Review Article

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Carbon and 2D nanomaterial smart hydrogels for therapeutic applications

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Abstract: Smart hydrogels, also known as environmentally responsive hydrogels, are a kind of intelligent polymer-based material network undergoing deformation and phase changes under external environmental stimuli. These special physicochemical properties make hydrogels great molecular systems for applications in controlled drug release. Particularly, hydrogels loaded with nanomaterials show strong potential in terms of mechanical properties and environmental responsiveness. In this context, the use of carbon and two-dimensional (2D) nanomaterials has attracted widespread attention, as they can trigger drug release. This review provides an overview of the current progress in the design of biocompatible and environmentally responsive hydrogels containing carbon and 2D nanomaterials, focusing on their preparation, properties, and advantages for drug release to treat different diseases such as cancer, diabetes, and inflammation.

Keywords: carbon nanotubes, graphene, carbon nanodots, graphene quantum dots, cancer

1 Introduction

Hydrogels are three-dimensional (3D) network structures that are chemically or physically crosslinked. Their high water content and 3D structure make them valuable in several biomedical applications, including drug and protein delivery [1–3], tissue engineering [4], and wound healing [5]. Hydrogels are particularly useful in drug delivery because of their porous structure, large storage capacity, and controllable physicochemical properties, such as water content, swelling behavior, and mechanical strength, which allow for controlled drug release, thus reducing the need for high dosage and repeated administration of traditional therapeutic drugs [6,7]. For example, they can limit the systemic toxic side effects of anticancer drugs by controlling their concentrations in the blood. Hydrogels have been used for diagnosis and therapy of various diseases, including cancer [8–16], severe infections [17–19], and diabetes [20–22]. Currently, over 30 injectable hydrogel products have received approval from the U.S. Food and Drug Administration and/or the European Medicines Agency for market use, primarily in the fields of cancer treatment and cosmetic enhancements [23].

Hydrogels can be divided into synthetic and natural hydrogels. Synthetic hydrogels are mostly based on synthetic polymeric materials, such as polyvinyl alcohol (PVA), polyacrylic acid, and polymethyl methacrylate, which have the disadvantage of complex synthetic processes, high energy consumption, and cost for their synthesis. In addition, the lack of biodegradability and biocompatibility is also a significant obstacle to the further development of traditional hydrogels. However, the rapid development of green materials in the past decade has allowed the synthesis of new types of hydrogels [24,25]. Natural polymers, such as alginate (Alg), chitosan (CS), agarose, and gelatin, have emerged as a promising solution to address the limitations of traditional hydrogels for biological applications. Being biocompatible, biodegradable, and amenable to various crosslinking methods for modification and stabilization, natural polymer hydrogels have been extensively developed for biomedical applications [26,27]. Hydrogels can also be categorized into nonresponsive hydrogels and environmentally responsive hydrogels (smart hydrogels). Although nonresponsive hydrogels can have the capacity to continuously release drugs, they lack the ability to control the drug concentration according to the needs of the patient [28,29]. Consequently, they are suitable only for the slow-release treatment of basic diseases, such as gastrointestinal diseases, and not for the precise

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treatment of serious diseases, including cancer and diabetes, requiring hydrogels to release medication or insulin in response to specific triggers, such as external stimuli or changes in glucose levels. Such hydrogels can help prevent hypoglycemia by releasing insulin only when the glucose levels are elevated. Following Wichterle's landmark publication in 1960, hydrogels have evolved from simple and inert materials to complex, sensitive, and responsive smart systems over time [30]. Smart hydrogels can be sensitive to small changes of the environment, such as temperature [31,32], pH [33,34], ion concentration [35,36], molecules (*e.g.*, enzymes) [37], glucose concentration [38], light [39,40], electric field [41], and pressure [42], and exhibit fast and reversible changes in structure, shape, or swelling behavior. While hydrogels with stimulus-response and site-specific drug delivery capabilities have shown great potential in biomedicine, there are still concerns that hinder their efficiency and translation into clinical applications. One of the most critical concerns is their mechanical properties. Indeed, poor mechanical properties can cause hydrogel collapse or breakage at the injection site, leading to uncontrolled drug release, potential toxicity, and undesired side effects [43]. Moreover, the low sensitivity and response rate of some smart hydrogels can also affect their drug delivery efficiency and disease treatment effectiveness. Therefore, there is a high demand for smart hydrogels that exhibit fast response characteristics and high mechanical strength.

Carbon-based nanomaterials and silica, metal, metal oxide, and polymer nanoparticles (NPs) offer diverse opportunities for site-directed and controllable delivery of drugs, proteins, and other bioactive molecules, thanks to their unique physicochemical properties, nanoscale features, controllable shapes, and various modification possibilities [44,45]. Nanomaterials and NPs can be successfully incorporated into hydrogel networks to generate nanocomposite hydrogels with improved physical, mechanical, and thermal properties [2,46,47]. Several strategies have been developed to load nanomaterials and NPs into hydrogels, as additives [48,49], or covalently bound to the hydrogel network [50]. Hydrogels loaded with nanomaterials have found applications in biomedicine (especially drug delivery), catalysis, and electronics [51]. Compared to traditional hydrogels, they exhibit a higher mechanical strength, elasticity and adhesion, an environmental sensitivity, a high drug loading capacity, and controlled release [47]. Moreover, hydrogels loaded with nanomaterials can promote cell adsorption and proliferation [52]. To date, many types of environmentally responsive hydrogels loaded with nanomaterials have been developed and fully valued in terms of drug loading capacity, controlled delivery, biocompatibility, and structural stability after injection, revealing their bright prospects for therapeutic applications [53].

Carbon-based and two-dimensional materials (2DMs) are highly promising for biomedical applications due to their unique structure and properties [54–56]. Furthermore, their high biocompatibility and biodegradability make them prime candidates for nanocomposite hydrogel research [57–66]. Carbon nanomaterials, including carbon nanotubes (CNTs), graphene, graphene oxide (GO), carbon nanodots (CNDs), graphene quantum dots (GQDs), and fullerene (C_{60}), exhibit excellent physical and chemical properties, such as a high mechanical strength, as well as thermal and electrical conductivity, making them suitable for various biomedical applications. They have been utilized as sensors and actuators [67,68] for photothermal therapy (PTT) and photodynamic therapy (PDT) [69] and as drug delivery systems [44,70] in diagnostic imaging [67] and tissue engineering [71]. The incorporation of carbon nanomaterials into hydrogels can significantly enhance their mechanical, electrical, and thermal properties [72]. 2DMs are ultrathin materials with high anisotropy and excellent optical, mechanical, and electrical properties. The loading of 2DMs into hydrogels can impart responsivity to specific stimuli [73,74].

Due to many similarities in the physical and chemical properties of carbon materials and 2D materials, including excellent mechanical strength, photothermal properties, and unique surface characteristics, they can be considered as a class of functionally similar materials. In this review, we focus on the recent advances of environment-responsive hydrogels loaded with carbon or 2DMs for therapeutic applications. We systematically discuss the preparation, biocompatibility, and drug-release capacity of these hydrogels, as well as their applications in cancer therapy, wound healing, antibacterial activity, and other diseases. Additionally, we explore their limitations and future challenges (Figure 1).

2 Carbon-based nanomaterial hydrogels

In this section, we discuss the preparation of hydrogels containing carbon nanomaterials and their performance in controlled drug release and disease treatment, focusing on the loading of GO, CNTs, CNDs, and GQDs into the hydrogels and the effect of different internal and external stimuli. The main studies, which are discussed in this review, are summarized in Table 1, as well as some additional studies.

2.1 GO-based hydrogels

GO-based hydrogels have garnered significant interest in drug delivery applications, where they are utilized for the controlled release of drugs. These hydrogels exhibit a high drug-loading capability and sustained release profile, effectively tackling challenges related to drug stability and therapeutic efficacy. Researchers are actively dedicated to enhancing their biocompatibility and tailoring their characteristics to address specific medical conditions, opening up promising avenues for drug delivery solutions in fields such as cancer therapy and tissue engineering.

2.1.1 Drug delivery

In recent years, GO has gained considerable attention for drug loading and delivery applications due to its large surface area and its ability to load aromatic molecules *via* π–π stacking and hydrogen bonding. For instance, the incorporation of GO into a carboxymethylcellulose hydrogel led to an enhanced loading capacity of doxorubicin (DOX) owing to π–π stacking and electrostatic interactions between DOX and GO [75]. The release of DOX from the hydrogel was around 55% at pH 6.8. Beyond DOX, other drugs can be adsorbed on GO thanks to its high surface area. An Alg hydrogel loaded with GO was designed for enzyme-triggered release of the antibiotic amoxicillin (AMOX) [76]. GO was used as an efficient carrier of AMOX that was conjugated on GO *via* a peptide linker (Leu-Leu-Gly) specific to the plant enzyme bromelain. Subsequently, GO-AMOX was crosslinked with Alg-containing bromelain to form a hydrogel. When the hydrogel was soaked in a solution of bromelain, the hydrolysis of the peptide bond resulted in a cumulative release of 90% of AMOX. In another study, an active targeted and pH-responsive injectable hydrogel was developed for the treatment of glioblastoma multiforme based on a thermosensitive CS-*g*-poly(*N*-isopropylacrylamide) (PNIPAM) hydrogel [77]. Cetuximab (CET), a monoclonal antibody targeting the epidermal growth factor receptor that is overexpressed on the surface of many cancer cells, was covalently conjugated onto polyethylene glycol (PEG)-functionalized GO to enhance its intracellular uptake through a ligand-mediated targeted drug delivery. Then, irinotecan (CPT-11) was loaded onto CET-PEG-functionalized GO surface and

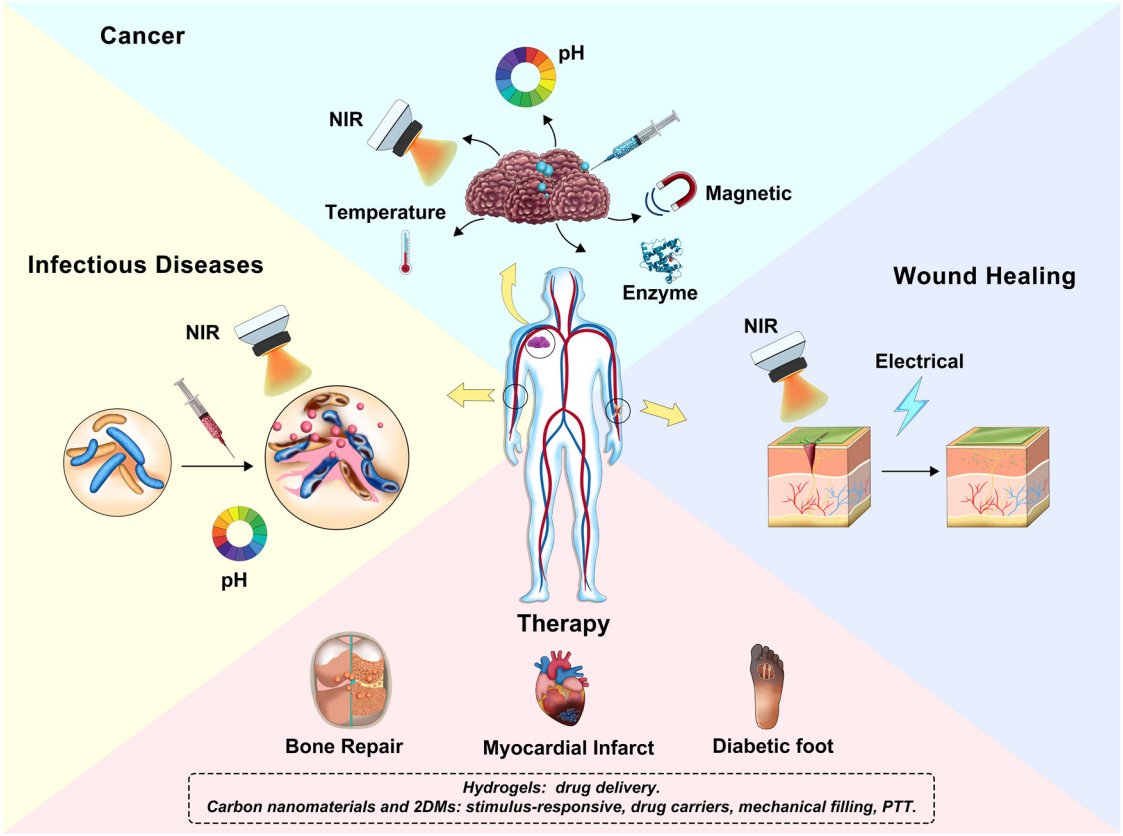

Figure 1: Therapeutic applications of hydrogels loaded with carbon or 2D nanomaterials.

Table 1: Carbon nanomaterials loaded in hydrogels for drug delivery

Carbon nanomaterials	Functions in the hydrogel	Drugs	Biological applications	Ref.
GO	Drug carrier	DOX, irinotecan, amoxicillin	Delivery of anticancer and antibiotic drugs; cancer cell treatment; antibacterial effect; tumor treatment	[75–77]
	Photothermal drug release	MTX, naringin, vancomycin, minocycline hydrochloride, tetracycline hydrochloride, ciprofloxacin, DOX	Delivery of anticancer, anti-inflammatory, and antimicrobial drugs; PTT; cancer cell treatment; antibacterial effect; wound healing; tumor treatment	[81–86]
	pH-responsive drug carrier	Tetracycline hydrochloride, DOX, diclofenac potassium, irinotecan	Delivery of anticancer, antimicrobial, and anti-inflammatory drugs; cancer cell treatment; tumor treatment	[53,75,77,84,87–89]
	Improvement of the mechanical properties	Tetracycline hydrochloride, bupivacaine hydrochloride, ibuprofen, ciprofloxacin	Delivery of antimicrobial, anti-inflammatory, anesthetic, and analgesic drugs; antibacterial effect; prolonged anesthesia duration; wound healing	[84,93–95]
CNTs	Drug carrier	DOX	Delivery of anticancer drugs, cancer cell treatment, PTT, tumor treatment	[101,102]
	Photothermal drug release	DOX, L-ascorbic acid, paclitaxel, doxycycline, ciprofloxacin hydrochloride	Delivery of anticancer, antimicrobial, anti-inflammatory and nerve repair drugs; cancer cell treatment; PTT; tumor treatment; antibacterial effect, wound healing; spinal cord injury repair	[101–109]
	Improvement of the mechanical properties	Doxycycline, ciprofloxacin hydrochloride, metformin	Delivery of antimicrobial and diabetes treatment drugs, wound healing, antibacterial effect	[108–111]
	Electroresponsive drug carrier	Curcumin, ketoprofen	Delivery of anti-inflammatory drugs	[110,113–116]
CNDs	Drug carrier	DOX, vancomycin, CpG oligodeoxynucleotides	Delivery of anticancer and antimicrobial drugs; cancer cell treatment; tumor treatment	[125–127]
	Photothermal drug release	5-Fluorouracil, DOX	Delivery of anticancer drugs, PTT/PDT, antibacterial effect, cancer cell treatment	[128,129]
	Improvement of the mechanical properties	Kanamycin sulfate; tetracycline	Delivery of antibiotic drug; antibacterial treatment; wound healing	[130,131]
GQDs	Drug carrier	DOX	Drug delivery for cancer treatment *in vitro*	[135,136]
	Photothermal drug release	DOX	Delivery of anticancer drug; tumor treatment	[138]
	pH-responsive drug carrier	Quercetin	Cancer cell treatment	[139]

Note: “Cancer cell treatment” refers to *in vitro* studies, while “tumor treatment” refers to *in vivo* animal experiments.

incorporated in the hydrogel along with stomatin-like protein 2 (SLP2) short hairpin RNA (shRNA) (Figure 2). The hydrogel prevented an abrupt release of CPT-11 in the extracellular environment and achieved a stable release in the acidic tumor microenvironment, eventually leading to tumor size reduction.

2.1.2 Photothermal drug release

Light-responsive hydrogels loaded with nanomaterials are promising due to their precise spatiotemporal control. In particular, PTT using hydrogels loaded with nanomaterials has received full attention for tumor treatment [78].

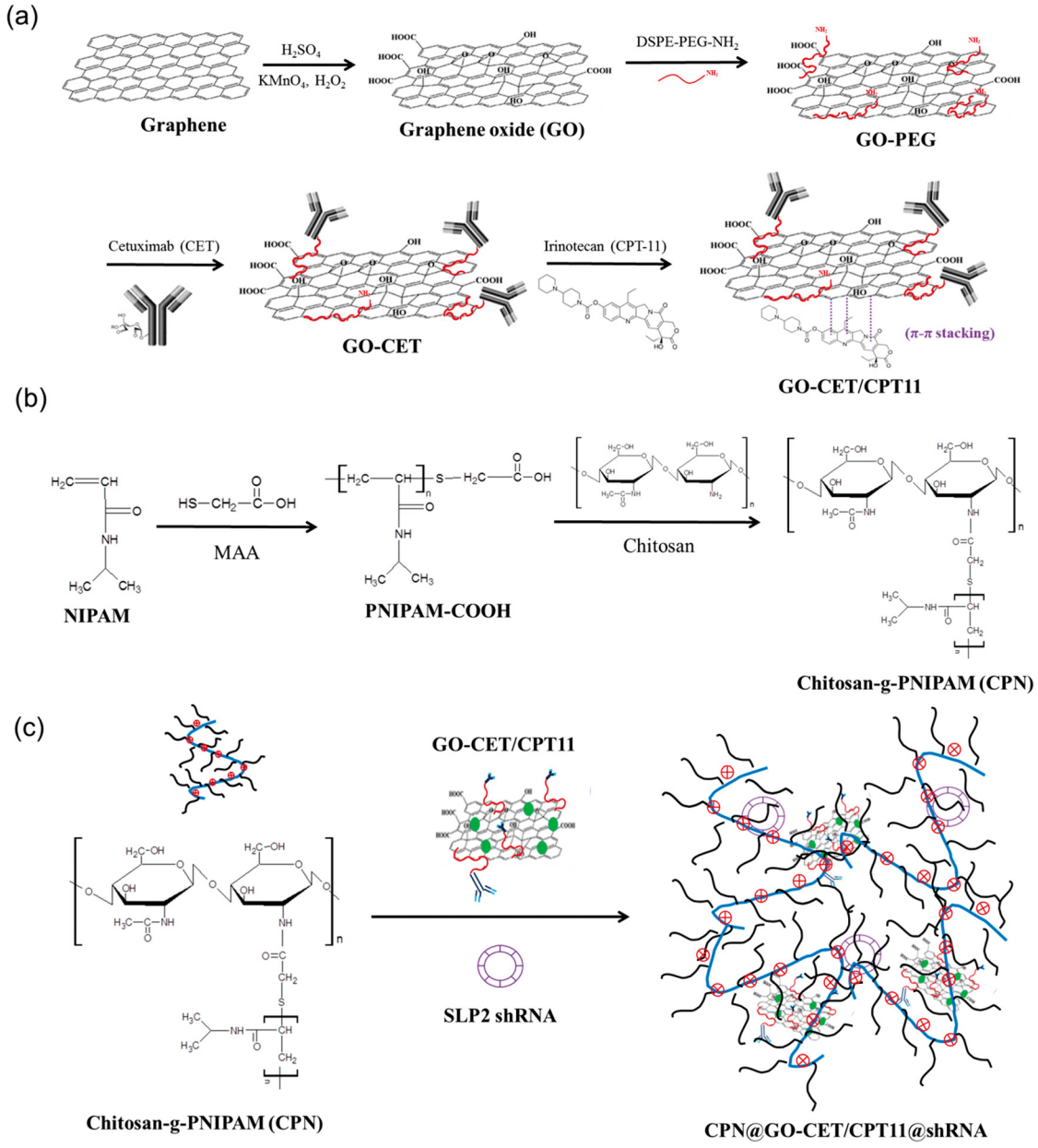

Figure 2: Synthesis of chitosan-*g*-PNIPAM-GO-CET/irinotecan/SLP2 shRNA hydrogel. The abbreviation used in the figure: *N*-isopropylacrylamide (NIPAM). (a) GO, prepared using the modified Hummers' method, was functionalized with *N*-(aminopropyl polyethyleneglycol)carbamyl-distearoyl-phosphatidyl-ethanolamine [1,2-distearoyl-sn-glycero-3-phosphoethanolamine-*N*-[amino(polyethyleneglycol)]] (DSPE-PEG-NH_2) to obtain GO-PEG. CET was subsequently conjugated to GO-PEG, yielding GO-CET. Finally, CPT-11 was loaded onto GO-CET via π–π stacking interactions, forming GO-CET/CPT-11. (b) PNIPAM-COOH was synthesized by free radical polymerization of NIPAM and mercaptoacetic acid (MAA). Subsequently, PNIPAM-COOH was grafted onto the CS backbone via amide bonds, forming CS-grafted-PNIPAM (CPN). (c) GO-CET/CPT-11 and SLP2 shRNA were embedded in the thermosensitive CPN hydrogel to form CPN@GO-CET/CPT11@shRNA. Reproduced with permission [77]. Copyright © 2020, International Journal of Molecular Sciences.

Compared with ultraviolet (UV, 200–400 nm) and visible (Vis, 400–700 nm) light, near-infrared (NIR) light (700–2,500 nm) has better tissue transparency and is the first choice for clinical treatment. Carbon-based nanomaterials have a high NIR light absorption and photothermal conversion efficiency, and they are actively used for PTT and diagnosis [69,79]. Over the past decade, GO has garnered significant attention due to its high NIR absorption and biocompatibility [80]. Hydrogels loaded with GO can release drugs when irradiated with NIR light. For instance, a study exploited π–π stacking interactions and hydrogen bonding to load naringin onto GO. Subsequently, naringin-loaded GO and MTX were co-encapsulated within a hydrogel network formed *via* a Schiff base reaction between oxidized Alg and carboxymethyl chitosan, resulting in a composite hydrogel with NIR-responsive release of naringin and MTX [81]. Under NIR (808 nm, 1 W) light irradiation, the temperature of the GO/carboxymethyl CS/oxidized Alg hydrogel increased to 50°C. Continuous NIR light irradiation accelerated the release of the drugs up to 91 and 86% for MTX and naringin, respectively. The hydrogel reduced the viability of osteosarcoma cells under NIR light irradiation, while the viability was high without irradiation. In another study, the researchers prepared an injectable, biodegradable, and self-healing hydrogel by crosslinking a thermoresponsive copolymer (PNIPAM) with dopamine-functionalized pectin hydrazide. GO was incorporated into the hydrogel to enable NIR-triggered drug release of vancomycin [82]. This hydrogel exhibited both pH-responsive and photothermal-responsive drug-release characteristics. Under acidic conditions (pH 5.4) and NIR light irradiation (1 W/cm^2, 10 min), the release rate of vancomycin exceeded 80%. The photothermal properties of the hydrogel and the effect of vancomycin effectively promoted burn wound healing by suppressing bacterial (*Escherichia coli* and *Staphylococcus aureus*) proliferation. An additional example involves the entanglement of chemically crosslinked Pluronic F127 diacrylate macromer with a solution of poly(lactide-*co*-glycolide) (PLGA)-GO to create a NIR-responsive double network shape memory hydrogel [83]. The hydrogel was immersed in ice to fix the shape (temporary curled shape), and upon NIR (8 W, 808 nm, r = 2 cm light spot) light irradiation, a more sustained release of minocycline hydrochloride was observed compared to the original shape. This phenomenon can be attributed to curling, which causes the molecular chains of the hydrogel to straighten, thereby affecting the drug-release kinetics. The drug-release rate was found to increase with temperature, likely due to an enhanced permeability of the hydrogel thanks to the heat generated by GO. This hydrogel could be a potential candidate for the development of an antibacterial scaffold. Another study reported the preparation of a novel mesoporous polydopamine (MPDA)@GO/cellulose nanofibril composite hydrogel, in which MPDA NPs were first coated with GO and then physically crosslinked into a cellulose hydrogel matrix to achieve controlled release of tetracycline hydrochloride [84]. GO improved the mechanical strength of the hydrogel, while both MPDA and GO imparted a drug-release capacity owing to their photothermal properties. As shown in Figure 3, under NIR (808 nm, 2 W/cm^2) light irradiation, the hydrogel temperature increase was dependent on the concentration of MPDA@GO and irradiation time. In particular, the hydrogel temperature could reach 56°C within 10 min of NIR irradiation when the concentration of MPDA@GO was 1 wt% (Figure 3a), and its photothermal conversion efficiency was 15% (Figure 3b). The drug-release rate from the MPDA@GO/cellulose nanofiber hydrogel was significantly enhanced after 10 min of NIR light irradiation (Figure 3c and d). Hence, the incorporation of GO as a photothermal agent in drug-loaded hydrogels allows accelerating drug release, offering great opportunities for efficient therapies, revolutionizing the landscape of drug delivery strategies.

2.1.3 pH-responsive drug release

GO can be functionalized with pH-sensitive groups to enable the selective release of drugs or other molecules (*e.g.*, vascular endothelial growth factor) in response to pH changes, which can be exploited in a variety of applications, including drug delivery and sensing. In this context, GO was loaded in a PEG/silk fibroin (SF) hydrogel to control the release of DOX *in vitro* [87]. Compared to the physiological environment, PEG/GO/SF hydrogel released more DOX in an acidic environment (pH = 5.4). This is attributed to the weakened π–π interactions and hydrogen bond rupture between DOX and GO at low pH because of a higher water solubility of the drug compared to physiological pH. Meanwhile, compared to free drugs, PEG/GO/SF hydrogel exhibited a stronger cytotoxicity against a breast cancer cell line (MCF-7) *in vitro*. Olate-Moya and Palza developed a supramolecular hydrogel for drug delivery, utilizing a polypseudorotaxane structure composed of PEG and α-cyclodextrin channel inclusion complex, in combination with GO [53]. DOX was loaded in the hydrogel thanks to electrostatic and π–π interactions with GO. Notably, the release of DOX was markedly higher under slightly acidic conditions (pH 5.5) than at physiological pH, likely due to the higher solubility of DOX at acidic pH and weaker interactions with GO. In contrast, no pH-dependent release was observed in polypseudorotaxane hydrogels not containing GO. In addition, a study leveraged the pH-sensitive drug-release properties of GO upon cellular uptake. A folic acid

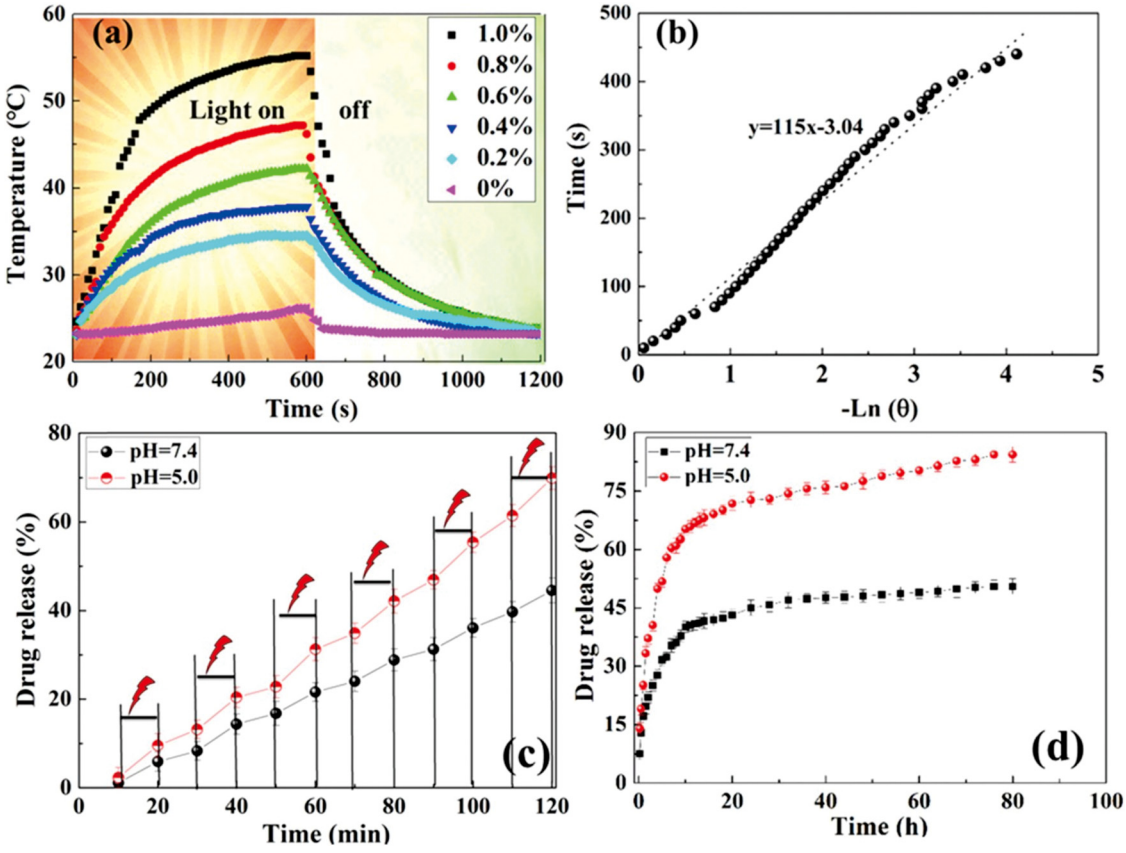

Figure 3: (a) Temperature increase of MPDA@GO/cellulose nanofiber hydrogels with different concentrations of MPDA@GO under irradiation at 808 nm and 2 W/cm^2. (b) Plot of the time data obtained from the hydrogel loaded with MPDA@GO 1.0 wt% for the cooling period *versus* −Ln(θ). (c) Drug release from the MPDA@GO(1:2)/cellulose nanofiber hydrogel at pH 5.0 or 7.4 under intermittent NIR light irradiation. (d) Drug-release profile of the MPDA@GO(1:2)/cellulose nanofiber hydrogel (MPDA@GO content of 0.6 wt%) over a long period of time at physiological pH (7.4) or pH 5.0. Reproduced with permission [84]. Copyright © 2020, ACS Applied Materials & Interfaces.

(FA)-functionalized GO (GO-FA) was prepared for targeted delivery of DOX. To enhance its delivery efficiency, GO-FA/DOX was encapsulated in an injectable, in situ-forming thermosensitive hydrogel composed of hyaluronic acid and CS-PNIPAM, enabling the precise intratumoral release of DOX [88]. The drug release from the hydrogel was pH-dependent, with a cumulative release rate of over 80% at pH 5.5 within 18 h, while it reached only 19% at physiological pH. Overall, pH-responsive GO-based hydrogels have been less developed than photothermal-responsive hydrogels, as it is more difficult to achieve precise drug release using pH as stimulus [89]. Nevertheless, they are an important component of responsive hydrogels for the comprehensive management of diseases [90]. Indeed, the pH levels in the body or target tissues can vary significantly depending on the disease state [91], making it difficult to achieve a consistent and controlled drug release. In contrast, NIR light provides a more precise control, as it allows for more predictable drug release by adjusting the GO loading in the hydrogels, NIR laser power, and duration.

2.1.4 Mechanical reinforcement

Enhancing the mechanical properties of hydrogels is a challenging task, and the incorporation of nanofillers, such as GO, has emerged as a promising approach to improve their strength through hydrophobic or electrostatic interactions [92]. A recent example is the incorporation of GO into a CS/β-glycerophosphate thermosensitive and pH-responsive injectable hydrogel loaded with bupivacaine hydrochloride (BH), a local anesthetic drug [93]. The study revealed that GO enhanced the physicochemical and mechanical properties of the hydrogel in a concentration-dependent manner, with the mechanical strength increasing from 6.32×10^{-5} MPa without GO to 20.87 MPa at 0.2% w/v GO concentration. BH was gradually released from the nanocomposite hydrogel containing 0.1% w/v GO, achieving 55 and 86% release at 6 and 24 h, respectively. *In vivo*, the BH-loaded nanocomposite hydrogel notably extended local anesthesia and exhibited a 6.5-fold increase in pain sensory reflex blockade compared to the BH

solution. These findings suggest that integrating GO markedly enhanced the physical and mechanical features of CS/β-glycerophosphate thermosensitive and pH-responsive hydrogels. The thermosensitivity arose from temperature-induced dehydration and increased physical crosslinking of polymer chains, while the pH-responsiveness was attributed to the neutralization of the amino groups of CS, facilitating *in situ* gel formation. These properties ensure prolonged local anesthesia for enhanced pain management efficacy. In another study, reduced graphene oxide (rGO) and ibuprofen were encapsulated into a methacrylated hyaluronic acid hydrogel for electrically triggered ibuprofen release [94]. The incorporation of rGO significantly improved the mechanical strength of the hydrogel. The elastic modulus increased from 1.86 to 5.77 kPa. GO has also been employed to enhance the mechanical properties of PNIPAM hydrogels loaded with ciprofloxacin, an antibiotic, enhancing their potential applications in wound dressings [95]. The incorporation of GO led to a significant 49-fold increase in the compressive strength of the hydrogel compared to pure PNIPAM hydrogel. A 99% release of ciprofloxacin was observed, resulting in strong antimicrobial activity against both *S. aureus* and *E. coli*. These results show that the favorable influence of GO on the mechanical properties of drug-carrying hydrogels is poised to propel the use of hydrogels in disease treatment, showing their potential as advanced therapeutic delivery systems.

In summary, thanks to its unique structural, physicochemical, photothermal, and mechanical properties, GO has been incorporated into various hydrogels for controlled drug delivery. However, some issues associated to the potential toxicity of GO have to be overcome before any translation to the clinic. Systematic toxicological studies are encouraged, as the studies on the toxicity of GO have led to contradictory results [96]. Other challenges relate to efficient targeted drug delivery and implementation of stimuli-responsive hydrogels [97].

2.2 CNT-based hydrogels

CNTs, including single-walled CNTs (SWCNTs) and multiwalled CNTs (MWCNTs), possess unique properties that have led to their use in diverse applications across various fields, including aerospace, electronics, and biomedical engineering [98]. Moreover, recent advancements in shape recovery stress, compressive properties, increased adsorption of drugs, and thermal and electrical conductivity of CNTs have made them highly smart and adaptable, allowing their use as functional and/or environmentally sensitive materials in various types of hydrogels, thereby enhancing their application potential [46].

2.2.1 Drug release

Due to their high surface area and the possibility of covalent and noncovalent functionalization, CNTs have been used as nanocarriers for drug delivery [70,99,100]. Their high drug loading capacity has led to extensive research on CNT-based hydrogels, allowing them to enhance the localized therapeutic effect of drugs. As an example, DOX-loaded FA-functionalized SWCNTs (SWCNT-FA/DOX) were incorporated into injectable silk hydrogels [101]. The DOX release was triggered under NIR (808 nm, 0.5 W) light irradiation. The concentration of released DOX was correlated with the amount of SWCNT-FA/DOX loaded in the hydrogels, rate of silk degradation, pH, and temperature. In another study, this hydrogel was administered at the periphery of the tumor in tumor-bearing mice, which was induced by the injection of 4T1 murine breast cancer cells [102]. The tumor showed a significant regression upon the application of an external electric field or a NIR light irradiation (simultaneously or separately), with no significant cardiotoxicity that is usually associated with free DOX treatment (Figure 4).

2.2.2 Photothermal drug release

Similar to graphene-based materials, CNTs can efficiently absorb NIR light, even at low doses, and generate high local temperature increase, making them suitable for PTT. In addition, this property also makes CNTs promising candidates for photothermally induced drug delivery [46]. Recent studies have highlighted the significance of externally controllable drug delivery systems in a broad spectrum of applications, encompassing tissue engineering and cancer chemotherapy. These systems enhance the localized dose and efficacy of chemotherapy drugs at the intended site while mitigating their adverse effects on healthy tissues. Our group developed fluorenylmethyloxycarbonyl (Fmoc)-protected aromatic amino acid derivative hydrogels loaded with a hydrophilic model drug (L-ascorbic acid) and carbon nanomaterials (oxidized CNTs or GO). The heat generated by the carbon nanomaterials upon NIR (808 nm, 2 W) light irradiation increased the temperature in the hydrogel rapidly, eventually causing the gel to collapse and release the drug (cumulative release rate between 63 and 82%) [103]. In another study, mesoporous silica-decorated MWCNTs modified with isobutyramide

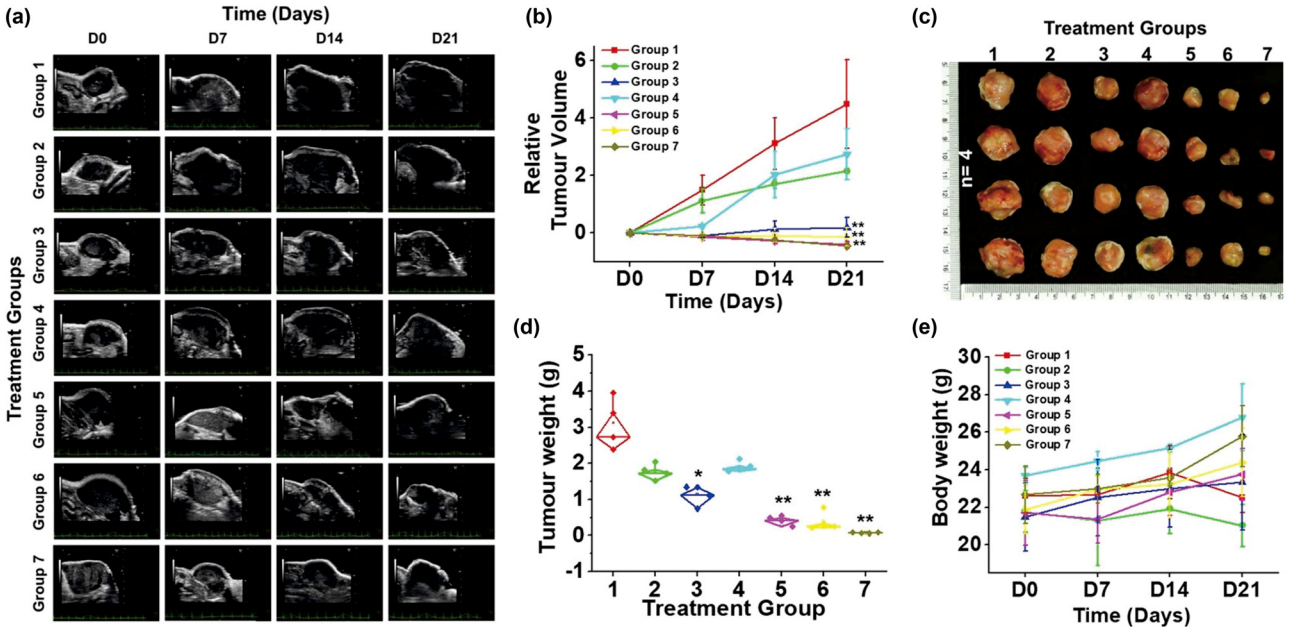

Figure 4: (a) Representative ultrasound images of tumors from all groups captured every 7 days for 21 days. (b) Tumor relative growth regression curve. (c) Comparison of tumor tissues in each treatment group. (d) Comparative analysis of tumor and mouse weight (e) among the treatment groups. Detailed information for each treatment group: (1) untreated, (2) DOX, (3) silk@DOX hydrogel, (4) silk@SWCNT-FA/DOX without stimulation, (5) silk@SWCNT-FA/DOX with NIR laser irradiation, (6) silk@SWCNT-FA/DOX with electric field, and (7) silk@SWCNT-FA/DOX with both NIR light and electric field stimulation. Reproduced with permission [102]. Copyright © 2020, ACS Applied Materials & Interfaces.

could load a high amount of DOX (≥80 wt%) [104]. Subsequently, the conjugate was coated with human serum albumin. DOX was released only under NIR light irradiation. The conjugate was incorporated in a hydrogel mimicking the extracellular matrix (Matrigel). Mouse mammary carcinoma cells (D2A1), which were localized on the top of the hydrogel, were killed by the photothermal effect of the CNTs induced by NIR light, coupled with the toxicity resulting from the released DOX. Such a drug delivery platform holds great promise as a novel component of implantable antitumor scaffolds that can respond to external stimuli promptly and locally, thereby improving disease management. In another work, a thermally sensitive injectable gelatin hydrogel loaded with SWCNT-(3-aminopropyl) trimethoxysilane was found to be nontoxic to gastric cancer cells, whereas it led to cancer cell death mediated by NIR (976 nm, 0.2 W/cm^2) light when DOX was incorporated in the hydrogel [105]. DOX/SWCNT-gelatin was subcutaneously injected in gastric tumor xenograft models in mice for combined chemotherapy and PTT. After 4 weeks of observation, DOX/SWCNT-gelatin demonstrated a significantly stronger tumor growth inhibition compared to free DOX (tumor growth ratio: 61 *vs* 166%). Moreover, hematoxylin and eosin staining revealed that the retention and duration of DOX in the tumor tissues were markedly higher in the DOX/SWCNT-gelatin group than in the free DOX group (Figure 5). Other hydrogels have been developed for NIR light-triggered drug delivery, such as a polycaprolactone-PEG-polycaprolactone copolymer thermosensitive hydrogel loaded with CS-coated MWCNTs [106]. The photothermal effect generated by the CNTs induced a gel-sol transition in the hydrogel, leading to the controlled release of DOX. The delivery of DOX was real time tracked by fluorescence imaging *in vivo*. Overall, similar to GO, photothermal-responsive hydrogels incorporating CNTs enable precise control of drug delivery, with drug-release behavior easily adjustable by managing laser power, irradiation time, and CNT concentration, thereby facilitating personalized disease treatment.

2.2.3 Mechanical reinforcement

Recently, CNTs have emerged as promising nanofillers for enhancing the mechanical properties of polymer matrices. The inclusion of CNTs as fillers in drug-carrying hydrogels can markedly enhance the mechanical strength of the hydrogels, imparting structural integrity for precise drug-release applications. This improved mechanical stability guarantees controlled and sustained drug release, resulting in more accurate and efficient drug delivery systems [46]. For instance, polydopamine-modified MWCNTs

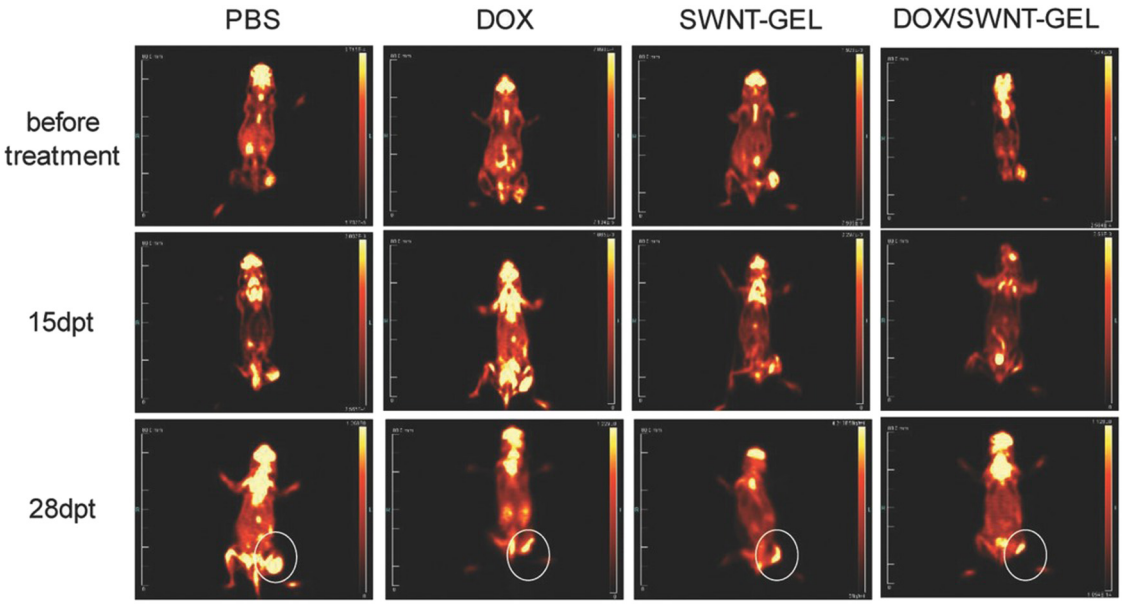

Figure 5: Micro positron emission tomography-computed tomography images of mice were obtained at various time points, including before treatment initiation, at 15 days posttreatment and at 28 days posttreatment. The white circles denote the positions of xenograft tumors in the respective groups. SWNT-GEL corresponds to the gelatin hydrogel loaded with SWCNTs. Reproduced with permission [105]. Copyright © 2015, Advanced Functional Materials.

were combined with gelatin-dopamine and CS to create composite hydrogels with high antimicrobial, adhesive, and mechanical strength [108]. The swelling and mechanical properties of the composite hydrogels were finely adjusted by altering the concentration of CNT-polydopamine. Meanwhile, the hydrogel loaded with the antibiotic doxycycline exhibited NIR-responsive drug-release behavior and demonstrated positive effects on infection control and wound healing when applied to full-thickness mouse skin wounds. This work highlights the significant potential of CNT-based hydrogels as versatile bioactive dressings for treating infected wounds. In another study, the impact of different concentrations of pristine MWCNTs on the mechanical properties of poly(methacrylic acid)-based hydrogels loaded with ^{14}C-sucrose was investigated [110]. ^{14}C sucrose was chosen due to its high water solubility, ease of diffusion, and traceability of the radioactive ^{14}C. Their results demonstrated a concentration-dependent enhancement in the mechanical strength upon the addition of MWCNTs, with a significant improvement observed at concentrations ranging from 0.05 to 0.5 wt%. The hydrogel pore size decreased from 300 μm (pristine MWCNTs: 0 mg/mL) to 150 μm (0.5 mg/mL), and the reduction in pore size indicated a higher crosslinking density between the polymer and nanomaterials, leading to enhanced mechanical strength. To improve the drug loading/release capabilities of hydrogels, carboxylated CS-modified MWCNTs were loaded in a temperature-sensitive hydrogel [poly (diethylacrylamide-*N*-hydroxymethylacrylamide)] containing the antibiotic ciprofloxacin hydrochloride, allowing to enhance both the fracture resistance and compressive strength of the hydrogels [109]. As the CNT content increased from 0.5 to 1 wt%, the energy storage modulus of the hydrogels increased from 0.052 to 0.176 MPa, confirming that the presence of the CNTs endowed the hydrogels with a superior mechanical strength. In addition, the hydrogel demonstrated adjustable drug loading capacity (from 982 to 1,424 μg/g) and enabled temperature-controlled drug release, achieving antibacterial rates higher than 90% against *E. coli* or *S. aureus*. Exosomes are vital contributors to promote skin regeneration and angiogenesis, and they can be co-administered with metformin, a frequently used drug for diabetes, to treat chronic diabetic wounds, which are a recognized global clinical challenge. However, their rapid clearance *in vivo* and short half-life hinder their clinical application. Therefore, to enhance the stability and delivery of metformin and adipose-derived mesenchymal stem cell exosomes, and to promote their synergistic effects in addressing the chronic diabetic wounds, Zhang *et al.* designed PEG hydrogels by crosslinking a PEG-SH derivative with Ag^{+} [111]. In addition, hydroxy-modified MWCNTs were introduced to form hydrogen bonds with thiols to enhance the mechanical strength of the hydrogels, ultimately resulting in a stable 3D structure. The adhesion strength between the PEG/Ag hydrogel and the skin was increased when the hydrogel

contained MWCNTs, thereby enhancing the stability and prolonging drug release. In a diabetic mouse model, the PEG/Ag/CNT hydrogel promoted wound healing and angiogenesis and mitigated inflammation in the periphery of the wound and vascular injury by inducing cell proliferation.

2.2.4 Electroresponsive drug release

CNTs are renowned for their exceptional electrical conductivity, and they have been used as conductive fillers in composite materials, for growing cells and tissues and for the development of electronic devices, leading to a variety of applications, including tissue engineering and biosensing [112]. The electrical properties of CNTs can also be exploited to trigger the release of drugs from hydrogels. This process typically involves the application of an electrical stimulus, which either alters the hydrogel structure or generates thermal effects through Joule heating, ultimately leading to the controlled release of the encapsulated drug. For example, electroconductive hydrogels containing pristine MWCNTs, gelatin, acrylamide, and PEG dimethacrylate were prepared by one-step radical polymerization and loaded with curcumin. The hybrid hydrogels exhibited a sensitive electrical response to external voltage with the release rate of curcumin reaching 100% within 48 h when the voltage reached 48 V [113]. The release of the drug was significantly dependent on the CNT content and voltage. Another innovative electroresponsive hydrogel was designed by combining pristine MWCNTs and poly(methacrylic acid), allowing a precise control of the release of a model drug ^{14}C sucrose *in vitro* and *in vivo* under an electrical stimulation [114]. After subcutaneous implantation in the upper dorsal region of mice, a rapid release of sucrose was observed 1 min after the electric field application, resulting in a high amount detected in blood after 10 min. Such an approach has the potential to personalize the management of chronic conditions requiring multiple dosage regimens.

An electrothermally responsive hydrogel was prepared by integrating pristine MWCNTs, which have excellent thermal properties in addition to high electrical conductivity, and CS in a thermoresponsive poly(NIPAAm-co-3,3′-(butane-1,4-diyl)bis(1-vinyl-imidazol-3-ium)) hydrogel [115]. The innovation in this study is the creation of a CNT sponge framework, utilizing CNTs as core units for electrical/thermal conduction and CS as shell unit and hydrophilic dispersant. This design allowed a homogeneous distribution and 3D connectivity of the CNTs. Approximately 37% of ketoprofen, loaded in the hydrogel and used for the treatment of musculoskeletal pain, was released after external electrical stimulus (~14 W) using a direct current power supply (1.7 V, ~8.1–8.2 A), due to the contraction of the gel by about 30%. In another study, oxyfluorinated MWCNTs were incorporated in PVA/polyacrylic acid hydrogels loaded with ketoprofen [116]. The drug-release behavior using a mouse skin model was notably influenced by the MWCNT content, oxyfluorination parameters, and voltage. The hydrogel showed no toxicity to L929 mouse fibroblasts in the absence of an electrical stimulation.

CNTs have shown great potential in drug-loaded hydrogels due to their unique properties, such as a high surface area and biocompatibility, and excellent electrical and thermal conductivity. The CNTs can trigger the release of drugs under external stimuli, such as NIR light irradiation and electrical stimulation, owing to their photothermal capacity and electrical conductivity. In addition, depending on the content of CNTs in the hydrogels, they can enhance their mechanical properties. However, the current research on CNT-based hydrogels still faces several limitations. One of the main challenges is the difficulty in achieving uniform dispersion of CNTs within the hydrogel matrix, which can affect the overall properties of the hydrogels. One possibility to overcome this limitation is to use functionalized CNTs with increased water dispersibility and higher interactions with the components of the hydrogels. Another limitation is the potential toxicity of CNTs, which requires careful consideration in the design of drug-loaded hydrogels. Surface functionalization of CNTs is an effective approach for reducing their potential toxicity [117–119]. In addition, there is a need for more studies to investigate the long-term stability, biocompatibility, and therapeutic efficacy of CNT-based hydrogels *in vivo*. Despite these limitations, the potential benefits of CNTs in drug-loaded hydrogels make them a promising area of research not only for targeted drug delivery but also for tissue engineering and regenerative medicine applications. Ongoing research efforts aim to overcome the current limitations and develop optimized CNT-based hydrogels that can provide precise and controlled drug delivery with minimal side effects.

CNTs and GO are prevalent carbon nanomaterials used in hydrogels. Hybrid hydrogels combining these materials exhibit promising potential for drug delivery systems. Drug-carrying hydrogels incorporating GO offer enhanced biocompatibility due to the presence of oxygen-containing functional groups, but often lack desired mechanical strength and electrical conductivity [120]. CNTs, conversely, possess excellent mechanical strength and electrical conductivity, providing structural integrity to the hydrogels and enabling various responsive drug-release

mechanisms. Their high aspect ratio and large surface area facilitate efficient drug loading, enhancing overall drug loading capacity. However, the potential long-term risks associated with the residence and accumulation of CNTs in the body necessitate careful consideration for their safe and effective use in drug delivery [121].

2.3 CND and GQD hydrogels

In the last years, CNDs have attracted significant attention due to their excellent excitation-dependent photoluminescence emission, good water dispersibility, ease of surface modification, low toxicity, and exceptional drug loading capabilities [122]. As a result, CNDs have found diverse applications in biomedical research, including drug delivery, wound healing, and tissue engineering [122,123]. Adding CNDs to hydrogels can enhance drug loading, provide fluorescent properties for real-time monitoring, strengthen the mechanical properties, and allow responsiveness to environmental changes [124]. For example, to minimize the toxic side effects of chemotherapeutic drugs and enhance their anticancer efficacy, a pH-responsive injectable hydrogel was developed by crosslinking CNDs, hydroxyapatite, and DOX through Schiff base bonds, hydrogen bonds, and ionic interactions [125]. The hydrogel displayed a high drug adsorption capacity and pH-dependent drug release and demonstrated efficacy in killing breast cancer cells (MCF-7) in a slightly acidic environment (pH 6.5).

Serious Gram-positive bacterial infections, such as osteomyelitis, present substantial challenges in clinical treatment. Developing efficient drug carriers to enhance the gastrointestinal absorption of vancomycin, a potent Gram-positive antimicrobial agent, is crucial. CNDs derived from *Aloe vera* leaves were used to formulate a hydrogel made of sodium Alg for regulating the delivery of vancomycin in the gastrointestinal tract [126]. The incorporation of CNDs led to a significant increase in drug loading in the hydrogel from 38 to 89 wt%, when compared to the gel with only vancomycin, owing to hydrogen bonding. The release of vancomycin from the sodium Alg/CND hydrogel was more pronounced at pH 1.5 (close to stomach pH), with a release rate of 72 wt%. This suggests a promising alternative to oral vancomycin administration. In another study, Pd single atom on catechol-grafted CNDs and immune adjuvant CpG oligodeoxynucleotides were added to an injectable hydrogel obtained by polymerization of PEG diacrylate for localized immunomodulation and catalysis-augmented immunotherapy in a subcutaneous rectal tumor-bearing mice [127]. In addition, CNDs have been employed in the preparation of photothermally responsive hydrogels for controlled drug release [128,129]. For instance, a NIR-responsive antimicrobial hydrogel was developed by encapsulating papaya leaf-derived CNDs in a thermosensitive PVA-melamine hydrogel loaded with 5-fluorouracil, intended for the treatment of metastatic melanoma and potential associated infections [128]. Upon exposure to NIR light at 980 nm (1.44 W/cm^2), rapidly warmed up to 42°C, leading to accelerated drug release. Biological experiments showed that, upon exposure to NIR light irradiation, the hydrogels completely inhibited the growth of melanoma cells and *Vibrio cholera* bacteria *in vitro*, in contrast to the nonirradiated group. Besides their role in controlling drug release, CNDs have been utilized as fillers to enhance the mechanical properties of hydrogels. Wang *et al.* developed a multifunctional injectable and self-healing hydrogel for wound infection treatment, based on the noncovalent self-assembly between kanamycin sulfate (an antibiotic)-derived CNDs and cationic guar gum (CG) [130]. Rheological testing confirmed the hydrogel self-healing properties, while the incorporation of CNDs significantly enhanced its mechanical strength. Remarkably, under 405 nm blue light irradiation for 5 min, the hydrogel completely inhibited the growth of *S. aureus* and *E. coli in vitro*. When injected into a bacterial infection model of a mouse skin wound, the CND-CG hydrogel effectively reduced inflammation and promoted wound healing. Furthermore, the excellent biocompatibility and biosafety of the hydrogel make it a promising candidate for wound dressing applications. A recent study reported the synthesis of CNDs derived from the natural plant resource, *Prunella vulgaris*, through a one-step hydrothermal process [131]. These CNDs were then uniformly integrated into a polyacrylamide/carboxymethylcellulose hydrogel matrix *via in situ* free radical graft polymerization, providing a multifunctional platform for wound management. The hydrogel exhibited a pH-sensitive photoluminescent behavior, with the maximum photoluminescence intensity observed at pH 5 (corresponding to the pH of acute wounds), while the photoluminescence intensity gradually decreased at both lower and higher pH values. This suggests that the hydrogel could serve as a tool for monitoring the healing process and detecting infections. In addition, the hydrogel provided complete protection against UV-C and UV-B radiation and blocked at least 83% of UV-A radiation, offering strong UV shielding for wounds. Notably, the hydrogel loaded with tetracycline was able to release the drug at a cumulative amount of 220 μg/mL over 33 h at pH 5. However, at pH 7, the release was only 100 μg/mL, indicating a potential pH-responsive antibacterial activity. Finally, no toxicity to mouse fibroblast

3T3 cells was observed *in vitro*, demonstrating the hydrogel's excellent biocompatibility. Therefore, this CND-based hydrogel holds great promise as an alternative to conventional wound dressings.

Overall, these studies revealed that incorporating CNDs into smart drug-carrying hydrogels has positive implications for enhancing hydrogel drug loading, improving mechanical properties, and enabling controlled release in response to specific conditions. However, limited animal experiments have been conducted, and their applicability *in vivo* remains unexplored.

GQDs are another type of carbon dots with remarkable biocompatibility, transparency, and electrical conductivity [132]. Due to these features, GQDs are emerging as innovative tools in fields such as photonics, composites, energy, and electronics. Moreover, GQD-based nanomaterials have demonstrated significant potential in biomedicine, particularly in diagnosis, drug delivery, NIR photo-induced PTT, as well as in bioimaging [133]. GQDs can serve as crosslinking agents through covalent bonding of the COOH groups with components of hydrogels, enhancing their mechanical properties and acting as drug carriers in smart hydrogel applications [133–137]. For instance, the incorporation of GQDs as crosslinkers into carboxymethylcellulose led to the formation of biocompatible and biodegradable hydrogel, exhibiting a 30% increase in tensile strength [135]. These hydrogels showed significant pH-responsive drug-release behavior, liberating a high amount of DOX (60%) at pH 7.4 compared to pH 2 (20%). In addition, *in vitro* experiments confirmed that the hydrogel exhibited excellent biocompatibility, while the DOX-loaded hydrogel showed significant cytotoxicity against human colorectal adenocarcinoma HT29 cells, suggesting their potential as oral agents for controlling drug release in the intestinal tract (pH 4–8.5). A recent study reported the development of CS/nitrogen-doped GDQ (NGQD) hydrogels with high DOX loading [136]. The NGQDs acted as a crosslinking agent, based on covalent and noncovalent interactions between the surface functional groups of NGQDs and the side chains of CS, resulting in superior mechanical properties of the CS/NGQD hydrogels. The loading of DOX in the hydrogel was found to gradually increase with increasing the NGQD amount, facilitated by the strong π–π interactions between the aromatic rings of DOX and the dots. Drug-release assays revealed that the control group (hydrogel without NGQDs) exhibited almost quantitative release at pH 5.0 within 10 h, whereas the CS/NGQD hydrogel showed a significantly lower DOX release rate. Indeed, the hydrogel released approximately 50% of the loaded drug within 10 h, which confirmed the controlled release effect exerted by the NGQDs, leading to an enhanced cytotoxicity against lung cancer cells (Figure 6). To address the limitations of monotherapies for advanced hepatocellular carcinoma, a therapy combining a hydrogel with GQDs and a CS coated with magnetic Fe_3O_4 NPs was developed [138]. The hydrogel was formed by conjugating DOX onto CS, followed by crosslinking between GQDs and magnetic CS through amide bonds. This hydrogel achieved over 70% DOX release in a mildly acidic environment under NIR light irradiation (808 nm, 2 W/cm^2, 5 min) , due to the Schiff base bond formed between DOX and CS, and the photothermal properties of GQDs. Both *in vitro* and *in vivo* experiments demonstrated that the photothermal performance of the hydrogel significantly enhanced the cytotoxicity of DOX against hepatoma cells (H22), ultimately improving tumor growth inhibition. In recent years, to improve the stability and bioavailability of quercetin and enhance its therapeutic effect for brain cancer, a hydrogel composed of CS, carboxymethylcellulose, GQDs, and zinc oxide NPs was designed for the release of quercetin [139]. CS and carboxymethylcellulose are pH-sensitive polymers used as hydrogelators. ZnO NPs served as mechanical fillers to enhance the hydrogel mechanical properties, while GQDs were employed to improve the ability of quercetin to penetrate the blood–brain barrier. Compared to a neutral environment (pH 7.4, release rate 45%), this hydrogel exhibited a quercetin release rate of more than 85% in an acidic environment (pH 5.4) over 100 h because of the protonation of the amino groups of CS. The hydrogel did not show toxicity to L929 fibroblast cells *in vitro*; the cell viability was 99% after 24 h incubation. However, the viability of human malignant glioma cells (U-87MG) incubated with the hydrogel decreased to 49%, which was significantly lower compared to the viability of the cells incubated with quercetin alone (65%). The anticancer effect on brain cancer cells with low toxicity to normal cells could make this GQD-based hydrogel a safe and effective drug carrier for the treatment of hard-to-treat cancers like brain cancer.

Therefore, incorporating GQDs into drug-loaded hydrogels offers advantages such as precise drug loading, controlled release, and enhanced biocompatibility, making them advantageous for biomedical applications. However, compared to GO and CNTs, GQDs may lack a sufficient mechanical reinforcement, which is a key property in certain applications, such as the development of robust injectable hydrogels for *in vivo* drug delivery and tissue engineering.

Although less studied than hydrogels incorporating CNTs and GO, CNDs, and GQDs have great potential to improve various properties of hydrogels and enable the design of new functional materials. For instance, incorporating CNDs and GQDs into hydrogels can enhance their mechanical strength, drug-loading capacity, and controlled drug-release behavior, making them promising candidates for precise drug delivery applications.

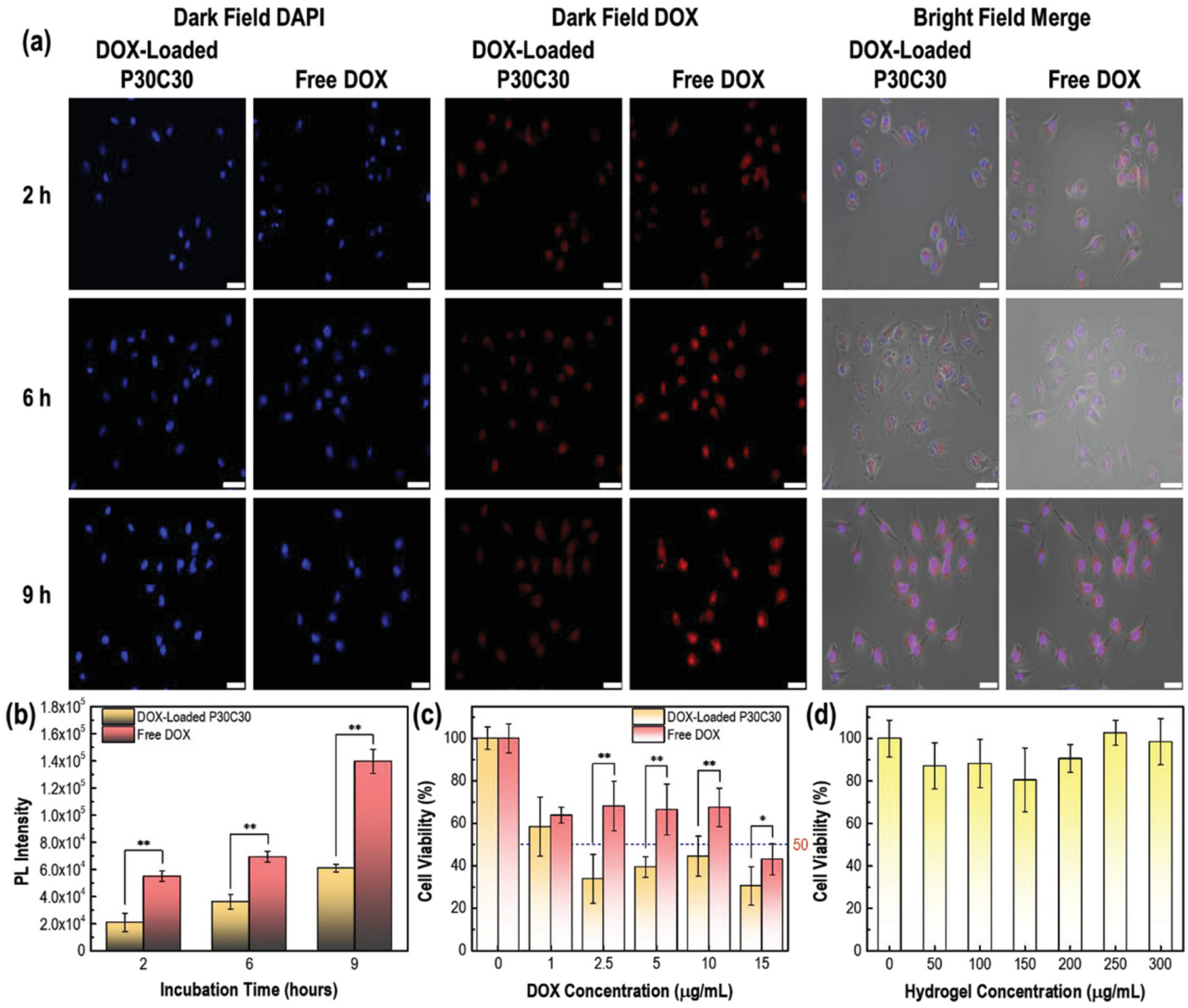

Figure 6: *In vitro* evaluation of P30C30 for DOX delivery. (a) Fluorescence microscopy images of A549 cells (lung cancer cells), (b) quantification of DOX fluorescence intensity using ImageJ software, (c) comparison of cell viability after treatment with DOX-loaded P30C30 *versus* free DOX (*$p < 0.05$, **$p < 0.01$; $n = 6$) and (d) assessment of cell viability of P30C30 in comparison with the normal cell line (L929). The sample designation P30C30 refers to a crosslinking time of 30 min (P30) for the CS solution, and a plasma crosslinking time of 30 min (C30) between CS and NGQDs. Reproduced with permission [136]. Copyright © 2023, Wiley.

3 2D material-based hydrogels

2DMs are an advanced class of materials characterized by their atomic-scale thickness, typically one or few atomic layers. Over the past 10 years, the unique properties of 2DMs have led to their wide use in various fields, including electronics, sensors, environmental science, and biomedicine [140]. Besides graphene, other 2DMs have been developed, including transition metal dichalcogenides (TMDs; *e.g.*, MoS_2, WSe_2, TiS_2), monoelemental materials called Xenes (selenium, boron, tellurium, bismuth, and phosphorus), metal sulfides (GaS, InSe, SnS, SnS_2), MXenes, and others. These materials exhibit excellent photodynamic and photothermal conversion properties, and offer diverse advantages in biomedical applications, such as biosensing, imaging, and therapy [141]. Moreover, the unique structure of 2DMs offers significant advantages as an attractive option for the development of smart composite hydrogels [142]. In this section, we emphasize the current development of hydrogels incorporating a variety of 2DMs as nanocarriers, mechanical fillers, and photothermal agents. Table 2 summarizes the recent development in 2DM-based hydrogels for drug delivery applications. The following sections on smart 2DM hydrogels will focus on TMDs, Xenes, layered double hydroxides (LDHs) and other materials, and responsive drug-loaded hydrogels. Specifically, we will present the effects of 2DMs on the drug

Table 2: 2DMs incorporated in hydrogels for drug delivery and myocardial infarction

Classifications	2DMs	Function in the hydrogels	Drug	Applications	Ref.
TMDs	MoS_2	Drug carrier; photothermal properties	DOX, immunoadjuvant R837	Delivery of anticancer drugs; PTT/PDT; tumor treatment; antibacterial effect	[146,148–150]
	MoS_2	Improvement of mechanical properties	Phenytoin	Antibacterial effect; wound healing	[151]
	WS_2	Photothermal properties	Ciprofloxacin	Delivery of antimicrobial drug; PTT; wound healing	[152]
Xenes	Black phosphorus	Photothermal properties; pH-responsive drug carrier	DOX; 4-octyl itaconate	Delivery of anticancer and anti-inflammatory drugs; PTT/PDT; antibacterial effect; tumor treatment; wound healing	[158,161]
	Antimonene	Photothermal properties	CS	Antibacterial effect; wound healing	[162]
	Germanene	Photothermal properties; drug carrier	DOX	Delivery of anticancer drug; PTT; antibacterial effect; tumor treatment; wound healing	[163]
LDHs and others	LDHs	pH-responsive drug carrier	Insulin; amoxicillin; ibuprofen	Delivery of antimicrobial and analgesic drugs; antibacterial effect	[167–169]
	MnO_2	Photothermal properties; improvement of the mechanical properties	DOX	Delivery of anticancer drug; PTT; tumor treatment; antibacterial effect; wound healing	[171]
	Ti_3C_2	Photothermal properties	DOX; Ag NPs	Delivery of anticancer drug; cancer cell treatment; antibacterial effect; wound healing	[172,177]
	$Ti_3C_2T_x$	Electrical conductivity and improvement of mechanical properties	/	Myocardial infarction (heart repair)	[178]
	Ti_3C_2	Improvement of mechanical properties	Chloramphenicol	/	[179]
	gC_3N_4	Improvement of the mechanical properties; pH-responsive drug carrier	Ciprofloxacin; quercetin; $Ag@TiO_2$ NPs	Delivery of anticancer and antimicrobial drugs; antibacterial effect; cancer cell treatment; wound healing	[173,181,182]

Note: “Cancer cell treatment” refers to *in vitro* studies, while “tumor treatment” refers to *in vivo* animal experiments.

release and their beneficial role in enhancing the drug loading capacity and improving the mechanical properties of hydrogels.

3.1 Transition metal dichalcogenide-based hydrogels

TMDs are a class of materials composed of transition metals combined with chalcogen elements, where each unit (MX_2) consists of a metal (M) layer sandwiched between two chalcogen (X) layers [143]. TMD nanosheets offer superior properties compared to conventional nanomaterials in biomedical research because they have a high mechanical strength and flexibility, a direct band gap, an extraordinary photoluminescence, and a good thermal stability, and they are chemically inert [144]. MoS_2 is the most extensively studied material in the TMD family due to its stable chemical properties, large specific surface area, and numerous active sites (*e.g.*, edges and S vacancies) [145]. In the recent years, the high photothermal conversion efficiency of MoS_2 has been exploited for PTT involving MoS_2-loading hydrogels [145,146]. For instance, a CuS@MoS_2 PVA hydrogel is an excellent example of TMD-based hydrogels with antibacterial properties able to promote wound healing [147]. By exposing this hydrogel to visible light (660 nm) and NIR light (808 nm), a synergistic photodynamic and photothermal effect was measured, resulting in the destruction of 99.3% of *E. coli* and 99.5% of *S. aureus*. In addition, this complex promoted wound healing by accelerating the expression of hypoxia-inducible factor-1 and vascular endothelial growth factor. Alternatively, Zheng *et al*. developed another dual-function NIR-responsive hydrogel for PTT and chemotherapy to treat colon cancer [148]. Injecting a mixed solution of CS and β-glycerophosphate led to the immediate formation of a hydrogel. Photosensitive MoS_2/Bi_2S_3-PEG nanosheets incorporated in the hydrogel enabled to release DOX under NIR light irradiation (808 nm, 1 W/cm^2). The NIR-controlled release of DOX allowed reducing the toxicity of the drug to normal tissues. The hydrogel was also able to inhibit the growth of colon cancer cells, with a viability of only ~13% after NIR light irradiation. In addition, it was found that the hydrogel exhibited good antimicrobial properties against *E. coli*, mitigating the risk of infections that may arise during chemotherapy treatments. Furthermore, several studies have integrated MoS_2 as a multifunctional material into hydrogels, enhancing the efficacy in controlling the onset of a disease. For example, MoS_2 was utilized as a photothermal and photodynamic agent, and a drug carrier to prepare a polypeptide-based hydrogel loaded with DOX, MoS_2, and $PC_{10}A$ polypeptide for PTT and PDT toward breast tumor (4T1) [149]. The primary function of MoS_2 in this study was to adsorb drug molecules and generate heat and reactive oxygen species. When the hydrogel was injected into mice and exposed to laser irradiation, it significantly enhanced the mice immune response against tumors, inhibited tumor growth, and prevented metastasis. In another study, defect (planar and edge atomic defects)-rich MoS_2 was combined with PNIPAM to obtain a responsive hydrogel [150]. Under NIR (600–1,000 nm, 250 W at a distance of 15 cm) light irradiation, MoS_2 acted as a crosslinker, reacting with thiol-functionalized PNIPAM *via* a defect-driven click chemistry, enabling precise control over the hydrogel properties. MoS_2 embedded in the hydrogel network acted as a platform to adsorb DOX through π–π stacking interactions, achieving high DOX loading efficiency (around 90 wt%). NIR light irradiation (808 nm, 1.5 W/cm^2) caused the hydrogel to shrink due to the photothermal effect of MoS_2, resulting in the release of DOX (over 75%) (Figure 7a and b). Cell viability experiments using MCF-7 cells showed that the anticancer activity was proportional to the concentration of liberated DOX *in vitro* (Figure 7c–e). In the current state of research, MoS_2 plays a pivotal role in smart hydrogels, offering multifunctional capabilities for advanced drug delivery and therapeutic applications. In addition to its excellent photothermal effect, MoS_2 can also serve to enhance the mechanical properties of hydrogels, thereby improving their applicability in the biomedical field. For example, to address the mechanical strength and antibacterial shortcomings of traditional dressings for diabetic foot wounds, a stress-responsive hydrogel was designed based on a zwitterionic polymer (sulfonated betaine methacrylate) using phenytoin (an antibacterial agent)-encapsulated beeswax NPs as crosslinker and keratin-exfoliated MoS_2 to enhance the mechanical properties [151]. When the MoS_2 concentration increased from 5 to 15 mg/mL, the tensile strength of the hydrogel significantly increased from 72 to 118 kPa. The hydrogel could release 38% of phenytoin after 100 stretching cycles (at 80% tensile strength). The hydrogel maintained more than 80% viability of L929 fibroblast cells after 7 days. In addition, *in vitro* experiments showed that the antibacterial activity of the hydrogel was closely related to the applied stretching force. Indeed, when the tensile strain increased from 20 to 80%, the hydrogel inhibition zone against bacterial (*S. aureus* and *E. coli*) proliferation grew from 7 to 18 mm. This characteristic makes the hydrogel particularly suitable for diabetic foot wounds, as it can release antibacterial phenytoin in response to the pressure generated on the foot. Furthermore, the *in vivo* healing rates (corresponding to the wound area post/pre-application ratio) of the hydrogel on days 4, 8, 12,

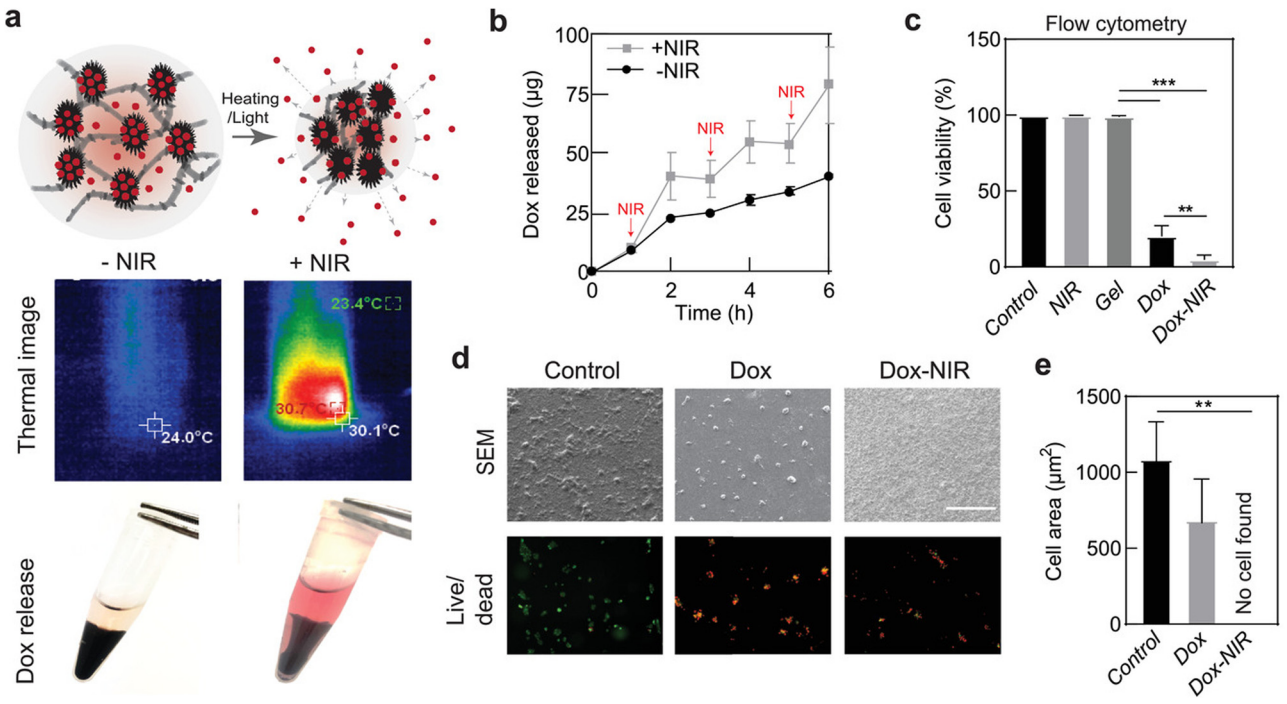

Figure 7: Drug delivery facilitated by NIR light exposure. (a) Schematic representation of drug release from PNIPAM-MoS_2 hydrogels. (b) Drug release triggered by NIR light irradiation over three cycles, with each cycle consisting of 10 min of NIR light exposure. (c) Effect of combined chemotherapy/PTT on MCF-7 cell viability evaluated by flow cytometry. (d) Representative scanning electron microscopy images and live/dead imaging of cells in different conditions. (e) Quantification of cell area on scanning electron microscopy samples. $^{**}p < 0.01$, $^{***}p < 0.001$. Reproduced with permission [150]. Copyright © 2021, Wiley.

and 16 were 18, 40, 62, and 91%, respectively, which was significantly better than the control group (50% healing rate on day 16). Notably, MoS_2 also induced macrophage polarization toward the anti-inflammatory M2 phenotype, promoting wound healing. This study highlights the multifunctionality of MoS_2 in hydrogels.

In addition to MoS_2, other materials such as WS_2 also exhibit high photothermal effects and can be utilized as photothermal agents for treating diseases [152,153]. A novel NIR-responsive antibacterial dressing material was designed by incorporating WS_2 nanosheets as photothermal agents and ciprofloxacin in a hydrogel composed of dodecyl-modified CS linked to PEG *via* a Schiff base bond [152]. Under NIR (808 nm, 0.5 W/cm^2) light irradiation, the WS_2 nanosheets generated a high temperature increase and ciprofloxacin was released at the wound site, ultimately leading to bacterial death. The hydrogel exhibited good antioxidant activity and could effectively block the inflammatory reaction caused by residual dead bacteria in the infected area, thereby avoiding secondary damage to the wounded tissue and promoting wound healing. Hence, the exploration of TMDs in smart drug-release hydrogels holds immense promise, ushering in a new era of innovative drug delivery systems with unparalleled precision and efficacy.

Overall, TMDs offer unique advantages in constructing smart drug-carrying hydrogels. Their tunable physicochemical properties and high surface area enable precise drug loading and controlled release, which are crucial for tailored therapeutic applications. In addition, TMDs inherent responsiveness to external stimuli, such as light and temperature, facilitating on-demand drug delivery, enhancing the treatment efficiency, and minimizing the side effects. However, challenges like potential toxicity and scalability issues must be addressed. Future research should focus on refining TMD-based hydrogel formulations, optimizing their biocompatibility, and developing scalable production methods. Integration with emerging technologies, like nanomedicine and bioinformatics, could pave the way for groundbreaking advancements in personalized and targeted drug delivery, revolutionizing the landscape of healthcare.

3.2 Xene-based hydrogels

Xenes are made of VA group elements (*i.e.*, P, As, Sb, Bi) or VIA group elements (*i.e.*, Se, Te) and consist of a single element arranged in a 2D structure [154]. Rapid

developments in the preparation of black phosphorus (BP) have brought Xenes to the forefront of researchers' attention [155]. Nowadays, Xenes are being investigated as promising therapeutic agents to address various challenges in the biomedical field [156]. For example, Xenes can be used for phototherapies, as they are promising for PTT and PDT against tumors, bacteria, and viruses [157–161]. An injectable, pH- and NIR light-responsive hydrogel was prepared by incorporating BP nanosheets into a crosslinked network of dibenzaldehyde-functionalized PEG and polyaspartylhydrazide polymer [158]. Following the injection, this hydrogel loaded with DOX was capable of achieving targeted drug release in the tumor area and providing effective PTT. In another study, a hydrogel with a photoresponsive shape memory performance and biodegradability was prepared using piperazinyl polyurethane, a thermally responsive polymer, and BP thin layers as photothermal nanofillers [159]. *In vitro* (human mesenchymal stem cells (hMSCs) and mouse fibroblast (L929) cells) and *in vivo* toxicity studies confirmed that the hydrogel possessed a good biocompatibility. When implanted subcutaneously in mice, the hydrogel displayed remarkable shape memory performance, swiftly changing its shape upon exposure to moderate 808 nm light irradiation (0.17 W/cm^2). Another hydrogel was designed for postoperative cancer therapy exploiting the photothermal effect of BP nanosheets and the thermosensitivity of triblock poly(lactide)-poly(ethylene glycol)-poly(lactide) copolymer [160]. This hydrogel not only exhibited excellent NIR photothermal performance and rapid NIR-induced sol-gel transition efficiency but also demonstrated good biodegradability and biocompatibility *in vitro* (hMSCs, L929, MCF-7, human cervical cancer cell (HeLa)) and *in vivo*. Under NIR (808 nm, 0.5 W/cm^2) light irradiation, the hydrogel effectively enhanced the therapeutic efficiency as a PTT agent and ultimately ablated residual cervical tumor tissues (Figure 8). Furthermore, its excellent photothermal antimicrobial properties prevented infections and made this highly efficient and biodegradable PTT system extremely promising for cancer treatment.

In a study exploring another type of Xenes, antimonene nanosheets (exfoliated from bulk antimony) were incorporated into a CS network to create a composite hydrogel with excellent antibacterial (*E. coli* and *S. aureus*) properties [162]. When incubated with bacteria, this hydrogel adhered to the surface of bacteria through the interaction of CS with the bacterial membrane. Subsequently, the intrinsic bactericidal properties of CS partly killed the bacteria. Upon irradiation using a NIR laser (808 nm, 1.5 W/cm^2), the antimonene nanosheets efficiently converted the light energy into localized heat, leading to the elimination of the residual bacteria. In another study, a mixed agarose/CS hydrogel was loaded with germanene as both drug carrier and photothermal agent [163]. The hydrogel displayed a high DOX loading capacity and NIR light responsiveness, showing good promises for postoperative oncology. The germanene nanosheets embedded into the hydrogel rapidly converted the NIR laser light into heat to kill the tumor and bacteria at the surgical site. At the same time, DOX released from the hydrogel synergistically destroyed residual 4T1 tumor cells. This multifunctional platform efficiently prevented both tumor recurrence and postsurgery wound infection.

Currently, Xene-containing hydrogels can be administered *in vivo* through surgical implantation, local injection, or systemic administration [164]. While most of these hydrogels are biocompatible, the metabolic pathways of Xenes within the body are still unknown. Therefore, future research should focus on studying the interactions between Xenes and the body, which will facilitate further development and *in vivo* applications of Xene-containing hydrogels.

3.3 LDH-based hydrogels

LDHs are materials that consist of a positively charged host layer with anions and water molecules embedded within interlayer channels as guests [165]. LDHs have shown great promise for biomedical applications due to their physicochemical advantages, including excellent biocompatibility, pH-sensitive biodegradability, highly tunable chemical composition and structure, and ability to easily form composites with other materials [165]. LDH-based drug carriers have been extensively studied in the field of anticancer, antibacterial, and wound therapy. Owing to their pH-sensitive biodegradability, LDHs can enable pH-sensitive drug release [166]. For example, a single electrodeposition process was used to prepare multilayered CS/LDH mixed hydrogels, which were loaded with insulin. The high sensitivity of LDHs to pH variations allowed avoiding a sudden release of insulin [167]. In another study, the pH sensitivity of a carboxymethylcellulose-based hydrogel can be adjusted by varying the amount of added LDHs [168]. Figure 9 shows that the hydrogel loaded with AMOX had the highest antibacterial activity against *S. aureus* and *E. coli* at a pH of 7.4, surpassing its performance in acidic environments. Furthermore, the hydrogel exhibited good biocompatibility with mammalian cells. Crucially, this approach tackles AMOX vulnerability to degradation in low pH environments, enhances its antibacterial efficiency, and mitigates associated side effects. These findings offer valuable insights into the optimized application of antimicrobial drugs.

LDHs were also employed to encapsulate ibuprofen into a hydroxypropyl-methylcellulose hydrogel, resulting in a

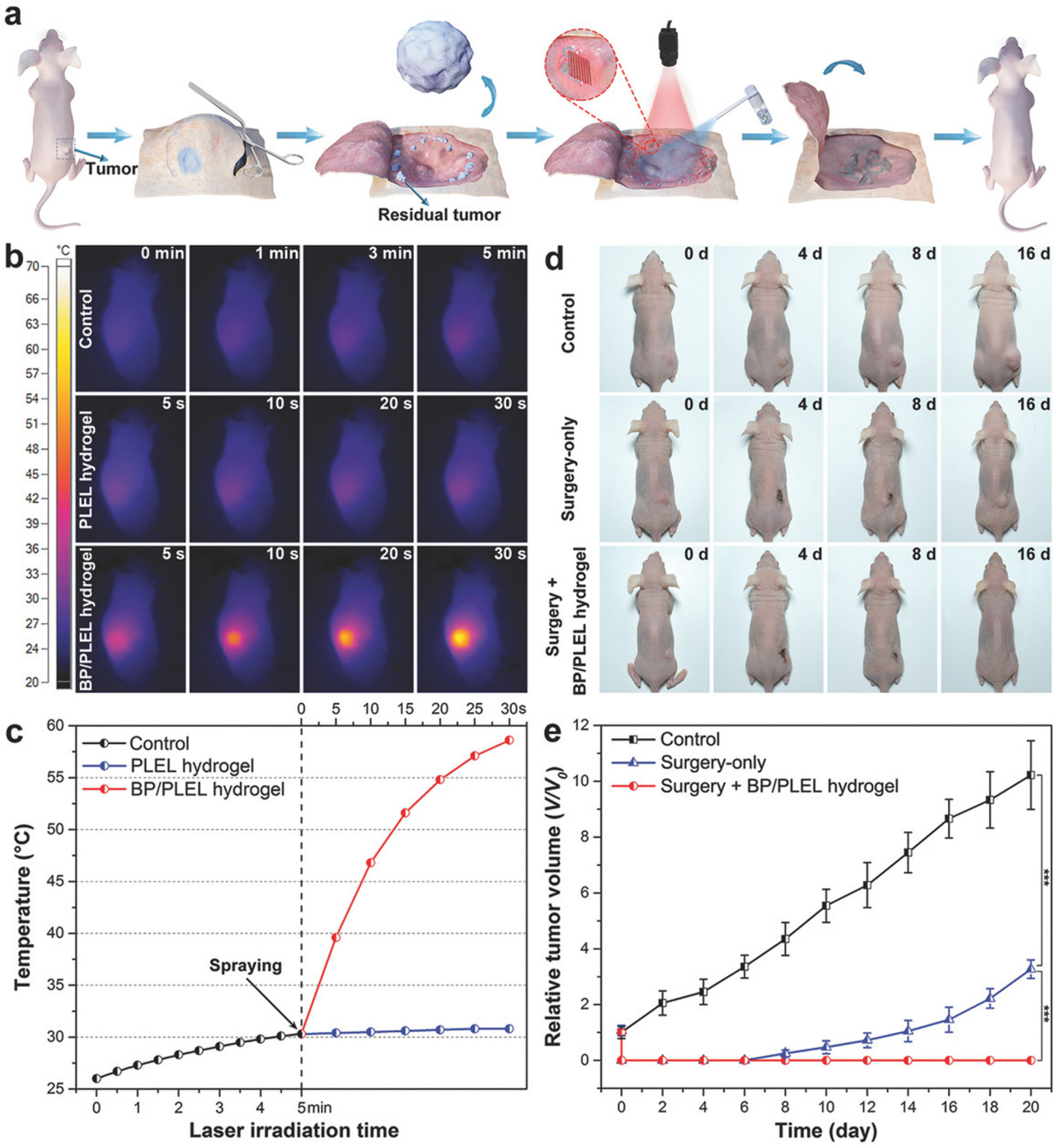

Figure 8: PTT for postoperative treatment of tumors. (a) The hydrogel was applied for PTT to eliminate residual tumor tissue after tumor resection surgery. (b) Infrared thermographic maps. (c) The temperature in the tumor-bearing nude mice gradually rose with time following the application by spraying, *via* a skin incision, of poly(lactide)-poly(ethylene glycol)-poly(lactide) (PLEL) and BP@PLEL hydrogel, coupled with irradiation using an 808-nm laser at 0.5 W/cm^2. (d) Representative images and (e) corresponding growth curves depicting tumor-bearing mice subjected to various treatments: no treatment, surgical intervention alone, and surgical intervention followed by PTT. Reproduced with permission [160]. Copyright © 2018, Wiley.

drug loading efficiency up to 54 wt% [169]. The release of ibuprofen was observed to be more pronounced in a weakly acidic environment mimicking intestinal fluid (pH 6.8).

Overall, LDH-based hydrogels have been recognized as effective systems for achieving long-lasting treatment of diseases and preventing relapse. These hydrogels overcome

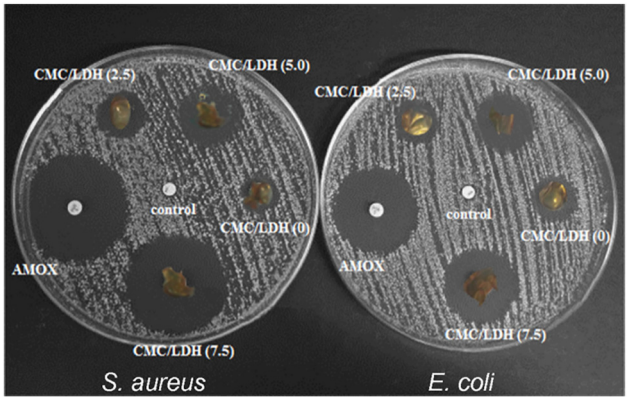

Figure 9: Antibacterial activity of a carboxymethylcellulose-based hydrogel loaded with LDH and AMOX against *S. aureus* and *E. coli*. under different pH conditions. The large diameter of the antibacterial ring indicated that the hydrogel effectively inhibited bacterial growth. Reproduced with permission [168]. Copyright © 2020, Elsevier.

issues such as clotting or vascular blockage caused by insufficient dispersion and stability of LDHs in body fluids, as well as other serious side effects that may arise [170]. On the other hand, the high drug-loading capacity of LDHs and their environmental responsiveness also endow hydrogels with precise drug-release behavior, suggesting the potential for personalized and precise therapeutic applications.

3.4 Other 2D nanomaterial-based hydrogels

In addition to the aforementioned 2DMs, transition metal oxide (TMOs), and nitrides [171], MXenes [172], and graphitic carbon nitride (gC_3N_4) [173] are also being explored for the development of smart hydrogels for the treatment of different diseases. TMOs are a class of materials that are composed of a single layer of transition metal atoms, typically in an oxide form, arranged in a two-dimensional lattice. TMOs have potential applications in hydrogels, as they are able to enhance their mechanical and functional properties [174]. TMOs possess a high surface area and exhibit strong binding energy *via* electrostatic and polar-π interactions, making them ideal candidates for carrying bioactive molecules such as anticancer agents and wound-healing compounds [174]. In addition, TMOs have broad absorption in the NIR region, enabling their use in PTT or as thermosensitive carriers for drug delivery, which can be spatially and temporally controlled for synergistic therapy [174]. A notable example is the covalent oxidative polymerization of catechol-functionalized CS mediated by 2D MnO_2 as a polymerization initiator to form light-responsive hybrid hydrogels (Figure 10a) [171]. The designed hydrogel was capable of alleviating the hypoxic tumor microenvironment by catalyzing the conversion of endogenous H_2O_2 into O_2 while simultaneously releasing the anticancer drug DOX and MRI-active Mn^{2+} owing to the catalytic and photothermal properties of MnO_2 (Figure 10b). The increased O_2 levels can help cancer cells overcoming multidrug resistance, thus improving the efficacy of DOX-mediated chemotherapy (Figure 10c). Furthermore, the photoreactive MnO_2 nanosheets endowed the hydrogel with high photothermal performance. The synthesized hydrogel was also able to significantly enhance wound healing *in vivo* in mice bearing a large subcutaneous melanoma tumor, particularly in the case of multidrug-resistant bacterial infections, by efficiently eradicating bacterial invasion and improving the oxidative and inflammatory microenvironment within the wound.

MXenes are an emerging class of the 2DM family, first described in 2011 by Gogotsi and collaborators [175,176]. MXenes have the formula $M_{n+1}X_nT_x$, where "M" denotes the transition metal, "X" denotes C and/or N elements, and "T" represents the surface termination element or group such as −O, −F and −OH, and n can range from 1 to 3 and x can range from 0 to 2 [175]. MXenes possess strong light absorption capability in the NIR region and conversion to heat, making them useful for applications such as tumor ablation or photothermal-responsive drug carriers [172]. 2D MXene (Ti_3C_2) nanosheets were integrated into a low melting point agarose hydrogel network, which was loaded with DOX [172]. Under NIR (808 nm, 2 W/cm^2) light illumination, the temperature in the MXene hydrogel rapidly reached 60°C within a few min despite the very low MXene concentration, resulting in the melting of the hydrogel, DOX release, and killing of melanoma cells. In view of tackling the crucial issue of chronic wound healing in healthcare, a smart drug delivery system with light and magnetic responsiveness was developed by incorporating MXene (Ti_3C_2)-wrapped Fe_3O_4@SiO_2 magnetic NPs into PNIPAM/sodium Alg double-network hydrogels loaded with Ag NPs (Figure 11a) [177]. Under the application of NIR (808 nm, 0.25 W/cm^2) light or alternating magnetic field, the temperature in the hydrogel increased significantly, causing shrinkage and controlled release of the encapsulated Ag NPs, which eliminated bacteria infecting deep wounds. Animal experiments demonstrated that this MXene-based hydrogel served as an effective drug delivery system for the healing of chronically infected wounds (Figure 11b). In the last years, MXene-based hydrogels are effective in repairing various electroactive tissues, such as cardiac, muscle, and nerve tissues. For example, conductive adhesive hydrogels for treating myocardial infarction were developed by incorporating 2D titanium carbide ($Ti_3C_2T_x$) MXene into hydrogels formed from gelatin and dextran aldehyde [178]. The hydrogel demonstrated material properties ideal for cardiac

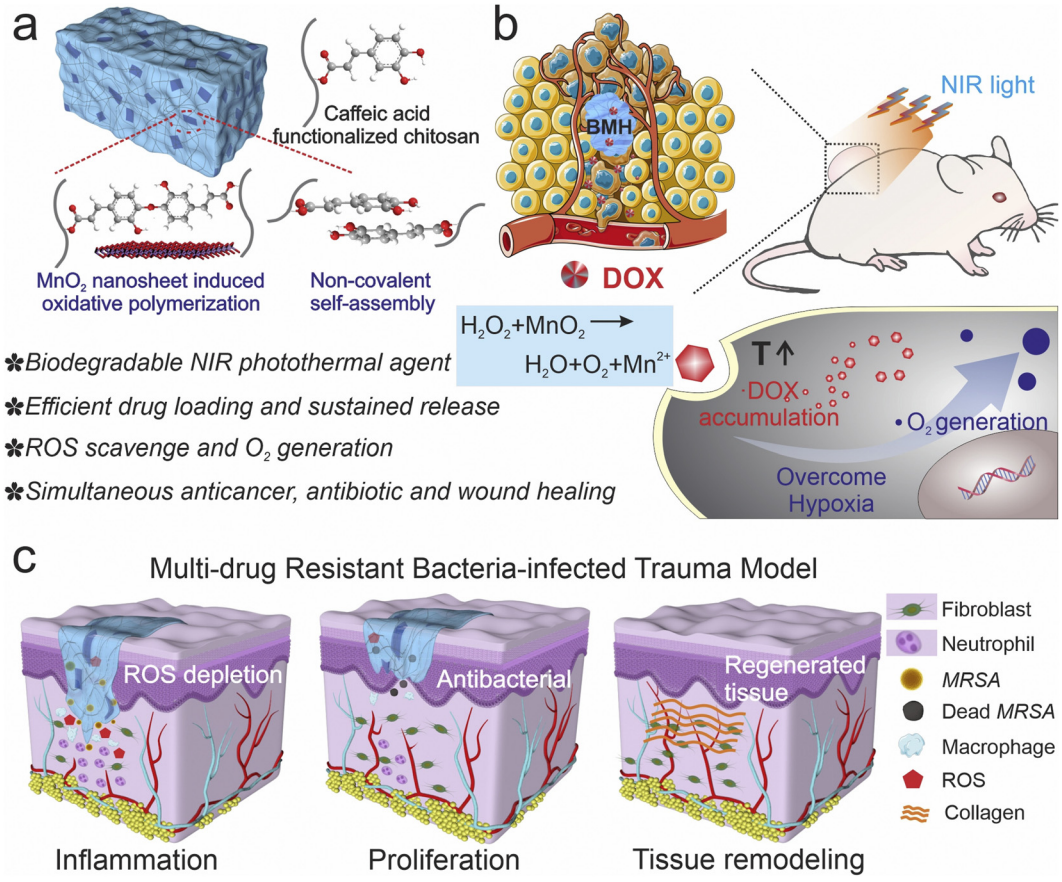

Figure 10: Schematic illustration of MnO_2/CS hybrid hydrogel for effective melanoma treatment and methicillin-resistant *S. aureus*-infected wound healing. (a) 3D illustration of the hydrogel showing the composition and structure and its advantages in simultaneous anticancer therapy and wound closure of multidrug resistance bacterial infection. (b) The hydrogel synergistically enhanced chemotherapy by decomposing endogenous H_2O_2 to accelerate O_2 generation and amplify intracellular DOX accumulation through PTT. (c) Illustration of how this hydrogel can effectively eradicate multidrug-resistant bacteria and improve the permanent oxidative and inflammatory microenvironment to accelerate wound healing *in vivo*. Reproduced with permission [171]. Copyright © 2020, Elsevier.

patch applications, such as high electrical conductivity (18.3 mS/cm), elasticity similar to cardiac tissue (30.4 kPa), strong tissue adhesion (6.8 kPa), high mechanical strength, and uniform MXene distribution. The hydrogel showed high cellular compatibility and promoted the maturation of cardiomyocytes *in vitro*. When injected into a rat model of myocardial infarction, the hydrogel effectively repaired the heart tissue and restored cardiac function, demonstrating its potential as a simple, safe, and efficient platform for myocardial infarction treatment. In addition, Ti_3C_2 can serve as a crosslinking agent to prepare Ti_3C_2/polyacrylamide hydrogel with enhanced mechanical properties [179]. When the Ti_3C_2 content increased from 0.0145 to 0.0436%, the Ti_3C_2/polyacrylamide hydrogel exhibited significantly improved mechanical properties, with the tensile strength increasing from 66.5 to 102.7 kPa, the compressive strength rising from 400.6 to 819.4 kPa, and the elongation at break increasing from 2158.6 to 3047.5%. More importantly, compared to a hydrogel (46.4 mg/g) prepared using an organic crosslinker (*N*,*N*′-methylenebisacrylamide), the Ti_3C_2/ polyacrylamide hydrogel had a uniform porous structure, resulting in a higher drug loading capacity (127.7 mg/g) and faster drug release. Therefore, the Ti_3C_2/polyacrylamide hydrogel showed a cumulative chloramphenicol, an antibacterial agent, release rate of 81% over 360 min, significantly higher than that of the polyacrylamide hydrogel (45%) prepared using the conventional organic crosslinker.

Graphitic carbon nitride is a 2D structure composed of carbon, nitrogen, and hydrogen atoms arranged in a honeycomb lattice structure. Due to its large surface area, biocompatibility, and unique chemical bonding properties, this material has gained popularity among researchers in biomedical applications, such as tissue engineering, wound dressings, and drug delivery [180]. A recent study used gC_3N_4 carrying ciprofloxacin incorporated into a PVA/ gelatin matrix to create a multifunctional drug delivery

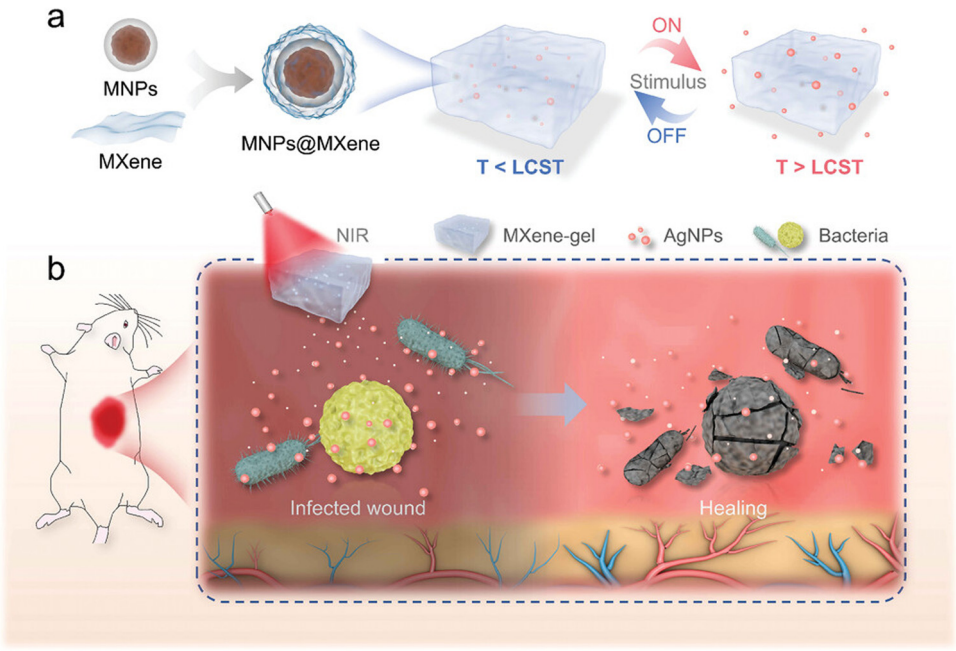

Figure 11: (a) Process to prepare the MXene-based hydrogel and drug-release mechanism under NIR light stimulation. (b) Strategy for treating wounds in diabetic rats exploiting the NIR-responsive hydrogel loaded with Ag NPs. Reproduced with permission [177]. Copyright © 2022, Wiley.

platform [181]. The addition of gC_3N_4 significantly increased drug loading, enhanced the mechanical strength of the hydrogel matrix, and improved its thermal stability. The hydrogel released 62% of ciprofloxacin within 120 min under physiological conditions (pH 7.4). In another study, gC_3N_4 was utilized to prepare a pH-responsive nanocomposite hydrogel containing CS, halloysite, and quercetin [182]. The incorporation of gC_3N_4 into the hydrogel increased the encapsulation efficiency of quercetin to 86%. The composite hydrogel demonstrated a 76% quercetin release at pH 5.4 and exhibited enhanced toxicity against breast cancer cells in comparison to free quercetin, showing its potential as a highly effective therapeutic delivery system. Burn injuries stand as a leading cause of disability globally. The challenge lies in treating wounds, which, due to substantial fluid loss and extensive tissue damage, compromise essential skin functions, making them exceptionally difficult to manage effectively [183]. To meet this challenge, a high-strength hydrogel was prepared for wound dressing, made of a mixed polymer composed of PVA and starch, gC_3N_4 as a filler, and silver-deposited titanium dioxide NPs as antibacterial agents [173]. Incorporating gC_3N_4 significantly enhanced the mechanical strength of the hydrogel. *In vivo* experiments were performed in albino mice. It was evidenced that third-degree wounds healed entirely within a mere 7 days, underscoring the remarkable potential of this wound dressing for the treatment of second- and third-degree burn injuries.

The use of 2DMs has significantly enhanced the properties and practicality of various hydrogels, indicating their potential for further development into commercially viable products and therapies. However, their high cost, difficulty of synthesis, and low yields still hinder their full translation. In addition, beyond therapeutic efficacy, the degradation and metabolism of 2DMs in the body require careful evaluation prior to clinical applications [184].

4 Clinical applications and challenges of carbon nanomaterial- and 2DM-based hydrogels

Several hydrogels have already obtained regulatory approval for healthcare applications, including cancer treatment, aesthetic corrections, and spinal fusion [23]. Until now, around 100 hydrogel formulations have received approval from the U.S. Food and Drug Administration (FDA) and/or the European Medicines Agency [23,185]. Among these, more than 50 are used for facial correction, 25 for spinal cord repair and fusion, 11 for wound dressings, and only 5 for drug delivery (prostate treatment). Notably, over 80 hydrogels are currently

undergoing clinical trials, primarily in the fields of joint repair, myocardial diseases, cancer therapy, and chronic kidney disease [185]. This underscores the vast potential of hydrogels for biomedical applications. However, carbon nanomaterial- or 2DM-based hydrogels have not received FDA approval or entered clinical trials yet, despite extensive laboratory evidence demonstrating their efficacy in treating diseases such as cancer, infection, and diabetes, and in promoting bone repair and wound healing [23,185,186]. A major challenge hindering their clinical translation is their potential long-term accumulation in the body, which may lead to unpredictable safety risks. Although many studies showed evidence that they have low toxicity, can be biodegraded, and do not cause severe short-term adverse reactions, their metabolic pathways *in vivo* remain poorly understood [187,188]. This uncertainty makes it challenging to meet the FDA's stringent safety requirements for biomaterials. Therefore, studies to assess the biocompatibility, degradability in the body and environmental conditions, [189–197] as well as the environmental impact of carbon nanomaterial- and 2DM-based hydrogels are necessary to advance their clinical applications. In particular, their interactions with tissue and potential long-term effects on cellular function must be thoroughly investigated. Ultimately, elucidating their metabolic pathways and excretion mechanisms from the body will be crucial for achieving clinical translation. The structural stability and functional modification of hydrogels in mass production remain difficult to control, making it challenging to establish standardized manufacturing processes and quality control systems [198]. Overall, currently available hydrogel products are still mainly concentrated in the cosmetic field, such as facial correction [23,199] and breast augmentation [200]. Developing low-cost and efficient smart hydrogels for drug delivery or disease treatment remains a huge challenge. The research and development process involves significant costs due to the construction of research platforms (such as equipment acquisition), researcher salaries, unpredictable research timelines, and clinical trial investments. Therefore, selecting safe, reliable, and widely studied materials (such as carbon nanomaterials and 2DMs) for development will greatly shorten the research and development cycle and reduce costs, thereby accelerating the industrialization of smart hydrogels for drug delivery and disease treatment.

5 Conclusion and future prospects

Smart hydrogels are essential in tissue engineering, drug delivery, and disease treatment, offering adjustable structures and diverse response modes depending on the environment [201]. They are particularly useful in drug delivery due to their versatility and adaptability to different needs. While smart hydrogels responsive to pH, temperature, light, and electrical stimulation have been successfully prepared, the development of copolymers using polysaccharide, proteins, and other biological molecules is still in its infancy, with slow responsiveness and low sensitivity, low mechanical strength, and low environmental adaptability being the main issues [29]. Although the introduction of NPs into hydrogels has been shown to effectively enhance their mechanical strength and improve responsiveness, there is still a significant gap between research and clinical application, which could be filled by exploiting the unique properties of carbon and 2DMs. In this context, this review primarily summarized the current research status of carbon-based nanomaterials and 2DMs in the development of smart hydrogels, with a focus on their potential applications in drug delivery and disease treatment. Carbon and 2D nanomaterials have been identified as important components in the advancement of smart hydrogels due to their high specific surface area, allowing the adsorption of large amount of drugs and unique physicochemical properties, endowing hydrogels with responsiveness to various stimuli, such as pH, temperature, light, and electric and magnetic field, thereby allowing superior therapeutic effects for cancer, infection and wound treatment.

There are still some limitations hindering the further development of carbon and 2DM-based smart hydrogels. Carbon and 2D nanomaterials can be functionalized to increase their biocompatibility and exhibit low toxicity to cells. Nevertheless, safety is one of the crucial aspects for clinical translation. More comprehensive *in vivo* studies, including immune responses and biodegradability, are required. Moreover, it is essential to understand the impact of the size, charge, and functionalization of the carbon and 2D nanomaterials on the performance of the hydrogels, in particular drug loading and release, as well as responsiveness to stimuli. In addition, the previous research mainly focused on the development of single-signal response carbon or 2D nanomaterial-based smart hydrogels, which might not be able to accurately control drug release in complex environment such as tumors. Therefore, the development of multifunctional and multi-signal responsive carbon/2D nanomaterial-based hydrogels for drug release and disease treatment will be the primary research direction and challenge in the future. For example, the development of carbon nanomaterial and 2DM smart hydrogels with synergistic effects (*e.g.*, pH/NIR dual-response, electric/NIR dual-response, and NIR/

magnetic dual-response) is highly needed to enhance their performance in complex environment such as tumors.

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Data availability statement: The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

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