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REVIEW ARTICLE

Chemotherapeutic Nano Formulations in Innovative Approach in Nose to Brain Delivery

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ABSTRACT
Brain delivery has gained attention in recent years as a new approach that bypasses the need to cross the blood-brain barrier and provides inexpensive access to brain diagnosis and treatment. Due to the unique structural features of the nasal cavity, intranasally administered drugs are delivered directly to the central nervous system. The most important advantage of this method is that it crosses the blood-brain barrier around the brain and prevents the entry of foreign substances into the central nervous system. Problems related to intranasal drug delivery are mainly due to the small volume of the nasal cavity and poor absorption of drugs in the nasal mucosa. These complications can be minimized by using properly designed drug carriers. The main characteristics that determine the effectiveness of effective drug delivery include delivery to the nasal olfactory region, prolonged retention in the nasal mucosa, reduced drug penetration in the nasal epithelium, and increased intranasal drug exchange. What is important in this research is nanoparticles, nasopharyngeal drug delivery, drug delivery to the damaged CNS and facilitating more efficient and targeted drug delivery.
Keywords: *Blood–Brain Barrier, Nose to Brain, Drug Delivery, Nano formulations.*

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INTRODUCTION

Improving the prognosis of central nervous system (CNS) diseases such as Parkinson's disease (PD), Alzheimer's disease (AD) and brain tumors is a more difficult challenge than diseases affecting other organs [1,2,3]. It has been reported that 90% of new CNS drugs prescribed are not approved by the US Food and Drug Administration (FDA) [4]. The existence of a complex blood-brain barrier (BBB) that limits the penetration of drugs into the CNS region is a major obstacle to the development of CNS therapies [5]. Furthermore, non-targeted delivery of diagnostic or therapeutic agents can cause significant damage to neurons and glial cells. Therefore, there is an urgent need for new delivery beds with therapeutic agents for the treatment of neurological disorders [6]. The human brain is one of the most complex and important organs that governs the most important functions of the human body, including voluntary movement, hormone secretion, organ function, and memory encoding. The human brain playing such a dangerous role is protected from inside and outside. Externally, the brain is protected by the skull and various membrane layers that act as shock absorbers, but internally it is mainly protected by the cerebrospinal fluid (CSF), the blood-CSF barrier, and the blood-brain barrier (BBB). . It protects the brain against infection, toxins and any physical damage [7]. Normally, all the above barriers are intact and protect the brain from all physical and chemical damage. However, it occurs in the presence of neurological diseases or other conditions involving the central nervous system (CNS), where there are chemicals that must be delivered to the brain [8]. Brain delivery has received attention in recent years as a novel approach that eliminates the need to cross the BBB and provides inexpensive access to the brain for diagnostic and therapeutic procedures. Some recent studies have reported the involvement of the intranasal route to deliver various hydrophilic, lipophilic and high molecular weight peptide/protein molecules through the nasal cavity directly to the brain [9,10]. Several advantages of the naso-brain route

have been proposed, including discretionary administration, increased patient tolerance, rapid onset of action, less systemic drug exposure, minimal side effects, and brain bioavailability. The mechanism by which the nose reaches the brain is still not understood. Some studies show that the nervous system that connects the nasal cavity to the brain transmits the nasal cavity to the CNS. Chemicals in the nasal cavity are thought to reach our brain through the axons of the olfactory nerve and the olfactory bulb. Thus, the trigeminal and olfactory systems are responsible for the transport of chemicals from the nasal passages to the olfactory bulb, frontal lobe, brain, and cerebrum [10,11].

Blood Brain Barrier (BBB):

The blood-brain barrier (BBB) consists of three layers: capillary pericytes, endothelium, and astrocyte foot processes [12]. The specialized endothelial cells of the BBB are fenestrated, have extensive tight junctions that severely limit cell permeability, and have few pinocytic vesicles that reduce the uptake of extracellular substances [13]. Therefore, the transport of the drug is blocked and only a small amount of the drug can reach the brain tissue. A therapeutic agent that is effective in vitro may not be active in vivo. Drug delivery to the brain is always a major challenge when existing treatments are not optimized [14]. Small lipophilic molecules with molecular weights less than 400 Da readily diffuse across the BBB, while larger or hydrophilic molecules do so due to specific mechanisms such as gating channels, protein and/or receptor binding, and energetics. It is difficult to depend on ATP. It has been shown to require support [15]. Two main approaches are used to deliver drugs to the brain: the molecular approach and the polymer carrier approach. In the molecular approach, drugs are delivered locally to brain cells and then activate enzymes that target the cells. However, the limited availability of such drugs and their associated metabolic pathways limit the applicability of this approach. Polymeric carrier approaches use polymeric nanoparticles not only to improve the physicochemical stability of therapeutic agents, but also to facilitate delivery via intravenous and enteral routes or brain device implantation [12].

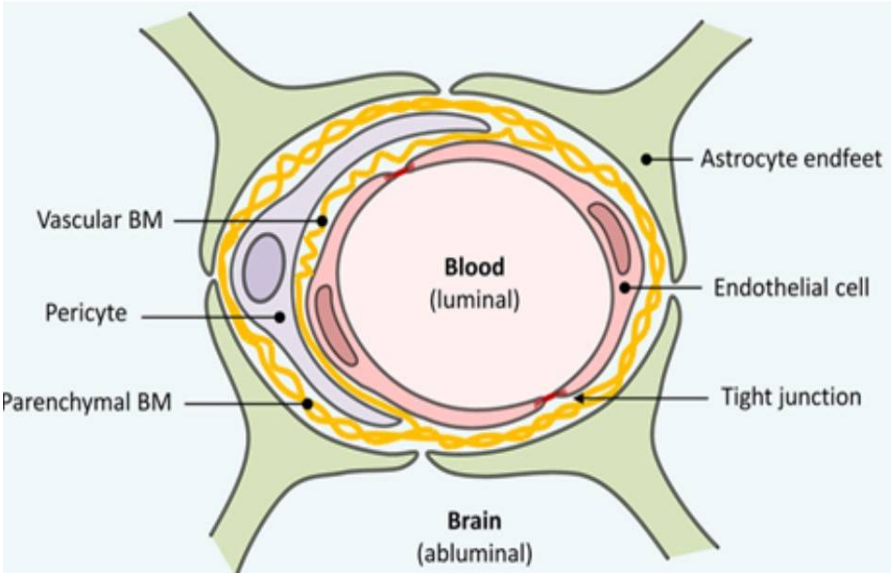

Figure 1: Anatomical Structure of the Blood Brain Barrier (BBB)

Nasal Cavity:

To understand the various mechanisms of drug absorption in the nasal cavity, it is necessary to know the anatomy and cellular structure of the nasal cavity.

Anatomy of Nasal Cavity:

The nasal cavity is 12 to 14 cm long, 5 cm high, has a total volume of 15 to 20 ml, and has a surface area of 150 to 200 cm 2 [16]. There are three types of nasal conchae: upper, middle and lower concha which are responsible for humidifying, filtering and heating the air inhaled through the nose [17,18]. The nasal cavity can be divided into three parts: nasal vestibule, airway, and respiratory tract (Figure 2) [18]. The nasal vestibule is located in the most anterior part of the nasal cavity and contains hair, fat, and sweat glands [19]. The airways are formed primarily by the middle and inferior nasal horns, which serve as airways to the lungs. The olfactory duct is located in the superior turbinate, covers an area of about 10 cm2, and contains olfactory receptors that respond to the sense of smell [18-20]. From the point of view of drug absorption by oral delivery, the respiratory and olfactory mucosa are the preferred sites.

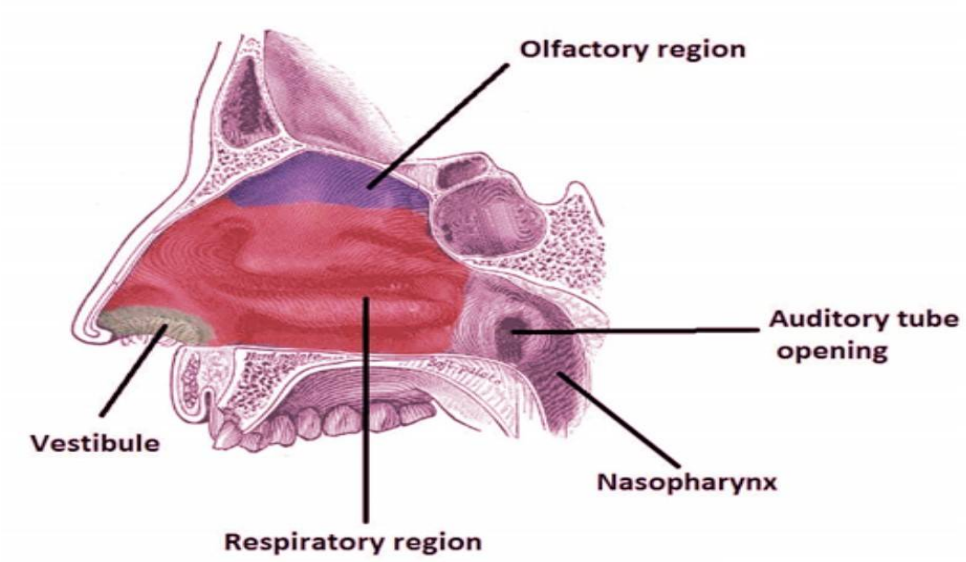

Figure 2: Anatomy of the Nasal Cavity

Respiratory Mucosa:

The airway mucosa comprises 80–90% of the total surface area of the human nasal cavity and is highly vascular, making it an important site for systemic drug absorption. The respiratory mucosa is composed of different types of cells and glands such as basal cells, goblet cells, layers of epithelial cells, and serous glands [21,22]. Basal cells are progenitor cells that can differentiate into other cell types of the epithelium and help anchor epithelial cells and goblet cells to the basal layer [23]. Goblet cells secrete mucus, which is composed of mucins (high molecular weight glycoproteins), water, salts, small groups of proteins, and lipids. Mucus forms a layer on the respiratory epithelium and acts as a first line of defense by trapping inhaled or irritating substances. Accessory cells help move this mucus toward the nasopharynx and cause mucus clearance (MCC). Serous glands secrete mucus and other antimicrobial proteins that are part of innate immunity [24,25].

Route of transmission from nose to brain:

The nasal cavity is classified into two parts by the nasal septum. Each half consists of three fields are nasal vestibule, respiratory tract and olfactory tract. The nasal vestibule is the entrance to the nose. It is covered with squamous epithelium and contains hairs (vibricei) and sebaceous glands [26]. The airways occupy most of the surface of the nose. It is lined with pseudo-stratified columnar epithelium (respiratory epithelium) and bears nasal tentacles. The nasal prongs are vascular structures containing sinuses and erectile tissue that humidifies and warms incoming air and causes venous stasis. The plantar area is located on the roof of the nasal cavity and about 7 cm from the nose. The epithelium is lined by connective columnar epithelium (olfactory epithelium) and contains olfactory nerves that cross the BBB and provide direct access to the CNS. Based on clinical studies, several transmission routes from the human nose to the brain have been suggested. Because of fundamental anatomical and physiological differences, evidence from animal studies cannot be easily translated to humans. However, clinical trials have demonstrated nose-to-brain transmission in humans. However, the route has not been confirmed. After inhalation, this material enters the nasal vestibule, where fibers, turbulence, and mucous membranes are exposed to filter particles larger than 12 μm [26]. The material passes through the nasal valves, which are made of nasal tentacles and cartilage, and enters the airways. Every 3 to 7 hours, the nasal cavity fills or fills up, which is caused by the selective autonomic nerve. Aging and increased tissue elasticity can cause temporary collapse of nasal valves [26]. The nasal valve is the smallest cross-sectional area of the nose, so slight changes in this area can affect airflow. This method reduces the amount of material reaching the plant area. However, 45% of drugs can be transported to the factory site using special equipment [27]. The rest of the drug is absorbed in the respiratory region, with the largest nasal area (about 130 cm2) and rich vascular supply [28]. The superior branch of the trigeminal nerve innervates the airway and enters the CNS through the eyelids. The CNS is a relevant target for drug transport [28,29]. Recent studies in the literature have shown that intranasal insulin can reach the extracellular components of the CNS and trigeminal nerve [30]. These findings suggest that intravenously injected macromolecules can cross the BBB and enter the CNS via the trigeminal nerve [31]. After removing the nasal valve, the drug enters the factory zone, the only place where the brain meets the outside world. The olfactory epithelium has been

proposed as a drug absorption site for nose-to-brain transport [32]. The area of the sole of a human foot is between 2 and 10 cm^2. However, the olfactory nerve can reach a wide area [33]. After the drug has passed through the olfactory epithelium, intracellular and intracellular transport occurs along the olfactory nerve. Transport occurs by passive cell diffusion for lipophilic drugs and mediated transport for hydrophilic drugs. Endocytosis and axonal transport play a minor role [32]. Olfactory neurons reach the cribriform plate of the ethmoid bone and the olfactory bulb of the CNS. The factory bulb provides sensory information to the amygdala, orbitofrontal cortex, and hippocampus. In the olfactory bulb, depending on the nature of the drug, it can enter the brain via axonal transmission, passive diffusion, or transporters. The extracellular pathway involves absorption of cerebrospinal fluid (CSF) from the paracellular space of the olfactory mucosa into the lamina propria and through the capillaries.

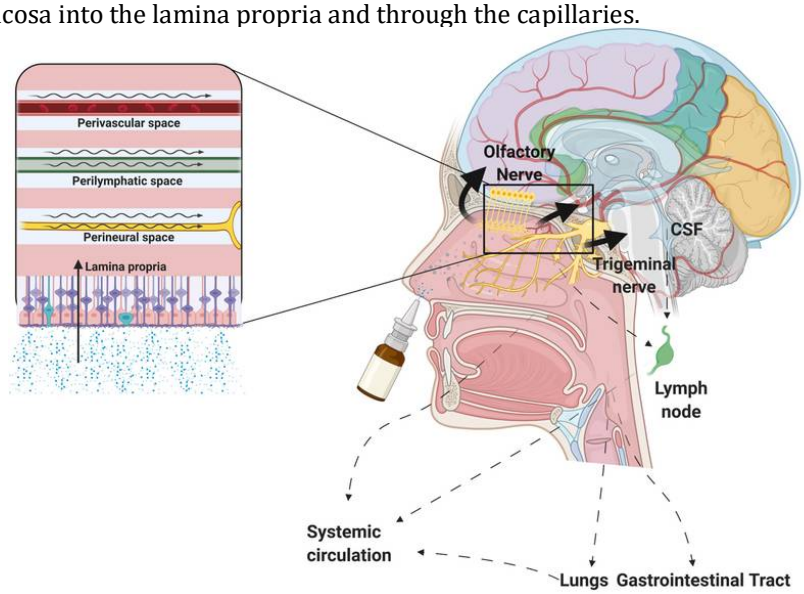

Figure 3: Nose to Brain Drug Delivery

A mass pump in the lamina propria, a superficial layer of loose connective tissue containing nerves, blood vessels, and lymphatic vessels, has also been shown to deliver material to the brain parenchyma [35]. The pulsatile pump mechanism relies on systolic arterial pressure waves passing through blood vessels to help cool and fill the vascular space [28]. The nose has a rich vascular supply from the ethmoid artery arising from the ophthalmic artery and the internal carotid artery [26]. Drugs can enter the CNS through the perivascular spaces of these vessels [28, 29]. Preclinical studies comparing intranasal and arterial injection have shown that substances injected intranasally within 20 minutes have higher concentrations in the perivascular space of the brain, the dura mater and the circle of Willis [26,35]. It is found in high concentrations deep in the neck and in points on the surface of the body. This suggests that CSF may be transported through the nasal cavity and lymphatic vessels. Minimally invasive intranasal medicine includes branches of the carotid, maxillary, ocular, and facial arteries. Vascular endothelial permeability is the major limiting factor of this pathway. In addition, the nasal cavity has its own independence. Parasympathetic transmission to the sphenopalatine ganglion is not possible [35]. Drugs that do not reach the sense of smell are enzymatically broken down and eliminated by mucociliary clearance. A small amount of residual drug may be reabsorbed into the systemic circulation through the respiratory mucosa. It probably doesn't matter [28].

Radiolabeled chemotherapeutic micelles:

Brain tumor cells express up to 500 times more folate receptors than normal cells because of their high nutritional requirements and constant requirement of folate for cell proliferation [36]. Methotrexate, an antimetabolite and anticancer drug, is closely related to folic acid and therefore binds to folate receptors [37]. Therefore, the authors decided to use the intranasal route to deliver radionuclide-conjugated methotrexate to the brain in a microelectric carrier as a treatment for GBM. We believe that formulations administered by the intranasal route may be the answer to unmet needs in the treatment of GBM. Also, we believe that the formula in the present study can be used to combine chemotherapy and radiotherapy to achieve a synergistic effect against cancer for the effective treatment of brain tumors [38].

NANO FORMULATIONS FOR BRAIN DISORDERS:

1] Polymeric Nanogels:

Polymeric nanogels are cross-linked hydrophilic or amphiphilic polymers formed by emulsification and subsequent solvent evaporation [39, 40]. Nanogel formulas are based on the principle of combining ionic and non-ionic polymers to form an interconnected network [41]. Polymeric nanogels are believed to provide better protection than other nanoformulations against drugs introduced during transport [42]. Polymeric nanogels are mainly used to deliver DNA, siRNA and oligonucleotides with an encapsulation efficiency of 40–60%. Nanogels have been shown to deliver oligonucleotides more efficiently to the brain than to the spleen or liver [43].

2] Polymeric Nanosuspensions:

Polymeric nanosuspensions are nanoformulations containing drugs that are stabilized using lipid mixtures or nonionic surfactants. Polymeric nanosuspensions have many advantages, including increased drug delivery, ease of fabrication, improved pharmacokinetics, and the possibility of surface modification [44]. However, polymer nanosuspensions are not considered to be the best formulations for the treatment of chronic diseases, as their preparation is very time-consuming and they have an unstable shelf life [45].

3] Niosomes:

Niosomes are nanoscale vesicles with a stable bilayer structure, composed mainly of nonionic surfactants and cholesterol. Niosomes are highly biocompatible and biodegradable [46]. They exhibit high chemical stability, long shelf life, low toxicity and low production cost. Niosomes can encapsulate lipophilic or hydrophilic drugs and deliver drug molecules in a sustained and/or controlled manner [47,48]. Niosomes have been reported to alter the organ distribution and metabolic stability of drugs [49]. Surface modification of niosomes has been shown to enhance the target specificity of cancer cell delivery systems. For example, modification of temozolomide-loaded niosomes with a targeting peptide, chlorotoxin, significantly increased the efficacy of temozolomide in targeting gliomas [50]. In one study, surface-modified niosomes containing boranzapine (an atypical antipsychotic) showed a 3-fold increase in the brain concentration of boranzapine compared to an intranasal solution of the drug [51]. To provide a novel pharmacological approach to ameliorate PD induced by subchronic MPTP administration in C57BL-6J mice, our research group developed a non-invasive intravenous delivery system consisting of chitosan-pentamidine-coated niosomes (inPentasomes). Studies have shown that the ability of pentasomes to inhibit the activity of glial-derived S100B rescues dopaminergic neuron loss and reduces the severity of neuroinflammation in the substantia nigra pathway, thereby reducing motor behavior in Parkinson's disease showed significant improvement [52]. Another similar study reported the preparation of pentamidine-coated drug-free cytosanglutamate niosomes for intracellular drug delivery using a thin layer hydration method. In this study, special attention was paid to observe the interaction of drug-free niosomes and pentamidine with mucin. Niosomal formulations have been shown to effectively deliver pentamidine or other potential drugs into the brain by intranasal injection [53]. In one study, Nisomes (an anxiolytic and serotonin receptor agonist) topical nasal gel of buspirone hydrochloride was used to overcome the challenges of short half-life (2-3 hours) and low oral bioavailability (4%). It is known to be formulated into formulations. The use of niosomes has been demonstrated to demonstrate the potential for intranasal delivery of buspirone hydrochloride from conventional gel formulations [54].

4] Nanospheres and Nanocapsules:

Nanospheres are solid core polymer matrices produced by microemulsion polymerization, while nanocapsules represent a vesicular system in which a dilute toxic polymer surrounds a drug compartment filled with oil [55,56]. Nanocapsules and nanospheres have the advantages of improving drug stability, facilitating surface modification and preventing systemic degradation. However, there are limitations such as complicated purification and storage and poor drug release pattern [57,58]. Nanocapsules containing indomethacin have been shown to protect hippocampal cultures against inflammation in vitro [59].

5] Silver nanoparticles:

Silver nanoparticles (AgNPs) have been shown to induce cytotoxicity in human skin, lung and fibroblast cells [60,61]. CNS-associated AgNPs have been shown to cross the BBB and accumulate in the brain after inhalation and ingestion [62–64]. Patchin et al observed rapid translocation of 20 nm silver nanoparticles into the olfactory bulb after 6 nm exposure and a slower decline in translocation of 110 nm silver particles [65]. The study reported that a very small amount of AgNPs was absorbed into the blood after intranasal injection, and the blood concentration was significantly higher after AgNO3 delivery, and the silver observed in the blood was due to the absorption of silver ions from the silver nanoparticles [66], for publication. AgNPs have been shown to induce cytotoxicity in neurons in vitro [67]. However, the exact mechanism by which AgNPs induce neurodegeneration is not well understood and this topic deserves further study. In contrast to the above data, the study demonstrated that AgNPs exhibited excellent anti-

inflammatory effects, reduced LPS-induced ROS, nitric oxide and TNFα production, and reduced microglial toxicity to dopaminergic neurons [68]. Therefore, further research is needed to find out how to design the next class of safe silver nanoparticles.

6] Dendrimers:

Dendrimes are a new class of highly branched nanoparticles that have a specific structure of molecular hooks and can target specific cells [69]. Two basic structures have been shown for dendrimers, one with a central core and radial polymeric branches and the other showing only a few branches without a core [70]. The unique structure of dendrites facilitates surface modification through adsorption and covalent bonding, which improves the ability of dendrites to carry various drugs [71,72]. Polyamine amine dendrimers have been shown to be used to create drug delivery systems with the potential to target cellular compartments in vitro and in vivo [73]. In addition, dendrimers can also be used as scaffolds for in vivo delivery of therapeutics and diagnostics.

7] Polymeric Nanoliposomes:

Polymeric nanoliposomes exhibit vesicular structures containing an inner water compartment and an outer layer of a lipid monolayer. The structural design of these nanoliposomes increases their stability and facilitates drug entrapment and escape from the reticuloendothelial system [74]. Although the efficacy of nanoliposomes against brain disorders is controversial, curcumin nanoliposomes have been reported to be particularly active against amyloid aggregates [75].

8] Polymeric Nanomicelles:

Polymeric nanomicelles have a hydrophobic core surrounded by a shell that forms a hydrophilic polymer block [76]. The nanoshell stabilizes and hides the polymeric cell from cellular interactions, and the core can encapsulate up to 30% of hydrophobic drugs [77,78]. Although polymeric nanomicelles are predicted to be effective for delivery of DNA molecules in vitro and in vivo, nanocell-mediated CNS drug delivery remains unclear. PEGylated phospholipid nanomicelles have been shown to abrogate amyloid-coated toxicity in vitro [79]. However, polymeric nanomicelles are not suitable for encapsulating hydrophilic drugs. It also has a shorter lifespan [80].

9] Gold nanoparticles:

Gold nanoparticles (AuNPs) are widely used as nanomaterials for drug delivery and imaging [81]. Studies have shown that AuNPs have low specificity due to the lack of selectivity to distinguish between target and non-target cells [82]. Researchers conjugated AuNPs with cell-targeting ligands to deliver therapeutic agents to target cells or tissues. The surface of AuNPs provides a platform for encapsulating various proteins, peptides, aptamers and antibodies [83]. However, this integrated method is very complex and the characteristic of the system limits its systemic application. In addition, some compounds are not suitable for clinical use due to toxicity due to the use of surfactants such as cetyltrimethylammonium bromide [84]. AuNPs can be used to infect neurons through two main routes: across the BBB and through the olfactory nerve. In this study, researchers successfully delivered multipurpose therapeutic gold iron oxide nanoparticles with miR-100 and antimiR-21 to mouse GBM using a nose-to-brain delivery route. [85]. A study reported the formulation of a transfersome-labeled nanoemulsion loaded with resveratrol and gold nanoparticles for intranasal brain targeting. Brain efficacy of these two nanoformulas was evaluated by investigating memory recovery in albino Wistar rats using water maze test and bioaccumulation study using computed tomography and histopathological examination. It was observed that transfersomes significantly improved behavioral and spatial memory performance in amnesic mice compared to nanoemulsion formulation and pure drug [86]. It has been reported that AUNPs can cause confusion, seizure activity, and impaired judgment after crossing the BBB.

10] Metal nanoparticles:

Metal nanoparticles have been the focus of recent research due to their potential applications in biomedical engineering and science [88]. Metal nanoparticles can be synthesized by combining several structural and surface modifications, opening new horizons for applications in magnetic separation, gene targeting, drug delivery, and especially in diagnostic imaging systems [89-91]. Many advanced modern imaging techniques such as MRI, CT, PET, SERS, and ultrasound require contrast agents to be effective. This need for contrast materials has led to the development of nanoparticles of gold, silver and magnetic iron oxide (Fe3O4) in nano dimensions [92,93,94].

POLYMER NANOPARTICLES:

Polymer-based NPs are probably the most common nanocarriers used for nose-to-brain delivery and are currently at the forefront of novel neuropharmacological therapies [95]. This type of nanocarrier is at the center of clinical research due to its chemical versatility, high drug loading capacity, and ease of surface functionalization with targets [96]. A variety of structures can be obtained using polymers such as NPs, micelles, nanocapsules, and dendrimers as building blocks [97–100]. In addition, drug delivery systems

can also be designed using synthetic and biological polymers. For example, biodegradable and biocompatible poly (caprolactone) (PCL), poly(lactic acid) (PLA), poly(lactic-glycolic acid) (PLGA) and poly(ethylene glycol)-poly (lactic acid-co -glycolic acid) (PEG-PLGA) is commonly used as a synthetic building block. Meanwhile, many biopolymers such as gelatin, pullulan, alginate, sodium hyaluronate, and human serum albumin (HAS) have been investigated. However, chitosan and chitosan derivatives, which have mucosal adhesion and cell penetration properties, are the most widely used polysaccharides in drug delivery systems [101]. Indeed, functionalized nanoparticles have previously been demonstrated for brain delivery, including coating with polymeric surfactants, mucoadhesive polymers, covalent attachment of biorecognition ligands targeting the olfactory region, and surface modification with cell-penetrating peptides [102,10]. The following section summarizes this class of functionalized polymeric nanoparticles and describes recent advances reported in the literature (Table 1).

Table 1: A summary of recent reports on polymeric nanocarriers for brain delivery via the intranasal route [95,96,101,102,103].

Polymer Nanoparticles	Drug	Disease	Particle size(nm)	Functionality	Main findings
Chitosan NP	Midazolam	Status epilepticus	241-381	Mucoadhesion	Superior brain-targeting efficiency
Chitosan-PLGA NP	Ropinirole hydrochloride	Parkinson's disease	468	Mucoadhesion	3.22 fold increase in permeability in sheep nasal mucosa
Lecithin/chitosan NP and PCL nanocapsules	Simvastatin	Glioblastoma	202-258	Mucoadhesion/ mucopenetration	Enhanced bioavailability
PSA NP	Thyrotropin releasing hormone	Suicidal depression	258	Degradable	It is useful for intranasal delivery in laboratory conditions
WGA-PEG-PLA NP	miR132	Alzheimer's	191	WGA active targeting	The bioavailability of genes in the brain increases significantly
OL-PEG-PLGA NP	Urocortin peptide	Parkinson's disease	85-115	OL active targeting	Increase brain absorption and increase neuroprotective effects
Bombesin-PEG-PCLTAT micelles	Camptothecin	Glioma	80	Bombesin/TAT active targeting/ cellpenetration	Improving treatment results in brain tumor bearing mouse models

LIPID-BASED NANOCARRIERS:

Lipid-based nanocarriers are surfactant-stabilized drug delivery systems composed of lipid and aqueous phases. These systems are composed of biocompatible and biodegradable components that have advantages in controlled release, drug protection, drug loading, stability and surface versatility. Lipid-based nanocarriers are specifically incorporated into biological membranes to facilitate nanoscale droplet fragmentation in the nasal mucosa and prolong residence time, thereby enhancing drug delivery to the brain after IN administration. It has great potential to improve fertility. [104]. Therefore, various lipid-based nanocarriers such as liposomes, nanoemulsions, lipid nanocapsules (LNC), solid lipid nanoparticles (SLN) and nanostructured lipid carriers can improve the bioavailability of some drugs through the nasopharynx. It has been proven that it can be used effectively. NLCs are due to their small size and the presence of emulsifiers. Liposomes and SLNs are the oldest studies for nose-to-brain delivery, and several NLC formulations have been reported in recent years. In addition, lipid-based nanocarriers modified with mucoadhesives or incorporated into adhesive-based formulations show promising results, improving contact with the nasal mucosa and increasing intranasal persistence. It is suggested that the passing speed will increase. The latest types of adsorbents for lipid-based nanocarriers reported in the literature are summarized in Table 2 and discussed in the following sections [105,106,107].

Table 2: A summary of recent reports describing the use of lipid-based engineered nanocarriers for intracerebral drug delivery via intranasal injection [104-107]

Lipid Nanoparticles	Drug	Disease	Particle size (nm)	Lipid excipients/ Emulsifiers/Other excipients	Main findings
Chitosan-coated NLC	Almotriptan malate	Migraine	255	Compritol®, Labrafil® / Tween® 80, Lauroglycol. L Chitosan	Increased Cmax of the drug in the brain
Multilamellar vesicles	Tramadol	Acute and chronic pain	167	Phospholipon® 90G/ Propylene glycol/Vitamin E	Advanced bioavailability
Chitosan-coated niosomes	Pentamidine	Parkinson's disease	300	DCP/Cholesterol/ Tween® 20/Chitosan	It is effective in mouse models of Parkinson's disease
NLC	Sumatriptan	Migraine headache	101	Stearic acid/ Cholesterol/ Triolein/ Brij® 35	3-fold increase in absolute brain bioavailability
NLC	Ketoconazole	Meningoencephalitis	102	Compritol® 888 ATO/ Miglyol 812 N/ Solutol® HS 15/ Tween® 80	Advanced brain targeting
NLC	Nicergoline	Dementia	111	Precirol® ATO 5/Sesame oil/ Tween® 80	Brain concentrations increased 1.60- and 4.57-fold when the same formulation was administered IV and IN, respectively.
NLC	Pioglitazone	Alzheimer's disease	211	Capmul MCM and tripalmitin/ Tween® 80/ Pluronic F68/ Stearyl amine	Improving drug permeability across the nasal mucosa. Increasing the concentration of the drug in the brain
LNC	Nimodipine	Acute subarachnoid haemorrhage	36	Labrafac/Lipoid® S75, Solutol® HS15.	Similar drug brain targeting with low blood drug concentration
Cubosomal mucoadhesive in situ nasal gel	Donepezil	Alzheimer's disease	137-231	Glycerol mono-oleate/ surfactant Poloxamer 407/ Gellan gum/ Konjac gum	Advanced bioavailability

INORGANIC NANOPARTICLES:

The versatility of the intranasal route has been studied using inorganic nanoparticles. These systems have different compositions (silver, gold, iron oxide, silicon, graphene, etc) and shapes (rods, prisms, spheres, stars, etc.). They design smart carriers for drug delivery, as their high chemical reactivity allows them to be combined with chemical or biological materials, adding new capabilities for drug delivery, bioimaging, photothermal therapy, and disease diagnosis. The best option for you. And other biomedical targets [108]. Several authors have evaluated different strategies to understand how inorganic nanoparticles are delivered to the brain. For this purpose, studies have been conducted to compare the size and shape of nanoparticles, external stimuli (infrasound, magnetic fields), peptides, etc. Therefore, to better understand the247otentiall applications of this system, the next section will focus on recent studies on the delivery of the most important inorganic NPs via the nasopharyngeal route (Table 3) [109,110].

Table 3: Summary of recent reports describing the use of inorganic NPs to achieve drug accumulation in the brain [108-110]

Carrier composition	Functionalization agent	Drug	Disease	Particle size (nm)	Main findings
CdSe/ZnS Quantum dots	PEG, phosphatidyl ethanolamine	n.r.	-	n.r.	Rapid uptake and axonal transport to the brain. Activation of microglial cells (proinflammatory response)
GNPr and GNS	PEG and D1 peptide	n.r.	Alzheimer	GNPr 78 GNS 47	Higher gold concentration (55 times) in the IN pathway compared to IV
Gold/iron oxide NP	β-cyclodextrin-chitosan (CD-CS) hybrid polymer and peptide PEG-T7	miRNAs and TMZ	Glioblastoma	53	Effective delivery of miRNAs and simultaneous systemic treatment with TMZ significantly improves survival in treated mice.
^{64}Cu-alloyed AuNC	n.r.	n.r.	-	5	Compared to IV administration, IN administration causes less accumulation of 64Cu-AuNC in organs (liver, spleen, lung, kidney, blood, heart). FUSIN improved targeting of brain regions targeted by FUS.
MSN	n.r.	Chrysin and Curcumin	Oxidative CNS disorders	220	pH-Dependent Release of Phytochemicals from MSNPs Nanoparticles with sizes less than 500 nm can be absorbed through olfactory cells

Table 4: Summary of reports describing the use of NC-based formulations to induce drug accumulation in the brain [111,114,116]

Drug	Disease	Particle size (nm)	Dosage form administered	Production method	Main findings
Breviscapine	Model drug	527	In situ gel formulation based on gellan gum	HPH	Preferential distribution of drugs to brain, cerebellum and OB
Clozapine	Psychosis	NS directly instilled in the nostrils	281	HSH	Increased mucosal permeability and cerebral accumulation
Resveratrol	Model drug	241	In situ gel formulation based on ionic-triggered DGG	Precipitation	Increased absorption in the brain compared to IV injection
Zotepine	Psychosis	330	NS directly instilled in the nostrils	HPH and precipitation	Increased drug accumulation in the brain while the plasma level is lower than the control group
Paeoniflorin	Parkinson's disease	156	NS directly instilled in the nostrils	Precipitation	Increasing mucosal penetration and reference distribution of drugs in the brain

DRUG NANOCRYSTALS:

Fabrication of pharmaceutical nanocrystals (NCs) is one of the most promising strategies for insoluble drug delivery. NCs are essentially crystalline NPs that are formed solely by the drug and stabilized by a surfactant layer [111]. Pharmaceutical NCs are often produced in liquid suspensions, and the final product is called a nanosuspension (NS), where solvent removal by freeze drying or spray drying yields a

solid, redispersible material. When drug particles are concentrated in the nanometer range, the specific surface area exposed to the solvent increases significantly, leading to increased dissolution rate, saturated dissolution, and bioadhesion [112]. NCs were first developed in the early 1990s to increase the bioavailability of water-insoluble drugs, and five NC-based products were approved by the FDA between 2000 and 2005. NCs, either lipid-based NPs or polymeric NPs, have several advantages, including: high drug loading, improved long-term stability, neutral pH-producing organic solvents, and enhanced manufacturing methods. All these aspects make NCs an attractive platform for tissue targeting, suggesting that many NCs have been used to accumulate drugs in specific tissues, including the CNS, via the nasopharyngeal route. When NC is administered orally, it increases drug diffusion across the mucosal barrier and prolongs particle survival and contact time in the mucosa. Most importantly, it has been reported that drug NCs can remain in the body as insoluble drug particles for several days, but this strongly depends on the route of administration, the size and shape of the NCs, and the physical and chemical properties of the drug. do. 115]. Due to the small amount of dispersion in the nasal cavity, NCs dissolve slowly and the particulate drug enters the CNS before dispersion. Table 4 presents a series of reports describing the use of NC-based oral formulations for brain targeting [116].

CONCLUSION

Recently, nasal-to-brain drug delivery has been considered as an alternative to the most common non-lingual delivery routes. Due to the unique structural features of the nasal cavity, oral drugs are delivered directly to the central nervous system. The most important advantage of this method is bypassing the blood-brain barrier around the brain and preventing foreign substances from entering the central nervous system. In addition, selective brain stimulation may circumvent the side effects of drug therapy. Problems related to intranasal drug injection are mainly due to the small volume of the nasal cavity and poor absorption of drugs in the nasal mucosa. These problems can be minimized by using properly designed drug carriers. As potential drug delivery systems, microemulsions offer excellent solubilization properties and the ability to enhance drug penetration across biological membranes.

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