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Development of Nanoformulations for Targeted Transport of CNS Drugs with Greater Pharmacological Activity via the Nose in to the Brain

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Abstract

The purpose of the paper is actively exploring the feasibility of using nanocarriers in the brain to treat various neurological disorders. These include Parkinson's disease, schizophrenia, epilepsy, Alzheimer's disease, brain cancer, multiple sclerosis, depression, cerebral ischemia, and cerebral malaria. Among the various approaches available, nose-to-brain drug targeting remains the most acceptable but difficult challenge due to the complex structure and multiple barriers presented by the CNS. The various nanoformulations including microemulsions, nanoemulsions, polymeric nanoparticles, micelles, solid lipid nanoparticles (SLNs), liposomes, and transferosomes are currently used for their advanced delivery approaches. The nanoformulations are capable of performing the desired functions of the advanced delivery and targeting approaches, i.e., enhancing nasal-to-brain delivery and penetration of the drug across the blood–brain barrier (BBB). These formulations are safe, stable, and capable of improving bioavailability and biocompatibility. These nanocarriers offer numerous advantages over conventional drug delivery systems, such as improved targeting and high drug loading capacity. Researchers and scientists worldwide are working tirelessly in various areas of CNS disorders with or without nanoformulations, and it is still an area that needs to be explored. This review focuses on the major approaches of brain targeting, including efficient delivery of the drug across the blood–brain barrier as well as navigation of the nanoformulations to the desired brain site in conjunction with the global prevalence of certain neurological diseases in the current situation.

Keywords: Nanocarriers; BBB; CNS Targeting; Intranasal drug delivery; Neurological disorders

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Introduction

The brain is a command center and one of the most important organs in humans, controlling all functions, both voluntary and involuntary [1]. The relevant information is also stored and transmitted to various organs. The brain is mainly protected by shielding a. the blood–brain barrier (BBB) and b. the endothelial cell. These shielding mechanisms protect the brain from harmful influences and maintain homeostasis [2]. According to 2015 statistics, Alzheimer's disease and other brain diseases are the top 10 causes of death worldwide [3].

The blood–brain barrier (BBB) is a unique shield against harmful substances that involves the tissues of neurons and blood vessels, allowing tissue function, regulation of transport, and protection [4]. It is made up of a variety of cells, including perivascular macrophages, pericytes, astrocytes, and capillary endothelial cells. Tight junctions (TJs) between endothelial cells, which include occludins, claudins, and junctional adhesion molecules, cause the BBB to be impermeable to many molecules. In addition to endothelial cells, the controlled permeability of the BBB is also influenced by specialized extracellular matrix and the basement membrane, which is made up of collagen type IV, laminin, fibronectin, tenascin, and proteoglycans [5].

Transcellular diffusion, also known as passive diffusion, as well as the saturable processes of facilitated diffusion and active transport are the routes by which substances cross the BBB that have received the most attention. Anatomically defined areas known as paracellular pathways, which allow trace amounts of circulating substances to enter the central nervous system, are being studied more and more [6]. There are passive and active components to the transcellular pathway. In the active transport of BBB, there are three different types of transport systems: carrier-mediated transport (CMT), which transports sugars, amino acids, metabolites, nutrients, organic anions and cations, and neurotransmitters; receptor-mediated transport (RMT), which transports large molecules such as proteins; and active efflux transport, which uses the ATP binding cassette (ABC) family. Therapeutic agents were ejected through the BBB due to the presence of various ABC transporters such as P-glycoprotein (P-gly) [7].

This BBB controls drug molecules in the brain. Almost every treatment acts only symptomatically, that is, it inhibits only the symptoms of the disease. Because they do not address the causative aspect of the disease, they are unable to effectively cure the disease. Researchers are working hard to develop new methods to effectively deliver the drug to the brain despite the presence of the BBB [8]. One of these strategies is the use of the nasal route, which allows drugs to be delivered effectively to the brain [9]. Both intravenous and intranasal drug delivery have been proposed ways to treat diseases affecting the central nervous system [10].

However, the amount of drug reaching the brain through the nose is less than 0.1% of the administered dose. These issues can be resolved, and nose-to-brain drug delivery has been shown to be improved by encapsulating medications into nanometer-sized particles [11].

Novel nanostructured drug delivery systems such as noisomes, liposomes, solid lipid nanoparticle (SLN), nanostructure lipid carrier (NLC), nanoemulsions, polymeric micelles, polymeric nanoparticles, dendrimers, etc., have been developed and investigated. Pharmaceuticals are transporters composed of various synthetic and natural polymers, poly (lactic-co-glycolic acid, or PLGA), gelatin, polylactic acid (PLA), chitosan, sodium alginate, etc. All these polymers are biodegradable, non-biodegradable, mucoadhesive, biocompatible, and non-toxic to human organs. Nasal delivery of active polymeric nanoparticles improves the overall drug performance, curative effect, solubility, bioavailability, BBB permeation, and drug loading capacity [10,12]. These developed nanosized carriers are much needed in pharmaceutical and biomedical regions.

It is possible to deliver drugs through the blood–brain barrier into the central nervous system by using a painless, non-invasive, and non-toxic delivery method called drug delivery through the nose into the brain. Penetration of the nanoformulation through the nasal epithelium allows the drug to reach the vicinity of the brain [13,14]. The BBB contains connective tissue, microvessels within the CNS fascicle, and the investing perineurium [15]. The microvessels play a critical role in regulating the permeability of the perineurium and endoneural capillaries, as well as the passage of drug molecules from the olfactory tract and trigeminal neural pathways into the CNS.

Intranasal Anatomy

The nose is a vital organ for the inhalation and exhalation of oxygen. It consists of two symmetrical nostrils lined with mucosa and a thick layer of mucus rich in blood vessels, as shown in **Figure 1** [16]. Particles entering from the outside are transmitted from the mucosa first to the nasopharynx and then to the esophagus and stomach. The process of drug absorption may occur in the nasal passages over a comparatively larger surface area. It is covered by ciliated or nonciliated mucosal epithelial cells composed of basal cells, goblet cells, and columnar cells. The digestive tract, which contains enzymes, proteins, and peptides, has less metabolic activity than the nose. The nasal route has the additional advantage of avoiding first pass metabolism and providing quick onset of action when compared to oral administration [16, 17].

Pathway of Intranasal Drug Delivery Systems

The nasal mucosa is the starting point for drug distribution pathways to the brain and has been extensively studied over the years. Simply put, the nasal orifice consists of three distinct regions: (1) the vestibule, (2) the respiratory region associated with the trigeminal region, and (3) the olfactory region, which has been studied extensively over the years. The vestibular regions are the anterior regions of the nasal orifice protected by cartilage with tiny hairs that help filter dust fragments from the swirling air and act on immunological responses [18, 19].

Molecules from the olfactory tract can be rapidly transported through the olfactory mucosa to the central nervous system by transcellular or paracellular transport systems that contain

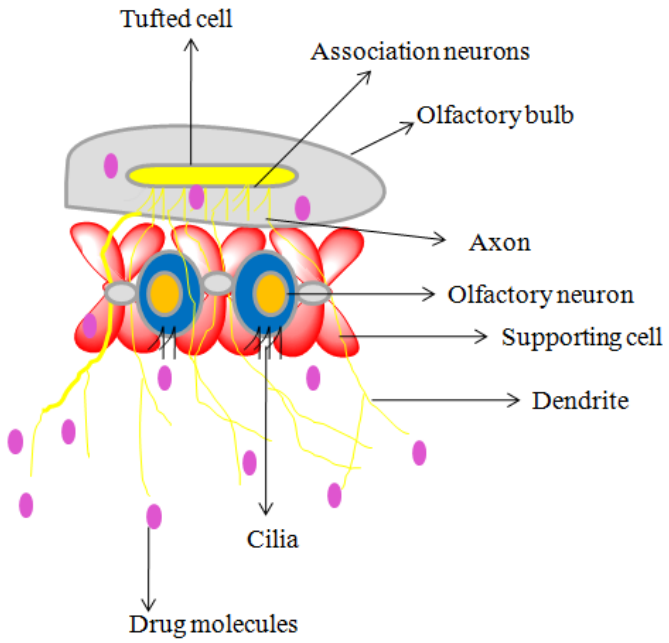

Figure 1 Olfactory nerve anatomy.

cilia and project downward from the olfactory epithelium into a mucosal layer. The Bowman's gland secretes more lipids through mucous secretions. The epithelial membrane in this region consists of three distinct layers: (1) sustentacular cells, which provide mechanical support to neighboring cells and from which basal cells arise; (2) the olfactory bulb, which consists of supporting cells and gives rise to olfactory neurons; and (3) sustentacular cells that are a type of cell found in the intestine. This is the most common and important specific pathway for drug delivery to the brain. Since most of the drug is likely lost through enzyme activity or mucociliary clearance (MCC), the brain will receive only a fraction of the total dose. The element also entered the systemic circulation where it was distributed to non-target tissues before being excreted [20, 21]. The respiratory region is habitat to the nose tubercle, a protrusion from the nasal cavity's lateral walls that creates turbulent airflow. This region is composed of four cell types: 1. basal cells, 2. wine goblets, 3. non-fibrillating columnar cells, and 4. fibrillating columnar cells. Drugs enter our systemic circulation either through the tissues or through the trigeminal canal in the respiratory system. This trigeminal nerve is more important for the transmission of sensory information [22]. However, when lipid-containing drugs are used, some of the drugs entering the systemic circulation may enter the brain via the BBB, as shown in **(Figure 2) .**

The exact pathways involved in nose-to-brain drug delivery system well known various routes are such as systemic, olfactory, and trigeminal nerve pathways. The systemic mechanism transported the drug being directly absorbed from epithelial cells (nasal) and the lymphatic system. The low molecular weight drug molecules can readily be absorbed into the circulatory system and later cross the blood–brain barrier (BBB) to reach the specific site [23]. Pinocytosis (active transport mechanism for reabsorption of the proteins) and endocytosis (the membrane engulfs the drug molecular and pinches off the drug-filled vesicle to transport it into the cell) are mechanisms for the internalization of drugs into the olfactory neurons and their intracellular axonal transport along the neurons into the olfactory bulb from which they are further distributed to different parts of the brain [24]. A better understanding of way how drug molecules are transported from the nasal cavity to the brain via the olfactory perivascular epithelium and trigeminal nerve pathway is required so it can to prevent crossing of the BBB, first-pass metabolism, and intestinal degradation.

Approaches for BBB Permeation

The BBB inhibits the release of drug molecules in the brain. Therefore, various nanocarriers are used to improve the efficacy of drugs in the CNS [25]. The BBB protects the brain through various restrictive layers, such as endothelial cells and tight protein junctions, etc. In an attempt to overcome these barriers, various novel drug delivery systems are being developed. Due to their small size, such nanocarriers promise to improve drug delivery in the brain. They are biocompatible, biodegradable, and have a lipid structure that provides high drug encapsulation efficiency. This is achieved by using a number of different transport framework processes, such as passive diffusion via paracellular and transcellular pathways and active diffusion via receptor- and carrier-mediated transport pathways, as shown in **Figure 3** [26]. This increases the amount of drug that can pass through the BBB. Small lipophilic compounds are the only

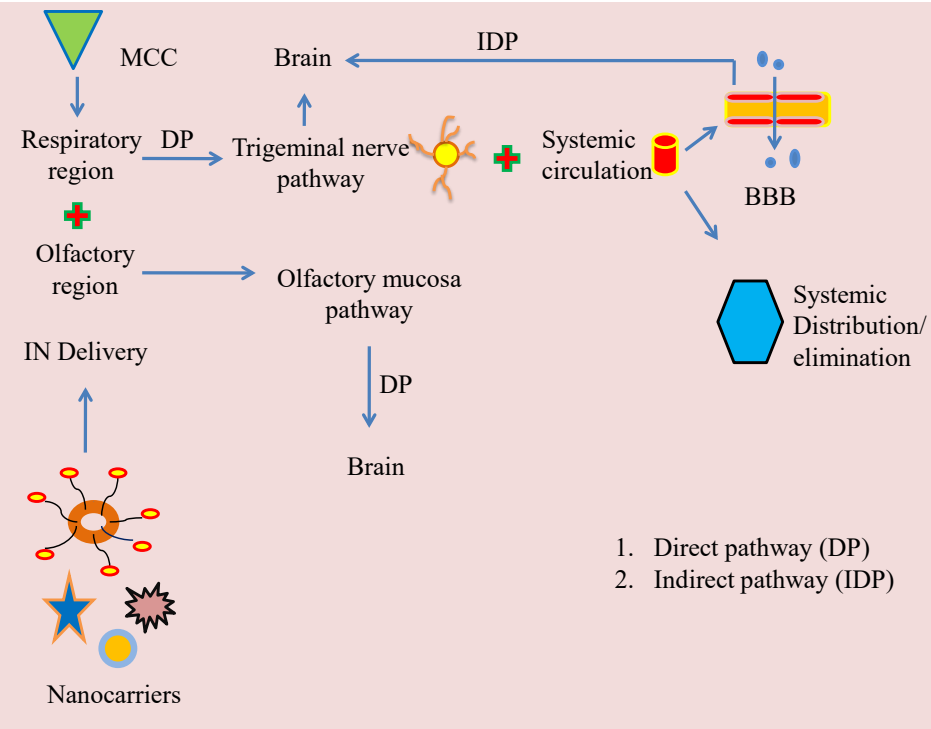

Figure 2 Nose-to-brain drug delivery system is depicted schematically.

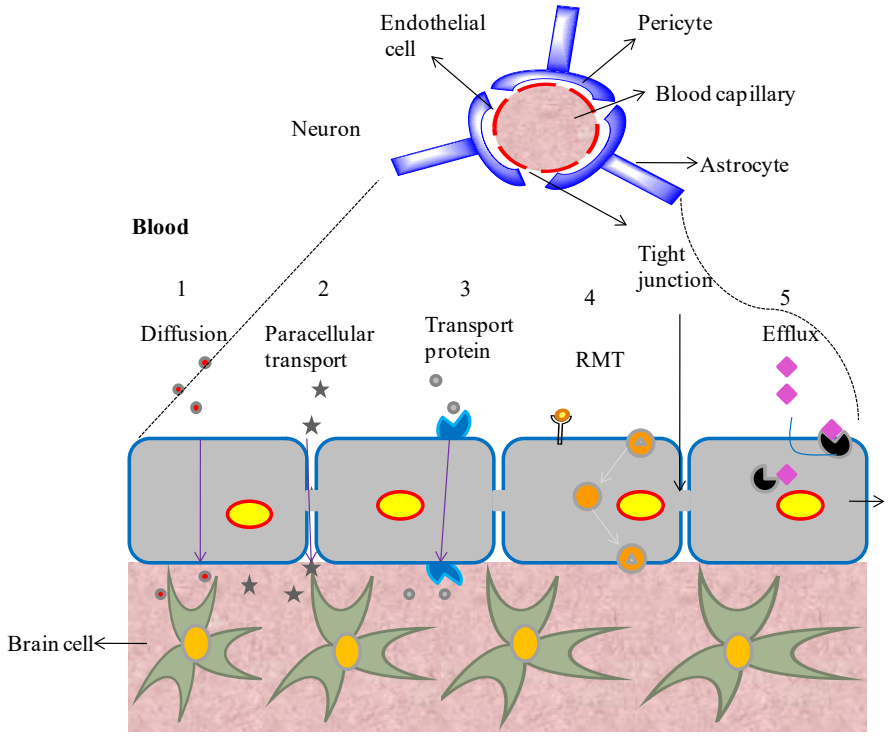

Figure 3 Transport across the BBB through different pathways such as: 1. diffusion; 2. paracellular; 3. transcellular; 4. transport proteins; 5. receptor-mediated transport; and 6. adsorption-mediated transcytosis.

ones that can pass through the transcellular pathway. Many studies have shown that the nanocarrier system increases the permeability of the BBB by partially opening the tight junctions covering different protective layers. Nanoformulation is a potential technique to improve the penetration of drug carriers into the brain [27]. Various small molecules, such as proteins, are used as drug carriers in nano-based formulations. They release drugs via the diffusion pathway or erosion of the matrix [28]. The NPs can overcome the BBB via various transport mechanisms, such as (1) membrane transcytosis, (2) transporter efflux, and (3) passive diffusion or an active transport system that transports the beneficial fragment to the CNS [29]. Liposomes are natural carriers composed of phospholipids in a bilayer structure. These transporter systems have increased interest in drug delivery to the brain as a promising strategy.

In addition, a new minimally invasive technique has been developed to simultaneously measure the temporal VEGF effects on the brain barrier's permeability to solutes and effective solute diffusion coefficients in the rat brain using multiphoton microscopy with a longer excitation wavelength for better penetration of brain tissue. Although it has been demonstrated that increasing cAMP levels can affect the permeability of peripheral microvessels, under various physiological and pathological circumstances, this technique can be used to assess cerebral microvessel permeability and solute diffusion coefficients in brain tissue. To create better drugs, drug carriers, and delivery methods for drugs into the brain, these quantified transport parameters can be used [30]. While other techniques include circulating the blood microbubbles (MB) and ultrasound (US), responses of the cortical cerebral vasculature to BBB opening were observed with varying acoustic peak negative pressure under a two-photon microscope using this sonication and MB contrast agent. Leakage was divided into three categories: fast, sustained, and slow based on a change in extravascular area intensity over time. Fast leakage occurred at all pressures and vessel sizes examined, showing a rapid increase to peak intensity during sonication and a subsequent decrease. All these findings point to a novel strategy for delivering potent therapeutic agents to the brain [31].

Nanoformulation for Nose-To-Brain Delivery

The BBB significantly impedes drug delivery to the brain. Nanotechnologies are the best new tools for finding new solutions to these challenges. The advantages of drug delivery systems that overcome the BBB and act on surrounding tissues are based on their ability to overcome the penetration barrier. In the last two decades, numerous nanoformulations have been developed for various purposes in pharmaceutical and biomedical sciences [15].

Developed nanocarriers such as SLNs, NLCs, liposomes, exosomes, niosomes, phytosomes, and other polymer-based nanocarriers can encapsulate sufficient amounts of therapeutic activity with improved efficiency and permeability, as shown in **(Figure 4)** [15,32].

Polymeric and metallic nanoparticles

Polymeric nanoparticles, especially those containing biodegradable polymers, show greater potential as nasal drug delivery systems. These NPs are colloidal in nature. The drug molecules are incorporated into the colloidal matrix via the

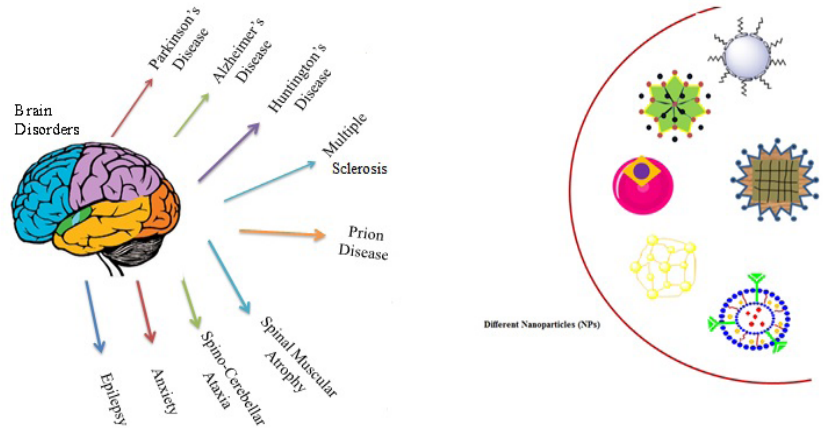

Figure 4 Structure of nanocarriers using different brain disorders.

conjugation or adsorption processes [33]. Polymeric NPs are small carriers with high drug encapsulation and can transport the drug to the target site in a controlled manner. The advantages of such NPs include improved cell uptake and targeted drug delivery to specific sites. Delivery of peptide drugs encapsulated in chitosan (CS) NPs provides better diffusion and improves the efficacy of delivery. Due to its low toxicity, biodegradability, biocompatibility, and mucoadhesive properties, it is an ideal formulatio. Since cilia are responsible for clearing the nasal epithelium, the mucoadhesive property of CS is particularly important for drug delivery through the nose to the brain. Chitosan increases the contact time and diffusion of drugs through the nasal mucosa. Ahmed et al. fabricated 2020 catechin (CH)-loaded CS-PLGA NPs that were used for nasal delivery to the CNS due to their tiny size, shape, and precise surface area and were linked to ligands for navigation. These NPs are under intense research due to their safety profile, biocompatibility, mucoadhesion ability, and enhanced drug availability through nasal delivery. In addition, polyvinyl alcohol nanoparticles (PVA-NPs) are used interchangeably through various modes of drug delivery due to their improved solubility, permeability, and compatibility with tremendous rheological properties in different forms and flexibility. Thymoquinone (THQ)-loaded PLGA nanoparticles were reported for the treatment of epilepsy due to their enhanced bioavailability to the brain. These formulations were prepared using the emulsion-solvent evaporation method. THQ achieves a higher therapeutic effect in the brain while avoiding unnecessary systemic drug delivery and lowering the dose required for therapeutic effect. PLGA NPs loaded with THQ enable the distribution of the bioactive drug in the brain and blood regions and improved pharmacokinetic profile.

Moreover, metallic nanoparticles have the potential to be used in the treatment of CNS disorders due to their unique physicochemical properties and dual role of therapeutic and diagnostic nature. These NPs were synthesized and modified in terms of shape and size, allowing conjugation of various surface ligands, which is helpful in targeted drug delivery for CNS disorders. According to the study, gold (Au) nanoparticles were used to treat Alzheimer's disease by modulating the fibrils with a microwave exposer. In addition, prepared AuNPs with transferrin were used as a targeting component to steadily increase the delivery of encapsulated drugs. For the healing of the AD, Yang et al. developed an H2O2-reactive preparation for the sustained release of mesoporous silica nanoparticles capped with gold metal (MSN-CQ-AuNPs) for the targeted delivery of clioquinol (CQ). The importance of polymeric and metallic nanoparticles as versatile carriers for CNS disorders is shown in **Table 1**.

Polymeric Micelles (PMs)

PMs are amphiphilic, circular nanostructures that form in an aqueous medium from a hydrophobic, self-assembled core and a hydrophilic shell. These hydrophobic cores form through hydrophobic interaction as well as other interactions such as electrostatic interaction and stereocomplexation. PMs have several advantages, including the ability to increase stability and improve bioavailability; improve solubility of hydrophobic drugs, the ability to overcome the P-glycoprotein (P-gp) efflux barrier, and excellent entrainment efficiency. p-gp is a transporter protein that prevents numerous drugs from reaching the CNS, intestine, and tumors. However, certain drawbacks have also been observed with such systems, such as the formation of bulky aggregates that are outside the apparent ideal size range for drug delivery systems, and the need for stability in aqueous dispersion, which can lead to phase separation, etc.. Pokharkar et al. used the solvent evaporation method to prepare a mixer of lurasidone HCL PMs. Thirty-two factorial designs were used to study the effect of excipients on micelle size and entrapment efficiency. By increasing the penetration and improving the residence time on the barrier surface, it was demonstrated that this PM mixture can overcome various barriers such as the BBB and poor solubility problems. Moreover, mixed micelles ensure that the drug is soluble in water, has a stable thermodynamic state, and has a greater therapeutic effect than other novel DDS systems such as lipid carriers, solid dispersions, nanocrystals, etc. In previous studies, rotigotine-loaded polymeric micelles were loaded into a thermosensitive gel and administered into the brain via the nose for the treatment of Parkinson's disease. The bioavailability of the drug is increased, the duration of the drug's residence in the brain is extended as well, and the concentration of the drug in the brain is increased. ROT-loaded micelles were optimized in terms

Table 1: Potential applications of nanocarriers for nose-to-brain delivery.

Disease	Therapeutic Agents	Nanocarriers	Advantages	Ref.
Alzheimer's Disease	Thymoquinone, a-Mangostin, Curcumine	PLGA nanoparticles, transferin liposome, nanoemulsion	Brain targeting ability increased, enhanced bioavailability, entrapment efficiency increased, controlled drug release, and protection from enzymatic degradation	[43–45]
Parkinson's Disease	Reveratrol, Levodopa, Levodopa + Carbidopa, Selegiline	Nanoemulsion, chlorotoxin modified liposome, nanoemulsion	Better targeting efficiency, better therapeutic effect, increased bioavailability	[46–49]
Glioblastoma	Doxorubicin, melatonin	PVA nanogel nanoparticle	Site-specific targeting, increased MLT concentration in the brain	[49,50]
Schizopherenia	Risperidone	Chitosan nanoparticle	Bio-efficacy enhancement	[51]
Prion's disease	Pomegranate seed oil	nanoemulsion, PEGylated nanoparticles	Highly neuroprotective effect, higher uptake by the brain	[36,52]

of particle size (88.62± 1.47 nm), entrapment efficiency (93.5%), and drug loading ability (19.9%).

Nanogel

Nanogels are three-dimensional polymer networks with nanoscale hydrogel structures. Due to its high water-absorption capacity, this polymeric gel swells in an aqueous medium. They have a large surface area and desirable properties such as biodegradability, increased permeability, and high drug loading due to their hydrophilic nature for brain delivery. To explore the potential of nanogels as a delivery system, nanogels loaded with venlafaxine were prepared using solvent evaporation techniques followed by ultrasonic treatment. The nanogel showed faster onset of action with controlled release. The formulation of such nanogels showed improved stability with particle size and zeta potential of 150 nm and −8.08 mV, respectively, and approximately 88% encapsulation of the drug. In addition, in vitro and ex vivo tests with the venlafaxine-loaded nanogel showed controlled release and improved permeation rate to the brain. This nanogel is mainly used for the treatment of depression. Similarly, Khan et al. developed a doxorubicin-loaded pH-responsive PVA nanogel for the targeted treatment of tumor cells. This formulation consists of disulfide and a surface modified with cyclo-RGD peptide. The drug delivery systems were found to be inactive under normal biological conditions and only allow release of the drug at the tumor site when the pH changes to allow effective targeting. It was also found that the negative effects of the surface-modified nanogel were reduced. Seok et al. prepared polysaccharide nanoparticles containing cyclodextrin and poly(-amino ester) for doxorubicin and insulin to act in the brain. In an in vitro BBB model, these cationic nanogels were shown to significantly improve BBB permeability. The nanogel was developed for the delivery of triphosphorylated nucleoside reverse transcriptase inhibitors (TPNRTIs) to the brain for HIV treatment. The nanogels were found to deliver the nucleic acid to the desired site and reduce the adverse side effects and neurotoxicity of the drug. Azadi et al. developed a nanogel loaded with methotrexate for the treatment of brain tumors. Chitosan, sodium tripolyphosphate, and polysorbate 80 were included in the nanogel formulation to provide a site-specific effect. The research showed an exceptional response as a candidate delivery system. Nanogel research may pave the way for a useful tool for brain delivery compared to other new delivery systems.

Dendrimer

Dendrimers are monodisperse, extremely branched, and symmetric macromolecules. These macromolecules are densely packed and improve the loading capacity and enable multi functionalization of the surface. The nano-sized dendrimers are the most suitable tools for targeting in the brain. In this way, Lu et al. developed an arsenic trioxide-loaded RGDPEG-modified polyamidoamine (PAMAM) dendrimer for targeting tumor cells in the brain. They observed reduced cytotoxicity due to peripheral surface modification. The therapeutic efficacy and pharmacokinetic studies of the drug revealed that the release of the drug increases over a longer period of time. Gothwal et al. developed a rivastigmine-loaded lactoferrin-modified polyamidoamine dendrimer to improve brain memory and treat neurodegenerative disorders. Applications of dendrimers as delivery systems for drugs intended for the brain have been reported.

Nanoemulsion/Microemulsion (Emulsions)

Emulsions are heterogeneous biphasic liquid systems with dispersed phases such as water in oil (w/o) or oil in water (o/w). These NEs with an aqueous liquid phase are appropriate for the delivery of hydrophilic as well as lipophilic drugs. The reason for this is the presence of the liquid phase. At the molecular level, this formulation is generally transparent, optically isotropic, homogeneous, or mixed. The corresponding substances, such as surfactants or co-surfactants, support the mechanism of action of NEs via RMT. NEs are formed when a force is applied. Moreover, the small size of NEs (200 nm) makes them a potential transport system, and their biocompatible and biodegradable nature makes them useful for targeting in the brain. Ruby et al. investigated the potential of memantine-loaded NEs for intranasal drug delivery via the BBB for the treatment of AD. The particle size of memantine-loaded NE was ˜11 nm and in vitro studies showed cell viability of 80% of drug release in simulated nasal fluid and 98% demonstrated potential antioxidant properties, which have been shown to be a good carrier system for intranasal delivery to the brain. Further, asenapine maleate nanoemulsion (ASP) was investigated with better outcomes. It was found to improve nasomucosal adhesion, drug efficacy, and locomotor activity. The importance of zolmitriptan (ZT) nanoemulsion for the treatment of migraine was also reported. This formulation increases the residence time and zeta potential while having no effect on the

size of the globules. The permeability coefficients of all tested formulations were observed higher than those of zolmitriptan solution through the nasal mucosa. Thus, it can be concluded that the developed formulation for intranasal delivery of zolmitriptan is a successful and safe tool for targeting in the brain.

Microemulsions have the potential to be used as a delivery system for the treatment of brain disorders. They are thermodynamically stable and improve brain targeting, drug absorption, and drug entry kinetics due to their bead size and lipophilic nature. They also have low viscosity. It was reported that donepezil (DPZ) ME is exceptionally developed for nasal delivery to the brain. It contains a reversible acetylcholinesterase inhibitor used to treat mild to moderate AD. A hyperbolic kinetic model is used in the ME, which ensures that the drug is released over a longer period of time. This is clear from the results of the in vitro release study of DPZ, and the results of the ex vivo permeation characteristics affirmed that the greatest permeability took place within the first four hours. Diazepam microemulsions were developed by phase separation method and optimized by Box–Behnken design. The pharmacokinetic and pharmacodynamic efficacy of the optimized MEs was evaluated. The parameters Cmax, Tmax, and AUC were accurately determined in brain tissue and plasma. It was found that microemulsions loaded with nasal diazepam were very capable of non-invasive delivery and had fewer side effects. The potential of rivastigmine (RHT)-loaded mucoadhesive MEs was developed for the dementia. Due to the hydrophilic nature of RHT, it is more difficult to target it to the brain because the molecule must cross the BBB and cell membrane. The BBB is a biological lipid membrane that acts as a barrier to the permeability of hydrophilic drugs and requires frequent oral administration to achieve therapeutic targets. RHT-loaded MEs increase brain uptake and bioavailability of RHT, which likely maximizes therapeutic effects while reducing dosing frequency. In vivo pharmacokinetic parameters also showed that intranasal administration of these MEs resulted in higher brain RHT concentrations compared with the control group. The MEs demonstrated that their system of drug delivery to the brain via the noninvasive intranasal route is highly suitable. This route is one of the largest novel drug delivery systems for brain diseases and was used in the demonstration.

Lipid-Based Nanocarriers

Lipid nanoparticles (LN) are lipidic structures with dimensions ranging from 50 to 1000 nm in a medium of biocompatible solid lipid mixtures. LN are divided into three subclasses: 1. lipid nanoparticles that are solid (SLN); 2. lipid carriers with nanostructures (NLC); and 3. lipid nanoemulsions (LNEs). LNEs with diameters ranging from 200 to 1000 nm were taken up by caveolae-mediated endocytosis. The general advantages of LNs include immediate uptake, no burst effect, and excellent acceptance. Advantages of LN nanoparticles compared to polymeric nanoparticles include drug loading capacity, smaller particle size, no leakage or ejection of drugs due to cargo delivery, and improved long-term stability. The nano size may improve nasal delivery via the brain because they contain protein P-gp efflux transporters that protect the drug molecule from extracellular transport and biological or chemical degradation, but allow the nano-sized molecules to escape. In addition, the bioadhesive nature of nanoparticles allows them to temporarily overcome the barriers of the mucosal epithelium to cross the nasal cavity (due to the use of surfactants in the formulation) and increase transport to the brain. In one study, the QbD approach was used to develop a novel hydrophilic SLN loaded with RHT. The method of homogenization and ultrasonic treatment was used to prepare RHT-SLNs. A high percentage of entrapped SLNs specified increased absorption of RHT. RHT SLNs exhibited better dispersion of the drug than a solution containing the crystalline form of the drug due to their lipophilic properties. This study was also supported by an in vivo evaluation in which nasociliary damage or cell necrosis was indicative of nasal administration.

Solid Lipid Nanocarriers (SLNs)

SLNs are one of the potential new colloidal carriers with bead sizes between 1 and 1000 nm. They have a higher melting point at room temperature. They are more likely to be accepted than other particles due to their lipid content and other versatile properties such as increased loading capacity, prolonged drug release, targeted drug release, and high probability. They are effective promising tools for a wide range of therapeutics for targeting in the brain. Patel et al. (2011) developed an intriguing formulation of risperidone (RSP)-loaded SLNs for the treatment of psychotic disorders. The efficiency of RSP entrapment in the SLNs was 59.65%, the average particle size was 148.0 nm, and the polydispersity index was 0.148, indicating that the SLNs approached a monodisperse stable system according to the in vitro studies. *In vitro* drug release for RS and RSLNs was 95.01% and 25.74%, respectively, in 7 h, indicating sustained drug release from RSP and SLNs compared to RS. After 24 h, RSLNs released 48.90% of the drug. In a recent study, solvent-free buspirone-loaded SLNs were developed for nasal CNS delivery optimized by three factors and a three-stage Box–Behnken design. All parameters studied, such as PDI, PS, and ZP, were within acceptable limits. Compared to BUS -Sol, BUS-SLNs showed more consistent and sustained drug release and better nasal residence. Studies on pharmacokinetics and targeting in the brain revealed that BUS-SLNs had higher drug awareness in the CNS than BUS-Sol.

Liposome-Based Nanocarriers

Liposomes are biodegradable polymers that can be used to transfer a variety of aquaphobic and hydrophilic (water-loving) small entities such as peptides, proteins, and RNAs without altering their base or protecting them from deprivation. The structure of liposome–phospholipid bilayers makes it easy to penetrate the BBB and deliver useful substances to the CNS. They are less toxic and can transport both hydrophilic and lipophilic compounds. On the other hand, liposomes have numerous limitations, such as rapid universal exclusion, rapid metabolism and deprivation of phospholipids, constant matter behind a large cargo space, inability to release drugs in a controlled manner, and the fact that they are very well suited for the uptake of lipophilic compounds. Liposomes are encapsulated by hydrophilic agents in the water core and protect the payload from deprivation. The advantages of liposomes are increased stability, improved biodistribution, and better pharmacokinetic profile. Several studies have developed

liposomal carriers containing temozolomide (TMZ), curcumin, and doxorubicin for the treatment of GBM compared to free agents. The brain-targeted liposome allows only lower doses. Thus, anticancer drug-loaded brain-targeted liposomes appear to be a promising new treatment option for GBM and other brain tumors. The gold-based theranostic liposomes decorated with transferrin and loaded with both drugs provide a versatile and useful platform. The method was used to prepare liposomes with a therapeutic drug (DCX) in the lipophilic bilayer and a therapeutic management (AuGSH) in the core. They were evaluated on a variety of parameters. Both nanoformulations achieved drug loading of about 70%. Both the specific and non-specific nanoformulations had slow and sustained drug release. Due to active transport via transferrin receptor-mediated endocytosis, transferrin-targeted gold liposomes had significantly higher transferrin levels of DCX (P0.0005) AuGSH in the brain than marketed Docel TM and non-targeted formulations. Transferosomes, composed of phospholipid bilayers and membrane-integrated edge catalysts, confer increased elasticity to the sacs, allowing them to travel across membranes to tiny fenestrations. Niosomes are composed of free polyoxyethylene fatty acids and cholesterol and have a large central core that can transport a large amount of active constituents. The cubic systems are composed of lipid bilayer structures and polymeric nonionic surfactants, with the exact ratio of phospholipids and surfactants determining the shape.

Nanostructure Lipid Nanocarriers (NLC)

Solid lipids mixed with liquid oil make up nanostructured lipid carriers, or NLCs. This combination increases residence time in the nasal cavity and leads to the formation of a less ordered lipid matrix with improved drug loading efficiency. Due to their rapid brain uptake, inhibition of P-gp-mediated drug efflux, controlled and sustained drug release, presence of physiological lipids, biocompatibility, biodegradability, long-term storage stability, and lower toxicity, NLCs have drawn a lot of attention for brain targeting.

Carbon Nanomaterials Used for Brain Delivery

A variety of carbon-based structures are included in the carbon-family nanomaterials, including two-dimensional graphene, nanodiamonds, single- and multiwalled carbon nanotubes (CNTs), fullerene in zero dimensions, and carbon dots (NDs). In order to deliver drugs to the brain, various structures are used as carriers. These structures often have advantageous mechanical, electrical, and optical properties. They have a number of benefits, including bioavailability, low toxicity, a large surface area, an incredibly small size even to cross the blood–brain barrier, and the existence of functionalizable surfaces. The use of carbon-based nanostructures in biomedicine is growing as a result of recent advances in nanotechnology.

Carbon Nanotubes

Carbon is hydrophobic by nature, forming tubular structures with a large surface area and high penetrating capacity. Their hydrophobicity provides a better route for drug delivery and improved penetration into biological membranes. They have unique physicochemical properties that make them potential targets for brain diseases. Multiple molecules can also be conjugated to their surface. They are an excellent drug delivery candidate for the brain because of all of these characteristics. Carbon-family nanomaterials include zero-dimensional carbon allotrope and dots, 1D carbon nanotube (CNT), 2D grapheme sheets, and nanodiamonds (NDs). The fullerene has a cage-like structure with clathrin-coated vesicles in which hexagons and pentagons are arranged. The sp2 hybridized carbon atom in fullerene's structure produces angle strain when bent, and these properties improve fullerene's biological activities. Graphene and all its derivatives play an important role in the brain and neurons.

Carbon Dots

Carbon dots are ideal for drug delivery to the brain because of their ability to form covalent conjugations with large molecules and because they are small. Carbon dots are better able to bind to receptors and penetrate cells. The nontoxic properties and surface nature of nanodiamonds make them ideal for targeted drug delivery. They are capable of binding to both organic and inorganic molecules. Although carbon dots have limited ability to overcome the BBB, they can do so with some modifications. They absorb ultraviolet light and transmit traces of visible light.

Fullerene

Fullerene is a graphitic carbon molecule with a zero-dimensional allotropic structure. In 1985 it was discovered by Harry Kroto. Buckminster Fuller was a famous architect. It is also known as buckyballs or fullerenes. The fullerene allotropes of carbon include C60, C70, C80, and C94. The surface functionalization is easy because the carbon atoms of fullerene interact with other molecular species with their own tendency. The partial solubility and agglomeration in the water medium were obstacles in biomedical applications. The problem is solved by changing the surface of the fullerenes. Functionalized fullerenes are useful as drug delivery nanocarriers. Chemotherapeutic agents can be loaded into fullerene, temozolomide, procarbazine, carmustine, and lomustine, and they play important roles against brain disorders. Neuroprotective properties of fullerene have been discovered, promising better diagnosis of neurological diseases. Fullerene increases locomotor activity and dopamine and serotonin turnover inside the brain after a single administration into the lateral ventricles. However, due to fullerene's poor BBB permeability, such activities are prohibited in intravenous injection.

Graphene-Based Brain Targeting

Graphenes are carbon-based nanomaterials in which each carbon atom is sp2 hybridized. Graphene is the first two-dimensional crystal of carbon atoms in which the layers are arranged alternately. The stacking method, which does not require surface functionalization, can be used to conjugate drug molecules onto graphene surfaces. Graphene derivatives have been introduced which have better properties than pure graphene. The low toxicity of grapheme and its adaptable physicochemical properties make it ideal for biomedical applications, especially for drug delivery. Very thin sheets of graphene oxide (s-GO) are used to modify neuronal synapses. The graphene oxide flakes possess the excellent

property of decreasing the availability of glutamate; thus, acting as an important excitatory neurotransmitter and mediating neuronal brain development and synapse maintenance. These developed s-GO sheets show excellent potential to become a specific modulator of synaptic transmission.

Future Prospects

Many CNS disorders go untreated because nanoparticles cause toxicity in human organs. Preclinical or early-stage clinical trials fail because the work is incomplete or discontinued, which is the first reason for the failure of brain disease treatment. Apart from this, there is currently no specified equipment or standard procedures in the world for the production of novel delivery systems. Researchers and scientists are currently working on this project. In addition, various novel nanocarriers are being developed using different methods, and we hope that these novel carrier systems will be successful in treating brain disorders in the future.

Conclusions

Targeting drugs to the brain is always a major challenge because of the complex structure and multiple barriers in the CNS. The presence of the BBB in the brain contributes to the protection against the penetration of external particles such as dust particles, bacterial and viral particles, as well as the restriction of the therapeutic agent to transport into the brain. Novel delivery systems such as microemulsions, nanoemulsions, polymeric nanoparticles, polymeric micelles, lipid-based nanocarriers, carbon nanotube SLNs, liposomes, and transferosomes of such nanocarriers are potential tools for solving brain disorder problems. Researchers and scientists are still working in this field. All these formulations are expected to be the safest, most stable, mucoadhesive, bioavailable, biocompatible, and profitable carrier systems for nasal delivery of CNS drugs. Due to the small size and pliability of nanoparticles, the biomedical sector has shown increased interest in these delivery systems over the past two years.

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