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Nanogels as Advanced Drug Delivery Systems: Preparation Strategies, Classification, Therapeutic Advantages, Limitations, and Biomedical Applications

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ABSTRACT:

Nanogels, nanoscale hydrogel particles, have emerged as highly versatile platforms in biomedical and pharmaceutical applications due to their unique physicochemical properties, such as high water content, tunable size, biocompatibility, and responsive behavior to environmental stimuli. This compressive review highlights recent advancements in nanogel synthesis methods, functionalization strategies, and their diverse applications in drug delivery, diagnostics, tissue engineering, and cancer therapy. Key challenges including stability, scalability, and targeted delivery are critically examined alongside future prospects for clinical translation. The review provides a cohesive understanding of the current state and potential of nanogels as smart nanocarriers in precision medicine. This **compressive review** highlights recent advancements in **nanogel synthesis methods**, **functionalization strategies**, and their diverse applications in **drug delivery, diagnostics, tissue engineering**, and **cancer therapy**. Key challenges including **stability, scalability**, and **targeted delivery** are critically examined alongside future prospects for clinical translation. The review provides a cohesive understanding of the current state and potential of nanogels as **smart nanocarriers** in **precision medicine**.

KEY WORDS: Nanogels, classification, nanocarriers, nanoscale hydrogel, drug delivery, scalability, methods.

INTRODUCTION:

The term 'nanogels' refers to nanoscale particles created by either physical or chemical cross linking of polymer networks that can swell in a compatible solvent. The designation "nanogel" was initially used to describe cross-linked bifunctional networks made up of a polyion and a nonionic polymer for the purpose of transporting polynucleotides . Nanogels are a type of nanoparticles made up of a hydrogel formed from cross-linked hydrophilic polymers, with a typical particle size ranging from 100 to 200 nm . The nanogel structure contains pores filled with either micromolecules or macromolecules. Characterized by their ability to swell and degrade, nanogels exhibit a flexible size, large surface area, and high water content . They are utilized for the controlled and sustained release of various biologically active agents and drugs. In their three-dimensional structures, nanogels can encapsulate drugs, polymers, and a dispersed liquid phase. From the perspective of materials, nanoparticles are typically composed of inorganic, lipid, and polymeric nanoparticles .Nanogels can be synthesized from polymer precursors or created through the heterogeneous polymerization of monomers.

ADVANTAGES:

- High biodegradability, which is essential to prevent accumulation of Nanogel material in the body's organs, which could result in toxicity and negative effects.
- High biocompatibility, which makes Nanogels a very promising approach to drug delivery systems.
- Ability to traverse the Blood Brain Barrier.
- Improved absorption through biological membranes as a result of their very small size.
- Nanogels can be readily delivered through parenteral and mucosal routes .
- The primary benefit of nanogels is the minimized premature leakage of the drug from the formulation.
- Nanogels can be delivered through several methods, such as oral, pulmonary, nasal, parenteral, intra-ocular, and topical administration routes.
- Nanogels can be used to formulate both hydrophilic and hydrophobic medications.

- Quick reaction to temperature and pH changes in the environment.

DISADVANTAGES:

• A costly method for totally eliminating the surfactants and solvents at the conclusion of the preparation process.

• Traces of surfactant or monomer may still be present and may have negative consequences.

• Aportion of the particles fall inside the micrometer range.

• The average size and weight make scaling up difficult.

CLASSIFICATION:

1. ON THE BASIS OF LINKAGE :

A)PHYSICAL CROSS LINKED GAS:

Weaker connections create physical gels or faux gels by either

Van der Waals forces,

Hydrophobic, electrostatic interaction,

Hydrogen bonding

The polymer composition, temperature, the medium's ionic strength, and the amounts of the polymer and cross-linking agent all affect how responsive these systems are.These strategies employ a range of techniques. mechanisms such as complexation of polymeric chains with opposite charges, self-assembly polymer chain formation and aggregation, and amphiphilic block association.

a)Liposome modified nanogel:

Simple tiny vesicles called liposomes have a lipid bilayer structure and an aqueous volume that is completely surrounded by a membrane made of lipid molecules. Liposomes include a variety of components, but the primary ones are cholesterol and phospholipid.It has been demonstrated that liposomes containing succinylated poly(glycidol)s effectively transport calcein to the cytoplasm by undergoing chain fusion below pH 5.5.

b)Micellar nanogel:

Polymeric micelles are tiny particles that have a special structure with a core and a shell, where the outer layer helps keep the core connected to the surrounding environment, and the core can dissolve a water-repelling medicine.Graft copolymers or supramolecular self-assembly of hydrophilic and hydrophobic blocks in an aqueous solution are the two methods used to create micellar nanogels. A hydrophilic core and a hydrophilic shell comprise micellar nanogels.

c) Hybrid nanogel:

A composite of nanogel particles distributed throughout organic or inorganic matrices is known as a hybrid nanogel.These nanogels can coat the surfaces of liposomes, particles, and solid surfaces like cells. They can also form complexes with different proteins, medications, and DNA.In particular, hybrid nanogels are important for delivering insulin and anticancer medications.The synthesis of nanogels in aqueous medium was carried out using amphiphilic polymers that self-assemble and aggregate, such as hydrophobized polysaccharides, pullulan-PNIPAM, and the hydrophobized Pullulan and hydrophobized Pullulan processes, with an emphasis on pullulan that contains cholesterol. CHP-based nanogels were investigated(.Because pullulan is easily chemically modified and is nontoxic, noncarcinogenic, nonmutagenic, and nonimmunogenic, it is mostly used in the food, cosmetics, and pharmaceutical industries.

B) CHEMICALLY CROSS LINKED GEL:

Chemical cross-linking creates an insoluble polymer network by forming covalent bonds under diluted circumstances by a cross-linking reaction of water-soluble polymers.Hydrogels that are chemically cross-linked are made by addition and condensation polymerisation, chain growth polymerisation, and gamma and electron beam polymerisation. Anionic and cationic polymerisation, as well as regulated and uncontrolled free radical polymerisation, are all included in chain-growth polymerization.The entire physicochemical characteristics of the gel systems can be altered thanks to these crosslinking locations. A few cross-linking agents that are versatile have been started.For instance, polymeric chains with pendant thiol groups were crosslinked using an environmentally safe chemical procedure to form a nanogel with a size range of 20 to 200 nm.

2. ON THE BASIS OF STRUCTURE:

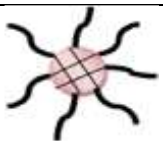
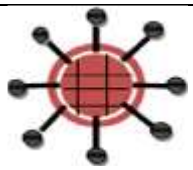
S.no	Types	Schematic structure	Network structure	Example
1.	Simple nanogel		a) Cross-linked b) Semi-interpenetrating polymer c) Self-assembled	Pullulan (CHP) nanogel, an artificial chaperone that contains cholesterol. Nanogel with quantum dots. CHSEG nanogel is an artificial chaperone cholesterol enzymatically synthesised glycogen.
2.	Hollow Nanogel		Interpenetrating polymer	Nanogel that is responsive and sensitive to stimuli.
3.	Core- shell nanogel		Cross-linked	Nanogel that is responsive and sensitive to stimuli.
4.	Hairy nanogel		Cross-linked	Nanogel that responds to stimuli.
5.	Multilayaer nanogel		Cross-linked	Nanogel that is responsive and sensitive to stimuli
6.	Functionalized nanogels		Cross-linked	Methacrylic acid polyethyleneglycol-b-poly [PEG-b-PMA] having PEG terminal aldehyde functionality.

Figure 1

3. ON THE BASIS OF STIMULI:

Environmental factors like temperature, pH, magnetic field, and ionic strength affect whether or not the nanogels will swell and how much they will swell or Deswell.Stimulus-sensitive nanogels get their name from the fact that any alteration to any of these stimuli will result in a change in the behaviour of the nanogels. Nanogels that respond to a variety of environmental stimuli are known as multi-responsive nanogels.

A) Thermosensitive nanogel

The shrinkage-swelling behaviour of temperature-responsive nanogels is a phenomena in which they alter size in response to changes in the ambient temperature.

B) **PH sensitive nanogel**:

The ionising groups in the design are principally responsible for the pH-dependent swelling-shrinking behaviour of nanogel; nevertheless, the pH value can modify the ionic behavior

C) Ultrasound sensitive nanoge:

The use of transdermal administration in the treatment of conditions affecting the central nervous system has grown significantly in the US

D) Magnetic response nanogel:

A magnetic field may be used to aid in the induction of hyperthermia. Moreover, magnetic targeting under a strong magnetic field is another application for these nanoparticles.

E) Reponse to multiple stimuli:

Dual or multi-stimuli responsive nanogels have attracted a lot of attention because of their improved capacity to continuously maintain controlled drug release.

F) Chain transfer polymerization:

The only processes that can be controlled by adding dithioester molecules to a polymer are those that involve reversible addition–fragmentation chain transfer (RAFT).

G) Photo – induced crosslinking polymerization:

Crosslinking between molecules brought on by radiation can produce atoms and radicals in a polymer that, when water molecules break down, generates nanogel.

H) Modification of nanogel for active targeting:

A ligand can reach the precise receptors on the cells or subcellular structures it was intended to influence through active targeting. Furthermore, biological materials such as proteins, peptides, polysaccharides, and tiny compounds.

ROUTE OF ADMINISTRATION:

- Oral
- Pulmonary
- Nasal
- Parenteral
- Intra-Ocular
- Topical.

PROPERTIES OF NANOGEL:

Biocompatibility and Degradability:

nanogel-based drug delivery systems are so biocompatible and biodegradable, this is a particularly promising field right now.These polymers are all naturally hydrophilic, nontoxic, stable, and biodegradable. The process by which a material is transformed into new products through biochemical processes or the activity of microorganisms like bacteria is known as biodegradation.

Swelling Property in Aqueous Media:

The fastest swelling and de-swelling properties of nanogels are their most advantageous feature. Soft nanomaterials are called nanogels.Similar to microgels, nanogels can incorporate polymers with high-affinity functional groups to both encapsulate and protect pharmaceuticals while controlling their release.

Higher Drug Loading Capacity:

Nanogels should have a higher loading capacity than traditional dosage forms, much like any other nano delivery technology. This is mostly because to the formulation's ability to swell, which permits it to absorb a significant amount of water.The drug-carrying efficiency is facilitated by these pendent functional groups of polymeric chains, which help to create hydrogen bonds or van der Waals forces of interactions within the gel network.

Particle Size:

The range of particle sizes of nanogels are commonly 20–200 nm in diameter, which is generally associated with being effective in evading fast renal elimination, while being small enough to refuse uptake through the reticuloendothelial system.Good permeation capabilities due to extreme small size. More specifically, it can cross the blood brain barrier (BBB).It’s small enough to cross (BBB) and in the same time avoid rapid clearance mechanisms.

Softness:

Nanogel softness is a critical parameter in the biomedical field because it affects their biodistribution properties. The chemical structure of the nanogel can be changed to alter its softness.

Solubility:

Nanogels are able to solubilize hydrophobic drugs and diagnostic agents in their core or networks of gel.

Preparation methods for nanogel:

Monomer polymerization at a consistent level:

As seen in Figure 2, this method creates a polymer colloidal suspension by homogeneously nucleating aqueous miscible monomers, which are employed to create better nanogels. This method is especially useful for controlling particle size. Nanogels with small particle sizes can be created by adding an ionic surfactant, which also improves the preparations' colloidal consistency. For instance, when creating nanogels, the amount of surfactant decreases while the particle size increases .

Donini and colleagues created a (PEG)-grafted poly(methacrylic acid) (PMA) nanosuspension in a water medium using the precipitation polymerization process. This method may not be applicable to biological particles and is only used for the hydrophobic and thermostable components .

As seen in Figure 3, some research used the inverse microemulsion (w/o) approach to polymerize monomers by building up cross-linkers to create a stable nanosystem. Luisi and Straub validated the focal copolymerization of monomers soluble in inverse micelles . A variety of polymers, including poly(2-hydroxyethyl methacrylate) and polyacrylamide (PAAm), are used to create water-soluble nanoparticles. and PAA, or polyacrylic acid . Diethylaminoethyl methacrylate nanogels that are pH-sensitive and employed as regulated drug delivery systems can also be made with this method . Atom transfer radical polymerization creates stable cross-linked nanogels in the inverse microemulsion process. To create nanogels with gradual drug release and chemical stability in the extracellular environment, a variety of disulfide cross-linkers were employed. Poly(oligo[ethylene oxide]-methyl methacrylate) polymer can be used to create biodegradable nanogels .

Interactive polymer self-assembly in physical form:

Nanogels, in which the drug and solvent interact via van der Waals forces and hydrogen bonds, are created by combining the physical self-accumulated mechanism of polymers with those of amphiphilic polymers. Micro- and macromolecules are confined within the nanogel network during the process of self-assembly . Numerous protein-loaded nanogels have been created using self-associating hydrophilic polymers. For instance, Akiyoshi et al. created insulin hydrogels using the cholesterol-modified pullulan method, achieving particle sizes of 20–30 nm. With this method, as illustrated in Figure 4, the size of the nanogels is controlled by the right concentration of the polymer and a variety of environmental conditions, including temperature, ionic strength, and pH. For instance, Yu et al. used a temperature-induced gelation approach to create nanogels of oppositely charged proteins including lysozyme, ovalbumin, and ovotransferrin. Ovalbumin or chitosan can be used to create nanogel using the pH-and temperature-induced gelation approach. Systems based on live radical polymerization, such as nitroxide-mediated polymerization processes and reversible addition–fragmentation chain transfer (RAFT), are employed to create amphiliphilic polymers. By changing the polymer's length, shape, and composition, amphiphilic polymers' micellar structure can be changed . The RAFT approach is frequently used to synthesize gene delivery systems because it produces particles of a small size that are appropriate for gene delivery . Additional options for modifying the micellar behaviors of the amphiphilic block copolymers are provided by the addition of additives, solvents, or temperature changes . Charged polymers mediate the interaction of oppositely charged colloids in a variety of settings.

A polyelectrolyte, for instance, is created when polyions combine with colloid particles such as proteins, micelles, and colloidal silica; these particles have a hydrodynamic size that is smaller than that of typical polymers with an indiscriminate walk shape. Three different kinds of complexes could emerge: complex coacervates, insoluble amorphous precipitates, and water-soluble intrapolymer complexes in which the colloid particles are attached to a polymer chain. Salt content, medium pH, and colloid-polymer mixing ratio are the primary determinants of the final type. The degree of ionization of polyelectrolyte nanogels determines how much their size changes. Due to the numerous dangling links, the charges of the nanogel particles are distributed throughout the network and have a smooth topology. The formation of the polyelectrolyte complex would be of interest because of similar biochemical variations that are found in different biological systems, even though the size of nanogels generally appears to be larger than the size of the polymers, even when the gel particles are completely collapsed. Additionally, the complex formation between oppositely charged polymers and polyelectrolyte nanogels would be enhanced. by a gel collapse due to the removal of network charges . Likewise, the complexation approach is thought to be a workable system for flavor protection by nanoencapsulation. This technique makes it easier to trap taste oils in a complex made up of two distinct biopolymers. Proteins and polysaccharides are the biopolymers used in this complexation technique; they can bond to one another via electrostatic forces. In most situations, single biopolymer nanoparticles are not preferred over polysaccharideprotein nanoparticles. Their strong chemical and colloidal defense is the real cause of this. Proteins typically have a positive charge below their isoelectric points (pI ≈ 5) and a negative charge above them. As a result, two phenomena can be seen when proteins and polysaccharides are combined in a liquid medium. There are reports of both soluble and insoluble compounds when the rate of attraction is higher. Additionally, the two biopolymers separate from one another when the rate of repulsion is larger. Depending on the presence of charge on the biopolymers as well as important variables like pH and ionic strength, one of these two phenomena will be reported .

Application of nanogel:

Nanogels can be applied through a variety of delivery methods, including parenteral, intraocular, topical, nasal, pulmonary, and oral. For instance, acetazolamide meant for ocular delivery was loaded into nanogels made of surfactant-based nanovesicles , curcumin for oral delivery was encapsulated into low density lipoprotein/pectin nanogels , and bio-inspired pulmonary surfactant-modified nanogels (a promising siRNA delivery system) and

nanogel-based antigen-delivery systems were employed for pulmonary and nasal applications, respectively . Some examples of nanogel uses are included below, together with information on indications, application areas, and some samples of commercially available goods.

Applications in autoimmune disorders

The fundamental requirement for treating autoimmune diseases is the capability of the delivery system to suppress the immune response.cells that contribute to the advancement of the disease by influencing the immune system. The integration of The incorporation of immunosuppressant medications into nanogels has been investigated for the treatment of autoimmune disorders, due to their capacity to pinpoint cells involved in autoimmune disorders and facilitating the systemic buildup of the administered medication.future science group www.future-science.com 709 Examine the work of Suhail, Rosenholm, Minhas, and others.A nanogel system was developed using mycophenolic acid complexed with nonmethylated β-cyclodextrin.through the fusion of liposomes with a diacrylate end-capped copolymer of poly(lactic acid-co-ethyleneglycol) for the goal of treatment for systemic lupus erythematosus.

Applications in the delivery of anti-inflammatory medications

Nanogel systems can be employed for the local administration of nonsteroidal anti-inflammatory medications. That system can address issues related to topical delivery systems, such as the relatively brief duration of interaction between active medications and the site of application, and this is achieved by holding water into the gel matrix, resulting in a consistent distribution of the nanogel. Spantid II and ketoprofen are two anti-inflammatory medications whose administration was effectively achieved using a nanogel made of poly-(lactide-co-glycolic acid).and chitosan. Oleic acid was utilized for surface modification.

Applications in vaccine administration

Nanogels have been employed as a new and efficient vaccine to improve the effectiveness and strength of vaccines distribution networks. The primary benefit of nanogels compared to traditional vaccine delivery is the safeguarding of thevaccines against enzymatic degradation. Nanogels modified on their surface with antibodies and additional ligands.can be used to improve the target specificity of the vaccine.

Applications in bone regeneration

Bone regeneration can be accomplished through the gradual and localized release of lithium and other medications.Lithium nanogels are created via micro-emulsion polymerization of polyacrylic acid and incorporated into the Matrix of biodegradable polyhydroxybutyrate has been developed for the controlled release of lithium into bone tissue.

Applications in antibacterial and antimicrobial drug administration

In the present 'postantibiotic' period, curing infections is becoming challenging due to the resistance to traditional antibiotics. Nanogel systems can be advantageous in addressing this issue, offering a focused and targeted delivery of the antimicrobial substance featuring rapid release properties. The method of mini-emulsion was employed for the synthesis of zinc (as ions) incorporated, dextran cross-linked polyacrylamide nanogels (i.e., nanogels derived from polysaccharides). Hyaluronic acid that is methacrylated served as the cross-linking agent. This nanogel was developed to specifically target the methicillin-resistant strains of Staphylococcus aureus

Conclusion:

Nanogels are promising, innovative, and smart drug delivery systems that address key limitations of traditional and modern therapeutics, such as nonspecific targeting and poor stability. Continuous research in this field is leading to the discovery of novel polymeric systems and advanced fabrication techniques that enhance the therapeutic potential of nanogels. These systems have shown great promise in targeted drug delivery for ocular, nasal, and vaginal applications, as well as in the diagnosis and treatment of a wide range of diseases, including diabetes, cancer, and neurodegenerative disorders. Their ability to efficiently deliver biopharmaceuticals and bioactive molecules makes them valuable carriers in modern medicine. Future research aims to design nanogels with specific targeting mechanisms for enhanced cellular uptake. Additionally, plant-based compounds, such as those derived from papaya, have demonstrated anti-inflammatory and immunomodulatory effects in preliminary in vitro and in vivo studies. However, clinical evidence remains limited, and further high-quality trials are needed to validate the therapeutic potential and safety of such natural extracts, particularly in the treatment of chronic inflammatory diseases (CIDs) and cancer.

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