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Nanogels as potential drug nanocarriers for CNS drug delivery

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Abstract

Hydrogel-based drug delivery systems (DDSs) have versatile applications such, as tissue engineering, scaffolds, drug delivery, and regenerative medicines. The drawback of higher size and poor stability in such DDSs are being addressed by developing nano-sized hydrogel particles, known as nanogels, to achieve the desired biocompatibility and encapsulation efficiency for better efficacy than conventional bulk hydrogels. In this review, we describe advances in the development of nanogels and their promotion as nanocarriers to deliver therapeutic agents to the central nervous system (CNS). We also discuss the challenges, possible solutions, and future prospects for the use of nanogel-based DDSs for CNS therapies.

Keywords

nanogels; nano-carriers; nanomedicine; drug delivery systems; brain drug delivery; CNS diseases

Emergence of nanogels in CNS drug delivery

The increasing prevalence of CNS diseases and dementia are considered major challenges in human health management, given their severe impact on the long-term health of patients. Health agencies and scientific reports have confirmed that around 1.5 million people have CNS disorders, and that 11% of serious diseases are accounted for by brain disorders [1,2]. Various drugs and therapeutic agents have shown not only efficacy, but also limitations according to individual patient's disease profiles. Thus, there is a constant demand for novel therapeutics to establish novel therapies for CNS diseases; however, there are significant challenges associated with the systemic administration of such therapeutics [3]. The blood–

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Teaser: Nanogels are nano-sized hydrogel particles that exhibit properties that are superior to conventional hydrogels and that have emerged as smart bioactive drug nanocarriers to deliver desired bioactives across the blood–brain barrier for the treatment and targeting of CNS diseases.

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brain barrier (BBB) and blood–cerebrospinal fluid barrier (BCSFB) restrict the site-specific delivery of therapeutics, which limits their efficacy against targeted diseases. In addition, the BBB can reduce the concentration of a drug that reaches the target site, reducing its ability to treat the target disease. The high-dose requirements of these drugs have intensified the need to develop nano-enabled DDSs [4], which have many advantages over conventional drugs and DDSs [5]. Such DDSs are able to bypass the BBB non-invasively. Moreover, their structure can be easily modified to encapsulate the desired drug, rendering them ideal for the treatment of CNS diseases.

There has been remarkable progress in developing DDSs for delivering novel therapies for the treatment of CNS diseases [6–10]. Various nano-enabled pharmacological approaches (i.e., nanomedicine in combination with a suitable delivery method) have been explored that can deliver various drugs across the BBB and the successful release of drugs with reduced adverse effects and maximum efficacy has been achieved [11]. The emergence of nanotechnologies that offer varied opportunities for disease prevention, diagnosis, and therapy has led to significant progress in the field of nanomedicine [6,9]. The range of approaches used in nanomedicine include various drug carriers, such as nanoparticles [12], nanocapsules [13], nanocomposite hydrogels [14], dendrimers [15], nanospheres [16], and liposomal drug delivery carriers [17]. However despite their properties that render them suitable pharmaceutical excipients for pharmacotherapy, they nevertheless suffer various limitations to their clinical applications, especially in CNS therapy.

Thus, there is a need to increase the development of DDSs with selective properties. For example, hydrogels (biocompatible 3D polymeric networks) have been used for CNS drug delivery [18], especially in CNS tissue engineering. Their easy synthesis using chemical and physical routes, desired functionality, tuneable shape and porosity, loading compatibility with biomolecules, biodegradability, and stimuli-responsive properties [19,20] have made them potential candidates for drug delivery. The diversity and applications of the various terms used for gels (i.e., hydrogels, microgels, and nanogels) have proven to be realistic platforms for CNS nanomedicine. Various forms of gels encompass films, crystals, liquids and particles in the nano range (i.e., ‘nanogels’), the latter of which have gained substantial research interest owing to their properties that render them suitable for CNS drug delivery [21]. However, conventional bulk hydrogels used as a DDSs exhibit limited ability to cross the BBB because of their micron-sized structure, resulting in inefficient drug delivery to the brain. This obstacle can be overcome by transforming hydrogel from microgels to nanogels, promoting this class of materials as suitable drug nanocarriers [22] to use to investigate novel therapeutics for CNS diseases. Figure 1 highlights the major issues involved with CNS delivery and how nanogel- and nanotechnology-based systems can improve CNS delivery. Nanogels are an exciting innovation in nanomedicine because their properties can be tailored to deliver the bioactive at the target site to achieve an effective therapeutic effect with minimum adverse effects. Nanogel technologies can also been improved in terms of their targeted delivery by better drug dosage concentrations, drug residence times, cellular uptake ability, and stability. Recent advances in nanomedicine have suggested several biomedical applications of nanogels, including the encapsulation of biomolecules, the oral delivery of nucleoside analogs, oligonucleotides or small interfering (si)RNA for the treatment of

cancers and viral infections, resulting in the design of nano-metallic composites for use in imaging and, most importantly, in CNS drug delivery [1].

Here, we provide insights into the potential applications of nanogel-based DDSs for achieving high drug loading, drug stability, sustained/on-demand drug release, and specific targeting of CNS disorders, including brain cancer and Alzheimer's disease (AD), targeting of HIV-1 in macrophages, and tissue engineering.

Nanogels as potential drug nanocarriers

Nanogels are potential drug nanocarriers with the capacity to reach the smallest capillary vessels because of their small volume, which enables them to penetrate tissues via transcellular pathways [23,24]. Nanogels show better encapsulation of drugs because of their interpenetrating network structure (Figure 2A) and can be delivered by various routes of administration, including oral, pulmonary, nasal, and intra-ocular routes. [25–28]. The most important aspect of nanogels in terms of their use as DDSs is their size, which directly influences their blood circulation time as well as their bioavailability within the body. Particles ranging from 5 nm to 10 nm are rapidly removed through extravasation and renal clearance on systemic administration, whereas 10–70-nm particles are small enough to penetrate small capillaries. Moreover, 70–200-nm particles exhibit the most prolonged circulation time. Particles with diameters >200 nm are usually stopped by the spleen via mechanical filtration and are phagocytically removed, decreasing their blood circulation time [29]. Thus, these reports suggest that 1–100-nm particles can be retained within endocytic vesicles to allow their entry into target cells via endocytosis. Nanogel-based nanocarriers have solved the limitation associated with controlling the distribution of drugs inside the body, increasing the efficiency of targeted drugs. These nanocarriers exhibit enhanced permeability and retention effects (EPR), probably because of the permeability of drugs across the barriers within the body, thus providing stable and responsive therapeutics [30,31]. Modulating their surface and size properties to respond to the various different pH levels inside the human body enables them to be delivered via different routes to target different organs. Nanogels have also gained significant attention because of their ability to respond to external stimuli, such as ionic strength [32], temperature [33], pH [34], and magnetic [35] and electric fields [36]. These nanocarriers respond to these stimuli by changing properties, such as by swelling or shrinking to change their volume, their flexibility, and refractive index. Click chemistry [37,38] (Figure 2B) is a useful approach to form gels with varying dimensions and appearances. Remarkably, click chemistry results in unique biorthogonal features, rendering them compatible with encapsulated bioactives and living cells. Furthermore, its high reactivity and selectivity for synthesis under mild conditions make it a suitable strategy for forming various types of gel [38]. The physical crosslinking of hydrogels is also an important approach for the synthesis of injectable nanogels, because of the weak forces and the formation of a 3D network that occurs because of secondary forces, including ionic interactions and H-bonding. By contrast, chemical crosslinking methods, which involve covalent bonding, are extensively used for the synthesis of nanogels because of their high stability and mechanical strength. Recent trends have emphasized the development of nanogels [39] based on natural and biodegradable polymers engineered using layer-by-layer [40], mini-emulsion techniques [41], as well as self-

assembly for the targeted delivery of various drugs [42], proteins, and nucleic acids. Nanogels are efficiently taken up by cells, improving the bioavailability and safety of such therapeutics *in vivo* [43]. Li *et al.* demonstrated biodegradable nanogels as an intracellular therapeutic delivery platform [44]. These materials are of great interest in nanomedicine because of their applicability for tissue engineering [45], cancer therapies [46], scaffold applications [47], imaging [48], theranostics [49], gene delivery [50], and pH-responsive behaviors [51].

Trends in nanogel-based drug delivery to the CNS

To highlight the emergence of nanogels in the field of CNS delivery, we focus on studies using hydrogels for the treatment of brain tumors and for tissue engineering, which render them ideal candidates for CNS delivery. Hydrogels containing therapeutic T lymphocytes for localized delivery to glioblastoma cells for brain tumor immunotherapy were developed using poly(ethylene glycol)-*g*-chitosan (PCgel) [52]. These gels released viable T lymphocytes with a suitable pore size. This study highlighted the cellular compatibility of PCgel with T lymphocytes, which retained their antiglioblastoma activity when encapsulated inside the PCgel. These gels also showed greater efficacy in killing glioblastoma cells compared with the Matrigel control, supporting the viability of such an approach for the localized immunotherapy for glioblastoma. Immunotherapy stimulates the immune system, which explicitly involves the rejection and destruction of tumors with minimal harm to the surrounding tissues and is a potential next-generation nanomedicine approach in the treatment of brain cancers [53].

Cholesterol-bearing pullulan (CHP) with a polysaccharide backbone and cholesteryl hydrophobic moieties was developed as a nanogel with a diameter of 20–30 nm using the self-association in aqueous solution approach. These nanogels were used to inhibit the formation of fibrils by amyloid β ($A\beta$), which is important in the pathology of AD [54]. Amphiphilic di-block co-polypeptide hydrogels were also explored as injectable depots providing the sustained delivery of bioactive proteins that exerted an effect on local CNS neurons inside the BBB [55]. ‘Thermosensitive hydrogels’ designed to be administered as injectable forms have attracted attention for spinal cord delivery because of the presence of the blood–spinal cord barrier (BSCB), which limits the passage of systemically administered drugs into the spinal cord [56].

Given the ability of hydrogels and nanogels to be injected into the intrathecal space, they are now being considered as candidates for the delivery of therapeutics and other biomolecules to the CNS. Successful delivery of therapeutic hydrogel formulation within the spinal cord tissue has shown to bypass the BSCB with high organ specificity and delivery efficiency. These injectable gels have added advantages over other carriers for the delivery of peptides and protein therapeutics, which have short half-lives in the circulation and are too large to cross the BSCB [57]. The potential of such gels has been explored for cell delivery to the brain by utilizing natural as well synthetic polymers. Many reports using synthetic injectable materials have demonstrated their *in vivo* cell transplantation applications for the treatment of spinal cord injuries.

Chitosan-based nanogels are well established in terms of their non-immunogenicity profile and biosafety. Methotrexate, a hydrophilic anticancer agent, exhibits poor permeability across the BBB. The surface functionalization of nanogels with polysorbate-80 have been evaluated by inducing the low-density lipoprotein (LDL) receptor-mediated endocytic pathway in brain endothelial cells [58]. Nanogels loaded with methotrexate when administered intravenously showed a 10–15-fold increase in the brain concentration of the drug compared with the equidose of free drug [59]. Reports suggested that ligands can be attached to nanogels for effective targeting to the brain. A recent report showed the use of angiopep as ligand for the brain-targeting delivery of PEG-block-poly(D, L-lactide acid) (PEG-PLA) micelles. A near-infrared (NIR) fluorescent signal detection method was used to visualize the accumulation of the micelles in the brain.

Nanogels have also shown potential for the delivery of activated nucleoside reverse transcriptase inhibitors (Nano-NRTI) to the brain. NRTIs in macrophages exhibit antiviral activity although the availability of enough NRTIs for targeting by macrophages is restricted. The CNS carries macrophages, which function as a storehouse for HIV-1. Efforts have been made to establish the antiviral activity of clinically approved NRTIs in macrophages [60], although this is limited by the mechanism of drug efflux in the BBB. Vinogradov *et al.* [60] demonstrated the preparation of nanogel networks with an even spatial distribution of cationic and neutral nanogel (NG1), representing a layered structure with an outer layer of cationic polymer NG-2 and NG-3 as well as a cationic core-neutral shell structure, NG-4. These various nanogel formulations exhibited a high neutral:cationic polymer ratio for lower cytotoxicity. The study showed that all nano-NRTIs demonstrated high efficacy of HIV-1 inhibition at a drug level as low as 1 mmol/l. This study highlights the ability of nanogels to carry antiretroviral drugs.

Nanogels based on these natural polymers fits into the category of materials suitable for such CNS applications. Their characteristic properties include their rigidity, porosity, biodegradability, compatibility of the surface with the CNS tissue and characteristics that are moldable with functionalization and other modifications. The pH and/or temperature sensitivity of nanogels have been explored using non-invasive magnetic resonance imaging (MRI) for the preoperative diagnosis of glioma. Jiang *et al.* [61] synthesized magnetic nanogels using monodisperse oleylamine-coated Fe₃O₄ nanoparticle-loaded poly(*N*-isopropylacrylamide-co-acrylic acid) nanogels. These gels demonstrated targeting on gliomas both *in vitro* and *in vivo*. Studies using a rat model with C6 gliomas showed that MRI/fluorescence imaging with high sensitivity and specificity could be acquired by application of these gels.

In a recent study, Nochi *et al.* [27] demonstrated the use of cCHP-based nanogels as a universal protein-based antigen-delivery vehicle for adjuvant-free intranasal vaccination. Such nanogels are formed by self-assembly in water and trap various proteins by hydrophobic interactions, exhibiting chaperon-like activity because of the hydration of the proteins without any aggregation, which can then be slowly released in their native form (Figure 3) [62]. This study revealed the potential of CHP nanogels as nanocarriers for protein delivery and provides scope for their application in cancer vaccine development. These types of study have focused on the development of adjuvant-free intranasal vaccines,

which induce antigen-specific CD8⁺ cytotoxic T lymphocyte responses and antibody production. CHP nanogels have also been explored as subcutaneous injections for carrying the cancer antigen HER2 (CHP-HER2) or NY-ESO-1 (CHP-NY-ESO-1) [63].

The greatest challenge in drug delivery is to deliver the drug cargo efficiently to the target site. There are many barriers that a cargo has to overcome before reaching its target site. The primary barrier in the brain is the BBB, which limits the access of various molecules and compounds to the brain from the periphery. This restriction is because of brain microvessel endothelial cells (BMVECs), which cover tight extracellular junctions and have little pinocytic activity [64]. Thus, there is a need to explore new nanocarriers for the effective delivery of drugs and biomacromolecules to the CNS for the treatment of neurological disorders. Many reports have demonstrated various strategies to inhibit drug efflux transporters expressed in the BBB by the use of Pluronic® block copolymers, which have the potential to transport substrates to the brain [65]. Other interesting strategies involve the development of nanoparticles bound with specific ligands that have the potential to target receptors mediated transcytosis as well as the functionalization of peptides and proteins by hydrophobic moieties for their efficient delivery to the brain.

Nanogel-based systems have shown the effective binding and encapsulation of negatively charged oligonucleotides, forming an aqueous stable dispersion of a polyelectrolyte complex with a particle size <100 nm [66,67]. An *in vitro* model that makes use of polarized monolayers of bovine BMVECs demonstrated the efficient transport of oligonucleotides encapsulated in nanogels across the BBB. The surface modification of the gels using transferrin or insulin demonstrated that the use of these gels resulted in a 15-fold increase in the accumulation of phosphorothioate ODN in the brain, whereas its accumulation in liver and spleen decreased twofold compared with free oligonucleotide [68]. Other important aspect that highlights the enhanced delivery of therapeutics to the brain is the interactions of the various polymers with membrane proteins in BMVECs. These polymers used efflux transporters, such as P-glycoprotein and multidrug resistance proteins.

Challenges for nanogel-based drug delivery systems

The potential of nanocarriers for the treatment of CNS disease have resulted in significant advances in the design of DDSs. The treatment of numerous neurological disorders and injuries to the CNS is hampered by the poor intrinsic regenerative capacity of these systems. The major challenge lies in the passage of these nanocarriers across the BBB, which restricts the diffusion of molecules into the brain by the diverse routes of administration, including oral and intravenous routes. The shape and size of lesions inside the CNS are important parameters that are dependent on the pathology of the injured tissue and site; nanogels could be used to fill in the void and their characteristics could be modulated for delivery through small-gauge needles. Other major challenges to the development of nanogel-based DDSs include: (i) the nano-ormulation must be capable of delivering enough of the drug to the target area in a controlled manner; (ii) the generation of biocompatible and biodegradable materials for the design of the nanoformulations; (iii) the DDS must be functional as a stimuli-responsive vehicle; and (iv) the DDS must be capable of acting as carrier for therapies combined with medical imaging attributes for diagnostics needed during surgery.

Other limitations to nanogels include the polydispersity of polymers and issues associated with their renal clearance, although this can be managed by altering the synthesis techniques and parameters used. Nanogels are also synthesized by the use of synthetic polymers (e.g., acrylic acid and its copolymers, polyacrylamide) and inorganic nanofillers, such as graphene, fume silica, and carbon nanotubes (CNT), although these can result in toxic by-products following their biodegradation. Thus, an appropriate concentration needs to be used that results in non-toxic effects and that can be safely cleared from the body. Moreover, very small particles (5–10 nm) are rapidly cleared via the renal system; thus, sorting similar-sized hydrogel particles is a possible solution to avoid rapid renal clearance.

The stability of the nanogel formulation is another important aspect to consider. Drug-loaded nanogels should be stable in terms of the drug inside the matrix and should not affect its integrity. Their responsiveness towards the various physiological pH environments inside the body is also important and has a significant effect on the release of their cargo, although this is still not fully understood.. Moreover, an intrinsic property of hydrogels as well as nanogels is that they swell in aqueous environments and other physiological fluids. They also have varying responses to external stimuli. Thus, there is a need to modulate the surface of nanogels for their use as DDSs for use in the brain. Thus, the biggest challenge is the tendency of nanogels to respond to external variation in the environment. Overall, the focus should be on the development of nanogels with rapid response onset times and the stability of the carriers [69]. In addition, the tuning of drug release kinetics for improved biodistribution of the drug is another challenge associated with nanogel-based systems. Early drug release or burst release are commonly faced challenges. Once addressed, this will enhance the therapeutic index of drugs encapsulated inside the nanogel acting as a drug nanocarrier. Nanogels have the capacity to overcome these challenges associated with drug delivery to the CNS by providing a minimally invasive, localized, void-filling platform for therapeutic use. Smallmolecule or protein drugs can be distributed throughout the hydrogel, which then acts as a depot for their sustained release at the target site. Nanogel-based delivery systems have been also explored as intranasal vaccine delivery systems. Recent research suggests that the nasal route can be used successfully to deliver therapeutics to the brain and it has been adopted as an alternative method for the transport of drugs into the cerebrospinal fluid in addition to the olfactory pathway. This pathway has also shown increased absorption of drugs by the CNS and brain [70].

Prospects

Future nanogel technologies are likely to involve more advanced functional systems with an innovative role in biomedical and nanotechnology [71]. Specifically targeted nanogels are the future of nanomedicine, which can be developed as new receptors and ligands are invented for the desired target tissue or organ. Recently, click-crosslinked hydrogels have proven to be more stable, with limited or no cytotoxic coupling agents, and without the formation of any side products. Modulation of synthesis methods for diagnostics and therapeutic purposes is required for optimal results. Nanogels show great promise for their application in diverse modes of administration, including aerosolic [61] as well as transdermal [72] and oral delivery [73]. These are the areas that should be pursued, in addition to the development of more efficient ultrasound/MRI contrast agents using

nanogels. Several challenges include the development of injectable systems with nm-sized particles, which can result in sustained drug release and multi-stimuli-responsive DDSs [74].

Emphasis on the use of more biodegradable and biocompatible polymers for the synthesis of nanogels is needed to completely eradicate any possible toxicity of the nanoformulations. Nanogel formulations that can be used as effective drug delivery vehicles must bear reducible bonds that can be cleared for faster intracellular release and a more efficient DDS; the targeted nanogel system should encapsulate a range of macromolecules, and hydrophilic as well as hydrophobic drugs; such systems must be capable of effectively binding with the targeted ligand or receptors and exhibit high stability of the encapsulated drug, keeping in mind the high therapeutic efficacy required for its sustained release. The typical advantage of nanogels compared with other carriers is their high degree of encapsulation as well as providing an ideal 3D environment for various macromolecules. Their various characteristics, from swelling to collapsing, enable them to respond to various external stimuli. Biodegradation is the most crucial characteristic of nanogels in terms of their clinical use. Thus, methods of synthesis that involve chemical crosslinking should be considered because they can be tuned to degrade at a required rate and, hence, are suitable for prolonged drug delivery to the injured site.

Nanogel technology opens the door to various approaches for the delivery of drugs across the BBB by either direct injection and implantations, or surface-modified nano-enabled delivery platforms via intravenous routes. In addition, magnetic-responsive nanogels also offer great promise for use in the delivery of drugs to the brain. Nanogel-based systems target the transcellular routes of drug transport in BMVECs. Thus, exploration of the specific peptides for targeting the drug as well as receptor-mediated transcytosis across the BBB are potential strategies for improving drug delivery to the brain. Nanogels can also be modified to develop therapeutic cargos that are able to traverse the BBB (Figure 4). Such modification is via receptor or ligand binding, as well as possibility of adding magnetic features to the nanostructure, which could enable these carriers to traverse other dynamic barriers in the body. Moreover, hydrophobic modifications of their surface render them more able to cross the BBB. Their unique ability to respond to external stimuli could also be utilized for the delivery of cargos using external stimulation, such as ultrasound and magnetic fields.

Concluding remarks

Nanogels exhibit characteristics of both nanoparticles and hydrogels that render them suitable for use as nanocarriers of both small bioactives and biomacromolecules. The 3D networks of hydrogels and the nanosized particles combine to result in greater therapeutic effects compared with conventional carriers. Here, we have provided an empirical framework highlighting the design, demands, and challenges that need to be confronted to realize the full potential of nanogel-based drug delivery to the brain. Presently, the major research focus in nanomedicine is on the design of nanogel formulations that could be used in personalized therapeutics, to better meet the need of individual patients.

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Highlights

- Nanogels are the nano-sized hydrogel particles exhibiting superior properties than the conventional bulk hydrogels.
- Nanogels are among exciting innovations in nanomedicine to deliver the bioactives at the target site.
- They are capable to achieve an effective therapeutic effect with minimum side-effects
- Nanogels based therapeutic cargo can be promoted as future CNS diseases therapy.

Figure 1.

Major issues involved with central nervous system (CNS) drug delivery and how nanogel and nanotechnology-based systems can improve the delivery of drugs to the CNS.

Figure 2.

Title. (a) Preparation of nanoformulations. (b) Preparation and potential biomedical applications of click hydrogels, and micro/nanogels. Reprinted, with permission, from [38].

Figure 3.

Use of cationic cholesterol-bearing hydrophobized pullulan (cCHP) nanogels as new antigen-delivery vehicles for intranasal vaccination. (a) A cCHP nanogel was generated from a cationic type of cholesteryl-group-bearing pullulan. (b) Superimposition of sagittal and transverse (photo insets) PET images on the corresponding CT images showing that intranasally administered cCHP nanogels carrying T18FU-labeled BoHc/A were effectively delivered to the nasal mucosa. (c) Direct quantitative study with T111InU-labeled BoHc/A further demonstrated that BoHc/A was retained in the nasal tissues for more than 2 days after intranasal immunization with the CHP nanogel. By contrast, most naked BoHc/A disappeared from the nasal cavity within 6 h of administration. Reprinted, with permission, from [27].

Figure 4.

Schematic presentation of the various suggested mechanisms by which nanogel-based drug delivery systems might cross the blood–brain barrier (BBB). Nanogel-based nanoformulations can be: (a) magnetic, to allow magnetically guided non-invasive delivery; (b) delivered to the brain via opening the BBB using external stimulation, such as focused ultrasound; (c) hydrophobic to achieve delivery to the brain; and (d) carry receptor-functionalized cargo that is able to cross the BBB.