Research Article

Nanogels As Advanced Platforms For Targeted And Smart Drug Delivery: Design Principles, Fabrication Strategies, Biomedical Applications, and Future Perspectives

Akansha Chandra[1], Amrita Gupta[2], Md Shamshir Alam [3], Sagun Rana [3], Abhilash [4], Mohd Ruman Khan [5], Rajendra Prasad [6], Priya Chaturvedi [7], Maksood Ali[8], Md Sarfaraz Alam [9*]

1. PhD scholar, Department of Pharmacy, School of Medical and Allied Sciences, Galgotias University, Greater Noida - 201310, Uttar Pradesh, India
2. Ram-Eesh Institute of Vocational and Technical Education (RIT), Knowledge Park-1, Greater Noida, Uttar Pradesh, INDIA
3. Department of Pharmacy Practice, Chandigarh College of Pharmacy, Chandigarh Group of Colleges (CGC) - Landran, Mohali – 140307, Punjab, India.
4. Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy, Bela, Ropar– 140111, Punjab
5. Invertis Institute of Pharmacy, Invertis University, Bareilly, India.
6. Department of Pharmacognosy, HIMT College of Pharmacy, Knowledge Park III, Greater Noida, Uttar Pradesh, INDIA
7. Maharishi school of Pharmaceuticals, Maharishi University of Information technology, Noida.
8. Managalayatan Institute of Pharmaceutical Education and Research, Manglayatan University, Mathura Rd, Aligarh, Beswan, Uttar Pradesh 202146.
9. School of Pharmacy, Manglayatan University, Mathura Rd, Aligarh, Beswan, Uttar Pradesh 202146.

***Corresponding Author;**
Prof. (Dr.) Md Sarfaraz Alam
School of Pharmacy, Manglayatan University Mathura Rd, Aligarh, Beswan, Uttar Pradesh 202146. Email Id: sarfaraz.alam@mangalayatan.edu.in

ABSTRACT:

Nanogels are innovative, smart delivery systems based on crosslinked polymer networks that offer high encapsulation capacity, stability, ease of preparation, minimal toxicity, and responsiveness to stimuli. They are prepared using various methods such as solvent diffusion, nanoprecipitation, emulsion evaporation, and reverse micellar methods. Nanogels are highly effective in chemotherapy, diagnostics, and organ-targeting for the delivery of bioactive substances. They are composed of natural and synthetic polymers, and their unique properties, including small particle size, stability, sustained, targetable release, and protective form degradation, make them more effective than conventional drug-delivery systems. Nanogels are responsive to environmental factors, such as pH, temperature, and ionic strength, and their permeability allows them to cross biological barriers. They have high drug-loading capacity and can be administered via various routes. Nanogels are biocompatible and have a wide range of applications including drug delivery, tissue engineering, protein delivery, and nucleic acid delivery. They are formulated using polymers, crosslinking agents, active pharmaceutical ingredients, surfactants, and stabilizers. Current scope of nanogel diagnosis and imaging therapy, drug delivery to the central nervous system, controlled release and diagnostics, regenerative medicine, and targeted drug delivery using smart delivery.

Keywords: Nanogel, Polymers, Characteristics, Preparation, Scope, Smart drug delivery systems.

INTRODUCTION

Nanogels may be expressed as highly cross-linked nanosized nanoparticles, which can be made up of ionic and non-ionic surfactant. The Ng's size ranged from 20 to 200 nm. Nanogels have unique properties such as three-dimensional, small particle size, high stability, sustained and targetable manner, high encapsulation efficiency, and protection from degradation, which make their drug delivery system (DDS) more effective and productive than conventional and micro-sized delivery. [1],[2],[3],[4] Nanogels are composed of both synthetic and natural polymers. They can swell by solvent absorption but are not dissolved because of the constituents of the polymeric network. [5], [6], [7], [8], [9] Nanogels have a porous structure that encapsulates small molecules, such as drugs or genes, and then releases them by changing their volume when external stimuli are applied. It can be administered through various routes, such as oral, nasal, topical, and parental. Nanogels have been developed as multipurpose drug delivery systems (DDS) for encapsulation.[9], [10], [11]

Classification of nanogels

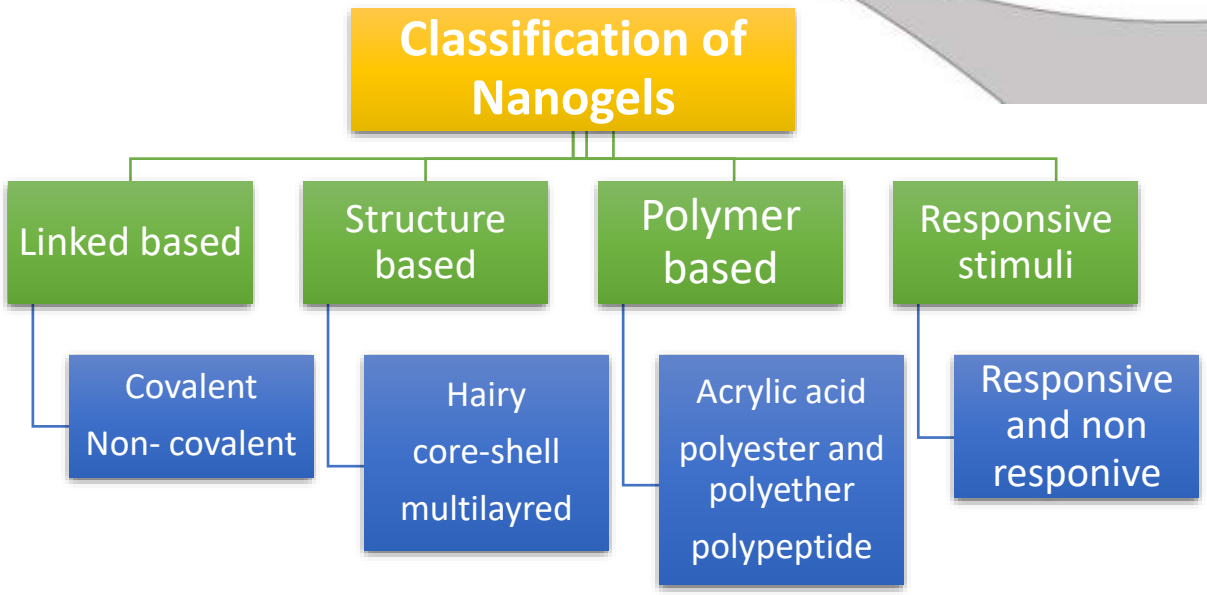

Figure 1: Classification of nanogels [12]

Table 1: Comparison of nanogels with nanocarriers

Property	Nanogels	Nanocarrier (like – liposome, micelle etc.)
Structure	Soft, Cross-linked polymer networks, swellable, permeable core-shell	Solid particles, vesicles, or micelles, rigid or less flexible [13]
Size	**10-100 nm** Tunable for barriers like Blood brain barrier	**10-200 nm** varies by type but less adjustable swelling[14], [15], [16]
Drug Loading	High (due to swelling and porosity); physical/chemical encapsulation	Moderate, and limited by surface or essential volume [17]
Stability	Admirable colloidal stability	Good, but susceptible to aggregation or faster dissociation
Stimuli Responsiveness	pH, temperature, enzyme-sensitive, controlled release, ionic strength	Varies - some responsive, but less inherent swelling control[18]
Biocompatibility	Highly Biodegradable and possess nominal toxicity	High, but Potential for immunogenicity[19]

Formulation of Nano Gels

Nanogels are made of a crosslinked polymeric network that can encapsulate both hydrophilic and hydrophobic drugs owing to their tunable nature. Their formulation typically involves the following key components:

1. Polymers

- **Natural Polymers**: cellulose, collagen, starch, natural silk, carboxymethyl starch, and proteins, hyaluronic acid.
- **Synthetic Polymers**: Polyvinyl alcohol, polypeptides, polyacrylates, polymethacrylates, poly (lactic acid), and poly sulfone.

- **Semi-Synthetic polymers:** PEG (polyethylene glycol), PNIPAAm (poly(N-isopropylacrylamide)), PVA (polyvinyl alcohol), carbomer.

2. Crosslinking Agents

- Chemical crosslinkers: Glutaraldehyde
- Di isocyanates
- Carbodiimides
- Polyepoxy compounds
- Acyl azide
- Physical crosslinking: sodium alginate, polyvinyl alcohol, gelatin, collagen, and agar.

3. Active Pharmaceutical Ingredients (APIs)

- Hyaluronic acid/β-glucan, methotrexate, lidocaine, valproic acid, acelofenac.

4**. Surfactants and Stabilizers**

- Sodium dodecyl sulfate (SDS)
- Sodium cholate (SC)
- Sodium dodecylbenzene sulfonate (SDBS) can be used as a surfactant.
- Dodecyl dimethyl ammonium bromide
- Polyvinyl alcohol these are a stabilizer that can be used in nanogels.

5. Solvents

- Water or other vehicles were used as solvents[20], [21], [22], [23], [24], [25], [26], [27]

Table 2: Advantages and disadvantages of natural and synthetic polymers used in NGs.

Natural polymer	
Advantages	**Disadvantages**
• Both Biocompatibility and biodegradability • Potential therapeutic effect (i.e., anticancer characteristics) • A sustainable and renewable supply • The possibility of biofunctionalization • High retention efficiency • Crosslinking agents is necessary to ensure people's safety and acceptance	• Variability from batch to batch • Insufficient mechanical power • Potentially intricate purifying procedures[26], [27]
Synthetic Polymers	
Advantages	**Disadvantages**
• Reproducible and controlled characteristics Adaptable rates of deterioration • Strong mechanical properties • Chemical alteration that is versatile Derivatisation and possible toxicity from synthetic residues that are not biodegradable	• Potential effects on the environment • Insufficient bioactivity • A challenging and unique synthesis process

Characteristics of nanogels

Biodegradability: Nanogels are biocompatible and degradable. Therefore, its accumulation in organs is avoided. It can be prepared using polymers such as chitosan, methylcellulose, ethyl cellulose, and various polysaccharides such as dextran and dextral. These polymers are non-toxic, hydrophilic, and biodegradable.[6]
Responsive Properties: Nanogels respond well to environmental factors, such as pH, temperature, and ionic strength. They have high tunability and stability and can sense and respond to external stimuli by showing changes in gel volume, water content, colloidal stability, mechanical strength, and other physical/chemical properties. The thermo-responsive polymers making up these nanogels are categorized into polymers possessing a lower critical solution temperature (LCST) and those with an upper critical solution temperature (UCST).[17], [28], [29], [30]
Permeability: Nanogels are capable of permeation by diffusion through tissues and, in some cases, through a particular transport system, creating a challenge in crossing the blood-brain barrier (BBB). Nanogels are emerging as promising nanocarriers for delivering therapeutic agents to treat central nervous system (CNS) disorders.
Surface area and drug loading capacity: Nanogels have become a research hotspot due to their smaller particle size, larger specific surface area, and higher loading capacity. Nanogels have better loading capacity than other dosage forms. Its swelling property allows it to absorb large quantities of water. Three loading methods were used in this study.

1. Physical entrapment
2. Controlled self-assembly
3. Covalent attachment of bioactive molecules.[31], [32]

Advantages of Nanogels

1. Nanogels exist in an internal aqueous environment and are inert in the bloodstream.
2. Nanogels are administered via various routes, including the nasal, intraocular, topical, parenteral, and nasal routes.
3. Drug loading in nanogels is relatively high compared to other nanocarriers because of the functional groups of the polymeric networks.
4. Nanogels were prepared to release the drug in a controlled pattern at the target site. Therefore, it is important to improve the therapeutic efficacy of the drug and avoid its adverse effects.
5. Nanogels are generally stress-free because mechanical energy is not active, and under harsh conditions, organic solvents are not introduced.
6. Nanogels can be formulated as polymeric micellar nanogel systems. It exhibited slow rates of dissociation stability over surfactant micelles. It had a longer retention time for the loaded drugs.
7. Nanogels have high efficacy in aqueous solutions and can swell.
8. Nanogels can be administered with both hydrophilic and hydrophobic drugs. This property can be highly influenced by the type of functional group in the polymeric networks.
9. Nanogels have high biocompatibility, which makes them a promising approach for drug delivery systems (DDS).
10. Nanogels carrying safe drug delivery into the cytoplasm of target cells.[33], [34]

Application

Nanogels for drug delivery

Recent advancements in nanomedicine have led to the development of nanogels (NGs) for drug delivery, gene therapy, and nanotheranostics (simultaneous diagnosis and therapy). The focus of 3d networks in nanogels is on the suitable incorporation of micro molecules or macromolecules.[35], [36] Polymeric nanogels are drug carriers present in the artificial environment, preventing the dosage of drugs by external stimuli, improving therapeutic efficacy, and reducing adverse effects. Nanogels are consumed in different ways, like hydrophilic and hydrophobic. Nanogels have a stimuli-responsive nature, high drug-loading capacity, physical stability, and controlled release of anti-inflammatory, antimicrobial, and anticancer drugs. This formulation of stimuli-responsive nano drug delivery systems is also known as a smart drug delivery system. They possess high water content, biocompatibility, and mechanical properties. They offer unique advantages for polymer-based DDS: high uniformity, minimal toxicity, and easy preparation owing to their high drug encapsulation capacity.[37], [38], [39], [40]

Tissue engineering

Recently, different types of nanogels, along with the synthetic procedure from nanogel carriers, have been the main focus to provide a good microenvironment for cell progress and tissue regeneration. A demanding study of clinical trials in the future will confirm that nanogels are suitable carriers of drugs.[41], [42], [43], [44]

Protein drug delivery

Proteins have poor stability, a short half-life, enzymatic degradation, and low permeability. Therefore, there is a need for pharmaceutical amendments for medicinal purposes. Encapsulation in a variety of polymers is the current way to prolong drug retention time. Natural and synthetic polymers of nanogels can deliver insulin with tremendous biocompatibility and enriched glucose-based approachability.[45], [46], [47]

Nucleic Acid drug delivery

Gene therapy is a special treatment for some hereditary diseases that involves the delivery of relaxing DNA and RNA arrangements. Both these remedies are significant medications for gene-related diseases. However, nucleic acids are negatively charged hydrophilic compounds that cannot penetrate cell surfaces, and their usage is limited by factors such as low transfection rates and short half-lives due to prompt enzymatic degradation.[48], [49]

Small molecule drug delivery

Nanogels have significant potential as drug delivery systems owing to their rational release, water solubility, biocompatibility, and degradability. Nanogels mainly focus on incapacitating the instability of protein drugs in order to achieve targeted drug delivery.[50], [51]

Biomacromolecule drug delivery

They have significant mass, complex structures, and biological functions. The stability and permeability of biomacromolecules are inspiring, and drugs are transferred by a variety of nanometre-sized drug delivery systems. It is composed of nanometre-scale hydrogels with outstanding drug-loading capacity, stability, and hydrophilicity.[52], [53]

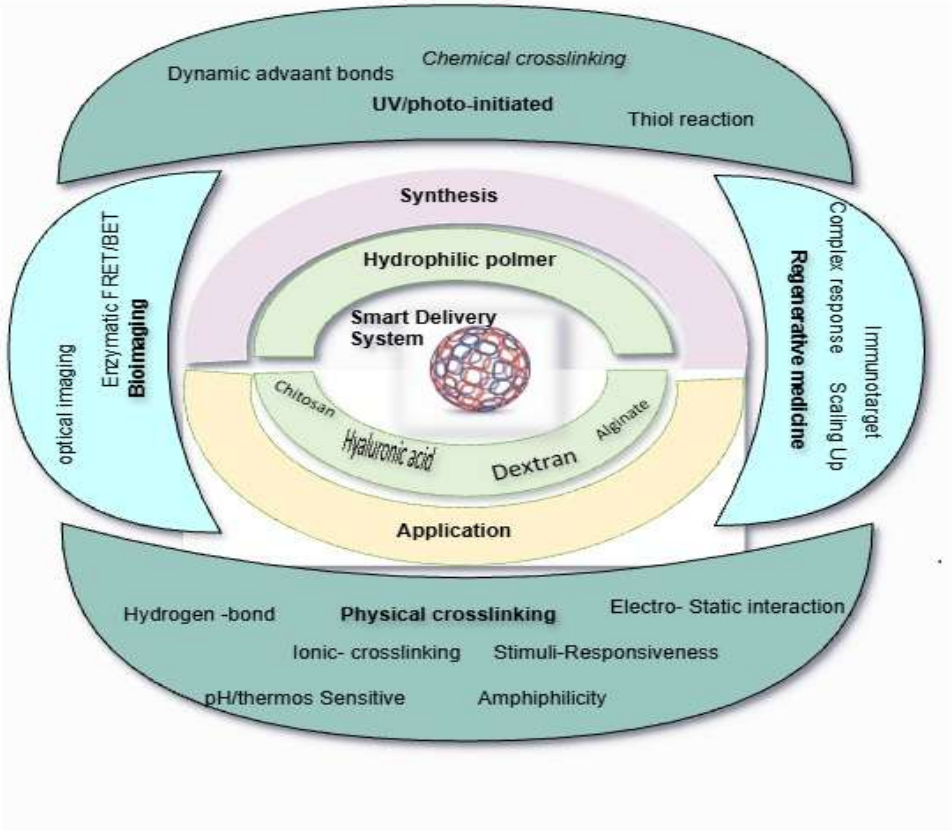

Figure 2: Schematic structure of nanogel possible synthesis

METHODS OF NANOGEL PREPARATION

These are the methods involved in the preparation of nanogels include -

1. Solvent diffusion method

2. Nano precipitated method
3. Evaporation of solvent method
4. Reverse micellar method
5. Modified diffusion emulsification method

1. Solvent diffusion method

An aqueous solution of the drug was solubilized in an organic layer. The polymer and gelling agents were dissolved in water to form the drug phase, which was added dropwise to the aqueous phase and homogenized for 30 min at 6000 RPM. Subsequently, the emulsion was homogenized into a nanodroplet and oil or water was formed. To form a nanogel polymer, triethanolamine was added, and the mixture was continuously stirring for an hour at 8000 RPM.

2. **Nano precipitation method**

When the organic phase containing both medication and polymer reacted with the surfactant aqueous layer, the polymer precipitated out after the removal of excess solvent, and the polymeric nanogel remained. A gelling agent and the necessary amount of nanoparticle dispersion were added, and the particles were moistened. After that, ph. It was stabilized using triethanolamine (TEA).

3. Evaporation of solvent method

In this method, during 2 h of treatment, the drug-polymer mixture was injected into the designated area of the aqueous phase. This process was performed with continuous stirring at 1000RPM by a magnetic stirrer. The nanosponges obtained were further subjected to filtration, followed by drying in a hot air oven at 40 °C for 24 h. Finally, the dried nanosponges were carefully transferred to vials for storage.

4. Reverse micellar method

In this method, the polymer medication and surfactant are dissolved in an organic solvent. It must be contained during the night after addition of the cross-linking agent. The nanoparticles were then purified and the solvent was evaporated to create a desiccated bulk. This was achieved by dissolving the gelling agent in water. When the nanoparticles and aqueous phase containing the gelling agent are combined, a nanogel is formed after neutralizing the modified substance.

5. Modified diffusion emulsification method

A polymer-containing solvent was mixed with the drug in a calculated ratio. The organic phases formed by the drug-polymer mixture were continuously mixed in the aqueous phase at 5000 – 10000 rpm. Then, the syringe is fitted with a needle and used to organic phase at a rate of 0.5 ml/minute to the aqueous stabilizer solution. The mixture was agitated for 6 min at rotational speeds ranging from 10000 to 20000 rpm. The suspension was then sonicated for 5-10 minutes. [54]

Mechanism of Drug Release from Nanogels

Nanogels release drugs via molecular-level processes like diffusion through swollen networks, swelling-induced expansion, polymer degradation/erosion, or stimuli-triggered bond cleavage. Diffusion-controlled release involves drug migration from the gel matrix driven by concentration gradients. Swelling-controlled release occurs as hydrophilic networks absorb water, enlarging pores for drug escape.[55] [56]

Degradation/erosion-controlled release hydrolyzes or enzymatically breaks polymer chains, liberating encapsulated drugs. Stimuli-triggered mechanisms include pH-induced protonation/deprotonation altering solubility, redox cleavage of disulfide bonds by glutathione (GSH), enzymatic hydrolysis of peptide links, or reactive oxygen species (ROS) oxidation.[56], [57], [58]

Stimuli-Responsive Nanogels

Stimulus	Mechanism	Example Application
pH	Protonation/deprotonation	Tumor targeting[56], [59]
Temperature	LCST/UCST transition	On-demand release[55], [56]
Enzyme	Enzyme-cleavable crosslinks	Cancer, inflammation [58]
Redox (GSH)	Disulfide bond cleavage	Intracellular delivery [58]
Light/Magnetic	External trigger (photothermal/heat)	Imaging & theragnostic [60]

These responses enable site-specific release by exploiting tumor microenvironments or external controls.[56], [60]

Characterization & Evaluation Parameters

1. Particle size (ideally <200 nm) and PDI (<0.3 for monodispersity, ensuring uniform biodistribution) are measured by DLS.[61] [58]
2. Zeta potential assesses stability (absolute value >|30| mV prevents aggregation) and cellular uptake (positive charge enhances endocytosis).[14], [61]
3. Drug loading efficiency (%DL = drug/polymer mass ×100; %EE = entrapped/initial drug ×100) quantifies payload.
4. In vitro release kinetics fit zero-order (constant rate), Higuchi (square-root time, diffusion), or Korsmeyer-Peppas (n<0.43 Fickian diffusion, 0.43<n<0.85 anomalous).
5. Stability studies evaluate storage (e.g., size retention at 4°C) and serum stability (minimal aggregation).[61] [14], [62]
6. In vitro cytotoxicity uses MTT (cell viability) and hemolysis (<5% for hemocompatibility).[56], [61], [63]

Clinical Translation & Regulatory Perspective

Over 50 FDA-approved nano-products exist, mostly liposomes (e.g., Doxil® since 1995 for doxorubicin delivery), but no nanogels due to translation gaps. Nanogels lack approvals from scale-up issues like batch reproducibility, GMP compliance, and polydispersity control. [13], [64], [65], [66]

Regulatory hurdles include toxicity profiling, biodistribution tracking, and degradation product safety; agencies demand human-relevant models. Liposomes succeed via established manufacturing, unlike nanogels' complex crosslinking. [64], [67], [68]

Challenges & Limitations

Key issues: protein corona formation accelerates immune clearance (e.g., MPS uptake), long-term toxicity/metabolite accumulation, and absent standardized models. Nanogels vs. liposomes: nanogels offer higher loading/stimuli-response but face faster clearance; liposomes have better translation (e.g., PEGylation evades immunity). [13], [65], [69]

Improvements: PEGylation, artificial corona pre-coating, AI-optimized synthesis for reproducibility.[69], [70]

Application	Nanogel Advantage	Compared System
Cancer therapy	High loading + stimuli release	Liposomes[71]
CNS delivery	BBB permeability, stability	Polymeric NPs [72]
Protein delivery	Protection from degradation	Micelles [56]
Gene delivery	Reduced toxicity, high EE	Viral vectors [70]

CURRENT SCOPE OF NANOGELS

Nanoparticle-composed gels in diagnosis and imaging therapy

Nanogels have significant features, such as flexibility, water consistency, biocompatibility, and liquidized vector qualities. Nanoparticle-composed gels account for the formation of different colors, corresponding atoms, and inorganic nanoparticles.

Nanogels-based drug delivery to the central nervous system (CNS)

Nanogels have emerged in the field of central nervous system (CNS) delivery. It uses hydrogels for the treatment of brain tumours and tissue engineering. These contain therapeutic T-lymphocytes for the localized delivery of glioblastoma cells for brain tumour immunotherapy. It was developed using polyethylene glycol gel.[73] [74]

Nanoparticles composed of gel as therapeutic vector

Solan nanoparticles composed of gel can have 30% weight and a greater number of organic particles and drugs through the vendor walls, electrostatic holding, and hydrophobic association with the chain of the polymer. The nanogel breakdown frames stable nanoparticles in which natural specialists become entrapped. [75], [76]

Drug delivery and controlled release

Nanogels are promising for drug delivery owing to their ability to encapsulate drugs. They controlled their release in a targeted manner. It is useful for the delivery of both hydrophobic and hydrophilic drugs, including poorly soluble drugs.[77]

Biomedical imaging and diagnostics

Nanogels have modernized imaging and diagnostic potential effects by integrating both therapeutic and diagnostic tendencies, and are known as theragnostic. Nanogels design multifunctional diagnostic agents (e.g., contrast agents, fluorescent probes, or MRI agents) with other drugs, enabling real-time monitoring of smart drug delivery and therapeutic efficacy. [78]

Tissue Engineering and Regenerative Medicine

Nanogels are attractive for tissue engineering and drug regeneration because they can simulate the extracellular matrix (ECM), which is crucial for cell adherence, development, and differentiation. Nanogels are biocompatible and biodegradable and make ideal 3d scaffolds that can support tissue regeneration. Tissue engineering and regenerative medicine (TERM) is a developing field that focuses on the development of alternative therapies for tissues.[79], [80]

Targeted Drug Delivery and Smart Nanogels

Nanogels are mostly customized and can be reformed for smart drug delivery in a specific and targeted manner. The advancement of smart nanogels has resulted in specific environmental cues in various areas of interest. Nanogels can be modified to release their goods only in specific tissues or under certain criteria, thereby decreasing off-targeting effects.[81], [82]

The scope of nanogels comprises the following aspects:

Nanogels are cross-linked polymers that can utilize large amounts of biological fluids while providing a 3D-dimensional structure.

Properties: Swelling and stimuli-responsiveness, such as pH, temperature, and light, but also recognition of the biocompatibility and degradability of specific molecules, high surface area, porosity, and tunable particle size and shape.

Drug delivery system (DDS) - targeted delivery, controlled release, improved bioavailability of poorly developed drugs, diagnostics, and biomarkers for disease identification.

Characterization techniques: These are evaluation techniques that help to identify the particular qualities of the subject. Similar to dynamic light scattering (DLS), scanning electron microscopy (SEM), transmission electron microscopy (TEM), and Fourier transform infrared spectroscopy (FTIR), we can find appropriate results and discussion of the nanogels using these techniques.

Future Perspectives

Improving stability and shelf life, enhancing targeting capabilities, mass production for industrial applications, concentrating on potential toxicity and environmental concerns, and developing multifunctional nanogels for theragnostic applications.

The scope of nanogels continues to increase as researchers explore new materials, synthesis methods, and applications in various fields, particularly biomedicine and environmental science.

Personalized medicine: As we understand genetics and diseases, smart biomarkers and nanogels can be used for specific therapies depending on the individual patient's genetic profile, offering personalized treatment plans for conditions such as cancer, autoimmune diseases, neurodegenerative disorders, and bone regeneration.

Combination therapy: Nanogels can deliver drugs in combination therapies, multiple therapies, or even in a single formulation for gene therapy to enhance the therapeutic outcomes for life-threatening diseases such as cancer or autoimmune disorders.

Regenerative medication—nanogels be used in regenerative medicine, developing cell regeneration, tissue repair, and organ regeneration through the sustained, controlled release of growth factors and genes.[83], [84]

DISCUSSION

Nanogels have unique properties in the biomedical field because of their extraordinary capability for drug encapsulation, uniformity, adjustable size, direct production, serum stability, and approachability to stimuli. This review outlines the methods used for nanogel preparation. Nanogels can be prepared using different techniques, such as emulsion solvent diffusion, nano-precipitation, emulsion evaporation of the solvent, reverse micellar, and modified diffusion emulsification methods. Thermosensitive nanogels, pH-sensitive nanogels, ultrasound-sensitive magnetic responses, chain transfer polymerization, photo-induced crosslinking polymerization, and modifications for active targeting are types of nanogels based on response to stimuli, and polysaccharides,

chitosan, pullulan, hyaluronic acid, alginate, cyclodextrin, gum acacia, and proteins are used in the preparation of nanogels.

CONCLUSION

Recently, nanogel-based nanoplatforms have impressively facilitated the coordination of smart drug delivery. In this review, we discuss the formulation, categorization, properties, and biological applications of nanogels in detail. Nanogels are formed by chemical crosslinking and physical self-building and can encapsulate compounds, drugs, proteins, DNA or RNA chains, and even small nanogels. The small size features of the carrier give them a special surface area and inner space, enhancing the stability of loaded drugs and extending their distribution time in the biological process. Responses or the cleavage of chemical bonds in the structure of nanogels have been proposed to generate controlled or sustained-release drugs.

Considering the design of particular chemical structures and various preparation procedures, nanogels can recognize various responses (pH-sensitive and temperature-sensitive) and permit the stimuli-responsive release of drugs in the mini-environments of many diseases.

DECLARATION OF INTEREST STATEMENT

The authors confirm that this article has no conflicts of interest.

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