Review

Nanogels as next-generation drug delivery systems: Design, advances, and biomedical applications

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Abstract

Background: Nanogels are next-generation smart and stimuli-responsive nanocarriers for drug delivery, characterized by high water capacity, excellent biocompatibility, tunable size, and environmental responsiveness. Their nanoscale cross-linked polymer networks enable the delivery and encapsulation of diverse therapeutic agents, such as small molecules, proteins, nucleic acids, and imaging agents. Emerging strategies have facilitated the synthesis of stimuli-responsive nanogels (e.g., redox-, pH-, temperature-, enzyme-responsive), multifunctional hybrid systems, and targeted drug delivery platforms tailored to disease-specific microenvironments. These nanogels have demonstrated promising applications in oncology, infectious diseases, ocular therapy, central nervous system targeting, gene therapy, and vaccine delivery. The integration of machine learning and artificial intelligence has further enabled predictive optimization and formulation. In addition, new approach methodologies, such as organ-on-a-chip and *in silico* models, provide human-relevant, ethical, and cost-effective approaches for evaluating safety, pharmacokinetics, and therapeutic efficacy. Although challenges related to scale-up, reproducibility, and regulatory approval remain, a number of nanogel-based products are advancing toward clinical application. **Objective:** This review explores the composition, functionalization, biomedical applications, and future prospects of nanogels, emphasizing their potential to enable precision medicine and drug discovery. **Conclusion:** Nanogels are promising platforms for precision and personalized medicine, offering routes for controlled, targeted, and intelligent drug delivery that can revolutionize future therapeutic strategies.

Keywords: Nanogels, Drug delivery systems, Stimuli-responsive polymers, New approach methodologies, Precision medicine

1. Introduction

Nanotechnology has opened up new avenues in drug delivery by enabling the development of platforms that overcome the drawbacks of conventional therapeutics, such as poor solubility, rapid systemic clearance, decreased bioavailability, and lack of target specificity.[1] Among the various nanocarriers investigated to date, nanogels have emerged as versatile drug delivery systems due to their nanoscale dimensions, soft hydrogel matrix, high water content, and tunable physicochemical properties.[2,3]

Nanogels are three-dimensional hydrophilic polymer networks formed through physical or chemical cross-linking. These structures can swell in aqueous environments while maintaining structural strength.[4] Their particle size typically ranges 20–200 nm, although this can be adjusted depending on the intended applications. Important features such as high surface area-to-volume ratio, colloidal stability, and multivalency enhance their therapeutic performance.[5] Unlike rigid nanoparticles, nanogels are less susceptible to rapid clearance by the mononuclear phagocyte system, although this function is highly dependent on surface modifications such as PEGylation or targeting ligand conjugation.[6]

1.1. Stimuli-responsive behavior

One of the most thrilling benefits of nanogels is their ability to respond to physiological or pathological stimuli. These smart systems are capable of undergoing controlled physicochemical

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alterations—swelling, shrinking, or degradation—in response to physiological stimuli such as pH, temperature, enzyme concentration, or redox potential.[7,8] The property allows site-selective and on-demand drug release, reducing systemic toxicity while maximizing therapeutic efficacy. For example, pH-sensitive nanogels remain stable in blood (pH ~7.4) but degrade or release their payload in the acidic microenvironment of tumors or endosomal compartments (pH 5.0–6.5).[9]

Nanogels can deliver a broad range of bioactive molecules, including small-molecule therapeutics, peptides, proteins, nucleic acids (DNA, small-interfering RNA [siRNA], messenger RNA), and vaccines.[10] Therapeutic agents can be either physically encapsulated or covalently conjugated within the nanogel matrix, enabling the delivery of hydrophilic, hydrophobic, and amphiphilic molecules, thereby boosting both therapeutic and diagnostic (theranostic) potential.[11] The overall development of nanogel-based drug delivery systems is schematically illustrated in Figure 1.

1.2. Polymers, functionalization, and applications

Recent advances in polymer chemistry, nanofabrication techniques, and biomedical engineering have driven the rapid development of nanogel technologies. Both natural polymers (e.g., chitosan, hyaluronic acid, dextran) and synthetic polymers (e.g., poly(ethylene glycol) [PEG], poly(N-isopropylacrylamide) [PNIPAM], poly(acrylic acid) [PAA]) have been exploited to engineer nanogels with tailored mechanical strength, degradation kinetics, biocompatibility, and targeting capability.[12]

Functionalization with targeted moieties, such as antibodies, peptides, aptamers, or folic acid, has significantly enhanced the selectivity of nanogels for drug delivery, especially in inflammatory diseases and cancer.[13] Due to their versatility, nanogels have been exploited in a wide range of therapeutic applications, including oncology, antimicrobial therapy, ophthalmology, transdermal drug delivery, neurodegenerative disease, gene therapy, and immunotherapy.[14,15] Furthermore, advancements in large-scale production, enhanced stability, and rigorous safety evaluations are facilitating the clinical translation of nanogel technologies.[16]

This review provides a comprehensive and up-to-date overview of nanogel-based drug delivery systems, with emphasis on their structural conformations, synthesis strategies, stimuli-sensitivity, drug loading and release characteristics, functionalization and fabrication techniques, therapeutic applications, safety and regulatory considerations, and their emerging role in precision medicine and theranostics.

2. Nanogel structure and composition

Nanogels are a specialized class of hydrogel-based nanocarriers composed of nanoscale cross-linked polymer networks. These structures can absorb considerable amounts of aqueous or biological fluids without dissolving. Their architecture is designed to achieve an optimal balance between structural stability and molecular flexibility, both of which are critical for stimuli responsiveness and sustained drug release.[17] The physical architecture and chemical composition of nanogels dictate their drug loading behavior, stimuli sensitivity, *in vivo* performance, and overall physicochemical properties. In general, nanogels are formed from one or more polymers that are cross-linked physically or chemically into a stable yet dynamic nanostructure. Their porous and hydrophilic matrix allows the encapsulation of a wide range of therapeutic agents, including antibiotics, nucleic acids, peptides, proteins, and anticancer drugs.[18] The core architecture of nanogels is shown in Figure 2.

2.1. Core architecture and morphology

The majority of nanogels are spherical or near-spherical particles with diameters ranging 20–200 nm, although their size can be tailored depending on the therapeutic application. Nanogels can be classified into the following structural types:

- Homogeneous networks: Uniform cross-linking throughout the gel matrix.
- Core–shell structures: Feature a distinct core and shell region, commonly used for surface functionalization or targeted delivery.

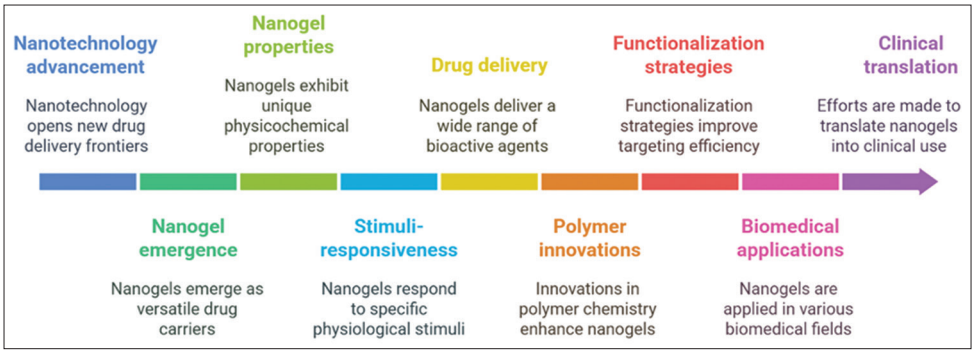

Figure 1. Nanogel drug delivery system development. Figure created by the authors.

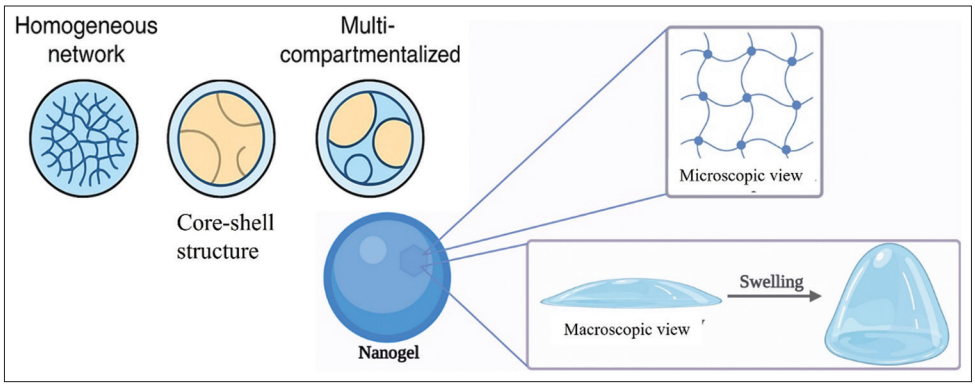

Figure 2. Core architecture of a nanogel. Figure created by the authors.

- Multi-compartmentalized nanogels: Designed for co-delivery or sequential release of multiple therapeutic agents.[19]

Internal pore size, degree of cross-linking, and polymer flexibility significantly affect drug loading and release profile. Highly cross-linked networks provide mechanical strength but may reduce drug entrapment efficiency. In contrast, lightly cross-linked nanogels enable higher drug loading but may exhibit accelerated drug release.[20]

2.2. Cross-linking strategies

Cross-linking is essential for forming a stable three-dimensional nanogel network and for tuning its responsiveness, degradation behavior, and drug retention capabilities. Nanogels are cross-linked using either physical (non-covalent) or chemical (covalent) techniques.

2.2.1. Physical crosslinking

Physically cross-linked nanogels are stabilized by reversible, non-covalent interactions, including:

- Hydrogen bonding: Formed between polar groups (–OH, –COOH, –NH_2) in aqueous solutions.
- Hydrophobic interactions: Drive the self-assembly of amphiphilic block copolymers into nanospheres.
- Electrostatic interactions: Facilitate the formation of polyelectrolyte complexes (e.g., chitosan–alginate systems).
- Van der Waals forces: Provide secondary stabilization.

These nanogels are typically prepared under mild conditions, making them suitable for encapsulating sensitive biomacromolecule drugs (e.g., siRNA, proteins). However, they may exhibit limited long-term stability *in vivo* and often require surface modification to improve circulation time and targeting.[21,22]

2.2.2. Chemical crosslinking

Chemically cross-linked nanogels form covalent bonds that provide enhanced structural stability, mechanical strength, and resistance to physiological conditions. Common chemical crosslinking methods include:

- Free-radical polymerization: Initiated thermally, by ultraviolet radiation, or via redox reactions (e.g., using acrylamide monomers).
- Disulfide bond formation: Facilitates redox-sensitive degradation in reductive intracellular environments.
- Click chemistry: Copper(I)-catalyzed azide–alkyne cycloaddition enables site-specific linkage formation.
- Enzymatic crosslinking: Utilizes enzymes such as transglutaminase or horseradish peroxidase for biospecific bond formation.[23]

Stimuli-labile bonds (e.g., Schiff bases, esters, hydrazones) enable controlled release in response to pH, enzyme activity, reactive oxygen species, or temperature.[24]

2.3. Nanogel polymer composition

The choice of polymer plays a critical role in determining the toxicity, biodegradability, stability, and drug compatibility of nanogels. Polymers used in nanogel fabrication can be classified as natural, synthetic, or hybrid.

2.3.1. Natural polymers

Natural polymers offer excellent biocompatibility and biodegradability. Common examples include:

- Chitosan: A cationic, pH-sensitive polymer with mucoadhesive, antimicrobial properties; suitable for nasal, oral, and ocular delivery.[25]
- Alginate: An anionic polymer that undergoes ionic crosslinking with Ca^{2+} to form reversible hydrogels; applications include wound healing and colon-targeted delivery.
- Gelatin: A temperature-responsive collagen derivative containing RGD motifs, facilitating cell adhesion.[26]
- Hyaluronic acid: An anionic polysaccharide that binds to CD44 receptors, making it effective for targeting cancer and inflammatory conditions.[27]

- Dextran: A neutral polysaccharide degraded by dextranase, suitable for passive and enzyme-responsive delivery systems.

Other biopolymers, such as starch, are valued for their biocompatibility, enzymatic degradability, and suitability for chronic infection or cancer therapy.

2.3.2. Synthetic polymers

Synthetic polymers can be chemically designed to achieve specific molecular weights, hydrophilicity, surface functionality, and degradation rates. Examples include:

- PEG: Enhances hydrophilicity, prolongs circulation time (via the stealth effect), and reduces immune recognition.[28]
- PNIPAM: Exhibits a lower critical solution temperature (LCST) near 32°C, which can be tuned through copolymerization to achieve thermally responsive behavior.[29]
- PAA: A pH-responsive polymer that swells in alkaline environments, making it suitable for colon-targeted delivery.[30]
- Poly(vinyl alcohol): Forms stable hydrogen-bonded networks with natural polymers and exhibits high biocompatibility.
- Poly(lactic-co-glycolic acid): The United States Food and Drug Administration (FDA)-approved, biodegradable copolymer widely used in hybrid nanogel systems.

Synthetic polymers enable fine-tuning of pharmacokinetic and physicochemical properties, facilitating optimization for clinical applications.

2.4. Hybrid and composite nanogels

Hybrid nanogels combine organic–inorganic materials or natural–synthetic polymer blends to enhance multifunctionality. Representative examples include:

- Magnetic nanogels: Incorporate Fe_3O_4 or other magnetically responsive nanoparticles for targeted drug delivery or magnetic resonance imaging tracking.
- Silica-based nanogels: Exhibit high mechanical stability, tunable porosity, and controlled degradability.
- Gold- or quantum dot-loaded nanogels: Enable photothermal therapy and optical imaging.
- Lipid–polymer hybrid nanogels: Offer high drug-loading efficiency, improved membrane fusion, and theranostic potential.[31]

These hybrid systems support real-time tracking, targeted delivery, and stimulus-responsive drug release, representing current trends in next-generation antimicrobial and multifunctional nanocarrier development. The most commonly used polymers in nanogel fabrication are listed in Table 1.

3. Synthesis methods

Nanogel synthesis involves the strategic selection of polymer precursors, cross-linking techniques, and reaction environments to produce nanoscale hydrogel structures that are biocompatible, stimuli-responsive, and capable of encapsulating drugs. Figure 3 presents an overview of commonly used synthesis methods. The key fabrication strategies employed in nanogel fabrication, along with their advantages and limitations, are described below, while Table 2 summarizes these methods for comparative reference.

3.1. Inverse emulsion polymerization

Inverse emulsion polymerization (water-in-oil) is a widely used method for synthesizing nanogels with controlled particle size and structure. In this method, an aqueous solution containing the monomer and cross-linker is dispersed into an organic continuous phase containing appropriate surfactants. The resulting nanoscale droplets function as microreactors in which polymerization is initiated using thermal or redox initiators (e.g., ammonium persulfate or azobisisobutyronitrile)[32] leading to the formation of homogeneously cross-linked nanogels.

(i) Advantages:

- Provides precise control over particle size distribution (typically 50–200 nm).
- Facilitates encapsulation of water-soluble drugs in the internal aqueous core.
- Allows surface functionalization for stimuli-responsive drug release (e.g., PNIPAM-based thermosensitive nanogels.[33,34]

(ii) Limitations:

- Requires rigorous purification to remove residual surfactants and solvents.
- Not ideal for labile biomolecules unless carefully formulated to prevent degradation.

3.2. Precipitation polymerization

Precipitation polymerization is a simple, surfactant-free, and scalable technique for nanogel synthesis. Water-soluble monomers (such as acrylic acid or methacrylates) and cross-linkers are dissolved in an aqueous solution. During polymerization, the growing polymer chains precipitate spontaneously, forming stable nanogels *in situ*.[35]

(i) Advantages:

- Eliminates the need for surfactants or emulsifying agents, simplifying purification and reducing cytotoxicity.
- Produces monodisperse nanogels with controlled porosity and swelling behavior, ideal for sustained drug release.[36]
- Suitable for large-scale manufacturing.

Table 1. Common polymers used in nanogel formulation[17-31]

Polymer	Source	Properties	Applications
Chitosan	Natural	Biodegradable, mucoadhesive, cationic, pH-sensitive	Oral/ocular delivery, gene/drug delivery
Dextran	Natural	Biocompatible, water-soluble, enzyme-degradable	Anticancer, vaccine delivery
Hyaluronic acid	Natural	Targets CD44 receptors, biodegradable, hydrophilic	Cancer targeting, tissue regeneration
Alginate	Natural	Ionically cross-linkable, pH-sensitive, biocompatible	Wound healing, oral drug delivery
Gelatin	Natural	Thermo-sensitive, biodegradable, cell-adhesive [Arginine–Glycine–Aspartic acid (RGD) motifs]	Tissue engineering, protein delivery
Poly (ethylene glycol)	Synthetic	Hydrophilic, stealth behavior, low immunogenicity	Surface modification, long-circulating nanogels
Poly (N-isopropylacrylamide)	Synthetic	Thermo-responsive (lower critical solution temperature of~32°C), reversible swelling	Thermo-triggered drug release
Poly (acrylic acid)	Synthetic	pH-sensitive, high swelling in alkaline pH	Colon-specific and pH-responsive systems
Poly (vinyl alcohol)	Synthetic	Chemically stable, hydrophilic, forms stable networks	Ophthalmic, topical applications
Poly (lactic-co-glycolic acid) (with hydrogels)	Synthetic	Biodegradable, controlled-release, United States Food and Drug Administration-approved	Hybrid nanogels for sustained drug delivery
Poly (ethylene glycol)–polycaprolactone block copolymers	Synthetic	Amphiphilic, biodegradable, self-assembling	Dual-drug or theranostic systems

Table 2. Summary of nanogel synthesis methods[32-42]

Method	Feature	Cross-linking type	Advantages	Limitations	Applications
Inverse emulsion polymerization	Nanodroplet reactors in the oil phase	Chemical	Size control, good encapsulation	Surfactant/solvent residue	Thermo-/pH-sensitive nanogels
Precipitation polymerization	Surfactant-free colloid formation	Chemical	Simple, scalable, no emulsifier	Post-loading needed	Poly (ethylene glycol)/ poly (acrylic acid)-based systems
Self-assembly techniques	Spontaneous polymer assembly	Physical (sometimes chemical)	Biocompatible, mild conditions	Mechanical instability	Protein/gene carriers, topical formulations
Click chemistry & advanced covalent strategies	Highly selective bond formation	Chemical (bio-orthogonal)	Functionalizable, efficient	Requires pre-functionalization	Theranostics, site-specific antimicrobials
Green synthesis	Eco-friendly aqueous reactions	Natural or enzymatic	Biodegradable, sustainable	Lower robustness	Antimicrobial gels, wound healing

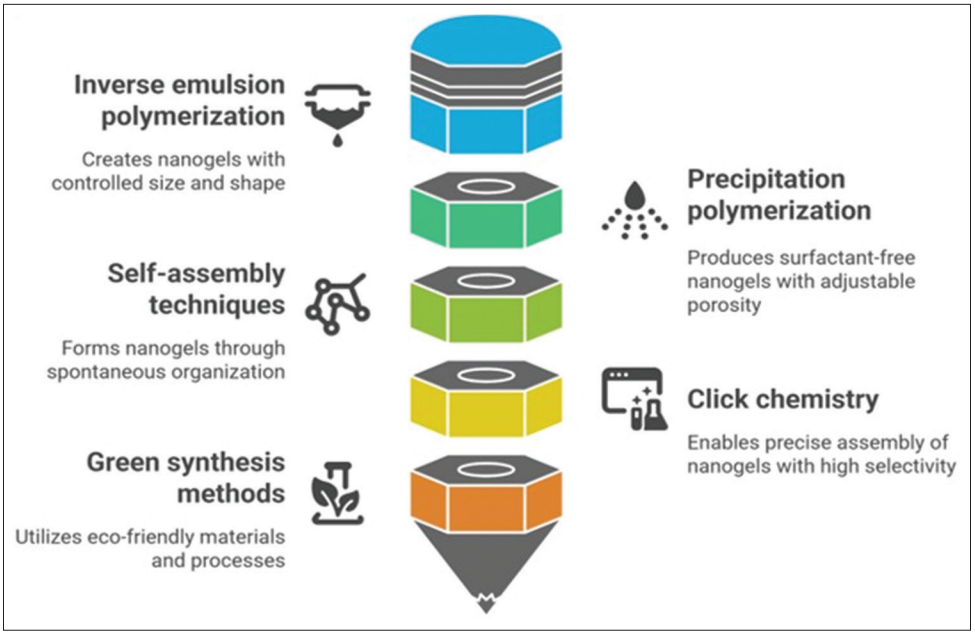

Figure 3. Overview of nanogel synthesis methods. Figure created by the authors.

(ii) Limitations
- Limited to hydrophilic monomers and solvents.
- Drug encapsulation efficiency may be lower compared to methods that enable simultaneous drug encapsulation.

3.3. Self-assembly techniques

Self-assembly relies on the spontaneous organization of amphiphilic block copolymers or biopolymers in aqueous media into nanogel structures through non-covalent interactions. Common examples include PEG-b-polylactide and chitosan derivatives forming micellar, vesicular, or network nanostructures stabilized by ionic interactions, hydrogen bonding, or secondary cross-linking.[37] Environmental stimuli such as pH, temperature, or ionic strength can further trigger gelation and stabilize nanostructures.

(i) Advantages:
- Conducted under mild conditions suitable for labile biomolecules (e.g., proteins, enzymes, siRNA).
- Avoids toxic initiators or solvents.[38]

(ii) Limitations:
- May exhibit insufficient mechanical strength unless post-cross-linked.
- Long-term stability may be limited without additional covalent stabilization.

3.4. Click chemistry and advanced covalent strategies

Click chemistry encompasses highly selective, efficient reactions that form covalent bonds with minimal by-products. Common reactions include azide–alkyne cycloaddition [Copper(I)-catalyzed Azide–Alkyne Cycloaddition (CuAAC), Strain-Promoted Azide–Alkyne Cycloaddition (SPAAC)], thiol–ene/yne reactions, Diels–Alder, and Michael additions.[39] These strategies enable modular and precise assembly of nanogels with defined monodisperse structure and functionalities.

(i) Advantages:
- High chemoselectivity and bio-orthogonality.
- Enable facile surface modification, ligand attachment, and integration of stimuli-responsive features.

(ii) Limitations:
- Certain reactions (e.g., CuAAC) require metal catalysts that must be completely eliminated before biomedical use.
- Pre-functionalization of polymer precursors can increase complexity.

3.5. Green synthesis methods

Green synthesis employs environmentally friendly reagents, natural cross-linkers, enzymes, and aqueous reactions that avoid toxic organic solvents. Common natural cross-linkers include citric acid, genipin, and oxidized dextran, whereas enzymes such as horseradish peroxidase and transglutaminase catalyze reactions under mild conditions. Biopolymers derived from plants, such as cellulose, gum arabic, and starch, are widely employed.[40,41]

(i) Advantages:
- Reduced environmental toxicity and high biocompatibility.
- Preserves the biological activity of labile therapeutic molecules.
- Suitable for clinical translation due to safety profile.[42]

(ii) Limitations:
- Limited scalability.
- Lower cross-linking density and mechanical strength limit long-term or load-bearing applications.

4. Stimuli-responsive nanogels

Stimuli-responsive nanogels are a sophisticated class of smart nanocarriers capable of altering their structural conformation or physicochemical properties in response to specific environmental stimuli. This adaptive behavior facilitates on-site, on-demand, and regulated drug delivery, enhancing therapeutic effectiveness while reducing systemic toxicity.[43] These nanogels can be designed to respond to internal physiological stimuli (e.g., pH, redox potential, enzyme concentration) or external stimuli (e.g., temperature, light, magnetic fields). Their unique capabilities make them particularly relevant in the treatment of infectious, inflammatory, and neoplastic diseases. The major categories of stimuli-responsive nanogels, along with their mechanisms and applications, are described and illustrated in Figure 4. The intelligent design of these nanogels enables precision and adaptive therapy and paves the way for advanced drug-loading strategies discussed in subsequent subsections. Table 3 summarizes the different types and their applications.

4.1. pH-responsive nanogels

pH-responsive nanogels exploit physiological pH variations across different biological compartments. For example, the bloodstream maintains a natural to slightly alkaline pH (~7.4), whereas tumor microenvironments and endosomal or lysosomal compartments exhibit acidic pH values (4.5–6.5). These nanogels are generally synthesized using weakly acidic or basic polymers such as polyacrylic acid, chitosan, or Eudragit. Drug release is triggered by protonation/deprotonation or pH-induced hydrolysis of acid-labile linkages (e.g., imine or hydrazone bonds).[44]

Applications:
- Colon-specific drug delivery (pH ~7).
- Targeted anticancer or antimicrobial delivery in acidic microenvironments.

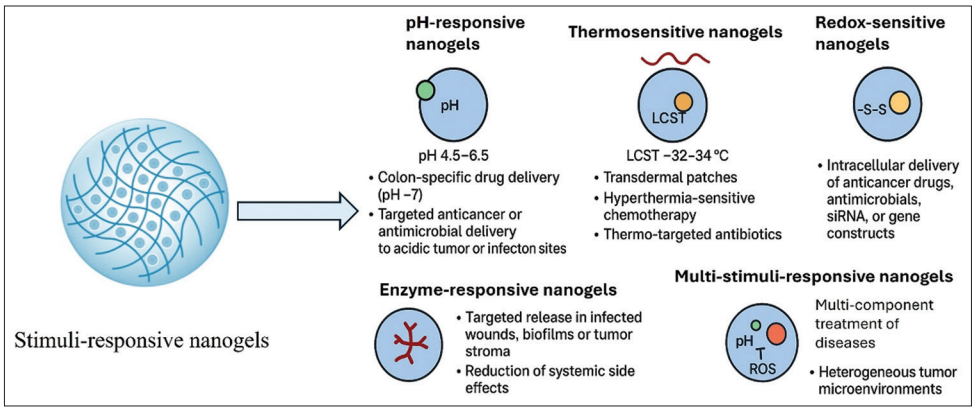

Figure 4. Types of stimuli-responsive nanogels. Figure created by the authors.
Abbreviations: LCST: Lower critical solution temperature; ROS: Reactive oxygen species.

Table 3. Summary of stimuli-responsive nanogels[43-48]

Stimulus	Mechanism	Polymer example	Application
pH	Ionization or bond cleavage under acidic/basic pH	Poly (acrylic acid), chitosan, hydrazone, Schiff base	Colon cancer, inflammation, infected tissues
Temperature	Coil–globule transition at lower critical solution temperature	Poly (N-isopropylacrylamide), Pluronic	Transdermal, hyperthermia-targeted therapy
Redox	Cleavage of disulfide or reactive oxygen species-labile bonds	Disulfide, thioketal, arylboronate	Intracellular delivery, cancer, infection
Enzyme	Enzymatic cleavage of peptide/ polysaccharide linkages	matrix metalloproteinase-sensitive peptides, dextran	Tumors, wounds, bacterial enzyme-targeted
Multi-stimuli	Sequential or synergistic response to two/more stimuli	Mixed linkers (pH/redox/reactive oxygen species/enzyme)	Precision drug delivery, resistant infections

pH-sensitive nanogels offer site-specific control, but other physiologic stimuli, including temperature, offer further opportunities for intelligent drug delivery.

4.2. Thermosensitive nanogels

Thermosensitive nanogels undergo reversible phase transitions at their LCST. Below the LCST, the nanogel network remains hydrated and swollen; above the LCST, it collapses and releases the encapsulated drug. PNIPAM is a commonly used thermoresponsive polymer with an LCST near physiological temperature (32–34°C). In pathological conditions such as fever, inflammation, or local hyperthermia, PNIPAM-based nanogels can undergo a coil-to-globule transition, enabling targeted, heat-activated drug release.[45]
Applications:

- Transdermal patches.
- Hyperthermia-sensitive chemotherapy.
- Thermo-targeted antibiotics.

While external control arises from thermal stimuli, intracellular redox milieus facilitate controlled cytoplasmic release of therapeutic agents.

4.3. Redox-sensitive nanogels

Redox-sensitive nanogels are sensitive to intracellular glutathione concentrations, which are substantially higher in tumor cells (~10 mM) compared to the extracellular environment (~2–20 μM). These nanogels often incorporate disulfide (-S–S-) bonds within the polymer network. Under reductive intracellular conditions, these bonds are cleaved, leading to rapid nanogel degradation and controlled drug release of the therapeutic payload.[46]
Applications:

- Intracellular delivery of anticancer drugs, antimicrobials, siRNA, or gene constructs.

In addition to redox sensitivity, enzymatic triggers provide disease-targeted degradation to facilitate highly localized release.

4.4. Enzyme-responsive nanogels

Enzyme-sensitive nanogels are formulated to degrade in a specific manner upon exposure to disease-related enzymes. Examples include matrix metalloproteinases in cancer, lysozyme in bacterial infections, trypsin in the gastrointestinal tract, and β-galactosidase in the colon. Nanogels may be formulated using cleavable peptide linkers or polysaccharide backbones that degrade on exposure to enzymes to release the drug of interest.[47]
Applications:

- Targeted release in infected wounds, biofilms, or tumor stroma.
- Reduction of systemic side effects.

To further enhance specificity, nanogels can be engineered to respond to multiple stimuli simultaneously.

4.5. Multi-stimuli-responsive nanogels

Multi-stimuli-responsive nanogels are responsive to two or more stimuli (e.g., pH, temperature, redox, reactive oxygen species, or enzyme activity) to achieve enhanced targeting and drug release regulation. Examples include:

- Redox + pH double-sensitive systems: Swell in acidic environments and biodegrade within the cell.
- Enzyme + temperature-sensitive systems: Release triggered by fever and bacterial enzymes.
- pH + reactive oxygen species-sensitive systems: Designed for oxidative stress-enriched microenvironments.[48]

Orthogonal cleavable linkers can be employed for the synthesis of multi-stimuli-responsive nanogels that are responsive to specific physiological stimuli. A few examples include disulfide linkers (reduction-sensitive), hydrazone linkers (pH-sensitive), and enzyme-cleavable peptide linkers. Nanogels can gain site-specific, spatially controlled, and temporally controlled drug release in intricate disease microenvironments by employing such linkers in combination. Applications:

- Multi-component treatment of diseases, for example, drug-resistant infections, heterogeneous tumor microenvironments.

5. Drug loading strategies

Drugs can be incorporated into nanogels through three principal strategies: Physical entrapment, ionic complexation, and covalent conjugation. Each method influences drug release kinetics, stability, and bioavailability differently, depending on the nature of the drug and the loading approach utilized.[49] Figure 5 illustrates these drug-loading strategies. While covalent conjugation is a viable method, physical entrapment and ionic complexation are the most commonly employed approaches, with conjugation primarily reserved for applications requiring tightly controlled release or enhanced stability. Table 4 provides these drug-loading methods, contrasting their mechanism, appropriate drugs, advantages, and limitations.

5.1. Physical entrapment

Physical entrapment involves incorporating the drug within the nanogel matrix during gelation or self-assembly. The drug is not covalently attached but is retained through non-covalent interactions such as hydrophobic interactions, hydrogen bonding, and van der Waals forces. This method is well-suited for small molecules, peptides, and nucleic acids since it allows for easy entrapment under mild conditions that maintain bioactivity. The primary advantage of physical entrapment is that it is a gentle and straightforward fabrication process, which is appropriate for labile biomolecules. The limitation, however, is the possibility of early drug release, particularly under shear stress or in well-hydrated conditions.

5.2. Ionic complexation

Ionic complexation is based on electrostatic interaction between oppositely charged drugs and polymers. The technique is more applicable to charged biomolecules, for example, siRNA, DNA, insulin, and some proteins. Electrostatic attraction facilitates effective loading and improves the stability of the encapsulated biomolecule. Ionic complexation is beneficial for strong drug retention without covalent modification, maintaining drug activity. Its performance can be ionic strength-, pH-, and physiologically condition-sensitive, which may cause premature release or aggregation if not sufficiently optimized.[50]

5.3. Covalent conjugation

Covalent conjugation takes the form of a chemical linkage of the drug to the polymer backbone by stimuli-sensitive linkers,

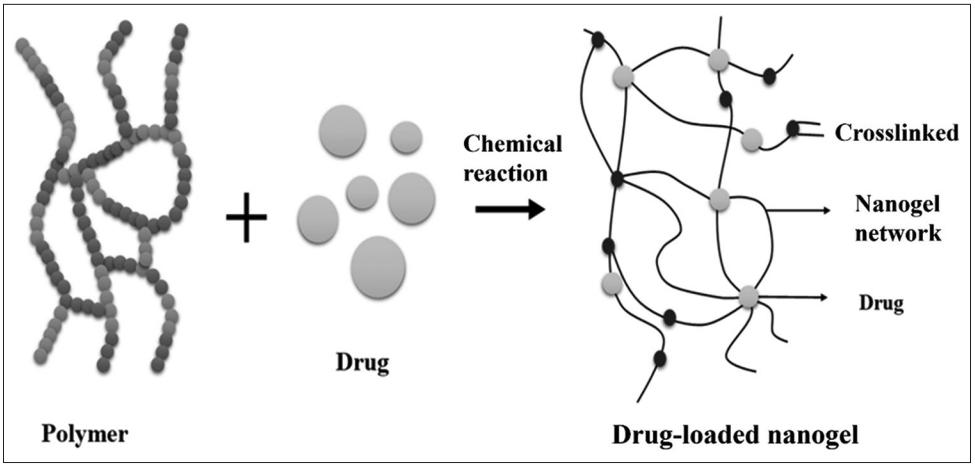

Figure 5. Drug loading strategies in nanogels. Figure created by the authors.

for example, ester, disulfide, or hydrazone linkage. Following drug linkage, the drug may be released in a controlled fashion at the site of action upon exposure to environmental stimuli such as pH, redox potential, or enzymes. It is well-suited to chemotherapeutics and peptides, wherein site-specific controlled release is critical. Its major benefit is controlled and targeted drug delivery with low systemic side effects. Nevertheless, complicated synthesis, possible toxicity of remaining reagents, and risk of drug bioactivity compromise are serious limitations to overcome in formulation.[51-53]

6. Biomedical applications of nanogels

Nanogel drug delivery systems are also receiving interest as second-generation carriers because of their biocompatibility, size tunability, stimuli-responsiveness, high drug loading capacity, and controlled release characteristics. Their capability to penetrate biological barriers and interact with tissues or cells selectively has helped them find additional applications in various therapeutic platforms. The major biomedical applications of nanogels, along with their mechanisms, advantages, and representative examples, are described below. Table 5 summarizes these therapeutic applications.

6.1. Anticancer drug delivery

Mechanism: Nanogels exploit the enhanced permeability and retention effect, as well as active targeting ligands (e.g., folate, transferrin), and stimulus sensitivity (e.g., pH, redox, enzymes) to deliver chemotherapeutics directly to tumor tissues.

Advantages: Nanogels minimize systemic toxicity of chemotherapeutic agents such as doxorubicin, paclitaxel, and cisplatin, facilitate cellular uptake via endocytosis, and regulate drug release selectively within the tumor microenvironment.

Examples: Hyaluronic acid-based nanogels target $CD44^+$ cancer cells. Redox-sensitive PEGylated nanogels release paclitaxel upon intracellular glutathione exposure.[54]

6.2. Antimicrobial and antifungal applications

Mechanism: Nanogels permeabilize bacterial membranes and biofilms and provide locally sustained therapeutic drug concentrations to treat resistant infection.

Advantages: They facilitate localized antibiotic or antifungal activity, decrease dosing frequency, and minimize systemic side effects.

Examples: Wound healing is promoted by chitosan nanogels with ciprofloxacin. Amphotericin B for the treatment of Candida albicans infections is delivered by dual-sensitive thermo-pH nanogels.[55]

6.3. Ocular applications

Mechanism: Precorneal residence time is prolonged by *in situ* gelling nanogels to deliver anterior/posterior segments of the eye.

Advantages: Enhance drug retention and bioavailability of ocular therapeutics.

Examples: Anti-inflammatory drug or anti-glaucoma drug in nanogels.[56]

6.4. Transdermal applications

Mechanism: Nanogels enhance drug deposition and skin permeability, with drug release controlled by pH- or temperature-sensitive systems.

Table 4. Comparison of drug loading strategies[49-53]

Method	Mechanism	Suitable drugs	Advantages	Limitations
Physical entrapment	Non-covalent incorporation	Small molecules, hydrophilic drugs	Simple, mild conditions	Risk of premature release
Ionic complexation	Electrostatic interactions	siRNA, proteins, peptides	High efficiency for charged drugs	Sensitive to ionic strength, pH
Covalent conjugation	Stimuli-cleavable chemical linkers	Chemotherapeutics, peptides	Precise and site-specific release	Complex synthesis, potential toxicity

Table 5. Therapeutic applications of nanogels

Application	Features	Examples
Anticancer	Enhanced permeability and retention effect, active targeting, stimuli-sensitive release	Doxorubicin, paclitaxel, cisplatin
Antimicrobial/antifungal	Enhanced biofilm penetration, local sustained release	Ciprofloxacin, amphotericin B
Ocular	Mucoadhesion, prolonged retention	Timolol, dexamethasone
Transdermal	Enhanced skin permeation, pH/thermo-responsive systems	Diclofenac, testosterone
Gene/RNA delivery	Protects nucleic acids, non-viral vector, cytoplasmic release	siRNA, CRISPR/Cas9
Vaccine delivery	Controlled antigen release, immune cell targeting	Influenza antigen, human papillomavirus, ovalbumin
Central nervous system targeting	Blood–brain barrier penetration, ligand-directed targeting	Levodopa, siRNA, antipsychotics

Abbreviations: CRISPR/Cas9: Clustered Regularly Interspaced Short Palindromic Repeats/CRISPR-associated protein 9; siRNA: Small interfering RNA.

Advantages: Increase systemic bioavailability, lower frequency of dosing, and increase patient compliance.

Examples: Responsive nanogel-based transdermal delivery of analgesic or hormone drugs.

6.5. Gene and RNA delivery

Mechanism: Nanogels encapsulate nucleic acids (DNA, siRNA, miRNA) through electrostatic complexation, enhance endocytic cellular uptake, and release cargo in the nucleus or cytoplasm through pH/redox-sensitive stimuli.

Advantages: Lower immunogenicity than viral vectors, high loading capacity, biocompatibility, and targeted delivery through ligand-functionalized nanogels.

Applications: siRNA delivery for gene silencing in cancer, inflammation, or viral infection.[57]

6.6. Vaccine delivery

Mechanism: Nanogels stabilize protein antigens, form depots at injection sites, are internalized by dendritic cells/macrophages, and facilitate antigen presentation to induce immunity.

Advantages: Controlled antigen release kinetics and targeting of lymphoid organs for maximum immunogenicity.

Applications: Nasal or transdermal COVID-19, influenza, or human papillomavirus vaccines in preclinical models.[58]

6.7. Central nervous system (CNS) targeting

Mechanism: Ligand-functionalized nanogels (transferrin, lactoferrin, apolipoprotein E) permeate through the blood–brain barrier (BBB) and stabilize drugs in plasma with release control.

Advantages: Particle size <200 nm, longer circulation time, improved BBB permeability, and targeted drug delivery to the CNS.

Applications: Antiepileptics, antipsychotics, neuroprotective agents, siRNA for neurodegenerative disorders (Alzheimer's, Parkinson's), and therapy of CNS infection such as cryptococcal meningitis.[59]

7. Future directions

Nanogels are emerging as next-generation drug carriers, driven by advances in precision medicine, intelligent material design, and artificial intelligence (AI). AI- and machine learning-assisted predictive modeling holds the potential to improve drug–polymer compatibility, release kinetics, and formulation parameters, thereby enhancing nanogel design efficiency while reducing the need for labor-intensive trial-and-error experimentation.[60] Another promising direction is the development of hybrid nanogels incorporating inorganic moieties such as gold nanoparticles, iron oxide, or quantum dots. These multifunctional systems are capable of simultaneous targeted therapy, imaging, and diagnostics, particularly relevant for oncology and infectious disease.[61,62]

Among the main translational research areas of interest is the development of targeted nanogels for precision medicine. These systems integrate ligands such as folate, transferrin, or CD44-binding ligands with stimuli-responsive cross-linkers to engineer patient-specific delivery profiles.[63-65] Furthermore, theranostic nanogels that combine imaging modalities broaden the scope of theranostics by enabling spatiotemporal drug release, real-time imaging, and image-guided therapy.[66-69] Concurrently, ethically suitable and human-relevant preclinical testing approaches are being embraced through new approach methodologies. These comprise next-generation *in vitro* platforms, organ-on-chip technologies, and AI-based *in silico* models, which collectively offer inexpensive, mechanistically enlightening, and ethical means of interrogating nanogel safety, pharmacokinetics, and toxicity, while facilitating the 3Rs principle (replacement, reduction, refinement) in preclinical research.

Importantly, beyond preclinical potential, nanogels are starting to transition to clinical and market applications. Certain generally recognized as safe (GRAS) polymers have entered clinical use for dermatological, ophthalmological, and oncological applications, suggesting therapeutic diversification.[70,71] Examples include dermal nanogels for chronic skin diseases, eye drop nanogels for drug delivery systems with sustained intraocular release, and injectable anticancer therapy drug delivery systems with controlled release. Although issues of large-scale production, sterilization, long-term stability, and regulation harmonization remain concerns, clinical advancements highlight the translational significance of nanogels.

In total, the destiny of nanogels is where nanotechnology, translational medicine, and computational design converge. As knowledge on stimuli-responsive polymers, hybrid multifunctional platforms, and AI-driven formulation design increases, nanogels can be expected to provide highly targeted, minimally invasive, and intelligent therapeutic interventions for multifactorial complex diseases. Their future clinical progression indicates a linear path from bench to bedside, affirming their position as a must-have platform in future drug delivery.

8. Conclusion

Nanogels have emerged as a strong and universal group of nanocarriers in the field of high-tech drug delivery systems,

providing a distinct and unique blend of nanoscale size, soft hydrophilic structure, controllable physicochemical behavior, and responsiveness to external stimuli. Three-dimensional cross-linked polymer matrices can effectively load an extensive range of therapeutic molecules, ranging from small molecules, peptides, and proteins to nucleic acids and vaccines, while improving solubility, stability, and bioavailability. Their ability to respond to intrinsic physiological signals such as pH, redox potentials, and enzymes or external stimuli such as temperature, light, or magnetism qualifies them as highly promising candidates for controlled, site-specific, and on-demand drug delivery. Significant progress has been made during the past decade in the design of nanogels with targeted delivery characteristics through surface functionalization with ligands (e.g., antibodies, aptamers, peptides) and biomimetic coatings. These developments have extended their therapeutic uses to oncology, microbial infection, ophthalmic disease, transdermal and mucosal drug administration, neurodegenerative disorders, and genetic disorders.

Nanogels offer several advantages over conventional delivery systems, including enhanced biocompatibility, reduced systemic toxicity, and improved therapeutic effectiveness, and therefore are of particular significance in evading the pitfalls of traditional drug delivery systems. The conjoining of the diagnostic and therapeutic functionalities within the same nanogel architecture, termed theranostics, has created new horizons for targeted and personalized therapy. Emerging directions such as AI-based design, machine learning-aided optimization of formulation, hybrid nanogels based on organic-inorganic hybrid building blocks, and four-dimensional stimuli-adaptive nanogels are transforming nanomedicine. Such advances not only enable the optimization of nanogel activity but also rationalize its drug development pipeline to clinical utility. Although they have tremendous promise, some issues need to be resolved to facilitate their clinical application and regulatory approval. A few of these are bulk manufacturing, reproducibility, sterilization, long-term stability, toxicity profiling, and harmonized regulatory guidelines. Positively, some nanogel systems based on GRAS or FDA-approved polymers are being investigated preclinically and clinically, especially in topical, ophthalmic, and cancer fields. In short, nanogels represent an innovative drug delivery platform that holds the promise for revolutionizing the delivery, monitoring, and tailoring of therapies. Their inherent flexibility, combined with advances in materials science, bioengineering, and computational design, places them at the epicenter of contemporary therapeutics. With the potential to advance toward targeted treatment and adaptive treatment regimens, nanogels are poised to fill the gap between benchside discovery and bedside delivery.

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Conflict of interest

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