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Controlled Drug Release Systems for Cerebrovascular Diseases

Celia Martín-Morales, Sofia Caspani, Manuel Desco, Célia Tavares de Sousa, and María Victoria Gómez-Gaviro**

This review offers a comprehensive exploration of optimized drug delivery systems tailored for controlled release and their crucial role in addressing cerebrovascular diseases. Through an in-depth analysis, various controlled release methods, including nanoparticles, liposomes, hydrogels, and other emerging technologies are examined. Highlighting the importance of precise drug targeting, it is delved into the underlying mechanisms of these delivery systems and their potential to improve therapeutic outcomes while minimizing adverse effects. Additionally, the specific applications of these optimized drug delivery systems in treating cerebrovascular disorders such as ischemic stroke, cerebral aneurysms, and intracranial hemorrhage are discussed. By shedding light on the advancements in drug delivery techniques and their implications in cerebrovascular medicine, this review offers valuable insights into the future of therapeutic interventions in neurology.

1. Introduction

Currently, research in the field of biomaterials is experiencing an important upswing. While prominent primarily for their applications in treatments like implants and medical devices, their utility extends far beyond, becoming essential for enhancing health and quality of life in numerous ways.

In this context, biomaterials play a vital role in medical applications, facilitating the support, enhancement, or substitution of impaired tissue or biological processes. This capability arises from the synergistic integration of medicine, biology, physics, chemistry, tissue engineering, and materials science.

Among all the applications currently being studied, the development of vectorization systems for controlled drug release has attracted increasing attention. Drug delivery is the process of administering a pharmaceutical compound to achieve a therapeutic effect in humans or animals. The search for materials that allow achieving this controlled release within the organism comes from the need to reduce the limitations that can currently be found in drug delivery, such as distribution, cellular uptake, toxicity, assimilation, and elimination associated with the compound's distribution mode. In this context, pharmacokinetics, which is the movement of drugs into, through, and out of the body, plays a crucial role in the design of a drug delivery system. It involves the time course of drug absorption, distribution, metabolism, and excretion, as briefly explained. Within this framework, absorption refers to the movement of a drug from its administration site to the bloodstream. Absorption of the drug through the plasma membrane can occur in two main ways: passive transport, and

C. Martín-Morales, M. Desco, M. V. Gómez-Gaviro
Unidad de Medicina y Cirugía Experimental, Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM)
Doctor Esquerdo 46, Madrid 28007, Spain
E-mail: desco@hggm.es; vgomez@hggm.es

S. Caspani
IFIMUP – Institute of Physics for Advanced Materials
Departamento de Física e Astronomia, Nanotechnology and Photonics of University of Porto
Faculdade de Ciências
Universidade do Porto, Rua do Campo Alegre s/n, Porto 4169-007, Portugal

M. Desco, M. V. Gómez-Gaviro
Departamento de Bioingeniería
Universidad Carlos III de Madrid
Leganés 28911, Spain

M. Desco, M. V. Gómez-Gaviro
Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM)
Madrid 28029, Spain

M. Desco
Centro de Investigaciones Cardiovasculares (CNIC)
Melchor Fernández Almagro
Madrid 28029, Spain

C. Tavares de Sousa
Departamento de Física Aplicada and IAdChem
Facultad de Ciencias
Universidad Autonoma de Madrid (UAM)
Campus de Cantoblanco, C/ Francisco Tomas y Valiente, 7, Madrid 28049, Spain

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active transport. The first one involves the movement of the drug across the cell membrane by diffusion, that is, from high to low-concentration regions, without requiring additional energy. In this mechanism, the rate of drug diffusion is directly proportional to the concentration gradient. On the other hand, active transport requires energy to facilitate the transport of drugs against a concentration gradient. After being absorbed, a drug undergoes distribution between the blood and extravascular fluids and tissues of the body. Drug distribution determines the quantity of drug that reaches a specific target site when compared to the rest of the body and plays a crucial role in drug efficacy and its associated toxicity. Various factors can affect the distribution of a drug, an important one being the presence of anatomical barriers such as the blood–brain barrier (BBB). Another factor that must be considered is the metabolism of drugs, which pertains to the fraction of drug that is lost during adsorption. Finally, the unchanged drug or its metabolites are excreted from the body through several mechanisms, such as urine, bile, sweat, and saliva, among others.[1]

Among the many advantages that can be found from the use of these controlled release systems compared to conventional drug delivery systems, the following should be highlighted.

Controlled-release drug delivery systems can be classified in several ways, one of which is based on their mechanisms of drug release, such as dissolution-controlled, diffusion-controlled, water penetration-controlled, chemically controlled, and nanoparticle-based systems.[2] Briefly, dissolution-controlled systems involve drugs that are either coated or encapsulated within slowly dissolving polymeric membranes, that is, reservoir systems, or matrices, that is, monolithic systems. In diffusion-controlled systems, inert water-insoluble polymeric membranes and matrices are employed to trap the drugs and control their release through diffusion. In the former system, the drug is located in the core and covered by a membrane, which can be either porous or nonporous, with characteristics such as thickness and porosity determining the rate of release. On the other hand, in matrix-controlled delivery systems, the drug can be either dissolved or dispersed throughout the matrix. Water penetration-controlled systems can be divided into osmotic pressure and swelling-controlled systems. Osmotic drug delivery systems use osmotic pressure for controlled drug release through osmosis, where water moves from lower to higher solute concentrations across a semipermeable membrane. Key components include the drug or osmogenic salt, a semipermeable membrane, and an outer coating material. Swelling-controlled drug delivery systems, on the other hand, use a hydrophilic polymer that transitions from a glassy to a rubbery state in water, allowing the drug to diffuse slowly from the swollen polymer matrix. Chemically controlled drug delivery systems use biodegradable polymers that degrade in the body via natural processes, eliminating the need for removal. They are classified into polymer-drug dispersion systems, where the drug is dispersed in the polymer and released as it degrades, and polymer-drug conjugate systems. Degradation occurs through bulk or surface erosion, influenced by factors such as polymer composition, structural defects, and molecular weight. Nanoparticles-based systems are systems capable of increasing the concentration of a drug without causing toxicity by selective targeting through stimuli-responsive delivery, being their mechanisms of drug release related to the specific type of nanoparticle.

These mechanisms can be either internal (chemical stimuli-responsive), such as pH, temperature, presence of enzymes, and redox potential changes, or external stimuli (physical stimuli-responsive) like light, temperature variations, ultrasound waves, and electric or magnetic field.[3] In addition, previous studies have demonstrated that the effectiveness of drugs in such controlled release systems can be significantly increased when the pharmaceutical agent is encapsulated or attached to a polymer, lipid, or other substances that facilitate enhanced penetration of the substance to the targeted location within the organism[4] Moreover, the high surface to volume ratio of nanoparticles allows them to bind, adsorb and carry other substances, besides drugs, such as small moieties like proteins, peptides and oligonucleotides.

It is well known that NPs for controlled drug delivery use several mechanisms to enter the cells. Among all, endocytosis has been considered the major route for delivering drugs into cells and can be generally classified in two main mechanisms: Phagocytosis and pinocytosis.[5] The former one is a unique endocytic pathway mainly found in phagocytes, responsible for the uptake of large particles, whereas pinocytosis controls the swamping of fluids and molecules containing small particles within small vesicles. The latter one can be further divided into four main classes, namely macropinocytosis, clathrin-mediated endocytosis, caveolin-mediated endocytosis, and clathrin- and caveolin-independent endocytosis. The mechanisms generally used to internalize nanosize materials, such as nanoparticles, are Clathrin- and caveolae-mediated endocytosis, which are receptor-mediated processes.[6] Nanoparticles that use the endocytic pathway to enter cells are usually degraded by hydrolytic enzymes present in the lysosomes. The process of endocytosis involves the internalization of substances into an endocytic vesicle, which then fuses with the early endosomal compartment. This compartment matures into a late endosome and eventually accumulates in the lysosome. During this maturation process, the pH of the endosome progressively decreases from a physiological pH of 7.4 to approximately pH 6.5 in the early endosome (EE), pH 6.0 in the late endosome, and pH 5.0 in the lysosome.[7] Studies have shown that the critical rate-determining step in the delivery of therapeutics is the escape from the endocytic pathway. Failure to escape results in entrapment and potential degradation within the lysosome.[8] A major challenge in the development of a nanoparticle is, therefore, to produce a nanosystem with the ability to escape from endosomes, thus avoiding endosomal degradation. In this context, endosomolytic agents, characterized by the ability to escape from endosome/lysosome to the cytosol, have been widely studied. Examples include peptides, proteins, toxins, polymers, or small chemical compounds, as presented in the following sections. The purpose of nanoparticles is, therefore, to escape from endosome to enter cells. Although they have the same mission, different nanoparticles employ different mechanisms to avoid endosomal degradation, which can be primarily divided into 3 strategies as follows: Strategies for promoting endosomal/lysosomal escape, strategies for crossing directly the cell membrane without entering endosomes or lysosomes, and strategies that utilize different pathways to escape

lysosome thus avoiding degradation.[9] In this subsection, the main mechanisms for promoting endosomal escape, such as osmotic lysis, proton sponge effect, swelling effect, pH-responsive, and membrane destabilization induced by pore formation, membrane disruption or fusion and photochemical internalization,[10] are briefly presented. The proton sponge effect relies on the buffering action of materials within a physiologically relevant pH range. In this process, protonated amino groups in cationic materials bind with protons delivered by proton pumps, causing them to remain continuously active. Each proton influx is accompanied by a chloride ion and a water molecule, leading to osmotic swelling. This swelling eventually causes the lysosomes to rupture, releasing the cationic nanocarriers into the cytoplasm.[11] This strategy is usually applied to polycationic materials such as PEI[12] and PAMAM dendrimers,[13] among other materials containing secondary or tertiary amines. Because of the incorporation of protonable amino groups, such materials become protonated and produce the so-called "proton sponge" effect at low pH (4 to 5.5) of endosomes or lysosomes. However, studies have reported that such nanocarriers present limited ability of endosomal escape. In fact, since few lysosomes per cell are able to fluctuate, only 1% of these systems can achieve escape.[14,15] Osmotic lysis, similarly, to the proton sponge effect, is another mechanism that involves the swelling and rupture of the endosome due to osmotic pressure, usually caused by the disassembly of pH-responsive nanoparticles at lower pH. Examples of nanoparticles that employ such mechanisms to escape from endosomes are ammonium-based amphiphilic triblock polymers coated nanomicelles[16] and calcium phosphate (CAP) inorganic nanoparticles,[17] for instance. Endosomal/lysosomal escape can also be induced by the swelling effect caused by pH-responsive materials that swell at lower pH in lysosomes after endocytosis. A swelling nanoparticle is similar to an open umbrella, as introduced in 2012 by Szoka et al.,[18] in which the rapid volumetric expansion of the nanoparticle results in membrane disruption promoting lysosomal escape. Even though several studies have been performed, supporting the hypothesis that the rupture of the membrane is caused by the mechanical strain of particle swelling, the effect of swelling is still unclear.[19] Another mechanism of endosomal/lysosomal escape involves the destabilization of the membrane which can be caused by several factors, such as pore formation, membrane disruption, membrane fusion and photochemical internalization. Membrane pore formation can be attributed to the direct interaction of polymers or peptides with membranes, resulting in diffusion of therapeutic drugs from endosomal/lysosomal compartments. In this context, as the pH of endosomes decreases, the proteins or peptides present in toxins accumulate in EEs. This triggers a conformational change in the transmembrane domain, causing it to insert into the endosomal/lysosomal membrane and form various types of pores, such as barrel stave and toroidal pores.[20] Furthermore, the disruption of the membrane can be attributed to increased membrane instability, which is caused by electrostatic interactions between the material and the endosomal membrane itself. The main mechanism driving membrane disruption occurs when the material becomes positively charged in an acidic environment. This change allows it to form ion pairs with the negatively charged endosomal membrane, leading to membrane destabilization and the subsequent release of drugs.[21] In this context, ionizable lipids used as delivery vehicles can mediate endosomal escape, by becoming protonated as the endosome matures, resulting therefore in phase transformation followed by membrane disruption.[22] Furthermore, physical and mechanical characteristics, such as ultrasound, temperature and magnetism can also be employed to enhance endosomal/lysosomal escape. Membrane fusion is another mechanism of endosomal escape, which arises from various fusogenic agents, such as proteins, lipids, ligands, metals and polymers. involves the fusion of nanoparticles or carriers with the endosomal membrane, facilitating their release into the cytoplasm. The fusion process is initiated by a conformational change in the fusion peptides or proteins, triggered either by interaction with specific cellular receptors or by a pH change.[23] Among fusiogenic agents, Dioleoyl-phosphatidyl ethanol-amine (DOPE) is the most commonly used membrane fusion agent.[24] Endosomal/lysosomal escape of several types of nanocarriers can also be promoted by photochemical internalization, which is a light-triggered technique.[25] This innovative mechanism harnesses light activation to disrupt endocytic structures, typically utilizing a light-sensitive small molecule. Upon illumination, this molecule generates significant quantities of oxidizing active substances, which disrupt the endosomal/lysosomal membrane, facilitating the release of encapsulated drugs.

Given the above-mentioned considerations, the optimal nanoplatform employed for both therapy and diagnosis, therefore, consists of, at least, three types of polymers, with the majority of systems being polymeric. One polymer must be responsive to either external or internal stimuli, another is essential for ensuring biocompatibility, and the final one imparts physicochemical stability to the colloidal system.[26]

To achieve this goal, numerous systems have been proposed as possible controlled release vectors. The selection of a specific system depends on factors such as the drug to be encapsulated, the targeted organ for release, physiological conditions, route of administration (topical, parenteral, enteral, inhaled, or ophthalmic), and numerous other considerations. Evaluation of these factors determines the suitability of each system, with adjustments made accordingly, tailored to the individual case.

In this review, the different controlled drug delivery systems that have been recently studied will be explained, with special emphasis on the applications related to these biomaterials in cerebrovascular diseases.

Moreover, it is essential to consider not only the advantages of these systems over conventional systems but also the advantages they can bring more specifically to the treatment of cerebrovascular diseases. First, the administration of newer and more complex therapies may become possible, such as proteins. In addition, the systemic toxicity can be reduced, the drug can be accumulated at the site with high selectivity and biocompatibility, and what's more, it is possible to get across the BBB without damaging it. Compared to other ways of drug delivery in this type of disease, controlled release systems are safer and more effective in brain tumors, brain abscesses, etc.[27,28]

Cerebrovascular diseases, as their name implies, encompass pathologies affecting the vascular system of the brain. These disorders typically manifest as either ischemic or hemorrhagic events, including conditions like stroke, carotid stenosis, aneurysms, and vertebral stenosis, among others. Despite various diagnostic methods available for detecting such diseases,

they remain a leading cause of death globally. Hence, there is a pressing need to further advance research in this domain.

Specific challenges and bottlenecks in current pharmacotherapy for cerebrovascular diseases.

The advancement of genomic technologies and the rise of personalized medicine and targeted treatments have in recent years led to a greater understanding of cerebrovascular diseases, as well as the possibility of curing more patients with lower associated risks.

However, pharmacotherapy for cerebrovascular diseases faces numerous challenges and bottlenecks, significantly impacting the development and effectiveness of treatments, such as the penetration of the BBB, drug delivery efficiency, side effects and toxicity, heterogeneity of cerebrovascular diseases, drug resistance, inflammatory and immune responses, and economic issues, among others. The BBB is a selective permeability barrier that protects the brain but also restricts the passage of many therapeutic agents. In this context, nanoscience has been considered an innovative and possible solution to effectively deliver therapeutics to the brain. At present, effective drug delivery across the BBB remains a significant hurdle, since almost all macromolecular drugs and more than 98% of small molecules have failed to cross the BBB. Systemic administration of nanoparticles is a potential approach to ensure efficient drug delivery to specific brain regions, but it presents drawbacks related to their production scalability in industrial settings. Moreover, their impact on the central nervous system remains largely uncertain, and they may provoke systemic side effects. Furthermore, the heterogeneity of cerebrovascular diseases complicates the development of universal therapies, emphasizing the need for personalized treatments tailored to individual profiles. Drug resistance further reduces treatment efficacy over time, necessitating new drugs and combination therapies. Inflammatory processes involved in cerebrovascular diseases are complex to modulate, requiring targeted immunomodulatory therapies. Finally, economic and accessibility issues limit the availability of advanced therapies, especially in low-resource settings, calling for policies to reduce costs, enhance healthcare infrastructure, and develop cost-effective treatments through public–private partnerships.[29]

The medical approaches proposed to curb these diseases are also numerous. To date, the effective therapy for ischemic stroke is to restore cerebral blood flow via intravenous thrombolysis, mechanical thrombectomy, and administration of tissue plasminogen activator.[30] In this context, a major challenge to be taken into account is the short therapeutic time window to deliver therapeutics to the brain, otherwise resulting in further complications.

At present, most treatments on the market focus on the impending effects of cerebrovascular disease, without taking into account the subsequent side effects. Priority is given to restoring blood flow, which in many cases, saves the patient's life, but does not cure the disease. In the context of ischemic stroke, even if patients receive treatment in time, reperfusion injury is difficult to avoid. Therefore, to prevent damage after reperfusion and extend the therapeutic window, several neuroprotective drugs, with anti-inflammatory and antioxidant stress effects, have been widely studied in vitro and in vivo experiments, confirming their efficacy in ischemic stroke models. However, such drugs failed clinical translation, because of insufficient concentration and rapid elimination.[31] In fact, the currently applied systemic approach is not targeted to a specific area of the body. As drugs travel toward the affected area of the brain, they may interact with other parts of the body, potentially reducing the amount of drug reaching the intended organ and causing side effects in other organs.[32]

A leading strategy proposed in recent years involves the use of biomaterials that respond to specific stimuli, as previously mentioned. These materials have the capability to target diseased tissue directly and adapt their physicochemical and morphological properties in response to changes in their environment. Stimuli can be internal such as pH, ROS, enzymes, etc., or external such as magnetic or electric fields. Therefore, controlled release systems are an important possibility in the study of the treatment of these diseases, which could provide viable and minimally invasive solutions to these diseases in the coming years. At present, there are different types of nanocarriers applied for the treatment of ischemic stroke, including liposomes micelles, poly (lactic-*co*-glycolic acid) (PLGA), dendrimers, extracellular vesicles (EVs), and polymeric and inorganic nanoparticles. Their advantages, challenges, therapeutic molecules, and injection methods in ischemic stroke will be discussed in the next sections.

2. Different Vectorization Systems for Drug Delivery: Organic

Vectorization systems for drug delivery can be generally distributed into two main big categories: Organic systems, which include micelles, dendrimers, polymeric micro- and nanoparticles, and liposomes, among others, and inorganic ones, composed of nanoparticles consisting of inorganic components. This section reviews the most representative organic vectorization systems addressed toward applications in cerebrovascular diseases.

2.1. Micelles

Micelles, mostly polymeric, represent a captivating category of amphiphilic nanostructures formed through the self-aggregation of amphiphilic molecules in water above a specific critical concentration known as the critical micelle concentration (CMC). With both hydrophilic and hydrophobic regions, micelles feature hydrophobic heads clustered at the core, accommodating hydrophobic drugs, while the sub-100 nm hydrophilic tails form the shell,[33] ensuring stability, protection, prolonged circulation in vivo[34,35] and minimum protein adsorption,[34,36] among other benefits.[33]

Moreover, among nanocarriers, micelles have garnered substantial attention as carriers for targeted drug delivery in treating brain cancer, after appropriate surface functionalization.[37] Their nano-scale dimensions evade easy recognition and clearance by the phagocytic system, while their hydrophilic shells promote enhanced permeability and retention effects.

Although micelles have numerous advantages, as previously mentioned, these systems also have limitations, such as insufficient stability upon dilution in the bloodstream (even though it is higher than in other formulations), complex characterization, and scalability of their production. Moreover, in drug

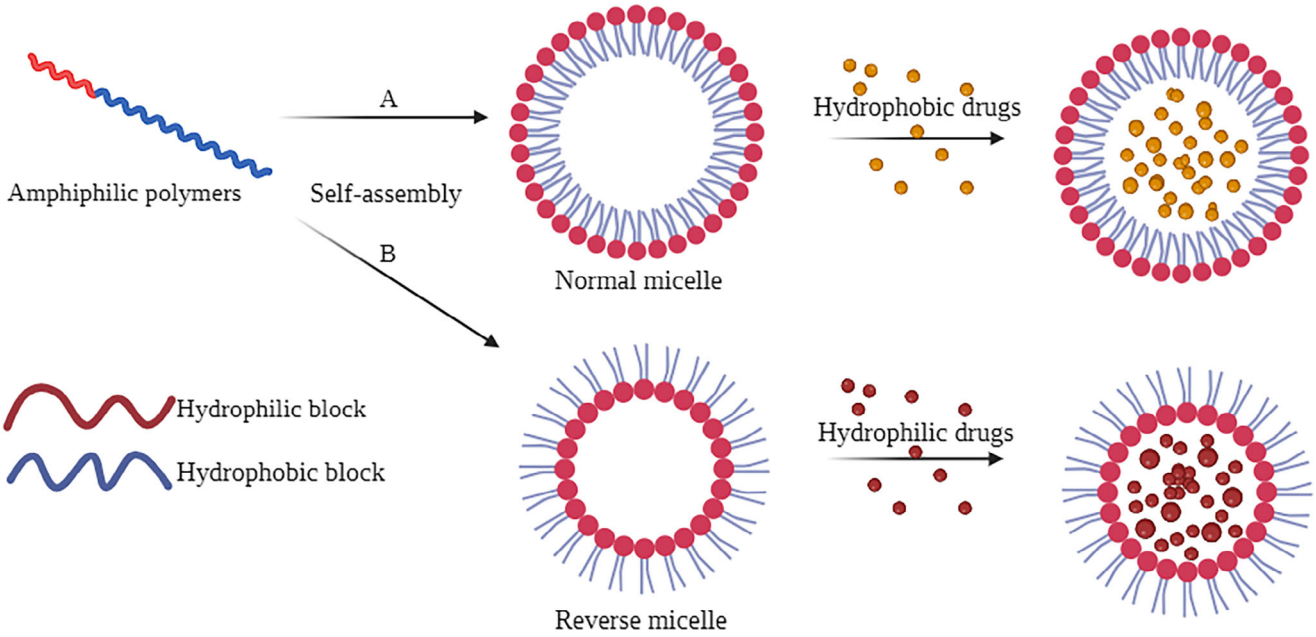

Figure 1. Synthesis of polymeric micelles and drug inclusion for controlled release. A) Normal micelle formation, with the hydrophilic side facing outward. Hydrophobic drugs are introduced into this type of micelles. B) Reverse micelle formation, with the hydrophilic part toward the inside. Hydrophilic drugs are encapsulated in these micelles.

delivery, the selection of targeting moieties mainly employs receptor-mediated targeting strategies, such as polypeptides and monofunctional antibodies, affecting the enhancement of targeting efficiency.[38,39]

The CMC value is the most important parameter to define micelles' thermodynamic stability. Above the CMC, the equilibrium is dynamic. Polymeric micelle's main advantages can be found in their lower CMC.[37]

2.1.1. Types of Polymeric Micelles

Several factors play pivotal roles in regulating the formation of diverse types of polymeric micelles. The choice of the polymer, whether it's diblock, triblock, multiblock copolymers, grafting polymers, or stimulus-sensitive polymers, for instance, dictates the self-assembly process leading to distinct polymeric micelles.[35] Yet, beyond polymer selection, other critical elements influence the formation of these systems, including pH, polymer concentration and ratios, and solvent properties, among others. Within this framework, diverse types of micelles can be synthesized. Broadly, they can be categorized as 'standard' micelles, where the hydrophilic segment of the amphiphilic polymer faces outward, while the lipophilic segment resides in the core of the micelle. Conversely, micelles with the hydrophilic segment inward and the lipophilic segment outward are termed reverse micelles. Additionally, by incorporating solubilizers into surfactant micelles, mixed micelles can be prepared.[35] Moreover, micelles can be generally categorized based on their shape, either as spherical or cylindrical, with spherical micelles being the most commonly employed for drug release.[40] Furthermore, block copolymers, the primary constituents, can be categorized into three types based on the intermolecular forces governing segregation in an aqueous medium:

- Amphiphilic micelles: hydrophobic interactions
- Polyon complex micelles: electrostatic interactions
- Micelles formed by metal complexation

The mode of drug encapsulation is also significant, primarily falling into two groups: chemical covalent bonding or physical encapsulation methods. This classification influences the localization of the drug within the micelle. Typically, non-polar compounds reside in the core, polar compounds in the shell, and those with intermediate polarity are encapsulated between the core and the shell (**Figure 1**).[35]

2.1.2. Innovative Applications of Micelles in Cerebrovascular Diseases

Currently, micelles find diverse applications, particularly as carriers for drugs, with their relevance in cerebrovascular diseases being particularly notable. In this context, a recent study has focused on designing a novel prodrug nanocarrier based on PEG and diosgenin derivatives aimed at inhibiting thrombosis.[41] This study highlighted that incorporating the prodrug into micelles could enhance efficacy in preventing thrombus formation, both arterial and venous, compared to other therapies. Administered by tail intravenous injection, the prodrug micelles exhibited favorable drug release kinetics, facilitated by nanocarrier cleavage under acidic conditions at thrombosis sites, enabling rapid diosgenin release, thereby aiding thrombosis inhibition.[41]

As a conclusion, this research underscored the suitability of prodrug micelles as a drug delivery system, eliminating the necessity for additional carriers.[41]

Another noteworthy application of these micelles, which has recently garnered considerable attention, is their utilization as drug nanocarriers in the treatment of ischemic stroke. In this context, the research conducted by Lu, Yifei, et al.[42] aimed to enhance the efficacy of thrombolytic therapy and reduce reperfusion injury in stroke treatment. To achieve this goal, the proposed strategy involved the neuroprotection and maximization of the rate of brain reperfusion. For such purpose, a polymeric micelle system (CREKA-PEG-LysB/Rapamycin, designated CPLB/RAPA) with neurovascular targeting and mTOR inhibiting functions was created. CREKA (peptide C) is a specific fibrin-binging peptide employed to facilitate micelle retention in the neurovascular unit of ischemic brain areas due to fibrin's role as the major component of microthrombi. Conversely, mTOR, the mammalian target of rapamycin, has been proved to play an active role in ischemic stroke. Therefore, inhibition of this pathway could induce productive autophagy, enhancing neuron survival and diminishing neuroinflammation.[42] To achieve this objective, different micelle formulations were prepared using dialysis methods, ultimately yielding spherical particles with a uniform size distribution of ≈65 nm in diameter.

By incorporating ROS-sensitive compounds, micelles were designed to undergo disassembly in oxidative environments, facilitated by polymer degradation and conversion into the more water-soluble PEG-polylysine. In this context, several parameters have been investigated concerning particles size and their capability to deliver drugs accurately, including incubation time, H_2O_2 concentration in the media, and micelle modifications. The mechanism by which the micelles achieved the objective started with the retention of micelles in the ischemic zone via microthrombus binding. It followed the penetration into the brain by damaged BBB crossing, with subsequent release of the drug due to the reactive oxygen species (ROS) within the oxidative microenvironment.[42]

In summary, microthrombus-binding polymeric micelle systems have been developed, providing direct protection to neurons and functional modulation of microglia and endothelium while preserving the integrity of the BBB.[42] In another work, Song et al., synthetized micelle nanoparticles by using 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-*N*-[methoxy (polyethylene glycol)-2000] (DSPE-PEG2000) as the carriers, angiopep-2 (Ang) to modify the surface, and isoliquiritigenin (ISL) to encapsulate in the center of the nanoparticle. As a result, the micelle nanoparticles were able to successfully cross the BBB and accumulate in the ischemic brain areas, with subsequent release of ISL to alleviate neuronal apoptosis. Moreover, such systems provided longer circulation times of the drug itself and higher biocompatibility.[43]

Besides treatment, micelle nanoparticles can also be employed for disease monitoring and diagnosis. In this framework, Shiraishi et al. fabricated a Gadolinium-based polymeric micelle to serve as an MRI contrast agent. The result of this study highlighted a clearer contrast of the MR scans of the ischemic hemisphere at 30 min post intravenous injection compared to standard contrast.[44]

More recently, efforts have been directed toward developing functionalized polymeric micelles for delivering therapeutics to the brain to address Alzheimer's disease. In this framework, Agwa et. al synthetized polymeric micelles for targeted delivery of conjugated linoleic acid to the brain via an oral route. In this work, to achieve effective brain targeting, linoleic acid was covalently attached to lactoferrin (Lf) through an amide bond formed by a carbodiimide coupling reaction. As a result, the functionalized polymeric micelles presented a 2.8-fold increase in drug concentration in brain tissue compared to other organs, without causing any toxic effects.[45]

The limited availability of anti- Alzheimer's disease drugs with the potential to provide symptomatic relief without disease progression has underscored the necessity of developing new alternatives. This includes therapies based on peptide and siRNA, which offer greater potency and selectivity in regulating epigenetic changes and reducing amyloid plaque accumulation in the brain by binding with amyloid-β, a hallmark of Alzheimer's disease. However, challenges such as poor in vivo stability, inefficient cellular uptake, limited oral bioavailability, susceptibility to degradation by endopeptidases, and unfavorable pharmacokinetic profiles have hindered the clinical administration of these therapeutics. To address these challenges, the unique functional properties and prolonged retention effect of polymeric micelles have been harnessed for the effective delivery of these therapeutics in managing Alzheimer's disease.[46] As previously mentioned, PEGylation is one of the approaches used for augmenting micelle's metabolic stability and reducing immunogenicity. Additionally, functionalized cross-linked and hybrid micellar systems have been employed to facilitate effective amyloid-β targeting by overcoming transport barriers.[47] Furthermore, therapies based on phytoconstituents with the ability to regulate hippocampal expression have gained attention as an effective strategy for treating Alzheimer's disease. For instance, Yang et al. co-functionalized PEG-PLA-based polymeric micelles with neural cell adhesion molecule mimetic peptide C3 and triphenylphosphonium via thiol-maleimide coupling reaction for neuronal-mitochondria targeting of resveratrol. These co-functionalized micelles showed 3.9-fold higher fluorescence in the brain than their non-functionalized counterparts. Further, in vivo studies revealed an enhanced concentration of the co-functionalized polymeric micelles in brain neurons of transgenic mice compared to the hippocampus and cortex regions after intravenous administration.[48]

In conclusion, considering the structure and properties of micelles, it can be inferred that such nanocarriers offer promising potential for enhancing treatments associated with cerebrovascular diseases. Their straightforward synthesis and lack of requirement for surface functionalization render them an attractive option. However, future efforts could focus on enhancing their stability in the bloodstream to optimize efficacy, potentially enabling longer-term therapies without necessitating invasive interventions for patients.

2.2. Liposomes

Liposomes are micro-particulate or colloidal carriers, usually 0.05–5.0 μm in diameter, formed by self-assembly of amphiphilic lipid molecules in solution, used as artificial biological membranes.[49] Liposomes consist of a liposomal membrane, which can be composed of one or more lipid bilayers known as lamellas. These bilayers typically enclose an inner aqueous core, with the polar head groups oriented toward the inner and outer aqueous phases. The bilayers can exhibit either concentric or non-concentric organization.[50,51]

Thanks to their structural versatility as well as their biocompatibility, biodegradability, non-toxicity, and non-immunogenicity, liposomes are considered powerful drug delivery systems. Their ability to accommodate both hydrophobic and hydrophilic compounds enables significant efficacy in various therapeutic applications, including cancer therapy.[52–54] While liposomes are primarily composed of glycerophospholipids, they can also be derived from cholesterol, non-toxic surfactants, and even membrane proteins.[53]

2.2.1. Types of Liposomes

Although liposomes can be classified in various ways, one of the most common approaches is related to the number of layers and size. In terms of layers, liposomes are broadly categorized into those with a single layer and multilayered. Within these categories, there exist different types of liposomes, with notable examples including niosomes, novasomes, and nryptosomes, among others. Remarkably, niosomes have been shown to enhance the oral bioavailability of drugs with low absorption efficiency.[53] Novasomes, on the other hand, are capable of encapsulating both hydrophilic and hydrophobic drug molecules, with bilayer encapsulation being particularly effective in preventing incompatibility issues related to surface charge properties. They are highly relevant in medical research, including vaccine development as well as in the cosmetics industry.[53]

Another common classification method is based on the synthesis method. Liposomes can be prepared using various methods such as Reverse phase evaporation method, microfluidic channel method, Stable unilamellar vesicles (SPVL), Frozen and Thawed (FATMLV), thin film hydration method (Bangham method), Vesicles prepared by extrusion technique (VET), supercritical fluid method and Dehydration–Rehydration method (DRV), among others (**Figure 2**).[55,56]

2.2.2. Innovative Applications of Liposomes in Cerebrovascular Diseases

Liposomes find application in various fields, including cancer treatment and cerebrovascular diseases. In recent years, liposomes have been investigated in the context of cerebral infarction-associated thrombolysis. In the study developed by Liu, W., et al.,[57] the inflammatory response provoked by cerebral ischemia-reperfusion prompted neutrophiles to release drugs at the site of the ischemic penumbra. Building on this understanding, they developed liposomes loaded with a neuroprotective agent, utilizing neutrophils as carriers to enhance BBB penetration. Experiments using mice as a model have demonstrated that liposomes with tailored properties could serve as effective drug delivery systems to the ischemic region of the brain. Unlike passive targeting approaches employed by conventional nano agents, the interaction between these carriers and inflammatory factors enables superior drug delivery to damaged brain areas. The process by which liposomes achieve their goal is similar to that described for micelles. First, an inflammatory response occurs, and the neutrophils penetrate the BBB. Then, the drug is released due to another inflammatory response, and the neuroprotection starts to take effect on the damaged nerve cells. Additionally, it offers an effective means for facilitating the passage of poorly soluble drugs through the BBB.[57]

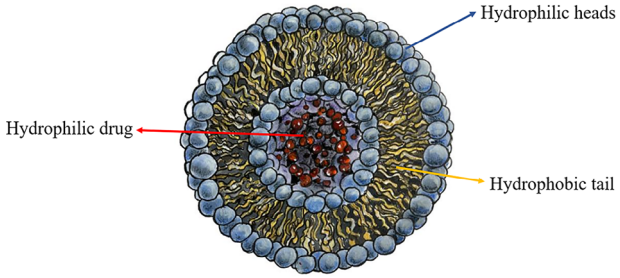

Figure 2. Representation of the structure of a liposome with an encapsulated drug inside it. It can be differentiated the polar heads, in blue; the hydrophilic part in yellow, and the encapsulated polar drug in red. Original illustration by Celia Martín-Morales.

Another research conducted by Al-Ahmady.[58] discovered two opportunities for therapeutic intervention through targeted liposomal transport across the BBB following ischemic stroke. The study demonstrated that liposomes administered intravenously in mice accumulated selectively in the ischemic brain area during both early (0.5 and 4 h) and delayed (24 and 48 h) time points after ischemic stroke, followed by absorption by microglia within two to three days after the event. Within the same context, Wang et al. delved into diverse liposome formulations, specifically developing polyethylene glycol (PEG)/cRGD double-modified liposomes encapsulating 9-AA (9-AA/L-PEG-cRGD). Their liposome delivery system exhibited both anti-neuroinflammatory and anti-ischemic brain injury effects. In mice subjected to middle cerebral artery occlusion (MCAO) and treated with 9-AA/L-PEG-cRGD double-modified liposomes via intraperitoneal injection, a dose-dependent reduction in infarct volume was observed. Moreover, the liposomes demonstrated superior neuroprotective effects compared to the administration of free 9-AA alone. This research underscores the potential of the 9-AA/L-PEG-cRGD liposome formulation as a promising strategy for mitigating neuroinflammation and reducing brain injury in the context of ischemic stroke.

In recent years, researchers have directed their efforts toward developing nanoparticle-based drug delivery systems to improve the targeting efficiency and circulation time of low-dose tPA, aiming to minimize its potential neurotoxic effects. In response to this challenge, Xingping Quan et al. designed a targeted drug delivery system named APLT-PA, which consisted of a fusion between platelet membranes and PEGylated liposomes loaded with tPA and chemically modified the annexin V protein. This

ingenious system was engineered to selectively target activated platelets within thrombi, enabling accurate and efficient drug delivery. As a result, the authors demonstrated that APLT-PA promoted fibrinolysis and antiplatelet activation, thus presenting a promising approach for addressing acute ischemic stroke while potentially alleviating the side effects linked to tPA injection.

In a more recent study, Michael R. Arul et al. successfully engineered PEGylated liposomal nanocarriers ranging from 50 to 80 nm in size, encapsulating both 5BDBD and Nile red dye. The chemical compound 5BDBD (5-(3-Bromophenyl)-1,3-dihydro-2H-Benzofuro[3,2-e]-1,4-diazepin-2-one) is known to inhibit P2X, a receptor that is activated during stroke and exacerbates post-stroke damage. This nanoparticle formulation has revealed an encapsulation efficacy of >80% and drug release over 48 h together with enhanced drug solubility, leading to improved BBB permeability and bioavailability. In in vivo studies, performed on a mouse stroke model, tail vein injection of such nanocarriers has shown good biodistribution to the injured brain and a significant reduction, ≈50%, in infarct volume. The fluorescent nano formulations developed in this study represent, therefore, a promising platform technology for the delivery of therapeutic agents for stroke.

Besides Ischemic Stroke, liposomes can also be employed in the treatment of Alzheimer's disease, the most prevalent and progressive form of dementia.[59] In this research, liposomes functionalized with a glut-1 targeting ligand mannose (MAN) and a cell-penetrating peptide were employed to deliver ApoE2 encoding plasmid DNA (pApoE2) to the brain. ApoE2 is known to have beneficial effects in preventing Alzheimer's development. Furthermore, the liposomes, besides being non-toxic, were observed to enhance their transport across the BBB, leading to improved internalization and expression of the therapeutic ApoE2 gene in the targeted brain cells.

In summary, liposomes represent a promising class of organic nanocarriers for therapy in cerebrovascular diseases. Their dual hydrophobic and hydrophilic nature enhances their versatility and potential application in various therapeutic contexts. Typically, functionalization is necessary to facilitate their incorporation across the BBB, as demonstrated in previous cases. Looking ahead, there is growing interest in utilizing liposomes for intranasal administration across a broad spectrum of diseases where effective therapies are urgently needed. Consequently, liposomes hold significant potential to reshape the future landscape, potentially reducing the prevalence of conditions such as strokes and Parkinson's disease, which currently rank among the leading causes of death.

2.3. Dendrimers

Dendrimers represent another type of controlled release system that is currently being studied. These polymeric structures exhibit a highly branched, radially symmetric configuration and are typically monodisperse. Comprising a core, main polymer chains, and side branches known as dendrons, dendrimers resemble a tree-like structure.[60] Their characteristics, such as bioavailability, low toxicity, non-immunogenic, and solubility make them a good choice for biomedical applications.[61]

The surface functionalization of dendrimers with various functional groups allows the modification of their physicochemical properties. Coupled with the structural arrangement that facilitates drug placement within the spaces between dendrons, this versatility allows for tailoring the system to specific applications. Consequently, dendrimers present a viable option for loading and delivering drugs to target sites (**Figure 3**).[62]

2.3.1. Types of Dendrimers

Dendrimers can be classified according to several parameters, as it can be shown in **Tables 1–3**.[63,64]

2.3.2. Innovative Applications of Dendrimers in Cerebrovascular Diseases

Dendrimers have unique characteristics due to their singular structure, allowing them to cross the BBB and release drugs into the brain., One notable example is poly(amidoamine) (PAMAM) dendrimers, which have spurred extensive research into treatments for cerebrovascular diseases. In this context, Sofia D. Santos et al. synthetized PEG-coated PAMAM dendrimers of different generations to reduce cytotoxicity and increase blood circulation half-life, aiming to safely deliver drugs in vivo in a stroke scenario. Additionally, Rhodamine B isothiocyanate (RITC) was covalently attached to the dendrimer backbone to serve as a surrogate drug and tracker. In this work, the authors concluded that PEGylation effectively increased PAMAM biocompatibility and facilitated BBB crossing. In the specific case of PEGylated G4 PAMAM dendrimers, the optimized nanovector formulation, contrary to unmodified dendrimers, showed no hemolysis upon intravenous administration. Moreover, such nanosystems were able to successfully reach the brain, having been detected in neurons of the ischemic cortex 24 h post administration. The results of this study suggested that the proposed nanovector formulation holds promise as an effective delivery vector for therapeutics to the injured brain after stroke, reaching the ischemic neurons.[65] In another study conducted by Dang et al., a dual-targeting nanosystem was developed, comprising PEG-coated calendula-loaded PAMAM dendrimers. This nanosystem was designed to target ischemic brain inflammation sites with the aim of exerting anti-inflammatory and anti-apoptotic effects. Furthermore, such nano-formulation underwent additional modification by incorporating two targeting peptides: the low-density lipoprotein receptor (Angiopep-2) and neutrophils. By leveraging the high BBB-transport capacity of Angiopep-2 and the affinity of *N*-acetylated PGP for CXCR2 receptors expressed on infiltrating neutrophils, the nano-formulation demonstrated enhanced efficiency in crossing the BBB and exhibited superior anti-stroke activity.[66]

Whitin PAMAM dendrimers, Huang et al. developed 1,3-propane sultone (1,3-PS)-modified generation 5 PAMAM (PG5) dendrimers (Au-G5.NHAc-PS) as a carrier for gastrodin (GAS) to address cerebral ischemia–reperfusion injury.[67] Compared to the GAS group, the Au-G5.The NHAc-PS/GAS group showed superior effects in suppressing inflammatory responses and reducing brain damage. Among all dendrimer's generations, PG2 is

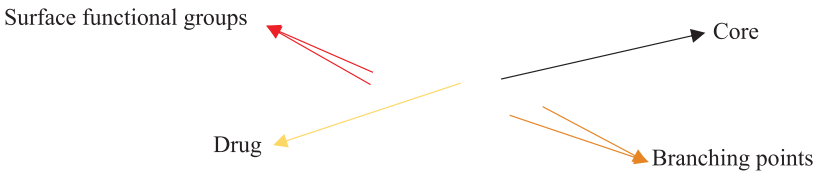

Figure 3. Representation of the structure of a dendrimer with an encapsulated drug inside it. It consists of a core, which determines size, directionality, and multiplicity, an intermediate zone in which the branching units are located, and terminal groups at the end. Original illustration by Celia Martín-Morales.

Table 1. Advantages of the use of drug delivery systems compared to conventional ones.

Advantages of the use of controlled release systems	Disadvantages of the use of controlled release systems
Reduced local or systemic side effects and increased therapeutic efficacy due to the controlled release of the drug at the required site.	Possible delayed effect respected to the administration.
Protection of the active substance against reactions (chemical, enzymatic, or immunological) within the organism increases the drug's half-life in circulation.	Unpredicted correlation between in vitro released and in vivo released and higher cost.
Improvement in the bioavailability of the drug for a longer period, avoiding wastage of the active compound itself from the site of administration to the specific site, including hard-to-reach places.	Some inadequate formulations could provoke a surge because of the dose release.
Improvement in the solubility of active compounds to adapt to the organism's needs.	Difficulties on the adjustment of the appropriate dosage.
Toxicity to certain organs is reduced, and continuous small amounts of the active substance may be less painful than introducing large doses.	Not all drugs are able to extended-release materials.
Fluctuation in drug levels can be reduced.	Possible toxicity.

Table 2. Classification of dendrimers by their properties.

Classification of dendrimers by their properties	
Hydrophilic	Incorporating hydrophilic polymers or surface modifiers allows dendrimers to form entities that interact with polar groups.
Hydrophobic	Conversely, unlike hydrophilic polymers, these dendrimers interact with non-polar groups.
Amino-acid base	the internal structure, formed by amino acid blocks, generates stereospecific sites within the dendrimer, where the substance to encapsulate can be attached noncovalently.
Glycodendrimers	created to generate more interactions between the dendrimer and cellular surface, due to the high interaction of the carbohydrate
Biodegradable	by the inclusion of ester groups, it is possible to generate dendrimers able to be quickly and efficiently eliminated through urine to avoid nonspecific toxicity.
Asymmetric	using click chemistry is possible to generate a nonuniform orthogonal dendritic architecture, which sometimes may offer better pharmacokinetic properties.

Table 3. Classification of dendrimers by their structure.

Classification of dendrimers by their structure	
Simple	simple monomeric units
Crystalline	formed by mesogenic monomers
Chiral	Consist of a chiral core and four different branches that are chemically similar
Micellar	these polymers are aromatic and water-soluble, like micellar structures
Hybrid	dendrimers formed by columnar and cubic-like organized structures resulting in dendritic structures
Metallodendrimers	dendrimer with metal atoms in its structure
Amphiphilic	by the segregation of the chain, dendrimers with polar and non-polar sides can be generated
Multiple antigen peptide dendrimers	the dendron-like structure formed by polylysineskelton, having many applications such as vaccine formation
Multilingual dendrimers	dendrimer containing multiple copies of a specific group of functions on the surface

the most efficient in treating ischemic stroke, due to its lower cytotoxicity and more efficient drug delivery capability. In this framework, Jeon et al. employed PAMAM G2-Dexa as a carrier and synthesized dexamethasone-conjugated PAMAM G2-Dexa to deliver the hemeoxygenase-1 gene into cerebral ischemic areas. This approach effectively suppressed inflammation and decreased brain infarct volume.[68]

In a recent study, these nanocarriers were employed to transport a neuroprotective agent (2-MPPA), which exhibited limited BBB permeability due to its hydrophilicity, for the treatment of perinatal brain injury. The utilization of PAMAM dendrimers facilitated enhanced penetration of the drug through the barrier, enabling rapid diffusion into the brain tissue. This mechanism facilitates the incorporation of the drug and the uptake by phagocytic-activated glia.

By using a combination of many techniques, including both in vitro and in vivo processes, the authors have demonstrated that the incorporation of the drug into PAMAM dendrimers generated an increase in the concentration of the pharmaceutical in the brain, which led to greater efficacy of the treatment and caused less damage to the patient.[69]

On a different work, in response to the urgent need for effective Alzheimer's disease treatments, Igartúa, Daniela E et al. proposed a novel combined therapy involving tacrine and PAMAM dendrimers co-administered via non-traditional routes, to mitigate the toxicity associated with extensive first-pass metabolism. This study outlined a method to prepare DG4.0-TAC and DG4.5-TAC suspensions while preserving the solubility and stability of Tacrine (TAC) and evaluated the effects of this co-administration through ex vivo, in vitro, and in vivo experiments. As a conclusion, the combination of TAC with DG4.0 or DG4.5 dendrimers proved to be less toxic, more biocompatible, and equally effective compared to free TAC at the tested concentrations. This approach holds promise for incorporation into clinical trials, potentially improving current treatment strategies.

Given the characteristics and potential applications of dendrimers, it can be concluded that, despite the complexity of their synthesis and potential structural imperfections, these systems facilitate the penetration of drugs across the BBB. The future of these nanocarriers involves not only their employment in therapies to enhance drug efficacy but also the exploration of synthesis and processing methods aimed at achieving greater control of the dendrimer structure.

2.4. Hydrogels

Hydrogels represent a versatile class of water-expandable 3D polymer networks with customizable physicochemical properties, making them ideal for tissue replacement in brain diseases. The following attributes make them particularly promising. First, hydrogels exhibit excellent biocompatibility and biodegradability, mimicking the soft tissue properties of the brain. They provide a conducive environment for stem cells, reducing toxicity and minimizing tissue damage. Second, their stable 3D structure surpasses the limitations of 2D cellular studies. Hydrogels offer high drug-carrying capacity and controlled-release properties, enhancing sustained drug effects within brain tissue by regulating release rates. Moreover, hydrogels improve drug stability, shield drugs from enzymatic degradation, and increase drug concentration and availability in the brain. They overcome traditional delivery barriers, enhancing drug efficacy. Last, their plasticity and injectability enable direct injection into defect sites in the brain, conforming to desired shapes. This facilitates drug delivery through local or systemic routes, reducing surgical trauma and patient discomfort. In summary, hydrogels hold significant potential for brain drug delivery, offering an efficient and versatile approach to addressing brain disorders. In this context, hydrogels employed for addressing brain disorders can be derived either from natural or synthetic sources. Wang et al., for example,[70] developed a novel hydrogel, OD-PP@SeNPs, designed to respond to the inflammatory microenvironment. This hydrogel comprised phenylboronic acid-grafted polylysine, oxidized dextran, and selenium nanoparticles. Utilizing Schiff base bonds, phenylboronate ester bonds, and hydrogen bonds, the hydrogel exhibited dual responsiveness to ROS and pH, facilitated by its triple-network structure. OD-PP@SeNPs demonstrated ROS scavenging and pH-regulating capabilities, providing protection to cells against oxidative stress. Additionally, it promoted the polarization of macrophages toward the M2 phenotype, thereby reducing inflammatory cytokines via the PI3K/AKT/NF-κB and MAPK pathways. These mechanisms contributed to its anti-inflammatory effects, effectively reshaping the inflammatory microenvironment. Moreover, in the context of regenerative medicine, angiogenesis plays an important role in organ and tissue regeneration. Stem cells, as previously mentioned, directly stimulate vascular growth. Encapsulation of stem cells, or their derived exosomes, in hydrogels, has already demonstrated higher differentiation efficiency. In this framework, Zhang et al.,[71] for example, developed a chitosan-based hydrogel to target lower limb ischemia. As a result of this study, the authors reported an increase in the stability of proteins in exosomes, as well as an augmented retention of exosomes in vivo.

Hydrogels and their cross-linking agents come in various forms, each with distinct mechanisms, and have been pivotal in addressing diseases such as vascular diseases. Initially serving as scaffolds and drug carriers, hydrogels have evolved to regulate disease origins through microenvironmental intervention. Their behavior and products can be tailored for different disease microenvironments, including degradation, gelation, ROS scavenging, nanoparticle transformation, cargo release, and oxygen generation, presenting hydrogels as a promising strategy for future therapeutic approaches. However, challenges remain for widespread preclinical and clinical applications. One challenge lies in exploring suitable injection approaches, as hydrogels, while effective as drug carriers, face limitations in mimicking physiological homeostasis, especially for cellular active substances like growth factors. Achieving precise release profiles and dose control for cell lifespan extension remains elusive. Additionally, for solid hydrogels used as scaffolding materials during long-term implantation, the effects of reduced mechanical strength and volume expansion on the body require systematic investigation. Further refinement and exploration of the potential toxicity, degradation rate, degradation product toxicity, and thrombus induction of chemical cross-linking agents, along with a standardized production process, are crucial before widespread clinical use.[72,73]

2.5. Microspheres

Microspheres are solid spherical particles typically ranging in size from 1 and 1000 μm, predominantly composed of synthetic polymers or proteins. They are biodegradable and find extensive applications in the controlled release of drugs, vaccines, antibiotics, and hormones.[74] These microspheres can be categorized into microcapsules, where the entrapped substance is enclosed by a distinct capsule wall, and micromatrices, where the entrapped substance is dispersed throughout the microsphere matrix.

These biomaterials can be classified in various ways depending on their application or behavior. Based on their applications, microspheres can be distinguished between nanosystems designed for therapy and diagnosis. On the other hand, they can be classified based on their behavior, as presented in the following section, with categories including bioadhesive, magnetic, floating, and polymeric microspheres, among others.[74–76]

Microspheres offer numerous advantages, including a consistent and prolonged therapeutic effect, as well as a reduction in the intensity of adverse effects due to improved drug utilization, leading to enhanced bioavailability.[75]

Although this system has many advantages, however, it's important to consider its limitations, such as the influence of process conditions like changes in temperature, pH, and solvent addition among others, which may influence the stability of the core particles to be encapsulated.[75]

2.5.1. Types of Microspheres

(a) Bioadhesive microspheres

Adhesion is the tendency of certain substances or materials to stick and bind to each other. In the context of drug delivery, this concept is often utilized by exploiting the adhesive properties of water-soluble polymers, allowing the drug to adhere to the membrane. When this interaction occurs between the drug delivery device and mucosal membranes such as buccal, ocular, or rectal, among others, it is termed bio adhesion.[74] Microspheres designed for bio adhesion are known for their strong interaction with the adsorption site, allowing them to remain in a specific place for long periods, thereby enhancing therapeutic efficacy.[77]

(b) Magnetic microspheres

Controlled drug release vehicles, such as magnetic microspheres, offer significant advantages by providing selective targeting to the desired release site through external stimuli, such as a magnetic field. By incorporating materials such as chitosan or dextran, for instance, these microplatforms ensure safe and consistent drug release. Magnetic microspheres are further divided into two main groups: those utilized for therapeutic purposes, like chemotherapy, and those employed for diagnostic applications, such as superparamagnetic iron oxide microspheres for visualizing specific tumor sites.[74,77]

(c) Floating microspheres

These microspheres are termed "floating" due to their ability to float in gastric fluid, owing to their lower density compared to the medium. This unique characteristic enables a slow and controlled release of the drug at the desired rate, reducing the risk of uncorrected drug release and dose dumping. Consequently, a sustained therapeutic effect is achieved, allowing for a reduction in the frequency of doses.[74,77]

(d) Polymeric microspheres

The numerous types of polymeric microspheres can be categorized into two main groups: biodegradable polymeric microspheres and synthetic polymeric microspheres.

Biodegradable Polymeric Microspheres consist of natural biodegradable polymers that can be decomposed by microorganisms such as bacteria or fungi within a short period of time, ultimately transforming into nutrients, carbon dioxide, biomass, and water. This category includes polymers such as starch, which are, besides biodegradable, also biocompatible and bio-adhesive in nature. Their significant swelling capacity in aqueous environments allows these polymers to extend residence time upon contact with mucous membranes. Moreover, the polymer concentration and its release pattern regulate the rate of drug release. Despite their numerous advantages, these polymers face challenges in achieving effective drug loading efficacy and controlling drug delivery.[74,77,78]

Synthetic Polymer Microspheres find extensive use in clinical applications, serving as bulking agents, fillers, embolic particles, or delivery vehicles. Despite their safety and biocompatibility, these biomaterials have been observed to migrate away from the injection site, which can potentially lead to complications such as embolism and further organ damage.[74,77]

(e) Radioactive microspheres

This group of microspheres is employed in radioembolization treatment, where they're injected into the arteries to increase radioactivity in target tumors while sparing surrounding normal tissues. These radioactive microspheres come in various forms, each with distinct mechanisms for delivering medication.[77]

2.5.2. Innovative Applications of Microsphere in Cerebrovascular Diseases

Microspheres could be another interesting biomaterial to be used as a drug delivery system in the diagnosis and treatment of cerebrovascular diseases. In ischemic stroke research, Cui, Y., et al. explored the use of sodium alginate microspheres to generate an ischemic stroke model in a miniature pig by blocking the skull base retia. This study aimed to provide, by using miniature pigs, a stable and reliable model for investigating the pathogenesis, pathophysiologic changes, and other molecular characteristics of cerebral infarction-induced brain ischemia, as well as for developing treatments. As a result, an ischemic stroke model was successfully established, being able to occlude the retia mirabile with sodium alginate microspheres. Unlike other potential methods, in this case, the animals survived and retained the ability to stand and walk, albeit without the capacity to maintain body balance or navigate barriers, as required to replicate stroke conditions. In another study, Ming-Jun Tsai et al.[79] manufactured chitin/PLGA embolic microparticles with different sizes and investigated their patterns of cerebral infarction in rats induced by the artificial emboli. In this context, all the developed microparticles presented an 80% or higher success rate of inducing stroke, with good reproducibility. Moreover, microparticle sizes ranging from 212 to 250 μm resulted in extensive diffuse infarction predominantly affecting the ipsilateral hemisphere, encompassing regions such as the cortex, hippocampus, basal ganglia, thalamus, midbrain, and cerebellum. Conversely, microparticles sized between 75 and 90 μm led to the formation of isolated infarcts, primarily in the subcortical region, resembling lacunar stroke observed in humans. Furthermore, microparticles sized between 38 and 45 μm frequently crossed to the contralateral hemisphere, causing diffuse infarctions in both hemispheres. Overall, the research established embolic stroke animal models, including a novel model predominantly expressing lacunar

infarction, through intravenous injection of chitin/PLGA microparticles.

The mouse model of multiple cerebral infarctions can be considered a recent development in the animal model of cerebral ischemia. To investigate its effectiveness, Shen, Yi et al.[80] developed fluorescent microspheres with sizes ranging from 45 to 53 μm in diameter. Six hours post injection, fluorescent microspheres were visualized directly using a fluorescence stereomicroscope, both on the brain's surface and within brain sections. Fluorescence histochemistry and immunohistochemistry assays revealed that the microspheres were predominantly distributed in the cerebral cortex, striatum, and hippocampus ipsilateral to the injection site. Microinfarcts were detected in brain regions where the fluorescent microspheres accumulated. The histopathological changes indicated that the animal model of multiple cerebral infarctions effectively replicated the cellular changes observed in multifocal microinfarcts. Thus, this model can be considered a valuable tool for studying the pathogenesis of ischemic stroke and assessing potential therapeutic interventions.

More recently, within therapeutic purposes, Tamar Memanishvili et al. developed Poly(ester amide) (PEA)-derived microspheres loaded with VEGF to be used as vehicles to reach the brain. The study concluded that grafted PEA MS could act as efficient vehicles, with anti-inflammatory action, for long-term delivery of growth factors into the injured brain.

Therefore, microspheres offer versatility in cerebrovascular disease research, serving as drug delivery systems and enabling the creation of stroke models with minimal invasiveness and harm to animals. Their application spans from studying pathogenesis and pathophysiological changes to evaluating therapeutic interventions, making them valuable tools in advancing our understanding and treatment of cerebrovascular diseases.

The diverse properties and customizable nature of microspheres make them highly versatile in various applications. For instance, magnetic microspheres offer the advantage of targeted therapy by responding to external stimuli, which is particularly valuable in treatments requiring precise localization. In the context of diseases like stroke, microspheres hold promise as efficient drug carriers that can be guided to specific areas of the brain using magnetic fields. Neil G Harris et al.,[81] for instance, developed starch microspheres to quantitatively assess early BBB dysfunction after ischemic-reperfusion injury in rats. This targeted approach enhances the efficacy of treatment while minimizing off-target effects, highlighting the potential significance of microspheres in advancing therapeutic strategies for cerebrovascular diseases.

2.6. Polymeric Nanoparticles

Nanoparticles represent the simplest form of structures with dimensions typically ranging from 1 to 100 nanometers.[82] Among the different types of nanoparticles, polymeric nanoparticles (PNPs) have been recently considered attractive biomaterials because of their small size, having being studied as a possible treatment for diseases like ocular disorders or COVID-19, among others.[83] The possibility to modify both size and surface properties makes PNPs a promising option for ensuring targeted drug delivery. In addition, these nanocarriers offer several advantages, including favorable pharmacokinetics, potential reduction of adverse effects, and mitigation of drug resistance. For such nanosystems, biodegradability and biocompatibility are crucial considerations, as naturally degradable polymers can be eliminated through metabolic pathways. Moreover, PNPs can also be tailored to enhance specific properties, for example, by incorporating compounds like polyethylene glycol (PEG), which mimics natural body scaffolds, promoting cell signaling and adhesion.[84–86] Given their versatile properties, PNPs hold promise for various biomedical applications, including research into cerebrovascular diseases.

2.6.1. Types of Polymeric Nanoparticles

Polymeric nanoparticles can be generally classified into two main groups, namely nanospheres and nanocapsules.

(a) Nanospheres

Nanospheres, as their name suggests, are like microspheres but smaller in size, typically ranging between 100 and 1000 nm. They consist of dense polymeric matrices in which drugs are physically and uniformly dispersed.[87,88] Although nanospheres share similarities with microspheres in terms of properties and applications, they also exhibit distinct advantages and disadvantages., they also exhibit distinct advantages and disadvantages. One notable advantage of nanospheres is their ability to undergo direct endocytosis, facilitating the accumulation of nanoparticle-encapsulated drugs within cells. This property can potentially reduce cytotoxicity by enabling the use of lower drug doses for equivalent therapeutic effects. Additionally, nanospheres can traverse small capillarity vessels, avoiding rapid clearance by phagocytes and thereby increasing their residence time in the body. Moreover, nanosphere-based colloidal systems generally display higher stability, as well as better injectability and moldability, compared to those based on microspheres.

Therefore, nanospheres are increasingly being used as tools for cellular delivery, cell imaging, and intracellular gene delivery.

Despite their many advantages, there are certain disadvantages to be highlighted compared to microspheres. For instance, generating nanospheres at larger scales can be challenging and costly. Additionally, their intrinsic high surface area renders them less stable in vitro and in vivo, as they interact more extensively with the physiological environment. Moreover, nanospheres have a tendency to aggregate, further complicating their use.[89]

However, despite these drawbacks, the applications of nanospheres in drug delivery systems are similar to those of microspheres, albeit with some differences as previously mentioned.

(b) Nanocapsules

Nanocapsules resemble nanosized vesicular systems, with the drug encapsulated within an internal cavity, either as a liquid or solid. This cavity consists of a liquid core surrounded by a polymeric membrane. Typically utilized for encapsulating hydrophobic drugs, nanocapsules offer several advantages as delivery systems, including protection, drug selectivity, targeting,

and minimized toxicity. Compared to nanospheres, nanocapsules offer some distinct advantages. They contain a lower polymer content, providing better protection against degradation factors and minimizing tissue irritation. Additionally, nanocapsules can load a higher amount of drug due to their lower polymer content. In summary, the primary distinction between nanospheres and nanocapsules relies in their structural composition. While nanospheres incorporate active substances within the polymers that form them, constituting a matrix system, nanocapsules encase the active substance within their core.[90–92]

2.6.2. Innovative Applications of Polymeric Nanoparticles in Cerebrovascular Diseases

Nanoparticles, particularly poly(lactic acid-glycolic acid) (PLGA) copolymer-based PNPs, hold significant promise in the diagnosis and treatment of strokes, the second leading cause of death globally. PLGA nanoparticles offer versatility due to the adjustability of the lactic acid and glycolic acid ratio. Recent research has shown that these nanostructures can penetrate the BBB, allowing for the internalization of drugs within the PNPs. This capability opens various treatment avenues for ischemic stroke, including thrombolytic therapy, anti-oxidative stress, and anti-apoptosis strategies. In this framework, Choi et al. developed PLGA-based nanoparticles to load and deliver PTEN-induced kinase 1 (PINK1) siRNA (PINK1 NPs). As a result of this study, the authors concluded that PINK1 siRNA NPs were able to decrease infarct volume and behavioral deficiency by inhibiting microglia responses in photothrombotic ischemic mouse models. Another interesting example was reported by Cheng Wang et al.,[93] which developed biomimetic nanocarriers comprised of fat extract (FE) encapsulated PLGA core enclosed by RGD peptides decorated plasma membrane of PLTs. From this study, the authors concluded that the nanosystem, besides targeting damaged and inflamed blood vessels, also presented rapid accumulation in the lesion area of the ischemic brain. In addition, RGD-PLT@PLGA-FE kept a sustained release behavior of FE at the lesion site, effectively increased its half-life, and promoted angiogenesis and neurogenesis by delivering neurotrophic factors including BDNF, GDNF, and bFGF to the brain, which ultimately resulted in blood flow increase and neurobehavioral recovery.

Another example is the case of treatment with dihydrotanshinone I (DHT), a natural compound investigated for its multiple bioactivities and especially for acting against hydrogen peroxide-induced oxidative damage in PC12 cells, which can be used in the treatment of stroke. This compound was encapsulated with bovine serum albumin to produce an improvement in bioavailability and could be administered by intravenous injection. The results of this research revealed that not only does DHT have significant ameliorating effects in rats subjected to stroke, but that the nanoparticles created with the serum albumin and this drug were significantly lower than those of the unencapsulated drug, demonstrating a better effect on therapy. In addition, it is important to mention that the rats treated with the nanoparticles improved the recovery of cerebral flow in the ischemic hemisphere, and also repaired the damage to the cortex and hippocampus after cerebral infarction.[94]

These approaches open the door to minimally invasive treatment options for stroke, offering hope for improved outcomes and quality of life for patients and effective carriers for delivering drugs to the brain.[95,96]

2.7. Extracellular Vesicles

EVs are small membrane-bound particles released by cells into the extracellular environment. They play important roles in intercellular communication by transferring proteins, lipids, RNA, and DNA between cells. EVs can be classified based on their biogenesis and size into several types, with the main categories being exosomes, microvesicles, and apoptotic bodies. Exosomes are small vesicles (30–150 nm) derived from the endosomal pathway. They are formed by inward budding of the membrane of late endosomes, resulting in multivesicular bodies that can fuse with the plasma membrane to release exosomes into the extracellular space. Microvesicles, also known as ectosomes or shedding vesicles, are larger than exosomes (100 to 1 µm) and are formed by direct outward budding and fission of the plasma membrane. Apoptotic bodies are larger vesicles (up to 5 µm) released during programmed cell death (apoptosis), containing fragmented cellular material from the dying cell.[97]

2.7.1. Innovative Applications of EVs in Cerebrovascular Diseases

As natural intercellular shuttles, EVs offer several advantages over traditional nanomaterials, including superior biocompatibility, biodegradability, low toxicity, and low immunogenicity. Considering these advantages, EVs are regarded as one of the most promising candidates in nanomedicine for the treatment of ischemic stroke. In this context, EVs can be further divided into four main groups, namely neutrophil membrane-derived nanovesicles, Monocyte/macrophage membrane-derived nanovesicles, platelet membrane-derived nanovesicles, and mesenchymal stem cell-derived exosomes,[98] as briefly presented below accompanied by some examples. Neutrophils are critical players in ischemic stroke and thrombosis, making them significant targets for prevention and treatment strategies. After an ischemic stroke occurs, neutrophils are recruited and begin infiltrating the ischemic brain within 12 h, reaching their peak presence at 24 h, and then gradually decreasing over the next three days.[99] Building upon the interaction between neutrophils and vascular endothelial cells, a recent study engineered magnetic nanoprobes camouflaged with neutrophil membranes (NMNPs). These nanoprobes featured a core of superparamagnetic iron oxide (SPIO) encapsulated within poly(lactic-*co*-glycolic acid) (PLGA), ensuring both safety and selectivity as a nanoprobe for neuroinflammation induced by stroke[100] In another interesting investigation, Mu et al., recently developed a nanoparticle that utilizes neutrophils in the bloodstream as carriers to transport drugs to ischemic brain lesions. Specifically, the surface of the nanoplatform was modified with the peptide cinnamyl-F-(D) L-F(CFLFLF), which selectively binds to the formyl peptide receptor found on neutrophil surfaces. Following intravenous administration on days 2 and 4 post-MCAO in mice, the modified nanoparticles effectively adhered to neutrophil surfaces in peripheral

blood. Subsequently, these nanoparticles were transported to ischemic brain lesions alongside neutrophil migration, facilitating the release of ligustrazine to enhance ischemic stroke prognosis. Despite their efficacy as transport carriers in ischemic stroke, studies predominantly focus on the acute phase of the condition, neglecting the recovery phase.[101] After ischemic stroke onset, peripheral monocytes rapidly infiltrate into ischemic lesions and differentiate into macrophages, accumulating within the lesions by day 1 and peaking at day 3. To mitigate the swift recruitment of monocytes, nanoparticles derived from monocyte cell membranes are engineered to directly bind with inflamed vascular endothelial cells. This approach aims to diminish the accumulation of monocytes in the peripheral blood within the ischemic brain area.[102] An example of this nanosystem is given by Wang and his group, which engineered rapamycin nanoparticles coated with monocyte membranes (McM/RNP). Upon intravenous administration to MCAO/R mice, McM/RNPs effectively reduced the accumulation of monocytes on inflamed endothelial cells and suppressed microglial proliferation in the ischemic brain region. Furthermore, a biosafety evaluation in vivo indicated that McM/RNPs did not manifest any discernible side effects or immunotoxicity following treatment.[103] Another factor involved in the formation of thrombosis in ischemic stroke is Platelet, and it has been considered a viable target for ischemic stroke treatment.[104] In this framework, a recent study by Wang et al. leveraged both the targeting capabilities of platelets (PLTs) to stroke lesions and Arg-Gly-Asp (RGD) peptides to angiogenic blood vessels to develop a biomimetic nanocarrier for precise fat extract (FE) delivery in stroke treatment. These biomimetic nanocarriers, named RGD-PLT@PLGA-FE, consist of an FE-encapsulated poly(lactic-*co*-glycolic acid) (PLGA) core surrounded by a PLT plasma membrane decorated with RGD peptides. RGD-PLT@PLGA-FE not only targeted damaged and inflamed blood vessels but also rapidly accumulated in the ischemic brain lesion area. Additionally, it ensured sustained release of FE at the lesion site, enhancing its half-life and promoting angiogenesis and neurogenesis by delivering neurotrophic factors like BDNF, GDNF, and bFGF to the brain. This ultimately led to increased blood flow and improved neurobehavioral recovery.[93] Thromboembolic stroke, caused by platelet activation and thrombus formation in cerebral vessels, has high global morbidity and mortality. Standard treatment with tissue plasminogen activator (tPA) within 4.5 h are known to potentially cause serious side effects, including hemorrhagic transformation. In this context, a novel delivery system, APLT-PA, combining Annexin V and platelet membrane, has been developed to improve targeting and therapeutic effects while reducing hemorrhage risk. APLT-PA targets activated platelets and thrombosis sites due to its binding properties. In mice with acute ischemic stroke, a single dose of APLT-PA resulted in significant thrombolysis and improved neurological function within seven days. This study introduced a safe, precise thrombolytic treatment and offered new strategies for developing cell-mimetic nanomedicines for biomedical applications.[105] Furthermore, since stem cells (SC) have been widely used to treat inflammatory diseases due to their regulation capacities, mesenchymal stem cell-derived exosomes have been extensively investigated for ischemic stroke treatment. Clinical trials have already been performed, enhancing the suitability of such cells in the context of the damaged brain.[106] In this framework, to overcome the main limitations of poor targeting of the ischemic lesion, magnetic extracellular nanovesicles derived from iron oxide nanoparticles-harboring mesenchymal SC have shown to improve the ischemic-lesion targeting and therefore the therapeutic outcome.[107] To assess the role of EVs in cerebrovascular diseases, an ongoing clinical trial is being performed. In this context, Cereda et al., are currently investigating the role of EVs as biomarkers for detecting brain ischemia in patients with transient ischemic attacks.[108]

3. Different Vectorization Systems for Drug Delivery: Inorganic

The current section resumes vectorization systems composed of inorganic materials.

3.1. Gold Nanoparticles

Gold nanoparticles (AuNPs) have emerged as one of the most significant nanoparticle systems in contemporary research due to their intrinsic tuneable optical properties, ease of synthesis, and chemical stability, making them versatile for both treatment and diagnosis applications. Their tuneable properties, including size, shape, and functionalization, enable a wide range of biomedical uses, particularly in targeted drug delivery systems. Various types of AuNPs, such as spherical AuNPs, gold nanorods, and gold composites, offer distinct advantages for drug delivery. However, concerns regarding their toxicity pose limitations in clinical applications. Nevertheless, recent advancements have demonstrated their significant impact in cancer therapy, molecular diagnosis, and immunotherapy. AuNPs serve as effective nanocarriers due to their ability to bind drugs to their surface via covalent or noncovalent interactions. Additionally, their surface can be readily modified to enhance drug encapsulation and delivery. Furthermore, AuNPs enable controlled drug release through interactions with cells or organs, triggered by external stimuli such as pH or enzymes, providing precise control over drug release kinetics.[109–111] Overall, AuNPs represent a promising platform for drug delivery, offering tailored solutions for various biomedical challenges and paving the way for innovative therapeutic strategies (**Figure 5**).

3.1.1. Innovative Applications of Gold Nanoparticles in Cerebrovascular Disease

AuNPs hold significant relevance in ischemic stroke research, offering potential benefits in scavenging ROS which play an important role in this type of cerebrovascular disease.

AuNPs have shown a noteworthy neuroprotective effect, being able to contribute to brain tissue repair and functional recovery in several ways. They could carry neuroprotective drugs to enhance neuronal survival and recovery or deliver anti-inflammatory agents to reduce post-stroke inflammation. Additionally, AuNPs may inhibit apoptosis in neurons, thereby preserving cell viability and limiting damage. Furthermore, they might promote the

Figure 4. Representation of the structure of a gold nanoparticle with an encapsulated drug inside it. The polymer's strain in yellow can be differentiated, and the encapsulated polar drug in red. Original illustration by Celia Martín-Morales.

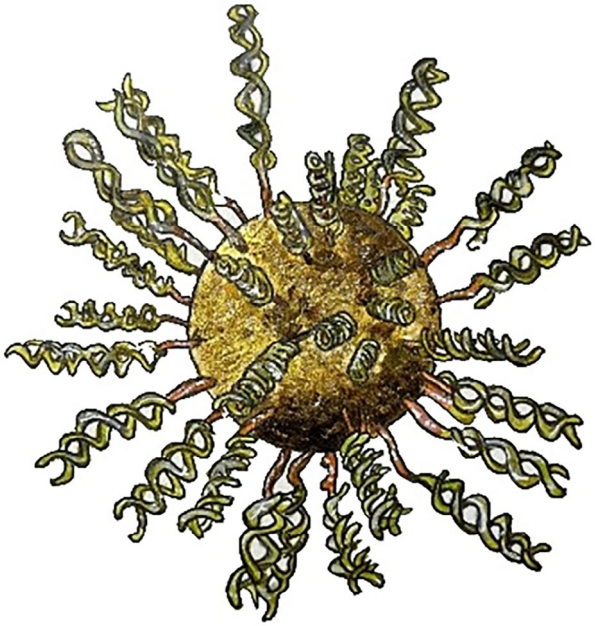

Figure 5. Representation of the structure of a gold nanoparticle with nucleic acids conjugated on the surface. The gold nanoparticle can be seen in gold, with the structure previously described in Figure 4, with nucleic acids (polymers formed by the repetition of nucleotides, joined by phosphodiester bonding). Original illustration by Celia Martín-Morales.

regrowth of damaged neuronal axons, crucial for restoring connectivity in the brain. Moreover, AuNPs could serve as carriers for thrombolytic agents, targeting and dissolving blood clots, which can cause ischemic strokes. Additionally, they may enhance brain tissue regeneration and repair, further promoting recovery from stroke-induced damage. Overall, the multifaceted therapeutic capabilities of AuNPs make them promising candidates for the development of novel stroke treatments aimed at enhancing neuronal survival, reducing inflammation, and promoting brain tissue repair and recovery.

In this context, Zheng et al.[112] investigated the antioxidant effects on focal ischemic stroke-induced rats, studying sizes between 5 and 20 nm. In this investigation, it was found that AuNPs with a size of 20 nm presented significant neuroprotective effects.[38,113] Another study conducted by Zheng et al.[112] explored the mechanism of injured rats' cortical neurons, induced by oxygen–glucose deprivation/reperfusion. The authors concluded 20-nm Au NPs improved cell viability, alleviated neuronal apoptosis, and increased mitochondrial respiration, while opposite effects were observed for 5-nm NPs. In another work, Nazarian et al.,[114] assessed the neuroprotective effect of AuNPs and mesenchymal stem cells in ischemic stroke rats. As a result, the brain infarct volume significantly decreased the Brain-derived neurotrophic factor (BDNF) and Neuronal nuclear protein (NeuN) expression, and an increase in glial cell-derived neurotrophic factor (GDNF) when administrating the nanosystems. These results demonstrated that the administration of stem cells and Modafinil-coated AuNPs at the same time had a good effect on ischemic brain injuries. More recently, Huang et al.[67] developed a novel drug delivery system composed of gastrodin-modified AuNPs wrapped with dendrimers, exploring its potential therapeutic effect against cerebral ischemia-reperfusion injury (CIRI). As a result, the favorable surface morphology, sustained drug release ability, lack of measurable toxicity, and good biocompatibility indicated the potential therapeutic effect of the developed nanosystem. Such a delivery system was considered successful thanks to the modification of the PAMAM, leading to the penetration of the BBB. This nansystem reduced the cell proliferation and increased the apoptosis level, and what is more, it achieved the downregulation of immune factors in LPS-induced astrocytes and hypothalamic neurons. Furthermore, TNF-α, IL-1β, and IL-6 could be suppressed by the biomaterial in LPS-activated glial and cerebral nerve cells, achieved by the inhibition of the β-actin signaling pathway.

These findings suggest that the encapsulated drug was able to exert anti-inflammatory and antiapoptotic effects in the context of CIRI. Beyond stroke research, AuNPs are widely investigated as a potential therapeutic strategy in the treatment of Alzheimer's disease, being employed in several ways, namely neuroprotective agents, neurogenesis promotors, immune response modulators, antioxidant and anti-aggregation agents, among others. In this framework, Yang et al.,[115] developed an innovative hybrid system composed of gold nanoparticle-decorated porous metal–organic framework MIL-101(Fe) (AuNPs@PEG@MIL-101) to inhibit amyloid β (Aβ) deposition. The nanosystem exhibited the potential to decrease intracellular Aβ40 aggregation and reduce the amount of Aβ40 that is immobilized on the cell membrane. In cellular models using PC12 cells, AuNPs@PEG@MIL-101 demonstrated protective effects against Aβ40-induced microtubular defects and cell membrane damage. Recent research include the study of innovative detection methods to enhance the sensitivity of Aβ detection and the development of nanosystems for inhibiting amyloid fibril formation,[116,117] among others.

Furthermore, Gold nanoparticles can be employed as drug carriers in biomedicine, with applications ranging from cancer treatment to various diseases. Their excellent optical properties and the ability to undergo diverse surface functionalization make them highly promising for future developments in nanomedicine (Figure 5).

3.2. Magnetic Nanoparticles

Among all nanoparticles, magnetic nanoparticles have attracted increasing attention in the field of biomaterials for drug delivery

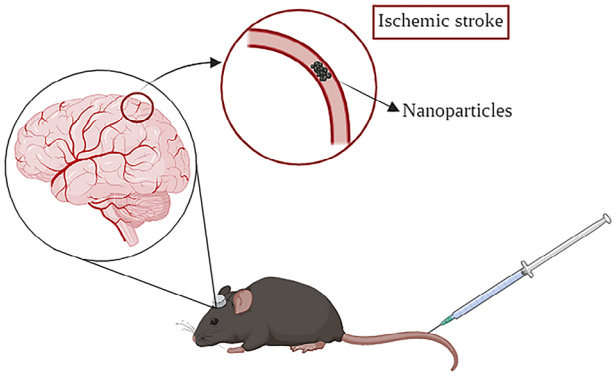

Figure 6. Schematic of ischemic stroke-induced with ferromagnetic NPs in rodents. NPs are administered through the tail, a magnetic microdevice is attached to the mouse sculpture, and the NPs concentrate under the magnetic device occluding blood vessels. Illustration created by Celia Martín-Morales.

systems due to their ability to be concentrated at specific points in the body using a magnetic field. These nanomaterials offer several advantageous properties as nanocarriers, including high surface-area-to-volume ratio, versatility, and, most notably, their responsiveness to magnetic stimuli. Beyond drug delivery, magnetic nanostructures find applications in imaging, spectroscopy, and as contrast agents either in resonance imaging or nuclear magnetic resonance. Although these nanocarriers can be composed of pure metals and their alloys, iron oxides, such as magnetite (Fe_3O_4), have become increasingly popular due to their superior biocompatibility, lower toxicity, and greater colloidal stability. These nanoparticles can be synthesized using various methods, such as coprecipitation, hydrothermal, and sol-gel, microemulsion, among others. Additionally, functionalization processes can easily modify their surface properties by incorporating desired functional groups.[118,119]

3.2.1. Innovative Applications of Magnetic Nanoparticles in Cerebrovascular Disease

Magnetic nanoparticles, besides their widespread applications, have gained particular attention in the field of cardiovascular disease. Within ischemic stroke, such particles have widely been proposed as carriers to increase the efficacy of targeted delivery of stem cells. In this framework, by combining ferrimagnetic iron oxide nanoparticles with magnetic fields, researchers were able to selectively administer stem cells with greater precision. In the study, rats with induced cerebral artery occlusion were used to mimic a stroke model and magnetic nanoparticles were targeted using a magnet. After 35 days, the groups treated with magnetic nanoparticles showed improved performance in behavioral tests compared to the control group. These findings suggest that the use of magnetic nanoparticles can enhance the efficacy of delivery systems for ischemic stroke treatment (**Figure 6**).[120]

The utilization of magnetic nanoparticles extends to the generation of ischemic stroke animal models, addressing the need for reproducible and non-invasive models for studying and treating this pathology. An innovative approach in this regard is demonstrated by the research carried out by Jie-Min Jia et al.[121]Their study introduced a technology for inducing the aggregation of magnetic nanoparticles to occlude blood flow in microvessels. This method involved the use of micromagnets to direct commercial magnetic nanoparticles to the mouse brain, enabling selective and minimally invasive occlusion of vessels of interest. This development offers new possibilities for the in-depth study of ischemic stroke and the exploration of alternatives for diagnosis and treatment.[121] In the same context, Li et al.[122] developed an innovative stroke model in mice that employed thrombin-functionalized magnetic nanoparticles to embolize blood vessels. In this study, the MNP@Thrombin accumulated in the carotid artery and induced thrombus formation, leading to the occlusion of the cerebral artery. As conclusion, these results suggested that this new method was able to block hemisphere blood flow and damaged neural function, providing an easy and minimally invasive process for a new stroke model.

Recent advancements in the design and synthesis of multifunctional nanostructures incorporating magnetic hold significant promise in the treatment of cardiovascular diseases through magnetically assisted targeted drug delivery. Magnetic nanoparticles, in particular, have emerged as safe MRI/ MPI contrast agents and effective drug carriers for treating cardiovascular ailments. By loading drugs onto magnetic nanoparticles, it becomes feasible to track and target drug delivery more precisely, contingent upon the type of contrasting agent utilized. In this framework, for instance, Peter et al.,[123] investigated MPI capabilities in detecting ischemic lesions in a murine model of ischemic stroke. The administration of superparamagnetic iron oxide nanoparticles as a contrast agent enabled magnetic particle imaging (MPI) imaging to achieve signal strength comparable to that of a small animal MRI scanner in detecting ischemic brain regions. Notably, MPI imaging exhibited shorter acquisition times and higher resolution compared to traditional MRI scanning methods. These attributes are pivotal as they enhance the ability to accurately predict the patient's condition, offering potential benefits for diagnosing and managing ischemic stroke. In another example, Suzuki et al.[124] developed ultrasmall superparamagnetic iron oxide nanoparticles coated with fucoidan, a polysaccharide to be used for molecular imaging of thrombus via magnetic resonance imaging (MRI) in arterial thrombus. This contrasting agent demonstrated the ability to image P-selectin, an adhesion molecule recognized as a molecular component of atherothrombotic disease, in a rat model of elastase-induced vascular injury. In a recent study, Sillerud et al.[125] developed novel anti-Iba-1-targeted superparamagnetic iron–platinum (FePt) nanoparticles to measure the spatiotemporal changes of the microglial/macrophage activation in living rat brain for four weeks post-stroke. The peak activation of microglia/macrophages was observed seven days post-stroke, and the activation decreased by two weeks, continuing to four weeks. These findings highlighted that nanoparticle-enhanced MRI could offer a novel approach for monitoring the dynamic progression of neuroinflammation in living animals during stroke development and treatment. Magnetic nanoparticles are currently one of the most cutting-edge fields of research, involving vast applications and promising prospects. Their magnetic properties, coupled with the ability to tailor their size, shape, and functionalization, position them as leading candidates in

biomedicine, particularly in conditions like cerebrovascular diseases such as stroke.

By harnessing external magnetic fields, these nanoparticles can be precisely manipulated, paving the way for less invasive, highly targeted, and more efficacious treatments. As such, magnetic nanoparticles hold immense potential for shaping the future landscape of nanotechnology in healthcare.

Moreover, a recent clinical study focused on the design of a novel nanosystem, named Pulse NanoMED system, comprising iron nanoparticles and a small, portable, magnetic workstation. The aim of the trial is to test the safety and feasibility of the Pulse NanoMED System in ischemic stroke patients. The potential clinical benefit of early recanalization will be visually assessed by a core laboratory by comparing baseline DSA, CTA, or MRA images with images taken at set timepoints.[126] Iron nanoparticles were further explored in combination with an external rotating magnet to overcome stagnant blood flow which limits access of clot-dissolving medication to the clot.[127]

3.3. Mesoporous Silica Nanoparticles

Mesoporous silica nanoparticles (MSNs) have emerged as a promising option for developing controlled drug delivery systems tailored for targeted diagnosis and treatment of cancer. MSNs feature a porous structure, with pore sizes ranging between 2 and 50 nm, exhibiting precise organization. With their high surface-to-volume ratio, tuneable pore size and surface properties, and low toxicity, MSNs offer a versatile platform for drug delivery applications. They effectively protect encapsulated drugs, ensuring controlled release, enhanced circulation time, and improved drug stability. Moreover, the surface of MSNs is readily modifiable with polymers like polyethylene glycol (PEG), lipid bilayers, or various coatings, enabling enhanced particle stability in vivo and responsiveness to external stimuli such as pH changes (**Figure 7**).[128–130]

3.3.1. Innovative Applications of MSNs in Cerebrovascular Diseases or Neurological Disorders

Despite the challenges associated with drug delivery to the brain and central nervous system, MSNs are emerging as promising options for treating neurodegenerative diseases such as Alzheimer's, depression, and Parkinson's disease. For example, some researchers have explored the application of MNS in Alzheimer's disease, a neurodegenerative condition characterized by elevated levels of proteins such as β-amyloid (Aβ), leading to the formation of plaques in the brain. By developing magnetic MSNs conjugated with plaque-targeting agents, researchers have demonstrated the ability to selectively target and disperse Aβ plaques using external magnetic stimuli. This approach holds promise for developing targeted therapies for Alzheimer's disease and other neurodegenerative disorders.[129]

Developing new nanoparticle-based drug delivery systems represents a promising approach to address the complexities associated with AD. These systems aim to target both amyloid plaques and trace metal ions, such as copper, which are also implicated in AD pathology. By incorporating bifunctional molecules into nanoparticles, researchers seek to enhance the efficacy of drug

Figure 7. Representation of the morphology of a mesoporous silica nanoparticle. It can be appreciated in red the encapsulated drug. The black surface is the silica nanoparticle itself, where pores of different sizes can be distinguished. The drug is released upon application of an external stimulus. Original illustration by Celia Martín-Morales.

transporters while minimizing the toxicity associated with traditional chelation therapy. One of the key mechanisms underlying AD pathogenesis involves the formation of ROS by the interaction between amyloid-beta (Aβ) and copper ions. These ROS contribute to oxidative stress, which can have deleterious effects on cellular components such as DNA, proteins, and lipids. In a reducing environment, the Aβ-Cu complex may react with oxygen to produce hydrogen peroxide, exacerbating oxidative damage. Efforts are underway to detect oxidative stress using nanoparticle-based approaches that leverage the surface chemistry of cellular oxidants like hydrogen peroxide (H_2O_2). By developing nanoscale platforms capable of targeting amyloid plaques, sequestering metal ions, and detecting oxidative stress, researchers aimed to advance the diagnosis and treatment of AD. In this context, Yang et al. synthetized gold-capped MSNs with an H_2O_2-responsive controlled release system to deliver metal chelator CQ (clioquinol) targeting toxic Aβ plaques involved in Alzheimer's disease.[115] The innovative aspect of this approach relied in its ability to release CQ in response to high H_2O_2 levels, which are characteristic of environments containing Aβ plaques. By selectively releasing CQ in the vicinity of Aβ plaques, the system minimized interference with normal metal homeostasis and reduced the risk of adverse side effects associated with traditional metal chelators. The study demonstrated that Au-MSN-CQ particles were more effective than bare MSN-CQ particles in decreasing Aβ self-assembly and inhibiting Cu^{2+}-induced Aβ40 aggregation. Moreover, Au-MSN-CQs exhibited benefits such as minimized ROS-mediated apoptosis caused by Aβ40-Cu^{2+} complexes, as well as reduced cell membrane disruption and microtubular defects. Importantly, this research highlights the potential of functionalized MSNs for efficient BBB penetration, suppression of Aβ aggregation, and excellent biocompatibility,

positioning them as promising delivery vehicles in the pharmaceutical industry. This study represents a significant step forward in the development of targeted therapies for AD, offering a novel approach to address the complex pathophysiology of the disease.

On a different approach, the study conducted by Karimzadeh et al.[131] represents a significant advancement in the development of drug delivery systems for Alzheimer's disease (AD) treatment, focusing specifically on the delivery of rivastigmine hydrogen tartrate (RT), a therapeutic drug that inhibits acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) metabolism in the central nervous system (CNS). One of the major challenges in AD treatment is the delivery of drugs like RT to the brain, given their hydrophilic nature and the biological barriers that restrict their access. Karimzadeh et al. addressed this challenge by developing high-porosity mesoporous silica nanoparticles (P1-MSNs) and functionalizing them using succinic anhydride (S-P1-MSN) and 3-aminopropyltriethoxysilane (APTES), resulting in AP-CO-P1-MSNs. They found that the functionalized nanoparticles exhibited higher entrapment efficiency and RT loading percentages compared to non-functionalized ones. In simulated gastric and body fluids, the release rate of RT from the functionalized particles was slower than that from non-functionalized nanoparticles. However, when orally administered, sustained release of RT was observed from the functionalized particles. Although the cytotoxicity associated with bare MSNs was negligible, treatment with functionalized MSNs resulted in a reduction in cell viability, possibly due to the easy access and accumulation of these particles in multiple cell components. Overall, this research demonstrated the promise of functionalized mesoporous silica nanoparticles as effective drug delivery vehicles for AD treatment, offering sustained release of therapeutic agents and potential applications in targeted drug delivery and disease diagnosis. Within the context of cardiovascular diseases, in the last years, MSNs have recently attracted increasing attention for drug delivery to the brain because of their exceptional biocompatibility, large surface area, high loading capacity, and ability to cross the BBB via transcytosis. In this framework, Zou et al.[132] developed lactoferrin functionalized hollow mesoporous manganese doped silica nanoparticles (LHMMSN) for the delivery of resveratrol (RES). The encapsulation of RES into LHMMSN ensured efficient delivery and sustained release of the therapeutic agent. In vitro and in vivo experiments demonstrated the efficacy of LHMMSN-RES in modulating oxidative stress, inflammation, and apoptosis in brain tissue. Specifically, LHMMSN-RES was found to increase the activity of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px), while reducing levels of ROS and malondialdehyde (MDA), markers of oxidative stress. Moreover, it enhanced the expression of anti-inflammatory (IL-10) and anti-apoptotic (bcl-2) factors, while reducing the expression of pro-inflammatory (TNF-α, IL-1β, IL-6) and pro-apoptotic (BAX, Cleaved caspase-3) factors in brain tissue. Overall, LHMMSN-RES demonstrated the ability to mitigate inflammation and protect nerve cells by inhibiting oxidative stress, leading to improved motor function recovery in rats with MCAO. This approach holds potential for the development of novel therapeutics for cerebral ischemia and other neuroinflammatory conditions. Furthermore, oxidative stress acts as a trigger in the course of neurodegenerative diseases. In this context, Resveratrol (RSV) is effective at reducing excess ROS and reactive nitrogen species in the CNS. However, its delivery to the brain via systemic administration is inefficient. In light of these considerations, Shen et al. developed Polylactic acid (PLA)-coated mesoporous silica nanoparticles, conjugated with a ligand peptide targeting the low-density lipoprotein receptor to enhance transcytosis across the BBB to deliver RSV. In vitro results confirmed the enhanced transcytosis of the nanosystem across the BBB.[80]

Table 4. Classification of dendrimers by the synthesis method.

Classification of dendrimers by the synthesis method	
Divergent growth method	Convergent growth method
the dendrimer is built from the core to the periphery starting from a multifunctional core	the dendrimer is assembled by coupling dendrimer entities into a multifunctional core (inward)

Intracerebral hemorrhage (ICH), caused by the sudden rupture of an artery within the brain, is a devastating subtype of stroke, which currently has no effective treatment. In this framework, Cha et al.[133] synthetized lipid-coated magnetic mesoporous silica nanoparticles doped with ceria nanoparticles (CeNPs) for ROS scavenging and iron oxide nanoparticles for MRI contrast enhancement. The lipid bilayer coating provides stability and facilitates cellular uptake of the nanoparticles. In vitro studies have demonstrated the potent anti-oxidative and anti-inflammatory properties of LMCs loaded with CeNPs. Upon intracerebral injection in a rodent ICH model, LMCs were able to reach the peri-hematomal area, where they were engulfed by macrophages. MRI imaging of the brain confirmed the localization of LMCs in the target region. Furthermore, LMC treatment led to a reduction in inflammatory macrophage infiltration and consequent brain edema, ultimately resulting in improved neurological outcomes in the animals with ICH. This theragnostic approach, combining therapeutic and diagnostic functions, represents a significant advancement in the management of ICH. Overall, LMCs represent a promising nanobiomaterialfor the treatment of ICH, offering a multifunctional platform for targeted therapy and non-invasive monitoring of disease progression. Further research and development of LMC-based theragnostic strategies may lead to improved outcomes for patients with ICH.

The adaptability and versatility of nanoparticles, particularly mesoporous silica nanoparticles (MSNs), offer immense potential in various biomedical applications. By fine-tuning their particle and pore size, as well as pore volume, tailored nanocarriers can be designed to address specific therapeutic needs. This versatility extends their utility across diverse fields, ranging from bone regeneration to targeted drug delivery for cerebrovascular diseases like stroke. One of the key advantages of MSNs is their ability to encapsulate drugs within their porous structure, allowing for precise control over drug release kinetics. Moreover, their surface can be easily modified to enhance biocompatibility, target specific sites, or respond to external stimuli, such as changes in pH or temperature. As our understanding of nanoparticle behavior and its interactions with biological systems continues

Table 5. Advantages and disadvantages of various drug delivery systems.

Type of system	Advantages	Disadvantages	Ref.
Polymeric Micelles	-Due to its high molecular weight, does not dissociate rapidly -Immediate transition to self-assembly when coming in contact with an aqueous environment -High stability -Longer shelf life than other systems -Inexpensive and easy to synthesize	-Potential toxicity -Low drug loading efficiency -Poor stability in the gastrointestinal environment -Non-targeting ability, they have to be functionalized	[34, 37, 46, 135]
Liposomes	-Amphiphilic: can encapsulate hydrophilic and hydrophobic drugs -Increased efficacy and therapeutic index of drugs and reduce the toxicity of the encapsulated agent -At high temperatures can maintain its structure -Highly biocompatible, biodegradable, flexible, non-toxic-non-immunogenic for system -Reduce the exposure of sensitive tissues to toxic drugs -Excellent cell internalization mechanism	-Low solubility in blood -Shorter half-lives -Low drug loading efficiency -Leakage and fusion of encapsulated drug/molecules -Production cost is high	[136–139]
Dendrimers	-High loading capacity of the drug -High bioavailability of the attached drug united by covalent or non-covalent bonds -High penetrability of biological barriers and cell membranes -Increase of the therapeutic efficacy and specificity action -Biodegradable -Versatility and easy-to-modify features such as size, shape, or functional groups in the surface -Prolonged half-life and reduced toxicity of the drug -Internal cavities generated by the gap left by the dendrons allow the introduction of drugs into there	-Due to the synthesis processes, some defects can be generated on the surface. Also, it is necessary to clean the product after each step of preparation. And, depending on the method used to synthetize, it can be difficult to control the structure. -Difficulties in the control of the release of drugs -A lower drug liberation potential	[13, 140, 141]
Nanospheres and Nanocapsules	-The use of natural polymers such as chitosan can improve the biocompatibility and biodegradability -High reactivity of particle surface -These systems can pass through the smallest capillary -Long half-life	-More possibility of aggregation -They could be toxic -Low control of drug release rates -Inactivation of drugs due to the fabrication processes -The ratios between its small size and a large surface area to volume can produce a burst release	[89–91]
EVs	Biocompatibility, biodegradability, low toxicity, low immunogenicity.	Without appropriate functionalization, these nanosystems lack of specificity, mainly accumulating in peripheral tissues or organs, such as the spleen, liver, and gastrointestinal tract	[97, 107]
Microspheres	-Provide constant and prolonged therapeutic effect -Low size than others leads to an increase in surface area -Reduces the dosing frequency and thereby improves patient compliance -They could be injected into the body due to their shape and size -Easier estimation of diffusion and mass transfer behavior -Improve bioavailability and reduce the incidence or intensity of adverse effects -Coating of the drug with polymers helps the drug from enzymatic cleavage and hence found to be the best for drug delivery -Reduce the reactivity of the core about the outside environment -Simple injection due to the small size and shape -Control of drug decomposition	-Release rate of the controlled release dosage form may vary from a variety of factors -Differences in the release rate from one dose to another -The cost could be higher than those of standard formulations -The fate of polymer additives such as plasticizers, stabilizers, antioxidants, and fillers -Less reproducibility -Process conditions like changes in temperature, and pH…may influence the stability of core particles to be encapsulated	[74, 142, 143]
Magnetic nanoparticles	-The size is variable -Easy functionalization of the surface -These types of nanocarriers can be controlled by an external magnetic field (remote control), and also their vibration, rotation, and translational movement can be controlled. -Super paramagnet nanoparticles can be generated to use for biomedical applications -By coating the nanoparticles, the half-life can be increased -Easy synthesis with high reaction yields and low-cost -Non-toxic, biocompatibility, bioavailability. -Advantages for in vivo use, promoting angiogenesis and revascularization in ischemic regions guided using a magnetic field	-Magnetic nanoparticles may have a lower chemical stability under biological environment conditions, resulting in aggregation -Once the magnetic field is removed, the nanoparticles do not retain any residual magnetism -Large-size particles are required for some specific applications	[118, 144, 145]

(*Continued*)

Table 5. (Continued)

Type of system	Advantages	Disadvantages	Ref.
Gold nanoparticles	-Easy functionalization -High chemical reactivity -High X-ray absorption coefficient, localized surface plasmon resonance, and radioactivity -Good electronic and optical properties -Longer circulatory halftime -Biocompatibility, enhanced binding affinity, and low phototoxicity	-If gold nanoparticles are not modified, they are toxic in the blood. It is necessary to PEGylated -Low solubility	[82, 111]
Mesoporous silica nanoparticles	-This type of nanoparticle avoids the premature release of the drug, improving efficiency and reducing potential side effects -Robustness, mechanical strength, tuneable degradability, thermal and chemical stability -Extended pore size -It is easy to incorporate two or more drugs in a single nanoparticle	-The pore size and volume of pores in the material may be a limiting factor for the molecules that could be encapsulated there	[146–148]

The colors in the table represent blue for the organic biosystems and green for the inorganic biosystems.

to evolve, MSNs are poised to play a pivotal role in the future of medicine. In conclusion, MSNs represent a promising avenue for the development of advanced therapeutic strategies. Their versatility, coupled with their ability to encapsulate and deliver therapeutic agents, holds great promise for addressing a wide range of diseases. With ongoing research and technological advancements, MSNs are expected to emerge as indispensable tools in the fight against various medical conditions in the coming years.

4. Drug Delivery to the Brain for Cerebrovascular Diseases

The brain, a delicate organ shaped by evolution, boasts highly efficient protective mechanisms. Unfortunately, these same defenses that shield it from harmful substances can hinder therapeutic treatments. Many pharmaceuticals fall short in treating cerebral diseases because of our struggle to deliver and maintain them effectively within the brain. Enhancing drug delivery methods to the brain has become a priority. Despite intensive research efforts, patients afflicted with fatal or debilitating CNS diseases, such as cerebrovascular diseases and neurodegenerative disorders, for instance, far outnumber those succumbing to systemic cancer or heart disease. The failure of many potentially effective therapies often lies not in their lack of potency, but in shortcomings in drug delivery methods. In fact, even though all CNS diseases have different causes, they all share common characteristics in terms of targeted delivery, and these characteristics are the BBB and the blood-cerebrospinal fluid barrier (BCSFB).

4.1. Blood–Brain Barrier (BBB)

The regulates the passage of molecules between the blood and the central nervous system, selectively allowing or restricting their entry. It consists of brain capillary endothelial cells, astrocyte foot processes, neurons, pericytes, and extracellular matrix. Despite not being a single physical entity, the BBB is a combination of physiological properties of endothelial cells that limit vessel permeability. Its importance is evident in conditions like ischemic stroke, where its behavior varies across different stages. here are three main stages of ischemic stroke: hyperacute (<6 h), acute (6–72 h), subacute (>72 h), and chronic stages (>6 weeks), each characterized by distinct BBB status. The hemodynamic changes in the barrier have both positive and negative aspects. While they may facilitate hemorrhagic transformation, they also promote neo angiogenesis and enable the delivery of therapeutic agents. Hence, understanding the dynamics of the BBB in various cerebrovascular diseases is crucial for effective management.

4.2. Blood-Cerebrospinal Fluid Barrier (BCSFB)

The second barrier encountered by systemically administered drugs before entering the central nervous system is known as the BCSFB. The BCSFB regulates the passage of blood-borne molecules into the cerebrospinal fluid (CSF), which can exchange molecules with the brain parenchyma's interstitial fluid. Physiologically, the BCB is primarily located in the epithelium of the choroid plexus, which restricts the passage of molecules and cells into the CSF. Additionally, the arachnoid membrane, situated between the dura and pia mater on the external surface of the brain, forms another component of the barrier system. The arachnoid membrane is generally impermeable to hydrophilic substances and functions passively in forming the Blood-CSF barrier. In contrast, the choroid plexus actively produces CSF and regulates the concentration of molecules within it. The choroid plexus consists of highly vascularized tissue masses protruding into pockets formed by ependymal cells. These cells, which line the ventricles, have microvilli on the CSF side, basolateral interdigitations, and abundant mitochondria. Although the capillaries of the choroid plexus are fenestrated and non-continuous, allowing free movement of small molecules, tight junctions between adjacent choroidal epithelial cells prevent most macromolecules from effectively passing into the CSF from the blood. However, these epithelial-like cells have a lower resistance compared to cerebral endothelial cells. Furthermore, the BCSFB is strengthened by an active organic acid transporter system in the choroid plexus, which actively removes CSF-borne organic acids into the blood. Consequently, therapeutic organic acids like penicillin, methotrexate, and zidovudine are actively removed from the CSF, inhibiting their diffusion into the brain parenchyma.

Moreover, disparities often exist between the composition of the CSF and brain interstitial fluid, suggesting the presence of a CSF-brain barrier. This barrier is attributed to the considerable diffusion distances required for equilibration between the CSF and brain interstitial fluid, making entry into the CSF not a guarantee of a drug's penetration into the brain (**Tables 4** and **5**).[129,134]

5. Advantages and Disadvantages of Drug Delivery Systems

6. Conclusion

The recent advancements and prospects of various drug delivery systems for cerebrovascular diseases have been extensively reviewed. Nanocarriers, based on different materials, such as polymers or silica have been investigated, being categorized into organic and inorganic biomaterials. Their potential applications as drug vehicles have been explored based on their unique characteristics and properties. The advantages and limitations of each system have been elucidated to guide the selection of the most suitable nanocarrier for specific studies. While these biomaterials offer significant promise in nanomedicine, they often face limitations, with control of release rate being a common challenge. Surface functionalization of nanovehicles can enhance their performance and selectivity, influencing factors like solubility and toxicity. Functional groups tailored to meet specific requirements play a crucial role in modulating interactions with the medium.

Many of these biomaterials are engineered to release drugs in response to specific stimuli, either internal or external. These stimuli, such as pH, enzymes, or magnetic fields, enable precise and controlled drug release at the target site. This feature underscores the growing significance of nanosystems in nanotechnology and biomedicine, offering less invasive and more personalized diagnostic and treatment options while mitigating adverse effects associated with conventional therapies. Future research directions should focus on developing tuneable delivery systems for personalized treatment, considering individual patient conditions, and optimizing drug dosages. Additionally, investigating the feasibility of using nanocarriers for continuous drug administration could revolutionize treatment protocols, reducing the need for frequent patient intervention.

Moreover, enhancing the speed and precision of drug release mechanisms holds promise for further advancements in nanotechnology within the biomedical sector. The potential of nanotechnology to combat diseases like stroke or Alzheimer's disease is substantial, raising hope for significant breakthroughs in the near future.

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Conflict of Interest

The authors declare no conflict of interest

Keywords

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María Victoria Gómez-Gaviro is a Pharmacologist and got her PhD at Hospital U. la Princesa, Madrid, in 2004. Then, she moved to the National Institute for Medical Research, MRC, London, to study the regulation of neural stem cells by the endothelium, funded by a postdoctoral Marie Curie fellowship. In 2010 she returned to Hospital U. Gregorio Marañon, Madrid, funded by a second Marie Curie fellowship, where she is leading her research group focused on bio-optical and bioengineering techniques applied to the study of the brain, neural stem cell niches, and cerebrovascular diseases. In the last 10 years, she has published more than 20 peer-reviewed articles as a senior author and is PI of several competitive grants. She is very involved in teaching and dissemination activities.