REVIEW PAPER

The use of nanocarriers for drug delivery through the blood-brain barrier

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ABSTRACT

Due to its importance, the central nervous system (CNS) is protected by the blood–brain barrier (BBB), a multicellular structure that controls the passage of molecules and ions and acts as a barrier for toxins and pathogens. However, the BBB represents an obstacle to achieving the delivery of therapeutic substances into the nervous system to treat neurological diseases. Strategies such as modulation, bypass of the BBB, and changes in the physical–chemical parameters of drugs can be used to enhance permeation. However, all of these methods have some drawbacks, and another growing strategy involves the use of drug nanocarrier systems. This review identifies the main nanocarriers administered orally or parenterally to increase BBB permeation. The literature describes the use of polymeric nanoparticles, micelles, liposomes, solid lipid nanoparticles, dendrimers, nanostructured lipid carriers, inorganic nanoparticles, nanoemulsions, and hybrid systems. However, polymers are widely applied. Ligand conjugation represents a common strategy for increasing cellular uptake, and the mechanisms involved are receptor-mediated and adsorptive-mediated transcytosis. Despite the potential and promising data for applying this strategy to treat CNS diseases, no commercial nanoformulations with these characteristics are available to treat CNS diseases.

Keywords: *Drug delivery systems, Nanoparticles vectorization, Nanotechnology, Blood-brain barrier, Brain*

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Abbreviations: *ABC - ATP-binding cassette; ARSACS - Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay; AUC – area under curve; BBB – blood-brain barrier; CNS-Central Nervous System; EGCG - epigallocatechin-3-gallate; HSPC - hydrogenated phosphatidylcholine; LRP - Lipoprotein Receptor-related Protein; NLC – nanostructured lipid carriers; NS – Not Specified; O/W – oil-in-water; O/W/O – oil-in-water-in-oil; PAMAM – Polyamidoamine; PBCA – poly-butyl-cyanoacrylate; PCL – polycaprolactone;; PEG – polyethylene glycol; PEI – polyethylenimine; PEtOz - poly(2-ethyl-2-oxazoline); PGA- poly-γ-glutamic acid; Pgp – P glycoprotein;; PLA - polylactic acid; PLGA - poly(L-lactic acid-co-glycolic acid); RVG - Rabies virus glycoprotein; SLN – solid lipid nanoparticles; W/O - water-in-oil; W/O/W – water-in-oil-in-water*

INTRODUCTION

The central nervous system (CNS) is composed of the encephalon, which includes the brain, cerebellum, brainstem, and spinal cord. Its primary function is to integrate body information and regulate both voluntary and autonomic movements. Neurons, the main cell type in the CNS, are responsible for transmitting information. However, other cell types, such as astrocytes and oligodendrocytes, also play crucial roles in this complex system [1].

Due to its complexity and importance, the CNS is protected by the blood–brain barrier (BBB). The primary structure of the BBB consists of endothelial cells connected by tight junctions surrounded by pericytes and astrocytes (Fig. 1) [2]. Endothelial cells are essential for regulating transport and forming blood vessels. Pericytes, which are located around blood vessels, help maintain vessel integrity and promote angiogenesis (Fig. 1) [3].

Glial cells are responsible for the protection, maintenance, and support of the CNS, and they are divided into three types: astrocytes, microglia, and oligodendrocytes. Microglia play a crucial role in the immune response and phagocytosis, and they also help maintain the integrity of the BBB. Oligodendrocytes, on the other hand, produce the myelin sheath around neurons' axons, which facilitates information propagation. They are not associated with the BBB [4]. Astrocytes are the most abundant type of glial cell in the brain. They provide nutrients to neurons, maintain the ionic balance, regulate the release of neurotransmitters, and control synaptic transmission. Within the BBB,

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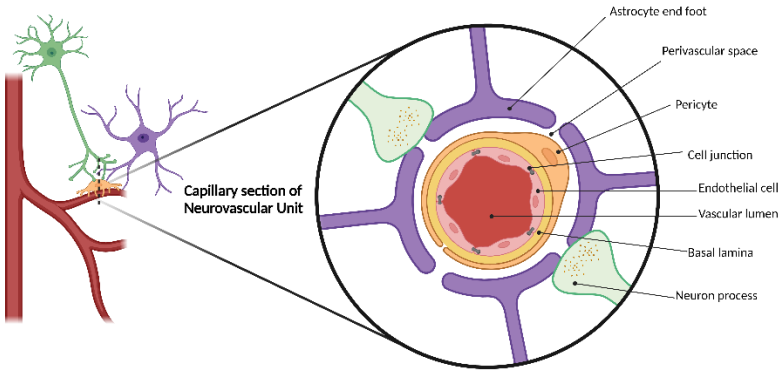

Fig. 1. Representation of the components of the blood–brain barrier (BBB). This structure comprises cell junctions between endothelial cells and other cell types, such as pericytes and astrocytes. Created with BioRender.com.

astrocytes are located between endothelial cells and neurons, covering a significant portion of blood vessels, which is crucial for maintaining the BBB structure. Additionally, astrocytes produce proteins necessary for cell junctions (Fig. 1) [2,5].

The primary functions of the BBB include maintaining CNS homeostasis; controlling the entry of nutrients, molecules, and xenobiotics; and regulating the ionic balance and composition of neurotransmitters. Similar to other cellular barriers in the body, for a substance to enter the CNS, it must permeate the BBB via paracellular or transcellular transport [2]. The latter can be facilitated. Transport across the BBB is determined by the structural characteristics of chemical substances (Fig. 2).

Due to the lipophilic nature of the BBB, small hydrophilic molecules can permeate via paracellular transport in aqueous media (Fig. 2a). In this type of transport, cell junctions impede the permeation of larger hydrophilic molecules [6]. In contrast, small uncharged lipophilic molecules and gases can permeate the membrane via transcellular transport (passive diffusion) [2,7] (Fig. 2b).

Some more complex or polar molecules, such as amino acids, carbohydrates, lipids, and polar ions, require alternative mechanisms to traverse the BBB. Thus, molecules that cannot permeate the BBB by diffusion utilize the transporters present in the membrane (Fig. 2c) [2,8]. Another permeation mechanism, transcytosis, involves the encapsulation of substances within endosomes and can be divided into three types (Fig. 2d-f). The first type is receptor-mediated transcytosis. After interacting with a ligand, a caveola forms, followed by a vesicle that internalizes the ligand and the receptor, transporting them to the other side. The receptor and ligand then dissociate either inside the vesicle or after exocytosis. Specific receptors for ligands such as transferrin, lipoproteins, folic acid, and glucose facilitate this type of transport. The second type is adsorptive-mediated transcytosis, which occurs when highly positively charged molecules, such as albumin, interact with the cell surface, inducing endocytosis followed by transcytosis. The third type is cell-mediated transcytosis, which occurs during episodes of inflammation when immune cells, such as monocytes, pass through the endothelial cells of the CNS to support the protection of the region [6,9].

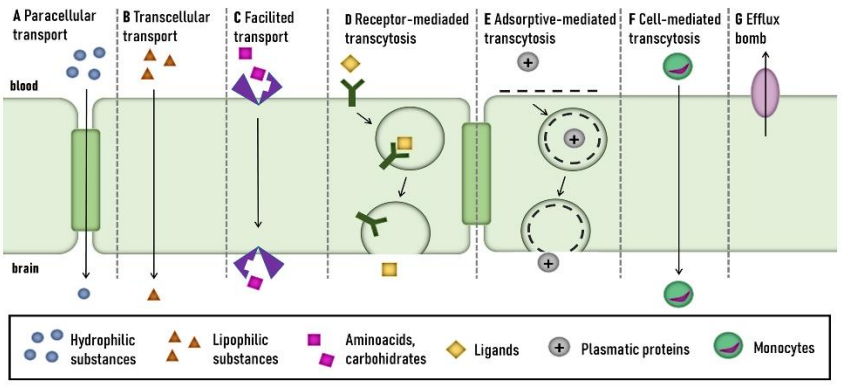

Fig. 2. Graphic representation of the types of transport of molecular substances through the BBB. a) Paracellular transport; b) transcellular transport; c) facilitated transport; d) receptor-mediated transcytosis; e) adsorptive-mediated transcytosis; f) cell-mediated transcytosis; and g) efflux bomb.

The last type of transport takes advantage of the concentration gradient, allowing substances to move from areas of high concentration to areas of low concentration, such as from the blood into the CNS. Conversely, some substances are transported against their concentration gradient by coupling their movement to the passive transport of another molecule, such as an ion. Additionally, efflux pumps powered by ATP, known as ATP-binding cassette (ABC) transporters, transport substances against their concentration gradients using energy from ATP hydrolysis. The most well-known transporter of this class is P-glycoprotein (Pgp), which transports substances from inside to outside the brain. Although Pgp is a protective mechanism for the CNS, it represents an obstacle to bioactive molecule delivery (Fig. 2g) [2,10].

The CNS is susceptible to various neuronal disorders, which can, in some cases, disrupt the BBB. However, the BBB structure remains intact in most instances, serving as a barrier for drugs [1,11]. The 2015 Global Burden of Disease, Injuries, and Risk Factors Study revealed that neurological disorders are the world's foremost cause of disability. In 2016, these diseases accounted for the greatest number of disability-adjusted life-years (DALYs), at 276 million, and were the second leading cause of death, with 9 million deaths[12].

Furthermore, during 2020-21, evidence emerged regarding the neurological effects of COVID-19, an emerging disease that led to a pandemic and raised alarms among health organizations, governmental authorities, and the global population due to the rapid transmission and infection of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Therefore, the severe neurological complications of this disease represent another public health challenge in the context of the CNS [13,14].

Given the various diseases that affect the CNS, drugs must be administered and act within this system. Therefore, these drugs must be able to cross the BBB. However, the physicochemical properties of the BBB make drug permeation challenging, and permeation is further complicated by protective mechanisms such as Pgp [15].

Therefore, for a drug to act in the brain region, strategies to bypass the BBB are needed. These strategies include modulation of the BBB, local administration, alteration of the physicochemical properties of bioactive substances, and the use of drug delivery systems.

One approach to enable drug permeation into the CNS is to increase paracellular transport by temporarily disrupting the membrane, either chemically or physically. Chemically, hypertonic solutions can dehydrate endothelial cells and widen cell junctions, facilitating the diffusion of water-soluble substances. However, this method has limitations, such as the necessity of administering anesthesia to the patient during the procedure [16]. Another strategy to bypass the BBB is the use of focused ultrasound. This technique transmits ultrasound waves that converge on a target region, creating microbubbles that can deform cell junctions and facilitate the passage of active substances. Monitoring this process is essential and requires specialized professionals and hospital facilities, which incurs additional financial costs [17].

Another strategy to bypass the BBB is to change the administration route from oral to local (intracerebroventricular or intrathecal injections) or nasal administration. The local administration approach is often used for anesthesia or for treating tumors. However, it is unsuitable for treating chronic diseases because it is more invasive and costly [18,19]. On the other hand, nasal administration is advantageous due to the proximity of the nasal cavity to the brain and its connections via the olfactory and trigeminal nerves. However, despite being more convenient for patients, nasal formulations face manufacturing challenges. Additionally, the dose reaching the CNS is affected by mucociliary clearance and the region's high blood flow, which contribute to rapid drug elimination and systemic distribution, respectively [20,21].

Another approach is to modify the chemical structure of a drug [7,22]. However, altering the physicochemical parameters of bioactive substances can reduce the interaction of a drug with its therapeutic molecular target, leading to a loss of activity [2].

The combination of drugs with delivery systems that can bypass the CNS is a growing strategy in the literature [8]. This strategy allows the modification of pharmacokinetic parameters, adjustment of particle size, increased solubility, and protection of the drug from metabolism. Additionally, it increases the drug concentration at the site of action and enables controlled drug release, thereby reducing toxicity and adverse effects [23]. The nanocarrier structure must be biocompatible, biodegradable, and resistant to enzymes and pH variations [24]. One of the greatest advantages of nanocarriers is the potential for surface functionalization with specific ligands that enhance targeting, enabling

receptor-mediated or adsorptive-mediated transcytosis [25].

The application of these systems can increase patient adherence to treatment and reduce hospital service costs. This approach simplifies the therapeutic regimen, often eliminating the need for administration in a hospital environment, as is required for BBB modulation [23].

Currently, the development of nanocarriers faces challenges such as high production costs, the transition from laboratory- to industrial-scale production, and unclear regulations from global regulatory agencies. However, this growing field is driving the advancement of production methods and procedures, which will eventually reduce costs and facilitate large-scale manufacturing. Furthermore, the development of specific legislation for nanomedicines can direct efforts toward rational industrial development following recommended quality and safety specifications, in addition to strengthening the area of nanomedicine [26,27].

In this review, data from recent research articles were collected to show that associating drugs with carriers effectively facilitates their passage through the BBB. This process allowed the identification of the main systems and strategies used for this purpose.

CNS drug nanocarriers

The primary structures described in the literature that enhance BBB permeation include polymeric nanoparticles, micelles, solid lipid nanoparticles, liposomes, dendrimers, nanostructured carriers, nanoemulsions, and hybrid systems (Fig. 3).

Additionally, functionalizing the nanocarrier surface before or after its formation is employed to increase its circulation time and penetration into the CNS. This functionalization is achieved by targeting receptors overexpressed in specific cells, such as brain endothelial cells, thereby directing the nanocarriers to the site of action [28]. The polymer PEG is widely used not only to increase the circulation time but also to decrease immunogenicity [29]. The second strategy takes advantage of mediated transcytosis, as mentioned before. Molecules are conjugated to the nanocarrier surface to bind to receptors on the cell membrane, thereby facilitating their entry [30].

Polymeric nanoparticles

Polymeric nanoparticles represent a widely used drug delivery system due to their ability to control the release of bioactive substances, protect drugs from metabolism, and enhance drug bioavailability and permeability [31,32]. According to Nowak et al. (2020), a size of approximately 200 nm is efficient for CNS delivery [33,34]. [35] To date, no pegylated nanosystems have been approved for clinical use; only pegylated proteins, such as Plegridy® and Copaxone®, have been approved as therapeutic alternatives for treating patients with multiple sclerosis [36].

Polymeric nanoparticles are classified as nanocapsules or nanospheres based on their structural organization. Nanocapsules have an oily or aqueous center containing the drug surrounded by a polymeric layer. In contrast, nanospheres consist of a polymeric matrix in which the drug is either dispersed throughout or attached to the surface [31,32].

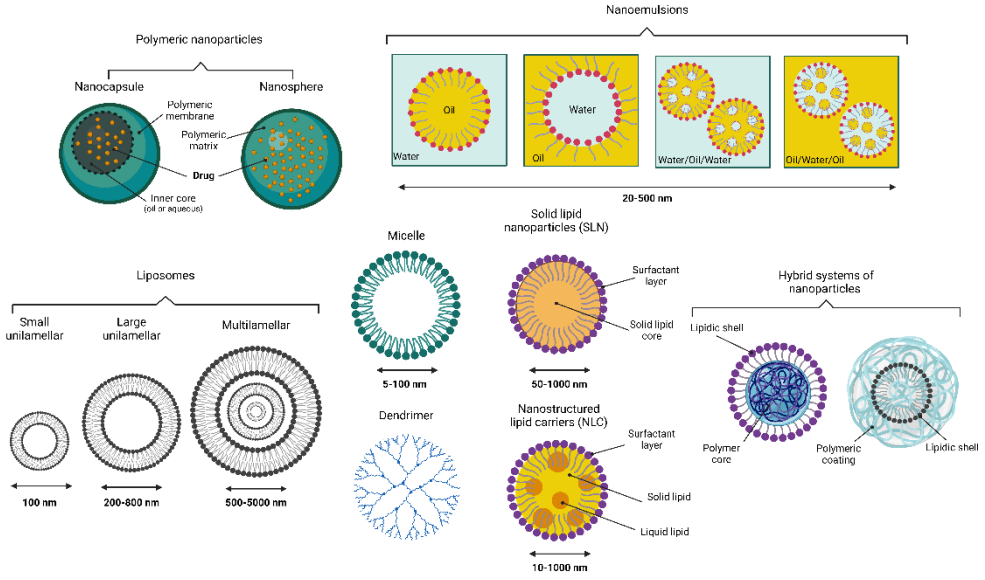

Fig. 3. Representative structures of the main nanocarriers employed for drug permeation of the BBB. Created with BioRender.com.

The polymers used must be biocompatible and biodegradable, meaning that they are generally nontoxic and do not generate harmful metabolites in the body. They often contain chemical bonds, such as ester, amide, and anhydride bonds, susceptible to hydrolysis and enzymatic cleavage. These polymers can be natural, such as chitosan and albumin, or synthetic, such as polylactic acid (PLA), polyethylene glycol (PEG), and polycaprolactone (PCL). In addition, poly(L-lactic acid-co-glycolic acid) (PLGA), a copolymer, is widely used in formulations for treating CNS diseases [31,32,37] since its hydrolysis generates the monomers lactic acid and glycolic acid, which are endogenous substances that are easily excreted [38]. Table 1 summarizes the research on polymeric nanoparticles for CNS drug delivery.

One example is PLGA nanoparticles produced to carry NL-1 for future stroke treatment [33]. NL-1 is a hydrophobic drug that binds the mitoNEET protein, which is present in the outer membrane of mitochondria and interacts with molecules involved in cellular respiration, playing an important role in organelle function [68].

In this study, the research group used a BALB/c mouse brain cell line (bEnd.3) to evaluate nanoparticle uptake. They found a significantly greater uptake of nanoparticles, likely due to their high fluorescence intensity and involvement in caveolae formation. Mechanisms such as phagocytosis and receptor-mediated endocytosis were found to be irrelevant to the transport process [33].

PLGA nanoparticles reportedly permeate the BBB *in vitro* [43,44] and *in vivo*, corroborating their application [39–42].

The effectiveness of other polymers, such as poly-γ-glutamic acid (PGA) [45] and poly(amidoamine) [46], has been reported *in vitro*, and others, such as PCL [47–50] and poly-butyl-cyanoacrylate (PBCA) [51], have already shown applicability in the CNS *in vivo*.

Regarding natural polymers, albumin nanoparticles have already been reported to increase drug permeation through the BBB in both *in vitro* and *in vivo* studies following parenteral administration to rodents [52–56]. Zhang et al. (2020) employed borneol and PEG to functionalize albumin nanoparticles. Borneol, a substance from traditional Chinese medicine, enhances absorption across cell membranes. It is suggested to increase

Table 1. Summary of the polymeric nanoparticles used in the research included in this review. ATR—ataxia telangiectasia-related; EGCG—epigallocatechin-3-gallate; NAP—NAPVSIPQ; NS—not specified; TPGS—D-a-tocopherol polyethylene glycol 1000 succinate.

Polymeric nanoparticles					
Polymer	**Functionalization**	**Drug**	**Disease**	**Biological analysis**	**Reference**
PLGA	-	NL-1	Stroke	*In vitro*	[33]
PLGA	TPGS	paclitaxel	cancer	*In vivo*	[39]
PLGA	-	VEGF	Parkinson's disease	*In vivo*	[40]
PLGA	folic acid	methotrexate	cancer	*In vivo*	[41]
PLGA	-	carbamazepine	refractory epilepsy	*In vivo*	[42]
PLGA	-	coumarin C75	Parkinson's disease	*In vitro*	[43]
PLGA	-	lutein	Alzheimer's disease	*In vitro/In vivo*	[44]
PGA	OX26 monoclonal antibody	ginsenoside rg1	cerebral infarction	*In vivo*	[45]
Poly(amidoamine)	-	-	NS	*In vitro*	[46]
PCL	-	lamotrigine	epilepsy	*In vivo*	[47]
PCL	-	4L	glioma	*In vivo*	[48]
PCL	polysorbate 80	nevirapine	HIV	*In vivo*	[49]
PCL	-	busulfan or etoposide	cancer	*In vivo*	[50]
PBCA	-	dopamine	Parkinson's disease	*In vivo*	[51]
albumin	-	andrographolide	Alzheimer's disease	*In vivo*	[52]
albumin	-	nerve growth factor	brain recovery after stroke	*In vitro/In vivo*	[53]
albumin	-	andrographolide	Alzheimer's disease	*In vitro*	[54]
albumin	-	citicoline	brain recovery after stroke	*In vitro*	[55]
albumin	substance P	paclitaxel	glioma	*In vivo*	[56]
albumin	PEG/borneol	itraconazole	meningitis	*In vitro/in vivo*	[57]
PLGA-PEG	-	dexibuprofen	Alzheimer's disease	*In vitro/In vivo*	[58]
PLGA-PEG	-	paclitaxel and R-flurbiprofen	glioblastoma	*In vivo*	[59]
PLGA-PEG	lactoferrin	shikonin	glioblastoma	*In vivo*	[60]
PLGA-PEG	-	EGCG/ ascorbic acid	Alzheimer's disease	*In vitro/in vivo*	[61]
PLA-PEG	TPL	NAP	Alzheimer's disease	*In vitro/In vivo*	[62]
Dextran-PLA	-	angiotensin II and octaneuropeptide	NS	*In vitro/In vivo*	[63]
PEG-PDL-DO	-	ATR inhibitor	cancer	*In vivo*	[64]
PBCA-PEG	-	coumarin-6	NS	*In vitro/In vivo*	[65]
Polymers P-2P-PEG	REG peptide	paclitaxel	cancer	*In vitro*	[66]
PEG-PCL	angiopep-2	doxorubicin	glioma	*In vitro/In vivo*	[67]

cell membrane fluidity, reversibly open gap junctions, and inhibit efflux pumps, thereby facilitating the permeation of other substances [69]. These nanoparticles carry the antifungal itraconazole, which has limited application in the treatment of cryptococcal meningitis due to its low permeability across the BBB. Compared with nanoparticles without this substance, borneol increased the permeability of bEnd.3 cells by approximately 1.72 times. The integrity of the cells treated with borneol-containing nanoparticles decreased due to loosened cell junctions. However, cell integrity was restored four hours after borneol removal, indicating a short and reversible process, unlike what occurs during disease treatment. Furthermore, cell internalization may occur through clathrin-mediated and energy-dependent mechanisms. Conjugated nanoparticles were also detected in the brains of mice after intravenous injection, confirming the benefits of these functionalized nanoparticles for BBB permeability [57].

As mentioned, combined polymers can also be employed to leverage their advantages. For example, nanoparticles of PLGA coated with PEG have been used to carry dexibuprofen, aiming to reduce the inflammatory process associated with Alzheimer's disease [58], and memantine has been used to treat the same condition [70]. Neither study documented cytotoxicity in brain-related cells such as bEnd.3 cells, astrocytes, or PC12 cells (a cell line derived from rat adrenal medulla pheochromocytoma with an embryonic neural crest origin) when exposed to different concentrations of the nanoparticles. An *in vitro* model was established with bEnd.3 cells and astrocytes to study BBB permeation, and the nanoparticles exhibited permeation through the basolateral membrane of the cells. Additionally, they reached the brain after oral administration in mice [58,70]. PLGA-PEG nanoparticles have also been employed to transport substances with low permeability through the BBB, increasing their concentrations in the brain [71] and advancing the development of treatments for other neurodegenerative diseases [61].

Other potential combinations have also been evaluated for treating CNS diseases, including combinations of natural and synthetic polymers such as dextran-PLA [63] and combinations of synthetic polymers such as PLA-PEG [62], PEG-poly(ω-pentadecalactone-co-p-dioxanone) (PDL-co-DO) [64], PBCA-PEG [65], and the polymers P and 2P (derivatives of glutaric acid and 1,8-octanediol) with PEG [66] and PEG-*b*-PCL [67].

Micelles

Another type of nanocarrier that has been described in the literature to enhance BBB permeation is micelles. Micelles are formed by amphiphilic structures, such as phospholipids and copolymers, which, together with surfactants, aggregate in concentrations above the critical micellar concentration in colloidal dispersions with particle sizes ranging from 5 to 100 nm. Depending on the solubility of the drug, it may be located inside the micelle core, in the intermediate region, or on the micelle surface [72].

While nanoparticles maintain a static and stable structure, they form a dynamic structure where surfactants or amphiphilic copolymers can be exchanged with free surfactants [73]. The production of micelles using polymers allows for surface modification and vectorization [72]. Micelles carrying paclitaxel [74] and estradiol [75] are commercially available for treating breast cancer and vasomotor symptoms, respectively. Table 2 summarizes studies that have used micelles as drug carriers for brain delivery.

Table 2. Summary of the micelles used in the research mentioned in this review. CREKA—specific fibrin-binding peptide; HE—histidine–glutamic acid repeats; RG—arginine–glycine repeats.

Polymer	Functionalization	Drug	Disease	Biological analysis	Reference
PEtOz-SS-PCL	-	doxorubicin	cancer	*In vivo*	[76]
PCL-PEI	tLyp1	curcumin	cancer	*In vitro/In vivo*	[77]
PLGA-ganglioside	-	doxorubicin	cancer	*In vivo*	[78]
gangliosides	-	doxorubicin	cancer	*In vivo*	[79]
DPSE-PEG	neuropeptide Y	doxorubicin	cancer	*In vivo*	[80]
PEG-PLA	integrin ligand	doxorubicin	cancer	*In vivo*	[81]
pluronic	glucose/folic acid	doxorubicin	cancer	*In vitro/In vivo*	[82]
CPSO	HE/RG	paclitaxel	cancer	*In vitro/In vivo*	[83]
DSPE-PEG	pep-1/borneol	carmustine	cancer	*In vitro/In vivo*	[84]
Paclitaxel-SS-octadecanol	CGKRK/borneol	paclitaxel	cancer	*In vitro/In vivo*	[85]
camptothecin/gemcitabine	-	camptothecin/gemcitabine	cancer	*In vivo*	[86]
camptothecin-PEG	RGD	camptothecin	cancer	*In vivo*	[87]
endomorphin-octadecanol	-	endomorphin	pain	*In vivo*	[88]
lactoferrin-linoleic acid	lactoferrin	linoleic acid	Alzheimer's disease	*In vivo*	[89]
PEG-PCL	borneol	vinpocetine	NS	*In vivo*	[90]
PEG-poly-lysine	CREKA	rapamycin	stroke	*In vivo*	[91]
calixarene	-	dauricine	intracerebral hemorrhage	*In vivo*	[92]

Li et al. (2017) employed a micelle production strategy using the polymers poly(2-ethyl-2-oxazoline) (PEtOz) and PCL connected by a disulfide bond (PEtOz-SS-PCL) to enhance the permeation of doxorubicin through the BBB. The PEtOz portion is hydrophilic, and the PCL portion is hydrophobic, interacting with the drug doxorubicin. Both polymers are biocompatible and biodegradable. In the cytoplasm, the polymer is cleaved by a reductive thiol such as reduced glutathione, and becomes oxidized, facilitating drug release [76,77,88]. Thus, three hydrophobic chains of different sizes are produced, namely, PEtOz-SS-PCL23, PEtOz-SS-PCL33, and PEtOz-SS-PCL43, with doxorubicin-loaded particle sizes of 162.4 nm, 137.8 nm, and 88.4 nm, respectively. The average particle size of PEtOz-SS-PCL decreases with an increasing degree of PCL polymerization. This decrease might occur due to the larger hydrophobic chain size, resulting in stronger interaction with the encapsulated drug, causing the inner core to shrink, and consequently reducing the micelle size [76].

The fluorescence intensity in the brain was measured after intravenous administration in mice implanted with glioma cells to assess the entry of the formulations into the brain. No fluorescence was observed after the administration of free doxorubicin, unlike the drug-loaded carriers. The micelles that exhibited the most intense fluorescence were those of PEtOz-SS-PCL43, indicating that a smaller particle size facilitates entry and retention in the CNS. These formulations were also the most effective at reducing gliomas after intravenous administration. This study revealed the influence of particle size on drug release and how it can enhance drug delivery to the brain [76].

Micelles of different materials carrying doxorubicin reach the brain since the drug exerts its antitumor effect on mice after intravenous administration [77–81].

Pluronic is a class of polymers used in micelle production due to its amphiphilic nature [82]. It also inhibits ABC transporters by reducing intracellular levels of ATP [93]. Niu et al. (2020) proposed doxorubicin-loaded Pluronic p105 micelles functionalized with glucose and/or folic acid to bind to the BBB receptors GLUT1 and FR, respectively. GLUT1 receptors transport glucose molecules from blood vessels to the CNS, while FR is expressed in tumor cells [94].

The authors observed greater entry of micelles conjugated with glucose and dual-conjugated micelles into the cells, indicating that the presence of glucose molecules on the micelle surface increases uptake by BBB cells. The mechanisms involved in this process include not only GLUT1 but also caveolae-mediated endocytosis and micropinocytosis. A pharmacokinetic study was conducted in rats after intravenous administration. In the brain, dual-conjugated micelles were present at the highest concentration, followed by glucose-modified micelles, corroborating the *in vitro* results. Furthermore, after *in vivo* administration, the plasma and brain drug concentrations increased for micelles compared to the free drug. Thus, glucose or the combination of ligands in the functionalization of doxorubicin micelles enabled efficient permeation of the BBB [82].

Other successful cases of drug delivery to the brain included vinpocetine-loaded micelles composed of PEG, PCL, and Pluronic P123, which were administered orally to rats. The addition of borneol to the surface further facilitated permeation across the BBB [90].

Paclitaxel was incorporated into micelles composed of cholesterol polyoxyethylene sorbitol oleate (CPSO), a derivative of polysorbate 80. Polysorbate can mimic ligands of LDL receptors, thereby facilitating BBB permeation [95]. Competitive inhibition was introduced in bEnd.3 and lung adenocarcinoma (A549) cells, which express high levels of LDL receptors, to evaluate the involvement of LDL receptors in the uptake mechanism of CPSO micelles. The results revealed that micelle uptake was reduced in an LDL concentration-dependent manner, indicating that receptor-mediated transcytosis was the mechanism involved. Furthermore, after intravenous administration in mice, the micelles reached the brains of the animals. Compared with free paclitaxel, micelles containing paclitaxel reduced the tumor volume more effectively. This improvement in antitumor efficacy is attributed to the encapsulation of paclitaxel, which prolongs the circulation time and increases accumulation in tumor sites [83].

Carmustine, an alkylating agent, was encapsulated in micelles for the treatment of gliomas. These micelles were functionalized with borneol and pep-1, an interleukin-13 receptor-binding peptide highly expressed in cancer cells. Borneol increased the micelle permeation of HBMECs, while pep-1 influenced the endocytosis mechanism in BT325 glioma cells. After intravenous administration in mice, the dual-functionalized micelles reached the brain, reduced the tumor size, and increased the survival of the animals from 49

days (for those treated only with carmustine) to 53 days [84].

An interesting type of micelle includes a drug directly linked to a polymer, forming an amphiphilic structure. This strategy is used for paclitaxel conjugated with octadecanol through disulfide bonding. These micelles were further conjugated with borneol and the CGKRK peptide, which binds to receptors present in glioma cells [85]. In other studies, the drugs camptothecin and gemcitabine were conjugated via disulfide bonds to form micelles [86]. Additionally, PEG and a cell-penetrating peptide consisting of arginine–glycine–aspartate (RGD) was conjugated [87]. Other studies have employed a disulfide bond between an endomorphin derivative and octadecanol for pain treatment [88] and an amide bond between lactoferrin and linoleic acid for the treatment of Alzheimer's disease [89]. In the body, these bonds can be cleaved by endogenous constituents such as glutathione or amidase, releasing bioactive substances in the brain after intravenous administration [87,88] or oral administration [85,89]. After the intravenous administration of micelles containing camptothecin and gemcitabine to mice, the drug-forming micelles had a short half-life and did not accumulate in the brain or other organs, despite their *in vitro* and *in vivo* efficacy [86]. In this case, polymer functionalization would be satisfactory for increasing the circulation time of the nanoparticle, or ligand conjugation would enhance permeation across the BBB via receptor-mediated transcytosis [28].

Another example is rapamycin encapsulated in PEG micelles functionalized with a polylysine derivative conjugated with the fibrin-binding peptide CREKA to enhance microcirculation perfusion in stroke situations [91]. Finally, dauricine was encapsulated in calixarene phosphate micelles for the treatment of intracerebral bleeding [92].

Drug delivery systems formed by polymers, whether polymeric nanoparticles or micelles are widely used, indicating a trend in this field. As previously discussed, different types of polymers, both natural and synthetic, can be combined, and new polymers can be designed to construct nanocarriers if they are biodegradable and biocompatible. Furthermore, these polymers have functional groups that can be linked to ligands on the surface to increase their interactions with cell membranes and facilitate vectorization to the CNS. Thus, polymers are versatile for forming suitable micelles for drug delivery to the brain.

Liposomes

Liposomes are used to carry bioactive substances, forming spherical structures with bilayers that encapsulate an aqueous phase in their interior. They can be classified based on the number of layers and their size: multilamellar liposomes, which have several bilayers and range in size from 500 to 5000 nm; small unilamellar liposomes, which are composed of a single bilayer and measure approximately 100 nm; and large unilamellar liposomes, which also have a single bilayer but are larger in size, ranging from 200 to 800 nm (Fig. 3) [96].

Due to their composition, liposomes can encapsulate hydrophilic drugs in their interior or incorporate lipophilic drugs within their lipid bilayer. Additionally, to facilitate liposomes reaching the target tissue, molecules can be added to their surface to enhance their recognition by cells of interest and minimize capture by the liver and spleen. This strategy reduces clearance and prolongs the circulation time [23,96].

Doxil®, a liposome containing doxorubicin, was the first approved nanocarrier for drug delivery [97]. Currently, other formulations for cancer treatment, such as Myocet®, which also carries doxorubicin [98], and DaunoXome®[99], which carries daunorubicin, are on the market. Additionally, liposomes are commercially available for treating diseases other than cancer, such as Onpattro® for the treatment of hereditary transthyretin-mediated amyloidosis [100]. Table 3 shows some examples of liposomes currently under study.

Table 3. Summary of the liposomes in the research mentioned in this review.

Liposomes				
Functionalization	**Drug**	**Disease**	**Biological analysis**	**Ref**
-	verapamil and riluzole	amyotrophic lateral sclerosis	*In vitro*	[101]
transferrin	dopamine hydrochloride	Parkinson's disease	*In vitro*	[102]
maltodextrin	levodopa	Parkinson's disease	*In vitro*	[103]
TAT	curcumin, quercetin, rosmarinic acid, and neural growth factor	Alzheimer's disease	*In vitro/In vivo*	[104]
angiopep-2/TAT	doxorubicin	glioma	*In vitro*	[105]
lactoferrin	daunorubicin and honokiol	glioma	*In vitro/In vivo*	[106]
RGD and glucose	paclitaxel	glioma	*In vitro/In vivo*	[107]
-	docetaxel	glioma	*In vivo*	[108]
Penetratin and transferrin	5-fluorouracil	glioblastoma	*In vitro*	[109]
mannose analog	curcumin and quinacrin	glioma	*In vitro/In vivo*	[110]
-	pentamidine	African trypanosomiasis	*In vitro*	[111]

Docetaxel was encapsulated in liposomes and administered intravenously to rats. Compared to that of the nonencapsulated drug, the concentration in the brain was slightly higher up to 2 hours. However, after four hours, the concentration of docetaxel from the liposomes increased, even though no functionalization was applied. This process is associated with the slower and sustained release of the drug from the liposomes or can be linked to the lower excretion of liposomes compared to the free drug [108], potentially reducing the number of doses.

The application of liposomes as drug carriers for treating CNS diseases has been intensively studied. Lopalco et al. (2018) compared transferrin-functionalized liposomes with nonfunctionalized liposomes for the delivery of dopamine hydrochloride to the CNS to treat Parkinson's disease. Transferrin binds to Tf receptors present in the BBB, enhancing the transportation of the active substance to the CNS. This strategy was applied because dopamine does not cross the BBB due to its polarity and ionization state at physiological pH. The permeability of dopamine-containing particles functionalized with transferrin in hCMEC/D3 cells was five times greater than that of liposomes without transferrin. The proposed transport mechanism involves receptor-mediated endocytosis, where transferrin binds to Tf receptors expressed on cell surfaces, causing endocytosis and transporting liposomes in endosomal vesicles across the membrane [102].

Gurtuk et al. (2017) encapsulated levodopa in liposomes containing maltodextrin to prevent its conversion into dopamine before reaching the brain. This functionalization favors stability and increases bioavailability. In a permeability test with a parallel artificial membrane, liposomes with maltodextrin allowed greater permeation of levodopa than the drug solution. In addition, the presence of glutathione inside the liposomes further favored permeation due to its antioxidant effect, enhancing system stability [103].

Liposomes containing verapamil and riluzole have been used to treat amyotrophic lateral sclerosis (ALS), another neurodegenerative disease [101]. Riluzole efficiently treats this disease but is a substrate for Pgp [101]. Moreover, the anti-arrhythmic agent verapamil is a Pgp inhibitor [112]. In bEnd.3 cells and C8D1A astrocytes, liposomes containing verapamil and riluzole reduced Pgp expression in a verapamil dose-dependent manner, reaching up to 40 μg/ml of the drug. Then, the cells were stimulated with both TNFα and hydrogen peroxide, which increased Pgp expression. Treatment with the nanoformulation led to a reduction in Pgp expression at a concentration of 30 μg/ml verapamil. An assessment of riluzole uptake by bEnd.3 cells revealed an increase when riluzole was delivered via liposomes, suggesting that Pgp was inhibited [101].

Due to the oxidative mechanisms involved in neurodegenerative diseases, antioxidants could be helpful in their treatment. Therefore, liposomes containing curcumin, quercetin, rosmarinic acid [113], and neural growth factor were formulated. The surface was modified by adding the cell-penetrating peptide TAT, which is positively charged and can interact with negatively charged cell membranes, in addition to cardiolipin and phosphatidic acid, which have an affinity for amyloid plaques, to the membrane. The modified liposomes increased permeability in a BBB model composed of human astrocytes, human pericytes, and HBMECs. The same effect was observed in rats that received liposomes intravenously. In addition, the levels of oxidation markers and aggregating proteins were reduced [104].

Han et al. (2017) produced liposomes containing doxorubicin coated with PEG to prolong the circulation time in the bloodstream and vectorized them with angiopep-2 and TAT. Angiopep-2 is a peptide ligand for lipoprotein receptor-related protein (LRP) present in the BBB and glioma cells that improves liposome delivery. The TAT peptide was selected not only for its ionic characteristics but also for its ability to enhance cell uptake when LRP receptor saturation occurs. In addition to dual-functionalized liposomes, liposomes were functionalized with only angiopep-2 or TAT and with no peptides on their surface. BBB permeability was evaluated in bEnd.3 cells by measuring fluorescence. The fluorescence intensity of the dual-functionalized particles was approximately 3.3 times higher than that of the TAT-conjugated particles, followed by that of the angiopep-2-conjugated and nonconjugated particles. After passing through the bEnd.3 cell layer, liposomes were captured by U251 cells (derived from malignant glioblastoma tumors) [105]. Compared with free doxorubicin and single-functionalized nanoparticles, dual-functionalized liposomes had a more significant antiproliferative effect. Transmission electron microscopy of U251 and bEnd.3 cells revealed that dual-functionalized liposomes were internalized via endocytosis in U251 cells and then released the drug, leading to glioma cell death. In bEnd.3 cells, vesicles with

intact cellular components, such as nuclear and cellular membranes, were observed after exposure to functionalized liposomes, indicating nanoparticle transcytosis without cell disruption. The two ligands used in the functionalization of liposomes had a synergistic effect on the delivery of the active substance to exert an antiproliferative effect, suggesting potential therapeutic applications [105].

Other liposome modifications, such as the addition of lactoferrin [106], RGD, glucose [107], transferrin, penetratin [109] and mannose [110], have been used.

One study compared liposomes and PCL nanoparticles for the transport of pentamidine, a drug used to treat African trypanosomiasis, an infection caused by the parasite *Trypanosoma brucei* [111]. Pentamidine has many adverse effects, such as nausea, abdominal pain, and altered blood glucose levels [114]. Its administration is intramuscular and requires hospitalization, which leads to low patient adherence to treatment. Furthermore, its low bioavailability increases the difficulty of achieving sufficient doses to treat neurological disorders. Liposomes transported 87% of pentamidine, while polymeric nanoparticles transported 66% of pentamidine in an *in vitro* model created with bEnd.5 (BALB/c mouse brain endothelial) cells [111]. Despite these differences, further studies are needed to assess the antiparasitic effect on more complex organisms.

Solid lipid nanoparticles (SLNs)

Another type of lipid-based drug delivery system is solid lipid nanoparticles (SLNs). Like liposomes, SLNs are lipid nanoparticles, but SLNs are formed from solid lipids such as triglycerides and waxes. They have a solid matrix with a hydrophobic character in which lipophilic drugs can be dispersed [112,113].

Compared with liposomes, SLNs offer greater control over drug release, especially for drugs that may not be efficiently encapsulated in liposomes. The particle size can vary between 50 and 1000 nm (Fig. 3). Polymers can also be used for conjugation with ligands and to protect nanoparticles from the immune system [112,113]. Another advantage of SLNs over polymeric nanocarriers is that they do not require organic solvents for production, which reduces their environmental impacts and toxicity [114]. SLNs have also been proposed to enhance drug permeation across the BBB, as shown in the examples in Table 4.

In a study by Loureiro et al. (2017), resveratrol and grape extract were encapsulated in various solid lipid nanoparticles (SLNs) for the treatment of Alzheimer's disease. These nanostructures were conjugated with the OX26 antibody, which recognizes transferrin receptors. Compared to unconjugated SLNs, the antibody increased permeability fourfold and significantly increased intracellular accumulation in an *in vitro* model consisting of human brain-like endothelial cells [115]. In a human brain microvascular endothelial cell model, SLNs containing borneol in their formulation exhibited increased permeation compared with SLNs without borneol, even in the absence of a specific drug. However, Song et al. (2018) reported that the reduction in cell integrity was reversible. After intravenous administration of SLNs containing borneol in mice, higher concentrations were observed in the brain than in the brain of mice not receiving borneol, corroborating previous *in vitro* results [69].

Table 4. Summary of the SLNs used in the research mentioned in this review. PEG-2-PE—1,2-Dipalmitoyl- sn-glycero-3-phosphoethanolamine-*N*-[methoxy (poly (ethylene glycol)-2000].

Solid lipid nanoparticles					
Material	**Functionalization**	**Drug**	**Disease**	**Biological analysis**	**Reference**
cetyl palmitate	OX26 antibody	resveratrol and grape extract	Alzheimer's disease	*In vitro*	[115]
Dioleoyl phosphoethanolamine	borneol	NS	NS	*In vitro/In vivo*	[69]
precirol 5 ATO, palmitic acid, and Gelucire 53/13	-	α-asarone	inflammation	*In vitro/In vivo*	[116]
mixture of mono-, di- and triglyc-erides of behenic acid	-	andrografolide	inflammation	*In vitro/In vivo*	[117]
PEG-2-PE	-	kiteplatin and its derivatives	glioblastoma	*In vitro*	[118]
oleanolic acid	-	paclitaxel	brain metastase	*In vivo*	[119]
stearic acid	angiopep-2	docetaxel	glioma	*In vivo*	[120]
stearic acid	-	curcumin	epilepsy	*In vivo*	[121]
trimyristin and lipoid S75	-	oxime	organophosphate poisoning	*In vivo*	[122]
stearic acid	-	dimethyl fumarate	multiple sclerosis	*In vivo*	[123]
myelin lipids	anti-Contactin2 or anti-Neurofascin	methylprednisolone	multiple sclerosis	*In vivo*	[124]
Kokum butter	-	nevirapine	HIV	*In vivo*	[125]

Using bEnd.3 cells, Ramalingam et al. (2020) evaluated the transport of the natural product α-asarone, which has anti-inflammatory effects, into the brain. *In vitro* evaluations showed that nanoparticles promoted a 3.9-fold increase in the permeability of the active substance compared to that of the free drug. This finding was further supported by an increase in the α-asarone concentration in the brain within 30 minutes after intravenous administration in mice [116]. In another study, a notable cellular model was used to evaluate neuroinflammation. CMEC/D3 cells were incubated with free andrographolide, an anti-inflammatory compound, and solid lipid nanoparticles (SLNs) containing this molecule. Encapsulation increased the permeation of andrographolide by approximately three times compared to that of the free substance. Subsequently, after intravenous administration to rats, the nanoparticles were detected in the animals' brains [117]. In efforts to develop glioma treatments, kiteplatin and its derivatives were encapsulated in solid lipid nanoparticles (SLNs), exhibiting increased drug permeation across the BBB [118]

Nanostructured lipid carriers (NLCs)

NLCs are another lipid drug delivery system considered the second generation of SLNs (Fig. 3). The difference is that a liquid lipid is incorporated into the solid matrix, providing an amorphous character to the solid lipid. This property enhances drug incorporation and controlled release and improves system stability [112,114]. Therefore, NLCs are one of the types of nanoparticles of interest when discussing BBB permeation (Table 5).

The development of drugs and pharmaceutical formulations for treating multiple sclerosis has been the focus of many scientific studies. Kumar et al. (2017) developed NLCs to carry dimethyl fumarate, a drug approved for treating multiple sclerosis with low cerebral permeability and potential gastrointestinal irritation. The uptake of the nanocarriers by neuroblastoma cells (SH-SY5Y) was compared to that of a pure dye used as a marker for cell nuclei, revealing that dimethyl fumarate NLCs had a permeation rate 50 times higher than that of the dye. Given the preference for an oral formulation, the permeation in intestinal epithelial cells (Caco-2) was also evaluated, revealing a 12-fold increase for the nanoparticles compared to the pure dye. In a pharmacokinetic study in rats conducted after the oral administration of free dimethyl fumarate or dimethyl fumarate loaded in NLCs, the cerebral bioavailability and the half-life of the nanocarrier system were 12.81 and 1.40 times higher, respectively, than those of the free drug [126].

Another neurodegenerative disease that has sparked interest in the formulation of NLCs is autosomal recessive spastic ataxia of Charlevoix–Saguenay. NLCs containing the antioxidant idebenone permeated the cellular BBB model prepared using bEnd.3 cells and astrocytes. Moreover, SH-SY5Y cells and fibroblasts from both healthy individuals and patients with the disease were able to internalize NLCs. Finally, the nanoparticles effectively reduced reactive oxygen species levels in fibroblasts [127].

As previously mentioned, the transferrin receptor plays a crucial role in BBB permeation, and its ligands can enhance this process. Therefore, transferrin receptor antibodies (OX26) were conjugated to NLCs carrying salvianolic acid B and baicalin to reduce neuronal damage after cerebral ischemia [128]. The presence of the antibody increased uptake by bEnd.3 cells, suggesting receptor-mediated endocytosis. Furthermore, an evaluation in mice after intravenous administration showed an increase in baicalin levels in the brain when baicalin was carried by NLCs conjugated with OX26. Salvianolic acid B was detected only in the brain when it was administered in the conjugated NLCs [128].

Table 5. Summary of the NLCs used in the research mentioned in this review. ARSACS—autosomal recessive spastic ataxia of Charlevoix–Saguenay.

Nanostructured lipid carriers					
Material	**Functionalization**	**Drug**	**Disease**	**Biological analysis**	**Reference**
stearic acid and tocopherol acetate	-	dimethyl fumarate	multiple sclerosis	*In vitro/In vivo*	[126]
oleic acid and cetyl palmitate	-	idebenone	ARSACS	*In vitro*	[127]
soy lecithin S100	OX26 antibody	salvianolic acid B and baicalin	cerebral ischemia	*In vitro/In vivo*	[128]
various oils	docosahexaenoic acid and transferrin	darunavir	HIV	*In vitro/In vivo*	[129]
oleic acid	-	temazepam	insomnia	*In vivo*	[130]

Table 6. Summary of the dendrimers used in the research mentioned in this review.

Dendrimers					
Material	**Functionalization**	**Drug**	**Disease**	**Biological analysis**	**Reference**
PAMAM	-	sinomenine	neuroinflammation	*In vivo*	[132]
PAMAM	-	minocycline	neuroinflammation	*In vivo*	[133]
PAMAM	lactoferrin	rivastigmine	Alzheimer's disease	*In vivo*	[134]
PAMAM	angiopep-2	doxorubicin	glioma	*In vitro*	[135]
PAMAM	RGD	arsenic trioxide	glioma	*In vitro*	[136]
PAMAM	RGD and TGN	arsenic trioxide	neuroinflammation	*In vivo*	[137]
poly(epsilon-lysine)	-	flurbiprofen	Alzheimer's disease	*In vitro*	[138]

In another study using NLCs, darunavir was encapsulated to treat brain damage caused by HIV infection [129]. In addition to transferrin, the NLCs containing darunavir also encapsulated docosahexaenoic acid, which acts as a ligand for receptors in the BBB, enhancing the permeation of the brain. In the *in vitro* model of the BBB, NLCs containing 15% docosahexaenoic acid and transferrin exhibited 8.99-fold greater permeation than the free drug. Furthermore, the drug-loaded nanoparticles reduced the virus concentration, as indicated by capsid protein suppression *in vitro*, more effectively than the free drug, an effect derived from darunavir. In mice, the drug concentration in the brain increased when encapsulated in NLCs together with docosahexaenoic acid and conjugated with transferrin [129].

Temazepam-loaded NLCs were directly tested for the treatment of insomnia in rats. Compared with a suspension of temazepam, the area under the curve (AUC) for the concentration in the brain was 3.4 times higher after oral administration, indicating the practical application of this nanocarrier system [130].

Dendrimers

Dendrimers are nanocarriers composed of polymers with a branched structure, resembling a tree-like organization. Each monomer is called a dendron and is divided into generations, which are determined by the number of branches from the core to the surface. Therefore, the greater the number of generations present in the dendron, the larger the size of the dendrimer. These nanostructures are typically constructed from polyamidoamines (PAMAM). However, polyamines, polypeptides, and polyesters can also be used [131]. Dendrimers can also be applied as drug carriers for brain delivery (Table 6).

Four-generation [132] and six-generation [133] PAMAM dendrimers loaded with sinomenine and minocycline, respectively, have shown efficacy as proposed treatments for neuroinflammation. These formulations were administered intravenously to rabbits, and not only did they reach the brain but they also penetrated microglia, reducing the levels of proinflammatory mediators. However, importantly, the permeation of the dendrimer structures could be facilitated by BBB damage caused by the inflammatory process [132,133].

Another strategy involves the functionalization of dendrimer structures. For example, PAMAM dendrimers were functionalized with peptides that bind to membrane receptors, thereby facilitating entry into the brain. This approach has generated considerable interest [134–137].

As mentioned, PAMAM dendrimers are widely used. However, other substances can also be employed in dendrimer production, as described in the work of Al-azzawi et al. (2018), where poly (epsilon-lysine) dendrimers were utilized for delivering flurbiprofen in Alzheimer's disease treatment. The dendrimers showed no toxicity in bEnd.3 cells and exhibited greater permeation than free flurbiprofen in the same cell type after 4 hours of testing—12% versus 8.5%, respectively. Additionally, hydrolysis products were detected during the evaluation of degradation in an acidic environment, indicating the biodegradability of these nanocarriers [138].

Nanoemulsions

Emulsions are dispersion systems formed by two immiscible phases, where one phase is dispersed as liquid droplets (internal phase) and the other phase is the continuous phase (external phase) surrounding them. When water forms the continuous phase, the system is termed oil-in-water (O/W); conversely, if oil forms the continuous phase, it is termed water-in-oil (W/O). Additionally, water-in-oil-in-water (W/O/W) and oil-in-water-in-oil (O/W/O) systems can be produced. An emulsifier is added to the formulation to stabilize these droplets in the immiscible phase [139]. The droplets in emulsions typically range in size from 20 to 500 nm (Fig. 3) [140]. Table 7 summarizes some examples related to brain action.

Table 7. Summary of the dendrimer nanoemulsions used in the research mentioned in this review.

Nanoemulsions					
Type	**Functionalization**	**Drug**	**Disease**	**Biological analysis**	**Reference**
O/W	-	cefuroxime	meningitis	*In vitro/In vivo*	[141]
O/W	lactoferrin	indinavir	HIV	*In vivo*	[142]
O/W	-	valproic acid	epilepsy	*In vitro/In vivo*	[143]
W/O/W	borneol	metformin	Alzheimer's disease	*In vivo*	[144]

Harun et al. (2018) proposed an O/W nanoemulsion to enhance the permeation of cefuroxime for treating meningitis. The formulation showed no toxicity in hCMEC/D3 cells. Following parenteral administration in rats, the drug concentration in nanoemulsions was 1.4 times higher than that of free cefuroxime [141]. An O/W nanoemulsion system carrying indinavir was also proposed to treat HIV-associated neurocognitive disorders [142]. Indinavir has low water solubility and limited permeation across the BBB due to its recognition by the Pgp efflux pump. Polysorbate 80 was incorporated into the formulation to inhibit the efflux pump, and lactoferrin was included to modulate the immune system and facilitate receptor-mediated permeation. Rats received an intravenous injection (5 mg/kg drug), and the concentration of indinavir in the brain was 4.1 times higher when it was delivered via the nanoemulsion than when it was delivered as the free drug. Furthermore, the presence of lactoferrin in the nanoemulsion further increased the brain concentration of indinavir by 1.6 times [142].

Although valproic acid permeates the BBB via transporter-facilitated transport, O/W nanoemulsions containing this drug were formulated to evaluate permeation in hCMEC/D3 cells and human CC-2565 astrocytes *in vitro* and to assess increased bioavailability in the brain *in vivo* following an intraperitoneal injection in rats (60 mg/kg). The nanoemulsion permeated the BBB 1.18 times more effectively than the free drug in the *in vitro* experiment. Furthermore, *in vivo*, the nanoemulsion generated an AUC that was 4.38 times higher in the brain, indicating significantly increased bioavailability [143].

Hong et al. (2019) formulated metformin in nanoemulsions (W/O/W) to enhance drug delivery to the CNS. Metformin, which is conventionally used to treat type 2 diabetes mellitus, has been shown to inhibit Aβ protein aggregation and tau phosphorylation, making it a potential treatment for Alzheimer's disease [145]. Furthermore, the nanoemulsions contained borneol to increase drug permeability across the BBB. In the *in vivo* study, rats received 50 mg/kg of metformin and borneol in the formulation via intragastric administration. The results showed 1.3- and 4.0-fold increases in the AUC and half-life, respectively. An analysis of the brain tissue revealed that the concentrations of the borneol/metformin nanoemulsion were 1.2 and 2 times higher than those of the nanoemulsion containing only metformin and the free drug, respectively. Therefore, the ability of borneol to increase the BBB permeability of drugs is demonstrated. However, these vectorizations do not impact cellular uptake [144]. It would be interesting to complement this assay because borneol can facilitate the action of nanoemulsions on amyloid aggregates, which are located extracellularly. However, its effect on tau protein neurofibrillary tangles inside cells may be limited [146].

Hybrid systems of nanoparticles

Hybrid nanoparticle systems combine different types of nanocarriers to amplify their advantages and mitigate their disadvantages (Fig. 3) [147]. Hybrid systems represent promising structures that combine characteristics of two different systems. For example, nanoparticles surrounded by phospholipids benefit from the outer layer, which increases biocompatibility, leading to a longer half-life and extended circulation time to reach the target site. Meanwhile, the content inside the system enables more controlled release of the drug (Table 8). Among the hybrid systems used to enhance permeation across the BBB, nanoparticles encapsulated within liposomes or lipid layers, as well as delivery systems that incorporate cyclodextrins, are notable.

Table 8. Summary of hybrid systems of nanoparticles as examples in this review.

Nanoparticles	Material	Functionalization	Drug	Disease	Biological analysis	Reference
liposome/polymeric nanoparticle	phospholipid/albumin	T807/TPP	curcumin	Alzheimer's disease	*In vitro/In vivo*	[148]
liposome/polymeric nanoparticle	phospholipid/PLGA	T807	curcumin	Alzheimer's disease	*In vitro/In vivo*	[149]
liposome/polymeric nanoparticle	phospholipid/PLGA	CDX	doxorubicin	glioma	*In vivo*	[150]
liposome/NLC	phospholipid/ oleic acid	TPP/RVG	resveratrol	Alzheimer's disease	*In vitro/In vivo*	[151]
liposome/polymeric nanoparticle	HSPC/PLGA	-	paclitaxel	glioma	*In vitro/In vivo*	[152]
liposome/polymeric nanoparticle	DSPE-PEG/PLGA	angiopep-2 and AS1411	doxorubicin	glioma	*In vitro*	[153]
cyclodextrin/liposome	oligosaccharide /phospholipid	-	estetrol	cerebral ischemia	*In vitro*	[154]

One strategy to enhance polymeric nanoparticle compatibility with the organism´s cell is to involve them with red blood cells, a cell type with greater ease of extraction. Both albumin [148] and PLGA [149] nanoparticles have been incorporated into red blood cells to deliver curcumin to the brain for the treatment of Alzheimer's disease. In both studies, the researchers functionalized the nanoparticles with T807, an imaging agent that interacts with tau protein, demonstrating the ability of these structures to permeate the BBB and facilitate uptake by hippocampal cells [148,149]. In the albumin nanoparticles enclosed within red blood cells, there was also conjugation with TPP, a ligand capable of interacting with the negatively charged membrane of mitochondria. However, this was found to be unnecessary for permeation across the BBB [148]. The presence of the T807 agent in the nanoparticle increased the concentration of curcumin in the brain by 6.3 times compared to free curcumin after intravenous injection. This effect may be attributed to the T807's positive charge, which enhances its interaction with the negatively charged cell membrane [149].

PLGA nanoparticles carrying doxorubicin, surrounded by red blood cells and conjugated with the CDX peptide, have also been formulated [150]. The CDX peptide, composed of sixteen amino acid residues and developed through structure-based design, binds to nicotinic receptors involved in receptor-mediated transcytosis in brain endothelial cells [155]. The explained mechanism enabled the nanoparticles to permeate rat brain capillary endothelial cells. Furthermore, the presence of the CDX peptide facilitated the entry of nanoparticles into the tested cells. *In vivo*, CDX-conjugated nanoparticles showed greater distribution in the mouse brain after intravenous injection than unconjugated nanoparticles, resulting in an increase in survival from 23.5 to 28.5 days and greater induction of apoptosis [150].

NLCs surrounded by red blood cells and conjugated with TPP and a 29-amino acid rabies virus glycoprotein (RVG29) were formulated to carry resveratrol. These structures aimed to reduce ROS levels in Alzheimer's disease models [151]. RVG29 can bind to nicotinic receptors, facilitating interactions with neuronal cells [156]. The *in vitro* model used to assess BBB permeation involved polymeric nanoparticles surrounded by red blood cells. The RVG29 peptide was crucial for BBB permeability, while the TPP peptide influenced uptake by HT22 cells. *In vivo* testing reproduced these results after the intravenous injection of 5 mg/kg in rats. This formulation led to cognitive improvements in the tested animals and reduced levels of the β-amyloid protein [151].

In some cases, a layer of phospholipids is used to surround polymeric nanoparticles, forming lipid-polymeric nanoparticles [157], such as in the use of a PLGA core and a hydrogenated phosphatidylcholine (HSPC) phospholipid layer to carry paclitaxel conjugated with RVG. A cell capture assay indicated that nanoparticles inside macrophages could be transferred to glioma cells. No significant capture by neurons was observed, reducing the risk of neurotoxicity. The nanocarriers loaded with the drug were cytotoxic in U87 glioblastoma cells, and no toxicity was observed in the absence of the drug. Twenty-four and 48 hours after intravenous administration in mice, the nanoparticles reached the brain and reduced tumor progression [152].

In another case, the PLGA polymer was combined with lecithin and DSPE-PEG, a phospholipid, to carry doxorubicin. The nanoparticles were conjugated with angiopep-2, AS1411, or both [158]. AS1411 is a DNA aptamer that binds to nucleolin, a protein highly expressed in the plasma membrane of glioma cells [158]. In the fluorescence capture assay, brain capillary endothelial cells captured nanoparticles containing both peptides and only angiopep-2 on the surface. However, in the case of C6 glioma cells, doubly conjugated nanoparticles showed more significant fluorescence than nanoparticles conjugated with

AS1411 alone. Therefore, the two ligands have synergistic effects on the tested cells. Furthermore, compared with nanoparticles lacking angiopep-2 and the free drug, nanoparticles conjugated with angiopep-2 enabled 4.3 times greater transport of doxorubicin across the BBB in an *in vitro* model. In the glioma cell evaluation, dual-conjugated nanoparticles and those containing only AS1411 showed significantly greater cytotoxicity (IC50 values of 0.91 µM and 0.78 µM, respectively) than nanoparticles conjugated with angiopep-2 and the free drug. This finding indicates the importance of the AS1411 peptide in glioma cells. This study further revealed that dual conjugation of nanoparticles in the development of formulations with nanocarriers can produce a synergistic effect [158].

When applied to the CNS, cyclodextrins are often associated with another type of delivery system, forming a hybrid structure. Cyclodextrins are composed of α-1,4-D-glucopyranose oligomers, which are derived from the cleavage of D-glucopyranose polymers found in starch [159,160]. Unlike the nanocarriers mentioned previously, cyclodextrins have a cup-like structure with a water-soluble exterior due to the presence of hydroxyl groups and a hydrophobic interior. In the commercial market, formulations are available for oral administration, such as limaprost, an analog of prostaglandin E1, in α-cyclodextrin, and piroxicam in β-cyclodextrin [159,160].

Palazzo et al. (2019) proposed the use of drug-loaded cyclodextrins inside liposomes to treat cerebral ischemia in premature babies. The chosen active substance was estetrol, an estradiol metabolite with antioxidant and neuroprotective effects. Cyclodextrins form a complex with estradiol, which is then located inside liposomes, preserving the integrity of the lipid bilayer and achieving a slower and more controlled release of the active substance. Furthermore, when evaluating permeation across the BBB with hCMEC/D3 cells, the hybrid system showed a transport rate up to 10 times higher than that of free estetrol over 6 hours. The authors suggested that BBB transport occurs due to adsorptive-mediated transcytosis, facilitated by the interaction between the positive charge on the surface of the systems and the negative charge on the BBB [154].

As shown in Tables 1-8, the predominant types of nanoparticles produced are polymeric nanoparticles and micelles. These drug delivery systems consist of synthetic or natural polymers (micelles can also be composed of phospholipids), which can be combined to maintain biocompatibility and biodegradability. Moreover, polymers have functional groups at their ends that allow for nanoparticle conjugation by binding to ligands that interact with membrane receptors. Thus, polymers are versatile and can be applied in nanocarrier formulations.

The conjugation of nanoparticles with ligands represents a powerful strategy for enhancing cellular uptake. Once again, the mechanisms of receptor-mediated and adsorptive-mediated transcytosis are highlighted. For instance, dual conjugation is particularly intriguing for cancer treatment, utilizing one ligand for brain cell uptake and another for tumor cell uptake, thereby enhancing drug delivery to the target.

To date, no formulation with the nanocarriers described in this study has been developed for treating diseases affecting the CNS [26,27]. Some of the research included in this paper presents only *in vitro* results, necessitating more advanced biological assays to analyze their therapeutic applications. Studies that include *in vivo* experiments have reported promising results by formulating nanocarriers that increase drug concentrations in the brain and show indications of therapeutic efficacy. Consequently, these formulations could undergo further biological evaluations, such as a determination of the permeation mechanism through the BBB, toxicity evaluations, and optimizations, to enable their industrial applications and use in treating diseases affecting the CNS.

CONCLUSIONS

The CNS is protected by the BBB, which plays a critical role in maintaining homeostasis. However, neurological disorders are significant contributors to disability and mortality worldwide, and the BBB poses a challenge to the delivery of drugs needed for treatment. Therefore, strategies such as BBB modulation, bypassing the BBB, and altering the physicochemical properties of drugs and drug delivery systems are essential.

Polymeric nanoparticles and micelles are among the most extensively studied nanocarriers for drug delivery. Conjugating nanoparticles to increase uptake by brain endothelial cells has broad applications, primarily through receptor-mediated transcytosis and adsorption mechanisms. Research on nanoparticles has primarily focused on brain cancers and neurodegenerative diseases, but studies have also focused on infections,

inflammation, stroke, epilepsy, and cerebral ischemia.

Although commercially available nanocarrier formulations for CNS diseases are currently lacking, the literature increasingly describes the advantages of these formulations in delivering drugs across the BBB. Moreover, nanoformulations targeting other diseases are already on the market, highlighting the potential application of this approach in the treatment of brain diseases.

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CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Material preparation, data collection and writing the first draft of the manuscript were performed by R. A. Conceição. The visualization and writing review were performed by J. V. V. Silva. The writing review and edition, and supervision were performed by L. D. Prado and B. F. C. Patricio. All authors read and approved the final manuscript.

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