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Nanogel technology: preparation strategies and therapeutic uses

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ABSTRACT

Nanogels also known as nanohydrogels are a class of 3D network comprised of natural synthetic, or hydrophilic polymers. The high-water content allows them to swell an enable them to catch hold of macromolecules and drug moieties that respond to external stimuli. The three-dimensional network enhances their stability and tunability with reduced side effects and degradation. The extensive research in miscellaneous field has produced various nanogels with distinct characteristics. Therefore, the simplification of these novel methodologies and their practical applicability would assist in designing nanogels with versatile properties, thereby enhancing drug delivery and targeting efficiency in biomedical and theranostic applications. In addition, the investigations would be helpful to resolve the limitations in conventional therapies such as side effects decreased stability cytotoxicity, non-targeted drug delivery etc. The surface modification results in drug targeting, and enhanced circulation time which increases the bioavailability of the drug molecules. The nanogels because of their biodegradability, biocompatibility, small size, stimuli responsive drug delivery, enhanced drug loading capacity, and tailored functionalities enable their potent applicability towards various fields. In this current comprehensive review, we discuss the updated technologies for the preparation of nanogels and their applicability in treating various diseases and pathological complications.

Keywords: Cross linking; drug delivery; drug release; nanogels; polymerization.

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INTRODUCTION

The term nanocarriers refers to Nano dispersion systems fabricated from various natural or synthetic polymers and inorganic materials including nanogels, nanoemulsions, and nanoparticles. These materials range from 1-1000nm that allows them to disperse or dissolve in a suitable solvent system and exhibits enhances stability with drug delivery characteristics. The advancements in nanotechnology has developed several advantages such as decreased adverse reactions, enhanced efficacy, drug loading and stability. These exclusive advantages enabled these materials to prefer in wide fields of interest such as tissue engineering, biomedical imaging, biosensing, and drug delivery. The nanomaterials encapsulated with various drug candidates that can be solubilized, absorbed, targeted, internalized in the targeted organs and tissues to produce the required therapeutic effect with reduced cytotoxicity. The nanocarriers loaded with versatile antimicrobials are used in food and packaging industry for preserving the safety and efficacy of the material. Therefore, the nanomaterials are widely used in miscellaneous fields including biopharmaceuticals due to their unique and potent drug delivery characteristics. Among these nanogels have gained significance due to their optimized size with enhance surface area, and biocompatibility. The nanogels can absorb abundant amounts of water and still can remain stable with high structural integrity. This polymeric network enables them to encapsulate both smaller as well as larger biomolecules and responds to signals that offer controlled drug release with real time visualization of drug distribution and therapeutic activity. This enables the nanogels to monitor the therapeutic activity along with the treatment such as gene therapy, drug delivery, tissue imaging, and imaging. The nanogels can be synthesized through physical and chemical methods in which the chemical methods involve establishment of permanent, rigid, and persistent links within the polymeric network while the physical methods involve establishment of

self-assembling technologies through non-covalent binding. The selection of appropriate method is useful to produce the nanogel with predefined specifications. At the same time the selection of a suitable polymer is highly critical in the fabrication of nanogels because several polymers lack biocompatibility, biosafety, and stability. The nanogels exert the required therapeutic action by means of various methodologies such as stimuli responsive, pH responsive, enzyme responsive, ROS responsive, magnetic responsive, near infra-red responsive, 3D printable and injectable nanogels [52]. In addition, the nanogels possess certain degree of elasticity, impact resistant and stability that enable them to withstand with the external stress to a certain extent [53]. The nanogels can be administered through various routes such as oral, nasal. pulmonary, parenteral and intraocular and the drug release relies on the composition of dosage from and through specific mechanism involved [54]. Apart from drug delivery, the nanogels also play a vital role in tissue engineering as they can behave as scaffolds for cell growth and in bioimaging through enhancement of resolution and specificity [55]. However, in the presence of external stimuli, these nanogels undergo structural changes, charge alteration, chemical reactions, and photo sensitization reactions with in the structure of nanogel that allows spatiotemporal drug release [56]. The versatility offered in the synthesis of nanogels allow substantial chemical design that produces controlled delivery triggered by endogenous or exogenous stimuli. However, there are no reported nanogels approved for various diseases as they are still under clinical trials in India. It is expected that the extensive research in the filed of nanotechnology provides novel platform to explore nanogels with robust and versatile properties [57, 58].

Methods of preparation:

I. Chemical Cross-linking method: One of the most widely used measures to prepare nanogels is chemical cross-linking due to the possibility of forming stable covalent bonds that do not allow premature dissociation in circulatory circulation. In this method, polymer strands are linked in three-dimensional network via a variety of chemical reactions, creating nanogels with adjustable nanoscale size. The methodology starts with the selective choice of water-soluble polymers, which are either natural or synthetic and have functional groups like hydroxyl, carboxyl, or amine functional groups. These groups act as reactive points where conjugation with crosslinkers can occur that, under controlled reaction conditions, covalently attaches the polymer chains resulting in a strong network structure. Technically, chemical cross-linking has a number of advantages, namely, it increases the mechanical stability, increases the retention of drugs, and enables the control of the particle size by changing the concentration of the polymer, the concentration of surfactants, and the reaction kinetics. Besides, the ability to incorporate stimuli-responsive crosslinkers allows nanogels to respond to stimuli including pH, redox potential, or enzyme activity, which can be used with a wide variety of targeted drug delivery applications. New developments are also hybrid nanogels, in which polymeric scaffolds are merged with inorganic nanoparticles (e.g., gold, silica, or iron oxide), forming multifunctional systems that have therapeutic delivery and imaging and diagnostic properties (theranostics). Chemically cross-linked nanogels have better structural integrity and clinical translatability than physically cross-linked gels, but there are still issues with scaling, reproducibility, and regulatory approval.

1. Free Radical Polymerization: The free radical polymerization method of nanogel preparation is uncontrolled free radical cross-linking and copolymerization of monomers in which both, cross-linking and copolymerization take place concurrently. The reaction is conducted in nanosized droplets of the surfactant and co-surfactant systems which are the stabilizers and form monomer micelles which are mini-reactors. Polymerization within such droplets is triggered by a suitable free radical initiator, e.g., thermal, photochemical, redox initiators. The stability and size of the resulting nanogels is determined by such critical parameters as the type and concentration of surfactant applied, the proportion of co-surfactant, and the period and intensity of shear stress on the emulsification process. To prevent undesired macro-gelation, methods of templating are used, and the emphasis is on heterogeneous polymerization under colloidal conditions, mini- or microemulsion polymerization, dispersion polymerization, or precipitation methods. Lastly, the nanogels are separated, purified and characterized to guarantee reproducibility and controlled physicochemical characteristics [1]. However, the various templating approaches for the preparation of nanogels can be enumerated as follows

1.1 Mini emulsion: monomers are dispersed into droplets of a specified size (50-100 nm) through high shear stress produced by mechanical shear forces like ultrasonicators or high-pressure homogenizers. To stabilize these droplets against coalescence and Ostwald ripening, relatively high concentrations of surfactants and co-stabilizers are added to stabilize these droplets. Free radical initiator (thermal, photochemical, or redox) is added and polymerization is carried out within each of the droplets, which is a mini-reactor. The outcome is a narrowly dispersed nanogels with size and morphology control.

1.2 Microemulsion: Microemulsion polymerization is based on the self-assembling of thermodynamically stable droplets in the size regime of 10150 nm without shear stress. To stabilize the microemulsion

system, the use of surfactants and co-surfactants are necessary. After forming the droplets of monomers, a free radical initiator is introduced and the polymerization occurs in these nanosized domains. The technique is specifically applicable to vinyl-functionalized monomers and yields highly uniform nanogels that are very stable.

1.3 Dispersion polymerization: Dispersion polymerization In dispersion polymerization, at the beginning of the reaction, all the components of the reaction (monomers, initiators, stabilizers) are dissolved in the reaction medium. The growing polymer chains become insoluble and precipitate out, forming particles that are stabilized by colloidal stabilizing agents, as polymerization proceeds. The monomer concentration and stabilizer concentration allow tuning the particle size which is usually in the range of 0.1-15 μm. The technique produces strong dispersions of nanogels that are well dispersed and reproducible.

1.4 Precipitation polymerization: The process of precipitation polymerization starts in a homogenate of monomers and initiators. During the polymerization, the chains of polymer forming are insoluble and precipitate, and cross-link, creating nanogels. In contrast to other techniques, no surfactants are needed in the precipitation polymerization, but the particle size (100600 nm) is regulated by the monomer concentration. The resulting nanogels are generally irregular shaped but can be optimized by changing reaction conditions.

2. Click Chemistry: Nanogels are produced in mild and biocompatible conditions using click chemistry to cross-link polymer chains. The organic phase is usually polymers bearing azide or alkyne groups and the aqueous phase offers a reaction and stabilization medium. The azide-alkyne click reaction forms robust 1,2,3-triazole bonds, forming a three-dimensional nanogel network. Key variables are the catalyst used (copper-catalyzed or copper-free), temperature, and the concentration of functional groups on the polymer. While copper catalysis speeds up the reaction, it could leave harmful metal residues, so copper-free catalysis is preferred for medical applications. This approach maintains the integrity of delicate biomolecules, like proteins, drugs or even cells, making it suitable for next-generation drug delivery systems. This yields a robust, biocompatible nanogel of desired size and shape [9, 10].

3. Emulsion Polymerization: A very strong method of producing nanogels is emulsion polymerization, where immiscible phases (aqueous and organic) are stabilized in nanoscale droplets by surfactants. Monomeric precursors in these droplets are polymerized under controlled conditions to produce crosslinked hydrogel nanoparticles. Three mechanistic phases are involved in the process; nucleation, during which primary radicals are used to form the particles; growth, which entails the propagation and expansion of polymer chains in the micellar domains; and crosslinking polymerization, which forms a three-dimensional network of polymer molecules covalently bonded together. Initializing can be done either through photopolymerization (activation of monomers through UV/visible light in droplets) or through thermal/radiation-induced generation of free-radicals, depending on the location of reactants in dispersed and continuous phases. Surfactants are essential in stabilization of interfaces and diffusion of monomers between phases to provide homogeneous network structure and uniform distribution of particle size.

3.1 Inverse mini emulsion polymerization technique: The preparation of nanogels by the inverse miniemulsion polymerization process starts with the creation of kinetically stable water-in-oil droplets by dispersing an aqueous monomer or precursor solution in an organic continuous phase with the aid of surfactants and mechanical mixing. The droplets are nanosized reactors with free radical initiators that induce polymerization and covalent cross-linking to create stable nanogels. The solvophobic driving forces enable the droplets to encapsulate hydrophilic cargo, e.g. proteins or nucleic acids, effectively because of the solvophilic environment of their aqueous interior and yields a high loading capacity. The nanogels trapping the cargo physically via covalent cross-links ensure that the cargo does not leak out on redispersal in water and the functional groups on the cross-linker can be suitably designed to allow stimulus-responsive release. Surfactant type and concentration, shear stress intensity, choice of initiator and solvent are critical parameters that require careful optimization to regulate the size of the droplets, their stability, and biocompatibility. Despite the benefits of this technique in encapsulation efficiency and controlled release, there exist difficulties associated with the fact that organic solvents and reactive monomers are used that can in the event that they are not managed can interfere with the biological activity of sensitive cargo [5, 6].

3.2 Reverse micro emulsion polymerization technique: Reverse microemulsion polymerization Reverse microemulsion polymerization starts by forming a thermodynamically stable water in oil dispersion system, with aqueous monomer or precursor solutions, which is encased by a vast number of oil-soluble surfactants and co-surfactants. These micellar droplets serve as nanoscale reactor, which offers a homogenous environment in which the polymerization takes place. The droplets are then introduced into the system where a free radical initiator is added to cause polymerization and cross-linking of the droplets to create nanogels. The microemulsions stability is ensured by the close attention to the concentration of surfactants, co-surfactants ratio and the polarity of the solvent to

prevent the process of coalescence of droplets and to maintain the monodispersity of droplets. The method has been used successfully to construct chitosan-based nanogels that can be loaded with doxorubicin to target tumours with the hydrophilic drug being easily entraped in the aqueous core by solvophobic forces. The physical entrapment of the drug by covalent cross-links reduces leakage after redispersion in aqueous media, and functional cross-linkers can be designed to release the drug in response to stimuli. Although these have such benefits, there are limitations such as the use of organic solvents and reactive monomers which can affect the biological activity of biodegradable cargo therefore to maintain biocompatibility, optimization of the reaction conditions and purification steps is necessary [8].

4. pH Shift Method: Nanogels are prepared via seeded precipitation polymerization where monomers such as N-isopropylacrylamide (NIPAM) are co-polymerized with co-monomers and crosslinkers such as N,N'-methylenebisacrylamide (BIS) to produce a hydrogel network. The organic phase (monomer and crosslinker dissolved in appropriate solvent) and the aqueous phase (reaction medium containing initiators) are used for the syntheses. The nanogels are then functionalized with pH-responsive groups like phenylboronic acid (PBA) or N-methylallylamine, which control the swelling and shrinking behavior. Key factors include the monomer and initiator concentrations, the polymerization temperature, and the presence of pH-sensitive groups. Following synthesis, the nanogels undergo a Volume Phase Transition (VPT) in response to changing pH: they are hydrophilic at physiological pH (e.g., 7.4) for circulation in the bloodstream and collapse to become hydrophobic under acidic conditions (e.g., 6.5, as in solid tumor tissue), releasing any drug cargo. This dynamic hydrophobicity also forms Pickering emulsions that demulsify at acid pH to release drugs. Therefore, the pH-shift approach does not produce nanogels, but rather generates stimuli-responsive nanogels for biomedical applications [11, 12].

5. Modified Pullulan Technique: In the modified pullulan method, the pullulan is first chemically modified by adding functional groups like aldehyde, carboxyl or methacrylate groups that form reactive sites to be covalently bonded. The altered polymer is then dissolved in a water solution to create a homogenous solution, whereby distribution of these reactive groups is even. An appropriate chemical cross-linker, such as glutaraldehyde, divinyl sulfone, or methacrylate-based initiators is incorporated which leads to the formation of cross-linkage between pullulan chains. The initiators or catalysts of free radicals can be added to enhance the reaction thus creating a stable three-dimensional network of nanogel. Conditions of reaction, including pH, temperature and concentration of cross-linker are regulated to control particle size, mechanical stability, and strength. After formation, purification of the nanogels is by dialysis or centrifugation to eliminate the unreacted monomers, cross-linkers, and by-products. Lastly, the nanogels are described in terms of particle size, morphology, swelling behavior, and drug-loading capacity, which will guarantee reproducibility and applicability in biomedical uses [3, 4].

II. Physical Cross-linking methods:

1. Hydrogen bond: Nanogels can be synthesized by dispersing an oil-containing surfactant (e.g. Span/Tween mixture with a desired HLB value) in a reaction vessel under constant stirring at ~40 °C. An aqueous solution of a polymer (e.g. sodium alginate) is then added dropwise to the oil phase using a peristaltic pump, with key variables being the stirring speed (500-1000 rpm) and rate of addition to avoid aggregation. Once the emulsion is formed, a solution of bioactive molecules and crosslinking ions (e.g., glycyrrhizic acid with Zn^{2+} or Ca^{2+}) is slowly added, resulting in hydrogen bonding and ionic crosslinking that induces gel formation. Hydrogen bonding in this case is a special type of intermolecular attraction between an electronegative atom (O, N, F) and a group (such as amine or hydroxyl) which is weaker and reversible than a covalent bond. This allows for the nanogels to be responsive to environmental changes such as pH and temperature; for example, acidification will protonate biomaterial functional groups, promote hydrogen bonding, and change the gel properties. Examples of such systems include polymers such as PVA or gelatin, although the mechanical strength is generally weaker than those crosslinked by covalent bonds. Finally, nanogels are recovered by centrifugation, washed and freeze-dried, producing responsive nanogels that show biocompatibility and adaptability, suitable for drug delivery [13, 14].

2. Ionic cross-linking method: In general, the cross-linking preparation of nanogels involves the simple mixing of a natural polysaccharide (e.g., chitosan, alginate or hyaluronan) with a suitable ionic or metal cross-linker. For instance, chitosan nanogels are formed by the interaction of positively charged amino with negatively charged tripolyphosphate, alginate nanogels are produced by the interaction of the guluronic acid block of alginate with divalent cations such as calcium, to form an "egg-box" structure, and hyaluronan nanogels are assembled through coordination with cisplatin (cross-linker and drug). In each case, conditions including pH, polymer and cross-linker concentrations, temperature, and order of polymer and cross-linker addition are fine-tuned to control the size, drug loading and release of the nanogels to produce a safe and modifiable drug delivery vehicle [15, 16, 17].

3. hydrophobic interaction: The synthesis of nanogels through hydrophobic interactions is a

complex self-assembly process based on the desire of amphiphilic copolymers to seek a state of lowest energy. The polymers have a hydrophilic backbone with hydrophobic side chains or a block of hydrophilic and hydrophobic segments. The addition of these polymers to an aqueous environment results in a "solvophobic" effect on the hydrophobic regions, which cluster in order to limit the impact on the hydrogen-bonded structure of the water molecules. The physical cross-linking results in the formation of three-dimensional network. As these interactions are physical, the nanogels formed can be reversible and responsive to external stimuli such as temperature and pH, which can affect the hydrophobic/hydrophilic balance. The structure of the nanogel generally has a dense hydrophobic core that can be loaded with high efficiency for lipophilic drugs, and a hydrophilic corona shell that serves as a "stealth" protective shell. The architecture prevents the adsorption of proteins at the terminal region and imparts enhanced stability to the nanogel in the presence of biological fluids. This technique eliminates the need for potentially harmful surfactants and cross-linking agents, and is therefore a "green" and biocompatible approach to prepare targeted drug delivery systems [18, 19, 20, 21].

III. Microfluidic technology:

1. Photolithographic technique: This technique is exclusively preferred for the preparation of nanogels because it produces the nanogels with precise particle size, composition, morphological attributes, and enables the loading of various bio actives and pharmaceutical active constituents. However, various stages are involved in the preparation of nanogels in which a substrate is prebaked with a photoresist to fixed on a wafer coated with a low-surface-energy polymer (UV-cross linkable) which forms the substrate. The silicon wafer is then pressed by the polymer in the form of specific shapes under the influence of a quartz base and subjected to intense UV light that triggers cross-linking. When the quartz is removed, patterned particles are left, which are joined together by a thin residual layer of a film. Oxygen plasma treatment eliminates this interconnecting layer, oxidizing and dissolving it in a clean manner. The released fabricated nanogel particles are finally released by dissolving the substrate in a water buffer, which produces uniform structures with accurate geometry and reproducibility [2].

IV. Template Assisted Method:

1. Micro template polymerization: Microtemplate polymerization involves loading a monomer and crosslinking agent into a microstructured template, and entrapping the compounds into specified cavities or grooves. The hydrogel nanoparticles are then formed in the template by free radical polymerization, usually triggered by light irradiation or photoinitiators. After polymerization, the nanogels are then removed carefully out of the template to obtain particles of very controlled size, shape and composition. The technique enables the integration of cells or bioactive molecules during fabrication, and is therefore versatile in biomedical applications. Other variants include photolithographic microtemplate polymerization which employs non-wetting substrates with micro-holes, and UV lighting to achieve high precision control whereas grooved templates offer fixed geometries to reproducible particle formation. Despite the ability of this method to produce nanogels with varied morphologies and dimensions below 200 nm, the method demands strict regulation of the properties of the templates and substrates, and usually, polymethylsiloxane or photocurable perfluorinated polyether are used to achieve accuracy and reproducibility [7].

Applications:

Transdermal drug delivery*:* nanogels serve as a prominent platform for the successful delivery of various therapeutic agents through transdermal route to produce controlled and sustained drug release and encompass the issues involved in oral drug administration such as first pass metabolism [23]. Nanogels are preferred in chronic diseases such as cancer in which the drug molecules can be targeted and accumulated at the diseased sites. The therapeutic effect can be produced using various stimuli responsive mediators such as heat, light temperature, and redox that enables the controlled release of the drug molecules. This prevents the accumulation of drug molecules in the non-targeted regions and reduces the side effects. Therefore, the drug molecules that possess enzyme degradability, low biological half-life can be cross linked with the suitable chemicals or physically fabricated into the nanogel systems [22]. Nanogels are exclusively preferred in treating analgesic and anti-inflammatory conditions because of enhanced penetration towards the inflamed tissues that reduced the side effects and enables sustained drug delivery. In addition, they are also biocompatible, exhibit high drug loading capacity, targeted drug release triggered by enzymes or pH in the inflammated tissues which reduces the dosing frequency when compared to the other novel dosage forms like liposomes, niosomes, which makes it valuable in testing chronic pain and inflammatory conditions [24].

Nanogels in CNS drug delivery: Nanogels are preferred in delivering various drug molecules to CNS system. The 3D network and hydrophilic cross-linked polymeric network enabled them to entrap water molecules or biological entities and overcome the limitations of conventional drug delivery systems and emerge as the novel drug delivery system [25]. The conventional drug delivery systems are facing a critical challenge such as delivery of drugs across the blood brain barrier, blood-cerebro spinal fluid barrier which can be effectively overcome using

nanogels. The novel nanogel technologies can be tailored to deliver numerous therapeutic agents at the targeted site with minimum adverse effects. They can provide optimized drug concentrations with enhanced cellular uptake, drug residence time, and stability [26]. The nanogels can be engineered to enhance their physiochemical properties that renders them to cross the physiological barriers and emerge as the most suitable platform for the management of various neurological conditions. The naogels produce the therapeutic effect over the CNS through surface modification such as conjugation of ligands, stimuli responsive mechanism, encapsulation, and enhanced neuroprotective activity [27, 28].

In Autoimmune disorders: Autoimmune diseases pose a serious problem to the modern medicine because of their complicated mechanisms that hinders the diagnosis and treatment. The incidence of autoimmune disorders is increasing globally and exerting strain on the health care professionals and financial resources. The hurdles are effectively overcome by the nanomaterials that exhibit exclusive advantages such as enhanced biocompatibility, bioavailability, and drug permeability across the biological membranes. However, the face numerous challenges including stability, safety, and efficacy [29]. The chronic diseases such as rheumatoid arthritis can be treated with nanogels that can be engineered with cationic charged polymeric coating that enable them to deeply penetrate into the cartilage tissues and bind with the negatively charged neutrophil extracellular traps. This conjugation encourages degradation of neutrophil extracellular traps via DNase I that significantly reduces the inflammation [30]. In another approach, the Hyaluronic acid conjugated nanogels to deliver tacrolimus to the inflamed joints. The disulfide bonds of the nanogel enable the release of tacrolimus in a controlled fashion in response to enhanced glutathione levels in the activated macrophages. Simultaneously, the *in-vivo* experimentations reveal the targeted properties of nanogels with enhanced therapeutic efficacy [31]. In a similar fashion, the treatment of Lupus erythematous results in autoimmunity which can be treated effectively with mmycophenolic acid nanogels. The investigative found that the nanogel reduced the kidney damage in comparison to the free mycopheolic acid solution. However, the nanogel combated in the critical kidney damage conditions and extended the survival time from 4 to 12.5 weeks. They reduced the inflammatory cytokinins such as IFN-γ and IL-12 and generated the autoinflammatory activity [32]. Therefore, in view of the above discussions, it can be inferred that the nanogels are quite effective in treating the autoimmune disorders effectively.

Treatment of diabetes: Diabetes in the chronic disease which require measurement of glucose levels regularly to enhance the life style of diabetic patients. The glucose levels are monitored using nanomaterials such as metal nanoparticles and carbon nanostructures that provides relevant information regarding glucose levels. The nanotechnology adopts glucose sensor sensitivity, and temporal response that encourages continuous in-vivo glucose monitoring. However, the nanomaterials function through closed-loop insulin delivery charges that releases insulin at a predefined rate based on the blood glucose levels [33]. However, the oral insulin treatment is one of the promising strategies to improve the hypoglycemia and insulin resistance. The experimental findings of Ma and associates [34] on diabetic mice with oral nanogels comprising carboxylbetaine zwitterion with ursodeoxycholic acid upon emulsification followed by UV crosslinking produced significant results in the mice. The nanogels stimulated GLP-1 secretion which overcome the mucus barrier and facilitated the intestinal permeation. The carboxylbetaine zwitterion and ursodeoxycholic acid in a fixed ratio enhanced the permeation through ASBT and PAT1 pathways which internally enhanced the intestinal absorption. Further the nanogels increased the binding with TGR5 receptors that increased the secretion of GLP-1 and insulin which normalized the insulin levels with in 18hrs. similarly, Li and associates [35] developed dual responsive nanogels to regulate insulin delivery in diabetic conditions. The nanogels are composed of poly(cyclic phenylboronic ester and poly(ethylene glycol) in dual sanative groups and synthesized using click chemistry. The investigations carried over the mice via transdermal application of nanogel generated H_2O_2 at elevated glucose levels which further undergone oxidation and hydrolyzed the phenylboronic ester groups. These nanogels enhanced the half-life with excellent biocompatibility and justified the potentiality of nanogels in diabetic wounds.

In protein and Peptide delivery: Nanogels are used for the encapsulation of a variety of drug molecules that allows a controlled and stimuli responsive release. The Rosa and colleagues [45] have prepared nanogels made from a mixture of Fmoc-diphenylalanine and cationic amphiphilic peptides. Two different nanogels were formulated using amphiphilic peptides of varying chain lengths. The cationic nature of the amphiphilic peptides conferred a positive surface charge to the nanogels, while two different surfactants, namely Tween 80 and Span 80, were employed to enhance their stabilization. The nanogels were experimented with various drug molecules including Alexafluor 430 an anionic molecule to evaluate their attachment and detachment behavior with the nanogels and inferred that the nanogels were safe and effective for drug delivery applications. Similarly, Massi and et.al. [46] have developed peptide-crosslinked temperature sensitive nanogels for the controlled delivery of proteins moieties. These nanogels respond to MM7,

an enzyme which is extremely produced in the diseases like cancers and inflammation. The investigation admixed N-isopropylacrylamide and N-cyclopropylacrylamide at an optimized temperature that effectively encapsulated the proteins. The nanogels thus produced were stabilized using peptide linkers which tend to break down effectively and release the drug molecules at the desired pH. Apart from the above, the investigators have also developed peptide grafted nanogels comprising hyaluronic acid-R954 and chitosan BQ123 as intraarticular injection for the treatment of osteoarthritis. These nanogels exhibited sustained drug release in the synovial fluid for 3 months and reflected a promising osteoarthritis therapy [47]. Therefore, these investigative findings strongly highlight the immense potential of nanogels as promising and efficient carriers for protein and peptide drug delivery applications.

In delivery of Oligonucleotides: Hu and et.al. [48] have developed self-cleavable DNA nanogel comprising splice-switch oligonucleotide which can undergo cleavage under acidic conditions and liberated the motif architecture that disintegrated the nanogel and release the splice-switch oligonucleotide resulting anticancer outout.. In this fashion, Vinogradov, and et.al [49] have proposed NanoGel™, a hydrophilic polymeric network synthesized by crosslinking polyethyleneimine and carbonyldiimidazole activated polyethylene glycol via emulsion solvent evaporation technique. In this formulation, Antisense phosphorothioate oligonucleotides that were specific to human mdrl 1 gene was incorporated which effectively reduced the diameter of particle size to 80nm and neutralized the zeta potential. The internalization of nanogels in human oral epidermoid carcinoma cells increased rapidly when compared to free antisense phosphorothioate oligonucleotides and successfully inhibited the expression of P-glycoprotein efflux pump in multi drug resistant cell lines. In continuation to the above, Liwinska, and et.al [50] have fabricated three segment oligonucleotide hybrids that are biodegradable for an effective cancer treatment. The formulation released the drug molecules by altering the gel network and DNA confirmation in the oscillating fashion and secondly through degradation of cross liners via denaturation. The DNA helix in the nanogels resulted three times increase in the encapsulation of anticancer moieties. The drug release potency of nanogel varied with temperature, and the results proved a 98% drug release at extreme hyperthermia conditions while it was restricted to 78% at low hyperthermia conditions. The release of drug molecules in association with DNA strands evoked the new possibilities in drug therapy.

Antimicrobial properties: The bacterial infections pose a serious problem in certain diseases like diabetes mellitus which should be treated immediately to prevent any serious consequences. The investigations of Luo and colleagues [36] enumerated the development of antibiotic florfenicol loaded cross linked nanogels fabricated using oxidized hyaluronic acid and N, O-carboxymethyl chitosan. The nanogels were pH responsive and released the florfenicol quickly at the infected wounds that accelerated the diabetic wound healing. The glucose oxidase effectively oxidized the high glucose concentrations that increased the Reactive Oxygen Species that resulted in the cellular damage. Similarly, Chow and et.al. [37] developed injectable insulin loaded gel comprising integrated lysozyme and carboxymethyl hexanoyl chitosan for optimized biodegradation and insulin release. The rate of biodegradation relies on the concentration of lysozyme and found to be cytocompatible. Furthermore, Wang and et.al. [38] developed glucose sensitive cross-linked 3D gels comprising phenyl boronic acid for the effective treatment of diabetes. The investigative findings revealed the outstanding biocompatibility, tunable size enhanced surface area for bioconjugation, and injectability. These exclusive features enabled the nanogels as an effective platform for the treatment of diabetes.

Nanogels in diagnostic and imaging: Nanogels are water-based solutions comprising hydrogel particles of nanoscale and interconnected by means of polymeric network. Apart from their biocompatibility, the vast advantages provided by the nanogels such as enhanced surface area, tunable size and bioconjugation enable them to encapsulate various drug moieties, genetic material, proteins and viable cells while maintaining outstanding stability. apart from these, they can also be surface engineered to alter their stimuli responsiveness towards pH, ionic strength, and temperature [39]. The specific size and exclusive properties offered by the nanogels enable them to undergo Reticular Endothelial System uptake that offers enhanced circulation, pharmacokinetics, and biomolecular imaging [40]. The comprehensive review of sivaram and et.al [40] exaggerates that nanogels composed of mucoadhesive polymers can prolong residential time, while artificial chaperons facilitate alignment the proteins and enzymes into specific conformation for producing the biological activity. Nanogels improve MRI imaging by delivering T1, T2, and 19F contrast agents with enhanced relaxivity and environment-responsive signal activation for targeted, high-contrast imaging. Radiolabelled nanogels containing isotopes such as Copper-64, Gallium-68, and Iodine-124 enhance PET imaging by improving tumor visualization and metastasis detection through efficient accumulation in diseased tissues. Nanogels carrying quantum dots, metallic nanoparticles, and fluorescent dyes especially NIR nanogels enable deep tissue imaging, sentinel lymph node detection, and real-time monitoring of drug delivery. Nanogels improve diagnostic imaging through prolonged

circulation, stimuli-responsive targeting, multimodal imaging capabilities, and theranostic applications that combine real-time disease diagnosis with targeted drug delivery.

Nanogels in MR contrast agents: Jiang and et.al. explored pH and temperature sensitive magnetic nanogels for the glioma imaging and tumor margin detection via Cy5.5 labelled lactoferrin. The hydrophobicity and shrinking characteristics of nanogels in the tumor environment enhances the tumor internalization. The lactoferrin guides the active targeting of moieties towards the glioma cells that can be visualized using MRI and Fluorescence imaging [41]. Similarly, Zhang and et.al [42] developed the multifunctional biodegradable nanogels encapsulated with fluorescent dextran and Fe_3O_4 nanoparticles. These nanogels exhibited exclusive characteristics such as enhanced cellular internalization, decreased interaction with the macrophages and immune system recognition which enabled disulfide bond cleavage, and allowed controlled drug release that tuned the MRI imaging characteristics. Similarly, Wang and et.al. [43] developed tumor targeted stimuli responsive magnetic responsive imaging contrast agent via polymeric nanogel system for the detection of early stage tumors. The nanogel comprises gadolinium chelates in association with pH sensitive and hypoxia targeting components that are used for the magnetic resonance imaging. They designed the mechanism in such as way that the nanogel generates low MRI signal at the normal biological conditions and when one it reaches the biological pH, then it gets activated and generates a potent MR signal helps in early stage diagnosis of tumors. Furthermore, Jiang and et.al [44] developed a smart nanogel system (PCG-Fe/Dihydroartemisinin) capable of co-delivering Fe^{3+} and Dihydroartemisinian (DHA) for ferroptosis cancer therapy and MRI diagnosis was developed. The nanogel was found to release the iron and DHA in a pH and esterase responsive manner to achieve efficient delivery in the interior of tumour cells. Fe^{3+} and DHA acted synergically to destabilize the intracellular iron homeostasis, increasing the labile iron pool and inducing the degradation of ferritin, and thus excessive generation of ROS in the cell via the Fenton reaction. Depletion of glutathione further impaired GPX4 activity and increased lipid peroxide level and ferroptosis in the tumor cells. The nanogel also showed 76.8% tumor inhibition with 2.4-fold greater MRI signal intensity than free iron in 4T1 breast tumor-bearing mice, highlighting its potent therapeutic and diagnostic potential.

CONCLUSION

Nanotechnology based formulations have potent applicability towards pharmaceutical and biomedical fields. The nanogels are a breakthrough in effective transportation of various therapeutic agents to the targeted areas in diseased areas. The unique characteristics of nanogels with structural modifications has emerged these as a novel platform to deliver various cargoes. the research on nanogels with novel properties is at fast pace which enabled controlled drug release that was useful for the treatment of various diseases. Although nanogels offer significant opportunities for encapsulating diverse drug molecules in nanoscience, challenges such as purity, safety, biological fate, biodistribution, selection of biocompatible and biodegradable polymers, scalability of production, and cost-effectiveness must be addressed to improve clinical outcomes. The mechanical properties of nanogels should be carefully evaluated to generate a precise data. Studying the release kinetics is essential for optimizing precursors, synthetic procedures, and cross-linkers, thereby facilitating the translation of nanogels from clinical trials to practical clinical applications. Despite the progress in nanogel research, their pharmacodynamics, pharmacokinetics, and metabolism should be carefully addressed to enhance the patient acceptability and efficacy of the dosage form.

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REFERENCES

1. Manimaran, V., Nivetha, R.P., Tamilanban, T., Narayanan, J., Vetriselvan, S., Fuloria, N.K., Chinni, S.V., Sekar, M., Fuloria, S., Wong, L.S., Biswas, A., Ramachawolran, G., Selvaraj, S., 2023. Nanogels as novel drug nanocarriers for CNS drug delivery. Front. Mol. Biosci. 10, 1232109. https://doi.org/10.3389/fmolb.2023.1232109
2. Chacko, R.T., Ventura, J., Zhuang, J., Thayumanavan, S., 2012. Polymer nanogels: A versatile nanoscopic drug delivery platform. Advanced Drug Delivery Reviews 64, 836–851. https://doi.org/10.1016/j.addr.2012.02.002
3. Zhang, T., Yang, R., Yang, S., Guan, J., Zhang, D., Ma, Y., Liu, H., 2018. Research progress of self-assembled nanogel and hybrid hydrogel systems based on pullulan derivatives. Drug Delivery 25, 278–292. https://doi.org/10.1080/10717544.2018.1425776
4. Ferreira, S.A., Coutinho, P.J.G., Gama, F.M., 2011. Synthesis and Characterization of Self-Assembled Nanogels Made of Pullulan. Materials 4, 601–620. https://doi.org/10.3390/ma4040601
5. Raghupathi, K., Eron, S.J., Anson, F., Hardy, J.A., Thayumanavan, S., 2017. Utilizing Inverse Emulsion Polymerization To Generate Responsive Nanogels for Cytosolic Protein Delivery. Mol. Pharmaceutics 14, 4515–4524.

https://doi.org/10.1021/acs.molpharmaceut.7b00643

6. Oh, J.K., Tang, C., Gao, H., Tsarevsky, N.V., Matyjaszewski, K., 2006. Inverse Miniemulsion ATRP: A New Method for Synthesis and Functionalization of Well-Defined Water-Soluble/Cross-Linked Polymeric Particles. J. Am. Chem. Soc. 128, 5578–5584. https://doi.org/10.1021/ja060586a
7. Li, C., Obireddy, S.R., Lai, W.-F., 2021. Preparation and use of nanogels as carriers of drugs. Drug Delivery 28, 1594–1602. https://doi.org/10.1080/10717544.2021.1955042
8. Zhang, Y., Bland, G.D., Yan, J., Avellan, A., Xu, J., Wang, Z., Hoelen, T.P., Lopez-Linares, F., Hatakeyama, E.S., Matyjaszewski, K., Tilton, R.D., Lowry, G.V., 2021. Amphiphilic Thiol Polymer Nanogel Removes Environmentally Relevant Mercury Species from Both Produced Water and Hydrocarbons. Environ. Sci. Technol. 55, 1231–1241. https://doi.org/10.1021/acs.est.0c05470
9. Blagojevic, L., Kamaly, N., 2025. Nanogels: A chemically versatile drug delivery platform. Nano Today 61, 102645. https://doi.org/10.1016/j.nantod.2025.102645
10. Yi, G., Son, J., Yoo, J., Park, C., Koo, H., 2018. Application of click chemistry in nanoparticle modification and its targeted delivery. Biomater Res 22, 13. https://doi.org/10.1186/s40824-018-0123-0
11. Li, Zheng, Yang, X., Li, Zifu, 2025. Nanogels with volume phase transition for biomedical applications. Nat Commun 16, 11237. https://doi.org/10.1038/s41467-025-67780-8
12. Wei, P., Gangapurwala, G., Pretzel, D., Leiske, M.N., Wang, L., Hoeppener, S., Schubert, S., Brendel, J.C., Schubert, U.S., 2019. Smart pH-Sensitive Nanogels for Controlled Release in an Acidic Environment. Biomacromolecules 20, 130–140. https://doi.org/10.1021/acs.biomac.8b01228
13. Chen, Y.-B., Qiao, T., Wang, Y.-Q., Cui, Y.-L., Wang, Q.-S., 2022. Hydrogen bond-enhanced nanogel delivery system for potential intranasal therapy of Parkinson's disease. Materials & Design 219, 110741. https://doi.org/10.1016/j.matdes.2022.110741
14. Choi, Y., Koh, H.Y., Han, J.Y., Seo, S., 2025. Synthesis of Hydrogel-Based Microgels and Nanogels Toward Therapeutic and Biomedical Applications. Applied Sciences 15, 1368. https://doi.org/10.3390/app15031368
15. Wang, H., Deng, H., Gao, M., Zhang, W., 2021. Self-Assembled Nanogels Based on Ionic Gelation of Natural Polysaccharides for Drug Delivery. Front. Bioeng. Biotechnol. 9, 703559. https://doi.org/10.3389/fbioe.2021.703559
16. Mauri, E., Giannitelli, S.M., Trombetta, M., Rainer, A., 2021. Synthesis of Nanogels: Current Trends and Future Outlook. Gels 7, 36. https://doi.org/10.3390/gels7020036
17. Mashabela, L.T., Maboa, M.M., Miya, N.F., Ajayi, T.O., Chasara, R.S., Milne, M., Mokhele, S., Demana, P.H., Witika, B.A., Siwe-Noundou, X., Poka, M.S., 2022. A Comprehensive Review of Cross-Linked Gels as Vehicles for Drug Delivery to Treat Central Nervous System Disorders. Gels 8, 563. https://doi.org/10.3390/gels8090563
18. Su, Y.-C., Chen, Y.-C., Lo, Y.-H., Chang, C.-H., Chen, Y.-F., 2025. Hydrophobic interactions enhance doxorubicin delivery from hyaluronic acid nanogels. European Journal of Pharmaceutics and Biopharmaceutics 210, 114676. https://doi.org/10.1016/j.ejpb.2025.114676
19. Sultana, F., Manirujjaman, M., Haque, Md.I.-U.-, Arafat, M., Sharmin, S., 2013. An Overview of Nanogel Drug Delivery System. J App Pharm Sc. https://doi.org/10.7324/JAPS.2013.38.S15
20. Zhang, X., Malhotra, S., Molina, M., Haag, R., 2015. Micro- and nanogels with labile crosslinks – from synthesis to biomedical applications. Chem. Soc. Rev. 44, 1948–1973. https://doi.org/10.1039/C4CS00341A
21. Myint, S.S., Laomeephol, C., Thamnium, S., Chamni, S., Luckanagul, J.A., 2023. Hyaluronic Acid Nanogels: A Promising Platform for Therapeutic and Theranostic Applications. Pharmaceutics 15, 2671. https://doi.org/10.3390/pharmaceutics15122671
22. Attama, A.A., Nnamani, P.O., Onokala, O.B., Ugwu, A.A., Onugwu, A.L., 2022. Nanogels as target drug delivery systems in cancer therapy: A review of the last decade. Front. Pharmacol. 13, 874510. https://doi.org/10.3389/fphar.2022.874510s
23. Soni, K.S., Desale, S.S., Bronich, T.K., 2016. Nanogels: An overview of properties, biomedical applications and obstacles to clinical translation. Journal of Controlled Release 240, 109–126. https://doi.org/10.1016/j.jconrel.2015.11.009
24. Bawa, P., Pillay, V., Choonara, Y.E., Du Toit, L.C., 2009. Stimuli-responsive polymers and their applications in drug delivery. Biomed. Mater. 4, 022001. https://doi.org/10.1088/1748-6041/4/2/022001
25. Kaushik, A., Jayant, R.D., Bhardwaj, V., Nair, M., 2018. Personalized nanomedicine for CNS diseases. Drug Discovery Today 23, 1007–1015. https://doi.org/10.1016/j.drudis.2017.11.010
26. Vashist, Arti, Kaushik, A., Vashist, Atul, Bala, J., Nikkhah-Moshaie, R., Sagar, V., Nair, M., 2018. Nanogels as potential drug nanocarriers for CNS drug

delivery. Drug Discovery Today 23, 1436–1443. https://doi.org/10.1016/j.drudis.2018.05.018

27. Zhang, Y., Zou, Z., Liu, S., Miao, S., Liu, H., 2022. Nanogels as Novel Nanocarrier Systems for Efficient Delivery of CNS Therapeutics. Front. Bioeng. Biotechnol. 10, 954470. https://doi.org/10.3389/fbioe.2022.954470

28. Stawicki, B., Schacher, T., Cho, H., 2021. Nanogels as a Versatile Drug Delivery System for Brain Cancer. Gels 7, 63. https://doi.org/10.3390/gels7020063

29. Ong, E.X.N., Ng, C.Y.J., Cao, L., Li, X., Li, P.P., Tan, N.S., Liao, Z., Zhao, Y., 2026. Nanoparticles for autoimmune diseases: advancing diagnostics and therapeutic solutions. Acta Pharmacol Sin. https://doi.org/10.1038/s41401-026-01794-w

30. Jin, Y., Yang, N., Chen, S., Wei, Y., Wei, X., Zhu, Y., Sun, C., 2025. Bioinspired catalytic nanogel as an inflammatory cascade-targeted therapeutic for rheumatoid arthritis. J Nanobiotechnol 23, 623. https://doi.org/10.1186/s12951-025-03642-1

31. Li, Y., Wang, X., Gao, Y., Zhang, Ziyi, Liu, T., Zhang, Zhuo, Wang, Y., Chang, F., Yang, M., 2024. Hyaluronic acid-coated polypeptide nanogel enhances specific distribution and therapy of tacrolimus in rheumatoid arthritis. J Nanobiotechnol 22, 547. https://doi.org/10.1186/s12951-024-02784-y

32. Look, M., Stern, E., Wang, Q.A., DiPlacido, L.D., Kashgarian, M., Craft, J., Fahmy, T.M., 2013. Nanogel-based delivery of mycophenolic acid ameliorates systemic lupus erythematosus in mice. J. Clin. Invest. 123, 1741–1749. https://doi.org/10.1172/JCI65907

33. DiSanto, R.M., Subramanian, V., Gu, Z., 2015. Recent advances in nanotechnology for diabetes treatment. WIREs Nanomed Nanobiotechnol 7, 548–564. https://doi.org/10.1002/wnan.1329

34. Ma, Y., He, M., Yuan, Z., Huang, D., Qian, H., 2025. Non-insulin ultra-simple nanogels stimulate GLP-1 secretion through TGR5 for oral diabetes treatment. Chemical Engineering Journal 524, 169543. https://doi.org/10.1016/j.cej.2025.169543

35. Li, C., Liu, X., Liu, Yong, Huang, F., Wu, G., Liu, Ying, Zhang, Z., Ding, Y., Lv, J., Ma, R., An, Y., Shi, L., 2019. Glucose and H2 O2 dual-sensitive nanogels for enhanced glucose-responsive insulin delivery. Nanoscale 11, 9163–9175. https://doi.org/10.1039/C9NR01554J

36. Luo, W., Jiang, Y., Liu, J., Algharib, S.A., Dawood, A.S., Xie, S., 2025. Nanogel Dressing with Targeted Glucose Reduction and pH/Hyaluronidase Dual-Responsive Release for Synergetic Therapy of Diabetic Bacterial Wounds. Gels 11, 380. https://doi.org/10.3390/gels11060380

37. Chou, H.-S., Larsson, M., Hsiao, M.-H., Chen, Y.-C., Röding, M., Nydén, M., Liu, D.-M., 2016. Injectable insulin-lysozyme-loaded nanogels with enzymatically-controlled degradation and release for basal insulin treatment: In vitro characterization and in vivo observation. Journal of Controlled Release 224, 33–42. https://doi.org/10.1016/j.jconrel.2015.12.036

38. Wang, C., Lin, B., Zhu, H., Bi, F., Xiao, S., Wang, L., Gai, G., Zhao, L., 2019. Recent Advances in Phenylboronic Acid-Based Gels with Potential for Self-Regulated Drug Delivery. Molecules 24, 1089. https://doi.org/10.3390/molecules24061089

39. Benjamin, S.R., Sales, A.J.M., Panicker, P.S., Bampoky, N.A., Nunes, P.I.G., 2025. Nanogels in diagnostics: Sensing and imaging applications, in: Nanogels. Elsevier, pp. 191–221. https://doi.org/10.1016/B978-0-443-30016-5.00004-5

40. Chan, M., Almutairi, A., 2016. Nanogels as imaging agents for modalities spanning the electromagnetic spectrum. Mater. Horiz. 3, 21–40. https://doi.org/10.1039/C5MH00161G

41. Sivaram, A.J., Rajitha, P., Maya, S., Jayakumar, R., Sabitha, M., 2015. Nanogels for delivery, imaging and therapy. WIREs Nanomed Nanobiotechnol 7, 509–533. https://doi.org/10.1002/wnan.1328

42. Jiang, L., Zhou, Q., Mu, K., Xie, H., Zhu, Y., Zhu, W., Zhao, Y., Xu, H., Yang, X., 2013. pH/temperature sensitive magnetic nanogels conjugated with Cy5.5-labled lactoferrin for MR and fluorescence imaging of glioma in rats. Biomaterials 34, 7418–7428. https://doi.org/10.1016/j.biomaterials.2013.05.078

43. Zhang, L., Xue, H., Cao, Z., Keefe, A., Wang, J., Jiang, S., 2011. Multifunctional and degradable zwitterionic nanogels for targeted delivery, enhanced MR imaging, reduction-sensitive drug release, and renal clearance. Biomaterials 32, 4604–4608. https://doi.org/10.1016/j.biomaterials.2011.02.064

44. Wang, T., Zeng, Q., Tang, J., Sui, M., Liu, X., Shen, Y., 2015. A tumor-targeting MRI contrast agent based on hypoxia and pH-responsive nanogel. Journal of Controlled Release 213, e104–e105. https://doi.org/10.1016/j.jconrel.2015.05.175

45. Jiang, J., Peng, Y., Qiu, L., 2024. Nanovesicle-templated nanogel: A dual-modal platform integrating intracellular iron homeostasis disruption for ferroptosis and MRI-guided tumor diagnosis. Chemical Engineering Journal 499, 156019. https://doi.org/10.1016/j.cej.2024.156019

46. Rosa, M., Rosa, E., Castelletto, V., Hamley, I.W., Morelli, G., Accardo, A., Diaferia, C., 2025. Evaluation of cationic peptide-based nanogels as delivery systems for negatively charged molecules: a for-

mulative study. Sci Rep 15, 36875. https://doi.org/10.1038/s41598-025-20945-3

47. Massi, L., Najer, A., Chapman, R., Spicer, C.D., Nele, V., Che, J., Booth, M.A., Doutch, J.J., Stevens, M.M., 2020. Tuneable peptide cross-linked nanogels for enzyme-triggered protein delivery. J. Mater. Chem. B 8, 8894–8907. https://doi.org/10.1039/D0TB01546F

48. Manivong, S., Garcia-Ac, A., Mahrouche, L., Guerra, F., Séguy, L., Sirois, P., Banquy, X., Roullin, V.G., Moldovan, F., 2025. Peptide-grafted nanogels for sustained endothelin and bradykinin blockade in osteoarthritis. International Journal of Pharmaceutics 683, 126089. https://doi.org/10.1016/j.ijpharm.2025.126089

49. Hu, Y., Chen, F., Lu, H., Tan, S., Ke, Y., Loh, W.W., Soh, E.J.H., Taniya, A., Tabaglio, T., Wee, D.K.B., Ying, J.Y., 2024. A splice-switch oligonucleotide loaded self-cleavable DNA nanogel. Chem. Commun. 60, 11516–11519. https://doi.org/10.1039/D4CC01942C

50. Vinogradov, S., Batrakova, E., Kabanov, A., 1999. Poly(ethylene glycol)–polyethyleneimine NanoGelTM particles: novel drug delivery systems for antisense oligonucleotides. Colloids and Surfaces B: Biointerfaces 16, 291–304. https://doi.org/10.1016/S0927-7765(99)00080-6

51. Liwinska, W., Stanislawska, I., Lyp, M., Mackiewicz, M., Stojek, Z., Zabost, E., 2017. A degradable nanogel drug carrier crosslinked with three-oligonucleotide hybrids for two-way drug release in mild and high hyperthermia treatment. J. Mater. Chem. B 5, 4713–4724. https://doi.org/10.1039/C7TB00092H

52. Wang, T., Zhao, W., Wu, Y., Wang, X., Kayitmazer, A.B., Ahmad, A., Ramzan, N., Si, Y., Wang, J., Xu, Y., 2023. Nanogel-Reinforced Polyacrylamide Hydrogel for Potential Vascular Adhesion. ACS Appl. Polym. Mater. 5, 1169–1179. https://doi.org/10.1021/acsapm.2c01649

53. Keshari, R., Muddala, G., Mishra, A., Srivastava, R., Kumari, P., 2026. Next-generation tissue regeneration through theranostic nanogels: rewiring repair pathways for precision and personalised therapy. International Journal of Pharmaceutics 696, 126813. https://doi.org/10.1016/j.ijpharm.2026.126813

54. Gao, J., An, B., Gong, H., Fu, H., Yu, H., 2025. Raw materials, preparation methods and applications of nanogels. Food Research International 222, 117695. https://doi.org/10.1016/j.foodres.2025.117695

55. Tayebi-Khorrami, V., Fadaei, M.S., Dabbaghi, M.M., Azimi, E., Kalalinia, F., Fadaei, M.R., Hashemi, M., 2025. Overview of the application of nanogels in wound healing. Journal of Drug Delivery Science and Technology 112, 107268. https://doi.org/10.1016/j.jddst.2025.107268

56. Pareek, A., Kumar, S., Kapoor, D.U., Prajapati, B.G., 2025. Advancements in superparamagnetic nanogels: A dual-role platform for diagnosis and targeted drug delivery. International Journal of Pharmaceutics 677, 125683. https://doi.org/10.1016/j.ijpharm.2025.125683

57. Musa, M., Sun, X., Shi, J., Li, J., Zhang, S., Shi, X., 2025. Intelligent responsive nanogels: New Horizons in cancer therapy. International Journal of Pharmaceutics 669, 125050. https://doi.org/10.1016/j.ijpharm.2024.125050

58. Dhanawat, M., Garima, Wilson, K., Bhushan, B., Chalotra, R., Gupta, S., Chaubey, P., 2025. Smart Stimuli-responsive Nanogels: A Potential Tool for Targeted Drug Delivery. CPD 31, 1696–1709. https://doi.org/10.2174/0113816128353985241231111149

59. Farjadian, F., Mirkiani, S., Ghasemiyeh, P., Rahbar Kafshboran, H., Mehdi-Alamdarlou, S., Raeisi, A., Esfandiarinejad, R., Soleymani, S., Goshtasbi, G., Firouzabadi, N., Mohammadi-Samani, S., Hossein Morowvat, M., Doroudian, M., 2024. Smart nanogels as promising platform for delivery of drug, gene, and vaccine; therapeutic applications and active targeting mechanism. European Polymer Journal 219, 113400. https://doi.org/10.1016/j.eurpolymj.2024.113400