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Nose To Brain Drug Delivery: Advancements On Skipping The Blood-Brain Barrier Review Article

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ABSTRACT

Introduction: Treatment of Brain Disorders like Alzheimer's, Parkinson's, etc. has been challenging due to a variety of obstacles in the way for effective delivery of the drugs to the brain. Intranasal drug delivery (INDD) is a non-invasive and convenient route of drug intake and hence has been useful for drugs targeting neurological (brain) disorders. This method bypasses the Blood-Brain Barrier (BBB), delivering the medication directly to the brain. The Intranasal route is the direct transportation of drugs via the Olfactory and Trigeminal nerve pathways to the brain overcoming the BBB. An enormous range of Macromolecular to Micromolecular medications can be delivered to the CNS via this pathway.

Areas Covered: Present review highlights the Anatomy and Physiology of the Nasal Cavity, the pathway of haulage across the nasal epithelium, and the potential of the intranasal drug delivery. The review also discusses various pros and cons of this route, the available traditional and novel INDDS's, techniques, devices, and presently available medications for the treatment of Brain Disorders.

Expert Opinion: Nose to Brain Drug Delivery or INDDS offers a non-invasive, safe, and convenient route of direct drug administration to the brain. This route helps increase the bioavailability of the drug and even reduces the amount of drug concentration required in contrast to the traditional drug delivery systems. Bypassing the BBB is an important factor due to the low permeability of some drugs, and INDDS helps overcome this barrier.

Keywords: nose to brain, intranasal drug delivery, blood-brain barrier, olfactory, vascular, and trigeminal nerve pathways.

1. INTRODUCTION

CNS disorders like Alzheimer's, Parkinson's, Schizophrenia, Migraine, Dementia, Meningitis, etc. require direct drug delivery to the brain. The nasal route has been employed in treating local disorders like nasal

infections, congestions, sinusitis, allergy, etc. The nasal route is considered as a secure, non-invasive, and suitable route to target faster drug delivery with comparatively less drug concentration and higher absorption[1]. The olfactory and trigeminal nerves provide a connection amid the Cerebrospinal Fluid (CSF) and the nose, which is the basic criteria of intranasal drug delivery and what makes the direct drug delivery to the brain possible. Some of the challenging drugs like micromolecular drugs, polar compounds, peptides, proteins, polysaccharides, etc. can also be delivered efficiently by the INDDS. Several pieces of evidence of Intranasal drug transport have been reported by several scientists all around the globe, with Illum Lisbeth extensively reviewing the nasal drug delivery possibilities, pros, and cons [2]. The nasal mucosa is highly vascularised, having a porous endothelial membrane, is readily accessible, has a vast surface area for extensive drug amalgamation, rapid onset of action, high blood flow per cm^3. It also delivers the drug directly to the systemic circulation and the brain, avoiding the hepatic first-pass metabolism. INDDS also enhances the bioavailability of the drug due to this reason [3]. High drug absorption across the nasal mucosa is a distinctive feature, and the best route to aim drug delivery to the brain [4-6].

Many authors have reviewed a variety of aspects of intranasal drug delivery, and various methods have been suggested to illustrate the extent of drug delivery to the brain. The drug targeting efficiency (DTE%)[5] computes the overall drug accumulation in the brain following intranasal administration vs. the systemic administration. The drug transport percentage (DTP%)[6] from nose to brain computes the relative amount of drug that reaches the brain via direct routes, i.e., olfactory and trigeminal. To enumerate the efficiency of drug delivery to the brain after intranasal drug administration, %DTE and %DTP have been used.

The following review discusses the anatomy and physiology of the nose, the pathway of transport across the nasal epithelium, and the potential of the intranasal drug delivery. The report also discusses various pros and cons of this route, the available traditional and novel INDDS's, techniques, devices, and presently available medications for the treatment of Brain Disorders. The pros and cons of the nose to brain drug delivery are listed in Table 2.

2. INTRANASAL ROUTE OF DRUG DELIVERY

2.1 ANATOMY AND PHYSIOLOGY OF THE NOSE

Breathing and olfaction are the main functions of a nasal cavity. It is lined with mucus and hair, which function trapping inhaled particles and pathogens. Mucociliary clearance (MCC), the resonance of sounds, metabolism, and immunological activities are some other essential functions [7]. The nasal cavity has a total surface area of 150 cm^2 [8] and a total volume of 15-20 mL. The nasal septum divides the nasal cavity into two symmetrical parts along the center, which open at the face as nostrils [9]. Each cavity can be segregated further into four divisions: the nasal vestibule, atrium, the olfactory expanse, and the respiratory expanse [10].

2.2 THE RESPIRATORY EXPANSE

The respiratory expanse is also known as "Conchae" and is a major part of the nasal cavity. The respiratory mucosa composes of the epithelium, basement membrane, and lamina propria[10]. The respiratory epithelium consists of four types of cells: ciliated and non-ciliated columnar cells, basal cells, and goblet cells, as well as mucus and serous glands [7]. The epithelial cells are covered with microvilli (about 300-400 per cell) and also have some fine projection called cilia. Microvilli augment the surface area while cilia are necessary to carry the mucus towards the nasopharynx. The secretory glands and the goblet cells are responsible for secreting mucus and thus forming a thin layer covering the nasal epithelium. The sectretory granules called goblet cells are packed with mucin, a glycoprotein that determines the mucus viscosity. The mucus layer is renewed every 15-20 minutes. The thickness of the mucus layer is 5µm and has two discrete layers: exterior (viscous and thick) and interior (fluid and serous)[10]. The nasal mucus layer consists of 95% water, 2.5-3 % mucin, and 2% of electrolytes, proteins, lipids, enzymes, antibodies, sloughed epithelial cells, and bacterial products [13-15]. Nasal mucus has various obligatory functions such as humidification, warming of inhaled air. The respiratory mucosa is also rich in dendritic cells imperative for the local immune response (IgA) [12]. The mucus layer is moved along by the cilia termini during the energy dependant stroke phase movement. Cilia are up to 7µ in length when fully extended but folds to half its length during the recovery phase. The cilia thump with a rate of recurrence of 1000 strokes/min. This synchronized movement of cilia results in mucus advancement in one direction only, i.e., frontal to the latter part of the nasal cavity up to the nasopharynx. Thus, particles applied to the nasal respiratory mucosa are hauled on the mucus to the back of the throat. The flow rate of mucus is 5 mm/min [9][2][13].

2.2.1 Mucociliary Clearance

The purpose of mucociliary clearance is to get rid of foreign particles and substances from the nasal cavity and to stop them from reaching the lower airway passage. It protects the lower airway passage from all kinds of noxious and harmful substances[14]. The mucociliary clearance has been described as the "Conveyer belt" in which cilia provides the strength and energy, and mucus acts as the sticky belt that entraps and eliminates the foreign particles[15]. The competence of mucociliary clearance is reliant on the physiological control of the cilia and the rheology of the mucus layer. The mucus layer is pushed towards the nasopharynx by the cilia. A single cilium sways uphill during its stroke, and its tip infiltrates the mucus. The cilium transfers its force to the mucus layer, which continues moving downwards slowly towards the periciliary fluid[16]. Eventually, other cilia join in the mucus layer, transfer their energy, and the effective ciliary strokes keep moving the mucus layer forward in the direction of the nasopharynx, where it is ingested [17]. Mucociliary transport time in humans is typically 12-15 minutes[18]. Transit times more than 30 minutes are considered deviant and indicate damaged mucociliary clearance[21-23]. The standard pace of nasal clearance is about 8mm/min, ranging from less than 1 to more than 20 mm/min[18]. In a study with 46 relevant subjects, mucociliary transfer was found to be free of sex or age factor[19]. The first clearance phase lasts for about 15-20 minutes, in which approximately 50% of the taken dose is eliminated from the respiratory mucosa[20]. The subsequent phase is sluggish and eradicates part of the nasal spray that is sedimented at the non-ciliated vestibule and anterior septum.

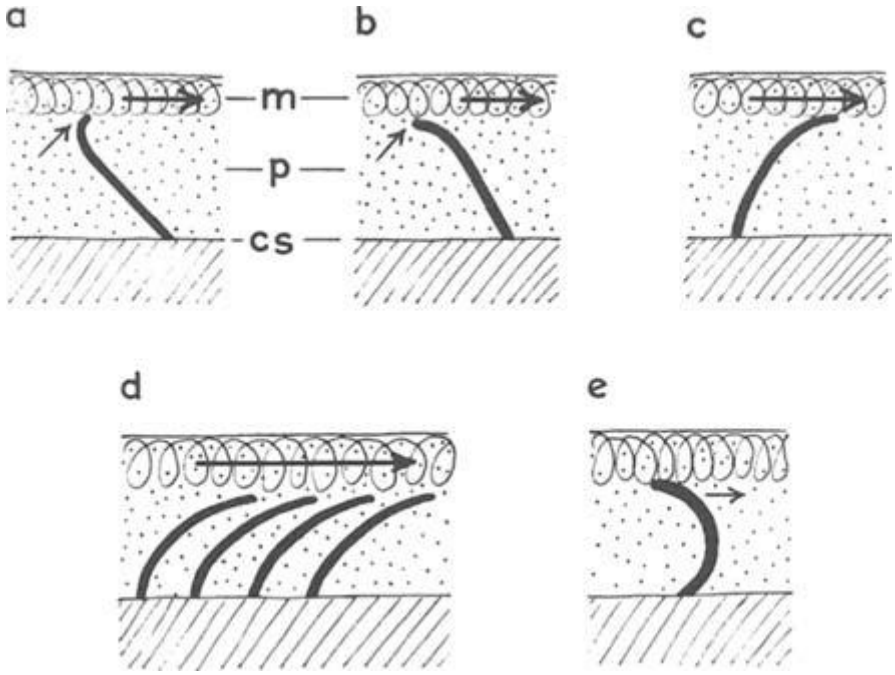


Fig. 1 Relationship among cilia and mucus layer in different circumstances.
Initially, at the commence of the stroke, the cilium enters the tip of the mucus (a) rather than sideways (b), at the lapse of the stroke (c) the cilium stops to move right, but the mucus continues getting propelled and is separated from the tip of the cilium. During the relaxation phase (d), the cilia lie with their tips at the course of mucus movement; if the mucus starts moving left, it would be wedged in the cilia tips. If the cilia bend too back during its effectual stroke (e), it will no longer propel the mucus.
(m: mucus, p: periciliary layer and cs: cell surface); From [16] Sleigh et al. (1988).

2.3 THE OLFACTORY EXPANSE

The olfactory expanse is situated laterally on the roof of the nasal cavity and extends down to the septum and lateral wall. In human beings, the olfactory expanse is about 10 cm^2, a mere 10% of the total nasal area of 150 cm^2[10][21]. The epithelial layer of the olfactory expanse predominantly contains three types of cells, namely, olfactory neural cells, the sustentacular or supporting cells, and the basal cells. Basal cells are the progeny of supporting cells, which also provide and sustain other cells through the anchorage. The olfactory neural cells/axons/unmyelinated cells are interspaced between the supporting cells. They derive at the olfactory bulb in the CNS and lapse at the apical surface of the olfactory epithelium[9]. The pH of mucosal secretions ranges from 5.5 to 6.5 in adults and 5.0 to 6.7 in children[22], which ensnare the foreign particles and is removed by the cilia from the nasal cavity. It comprises of 95% water, 2% mucin, 1% salts, 1% other proteins such as albumin, immunoglobulins, lysozymes and lactoferrin, and <1% lipids travels through the nose at an approximate pace of 5 to 6 mm/min clearing the nose of foreign particles within every 15 to 20 minutes[21][23][24]. The lamina propria of the olfactory epithelium is positioned underneath the epithelial stratum and has the blood vessels, Bowmans glands (mucus-secreting acinar glands), nasal lymphatics, and a neuronal reserve that consists of olfactory axon bundles, nerve fibers and the maxillary branch of the trigeminal nerve[10][21][25][26]. These nerves are accountable for the

transport of drugs to the CNS along the neural conduit. The Bowmans glands are under the control of the parasympathetic nervous system. The Bowmans glands produce nasal secretions in the lamina propria and squirt them through a tube-like opening into the luminal bay.

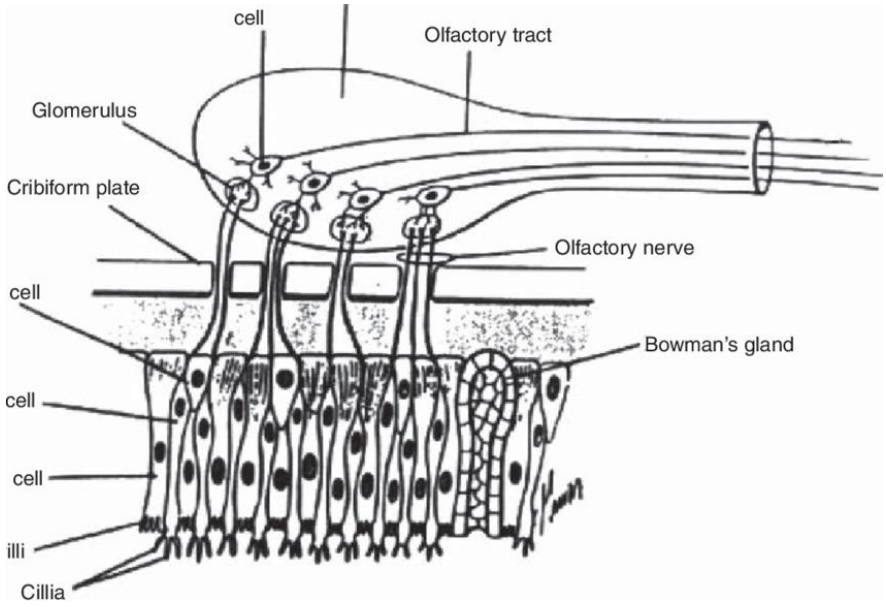


Fig. 2 Olfactory expanse screening the olfactory epithelium, bulb and tract;
From. [9] **Mistry et al. (2009).**

The olfactory neurons in the lamina propria of the olfactory epithelium taper jointly and are en-sheathed by Schwann cells (or glial cells). These are identified as filia olfactaria [27]. Several enzymes, like Cytochrome P450 enzyme isoforms (CYP1A, CYP2A, and CYP2E), carboxylesterases, and glutathione S-transferases are found in the nasal cavity[28][29].

2.4 THE NASAL FOYER

The nasal foyer is the zone just inside the nostrils and has an area of roughly 0.6 cm^2. This region is located anterior to both of the nasal cavities and contains nasal hair (or vibrissae) for straining out the foreign air particles. The nasal vestibule contains the nasal valve, which is the slimmest segment in the respiratory area, which accounts for 80% of the nasal resistance and 50% of the airway resistance. The nasal vestibule contains transitional stratified squamous epithelium with sebaceous glands devoid of ciliated cells chiefly responsible for filtrage of inhaled air and is of negligible interest as per the nasal drug absorption[8][10][21][[23]. These nasal vestibular features are looked-for to afford high resistance against environmental matter, but at the same time, the absorption of material, including drugs, becomes very tricky in this area[30].

2.5 THE ATRIUM

The atrium is the area amid the nasal foyer and the respiratory expanse. The frontal section of the atrium is comprised of stratified squamous epithelium, and the latter is comprised of pseudostratified columnar cells presenting microvilli[7][31].

Table 1. Human nasal epithelial characteristics [2][8][32][33]

Nasal Section	Epithelium Characteristics & Function	Surface area	Permeability	Vascularization
Respiratory expanse	▪ Columnar ciliated cells: Support & mucociliary clearance ▪ Columnar non-ciliated cells: Support ▪ Goblet cells: Mucus discharge ▪ Basal cells: Progenitor of other cells	~ 130 cm^2	Good	Very high
Olfactory expanse	▪ Sustantacular cells: Support ▪ Olfactory neural (receptor) cells: Olfactory perception ▪ Basal cells: Progenitor of other cells	~15 cm^2	Direct access to CNS	High
Nasal foyer	▪ Stratified squamous & keratinized epithelial cells with hair: Support and Defence	~0.6 cm^2	Poor	Low
Atrium	▪ Stratified squamous cells: Support ▪ Pseudostratified cells: Support	NA	Reduced	Low

3. INTRA-NASAL DRUG DELIVERY PATHWAYS AND MECHANISMS

The exact procedure underlying the nasal drug delivery (INDD) to the CNS is not fully known, a promising piece of proof validates that pathways concerning nerves linking the nasal passage to the brain and spinal cord are undoubtedly vital. Also, the pathways, including the CSF, vasculature, and lymphatic systemic, has been employed in the transportation of molecules from the nasal passage to the CNS. It's highly possible that a blend of these pathways is accountable, even though one may outweigh, depending on properties like remedial properties, features of the formulation, and the drug delivery tool used.

3.1 The Olfactory Nerve Pathway

A therapeutic may briskly gain access to the CNS subsequent intranasal administration along the olfactory nerve pathway from the nasal cavity directly to the CNS. Olfactory nerve pathways are the foremost part

of the INDD, substantiated by the fact that fluorescent tracers are linked with the olfactory nerves as they travel across the cribriform plate [34], drug concentrations in the olfactory bulbs are maximum CNS concentrations generally [40-46] and a stout positive association exists among concentrations in the olfactory epithelium and the olfactory bulbs[36]. Olfactory pathways appear in the upper region of the nasal passage, i.e., the olfactory expanse where the olfactory receptor neurons (ORNs) are inter-dispersed amid the supporting cells, microvillar cells, and basal cells. ORNs channel the sense of smell by transmitting sensory info to the CNS. The ORN dendrites penetrate the mucus layer of the olfactory epithelium; axons widen inwards via the lamina propria and crossing the punctures in the cribriform plate, which splits the nasal and cranial cavities. The ORN axons surpass the subarachnoid space having CSF and end in the mitral cells of the olfactory bulbs[48-50]. These exclusive attributes of ORNs contribute to the fact that the olfactory nerve pathway has a vibrant cellular milieu essential for intra-nasal drug transport to the CNS. ORNs usually regenerate every 3 to 4 weeks from basal cells in the olfactory epithelium because of uninterrupted contact with toxins from the external surroundings [38]. The unique milieu of the olfactory epithelium makes it likely for the intranasal drugs to reach CNS via extracellular and intracellular means of transport. Extracellular transport involves swift passage of molecules amid cells in the nasal epithelium. It takes just 30 minutes for the molecules to arrive at the olfactory bulbs and other areas of the CNS after INDD[39][40]. Transport mostly involves bulk movement and bulk flow mechanism[35][41] within channels created by olfactory en-sheathing cells (OECs). Intracellular transport involves molecule uptake by ORNs by inert diffusion, receptor-mediated endocytosis, or adsorptive endocytosis, trailed by slow axonal transport taking numerous hours to days for a drug to reach the olfactory bulb and other brain areas[55-57]. Intracellular transport has been verified for small and lipophilic molecules like gold particles[43], aluminium salts[44], etc. Intracellular transport is important for some therapeutics but is not the preferred or major mode of transport to the CNS. The bulk of published intranasal studies exhibit the fast and rapid delivery, with high CNS drug concentrations, with effects immediately or in an hour after INDD, validating extracellular transport mechanism[40-41][43-44][60-61]. The receptor-mediated transport cannot be held responsible for broad-spectrum drugs or molecules to be conveyed to the CNS. Some large molecules like galanin-like peptide (GALP) display saturable transportation pathways[45], for other large molecules like NGF and IGF-I, intranasal delivery to the brain is non-saturable, and non-receptor mediated[35][47].

3.2 The Trigeminal Nerve Pathway

The other important pathway for INDD is via the trigeminal nerve. It is largest nerve among all cranial nerves. The trigeminal nerve innervates the olfactory and respiratory epithelium of the nasal passage and come into the CNS in the pons[48][49]. Also, a minute portion of the trigeminal nerve also terminates in the olfactory bulbs[50]. The trigeminal nerve transmits sensory information from the nasal cavity, the oral cavity, the eyelids, and the cornea to the CNS. It is comprised of three divisions: the ophthalmic nerve, the maxillary nerve, and the mandibular nerve[48][49]. The mandibular nerve performs both sensory and motor roles, whereas the ophthalmic and maxillary nerve performs the only sensory role. All three divisions meet at the trigeminal ganglion, which includes the cell bodies of these sensory nerve fibers. The afferent neurons at the trigeminal ganglion join to create a single incoming nerve that penetrates the brain stem at the pons. The ophthalmic and maxillary nerves are quite important for INDD since neurons from these branches pass directly through the nasal mucosa. The ophthalmic nerve innervates the

posterior nasal mucosa, and the frontal portion of the nose and the maxillary nerve innervates the lateral walls of the nasal mucosa. In fact, these nerves have confirmed to deliver IGF-1(MW 7.65kDa) to the brain stem and the spinal cord in the vivo rat model[35]. The mandibular nerve stretches to the jaw and teeth having zero neural contribution to the nasal cavity. A significant and distinctive characteristic of the trigeminal nerve is that it goes in the brain from the respiratory epithelium of the nasal passage at two locations: (a) frontal shredded foramen near the pons (b) through the cribriform plate near the olfactory bulbs entering both the terminal and rostral brain areas following INDD. INDD along the trigeminal nerve was first demonstrated for I-IGF-1[51], where elevated levels of radioactivity were seen in the trigeminal nerve divisions, trigeminal ganglion, pons, and olfactory bulbs, with unswerving delivery among the trigeminal and olfactory nerves[35]. Since one point of entry of the trigeminal nerve in the brain is via the cribriform plate beside the olfactory pathway, it is intricate to determine whether the governed drug reached the olfactory bulb and rostral brain regions via the trigeminal or the olfactory pathway or both were equally involved, bypassing the BBB. INDD done with other proteins and peptides like interferon-b1b (IFN-b1b)[52][53], hypocretin-1[36][52] and peptoids [54], found parallel high radioactivity amounts in the trigeminal nerve.

3.3 The Vascular Pathways

Initially, the intranasal itinerary has been used to deliver drugs to the systemic circulation via absorption by the capillary blood vessels lying beneath the nasal mucosa. The medications can also be delivered transnasally via the blood vessels supplying the nasal cavity and from systemic circulation after intranasal administration. The nasal mucosa gets blood supply from divisions of maxillary, ophthalmic, and facial arteries arising from the carotid artery and is highly vascularized[48][55]. The olfactory mucosa gets blood from the ophthalmic artery (small branches like the anterior and posterior ethmoidal artery), while the respiratory mucosa gets blood from the sphenopalatine artery (a branch of the maxillary artery)[56]. The relative density of blood vessels is higher in the respiratory mucosa compared to the olfactory mucosa, making the previous region an ideal site for absorption into the blood[56]. The respiratory region has an amalgamation of fenestrated and continuous endothelium, permitting the passage of both small and large molecules into the blood through the BBB to the brain [57][58]. Small lipophilic drug molecules more easily enter the bloodstream crossing the BBB in contrast to hefty hydrophilic drug molecules like peptides and proteins. There is another possibility drugs can enter the blood supply in the nasal passage where they are quickly relocated to the carotid arterial blood supply supplying the brain and spinal cord, a process known as counter-current transfer[71-73] instead of being disseminated throughout the systemic circulation. Drug molecules may also enter the brain via perivascular spaces in the nasal cavity or after getting to the brain parenchyma to be circulated throughout the brain. These perivascular spaces are enriched with blood vessels and are bound by the basement membrane of the adjoining tissue[60]. The perivascular spaces are the sites in the brain where neuron derived substances are cleared from brain interstitial fluid by entering perivascular channels allied with cerebral blood vessels[60]. An increasing number of shreds of evidence suggests this pathway involving perivascular channels is a potential nose to brain drug transport mechanism[75-78]. Perivascular transport is a mass flow transport mechanism rather than just diffusion [62][63], and the arterial beats are also a driving force for this transport[64][65]. Intranasally applied drugs can move into perivascular spaces in the nasal cavity, and the widespread circulation within the CNS could be due to this perivascular transport mechanisms[35]. Quite a few

intranasal studies have shown that high levels of drugs exist in the the cerebral blood vessels and the carotid arteries even after blood perfusion, clearly predicting that intranasally delivered drugs do have admittance to these spaces[35][53][36].

3.4 The CSF and Lymphatic Pathways

The subarachnoid space containing CSF, perineurial spaces encompassing olfactory nerves and nasal lymphatics are connected via pathways and they provide a gateway for intranasally applied therapeutics to the CSF and other areas of the CNS[36]. CSF is formed by special ependymal cells in the choroid plexus by ventricles of the brain. CSF is a secretory fluid meant to cushion the brain[22]. Several reports have documented that tracers injected into the CSF drain to the underside of the olfactory bulbs into networks related with olfactory nerves passing through the cribriform plate and get to the nasal lymphatic system and cervical lymph nodes[83-87]. Medications may reach the brain via theses pathways after INDD travelling from the nasal passage to the CSF to the interstitial spaces in the brain to the perivascular spaces for circulation all through the brain. These drainage pathways are noteworthy in many animal species (sheep, rabbits, and rats), accounting for roughly 50% of CSF clearance[61][51][67]. Many intranasal studies have demonstrated that drug the transport depends on the lipophilicity, molecular weight, and degree of ionization of drug molecules and the drug molecules s gain direct access to the CSF from the nasal cavity, followed by subsequent supply to the brain and spinal cord [72-75]. In the last two decades, there have been studies stating the presence of a purposeful and structural link between the extra-cranial lymphatics (nasal submucosal and cervical lymphatics) and the subarachnoid space via the perineural spaces and the cribriform plate[76]–[79]. Walter et al. demonstrated this connection from their experiment on the rat model[71]. An antigen was injected into the subarachnoid space and this injected antigen also appeared in both superficial and deep cervical lymph nodes, signifying the drainage of this antigen from the subarachnoid space to extra-cranial lymphatic vessels alongside the olfactory nerves. Also, trigeminal-mediated transport mechanism also play a significant role in the distribution of intranasally administered drugs to brain areas [35][52]. It is quite complicated to differentiate between different pathway contributions into the CNS after INDD.

Table 2. Pros and Cons of Nose to brain intranasal drug delivery

Pros	Cons
▪ Rapid, safe, convenient and non-invasive	▪ Rapid drug elimination
▪ Avoids GIT drug degradation	▪ High chances of variability in drug concentrations across the brain and spinal cord
▪ Avoids first pass metabolism	▪ Absorption enhancers added in the formulations may cause toxicity
▪ Enhances bioavailability	▪ Frequent application of drugs/medications at the nasal mucosa may cause damage like infection
▪ Excellent bioavailability for micromolecular drugs	▪ Macromolecular drugs have low permeability

▪ Rapid drug absorption due to high vasculature and permeability	▪ Nasal congestion may hinder this method of drug delivery
▪ Patient compliance since self medication is possible	▪ Some drug molecules may irritate the nasal mucosa or may be vulnerable to enzymatic degradation
▪ Bypasses the BBB and no therapeutic modification required in the drug for INDD	▪ Improper drug administration may result in loss of dosage form
▪ Alternative for parenteral drug administration	▪ Drug transport mechanisms are still unclear

4. Different types of Dosage Forms for Intranasal Delivery

The dosage form selection depends on factors like the proposed indication, the drug being used, patient population, and lastly, market preferences. The sedimentation of the drug and sedimentation area are the functions of the delivery system and delivery tool. This section describes the types of drug delivery systems.

4.1 Nasal Drops

Nasal drops are the easiest and most suitable systems developed for nasal delivery. This system of delivery is mainly used for provisional aid in congestion in the nose caused by a common cold, hay fever, sinusitis, allergies, etc. and can be in the form of a solution or suspension. Nasal drops usually work by narrowing the blood vessels in the nasal cavity, reducing swelling and congestion. The main drawback of this system is the lack of dose precision, and therefore, nasal drops are somewhat not suitable for prescribed products[80]. Nasal drops deposit human serum albumin in the nostrils more capably than nasal sprays[81].

4.2 Nasal Aerosols

Nasal aerosols can be prepared as a solution or suspension. A nasal aerosol usually has metered-dose pumps and actuators and hence, can release an exact dose from 25 to 200µL[82]–[84]. The type of pump and actuator compilation depends on the particle size and morphology (in suspensions) of the drug and thickness of the preparation. Solution and suspension aerosols are preferred over the powder aerosols since powder causes mucosal irritation[85].

4.3 Nasal Gels

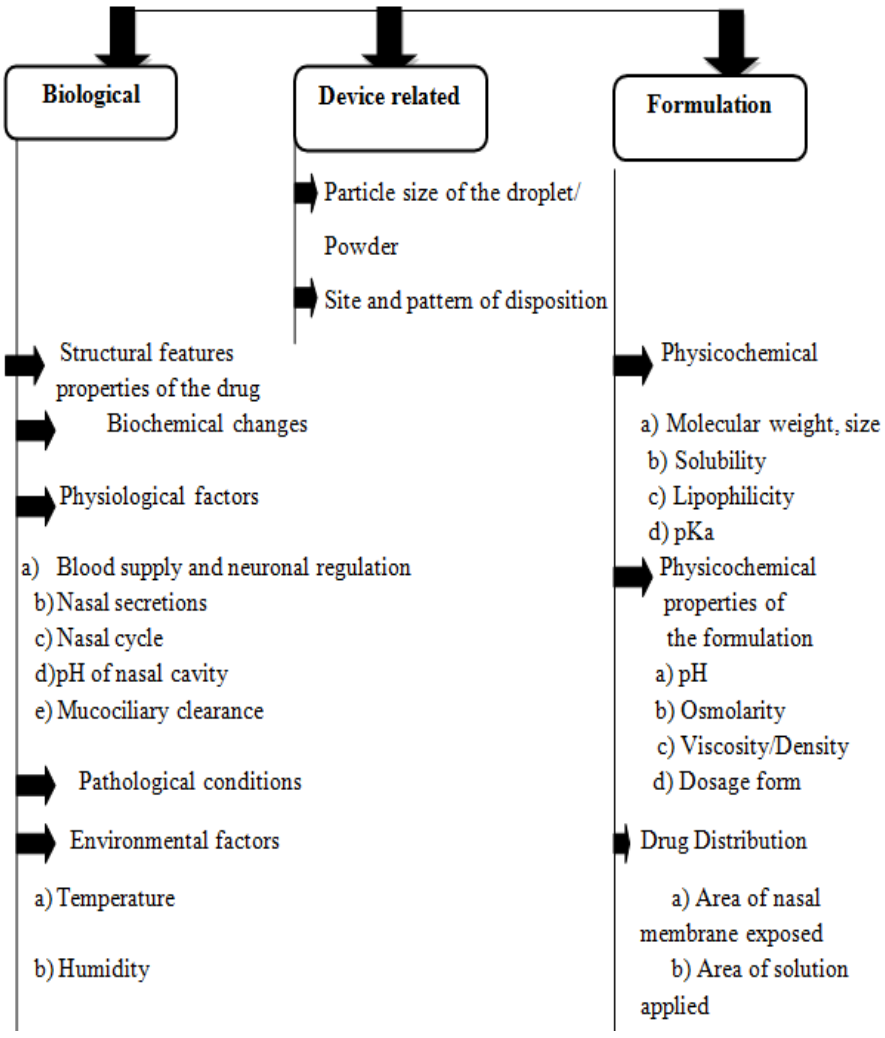
Nasal gels are thick solutions or suspensions. Until recently, precise dosing devices have been developed, and that has increased the researcher's interest in this system. The advantages of this system include long dwelling time in the nasal cavity due to high thickness, subsequently less wastage due owing to low post-nasal dripping, the addition of soothing excipients which significantly reduces irritation, and better drug absorption because of close connection amid the drug and the nasal mucosa[86]. Vitamin B12 and apomorphine gels have been successfully used to achieve required curative concentrations subsequent to nasal administration[87]. Thermo reversible gels using temperature- receptive polymers like

poloxamers and pH-sensitive gels employing pH-sensitive polymers like polycarbophil offer the advantage of more accurate dosing over conventional gels[88]–[91].

4.4 Nasal Powders

Powder dosage forms are formulated mainly due to the drug instability in the solution or suspension form. The main benefits of this delivery system are the absence of preservatives and the superior stability of the formulation. A few factors have to be considered before selecting this dosage form like solubility, particle dimension, aerodynamic properties, and the possibility of nasal irritation of the active drug and excipients. One advantage of this system is the topical application of the drug. Still, the possibility of nasal irritancy and accurate metered dose delivery are the challenges for formulation scientists and manufacturers who are interested in making a device powder dosage forms[92].

Fig. 3 Factors affecting nasal drug absorption. From Fulara et al. [93]



5. NOVEL FORMULATIONS FOR NOSE TO BRAIN DRUG DELIVERY

For the formulation of a nasal formulation with necessary attributes and performance, the drug properties, nasal physiology, and the delivery system should be considered from the early stage of

development. The focus should be on enhancing the residence time, therefore, ensuring efficient drug absorption.

5.1 Mucoadhesive Solutions

These solutions mainly comprise chitosan, cellulose polymers, polycarbophil, poloxamers, etc. and hence, augment drug permeation nasally[94]. The mucoadhesive systems have higher dwelling time and better drug absorption due to high viscosity and mucoadhesive properties. Chitosan and its derivatives are efficient and safe absorption enhancers that significantly improve the delivery of hydrophilic macromolecules such as peptides and protein [95][96]. If compared to gel or powder formulations, these systems offer a disadvantage of post-nasal dripping and frontal leakage.

5.2 Microspheres

Microspheres have more extended contact with the nasal mucosa, which enhances the rate of drug absorption[94]. Microspheres are usually prepared using biocompatible materials, such as starch, albumin, dextran, hyaluronic acid, chitosan and gelatine, hydroxypropyl methylcellulose, carbopol 934P and various combinations of these polymers[97]–[99]. These polymers with the nasal secretions form a gel, which is cleared gradually from the nasal cavity. The toxicity of the polymers on the nasal cavity should be thoroughly assessed. Starch microspheres have been successfully used for insulin, gentamicin, human growth hormone, metoclopramide, and desmopressin[100]. Starch microspheres dry up the nasal mucosa due to moisture uptake by the microspheres resulting in reversible "shrinkage" of the cells, causing a temporary physical separation of the tight (intercellular) junctions that increases the absorption of drugs[101]–[103]. The incorporation of insulin from bioadhesive DEAE-dextran microspheres was studied by Illum et al. [101]. The brain delivery of clonazepam from gelatin-chitosan based nasal mucoadhesive microspheres in rats was studied by Shaji et al. [104]. Nasal chitosan microspheres for improved and prolonged delivery of rokitamycin to the brain for treating granulomatous amoebic encephalitis was developed by Rassu et al. [105].

5.3 Microemulsions

Microemulsions are optically isotropic and thermodynamically stable fluids containing multiple components like oil, water, and surfactant. These emulsions offer several advantages over other dosage forms like higher solubilization of lipophilic drugs, thermodynamic stability, ease of preparation and handling, stabilization of hydrolytically vulnerable compounds, and provide huge surface area for enhanced drug absorption. A mucoadhesive microemulsion will offer an additional advantage of longer dwelling time in the nasal cavity, illustrating swift and complete absorption of drugs. Improved transport of various drugs to the brain across the nasal cavity using mucoadhesive microemulsions for the management of multiple brain or brain associated disorders was reported by Misra et al. [21][89], [91][94]. Nanoemulsion and gel formulations of rizatriptan benzoate for the treatment of migraine was developed by Bajaj et al. [106].

5.4 Liposomes

Various routes were used to deliver liposomes. Liposomes containing quercetin decreased anxiety-like behavior, and increased spatial memory was reported by a study on rats by Wattanathorn et al. [106]. A

nasal micellar or liposomal preparation for the delivery of fibroblast growth factor to the brain was described in a US Patent 6342478 [107]. Multilamellar liposomes have been used for the intranasal delivery of nifedipine by Vyas et al. [108]. Shim et al. prepared a free-flowing proliposomal preparation containing propranolol hydrochloride and evaluated its potential for transnasal delivery of propranolol to sustain its plasma concentration[109].

5.5 Nanoparticles

Nanoparticles have properties like controlled drug release and targeting efficiency, which is ideal for drug delivery and has been used for the development of carriers to cross the blood-brain barrier[110]. Chitosan-based nanoparticles enhance nose-to-brain delivery of drugs compared to equivalent drug solutions formulations due to the protection of the drug from degradation or efflux back into the nasal cavity demonstrated by Illum et al. [9]. Estradiol containing chitosan nanoparticles show improved nasal absorption and brain targeting, demonstrated by Tang et al. [111]. Ali et al. has also reported that chitosan nanoparticles for the nose to brain delivery of a piperidine cholinesterase inhibitor have also been formulated [112]. Alonso et al. demonstrated the potential of low molecular weight chitosan nanoparticles as carriers for nasal vaccine delivery in mice[113]. The in vivo efficacy of plasmid DNA loaded chitosan nanoparticles for nasal mucosal immunization against hepatitis B was evaluated by Vyas et al., and he also demonstrated intranasal administration as a potential route for vaccine delivery[114]. PEG-PLA nanoparticles as potential nasal carriers for drug/vaccine administration has been demonstrated by Alonso et al. [113]. N-trimethyl chitosan (TMC) nanoparticles were evaluated as a potential carrier for the nasal delivery of proteins by Jiskoot et al. [115].

5.6 Nasal Insertions

The nasal inserts are the solid dosage form that offers prolonged systemic drug delivery via the nasal route and is bioadhesive in nature [116]. The absorption of the nasal fluid from the mucosa and to form a gel in the nasal cavity is the basic working principle behind nasal inserts to avoid irritation. The resultant gel sticks to the nasal mucosa and acts as a release control matrix allowing sustained drug delivery. The method of preparation of the in-situ nasal inserts is by lyophilization of aqueous solution of drug-polymer as the carrier and other excipients if needed. The porous structure of the gel is an imperative parameter to ensure fast hydration and gelation at the nasal mucosa. For the delivery of the influenza vaccine, hydrophilic polymer-based nasal inserts have been reportedly used by Bodmeier et al. [117].

6. INTRA-NASAL DRUG DELIVERY TECHNIQUES

Various nasal drug administration techniques are employed, and each has a different way of deposition within the nasal epithelium and delivery along the various conduits to the brain. Several nasal drug delivery techniques are mentioned in this section.

6.1 Snorting

Drug addicts used this method of delivery for ages and are the basis of intranasal drug delivery. Snorting involves snuffling a highly concentrated powder form of a drug (heroin or cocaine) speedily into the nostril. This results in the deposition of the drug in the nasal mucosa and its transfer to the circulation and brain.

6.2 Drug Delivery using a Syringe or Dropper

This method involves putting a few droplets of the medication (i.e., liquid form) into the nose via a syringe or a dropper passing through to the nasal cavity. The syringe acts as a measuring device. The efficiency of the nasal dropper can be highly variable, though some authors believe that this is an effective method of nasal delivery[118]–[120]. This method results in non-uniform dosing of medication on account of post-nasal dripping and frontal leakage [135][137]. This method has demonstrated to be an efficient way to deliver sufficient doses of medications.

6.3 Atomized Drug Delivery

The pharmaceutical industry has recently and widely accepted this method due to improved usability and bioavailability. This technique is a combination of a syringe or pumps delivering a unit dose having a spray tip dispensing medication as fine particles into the nose. Broader distribution of drugs across the nasal mucosa is made possible by this method of delivery, resulting in increased bioavailability of the drug[118][121]–[125]. This method is very patient compliant and takes a very short time to take the medication. Post-nasal dripping and frontal leakage are negligible because the drug is atomized and sprayed as a mist. This is the reason why major pharmaceutical companies package the nasal formulations with a spray pump.

Fig. 4 Current formulations for nasal drug delivery. From [126]

Indication	Active pharmaceutical ingredient	Formulation
Analgesia	Diamorphine hydrochloride Fentanyl citrate	Powder and diluent for reconstitution-aqueous spray Nasal spray, solution
Acute treatment of migraine	Sumatriptan Zolmitriptan	Nasal spray, solution Nasal spray, solution
Endometriosis Ovarian stimulation	Nafarelin acetate	Nasal spray, solution
Nasal congestion (associated with sinusitis, common cold, rhinitis and other UTIs) Symptomatic relief of rhinorrhoea	Xylometazoline hydrochloride Oxymetazoline hydrochloride Azelastine Hydrochloride Ephedrine Ipatropium bromide	Nasal spray, solution, nasal drops Nasal spray, solution Nasal spray, solution Nasal drops Nasal spray, solution
Prophylaxis and treatment of perennial and seasonal allergic rhinitis	Budesonide, beclometasone dipropionate (and monohydrate (micronized), Mometasone furoate Triamcinolone acetonide Fluticasone propionate Fluticasone furoate Fluticasone with azelastine HCl Sodium cromoglicate	Nasal spray suspension Nasal spray suspension Nasal spray suspension Nasal spray suspension Nasal spray suspension Nasal spray suspension Nasal spray suspension, spray solution
Prostatic carcinoma (hormone -dependent)	Buserelin acetate	Nasal spray, solution
Nasal congestion	Levomenthol	Nasal ointment
Nasal infection	Neomycin sulfate and Chlorhexidine dihydrochoride	Nasal cream
Nicotine withdrawal symptoms	Nicotine	Nasal Spray Solution
Nocturia associated with multiple sclerosis The diagnosis and treatment of vasopressin-sensitive cranial diabetes insipidus. Establishing renal concentration capacity.	Desmopressin acetate	Nasal Spray Solution
Vaccinations	Influenza vaccine	Nasal spray suspension

7. FUTURE PERSPECTIVES

This review has discussed the nasal physiology, various drug delivery pathways, and mechanisms involved in the INDDS. Different novel approaches have been employed in enhancing drug incorporation via nasal mucosa and have been reviewed. Still, some alternative strategies can be investigated for effective drug

delivery across the nasal passage. It is evident that pathways along the trigeminal nerves, perivascular channel, CSF, and lymphatic channels are as noteworthy as the olfactory pathway. Drug transport takes place by dispersion, bulk surge, perivascular thrust, and other mechanisms. This review has also enlisted the aspects that affect the nasal drug absorption. Mucoadhesive microemulsions have great potential for targeted drug delivery to the CNS following INDD. Still, to improve the delivery efficacy and to target medications to the specific brain areas requiring treatment, some additional strategies will be required. For example, for the treatment of Parkinson's disease, formulations targeting the trigeminal nerve may be useful in delivering the drug correctly to the brainstem and cerebellum. For treating Alzheimer's disease, dementia, and personality disorders, formulations that target the olfactory nerve are required for delivering medications to the olfactory bulbs and frontal cortex.

8. CONCLUSION

The nose to brain drug delivery has proven to be very useful in the light of the available and successful formulations available in the market. Excellent results were seen with small molecules as well as large molecules like peptides, proteins, hormones, and stem cells. A delivery system becomes successful if it is available for large scale industrial production. The BBB offers a great hindrance to the CNS drug delivery. Direct nose to brain drug delivery provides a way to get through these potential obstacles offered by BBB. INDD skips the BBB and effectively delivers the medication to the CNS along with the reduction of systemic exposure and, therefore, reduction of systemic side effects. INDD is a non-invasive, safe, patient compliant, and rapid method of drug delivery, making it an attractive option in the present scenario. These findings have proven to be very useful for developing therapeutically effective medications in the treatment of chronic neurological disorders like brain tumors, epilepsy, migraine, and other neurodegenerative diseases that are otherwise difficult to treat.

9. EXPERT OPINION

BBB is a highly selective semi-permeable membrane that prevents solutes in the blood from reaching into the extracellular fluid of the CNS. The BBB protects the brain and spinal cord from various circulating toxins and pathogens while allowing the essential nutrients to pass through. The BBB is the foremost hurdle in delivering the medications to the brain, restricting the drug diffusion from the circulation to the CNS. It presents a significant obstruction to polar and large molecules like proteins and peptides and hence, maybe the reason for the failure of neuro medications because of their inability to achieve the required CNS concentration due to systemic circulation, gut, and first-pass metabolism. INDD is a practical, safe, convenient, non-invasive, rapid, and patient compliant method of drug delivery as compared to other drug delivery routes and bypasses the BBB effectively targeting the CNS. There are two main pathways of this type of drug delivery, i.e., olfactory and trigeminal nerve conduits. The olfactory and trigeminal nerve conduits connect the nasal passage to the brain and spinal cord together with the pathways involving CSF and lymphatic systems and target the CNS via the nasal cavity. A blend of these pathways is accountable for drug delivery, although anyone pathway may outweigh. Many researchers have stated the utility of the INDD in humans to treat various brain diseases with minimum superfluous systemic drug disposition in contrast to other routes of drug administration, both oral and parenteral. There is still a need for a device that selectively delivers the medication at the olfactory expanse in the nasal cavity. More investigation is needed to find ways of delivering drugs to the specific brain areas effective in the intended

neurological disease such as the brainstem and cerebellum in Parkinson's disease while the frontal cortex in Alzheimer's disease, dementia, or personality disorders. Since most of the effective CNS drugs are hydrophilic, which makes it hard for them to penetrate the BBB, there are still many challenges remaining. Surface modification of delivery systems may help overcome this problem and enhance direct nose to brain drug delivery. Finally, taking into consideration all the possible benefits of INDD, it is an effective substitute for various insidious methods and could be greatly explored in the near future for the development of novel drug delivery systems. The epoch of nasal drug delivery is emerging fast. However, to make this route more popular and efficient, the field needs to be explored more.

10. DECLARATION OF INTEREST

The author(s) confirm that this article content does not disagree in the context of interest. No payment received for the preparation of this manuscript.

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