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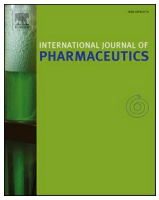

Review

Intelligent responsive nanogels: New Horizons in cancer therapy

MiriGuli Musa [a,1], Xinxin Sun [b,1], Jianbin Shi [b], Jing Li [c,*], Shenwu Zhang [b,*], Xianbao Shi [a,*]

[a] Department of Pharmacy, The First Affiliated Hospital of Jinzhou Medical University, Jinzhou, China
[b] Department of Pharmaceutics, Wuya College of Innovation, Shenyang Pharmaceutical University, Shenyang 110016, China
[c] School of Pharmacy, Shenyang Medical College, Shenyang, Liaoning Province, China

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ABSTRACT

Biologically engineered nanogels formed through sophisticated intramolecular crosslinking processes represent the forefront of next-generation drug delivery systems. These innovative systems offer many advantages, like adjustable size, satisfactory biocompatibility, and minimal toxicity. Their unique attributes facilitate deep penetration and long-term retention of drugs in tumors, effectively enhancing the anti-tumor effects. Nonetheless, the rapid disintegration of nanogels and the subsequent triggering of drug release at the tumor site pose significant challenges in achieving more effective and precise tumor treatments. Therefore, increasing research has been dedicated to exploring stimulus-responsive nanogels for enhancing tumor therapy. This review aims to encapsulate the research advancements in emerging stimulus-responsive antitumor nanogels. Firstly, a detailed exposition is provided on various endogenous stimulus-responsive nanogels, encompassing factors such as pH, hypoxia, enzymes, reactive oxygen species (ROS), and glutathione (GSH). Secondly, various nanogels triggered by exogenous stimuli such as light, ultrasound, temperature, and magnetic fields are elaborately presented. Furthermore, nanogels with multifaceted stimulus-responsive properties are also skillfully designed. Finally, the future directions, application prospects, and challenges of intelligent responsive nanogels in cancer treatment are highlighted.

1. Introduction

Cancer, a persistent threat to human health, necessitates a comprehensive reassessment of current therapeutic strategies (Machlowska et al., 2020; An et al., 2024). Conventional approaches, including surgery, chemotherapy, radiotherapy, and novel interventions, despite their widespread application, face inherent limitations exacerbated by the heterogeneous and intricate nature of tumors. These conventional approaches frequently lack specificity, resulting in unintended damage to healthy tissues and systemic toxicity (Mishra et al., 2024). Furthermore, these methods may fail to effectively target heterogeneous populations of cancer cells, thereby promoting the emergence of drug-resistant clones and disease recurrence (Gupta et al., 2024). Acknowledging the limitations of these current anticancer treatments underscores the pressing need for more precise, efficient, and targeted therapeutic strategies (Garcia-Oliveira et al., 2021).

In response to these challenges, cutting-edge drug delivery systems are being explored to target cancer cells selectively (Sun et al., 2023; Zhang et al., 2022). Notably, nanoparticle-based carriers hold promise by ensuring a controlled release of therapeutic agents, optimizing localization, and reducing exposure to healthy tissues (Zeng et al., 2023; Zhang et al., 2022; Sun et al., 2023). In particular, nanogels have garnered significant attention due to their unique properties and potential applications (Idumah, 2024). Nanogels are nanometer-sized hydrogel particles formed from polymer networks cross-linked through physical or chemical methods, combining the advantageous properties of both hydrogels and nanoparticles. With diameters typically ranging from 20 to 200 nm, nanogels share a comparable size to traditional nanoparticles, enabling them to navigate physiological barriers more effectively than larger hydrogels. This optimal size range also provides a higher surface area, facilitating efficient material exchange and interactions with their surroundings. Structurally, their polymer networks can absorb significant amounts of water, imparting gel-like properties, shape retention, and a degree of elasticity. Functionally, nanogels are responsive to environmental stimuli, such as temperature, pH, and ionic strength. These distinctive attributes make nanogels highly promising as drug carriers in drug delivery systems, where they can encapsulate therapeutic agents within their polymer networks and

* Corresponding authors.
E-mail addresses: dddefghijklmn@163.com (J. Li), zhangshenwu@aliyun.com (S. Zhang), sxbsln@163.com (X. Shi).
[1] These authors contributed equally to this work.

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enable controlled release. The nanogel drug delivery system seamlessly amalgamates the merits of nanotechnology and smart hydrogels (Pinelli et al., 2022). Its advantages, such as high drug loading, targeted delivery, extended blood circulation, responsiveness, and controllability, herald new prospects in the field of drug delivery (Rajput et al., 2023). The unique structure and functionality of nanogels facilitate the precise delivery of drugs to specific cells, tissues, or organs, consequently diminishing systemic side effects and enhancing the efficacy and safety of treatment (Suhail et al., 2019). This innovative technology represents a paradigm shift toward a more effective, precise, and personalized direction in cancer treatment and other disease therapies.

One of the most notable features of nanogels is their stimulus-responsive release mechanism, which offers a range of intelligent solutions for precise drug delivery (Abedi et al., 2023). During the drug delivery process, nanogels respond to environmental stimuli such as pH, temperature, specific ion concentrations, or light exposure (Luo et al., 2023). These responses induce structural changes, chemical reactions, charge alterations, or light sensitivity within the nanogels, allowing for spatiotemporal control over drug release (Bhaladhare and Bhattacharjee, 2023). This intelligent release system, carefully engineered for tumor targeting, offers several advantages (Ashwani et al., 2023). First, it enables the precise targeting of cancer cells, thereby minimizing damage to healthy tissues and reducing adverse effects during treatment (Huang et al., 2018; Mohammadi et al., 2020). Second, due to their stimulus responsiveness, nanogels can release drugs at optimal times, further enhancing the spatiotemporal control of therapy (Lee et al., 2023; Yan et al., 2024). Additionally, this system has the potential to prolong drug retention within tumor tissues, thereby extending the duration of drug efficacy (Stawicki et al., 2021). The properties of nanogel drug delivery systems open new possibilities for cancer treatment, providing strong support for the development of more intelligent and efficient anti-tumor therapies (Shen et al., 2022; Katopodi et al., 2024). The integration of advanced nanotechnology with stimulus-responsive release mechanisms places nanogels at the forefront of tumor-targeted drug delivery, presenting a promising and forward-looking approach to the future of cancer therapy.

In recent years, the broad applicability of tumor-specific stimulus-responsive nanogels has garnered significant attention in the field of cancer treatment. As some order begins to emerge from this complex landscape, it is timely to review the latest advances in this area. This review first discusses the classification and typical examples of endogenous stimuli-responsive nanogels that are driven by factors within the tumor microenvironment (TME), such as pH, biomolecules, ROS, and hypoxia (Fig. 1). Next, we highlight various exogenous stimulus-based nanogels, including those responsive to light, ultrasound, and magnetic fields. Additionally, multi-stimulus-responsive nanogels, their therapeutic applications, preparation methods, and release mechanisms are further summarized. Finally, we explore the prospects and challenges associated with these intelligent-responsive nanogels. Ultimately, this review provides valuable insights for the rational design of gel-based nanosystems, aimed at enhancing the efficacy of therapies for solid tumors.

2. Preparation and characterization of nanogels

Nanogels exhibit the characteristics and functionalities of both nanoparticles and hydrogels (Duan et al., 2023). Nanoparticles provide several advantages, including enhanced selectivity in drug delivery, improved drug solubility and stability, synergistic delivery of multiple drugs, increased bioavailability, and facilitation of sustained or controlled drug release (Li et al., 2024). Hydrogels are composed of three-dimensional polymer networks containing aqueous moieties, and this 3D structure imparts a stable drug-carrying capacity to hydrogels (Dhara, 2024; Ettoumi et al., 2024; Fan et al., 2024). Furthermore, a significant advantage of nanogels over other solid drug carriers is their size, which ranges from the nanometer to micrometer scale. This

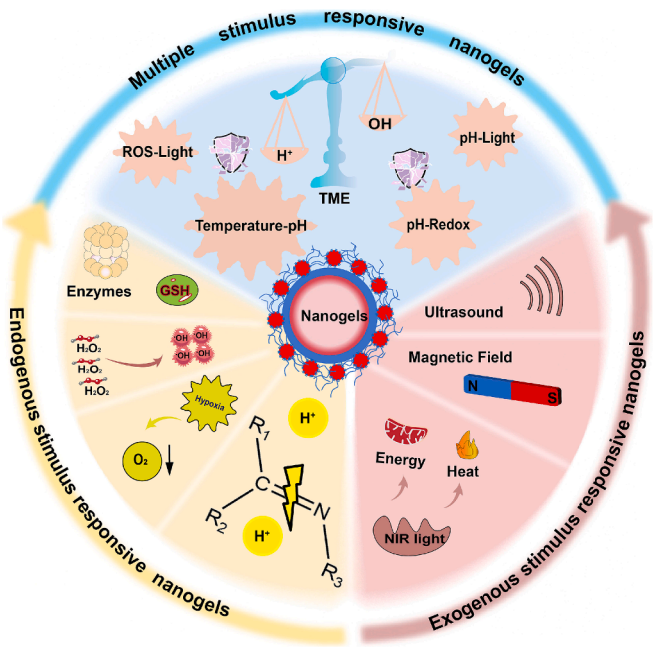

Fig. 1. Schematic representation of tumor-specific responsive nanogels for cancer treatment.

exceptionally small size facilitates better cellular uptake and enhances drug absorption. Nanogels are known to possess good mechanical stability, drug-carrying capacity, slow and controlled release properties, and the ability to respond to physical and chemical changes (Shirvalilou et al., 2024).

Nanogels are formed by physical or chemical cross-linking of carrier materials. Therefore, the carrier material plays a crucial role in the preparation of nanogels. Commonly used carriers are some polymers, such as polysaccharides, acrylamides, acrylics, and some cationic polymers. Based on the cross-linking of the polymer, the preparation methods are classified as physical cross-linking and chemical cross-linking as shown in Table 1 (Ma et al., 2024). The nanogels prepared by physical cross-linking were achieved by self-assembly of the polymer in aqueous solution. The polymers mixed in aqueous solution undergo cross-linking through hydrogen bonding, van der Waals forces,

Table 1
Classification of nanogel preparation methods.

Crosslinking type	Active force		Reference
Physical crosslinking	Hydrogen bonding, Van der Waals forces		(Xia et al., 2024)
	Hydrogen bond		(Fan et al., 2024)
Chemical crosslinking	Radical polymerization	Emulsion polymerization	(Du and Fielding, 2024; Liao et al., 2024; Hijazi and Islam, 2024)
		Precipitation polymerization	(Yan et al., 2024; Cai et al., 2024; Wang et al., 2024; Xia et al., 2024)
		Dispersion polymerization	(Mazzali et al., 2024)
	Chemical reaction method	Schiff base method	(Bernal-Cepeda et al., 2024; Yu et al., 2024)
		Michael's addition	(Yabuuchi et al., 2024; Filipek et al., 2024)
		Click on chemical reaction	(Li et al., 2024; Wang et al., 2024; Hatami et al., 2024)

hydrophobic forces, and electrostatic interactions to form nanogels. Fan (Fan et al., 2024) et al. prepared hydrogen-bonded cytosine-enabled supramolecular polymer nanogels for enhanced targeting of cancer cells, thereby improving drug efficacy.

Chemical cross-linking can be classified into two primary categories: free radical polymerization and chemical cross-linking through chemical reactions. Chemical cross-linking is typically stronger than physical cross-linking, and its preparation methods are both complex and diverse. The most widely employed chemical cross-linking method is free radical polymerization, which includes techniques such as emulsion polymerization, precipitation polymerization, and others. Free radical polymerization involves dissolving monomers in either a homogeneous or heterogeneous system, in the presence of a free radical initiator and stabilizer, leading to the formation of a three-dimensional nanogel network. The size of the nanogel can be controlled by adjusting the ratio of stabilizers, surfactants, and other relevant modifiers. Another widely used method of chemical cross-linking is achieved through chemical reactions, such as click chemistry. Common chemical methods for nanogel cross-linking include the Schiff base reaction of aldehydes with amines or hydrazides, the Michael addition of thiols to α, β-unsaturated carbonyl compounds, and click chemistry involving nitriles and alkyne rings. For instance, the Schiff base reaction takes place in an acidic environment, enabling nanogels to release drugs in acidic conditions, such as those found in tumors. Carneiro (Carneiro et al., 2021) et al. synthesized dextran-grafted poly (N-isopropyl acrylamide) (PNIPAM) copolymers using the Schiff base generation method and prepared nanogels for delivery of adriamycin from this copolymer.

Due to the acidic and hypoxic oxygen physiological environment of TME, the characteristics of nanogels to respond to these physiological stimuli have been found extensive application in tumor therapy (Liao et al., 2024). Nanogels carrying anticancer drugs infiltrate the TME and rupture their structure under physiological stimuli to achieve the concentrated release of drugs at the tumor site (Fig. 2) (Song et al., 2017; Shang et al., 2022; Kumar et al., 2021). This property not only improves the accumulation and precise release of drugs at the tumor site but also reduces drug-related side effects and enhances patient compliance (Dalir Abdolahinia et al., 2022).

From therapeutic modalities, nanogels have a wide range of applications in therapeutic areas such as chemotherapy, radiotherapy, photodynamic therapy (PDT), photothermal therapy, and gene therapy (Fig. 2). Most commonly, nanogels are used as a well-targeted delivery system to encapsulate chemotherapeutic drugs, increase the water solubility of the drugs, protect the drugs from enzymatic degradation, and target the drugs to the tumor site through the enhanced permeability and retention (EPR) effect in the tumor tissues (Yan et al., 2024). Secondly, nanogels can be combined with radiotherapy to sensitize the effect of radiotherapy. In radiotherapy, they can absorb the energy of radiation to generate free radicals or heat, which can enhance the killing effect of tumor cells (Shi et al., 2024). In addition, nanogels can be loaded with photosensitizers and delivered deep into the tumor tissue, where the photosensitizers will generate ROS under light irradiation at specific wavelengths to induce apoptosis of the tumor cells; At the same time, nanogels can be loaded with photothermal converting materials to convert light energy into heat energy under near-infrared light irradiation to raise the local temperature of the tumor tissue, resulting in thermal damage and death of the tumor cells (Li et al., 2024). Finally, nanogels can be used as gene carriers to deliver therapeutic genes to tumor cells, protect the genes from nuclease degradation, and enhance binding and uptake by surface modification (Hatami et al., 2024). In conclusion, nanogels combined with various cancer treatment strategies not only solved the problems of low drug solubility and poor stability but also improved drug targeting and enhanced the EPR effect (Table 2).

In this review, we have classified stimulus-responsive nanogels into two main categories based on the ability of the nanogels to respond to

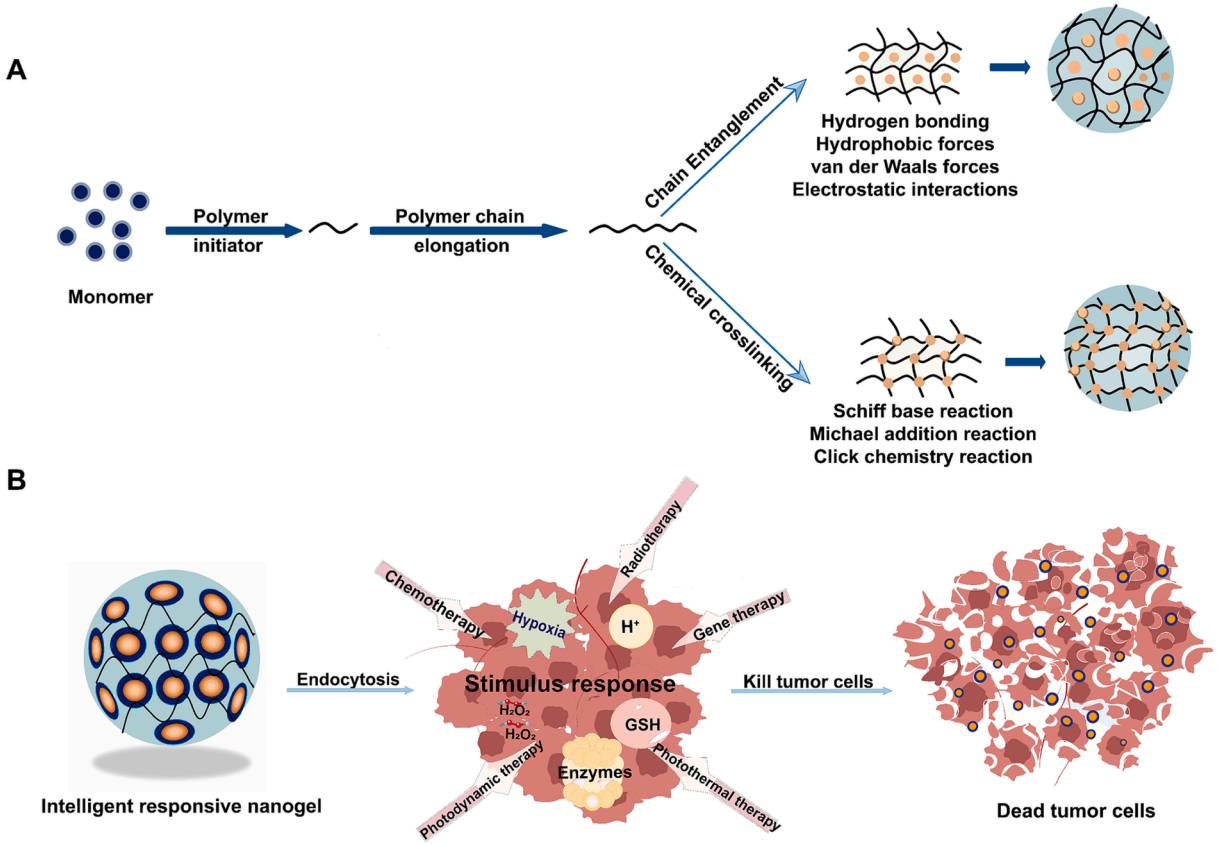

Fig. 2. A. Formation mechanism of physically cross-linked nanogels and chemically cross-linked nanogels; **B.** Therapeutic methods of nanogels in cancer cells.

Table 2
Therapeutic effects of stimuli-responsive nanogels.

Types of nanogels	Composition of nanogels	animal model	Treatment results	Reference
Endogenous stimulus–response	PBA-PAL and mPEG-DA	Tumor transplantation mouse model	Increased up to three times at lower pH	(Chen et al., 2023)
	PFP-based activated esters	Zebrafish xenograft tumor model	Demonstrated a strong tumor inhibitory effect	(Van Driessche et al., 2018)
	Bovine serum albumin, CMC-SS, and PCB	Mouse embryonic fibroblast tumor model	Tumor inhibition increased from 24 % to 90 %	(Liao et al., 2024)
Exogenous stimulus–response	IMs	4 T1 BALB/c female mouse tumor model	The treatment group had the lowest tumor weight and the highest inhibition rate of 59 %	(Xu et al., 2023)

TME, endogenous stimulus–response and exogenous stimulus–response. The endogenous stimuli include pH, biomolecules, ROS, and hypoxia, and the exogenous stimuli include light, ultrasound, and magnetism.

3. Endogenous stimuli-responsive nanogels

A diverse array of nanogels can be intricately designed to respond to internal environmental stimuli, with a particular focus on tailoring them for the TME. The TME possesses distinctive characteristics that render it particularly amenable to the incorporation of endogenous stimuli-responsive features (Wang et al., 2024). Notably, these endogenous stimuli include pH, biomolecules such as GSH, enzymes, ROS, and hypoxia. Aligned with these unique attributes of the TME, numerous nanogels, primarily intended for drug delivery, are formulated and released through the cross-linking of polymers using cross-linking agents sensitive to these stimuli (Chakroborty et al., 2024). This strategic design enables a targeted and responsive approach, ensuring that the nanogels can effectively navigate and respond to the dynamic conditions within the TME.

3.1. pH-responsive nanogels

3.1.1. pH-sensitive chemical bonding

Chemotherapeutic agents demonstrate toxicity due to their non-selective targeting, resulting in the destruction of both cancerous and normal cells (Johnson and Keyes, 2024). Cancer cells generate an acidic microenvironment within tumors due to their elevated proliferation rate and intense glycolytic activity, which leads to lactic acid accumulation (Oudin and Weaver, 2016). The encapsulation of drugs in pH-responsive polymers not only mitigates systemic toxicity but also enhances drug accumulation at the tumor site, thereby improving therapeutic efficacy. In general, the drugs and polymer carriers are conjugated through chemical bonds that undergo hydrolysis in an acidic environment, which begin to cleave upon exposure to the TME, thereby releasing the drugs. Common acid-labile bonds include Schiff base (imine) bonds, boronic acid esters, o-ester bonds, and hydrazone bonds (Yan et al., 2024).

3.1.1.1. Imine bonds. The imine bond resulting from the condensation reaction between an aldehyde or ketone with amino groups changes reversibly at low pH (Chen et al., 2024). The imine bond formed by primary amines and aldehydes is hydrolyzed at pH below its pKa, while above this value Schiff bases bonds are considered stable. PNIPAM is a thermoresponsive polymer close to the normal temperature of the human body (Ashraf et al., 2016). Carneiro (Carneiro et al., 2021) et al. prepared a dual pH/temperature-responsive nanogel for transporting the anticancer drug doxorubicin (DOX) through synthetic methods such as free radical polymerization, atom transfer radical polymerization employing the characteristics of Schiff base, and PNIPAM. The researchers synthesized dextran-grafted PNIPAM copolymers with dual-responsive properties to both heat and pH through a Schiff-based bond, thereby facilitating the targeted delivery of the anticancer drug DOX to the tumor site and enhancing drug accumulation. The DOX release curve showed values of 34.9 ± 4.8 % at pH 7.4 and 59.1 ± 2.1 % at pH 5.0. Experimental results indicated that the imine bond was less stable in the TME, leading to the cleavage of bonds between DOX and the copolymer, as well as between oxidized dextran and PNIPAM-NH_2, thus facilitating a significant release of DOX and enhancing drug targeting and efficacy.

As previously mentioned, Schiff base bonds are easily hydrolyzed and unstable in acidic environments; therefore, the drug carriers were designed to be pH-responsive. However, this method results in a relatively slow drug release rate. To improve its release rate, Yu (Yu et al., 2020) et al. prepared pH/GSH dual stimuli-responsive dextran nanogels for delivery of DOX by forming disulfide-containing Schiff bases bonds through the reaction of aldehyde dextran and hemiamine in a water-in-oil reverse microemulsion. Dextran nanogels were prepared by using polyaldehyde dextran and hemiamine to form disulfide-containing Schiff bases bonds, wherein DOX was covalently bound to the aldehyde group on the dextran nanogels through Schiff base bonding to facilitate drug-carrier binding. DOX served as a model drug for studying the release profile of the nanogel. As depicted in Fig. 3, the experimental results revealed that the release of DOX was only about 9 % after 158 h at pH 7.4 or under low GSH concentration; the cumulative release of DOX reached 23.86 % after 158 h of incubation at pH 6.5; and at pH 5.0, the release was 40 %. The release of DOX under conditions of high GSH content was 56 % and 75 %, respectively. The release of the DOX-loaded nanogel at the tumor site was significantly increased, thereby enhancing the local accumulation and sustained release of the drug. This approach improved therapeutic efficacy while minimizing side effects.

3.1.1.2. Borate bond. Borate bonds, as commonly used chemical bonds with acid instability, are pH-responsive like Schiff bases bonds, but borate release is maximal in acidic TME and minimal at normal physiological pH, a feature that prevents premature release of the drug, improves drug accumulation in tumor tissues, and enhances therapeutic efficacy.

The preparation of pH-responsive nanogels using boric acid commonly involves two methods. The first method involves introducing the borate ester into the carrier through the condensation reaction between boronic acid and diol, and the second method entails covalently linking the drug to the carrier *via* the borate ester (Yu et al., 2023). Based on the above-mentioned theories, Chen (Chen et al., 2023) et al. synthesized hydrophobic polyesters containing multiple pendant phenylboronic acid groups through ring-opening polymerization and click chemistry. Subsequently, catechol-modified hydrophilic compounds were synthesized by attaching dopamine to carboxyl-terminated polyethylene glycol. The anticancer drug paclitaxel (PTX) was then loaded into the prepared amphiphilic compound *via* a self-precipitation method. The resulting nanogels, which contained phenylboronic acid groups, exhibited resistance to the acidic TME, and hydrolysis of the boronic acid bonds led to the rupture of the nanogels, facilitating the release of PTX at the tumor site. This was confirmed by establishing a tumor model of the human prostate cancer cell line (DU145) in BALB/c nude mice and evaluating the therapeutic effects of the nanogel on the tumor-bearing mouse model. Observation of the drug release profile demonstrated that PTX release increased up to threefold at pH 7.4 and 5.5, resulting in release percentages of 20 % and 60 %, respectively. Furthermore, investigation of the antitumor activity revealed that

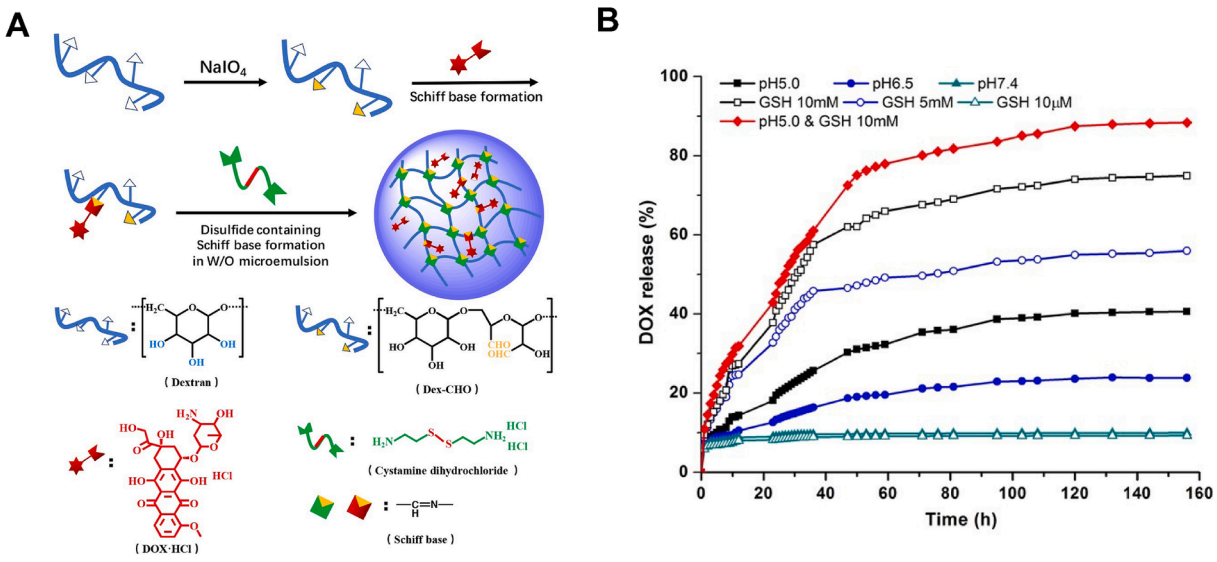

Fig. 3. A. Schematic illustration for the preparation of pH/reduction dual sensitive dextran nanogel via disulfide containing Schiff base formations in W/O microemulsion; B. Time-dependent cumulative DOX release of DOX@Dex-SS nanogels. DOX: Doxorubicin, DOX@Dex-SS: dextran-based (Dex-SS) nanogels. Reprinted with permission from Yu et al. (2020) (Yu et al., 2020). Copyright (2020), Elsevier.

administration of free PTX and PTX-loaded nanogels inhibited tumor growth, whereas PBS-treated mice exhibited rapid tumor growth. These findings suggest that the nanogels enhance their effectiveness within the TME and exhibit improved anticancer activity.

Emodin possesses anticancer and antimicrobial properties and has significant therapeutic effects on various cancers such as colorectal cancer, breast cancer, and glioma. However, it has serious toxic side effects such as hepatotoxicity. To reduce its side effects and improve patient compliance, based on the above-mentioned first route of preparing pH-responsive nanogels using boric acid, Zheng (Zheng et al., 2021) et al. prepared nanopredrugs for the *in vivo* transport of emodin. They synthesized pH-responsive nanopredrugs by conjugating rhodopsin with poly (ethylene glycol) polyethyleneimine with acid-sensitive borate bonds. The borate bond in the nanomedicine started to break down and release emodin in the acidic TME. Leveraging the acidic TME, a pH-responsive drug delivery system facilitates enhanced drug accumulation in tumor tissues, thereby significantly improving therapeutic efficacy. Similarly, bacteria grow faster in acidic environments, and the release of pH-responsive drugs would inhibit bacterial growth more effectively. As shown in Fig. 4, the experimental results indicated that the bacterial inhibition rates of emodin against *Escherichia coli* and *Staphylococcus aureus* were 73.7 % and 34.4 %, while the inhibition rates of anti-tumor small-molecule prodrugs were 96.0 % and 78.0 % at pH 5.0.

3.1.1.3. O-ester bond. The acid-cleavable neighboring ester (O-ester) bond is more stable than the boronic acid ester bond, which exhibits minimal hydrolyze at normal physiological pH, but undergoes some

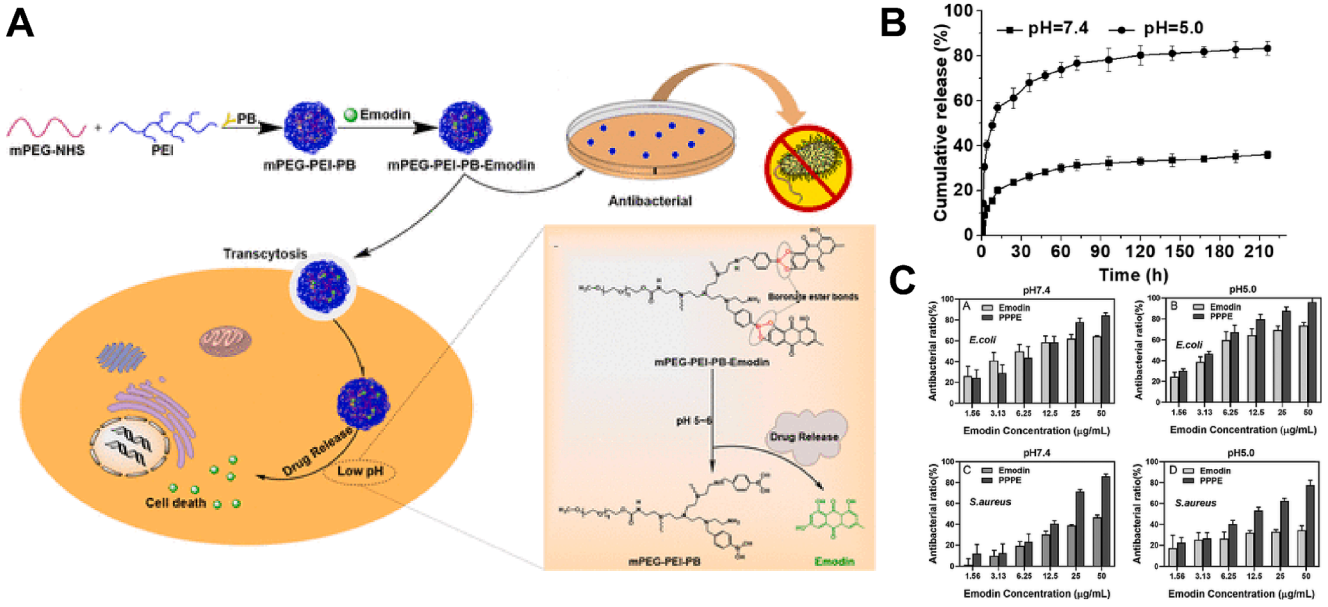

Fig. 4. A. pH-sensitive boronate ester bridged emodin nano-prodrug for the anticancer drug-delivery system; Antibacterial activity of the nano-prodrug; Illustration of the drug-release mechanism of the PPPE under weak-acidic environment; B. pH-responsive drug-release profiles of emodin from PPPE under different pH values (7.4 and 5.0); C. Quantitative results of antibacterial activity toward E. coli and S. aureus with emodin and PE prodrug at pH 7.4 and pH 5.0. PPPE: PEGylated polyethylenei-mine-PB-emodin. Reprinted with permission from Zheng et al. (2021) (Zheng et al., 2021). Copyright (2021) American Chemical Society.

hydrolysis in acidic environments (Yu et al., 2024). As previously discussed, the primary advantage of the boronic acid ester bond over the Schiff base bond is its ability to facilitate targeted drug release, thus preventing premature drug release. The key advantage of the O-ester bond over the boronic acid ester bond lies in its superior stability and enhanced sensitivity to acidic environments, in contrast to acid-unstable bonds. The synergistic combination of these properties enables the precise and controlled release of drugs. Natural polysaccharides, such as chitosan (CS), contain O-ester bonds, making them suitable candidates for incorporation into nanomedicine carriers (Fu et al., 2018). Based on the above characteristics, Li (Li et al., 2019) et al. prepared two types of nanogels—acid-sensitive and acid-insensitive—for the delivery of DOX. These nanogels were prepared by directly cross-linking carboxymethyl chitosan (CMCS) with two different cross-linking agents: an acid-sensitive bi (epoxy)-terminated cyclic O-ester compound and an acid-insensitive ethylene glycol diglycidyl ester, respectively. The fabrication process utilized the straightforward technique of solvent evaporation from an emulsion. DOX, serving as the model drug, was loaded into the nanogels *via* O-ester bonding. The researchers investigated the degradation behavior of the nanogels and the release profile of DOX under three different pH conditions. The results demonstrated a minimal drug release (11.70 %) at pH 7.4, while significantly higher release rates of 67.2 % and 95.1 % were observed at pH 6.5 and pH 5.0. To evaluate anti-tumor efficacy, a growth inhibition assay was conducted on tumor-like multicellular spheroids. The results showed a progressive reduction in spheroid diameter upon treatment with the pH-responsive DOX-loaded nanogel, reaching its smallest size by day 7. The advantage of pH-sensitive nanogels for release in acidic TME was highlighted by comparing two nanogels that were not equally sensitive to pH. Meanwhile, this pH-responsive behavior significantly enhanced antitumor activity and the therapeutic effect of DOX.

3.1.1.4. Hydrazone bond. Similar to the O-ester bond, the hydrazone bond remains stable in a neutral environment but can be hydrolytically ruptured under acidic conditions (Yan et al., 2024). Therefore, polymers containing hydrazone bonds function as effective carriers for nanomedicines, facilitating the delivery of anticancer drugs into the human body. This strategy facilitates the targeting and eradication of tumor cells while minimizing the toxic side effects of the drugs. Capitalizing on the acid sensitivity of the hydrazone bond, Van Driessche (Van Driessche et al., 2018) et al. proposed a direct method based on polymer-activated ester scaffolds followed by hydrazone bonding to connect the synthesized amphiphilic polymers and nanoparticle-DOX couplers. DOX was chemically coupled *via* bonds hydrolyzed by acid to produce stable DOX-loaded nanogels. The zebrafish xenograft tumor model was utilized to predict the anti-tumor activity by measuring the inhibitory ability of DOX-carrying nanogel against the growth of zebrafish embryo transplanted B16 murine melanoma cells. The experimental results showed that the nanogel was able to reduce tumor growth and demonstrated a strong tumor inhibitory effect.

3.1.2. pH-sensitive functional polymers based on ionic interactions

Functional polymers based on ionic interactions are primarily synthetic polymers that offer advantages such as design flexibility, functional versatility, stability, and ease of synthesis and processing. Among the various types of ionic polymers, cationic polymers and charge-converting polymers are most commonly used in nanogel formulations (Huh et al., 2012). Cationic polymers are highly water-soluble and possess positive electrostatic properties, enabling them to interact electrostatically with negatively charged substances. This property also facilitates endosomal escape *via* the proton sponge effect, which disrupts the nanogel structure and promotes drug release (Mehta et al., 2024). Charge-converting polymers, on the other hand, undergo charge transformation in response to specific environmental conditions, such as pH or redox changes. These polymers are typically made by polymerizing monomers with ionizable groups that can be protonated or deprotonated under different conditions. This protonation/deprotonation process alters the polymer's charge, causing the nanogel to either swell or rupture, thereby releasing the encapsulated drug. Leveraging these characteristics, nanogels can be engineered to undergo endosomal escape or charge transformation in response to the TME. This enhances drug accumulation and release at the tumor site, minimizes toxicity to healthy tissues, and improves both delivery efficiency and therapeutic efficacy. Specific examples of these two types of functional polymers are discussed below.

3.1.2.1. Cationic polymers. Cationic polymers in nanogels mainly achieve drug release through the proton sponge effect. After reaching the target cell, the nanomedicine enters the intracellular environment through endocytosis. However, the majority of nanoparticles are unable to escape from the inner core and bypass the endosomal barrier (Beach et al., 2024). To address this issue, it is suggested to utilize the plasmonic sponge effect to disrupt the membrane, facilitating the endosomal escape of drugs or nanoparticles. In the proton sponge effect, polybases with pKa between extracellular and lysosomal pH (4.5–7.4) buffer the endosomal pH, altering the osmotic pressure of the endosome and causing it to rupture (Sikder et al., 2024). Cationic polymers demonstrate pH-responsiveness in acidic conditions and can form complex structures with therapeutic macromolecules through electrostatic interactions. These compounds can be directed to the tumor-targeted site, where they are activated by a mildly acidic microenvironment, triggering the release of the drug in TME.

Gene therapy is already widely utilized. Certain cationic buffer polymers are favored for their capacity to overcome the endosomal barrier and for their targeted release in acidic environments. Spencer (Spencer et al., 2021) et al. prepared a cationic nanogel system based on 2-(diethylamino) ethyl methacrylate for delivery of siRNA *via* emulsion DOX. By coupling cationic nanogels carrying drug molecules with siRNA, renal filtration and hepatic uptake are avoided, prolonging drug retention time and reducing DOX off-targeting toxicity. Furthermore, cationic polymers demonstrate responsiveness to an acidic TME, facilitating controlled drug release. This experiment evaluated the cytocompatibility of nanogels using a mouse fibroblast cell line, a human hepatocellular carcinoma cell line, an eGFP-expressing human breast cancer cell line, and a DOX-resistant breast cancer cell line. The nanogels were tested at four concentrations (1, 5, 25, and 125 μg/mL) over 48 h. The results demonstrated higher toxicity in the MCF-7/A DOX-resistant human breast cancer cell line (MCF-7/ADR) , while cytocompatibility trends were consistent across the remaining three cell lines. Clegg (Clegg et al., 2021) et al. similarly utilized the cationic polymer poly (acrylamide-co-methacrylic acid) nanogels, which were modified in a modular fashion with bioactive peptides. Peptides, proteins, or nucleic acid ligands targeting receptors overexpressed in tumor cells were integrated with the nanogels. Integration of ligand targeting with the nanogel reduces off-target effects. As previously mentioned, the phenomenon wherein endosomes disrupt cation networks and multimers is termed the proton sponge effect. Utilizing the plasmonic sponge effect, unmodified nanogels are responsive to the pH environment, enabling encapsulation of complex hydrophilic small molecule payloads, and demonstrate non-toxicity to a broad range of cell lines at high doses (0.5 wt% in the culture medium). This drug model was applied to colorectal cancer by selecting a peptide to target colorectal cancer cells and examining the effect of peptide mass percentage on target cell co-localization and endosomal escape. Experimental evidence demonstrated that the peptide is encapsulated within a nanogel and its spatial arrangement may influence its targeting ability or its interaction with endosomal membranes.

Similarly, Sahu (Sahu et al., 2019) et al. accomplished pH-triggered transdermal targeted delivery of anti-skin cancer drugs *via* the interaction between cationic charge and acidic TME. Pluronic F127 was used as a raw material and the surface was modified with Transcutol as a

nonionic permeation enhancer, Subsequently, the nanogel was loaded with DOX through an ionic gelation mechanism. *In vitro* experiments to assess the release pattern of the nanogel were conducted using the dialysis bag method in PBS at pH 4.0, 5.0, 6.0, and 7.0 at 37 °C. The results indicated that approximately 15–25 % of the nanogel was released at pH 7.0 with no further release observed thereafter, significant release was observed at pH 4.0 and 5.0.

3.1.2.2. Charge-converting polymers. Apart from cations and acidic environments triggering the release of nanogels, another prevalent mechanism relies on charge-converting polymers, resulting in a pH-response release of nanogels. This response mechanism involves the formation of cations and anions through deprotonation or protonation of pH-sensitive polymers. Charge-converting between cations and anions induces alterations in the swelling properties of the nanogel, thereby facilitating the release of the drug encapsulated within the nanogel.

CS and poly(methacrylic acid) (PMAA) are both functional polymers (Samel-Garloff et al., 2024). CS becomes protonated to form cations under acidic conditions and PMAA becomes deprotonated to form anions under alkaline conditions. Based on these two pH-sensitive polymers, Bhattacharjee (Bhattacharjee et al., 2023) et al. prepared CS/PMAA nanogels through a two-step process. The first step involved the polymerization of methacrylic acid monomers with initiators and cross-linkers to form covalently cross-linked networks. The second step used secondary forces such as hydrogen bonding to form a complex between CS and PMAA. The prepared complexes between CS and PMAA carry repulsive forces due to the opposite charges, which significantly influence the swelling properties of the nanogel. This reversible pH-stimulated volumetric phase transition enables controlled and targeted drug delivery, leading to improved efficacy and reduced side effects.

Charge-reversible nanogels are typically created through stimulus-triggered protonation/deprotonation or the covalent cleavage of key functional groups. However, covalent bond cleavage takes a longer time, often leading to premature release of the nanogel before the process is complete. Therefore, protonation/deprotonation, triggered by a stimulus, is more effective for controlled release. Building on this, Li (Li et al., 2021) et al. developed nanogels with enzymatic degradation using a microemulsion method and glutaraldehyde as a cross-linking agent. These nanogels exhibited pH-triggered charge reversal properties after treatment with an alkaline solution, enabling efficient delivery of the chemotherapeutic drug DOX. Their release profile showed slow drug release at pH 7.4, with only 17.45 % of DOX released after 24 h. At pH 6.5, DOX release increased to 36.53 %, attributed to the negative charge of DOX and the nanogel's charge reversal. Additionally, tumor penetration studies using a multicellular spheroid model revealed that pH-responsive charge reversal enhanced the nanogel's tumor penetration *via* active transport.

3.1.3. pH-sensitive coatings

Carbon nanotubes were previously found extensive applications in automotive and aerospace industries for enhancing performance, self-repair, and durability (Dallaev, 2024). Over time, stable forms of carbon nanotubes (e.g. functionalized carbon nanotubes), including functionalized variants, have found application in nanotechnology as potent drug delivery systems for targeted or localized therapeutic delivery. Carbon nanotubes are pH-sensitive and drugs are complexed with carbon nanotubes through hydrophobic interactions and subsequently begin to be released under lysosomal low pH conditions (Alves da Silva et al., 2024). Seyfooria (Seyfoori et al., 2019) et al. prepared pH/magnetic dual-responsive nanogels for transporting DOX by coating CS nanogels on the surface of magnetic nanoparticles $MnFe_2O_4$ based on carbon nanotubes. They chose pH 5.3 and pH 7.4 to employ the pH of TME and normal physiology. The observed drug loading of DOX was 71 % and 92 % at pH 5.3 and 7.0, respectively. The experimental results demonstrated that the drug loading of the nanogel was greater in an acidic environment, correlating with stronger antitumor activity.

Fattahi (Fattahi et al., 2024) et al. developed pH/magnetic-responsive nanogels using $CuFe_2O_4$ instead of $MnFe_2O_4$. $CuFe_2O_4$ nanoparticles were first synthesized, then coupled with PMAA *via* reflux precipitation polymerization. Next, $CuFe_2O_4$@PMAA was functionalized with amino-modified lignin through a Mannich reaction, creating a nanogel for curcumin (CUR) delivery in breast cancer treatment. The polymer structure of the resulting nanogel, abundant in carboxylic acid groups, enabled it to shrink or swell in response to pH changes. Drug release studies revealed that 79 % of CUR was released after 120 h at pH 5.6, while only 50 % was released at physiological pH (7.4). This metal oxide-coated nanogel not only enhanced the nano-delivery system but also provided dual pH/magnetic responsiveness, improving drug release control, preventing premature leakage, and increasing drug accumulation at the tumor site, ultimately enhancing therapeutic efficacy.

3.2. Biomolecule-responsive nanogels

Biomolecules, unique to living organisms, can respond to the TME, including GSH, and enzymes, among others. For example, the concentration of GSH in the TME is 7–10 times higher than that in normal cells (Wang et al., 2024). Thus, polymers containing sulfhydryl groups can be introduced into nanogels. Upon reaching the tumor site, the nanogel carries the anticancer drug in response to the high concentration of GSH and releases the drug in the tumor site (Janus-Faced, 2014). Within the TME, various enzymes such as hyaluronidase, and matrix metalloproteinases (MMPs), among others (Liu et al., 2021); overexpressed in tumor cells, making them potential targets for the development of enzyme-sensitive nanogels.

3.2.1. GSH-responsive nanogels

Tumor cells exhibit increased ROS production attributed to mitochondrial dysfunction, metabolic alterations, and frequent gene mutations (Weinberg et al., 2019). The inherent disulfide bonds in the GSH molecule exhibit high stability, rendering disulfide-coupled nanogels of anticancer drugs stable in somatic circulation (Li et al., 2024). Upon entering tumor cells, the drug-loaded nanogel is reduced to sulfhydryl groups due to the high concentrations of GSH, resulting in the structural disintegration of the nanogel and the subsequent release of the drug. In contrast to disulfide bonds, Se-Se bonds possess weaker bond energy (172 kJ/mol) compared to S-S bonds (240 kJ/mol) and are readily cleaved by external stimuli (Yan et al., 2024); thus rendering disulfide bonds more sensitive to external stimuli and exhibiting a faster reaction speed. Tian (Tian et al., 2020) et al. used reflux precipitation polymerization to copolymerize nanogels with 2-methacryloyloxyethylphosphorylcholine and diselenodiamine-containing bonded cross-linkers. The diselenide bond contained in the cross-linker conferred redox instability to the nanogel so that the drug-carrying nanogel started to break up and release the drug upon entering the TME. DOX was employed as a model anticancer drug to evaluate the drug release profile of the nanogels. The experimental results demonstrated that the release of DOX was 88.3 % and 82.2 % under redox conditions of 10 mM GSH and 0.01 % hydrogen peroxide (H_2O_2), respectively. In contrast, the release of DOX from the non-degradable nanogel, used as a control, was less than 20 %. The experimental results indicated that the diselenide-bonded cross-linker with redox response promoted the accumulation and release of DOX and significantly improved the drug efficacy.

3.2.2. Enzyme-responsive nanogels

Advanced drug delivery systems can detect biological stimuli, such as specific enzymes, within pathological environments, facilitating responsive delivery and thus paving the way for controlled and targeted drug delivery. Overexpressed enzymes, such as hyaluronidase and MMPs found in tumors or other inflammatory sites, could serve as viable targets for designing enzyme-sensitive nanogels (Gębalski et al., 2024). To reduce adverse drug reactions, nanocarriers can be utilized and

modified with enzyme-unstable bonds to enable on-demand enzyme-responsive drug release.

Hyaluronidase is a broad term for an enzyme that hydrolyzes HA, reducing its activity in the body, and consequently enhancing tissue permeability with fluid (Bokatyi et al., 2024). HA is a naturally occurring acidic glycosaminoglycan that exhibits outstanding viscoelastic properties, high water solubility, biocompatibility, hydrophilicity, and minimal immunogenicity. Le (Le et al., 2022) et al. developed a novel nanogel by mixing HA with a thermo-responsive amine-terminated polyether and either diethylaminoethyl dextran or poly L-lysine in water. Additionally, the anticancer drug CUR was encapsulated within the nanogel as a drug model. Due to hyaluronidase overexpressed in TME, the nanogel loaded with CUR commenced degradation and subsequent CUR release upon reaching the tumor site.

The expression levels of hyaluronidase are markedly elevated in numerous tumor tissues, playing a crucial role in tumor development and metastasis. Similarly, MMPs are expressed in various types of cancers and play pivotal roles in tumorigenesis, progression, invasion, and metastasis by regulating signal transduction and the TME. MMPs comprise a large family of proteases with metal ions in their active centers (Baidya et al., 2024). Depending on the structural domains, MMPs can be classified into various isoforms, with the most prevalent being matrix MMPs. Using the response of MMPs to the TME, Singh (Singh et al., 2021) et al. synthesized an MMPs-sensitive nanogel employing a prepolymer approach. The nanogel was crosslinked by an MMP-2 and MMP-9 substrate and loaded with the radiopharmaceutical, capable of being integrated into the DNA of tumor cells upon release. Upon accumulation at the tumor site, the nanogel responds to elevated concentrations of MMP-2 and MMP-9 in the TME. Zymograms conducted under the tested conditions revealed the highest MMP-2 and MMP-9 activities in the co-culture medium of human glioblastoma cells (U-87 cells). To assess degradation under physiological and pathological conditions, the degree of nanogel degradation corresponded to the MMP-2 activity detected *via* enzymatic profiling, as observed through phosphoroplastometry, with the highest degree of degradation of the nanogels when co-cultured with U-87 cells. Experimental studies have shown that this nanogel demonstrates exceptional stability and therapeutic efficacy in glioma treatment, addressing the challenge of restricted drug permeability across the blood–brain barrier and mitigating drug-related adverse effects.

3.3. ROS-responsive nanogels

ROS plays a crucial role in cell growth, proliferation, and signaling processes, such as H_2O_2, superoxide, and hydroxyl radicals. Typically, ROS levels remain low in the cell due to timely scavenging by antioxidants such as GSH, superoxide dismutase, and peroxidase. Conversely, in tumor cells, the metabolic level of ROS significantly increased due to ROS overproduction, resulting in oxidative stress stemming from the mutual antagonism between ROS and antioxidant systems (Ferraz et al., 2024; Black, 2024). Furthermore, continuous ROS production under the influence of exogenous and endogenous factors exacerbates oxidative stress, which induces apoptosis and necrosis once the ROS level surpasses the tolerance capacity of the tumor cells. However, this phenomenon does not occur in normal cells. Therefore, the selective targeting of tumor cells through ROS regulation while sparing normal cells represents an effective anti-tumor strategy.

The primary mechanism of PDT involves enhancing intracellular oxidative stress through ROS generation to eliminate cancer cells (Ming et al., 2021). However, PDT is limited by the inefficiency of ROS generation in tumors and the lack of specific targeting. Additionally, malignant cells commonly exhibit upregulation of GSH levels, which can scavenge ROS produced during PDT, thereby rendering tumor tissues highly resistant to treatment and reducing the therapeutic efficacy of PDT (Liu et al., 2023). GSH can be depleted *via* a sulfhydryl click reaction, in which ROS production inhibits enzymes involved in GSH biosynthesis, leading to a direct or indirect reduction in GSH concentrations (Hu et al., 2020). Based on the above methods and theories, Liao (Liao et al., 2024) et al. synthesized multifunctional nanogels by incorporating bovine serum albumin, carboxymethylcellulose sodium (CMC-SS), and a natural photosensitizer peridinin-chlorophyll-protein complex (PCB). As shown in Fig. 5, CMC-SS was employed to decrease intracellular GSH levels in malignant cells and disrupt the redox homeostasis of tumor cells. Mouse embryonic fibroblasts were utilized as a tumor model to evaluate the tumor inhibition effect of nanogels loaded with photosensitizers. The results demonstrated tumor inhibition rates of 24 % in the control group and 90 % in the experimental group, respectively, indicating that the multifunctional nanogels synthesized with natural photosensitizers exhibit significant anti-tumor activity within the TME, thereby enhancing therapeutic efficacy. $CD8^+$ T cells have emerged as essential components of tumor immunotherapy due to their potent cytotoxic activity against tumor cells (Chen et al., 2016). Nonetheless, the immunosuppressive TME hampers the anti-tumor immune response required for $CD8^+$ T cell activation. The novel immunomodulators to improve immunosuppression and reactivate T-cell-mediated anti-tumor immunity within TME were identified. For *in vivo* delivery of these immunomodulators, Tian (Tian et al., 2023) et al. achieved the synthesis of a block copolymer (PEGb-NH_2) *via* reversible addition-fragmentation polymerization and then introduced a thiol linker on PEG-NH_2 *via* highly reactive acyl chlorides and free amino groups for rapid ROS cleavage. Subsequently, the ROS-responsive phenolic polymer (PM) was synthesized by coupling the crosslinked polymer with metformin (Met) and 3,4 dihydroxybenzaldehyde on the hydrophobic side chain *via* acid-sensitive imine bonds. This nanogel carries two repurposed immunomodulators, imiquimod, and Met, which collectively remodeled the immunosuppressive TME. This remodeling is achieved through several mechanisms, including promoting dendritic cell maturation, repolarizing M2-like tumor-associated macrophages, and down-regulating PD-L1 expression. These actions work together to effectively promote $CD8^+$ T cell infiltration and activation, ultimately enhancing anti-tumor immune responses when combined with anti-PD-1 antibodies. To verify the autodegradation of the nanogel in TME and the ROS responsiveness of PM, they prepared a solution at pH 6.8 containing 100 μM H_2O_2 to simulate TME and incubated it with the nanogel for 6 h. TEM images were subsequently employed to confirm the disruption of the previously well-assembled structures. After co-incubation with H_2O_2, the amount of ROS generated was four times higher than that of the H_2O_2 alone group. Self-degradation of nanogel ultimately led to the rapid release of the drug. Imiquimod was released by more than 50 % within 4 h in a solution at pH 6.8 containing 100 μM

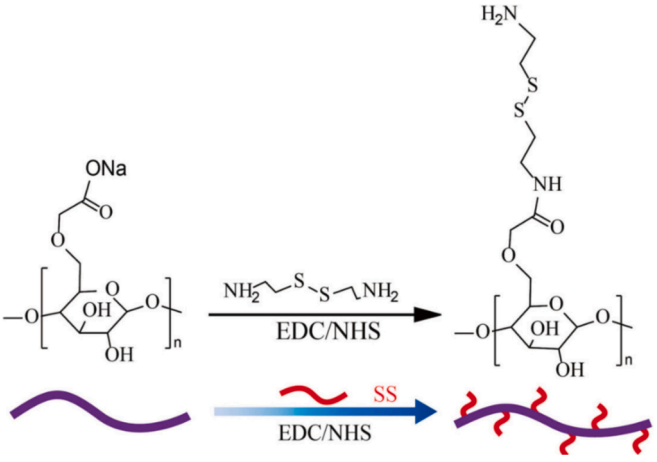

Fig. 5. Schematic diagram of CMC-SS synthesis; CMC-SS: carboxymethylcellulose sodium. Reprinted with permission from Liao et al. (2023) (Liao et al., 2024). Copyright (2023), Elsevier.

H_2O_2. At pH 5.5, the release of Met from the nanogel was upwards of 80 %, whereas at pH 6.8, it was 50 %, and at pH 7.0, it was negligible. The highest release of Met from nanogel occurred in an acidic environment, suggesting improved efficacy against tumors.

3.4. Hypoxia-responsive nanogels

In tumors, restricted blood perfusion due to local spatial constraints and delayed angiogenesis often results in the development of a hypoxic microenvironment within the tumor region (Li et al., 2024). To a certain extent, the hypoxic microenvironment can inhibit tumor growth by suppressing their energy metabolism. The azobenzene bond is highly sensitive under a low oxygen environment, which can cause drug release through the breakage of the azobenzene bond (Cheng et al., 2021). In recent years, azobenzene derivatives have been widely studied as basic materials for constructing hypoxia-responsive nanocarriers.

Based on this feature, Peng (Peng et al., 2021) et al. synthesized azobenzene-containing cross-linker (MPC) by amidation reaction of azobenzene-4,4′-dicarboxylic acid with 2-aminoethyl methacrylate hydrochloride. ^{H} PMPC nanogels were prepared by copolymerization of MPC with azobenzene cross-linker *via* reflux precipitation polymerization for the transport of DOX. It was found by transmission electron microscopy that the hydrodynamic size of ^{H} PMPC remained almost unchanged after 7 days of incubation in a cell culture medium, which indicated that the nanogel had good stability. They analyzed the anti-tumor activity of DOX-carrying nanogels using human hepatocellular carcinoma cell (HepG2) hormonal nude mice as a tumor model, with DOX serving as a drug model. Observation of the release profile revealed that the nanogel exhibited a release rate of 86.3 % attributed to the cleavage of the hypoxia-sensitive azobenzene bond. Additionally, the nanogel demonstrated superior anti-tumor efficacy compared to the control group.

In our previous work, our focus has primarily been on achieving targeted release of nanogels, with less emphasis on increasing drug loading while maintaining targeted release. If we can achieve both the targeted release of drugs and increased drug loading, then we get two birds with one stone. The development of multifunctional drug delivery systems capable of carrying multiple drugs to treat multiple diseases is essential but still challenging. Zhang (Zhang et al., 2019) et al. developed a nanogel loaded with 5-aminolevulinic acid, a hydrophilic prodrug of protoporphyrin IX (PpIX), and tirapamine (TPZ), a water-soluble, hypoxia-responsive drug. PpIX could consume oxygen to generate toxic mono-linear oxygen in the light-irradiated TME, activating the hypoxia-dependent cytotoxicity of TPZ, thus accelerating the conversion of nontoxic TPZ to highly toxic TPZ radical conversion. TPZ, a hypoxia-responsive drug, was transported to the tumor site by loading it into a nanogel along with PpIX for nanoprobing. When the nanogel reached the tumor site, the hypoxic characteristics of the TEM triggered the release of TPZ. The apoptosis rate of human lung adenocarcinoma cell line A549 (A549 cells) increased dramatically from 26.6 % to 90.5 % after irradiation with near-infrared light, indicating that this nanogel has high anti-tumor activity. They investigated the anti-tumor ability of the nanogel in the mentioned body using hormonal mice as a tumor model. The experimental results demonstrated that free TPZ displayed minimal anti-tumor activity. However, the tumor inhibition rate in mice treated with the nanogel system and laser irradiation reached 86.1 %. These results clearly demonstrate that the combination of hypoxia-responsive TPZ and the nanogel system not only enhanced drug accumulation at the tumor site but also improved anti-tumor efficacy, thereby increasing therapeutic outcomes.

With the diversification of tumor therapeutic modalities, the above-mentioned dual-responsive nanogels containing hypoxia-stimulated responses have been applied to the delivery of protein drugs (Tian et al., 2024). Protein drugs represent an effective method of cancer treatment, and most protein therapies exhibit anticancer activity by binding to receptors on tumor cells, such as trastuzumab binding to human epidermal growth factor receptor 2 on cancer cells (Ren et al., 2024). However, systemic administration of protein drugs may cause serious side effects. Therefore, achieving efficient delivery of protein drugs *in vivo* with reduced side effects is a current challenge. Interleukin-12 (IL-12) is a potent immunotherapeutic cytokine with antitumor activity (Xin et al., 2024). However, IL-12 therapy is also associated with significant systemic side effects (Xu et al., 2024). Therefore, there is a need to develop delivery systems capable of effectively encapsulating proteins and releasing them slowly as required. The sustained release would prolong the therapeutic effects of the released cytokines, thereby minimizing potential systemic side effects. The tumor-specific hypoxic microenvironment influences cellular metabolism, leading to angiogenesis and reduced drug cytotoxicity (Liang et al., 2024). Therefore, Zhang (Zhang et al., 2020) et al. prepared polyethylene glycolated HA nanogels with low oxygen and enzyme reactivity and demonstrated that the nanogels could selectively release IL-12 in the TME. Nitroimidazole was sensitive to hypoxic environments and could be converted to hydrophilic aminoimidazole in hypoxic environments, which facilitated the release of encapsulated IL-12. They chose to use melanoma mice as a model to investigate the anti-tumor efficacy of hypoxia-responsive nanogels. The experimental data indicated that IL-12 was released at a concentration of 150 ng over 96 h. The degradation of the nanogel was attributed to both its sensitivity to the hypoxic environment and the presence of hyaluronidase, which accelerated nanogel degradation and, consequently, enhanced drug release.

4. Exogenous stimuli-responsive nanogels

Exogenous stimuli mainly include light, magnetic, ultrasound et al (Xiao et al., 2024). The release mechanism is the same as that of endogenous stimulation, but endogenous stimulation is mainly achieved by using the TME, while exogenous stimulation causes drug release by artificially giving some external stimuli. Below, we give some typical examples of exogenous stimulation-responsive nanogels respectively (Fig. 6).

4.1. Light-responsive nanogels

Light irradiation-triggered nanogels have demonstrated significant

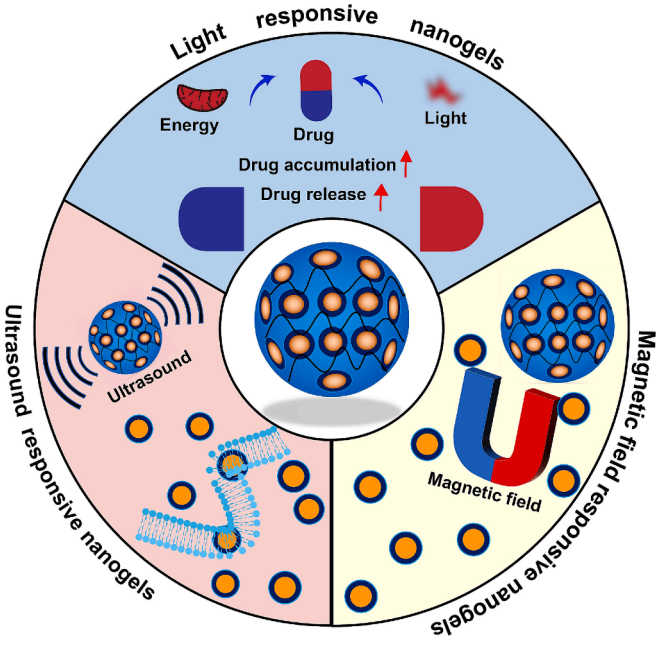

Fig. 6. Schematic representation of exogenous stimuli-responsive nanogels for cancer treatment.

potential in achieving precise, site-specific drug release for diagnostic and therapeutic purposes. The primary mechanism of action involves photosensitive nanocarriers delivering drugs to the targeted site through passive accumulation, active targeting, and internalization (Zhao et al., 2019). Nanogels are encapsulated or loaded with bioactive agents or therapeutic drugs that undergo physicochemical or conformational changes upon receiving light, thereby modulating the release of the drug at a specific site in a controlled manner. Among the most common modes of release are photothermal and photodynamic.

4.1.1. Light-heat responsive nanogels

Photothermal-based nanogel drug delivery systems require the conversion of photonic energy into thermal energy for the controlled release of antitumor drugs to the target site (Jain et al., 2021). Drug release *via* photothermal is achieved in two main ways. The first one is achieved by using materials involving heat/temperature sensitive materials such as PNIPAM, where the heat generated by the light triggering undergoes physicochemical changes to disrupt the structure of the nanogel thereby achieving drug release (Bhaladhare and Bhattacharjee, 2023). The second approach involves photosensitive materials, such as gold nanoparticles (AuNPs), which absorb photon energy and generate heat through photoexcitation.

Drug release through the introduction of photosensitizers and heat-sensitive materials is very popular. To achieve effective and safe antitumor therapy, Yao (Yao et al., 2021) et al. prepared thermosensitive PNIPAM nanogels by soapless emulsion polymerization and loaded them with large amounts of the photosensitizer indocyanine green (ICG) and the anticancer agent 5-fluorouracil (5-Fu), which were used to efficiently realize synergistic chemotherapy and photothermal/PDT for tumors. By comparing the anti-tumor activity of chemotherapy alone and combined PDT, it was observed that the apoptosis rate of HeLa cells was approximately 45.9 % after 24 h of co-culture with 5-Fu@PNIPAM. In contrast, the apoptosis rate of cells subjected to laser irradiation was 46.2 % in the ICG-PNIPAM group. Furthermore, the percentage of apoptotic cells in the 5-Fu@ICG-PNIPAM-laser group was 80 %, significantly higher than that observed with single chemotherapy or photothermal/PDT treatment. These experimental results suggest that the combined photothermal and photodynamic therapies are more effective than single chemotherapy treatment. Xu (Xu et al., 2023) et al. also prepared a GSH/ROS/photothermal multiple reaction nanogel systems (IMs) with the photosensitizer ICG. Se-Se bond breaking could disrupt the redox homeostasis of tumor cells, inducing oxidative stress, synergistically enhancing caspase-3 cleavage, and ultimately regulating cellular pyrokinesis. They first evaluated the photothermal properties of IMs, and the results after 5 min of 808 nm laser irradiation showed that IMs have concentration-dependent photothermal properties. The drug penetration ability was verified by intravenously injecting IMs (ICG concentration of 5.0 mg/kg) into mice, and *in vivo* phase transition temperature ability was explored, the tumor temperature of mice increased from 35 °C to 51.7 °C, indicating that IMs had good *in vivo* photothermal transformation. They used 4 T1 murine breast cancer cell hormonal balb/c mice as a tumor model to examine its anti-tumor activity. The results showed that the mice in the treatment group had the lowest tumor weight and the highest inhibition rate of 59 %. This result indicated that the treatment group had the highest anti-tumor activity and better efficacy.

The thermosensitive polymer PNIPAM mentioned above plays an important role in the preparation of nanogels, but this polymer may have toxicity (Li et al., 2023). As a photoresponsive nanomaterial, AuNPs can generate heat under laser radiation for the photothermal ablation of tumor cells (Consoli et al., 2024). It is widely used in cancer diagnosis and therapy due to its ease of production, biocompatibility, and low toxicity (Ghafari et al., 2024). CS, as a natural polymer, not only covers the surface of AuNPs but also forms AuNPs in an additive-free manner (Faid et al., 2023). Ziaei (Alioghli Ziaei et al., 2023) et al. used an additive-free process to prepare DOX-loaded CS /AuNP nanogels using sodium pentasodium triphosphate (TPP) to treat breast cancer. The experimental results showed that the DOX-loaded nanogel caused a higher mortality of human breast cancer cell line MCF-7 compared to the same concentration of free DOX. Observation of the release curves at pH = 5.8 and pH = 7.4 showed that the release rate of DOX at these two pH values was 99 % and 73 %, respectively, indicating that the composite nanogel exhibited photothermal properties as well as pH responsiveness.

4.1.2. Light-kinetic energy responsive nanogels

Generally, photodynamic responsive nanogels are commonly used in clinical PDT, but they are becoming more and more versatile as medical treatments become more advanced. Preparation of nanogels requires cross-linking agents, but some of the cross-linking agents may be toxic, thus increasing the toxicity of the nanogels (Neamtu et al., 2017). Therefore, the researchers proposed to crosslink the nanogels with light energy. The most widely studied photocrosslinking technique is two-photon polymerization micromachining. However, two-photon polymerization only occurs at higher energy densities and is eliminated because of expensive equipment (Nguyen and Narayan, 2017). By observing the gaussian distribution of light energy, researchers learned that the middle is where the laser energy is the strongest, and it is possible to control the micro reaction area by adjusting the laser energy at the focus (Chen et al., 2019). In this case, the morphology of the crosslinked nanogel could be controlled by combining self-emulsification of the monomer and spatial control of the focus (Wang et al., 2021). An increase in laser power leads to an increase in energy density, and with an increase in cross-linking density, the number of double-bond cross-links between micellar aggregates and within the micelles increases. Therefore, nanogels can be prepared by balancing the double bond cross-linking between micellar aggregates and within micelles. Based on these theories and assumptions, Wang (Wang et al., 2021) et al. prepared a photodynamically responsive nanogel by combining the self-emulsification of poly (ethylene glycol) diacrylate monomers with a small irradiation region of laser light. This kind of nanogel is controlled by a laser to control the reaction area and the size of the nanogel by controlling the laser energy without a cross-linking agent, thus realizing the direct cross-linking of the nanogel. This approach is controllable on the one hand, and on the other hand, the toxicity of the cross-linking agent can be avoided, thus ensuring the safety of the nanogel. Escobedo (Escobedo et al., 2020) et al. similarly achieved drug release using an optokinetic model. As depicted in Fig. 7, by studying the release of the model drug Rhodamine B, it was observed that as the percentage of IEM increased from 0 % to 10 % and then to 100 %, the release of Rhodamine B decreased from 80 % to 50 % and then to 15 %. The above results indicated that this photodynamic model prepared nanogel improved the drug release. However, it was not found that the method of controlling the morphology and size of the nanogel by laser energy is not currently applied to cancer therapy, so the mechanism needs to be explored in depth for this feature at a later stage.

With the increasing number of oncology treatment modalities, the diversity of treatment-related materials has expanded significantly. Among these, PDT has emerged as a prominent approach, particularly when driven by photosensitizers, offering both therapeutic and diagnostic potential. Upon injection into an organism, photosensitizers preferentially accumulate in tumor tissues or lesions due to the EPR effect characteristic of tumor vasculature. Following light irradiation of the lesion, the photosensitizer generates ROS through energy transfer. These ROS are pivotal in inducing tumor cell death, thereby exerting both therapeutic and diagnostic effects.

Despite the advancements in tumor treatment strategies, including PDT, each method has inherent limitations that constrain its efficacy. To address these challenges, Liu (Liu et al., 2020) et al. proposed using nanogels as carriers to enhance PDT outcomes. They encapsulated the photosensitizer chlorin e6 (Ce6) and the histone deacetylase inhibitor (SAHA) into nanogels, aiming to improve the therapeutic efficacy against prostate cancer while enabling tumor imaging. Their study

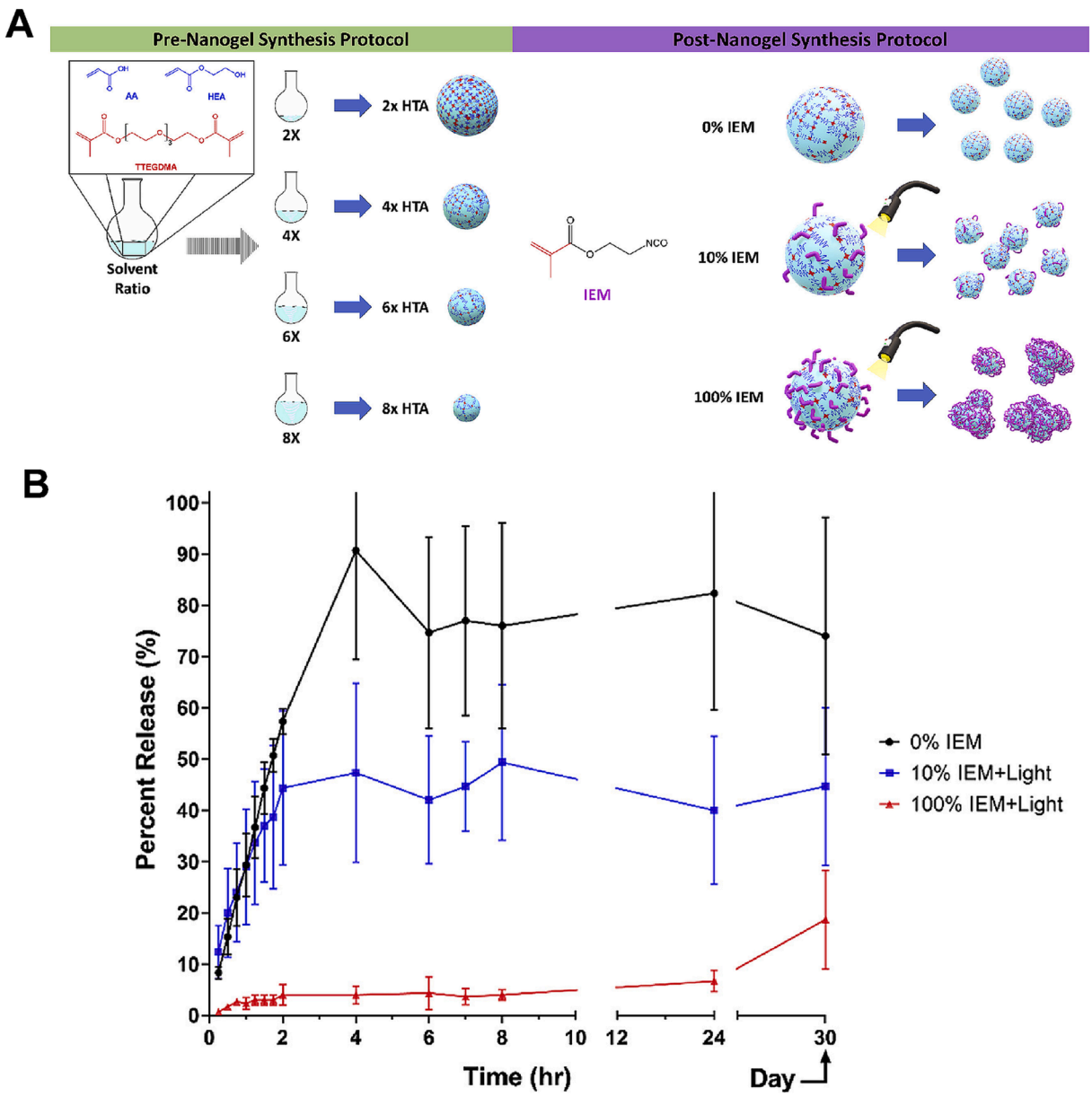

Fig. 7. A. Nanogels with tunable properties were synthesized from 2-hydroxyethyl acrylate (HEA), tetraethylene glycol dimetha-crylate (TTEGDMA), and acrylic acid (AA) monomers to form crosslinked nanogel net-works (HTA nanogel) for drug delivery; B. Rhodamine B (RhB) release over time in phosphate-buffered saline over 30 days from 0 %, 10 %, and 100 % IEM 4X HTA nanogels after a one-time light exposure (365 nm, 10 mW/cm^2, and 30 s) at the beginning of the period. Reprinted with permission from Escobedo et al. (2020) (Escobedo et al., 2020). Copyright (2020), Elsevier.

involved intravenously injecting mice with different formulations—Ce6, SAHA, Ce6-loaded nanogels, and Ce6- and SAHA-loaded nanogels—followed by light activation at the tumor site. Experimental results revealed that tumor volume increased significantly in the control group and was only slightly inhibited in the Ce6 and Ce6 + SAHA groups. In contrast, tumor growth was more effectively suppressed in the Ce6-containing nanogel group and most significantly inhibited in the group receiving nanogels loaded with both Ce6 and SAHA. These findings underscore the potential of combining nanogels with PDT to achieve enhanced tumor suppression.

Beyond therapeutic applications, Ce6-loaded nanogels also demonstrate potential in tumor imaging. Shin (Shin et al., 2023) et al. developed fucoidan-based nanogels (CFN-gels) incorporating Ce6 and evaluated their performance in PDT and tumor imaging. The CFN-gels exhibited superior accumulation efficiency in cancer cells and sustained high fluorescence signals under near-infrared light compared to commercially available fluorescent materials. Using a near-infrared fluorescent diagnostic and therapeutic system with multiple light sources, they further demonstrated the CFN-gels' capability for image-guided surgery and identification of lymph node metastases in colorectal cancer. These findings highlight the dual utility of photosensitizer-loaded nanogels, which not only enhance drug delivery and tumor site drug accumulation but also provide valuable applications in surgical guidance and tumor imaging.

4.2. *Magnetic field-responsive nanogels*

Drug-loaded magnetically responsive nanogels are easy to agglomerate due to their superparamagnetic properties, high surface hydrophobicity, and elevated surface area-to-volume ratio (Mandal et al., 2020). The drug accumulated and concentrated at the target site under an applied magnetic field, subsequently being released to the tumor site

in response to the magnetic field.

Chemotherapy, the mainstay of tumor treatment, has some serious side effects of chemotherapy drugs. To reduce its side effects and improve its efficacy, Mandal (Mandal et al., 2020) et al. modified it with amino silane-coated magnetic nanoparticles based on modified pH and redox-responsive nanogels to confer magnetic field response properties. The nanogel was esterified from –COOH of a pre-synthesised amphiphilic four-armed block copolymer and –OH of a redox-responsive crosslinker. On this basis, they were further modified with amino silane-coated magnetic nanoparticles to impart magnetic field-responsive properties. It was learned by evaluating the magnetic behavior of the nanogels by monitoring the magnetization intensity versus the applied magnetic field (M−H) in the presence of an external field of 30 kOe at room temperature. As depicted in Fig. 8, the results showed a significant increase in saturation magnetization intensity from 1.37 emu/g to 10.7 emu/g. Using DOX as a drug model, they studied the drug release behavior in simulated physiological and cancer cell environments. The experimental results showed that the release rate increased from 8 % to 65 % within 1 h in the presence of a magnetic field at pH 5.0 and GSH 10 mM. This result illustrates that the release rate of magnetically modified nanogels in tumors is greatly increased, which in turn increases the antitumor ability and improves the efficacy.

4.3. Ultrasound-responsive nanogels

Ultrasound is a low-cost, non-invasive technology that allows precise focusing of the beam on the diseased tissue. Ultrasound-induced acoustic cavitation enhances cell membrane permeability and skin porosity, thus facilitating drug delivery. The frequency of ultrasound regulates the depth of penetration and cavitation effect (Shen et al., 2018). Cavitation is a non-thermal effect that causes bubbles to suddenly increase in size under the action of ultrasound. When ultrasound is used as a trigger, it can be precisely focused on tissue sites or drug carriers to achieve controlled drug delivery and release. Based on the above characteristics, Shen (Shen et al., 2018) et al. prepared copolymers with lower critical solution temperature (LCST) using reversible addition-fragmentation chain transfer polymerization and ethylcarbodiimide/succinimide coupling, followed by the formation of copolymer micelles containing PNIPAM cores and PEI shells. The shells were crosslinked with a disulfide-containing crosslinker to obtain spherical nanogels. The anticancer drug DOX hydrochloride and ultrasound-sensitive PFH were encapsulated in the global nanogel. Ultrasound induced the PFH liquid to become microbubbles and cavitation. Under the action of ultrasound, these microbubbles are made to increase suddenly as the trigger signal of ultrasound, which can accurately gather at the tumor site, thus causing the targeted release of DOX. Cytotoxicity assay by CCK-8 assay revealed that the cell survival rate was more than 85 % at a wide range of concentrations, indicating minimal toxicity. To verify the release behavior, three conditions such as unstimulated release at 37 °C, addition of GSH, and ultrasound were chosen for the nanogel frontal release behavior. The experimental results showed that the release of DOX was less than 15 % in the first 4 h. When GSH was added, the cumulative release of

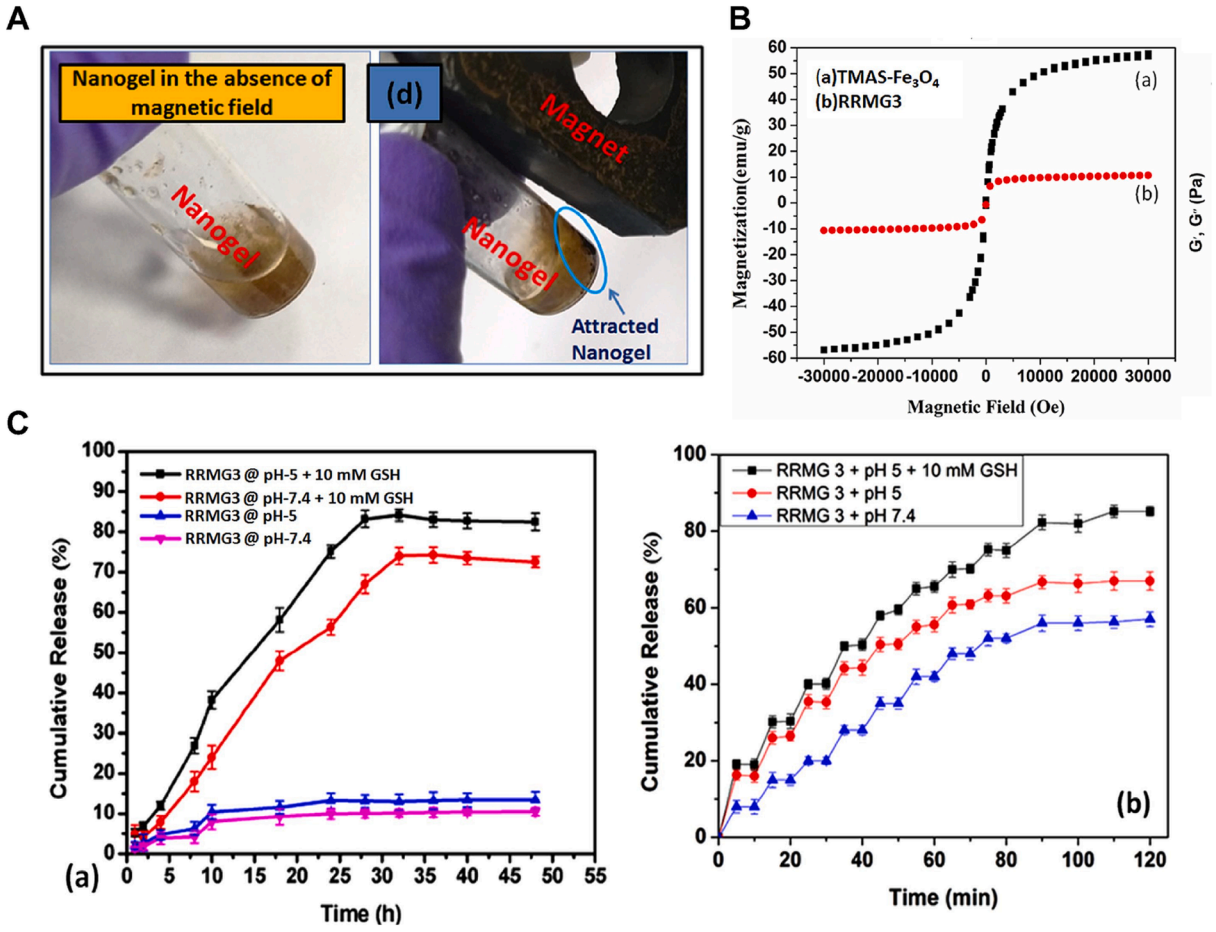

Fig. 8. A. Magnetic field response of the magnetic nanogel; B. Magnetization versus field (M−H plot) of TMAS coated Fe_3O_4 and RRMG3; C. In vitro DOX release from nanogel at two different buffers pH (5.0 and 7.4) in the presence and absence of 10 mM GSH concentration and DOX release from RRMG3 in high frequency alternating magnetic field (HFAMF) at two different pH (pH 5.0 and pH 7.4) in presence of (pH 5.0 and 10 mM GSH). DOX: Doxorubicin, TMAS: (3-aminopropyl) trimethoxysilane, RRMG: reduction responsive magnetic nanogel. Reprinted with permission from Mandal et al. (2020) (Mandal et al., 2020). Copyright (2020) Elsevier.

DOX rapidly increased from 15 % to about 60 % in the second 4 h. The release of DOX was also increased by the addition of GSH. Finally, ultrasound acted to promote cavitation, and DOX was completely released. This result suggests that ultrasound-responsive behavior promotes the release of DOX to improve anti-tumor activity and achieve better efficacy.

5. Multiple stimuli-responsive nanogels

As mentioned above, stimulus-responsive nanogels change their structure, dissolve, or even rupture in the TME or respond to some exogenous stimuli, leading to drug release (Hajebi et al., 2019; Lyu et al., 2017) (Table 3). Many endogenous and exogenous stimuli enhance the drug delivery capacity and targeting efficiency of nanogels. To further improve their responsiveness to stimuli and achieve more precise and controlled drug release, thereby enhancing therapeutic efficacy, researchers have proposed the development of multifunctional stimulus-responsive nanogels through multiple modifications (Cao et al., 2016). The preparation of multiple stimulus-responsive nanogels is also achieved by cross-linking agents, grafting of amphiphilic polymers, and so on. However, the difference is that instead of giving a single stimulus, the nanogel is modified to make it multiple stimulus-responsive, which increases its drug-loading capacity and improves the therapeutic efficacy. Next, we will list typical examples of dual stimulus-responsive nanogels (pH-light, ROS-light, temperature-light, pH-GSH) and multiple stimulus-responsive nanogels.

5.1. Dual stimulus-responsive nanogels

5.1.1. pH-light dual stimulation responsive nanogels

We have previously mentioned several ways in which nanogels deliver DOX. Crucially, AuNPs are photoresponsive nanomaterials that can generate heat in response to laser radiation for the photothermal ablation of tumor cells. Based on these advantages, AuNPs have been widely used in cancer diagnosis and treatment (Arifuzzaman et al., 2024). Therefore, Ziaei (Alioghli Ziaei et al., 2023) et al. proposed to coat biocompatible polymers on the surface of AuNPs to form pH/light dual-responsive nanogels. They used an additive-free preparation process to prepare DOX-loaded CS/AuNP nanogels with β-glycerophosphate salt as an ionic cross-linking agent *via* the Schiff base reaction principle and sodium pentabasic TPP. The pH-responsive drug release behavior was investigated, and the experimental results demonstrated that 99 % and 73 % of DOX were released after 48 h at pH 5.8 and pH 7.4, indicating that the nanogels exhibited pH-responsive behavior in acidic environments. This nanogel, loaded with the anticancer drug DOX, can release the drug in response to both light and pH, thereby improving the drug's properties and enhancing its therapeutic efficacy.

5.1.2. ROS-light stimulation responsive nanogels

The main applications of such nanogels are tumor imaging and apoptosis of cancer cells. Shen (Shen et al., 2022) et al. designed carbon nanogels endowed with dual functionalities for ROS imaging and PDT through self-assembled chemiluminescent carbonized polymer dots. The main mechanism is through the assembly of polymer couplers and near-infrared chemical light (CL) donors with photodynamic capabilities. The result is that ROS generated in the TME triggers chemically triggered electron exchange luminescence in the chemical reaction between peroxalate and H_2O_2, giving the nanogels ROS bioimaging capabilities. Part of the excited state electrons is transferred to the surrounding H_2O_2 or dissolved oxygen, leading to the generation of type I and type II photochemical ROS from hydroxyl radicals or singlet oxygen, which leads to apoptosis of tumor cells. The ability of the nanogels to generate ROS in aqueous solution was evaluated under light irradiation. The experimental results showed that ROS could be effectively generated in aqueous solution under light irradiation, and these ROS could be used as effective toxins of nanogels for PDT. It was learned by examining the CL properties of nanogels in aqueous solution that the CL signals of 50 μL of nanogels in the presence of 1 mL H_2O_2 were higher than those of the corresponding blanks, which indicated that the nanogels had a higher responsiveness sensitivity to ROS. The dynamic CL of the nanogel in this model was determined by establishing an inflammatory mouse model by intraperitoneal injection of Zymosan A. The results showed significantly strong and sustained luminescence in mice after 0.5 ml injection. Antitumor activity of the nanogel was assessed in hormone-treated mice, and the experimental data indicated that the tumor volume in the

Table 3
Types of nanogels, their response to stimuli, and anti-cancer drugs delivered.

No.	Constituents of nanogels	Responsive	Release Mechanism	Used Cargo	Reference
1	Dextran-grafted poly n-isopropyl acrylamide	pH	Breakage of Schiff base bonds	DOX	(Carneiro et al., 2021)
2	PBA-PAL and mPEG-DA	pH	Breakage of the borate bond	PTX	(Chen et al., 2023)
3	Pentafluorophenyl (PFP)-based activated esters	pH	Breakage of the hydrazone bond	DOX	(Van Driessche et al., 2018)
4	chitosan (CS)/polymethacrylic acid (PMAA)	pH	Swelling due to protonation of $–NH_2$ and deprotonation of –COOH	_	(Bhattacharjee et al., 2023)
5	Polyethylene glycol methyl methacrylate (OEGMA) and di (ethylene glycol) methyl methacrylate (MEO_2MA)	pH-Redox	Disulfide bond (− s − s −) breaking in a reducing environment	DOX	(Yang et al., 2022)
6	Ethylene oxide-propylene oxide	Enzyme	Degradation of nanogels induced by matrix metalloproteinases	5-[125I] Iodo-4″-thio-2″-deoxyuridine ([^{125}I] ITdU)	(Singh et al., 2021)
7	CMCS	Redox	Breakage of diselenide bonds (Se–Se)	DOX	(Wang et al., 2022)
8	Amphiphilic phenolic polymers	ROS	ROS-induced degradation of nanogels	Imiquimod (Imi) and Metformin (Met)	(Tian et al., 2023)
9	Polyethylene glycolic hyaluronic acid	Hypoxia	Degradation of nanogels	Interleukin-12 (IL-12)	(Zhang et al., 2020)
10	PNIPAM	photothermal	Endocytosis of nanogels	5-Fluorouracil (5-Fu)	(Yao et al., 2021)
11	Polymethacrylic acid (PMAA)	Ultrasound	Disintegration of nanogels	–	(Shen et al., 2018)
12	Pentaerythritol-poly(ε-caprolactone)-b-polyacrylic acid, 2-hydroxyethyl disulfide and amino silane	Magnetic	Disintegration of nanogels	DOX	(Mandal et al., 2020)
13	Chitosan/gold nanoparticles (CS/AuNPs)	pH, Light	Self-degradation of nanogels in TME	DOX	(Alioghli Ziaei et al., 2023)
14	Polyvinyl lactam	pH, Temperature	Breakage of Schiff base bonds and high-temperature	DOX	(Chang et al., 2021)
15	Glucose $C_6H_{12}O_6$	pH, GSH	Breakage of Schiff base and disulfide bonds	DOX	(Yu et al., 2020)

nanogel-treated group was smaller than that in the saline control group, suggesting the therapeutic efficacy of the nanogel.

We mentioned in our previous elaboration that the photosensitizer ICG has good light responsiveness. The nanogel loaded with photosensitizer and therapeutic drug achieves precise drug release through multiple responses, which not only improves drug efficacy but also reduces side effects. Temozolomide (TMZ), a first-line drug for the treatment of glioblastoma multiforme, is difficult to accumulate due to its inefficient extravasation caused by the blood–brain barrier. Zhang (Zhang et al., 2022) et al. proposed a ROS/light dual stimulation-responsive nanogel loaded with the photosensitizer ICG and the chemotherapeutic drug TMZ. The nanogels were camouflaged with apolipoprotein E peptide-modified erythrocyte membranes to further prolong blood circulation and active tumor targeting. GBM stem cell-derived mouse models were used to observe the dual-response release behavior of the nanogels. The experimental results demonstrated that when irradiated with 808 nm near-infrared light, the release of TMZ and ICG was localized at the tumor site, with ICG generating ROS, thereby inhibiting GBM tumor cell proliferation. Furthermore, the irradiated nanogel exhibited a softer and looser structure, indicating a structural transformation.

5.1.3. Temperature and pH-responsive nanogels

In the previous elaboration of individual stimulus-responsive nanogels, we mentioned that one of the ways to achieve pH response is through the plasmonic sponge effect. Also in the previous section, we mentioned thermosensitive polymers such as PNIPAM. Abedi (Abedi et al., 2021) et al. proposed a pH/temperature-responsive nanogel for the treatment of colon cancer. We already know that PNIPAM is recognized as a thermosensitive polymer, but its LCST is narrow and lower than the human body temperature, so it is necessary to adjust the LCST around it so that it can be polymerized with different polymerized monomers. N, N'-dimethylamino ethyl methacrylate (DMAEMA) is a water-soluble cationic monomer containing tertiary amine groups, which can be polymerized with PNIPAM *via* free radical polymerization, thus enabling drug release in the acidic environment of tumors. DOX and CUR, two widely used anticancer drugs, are often limited by high side effects and low bioavailability. To overcome these challenges, efficient delivery systems are required to ensure their effective delivery, minimize side effects, enhance therapeutic efficacy, and improve patient compliance. To achieve the combined use of DOX and CUR, they prepared pH/thermosensitive biocompatible hydrogel poly (NIPAAm-co-DMAEMA) and transformed it into a smart nanogel for the co-delivery of DOX and CUR drugs. Drug release profiles were made at two pH values (7.4 and 5.8) and two temperatures (37 °C and 40 °C) under precipitation conditions to discuss the release ability. Firstly, a single-drug release test was conducted, where the release of DOX at pH 5.8 and 40 °C was 42 %, which was higher than at pH 7.4. However, in the two-drug release test, the DOX release rate reached 98 % at pH 5.8 and 40 °C. In contrast, when the temperature was lowered to 37 °C under the same pH conditions, the DOX release rate decreased to 70–80 %. This suggested that dual-drug release is more effective. At pH 7.4 and 37 °C, the release rate of CUR was only 28 %, but it increased to 49 % at 40 °C under acidic conditions. At 40 °C and pH 5.8, drug release was 80 %, compared to 60 % at physiological pH (pH 7.4) and 37 °C. These results from both sets of experiments demonstrated that temperature and pH are the two major influencing factors and provide strong evidence that the dual-drug formulation is more potent, with superior anti-tumor efficacy compared to the single drug.

Polyamidoamine dendritic macromolecules are characterized by well-defined structural architecture, strong branching, and ease of surface modification, which improves the bioavailability of hydrophobic molecules, and their ultra-small size and strong cationic properties make them effective nanocarriers. These features can improve drug permeability within the tumor and promote tissue penetration and cellular internalization. Based on the above theory, Li (Li et al., 2021) et al. prepared a temperature/pH dual-responsive nanogel by precipitation polymerization. As shown in Fig. 9, the surface of nanogel was functionalized with cationic dendritic macromolecules, a modification that has been shown to mitigate undesired liver retention while concurrently augmenting the accumulation of nanogels within tumor sites. The thermal response properties of nanogels containing different dendritic molecular weights were verified by dynamic light scattering measurements. The experimental results showed that at temperatures higher than the volume phase transition temperature, the nanogels started to crumple and collapse, achieving DOX release. The drug release behavior of DOX-loaded nanogels in PBS (pH 7.4, pH 6.8) and acetate buffer (pH 5.5) was observed using hormonal mice as an animal model and DOX as a drug model, and it was found that DOX was released slowly at pH 7.4, and rapidly at both pH 6.8 and pH 5.5, and the release of DOX was higher at pH 5.5. The anticancer activity of the nanogels against human ovarian adenocarcinoma cell line SK-OV-3 (SKoV3 cells) was assessed by CCK-8 proliferation assay and it was learned that a concentration-dependent cell proliferation inhibition effect was exhibited. Moreover, under the same concentration of DOX, the activity of cells treated with nanogel modified by dendrimer was the lowest, indicating its good anticancer activity.

We mentioned the thermal polymer PNIPAM in the above discussion, but PNIPAM is non-biodegradable. Therefore, Ghaeini-Hesaroeiye (Ghaeini-Hesaroeiye et al., 2020) et al. came up with the idea of replacing PNIPAM with the FDA-approved biopolymer poly (L−propionyl ester), which is biodegradable and has good biocompatibility. They prepared copolymers of poly (L−propionyl ester)-grafted chondroitin sulfate with different L−propionyl ester contents by ring-opening polymerization and prepared pH/temperature dual-responsive nanogels. To examine the pH sensitivity and temperature sensitivity of the nanogels, the *in vitro* cumulative drug release of the nanogel samples was evaluated under four different conditions. A pH value of 7.4 led to 25 % release of the peptide substance after seven days at 37 °C, while the release was 63 % at 42 °C. When the pH was 5.4 and the temperatures were 37 °C and 42 °C, the peptide substance was released 95 % and 98 % respectively. The experimental results demonstrated that the nanogel was temperature-sensitive at physiological pH and pH-sensitive at both temperatures. This next example will similarly use a thermosensitive and surface modification of the polymer to make the nanogel dually responsive to pH/temperature.

There is another thermal polymer, poly (vinyl caprolactam) (PVCL), which is also widely used. Farjadian (Farjadian et al., 2019) et al. prepared temperature/pH dual responsive nanogels by an ideal reversible addition-fragmentation polymerization method using amphiphilic non-toxic polymer PEG as a cross-linking agent, and by attaching anticancer drug DOX to a backbone made of hydrophilic temperature-sensitive polymer PVCL through a pH-responsive Schiff base bond. The release of DOX was evaluated in a simulated medium under varying pH and temperature conditions. At pH 7.4 and 37 °C, 37 % of DOX was released, whereas at 40 °C and pH 5.0, up to 80 % was released. This method enabled targeted and controlled release of DOX, thereby enhancing drug efficacy and minimizing side effects.

5.1.4. pH-GSH responsive nanogels

The pH-responsive mechanism of the dual pH and GSH-responsive nanogels is mainly achieved by acid-unstable bonds such as Schiff base bonds or stilbene bonds, whereas the GSH responsiveness is mainly achieved by the incorporation of cross-linking agents containing disulfide bonds.

We mentioned in the single stimulus response section that Schiff base bonds are hydrolyzed by acid and that Schiff base bond rupture can be achieved by the acidic environment of the TME. Zhang (Zhang et al., 2020) et al. prepared pH/GSH dual-responsive nanogels using a single-emulsion technique by first obtaining pH-sensitive Schiff base bonds (imine bonds) by oxidizing dextrose anhydride and then cross-linking DOX with cystamine. The triple-negative breast cancer cell line MDA-

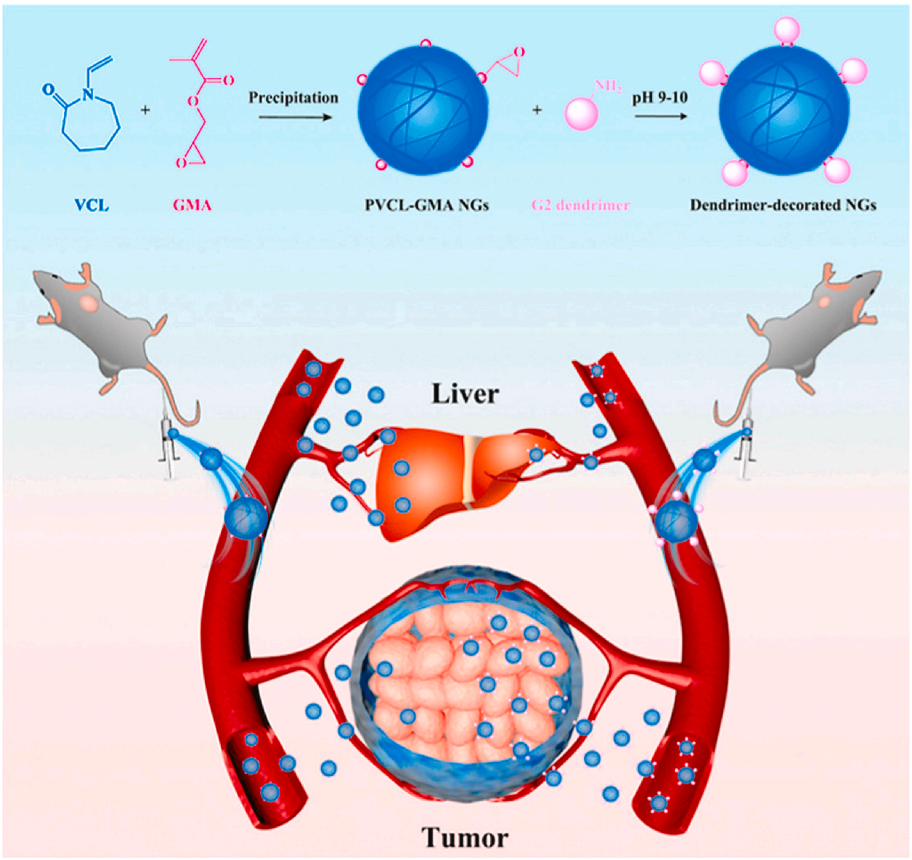

Fig. 9. Schematic illustration of the preparation of dendrimer-decorated PVCL-GMA nanogels for efficient drug delivery *in vivo*. PVCL: poly (vinyl caprolactam). Reprinted with permission from Li et al. (2021) (Li et al., 2021). Copyright (2021), Elsevier.

mb −231 was used as a tumor model to study various aspects of its properties. The *in vitro* release of the dual-sensitive nanogels was investigated by simulating the low pH and high GSH concentration of TME. The experimental results showed that the nanogels exhibited accelerated release at pH 6.5 and 5.0 when the pH was divided into 5.0, 6.5, and 7.4. The addition of GSH resulted in a release rate of 90 % within the first 24 h. The uptake of the nanogels in cancer cells and control 3 T3 cells was assessed using FACS at the same DOX concentration. The IC_{50} values were lower in the cancer cells, indicating good anti-tumor activity.

Yu (Yu et al., 2020) et al. also prepared pH/temperature dual-responsive nanogels for DOX transport using Schiff base bonds and disulfide-containing cross-linking agents but unlike the example above they utilized the formation of disulfide-containing Schiff base disulfide bonds between a poly aldehyde dextran and a hemiamine, which were synthesized directly in a one-step process. The pH responsiveness and release behavior were assessed using scanning electron microscopy. The results indicated no significant change in the nanogels at pH 7.4, whereas significant degradation occurred at pH 6.5 and 5.0. After 12 h of treatment at pH 5.0, most of the nanogels softened and collapsed. The GSH-treated nanogels were also degradable and most of the nanogel particles collapsed due to −s-s- bond breakage after 12 h of GSH at 10 mM. After incubation in a buffer solution at pH 5.0 with 10 mM GSH, the nanogels were almost completely dissolved. The drug loading and *in vitro* release profiles of the nanogels were investigated at different pH and GSH concentrations using DOX as a model drug. pH 7.4 and low GSH concentration (10 μM) showed a slow release of DOX, with only about 9 % of DOX being released after 158 h. The release of DOX was 23.86 % at pH 6.5 and 40 % at pH 5.0. The release of DOX was 23.86 % at pH 6.5 and 10 mM. The release of DOX after 158 h of incubation at GSH concentrations of 5 mM and 10 mM was 56 % and 75 %, respectively. The results above not only demonstrate the dual-responsive nature of the nanogels but also highlight the rapid release of DOX at pH 5.0 and elevated GSH levels.

The ozonium bond, like Schiff bases, is hydrolyzed by acid, i.e. it can be hydrolytically ruptured at lower pH and therefore possesses pH responsiveness. Alkanawati (Alkanawati et al., 2021) et al. used a bio-orthogonal reversible reaction to create disulfide and sulfur bonds in the cross-linking agent to prepare pH/temperature dual-responsive nanogels loaded with albumin. By observing the release profiles at different pH, it was learned that less than 15 % of the proteins were released at pH 7.4, but about 60 % and 75 % of the encapsulated proteins were released after 1 day of incubation in buffers at pH 6.2 and 5.2. The nanogels were evaluated for their cellular interactions and demonstrated no cytotoxicity after 24 h of incubation.

All three examples above achieved pH-responsiveness of nanogels by hydrolysis of acid-unstable bonds, and there is another way to obtain pH-responsive nanogels by modification of pH-sensitive polymers. Yang (Yang et al., 2022) et al. used glycidyl methacrylate to modify CMCS. The double bonds on the side groups of CMCS were polymerized and crosslinked with N-N'-bis(acryloyl) cysteamine-containing disulfide bonds and modified with folic acid to obtain pH/GSH dual-responsive nanogels for targeted delivery of DOX. Observation of the release curves at different pH and different concentrations of GSH showed that the cumulative release of DOX was about 13.8 % after 48 h at pH 7.4, while it increased to about 23.2 % at pH 5.2. With increasing GSH concentration, the 10 h DOX release increased from 11.3 % to 48.7 % at pH 7.4. At pH 5.2, 10 h DOX release increased from 17.6 % to 60.3 % after 48 h, DOX release was 55.3 % and 65.1 % at the two pH conditions, respectively. The release trend showed that the acidic and GSH sensitive environment is very favorable for the release of DOX. The increased release of DOX indicated increased potency and antitumor ability.

5.2. Multiple stimulus-responsive nanogels

Dual stimuli-responsive nanogels have been improved based on single stimuli-responsive nanogels. If dual stimulation does not satisfy the delivery needs, then a third modification can be made in the same manner to make the nanogel multi-stimulus responsive. Multi-stimuli-responsive nanogels further improve their structure and function without increasing their toxicity and making them more multifunctional, thus improving the transport efficiency of anti-tumor drugs in the body, increasing their efficacy while reducing their side effects and improving patient compliance.

Li (Li et al., 2021)et al. synthesized PVCL-based nanoparticles with core/shell structure using a one-step synthesis method with adjustable amino content. The formed cationic nanoparticles exhibited thermal/pH/redox multi-responsive behavior and were used for modification or/and loading of various functional agents (fluorescent dyes, targeting molecules, metal ions, nanoparticles, and pharmaceuticals) in a modular fashion to build versatile nanoplatforms. The disintegration was observed experimentally at different pH and different temperatures. The experimental results show that the diameter of the nanogel decreases with increasing temperature and its electrophoretic mobility increases from 0.051 to 1.72 at pH 10.0–3.0. The weight of the nanogel decreases rapidly with a mass loss of 48 % in the first 4 h in the GSH environment. The mass loss of the nanogel is about 93 % after 20 h. The nanogel is also found to be in good condition in the GSH environment, which is a good choice for the treatment of nanogels. These three results indicate its pH/temperature/GSH multiple stimulus responsiveness. Observation of its release profile showed that DOX was released rapidly at pH 5.5 and pH 6.5, and the cumulative release reached 44.1 % and 32.1 % after 24 h, respectively, which was higher than that at pH 7.4 (8.7 %).

Rezanejade Bardajee (Bardajee et al., 2020) et al. used two approaches to improve κ-carrageenan-based as a slow-release drug delivery system for levodopa, combining both approaches to prepare thermally, pH, and magnetic field responsive nanogel drug delivery systems. They used metal oxide nanoparticles (e.g. Fe_3O_4 nanoparticle) as cross-linkers in the κ-carrageenan hydrogel matrix for its magnetic field responsiveness. It was also passed through PNIPAM and poly (acrylic acid), thus inducing pH-responsive and thermo-responsive properties as shown in Fig. 10. Firstly, they measured the magnetic responsiveness of the nanogels and learned that the degree of swelling was slightly reduced in the presence of a magnet. Secondly, we verified its temperature responsiveness and learned that at elevated temperatures, PNIPAM breaks its hydrogen bond with water and undergoes a reversible bulk phase transition temperature, leading to the rupture of

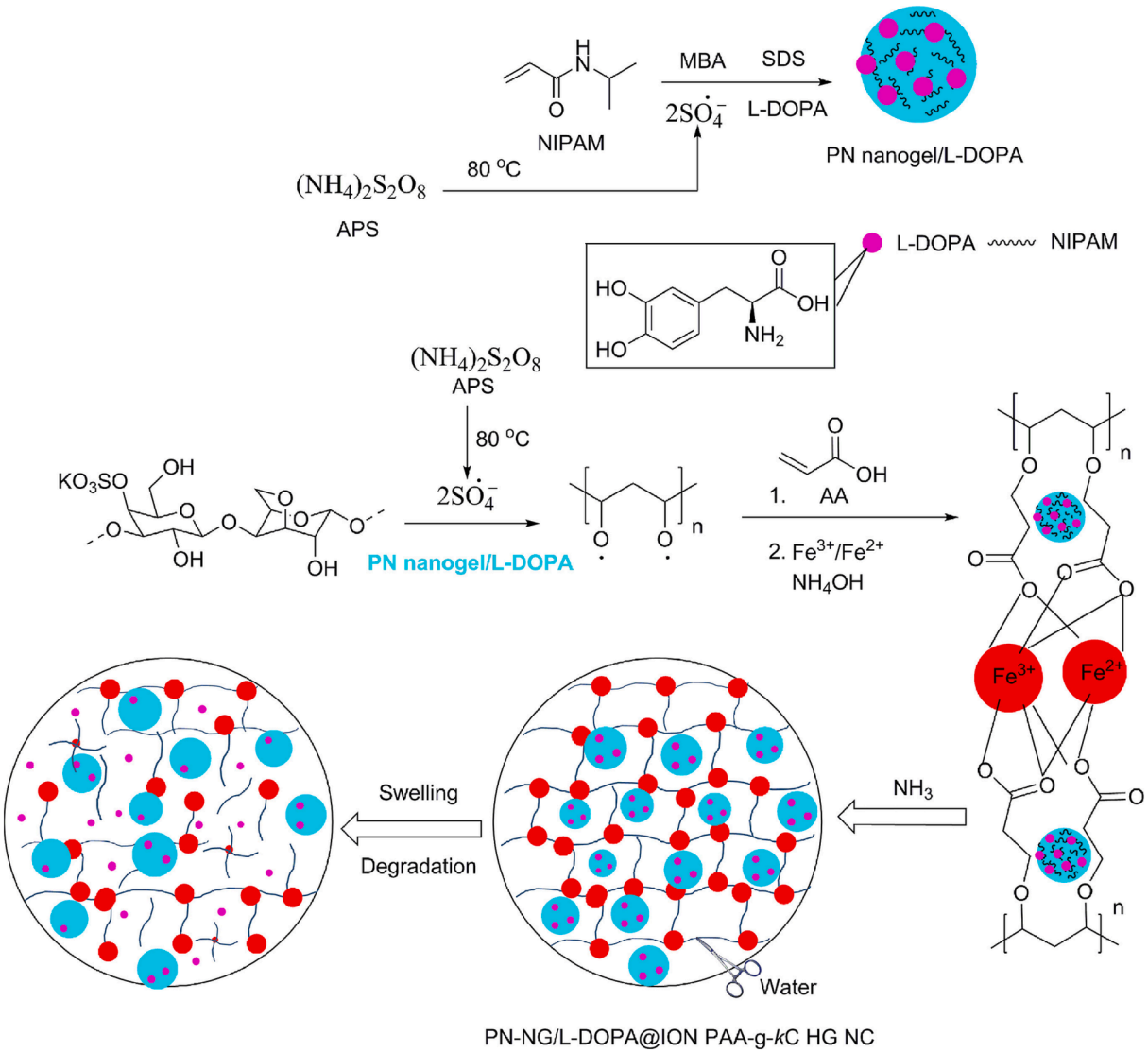

Fig. 10. Proposed mechanism for preparation of PN-NG/L-DOPA@ION PAA-g-κC HG NC and drug release profile. L-DOPA: levodopa, PAA: poly (acrylic acid), κC: κ-carrageenan, NC: nanocomposite. Reprinted with permission from Rezanejade Bardajee et al. (2020) (Bardajee et al., 2020).Copyright (2020), Elsevier.

the nanogel and consequently drug release. Finally, the solubility of the nanogel at different pH values was studied. The experimental results showed that the swelling of the nanogel was very low (about 120 g/g) at pH 2.0, increased to 730 g/g at pH 2.0–9.0, but decreased again at pH 9.0. It indicates that the nanogel has good swelling properties at pH 2.0–9.0. Using levodopa as a drug model molecule and observing its release profile it was learned that the release behavior of the nanogel at pH = 7.4 at 25 °C and 37 °C showed a faster release rate at 37 °C than at 25 °C, with a release rate of 97 % at 37 °C and 84 % at 25 °C after 11 days.

To improve the transport efficiency of DOX, Mandal (Mandal et al., 2020) et al. proposed a triple-responsive nanogel. They prepared a pH-magnetic field- and redox-responsive nanogel by esterifying the carboxyl groups of an amphiphilic copolymer with the hydroxyl groups of a redox-responsive cross-linker and then modifying its surface with a magnetic aminosilane. The degradation properties were examined by HRTEM analysis. The nanogel before GSH treatment showed a well-defined spherical morphology. The structure of the nanogel was gradually degraded after 10 min, 1 h, and 24 h of treatment, and finally lost its spherical-like morphology. Observation of its *in vitro* cytocompatibility against C6 glioma and high-temperature keratinocytes cell lines (HaCaT) revealed more than 80 % cell viability at a sample concentration of 20 μg/mL. Cytotoxicity of the degraded nanogels on C6 glioma and human adult low-calcium HaCaT cells was evaluated using the MTT assay. The results indicated that cell viability exceeded 80 % for both cell types. The release behavior of DOX, as a model anticancer drug, was further investigated in simulated physiological and cancer cell environments. The release of DOX from DOX-loaded nanogels was 12 % at pH 7.4 but was enhanced to 74 % in the presence of 10 mM GSH. However, the release was highest at 18 % at pH 5.0 but enhanced to 91 % in the presence of 10 mM GSH.

6. Conclusion and prospects

Based on the unique characteristics of the TME, such as low oxygen, acidic pH, permeability, and strong retention effect, researchers have introduced intelligent nanogels that respond to TME stimulation. The main functions of intelligent nanogels include responding to multiple disease signals, manipulating diagnostic and therapeutic effects, releasing drugs precisely, allowing for multi-drug combinations (chemotherapeutic agents, antigens, nanoprobes, photosensitizers, etc.), breaking through the TME barrier, and regulating and remodeling the TME. The application of intelligent nanogels in tumor therapy is mainly to achieve targeted drug delivery as a carrier. We have classified intelligent nanogels into two main categories, endogenous (pH, biomolecules, ROS, hypoxia) and exogenous (ultrasound, light, magnetism) stimuli, based on the response mechanism. Intelligent nanogels show outstanding advantages such as high drug loading capacity, long blood circulation time, recognition by target cells, and stimulation of sensitive degradation.

However, intelligent nanogels have yet to reach clinical application, primarily due to several significant technical barriers. First, evaluating nanogels as tumor-targeting carriers is highly complex. Blood concentration measurements alone are insufficient to fully characterize their behavior, and there is a lack of comprehensive methods to assess their distribution, transport, and interactions within tumors and with cells. Second, achieving controlled drug release remains a challenge. When stimulus-responsive nanogels encounter triggers, such as an acidic environment, they may release drugs unpredictably, complicating control over the release site and dosage. Third, these nanogels often exhibit low drug-loading capacity, which limits their therapeutic efficacy. Lastly, the high cost of production and the current challenges in large-scale manufacturing further hinder their widespread clinical use.

Based on these four drawbacks, their clinical applications need to be rationally designed. Firstly, nanogels should have a safety profile. Pharmacokinetic and pharmacodynamic characteristics need to be clearly described, drug metabolism and drug interactions need to be explored, and drug activity needs to be assessed. Complete clinical data should be available to ensure their safety before they can be used in the clinic. Secondly, it is important to reduce the cost while ensuring its safety. High cost can affect the popularity of nanogels, thus limiting their clinical application. Finally, finding the right route of administration is key to the clinical use of nanogels. Currently, more research has been done on injectable drug delivery, but this method is also not mature enough, thus limiting its clinical application.

In the future development process, we hope to fully understand all aspects of the nanogel's performance and safety, optimize the carrier structure, and further explore the intelligent nanogel so that it can enter the clinical application stage as soon as possible.

CRediT authorship contribution statement

MiriGuli Musa: Writing – original draft, Project administration, Formal analysis, Conceptualization. **Xinxin Sun:** Writing – review & editing, Project administration, Formal analysis, Conceptualization. **Jianbin Shi:** Writing – review & editing. **Jing Li:** Writing – review & editing. **Shenwu Zhang:** Writing – review & editing, Resources, Formal analysis, Conceptualization. **Xianbao Shi:** Writing – review & editing, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

The authors do not have permission to share data.

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