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Review Article

Nanogels: Emerging Smart Platforms for Drug Delivery

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ABSTRACT

Nanogels are nanoscale hydrogel-based drug delivery systems that have gained remarkable attention in recent years due to their unique physicochemical properties and clinical potential. Characterized by high water content, tunable swelling behavior, biocompatibility, and capacity for surface modification, nanogels provide an efficient platform for controlled and site-specific delivery of a wide range of therapeutic agents. Their ability to encapsulate small molecules, proteins, peptides, nucleic acids, and vaccines, while protecting them from enzymatic degradation, makes them superior to many conventional nanocarriers. Importantly, nanogels exhibit stimuli-responsive behavior, releasing drugs in response to environmental cues such as pH, temperature, redox potential, or enzymatic activity, thereby enabling precision medicine. Significant progress has been made in the application of nanogels for cancer therapy, gene delivery, diabetes management, ophthalmic formulations, and brain-targeted treatments. Furthermore, the integration of nanogels with diagnostic agents has opened avenues for theragnostic applications. Despite their immense promise, challenges related to large-scale production, reproducibility, long-term safety, and regulatory approval remain obstacles to clinical translation. This review provides a comprehensive overview of nanogel systems, highlighting their preparation strategies, classification, drug loading and release mechanisms, therapeutic applications, safety considerations, and future directions.

INTRODUCTION

The past few decades have witnessed remarkable advances in drug delivery technologies, with the overarching goal of improving therapeutic efficacy, minimizing adverse effects, and enhancing patient compliance. Among the various nanocarriers investigated, including liposomes, polymeric nanoparticles, dendrimers, and micelles, nanogels have emerged as a particularly promising class of smart delivery vehicles. Nanogels are nanosized hydrogel particles composed of crosslinked hydrophilic polymers that retain the inherent water-absorbing properties

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of bulk hydrogels, while offering the advantages of nanoscale dimensions[1,2]. The nanoscale size of nanogels (typically 20–200 nm) enables efficient circulation, tissue penetration, and, in certain cases, the ability to cross biological barriers such as the blood–brain barrier. Their soft and highly hydrated network provides a suitable environment for the incorporation of both hydrophilic and hydrophobic drugs, biomacromolecules, and genetic materials. Unlike conventional polymeric nanoparticles, nanogels exhibit superior swelling behavior, responsiveness to external stimuli, and high drug-loading efficiency, making them highly versatile for a wide range of therapeutic applications[3]. One of the most attractive features of nanogels is their stimuli-responsiveness. Smart nanogels can undergo reversible changes in structure and properties in response to environmental factors such as pH, temperature, ionic strength, redox potential, or specific enzymes. For example, pH-sensitive nanogels can release drugs preferentially in acidic tumor tissues or intracellular compartments, while thermo-sensitive nanogels can respond to mild hyperthermia at the diseased site. These "intelligent" release profiles not only improve drug bioavailability but also reduce off-target toxicity[4-5]. Despite these advantages, the clinical translation of nanogels remains limited. Issues such as reproducibility in synthesis, scalability of production methods, long-term safety, and regulatory approval must be addressed before nanogels can achieve widespread clinical use. Nevertheless, ongoing research into hybrid nanogels, bioinspired systems, and theranostic platforms is rapidly expanding the potential of these versatile carriers. This review provides a comprehensive analysis of nanogels as emerging smart platforms for drug delivery. It begins with an overview of their structural features and preparation methods, followed by their classification based on crosslinking, materials, and stimuli-responsiveness. Mechanisms of drug loading and release are discussed in detail, with emphasis on how these mechanisms contribute to controlled and targeted therapy[3]. The review further highlights key therapeutic applications, recent innovations, toxicity considerations, and future perspectives.

2. Nanogels: Definition and Properties

Nanogels are defined as hydrogel nanoparticles formed through the crosslinking of hydrophilic or amphiphilic polymers at the nanoscale. They are typically spherical in shape, with a particle size ranging from 20 nm to several hundred nanometers, depending on the preparation method and polymer type. Unlike conventional hydrogels, which are macroscopic and primarily used for topical or implantable applications, nanogels possess nanoscale dimensions that allow for systemic administration, enhanced tissue penetration, and intracellular delivery.

The unique properties of nanogels make them highly attractive for drug delivery applications:

- **High Water Content and Swelling Ability:** Nanogels are composed of polymeric networks that can absorb large amounts of water while maintaining structural integrity. This confers a soft and hydrated structure, mimicking biological tissues and enhancing biocompatibility.

- **Biocompatibility and Biodegradability:** Many nanogels are prepared from naturally derived or FDA-approved synthetic polymers such as chitosan, dextran, poly(N-isopropylacrylamide) (PNIPAAm), and polyethylene glycol (PEG). Their breakdown products are generally non-toxic and easily eliminated from the body.

- **High Drug Loading Capacity:** The porous and swollen structure of nanogels provides large internal volume and surface area, allowing encapsulation of small molecules, macromolecules, and biomolecules. Drugs can be incorporated via physical entrapment, electrostatic interactions, or covalent attachment.

- **Stimuli-Responsive Behavior:** Nanogels can be engineered to respond to environmental triggers such as pH, temperature, redox state, or enzymatic activity. This enables controlled and site-specific drug release, which is particularly beneficial in cancer, infection, and inflammatory diseases[6].

- **Colloidal Stability:** Unlike many other nanocarriers, nanogels are highly stable in aqueous media due to their hydrophilic nature and crosslinked structure. This stability enhances their circulation time and prevents premature drug leakage.

- **Surface Modifiability:** Functional groups on the polymer backbone allow for conjugation of targeting ligands, imaging probes, or protective coatings. This facilitates active targeting, stealth behavior (via PEGylation), and theranostic applications.

In summary, nanogels integrate the softness and water-rich environment of hydrogels with the small size and surface versatility of nanoparticles, thereby establishing themselves as "smart" carriers capable of personalized and precision drug delivery[7-13].

3. Methods of Preparation

The synthesis of nanogels involves various chemical and physical techniques designed to control particle size, crosslinking density, and functionality. Preparation methods can broadly be categorized into **polymerization-based methods**, **crosslinking strategies**, and **self-assembly approaches**[2-4, 8, 21, 23].

3.1 Emulsion Polymerization

Emulsion polymerization is one of the most widely used techniques for nanogel preparation. Hydrophilic monomers are polymerized in an aqueous phase, with surfactants or stabilizers ensuring nanoscale particle formation. Variations include:

- **Inverse mini-emulsion polymerization:** Polymerization occurs within water-in-oil droplets, producing nanogels with controlled sizes and narrow polydispersity.

- **Precipitation polymerization:** Hydrophilic monomers polymerize in a poor solvent, causing spontaneous nucleation and gel particle formation.

Advantages: precise control over particle size and morphology.
Limitations: use of surfactants and initiators may leave toxic residues.

3.2 Physical Crosslinking

Physical crosslinking relies on non-covalent interactions such as hydrogen bonding, ionic interactions, or hydrophobic associations. Examples include chitosan–tripolyphosphate nanogels (ionic crosslinking) and polypeptide nanogels formed via hydrophobic assembly.

- Advantages: mild conditions, suitable for sensitive biomolecules.

- Limitations: weaker stability compared to chemically crosslinked nanogels.

3.3 Chemical Crosslinking

In chemical crosslinking, covalent bonds are formed between polymer chains using crosslinkers (e.g., glutaraldehyde, carbodiimide). This method offers robust stability and controlled network density. However, residual crosslinkers may be cytotoxic, requiring careful purification.

3.4 Self-Assembly Approaches

Block copolymers or amphiphilic polymers can spontaneously self-assemble into nanogels in aqueous media through hydrophobic and hydrophilic interactions. This method is widely applied in preparing stimuli-responsive nanogels with tailored architectures.

3.5 Microfluidics-Based Synthesis

Microfluidics technology has recently emerged as an advanced method for preparing uniform nanogels with precise control over size and composition. By manipulating flow rates, shear forces, and mixing parameters, highly monodisperse nanogels can be fabricated, which is critical for reproducibility and scale-up.

Comparison of Methods:

- Emulsion-based techniques: high reproducibility but potential toxicity issues.
- Physical crosslinking: biocompatible, but less stable.
- Chemical crosslinking: stable, but purification required.
- Self-assembly: versatile and stimuli-responsive.
- Microfluidics: scalable and precise but requires advanced instrumentation.

4. Classification of Nanogels

Nanogels can be classified based on several parameters, including their mode of crosslinking, responsiveness to external stimuli, and the type of polymers employed. Such classification helps in tailoring nanogels for specific therapeutic purposes[21-28].

4.1 Based on Crosslinking

Physically Crosslinked Nanogels: These are formed through non-covalent interactions such as hydrogen bonding, ionic interactions, or hydrophobic associations. They are generally biocompatible and suitable for encapsulating sensitive biomolecules like proteins and nucleic acids. However, their structural stability may be compromised under physiological stress. *Example:* Chitosan–tripolyphosphate nanogels for insulin delivery.

Chemically Crosslinked Nanogels: These nanogels are synthesized through covalent bonding using crosslinkers such as glutaraldehyde or carbodiimide. They offer robust stability and resistance to dissolution in physiological fluids. However, concerns regarding residual crosslinker toxicity and purification processes must be addressed.
Example: PEG–poly (acrylic acid) nanogels for controlled anticancer drug release.

4.2 Based on Stimuli Responsiveness

Nanogels can be engineered to respond selectively to microenvironmental cues, thereby enabling smart drug release[6,14,22].

pH-Sensitive Nanogels: Designed to release drugs in acidic or alkaline environments. Particularly useful for tumor tissues (acidic extracellular pH) and intracellular compartments such as lysosomes[6,14,22].

Example: Polyacrylic acid nanogels releasing doxorubicin in tumor microenvironments.

Temperature-Sensitive Nanogels: Composed of thermo-responsive polymers such as PNIPAAm, which exhibit phase transitions around body temperature. This property is useful in hyperthermia-triggered drug release[6,14,22]. *Example:* PNIPAAm-based nanogels delivering paclitaxel.

Redox-Sensitive Nanogels: Utilize disulfide linkages that cleave under the reductive environment of the cytosol (high glutathione levels), enabling intracellular drug release. *Example:* Redox-responsive nanogels for siRNA delivery[6,14,22].

Enzyme-Sensitive Nanogels: Designed to degrade in the presence of disease-specific enzymes, such as matrix metalloproteinases overexpressed in cancer and arthritis. *Example:* Collagenase-degradable nanogels for localized drug release[6,14,22].

Multi-Stimuli Responsive Nanogels: Combine two or more stimuli (e.g., pH/temperature, redox/enzyme) to provide greater specificity and controlled release[6,14,22].

4.3 Based on Polymer Type

Natural Polymer-Based Nanogels: Utilize polymers such as chitosan, dextran, alginate, gelatin, and hyaluronic acid. These offer high biocompatibility and biodegradability but may exhibit batch variability.

Synthetic Polymer-Based Nanogels: Include PEG, PNIPAAm, polyvinyl alcohol (PVA), and polycaprolactone (PCL). These provide precise control over molecular weight, crosslinking, and functionalization, ensuring reproducibility.

Hybrid Nanogels: Combine natural and synthetic polymers or integrate nanomaterials (e.g., gold nanoparticles, magnetic nanoparticles) within nanogels. These systems are particularly promising for theranostic applications.

5. Drug Loading and Release Mechanisms

The therapeutic success of nanogels largely depends on their ability to efficiently load drugs and release them in a controlled manner at the desired site[14-20,30].

5.1 Drug Loading Strategies

Physical Entrapment: Drugs are physically incorporated into the nanogel network during swelling or polymerization. Suitable for hydrophilic drugs but may suffer from burst release.

Electrostatic Interactions: Ionic drugs interact with oppositely charged functional groups within the nanogel matrix. Commonly used for nucleic acids, peptides, and proteins. *Example:* siRNA loading into cationic chitosan nanogels[5-9].

Hydrophobic Interactions: Amphiphilic nanogels can encapsulate hydrophobic drugs within their hydrophobic domains, improving solubility and stability.

Covalent Conjugation: Drugs are chemically bound to the nanogel via cleavable linkers (e.g., ester, disulfide). This approach ensures high drug stability and controlled release triggered by enzymatic or redox conditions.

5.2 Drug Release Mechanisms

Diffusion-Controlled Release: Encapsulated drug molecules diffuse out of the swollen nanogel

matrix gradually, depending on polymer porosity and crosslinking density.

Degradation-Induced Release: Biodegradable polymers break down under physiological conditions or enzymatic action, leading to sustained release.

Stimuli-Triggered Release:

- pH-sensitive: drug release accelerated in acidic or alkaline environments.
- Temperature-sensitive: polymer collapse or swelling induces drug release.
- Redox-sensitive: cleavage of disulfide bonds in the reductive cytosol.
- Enzyme-sensitive: degradation of polymeric backbone by specific enzymes.

Burst Release vs. Sustained Release: Nanogels may exhibit an initial burst release due to loosely bound drugs at the surface, followed by a sustained release phase controlled by diffusion or degradation. Optimizing crosslinking density and surface chemistry can reduce burst effects[7-10.]

6. Applications of Nanogels in Drug Delivery

Nanogels have gained prominence as versatile carriers due to their tunable physicochemical properties, ability to encapsulate diverse therapeutic agents, and responsiveness to physiological stimuli. Their application spans across multiple therapeutic domains, including oncology, endocrinology, neurology, ophthalmology, dermatology, and vaccine delivery[2,8,9,10,15].

6.1 Nanogels in Cancer Therapy

Cancer remains one of the leading causes of mortality worldwide, and conventional chemotherapeutic regimens are often associated with systemic toxicity, multidrug resistance (MDR), and poor tumor selectivity. Nanogels address these challenges through enhanced permeability and retention (EPR) effect, active targeting, and stimuli-triggered drug release[15.]

Targeted Drug Delivery: Nanogels can be surface-modified with ligands such as folic acid, transferrin, or antibodies to specifically target overexpressed receptors on tumor cells. This enhances cellular uptake and reduces off-target toxicity[15.]

Overcoming MDR: Nanogels facilitate co-delivery of chemotherapeutic drugs and MDR modulators (e.g., siRNA or efflux pump inhibitors) to sensitize resistant cancer cells[15].

Stimuli-Responsive Release: Tumor-specific conditions such as acidic pH, elevated glutathione levels, and enzyme overexpression are exploited by nanogels to achieve localized drug release[8].

Examples:

- Doxorubicin-loaded pH-sensitive polyacrylic acid nanogels for breast cancer therapy.
- Paclitaxel-loaded PNIPAAm nanogels responsive to mild hyperthermia for solid tumors.
- Redox-sensitive nanogels co-delivering cisplatin and siRNA to enhance apoptosis in resistant ovarian cancer cells.

6.2 Protein and Peptide Delivery

Proteins and peptides are highly effective therapeutic agents but are limited by short half-life, enzymatic degradation, and poor membrane permeability. Nanogels provide a hydrated and

protective environment, preserving their bioactivity and enabling controlled release[27].

Insulin Delivery: Chitosan-based pH-responsive nanogels have been developed for oral insulin administration, protecting insulin in the stomach and releasing it in the intestine.

Growth Factors: Nanogels loaded with epidermal growth factor (EGF) or vascular endothelial growth factor (VEGF) have shown promise in wound healing and tissue regeneration.

Vaccines: Protein antigens encapsulated in nanogels enhance immune response by providing sustained antigen release and better uptake by antigen-presenting cells.

6.3 Gene and Nucleic Acid Delivery

Nanogels are particularly suited for gene delivery due to their ability to condense nucleic acids, protect them from nuclease degradation, and enhance cellular internalization[16].

siRNA and miRNA Delivery: Cationic nanogels form electrostatic complexes with negatively charged siRNA/miRNA, facilitating endosomal escape and gene silencing[21].

DNA and Plasmid Delivery: Nanogels improve transfection efficiency with lower cytotoxicity compared to viral vectors and cationic lipids.

Gene Editing: Nanogels have recently been explored as carriers for CRISPR-Cas9 systems, offering precise genome editing capabilities.

Examples:

- Polyethylenimine (PEI)-modified nanogels for siRNA-mediated knockdown of oncogenes.
- Hyaluronic acid nanogels delivering plasmid DNA for regenerative medicine.

6.4 Ocular Drug Delivery

Ocular diseases such as glaucoma, uveitis, and age-related macular degeneration require sustained and targeted delivery to overcome rapid clearance from tear fluid and barriers such as corneal epithelium[21-23]. Nanogels provide mucoadhesion, prolonging residence time in the ocular cavity. They enable sustained release, reducing the need for frequent administration.

Examples:

- Timolol maleate-loaded chitosan nanogels for glaucoma treatment.
- Dexamethasone-loaded nanogels for intraocular inflammation.

6.5 Transdermal and Topical Applications

Nanogels enhance drug penetration across the stratum corneum and provide controlled drug release for dermatological and systemic therapy[10].

Anti-inflammatory Therapy: Diclofenac-loaded nanogels for topical pain relief with sustained action.

Dermatological Disorders: Nanogels loaded with corticosteroids or antifungal agents for eczema, psoriasis, and fungal infections.

Cosmeceuticals: Vitamin E and retinoid-loaded nanogels for anti-aging and skin hydration.

6.6 Brain Drug Delivery

Crossing the blood–brain barrier (BBB) remains one of the greatest challenges in CNS drug delivery. Nanogels offer advantages due to their small size, surface modifiability, and stimuli-responsive behavior[18,29].

Strategies:

- Surface conjugation with ligands such as transferrin or lactoferrin to exploit receptor-mediated transcytosis.
- Redox-sensitive nanogels releasing drugs in the reductive intracellular environment of neuronal cells.

Applications:

- Curcumin-loaded nanogels for Alzheimer's disease.
- Dopamine-loaded nanogels for Parkinson's therapy.
- Temozolomide nanogels for glioblastoma treatment.

6.7 Other Emerging Applications

Diabetes Management: Oral insulin nanogels improving bioavailability and glycemic control.

Infectious Diseases: Antimicrobial peptide-loaded nanogels for combating drug-resistant bacterial infections.

Immunotherapy and Vaccines: Nanogels as adjuvants for cancer immunotherapy and viral vaccines (including potential applications in COVID-19).

Theranostics: Hybrid nanogels integrated with imaging agents (MRI contrast, fluorescence probes) enabling simultaneous diagnosis and therapy[4,7,11].

7. Toxicity and Safety Concerns

For successful clinical translation, it is essential that nanogels exhibit minimal toxicity, high biocompatibility, and favorable pharmacokinetic behavior. While nanogels are generally considered safer than many other nanocarriers, certain issues need to be carefully evaluated[3,21.23.14].

7.1 Biocompatibility and Immunogenicity

Polymer Source: Naturally derived polymers such as chitosan, dextran, and hyaluronic acid are inherently biocompatible and degrade into non-toxic byproducts. Synthetic polymers, however, may require extensive biocompatibility testing to rule out cytotoxicity.

Immunogenicity: Surface charge and functionalization influence immune recognition. Positively charged nanogels may interact with serum proteins, leading to complement activation or unwanted immune responses. PEGylation or coating with hydrophilic polymers reduces immunogenicity.

7.2 Hemocompatibility

Nanogels must demonstrate compatibility with blood components to avoid hemolysis, platelet aggregation, or clot formation. Ionic nanogels, especially cationic ones, require careful optimization to minimize red blood cell disruption.

7.3 Degradation and Clearance

Biodegradability: Ideally, nanogels should degrade into non-toxic, excretable byproducts through hydrolysis or enzymatic action.

Clearance: Particle size and surface chemistry determine renal or hepatic clearance. Nanogels >200 nm may accumulate in the reticuloendothelial system (RES), potentially leading to organ toxicity.

7.4 Long-Term Toxicity

Chronic administration studies are limited. Long-term accumulation, interactions with the immune

system, and effects on normal cellular processes remain concerns. Hence, extensive *in vivo* toxicity, biodistribution, and pharmacokinetic studies are crucial prior to clinical application[25].

7.5 Regulatory Challenges

Despite encouraging preclinical data, very few nanogel formulations have entered clinical trials. Standardized protocols for safety assessment, regulatory guidelines, and manufacturing consistency are still evolving, which delays clinical adoption.

8. Recent Advances in Smart Nanogels

Nanogels are undergoing rapid innovation with the integration of advanced materials science, biotechnology, and computational tools[6,14,22]. Some key advances include:

8.1 Nanogels in Immunotherapy and Vaccines

Nanogels are being designed as **vaccine adjuvants** to enhance antigen presentation and immune activation. Protein and peptide antigens encapsulated in nanogels show prolonged immune stimulation[16].

Example: Nanogel-based adjuvants developed for cancer immunotherapy and experimental viral vaccines.

8.2 Theranostic Nanogels

Theranostic nanogels combine therapeutic and diagnostic functions in a single platform. They can carry anticancer drugs along with imaging agents such as fluorescent dyes, MRI contrast agents, or radionuclides. This enables simultaneous tumor localization, therapy monitoring, and therapeutic intervention[4,7,11].

8.3 Hybrid and Multifunctional Nanogels

Integration of inorganic nanomaterials (gold nanoparticles, quantum dots, iron oxide) with nanogels has created hybrid systems. These allow for **photothermal therapy, magnetic targeting, and multimodal imaging** in addition to drug delivery[4,7,11,26].

Example: Gold nanogel composites for combined chemotherapy and photothermal ablation of tumors.

8.4 Bioinspired and Biomimetic Nanogels

Inspired by biological systems, bioinspired nanogels mimic natural cellular structures and interactions. Coating nanogels with cell membranes (erythrocytes, leukocytes, platelets) enhances immune evasion and targeting[13,27.28]. These biomimetic systems are advancing toward personalized nanomedicine.

8.5 AI-Driven Nanogel Design

Artificial intelligence and computational modeling are increasingly used to predict polymer behavior, optimize crosslinking density, and simulate drug release kinetics. This accelerates the design of personalized nanogel systems for patient-specific therapy[17].

9. CONCLUSION

Nanogels have established themselves as one of the most versatile and intelligent drug delivery systems in modern pharmaceutical research. Their unique combination of nanoscale size, high water content, tunable crosslinking, and stimuli-responsive properties enables them to encapsulate and protect a wide range of therapeutic agents while ensuring controlled and site-specific release. Applications in cancer therapy, protein and peptide delivery, gene therapy, ocular formulations, transdermal systems, and brain-targeted drug delivery clearly highlight their

translational potential. Recent advances such as hybrid nanogels, bioinspired coatings, theranostic systems, and AI-driven design strategies further expand the functional scope of nanogels beyond conventional drug carriers, moving toward personalized and precision medicine. However, despite promising preclinical data, clinical translation is still hindered by challenges related to large-scale manufacturing, long-term safety, and lack of standardized regulatory guidelines. Overall, nanogels represent a rapidly evolving frontier in nanomedicine. Continued interdisciplinary research combining polymer chemistry, biotechnology, nanotechnology, and computational approaches will be crucial to unlock their full clinical potential. With focused efforts in addressing safety, scalability, and regulatory hurdles, nanogels are poised to become next-generation smart platforms for effective and patient-centered drug delivery.

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