CHAPTER

9

Nose-to-brain drug delivery: an alternative approach for effective brain drug targeting

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1. Introduction

The oral and parenteral routes are most prevalent routes of drug administration. The benefits of these routes are well known, but apart from that, both the strategies have many limitations, especially in the case of brain disorder. The parenteral route is a painful method of drug administration and also needs expert assistance for administration. On the other hand, the oral route is patient friendly. However, the drug administered via this route should follow the normal distribution pattern of body fluid and needs to cross the blood–brain barrier (BBB), which results in significantly lower drug concentration in the brain [1,2]. Also, it is associated with hepatic first-pass metabolism, which causes degradation of many drugs and bioactives. Along with this, many other factors confine the central nervous system (CNS) acting drug's concentration, reaching the brain from the systemic circulation, and hinders the efficacy of the drug and increases the peripheral side effect [1]. Thus, to improve the therapeutic efficiency and minimize the side effects, an alternative and direct

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delivery route to delivering drugs to the brain is highly desirable.

The intranasal route offers a direct nose-to-brain passage via olfactory and trigeminal nerves and minimizes the exposure of the drug to general circulation [3]. In the past 2 decades, the nose-to-brain delivery was explored as a promising approach in the treatment of CNS disorders [4]. Previously, nasal drug delivery was often used for local and systemic therapies due to high vascularization [5]. Later, scientists recognized that the direct connection between the brain and nasal cavity through olfactory and trigeminal neurons could be utilized for better brain targeting of drugs. The concept of nose-to-brain drug delivery was discovered by W. H. Frey II in 1989 [3]. Initially, the application of intranasal route was limited to brain targeting of insulin or insulin-like growth factor [6]. However, studies have proven its suitability for many other large-molecular-weight substances like proteins, peptides, and other bioactives [4]. Although some contradictions are also there, among different group of scientists across the globe [7], such paradoxes require a complete understanding of the technology, establishment of uniform research protocols, availability of proper clinical facilities, and better communication between the researchers of the different regions [8]. Some commercially available intranasal formulations for the treatment of various CNS disorders are listed in Table 9.1.

The intranasal (i.n.) route is preferred over another route of drug administration for brain targeting due to its ability to directly deliver the drug via neuronal pathways (olfactory and trigeminal nerve pathway). It bypasses the BBB and the hepatic first-pass metabolism, the two significant barriers of drug transport to the brain from the periphery [9]. This route is suitable for various proteins, lipids, and drug moieties that are susceptible to enzymatic degradation and harsh acidic environment of the gastrointestinal tract. The high vascularization and neuronal network of the nasal cavity facilitate the drug absorption and improve the bioavailability in the brain as compared to the oral route. The drug is instilled in the deeper region of the nasal cavity, primarily absorbed via olfactory and trigeminal neurons, and reaches to the olfactory bulb via cellular transport [4]. The systemic absorption is a secondary route in which a limited amount of drug is entered and follows the regular path (crossing the BBB) to enter into

TABLE 9.1 List of commercially available conventional intranasal products for the treatment of brain disorders.

Product	Active ingredient	Dosage form	Indication	Company name	References
Migranal	DHE-45[a]	Nasal spray	Migraine	Xcel Pharm	[26,27]
Stimate	Desmopressin acetate	Nasal spray	Haemophillia A	Rhone Poulenc Rorer	[28,29]
Syneral	Nafarelin acetate	Nasal spray	Central precocious puberty	Roche lab	[30,31]
Stadol	Butorphanol tartrate	Nasal spray	Migraine	ESi Lederle, Roxane labs	[32,33]
Zoming	Zolmitriptan	Nasal spray	Migraine	Astra Zeneca	[34,35]
DDAVP	Desmopressin acetate	Nasal spray	Head trauma, polydipsia, and polyurea	Ferring Pharma, Aventis Pharma	[35,36]

[a] *Dihydroergotamine mesylate.*

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the brain. Thus, owing to the minimum peripheral exposure of drug, it also reduces the systemic side effects of CNS-acting agents. The use of suitable permeation enhancer or amalgamation with the novel carrier system enables the entry of large proteins and peptides and improves brain targeting efficiency of i.n. route [10]. As cellular transport is the primary path of drug absorption, this route is suitable for both the lipophilic and hydrophilic molecules. In comparison to the parenteral, surgical, and other invasive strategies, the nasal route offers a noninvasive, patient-friendly technique, which is also convenient for the unconscious, pediatric, and geriatric patients [2].

However, there are also some limitations that reduce the efficiency of i.n. route. First of all, the mucociliary clearance and low drug retention in the nasal cavity reduce the drug permeation across the nasal mucosa. Also, nasomucosal enzymes cause degradation of various proteins, peptides, and bioactives. Secondly, due to the small volume of the nasal cavity, only a small amount of drug can be instilled at once. Moreover, the head position greatly affects drug absorption through the neuronal system. So, sometimes the patient needs to lie down or hold up their head during administration. Thirdly, the high vascularization facilitates systemic absorption, which sometimes causes peripheral side effects and reduces the drug concentration in the brain. Finally, the nasal epithelium is less permeable for the polar drugs, which can be overcome by the use of suitable permeation enhancer. However, the excess of permeation enhancer causes irritation to nasal mucosa [9].

Due to such disadvantages, novel carrier systems are used for nose-to-brain delivery, which circumvents the boundaries and increases drug targeting to the brain. This chapter briefly discusses some common CNS disorders, present therapies, and challenges to brain drug delivery [11].

2. Common brain disorders

2.1 Alzheimer disease

Age progression causes irreversible loss of nerve cells in the brain. This may result in difficulty remembering things, with slight confusion, thinking and responding slowly, etc. but severe memory loss, cognition and learning disability, difficulty in speech, abnormal behavior, and disturbing daily activity are the common signs of Alzheimer disease (AD) [2,12]. Alzheimer is a progressive, irreversible neurodegenerative disorder that slowly destroys the brain cells responsible for memory, learning, cognition, and other routine activities [4]. AD is mostly seen in old age but also sometimes observed in young people, known as the younger stage AD. AD is the most common cause of dementia, around 60%–70% of all cases noticed worldwide. As per the Alzheimer Association Report 2017, around 47 million in the world population were suffering from dementia, of which 37 million were reported to have AD. It is considered the sixth major cause of death in the United States, and the statistics are supposed to reach to 131 million people by 2050 [13].

AD was first discovered by the German doctor Alois Alzheimer in 1906, during the treatment of his patent named August D. who was suffering from behavioral abnormalities and memory loss. He observed shrinkage in the brain of the patient in the autopsy. Afterward, in 1910, a psychiatrist Dr. Emil Kraepelin, a colleague of Dr. Alzheimer, named the disease as "Alzheimer's Disease" to honor his discovery. Then, in 1994, after a very long time, the U.S. Food and Drug Administration (FDA) approved "Cognex" as the first AD drug. From then, until now, we have had only have five FDA-approved drugs, including donepezil, galantamine, tacrine (Cognex), rivastigmine, and memantine. Although, there are various natural and synthetic compounds available that are reported to have a promising anti-AD effect, others are still

under research such as curcumin, quercetin, piperine, S14G-Humanin, nerve growth factor (NGF), insulin, α-mangosteen, tarenflurbil, deferoxamine, risperidone, etc. Based on their mechanism of action, the anti-AD drugs are of two types:

(1) *Symptomatic drug:* The drug molecules that just reduce the symptoms of the disease and improve brain functions, including cognition, memory, and learning, fall into this category. These are mainly the acetylcholine esterase (AChE) inhibitors, which facilitate neurotransmission, e.g., donepezil, galantamine, rivastigmine, risperidone, piperine, etc.

(2) *Targeted drug:* The drug molecules that mainly act on the pathological factors responsible for AD or directly act on the target sites of the disease are considered as a targeted drug substances, e.g., deferoxamine, tarenflurbil, curcumin, NGF, H102 peptide, etc. [4].

2.2 Parkinson disease

Parkinson disease (PD) is a chronic neurodegenerative disorder that primarily affects the motor system of the CNS. PD is mainly characterized by loss of various motor functions of the brain, including movement difficulty, rigidity, shaking, difficulty in walking, etc. Similar to AD, the patient with PD also experiences behavioral abnormalities and dementia at the advanced stage of the disease. Along with this, one may also suffer from anxiety, depression, sleep, and sensory disbalance and emotional anomalies [14,15].

PD has been well known to human beings since ancient times. In ancient medical system it is known as "Shaking palsy" (Western medicine system) and "Kampavata" (in Ayurveda). In the year 1817, the disease was named PD after Dr. James Parkinson. Further, in 1912, a German pathologist, Dr. Friedrich H. Lewy, reported the existence of neuronal cytoplasmic inclusion in the brain region. Such bodies are named as Lewy bodies in honor of this scientist. In 1919, Tretiakoff observed neurodegeneration in the substantia nigra of the midbrain in PD patients. Afterward, the role of dopamine and its diminution from the basal ganglia was reported in 1950. In the present scenario, PD is considered as the second major neurodegenerative disorder associated with aging after AD [16]. The statistics indicate around 7 to 10 million people suffering from PD worldwide. The disease prevalence is 41 per 100,000 after a person is in their forties, which increases to approximately 1900 per 100,000 after one is in their eighties. The global burden of PD has more than doubled in the last 26 years, from 2.5 million in 1990 to 6.1 million in 2016.

Currently there is no complete cure for the PD; the available treatments only improve the symptoms of the disease. The primary and basic treatment of PD includes the combined therapy of levodopa with a dopamine agonist or other synergistic drugs like MAO-inhibitor, dopa decarboxylase inhibitor, COMT inhibitor, etc. But with the disease progression, these medicines become ineffective or sometimes produce other complications [17]. In extreme cases, surgery (deep brain stimulation) is also preferred to reduce the severity of the disease. Rehabilitation and diet may also help as alternative approaches. To find out a proper therapy for the treatment of PD, various experiments are being conducted. The research data suggest gene therapy, cell-based therapy as promising approaches to restore the brain function. At the same time, various novel drug delivery approaches can also be a promising way to improve the efficacy of existing drugs [18].

2.3 Migraine

Migraine is a headache disorder in which the patient is suffering from recurrent, pulsating, moderate to severe headache starting from either half of the brain, which may migrate to the other half or the whole brain and lasts from 2 h to 3 days. Sometimes it may be associated with vomiting, nausea, and light, sound, or smell sensitivity [19]. Moreover, about one-third of migraine patients experience auras, which are visual disturbances that signal the headache. Genetic and environmental factors are believed to be the two major cause of migraine. It is reported that about two-thirds of migraine cases are genetically based. The occurrence of migraine also varies with gender; females are more prone to the disease in comparison to males, and this ratio increases after puberty. The study shows that around 75% of migraine patients are females [20].

Migraines have been well known from since early human civilization. In the ancient world (7000 BCE) trepanation (drilling a hole in the skull) was the preferable treatment for migraine. The people at that time believed this procedure let the evil spirits escape from the mind. In the 17th century, William Harvey also recommended trepanation as effective migraine therapy. It was 1868 when a fungus "ergot" was first used in the treatment of migraine. Afterward, in 1918, ergotamine was successfully isolated from ergot and used in the treatment of migraine. Then, in 1959, methysergide was synthesized, and sumatriptan (the first triptan) was developed in 1988 [21].

Migraine is generally divided into two types: (1) migraine with aura, and (2) migraine without aura. The pathophysiology of migraine disease is not well known; some researchers believe that the CNS is primarily responsible for the pain, whereas others believe that the peripheral system including sensory neurons and blood vessels play an important role in disease initiation. The primary treatment utilizes regular analgesics like paracetamol, ibuprofen for the headache, and common medicines for nausea. If these are ineffective, the triptans and ergotamines are prescribed. Sometimes, caffeine may also be used for severe pain. Current research on migraine therapy focusses on the use of calcitonin gene related peptides (CGRPs), such as telcagepant and olcegepant, which claim to act on the pathophysiology of the pain. Unfortunately, the phase III clinical trial conducted by Merck on telcagepant failed in 2011. Now there is also study of CGRP monoclonal antibodies for effective migraine therapy [22].

2.4 Schizophrenia

Schizophrenia is a polygenic psychiatric disorder characterized by behavioral disturbance, cognitive, and perceptual abnormalities. It is generally observed beginning in young adulthood and lasts for a long time. The person suffering from schizophrenia mainly experience false belief, unusual visions and thinking, confused responses, emotional insecurity, lack of motivation, hallucinations, and reduced social activities. Sometimes the patient hears imaginary voices and has visions that do not exist in reality. Along with this, depression, anxiety, and poor mental health are the secondary symptoms of schizophrenia [23,24].

Various environmental (including modern lifestyle, cannabis addiction, nutritional deficiency during pregnancy, and parental age) and genetic factors are the prime causes of schizophrenia. The diagnosis is primarily based on the behavior of the person and observation of the family members. The antipsychotic medicines at their lowest possible dose are preferred for the treatment of schizophrenia. Depending upon the symptoms and response of the patient to the medications, antidepressants and antianxiety drugs are prescribed in combination. Along with this, proper counseling, rehabilitation, emotional support, and job training assist in

fast recovery. In severe conditions, either voluntary or involuntary hospitalization is also observed [25]. Statistics show that worldwide around 0.3%−0.7% of the population experience schizophrenia during their lifespan. It is observed that men are more prone to the disease as compared to women. Around 20% of people respond to therapy and recover completely; however, in 50% of the cases, the patient fails to recover and has to live with schizophrenia for the rest of their life. An average lifespan with the disease is about 10−25 years [26].

2.5 Autism

Autism is a complex, heterogeneous developmental and psychological disorder caused by the anomalous connection between different brain regions. The common symptoms of autism are abnormal social behavior, difficulty in social interaction, inability in general communication, stereotypical behavior, poor social skills, and cognitive impairment. The disease symptoms are mostly observed in childhood and gradually increase with age [31]. The term "autism" originates from the Greek word *autos*, which means isolated behavior, so autism is a neurodevelopmental syndrome in which an individual isolates themself from the surrounding culture. Reports from the U.S. Centers for Disease Control and Prevention (CDC) claim the rate of disease prevalence was approximately 1.5% in developed countries in 2017. It was observed that boys are more prone to the disease than girls. Also, it is more frequently observed in white children than children of color [27].

Autism was first described in 1943, by Leo Kanner, as the inability of an individual to create normal social, emotional interaction with the family and society. Kanner reported behavioral abnormalities of 11 children in his report [28]. The first case of autism was reported by Kanner in 1938. At that time, the disease was confused with other similar syndromes like infantile schizophrenia. In 1960, the autism term was established as a separate syndrome [29].

Genetic and environmental factors are the primary cause of autism. Along with this, any kind of drug, cocaine or alcohol addiction, and some infections (like Rubella) during pregnancy may also be responsible for autism. It is believed that these factors may cause abnormal synaptic and neural connections, which cause misinterpretations of the signals and are responsible for repetitive behaviors [30]. There are controversies among various scientists about the mechanism behind the disease, and the exact mechanism is still unknown. The diagnosis of the disease is mainly based on behavioral observation and interaction with the family and the affected child. The two commonly used diagnostic techniques are:

(1) ADI-R (Autism Diagnostic Interview-Revised)
(2) ADOS (Autism Diagnostic Observation Schedule)

The primary treatment of the child with autism is mainly psychological and emotional support. The education system, family, and healthy surroundings ensure better results. Improving the confidence and IQ level by giving some responsibility to the child will be beneficial most of the time. If the behavioral therapy fails, sometimes along with the behavioral therapies some medicines, including antipsychotic, anticonvulsant, antianxiety, and antidepressant drugs may be given for treatment. Proper nutrition, quality lifestyle, personality development classes, and music therapy may also be helpful [31].

2.6 Cerebral palsy

Cerebral palsy (CP) is a group of neurological disorders that limits body activity and causes permanent movement disability. CP can be defined as "set of permanent neurological

disorder resulted in distort posture, immobility of some or whole body and limited physical movement and activities which are attributed to a non-progressive disturbance that occurs in infant's brain or developing fetus" [32]. The symptoms of cerebral palsy may vary from very mild to severe spasms or movement disability. The person/child with mild CP may experience slight to severe difficulty in the movement of one arm or leg or one side of the body, with the complete or partial sensory loss at that side, sometimes associated with focal epilepsy. In some cases, the spasm and dyskinesia are experienced in all four limbs of the patient. Moreover, visual impairment and learning difficulties can also be observed occasionally. The individual with CP mostly becomes dependent on a wheelchair and needs assistance for mobility [33].

CP is a neurological syndrome in which some lesions are formed in the brain during the developmental stage due to motor impairment. The disease was first reported in 1862, by William Little (an orthopedic surgeon). From then various attempts have been made to define and classify the disease, and recently, a proper definition was proposed by the International Executive Committee for the definition of cerebral palsy; cerebral palsy is described as a group of permanent disorders of the development of movement and postures, causing activity limitation, that are attributed to a nonprogressive disturbance that occurred in the fetal or infant's brain. The motor disorder of cerebral palsy is often accompanied by disturbance of sensation, perception, cognition, communication, and behavior, by epilepsy and by secondary musculoskeletal problems [34,35].

2.7 Meningitis

Acute inflammation in the protective covering of the brain and spinal cord, meninges is known as meningitis. It is characterized by severe headache, pain in back and neck muscle, muscular stiffness [36]. The common symptoms of the disease are fever, shivering, cold, lethargy, nausea, vomiting, blotchy or red rashes, loss of appetite, etc. The young population experiences very casual, nonspecific symptoms like drowsiness, irritation, etc. The presence of rashes indicates the bacterial, viral, or any other infection-generated meningitis [37]. Meningitis may directly affect the brain and spinal cord; hence is considered as a life-threatening disorder. It is diagnosed by cerebrospinal fluid examination (CSF). The primary treatment of disease utilizes various antibiotics or sometimes antiviral drugs, followed by corticosteroids in severe conditions. The pneumococcal, meningococcal, mumps, and Hib vaccines are also used sometimes. If it is not treated immediately, it may cause severe complications like epilepsy, deafness, cognitive deficits, etc. [38,39].

2.8 Myasthenia gravis

Myasthenia gravis is a chronic neuromuscular disorder that weakens the skeletal muscle, more specifically affects the facial muscle and eye. Histologically it is an autoimmune disorder that forms antibodies to destroy or block the nicotinic cholinergic receptors present at the neuromuscular junction [40,41]. This interferes with the signal transmission from nerve to muscles and causes muscular contraction. It affects approximately 200 persons per million population, of which women under 40 years and men over 60 years are more susceptible to the disease. In most of the cases, acetylcholine esterase inhibitors (like pyridostigmine, neostigmine) and various immunosuppressants (like prednisone, azathioprine) are useful for treatment. In some severe conditions, the surgical removal of thymus gland can also be effective [42,43].

2.9 Stroke

Stroke is a physiological condition in which brain cell death occurs due to poor blood flow or excessive bleeding in the brain. In other words, it is a kind of brain attack in which the deficiency of oxygen in brain cells results in nerve cell death and thus affect memory and other body functions like body movement, muscle control, senses, etc. regulated by that particular part of the brain [44]. Stroke may be divided into two types:

- Ischemic stroke: Blockage in the brain blood vessels that causes lack of blood flow
- Hemorrhagic stroke: Bleeding into the brain due to blood vessel damage or rupture, resulting in bleeding in the interstitial or cerebrovascular space [45].

Tobacco smoking, high blood pressure, high blood cholesterol, diabetes, and arterial fibrillation are the common risk factors responsible for stroke. The common symptoms are partial or whole-body paralysis or numbness of specific body parts like legs, arms, or face, difficulty in speaking, walking, vision loss or blurred vision, loss of the sensation, headache, vertigo, fatigue, etc. The disease can be diagnosed by MRI or CT scanning, sometimes associated with ECG. Stroke is considered as an emergency medical condition and is treated with statins, aspirin, surgery to remove a blockage in case of ischemic stroke, and warfarin for hemorrhagic stroke [46,47].

3. Anatomy of the nasal cavity

The human nasal cavity consists of three subsequent regions with different functions: the vestibular, respiratory, and olfactory regions. The vestibular region is the frontal-most part of the nose, containing hairy structures and mucus linings. It actively participates in the first line of body defense that prevents the entry of foreign particles, microbes, parasites, and harmful toxins into the body [9]. The respiratory region is situated in the middle of the nose. It covers the largest area (approximately 130 cm^2) of the nasal cavity and is composed of goblet cells, basal cells, and columnar epithelial cells (ciliated and nonciliated). The higher surface and high vascularization make it a prime region for drug absorption in the systemic circulation [4]. It is also supplied with trigeminal sensory neurons, which are responsible for signal transmission to the brain [48]. Next to this, the olfactory region is situated on the roof of the nose beneath the cribriform plate of the skull. It is comprised of olfactory nerve cells, basal cells, supporting cells, microvillar cells, and trigeminal neurons in small proportion. The olfactory region is responsible for direct connection with the brain via olfactory and trigeminal neurons, which facilitate the drug transport to the brain [8].

4. Nose-to-brain drug transport pathways

Due to the direct connection with the brain, the nasal cavity holds great potential for brain targeting without the interference of the BBB and other peripheral factors. The drug transport mostly takes place via a neural pathway (olfactory and trigeminal nerves) and through vascular route. In addition, CSF and lymphatic system are also involved in the passage of drug from nose-to-brain to a lesser extent [9]. Different brain transport mechanisms are discussed next.

4.1 Neuronal pathway

The nasal cavity is supplied with two types of neurons: (1) olfactory receptor neurons, and (2) trigeminal sensory neurons. The olfactory nerve is primarily responsible for smell senses and the trigeminal nerve transfers other senses from the nasal mucosa to the brain. It offers a direct way to access the brain and, hence, is considered a major pathway of nose-to-brain

transport of drug [48]. The drug transfer via these two nerves is explained below.

4.1.1 Olfactory nerve pathway

The olfactory mucosa is enriched with olfactory receptor neurons. When the drug reaches the olfactory region, it interacts with the nerve endings of olfactory receptor neurons and translocates to CNS along the axonal length of olfactory neurons. The nerve bundle crosses the cribriform plate of ethmoid bone then enters the olfactory bulb [8]. The passage of drug cargo to the olfactory receptor neurons takes place by transcellular or paracellular transport. Olfactory nerves deliver the bioactives to the olfactory bulb and CSF. Further, the drug is distributed to a different region of the brain after mixing with interstitial fluid [49]. The axonal pathway is also known as the intraneural route of drug transport to the brain, which is a slow process, taking hours to days for drug transfer. In contrast, the paracellular or perineural channel, i.e., transfer between the epithelial or neural cells, is a faster way of drug passage to the brain, which only takes a few minutes [50–52]. This route innervates the deeper brain regions like cerebrum, cerebellum, and cortex.

4.1.2 Trigeminal sensory nerve pathway

Trigeminal nerve pathway connects the nose to the posterior region of the brain, including medulla, pons, and spinal cord. It also has access to the olfactory bulb to a minor extent. The drug transport through the trigeminal nerve pathway takes place either by the axonal route (intracellular transport) or via endocytosis. The trigeminal nerve is the fifth cranial nerve and is considered as one of the largest neurons of CNS, comprised of maxillary, mandibular, and ophthalmic neurons. Among these, the maxillary and ophthalmic neurons are primarily responsible for nose-to-brain connection [8]. Trigeminal nerves are chiefly found in the respiratory region of the nasal cavity and in the dorsal olfactory region to a lesser extent. The drug in the respiratory and olfactory region of the nose is diffused from the nasal mucosa to the trigeminal nerve endings and translocated to the different part of the brain such as the brain stem, medulla, pons, olfactory bulb, and also the forebrain [53].

4.2 Vascular pathway

The large absorption surface area and high vascularization of the nasal cavity, particularly the respiratory region, facilitate the drug absorption to the systemic circulation. Once a drug enters into general circulation, it reaches the CNS/brain via a conventional path, i.e., by crossing the BBB as per the blood distribution ratio [54]. The respiratory epithelium allows the entry of both small and large, polar and nonpolar moieties to the blood through paracellular and transcellular transport. Subsequently, the small, lipophilic molecules can cross the BBB and enter into the brain [8].

5. Strategies to enhance nasal absorption

5.1 Permeation enhancers

Apart from the physicochemical properties of drug and carrier systems, the nasal absorption and bioavailability of the drug in CNS depend on the permeability of nasal mucosa. The paracellular transport only allows the passage of small hydrophilic molecules, whereas the transcellular route permits the way for low-molecular-weight lipophilic substances. In such condition, owing to larger size, solubility, and polarity, most of the hydrophilic drugs, proteins, and peptides get stuck in the nasal cavity. Improvement in nasal permeability could resolve such an issue and facilitate the transfer of bioactives via extracellular transport through olfactory and trigeminal neurons [8].

The permeation enhancers, including tight junction modifiers, polymers, lipids, cyclodextrin, bile salts, surfactants, etc. possess the ability

to improve the permeability of nasal epithelium. Such compounds dissolve the membrane lipid and thereby reversibly modify the permeability [55,56]. Other common mechanisms by which the permeation enhancer exerts their activity are given below:

- By improving the contact between nasal epithelium and drug-carrier system
- By reducing the mucociliary clearance
- By solubilizing the drug
- By minimizing elasticity of the mucus layer
- And by inhibiting the metabolizing enzymes

Examples of some permeation enhancers used in intranasal formulations are saponins, Laureth-9 (surfactant); fusidic acid derivatives, trihydroxy salts (bile salts); oleic acid, caprylate, laurate (fatty acid); EDTA, salicylic acid (chelators); phospholipids, etc. [57,58].

Sometimes, permeation enhancers may irritate the nasal mucosa and produce toxicity, which can be minimized by using suitable permeation enhancers at the appropriate concentration. In addition, this improves the drug permeation in the vascular region, which often leads to severe peripheral side effects [56].

5.2 Enzyme inhibitor

Most of the protein, peptide, and some drug moieties are highly susceptible to enzymatic degradation during transport through an epithelial barrier or in the nasal cavity, which reduces their bioavailability in the brain region. The nasal mucosa is enriched with both exopeptidase and endopeptidase enzymes. The exopeptidases are commonly used, belonging to mono- and diaminopeptidase classes, which cleave the peptides at C- and N-terminals. In contrast, endopeptidase enzymes like cysteine, serine, etc. break the internal peptide bonds [59]. Thus, various enzyme inhibitors are coadministered or added into the nanocarrier system to prevent the nasal metabolism or degradation of the drugs/bioactives. Commonly, the enzyme inhibitors belong to the class of proteases or peptidases [1]. In addition, some absorption enhancers, such as different salts and fusidic acid derivatives, also act as enzyme inhibitors [60]. Along with this, aprotinin, boroleucin, amastatin, borovaline, trypsin, and bestatin inhibitors are other important compounds used to protect drugs from nasal enzymatic degradation [57].

6. Novel drug delivery approaches

6.1 Polymeric nanoparticles

Polymeric nanoparticles primarily consist of polymeric matrix in which the therapeutically active agents are either entrapped, encapsulated, or chemically conjugated [61–63]. The size of polymeric nanoparticle is usually larger than the micelle, i.e., 100–200 nm with higher Poly Dispersity Index (PDI) [64]. It offers a biocompatible, biodegradable, stable, and cost-effective carrier system with controlled or sustained release of the drug [65]. The polymer used may be of natural (like collagen, albumin, gelatin, alginate chitosan, etc.) or synthetic origin (like polycaprolactones or polyacrylates), which affect the biocompatibility, drug loading, release, toxicity, and stability profile of the nanoparticle [66]. Owing to the flexible characteristics, the synthetic polymers sometimes are more beneficial than the natural polymers [67]. Chitosan imparts mucoadhesiveness to the nanoparticle and hence increases the retention time in nasal mucosa as well as reduces the mucociliary clearance. In addition, it loosens the tight junction between endothelial cells, hence, facilitates the drug transfer via a paracellular route from the nasal cavity to the brain [68]. Various studies done using polymeric nanoparticles as carrier for direct nose-to-brain delivery of drug are discussed in Table 9.2.

TABLE 9.2 Polymeric nanoparticles for nose-to-brain delivery of therapeutics.

Drug	Polymer	Particle size	Objective	References
Tarenflurbil	PLGA	133.13 nm	Improve bioavailability of tarenflurbil in the brain	[78]
Huperzine A	Chitosan-PLGA	153.2 nm	Targeting to the brain via lactoferrin conjugation	[79]
bFGF	PEG-PLGA	104.8–118.7 nm	Effective targeting of proteins and peptides to the brain	[80]
Rivastigmine	Chitosan	143.1 nm	Improve bioavailability and nasal uptake of rivastigmine	[81]
Galantamine	Chitosan	190 nm	Improve galantamine entrapment into chitosan nanoparticle	[69]
Galantamine	Chitosan	48.3–68.3 nm	Enhance therapeutic efficiency of galantamine and alter its pharmacological and toxicological profile	[69]
Piperine	Chitosan	248.5 nm	Brain targeting of bioactive via nasal route	[82]
Neuroprotective peptide (NAP)	PEG-PCL	70–90 nm	To determine the brain targeting potential of lactoferrin-modified nanoparticle	[83]

Hanafy et al. developed i.n. galantamine-chitosan complex nanoparticle for the treatment of AD and investigated the effect of drug-polymer complexation on the pharmacological behavior of the drug. The in vivo study on male Wistar rats demonstrated no negative effect on the pharmacological profile of galantamine. It significantly increases the therapeutic potency of the drug by reducing the AChE level. At the same time, no toxicity or adverse effect was observed [69]. Further, various other works have investigated the application of i.n. chitosan nanoparticle for the treatment of cerebral ischemia [70], PD [71], schizophrenia and bipolar disorders [72], neural pain [73], and other brain disorders.

Another important synthetic polymer is poly(lactic-co-glycolic acid) (PLGA), widely used and approved by the FDA for preparation of nanoparticles. It is suitable for both the hydrophilic and lipophilic moieties and offers a biodegradable, controlled-release drug carrier system [74]. Sharma et al. developed midazolam-loaded PLGA-nanoparticle for direct nose-to-brain delivery of the antianxiety drug. The ex vivo study shows higher drug permeation and in vivo investigation demonstrated considerable improvement in bioavailability and therapeutic efficiency of the drug [75]. Similarly, Seju et al. utilized PLGA-nanoparticle for nose-to-brain delivery of an antipsychotic drug, olanzapine. The PLGA improved contact with nasal mucosa and facilitated drug absorption and enhanced drug permeation. It also increased the therapeutic efficiency of the drug [76].

Tong et al. explored the ability of mucoadhesive PLGA-chitosan-based nanoparticle for brain delivery of an antidepressant drug, desvenlafaxine. The drug was loaded into the i.n. mucoadhesive nanoparticle, to improve its concentration in the brain and its therapeutic efficiency. The combination of PLGA and chitosan imparts excellent bioadhesion to the formulation and, thus, facilitates drug absorption. They found that the formulation considerably improved the drug pharmacokinetic and pharmacodynamic behavior and relieved the symptoms of depression [77].

6.2 Lipidic nanoparticles

Unlike the polymeric nanoparticles, lipid nanoparticles are colloidal, nanosized materials composed of natural or synthetic lipid or combination of lipid, stabilized with an appropriate surface acting agent [84,85]. Solid lipid nanoparticles (SLNs) and nano lipid carriers (NLCs) are the most promising and modern lipid nanoparticles, extensively used for brain targeting of pharmacologically active substances [86]. Lipid nanoparticles offer advantages over other nanocarriers like biocompatibility, biodegradability, higher drug permeation, compatibility with a wide range of both hydrophilic and hydrophobic molecules, less toxicity, controlled and prolonged release, etc. However, low drug encapsulation and susceptibility to degradation upon storage are the limitations of lipid nanocarrier. But, the next-generation carrier system like SLNs and NLCs resolve these issues and hence have become popular among researchers for brain targeting [13]. A typical structure of SLN is shown in Fig. 9.1. Rassu et al. utilized SLN for intranasal administration of BACE1-siRNA to the brain for the treatment of AD. They developed chitosan-coated, positively charged SLN for prolonged delivery of the drug to the brain. The chitosan-modified nanoparticle increases the drug permeation and provides controlled and prolonged release of the drug [87]. Further, Youssef et al. developed almotriptan-loaded SLN and incorporated it into mucoadhesive in situ gelling system to treat migraine. The in situ gel imparts mucoadhesiveness to the formulation and facilitates constant and higher drug absorption for a prolonged duration. The SLN successfully delivered the drug to the brain with higher drug concentration. The formulation didn't impart any toxicity or irritability to the nasal mucosa [88]. Yasir et al. worked on i.n. delivery of haloperidol- (antipsychotic agent) loaded SLN. The intranasal SLN demonstrated higher drug targeting efficiency than the oral formulation and a significant improvement in the local drug concentration in the brain [89].

NLCs are considered as second-generation SLNs, as they overcome the limitation of poor drug loading and stability issues [13]. A general structure of NLC is shown in Fig. 9.2. Various research has focused on the utilization of NLC as a carrier system for treatment of a variety of CNS disorders like AD, PD, epilepsy, schizophrenia, migraine, depression, anxiety, bipolar disorder, etc. Some of the examples are discussed in this section. Wavikar et al. developed rivastigmine-loaded NLCs using in situ gelling

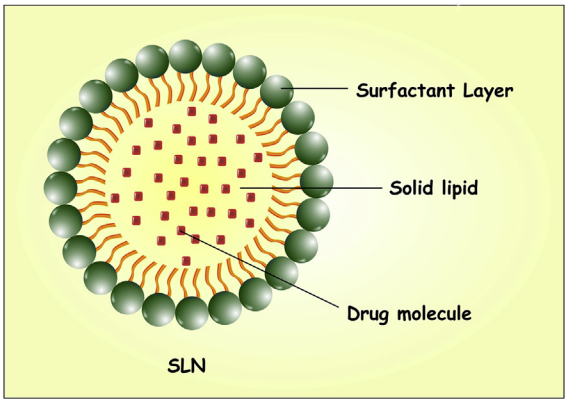

FIGURE 9.1 A general structure of solid lipid nanoparticle (SLN).

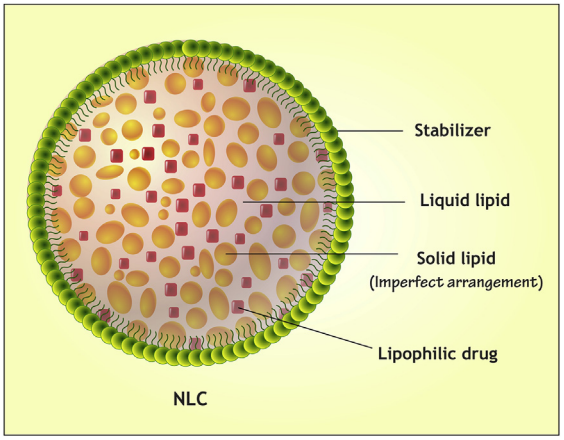

FIGURE 9.2 General structure of NLC.

systems for the treatment of the neurodegenerative disorder. The NLC-based intranasal in situ gel demonstrated two-fold higher nasal permeation and three-fold higher enzyme inhibition activity [90]. Further, Khan and team investigated the brain targeting efficiency of temozolomide-loaded NLCs and found a considerable improvement in the drug concentration in the brain [91]. Apart from these, various other works focusing on the use of lipid nanocarrier for intranasal drug delivery to the brain are discussed in Table 9.3.

6.3 Inorganic nanoparticles

Inorganic nanoparticles are mainly composed of various metals or metal oxides and hold great potential as diagnostic and therapeutic agents. Studies demonstrated the application of different inorganic nanoparticles like gold nanoparticle, mesoporous silica nanoparticle, carbon nanotubes, quantum dots, magnetic nanoparticles, etc. as radio or fluorescent-labeled agent for biochemical analysis and as a carrier system for effective brain targeting. Depending on the nature of the material used, the individual nanoparticle holds unique novel properties like targeting to a specific site, controlled and prolonged release of the active molecule, external control, and regulation of in vivo behavior, high drug loading, etc. [114]. Although for brain targeting (Table 9.4), the inorganic nanoparticles have not been much explored for direct nose-to-brain delivery of therapeutics. This may be because of some complexities, such as irritant behavior to the nasal mucosa and toxicity profiles of inorganic nanoparticles [115].

6.4 Liposomes

Liposomes are referred to as spherical lipidic vesicles made of a concentric bilayer of phospholipid with aqueous core material. The lipid content of liposome mimics the physiological membrane and thus offers a biocompatible and biodegradable carrier system [12]. The lipid gets self-assembled as a nano-sized vesicle enclosing an aqueous core when immersed into the aqueous solution. It is suitable for both the hydrophilic and hydrophobic moieties; the hydrophilic drugs are encapsulated into the aqueous core while the lipophilic molecules get intercalated between the lipid bilayer (Fig. 9.3) [128]. It offers a nontoxic, biocompatible, and highly lipophilic carrier system for brain targeting, which has the ability to protect the bioactive substances from enzymatic degradation and the surrounding environment [129]. Application of liposome as carrier for nose-to-brain delivery of therapeutics is explained in Table 9.5.

Nageeb El-Helaly et al. developed an electrostatically stable stealth liposome for brain targeting of rivastigmine via the intranasal route to treat neurodegenerative disorders like AD. Research shows that stability is the challenge for liposomal preparation. Hence, the author used DDAB[1] for electrostatic stability and PEG-DSPE to provide stealth nature and improve the stability of the formulation. The resultant carrier system shows significantly higher drug permeation, and pharmacokinetic behavior thus increases the bioavailability of the drug in the brain [130]. Another interesting approach is the development of ghrelin-loaded surface-modified intranasal liposome with chitosan to treat cachexia. The liposome was coated with N-(2-hydroxy) propyl-3-trimethyl ammonium

[1] Didecyldimethyl ammonium bromide.

TABLE 9.3 Lipidic nanoparticles for nose-to-brain delivery of therapeutics.

Drug	Lipid or oil phase	Particle size	Objective	References
Microemulsion				
Rivastigmine	Capmul MCM	53–55 nm	Improve pharmacokinetic profile and brain bioavailability of rivastigmine	[92]
Paliperidone	Oleic acid, Polyoxyl 40 hydrogenated castor oil and Caprylocaproyl polyoxylglycerides	27.31 nm	To develop paliperidone-loaded intranasal microemulsion for treatment of schizophrenia	[93]
Olanzapine	Oleic cis-9-octadecenoic acid	23.87 nm	Effective treatment of schizophrenia	[94]
Buspirone hydrochloride	Isopropyl myristate	35.7–36.2 nm	Improve drug concentration and bioavailability in the brain	[95]
Tramadol	Isopropyl myristate, Polyethylene glycol-400, Propylene glycol	16.69 nm	Improve therapeutic efficiency of drug	[96]
Curcumin	Capmul MCM, DHA rich oil	<20 nm	To evaluate role of DHA in brain delivery of curcumin via i.v. and i.n. route	[97]
Quetiapine fumarate	Capmul MCM	35.31 nm	Effective brain targeting bioavailability of drug	[98]
Solid lipid nanoparticle (SLN)				
Quetiapine fumarate	Solid lipid: Glycerol monostearate	117.8 nm	Improve therapeutic efficiency of drug to treat schizophrenia and antipsychotics	[99]
Vincristine sulfate	Solid lipid: Cetyl palmitate	100–169 nm	Enhance brain delivery of drug	[100]
Ganciclovir	Solid lipid: Glyceryl monostearate	113.7–142.5 nm	Investigate tissue distribution of drug in the brain	[101]
Rivastigmine	Solid lipid: Tocopherol succinate	15.6 nm	Improve brain targeting of drug in the brain	[102]
Rosmarinic acid	Solid lipid: Glyceryl monostearate and soy lecithin	149.2 nm	Evaluate the brain targeting efficiency of SLN	[103]
Ondansetron HCl	Solid lipid: Glyceryl monostearate	320–498 nm	Investigate CNS targeting efficiency of ondansetron-loaded SLN	[104]
Haloperidol	Solid lipid: Glyceryl monostearate	115–156 nm	Study the stability and effect of SLN on brain targeting efficiency	[89]
Tarenflurbil	Solid lipid: Glyceryl monostearate	89.21 nm	Improve concentration of drug in the brain via intranasal administration	[78]
Rivastigmine	Solid lipid: Compritol 888 ATO	82.5 nm	To develop rivastigmine-loaded SLN by applying quality by design approach	[105]
Nano lipid carrier (NLC)				
GDNF	Solid lipid: Precirol ATO Liquid lipid: Mygliol	205.9 nm	To evaluate neuroprotective and regenerative behavior of Chitosan-TAT-based nasal NLC	[106]

TABLE 9.3 Lipidic nanoparticles for nose-to-brain delivery of therapeutics.—cont'd

Drug	Lipid or oil phase	Particle size	Objective	References
Clonazepam	Solid lipid: Compritol 888 Liquid lipid: Oleic acid and glyceryl monooleate	209.6–288.8 nm	Improve brain targeting of drug via nasal olfactory mucosa	[107]
Artemether	Solid lipid: Trimyristin Liquid lipid: Medium chain triglycerides	123.4 nm	Optimize drug-loaded NLC via central composite design	[108]
Protein	Solid lipid: Precirol ATO5 Liquid lipid: Mygliol	114 nm	Design and optimize chitosan-coated NLC for brain targeting	[109]
Duloxetine	Solid lipid: Glyceryl monostearate Liquid lipid: Capryol PGMC	137.2 nm	Evaluate brain targeting efficiency of NLC upon nasal administration	[110]
Efavirenz	Solid lipid: Precirol ATO 5 Liquid lipid: Captex P 500	162 nm	Develop and optimized efavirenz-loaded NLC for effective brain targeting via nasal route	[111]
Rivastigmine	Solid lipid: Glyceryl monostearate and Capmul MCM C8 (3:2) Liquid lipid: Stearic acid	123.2 nm	To explore the brain targeting efficiency of NLC	[112]
Temozolomide	Solid lipid: Gelucire Liquid lipid: Vitamin E	141.28–220.11 nm	To optimize brain pharmacokinetic and drug efficiency via spinographic imaging after i.n. administration to brain	[91]
Embelin	Solid lipid: Cetyl palmitate Liquid lipid: Octyldodecanol	152 nm	Investigate brain targeting efficiency of NLC for treatment of epilepsy	[113]

chitosan chloride to impart surface charge (anionic) to the carrier system. The surface modification with negatively charged polymer facilitates interaction with the nasal mucosa, thus improving the drug permeation. It was delivered as an aerosol preparation. The prepared formulation enhances the brain targeting efficiency and shows higher bioavailability of the drug [131]. In the same sequence, Upadhyay et al. tried to improve the bioavailability of quetiapine fumarate for the treatment of schizophrenia. The oral administration of quetiapine fumarate is hindered by hepatic first-pass metabolism. Hence, the author developed an intranasal to avoid gastrointestinal degradation and improve the therapeutic efficiency of the drug. The liposome significantly enhances the nasomucosal permeability of drug and provide a safer means of drug targeting [132]. In addition, Bender et al. developed GDNF[2]-loaded liposome for intranasal delivery to the brain to treat PD. The intranasal liposome successfully targets the bioactive to the brain and significantly improves overall bioavailability of GDNF [133]. Apart from these, a number of studies have been conducted by using liposome as a carrier system for direct nose-to-brain targeting of the drug by using various surface-acting agents, targeting molecules and other modifications to improve the efficiency of the system.

[2] Glial cell line–derived neurotrophic factor.

TABLE 9.4 Application of inorganic nanoparticle for nose-to-brain delivery of therapeutics.

Drug	Type of inorganic nanoparticle	Metal/metal derivatives	Particle size	Objective	References
–	Quantum dots	CdSe/ZnS nanocrystals	15–20 nm	To explore suitability of quantum dots for nose-to-brain delivery	[116]
–	Quantum dots	CdSe/ZnS	95.3 nm	Brain targeting of diagnostic agent for in vivo imaging of brain	[117]
–	Quantum dots	Cadmium selenide	20–25 nm	Study microglial activation by nanoparticulate stimulation, in vivo imaging	[118]
hNgR-Fc protein	Gold nanoparticle	Gold	15 nm	Improve brain targeting and therapeutic efficiency of protein and peptide	[119,120]
–	Gold nanoparticle	Gold	13 nm	Study the biodistribution, safety, and efficacy of gold nanoparticle after intranasal administration	[121]
Resveratrol	Gold nanoparticle	Gold	10.30 nm	Effective brain targeting of resveratrol and as biomarker agent	[122]
–	Mesoporous silica nanoparticle	Silica	220 nm	Investigate the application of mesoporous silica nanoparticle as carrier for nose-to-brain drug delivery	[123]
–	Silica nanoparticle	SiO_2	115 nm	Evaluate the adverse effect of silica nanoparticle on brain	[124]
–	Carbon nanotube	–	5–15 nm	Study the effect of carbon nanotube on function and viability of brain macrophages	[125]
Mesenchymal stem cells	Magnetic nanoparticle	Iron oxide	5.22 nm	Improve homing of stem cell	[126]
Carmustine	Magnetic nanoparticle	Iron (II) chloride tetrahydrate and iron (III) chloride hexahydrate	30–50 nm	Effective nose-to-brain drug delivery via olfactory nerve pathway	[127]

Such extensive utilization suggested liposome as a potential carrier system for nose-to-brain delivery of therapeutic agents.

6.5 Nanoemulsions

Nanoemulsions are nanosized w/o or o/w emulsion of two immiscible liquids stabilized with suitable surfactant. The standard globule size of nanoemulsion was supposed to less than 100 nm. However, 300 nm is also reported in some literature. The smaller droplet size imparts transparent or milky white appearance to the nanoemulsions [144,145]. It possesses a higher surface area than the other carrier system, and also the smaller size is responsible for the stable formulation without any sign of sedimentation, creaming, coalescence, etc. It improves the solubility of poorly soluble drug substances. In addition, it has the ability to protect the drug from the surrounding environment (pH and physiological condition), oxidation, and enzymatic degradation [145].

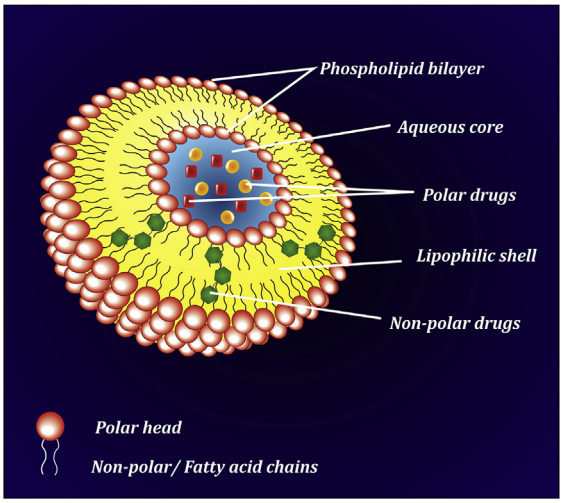

FIGURE 9.3 A typical structure of liposome.

Various preclinical and clinical investigations demonstrated nanoemulsion as a promising carrier system that promotes the permeation of small lipophilic molecules across the nasal epithelium (Table 9.6) [86]. Columbo et al. studied the efficiency of kaempferol in treatment of glioma when delivered intranasally by encapsulating in the mucoadhesive nanoemulsion. The formulation improves the nasal permeation and preserves the antioxidant potency of the drug. The in vivo study indicated 4.5–5-fold higher drug concentration in the brain. Moreover, the higher cytotoxicity to the tumor cell makes it a suitable candidate for the treatment of glioma [150]. Further, the intranasal nanoemulsion was also investigated for schizophrenia treatment. Boche et al. developed quetiapine

TABLE 9.5 Application of liposome for nose-to-brain delivery of therapeutics.

Drug	Lipid	Particle size	Objective	References
Rivastigmine	Egg phosphatidylcholine	178.9 nm	Improve brain distribution of drug and reduce systemic side effects via i.n. route	[134]
Galantamine hydrobromide	Soy phosphatidylcholine	112 nm	Evaluate the AChE inhibition activity of drug	[135]
Rivastigmine	Soy lecithin	10 μm	For effective delivery of drug to the brain via nasal route	[136]
Cyclovirobuxine D	Soy lecithin	72.03–86.5 nm	To evaluate brain targeting efficiency of polysorbate 80-coated liposome and to increase bioavailability of drug in the brain	[137]
H102	Egg phosphatidylcholine, DSPE-PEG	112.2 nm	Enhanced brain targeting of peptide	[138]
Ferric ammonium citrate	Soy lecithin	40 nm	For effective delivery of iron to the brain	[139]
bFGF	Soy phosphatidylcholine	128 nm	Prevent cerebral ischemia in stroke patients	[140]
Donepezil	Distearyl-sn-glycerol-3-phosphocholine (DSPC)	102 nm	Enhance brain bioavailability of drug for effective treatment of AD	[141]
Rivastigmine	CPP, DSPE-PEG-NHS	178.9 nm	Improve brain distribution and reduce side effect of drug	[134]
Risperidone	Soy phosphatidylcholine	91–106 nm	Effective brain targeting of risperidone to treat schizophrenia	[142]
Ghrelin	Soy lecithin	10 μm	Improve brain delivery of ghrelin	[143]

TABLE 9.6 Application of nanoemulsion for nose-to-brain delivery of therapeutics.

Drug	Oil phase	Globule size	Objective	References
Riluzole	Sefsol	23.92 nm	Improve brain bioavailability of riluzole	[146]
Cyclosporine-A	Flaxseed oil	272 nm	Investigate biodistribution and pharmacokinetics of drug in brain upon i.n. administration	[147]
Selegiline	Grape seed oil and Sefsol 218 (1:1)	61.43 nm	Effective brain delivery and improved bioavailability to treat Parkinson disease	[148]
Tramadol	Isopropyl myristate	136.3 nm	Improve therapeutic efficiency of drug	[96]
Quetiapine fumarate	Capmul MCM	144 nm	Improve brain targeting via intranasal route	[149]
Kaempferol	Egg lecithin and medium-chain triglycerides	170.4 nm	Develop mucoadhesive nasal formulation for effective brain targeting	[150]

fumarate—loaded nanoemulsion and investigated its brain targeting efficiency. Significantly higher drug transport and targeting efficiency were observed by direct nose-to-brain delivery of nanoemulsion [149]. Brain delivery of zolmitriptan, an antimigraine drug—loaded bioadhesive nanoemulsion via intranasal route was studied by Abdou et al. The nanoemulsion successfully delivered the drug to the brain at high concentration and rapid onset of action was achieved, which is essential for migraine therapy. Study shows significant improvement in pharmacokinetic behavior of the formulation in the brain [151]. Similarly, Parikh et al. utilized nanoemulsion to improve the bioavailability of riluzole for the treatment of amyotrophic lateral sclerosis, a progressive neurodegenerative disorder. It is prone to P-glycoprotein efflux transportation and restricted by the BBB. The intranasal nanoemulsion improves brain bioavailability of the drug and, hence, the therapeutic efficiency [146]. Along with these, numerous other studies confirm that the intranasal nanoemulsion presents a potential carrier system for the treatment of CNS disorders.

6.6 Dendrimers

Dendrimers are nanosized, three-dimensional complex polymeric structures with higher surface functionalization and high drug-loading efficiency (Fig. 9.4) [13]. Win-Shwe et al. evaluated the brain targeting efficiency of PAMAM dendrimer after administration of a single intranasal dose on mice model. The animal organs (different parts of brain including the hippocampus, olfactory bulb, cerebrum, and cortex, and blood samples) were evaluated for the presence of a biomarker. The study indicated the transfer of carrier system takes place via olfactory neuron path as well as through systemic circulation upon intranasal administration. The intranasal PAMAM dendrimer shows significant brain targeting ability (Table 9.7) [152].

Earlier, Perez utilized PAMAM dendrimer for brain delivery of siRNA[3]. They developed siRNA-complexed dendrimer incorporated into in situ mucoadhesive chitosan-based nasal gel. To check the brain targeting efficiency, the prepared drug carrier system was radiolabeled.

[3] 32P-small interference RNA.

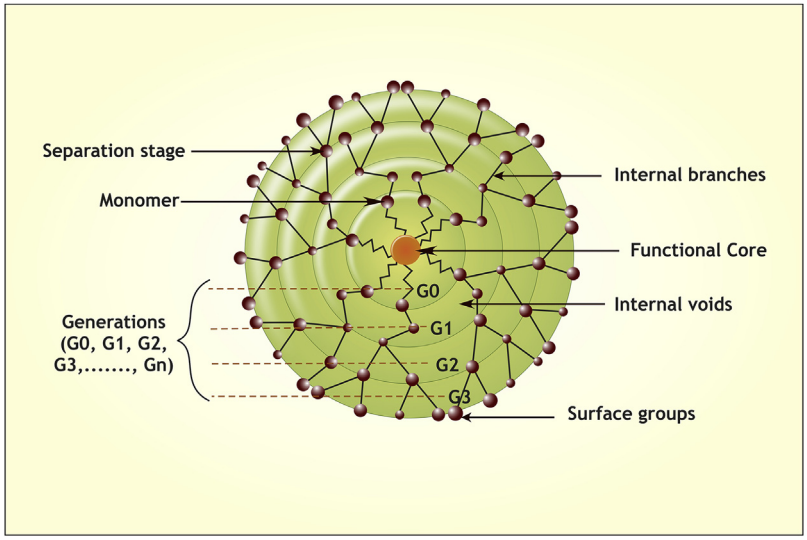

FIGURE 9.4 Basic structure of dendrimer showing different generations and function surface groups with highly branched structure.

TABLE 9.7 Application of dendrimer for nose-to-brain delivery of therapeutics.

Drug	Polymer	Particle size	Objective	References
–	PAMAM-NH2 (G4)	5.7 nm	To study the neurotoxicity of PAMAM dendrimer after intranasal administration	[152]
siRNA	poly(amidoamine) (G7)	–	To study the radioactivity of brain after nasal administration of si-RNA-loaded dendriplex	[153]
Paeonol	PAMAM	72.4–96.5 nm	Improved brain targeting of drug	[154]

The thermoresponsive in situ gel increases the nasal retention time of the system and facilitates drug absorption via nasal mucosa. At the same time, the dendrimer improves brain targeting efficiency via an olfactory neural pathway, and hence, higher radioactive material was observed in the olfactory region [153]. Recently, another study done by Xie et al. also relies on the findings of the above studies. They also synthesized PAMAM dendrimer and merged this nanocomposite with in situ gelling systems. They observed a significant amount of dendrimer nanocomposite in the brain, which further increases by using in situ gelling system upon intranasal administration. The brain targeting was achieved by neuronal pathway. All these studies show that the dendrimer serves as a potential carrier system for brain targeting via intranasal route [154]. However, systematic investigations are needed to establish an approach for commercial application.

7. Recent advancements in the clinical trials of nanoparticles via the nose-to-brain delivery

The delivery of drugs using conventional dosage form such as solution or suspension via the nose-to-brain delivery has been studied in clinical trials. There is a lack of clinical trials that are focused on the nose-to-brain delivery of drug-loaded nanoparticles. One of the promising delivery systems is nanoemulsions, which represent a promising strategy for nose-to-brain delivery for the treatment of CNS diseases. Technion developed an electronic nose-based nanomaterial for diagnosis of diseases such as cancer, kidney failure, etc. via breath samples. This trial is completed (NCT01206023). However, the results of this trial were not published at the time of writing. In addition to pharmacokinetic and pharmacodynamic studies under clinical trial, the toxicity of nanoparticles should be tested to calculate the benefit-to-risk ratio. It is expected that with the advancement of formulation strategies for the nose-to-brain delivery, these nanoparticle-based delivery systems will be tested under clinical trials in the near future.

8. Summary

Nose-to-brain route offers a potential, alternative, and noninvasive way of drug targeting to the brain that evades the interference of BBB and minimizes the peripheral side effects of the drug. The efficient drug targeting, minimum systemic exposure, ability to circumvent the BBB, patient convenience over the parenteral route, and reduced systemic side effects make this route of administration superior over the oral and parenteral route of drug administration. However, low bioavailability, rapid clearance, enzymatic degradation, and systemic absorption through respiratory tract limit its application. Thus, the use of novel carrier system and surface-modified or targeted formulations are used for more effective intranasal delivery to the brain. The novel carrier system made of mucoadhesive polymers or high-viscosity formulation increases the retention time and reduces the mucociliary clearance of the drug. The use of permeation enhancer facilitates the drug absorption. Similarly, nanocarriers also protect the drug from enzymatic degradation and assist in enhancing the absorption. In addition, the surface-modified nanocarrier system promotes drug targeting to a site of action. Moreover, the proper nasal administration technique is also essential to facilitate neural absorption from the dorsal olfactory region of the nasal cavity to the brain. Currently, most of the nanocarrier-based intranasal strategies are under clinical or preclinical investigation stages. A systematic understanding of nasal drug targeting and amalgamation with a novel nanocarrier system is hoped to offer better treatment of chronic CNS disorders.

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References

[1] Hussain AA. Intranasal drug delivery. Adv Drug Deliv Rev 1998;29(1–2):39–49.
[2] Shadab Md, Bhattmisra SK, Zeeshan F, Shahzad N, Mujtaba MA, Srikanth Meka V, et al. Nano-carrier enabled drug delivery systems for nose to brain targeting for the treatment of neurodegenerative disorders. J Drug Deliv Sci Technol 2018;43:295–310.
[3] William H, Frey I. Inventor Neurologic Agents for nasal administration to the brain. US1991 1990-12-04.
[4] Agrawal M, Saraf S, Saraf S, Antimisiaris SG, Chougule MB, Shoyele SA, et al. Nose-to-brain drug delivery: an update on clinical challenges and progress towards approval of anti-Alzheimer drugs. J Control Release 2018;281:139–77.

[5] Graff CL, Pollack GM. Nasal drug administration: potential for targeted central nervous system delivery. J Pharm Sci 2005;94(6):1187−95.
[6] van den Berg MP, Merkus P, Romeijn SG, Verhoef JC, Merkus FW. Uptake of melatonin into the cerebrospinal fluid after nasal and intravenous delivery: studies in rats and comparison with a human study. Pharm Res 2004;21(5):799−802.
[7] Al-Ghananeem AM, Traboulsi AA, Dittert LW, Hussain AA. Targeted brain delivery of 17 beta-estradiol via nasally administered water soluble prodrugs. AAPS PharmSciTech 2002;3(1):E5.
[8] Dhuria SV, Hanson LR, Frey 2nd WH. Intranasal delivery to the central nervous system: mechanisms and experimental considerations. J Pharm Sci 2010;99(4): 1654−73.
[9] Selvaraj K, Gowthamarajan K, Karri V. Nose to brain transport pathways an overview: potential of nanostructured lipid carriers in nose to brain targeting. Artif Cells Nanomed Biotechnol 2018;46(8):2088−95.
[10] Ali J, Ali M, Baboota S, Sahani JK, Ramassamy C, Dao L, et al. Potential of nanoparticulate drug delivery systems by intranasal administration. Curr Pharmaceut Des 2010;16(14):1644−53.
[11] Samaridou E, Alonso MJ. Nose-to-brain peptide delivery - the potential of nanotechnology. Bioorg Med Chem 2018;26(10):2888−905.
[12] Agrawal M, Ajazuddin, Tripathi DK, Saraf S, Saraf S, Antimisiaris SG, et al. Recent advancements in liposomes targeting strategies to cross blood-brain barrier (BBB) for the treatment of Alzheimer's disease. J Control Release 2017;260:61−77.
[13] Agrawal M, Saraf S, Saraf S, Antimisiaris SG, Hamano N, Li SD, et al. Recent advancements in the field of nanotechnology for the delivery of anti-Alzheimer drug in the brain region. Expert Opin Drug Deliv 2018;15(6):589−617.
[14] Kalia LV, Lang AE. Parkinson's disease. Lancet (London, England) 2015;386(9996):896−912.
[15] Schneider RB, Iourinets J, Richard IH. Parkinson's disease psychosis: presentation, diagnosis and management. Neurodegener Dis Manag 2017;7(6): 365−76.
[16] Goetz CG. The history of Parkinson's disease: early clinical descriptions and neurological therapies. Cold Spring Harb Perspect Med 2011;1(1):a008862.
[17] Opara J, Malecki A, Malecka E, Socha T. Motor assessment in Parkinson's disease. Ann Agric Environ Med 2017;24(3):411−5.
[18] Orimo S. New development of diagnosis and treatment for Parkinson's disease. Rinsho Shinkeigaku Clin Neurol 2017;57(6):259−73.
[19] Oakley CB, Kossoff EH. Migraine and epilepsy in the pediatric population. Curr Pain Headache Rep 2014; 18(3):402.
[20] Zarcone D, Corbetta S. Shared mechanisms of epilepsy, migraine and affective disorders. Neurol Sci 2017;38(Suppl. 1):73−6.
[21] Swaminathan A, Smith JH. Migraine and vertigo. Curr Neurol Neurosci Rep 2015;15(2):515.
[22] Wells RE, Turner DP, Lee M, Bishop L, Strauss L. Managing migraine during pregnancy and lactation. Curr Neurol Neurosci Rep 2016;16(4):40.
[23] Khandaker GM, Dantzer R. Is there a role for immune-to-brain communication in schizophrenia? Psychopharmacology 2016;233(9):1559−73.
[24] Tomasik J, Rahmoune H, Guest PC, Bahn S. Neuroimmune biomarkers in schizophrenia. Schizophr Res 2016;176(1):3−13.
[25] Meltzer HY. New trends in the treatment of schizophrenia. CNS Neurol Disord − Drug Targets 2017;16(8):900−6.
[26] Seidman LJ, Mirsky AF. Evolving notions of schizophrenia as a developmental neurocognitive disorder. J Int Neuropsychol Soc 2017;23(9−10):881−92.
[27] Bhat S, Acharya UR, Adeli H, Bairy GM, Adeli A. Autism: cause factors, early diagnosis and therapies. Rev Neurosci 2014;25(6):841−50.
[28] Chaste P, Leboyer M. Autism risk factors: genes, environment, and gene-environment interactions. Dialogues Clin Neurosci 2012;14(3):281−92.
[29] McPartland J, Volkmar FR. Autism and related disorders. Handb Clin Neurol 2012;106:407−18.
[30] Dolen G. Autism: oxytocin, serotonin, and social reward. Soc Neurosci 2015;10(5):450−65.
[31] Lai M-C, Lombardo MV, Baron-Cohen S. Autism. Lancet 2014;383(9920):896−910.
[32] Graham HK, Rosenbaum P, Paneth N, Dan B, Lin JP, Damiano DL, et al. Cerebral palsy. Nat Rev Dis Prim 2016;2:15082.
[33] Colver A, Fairhurst C, Pharoah PO. Cerebral palsy. Lancet (London, England) 2014;383(9924):1240−9.
[34] Novak I, Morgan C, Adde L, Blackman J, Boyd RN, Brunstrom-Hernandez J, et al. Early, accurate diagnosis and early intervention in cerebral palsy: advances in diagnosis and treatment. JAMA Pediatr 2017;171(9):897−907.
[35] Gulati S, Sondhi V. Cerebral palsy: an overview. Indian J Pediatr 2018;85(11):1006−16.
[36] Putz K, Hayani K, Zar FA. Meningitis. Prim Care 2013;40(3):707−26.
[37] Rosenberg J, Galen BT. Recurrent meningitis. Curr Pain Headache Rep 2017;21(7):33.

[38] Christie D, Rashid H, El-Bashir H, Sweeney F, Shore T, Booy R, et al. Impact of meningitis on intelligence and development: a systematic review and meta-analysis. PLoS One 2017;12(8):e0175024.
[39] Murthy H, Anasetti C, Ayala E. Diagnosis and management of leukemic and lymphomatous meningitis. Cancer Control 2017;24(1):33–41.
[40] Drachman DB. Myasthenia gravis. Semin Neurol 2016;36(5):419–24.
[41] Gilhus NE. Myasthenia gravis. N Engl J Med 2016; 375(26):2570–81.
[42] Gilhus NE, Verschuuren JJ. Myasthenia gravis: subgroup classification and therapeutic strategies. Lancet Neurol 2015;14(10):1023–36.
[43] Sieb JP. Myasthenia gravis: an update for the clinician. Clin Exp Immunol 2014;175(3):408–18.
[44] Hankey GJ. Stroke. Lancet (London, England) 2017; 389(10069):641–54.
[45] McDermott M, Jacobs T, Morgenstern L. Critical care in acute ischemic stroke. Handb Clin Neurol 2017;140: 153–76.
[46] Singh V, Prabhakaran S, Chaturvedi S, Singhal A, Pandian J. An examination of stroke risk and burden in South Asians. J Stroke Cerebrovasc Dis 2017; 26(10):2145–53.
[47] Nakanishi K, Homma S. Role of echocardiography in patients with stroke. J Cardiol 2016;68(2):91–9.
[48] Crowe TP, Greenlee MHW, Kanthasamy AG, Hsu WH. Mechanism of intranasal drug delivery directly to the brain. Life Sci 2018;195:44–52.
[49] Sekerdag E. Chapter 5 – nasal physiology and drug transport. In: Gürsoy-Özdemir Y, Bozdağ-Pehlivan S, Sekerdag E, editors. Nanotechnology methods for neurological diseases and brain tumors. Academic Press; 2017. p. 93–102.
[50] Frey WH, Liu J, Chen X, Thorne RG, Fawcett JR, Ala TA, et al. Delivery of 125I-NGF to the brain via the olfactory route. Drug Deliv 1997;4(2):87–92.
[51] Frey WHLJ, Thorne RG, Rahman YE. Intranasal delivery of 125 Ilabeled nerve growth factor to the brain via the olfactory route. In: Iqbal KMJ, Winblad B, Wisniewski HM, editors. New York (NY): John Wiley and Sons Ltd; 1995.
[52] Chen XQ, Fawcett JR, Rahman YE, Ala TA, Frey IW. Delivery of nerve growth factor to the brain via the olfactory pathway. J Alzheimer's Dis 1998;1(1):35–44.
[53] Liu XF, Fawcett JR, Hanson LR, Frey 2nd WH. The window of opportunity for treatment of focal cerebral ischemic damage with noninvasive intranasal insulin-like growth factor-I in rats. J Stroke Cerebrovasc Dis 2004;13(1):16–23.
[54] Schaefer ML, Bottger B, Silver WL, Finger TE. Trigeminal collaterals in the nasal epithelium and olfactory bulb: a potential route for direct modulation of olfactory information by trigeminal stimuli. J Comp Neurol 2002;444(3):221–6.
[55] Chen SC, Eiting K, Cui K, Leonard AK, Morris D, Li CY, et al. Therapeutic utility of a novel tight junction modulating peptide for enhancing intranasal drug delivery. J Pharm Sci 2006;95(6):1364–71.
[56] Davis SS, Illum L. Absorption enhancers for nasal drug delivery. Clin Pharmacokinet 2003;42(13): 1107–28.
[57] Alagusundaram M, Chengaiah B, Gnanaprakash K, Ramkanth S, Madhusudhana Chetty C, Dhachinamoorthi D. Nasal drug delivery system – an overview. Int J Res Pharm Sci 2010;1(4):454–65.
[58] Ramesh RP, Patil MC, Obire O. Nasal Drug delivery in Pharmaceutical and biotechnology: present and future. e-J Sci Technol 2009;3:1–21.
[59] Lee VH. Enzymatic barriers to peptide and protein absorption. Crit Rev Ther Drug Carrier Syst 1988; 5(2):69–97.
[60] Donnelly A, Kellaway IW, Taylor G, Gibson M. Absorption enhancers as tools to determine the route of nasal absorption of peptides. J Drug Target 1998; 5(2):121–7.
[61] Ameller T, Marsaud V, Legrand P, Gref R, Barratt G, Renoir J-M. Polyester-poly(ethylene glycol) nanoparticles loaded with the pure antiestrogen RU 58668: physicochemical and opsonization properties. Pharm Res 2003;20(7):1063–70.
[62] Gref R, Domb A, Quellec P, Blunk T, Muller RH, Verbavatz JM, et al. The controlled intravenous delivery of drugs using PEG-coated sterically stabilized nanospheres. Adv Drug Deliv Rev 1995;16(2–3): 215–33.
[63] Soppimath KS, Aminabhavi TM, Kulkarni AR, Rudzinski WE. Biodegradable polymeric nanoparticles as drug delivery devices. J Control Release 2001;70(1–2):1–20.
[64] Kwon GS. Diblock copolymer nanoparticles for drug delivery. Crit Rev Ther Drug Carrier Syst 1998;15(5): 481–512.
[65] Naahidi S, Jafari M, Edalat F, Raymond K, Khademhosseini A, Chen P. Biocompatibility of engineered nanoparticles for drug delivery. J Control Release 2013;166(2):182–94.
[66] Martins S, Sarmento B, Ferreira DC, Souto EB. Lipid-based colloidal carriers for peptide and protein delivery–liposomes versus lipid nanoparticles. Int J Nanomed 2007;2(4):595–607.

[67] Vllasaliu D, Exposito-Harris R, Heras A, Casettari L, Garnett M, Illum L, et al. Tight junction modulation by chitosan nanoparticles: comparison with chitosan solution. Int J Pharm 2010;400(1−2):183−93.

[68] Genta I, Perugini P, Modena T, Pavanetto F, Castelli F, Muzzarelli RAA, et al. Miconazole-loaded 6-oxychitin−chitosan microcapsules. Carbohydr Polym 2003;52(1):11−8.

[69] Hanafy AS, Farid RM, Helmy MW, ElGamal SS. Pharmacological, toxicological and neuronal localization assessment of galantamine/chitosan complex nanoparticles in rats: future potential contribution in Alzheimer's disease management. Drug Deliv 2016; 23(8):3111−22.

[70] Ahmad N, Ahmad R, Naqvi AA, Alam MA, Ashafaq M, Samim M, et al. Rutin-encapsulated chitosan nanoparticles targeted to the brain in the treatment of Cerebral Ischemia. Int J Biol Macromol 2016; 91:640−55.

[71] Raj R, Wairkar S, Sridhar V, Gaud R. Pramipexole dihydrochloride loaded chitosan nanoparticles for nose to brain delivery: development, characterization and in vivo anti-Parkinson activity. Int J Biol Macromol 2018;109:27−35.

[72] Shah B, Khunt D, Misra M, Padh H. "Application of Box-Behnken design for optimization and development of quetiapine fumarate loaded chitosan nanoparticles for brain delivery via intranasal route* ". Int J Biol Macromol 2016;89:206−18.

[73] Javia A, Thakkar H. Intranasal delivery of tapentadol hydrochloride-loaded chitosan nanoparticles: formulation, characterisation and its in vivo evaluation. J Microencapsul 2017;34(7):644−58.

[74] Sharma D, Sharma RK, Sharma N, Gabrani R, Sharma SK, Ali J, et al. Nose-to-brain delivery of PLGA-diazepam nanoparticles. AAPS PharmSciTech 2015;16(5):1108−21.

[75] Sharma D, Sharma RK, Bhatnagar A, Nishad DK, Singh T, Gabrani R, et al. Nose to brain delivery of midazolam loaded PLGA nanoparticles: in vitro and in vivo investigations. Curr Drug Deliv 2016;13(4): 557−64.

[76] Seju U, Kumar A, Sawant KK. Development and evaluation of olanzapine-loaded PLGA nanoparticles for nose-to-brain delivery: in vitro and in vivo studies. Acta Biomater 2011;7(12):4169−76.

[77] Tong GF, Qin N, Sun LW. Development and evaluation of Desvenlafaxine loaded PLGA-chitosan nanoparticles for brain delivery. Saudi Pharm J 2017; 25(6):844−51.

[78] Muntimadugu E, Dhommati R, Jain A, Challa VG, Shaheen M, Khan W. Intranasal delivery of nanoparticle encapsulated tarenflurbil: a potential brain targeting strategy for Alzheimer's disease. Eur J Pharm Sci 2016;92:224−34.

[79] Meng Q, Wang A, Hua H, Jiang Y, Wang Y, Mu H, et al. Intranasal delivery of Huperzine A to the brain using lactoferrin-conjugated N-trimethylated chitosan surface-modified PLGA nanoparticles for treatment of Alzheimer's disease. Int J Nanomed 2018;13:705−18.

[80] Zhang C, Chen J, Feng C, Shao X, Liu Q, Zhang Q, et al. Intranasal nanoparticles of basic fibroblast growth factor for brain delivery to treat Alzheimer's disease. Int J Pharm 2014;461(1−2):192−202.

[81] Fazil M, Md S, Haque S, Kumar M, Baboota S, Sahni JK, et al. Development and evaluation of rivastigmine loaded chitosan nanoparticles for brain targeting. Eur J Pharm Sci 2012;47(1):6−15.

[82] Elnaggar YS, Etman SM, Abdelmonsif DA, Abdallah OY. Intranasal piperine-loaded chitosan nanoparticles as brain-targeted therapy in Alzheimer's disease: optimization, biological efficacy, and potential toxicity. J Pharm Sci 2015;104(10): 3544−56.

[83] Liu Z, Jiang M, Kang T, Miao D, Gu G, Song Q, et al. Lactoferrin-modified PEG-co-PCL nanoparticles for enhanced brain delivery of NAP peptide following intranasal administration. Biomaterials 2013;34(15): 3870−81.

[84] Cunha S, Amaral MH, Lobo JMS, Silva AC. Lipid nanoparticles for nasal/intranasal drug delivery. Crit Rev Ther Drug Carrier Syst 2017;34(3):257−82.

[85] Cunha S, Almeida H, Amaral MH, Lobo JMS, Silva AC. Intranasal lipid nanoparticles for the treatment of neurodegenerative diseases. Curr Pharmaceut Des 2017;23(43):6553−62.

[86] Khan AR, Yang X, Fu M, Zhai G. Recent progress of drug nanoformulations targeting to brain. J Control Release 2018;291:37−64.

[87] Rassu G. Nose-to-brain delivery of BACE1 siRNA loaded in solid lipid nanoparticles for Alzheimer's therapy. Colloids Surf B Biointerfaces 2017;152: 296−301.

[88] Youssef N, Kassem AA, Farid RM, Ismail FA, El-Massik MAE, Boraie NA. A novel nasal almotriptan loaded solid lipid nanoparticles in mucoadhesive in situ gel formulation for brain targeting: preparation, characterization and in vivo evaluation. Int J Pharm 2018;548(1):609−24.

[89] Yasir M, Sara UV. Solid lipid nanoparticles for nose to brain delivery of haloperidol: in vitro drug release and pharmacokinetics evaluation. Acta Pharm Sin B 2014; 4(6):454−63.

[90] Wavikar PR, Vavia PR. Rivastigmine-loaded in situ gelling nanostructured lipid carriers for nose to brain delivery. J Liposome Res 2015;25(2):141−9.

[91] Khan A, Imam SS, Aqil M, Ahad A, Sultana Y, Ali A, et al. Brain targeting of temozolomide via the intranasal route using lipid-based nanoparticles: brain pharmacokinetic and scintigraphic analyses. Mol Pharm 2016;13(11):3773–82.
[92] Shah B, Khunt D, Misra M, Padh H. Formulation and in-vivo pharmacokinetic consideration of intranasal microemulsion and mucoadhesive microemulsion of rivastigmine for brain targeting. Pharm Res 2018; 35(1):8.
[93] Patel MR, Patel RB, Bhatt KK, Patel BG, Gaikwad RV. Paliperidone microemulsion for nose-to-brain targeted drug delivery system: pharmacodynamic and pharmacokinetic evaluation. Drug Deliv 2016;23(1): 346–54.
[94] Patel RB, Patel MR, Bhatt KK, Patel BG, Gaikwad RV. Evaluation of brain targeting efficiency of intranasal microemulsion containing olanzapine: pharmacodynamic and pharmacokinetic consideration. Drug Deliv 2016;23(1):307–15.
[95] Bshara H, Osman R, Mansour S, El-Shamy Ael H. Chitosan and cyclodextrin in intranasal microemulsion for improved brain buspirone hydrochloride pharmacokinetics in rats. Carbohydr Polym 2014;99:297–305.
[96] Lalani J, Baradia D, Lalani R, Misra A. Brain targeted intranasal delivery of tramadol: comparative study of microemulsion and nanoemulsion. Pharm Dev Technol 2015;20(8):992–1001.
[97] Shinde RL, Devarajan PV. Docosahexaenoic acid-mediated, targeted and sustained brain delivery of curcumin microemulsion. Drug Deliv 2017;24(1): 152–61.
[98] Shah B, Khunt D, Misra M, Padh H. Non-invasive intranasal delivery of quetiapine fumarate loaded microemulsion for brain targeting: formulation, physicochemical and pharmacokinetic consideration. Eur J Pharm Sci 2016;91:196–207.
[99] Li JC, Zhang WJ, Zhu JX, Zhu N, Zhang HM, Wang X, et al. Preparation and brain delivery of nasal solid lipid nanoparticles of quetiapine fumarate in situ gel in rat model of schizophrenia. Int J Clin Exp Med 2015;8(10):17590–600.
[100] Aboutaleb E, Atyabi F, Khoshayand MR, Vatanara AR, Ostad SN, Kobarfard F, et al. Improved brain delivery of vincristine using dextran sulfate complex solid lipid nanoparticles: optimization and in vivo evaluation. J Biomed Mater Res A 2014; 102(7):2125–36.
[101] Ren J, Zou M, Gao P, Wang Y, Cheng G. Tissue distribution of borneol-modified ganciclovir-loaded solid lipid nanoparticles in mice after intravenous administration. Eur J Pharm Biopharm 2013;83(2): 141–8.
[102] Malekpour-Galogahi F, Hatamian-Zarmi A, Ganji F, Ebrahimi-Hosseinzadeh B, Nojoki F, Sahraeian R, et al. Preparation and optimization of rivastigmine-loaded tocopherol succinate-based solid lipid nanoparticles. J Liposome Res 2018;28(3):226–35.
[103] Bhatt R, Singh D, Prakash A, Mishra N. Development, characterization and nasal delivery of rosmarinic acid-loaded solid lipid nanoparticles for the effective management of Huntington's disease. Drug Deliv 2015;22(7):931–9.
[104] Joshi AS, Patel HS, Belgamwar VS, Agrawal A, Tekade AR. Solid lipid nanoparticles of ondansetron HCl for intranasal delivery: development, optimization and evaluation. J Mater Sci Mater Med 2012; 23(9):2163–75.
[105] Shah B, Khunt D, Bhatt H, Misra M, Padh H. Application of quality by design approach for intranasal delivery of rivastigmine loaded solid lipid nanoparticles: effect on formulation and characterization parameters. Eur J Pharm Sci 2015;78:54–66.
[106] Hernando S, Herran E, Figueiro-Silva J, Pedraz JL, Igartua M, Carro E, et al. Intranasal administration of TAT-conjugated lipid nanocarriers loading GDNF for Parkinson's disease. Mol Neurobiol 2018;55(1): 145–55.
[107] Abbas H, Refai H, El Sayed N. Superparamagnetic iron oxide-loaded lipid nanocarriers incorporated in thermosensitive in situ gel for magnetic brain targeting of Clonazepam. J Pharm Sci 2018;107(8):2119–27.
[108] Jain K, Sood S, Gowthamarajan K. Optimization of artemether-loaded NLC for intranasal delivery using central composite design. Drug Deliv 2015;22(7): 940–54.
[109] Gartziandia O, Herran E, Pedraz JL, Carro E, Igartua M, Hernandez RM. Chitosan coated nanostructured lipid carriers for brain delivery of proteins by intranasal administration. Colloids Surf B Biointerfaces 2015;134:304–13.
[110] Alam MI, Baboota S, Ahuja A, Ali M, Ali J, Sahni JK. Intranasal administration of nanostructured lipid carriers containing CNS acting drug: pharmacodynamic studies and estimation in blood and brain. J Psychiatr Res 2012;46(9):1133–8.
[111] Pokharkar V, Patil-Gadhe A, Palla P. Efavirenz loaded nanostructured lipid carrier engineered for brain targeting through intranasal route: in-vivo pharmacokinetic and toxicity study. Biomed Pharmacother 2017; 94:150–64.
[112] Wavikar P, Pai R, Vavia P. Nose to brain delivery of rivastigmine by in situ gelling cationic nanostructured lipid carriers: enhanced brain distribution and pharmacodynamics. J Pharm Sci 2017;106(12): 3613–22.

[113] Sharma N, Bhandari S, Deshmukh R, Yadav AK, Mishra N. Development and characterization of embelin-loaded nanolipid carriers for brain targeting. Artif Cells Nanomed Biotechnol 2017; 45(3):409−13.
[114] Wang F, Li C, Cheng J, Yuan Z. Recent advances on inorganic nanoparticle-based cancer therapeutic agents. Int J Environ Res Public Health 2016;13(12).
[115] Shiga H, Yamamoto J, Miwa T. [Clinical diagnosis of the olfactory nerve transport function]. Yakugaku Zasshi 2012;132(11):1263−6.
[116] Hopkins LE, Patchin ES, Chiu PL, Brandenberger C, Smiley-Jewell S, Pinkerton KE. Nose-to-brain transport of aerosolised quantum dots following acute exposure. Nanotoxicology 2014;8(8):885−93.
[117] Gao X, Chen J, Chen J, Wu B, Chen H, Jiang X. Quantum dots bearing lectin-functionalized nanoparticles as a platform for in vivo brain imaging. Bioconjug Chem 2008;19(11):2189−95.
[118] Lalancette-Hebert M, Moquin A, Choi AO, Kriz J, Maysinger D. Lipopolysaccharide-QD micelles induce marked induction of TLR2 and lipid droplet accumulation in olfactory bulb microglia. Mol Pharm 2010; 7(4):1183−94.
[119] Wang YT, Lu XM, Zhu F, Huang P, Yu Y, Zeng L, et al. The use of a gold nanoparticle-based adjuvant to improve the therapeutic efficacy of hNgR-Fc protein immunization in spinal cord-injured rats. Biomaterials 2011;32(31):7988−98.
[120] Velasco-Aguirre C, Morales F, Gallardo-Toledo E, Guerrero S, Giralt E, Araya E, et al. Peptides and proteins used to enhance gold nanoparticle delivery to the brain: preclinical approaches. Int J Nanomed 2015;10:4919−36.
[121] Ye D, Zhang X, Yue Y, Raliya R, Biswas P, Taylor S, et al. Focused ultrasound combined with microbubble-mediated intranasal delivery of gold nanoclusters to the brain. J Control Release 2018;286: 145−53.
[122] Salem HF, Kharshoum RM, Abou-Taleb HA, Naguib DM. Brain targeting of resveratrol through intranasal lipid vesicles labelled with gold nanoparticles: in vivo evaluation and bioaccumulation investigation using computed tomography and histopathological examination. J Drug Target 2019: 1−34.
[123] Lungare S, Hallam K, Badhan RK. Phytochemical-loaded mesoporous silica nanoparticles for nose-to-brain olfactory drug delivery. Int J Pharm 2016; 513(1−2):280−93.
[124] You R, Ho YS, Hung CH, Liu Y, Huang CX, Chan HN, et al. Silica nanoparticles induce neurodegeneration-like changes in behavior, neuropathology, and affect synapse through MAPK activation. Part Fibre Toxicol 2018;15(1):28.
[125] Villegas JC, Alvarez-Montes L, Rodriguez-Fernandez L, Gonzalez J, Valiente R, Fanarraga ML. Multiwalled carbon nanotubes hinder microglia function interfering with cell migration and phagocytosis. Adv Healthc Mater 2014;3(3):424−32.
[126] Yun WS, Choi JS, Ju HM, Kim MH, Choi SJ, Oh ES, et al. Enhanced homing technique of Mesenchymal stem cells using iron oxide nanoparticles by magnetic attraction in olfactory-injured mouse models. Int J Mol Sci 2018;19(5).
[127] Akilo OD, Choonara YE, Strydom AM, du Toit LC, Kumar P, Modi G, et al. AN in vitro evaluation of a carmustine-loaded Nano-co-Plex for potential magnetic-targeted intranasal delivery to the brain. Int J Pharm 2016;500(1−2):196−209.
[128] Barratt GM. Therapeutic applications of colloidal drug carriers. Pharm Sci Technol Today 2000;3(5): 163−71.
[129] Torchilin VP. Recent advances with liposomes as pharmaceutical carriers. Nat Rev Drug Discov 2005; 4(2):145−60.
[130] Nageeb El-Helaly S, Abd Elbary A, Kassem MA, El-Nabarawi MA. Electrosteric stealth Rivastigmine loaded liposomes for brain targeting: preparation, characterization, ex vivo, bio-distribution and in vivo pharmacokinetic studies. Drug Deliv 2017; 24(1):692−700.
[131] Salade L, Wauthoz N, Deleu M, Vermeersch M, De Vriese C, Amighi K, et al. Development of coated liposomes loaded with ghrelin for nose-to-brain delivery for the treatment of cachexia. Int J Nanomed 2017; 12:8531−43.
[132] Upadhyay P, Trivedi J, Pundarikakshudu K, Sheth N. Direct and enhanced delivery of nanoliposomes of anti schizophrenic agent to the brain through nasal route. Saudi Pharm J 2017;25(3):346−58.
[133] Bender TS, Migliore MM, Campbell RB, John Gatley S, Waszczak BL. Intranasal administration of glial-derived neurotrophic factor (GDNF) rapidly and significantly increases whole-brain GDNF level in rats. Neuroscience 2015;303:569−76.
[134] Yang ZZ, Zhang YQ, Wang ZZ, Wu K, Lou JN, Qi XR. Enhanced brain distribution and pharmacodynamics of rivastigmine by liposomes following intranasal administration. Int J Pharm 2013;452(1−2):344−54.
[135] Li W, Zhou Y, Zhao N, Hao B, Wang X, Kong P. Pharmacokinetic behavior and efficiency of acetylcholinesterase inhibition in rat brain after intranasal administration of galanthamine hydrobromide loaded flexible liposomes. Environ Toxicol Pharmacol 2012;34(2):272−9.

[136] Arumugam K, Subramanian GS, Mallayasamy SR, Averineni RK, Reddy MS, Udupa N. A study of rivastigmine liposomes for delivery into the brain through intranasal route. Acta Pharm 2008;58(3):287–97.
[137] Wei H, Liu T, Jiang N, Zhou K, Yang K, Ning W, et al. A novel delivery system of Cyclovirobuxine D for brain targeting: angiopep-conjugated polysorbate 80-coated liposomes via intranasal administration. J Biomed Nanotechnol 2018;14(7):1252–62.
[138] Zheng X, Shao X, Zhang C, Tan Y, Liu Q, Wan X, et al. Intranasal H102 peptide-loaded liposomes for brain delivery to treat alzheimer's disease. Pharm Res 2015;32(12):3837–49.
[139] Guo X, Zheng H, Guo Y, Wang Y, Anderson GJ, Ci Y, et al. Nasal delivery of nanoliposome-encapsulated ferric ammonium citrate can increase the iron content of rat brain. J Nanobiotechnol 2017;15(1):42.
[140] Zhao YZ, Lin M, Lin Q, Yang W, Yu XC, Tian FR, et al. Intranasal delivery of bFGF with nanoliposomes enhances in vivo neuroprotection and neural injury recovery in a rodent stroke model. J Control Release 2016;224:165–75.
[141] Al Asmari AK, Ullah Z, Tariq M, Fatani A. Preparation, characterization, and in vivo evaluation of intranasally administered liposomal formulation of donepezil. Drug Des Dev Ther 2016;10:205–15.
[142] Narayan R, Singh M, Ranjan O, Nayak Y, Garg S, Shavi GV, et al. Development of risperidone liposomes for brain targeting through intranasal route. Life Sci 2016;163:38–45.
[143] Salade L, Wauthoz N, Vermeersch M, Amighi K, Goole J. Chitosan-coated liposome dry-powder formulations loaded with ghrelin for nose-to-brain delivery. Eur J Pharm Biopharm 2018;129:257–66.
[144] Ahmad E, Feng Y, Qi J, Fan W, Ma Y, He H, et al. Evidence of nose-to-brain delivery of nanoemulsions: cargoes but not vehicles. Nanoscale 2017;9(3):1174–83.
[145] Comfort C, Garrastazu G, Pozzoli M, Sonvico F. Opportunities and challenges for the nasal administration of nanoemulsions. Curr Top Med Chem 2015;15(4):356–68.
[146] Parikh RH, Patel RJ. Nanoemulsions for intranasal delivery of riluzole to improve brain bioavailability: formulation development and pharmacokinetic studies. Curr Drug Deliv 2016;13(7):1130–43.
[147] Yadav S, Gattacceca F, Panicucci R, Amiji MM. Comparative biodistribution and pharmacokinetic analysis of Cyclosporine-A in the brain upon intranasal or intravenous administration in an oil-in-water nanoemulsion formulation. Mol Pharm 2015;12(5):1523–33.
[148] Kumar S, Dang S, Nigam K, Ali J, Baboota S. Selegiline nanoformulation in attenuation of oxidative stress and upregulation of dopamine in the brain for the treatment of Parkinson's disease. Rejuvenation Res 2018;21(5):464–76.
[149] Boche M, Pokharkar V. Quetiapine nanoemulsion for intranasal drug delivery: evaluation of brain-targeting efficiency. AAPS PharmSciTech 2017;18(3):686–96.
[150] Colombo M, Figueiro F, de Fraga Dias A, Teixeira HF, Battastini AMO, Koester LS. Kaempferol-loaded mucoadhesive nanoemulsion for intranasal administration reduces glioma growth in vitro. Int J Pharm 2018;543(1–2):214–23.
[151] Abdou EM, Kandil SM, Miniawy H. Brain targeting efficiency of antimigrain drug loaded mucoadhesive intranasal nanoemulsion. Int J Pharm 2017;529(1–2):667–77.
[152] Win-Shwe TT, Sone H, Kurokawa Y, Zeng Y, Zeng Q, Nitta H, et al. Effects of PAMAM dendrimers in the mouse brain after a single intranasal instillation. Toxicol Lett 2014;228(3):207–15.
[153] Perez AP, Mundina-Weilenmann C, Romero EL, Morilla MJ. Increased brain radioactivity by intranasal P-labeled siRNA dendriplexes within in situ-forming mucoadhesive gels. Int J Nanomed 2012;7:1373–85.
[154] Xie H, Li L. An available strategy for nasal brain transport of nanocomposite based on PAMAM dendrimers via in situ gel. Nanomater (Basel) 2019;9(2).