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iajpb.editor@gmail.com
editor@iajpb.com

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NOSE TO BRAIN A MUTLIFACETED MODE OF DRUG DELIVERY SYSTEM

[1]Dr. G. Thirupathi,[2]Mr. V. Sanjeev,[3]Mrs. Syed Husna Fathima
[1]Professor,[2,3]Assistant Professor
[1,3]Department of Pharmacology
[2]Department of Pharmaceutics
Vaagdevi Institute of Pharmaceutical Sciences, Bollikunta, Warangal. Telangana.

Abstract:

It has always been difficult to treat neurodegenerative illnesses and other abnormalities of the central nervous system (CNS). Due to the blood-brain barrier's (BBB) nature, therapeutic molecules cannot fully penetrate the brain after being administered orally or parenterally. This, along with hepatic metabolism, drug elimination, and drug inactivation during the drug's journey through the systemic circulation, reduces treatment efficacy, necessitates high dosages, and frequently results in unfavorable side effects. Drug concentration in the brain is increased through nose-to-brain delivery, which circumvents the blood-brain barrier and permits the direct movement of medicinal compounds. The processes of nose-to-brain drug delivery are described in this study, along with recent developments in the field, with a focus on techniques based on nanotechnology.

Keywords: nasal administration, brain-targeting, CNS illnesses, neurodegenerative diseases, nanomedicine, and nanotechnology

1. Introduction

The brain is one of the most complex, vital organs that accepts signals from sensory organs and regulates most body functions. It controls voluntary and involuntary movements, hormone secretion, memory encoding, and the functions of many other organs [1]. Since the brain has such a critical role in the human body, it is protected externally and internally. It is protected by a skull with different membrane layers that prevent external damage and is internally protected by cerebrospinal fluid (CSF), the CSF-blood barrier, and the blood-brain barrier (BBB). These barriers help maintain the homeostasis of the brain and prevent physical damage, infections, endotoxins, and any harmful effects [2,3].

The integrity of these protective mechanisms may be altered for various reasons such as trauma, mutation, aging and may lead to neurological disorders. As the brain regulates the whole body, the damage of this control center has a detrimental effect on both physical and mental health. According to the World Health Organization (WHO), death due to Alzheimer's disease and other dementias more than doubled between 2000 and 2019, making it the 7th leading cause of death globally [4]. Not only dementia but also other neurological disorders, such as stroke, epilepsy, and Parkinson's disease, are significant causes of hospitalization and mortality worldwide. In 2016, neurological disorders were the leading cause of disability-adjusted life-years (sum of years of life lost and years lived with disability) and the second leading cause of death [5]. Patients suffering from chronic

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neurological disorders may also end up facing depression and suicidal ideation [6].

Researchers have invented several different therapeutic agents to treat these devastating neurological disorders. Still, these agents are mainly used for slowing down the progression of disease and cannot completely reverse the condition [7]. One of the main reasons for this limited therapeutic effect is the presence of the BBB, which blocks more than 98% of neurotherapeutic molecules into the central nervous system (CNS) [8]. The BBB consists of endothelial cells of capillaries, astrocyte end-feet surrounding the outside of brain capillary endothelial cells, and pericytes embedded in the capillary basement membrane. The capillaries are non-fenestrated vessels with tight junctions, limiting the paracellular pathway of these therapeutic molecules [9]. Moreover, P-glycoprotein and other ATP-binding cassette transporters prevent the accumulation of the therapeutic drugs and pump those molecules out of the brain [10,11]. Due to the tight junctions that limit the paracellular route of drug delivery, the most possible pathways for drug transport to the CNS are the transcellular route (limiting the drug molecule to be highly lipophilic and molecular weight < 500 Da), receptor-mediated endocytosis, and carrier-mediated transport. However, in order to employ these mechanisms of drug entry into the brain, a drug or delivery vehicle needs to meet specific criteria for this to occur [12–15]. In addition, circumventricular organs with permeable endothelial cells of capillaries as well as specialized permeable zones of the brain potentially can also be used for the delivery of therapeutics to the brain tissues [16].

Many researchers proposed alternative strategies to overcome this physiological barrier, such as intracerebroventricular injection and intrathecal injection. Intracerebroventricular and intracerebral injection allow neurotherapeutic molecules to reach a high concentration in the brain. Still, the injection solution and drug itself need to meet many conditions, such as pH, volume, diluents, and preservatives in order to be injected directly into the brain structures, which creates certain difficulties for using these alternative routes for the brain delivery [17]. Intrathecal injection is more common, especially in oncology, to treat cancer in CNS, but its application in neurology is still limited. Deep brain stimulation involves the implantation of electrodes in the brain to treat Parkinson's disease and has shown significant progress. However, this method is an invasive and costly technique [18]. Implantable drug reservoirs with prolonged drug release (e.g., GLIADEL® Wafer) are also used for local brain delivery [19,20].

Since all of the procedures described above are invasive and costly, the intranasal delivery system has attracted attention as a route for potential drug delivery to the brain. Traditionally, intranasal delivery is used to promote local effects for the treatment of rhinitis or allergy. However, due to its many favorable characteristics, including non-invasiveness, good patient compliance, and ease of administration, intranasal delivery has also been used for systemic delivery. Its application has been increasing in the market, as it has shown efficacy in the flu vaccine, pain and migraine management, smoking cessation, and other areas [21]. Many studies have shown that intranasal delivery of small and large molecules can directly target the brain. Olfactory mucosa is the region that BBB does not protect, and it has direct contact with the brain. Also, it has the

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potential to decrease the accumulation of therapeutic molecules in the major organs, such as the liver, spleen, and kidney, and therefore reduce systemic side effects [22,23]

The present review is a comprehensive synopsis and analysis of the current landscape of nose-to-brain (N2B) delivery for nanotherapeutics from a wide range of perspectives including but not limited to mechanistic biology, transport kinetics, formulations, and clinical applications in both recent & historical context. Herein, the anatomy of the nose and prospective pathways of N2B delivery, challenges associated with those respective routes, basic pharmacokinetic parameters and expressions are discussed in greater detail. Furthermore, the application of various nanotherapeutic approaches for N2B delivery is assessed amongst neurological and other CNS disorders.

2. Nasal Cavity

To understand the different mechanisms of drug absorption through the nasal cavity to the brain, it is essential to know the anatomical and cellular structure of the nasal cavity.

2.1. Anatomy of the Nasal Cavity

The nasal cavity extends around 12–14 cm in length, 5cm in height, has a total volume of 15–20mL, and a surface area of between 150 to 200 cm2 [24–26]. There are three kinds of turbinate: the superior, the middle, and the inferior turbinate, and they are responsible for humidifying, filtering, and warming the inspired air through nostrils [27,28]. The nasal cavity can be divided into three sections: the nasal vestibule, the respiratory section, and the olfactory section (Figure 1a) [28]. The nasal vestibule is located in the most anterior part of the nasal cavity, and it consists of hairs, sebaceous, and sweat glands [28,29]. The respiratory section is mainly dominated by the middle and the inferior turbinate, and it serves as a passage for air to the lungs. The olfactory area is located on the superior turbinate, covering about 10 cm2 , and contains olfactory receptors, which are responsible for the sense of smell [28,30,31]. In terms of drug absorption through intranasal delivery, respiratory and olfactory mucosa are the main sites of interest.

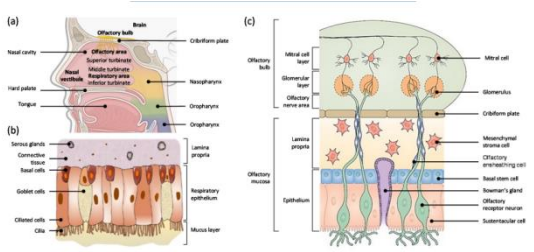

Figure 1. (a) Anatomy of the human nasal cavity. Squamous mucosa is located at the nasal vestibules. Respiratory mucosa is consisted of inferior, middle, and superior turbinate forming respiratory area. The olfactory mucosa is located underneath the cribriform plate in the olfactory area. (b) The respiratory mucosa. It is comprised of the lamina propria, respiratory epithelium, and a mucus layer. Within the respiratory epithelium, there are basal, goblet, and ciliated cells. Adapted with permission from [27], Elsevier, 2018. (c) The olfactory system consists of the olfactory mucosa, which is in the nasal cavity, and the olfactory bulbs, which are in the brain. The mucosa is composed of a pseudostratified epithelium containing olfactory receptor neurons (OSNs), Bowman's glands, sustentacular cells, basal cells, and the lamina propria. OSNs have receptors that can entrap molecules and transmit information to glomeruli in the olfactory bulb. These neurons are ensheathed by glia,

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known as olfactory ensheathing cells (OECs). After damage or during normal cell turnover, newly formed OSNs are guided back by OECs into the olfactory bulb, where they re-synapse with glomeruli. Adapted with permission from [32], Springer Nature, 2020.

2.2. Respiratory Mucosa

Respiratory mucosa consists of 80–90% of the total surface area in the human nasal cavity, and it is highly vascularized, making it a significant site for systemic drug absorption [25]. Respiratory mucosa consists of various cell types and glands, such as basal cells, goblet cells, ciliated epithelial cells, and serous glands (Figure 1b) [27,28]. Basal cells are progenitor cells that can differentiate into other cell types found within the epithelium and also help to attach ciliated and goblet cells to the basal lamina [33]. Goblet cells secrete mucus composed of mucin (high molecular weight glycoproteins), water, salts, a small group of proteins, and lipids [34]. Mucus forms a layer in the respiratory epithelium and serves as a first-line defense by entrapping any inhaled materials or irritants [35,36]. Ciliated cells help to remove this mucus towards the nasopharynx, which results in mucociliary clearance (MCC) [25,37]. Serous glands secrete watery fluid and other antimicrobial proteins, which serve as part of innate immunity [38].

2.3. Olfactory Mucosa

The olfactory mucosa is located on the top of the nasal cavity and takes up about 5~10% of the total surface area of the human nasal cavity [25]. The olfactory mucosa (Figure 1c) consists of olfactory receptor neurons, so-called olfactory sensory neurons (OSN), the olfactory epithelium, and the lamina propria [27,32]. The olfactory nerve is the first cranial nerve that transmits sensory information related to smell [39]. OSNs are non-myelinated neurons and located in the nasal epithelium. OSNs have direct contact with airborne substances through odorant chemoreceptors located in the apical surface of the olfactory mucosa, and each OSN expresses only one receptor [40]. Humans have approximately 400 olfactory receptors, whereas rodents have approximately 1000 olfactory receptors [41]. Each OSN forms thick axon bundles in the lamina propria, and these bundles become olfactory nerves. They innervate the cribriform plate and create synaptic connections with glomeruli of mitral and tufted cells in the olfactory bulb [40,42,43].

OSNs have direct contact with the environment, airborne irritants, and microbial agents, so these exogenous compounds may cause injury or cell death of OSN. To maintain its function, neurogenesis of OSNs occurs in the nasal epithelium to regenerate the neurons. A few studies have suggested that the life span of OSNs is between 30–60 days, and the systemic apoptosis of OSNs occurs to protect the brain from infections [28,40,44]. During the neuronal regeneration, there is a delay of tight junction formation, which causes some gap and allows some substance penetration [45].

Olfactory epithelium, just like respiratory epithelium, consists of ciliated columnar cells covered by a mucus layer. However, cilia in the olfactory epithelium are non-motile and longer than those in the respiratory epithelium [43]. In the olfactory epithelium, two types of basal cells account for neuronal regeneration: globose basal cells and horizontal basal cells. Globose basal cells are progenitor cells for OSNs, and they account for the homeostasis of normal tissue in olfactory mucosa [46,47].

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Horizontal basal cells are multipotent progenitor cells in the olfactory epithelium for normal turnover and help its regeneration from acute injury [48]. Not only basal cells but also supporting cells are present in the olfactory epithelium. Sustentacular cells (SUS) are supporting cells that enclose the OSNs in the olfactory epithelium region. Their primary function is to stabilize the structural and ionic integrity of OSNs [49].

Lamina propria of olfactory mucosa consists of numerous cell types and structures such as Bowman's glands (BG) and olfactory ensheathing cells (OEC) [50]. BGs innervate the olfactory epithelium and secrete a mucus layer in the olfactory system [51]. The exact composition of the olfactory mucus is still unknown, but a histological study showed that these glands are positive for periodic acid-Schiff staining, indicating the presence of neutral glycoproteins [28,52]. OECs are glial cells that enwrap non-myelinated bundles of OSN and help to promote the regeneration of OSNs [53].

3. Pathways for Nose-To-Brain Delivery

Drug transport through the olfactory mucosa has been studied to deliver therapeutic substances to the brain to treat CNS diseases. As described earlier, it has the significant advantage of bypassing BBB and reducing systemic exposure. The pathways for N2B delivery have not been fully understood, but many recent studies have suggested some major possible pathways. One way is the direct transport of drugs to the brain through neuronal pathways such as olfactory or trigeminal nerves. The other way is the indirect transport of drugs through the vasculature and lymphatic system, leading to the brain crossing BBB [54]. Drug absorption from nose to brain may not be limited by one single mechanism, but may involve several pathways.

3.1 Olfactory Pathway

Major routes of drug transport from the olfactory pathway can be subdivided into four different categories: intra-and extra-neuronal pathways and paracellular and transcellular pathways (Figure 2) [23,27,42].

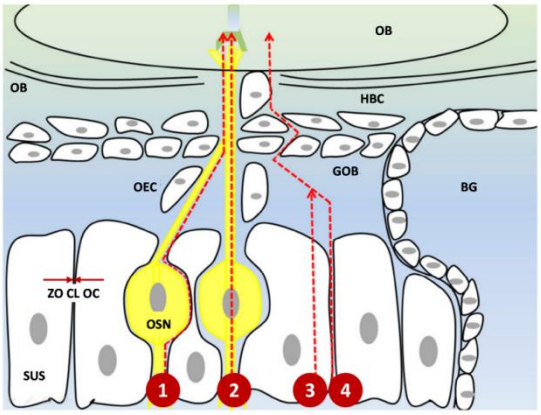

Figure 2. Four different routes of nose-to-brain drug delivery through olfactory mucosa. (1) Extra-neuronal pathway (2). Intra-neuronal pathway (3). Transcellular pathway (4). Paracellular pathway. The drug has to pass tight junctions (marked with red arrows) such as ZO, CL, and OC to travel through the intercellular space. N2B delivery is a mixture of these Figure 2. Four different routes of nose-to-brain drug delivery through olfactory mucosa. (1) Extra-neuronal pathway (2). Intra-neuronal pathway (3). Transcellular pathway (4). Paracellular pathway. The drug has to pass tight junctions (marked with red arrows) such as ZO, CL, and OC to travel through the intercellular space. N2B delivery is a mixture of these different pathways. Abbreviations: ZO: zonula occludens; CL: claudin; OC occludin; SUS: sustentacular cells; OSN: olfactory sensory neuron; OEC: olfactory ensheathing cell; GOB: globose

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basal cells; HBC: horizontal basal cells; BG: Bowman's gland; CP: cribriform plate; OB: olfactory bulb. Modified from [28].

2. Trigeminal Pathway

A trigeminal nerve is the fifth cranial nerve and is the largest cranial nerve which innervates both the olfactory and the respiratory mucosa. It has three different branches, consisting of the ophthalmic, maxillary, and mandibular nerves, and is responsible for delivering sensory and motor information of these areas to the spinal cord, the medulla, and the pons [27,58,61]. Among those branches, the ophthalmic and maxillary branches are involved for N2B delivery. Ophthalmic branches pass through the dorsal nasal mucosa and anterior part of the nose, and maxillary branches through the lateral wall of nasal mucosa [23,30]. Similar to the olfactory nerve pathway, drug transport via the trigeminal nerve occurs by multiple pathways. Once drug moieties reach the branches of the trigeminal nerve, they will merge at the trigeminal ganglion and enter the brain near the pons. Also, some portions of the trigeminal nerve are present near olfactory bulbs, so drug molecules can cross the cribriform plate and reach both the caudal and rostral areas of the brain [23,62].

3.3. Systemic Pathway

Drug transport of inhaled substances to the brain can occur indirectly through the respiratory epithelium via systemic circulation and the lymphatic system. Since the respiratory epithelium is highly vascularized with a combination of a continuous and fenestrated endothelium, it gives access to blood circulation. However, these substances need to cross the BBB to reach the CNS, which is the rate-limiting step. The systemic pathway mainly occurs for the small and lipophilic substances so that they can cross the BBB transcellularly [27,30,58].

4. Potential Challenges for Nose-To-Brain Delivery

Nose-to-brain delivery has many advantages, including bypassing BBB, less systematic side effects, and increasing patient compliance using a non-invasive approach. However, there are a few challenges, such as optimizing mucus penetration and mucociliary clearance (MCC).

4.1. Cilia and Nasal Mucus Transport

There are motile and non-motile cilia in the nasal cavity. Motile cilia are mostly present in the respiratory epithelium, whereas non-motile cilia are prevalent in the olfactory epithelium. Motile cilia have a motor protein called dynein, which generates motion, and non-motile cilia play roles in sensory function and transportation [28,63]. A small portion of respiratory mucosa is present in the olfactory region, allowing mucus transport in the olfactory region [64].

4.2. Mucociliary Clearance

Mucociliary clearance (MCC) is an interaction between the cilia and mucus layers, which helps inhaled toxic substances to adhere and transport toward the nasopharynx and gastrointestinal tract [68,69]. There is an inter-individual difference in MCC, but the speed is estimated to be 6 mm/min on average. MCC is one of the major factors to consider for N2B delivery since it can affect drug bioavailability. Drug formulation should be able to stay long enough to penetrate the mucus and adhere to the local nasal epithelium before being washed away.

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Once the inhaled molecules cross the mucus, they have good permeability to the nasal epithelium [70].

MCC can vary based on environmental and pathological factors. Decreased mucus viscosity, increased mucus production, and increased ciliary beat frequency will increase MCC. In contrast, the inhalation of sulfur dioxide, smoking, reduced temperature in the nasal cavity, and thickened mucus will decrease MCC. Asthma, rhinitis, allergy, and sinusitis can change MCC by affecting ciliary beat frequency or mucus production [69,71]. MCC can also be influenced by drugs that affect ciliary beat frequency. Anesthetics, cholinergic inhibitors, alpha-adrenergic receptor agonists, corticosteroids, and anti-histamine drugs inhibit MCC, whereas beta-adrenergic agonists and cholinergic agonists increase the ciliary beat frequency and stimulate MCC [70]. Therefore, N2B delivery may have variable bioavailability in the brain, depending on patients' physiological conditions and medications.

5. Pharmacokinetics of Nose-To-Brain Delivery

Drug absorption through N2B delivery, as distinct from a conventional pathway for brain delivery (oral, parenteral, and transdermal), requires specific pharmacokinetic indexes to measure its effectiveness. Drug targeting efficiency (DTE) is a parameter that represents the efficiency of the drug to reach the brain via the intranasal route relative to that obtained via the systemic route (1). AUC is the area under the curve representing drug concentration over time for the duration of the study [72]. Values can range from 0 to +∞, and the values above 100% indicate better efficient brain targeting through IN than IV, whereas values below 100% represent the opposite.

$$DTE(\%)_{(IN)} = \frac{\left(\frac{AUC_{Brain}}{AUC_{Blood}}\right)_{IN}}{\left(\frac{AUC_{Brain}}{AUC_{Blood}}\right)_{IV}} \times 100 \quad (1)$$

DTE does not describe which pathway contributed to the drug concentration in the brain. Instead, it implies that intranasal administration leads to higher brain bioavailability than intravenous administration.

To calculate whether intranasal delivery directly leads drugs to reach the brain or not, we can use direct transport percentage (DTP). DTP is a percentage of the dose reach to the brain via IN compared to the overall delivery of the drug to the brain (2). It represents the drug fraction from direct transport to the brain.

$$DTP(\%)_{(IN)} = \frac{AUC_{BrainIN} - F}{AUC_{BrainIN}} \times 100 \quad (2)$$

F is the brain AUC fraction from the systemic circulation (indirect pathway) (3).

$$F = \frac{AUC_{BrainIV}}{AUC_{BloodIV}} \times AUC_{BloodIN} \quad (3)$$

The values of DTP can range from -∞ to 100%. A positive DTP value indicates a contribution of the direct N2B pathway to the drug levels, whereas 0 or negative values indicate the drug prefers to be delivered to the brain through systemic circulation after IV administration. These quantitative data help build advanced PK-PD models to predict CNS concentration for N2B delivery [73]. One limitation of DTE and DTP is that poorly permeable drugs to BBB will lead to high values, so it does not always correlate to high bioavailability in the brain.

B%Brain IN/IV is used to measure the drug accumulation in the brain from IN

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compared to that of IV (4). Values above 100% indicate a better brain drug accumulation through IN administration.

$$B\%_{\text{Brain IN/IV}} = \frac{AUC_{\text{BrainIN}}}{AUC_{\text{BrainIV}}} \times 100 \quad (4)$$

Relative bioavailabilityBrain is a measure of brain drug accumulation with nanosystem IN compared to drug solution IN (5). Since many N2B delivery systems use nanocarriers to deliver drugs, it may be necessary to calculate the effectiveness of the nanosystem compared to that of free drug solution.

$$\text{Relative bioavailability}_{\text{Brain}} = \frac{(AUC_{\text{BrainIN}})_{\text{nanosystem}}}{(AUC_{\text{BrainIN}})_{\text{solution}}} \times 100 \quad (5)$$

Values above 100 will indicate a better drug accumulation with the nanosystem than the drug solution. Using this relative bioavailability concept, we can also compare the relative DTE and DTP of the nanosystem and drug solution using the following equations:

$$RDTE\% = \frac{DTE\%_{\text{INnanosystem}}}{DTE\%_{\text{INsolution}}} \times 100 \quad (6)$$

$$RDTP\% = \frac{DTP\%_{\text{INnanosystem}}}{DTP\%_{\text{INsolution}}} \times 100 \quad (7)$$

6. The Potential Role of Nanotechnology for Nose-To-Brain Delivery

Pharmaceutical nanotechnology has been widely used to deliver therapeutic molecules to the targeted area. The size of the particles is in the nano range (1–1000 nm), and these particles typically form a colloidal dispersion [74,75]. The use of nanotechnology in N2B delivery is very promising. It can increase the residence time of the drug at the site of absorption, promote its mucosal permeation and cellular internalization, increase drug solubility, control the release of the encapsulated drug, and reduce systemic side effects by decreasing the drug distribution to the non-targeted area. All these characteristics favor the use of nanoparticles (NPs) for N2B delivery [76].

Although nanotechnology has been widely used in drug delivery for its favorable characteristics, the effect and accumulation in the human body should not be neglected. Once nanocarriers enter the biological system, proteins, lipids, and other biological molecules in the body will be adsorbed on the surface of nanocarriers and form the so-called “biocorona” [77]. The biocorona can alter physicochemical properties such as size, shape, and hydrophilicity of original nanocarriers through nanoparticle-biomolecule interactions [78]. Also, the pharmacokinetic profile, such as cellular uptake, half-life, and distribution can be modified [79,80]. The biocorona can be recognized by complement receptors on macrophages and undergo increased cellular uptake and accumulated in the liver and spleen [81]. Some studies showed that metal-based nanoparticles may cause negative effects on the cardiovascular system and the nervous system. Increased inflammatory ytokines, arrhythmia, as well as increased oxidative stress and neurotoxicity could occur after the administration of titanium dioxide and silica nanoparticles, which are a commonly used nano-formulation in the industry [82,83]. Since peptides and lipids are present in the nasal mucus, there is a high chance that the inhaled nanoparticles will form the biocorona and may alter their physicochemical properties and cellular uptake. Therefore, the characteristics of the biocorona need thorough evaluations to effectively translate preclinical data to a safer and more efficient nanosystem for clinical application.

6.1. Lipid-Based Nanoparticles

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Lipid-based nanoparticles have been widely investigated for drug delivery systems. These NPs are amphiphilic, being able to transfer both hydrophilic and hydrophobic materials in one particle [85]. Lipid-based carriers are made from biocompatible, biodegradable lipids similar to those consisting of the cell membrane. These features allow them to penetrate the cells efficiently and limit their toxicity. Most commonly used lipid-based NP formulations are (Figure 3) liposomes, nanoemulsions formed with micelles, solid lipid nanoparticles (SLN), and nanostructured lipid carriers (NLC) [86,87]. These lipid-based NPs are often modified with polymers such as polyethylene glycol (PEG) or poloxamers. PEG is a hydrophilic polymer that is biocompatible and stabilizes NPs [88]. Furthermore, it acts as a mucus penetration enhancer by decreasing interaction with mucin [76]. Poloxamers, similar to PEG, are water-soluble, non-ionic surfactants and consist of a triblock copolymer of hydrophobic polypropylene glycol and two hydrophilic blocks of PEG. They have low toxicity, good drug release, and are compatible with many different chemicals, making them useful tools for drug delivery [89]. Poloxamer 407 (Pluronic F127) and 188 (Pluronic F-68) both have high contents of PEG (70% and 80%, respectively) and can help decrease mucus viscosity and increase penetration by interacting with lipid membranes and tight junctions [90,91].

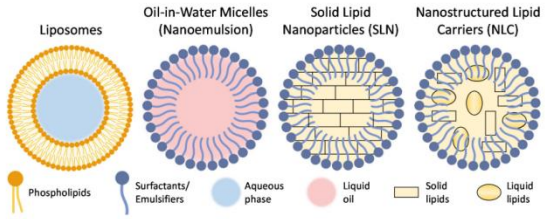

Figure 3. Most widely used lipid-based nanoparticles. Figure 3. Most widely used lipid-based nanoparticles.

6.1.1. Liposomes

Liposomes are one of the most widely used lipid-based NPs for drug delivery systems. Typically, a liposome has a single or several phospholipid bilayers, often with other lipids such as cholesterol or phosphatidylcholine. Using various types of lipids, the physical characteristics of liposome membranes may vary in terms of size and surface charge. For instance, neutral or slightly negatively charged liposomes can incorporate both hydrophilic (inside their aqueous core) or hydrophobic (inside the lipid membrane) active ingredients. In contrast, the positively charged liposomes can form multiplexes with negatively charged nucleic acid [94–98].

Many studies of N2B delivery have used a liposome as a nanocarrier to treat different types of CNS disorders [99–104]. Al Asmari et al. formulated a donepezil-loaded liposome using 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and PEG to evaluate the brain and plasma pharmacokinetics after intranasal administration [99]. Donepezil is a cholinesterase inhibitor, and it is a commonly used medication to treat Alzheimer's disease. In their study, the size of nanoparticles was 102 ± 3.3 nm, the surface charge was −28.31 ± 0.85 mV, the polydispersity index (PDI) was 0.28 ± 0.03, and drug encapsulation efficiency (EE) was 84.91 ± 3.31%. The drug release from the liposomes had biphasic characteristics: an initial rapid release phase for 2 h followed by a sustained release up to 8 h. The AUC of donepezil liposome through intranasal (IN) delivery was higher than the AUC of

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oral (PO) and IN of free donepezil. The bioavailability of donepezil delivered by liposomes via the IN route in the brain was two times higher than that of free IN donepezil ($p < 0.05$) but showed no significant difference in terms of half-life. The histopathological study showed no evident signs of injury in major organs such as the liver, lung, heart, spleen, kidney, brain, and olfactory bulb after nasal administration of the liposomal formulation of donepezil in rats. This study showed the promising role of liposome as a carrier for improving the bioavailability of donepezil to the brain with N2B delivery systems [99]. Hoekman and et al. developed a fentanyl-loaded liposome with an arginine-glycine-aspartate (RGD) peptide and underwent aerosolization for intranasal delivery [101]. Rats treated with RGD-liposome IN had a higher analgesic effect than those with free fentanyl IN (AUC 1387.1 vs. 760.1%) and 20% reduced plasma drug exposure (AUC0–120 208.2 vs. 284.8 ng·min/mL). The RGD peptide liposomes bind to integrin proteins on the nasal epithelium and eventually increase the retention of fentanyl in the nasal and olfactory epithelium [105]. In addition, the liposomes worked as a drug reservoir, as there was a significant increase in the overall analgesic effect without affecting the onset of action, but lasted six times longer than the free fentanyl solution. Intranasal liposomal delivery potentially showed increased drug concentration in the brain as well as a decreased systemic exposure [101].

Muntimadugu et al. formulated tarenflurbil-loaded solid lipid nanoparticles (SLN) and PLGA NPs for effective brain penetration. Tarenflurbil (TFB) is a β-amyloid-42 peptide lowering agent and modulates γ-secretase, an enzyme responsible for β-amyloid plaque formation. TFB PLGA NPs used in one study had a size of 133.13 ± 7.82 nm, ZP of −30.25 ± 2.11 mV, PDI of 0.21 ± 0.02, and encapsulation efficiency of 64.11 ± 2.21% [139]. TFB SLN had a size of 169.87 ± 10.98 nm, ZP of −23.13 ± 2.32 mV, PDI of 0.24 ± 0.04, and EE of 57.81 ± 5.32%. Both formulations showed a biphasic release pattern: ~55% of TFB was released from both formulations in 2 h with a sustained release for 48 h. Higher absolute bioavailability, DTE, and DTP were recorded in TFB PLGA NPs than those in TFB SLN. The effectiveness of PLGA NPs was markedly observed in 8 h and 24-h post-administration as the concentration of TFB in the brain was significantly higher in the PLGA NPs group than the SLN group ($p < 0.0001$ and $p < 0.01$, respectively) (Figure 4). Both formulations yielded significantly higher drug concentration in the brain than IV and PO tarenflurbil, with no significant drug concentration difference in the spleen and heart [139]. This study implied that tarenflurbil could be a more suitable substrate for polymeric NPs than lipid-based NPs for N2B delivery

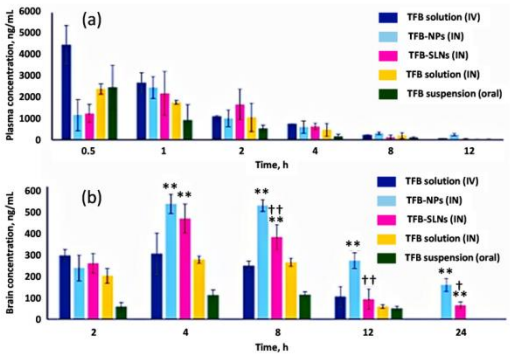

Figure 4. Plasma concentrations (a) and brain concentrations (b) of tarenflurbil (TFB). Values are expressed as mean ± SD (n = 4). ** $p < 0.0001$ when compared with TFB administered by IV solution, IN solution and oral suspension, †† $p < 0.0001$ when compared with TFB-NPs and † $p < 0.01$ when compared with TFB-NPs.

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Adapted with permission from [139], Elsevier, 2016

7. Physicochemical Properties

That Can Affect Nose-To-Brain Delivery 7.1. Particle Size Particle size is one of the most crucial factors in the N2B delivery system. As stated above, the diameter of the OSN is between 0.1–0.7 µm, which limits the particle size to the nano range [56]. Also, smaller particles have less resistance to the mucous membrane penetration, as mucus forms a mesh-like structure. There are several studies that show that particle size can be a limiting factor for N2B delivery. Mistry et al. formulated chitosan or polysorbate 80 coated polystyrene NPs with a 100 and 200 nm particle size [140]. The study showed that nonmodified polystyrene NPs and polysorbate 80 coated NPs with the particle size of 100 nm were more suitable for olfactory epithelial cells than those with 200 nm diameter. However, none of the formulations were found in the olfactory bulb. Based on this study, the authors concluded that the optimal nanoparticle diameter for axonal transport is less than 100 nm [140].

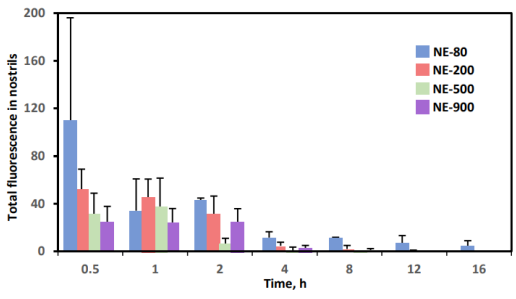

Figure 5. Quantification of total fluorescence of nanoemulsions (NE) with different sizes (80, 200, 500, 900 nm) in nostrils. Replotted using data from [141].

Not only can the charge of NPs increase the residence time, but it can also impact its delivery pathway. Bonaccorso et al. formulated rhodamine B labeled polymeric nanoparticles with an opposite surface charge to evaluate the bioavailability after intranasal administration in mice. The study used poly-lactide-co-glycolic acid (PLGA) NPs to make negatively charged nanoparticles, and used chitosan to make them positively charged. The mean size of both types of NPs was smaller than 250 nm. The negatively charged NPs arrived at the rostral subregions after 8 h of IN administration and were further transported to the caudal region in 24 h. However, positively charged NPs arrived in caudal sub-regions after 24 h of IN administration and were transported to the rostral area (Figure 6). Since the fluorescent signal from negatively charged NPs appeared in early time points, it is suggested that they were delivered via the olfactory pathway with both intra and extra-neuronal pathways. On the other hand, positively charged NPs transported through the trigeminal nerve as the fluorescent signal was strong after 48 h in the posterior brain. The author suggested that the surface charge influences the delivery pathway and the time to reach the brain [144].

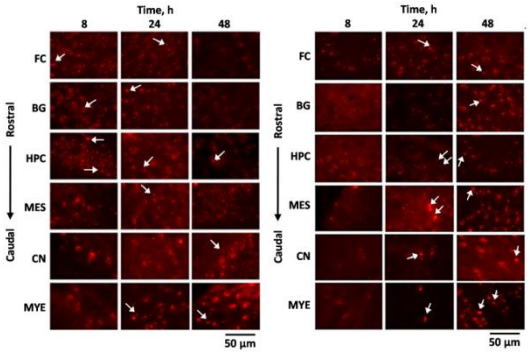

Figure 6. Localization of the negatively charged NPs (left panel) and positively charged NPs (right panel) after IN administration. Frontal cortex (FC); basal ganglia (BG); hippocampus (HPC); mesencephalon (MES); cerebellar nuclei (CN); myelencephalon (MYE). The white arrows indicate the presence of rhodamine-

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labeled NPs. Adapted with permission from [144], Elsevier, 2017.

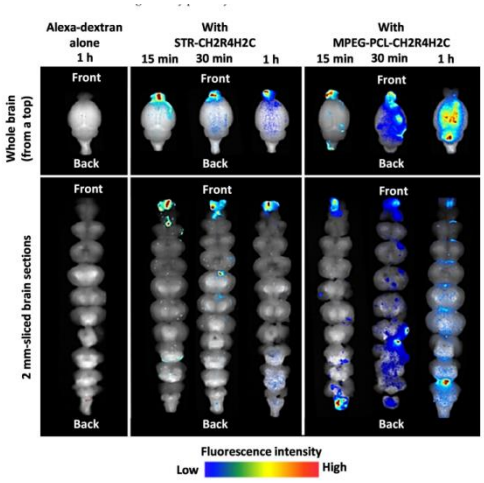

Figure 7. Dynamics of Alexa-dextran in brain tissue following IN administration of Alexa dextran alone, hydrophobic (STR-CH2R4H2C) and hydrophilic (MPEG-PCL-CH2R4H2C) in whole brain and 2 mm-sliced brain sections. Adapted with permission from [146], Elsevier, 20.

8. Therapeutic Applications of Nose-To-Brain Delivery

8.1. Epilepsy

Epilepsy is a chronic neurological disease that causes seizures and can be manifested at all ages, though the highest numbers of new cases occur in childhood and the geriatric population [147]. Epilepsy affects more than 65 million people globally, and about 4.6 million people are diagnosed each year [148,149]. According to the International League Against Epilepsy, there are six etiologies of epilepsy: (1) structural, (2) genetic, (3) infectious, (4) metabolic, (5) immune, and (6) unknown [150]. The cause of epilepsy is not limited to one specific etiology, as they can be combined. Also, the most common causes are different according to population and area. For example, children are more likely to suffer seizures from genetic disorders, whereas from the older generation it can be from an acquired injury. These physiological changes alter the number and properties of voltage or ligand-gated ion channels in the neuronal membrane and lead to hyperexcitation of neurons and, ultimately, a seizure [151]. The symptoms of epilepsy can differ based on the region of the brain and types of seizures. The symptoms include motor symptoms, such as twitching or shaking, sensory symptoms, such as numbness and tingling, and loss of consciousness. If the clinical and/or electrographic seizure lasts more than 5 min, it is called status epilepticus. This serious condition can cause severe morbidity and mortality [152]. Moreover, the elderly population can develop multiple complications such as fractures, depression, and anxiety. The general approach to treat epilepsy is antiseizure medications and benzodiazepines, but these agents are symptomatic treatments only [148]. Typical antiepileptic agents have many drug-drug interactions, as they can modify hepatic enzymes such as CYP3A4 and CYP1A2. This is significantly more problematic in the geriatric population, as they usually take multiple medications to control their chronic disease [153].

Table 1. Applications of nanoparticle in N2B delivery for treatment of epilepsy.

Drug	Nanocarrier	Lipids	Surfactant/ Co-Surfactant	Surface Modification	Size, nm	Z-Potential, mV	PDI	EE, %	DTE, %	DTE %	Ref.
Letrozole	Nanoemulsion	Triacetin	Tween 80,	PEG-400	95.59 ± 2.34		0.162 ±0.012	97.37 ± 1.33	-	-	[120]
Carbamazepine	Nanoemulgel	Oleic acid	Labrasol	Xanthan gum	45-146	-	-	-	-	-	[135]
Diazepam	PLGA Nanoparticle	-	Poloxamer 407		183.2	-	-	87.8	258	61.3	[136]
Oxcarbazepine	PLGA Nanoparticle	-	Tween 80	-	256.16 ± 2.04	−15.12 ± 0.56	0.144 ± 0.024	85.1 ± 2.1	-	-	[137]
	Emulsome	Triolein	Tween 80		120.4 ± 1.45* 101.5†	−34.1 ± 1.27* −6.72†	0.36*	81.19 ± 2.3* -	265.7	62.3	[138]
Amiloride	Nanoemulsion	Oleic acid	Tween-80/ Carbitol		89.36 ± 11.38	−9.83 ± 0.12	0.231 ± 0.018	98.28 ± 0.29	1993 ± 46	586.2 ± 11.6	[139]
Thyrotropin-release hormone	PLA Nanoparticle	-	PVA	-	108 ± 12	-	-	-	-	-	[140]
Lorazepam	PLGA Nanoparticle	-	Poloxamer 407		168.2	−18.4	0.08	83.8			[141]
Lamotrigine	Liposome	Phospholipon 90G/ Cholesterol	Tween 80	-	88.90 ± 1.56	-	0.247 ± 0.04	68.75 ± 0.02	-	-	[142]

Table 2. Applications of nanoparticles in N2B delivery for treatment of Alzheimer's disease.

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Drug	Nano-Carrier	Lipids	Surfactant/ Co-Surfactant	Surface Modification	Size, nm	Z-Potential, mV	PDI	EE, %	DTE, %	DTP, %	Ref.
Tanshinone	PLGA Nanoparticle		PF-68	-	135.13 ± 7.82	−30.25 ± 2.11	0.21 ± 0.02	64.11 ± 2.21	287.24	65.18	[139]
	SLN	Glyceryl monostearate/ Stearic acid /Soy lecithin	Tween 20		169.87 ± 10.98	−23.13 ± 2.32	0.24 ± 0.04	57.81 ± 3.32	160.15	45.41	
Donepezil	Liposome	DSPC, Cholesterol		PEG	102 ± 3.3	-28.31 ± 0.85	0.25 ± 0.03	84.91 ± 3.31	-	-	[99]
	Chitosan Nanosuspension	-	-	-	150–200	-	0.341	92–96	-	-	[175]
	PLGA Nanoparticle	-	-	PVA/Tween 80	-	89.47 ± 6.45	−36 ± 1.05	0.013 ± 0.002	86.65 ± 2.51	-	-	[179]
Galantamine	Thiolated Chitosan Nanoparticle	-	-	-	-	140.2–150	+27.2	0.216–0.225	87.65–89	-	-	[180]
	Liposome	SPC/Cholesterol	-		Propylene glycol	112 ± 6	−49.2 ± 0.7	-	83.6 ± 1.8	-	-	[181]
	SLN	Compritol 888 ATO	PF-127/ Tween 80		-	92.0 ± 3.91	−37.22 ± 1.1	0.380 ± 0.16	85.42 ± 0.63	-	-	[182]
Memantine	Nanoemulsion	Labrasol	Tween 20/Propylene glycol			~11	-19.6	0.66		136.78	37.05	[183]
Pioglitazone	NLC	Capmul MCM/ Tripalmitin	PF-68/ Tween 80		-	211.4 ± 3.54	+14.9 ± 1.09	0.257 ± 0.038	70.38 ± 4.5	-	-	[184]
Huperzine A	PLGA Nanoparticle			PVA		153.2 ± 13.7	+35.6 ± 5.2	0.229 ± 0.078	73.8 ± 5.7	-	-	[185]
Rivastigmine	Chitosan Nanoparticle	-	-	-	TMC/ Lactoferrin	185.4 ± 8.4	+26.4 ± 2.85	0.391 ± 0.065	85.3 ± 3.5	355 ± 13.5	71.66 ± 6.7	[186]
	Liposome	EPC/cholesterol	-	-	DSPE-PEG/ CPP	178.9 ± 11.7	-9.6 ± 2.4	0.333 ± 0.032	30.5 ± 4.0	-	-	[187]
RACE1 SIRNA	SLN	Witepsol E 85	PVA		RVG-9R/ Chitosan	335.76 ± 34.81 * 358.44 ± 25.09 #	-17.31 ± 0.68 * +10.54 ± 0.75 #	0.013 ± 0.007 * 0.028 ± 0.02 #	-	-	-	[188]
R-flurbiprofen	Albumin Nanoparticle	-	-	-	-	284.4 ± 14.9	-	0.404 ± 0.065	-	-	-	[189]

Meng et al. used lactoferrin (Lf) and N-trimethyl chitosan (TMC) as ligands to increase the efficiency of Huperzine A-loaded PLGA nanoparticles for the treatment of AD [185]. Huperzine A is a cholinesterase inhibitor that is not approved to be used in AD but can be used as a dietary supplement for memory enhancement. One of the major side effects of Huperzine A is gastrointestinal-related side effects such as nausea, vomiting, constipation, and diarrhea [194]. To decrease the drug's systemic side effects and achieve better brain targeting, the study used the N2B delivery method. The nanoparticles had a particle size of 153.2 ± 13.7 nm, ZP of +35.6 ± 5.2 mV, PDI of 0.229 ± 0.078, and EE of 73.8 ± 5.7%. Absorption of mucin to Lf-TMC nanoparticle was 86.9 ± 1.8%. This NP showed sustained release over 48 h and higher cellular uptake of Lf-TMC nanoparticles. Also, an in vivo study of Lf-TMC Huperzine A nanoparticles showed higher fluorescence intensity, longer residence time, and higher specificity to the brain than TMC nanoparticles and PLGA nanoparticles (Figure 8). Interestingly, the study further analyzed the drug distribution to the specific areas of the brain (olfactory bulb, cerebrum, cerebellum, hippocampus) and showed that AUCs of Lf-TMC NPs IN in all areas were significantly higher than those of TMC NPs IN and PLGA NPs IN [185]. The presence of Lf and TMC substantially increased the mucoadhesion and accumulation of the drug in the brain. Therefore, such nanoparticles can potentially be used for the effective N2B delivery

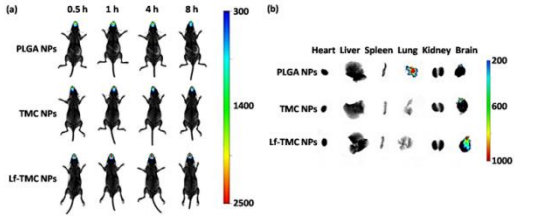

Figure 8. In vivo and ex vivo fluorescence images of organs of mice. (a) In vivo imaging of mice at 0.5, 1, 4, and 8 h after treatment with DiR-loaded PLGA NPs, TMC NPs, and Lf-TMC NPs at a dose of 0.5 mg DiR/kg of body weight via the intranasal route. (b) Ex vivo imaging of organs excised from mice at 8 h after the intranasal administration. Modified from [185].

10. Conclusions

The unique nature of the blood-brain barrier and the potential for negative side effects following systemic drug delivery have made drug delivery to the brain a substantial problem. Since it can get over the blood-brain barrier and boost the concentration of therapeutic molecules in the brain directly through olfactory and trigeminal pathways, nose-to-brain administration of molecules can be a potential approach. This strategy may eventually reduce the danger of systemic toxicity and reduce the necessary dosage of the medication. By delivering active molecules locally to the brain, several innovative nanoscale-based carriers may be able to give controlled release of treatments and increase the effect of medication targeting. While some FDA-approved treatments have recently been put on the market, such as Nayzilam®, Valtoco®, or ongoing N2B delivery clinical trials (ClinicalTrials.gov Identifier: NCT01767909, NCT03541356, NCT02503501), the majority of dosage forms that have been studied are drug

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solutions that need to be administered orally or parenterally. A deeper understanding of the N2B delivery system, including the pharmacokinetics and pharmacodynamics of intranasally administered active pharmaceutical ingredients and the development of an appropriate device that targets the olfactory region, is required in order to effectively translate the preclinical data to the clinical setting. N2B distribution via nanocarrier devices holds a lot of promise for treating CNS illnesses, despite certain difficulties.

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