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Novel Nanogel Formulation, Evaluation, and Applications: A Review

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Abstract
Nanogels — nanoscale, highly hydrated polymeric networks — combine the advantages of hydrogels (high water content, biocompatibility) and nanoparticles (tunable size, surface functionality) to form versatile carriers for drugs, biomacromolecules, genes and vaccines. Recent years have seen rapid innovation in materials, cross-linking chemistries, stimuli-responsive designs, and application-specific formulations (e.g., ocular, topical, wound, CNS, cancer). This review summarizes contemporary formulation approaches, critical physicochemical and biological evaluation methods, representative biomedical applications, and practical translational challenges (stability, scalability, regulatory hurdles). Emphasis is placed on "novel" aspects: green and bio-inspired chemistries, multifunctional stimuli-responsive nanogels, combination/theranostic systems, and strategies improving in vivo stability and targeting. Key gaps and future directions for clinical translation are highlighted.

Keywords: Nanogels, Applications, Formulation

Introduction

Nanogels (NGs) are three-dimensional crosslinked polymer networks with particle sizes typically ranging from 20–300 nm, providing unique advantages in therapeutic delivery and diagnostic applications due to their high-water content, deformability, and enhanced stability in biological systems (Siafaka et al., 2023). Their small size allows enhanced permeability and retention in tumors, while the gel-like matrix allows efficient encapsulation of hydrophilic and hydrophobic drugs (Vashist et al., 2024).

Novel nanogel research focuses on precision targeting, better stimuli responsiveness, improved biodegradability, and safer clinical translation (Manimaran et al., 2023).

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Materials and Design Considerations

Natural Polymers

Natural polymers such as chitosan, alginate, hyaluronic acid, and dextran are widely used due to biodegradability and minimal toxicity (Gadziński et al., 2022). Chitosan-based nanogels offer mucoadhesion and antimicrobial activity, while hyaluronic acid provides CD44-mediated targeting in cancer.

Synthetic Polymers

Synthetic polymers such as polyethylene glycol (PEG), poly(acrylic acid), and PNIPAM enable controlled mechanical properties and environmental responsiveness (Soni et al., 2015). Copolymer nanogels combine advantages of natural and synthetic polymers for improved performance.

Cross-linking Strategies

Two major crosslinking approaches are commonly used:

Chemical Crosslinking **Physical Crosslinking**

Chemical Crosslinking	Physical Crosslinking
Covalent bonds via free radical polymerization, click chemistry	Ionic interactions, hydrogen bonding, host–guest complexation
Stronger stability, long-term retention	Reversible interactions, improved stimuli-responsive release

Dual crosslinked systems integrate both benefits for biomedical applications (Suhail et al., 2022).

Novel Nanogel Formulation Approaches

Microfluidic Technology

Microfluidics offers precise control of nanoparticle size distribution, scalable production, and compartmental designs useful for multi-drug systems (Vashist et al., 2024).

Inverse Miniemulsion Polymerization

Allows uniform particle formation and tuning of crosslink density, benefiting hydrophobic drug encapsulation (Soni et al., 2015).

Ionotropic Gelation

Often used for chitosan or alginate nanogels by simple mixing with appropriate counterions (Gadziński et al., 2022). Ideal for protein and gene delivery.

Green Chemistry and Enzymatic Approaches

Current focus is on eliminating toxic organic solvents using enzyme-mediated crosslinking or photo-induced polymerization under mild conditions (Vashist et al., 2024).

Self-Assembly and Supramolecular Chemistry

Cyclodextrin host–guest interactions, peptide-driven assembly, and amphiphilic block copolymers yield structurally sophisticated nanogels (Siafaka et al., 2023).

Physicochemical Characterization and Evaluation

Particle Size and Morphology

Dynamic light scattering (DLS) measures hydrodynamic size and PDI, while TEM confirms morphology (Suhail et al., 2022). Sizes <200 nm favor tumor targeting.

Zeta Potential

Surface charge influences colloidal stability and cellular interactions (Soni et al., 2015). Slight negative/neutral charge is correlated with reduced immune clearance.

Swelling Capacity and Gel Fraction

Swelling influences drug loading and release kinetics. Network porosity determines diffusion behavior (Suhail et al., 2022).

Drug Loading and Encapsulation Efficiency

Factors such as polymer composition, hydrophobicity, and crosslinking density affect payload retention (Kumari et al., 2024).

Rheology and Mucoadhesion

Important for topical or ocular delivery to ensure retention at the administration site (Das et al., 2025).

In vitro Biological Studies

Cytotoxicity, hemocompatibility, cellular uptake, and transwell permeability are routinely assessed (Manimaran et al., 2023).

In vivo Pharmacokinetic and Therapeutic Evaluation

Biodistribution, release profile, and therapeutic efficacy must be validated in disease-specific models (Kumari et al., 2024).

Stimuli-Responsive Nanogels

pH-sensitive Nanogels

Used for tumor or intracellular drug release through acidic environment-triggered swelling (Siafaka et al., 2023).

Temperature-responsive Nanogels

PNIPAM systems collapse above LCST, expelling drug selectively (Soni et al., 2015).

Redox-Responsive Nanogels

Disulfide linkages cleave intracellularly upon exposure to glutathione, enabling cancer cell-specific release (Vashist et al., 2024).

Enzyme-responsive Nanogels

Overexpressed enzymes such as MMPs or hyaluronidases trigger controlled degradation at disease sites (Das et al., 2025).

Multi-Modal and Theranostic Systems

Dual drug/gene therapy and integrated imaging facilitate synergistic treatment and real-time tracking (Siafaka et al., 2023).

Biomedical Applications

Cancer Therapy

Nanogels improve drug solubility, facilitate tumor targeting, and reduce systemic toxicity. Co-delivery of siRNA and chemotherapeutics enhances tumor apoptosis (Manimaran et al., 2023).

Central Nervous System Drug Delivery
Surface-ligand modified nanogels efficiently cross the blood–brain barrier through receptor-mediated transport (Vashist et al., 2024).

Ocular Delivery
Nanogels provide prolonged retention, lower dosing frequency, and efficient targeting of ocular infections or inflammation (Soni et al., 2015).

Wound Healing and Dermatology
Nanogels form a protective moist layer, deliver antimicrobials, and promote collagen deposition (Kumari et al., 2024).

Vaccine and Immunotherapy Delivery
Nanogels enhance antigen stabilization and dendritic cell uptake, improving immune response (Siafaka et al., 2023).

Anti-Microbial and Anti-Biofilm Therapies
Nanogel-encapsulated antibiotics show improved penetration and reduced resistance emergence (Das et al., 2025).

Industrial and Cosmetic Applications
Nanogels with controlled rheology and hydrating capabilities are increasingly used in:

- Hair care formulations
- Moisturizers
- Skin regeneration products
- Sunscreens

Their biocompatibility and tailored penetration depth enhance product efficacy (Siafaka et al., 2023).

Stability, Safety, and Translational Barriers

Challenge	Impact	Strategies
Storage instability	Aggregation/contamination	Lyophilization, sterile processing
Cytotoxic residues	Safety issues	Green synthesis, thorough purification
Scale-up	Variable batch quality	Microfluidics, continuous manufacturing
Regulatory approval	Limited guidelines	Standardized testing and CQAs

Comprehensive chronic toxicity and immunogenicity evaluations remain mandatory before clinical translation (Vashist et al., 2024).

Future Prospects
Advances expected to shape the next decade include:

- **Personalized nanogels** tailored to patient biomarkers
- **Smart biosensing nanogels** with on-demand release capability
- **Gene editing delivery** using CRISPR-loaded nanogels
- **AI-guided formulation prediction** for precision engineering
- **FDA harmonized regulatory frameworks** for nanomedicines

Sustained collaboration between researchers, pharmaceutical industries, and clinical regulators will accelerate successful commercialization (Manimaran et al., 2023).

Conclusion
Nanogels represent a powerful and adaptable class of nanocarriers offering unique advantages in controlled delivery and precision medicine. Novel formulation methods combined with stimuli-responsive design have significantly improved their therapeutic success. Despite promising preclinical outcomes, critical efforts should focus on regulatory compliance, clinical validation, and manufacturing scalability. Overall, nanogel technology holds tremendous potential to transform therapeutics, diagnostics, wound management, and tissue engineering in the near future.

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