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REVIEW ARTICLE

Comprehensive Review on Nose to Brain Drug Delivery Through Nanocarriers

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ABSTRACT

Complex The central nervous system disorder (CNS disorder) is the second most lethal and disabling disorder in the 21st century in terms of mortality rates. With 1 in 6 people suffering from a neuroailment, the numbers are frequently rising significantly. The transport of neurotherapeutics to the brain was hampered by the two main anatomical barriers, the blood-brain barrier (BBB) and the blood-cerebrospinal fluid barrier (B-CSF-B). The BBB and B-CSF-B must be bypassed in order to effectively treat CNS diseases. Since the Vedic era in India, about 1500 BC, the nose has been used as an entrance point for the administration of medications for illness therapy. Recently, researchers and healthcare professionals have paid a lot of attention to the direct nose-to-brain administration method of delivering neurotherapeutics directly into the brain areas. Neurotherapeutics, both tiny and large compounds, can be quickly transported by olfactory and trigeminal nerve pathways thanks to a unique link between the nose and the brain. Thus, surface modification of nanocarriers, the employment of cutting-edge drug delivery devices, and direct nose-to-brain administration of neurotherapeutics all contribute to opening up new pathways for the development of effective nose-to-brain drug delivery. The goal of the current review, which is titled Nanocarriers for nose-to-brain medication delivery: Mechanism, Technological Advances, Applications, and Regulatory Updates, is to offer a thorough analysis of the literature on this topic. The blood-brain barrier may now be crossed with the use of technological and mechanical techniques. These methods can be used to create medications that are safer and more effective at treating debilitating brain illnesses.

Keywords: *Blood Brain Barrier, Central Nervous System, Nono particulate Drug Carrier, Nanocarriers, vesicular Nanocarrier*

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INTRODUCTION

In recent decades, nasal route has received significant attention for local and systemic delivery. Because of the impermeable nature of the tight endothelium Membrane known as the blood brain barrier, drug delivery to the brain has long been a significant difficulty. Several tight junctions and efflux transporters in the blood brain barrier prohibit -95 percent of chemicals from entering the CNS [1]. The Blood Brain Barrier (BBB) separates the central nervous system (CNS) from the rest of the body, creating a tightly controlled extracellular fluid environment that protects the brain parenchyma from plasma potentially CNS-toxic chemicals. This tight physiological barrier severely restricts medication diffusion into the extracellular space and is regarded as a bottleneck in brain drug research as well as a significant limiting factor for biotechnology-derived 'neurotherapeutics' potential developments and future applications [2]. The BBB can be circumvented by intra - ventricular or intra- cerebral administration. It is necessary to have a second understanding of morphological and physiological characteristics of the nose and their relation to direct nose to brain therapies administration in order to envision possible trials of nose to

brain medication delivery and its applicability in pharmaceutical and biomedical industries. This page will cover nasal anatomy and physiology, as well as the method used to transport Nanocarriers from the nose to the brain and other cellular systems [3].

Blood Brain Barrier

The minimal trans cellular transport occurs in BBB [4], the adult blood brain barrier (BBB) is made up of capillary endothelial cells (ECs) closely coupled with tight junctions (TJs) and adherent junctions (AJs) that restrict paracellular transport [5] and also have a weak pinocytosis activity [6,7]. In addition, the BBB is regulated by closely linked pericytes, perivascular astrocytic end-feet, and microglia [8]. By controlling the migration, proliferation and vascular branching of brain endothelial cells, these distinct cell types play critical roles in BBB initiation and progression. The basement membrane also acts as a structural support for pericytes and endothelial cells. The cell membrane of the astrocyte end-feet is continuous with the basal lamina [9]. With a Trans endothelial electrical resistance (TEER) of roughly 1500 X cm^2, the BBB provides substantial resistance to ion flow, which is 100 times greater than peripheral micro vessels [10]. The Active and passive transport channels can be found in the BBB penetration process [11]. Simple diffusion is an example of a passive transport route that indicates energy-independent processes [12]. The (EPR) enhanced permeability and retention effect is the most common way for medicines to diffuse passively in tumour cells [13]. On the other hand, active transport route includes receptors- and adsorbent endocytosis, as well as carrier-mediated transportation, all of which need adenosine triphosphate hydrolysis (ATP) [14]. In addition, the medication delivered varies depending on the NPs and processes utilization. For example, the carrier-mediated transport systems tiny then stereospecific pores limit to deliver a large-molecular medicines [15]. Instead, most carbon dots (CDs) are ultra-small (1-10 nm) and have a variety of surface functions [16]. Making them ideal for delivering big drug molecules via carrier-mediated transport by covalently conjugating with medicines [17].

Nasal anatomy

Breathing and olfaction are the two primary activities of the nasal cavity. Mucus and hair line the inside, acting as a filter for foreign substances and viruses. Mucociliary clearance (MCC), metabolism, immune activity and sound resonance are all important roles [18] .The nasal cavity is 150 cm^2 [19] in size and holds 15-20 mL of fluid. The nasal septum divides the nasal cavity into two spherical parts, each of which opens as nostrils in front of the face. [20]. each cavity is divided into four sections: the Atrium, nasal vestibule, olfactory region, and respiratory region [21].

Nasal physiology

We breathe in about 12 - 24 time a minute, inhaling approximately 10,000L of air a day of different temperature, humidity, and may contain dust and organisms. The nose performs different functions [22].

1) Olfaction.
2) Sensation.
3) Immunology.
4) Protection.
5) Filtration.
6) Air conditioning.
7) Maintaining air flow dynamics and speech.

TABLE 1. Qualitative morphometric Data for the nasal passages of humans [23]

	Human
Body weight	70 kg
Nasal cavity volume (V)	25 cm^3 cubic
Surface area per unit volume	6.4
Nasal cavity surface area (SA)	160 cm^2
Olfactory epithelium (area , %)	12.5 cm^2 , 8%

TABLE 2. Human nasal epithelium characteristics [24]

Region	**Vascularization**	**Permeability**
Nasal vestibule (0.6 Cm^2)	Low	Least permeable because of the presence of keratinized cells
Atrium	Low	Less permeable as it has small surface area and stratified cells are present anteriorly
Respiratory region (inferior turbinate, middle turbinate, superior turbinate)(130 Cm^2)	Very high	Most permeable region because of large surface area and rich vasculature
Olfactory region(10-20 Cm^2)	High	Direct access to cerebrospinal fluid
Nasopharynx	-	Receives the nasal cavity drainage

NASAL DRUG DELIVERY SYSTEMS

Nasal Drug Delivery Route

The nasal route has gained popularity since it is a non-invasive, direct approach for delivering medications to the brain that cannot be delivered via the oral route. The trigeminal and olfactory nerves have been proved to be safe and effective delivery channels for medicinal medicines to the brain. The trigeminal pathway is another important route for delivering therapeutic medicines to the brain. The ophthalmic and maxillary nerves control the mucosa of the nose and transfer signals from the nasal cavity to the brain. For drug delivery, several drug delivery systems for the brain or nerve cells commonly target these two branches [26]. The trigeminal nerve, which regulates the nasal cavity, runs from the brainstem to the caudal and rostral parts of the brain via the pons [27]. Fig 1. Pathways of Drug Distribution in the Nasal Cavity and CNS, Innervated By trigeminal and olfactory Nerves. Beginning in the olfactory bulb of the CNS, neuronal cells construct an informational pathway to the brain. Progenitor cells, supporting cells, and neuronal cells are the three types of cells that make up the olfactory epithelium. They are connected by strong connections and are located in the nasal cavity [28]. Because of the constant mobility between neural cells and basal cells, the ability to transfer drugs to the brain was improved [29]. Mucus-secreting glands, blood arteries, a branch of the trigeminal nerve, and an olfactory axon make up the lamina propria [30]. The olfactory bulb is responsible for delivering medication directly to the Amygdala , piriform cortex and hypothalamus through the nose [31]. Antidepressant treatment that involves direct intranasal medicine delivery to the brain has indeed been proposed. It would improve targeting by breaking through the BBB bottleneck. The availability of enzymes breaks down with in nasal pharmaceutical delivery route, rapid drug clearance, limited dosage volume, and rapid drug [32].

TABLE 3. Advantages and limitations of nose to brain drug delivery system [33]

Advantage	Limitation
There is no need to alter the therapy.	With increasing molecule size, delivery is likely to diminish.
Systemic exposure is reduced.	Irritation or injury to the mucosa may result.
Noninvasive, easy to administer	Nasal congestion might make it difficult to deliver.
The rate of drug degradation and metabolism is reduced to a minimum.	Delivery to various brain tissues is unknown.
May bypass the Blood Brain Barrier (BBB).	There is a lack of empirical research on the absorption, use, and metabolism of the central nervous system.

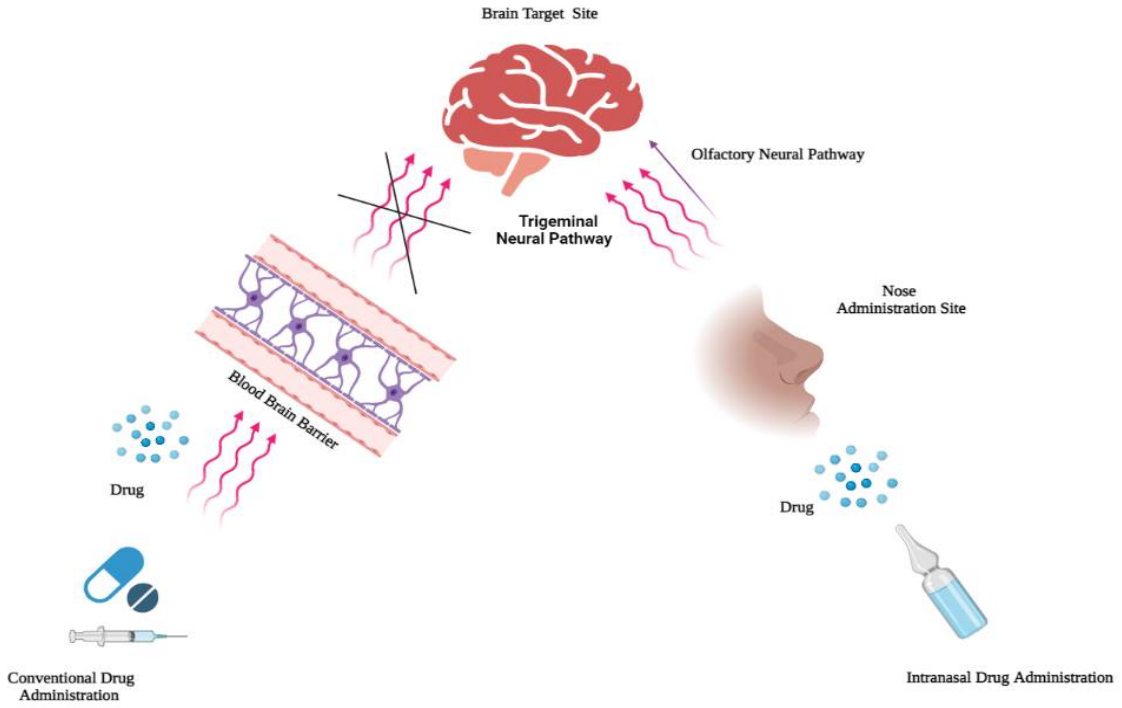

Fig 1. Pathways of Drug Distribution in the Nasal Cavity and CNS, Innervated By trigeminal and olfactory Nerves.

Mechanism of Nasal Drug absorption -

Several ways for demonstrating drug trans nasal absorption into the brain have been presented. On the other hand, the paracellular and transcellular pathways, are primarily considered.

Paracellular/extracellular mechanism - is a passive and slow water transport pathway that passes through the interstitial adherence junctions or open clefts of the nasal mucosa's epithelium [34, 35]. The paracellular mode of drug transport from the nose to the brain involves two extracellular pathways, one across the olfactory neurons and the other over the trigeminal nerve [36]. Therapeutics can penetrate other brain regions via simple diffusion after approaching the olfactory region or the trigeminal region, which is aided by a circulatory pulsation-driven perivascular pump. Molecular weight and Intranasal absorption of polar substances have an inverse log-log association, according to a paracellular process. Drugs with a molecular weight larger than 1000 Daltons have poor bioavailability, regardless of their lipophilicity [37]. The use of agents like chitosan to modify the tight connections between nasal epithelial cells in order to facilitate trans nasal medication absorption has also been tested [38].

Transcellular/intracellular mechanism - transports endocytosis, passive diffusion, or fluid phase endocytosis through a lipoidal pathway [39,40]. The trans nasal uptake of both small and big lipophilic substances is explained by this process. As a result, transcellular drug absorption is mostly determined by the drug compound's lipophilic nature, with highly lipophilic medicines likely to have accelerated trans nasal uptake. The transcellular method, on the other hand, is a slow process that takes hours for nasally delivered medicines to reach the olfactory region via intercellular axonal transport mediated by mechanisms such as endocytosis within olfactory neurons [34, 41, 42, 43].

TABLE 4. Considerations in efficient nose to brain drug delivery [44]

Physiochemical	Formulation	Physiological	Experimental
Molecular size.	PH.	Nasal blood flow.	Pattern of nasal deposition.
Molecular weight.	Viscosity.	Site and area of nose exposed.	Drug administration technique.
Partition coefficient.	Osmolality.	Nasal secretion and cycle.	Head position
Lipophilicity.	Type of nasal dosage form.	Mucociliary clearance.	Angle of spraying.
Solubility and dissolution rate.	Physical form of formulation.	Transporters and efflux system.	Volume of administration.
Chemical form of drug.	Pharmaceutical excipients.	Physical state of nasal mucosa.	Inhalation or sniffing.
Polymorphism.		Pathological conditions.	Frequency of administration.

Nanocarriers For Direct Nose to Brain Drug Delivery

The Blood Brain Barrier (BBB), which acts as a barrier in the passage of drug molecules, would limit the delivery of numerous therapeutics for the treatment of various brain ailments. As a result, intranasal drug delivery via the olfactory and trigeminal neural pathways, which bypasses the BBB, has eliminated the problem of traditional brain drug delivery. Different nano-mediated carriers, such as polymeric Nanoparticles, lipid Nanocarriers, inorganic Nanoparticles, and nano-Drug derivatives, have gotten a lot of attention in the research community in recent years. They have been successfully deployed to the brain intranasally due to several advantages and small vesicular size, resulting in improved bioavailability and thus maximum therapeutic potential [45]. Various Nanocarriers for the nose - to - brain drug delivery has been further discussed.

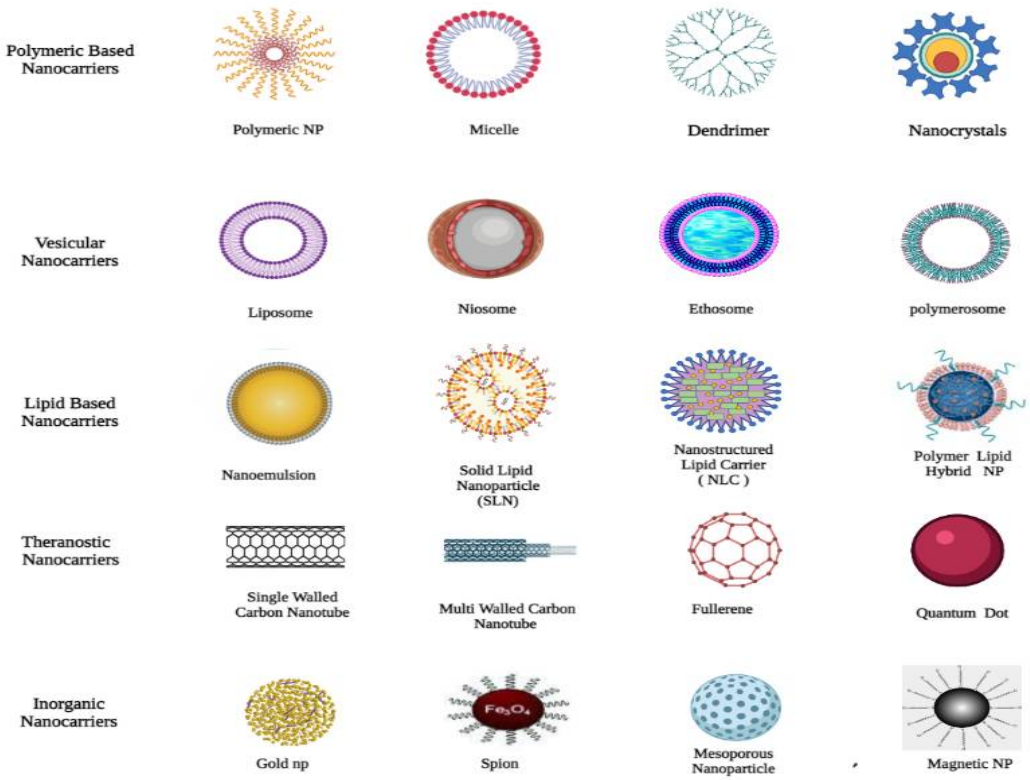

Fig 2. Types of Nanocarriers investigated For Nose to Brain Drug Delivery System

Nanoparticulate Carriers

These are carrier systems made with a variety of natural and synthetic polymers or both are ranging in size from 10 to 100 nanometres [46]. Nanoparticles can be modified with various ligands for site-specific drug delivery. Different Nanoparticulate carrier are summarized in the following section.

A) Polymer Based Nanocarriers.

Polymeric NP

The size of the polymeric NPs is by far the most important factor that affects their performance as drug delivery vehicles. In this regard, natural and synthetic polymeric NPs have recently been used as nose-to-brain delivery systems [47]. Polymeric NPs with 50–200nm sizes, as controlled drug delivery systems, increase the oral Bioavailability of hydrophobic drugs. This has been obtained by high half-lives, low toxicity, and improved capability of the NPs to cross the BBB [48].In addition to the many advantages of a polymeric NP delivery system for the intranasal route, a greater portion of the administered delivery platform reached systemic circulation where it can be opsonized releasing the components from where it reaches the BBB to face the polyglycol- protein efflux pumps.

Polymeric Micelle

Polymeric micelles are nanoscopic core/shell structures formed by amphiphilic block copolymers. Both the inherent and modifiable properties of polymeric micelles make them particularly well suited for nose to brain drug delivery purposes [49].In comparison to other micellar systems, polymeric micelles are the finest alternative drug carriers. The polymeric micelle core is engineered for optimal medication loading capacity and longevity [50]. The hydrolytic conversion of the hydrophobic block of the micelle to the hydrophilic component is required for controlled drug release [51] .The development of polymeric micelles is based on the design of the constituent block polymers. The polymer design needs to be optimized depending on the drug to be incorporated, which is in contrast with the conventional encapsulation technology for nanoparticle formulations such as liposomes [52].

Dendrimer

These are a type of polymeric material with a symmetrical nanoscale structure made up of tree-like atoms. The name "dendrimer" comes from two Greek words: "Dendron," which means "tree," and "meros," which means "part." Dendrimers are symmetric branching units constructed around a tiny molecule or linear polymer core in monodisperse marcomolecules [53]. Dendrimer's structure consists of three components:

- A initiator.

- repeating units or interior layers.
- Outer interior generations with exterior region.

Drug distribution to the brain can be divided into two categories: bypassing the BBB and traversing the BBB. Drug molecules can be physically enclosed in the internal cavities of dendrimer molecules or chemically attached to the terminal functional groups based on varied shapes and properties of dendritic polymers [54]. Dendrimers are globular macromolecules made up of branching monomers attached to a tiny core molecule. The advantages of utilizing dendrimers include size control, liquid solubility, and a wide range of functionalization options. However, dendrimer synthesis is time-consuming, and the scaffold has a significant impact on the balance of toxicity and biodegradability [55].The dendrimer, liposomes, nanocrystals carriers' aid in improving drug solubility and Bioavailability while also reducing off-target effects [56].

Nanocrystals and Nanogel

Drug nanocrystals are particles with a size in the nanometric, indicating that they are crystallized nanomaterials[57]. Approximately 40% of currently available medications have aqueous solubility issues, while 70% of compounds in the discovery pipeline are practically insoluble in water. Nanocrystals are a popular method for addressing the problem of poor water solubility and enhancing the Bioavailability of many medications [58]. For Nanocrystals the nasal region is the only direct link between the outside environment and the CNS. Drugs can be delivered to the brain via intranasal delivery, bypassing the BBB [59]. A medication delivery technology known as the nanogel is an option to consider for the forthcoming treatment of brain diseases [60]. A nanogel is a 3D hydrogel made up of nano-scopic micelles distributed in an aqueous phase ("nano-in-hydrogels") with the ability to integrate hydrophobic groups in the micelles' core while sustaining a hydrophilic environment [61]. Nanogels are prospective drug nanocarriers with the ability to infiltrate tissues via Trans cellular routes due to their small volume [62]. Nanogels have been shown to improve insulin delivery to the brain, resulting in a huge amount of insulin being found in the atrial and cerebellar areas of the mouse brain [63].When tested in an in vitro BBB model, this cationic nanogel dramatically enhances insulin BBB permeability [64].

B) Vesicular Nanocarriers.

Liposomes

Weissmann coined the word "liposome" after the lysosome because of its similarities [65]. Liposomes can be anywhere between 30 nm and 100 m in size. The liposome can be classified into three types based on the size and number of concentric lipid bilayers: (1) Multilamellar vesicle, (2) Oligo lamellar vesicle, and (3) liposome vesicle (Large and small micelles) [66]. Liposomes provide site-specific delivery, preserve drugs from enzymatic degradation, reduce side effects, and are a biodegradable and biocompatible delivery technology, increasing both academic and commercial interest in innovative drug delivery systems [67, 68]. Various studies, both in the lab and on a commercial scale, are being conducted on liposome as a viable carrier system for direct medication delivery from the nose to the brain. To aid therapeutic targeting to the brain, liposomes are sometimes surface modified with specific ligands or carrier molecules such as monoclonal antibodies, polyethylene glycol, glutathione, transferrin, lactoferrin, and others [69].

Niosomes

Niosomes are osmotically active, less poisonous, and chemically stable as a drug delivery system. As a ligand of the unique receptor, niosomes' active targeting to the desired tissue is arbitrated with different therapeutic ways. With the increasing availability of new strategies to cross BBB and target niosomes to the CNS, this technology has a bright future in pharmaceutical applications [70]. Rinaldi et al. conducted a fascinating investigation on chitosan glutamate niosomes, which are non-ionic surfactant nanoscale-vesicles recommended as preparations for nose-to-brain medication transport [71]. The investigation by Rinaldi et.al. The both Chitosan Glutamate -Niosome and Chitosan Glutamate -Niosome Particle produced via thin film hydration appear to have mucoadhesive characteristics in vitro. However, more research is needed to confirm the enhanced bioavailability and lower drug removal in the nasal cavity in vivo [72]. Khoee et al. investigated synthesized niosomes for dynorphin-B targeting drugs. The glucose compound N-palmitoyl glucosamine was used to synthesize niosomal formulation in this study. The improved niosomal formulation of dynorphin-B was given to mice intravenously (IV) and demonstrated a significant antinociceptive effect, far greater than that produced by Intravenous administration of the peptide in its pure form at the same concentration [73]. As a result, Niosomes are the next exciting generation of drug delivery carriers [74].

C) Lipid Based Nanocarriers.

Nanoemulsion and Nanostructured Lipid Carriers (NLC)

Nanoemulsions are a Nano sized, heterogeneous solution of water-in-oil or oil-in-water that has been stabilized by an appropriate emulsifier [75]. Nanoemulsions typically have a mean droplet size of 20 to 200 nm. Lipophilic medicines can dissolve in the oily phase, and when they are released into the aqueous phase, Nano precipitates with a large surface area can develop, resulting in a rapid dissolution rate [76, 77]. Nanoemulsions are frequently used in recent scientific investigations for direct drug transport from the nose to the brain, as well as for parenteral administration. Shobo et al. created a pretomanid loaded nanoemulsion for nasal administration in 2018 to improve the drug's brain penetration [78]. Furthermore, nanoemulsions can be made into nanoemulgels or in presence hydrogels to bypass the mucociliary clearance mechanism and extend the time spent in the nasal cavity [79].According to the available research, mucoadhesive nanoemulsion, which is primarily intended for transdermal and intranasal administration to the brain, has been comprehensively studied and found to be a viable carrier system that diminishes associated adverse effects, improves therapeutic potency, and provides a non-invasive patient-friendly strategy to access the brain [80].

Solid lipid Nanoparticles

SLNs (submicron colloidal carriers, 50–1000 nm) were first introduced in 1991. They are utilized to deliver both hydrophilic and lipophilic drug that are confined in a compatible material essence made up of a lipid or mixture of lipids and supported by surfactant in the external shell [81]. SLNs are a medication delivery technology that enhances brain uptake due to their lipophilic nature and small particle size. In an investigation by pardeshi et al. (2013) , Emulsification was used to make Ropinirole HCL loaded SLNs diffusion of solvents method are intended for nose to brain drug delivery [82]. The good physical stability and protection of integrated labile medicines from degradation are the major properties of SLN in terms of parenteral application [83]. SLNs are simple carrier systems based on solid lipids that is used to deliver a variety of medications, including peptides, proteins, and pharmaceuticals that are poorly water-soluble. SLNs will provide a new pathway for the transport of a wide range of therapeutic molecules into the brain, including analgesics, antianxiety, neuroleptics, antibiotics, medicines [84].

D) Theranostic Nanocarriers.

Quantum Dot - Quantum dot are colloidal nanostructured semiconductor materials that have a metalloid particle core and a nonreactive metallic shells that surrounds it [85, 86]. It also has a large surface area, which allows it to encapsulate a wide range of medicinal and diagnostic chemicals. As a result, it has the potential to be an effective carrier system for brain targeting. To aid brain targeting, bioactive compounds can be placed into the quantum dots' core, while the surface can be sintered with targeting ligands [87]. It's a promising diagnostic tool because of its long-term photostability, high brightness, and size-tunable short emission spectra [88]. Tang et al. (2017) developed a PEGylated quantum dot nanoprobe associated with aptamer 32 for brain tumour fluorescence imaging. It has the ability to bind exclusively to glioma cells, making it a viable tool for the detection, research, and surgical intervention of brain tumors [89]. Similarly, Yang et al. (2017) employed quantum dots as an useful diagnostic tool as well. They employed Cd-Se-ZnS nanocrystals in a pH-triggered polymeric particles as a fluorescent imaging nanoprobe to differentiate cerebral ischemia afflicted regions in the brain [90]. As a result, quantum dots have shown to be an incredibly effective diagnostic tool for brain problems.

Carbon Nanotube

Carbon nanotubes (CNTs) were first described as needle-like tubes made up of layers of graphitic sheets by Iijima in the early 1990s [91]. Because of its great mechanical strength, outstanding electrical, and thermal properties, single-walled and multiwalled carbon nanotubes (SWNTs or MWNTs), consisting of one or more layers of graphene, have primarily been used in industry [92]. Drug delivery into the brain is difficult and constrained attributed to the prevalence of the blood brain barrier (BBB) [93]. Yang et al. reported the first observation of f-CNTs in the brain when truncated SWNTs were fed orally to mice every day for 10 days [94]. In vitro and in vivo, CNTs have the inherent potential to traverse the BBB. Researchers produced an angiopep-2 (ANG) conjugated synthesized CNT for brain targeting in a study. CNTs' natural brain targeting paired with ANG targeting supports potential glioma treatment uses [95]. CNTs hold enormous potential and applicability in medical, biomedical, drug delivery and therapeutics. Ameliorating CNTs by functionalizing them before their biomedical application should be a recommended practice. The hazards after CNT treatments should be assessed with conventional treatment modalities for finalizing safe doses [96].

E) Inorganic Nanocarriers.

Gold Nanoparticle

Due to their ease of synthesis, great biocompatibility, well-defined surface composition, and simple molecular imaging using fluorescence resonance energy transfer, gold nanoparticle have become a prominent candidate for multifunctional gene carriers (FRET). Surface functionalization of AuNPs with positively charged compounds such as tertiary amine-containing molecules, amino acids and cationic peptides is a common approach for the creation of AuNP-based gene delivery vectors [97, 98]. The development of mixture monolayer protected gold nanoparticles, gold nanoparticle complexes and polymer, single -stranded DNA synthesized gold nanoparticles, and double-stranded DNA derivatized gold nanoparticles has been greatly facilitated by the advancement of gold nanoparticles for gene delivery [99,100]. Shan et al. reported a new gene delivering vector based on gold nanoparticles entrapped dentrimer . (Au DENPs) with considerably greater gene transfection efficacy than dendrimers without AuNPs entrapped, leading to more efficient associations between dendrimers and DNA [101].

Silica Nanoparticles

Silica can be found in a variety of forms, including silica particles, hollow silica particles, nanotubes, and mesoporous silica nanoparticles (MSN). Surface-modified Nanospheres could be used as gene delivery vehicles. They've been found to be useful for in vivo targeted brain therapy as well as successful therapeutic exploitation of neural stem/progenitor cells [102]. Because of their hierarchical porosity, unique structure, huge surface area, and excellent biocompatibility, synthesized dendrimer-like hybridized silica nanoparticles are also proposed as promising nanocarriers for drug and gene delivery [103]. The form and structure of the nanoparticles play a role in the efficiency of gene transfection [104]. MSNs modified with PEI were used to adsorb negative charge plasmid DNA onto the interface for loading and cellular transport, according to Xia et al. Others modified surfaces using cationic compounds like dendrimers and cationic lipids [105].

CONCLUSION AND FUTURE PERSPECTIVES

Effective treatment of neurodegenerative illness is frequently obtained due to the presence of BBB. The BBB is a significant impediment to the administration of a range of medications for the treatment of neurodegenerative disease and other neuroailments. This could be one of the main reasons why so many neurotherapeutics have failed to reach the pharmaceutical market. This raises the spectra of a potential hazard in the treatment of CNS illnesses. By bridging the BBB with Nanocarriers, recent research shows the necessity for joint research across chemical, biological, and pharmacological components. The increasing number of papers published over the last decade can be used to examine the expanding interest in nose-to-brain drug delivery. Intranasal administration is a noninvasive, safe, and convenient alternative to other traditional medication delivery methods. The route is ideal for the administration of Nanocarriers because it allows for direct delivery of drugs through the olfactory or trigeminal pathways. The direct flow of medication from the sub mucosal region of the nostril to the CSF in the brain can thus improve site specificity. This method of medication delivery from the nose to the brain is particularly appealing for Nanocarrier-mediated drug delivery. Nanocarrier administration via the nose-to-brain channel can provide a diverse platform with significant potential for resolving Nanocarrier's underlying problems. Several Nanocarrier-mediated drug delivery systems have been investigated for therapeutic delivery via the nose-to-brain route, including polymeric Nanoparticles, polymeric micelles, polymer-lipid hybrid Nanoparticles, and lipid-based Nanocarriers.

DECLARATION OF COMPETING INTEREST

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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