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# NASAL MUCOSA AS A NOVELISTIC PLATFORM FOR BRAIN TARGETTING

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## ABSTRACT

Many therapeutic drugs are difficult to reach the central nervous system (CNS) from the systemic blood circulation because the blood-brain barrier (BBB) and the blood-cerebrospinal fluid barrier (BCSFB) form a very effective barrier which prevents most molecules from passing through. BBB allows a selective entry of nutrients and minerals across it and limits the entry of foreign substances like drugs as well as neuropharmaceutical agents. To bypass BBB, drugs can be delivered through olfactory region for nose-to-brain targeting. . Intranasal administration of therapeutic agents (i.e., drug delivery via the nose) offers several advantages over oral, intravenous, and other routes of administration. Drugs can be rapidly absorbed through the large surface area of the nasal mucosa. Intranasal delivery is also non-invasive and essentially painless. This review provides an overview of strategies to improve the drug delivery to the brain via the nasal mucosa and recent advances in the field.

**Keywords**: Nasal route, absorption, Nasal drug delivery, Blood brain barrier, Brain targeting technology.

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# INTRODUCTION

Diseases of the Central Nervous System (CNS) such as schizophrenia, meningitis, migraine, Parkinson's disease and Alzheimer's disease require delivery of the drug to the brain for treatment. However such transport remains problematic, especially for hydrophilic drugs and large molecular weight drugs, due to the impervious nature of the endothelial membrane separating the systemic circulation and central interstitial fluid, the Blood–Brain Barrier (BBB) [1]. Hence, many therapeutic agents may have been abandoned because sufficient drug levels in the brain cannot be achieved via the systemic circulation. Macromolecular drugs such as peptides and proteins, termed 'biologics,' are too large and too hydrophilic to penetrate the BBB from the systemic circulation and would be rapidly degraded by gastrointestinal enzymes or the liver cytochromes, if taken orally. A non-invasive therapy would be desirable for patients particularly for diseases that require chronic dosing such as those related to dementia. It has been shown in the literature from animal and human investigations, that transport of exogenous materials directly from nose-to-brain is a potential route for by-passing the BBB [2]. This route, involves the olfactory or trigeminal nerve systems which initiate in the brain and terminate in the nasal cavity at the olfactory neuroepithelium or respiratory epithelium, respectively. They are the only externally exposed portions of the CNS and therefore represent the most direct method of non-invasive entry into the brain. Intranasal administration of therapeutic agents (i.e., drug delivery via the nose) offers several advantages over oral, intravenous, and other routes of administration. Drugs can be rapidly absorbed through the large surface area of the nasal mucosa, resulting in a rapid onset of action and avoiding degradation in the gastrointestinal tract and first-pass metabolism in the liver. Intranasal delivery is also non-invasive and essentially painless, which helps to increase patient comfort and compliance. Because of these distinct advantages, explorations into the practical applications of intranasal administration are becoming increasingly common and IN formulations of a wide variety of therapeutic agents now exist. Nasal administration is a logical choice for topical nasal treatments such as antihistamines and corticosteroids, and the nasal mucosa has also received attention as a viable means of systemic administration of analgesics, sedatives, hormones, cardiovascular drugs, and vaccines. Importantly, the nose also serves as a direct route to the brain. Intranasal administration of therapeutic agents (i.e., drug delivery via the nose) offers several advantages over oral, intravenous, and other routes of administration. Drugs can be rapidly absorbed through the large surface area of the nasal mucosa, resulting in a rapid onset of action and avoiding degradation in

the gastrointestinal tract and first-pass metabolism in the liver. Intranasal delivery is also non-invasive and essentially painless, which helps to increase patient comfort and compliance. Because of these distinct advantages, explorations into the practical applications of intranasal administration are becoming increasingly common and intranasal formulations of a wide variety of therapeutic agents now exist. Nasal administration is a logical choice for topical nasal treatments such as antihistamines and corticosteroids, and the nasal mucosa has also received attention as a viable means of systemic administration of analgesics, sedatives, hormones, cardiovascular drugs, and vaccines [3].Importantly, the nose also serves as a direct route to the brain. However, the quantities of drug administered nasally that have been shown to be transported directly from nose-to-brain are very low, normally less than 0.1%, and hence the system is not currently used therapeutically and no product is licensed specifically via this route [4]. The strategy of applying drugs that are encapsulated into particulate vectors (such as synthetic nanoparticles) to the olfactory epithelium could potentially improve the direct CNS delivery of drugs including biologics. If drugs could reach the CNS in sufficient quantity by this route, it could generate interest in previously abandoned drug compounds and enable an entirely novel approach to CNS drug delivery. Therefore, the aim of this review is to critically evaluate the evidence of nose-to-brain transport.

**Blood Brain Barrier Transport System**

Unlike peripheral capillaries that allow relatively free exchange of substance across cells, the BBB rigorously limits transport into the brain. BBB not only functions as a physical barrier, but also a biochemical barrier that expresses certain enzymes like peptidases along with several cytosolic enzymes and efflux p-glycoprotein system that helps effluxing drugs from the endothelial cells back into the blood which helps in its further protecting action towards the brain microenvironment [5]. Thus the BBB is often the rate-limiting factor in determining permeation of therapeutic drugs into the brain. BBB is physiologically guided by two types of membranes such as luminal membrane and abluminal membrane. Even so, BBB has been found to be permeable in transport of nutrients like blood glucose, proteins, peptides and related peptide drugs [6]. Various transport mechanisms at the BBB have been explained for the transport of these substances. The transport systems mainly operate in the luminal and abluminal membranes, i.e. in both directions, from blood-to-brain and brain-to-blood. But the blood-to-brain transport system is of considerable interest in drug delivery for targeting of drug molecules into brain as compared to brain-to-blood transport system.

**Conventional Brain Targeting Strategies**

The usual noninvasive approach to solving the brain drug delivery problem is to increase the lipophilicity of the drug. The water soluble parts of the drug restricts BBB transport conversion of water soluble drug into lipid soluble prodrug is the traditional chemistry driven to solution to the BBB problem [7]. Several drugs do not have adequate physiochemical characteristics such as high lipid solubility, low molecular size and positive charge which are essential to succeed in traversing BBB.

**Disruption of the BBB**

The thought behind this approach was to break down the barrier momentarily by injecting mannitol solution into arteries in the neck. The resulting high sugar concentration in brain capillaries take up water out of the endothelial cells, shrinking tem thus opening tight junction. The effect lasts for 20 to 30 minutes, during which drugs diffuse freely, that would not normally across the BBB. This method permitted the delivery of chemotherapeutic agents in patients with cerebral lymphoma, malignant glioma and disseminated CNS germ cell tumours. Physiological stress, transient increase in intracranial pressure and unwanted delivery of anticancer agents to normal brain tissues are the undesired side effects of this approach in humans [8,9].

**Intraventricular delivery**

Like other approaches intraventricular route also act as an approach to bypass BBB where therapeutic agents are instilled directly into cerebral ventricle. This route is best suited for meningioma treatment and metastatic cells of CSF as it distribute drugs mainly into ventricles and subarachnoidal area of brain [10]. Major advantage of this route is its lack of interconnection with interstitial fluid of brain unlike intracerebral delivery. Hence the drug achieves higher concentration in brain in comparison to that of its extravascular distribution [11]. But the major disadvantages are the chance of causing subependymal astrogliatic reaction due to high drug exposure at the ependymal surface of brain [12].

**Intracerebral (intraparenchymal) delivery**

Intracerebral delivery involves delivery of drug directly into parenchymal space of the brain [13]. Drugs can be injected directly (bolus or infusion) via intrathecal catheters, by controlled release matrices [14], microencapsulated chemicals [15] or recombinant cells [16]. The major problem with bolus injection is slower movement of compounds within the brain due to the limited diffusion coefficient. The reason is due to the closely packed arrangement of cells in both gray as well as white matter microenvironment and due to the concentration dependent diffusion phenomena in

brain [18]. Hence a large amount of dose is required for an appropriate drug concentration in parenchyma [17]. Alternatively the continuous infusion method can be used which uses convection enhanced diffusion (CED) phenomena to drive the drugs to a larger tissue region. It has been found that in comparison to bolus injection the CED has better ability to deliver the drug in large doses, maintaining drug concentration and distribution over time [18].

**Intrathecal delivery (intra-CSF drug delivery)**

Intrathecal route involves delivery of neurotherapeutic agents to brain by direct administration of drugs through intrathecal route into cisterna magna of brain. Though it is substantially less invasive than intraventricular administration, but this method fails to result in drug accumulation in parenchymal structures of the deep brain which is highly essential for sustained drug release [10]. The major disadvantage of this route is the chance of understood when etoposide administered through this route into the dogs led to ataxia and loss of muscle coordination [19]. Hence due to this, intrathecal route is best suited for drug delivery for treatment of spinal diseases and disseminated meningeal diseases but not for large parenchymal diseases like parenchymal tumors such as glioblastoma [20].

**Transnasal delivery**

Since long, intranasal route has been utilized for delivering drugs for systemic action as the drug directly reaches to blood by crossing the nasal mucosa [21]. In case of brain also, better targeting action can be achieved due to direct movement of drug from the sub mucosa space of the nose into the CSF compartment of brain (Fig. 1: describing different pathways for reaching the brain after intranasal administration) [22].

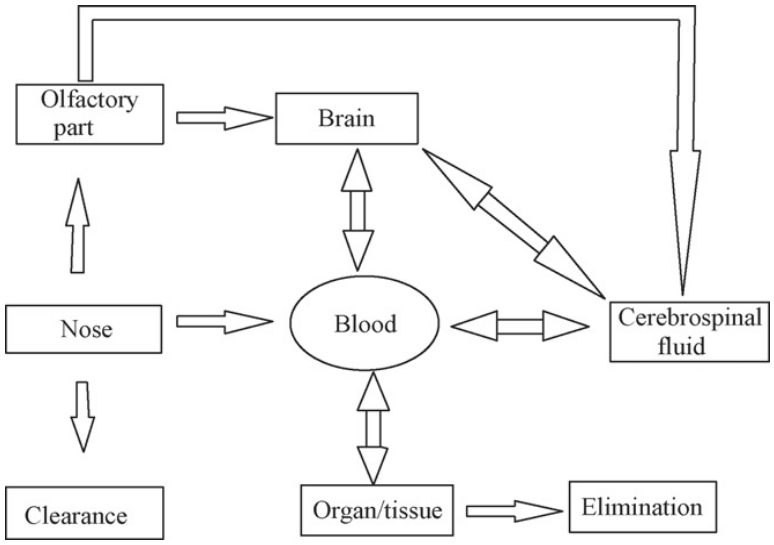


**Figure 1. Different pathways for reaching the brain after intranasal administration.**

Transnasal delivery is a non-invasive method of bypassing the BBB to deliver the drug substances and peptides to the CNS. The highly permeable nasal epithelium allows rapid drug absorption to the brain due to high total blood flow, porous endothelial membrane, large surface area and avoidance of first-pass metabolism. Transnasal method can deliver a wide variety of therapeutic agents (small molecules and macromolecules) to the CNS [23]. Many agents active in the CNS are more effective when given nasally and provide the advantage of small dose, self administration and avoidance of sterile techniques. It neither requires any modification of the therapeutic agent nor has the drug to be coupled to any carrier. Transnasal delivery has some limitations including damage of nasal mucosa on frequent use of this route, rapid clearance from nasal cavity by mucociliary clearance system, interference due to nasal congestion, elimination of some quantity of drug absorbed systemically via normal clearance mechanism and possibility of partial degradation or irritation to the nasal mucosa [24]. The respiratory region of the nose is considered to be the major site for drug absorption into the systemic circulation, where the compounds can be absorbed by transcellular pathways or paracellular passive absorption, carrier-mediated transport, and absorption through transcytosis pathways. The olfactory region, next to respiratory region, is the foremost site from where drug can be absorbed directly into the brain by different mechanisms including transcellular, paracellular, olfactory and trigeminal neural pathways [25]. The olfactory region of nasal mucosa contains olfactory cells which extend up into cranial cavity. When the drug formulation on nasal installation, comes in contact with the mucosa they are rapidly transported directly into the brain, skipping the BBB, and achieving very rapid cerebrospinal fluid levels [26,27]. Most of the lipid soluble molecules can readily enter the blood stream from the nasal mucosa and subsequently reach the CNS by crossing the BBB [28]. But majority of the pharmaceutical drug molecules are hydrophilic, which becomes another rate limiting barrier for drug targeting, as highly lipid soluble drug molecules show easier and better targeting ability due to higher partition coefficient. It has been reported that the drugs other than lipid soluble molecule can cross nasal mucosa if there is a local injury as that can lead to breakdown of the nasal mucosal barrier [29]. In the recent years several drugs as well as peptides have been delivered effectively using intranasal route. Nasal administration greatly decreased brain injury in a rat model of transient focal ischemia and profoundly decreased oxidative cell death [30]. Similarly intranasal administration of gallotannin, a poly (ADP-ribose) glycohydrolase (PARG) inhibitor showed a marked reduction in the frequency of ischemic brain injury in rats [31]. Olanzapine when delivered intranasally as mucoadhesive microemulsion formulation showed

better effectiveness of the route of drug delivery into brain [32, 33]. The delivery of buspirone hydrochloride as mucoadhesive formulation using chitosan and hydroxylpropyl beta cyclodextrin showed better brain concentration after intranasal administration in mice [34]. Similarly intranasal mucoadhesive microemulsion of sumatriptan showed better cerebral concentration and reduction in migraine headache [35].

## NASAL ANATOMY AND PHYSIOLOGY

### The external nose and the nasal cavity

The main functions of the nose are olfaction, regulation of humidity and temperature of inhaled air, and removal of large particulates including microorganisms fromthe inhaled air. In humans, the total surface area and volume of the two sides of the nasal cavity has been measured using computed tomography (CT) scans as 150.4cm2 (made possible by three protrusions or 'turbinates' within the cavity) and 13.0 ml, respectively [36]. The nasal septum divides the nasal cavity along the centre into two halves open to the facial side and to the rhinopharynx, through the anterior and via the posterior nasal apertures, respectively. Each nasal cavity can be divided into three regions; the nasal vestibule, the olfactory region and the respiratory region. The olfactory epithelium is located high in the nasal cavity in man. It partly overlies the cribriform plate, a bony structure that contains many pores that allow the passage of neuronal bundles from the olfactory epithelium to pass into the CNS. Olfactory epithelium may also lie partly on the nasal septum and on the superior turbinate. It is above the normal path of the airflow which means that odorant molecules normally reach the sensitive receptors by diffusion. The act of sniffing enhances the diffusional process by increasing the airflow rate and changing it from continuous to pulsatile in nature. This behaviour increases the turbulence within the nasal cavity and therefore allows greater interaction of the inspired air with the olfactory region at the roof of the nasal cavity. The respiratory region is dominated by the large inferior turbinate, the middle turbinate and further back in the nasal cavity, the superior turbinate.

### The respiratory epithelium and mucociliary clearance

The respiratory epithelium is composed of four types of cells, namely, non-ciliated and ciliated columnar cells, basal cells and goblet cells. These cells facilitate active transport processes such as the exchange of water and ions between cells and motility of cilia (where applicable). They may also serve to prevent drying of the mucosa by trapping moisture. About 15–20% of the respiratory cells are covered with a layer of long cilia, which move in a coordinated way to propel mucus towards the pharynx. Mucus (or nasal secretion) is a complex mixture of materials

consisting of approximately 95% water, 2% mucin, 1% salts, 1% of other proteins such as albumin, immunoglobulins, lysozymes and lactoferrin, and <1% lipids [38]. Mucus is present intwo layers on the epithelium in order to facilitate mucociliary clearance. A viscous gel layer, the 'mucus blanket' floats on the serous fluid layer. The viscous gel layer is moved along by the hook shaped cilia termini during the energy dependent 'effective stroke' phase of the ciliary motion. Cilia are up to 7µm in length when fully extended but can fold to half this length during the recovery stroke where the hook terminus detaches from the gel layer and moves immersed in the sol layer in the opposite direction to the gel layer movement. The cilia beat with a frequency of 1000 strokes per min. Hence the mucus moves only in one direction from the anterior to the posterior part of the nasal cavity to the nasopharynx. Therefore, particles applied to the nasal respiratory mucosa will be transported on the mucus to the back of the throat with a speed of 5mm per min [39].

**Olfactory epithelium and neuronal supply to the nasal cavity**

The olfactory epithelial layer predominantly contains three cell types: the olfactory neural cells, the sustentacular (also known as supporting) cells and the basal cells. Basal cells are progenitor Cells (of supporting cells) that also provides mechanical support via anchorage to other cells. The olfactory neural cells or the axons are un-myelinated and interspaced between the supporting cells (Fig. 2: Diagram of the olfactory area showing the olfactory epithelium, bulb and tract [37]).

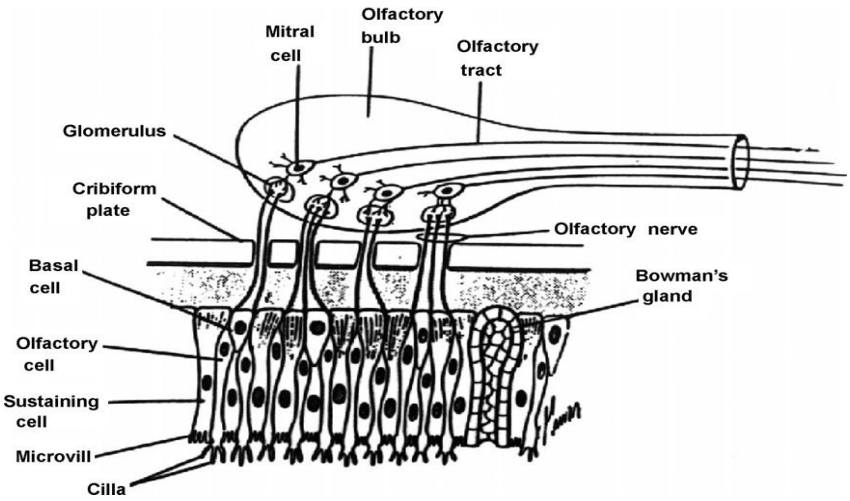


**Figure 2. Diagram of the olfactory area showing the olfactory epithelium, bulb and tract [37].**

They originate at the olfactory bulb in the CNS and terminate at the apical surface of the olfactory epithelium. The olfactory knob (or vesicle) protrudes out from and above the apical surface of the olfactory epithelium. Approximately 10–23 cilia project from the basal bodies of the knob, each of length up to 200_m. The cilia contain chemical detectors that, once activated

by odorants, initiate de-polarization of the olfactory axon by either direct ion-gated channels or cAMP operated ion-channels [40]. The cilia entangle with the thick brush border of microvilli of the supporting cells at the air/mucus/tissue interface. The cilia are non-motile in the olfactory region (in contrast to respiratory tissue) since they lack the dynein arms which contain the Mg2+-ATPase that generates the force for ciliary motility [41]. The *lamina propria* of the olfactory epithelium, which is located beneath the epithelial layer(s), contains the blood supply, mucus secreting acinar glands (Bowman's glands), nasal lymphatics, and a neuronal supply that consists of olfactory axon bundles, autonomic nerve fibres and the maxillary branch of the trigeminal nerve [42]. Bowman's glands are under the control of the parasympathetic nervous system. These acinar-type glands produce nasal secretions in the *lamina propria* and secrete them through a narrow tube-like opening into the luminal space. In the *lamina propria* the olfactory neurones taper together and are ensheathed by glial cells (or Schwann cells). These processes are called *filia olfactoria*. *Filia olfactoria* are unique features in the mammalian body in that around twenty axons are partitioned by the Schwann cell into fascicles. In this way a single Schwann cell may ensheathe around a hundred or so axons. This feature allows 10–15 nm sized spaces between axons that act as ionic reservoirs for action potential propagation. Hence, perineuronal transport of molecules to the olfactory bulbs is limited by the size of these spaces. Mesaxons are pores in the *filia olfactoria* structure that allow passage of extracellular fluid into the neuronal bundle structure.

**Junctional complexes**

Junctional complexes are cell-to-cell contact areas found between both respiratory and olfactory epithelial cells in the nasal cavity. There are three different types of these complexes; *macular adherens* (or desmosomes), *zonula adherens* and *zonula occludens* [43]; The *zonula occludens* are located closest to the luminal space above the z*onula adherens* with the *macular adherens* situated basolaterally in relation to the other two complexes. Thus, transport of drugs between cells (paracellular transport) is largely determined by the integrity of these (and in particular the *zonula occludens*) complexes for intact epithelia. The hydrophilic channel between epithelia, the tight junctions, are generally impermeable to molecules with a hydrodynamic radius greater than 4–8 Å. This is the normal diameter of a closed tight junction (depending on the 'leakiness' of the epithelium) which restricts the movement of molecules larger than this to pass between neighbouring cells [44]. Itwas found that in the nasal epithelia, the largest molecular weight drug that was transported paracellularly (albeit at very low amounts) without the addition of an

absorption enhancer was about 50 kDa. Even when tight junctions are opened, by application of certain absorption enhancers such as poly-l-arginine, they reach a maximum of about 15nm in diameter and hence are not expected to allow molecules larger than 150 kDa to pass through in significant quantities [45]. Hence, generally nanoparticles used in the literature are too large for this route to achieve feasible transport for drug delivery purposes.

## NOSE TO BRAIN PATHWAY

### Mechanisms

Two mechanisms are involved in the nasal delivery, a fast rate that depends on lipophilicity, and a slower rate that depends on molecular weight. The transport of SS-6 (an octapeptide) and horse radish peroxidase through rat's nasal cavity and their absorption studies are consistent with the non-specific diffusion of the penetrant molecules through aqueous channels located between the nasal mucosal cells, which impose a size restriction on nasal permeability. The data indicate that good bioavailability can be achieved for molecules up to 1000 Da (without enhancers) and good availability can be extended to at least 6000 Da with enhancers [44]. The transport mechanisms of different substances like insulin, mannitol or propranolol across the nasal mucosal tissue were studied. The transport of these substances occurs by a passive transport mechanism. The addition of deoxycholate (0.1%) reversibly increased the transepithelia conductance across the nasal membrane and enhanced the transport of mannitol and insulin [46]. The transport of tyrosine and phenylalanine across rat mucosa was also studied by using an in-situ per fusion technique [47]. It was found that both amino acids were absorbed by an active saturable transport process, which appeared to be Na+ dependent, and transport may have required metabolic energy as a driving force. Water-soluble substances such as sodium cromoglycate are absorbed well and nasal absorption probably depends on aqueous channel diffusion (pores) [48]. The molecular size of the compound will be a determinant in the rate of absorption in such a channel.

### Pathways

The olfactory epithelium is a gateway for substances entering the CNS and the peripheral circulation. The neural connections between the nasal mucosa and the brain provide a unique pathway for the non-invasive delivery of therapeutic agents to the CNS [49-50]. The olfactory neural pathway provides both an intraneuronal and extraneuronal pathway into the brain [49,50-54]. The intraneuronal pathway involves axonal transport and requires hours to days for drugs to reach different brain regions. While the extraneuronal pathway probably relies on bulk flow

**Table 1.Recent advances in nose to brain drug delivery [77]**

| Drug molecule | Function |
|---|---|
| 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 |
| Insulin like Growth factor (IGF-1) | Treatment of Diabetes Mellitus |
| 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 |
| Activity-dependent neuro-trophic Factor (ADNF12) | Treatment of Alzheimer disease |
| Vasopressin | Diagnosis and treatment of central diabetes insipidus prevention and treatment of postoperative abdominal distention |
| Cholecystokinin.(CCK) analog | CCK mediates a number of physiological http://en.wikipedia.org/wiki/Physiology processes, including digestion and satiety |
| 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 |
| Cocaine | CNS stimulant |
| Dopamine | Sympathomimetics |
| Progesterone | Supplementation of insufficient secretion of progesterone in women participating in fertilization programmes |
| 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. |
| Cephalexin | Prevention from bacterial infection |
| Meptazinol | Relief from pain |
| Folic acid | Treatment or prevention of Alzheimer's disease and stroke |
| Morphine | Relief from pain |
| Diazepam | Management of anxiety |

transport through perineural channels, which deliver drugs directly to the brain parenchymal tissue and/or CSF. The extraneuronal pathway allows therapeutic agents to reach the CNS within minutes [55-58]. Intranasal delivery of agents to the CSF is not surprising as CSF normally drains along the olfactory axon bundles as they traverse the cribriform plate of the skull and approach the olfactory submucosa in the roof of the nasal cavity, where the CSF is then diverted into the nasal lymphatics [59-61]. It had reported that the trigeminal neural pathway may also be involved in rapidly delivering protein therapeutic agents, such as insulin-like growth factor- 1 to the brain

and spinal cord following intranasal administration [51]. The transport of drugs across the nasal membrane and into the bloodstream may involve either passive diffusion of drug molecules through the pores in the nasal mucosa or some form of non-passive transport [62].

**Formulation Aspects**

**Mucoadhesive formulation**

The incorporation of mucoadhesive polymers into nasal formulation can increase the mucosal contact time and prolong the residence time of the dosage forms in the nasal cavity. The pharmacokinetic profiles of apomorphine after nasal administration were improved with mucoadhesive polymers of polyacrylic acid, Carbopol, and carboxymethylcellulose[63,64]. Hyaluronan is another example of mucoadhesive polymer used in a nasal formulation. It has demonstrated its ability to improve the brain penetration of a hydrophilic peptide via the nasal route [65]. *Chitosan* was also extensively studied by formulators due to the non-toxic nature and its absorption enhancing and mucoadhesive properties[66]. Chitosan enhanced the brain bioavailability of intranasally administered nerve growth factor by a 14-fold increase comparing with a preparation without chitosan[67]. Chitosan hydrochloride in combination with hydroxypropyl beta-cyclodextrin was used as mucoadhesive formulation in brain targeting studies on buspirone hydrochloride with a high drug targeting index[35]. Chitosan and hydroxylpropylmethyl cellulose can be formulated as mucoadhesive temperature-mediated in situ gel to enhance intranasal delivery of ropinirole, the dopamine D2 agonist, to the brain [68].

**Penetration enhancers**

Penetration enhancers are used to improve the permeability and bioavailability of the drug upon contacting the nasal mucosa. The bioavailability of nerve growth factor in the brain could be enhanced by intranasal administration of peppermint oil [69]. Intranasal administration of hexarelin, a growth hormone releasing neuropeptide for nose-to-brain targeting, was also enhanced by N-tridecyl-beta-D-maltoside as a permeation enhancer. Markedly greater hexarelin concentrations in olfactory bulb and olfactory tract on the treated side of brain tissues were observed [70].

**Liposomes**

Liposomes are soft vesicular structures formed by self-assembly of phospholipids which are the same materials as cell membranes. They can be formed in many shapes and sizes depending on lipid composition. Liposomes are often used as non-viral carriers for DNA delivery because of their dynamic properties of cellular membranes that interact with the biological environment [71].

Cationic liposomes were able to enhance the interferon-inducing and antiviral activity of ridostin (an interferon inducer) in experiments with cell cultures of L-929 [72]. Liposomes can also be coated with several thousand strands of polyethylene glycol (PEG) to extend the circulation time in the blood. About 1-2% of the PEG polymer tips are conjugated with a targeting monoclonal antibody which acts as a molecular Trojan horse, specific to brain receptor. This type of Trojan horse liposome is also called PEGylated immunoliposomes. The molecular Trojan horse then binds to a receptor on the BBB and brain cell membrane, triggering receptor-mediated transcytosis of the liposome across the BBB, and endocytosis into brain cells [73].

**Vasoconstrictor**

Phenylephrine hydrochloride, a short-acting vasoconstrictor showed remarkably reduced blood concentrations and increased CNS concentrations of hypocretin-1, a peptide involved in appetite and sleep regulation, and dipeptide L-Tyr-D-Arg, a morphine-like analgesic [74]. In this case, vasoconstrictor was used to enhance intranasal drug targeting to the CNS by limiting absorption into the systemic circulation and increasing the amount of neuropeptide available for direct transport into the CNS along olfactory pathways.

**Nanoparticles**

Intranasal drug delivery of didanosine-loaded chitosan nanoparticles for brain targeting has shown increased drug delivery to the brain [75]. Despite the positive experimental results in improving nose-to-brain delivery of nano-sized drugs in animal studies, it is still uncertain at this stage whether drug carried by the nanoparticles is being released in the nasal cavity or the nanoparticles carrying the drug are transported via the olfactory or the trigeminal nerves into the CNS where the drug is then released [76].

## CONCLUSION

Although major progress has been made regarding intranasal drug delivery, there is still a distinct lack of information regarding this topic. This novelistic route demands attention of scientists around the globe due to the rapid increase in the aging population and the increasing susceptibility of patients to neurological disorders around the world. Intranasal drug delivery has got the attention of many researchers due to its application in various diseases related to CNS. This system has clinical benefits like reduced dose hence lower incidence of systemic adverse effects, and more patient compliance. The advantages of intranasal delivery are numerous and very importantly it is rapid and non-invasive. It reduces systemic exposure and thus reduces the

side effects. It also bypasses the BBB and delivers the drug directly into the CNS. It acts as an alternative to parenteral and oral route for delivery of some drugs.

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