# Nose to brain: An advanced drug delivery system using nanovehicle as carrier

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**A B S T R A C T**

A little benefits offered by particles for nose-to-brain medication delivery have been called into question by a quantitative investigation. Determining the function of nanoparticles as nose to brain delivery medication delivery is therefore crucial. It is challenging for nanocarriers to overcome conventional formulations, such solutions or gels, if they are just utilised as an alternative to enhance certain qualities of the medications or formulations. Yet, nanovehicles have unique properties that increase the effectiveness of nose to brain delivery delivery, such as maintaining the solubilized state of medicines, prolonged or delayed release, and improved penetration due to surface changes.

Key words:
Lipid nanocapsules; nose to brain delivery; stroke

## Introduction

The physiological barrier like blood brain barrier (BBB) and cerebro-spinal fluid (CSF), insulate neurological system from our systemic circulation, equipoise homeostasis, and shield it from outside intruders [1]. While in a healthy state, the BBB prevents foreign substances avoid getting into the brain's extracellular fluid ensuring proper brain function. Using animal models, Paul Ehrlich and Edwin Goldman demonstrated in 1885 and 1913 correspondingly, that there is a barrier that prevents dyes from travelling from blood to the central nervous system (CNS) and vice-versa. The structural and physiological characteristics of the BBB and its crucial role in regulating drug entry into the Brain have been better understood as a result of subsequent research.

The BBB is made up of a network of closely knit endothelial cells that permit only selective entry of nutrients molecules and hormones while preventing the transit of infections, poisons, and foreign materials, such as medications. The medicinal agent must first cross the BBB before it may enter the systemic or oral circulation and reach the central nervous system. Compounds enter the brain primarily by passive diffusion and active transport through endothelial cells. Tight junctions prevent big molecules and the majority of low molecular weight molecules from passing through the BBB, leaving only tiny and highly lipophilic molecules through [4,5]. Moreover, each structure has particular surface receptors and transporter proteins that let the entry of necessary chemicals like the glucose transporter (GLUT-1), insulin receptor (IR), and transferrin receptors (TfR) and some others. Like in the situations of P-glycoprotein (P-gp) and proteins associated to multi drug resistance (MDR), certain efflux transporters on endothelium, however, can impede the absorption of many compounds inside the brain and compel medications to return it back into systemic circulation [1,5,6].

In order to treat CNS illnesses including Parkinson's disease (PD), Alzheimer's disease, sclerosis, schizophrenia, epilepsy, meningitis, and neuro-cysticercosis, among others, an appropriate quantity of the medicine supplied must enter the brain at therapeutic levels [7,8]. These illnesses often entail a wide spectrum of clinical signs that result in alterations of brain functioning and progressive destruction of neural system. Despite some of the available therapies for such disorders are successful, systemic medication distribution frequently comes with a heavy weight of side effects that have a severe impact on patients' quality of life. Although tremendous progress has been made in understanding the pathogenic mechanism behind these illnesses, there is still a need for more advanced therapies with fewer side effects. It has been claimed that an alternate method over the conventional oral routes and parenteral for the direct delivery of pharmaceuticals, is intranasal (IN) administration for delivery delivery as a means of achieving high drug levels in the brain. Anatomically speaking, the nasal cavity is an ideal location for drug administration since it is less invasive, has a quick beginning of action, and doesn't have the first pass impact on the liver [9]. The IN pathway has undergone substantial research to administer topical and systemic medicines since it has a surface area i.e.

approximately 160 cm2 (96.000 cm2 of which are made up of the microvilli) [10,11]. The size of olfactory region, which provides direct accessibilityF to the brain, is only around 5 cm2 (3,000 cm2 of which are made up of the microvilli) [11]. Moreover, a high-density microvasculature found in the IN cavity contributes to the distribution and absorption of medications. However, while creating medication formulations for this route, nasal physiology provides several difficulties that should be taken into account. Some of the characteristics that can prevent drug absorption by the IN route include the little amount of dossage that can be placed into the nose, mucociliary clearance (MCC), the existence of mucus layer, and enzymes. In context of this, nanotechnology drug delivery methods have demonstrated to be an effective means of promoting drug accumulation in the central nervous system (CNS) thoroughly an increase in olfactory area permeability. In this article, we'll critically examine current developments in the creation of the nanoparticles (NP) for IN-route medication into the brain (Fig. 1). The nature of nanocarriers, such as polymers, lipid, and inorganic NP, along with drug nanocrystals, will receive particular attention.

**Nose to brain delivery: Advantages, various Challenges and barriers**

Comparing IN route with intravenous (IV) and oral modes of delivery to the CNS, the IN route is non-invasive. Together with avoiding the BBB, this direct path to the CNS can lessen systemic adverse effects. The various parenteral routes and oral delivery require medications to first pass through a number of barriers in order to establish systemic circulation, and then they must pass through the BBB in order to reach CNS. Additionally, the IN route offers an alternative route for parenteral administration, as it bypasses first pass metabolism effect of drug and drug degradation, occur in gastroenteric system (like proteins and peptides). As a result, IN administration, primarily via sensory neuronal route or indirectly by passing over the BBB from the systemic circulation, can enable direct drug transport to the brain.

The vestibular region, the respiratory region, and the olfactory region are the three primary regions of the nose cavity (Fig. 1A). The first region is the outermost section of the nasal cavity and is lined with ciliated hairs and a mucous layer, which prevents infections, antigens, and foreign particles from entering. Subsequently, blood vessels and trigeminal sensory nerves are implanted in the respiratory area. Last but not least, the nasal cavity's top portion contains the olfactory area, which has an epithelium made of supporting cells, basal cells, and olfactory receptor cell (Fig. 1). By the olfactory cells located underneath the cribriform plate, this area is in intimate touch with the olfactory bulb in brain. Trigeminal nerves can also be found here [1,12,13].

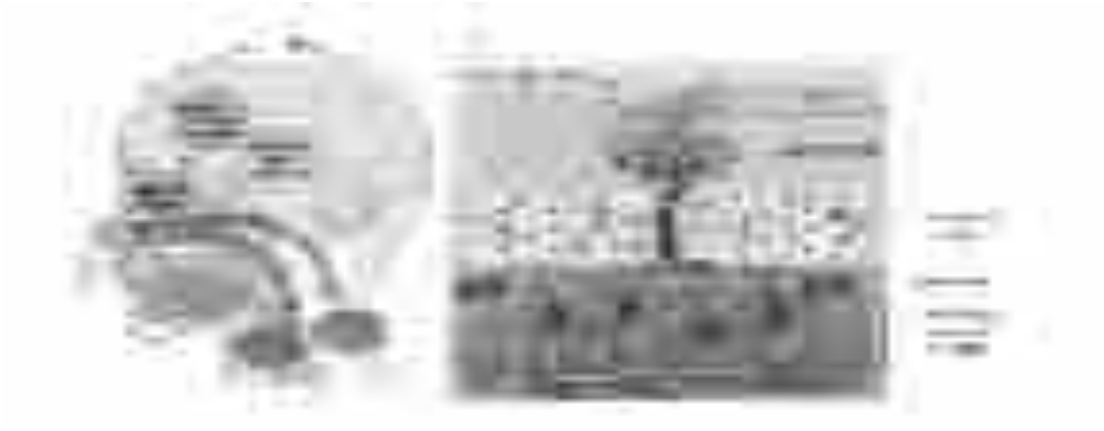

**Fig. 1.** (A)Nose to brain drug delivery system, (B) Anatomical structure of the intranasal route

A therapeutic formulation must defeat mucociliary clearance within the vestibular region after being placed within the nose. The medication can access the CNS after entering the interior nasal cavity by way of the trigeminal and olfactory nerves, or indirectly through into systemic circulation [6,8]. Direct delivery to the brain is made possible throughout the trigeminal and olfactory pathways of the nasal cavity, which has a favourable effect on the pharmacokinetic profiles of CNS medicines. When a medication enters the OB via the olfactory route, it may first travel via the olfactory mucosa or the CSF before mixing with the brain's interstitial fluid. After engaging with olfactory receptors present on the olfactory neurons, and therapeutic substances must pass via cribriform plate and olfactory neurons. Several olfactory nerve transport methods can transfer medications directly to the brain, including intraneuronal and extraneuronal pathways, where movement happens along axons and via perineural channels, subsiquently[9].

This trigeminal route transports therapeutically active chemicals to the brain stem and associated tissues by passing through segments of trigeminal nerves which feed the respiratory region and olfactory mucosa. These branches extend to the forebrain and hindbrain after entering the CNS at the level of the pons. This system permits extracellular transport by bulk flow and diffusion via perineuronal channel, vascular gaps, or lymphatic channels related with CSF and brain tissues, as well as intracellular transport across axons. Transport can take place either intracellularly or extracellularly depending on the physicochemical characteristics of the medication [10-11]. Nonetheless, the respiratory area has significant vascularization, which promotes systemic medication absorption.

Tiny, lipophilic molecules may enter the bloodstream and pass across the BBB more easily than large, hydrophilic ones can. The carotid artery, the brain, and the spinal cord can all be reached by the medication after it has entered the nasal blood vessels. Due to the BBB's restrictions on medication access to the CNS and the potential for unwanted side effects from systemic dispersion, this route is less recommended [12,13]. Notwithstanding the advantages and promise of nose to brain route of administration, the anatomy & physiological, and biochemical

properties of the target location provide considerable obstacles for medicines to enter the central nervous system (CNS).

When medications are taken by the IN route, one of the key obstacles is connected to the residency of mucus into nasal mucosa and ciliary activity as both variables might restrict with retention period of drug molecule into the nasal route and its transit of molecules towards the CNS. Moreover, the tiny volume that each nostril has available for formulation distribution may hinder an effective medication delivery to the brain [7,16]. Another significant restriction with this route, is that the dossage form required first be able to get to the olfactory epithelium due to its anatomical position. While creating a formulation for the nose to brain pathway, enzymes that cause metabolism are found in olfactory mucosa, that must be taken into account. In order to prevent fast removal owing to either mucociliary clearance or enzymatic degradation, or both IN formulations must have been made of compatible and odourless excipients.

Moreover, they need to have a pH that is compatible with the nasal mucosa, the right viscosity, and physiological tonicity [9,14]. As a result, many approaches have been investigated to address the problems with this administrative path. By prolonging the time of drug molecule into nasal mucosa will encouraging drug concentration within the CNS, the majority of these strategies intended to improve molecular absorption and permeability [17]. These techniques include permeation and absorption enhancer, cell-penetrating agents, muco-adhesive and muco-penetrating agents, enzyme inhibitors, polymeric hydrogel systems and nanosized drug delivery systems, as well as a combination of other techniques.

The amazing ability of nanosized-based systems, in particular, to circumvent the difficulties posed by the IN route and create drug accumulation in the brain without systemic dissemination, has been proven. The most recent developments in this area are shown below.

**NP as a carrier: nose to brain delivery**

Due to their functional features associated to the nanoscale size and material composition, nanoparticles based systems must have made tremendous progress in the search for therapeutic drug delivery techniques to the CNS. As a result, among other things, surface area, strength, sensitivity, and solubility enable them penetrate the BBB. There are non-invasive approaches, invasive methods, and alternate pathways that can be employed to deliver nanotechnology systems to the CNS [18]. The non-invasive techniques use internalised cellular processes that, in response to the Fcolloidal, chemical, or biological features, provide the transcellular channel for the transportation of nanoparticles based systems over the BBB. Intraventricular, intrathecal or interstitial injections, among other invasive approaches, are used to provide the nanoparticles based technology precisely into the brain tissue. As per colloidal, chemical, or biological features, the non-invasive approaches use endogenous cellular processes to make it easier for nanoparticles based systems to cross the BBB through the transcellular route. The invasive techniques include methods on the basis of interruption of the BBB using electro-magnetic, ultra-sound, chemical, or magnetic techniques, as well as direct intraventricular, interstitial or intrathecal injections of the nanoparticles system in the brain tissues, among other techniques.

The most effective strategy for delivering therapeutic compounds to the CNS remains the IN administration of nanoparticulate-based systems, notwithstanding all the difficulties encountered. Together, the benefits connected to the route of administration and the characteristics of nanoparticles might make it easier to deliver medications to the CNS. In this approach, one of the key elements that has to be managed in the development of IN formulations is the size of nanoparticulate-based systems. Moreover, drug loading, release, and stability can be impacted by particle size, which also affects toxicity, in vivo distribution of drug and CNS targeting. Pharmacokinetics parameters of nanocarriers, such as systemic circulation duration, absorption, and along with distribution, can also be influenced by particle size distribution [19]. Hence, smaller particle sizes and larger surface areas may result in a drug's being more soluble, interacting with the mucosa more strongly, or permeating the body more effectively than a drug in solution, all of which may be influenced by the makeup of the nanoparticulate system. Another crucial element that improves medication performance after injection is the surface charge of nano- carriers. Positive zeta potentials can facilitate improved interactions with the negatively charged, residue of mucin, which favours the formulation's prolonged retention in the nasal mucosa [20,21].

It has been shown that nanoparticle-based systems enhance medication permeability and absorption, as well as their entry and accumulation into the central nervous system (CNS) and uptake in the olfactory area. They can simultaneously shield therapeutic compounds from deterioration and stop outgoing transporters from delivering them outside the cell [9,19,20]. Also, the incorporation of various approaches with nanotechnology has made it possible to favour the absorption of IN nanoparticulate-based systems into the CNS. Pegylated molecules, one type of surfactant, are utilised to make drugs more permeable, and mucoadhesive polymers that may interact with mucin, including chitosan, are used to extend mucin's residence duration [23]. Cell penetrating peptides, may cause interaction with the biological membranes, on the other hand, are used to increase cellular uptake [23,24]. In a similar manner, other research have looked at the usage of biorecognition ligands to increase the transit of nanocarriers from the nose to the brain. For active brain targeting, lectins and other proteins with olfactory receptors are the industry standard.

**Nanoparticles based on polymers**

Because to their widespread application in nose-to-brain administration, polymer-based NP are presently at the vanguard of innovative neuropharmacological therapies [27]. These nanocarriers have become the subject of therapeutic study due to their chemical adaptability, high drug loading capacity and simplicity in surface function with targetting ligands [28]. Polymers can be used as building blocks to create a variety of structures, including dendrimers [32], micelles [30], nanocapsules [31], and polymer NP [29]. Moreover, drug delivery methods for IN might be created using biopolymers and synthetic polymers. For instance, synthetic building blocks made of biodegradable and biocompatible materials such as poly(capro-lactone), poly(lactic acid),

poly(lacticcoglycolic acid), and poly(ethyleneglycol)-poly(lacticcoglycolic acid) (PEG-PLGA) are frequently employed [21]. On the other hand, several biopolymers have been investigated, including gelatine, pullulan, sodium alginate, sodium hyaluronate and human serum albumin (HSA). Nevertheless, the most often used polysaccharides in nasal route delivery systems are chitosan and its derivatives, which have remarkable mucoadhesive and cell penetrating capabilities [33].

**Polymer nanoparticles that penetrate mucus**

Because to their muco- diffusive and penetration capabilities, surfactants like Tween 80 and Poloxamer 407 (Pluronic F127), have historically been utilised to coat polymer NP in IN formulations [21]. Rhodamine-loaded PLA and PLGA nanoparticles were made by Puglisi et al. using Tween 80 as a stabiliser, and their absorption in olfactory ensheathing cells was compared to that of chitosan nanoparticles [35-37]. Study indicated that Tween 80 was crucial in enhancing cellular absorption of the polymer NP, with the lowest absolute surface charge PLGA nanospheres exhibiting the highest performance. Recent research conducted by Del Favero et al. compared three nanoformulations for the nasal delivery of simvastatin, including polymer PCL nanocapsules stabilised with Tween 80, polymer PCL as nanocapsules which is coated with sodium caproyl hyaluronate, and hybrid lecithin [38,41].

**Mucoadhesive nanoparticles**

The main physiological process that dramatically reduces nose-to-brain transfer is mucociliary clearance. As a result, NP-based models that may interact with mucin and increase their time spent in the olfactory area have been studied for years [42]. Considering this, the workhorse of nose-to-brain transport has been chitosan NP or NP containing polyer coated with this polysaccharide [22]. The encapsulation of midazolam in chitosan NP is described in a recent case that has been reported in the literature [42]. Midazolam concentration in the brain was much greater with the nanoformulation than with the drug solution (DTE 271% vs. 191%), proving the effectiveness of these mucoadhesives and penetrating chitosan NP in targeting the brain.

A non-ergoline dopamine agonist having significant results in treatment of Parkinson's disease, rotigotine, was developed for IN administration via chitosan NP by Bhattamisra et al. [43]. In Sprague Dawley rats, this nanosystem demonstrated better brain accumulation capacity and drug bioavailability. An increase in level of alpha-synuclein is a crucial clinical indicator of Parkinson's disease. In order to show that rats given with rotigotine drug loaded with chitosan NP produced a large drop in the levels of this neuronal protein, 51.10 2.24 pg/mL, the authors found that this reduction was much greater compared to the rotigotine solution, 62.78 pg/mL.

Borge et al. suggested covering PLGA NP with chitosan and loading the anti-Parkinsonian medication ropinirole hydrochloride as a substitute to such polymer nanosystem [44]. These NP were given mucoadhesive characteristics by the chitosan armour, which significantly increased the drug's penetration into nasal mucosa of by around three times over unmodified PLGA NP.

Moreover, the effect of chitosan coating on the characteristics of HSA NP for nose-to-brain transport was recently investigated [45].

**Lipid-Based nanocarrier system**

The drug delivery systems called lipid-based nanocarriers are made of lipid and an aqueous phase and are stabilised by using surfactants. Such system provide advantages in terms of controlled release, sustained release, drug safety, drug loading, drug stability and surface adaptability and are made of biocompatible and biodegradable components. The ability of lipid-based nanocarriers to permeate biological membranes and to encourage partitioning of nanosized droplet in the nasal mucosa, which results in an extended residence period, makes them excellent candidates to improve brain drug delivery following IN administration [46].

**Nanocarriers based on lipids**

The oldest substances studied for nose-to-brain transport were liposomes and Solid lipid nanoparticles however in more recent years, several formulations of NLC have been described for this route. Additionally, mucoadhesive agents have shown promising results when added to lipid-based nanocarriers or when they are included in formulations that are mucoadhesive-based, indicating improved contact with the nasal mucosa and the potential for increased permeation rate and permanence in the nasal cavity [47].

**Solid lipid nanoparticles**

Solid lipid nanoparticles are colloidal structures with solid lipid core and a layer of surfactant covering that are helpful for regulated medication release and protection of drug over chemical degradation [48]. The bioavailability of several medications in the brain has been increased by a number of IN formulations based on Solid lipid nanoparticles. The most recent research focuses on HIV infections, Parkinson's disease, and Alzheimer's disease. In order to overcome the limited drug bioavailability via oral route, Solid lipid nanoparticles have been employed to encapsulate efavirenz for HIV infections treatment. After IN injection, Solid lipid nanoparticles shown 150 times more brain targeting effectiveness than a conventional oral formulation [49].
These findings were connected to formulation characteristics, such as lipid content and nanoscale size, and direct nose-to-brain delivery. In a different trial, Solid lipid nanoparticles were employed to encapsulate a combination with geraniol and ursodeoxycholic acid for the IN administration treatment of Parkinson's disease. This method got around some of the problems of geraniol, which has short half-life into the systemic circulation when taken orally and having poor solubility in water along with muco-irritation. It's interesting to note that rats given this Solid lipid nanoparticles formulation by IN injection had greater geraniol concentrations in their CSF without experiencing mucosal irritation, proving that it can help molecules pass from the nasal route to the CSF in the animal models [50].

The exploration of Solid lipid nanoparticles formulations incorporating mucoadhesive polymers and emulsifiers with strong penetration effects demonstrated a more effective brain

targeting for such a formulation. The inclusion of lipid components, Span® 60, and formulations with mucoadhesive properties from HPMC, which favour residency in the IN cavity and may facilitate passage over the BBB and function as uptake enhancers, respectively, were attributed to the increased drug delivery in large part [48, 51]. Almotriptan malate was created for brain administration through IN route, while mucoadhesive in-situ gel formulation using Poloxamer 407 and sodium carboxy methyl cellulose, such solid lipid nanoparticles demonstrated fast drug accumulation in the brain. In-situ gel formulation of the Solid lipid nanoparticles had a greater brain/blood dose ratio as compared to IN and IV administration of the drug, according to distribution studies. Moreover, AUC values up to 6 hours, which correspond to the brain's drug dose profile, supported the effectiveness of IN Solid lipid nanoparticles and IN drug formulation over IV drug delivery [52,53].

**Gold nanoparticles**

In addition to other CNS disorders, Gold NP have shown possible applicability for ageing, Alzheimer's disease, and parkinsonism diagnosis [54]. Nevertheless, after IV administration, the BBB restricts their accumulation in the Brain [55]. The IN route has been suggested as a means of getting over this barrier at the moment, however differing physicochemical properties of Gold NP will interfere with the transportation of nanoparticles to the CNS from the nasal cavity. The examination of NP in various sizes and forms might thus be useful in understanding this process. Gold nanoprisms (GNPr) and nanospheres (GNS) with comparable surface areas were used by Gallardo-Toledo et al. to measure their transit to the brain following IN administration [59].

**Conclusion**

The specifics of the BBB and possibility of negative side effects following systemic drug administration, medication delivery into the brain has proven to be a substantial difficulty. As it can cross the blood-brain barrier and raise in concentration of the therapeutic agent in the brain via direct transportation through olfactory and trigeminal pathways, nose to brain administration of therapeutic agents might be a promising approach. This strategy can reduce the amount of medication needed and may eventually reduce the danger of systemic toxicity. Localized delivery of active molecules into the brain, several innovative nanoscale-based carriers might increase the drug targeting impact and perhaps offer regulated release of treatments.

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