or cerebrospinal fluid (CSF) to treat central nervous system (CNS) disorders.[52] This method offers a rapid onset of action and the ability to bypass the blood-brain barrier. It mainly facilitates drug absorption in the CNS, CSF, and olfactory bulb.[53] The olfactory bulb projects to various brain regions, such as the amygdala, cortex, and hypothalamus, allowing for direct drug delivery to these areas. Additionally, the movement of basal and neural cells enhances drug delivery to the brain. The nasal epithelium helps protect the brain by preventing harmful substances from entering; these substances are trapped in the mucus layer of the nasal epithelium and removed by the ciliary movement. The olfactory epithelium is composed of neuronal cells, supporting cells, and progenitor cells connected by tight junctions.[54] With intranasal administration, the drug quickly reaches the olfactory bulb and subsequently the central nervous system (CNS). The transport of the drug through the olfactory mucosa

involves both intracellular and extracellular mechanisms. The drug must permeate the mucus gel layer, which can be influenced by passive diffusion through sustentacular cells, transcellular transport via endocytosis, and the paracellular route.[55]

5.2: The trigeminal nerve pathway :
This pathway involves transporting drugs to the brain via the trigeminal nerves. The trigeminal nerve, the largest cranial nerve, transmits thermo-sensory and chemosensory information to the ocular, oral, and nasal mucosa.[56] As the fifth cranial nerve, it is comprised of the ophthalmic, maxillary, and mandibular branches.[57] These trigeminal nerves innervate both the olfactory and respiratory mucosa, aiding in drug delivery to the brainstem and other brain regions. Although trigeminal nerve endings do not directly connect with the nasal cavity, the initial entry point is through the ophthalmic and maxillary branches, which innervate the dorsal nasal mucosa.[58] The mandibular branch, along with other trigeminal nerve branches, also extends into the pons of the brainstem.[53]Trigeminal pathways are linked to both the rostral and caudal regions of the brain, unlike the olfactory pathway, which is associated only with the rostral brain area.[59]The trigeminal nerve pathways involve both intracellular and extracellular transport mechanisms. Extensive research continues to investigate the detailed mechanisms of drug transport through the trigeminal nerves when administered via the nasal route.[54]

6: Factor affecting nasal drug delivery :
6.1: Molecular weight : Molecular weight is a key factor in determining how quickly a substance can permeate the mucosa. Compounds with a molecular weight between 300 and 500 Daltons can be effectively delivered from the nose to the brain.[60] However, larger molecules, such as proteins and peptides, achieve only limited brain targeting via the nasal route.[61] Using permeation enhancers like sodium lauryl sulfate and sodium glycocholate can help transport high molecular weight drugs through this route. For polar drugs, molecular weight is crucial in determining the rate of transport through the nasal membrane.[62] Hydrophilic molecules with a molecular weight under 300 Daltons can be transported efficiently through the paracellular route or by carrier-mediated transport. Lipophilic molecules, with molecular weights ranging from 300 to 1000 Daltons, and even those under 300 Daltons, generally move through passive diffusion. If the particles are very fine, they may end up in the lungs rather than being delivered to the brain through the nasal route.

6.2: Particle size: Particle size is a crucial factor affecting the effectiveness of nasal drug delivery to the brain. Smaller particles face less resistance when penetrating the mucus and migrating through the absorption pathways. Larger particles tend to be retained in the nasal mucosa, making their movement through the nasal route more challenging. Nanoparticles with sizes ranging from 100 to 200 nm can efficiently pass through olfactory epithelial cells. The delivery to the brain is highly dependent on particle size.[63]

6.3: Surface charge : The nasal mucosa carries a negative charge, which can lead to electrostatic interactions with positively charged particles or polymers.[64]This interaction may result in bio-adhesion, extending the residence time of the particles.[65] Polymers such as chitosan and its derivatives are commonly used in nanoparticle formulation. For targeting the brain via nasal delivery, chitosan and similar polymers possess a positive charge at the physiological pH of the nasal cavity.[66]Particles with a positive charge are likely to preferentially interact with the trigeminal pathways, whereas particles with a negative charge are more likely to target the olfactory nerve pathways.[67]

6.4: Polymorphism : Identifying the polymeric form of a drug is a critical aspect of nasal drug delivery and product development. Various polymorphs can affect the drug's dissolution and absorption within the nasal cavity. Each polymorphic form of a drug has distinct abilities to penetrate the nasal membrane. Therefore, for nasal formulations, it is essential to consider the purity and stability of these polymorphic forms.

6.5: PH : The pH of both the nasal mucosa and the drug affects the efficiency of nasal drug delivery to the brain. To avoid nasal irritation, bacterial growth, and mucosal damage, the formulation should ideally have a pH between 4.60 and 6.50. Only the non-ionized form of the drug can pass through the nasal mucosa.[68]

6.6:Partition Coefficient : Compounds with high molecular weight and hydrophilic properties struggle to cross the nasal mucosa because they are often removed by mucociliary clearance. While the nasal mucosa contains both hydrophilic and lipophilic components, lipophilic drugs generally have better transport across the nasal epithelium compared to hydrophilic drugs. The prodrug strategy has proven effective for delivering hydrophilic drugs from the nasal cavity.[69] For instance, a prodrug of levodopa is designed to improve its penetration through the nasal mucosa. Similarly, peptides and proteins, which are typically broken down by enzymes in the nasal mucosa, can be protected from degradation using prodrugs. An example is L-aspartate β-ester, a prodrug of acyclovir, which facilitates the drug's penetration through the nasal mucosa in its salt or ester form.[70]

Table 1. Research Carried Out to Delivery Drug Molecule to Brain from nose

Drug molecule	Function	Reference No:
Nerve Growth Factor (NGF)	Nerve growth factor plays an important role in the growth, survival, and preservation of cholinergic neurons in the central nervous system	[71,72,73]
Insulin like Growth factor (IGF-1)	Treatment of Diabetes Mellitus	[74]
Fibroblast growth factor (FGF)	FGFs are a family of molecules that stimulate cell growth in many areas of the body, and are involved in the growth of multiple tissues. They are also involved in the repair of adult tissues after injury and may mediate the cross-talk between different cell types in the brain. they can be seen as mediators of the property that neuroscientists call "neural plasticity" — the ability of the brain to adapt to stress, experience, disease and the effects of drugs	[75]
Activity-dependent neuro-trophic Factor (ADNF12)	Treatment of Alzheimer disease	[76]
Vasopressin	Diagnosis and treatment of central diabetes insipidus prevention and treatment of postoperative abdominal distention	[77]
Melanocortin melanocyte-stimulating hormone/ adrenocotropin (MSH/ACTH)	Melanocyte-stimulating hormone is a peptide hormone produced by cells in the intermediate lobe of pituitary gland.It stimulates the production and release of melanin by melanocytes in skin and hair	[78,79]
Cocaine	CNS stimulant	[80]
Dopamine	Sympathomimetics	[81]
Progesterone	Supplementation of insufficient secretion of progesterone in women participating in fertilisation programmes	[82]
Estradiol	Primary and secondary amenorrhoea , uterine hypoplasia, deficiency symptoms in young women after oophorectomy or radiological castration for non-carcinomatous diseases, gynaecological operations, dysfunctional bleeding	[82]
Cephalexin	Prevention from bacterial infection	[83]
Folic acid	Treatment or prevention of Alzheimer's disease and stroke	[84]
Morphine	Relief from pain	[84]
Diazepam	Management of anxiety	[84]

Conclusion:

The nasal drug delivery system offers a promising alternative for administering various systemically acting drugs that have poor bioavailability. It provides advantages over parenteral routes, including enhanced patient acceptability and compliance. The intranasal route is a convenient and accessible option for drug administration, with significant potential for developing safe and effective formulations for both short-term and long-term therapy. Nasal products can include treatments for acute and chronic conditions, as well as vaccines, offering improved local or systemic protection against infections. This route enables direct targeting of the brain, potentially achieving effective CNS therapy while minimizing systemic side effects. The nasal cavity, being highly vascularized, offers an excellent surface for drug absorption.

Recent advancements in sophisticated and nano-based approaches for effective brain targeting via the nasal route have been significant. Intranasal delivery to the central nervous system (CNS) is an appealing method due to its ease of use, patient tolerance, and ability to achieve high drug concentrations in the brain while minimizing systemic side effects. This non-invasive technique bypasses systemic circulation by utilizing intra- and extra-neuronal pathways, providing direct access to the brain. The benefits of intranasal delivery include a quicker onset of action, improved patient compliance, precise brain targeting, and reduced a systemic side effects. Despite its potential, nasal-to-brain drug delivery faces challenges such as enzymatic degradation of drugs by nasal enzymes, irritation of the nasal mucosa, and toxicity from penetration enhancers. These obstacles can be addressed through various nanotechnological approaches, including solid lipid nanoparticles, polymeric nanoparticles, nanostructured lipid carriers, microemulsions, nanoemulsions, and liposomes. Evidence supports

the use of chemically modified polymers for direct nose-to-brain delivery. These nano-vehicles can stabilize drugs through encapsulation, enhance nasal residence time, and provide controlled or sustained release. Researchers are still investigating how these polymeric nanoparticles deliver drugs to the brain—whether they are readily absorbed or release drugs near the apical surface. Therapeutic agents administered intranasally are effective in managing neurological disorders, and nanoparticles hold promise for targeting various brain conditions. The nasal route has numerous advantages that could make it a highly promising method for brain targeting in the future.

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