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Review Article

Nanogels In Modern Drug Delivery: Advancements In Functionalization, Emerging Applications, And Challenges Toward Clinical Use

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ABSTRACT

Nanogels are three-dimensional cross-linked polymer networks in a nanoscale size range that can retain large amounts of water while maintaining its structural integrity. Its capacity to absorb and release water without dissolving enables them to carry both hydrophilic and lipophilic drugs, protecting them against premature degradation and releasing them in a controlled manner. The current review discusses the classification of nanogels in relation to its structure, the chemistry of its crosslinking, their ability to respond to stimuli, and polymer composition used for its synthesis. It then covers swelling, the defining property of a nanogel, and the main driving element that governs the release of drug from the matrix to the tissue. The common preparation methods are described going from the older top-down approaches such as photolithography and PRINT to the more intricate bottom-up approaches such as emulsion polymerization, ATRP, RAFT, and microfluidic assembly. The latest developments in the field of functionalization of nanogels such as surface modification, biomimicking coating, and cell targeting are described, as well as their application in drug delivery, biosensing, gene delivery, cancer therapy, transdermal drug delivery and vaccines. Lastly, the review calls attention to the barriers still standing between nanogels and clinical use namely; difficulties in purification, poor batch-to-batch reproducibility, the absence of standardized toxicity testing, and the high cost of producing more advanced, functionalized nanogels. These issues will need to be resolved before the nanogels can move from the laboratory into real, affordable treatments.

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INTRODUCTION

Nanomedicine is an interface where nanotechnology, medicine, and pharmaceuticals are converged to produce multiple nanoscale drug delivery systems. Among the most recent of these is the nanogel, a 3D hydrogel particle of nanoscale dimensions formed through the physical or chemical crosslinking of polymers. Nanogels show relatively high encapsulation efficiency of both hydrophilic and hydrophobic therapeutics with increased stability, long circulation time, stimuli-responsiveness, alongside an innate capacity to swell while retaining their nanoscale size. These combined properties have enabled nanogels to find applications in diverse delivery routes including transdermal, ophthalmic, vaginal drug delivery, vaccine delivery, oncology, targeted protein delivery, delivery of genetic material, as well as their use as versatile nanocarrier for cancer therapy, imaging and diagnostics, hence playing a vital and diverse role in modern therapeutics.

Nanogels possess a highly hydrated and porous network that plays an important role in their physicochemical behavior. The high-water content is closely linked to the fluid transport qualities shown by bioactive compounds that are much smaller than the gel pore sizes.¹

The swelling effect arises from interactions between the nano scaffold and solvent molecules, in which polymer chains stretch upon absorbing water until the elastic restoring force counterbalances the deformation, leading to an equilibrium that enables uptake of more than 90% w/w of aqueous solution. These water retention characteristics improve ion diffusion and exchange, along with metabolites and biomolecules, promoting synergy with biological uses and making nanogels promising biocompatible options.²

The term "NanoGel" was initially introduced when it was developed as a hydrophilic polymer network through chemical bonding of polyethylene glycol and polyethyleneimine for delivering antisense oligonucleotides.³

2. CLASSIFICATION OF NANOGELS

2.1. Based on structure:

Based on their structure, nanogels can be broadly classified into different types depending on the arrangement of their polymeric networks and internal or surface features. The major structural types include multi-layered, core, hairy, and hollow nanogels, as illustrated here.

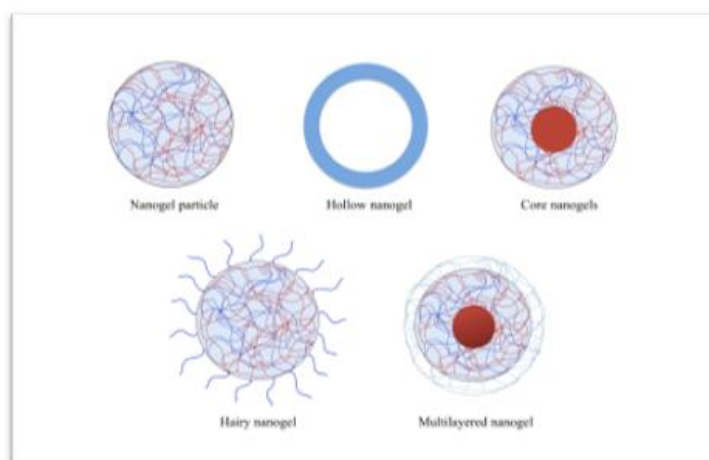


Fig -1 Structure based classification of nanogels

2.2. Based on linkage:

2.2.1. Physically crosslinked nanogels:

A controlled self-assembling reaction between similar or dissimilar polymer chains, driven by electrostatic interactions, van der Waals forces and hydrogen bonding, lead to the formation of physically crosslinked nanogels. These nanogels are relatively less stable compared to chemically crosslinked nanogels.^{4,1}

Hybrid nanogels form through the crosslinking of copolymer micelles via carbodiimide-activated glutamic acid groups combined with ethylenediamine, with PEG chains stabilizing the outer shell. This approach has been used for the co-delivery of cisplatin and paclitaxel in ovarian A2780 cells, remaining non-toxic up to 5 mg/mL while producing synergistic cytotoxicity when fully loaded.⁵

Liposomal nanogels, also termed "nanolipogels," instead use liposomes as crosslinking templates or hosts, with Michael-type thiol-maleimide addition linking liposome cores to thiolated PEG through

thioether-succinimide crosslinks; this system enabled GSH-triggered co-delivery of doxorubicin and cytochrome c with differential, degradation-mediated release profiles.⁶

Micellar nanogels form when amphiphilic block or graft copolymers self-assemble via hydrophobic association, as seen with cholesteryl-pullulan (CHP), or through stereocomplexation, as with enantiomeric PLA, to produce physically crosslinked cores. CHP nanogels enable stable complexation with insulin, anticancer drugs, proteins, and DNA, while PLA stereocomplex micellar nanogels exhibit dual temperature/reduction responsiveness with swelling tunable via polymerization degree.⁷

2.2.2. Chemically crosslinked nanogels:

While physically crosslinked nanogels are held together by weak forces, a reason for its low stability in the physiological environment, the chemically crosslinked nanogels are prepared by coupling the polymer chains with covalent networks which are irreversible and hence stable in the physiological conditions of the body.

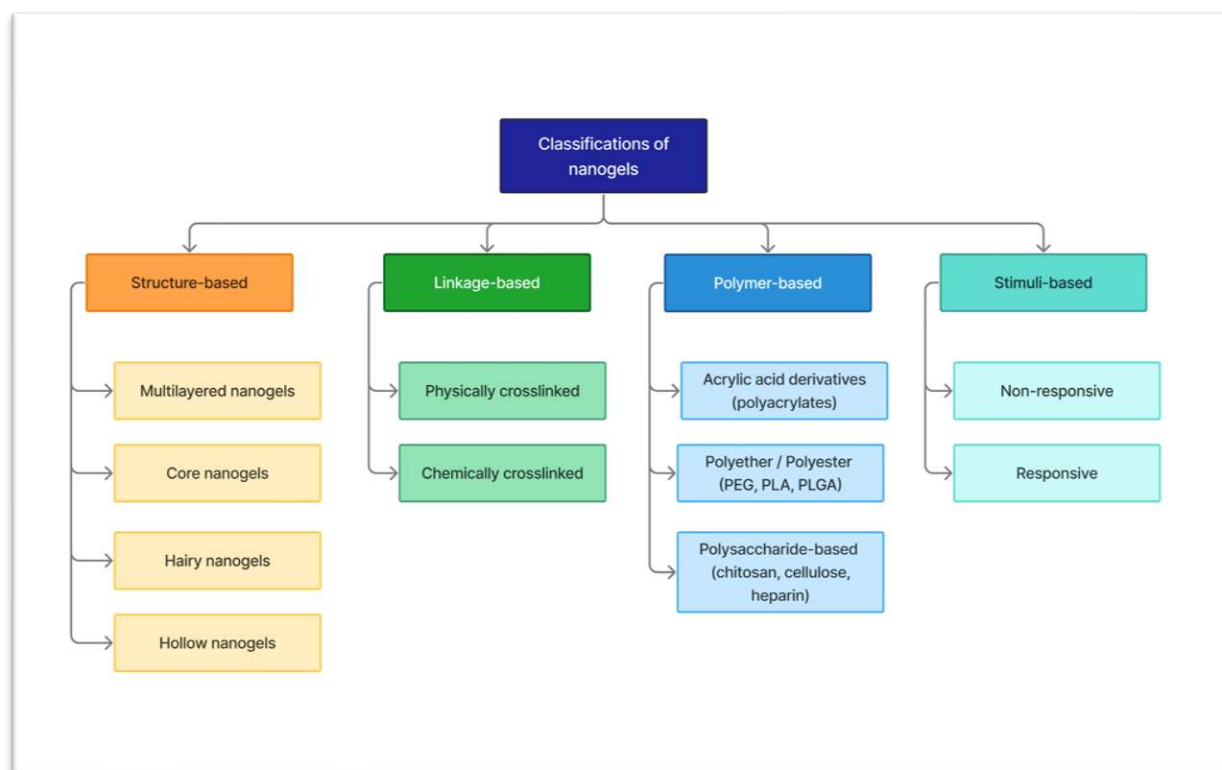


Fig -2 Classification of nanogels

2.2.3. Based on stimuli:

Nanogels are classified into responsive and non-responsive nanogels based on their reaction to external stimuli.

Non-responsive nanogels do not require any triggers for drug release as they swell by a simple absorption mechanism when in contact with body fluids and will release the loaded drug.

Responsive nanogels on the other hand will get influenced by external environmental factors to trigger the release of drug. The trigger can be various physical, chemical, or biological stimuli like pH, magnetic field, light, electricity, ultrasound, composition change of solvent or temperature change which may cause the nanogel to either swell or collapse, thereby releasing or stopping the release of drug.

pH-responsive nanogels will swell or collapse in response to the pH of the environment, ensuring more targeted delivery. Our bodies have different pH environments based on the location, healthy tissues have a pH around 7.4, the stomach has an acidic pH of 1.0-3.0, and the tumor tissue is comparatively more acidic than healthy tissue ranging from 6.5 - 7.0. Due to this variation in the pH, one can employ acidic or basic groups in their nanogel structure causing eventual protonation or deprotonation according to the target site's pH, prompting release of drug.

Thermo-responsive nanogels show responsiveness to change in temperature of the surrounding environment. They can be utilized for targeting tumor tissue due to their elevated temperature. Various polymers can be utilized that will either swell or collapse owing to any kind of change in the physiological temperature.

Thermo-sensitive nanogels are of 2 types, Negative temperature sensitive polymeric nanogel and positive temperature sensitive polymeric nanogel. The NTS polymeric nanogel will have a lower critical solution temperature or LCST. The polymers employed in this type of nanogel will have both hydrophilic and hydrophobic groups attached to them. When the physiological temperature is lower than LCST, then the hydrophilic groups and the water present in the surrounding fluid will form hydrogen bonds and the nanogel will swell causing the eventual release of drug, and when the temperature is higher than the LCST, the hydrophobic interactions will dominate the H-bonding causing the nanogel to collapse.^{8,9}

Positive temperature-sensitive polymeric nanogel will have an upper critical solution temperature or UCST. Here, the nanogel will swell when the physiological temperature is higher than the UCST, and the system will collapse when the temperature is lower than the UCST.^{9,10}

3. METHODS OF NANOGEL SYNTHESIS

As nanogels gained popularity in biomedical research due to their plethora of applications, a great number of synthesis methods are present and many still in ongoing research. If one wants to give a broad classification, the synthesis methods can come under one of these 2 headings: Top-down approach or Bottom-up approach.

3.1. Top-down approach:

The top-down approach comprises breaking down larger bulk materials into the desired nanostructure form. It relies on physical, chemical, or template-assisted deconstruction. While one can efficiently break down larger bulk material without using toxic organic solvents or mineral oils, this method is difficult to scale up, will cause imperfections to

the nanogel surface and are more suitable for micro-size formulation, hence is not being employed much in today's literature.

3.2. Bottom-up approach:

The bottom-up approach brings in single atoms or molecules and works up their way to form nanostructures by crosslinking using physical or chemical bonds.

3.2.1. Preparation of nanogels using polymeric precursors:

In aqueous solution, driven by the hydrophobic effect, amphiphilic copolymers self-assemble forming loose nanostructures, which then serve as an adaptable framework for preparing nanogels simply by crosslinking the assembly.¹¹ One can assemble the network with the help of crosslinkers, such as *disulfide bonds*, *amide bonds*, *imide bonds*, and *click chemistry*. They will act as permanent anchors, chemically crosslinking the network. These bonds upon reaction to different stimuli of the body's physiological environment, will degrade or dissolve leading to rapid release of drug. For example, disulfide bonds will remain intact in healthy tissue, but in cancer tissue, high levels of glutathione will break the S-S bond, causing the nanogel network to dissolve thereby releasing the drug.

3.2.2. Preparation of nanogels using monomers:

Monomer-based nanogel synthesis can proceed through conventional free radical polymerization, emulsion polymerization, and other classical routes; however, *controlled or living free radical polymerization* has garnered much attention owing to its ability to produce polymers with narrow MW distribution, uniform PDI (< 1.5), which eases in formation of homogenous polymer network with better drug loading capacity.¹²



The most widely used techniques here are ATRP - - Reversible Addition-Fragmentation Chain Atom Transfer Radical Polymerization and RAFT Transfer.

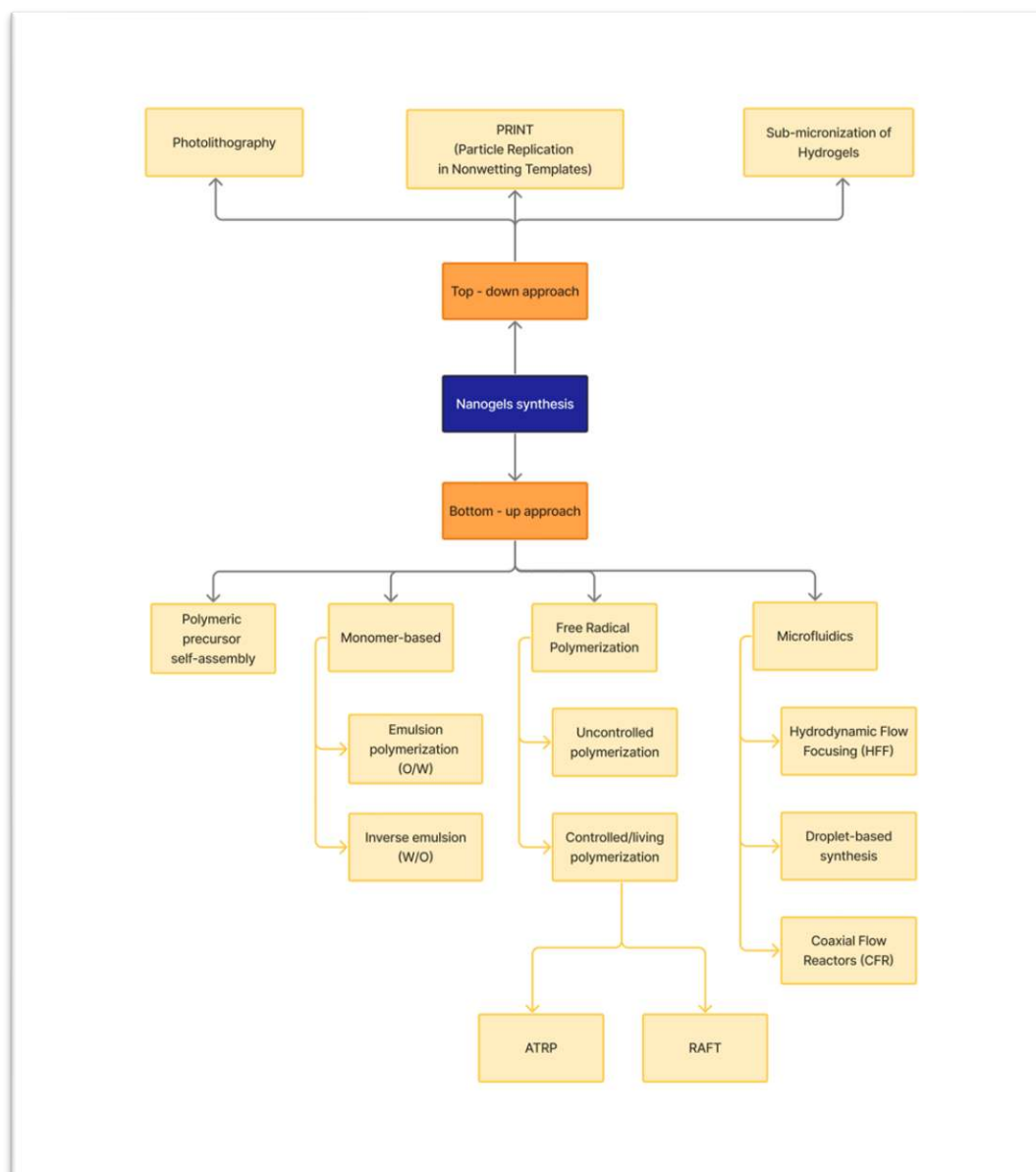


Fig -3 Methods of nanogel synthesis

ATRP or Atom Transfer Radical Polymerization is among the most dynamic and versatile CRP processes. ATRP has been used for years to prepare peptide/polymer conjugates, nanogels, hydrogels and polymer modified polysaccharides, and much more.¹³ The paramount feature of ATRP is the equilibrium it maintains between low concentrations of active radicals and a higher

number of dormant chains by undergoing a reversible redox process. A transition metal complex catalyzes the redox reaction, where one electron is oxidized with concomitant removal of a halogen atom from the dormant chain, R-X. The rate constant of activation k_{act} , and rate constant of deactivation k_{deact} govern the reaction, with k_p being the polymer chain propagation constant.

While termination reactions are a norm in conventional free radical polymerization are comparatively rare in a well-controlled ATRP.

Simakova et al¹⁴ when working with cationic nanogels have outlined the significant increase in the size of polymer droplets during its synthesis by polymerization in dispersed media due to Ostwald ripening and successfully synthesized cationic nanogels by ATRP using hydrophilic inimer under inverse microemulsion conditions. This study utilized a hydrophilic inimer in place of a regular monomer which resulted in swift initiation and facile nucleation resulting in nanogels polymer droplets with uniform size compared to the initial micelles.¹⁴

In one recent study, Kim et al¹⁵ prepared a novel enzyme nanogel via in situ ATRP with the aim to enhance thermal stability and electron conductivity of enzymes for application in highly sensitive glucose detection. They developed a uniform single-enzyme nanogel (ATRP-SEG) by growing a crosslinked polyacrylamide network directly from the enzyme's surface using atom transfer radical polymerization (ATRP) to significantly improve its lifespan and heat resistance. The ferrocene incorporated nanogel (Fc-ATRP-SEG) successfully showed higher sensitivity and half-life of 49 days, which was nearly 197 times longer than the free glucose oxidase.¹⁵

However, ATRP requires transition-metal catalysts, usually copper-based systems that can lead to residual metal contamination, toxicity, and purification requirements for biomedical applications. Its sensitivity to reaction conditions and the need for careful control over catalyst and ligand concentrations can also complicate process optimization and scale-up.

RAFT or Reversible addition-fragmentation chain transfer is yet another kind of controlled free radical polymerization, whose pivotal feature lies in its utilization of a Chain transfer agent or CTA. Thiocarbonylthio compound is usually the CTA or RAFT agent. RAFT polymerization is compatible with a broad range of monomers such as acrylates, acrylamides, butadiene, styrene and its derivatives, acrylonitrile when compared to its counterpart ATRP or NMP. It involves 3 steps, initiation, propagation and termination. During the first step, an initiator is added which generates radicals that react with the monomers, creating initial polymer radicals. The second step involves the addition of the CTA agent that the polymer radicals react with, leading to the formation of dormant chains. The dormant chains then fragment creating a new polymer radical which can then either start a new polymer chain by reaction with monomer or continue the growth of the parent chain. Termination again is a rarity here.¹⁶

Unlike ATRP, RAFT does not require transition-metal complexes for the polymerization process, thereby avoiding the potential toxicity and the tedious and complex metal-removing issues associated with ATRP polymerized nanogels. This becomes particularly important if the preparation is used for biomedical applications, wherein any residual metal components will adversely affect the human body and the biocompatibility of the final preparation.

RAFT polymerization due to its broad adaptability, tolerance for a wide array of monomers and gentle reaction environments gives rise to plethora of applications as in creating complex molecular architectures such as graft polymers, star-shaped polymers, hyper-branched polymers and finally the 3D hydrogel networks made of crosslinked polymers – nanogels.¹⁷

Injectable nanogels, being extensively studied due to their revolutionary solution to conventional problems relating to traditional drug delivery have found their way into the ROS-reduction antioxidant approach where a recent work by Basak et al¹⁸ has offered an innovative approach to cardiovascular problems by developing a novel nitroxide-based nanogel using RAFT polymerization. By taking PMA and GMA as monomers and designing a core-shell nanogel of size 20-40 nm using RAFT, they produced a system that exhibited improved shelf life by approx. 85% when compared to the native SOD enzymes.¹⁸

Kitayama et al¹⁹ developed a system for identifying and reporting target molecules for diagnosis, drug delivery, and food testing applications. They prepared a polymeric nanogel that can identify the most crucial protein- albumin by RAFT precipitation polymerization using PMPC as an anti-fouling base and dansyl groups as identifying and reporting units for albumin. The nanogels changed their fluorescent intensity when they successfully adsorbed albumin from human, bovine (cow), and porcine (pig) serum. The prepared nanogels successfully detected urinary serum albumin, a critical clinical marker to detect diabetic neuropathy, and was also applied for vegan food testing, where it again capably detected BVA contamination in real soy milk.¹⁹

As discussed above, RAFT provides greater flexibility in controlling the polymer composition and molecular weight, however on the expense of utilizing CTA agents; which will require an additional purification step in the synthesis process thereby increasing formulation complexity and

cost. Although, both techniques offer valuable control over nanogel structure and function, their reliance on specialized reagents, stringent reaction conditions, purification requirements, and scalability issues can hinder widespread accessibility and translation into cost-effective large-scale nanogel production.

3.2.4. Preparation of nanogels by microfluidics technology:

Microfluidics technology has revealed itself as a superior bottom-up approach in the preparation of NPs and eventually nanogels. This recent technology is labeled as a lab-on-chip device which consists of their characteristic flow channels spanning several hundreds of micrometres in width. Due to these microchannels, one can efficiently manipulate the flow of fluids, hence providing excellent control over particle size, polydispersity index, and overall uniformity of the solution. Its continuous flow nature eliminates the disadvantages concerning “all in a pot mixing”, which not only doesn't give control over various reaction parameters, materials morphology but also after the tedious process; still results in a broader and polydisperse mixture which is difficult to scale up for industries. Under microfluidics we have 3 fluid dynamic arrangements, hydrodynamic flow focusing or HFF, droplet-based synthesis, and coaxial flow reactors or CFR.

MICROFLUIDIC FLUID DYNAMIC ARRANGEMENTS FOR NANOGEL SYNTHESIS

Table -1

Arrangement	Mechanism
Hydrodynamic Flow Focusing (HFF)	Rapid mixing by diffusion → fast precipitation, controlled self-assembly



Droplet-based synthesis	2 immiscible liquids pressurized at junction → uniform microdroplets; crosslinking within droplets
Coaxial Flow Reactors (CFR)	3D core-sheath laminar flow; sensitive cargo (proteins/mRNA/cells) in inner capillary, antisolvent in outer tube

Nunziata et al²⁰ developed fluorescent PEG-Jeffamine nanogels through orthogonal click chemistry using continuous flow microfluidics and compared it with the organic batch. They used 2 fluorescent dyes, namely FTIC, which here in this study mimics the hydrophobic drug and RhB, that will mimic the hydrophilic one. The study concluded that both model compounds were encapsulated by the nanogel, and the EE% increased from 54.2% to 84.9% for FTIC and 92.1% to 95.9% for RhB. In addition to that, it showed increased circularity and monodispersity with size ranging from 90-110nm.²⁰

Unlike Nunziata²⁰ who used orthogonal click chemistry using continuous flow microfluidics to develop fluorescent PEG-Jeffamine nanogels and compared it with the organic batch, Mastella & Luin²¹ utilized another bioorthogonal click chemistry reaction- SPAAC, a catalyst-free reaction, which makes it suitable for the preparation of nanogels intended for biomedical applications. They applied this in a microfluidic assembly to generate polyglutamic acid-based nanogels. The essential parameters, Flow rate ratios (FRR), and Total flow rates of the microfluidic assembly were screened to evaluate at what flow rates one can obtain smaller and more uniform nanogels. The DOX-loaded (PGA)-based

nanogels were prepared which showed increased EE% of 65% and higher FRR and TFR showed greater uniformity and smaller size when compared to the traditional batch synthesis.²¹

Focusing on the development of microfluidic devices for one-step nanogel synthesis, Montalbo et al²² in their recent work engineered a fluorocarbon microfluidic chip for one-step flow synthesis of polymeric nanogels. The fluoropolymer coating is a high-performance elastomer that will provide excellent chemical resistance and thermal stability, hence is a great choice for using it to perform homopolymer synthesis and eventual crosslinking to form nanogels all in a single chip. The coating will also act as an antifouling surface, therefore avoiding unnecessary monomer sticking and fabrication is also easier when compared to a glass device. They fabricated this device using Fluorolink MD-70- a PFPE as fluoropolymer elastomer and introduced 2 mixers, one long channel for RAFT synthesis of stimuli-sensitive polymers which are then directed to an HFF junction for rapid mixing with the crosslinker to produce nanoparticles. The study concluded that the development of a fluorocarbon microfluidic chip had higher compatibility and easy and quick fabrication when compared to the PDMS or glass chips.²²

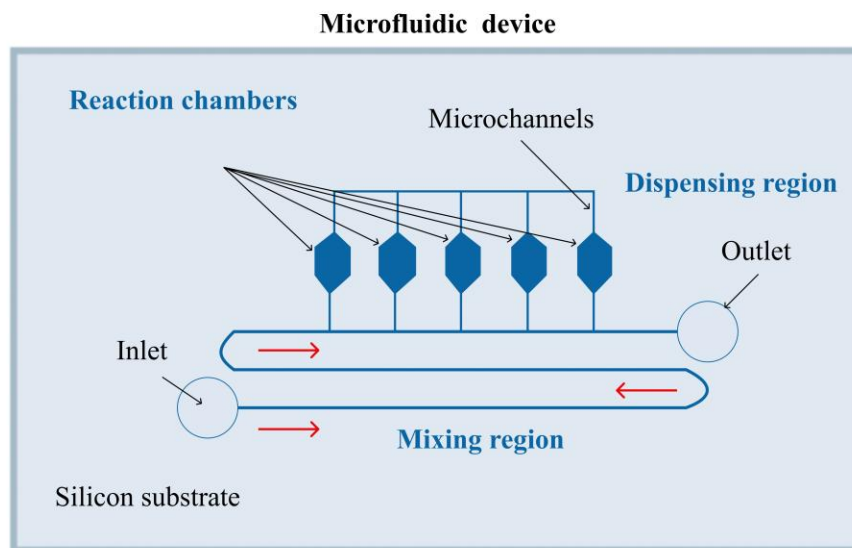


Fig 4 – Microfluidic Device

General schematic diagram of a microfluidic device layout for nanogel synthesis, illustrating the inlet port, mixing region, microchannel network, and dispensing/reaction chambers leading to the outlet port.

Further advancement in microfluidic nanogel synthesis was demonstrated by Giannitelli et al²³ in which a pressure-driven actuator system for synthesis of nanogels in droplet-based microfluidics was developed. They introduced a pneumatic micro-actuator in the HFF junction which allowed them to control the NP size in real time and ensured monodispersity. They directed their nanogel system for ovarian cancer using DOX as the anti-cancer agent, hence utilizing the polymer HA or Hyaluronic acid - a well-known marker for cancer cells and Polyethyleneimine. With this system they could achieve the size range of 92–190 nm and PDI of 0.015 which they argued was unfeasible in traditional batch synthesis.²³

Despite its precision, microfluidics fabrication carries real limitations that restrict its path towards

clinical translation. Throughput being the core issue. The device's performance depends on tightly controlled fluid flow in the order of microns, making the production limited due to low flow rates and output too low for most practical manufacturing volumes.⁵⁷ Thereby, directly conflicting with the large batch sizes which the pharmaceutical production generally requires. Apart from this, the channels in the device are usually prone to clogging owing to its micrometer size, affecting the intricate geometrics such as flow-focusing junctions used in the studies here. The chip materials themselves add to the limitations, wherein the PDMS- based devices, commonly used; suffer from limited solvent compatibility,⁵⁸ and the more recent fluoropolymer-coated chips though chemically more restrained, add to the cost and complexity.²² Complex architecture, precise syringe pumps and temperature control systems of this assembly pushes the overall implementation cost well above the conventional batch synthesis.⁵⁸

4. LOADING OF NANOGELS

The loading of cargo in nanogels is unarguably a decisive step in the development of nanogels as it governs encapsulation efficiency (EE%), drug-loading capacity (DLC%), release kinetics and in-vivo performance of the carrier. We can broadly classify the drug-loading strategies described in the literature for nanogels into physical entrapment, covalent conjugation, and controlled

self-assembly. A fourth route also available is the post-loading of a preformed nanogel by either diffusion or incubation, widely used when the payload or the nanogel network is sensitive to the synthesis conditions.^{24,25}

COMPARISON OF DRUG-LOADING STRATEGIES FOR NANOGEL DRUG DELIVERY SYSTEMS

Table-2

Strategy	Best-suited Drug Type	Advantage	Limitation	Ref
Physical entrapment	Hydrophobic small molecules, lipophilic drugs	Simple, single step; preserves native drug structure	Burst-release risk; batch-to-batch EE% variability	24,26
Covalent conjugation	Potent cytotoxic agents (e.g., doxorubicin)	Minimizes premature leakage; precise stimuli-triggered release	Needs reactive functional group; complex multi-step synthesis	25,27,28
Ionic/electrostatic complexation	Charged macromolecules (insulin, siRNA, pDNA)	High loading efficiency under mild aqueous conditions	Sensitive to pH/ionic strength; colloidal instability risk	29,30
Post-loading (diffusion/incubation)	Drugs unstable during network-formation conditions	Avoids exposure to organic solvents/radicals/heat	Lower loading capacity (diffusion-equilibrium limited)	25,31

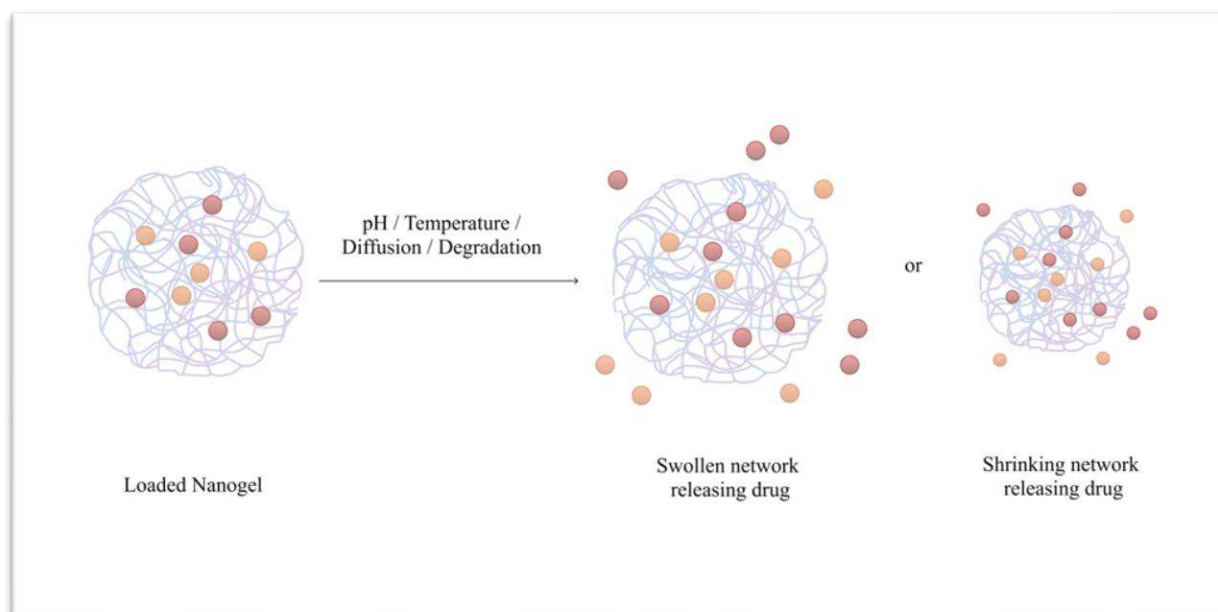


Fig- 6

Drug release from a loaded nanogel in response to pH, temperature, diffusion, or degradation, leading to either swelling or shrinking of the polymer network. Both will cause the release of cargo from the nanogel network

5. FUNCTIONALIZATION: AN EMERGING FRONTIER IN NANO GEL DESIGN

As discussed earlier, delivering a pharmaceutical agent to its target and governing its release such that the dose stays at therapeutic levels is ultimately the fundamental goal in pharmaceutical and biomedical research. Conventional nanogels show a great promise in drug delivery applications; however, research is moving forward towards functionalization of nanogels to fulfill the growing complex needs in biomedical research. Functionalization of nanogels, at present generally include; altering its surface chemistries, introducing target ligands, causing nucleophilic interactions, biomimetic coating, immobilizing proteins and antibodies onto the surface of

nanogels to impart specific properties to the system.

Functionalization is usually done by either of the 2 ways; one is we can functionalize them *during* its synthesis; the other is *after* the nanogel has been formed. The former procedure is beneficial in scaling since it only involves a single step; however, the main issue is the incomplete colloid formation as the functionalization will hinder the primary assembly process. The latter one avoids interference with the assembly however; an additional processing step will increase the complexity of scale-up.³²

Surface Functionalization is a pivotal strategy to improve the surface interactions with biological fluids, imparting the system with benefits such as anti-fouling surface, targeting, adherence to the target membrane which was specifically shown by Al-Awady et al³³ wherein berberine encapsulated in PAA-based nanogels surface functionalized with a cationic polyelectrolyte - PDAC, showed higher adherence to the cell membrane causing greater release of berberine on *E.coli* and

Chlamydomonas reinhardtii, thus substantially increasing the systems antimicrobial action.³³

While this study demonstrated how electrostatic surface functionalization can enhance antimicrobial effect, the cationic adherence is non-specific hence this specific study is better for achieving broad antimicrobial applications and not selective targeting.

Similarly, a surface functionalization strategy involving a metal-chelating agent was developed by grafting NTA, which is a conjugate of lysine,

onto the surface of PLA-based nanogels that can chelate transition metal ions like Ni^{2+} and Co^{3+} . With this surface modification, His-tag mediated docking can easily be explored in polymeric literature which was earlier only used in protein purification. Using His-Rhodamine as a model ligand, Co^{3+} -chelated nanogels demonstrated higher His-tag grafting density when compared with the Ni^{2+} -chelated nanogels, which is notable since Ni^{2+} -NTA chemistry is usually the default. In cisplatin delivery applications, again the former performed better in ovarian cancer cells than free drug in vitro.³⁴

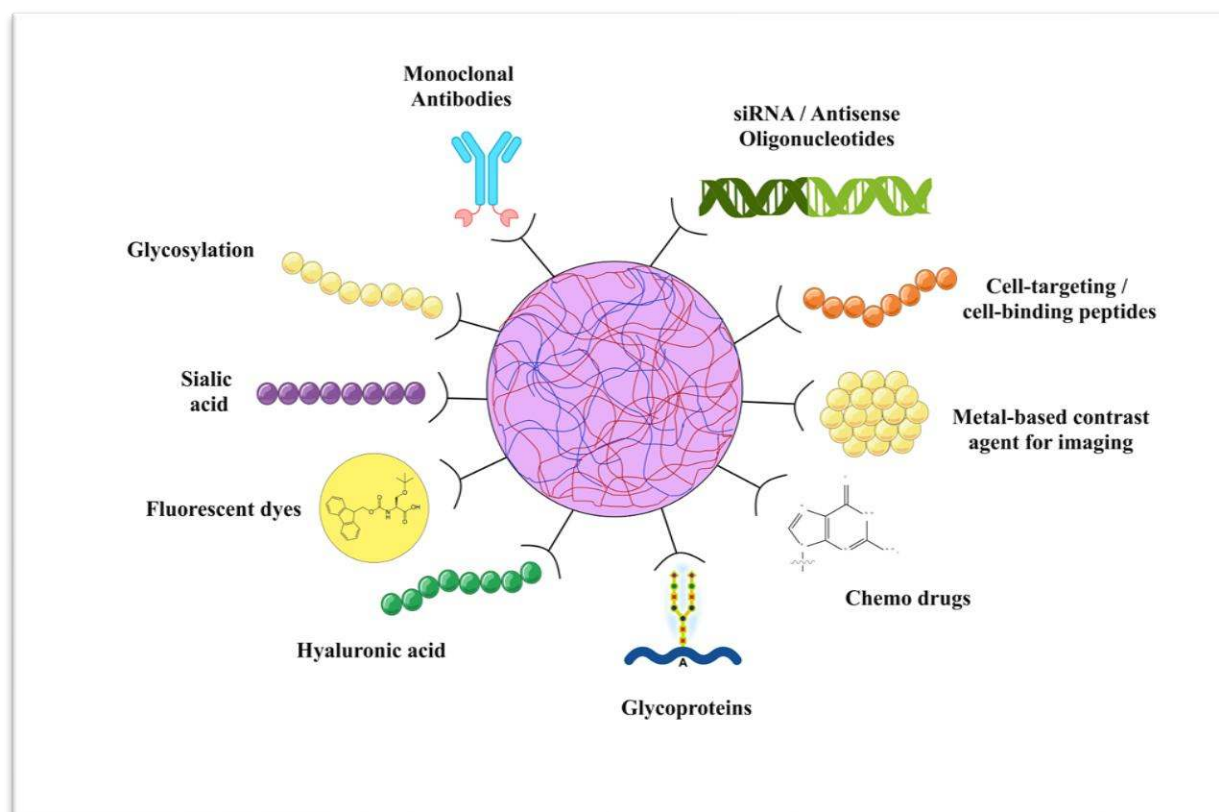


Fig -7

Functionalization strategies for nanogels, showing surface conjugation with targeting ligands Adapted from Narayanan et al⁵⁹ licensed under CC-BY 4.0.⁵⁹

Unlike surface functionalization achieved by attaching ligands, one can also functionalize the nanogel by controlling the spatial orientation of the existing monomers in the nanogel network. One such study was done by Cruz-González et al³⁵ where they prepared nanogels formed by NIPAm-

EG copolymers, in which the placement of the NIPAm monomer in the structure was random, confined to the core region, or localized at the surface of the nanogel. When NIPAm was placed at the surface of the nanogel, they noticed the formation of hydrophobic spots and Janus structures which exposed the hydrophilic EG segments at physiological temperature. On the other hand, when the localization was at the core, a VPTT value close to the one in pure pNIPAm gels was obtained, while when it was random or surface-localized, the VPTT was increased.³⁵ This goes on to show that not only the surface of the nanogels can be functionalized to achieve thermoresponsiveness but we can also engineer the internal structure of the nanogel, thus offering us an additional design with which we can tailor our desired nanogels.

Biomimetic surface functionalization is yet another kind of functionalization which has recently emerged as a newer and more advantageous strategy, where cell-derived materials are immobilized on the nanocarrier which will aid in camouflage, eluding immune system clearance, achieving targeting ability, which is by far difficult to achieve through normal conventional chemical conjugation strategy.

Liu et al³⁶ applied this approach by developing RBC membrane vesicle (RV)-camouflaged nanogels and further decorated it with luteinizing hormone-releasing hormone (LHRH) for targeted delivery of the drug HCPT in prostate cancer (LHRH-RV-NG/HCPT). The resulting NPs were around 100nm in size, which they highlighted as a size suited for passive tumor targeting by taking advantage of the EPR effect. Targeting the prostate cancer cells was ensured by the LHRH decoration, while RV coating helped lessen the premature drug release, allowing the drug to be accumulated at the tumor site. The CD47 protein also presents

on the NP surface, helped them evade immune clearance and thereby increasing the circulation time of the prepared nanogel. In-vivo experiments showed that these dual-layer biomimetic nanogels showed higher tumor accumulation and hence stronger anti-tumor activity when compared to the free drug and other nanocarriers.³⁶

However, layering multiple functional components onto a single nanogel, here, an RBC membrane coating and a targeting ligand increasing manufacturing complexity at each added step; each layer introduces its own batch-to-batch variability. The purification burden scales with the number of conjugation steps rather than any single one. This raises a genuine question of whether dual- or multi-layer biomimetic systems can be manufactured with the reproducibility required for regulatory approval.

Another study concerning the biomimetic surface functionalization was done by Li et al³⁷ where they formulated cancer nanovaccines, through the development of a dendrimer nanogel coated with CpG-functionalized exosomes taken from pancreatic cancer cells (Au@DNG@C-Exo). They loaded the core with drug doxorubicin along with gold NPs, for tumor imaging. The exosomes coated on the surface aided in homologous targeting, allowing the nanogel to enter the same type of cancer cells the exosomes were derived from. The drug release on reaching the tumor environment caused “immunogenic cell death”, a process that triggers the entire immune system to do the same, which was further increased by the CpG adjuvant. When tested in a pancreatic cancer mouse model, it not only suppressed the growth of tumor but also prevented formation of tumor on re exposure.³⁷

This durability comes at a structural cost distinct from conjugation-based strategies, because the exosomes must be derived from patient-specific

pancreatic cancer cell lines, each batch is inherently personalized rather than off-the-shelf, which limits standardization across patients and makes conventional large-batch manufacturing largely incompatible with this approach.

Recent literature shows that one can target not only the delivery of drugs but also the cell death pathway in anti-cancer therapeutics. One such study by Yang et al³⁸ where they designed M1 macrophage membrane-coated chitosan-ferrocene-sodium alginate nanogels, loaded with drug pravastatin (CFA/PRV@MM), to trigger ferroptosis, which is an iron-driven cell death due to lipid damage, as the preferred route for immunogenic cell death. Ferrocene increased the ROS and statin blocked another additional antioxidant route which in turn reduces the glutathione, thereby overcoming the tumor's usual resistance to ferroptosis. The study concluded that in the mouse breast cancer model this system effectively reduced tumors and triggered an immune response with minimal side effects.³⁸

The above studies highlight how one can combine biomimetic surface functionalization with varied components having specific applications to achieve a system that can effectively bypass the resistance that arises in conventional delivery systems, while also providing additional applications such as bioimaging, controlled drug release, making biomimetic functionalization a versatile platform for the forthcoming nanogel therapeutics.

However, none of the studies discussed above addressed reproducibility or scale-up feasibility, a gap that needs to be closed before this system can move towards clinical translation. Apart from the problems concerning the scale-up, one must also move their attention towards toxicity that arises when we decrease the size to nano-dimension, as many studies claim how different molecules act in

this specific dimension for example *Au* being entirely inert in original form is highly reactive in nano-form. Henceforth, the authors of this work want to highlight the largely unstudied platform that needs to be particularly addressed and researched on – Nanotoxicology.

6. APPLICATIONS

6.1. Nanogels for drug delivery:

Comb-like anionic polymers with hydrophobic alkyl side chains gave pH-sensitive nanogels loaded with camptothecin for oral delivery, with enhanced cell uptake and anti-tumor activity.³⁹ Nanogels synthesized through thiol-maleimide coupling and thiol-disulfide exchange as orthogonal approaches, functionalized with cell-targeting peptides, showed greater internalization in breast cancer cells and enhanced cytotoxicity in glutathione-rich cells.⁴⁰

6.2. Nanogels as biosensors:

Nanogels have also been found useful in biosensing due to their nanoscale dimensions, high water content, porous polymeric network, and responsiveness to environmental changes. Their polymeric network can be functionalized with enzymes, antibodies, or nanoparticles to selectively bind the target analyte and convert the interaction into an optical, electrochemical, or mass signal. Recent studies have shown the use of nanogels in the detection of clinically relevant biomarkers and pathogens. These findings show the potential of nanogels in the design of sensitive and selective biosensors.

6.3. Nanogels for gene delivery:

In addition to being used for drug delivery, cationic nanogels have also been investigated for their applicability as non-viral vectors for nucleic acid delivery and can act as an alternate delivery



approach compared to the conventional lipid-based delivery systems as well as viral vectors. One major advantage that the former offers over the latter is the possibility of tailoring the biodegradability of the system along with the reduced immunogenicity. The chitosan-based nanogels are especially popular as a choice for this kind of application due to the inherent property of positive charge that makes it capable of forming electrostatic complexes with negatively charged DNA/RNA molecules.

6.4. Nanogels used against cancer:

A variety of nanogel-based drug delivery systems have been tested in several areas of anticancer research. In each of them, the drug delivery system is based on the incorporation of an active agent into a nanogel by a particular method that allows achieving specific benefits like targeting, stability, or efficacy. Different drugs have been loaded using different methods, from simple physical entrapment to electrostatic binding, showing that even basic loading approaches can give strong anticancer effects.

6.5. Nanogels for vaccine delivery:

Nanogels have been recently proposed as promising candidates as vaccine carriers due to their capability to entrap and stabilize antigens, as well as delivering them in controlled manner. Different nanogel systems have been used to carry antigens alone or along with adjuvants, helping the immune system respond better.

6.6. Nanogels as carriers:

Nanogels have been extensively studied for use as drug delivery carriers owing to their small sizes, high water content, large surface areas, and stimulus-responsive nature. Nanogels consist of three-dimensional polymeric networks with enough space to encapsulate the drugs and at the same time protect them from degradation and allow their sustained release.

REPRESENTATIVE NANOGEL SYSTEMS ACROSS MAJOR BIOMEDICAL APPLICATIONS

Table -3

Application	Example Study	Key Finding	Formulation Feature	Ref
Drug delivery	Comb-like anionic C14 nanogel, camptothecin (oral)	Release: $7\pm 5\%$ at pH 1.2 (stomach) vs $78\pm 2\%$ at pH 7.4 (intestine), 24h	pH-sensitive, hydrophobic alkyl side chains	39
Drug delivery	Thiol-maleimide/thiol-disulfide nanogel, docetaxel	GSH-triggered release; peptide-functionalized $\rightarrow$ higher breast cancer cell uptake	Orthogonal redox-responsive crosslinking	40
Biosensing	CoA-responsive electrochemical nanogel sensor	Detected osteoarthritis-related biomarkers	Enzyme-functionalized coating	41
Biosensing	Nanogel-based SPR biosensor	Rapid detection of SARS-CoV-2-neutralizing antibodies	Antibody-specific molecular interaction surface	42
Gene delivery	Chitosan nanoparticle + GFP-reporter plasmid	~ 260 nm; crossed blood-brain barrier in vivo	Complex coacervation	43

Gene delivery	Chitosan NP + SARS-CoV-2 Omicron spike plasmid	Equal efficiency vs. commercial transfection reagent (HEK-293T)	Simple electrostatic complexation, no ligand	44
Anticancer	PNIPAM microgel with Ag and Fe ₂ O ₃ bimetallic nanoparticles (in-situ synthesis)	Cytotoxicity against human colon cancer cells (SW480), with selectivity over normal cells (NIH/3T3)	In-situ bimetallic NP integration, dual drug-delivery and catalytic functionality	45
Anticancer	Chitosan-albumin + doxorubicin	29 nm; protection against photodegradation, enhanced toxicity vs free drug	Electrostatic tight binding	46
Anticancer	Chitosan NP + thiocolchicoside + lauric acid	Apoptosis via Bax/Bcl-2 shift; dual anticancer/antimicrobial action	Dual-drug loading	47
Vaccine delivery	pNIPAM nanogel + OmlA antigen	~250 nm; induced OmlA-specific IgG in mice via nasal route	Thermoresponsive, macrophage uptake	48
Vaccine delivery	pNIPAM nanogel + ovalbumin	Biocompatible/immunogenic in murine & equine models	Cross-species evaluation	49
Vaccine delivery	Cholesteryl pullulan nanogel + TLR7/8 adjuvant	25 nm; increased CTL response, no free-adjuvant inflammation	Dual antigen + adjuvant co-delivery	50
Transdermal	Spanlastic nanogel, raloxifene	216% bioavailability vs oral suspension; improved bone mineral density (ovariectomized rats)	No skin irritation observed	51
Carrier platform	HA-based nanogel + cationic peptides	Physicochemical properties tunable by peptide cargo	Self-assembled, mild synthesis	52
Carrier platform	Nanogel + cell-penetrating peptide (UTI treatment)	Improved cellular uptake, antibacterial activity	Peptide-functionalized targeting	53
Carrier platform	Multi-target nanogel, spinal cord injury	Reduced neuroinflammation, improved repair (in vivo)	Dual-mechanism (anti-inflammatory + repair)	54

7. FUTURE CHALLENGES:

7.1. Clinical Translation:

Despite the considerable amount of research reviewed here, no nanogel formulation has yet received regulatory approval for systemic pharmaceutical use. The marketed nanogel-based products remain largely confined to the field of cosmeceuticals and are used for topical anti-aging and acne treatments rather than prescription drug

products administered systemically. This gap between research and clinical translation is not accidental; it can be directly associated with the limitations inherent in the very synthesis and functionalization methods reviewed in this article.

Conventional emulsion polymerization requires excess surfactant for stabilization of micelles, thereby increasing the purification burden and potential surfactant toxicity concerns. ATRP provides good control over polydispersity but uses

transition-metal catalysts, hence making residual metal contamination a biocompatibility concern and requiring additional, often incomplete, purification steps before the formulation can be considered for systemic administration. RAFT avoids metal catalysts but carries its own burden, requiring removal of thiocarbonylthio chain-transfer agents (CTA) associated with color, odor, and potential toxicity.⁴⁷ Therefore, RAFT-synthesized nanogels also require their dedicated CTA-removal step in its synthesis. Microfluidic fabrication offers excellent particle size and polydispersity control but is limited by high equipment costs and low production throughput, restricting its large-scale economic viability.⁵⁵

7.2. Nanotoxicology:

Reducing a therapeutic system to nanoscale dimensions not only affects the size of the system, but is capable enough to alter its biological reactivity, cellular uptake behavior, and biodistribution relative to the same material in bulk form. This change in behavior due to the nano-sizing of particles is central to nanotoxicology, and it applies directly to the functionalized nanogel systems discussed throughout this review. Particularly those incorporating metallic components (*Au NPs* for imaging), biomimetic coatings, or high-density surface ligand conjugation.

Although there have been numerous studies that show the impressive invitro and in vivo efficiency, discussed in this very review, not many studies have undertaken any sort of systematic and standardized nanotoxicological investigations. This is part of a greater problem that affects the entire field of nanomedicine -- lack of universal standardized protocols for nanotoxicological investigations. Thereby, making safety data difficult to analyze and assess. The nanoparticle safety depends on several parameters, such as size,

shape, surface charge, surface chemistry, distribution, and clearance, and there are no adequate long-term risk assessments done. Moreover, variations between animals and genetically and physiologically different populations of people make it unclear whether the safety and efficacy of the nanoparticles can be reliably reproduced. It becomes especially relevant for functionalized and advanced nanogels which have additional biomimetic or cell membrane coatings and thus introducing additional biological interactions and complexity. The application of some modern technologies, such as artificial intelligence analysis of nanotoxicology data, may assist in finding the physicochemical characteristics responsible for biological risks and help with safety assessment,⁵⁶ however these are still in early stage of development and require regulatory validation. Thus, standardized and harmonized toxicology evaluation for residual impurities, functionalization-related risks, biodistribution, clearance, and long-term toxicity is crucial for enhancing the reproducibility, regulatory approval and the clinical translation of nanogels.

7.3. Functionalization barriers:

The problems of synthesis-stage nanogels are further exacerbated when it comes to the functionalization stage. As it has been noted in the Functionalization section (5), the use of biomimetic tactics, such as cell membrane coating or patient-specific exosomes is the most efficient strategy in terms of specificity and immunity evasion, but at the same time requires the source, separation, and batch reproducibility challenges, which become more acute with increased volume of manufacturing process. Unlike small molecules, where synthesis will be relatively cheaper on a larger scale, biomimetic and multifunctional

nanogels run a risk of becoming more expensive to produce on mass scale.

7.4. Accessibility and affordability of nanogel therapeutics:

The growing complexity and cost of functionalized nanogels may hinder widespread use. Advanced systems, including biomimetic or patient-/donor-material-dependent nanogels, may be costly to manufacture. Therefore, these therapies may be concentrated in personalized or precision-medicine settings and only be available to patients with financial means or insurance coverage, not to the general population as affordable pharmaceutical products. This raises a critical question about whether nanogel therapeutics will have equal access to conventional medicines. Therefore, cost-effective, scalable, and standardized manufacturing strategies should be adopted early on in nanogel development to make them more affordable and accessible.

8. DISCUSSION & CONCLUSION

Nanogels have come a long way since they were first developed as a simple polymer network for carrying antisense oligonucleotides. Today, they can be built in many different structures, made from a wide range of polymers, and designed to respond to specific triggers in the body such as pH or temperature. Their biggest strength is the ability to swell while holding onto their nanoscale size, which gives them a level of control over drug release that many other carriers cannot match.

That said, this review also shows that nanogels are still far from being a finished technology. Every synthesis method comes with its own detriment, emulsion polymerization needs large amounts of surfactant that are hard to remove, ATRP leaves behind metal catalysts, RAFT leaves behind chain-transfer agents that need their own removal step,

and microfluidics, while precise, is expensive and slow to scale. Functionalization, especially biomimetic approaches using cell membranes or exosomes, gives nanogels better targeting and longer circulation time, but these methods are difficult to reproduce from batch to batch and get more expensive as production increases.

Most of the studies covered here show strong results in cells or animals, but very few of them look closely at toxicity once the material is brought down to the nanoscale, and there is still no standard way of testing this across the field. This makes it hard to compare safety data between studies or build confidence for regulatory approval. As a result, despite dozens of promising formulations in the literature, no nanogel has yet been approved for systemic drug delivery, and current marketed products are limited to topical cosmetic use.

Going forward, the field needs to focus less on adding more complexity to nanogels and more on making the synthesis, purification, and testing steps simpler, cheaper, and reproducible. Only once these practical barriers are addressed can nanogels move from being a promising research tool to an accessible drug delivery system used in the clinic.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest associated with this manuscript.

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