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Inorganic nanoparticle-based nanogels and their biomedical applications

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The advent of nanotechnology has brought tremendous progress in the field of biomedical science and opened avenues for advanced diagnostics and therapeutics applications. Several nanocarriers such as nanoparticles, liposomes, and nanogels have been designed to increase the drug efficiency and targeting ability in patients. Nanoparticles based on gold, silver, and iron are dominantly used for biomedical purposes owing to their biocompatibility properties. Nanoparticles offer an enhanced permeation into tissue vessels; however, their short half-life, toxicity, and off-site accumulations limit their functionality. The above shortcomings could be prevented by employing an integrated system combining nanoparticles with a nanogel-based system. These nanogels are 3D polymeric networks formed by physical and chemical crosslinking and are capable of incorporating nanoparticles, drugs, proteins, and genetic materials. Modification, functionalization, and introduction of inorganic nanoparticles have been shown to enhance the properties of nanogels, such as biocompatibility, stimuli responsiveness, stability, and selectivity. This review paper is focused on the design, synthesis, and biomedical application of inorganic nanoparticle-based nanogels. Current challenges and future perspectives will be briefly discussed to emphasize the versatile role of these multifunctional nanogels for therapeutic and diagnostic purposes.

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Introduction

About 95% of all new drug candidates have poor biopharmaceutical and pharmacokinetic properties.[1,2] The primary concerns with these drug candidates remain their poor solubility,

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off-site accumulation, side effects, and inability to reach the targeted site with the desired concentrations.[3,4] Nanotechnology offers a plethora of materials and tools that expand their applications in every arena of biomedical sciences, with particular interest in diagnostics and therapeutics.[5] The primary aim of the development of nanotherapeutics is to overcome the challenges faced by conventional therapeutic drugs used to treat pathological diseases.[6] Depending on the loading methods used for diagnostic and therapeutic molecules on nanomaterials, these molecules can be encapsulated, dissolved, covalently attached, or adsorbed onto the nanomaterial surface. Additionally, the enhanced permeation and retention (EPR) effect in cancer tissues also contributes to adding some specificity to these nanomaterials.[7] These interactions enable the design of various nano-sized drug carrier conjugates, such as liposomes, nanoparticles, and nanogels.[8,9] These nanocarriers serve as a framework for loading and releasing drugs without affecting the tissue vasculature and blood circulation and maintaining efficient pharmacological properties of the agents.[10] Due to the nanosize (1–100 nm) of these carriers, they are effectively internalised within the cells through normal uptake methods like endocytosis and transcytosis.[11] Nanocarriers have increased therapeutic efficiency, reduced health costs, and provide a convenient route of administration for drugs.[12] Although there has been an immense surge in the development of nano-based systems, the formation of an integrated system that is unaffected by the immune system while circulating within the blood vessels and has efficient targeted delivery without any collateral cellular damage remains a challenge.[13]

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Nanoparticles have advantages over large particles because of their small size, high surface-to-volume ratio and peculiar optical, magnetic, and electrical properties.[14,15] Along with the aforementioned properties, functionalization and conjugation with biomolecules or drugs have led to increased application of nanoparticles, both in diagnostics and treatment.[16] The large surface area of these nanoparticles enhances the vascular circulation lifetime, thus increasing the efficacy of drugs, making them more potent at lower concentrations. The surface functionalization and modification of nanoparticles lead to an increase in the selectivity of drugs, which also gives them immense potential for acting as multifunctional agents.[17] However, despite these benefits, nanoparticles are accompanied by toxicity due to their efficient penetration through bio-membranes and interference with cellular basal metabolic reactions.[18] Since these particles are easily translocated within the body through the circulatory and neural networks, they tend to accumulate within specific organs due to ineffective clearance pathways. The accumulation of these nanoparticles and the immune system affecting the therapeutic efficiency of nanoparticles are some of the major concerns in developing them into potential therapeutic candidates.[19,20] Thus, there is an immediate need to develop integrated systems to mitigate the shortcomings of nanoparticles without affecting their properties.

Nanogels are three-dimensional nano-sized polymeric structures synthesized through physical and chemical linkages. These nanogels have attracted much interest in the field of theranostics owing to their biocompatibility, high water content, enhanced vascular circulation lifetime, targeted drug delivery, and ability to carry different types of molecules and drugs.[3,21] Furthermore, nanogels are structurally diverse and, therefore, could be functionalized and modified on an on-demand basis, forming a 'smart' drug delivery system.[22] These stimuli-responsive nanogels are designed to undergo structural and physical modification in response to stimuli like light, pH, temperature, and ultrasound. The stimuli-directed responsiveness of some nanogels is primarily due to their internal aqueous environment and microporous structure.[23,24] Although numerous studies have been carried out to develop mono-responsive nanogels, the design and development of nanogels with specific functions and desired properties in a particular area remains to be fully explored. Ideally, the short half-life of nanoparticles in the circulatory system is due to their small size, so the most efficient way of drug delivery is to initially deliver a large-sized nanomaterial, which will release small-sized nanoparticles at the desired site.[25] Thus, delivering nanoparticles enclosed in a biocompatible nanogel is an effective method for targeted drug delivery. This review will discuss the synthesis and biomedical applications of nanogels enclosing inorganic nanoparticles, as shown in Fig. 1. Gold, silver, and iron nanoparticles will be of particular interest due to their biocompatibility, optical sensing, photothermal, radiotherapy, and magnetic properties.[15,26] Further discussion about the current progress and challenges these delivery

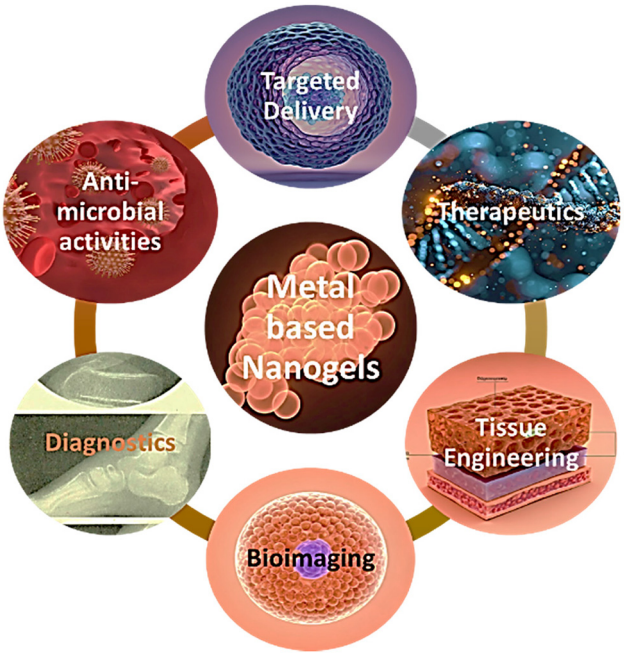

Fig. 1 Schematic diagram representing the various applications of metal-based nanogels.

systems face, followed by potential solutions, will provide extensive insight into the topic.

Nanogels

Nanogels are 3D polymeric hydrogel materials with nanoscale size. Nanogels can be further subclassified as nanohydrogels and nano-organogels. Nanohydrogels are polymers composed of nanosized hydrogels, offering several advantages such as biocompatibility, controlled drug release, and the capacity to accommodate a wide range of molecules.[27,28] Nano-organogels can also be used for the effective transportation of water-insoluble drugs.[29,30] These gels are formed through cross-linking hydrophilic polymers and can absorb large volumes of physiological fluids or water. Thus, properties like high water content, biocompatibility, tunable size, multivalent bioconjugation, and an internal network supporting the uptake of a wide range of biomolecules and complexes make them more beneficial than other nanocarriers such as liposomes, micelles, *etc*.[31] Nanogels hybridized with other polymers are known as hybrid nanogels and they tend to preserve the unique properties of each component. Hybrid nanogels fall into two categories: polymer–nanogel composites and nanomaterial nanogels, as shown in Fig. 2. Polymer–nanogel composites consist of interpenetrated networks and core–shell particles, whereas in nanomaterial nanogels, generally carbon-based nanomaterials are integrated into the nanogel structure, some examples include graphene, fullerenes, plasmonic materials, and carbon nanotubes.[32] Among them, magnetic nanogels have shown significant potential in the field of pharmaceuticals and biomedical science.

Synthesis

Nanogels can be formulated using various methods and materials [Fig. 3]. Among them, radical polymerization in an inverse emulsion is most commonly used. In this method, crosslinkers, catalysts, and monomers dispersed in aqueous solutions are stabilized by surfactants in the organic phase, forming droplets that polymerize into nanogels. Some frequently utilized monomers include acrylamide, pH-sensitive acrylic acids, and thermosensitive *N*-isopropylacrylamide (NIPAM).[33] Another method for forming nanogels involves the crosslinking (physical or chemical) of modified hydrophilic polymers through conjugating functional groups such as thiols and acrylates. Amphiphilic polymers, such as chole-

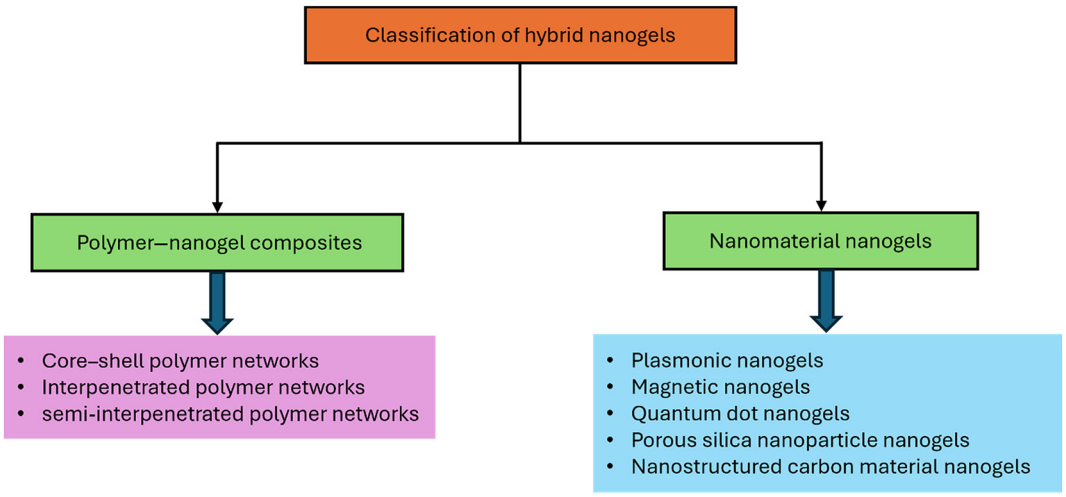

Fig. 2 Schematic diagram of the classification of hybrid nanogels.[32]

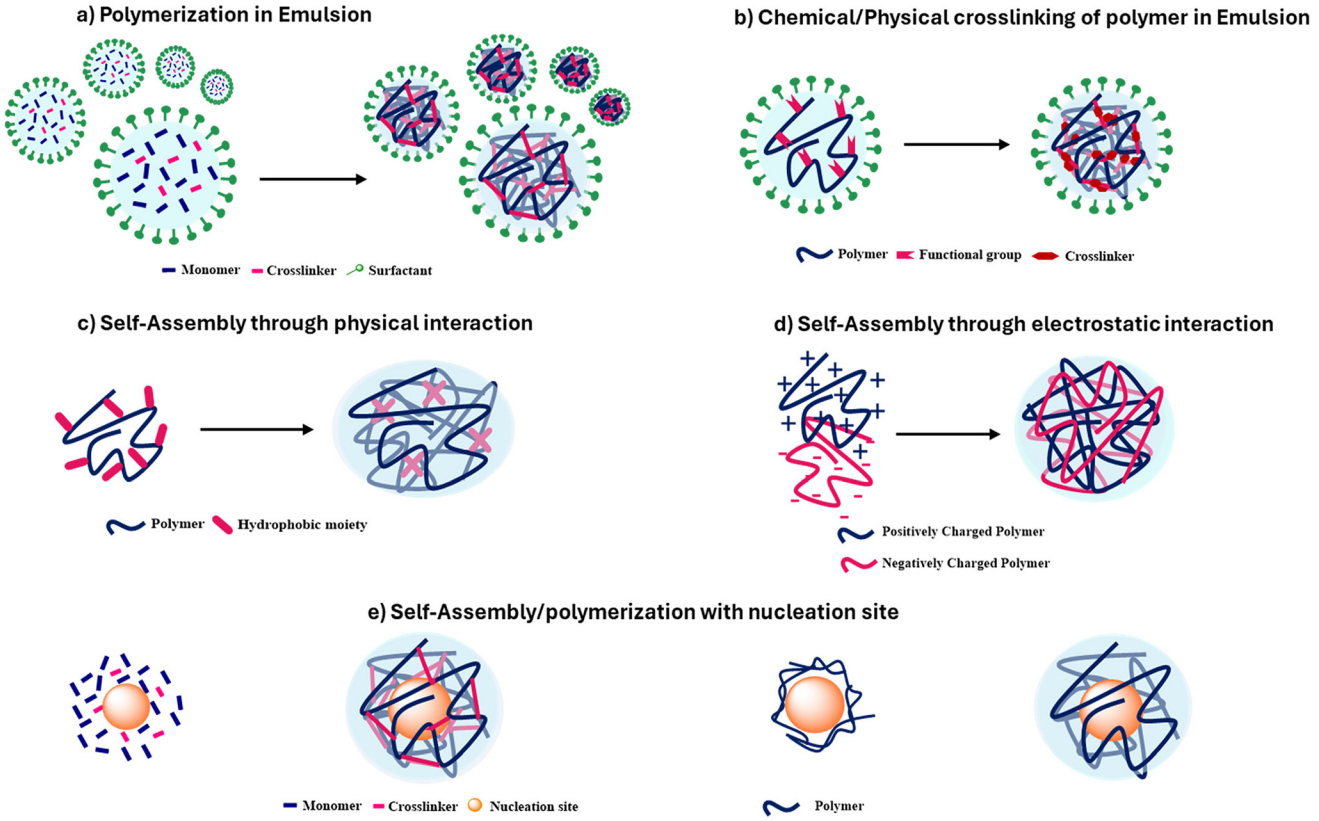

Fig. 3 Nanogel formulation strategies. (a) Hydrophilic monomers and crosslinkers in a water-in-oil emulsion stabilized using surfactants. Upon the addition of a catalyst, polymerization occurs within the emulsion droplets, forming nanogels. (b) Hydrophilic polymers modified with functional groups that allow physical/chemical crosslinking to form nanogels. (c) Polymers modified with hydrophobic moieties for self-assembly into nanogels. (d) Self-assembly of positively and negatively charged polymers through electrostatic interaction. (e) Polymerization of monomers and crosslinking shells or self-assembly of polymers modified with hydrophobic moieties in the presence of nucleation sites.[33]

sterol-modified pullulan, can also form nanogels through self-assembly. Both of the aforementioned methods can utilize natural polymers, such as non-immunogenic polysaccharides (chitosan, dextran, hyaluronan). The self-assembly method does not require surfactants for stabilization, making the procedure more robust and facile.[34,35]

However, since physical crosslinking is unstable, chemical crosslinking is required for *in vivo* applications. Additionally, nanogels can be generated by interacting two oppositely charged polymer chains through electrostatic interactions. This method is convenient and simple as it avoids the polymer modification steps essential in previous methods. However, nanogels formed solely through electrostatic interactions are not stable. Furthermore, nanogels can also be formed using nucleation sites. In this process, inorganic nanoparticles such as iron oxide nanoparticles (IONPs) or quantum dots serve as sites where polymers or monomers adsorb and polymerize.[36] These nucleation sites act as nanogel formation templates, generating nanogels with higher monodispersity. Each method for nanogel preparation has been detailed in various reports presenting comprehensive reviews.[36–38]

Inorganic nanocarriers. Nanoscale organic particles have been most frequently used for drug delivery, imaging, and therapeutics. Some examples of nanosized organic particles are liposomes, micelles, biomolecule-conjugated polymer nanoparticles, and polymersomes.[39–41] The biocompatibility and minimal side effects of organic nanoparticles are commendable.[42] However, in the past few years, inorganic nanomaterials have attracted the attention of researchers due to their distinct material and unique size-dependent physiochemical properties. Their inertness, stability, and functionalization properties also give them an edge over the common organic nanoparticles. Inorganic nanoparticles, mostly gold, silver, and iron, have been utilized in both preclinical and clinical trials for the diagnosis and treatment of numerous diseases.[43] Owing to the optical, magnetic, and electronic properties combined with the nanosized structure, they are found to be potential therapeutic and imaging agents.[44] Despite having the potential to solve the traditional drug limitations, such as delivering poorly soluble drugs, effective internalization, *etc.*, these inorganic nanoparticles are still accompanied by some drawbacks, such as premature leakage from the body instability in the *in vivo* system.[45] Thus, enclosing these nanoparticles within a biocompatible and target-specific carrier is an effective alternative for overcoming the shortcomings of nanoparticles.

Gold nanoparticle-based nanogels

Gold nanoparticles (Au NPs) are commonly used for theranostic purposes due to their size and shape-dependent electronic, optical, magnetic and catalytic properties.[46] Au NPs have distinct chemical and physical properties such as bioaccumulation, sensitivity, and resonance light scattering, significantly increasing their use in pharmaceutical and biomedical applications.[47] Some of the distinct features of Au NPs are their radiosensitivity, good conductivity, and photothermal activities, which make them suitable for use as biosensors and drug delivery systems (DDS) and sometime as metallodrugs.[48] Micro-environmental stimulations, including external stimuli, cause changes in the morphological structures of Au NPs, which induce resonance light scattering properties, the photothermal effect, and good conductivity. These characteristics make them an attractive option for targeted drug delivery.[49] The main drawbacks of using Au NPs in biosensing and DDSs are their aggregation tendencies and low stability for which several protective and stabilization agents have been synthesized. These agents may be polymer based, consisting of nanogels, latex particles and microgels.[50] The primary role of these stabilizing agents is to achieve effective dispersion of Au NPs without aggregation and play a prominent role in regulating the nanostructures of Au NPs.

Biomedical applications

Amongst the various protective agents, nanogels have attracted much attention due to their 3D networks and biocompatibility, which aid the *in situ* synthesis and stabilization of Au NPs.[51,52] Recently, several nanogels have been used as templates to promote the synthesis of Au NP nanogels. These polymeric nanogels comprising Au NPs are being utilized for different biomedical purposes such as anti-cancer agents, radiosensitizers, drug carriers[53] and bio-imaging applications, owing to their enhanced permeation and biocompatibility, retention and photoresponsive properties.[54,55] These Au NP nanogels can be synthesized primarily by two methods: (1) pre-synthesizing NPs followed by incorporating them into nanogels or posterior seed polymerization of nanogels and (2) *in situ* generation of NPs within the nanogels.[32]

Anticancer therapy. The interest in cancer research has shifted from individual to combinational therapies. In these combinational therapies, novel nanogel platforms have been designed with incorporated nanoparticles. These systems function by increasing the efficacy of drug delivery and combine phototherapy, radiotherapy, and chemotherapy as prominent anticancer treatment strategies. One such nanoplatform has been developed utilizing alginate nanogels co-loaded with Au NPs and cisplatin, providing a combined chemo-photothermal therapy.[56] This nanocomplex was found to display an enhanced anti-cancer effect on colorectal tumours. The *in vivo* studies revealed that these nanocomplexes received an increased thermal dose compared to the normal drugs and controls, owing to the optical properties of Au NPs embedded in the nanoplatforms. Additionally, these nanocomplexes have been found to mitigate tumor growth by 95%, and in combination with laser irradiation, have the potential to eradicate tumor residues, preventing cancer relapse.[56] Ziaei *et al.*[57] reported the synthesis of pH-sensitive nanogels composed of alginate and gelatin, incorporating DOX-loaded chitosan/gold nanoparticles (Au NPs) *via* a Schiff base reaction. These nanogels achieved a DOX loading efficiency of 72.6% and exhibited enhanced anticancer efficacy and biocompatibility compared to the drug alone. In some studies, an alginate-based nanoplatform was developed for co-delivery of Au NPs and cisplatin commonly referred as an ACA nanocomplex. This nanocomplex was found to significantly enhance the therapeutic ratio of chemo-radiation therapy on glioblastoma cells and a colon adenocarcinoma tumour model. The cause of cell death in these tumour models was predominantly through the apoptotic mechanism.[58,59] These ACA nanocomplexes have been demonstrated to enhance cytotoxicity towards adenocarcinoma cells and the brightness of computed tomography (CT) images and the contrast-to-noise ratio. Thus, these ACA nanocomplexes can be utilized as theranostic agents, which could act as anticancer agents and CT traceable nanocarriers, allowing the monitoring of drug delivery, local accumulation, and *in vivo* biodistribution.[60] Inanami *et al.* described the synthesis and analysis of PEGlyated nanogel-containing Au NPs (GNG). The pretreatment of GNG significantly radiosensitized various cancer cell lines, *i.e.*, murine squamous carcinoma SCCVII cells, human lung adenocarcinoma A549 cells and Chinese hamster V79 cells. The radiosensitization of the cells was further accompanied by ER stress-mediated induction of apoptosis and inhibition of the DNA repair mechanism.[61] Jia *et al.* reported a multifunctional nanoplatform designed utilizing diselenide-crosslinked poly(*N*-vinylcaprolactam) (PVCL) nanogel co-delivery of Au NPs and methotrexate. This nanomedicine may act as a potential theranostic agent where it enhances CT-mediated imaging along with chemotherapeutic and tumor remodelling capability.[62] Takeuchi *et al.* reported the fabrication of novel stealth radiosensitizers for cancer treatment. This nanomaterial enhanced the efficiency of radiation therapy in the pancreatic cancer mouse models. Similarly, Zhang *et al.* synthesized a polymer-coated nanogel encapsulating doxorubicin. This nanocomposite combines the properties of Au nanorods with the pH- and thermo-responsive characteristics of the polymer. Its efficiency in targeted accumulation and anticancer activity can be regulated through near-infrared (NIR)-mediated drug release or site-specific accumulation [Fig. 4].[63] These nanoplatforms can be utilized as nanogel tracers along with radiosensitizers, forming an effective nanomedicine.[64] Multifunctional poly(*N*-isopropylacrylamide) (PNIPAm) incorporating Au NP nanogels demonstrated thermal/photo-triggered release of 5 fluorouracil (5 FU), leading to enhanced anti-cancer activities. These PNIPAm nanogels also exhibited cellular imaging when observed through a dark field microscope. This multi-functionality of the synthesized nanoplatform confers it to develop as a potential theranostic nanomedicine.[65]

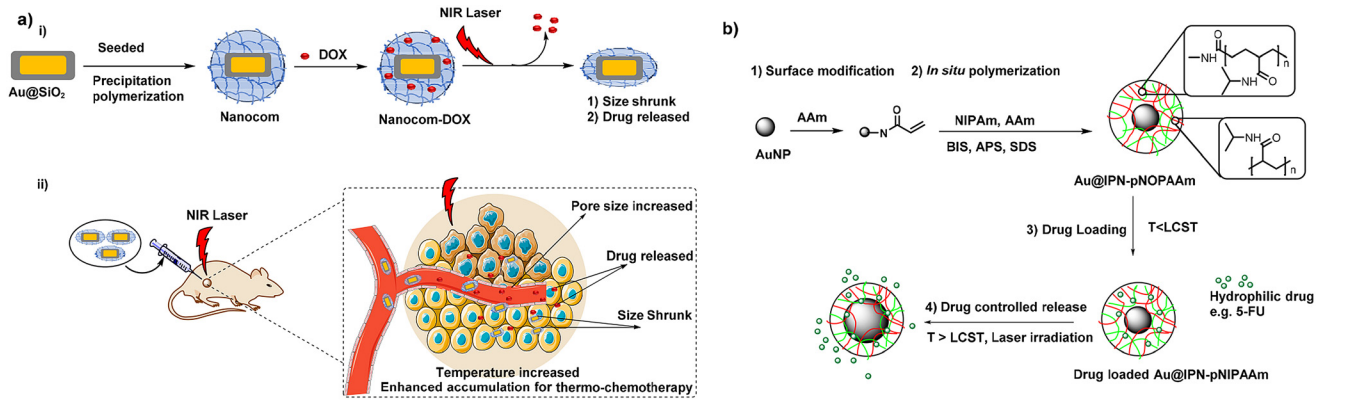

Fig. 4 (a) Synthesis of hybrid nanogels and NIR laser-induced targeted therapy using hybrid nanogels[63] and (b) schematic of the sequence of steps in the synthesis of hybrid Au@IPN–pNPAAm nanogels.[65]

Bio-imaging. These NGs embedded with Au NPs are also utilized for bioimaging purposes. Lysosome dextran polysaccharide nanogels were fabricated to stabilize Au NPs and were eventually used for cell imaging purposes.[52] Liu *et al.* developed a novel hybrid nanogel platform (CPTA) by conjugating cysteine-modified gold nanoparticles (Au NPs) with modified chitosan (CTS)/tripolyphosphate (TPP) nanoparticles (NPs) and polyacrylic acid (PAA). These nanogels function as theranostic agents, achieving a high drug encapsulation efficiency of 87%. They were designed to release the drug in the tumor microenvironment in response to acidic pH and the overexpression of the lysozyme enzyme. Furthermore, these nanogels can be easily tracked using CT imaging and were observed to accumulate in tumor cells. The CPTA nanogels demonstrated superior antitumor activity and biosafety compared to the drug alone.[66] Liu *et al.* described the synthesis of genetically engineered polypeptide–Au NP hybrid nanogels for targeted photoacoustic imaging. Triblock polypeptides $PC_{10}A$ and $PC_{10}ARGD$ were synthesized through self-assembly to form nanogels. $PC_{10}ARGD$ hybrid nanogels have shown remarkable targeted cellular photoacoustic imaging properties.[67] Poly(ethylene glycol) (PEG) nanogels entrapping Au NPs were used to study the cellular internalization and uptake of nanodevices through endocytosis in human umbilical vascular endothelial cells (HUVECs) and human mesenchymal stem cells (hMSCs).[68] Similarly, Oishi *et al.* synthesized Au NPs containing PEGlyated nanogels which were then conjugated with fluorescein isothiocyanate (FITC)-labeled Asp–Glu–Val–Asp (DEVD) peptides. Activated caspase-3 cleaves DEVD peptides release FITC and enhance fluorescence in apoptotic cells in human hepatocyte (HuH-7) multicellular tumor spheroids (MCTSs). Thus, these nanocomplexes can be utilized for rapid detection of cancer therapeutic response [Fig. 5].[69] Nakamura *et al.* reported the formation of PEGylated poly-[2-(*N*,*N*-diethylamino)ethyl methacrylate] (PEAMA) core nanogels with AuNPs post-synthesized by reduction of Au(III) ions. These nanocomposites were found to demonstrate selective and targeted anticancer activities in HeLa cells in response to photothermal therapy.[70] In another study by Shen *et al.*, the construction of a "smart" nanoplatform was synthesized using PVCL nanogels with embedded Au NPs and manganese dioxide (MnO_2) NPs. These intelligent nanoplatforms sensitize cancer cells towards radiotherapy (RT) by generating reactive oxygen species (ROS), causing significant DNA damage. This DNA damage is further prevented from repairing by relieving tumour hypoxia through continuous O_2 production. The *in vivo* studies demonstrated the targeted CT and magnetic resonance imaging-guided RT in tumor models.[71]

Silver nanoparticle-based nanogels. Silver nanoparticles (Ag NPs) possess superior electromagnetic, physical, and chemical characteristics, making them valuable in catalysis, nanodevices, and nanomedicine chemistry.[72] Au NPs and Ag NPs are commonly used to create stable NPs through colloidal and dissolution reactions. These NPs are beneficial for applications such as photonics, bioimaging, labelling, and surface-enhanced Raman scattering.[73] Additionally, Ag NPs are frequently utilized for biomedical, commercial, industrial, energy storage, and agricultural purposes.[74,75] Ag NPs exhibit several important biological and physiochemical properties, including wound healing, drug delivery, a high surface-to-volume ratio, easy functionalization, remarkable surface plasmon resonance, ease of formation of bio-composites and toxicity. The size, type, and crystallographic structures of these NPs significantly influence their efficacy in anti-microbial applications.[76,77] Due to their luminescence properties, Ag NPs are extensively researched for their effects on the fluorescence applications of medicinal drugs.[78]

Despite their exceptional properties, Ag NPs have some drawbacks in biological applications such as losing or deterioration in their anti-pathogenic properties in bacteria-rich environments.[79] To address this issue, various agents (organic, inorganic, biotic, and abiotic) and methodologies are applied to stabilize Ag NPs.[80–83] However, using Ag NPs in biomedical applications also presents several other challenges, such as toxicity, emergence of resistance, and regulatory restriction. Overcoming these challenges is crucial for the secure and efficient utilization of Ag NPs in biomedical applications. A comprehensive study is required to evaluate the long-term

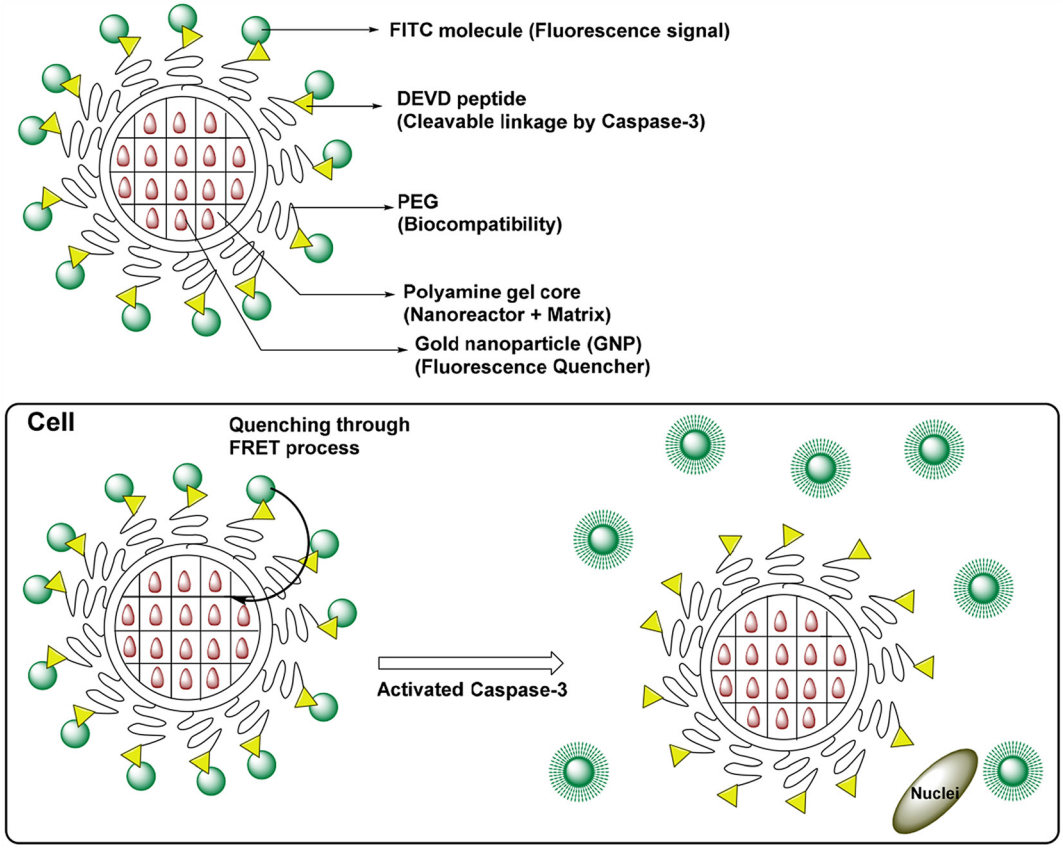

Fig. 5 Schematic illustration of the smart fluorescence-quenching apoptosis nanoprobe based on a PEGylated nanogel containing GNPs within the cross-linked PEAMA core and FITC-labelled DEVD peptides at the tethered PEG chain ends.[69]

effects of Ag NPs on human health and the environment. Addressing these challenges and understanding the long-term implications will enable the safe and effective use of Ag NPs in various applications.[84]

One approach to overcome the above challenges is to achieve a controlled release of Ag NPs locally by encapsulating them into nanogels. This can enhance cellular uptake while mitigating toxicity and other drawbacks.[85–87] Hybrid nanogels are typically formed by conjugating pre-synthesized Ag NPs with a polymeric network. These studies use hydrogels as templates for synthesizing or stabilizing Ag NPs *in situ*.[88,89] Recently, greener and simpler methods are being investigated for synthesizing Ag NP-containing hybrid nanogels.[90,91] Researchers have developed a hybrid nanogel with a lysosome-rich core and a dextran-rich shell, enabling the *in situ* synthesis of Ag NPs without reducing agents.[92] Lysosomes were found to stabilize Ag NPs and affect the loading capacity of nanogels by tuning the sizes of both nanogels and Ag NPs.[93] Similarly, greener Ag NPs in thermo-responsive nanogels were synthesized "*in situ*" utilizing the microwave-assisted irradiation technique.[94] Similarly, gamma radiation has also been used to synthesize Ag NP nanogels "*in situ*".[95] Additionally, electron beam irradiation of silver nitrate and polyacrylic acid has been used to synthesize Ag NP nanogels in a one step process. However, reports suggest that an increase in irradiation doses decreases the size of the prepared nanogels and augments their antibacterial activities due to the larger surface area for bacterial interaction of smaller Ag NPs.[90]

Biomedical applications

Nanoparticles, owing to their small size, are highly chemically reactive and are used as delivery systems for large amounts of drugs. However, the small size of NPs leads to ready oxidation and deposition, consequently losing their properties. Thus, they must be protected by some stabilizing agents, including polymers, polysaccharides, surfactants, *etc*. However, the activities of these loaded Ag NPs also depend on the type of polymer used. For instance, the anti-bacterial activities of PVA–Ag NPs are found to be significantly greater than those of PEG–Ag NPs.[96,97] Additionally, the nanogels are well responsive to the surrounding stimulus, thus are considered as "smart biomaterials" capable of responding to exogenous and endogenous stimuli.[98]

Anti-microbial activities. Several microorganisms have developed distinct strategies to protect themselves from unfavourable environments including immune responses and antimicrobial treatments. Among them, one strategy involves the

formation of biofilms. Biofilms are the accumulation of surface-associated microbial cells enclosed with the self-synthesized extracellular polymeric substance (EPS) matrix.[99] EPS covering blocks the supply of nutrients and oxygen, forcing the bacteria to undergo anaerobic metabolism and making the environment acidic. Low pH, high H_2O_2 concentration, and enzyme over expression are some of the special attributes of the biofilm microenvironment, which can be used for designing a targeted therapeutic agent.[100] Along with endogenous stimuli, exogenous stimuli such as radiation, magnetic field, ultrasound, and temperature can also be used to improve the specificity of drug delivery.[101,102]

Owing to the stimuli-responsive properties of nanogels, these can be utilized as anti-microbial agents. Recently, a photo-responsive nanogel was developed using chitosan- and aniline nanogels encapsulating Ag NPs. A controlled release of Ag NPs was observed under irradiation of hybrid nanogels at 405 nm, thereby displaying significant anti-bacterial activities.[91] Another photo-responsive nanogel was synthesized by surface immobilization of Ag NPs on polycaprolactone nanofibers. This hybrid nanogel releases the encapsulated Ag NPs upon light irradiation at 405 nm, demonstrating anti-bacterial activities on *S. aureus* and *E. coli* species.[86]

Biofunctionalized nanosilver (ICS-Ag) was formed using an itaconyl-chondroitin sulphate nanogel (ICSNG), which acted as an anti-microbial agent on medical devices. It acted as an anti-bacterial agent by destroying the bacterial cytomembrane and biofilm formation.[103] Recently, nanofibrillar silk microgels with Ag NPs decorated on the surface were developed, displaying significant eradication. The anti-bacterial action involved adhering bacteria to their surface and subsequently eliminating them. Additionally, these hybrid microgels were found to be non-hemolytic and non-cytotoxic toward mammalian cells.[104] A nanogel containing a lysosome core and a dextran shell enclosing Ag NPs was formed. The smallest Ag NPs-containing nanogel displayed the highest minimum inhibitory concentration (MIC), indicating the importance of NP size on anti-bacterial activities.[93] An Ag-embedded carboxymethyl cellulose (CMC) nanogel was prepared by reducing silver nitrate and fructose in the presence of CMC as a reducing agent. This nanogel showed anti-microbial activities against Gram-positive and Gram-negative bacteria, displaying approximately >99% colony reduction at 300 ppm silver content. Additionally, it exhibited anti-adhesion properties against *S. aureus* and *E. coli* species, indicating its potential use in anti-bacterial fabrics [Fig. 6].[105] A chitosan nanogel (AgNPs@CS/SCS) was used to synthesize Ag NPs *in situ*, showing remarkable anti-bacterial and biofilm ablation activities. Moreover, this nanogel demonstrated superior anti-microbial activity in the treatment of implants, along with good biocompatibility.[106]

Due to their exceptional antimicrobial and biocompatibility properties, these nanogels have strong potential for targeted drug delivery, treatment of drug-resistant microbial infections, biofilm ablation, and antimicrobial treatment of implants in clinical settings. Additionally, the antimicrobial properties of these Ag NP nanogels can be utilized to treat chronic and non-healing wounds, making them immensely useful for biomedical applications. However, the practical application in clinical settings and ease of production still need to be overcome.

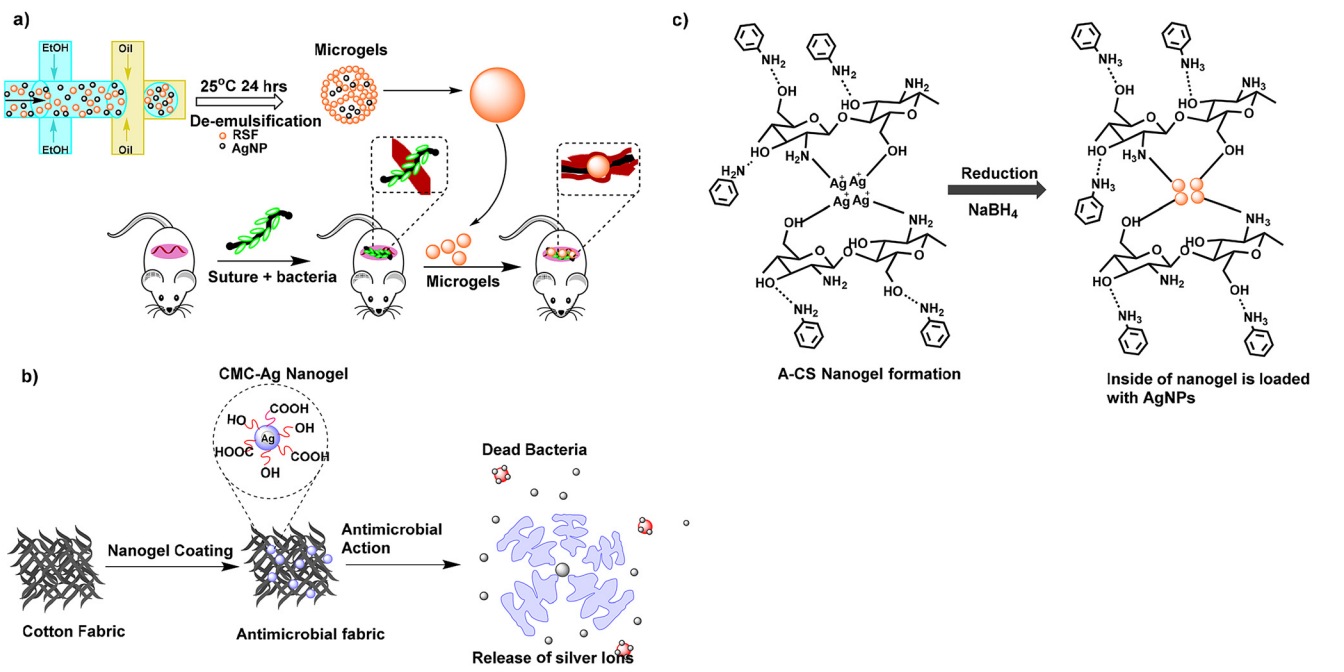

Fig. 6 (a) Biocompatible hybrid organic/inorganic microhydrogels promoting bacterial adherence and eradication *in vitro* and *in vivo*.[104] (b) Synthesis of silver nanoparticle-embedded nanogels for infection-resistant surfaces.[105] (c) Illustration of AgNP–nanogel formation.[91]

Wound healing activities. Wound healing is a complex process that intertwines the biological processes of the inflammatory reaction, proliferation, and remodelling.[107] Any abnormalities in these processes lead to poor wound healing.[108] The topical application of anti-bacterial agents on the wound or burn prevents infection, mitigates the wound eschar formation, and promotes the wound healing process.[109] Nanocrystalline silver-based wound dressings have been used for decades and are currently employed in the treatment of wounds, burn and chronic ulcers.[110] Thus, the advent of nanotechnology has enhanced the use of Ag NPs for wound healing purposes.

Recently, Ag NPs synthesized from *Ocimum sanctum* leaf extract encapsulated in nanogels were observed to exhibit noteworthy antibacterial and wound healing capabilities, promoting the green synthesis of nanogels. These nanogels showed significant wound healing of 96.20% on the14th day in comparison with the control. Additionally, they displayed effective anti-microbial inhibitory efficiency against *Staphylococcus aureus*, *E. coli*, and *Pseudomonas aeruginosa* species.[79] In another study, UV radiation was utilized for *in situ* synthesis of Ag NPs loaded into polypeptide nanogels for greener and simpler synthesis. These hybrid nanogels exhibited excellent antibacterial activities against Gram-positive and Gram-negative bacteria *in vitro* and displayed significant wound healing and antibacterial activities *in vivo.*[111]

The mycosynthesized Ag NPs from *Fusarium oxysporum* were used to form silver nanogels, which exhibited excellent wound healing and anti-bacterial activities in various wound models of albino Wistar rats.[112] Nanogels incorporating oleanolic acid-loaded silver nanoparticles demonstrated wound closure rates in albino rats equivalent to the standard pharmaceutical agent betadine.[113] A carbopol-based nano-silver gel was prepared using Ag NPs synthesized from *Saccharomyces boulardii* and *Clitoria teratea*, exhibiting a remarkable wound healing efficiency in rat wound models.[114,115] Ag NPs generated *in situ* within peptide nanogels Ac-IVZK-NH_2 and Ac-IVFK-NH_2 have shown excellent anti-bacterial and wound healing properties in normal micropigs.[116]

Despite significant progress in developing Ag NP-containing nanogels, challenges regarding their efficacy and cost remain major concerns. Current formulations may not consistently achieve the desired therapeutic outcomes and the production costs can be prohibitive for widespread clinical use. These issues highlight the need for continued research and optimization to enhance the performance and affordability of these nanogels. Therefore, extensive studies are required to fully explore and understand the potential of Ag NP-based nanogels in biomedical applications

Iron nanoparticle-based nanogels

Iron oxide nanoparticles (Fe NPs) are the most investigated materials for FDA-approved nanomedicines. Their biocompatibility, magnetic, and superconductive properties have made them suitable for multifunctional biomedical applications. These Fe NPs are less likely to be oxidized, therefore, have been used for *in vitro* diagnostic purposes for decades.[117] Mostly magnetic nanoparticles (MNPs) such as those made of hematite (α-Fe_2O_3), maghemite (γ-Fe_2O_3) and magnetite (Fe_3O_4) NPs are used as contrast agents, drug delivery vehicles and hyperthermia-based therapeutics.[118] The biocompatibility and ease of functionalization made them suitable for a wide range of diagnostic and therapeutic applications.[119] The properties of Fe NPs are dependent on their size, shape, coating, and stability.[120] NPs with sizes >200 nm or <10 nm are easily excreted from the body through the reticuloendothelial system and the basal lamina existing pores of kidneys, respectively.[121] Additionally, these MNPs have hydrophobic surfaces, which have large surface-to-volume ratios that tend to agglomerate to form large clusters of NPs. These large clusters can be exponentially influenced by the application of external magnetic fields, thus further elevating the attraction between magnetic particles and causing aggregation.[122,123]

The surface modifications of these MNPs remain crucial for enhancing their biocompatibility and reducing aggregation. Thus, MNPs with proper surface coating can stay in circulation for extended periods and remain mostly unrecognized by the body's immune system.[124] MNPs can be functionalized using organic and inorganic materials such as synthetic and natural polymers and surfactants to enhance the dispersibility of these particles.[125,126] NPs of less than 15 nm are of particular interest, considered to have superparamagnetic properties, and tend not to retain magnetism upon removal of the magnetic field, thus remaining unnoticed by the body's immunity.[127] Thus, encapsulating these Fe NPs into nanogels may be helpful in reducing their drawbacks and enhancing their wider applications in biomedical fields.

The two important techniques for the synthesis of magnetic nanogels are primarily through blending and *in situ* methods. The blending technique depends on covalent interactions to form stable intermediates which are subsequently cross-linked to form magnetic nanogels. Vijayan *et al.* fabricated magnetic nanogels through covalent interactions between negatively charged citric acid-coated Fe NPs and the positively charged 2-(dimethylamino) ethyl methacrylate.[128] Similarly, Chiu *et al.* synthesized a magnetic nanogel through photoinitiation polymerization of nanogels in the presence of citric acid-coated Fe NPs. However, this technique is accompanied by aggregate formation and low incorporation of Fe NPs into the gel [Fig. 7].[129] Another technique is *in situ*, which uses a micro/nanogel as a microreactor; however, controlling the properties of nanogels still remains a challenge. Another method is the grafting technique, where ligands are utilized to bind to the surface through functional group interactions such as carboxylic acid, phosphonic acid, *etc.*[130] These bonds formed in nanogels can withstand higher temperatures, thus making these nanogels suitable for hyperthermia treatment. Furthermore, a detailed study on synthetic methodologies for the synthesis of Fe NPs can be found in the review article reported by Patri *et al.*[131]

Biomedical applications

Magnetic nanogels (MNGs) can be utilized for various biomedical applications, including anticancer therapies and

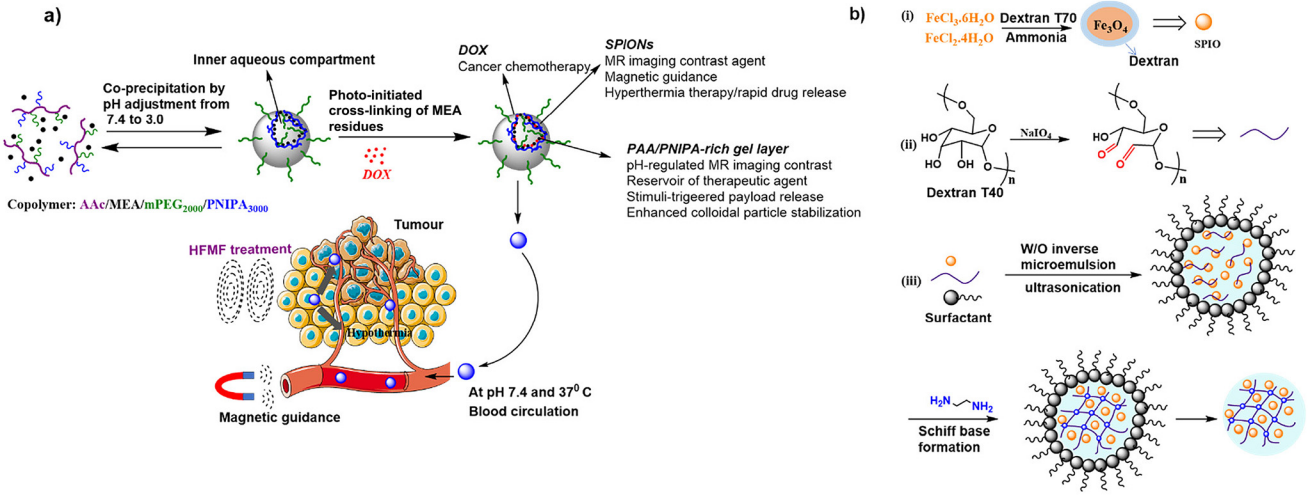

Fig. 7 (a) Development of DOX-loaded hollow nanogels serving as a multi-functional nanogel theranostic platform.[129] (b) Schematic illustration of the synthesis of Fe_3O_4 NP-encapsulated dextran nanogels: (i) preparation of dextran-coated Fe_3O_4 NPs *via* the co-precipitation method, (ii) periodate oxidation of dextran, and (iii) Dex–CHO solution blend with Fe_3O_4 NPs cross-linked with ethylenediamine in a W/O inverse microemulsion.[132]

protein and gene therapeutics. These NGs can also serve as contrast agents, making them a potential choice for magnetic-mediated imaging. The magnetic and hyperthermic properties of magnetic nanoparticles (MNPs) make them ideal for conjugation with NGs in the development of targeted and precision nanomedicines. Understanding the physical properties of these materials, particularly the time scale and interactions affecting the swelling and deswelling of MNGs, is crucial for their design.[133] Additionally, multi-stimulus responsive MNGs can be formulated by interacting with and grafting different polymers and copolymers. The targeting efficiency of these nanomaterials can be enhanced by grafting specific ligands, proteins, enzymes, and drugs, which can be released in response to external and internal stimuli. Here are some of the significant applications of MNGs (Fig. 8).

Anticancer therapy. Various stimuli-responsive MNGs have been fabricated for the delivery of several anticancer drugs and have shown effectiveness against various cell lines such as HT29 (human colorectal adenocarcinoma), HepG2 (hepatocellular carcinoma), B16F10 (mouse melanoma), HeLa (human cervical adenocarcinoma), and MCF7 (human breast adenocarcinoma).[135] Some MNGs, formed by coating the maghemite iron oxide core with PEG (polyethylene glycol)–polycarboxylate copolymers, can be used for magnetic-based separation of melanoma cells. These MNGs have shown prolonged circulation in blood vessels *in vivo*.[136] Additionally, hollow nanogels (NGs) containing iron oxide nanoparticles (IONPs) and anticancer drugs have been fabricated using an acrylic acid and 2-methacryloylethyl acrylate backbone attached with PEG and PNIPAM. These MNGs exhibit controlled release of anticancer drugs in response to pH and temperature fluctuations against the HeLa cell line.[129] Similarly, a nanogel system with an Au/Fe_3O_4 core, fabricated with a PEG copolymer and a PNIPAM gel layer, can be used for the delivery of methotrexate.[137] Furthermore, IONPs grafted with PNIPAM copolymer-based NGs are utilized to deliver cisplatin.[138]

More complex hybrid NGs have been developed for the formation of multifunctional NGs. These hybrid NGs are formed using an IONP core cluster with a porous carbon shell embedded with fluorescent carbon dots and an outer drug-loaded PNIPAM NG layer. The IONP core and carbon dot shells can be heated by the application of magnetic fields and near-infrared light, respectively. This heat leads to deswelling of the NGs, thereby selectively releasing drugs and enabling targeted imaging of B16F10 cells *in vitro*.[139] Similarly, IONPs grafted with chitosan-*g*-poly(*N*-vinylcaprolactam) lead to the formation of thermoresponsive NGs, which release doxorubicin in response to high-frequency magnetic fields. This NG platform displays hyperthermia and chemotherapy-mediated cytotoxicity against breast cancer cell lines. Recently, neutrophil-inspired magnetic peptide NGs containing IONPs and chloroperoxidase have been developed. These MNGs can upregulate the levels of H_2O_2 in cancer cells, which can be converted into singlet oxygen by chloroperoxidase, thereby causing anticancer therapeutic effects through magnetic hyperthermia and enzymatic treatment.[140]

Protein and gene therapeutics. Recently, a magnetic nanogel was developed to deliver growth factors (GFs) through nuclear base pairing. A biopolymeric nanogel was fabricated utilizing magnetite, heparin, and chitosan, which displayed rapid encapsulation of MNPs. The cellular delivery of GFs was confirmed by the absorption and release of bone morphogenetic protein-2 (BMP-2). This nanogel demonstrated the magnetic field-mediated release of BMP-2, which might hold great potential for application in tissue regeneration.[141] Poly(vinyl pyrrolidone) (PVP) nanogels were loaded with iron oxide nanoparticles (IONPs). These PVP nanogels being heat and pH responsive in nature were found to shrink in basic pH, thereby preventing the release of IONPs. However, in an acidic environment, these nanogels swell and tend to release NPs. These IONPs can be removed from the system by applying a small

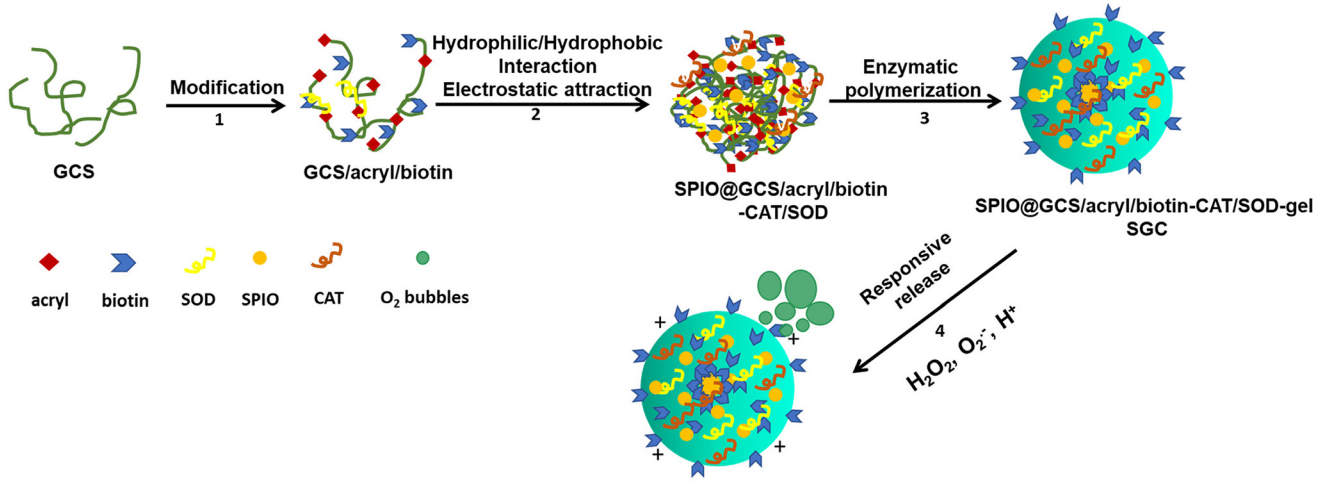

Fig. 8 Schematic illustration of SGC (SPIO@GCS/acryl/biotin-CAT/SOD-gel: (1) modification of acryl bonds and the biotin group on glycol chitosan (GCS), (2) interaction between the modified GCS and the superparamagnetic iron oxide particles SPIO, as well as electrostatic interaction of dual enzymes (CAT: catalase and SOD: superoxide dismutase), (3) efficient enzymatic polymerization of the hybrid system, and (4) responsive bubble generation and protonation effect due to pathological stimuli (H_2O_2, O_2, and H^+) for enhanced dual modality US/MR imaging.[134]

magnetic field, thus demonstrating hyperthermia treatment through IONP drug delivery.[142] Furthermore, pH-sensitive nanogels were utilised to deliver the anti-green fluorescent protein (GFP) siRNA and superparamagnetic IONPs to HeLa–GFP cells. IONPs were used to increase the cellular absorption of nanogels, which were then utilized as tracking agents. The siRNA was released in a pH-mediated manner and participated in gene down regulation. This multifunctional nanogel is capable of pH-mediated siRNA release causing gene downregulation, IONP-mediated resonance imaging, and potential hyperthermia treatment for cancer therapy.[143] A doxorubicin-loaded iron oxide poly(acrylic acid) nanogel was formulated for cancer theranostics. Additionally, a magnetic DNA nanogel was developed by synthesizing a DNA nanogel layer on magnetic nanoparticles (MNPs). These magnetic nanogels can easily target tumour sites through the application of an external magnetic field Recently, a MNG-exosome complex was fabricated for magnetic-mediated targeted delivery of mRNA and microRNA *in vitro.* This nanohybrid RNA vehicle was developed by hydrophobically fusing amphiphilic nanogels containing IONPs with exosomes derived from PC12 (rat pheochromocytoma) cells that carried mRNA and microRNA. These MNG–exosome complexes can be magnetically directed to adipose-derived mesenchymal stem cells, inducing differentiation into neuron-like cells.[144]

Magnetic resonance imaging (MRI). MRI is generally used for *in vivo* imaging techniques and non-ionization radiation is used just like ultrasound or PET imaging. Body systems contain large quantities of water molecules possessing protons which play a significant role in MRI signal production. Protons, under the influence of external magnetic fields, align themselves in the parallel direction of the magnetic field. However, due to radiofrequency, the spins get arranged in an antiparallel direction. The protons regain a parallel direction to the state of the external magnetic field once the radiofrequency is removed. This is known as longitudinal or T1 relaxation and magnetism can be restored through transverse of T2 relaxation. T2 contrast agents can improve the T2 of water by creating negative contrast in MRI imaging. MRI contrast agents' capability to elevate the contrast relies on relaxivity, leading to spin dephasing and relaxation times. Contrast agents improve the visibility of internal body structures in MRI.[145,146] The recently developed iron oxide nanoparticle-infused dextran-based magnetic nanogels exhibit superparamagnetic behavior comparable to individual iron oxide particles.[132] Similarly, a hybrid nanogel was prepared using glycol chitosan infused with iron oxide nanoparticles and two enzymes to obtain dual imaging abilities. Dual imaging capabilities refer to the ability of MRI and ultrasound combined together to diagnose the tumor in an animal model.[134] Polymeric nanogels with infusion of iron oxide help in the diagnosis of several pathological conditions through MRI. MRI detects such diseases by utilization of contrast agents. Iron oxide nanogels can be excellent contrast agents for the detection of pathological diseases such as malignant brain gliomas, whose detection immensely depends on MRI.[147,148] Overall, it is fairly understood that iron-oxide nanoparticle-loaded nanogels can be way better contrast agents than the existing ones.

Conclusion and future perspectives

In this review, we discuss the effects of conjugating nanogels (NGs) with inorganic nanoparticles. The most commonly used inorganic nanoparticles for biomedical applications include gold, iron, and silver. We provide a concise overview of the synthesis of various NGs containing these inorganic nanoparticles and elaborate on their applications in several biomedical

fields, such as anticancer therapy, diagnostics, and drug delivery. Additionally, we report on new platforms that exhibit multifunctional activities and enable the controlled and targeted release of drugs or cargoes. The development of novel smart gel systems has further accelerated the generation of advanced biomaterials for various applications. Functionalization and multi-stimuli responsiveness have enhanced the utilization of these NGs as targeted and selective theranostic nanomedicines. Despite significant progress in this field, the range of applications does not yet meet clinical practice standards, indicating the need for substantial improvements in current strategies. Moreover, the limited clinical data regarding the safety and efficacy of NGs are a notable concern. Issues related to the pharmacodynamics, metabolism, and pharmacokinetics of various nanomaterials must be resolved to advance nanomedicines from the bench to the bedside. Significant *in vivo* studies are required for various hybrid NGs to predict their clinical relevance and efficacy.

For the development of potent *in vivo* nanomedicines, more effective, tunable, and smart nano-biomaterials need to be developed. By introducing biodegradability, enhanced cellular interaction, and multifunctionalities, these NGs may become suitable for clinical treatments. Additionally, identifying the toxicity of these nanomaterials is crucial for facilitating measures for enhancing their safety. Furthermore, there should be a focus on the fabrication of self-regulating nanomaterials that can report information about the local physiological environment (*via* magnetic resonance or fluorescence) and can be controlled by both external and internal body manipulators.

Author contributions

SM performed conceptualization of the work, editing and proof reading. CS performed conceptualization, writing of the manuscript, and editing. RR helped in revision and figure preparation.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Conflicts of interest

There are no conflicts to declare.

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