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REVIEW

Stimuli-Responsive MXene Nanomaterials for Advanced Antitumor Drug Delivery Systems

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Abstract: MXene, a novel class of two-dimensional nanomaterials, has garnered significant attention for antitumor drug delivery due to its exceptional properties, including high specific surface area, excellent photothermal conversion efficiency, and tunable surface chemistry. Given the limitations of traditional cancer therapies, such as systemic toxicity and poor tumor targeting, MXene-based nanocarriers offer a promising solution. This review summarizes the intelligent responsive nano-drug delivery system constructed with MXene nanomaterials as a drug carrier material, as well as the research progress of endogenous stimulation (pH value and redox microenvironment), exogenous stimulation (photoheat and ultrasound), and multistimulus-responsive MXene nanomaterials. The aim is to provide valuable insights and inspirations for the further development of effective and safe MXene nanomaterials with antitumor properties.

Keywords: MXene, stimuli-response, antitumor, drug delivery system, review

Introduction

Cancer, a complex malignant disease characterized by uncontrolled cell proliferation and metastasis, remains one of the most formidable challenges in global public health.[1] According to the latest global cancer statistics, an estimated 20.9 million new cancer cases and 10 million cancer-related deaths occurred in 2020, with these figures projected to increase substantially in the coming decades due to population aging and lifestyle changes.[2] Traditional cancer therapies, including chemotherapy, radiotherapy, and surgery, have long served as the mainstays of clinical intervention, yet they are inherently constrained by critical limitations.[3,4] For instance, chemotherapy induces systemic toxicity because anticancer drugs circulating throughout the body affect both cancerous and healthy cells, leading to severe side effects such as nausea, alopecia, and immunosuppression.[5] Additionally, the emergence of drug resistance commonly reduces chemotherapeutic efficacy over time. Although radiotherapy is effective for local tumor treatment, it damages surrounding healthy tissues, causing long-term complications.[6] Surgery, while curative for early-stage cancers, is often infeasible for patients with advanced or metastatic disease. Emerging nanocarriers, such as liposomes, polymeric micelles, and inorganic nanoparticles, have shown improved drug delivery but still face challenges in precise control over drug release and biodegradation. MXene nanomaterials, with their unique physicochemical properties, offer a promising alternative for stimuli-responsive drug delivery, addressing these critical clinical needs.

MXene, a novel class of 2D nanomaterials, shows great potential for antitumor drug delivery due to its unique chemical and physical properties.[7–9] Compared with conventional chemotherapy systems, MXene-based drug delivery systems have distinct advantages: It not only boosts drug loading efficiency but also enables precise tumor-site delivery

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to ensure better therapeutic effects. Moreover, MXene uniquely integrates photothermal and photodynamic therapy functions; their synergy significantly enhances tumor-site efficacy, which conventional chemotherapy cannot achieve.[10,11] The origin of MXene dates back to 2011, when scientists first synthesized 2D transition metal carbide and nitride through selective etching from MAX phase materials.[12,13] The MAX phase is a class of layered compounds composed of transition metals, aluminum, and carbon or nitrogen, with good mechanical properties and electrical conductivity.[14] The MAX phase material—ternary layered ceramics defined by the general formula Mn+1AXn, where M denotes an early transition metal, A represents a group IIIA or IVA element, X stands for carbon, nitrogen, or their combination, and n takes values of 1, 2, or 3—is first soaked in hydrofluoric acid and then subjected to sonication for stripping: this process enables selective etching of the A-layer, thereby generating MXene layers with the general formula $M_{n+1}X_nT_x$ (where T_x refers to surface terminal functional groups, mainly including hydroxyl (-OH), fluorine (-F), and oxygen (-O)).[15,16] These MXene layers have metal-like conductivity and hydrophilic surface properties and are also known as “conductive clay”.[12,16] Moreover, the research on MXene is not limited to its basic physicochemical properties but expands to its potential applications in fields such as energy storage and electronic devices. For example, MXene yields excellent performance in electromagnetic interference shielding, supercapacitors, and lithium-ion battery anodes.[17–19] In the field of biomedicine, the load system built using MXenes can achieve precise regulation and sustained release of drugs, which cannot be achieved in the conventional drug delivery mode. For instance, MXenes have shown promising applications in antimicrobial therapy and bone tumor treatment by optimizing drug delivery processes.[20,21]

Stimulus response is a commonly used method to construct intelligent drug delivery systems.[22,23] The differences in the microenvironments between tumor and normal tissues, such as pH, redox reaction potential, and the types of enzymes and small molecule substances, can be used as endogenous stimulation signals. In addition, external physical stimuli, such as temperature and optical and magnetic fields, can be used as exogenous stimulation signals.[24–26] The current review mainly focuses on the application of MXene in various therapeutic modalities, such as photothermal therapy, photodynamic therapy, chemotherapy, etc., and emphasizes the physicochemical properties of MXene, including surface modification, light absorption capability, and surface plasmon resonance effects. However, it is noteworthy that despite the multitude of properties that make MXene a highly promising material for drug delivery, there remains a lack of comprehensive reviews on MXene as a carrier for responsive drug delivery systems.

Compared with previous reviews, this review focuses on stimuli-responsive MXene for antitumor applications. We will first introduce the basic structure and properties of MXene in detail, including its synthesis methods and surface modification strategies. Then, the construction and application of MXene-based intelligent responsive nano-drug delivery systems will be systematically reviewed, covering those responsive to endogenous stimuli, exogenous stimuli, and multiple stimuli. Through a comprehensive evaluation of MXene’s performance, mechanistic analysis, and the challenges faced within these systems, our research endeavors to provide fresh perspectives and innovative ideas for the further development and clinical application of MXene in the field of drug delivery (Figure 1).

Synthesis Approaches of MXene

MXene follows the general formula $M_{n+1}X_nT_x$, where M represents transition metal elements, including titanium (Ti), vanadium (V), molybdenum (Mo), etc. X is carbon (C) or nitrogen (N); n typically takes values of 1, 2, or 3, which determines the dimensionality of the material’s crystal structure. T_x denotes surface-terminal functional groups, mainly including hydroxyl (-OH), fluorine (-F), oxygen (-O), etc. Microscopically, its structure exhibits a typical two-dimensional layered morphology, composed of alternating stacks of transition metal carbide/nitride layers and surface functional groups, resembling a sandwich configuration. Precise control over the synthesis process is essential for tailoring MXene’s structural characteristics, surface properties, and functional capabilities.

Etching Technique

The etching approach, a cornerstone for MXene fabrication, relies on the selective dissolution of the A-layer (typically group IIIA or IVA elements) in MAX phase ceramic precursors by etchants. For instance, during the hydrofluoric acid (HF) etching of Ti_3AlC_2, the reaction $6HF + 2Al \rightarrow 2AlF_3 + 3H_2\uparrow$ facilitates the exfoliation of $Ti_3C_2T_x$.[27,28] Despite yielding high-crystallinity MXene, the corrosive nature of HF restricts its industrial scalability. Recently, milder etching

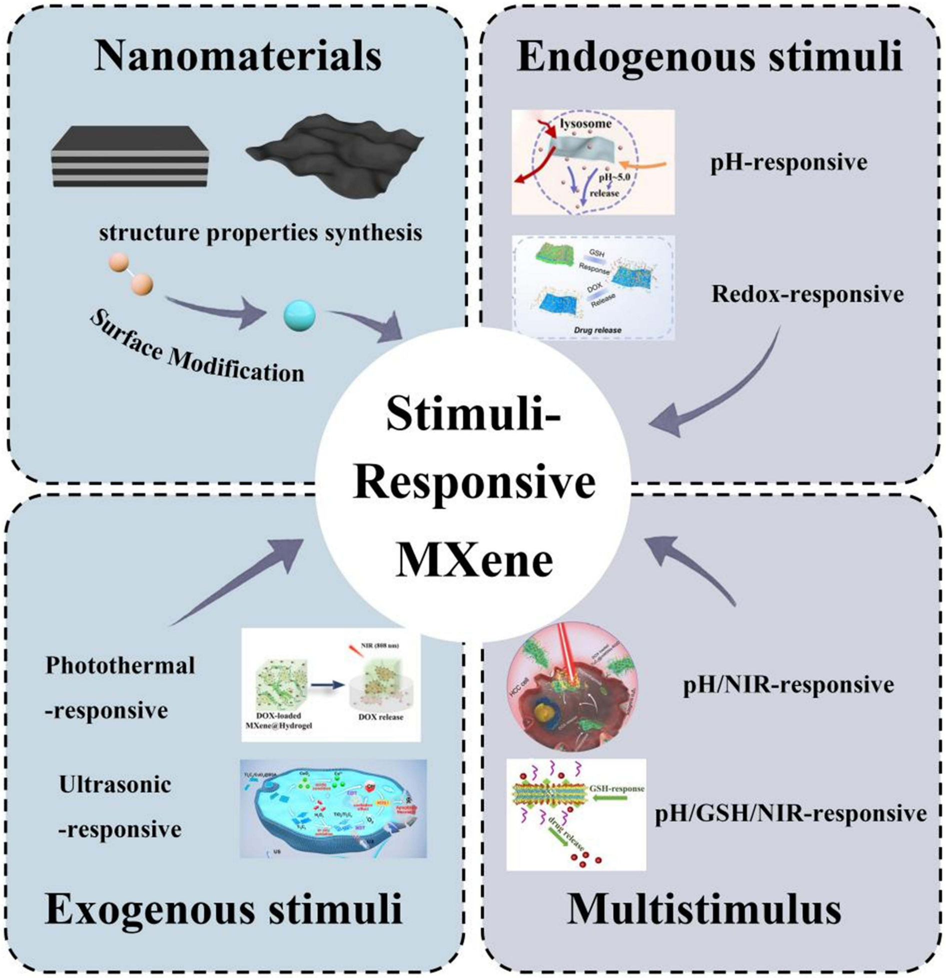

Figure 1 The main topics of review, including endogenous stimulus-responsive, exogenous stimulation-responsive, multistimulus-responsive of MXene drug delivery system.

systems, such as LiF/HCl (1:6 molar ratio) at 40°C for 24 h yielded 95% delamination efficiency. In this system, F^- ions from LiF in HCl solution complex with A-layer metals, promoting layer dissolution. $Ti_3C_2T_x$ synthesized via LiF/HCl maintains high crystallinity while reducing surface defects, and requires no specialized protective gear, enhancing safety and environmental compatibility.[29] Tuning LiF/HCl ratios, reaction temperature, and duration enables precise control over MXene layer number and surface functional group composition, crucial for functional applications.[30]

Ionic Liquid - Based Method

Ionic liquids (ILs), characterized by low vapor pressure, high tunability, and thermal stability, serve as ideal media for MXene synthesis. In IL-based etching, cations and anions interact specifically with MAX phase surfaces, driving A-layer exfoliation. For example, the imidazolium cation of [BMIM][BF_4] adsorbs onto the MAX phase, weakening A-layer transition metal bonding and enabling controlled MXene exfoliation. Compared to conventional etchants, ILs allow precise regulation of MXene surface properties through structural design. Functionalized ILs have been used to prepare -NH_2- rich MXene, enhancing bioconjugation and offering new strategies for targeted drug delivery.[31]

Electrochemical Route

The electrochemical method employs an electrolytic cell to accelerate MAX phase exfoliation via electric field application. During anodic oxidation, the MAX phase anode oxidizes in the electrolyte, with electrons transferred to the cathode and A-layer metals ionized into solution, yielding MXene.[32] Using Na_2SO_4 as electrolyte, few-layer MXene can be rapidly synthesized by etching Ti_3AlC_2 at 3–5 V for 1–2 h. This method enables precise control of MXene thickness and morphology by adjusting current density and electrolysis time.[33] Adding trace surfactants (eg, sodium dodecyl sulfate) to the electrolyte suppresses MXene aggregation, producing monodisperse single layer MXene, which facilitates high-end biomedical applications.[34] Additionally, in-situ surface modification during electrolysis endows MXene with additional functionalities.[35]

Comparison of MXene Synthesis Approaches

Different MXene synthesis methods vary significantly in preparation efficiency, product performance, safety, and scalability. To clarify their application scenarios, the mainstream synthesis technologies are compared across multiple dimensions in Table 1.

Surface Modification Strategies of MXene

The surface properties of MXene play a pivotal role in determining its functionality and applicability in various biomedical fields, especially in antitumor drug delivery systems. To fully exploit the potential of MXene and overcome its inherent limitations, such as poor biocompatibility and lack of targeting ability, surface modification strategies have emerged as indispensable approaches. These strategies endow MXene with enhanced properties, including improved stability, targeted delivery capabilities, and stimuli-responsiveness.

Non-Covalent Modification

Non-covalent modification methods, such as hydrogen bonding, electrostatic interactions, and π-π stacking, are able to achieve efficient modification of MXene's surface without destroying its structure, thus enhancing its performance in tumor therapy. For example, non-covalent modification of $Ti_3C_2T_x$ MXene membranes by solvent treatment significantly enhances their performance in ion sieving by utilizing a hydrogen bonding network to firmly decorate the channels.[36] In addition, the non-covalently modified MXene can not only be used as a synergistic treatment platform for photothermal/photodynamic/chemotherapy but also realize multimodal therapy by loading drugs or nanoenzymes. For example, the Ti_3C_2-DOX nanoplatform modifies adriamycin (DOX) and hyaluronic acid (HA) on the surface of Ti_3C_2 MXene by layer-by-layer self-assembly technique, which achieves efficient tumor killing.[37]

Covalent Modification

The MXene surface is rich in functional groups such as -OH, -F and -O, which can participate in various chemical reactions to realize covalent modifications of MXene.[38,39] Organic ligands (eg, organic salts, catechols, phosphonates, carboxylates, and silanes) are used to functionalize the MXene surface through covalent or non-covalent bonding interactions to modulate the physicochemical and mechanical properties of MXene.[40] For example, covalent attachment of ω-PEG6-COOH ligands to Ti_3C_2 MXene lamellae by esterification reaction can significantly improve their dispersibility in both nonpolar and polar solvents.[41] In addition, aryl diazonium salts can increase the interlayer space of MXene-based nanomaterials by forming stable Ti-O-C bonds covalently anchored to the Ti_3C_2 MXene surface, enhancing the dispersion and improving the specific surface area.[42]

Table 1 Comparison of Mainstream MXene Synthesis Approaches

Synthesis Method	Synthesis Cycle	Product Layer Number/ Crystallinity	Surface Functional Group Controllability	Toxicity Risk
HF Etching Method	2-6h	Few layers (1–5 layers)/High	Low (mainly -F)	High (HF corrosiveness)
LiF/HCl Etching Method	8-12h	Few layers (2–8 layers)/Relatively high	Medium (adjustable -OH/-F)	Low (no free HF)
Ionic Liquid - based Method	12-24h	Single layer/Medium	High (can introduce $-NH_2$, etc).	Low (IL recyclable)
Electrochemical Route	1-3h	Single layer - multi - layer/Medium	Medium (in - situ modification possible)	Low (no toxicity of electrolyte)

Endogenous Stimulus-Responsive MXene Drug Delivery System

The endogenous stimulus-responsive drug delivery system is an intelligent drug delivery system that can identify a specific cellular microenvironment in vivo to accommodate changes in biological tissue and achieve targeted release of the drug.[43–45] This system mainly uses natural conditions or bioactive molecules existing in the body, such as pH, reactive oxygen species (ROS), enzyme activity, and temperature, as stimulation sources to provide appropriate trigger signals for irritant response agents.[46,47] As a 2D material composed of transition metal carbide, nitrogen carbide, or carbon nitrogen carbide, MXene has a high specific surface area, good biocompatibility, and low toxicity, all of which make it a potential drug delivery candidate in the field.[48]

pH-Responsive Drug Delivery System

A pH-responsive drug delivery system is an intelligent drug delivery technology designed to control drug release through pH changes in the local microenvironment. This system is suitable for tumor therapy because many tumor microenvironments have a lower pH than normal tissues.[49–51] For example, the pH outside of tumor cells is usually around 6.8 and that inside cells, such as lysosomes or endosomes, is even lower, around 5.0.[52,53] This pH gradient can be used to trigger drug release.

When designing pH-responsive drug delivery systems, researchers often use pH sensitivity to achieve controlled drug release.[54,55] By binding a drug to an amphiphilic polymer, its surface charge can be altered under specific pH conditions, thus facilitating intracellular uptake and subsequent release of the drug.[56,57] For example, Li et al designed a mild photothermal platform for heat shock protein (HSP) inhibition based on MXene that utilizes Ti_3C_2. The high photothermal conversion ability of nanosheets and quercetin (Qu) as an HSP70 inhibitor released Qu molecules in the acidic environment by pH and depleted the level of HSP70 in tumor cells, thus improving the sensitivity of tumor cells to heat-induced stress, and the rapid release of Qu can be observed in the acidic environment at pH=5.0, with a cumulative drug release rate of 91.34% at 48h (Figure 2).[58] Lu et al synthesized a new 2D material, IL-$Ti_3C_2T_x$ MXene nanosheet, which exhibits strong absorption in the near-infrared region (NIR), with a photothermal conversion efficiency of up to 63.91%, making it a potential photothermal therapeutic agent. The nanosheet has significant pH sensitivity, which can effectively release drugs in the acidic tumor microenvironment and enhance the tumor therapeutic effect.[59]

Another strategy is to use pH-sensitive chemical bonds, such as acid-sensitive hydrazone or imine bonds, which break under acidic conditions to trigger drug release.[60,61] For example, MXene was introduced into the polyurethane matrix modified by the chemical aminolysis technology to form the Mxene@APU/PCL film. The release of rutin from the matrix at the rate of 79.3% at pH 5.6.[62]

Redox-Responsive Drug Delivery System

The redox reaction plays an important role within the cell, not only participating in normal physiological processes, such as signaling, cell proliferation, and differentiation, but also being closely related to the occurrence and development of various diseases.[63–65] For example, ROS as an important oxidant, plays a key role in cell signaling. However, its overproduction can generate oxidative stress, which can lead to various pathological states, including cancer, diabetes, atherosclerosis, and autoimmune diseases.[66–68] Therefore, the development of drug delivery systems that can respond to changes in redox status in vivo is important for improving the specificity and efficacy of drug therapy.

Recently, drug delivery systems based on redox responsiveness have been favored by researchers for their ability to achieve spatiotemporal control of drug release. These systems generally use ROS-and glutathione (GSH)-sensitive chemical bonds or functional groups, such as disulfide, selenium, and thioether bonds, to design drug carriers, such as nanocarriers or microspheres [32–34]. When these vectors are exposed to high concentrations of ROS or GSH, specific chemical bonds or functional groups are broken or oxidized, thus triggering drug release.[69–71] For example, Wu et al loaded DOX onto $Ti_3C_2T_x$ MXene under intermolecular forces and then assembled a PMAsh shell layer-by-layer on $Ti_3C_2T_x$-DOX by using the disulfide bond cross-linking method. Once the drug-loaded nanosystems were internalized by the tumor cells, the PMAsh shells were deconstructed upon encountering GSH to release the DOX drug. As a result, the DOX release rate was 8.2% after 24 h in the pH 5.5 solution. When exposed to the slightly acidic environment at pH 5.5 containing GSH, the DOX release rate

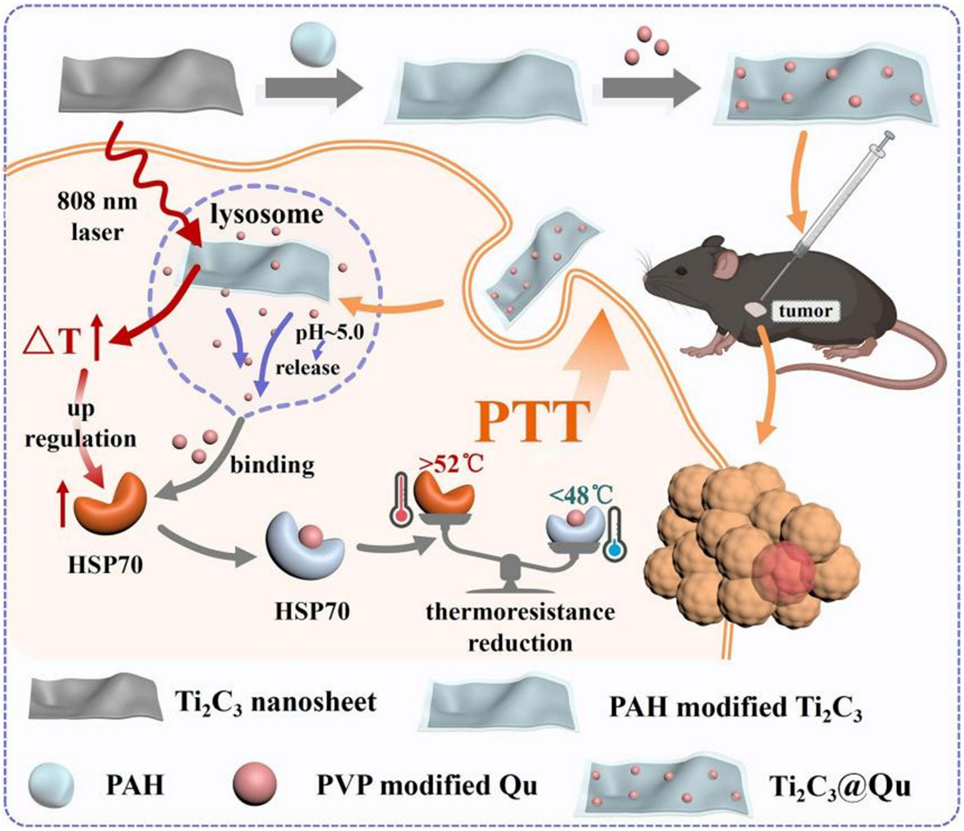

Figure 2 Schematic illustration of the pH-responsive Ti_3C_2@Qu for sensitised photothermal therapy.[57] Copyright 2024, Elsevier.

increased dramatically to 39.5% after 24 h. (Figure 3a).[72] Chen et al developed a MXene/silver nanoparticle ($Ti_3C_2T_x$/Ag) film, which presented the combination of $Ti_3C_2T_x$ MXene and the excellent surface-enhanced Raman scattering (SERS) properties of noble metal materials, as a nanocarrier for traceable drug delivery. When the anticancer drug DOX was loaded onto the $Ti_3C_2T_x$/Ag film surface, drug tracking and monitoring were achieved using SERS. When the concentration of GSH was as high as 50 mM, the intensity of 4-MBA decreased to about 20% of the original intensity after 12 h, which indirectly reflected the roughly 80% reduction in the original loading of DOX (Figure 3b).[73]

Exogenous Stimulation-Responsive MXene Drug Delivery System

Exogenous stimulus responsiveness usually refers to the ability of the system to respond to external stimuli, such as temperature, pH, light, magnetic fields, or ultrasound, which triggers drug release. It is fundamentally distinct from endogenous stimulus responsiveness—the latter relies on intrinsic biological cues inherent to the tumor microenvironment (eg, acidic pH ~6.8–5.0, high intracellular glutathione (GSH) levels) to autonomously trigger drug release without external intervention. In contrast, exogenous systems require active, controllable external triggers to regulate release timing and location, avoiding passive activation in normal tissues and enhancing targeting precision. Notably, pH, often mistakenly categorized as an exogenous stimulus, belongs exclusively to endogenous cues: it is a naturally occurring microenvironmental difference between tumors and normal tissues (normal tissue pH ~7.4), not a physically controllable external signal like light or ultrasound.

With high photothermal conversion efficiency, MXene is able to efficiently convert absorbed light energy into heat.[74] Under NIR, the heat generated by MXene can trigger the release of drugs for precise treatment. In addition, recent research advances have shown that MXene materials possess the characteristics to act as acoustic sensitisers and have significant potential in ultrasound-responsive drug delivery systems.[75]

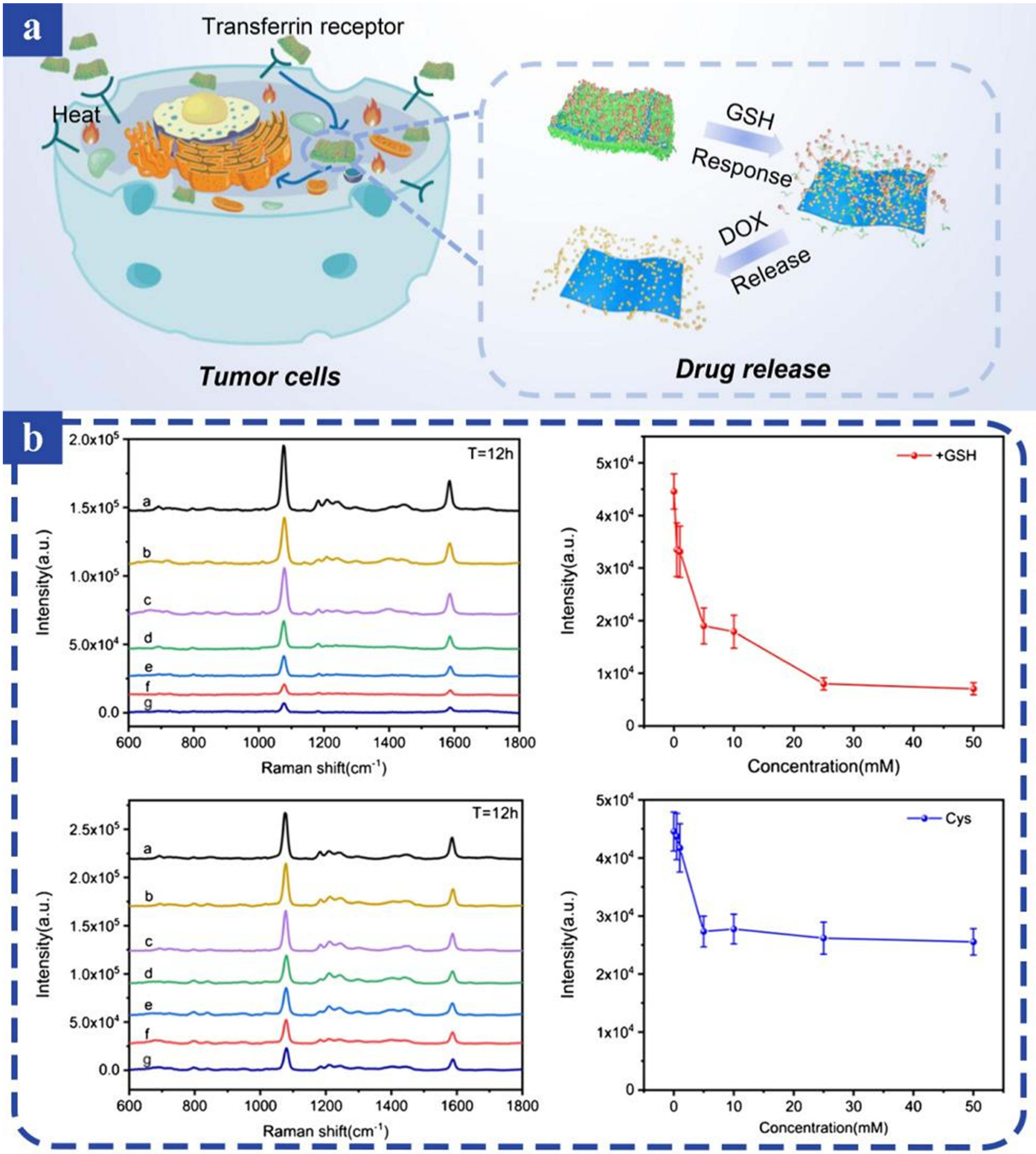

Figure 3 (**a**) Schematic representation of GSH-responsive $Ti_3C_2T_x$ -DOX-PMAsh-Tf nanodrugs.[71] Copyright 2023, American Chemical Society. (**b**) DOX release profiles of HAP/CS/HA/MXene/AuNRs upon NIR laser irradiation.[72] Copyright 2021, Elsevier.

Photothermal-Responsive Drug Delivery System

A photothermal-responsive transmitter system is a novel transmitter technology that uses the photothermal effect to achieve precise release and control of drugs.[76,77] It is mainly based on the phenomenon of photothermal conversion, that is, the absorption of light energy of substances to produce temperature rise, which triggers the phase change or chemical

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reaction of substances. This technique enables precise control of the drug delivery system by rationally regulating the intensity, time, and wavelength of the illumination.[78–80]

The photothermal conversion capability of MXene is mainly derived from its unique electron-phonon and phonon-phonon coupling processes. The strong electron–phonon coupling in MXene can lead to lattice heating on a timescale of several femtoseconds to nanoseconds. Furthermore, by controlling its thickness, chemical surface terminals, sheet size, and annealing conditions, thermal boundary conductivity can be effectively regulated to optimize thermal dissipation, which is critical for heat management in engineered photothermal and thermoelectric applications.[81,82]

In addition, MXene is characterized by a high surface area, good biocompatibility, wide spectral absorption range, and efficient photothermal conversion. These properties afford it great potential in photothermal therapy (PTT) and photothermal-responsive drug delivery, especially in the non-invasive treatment of cancer and other diseases. For example, Dong et al prepared a drug-loaded MXene/agarose hydrogel with nanosheets and therapeutic drugs embedded in a low-melting-point agarose hydrogel network (MXene@Hydrogel). With low concentrations of MXene (20 ppm), MXene@Hydrogel can rapidly rise to 60°C with NIR irradiation and melt to release the encapsulated drug (Figure 4a).[83]

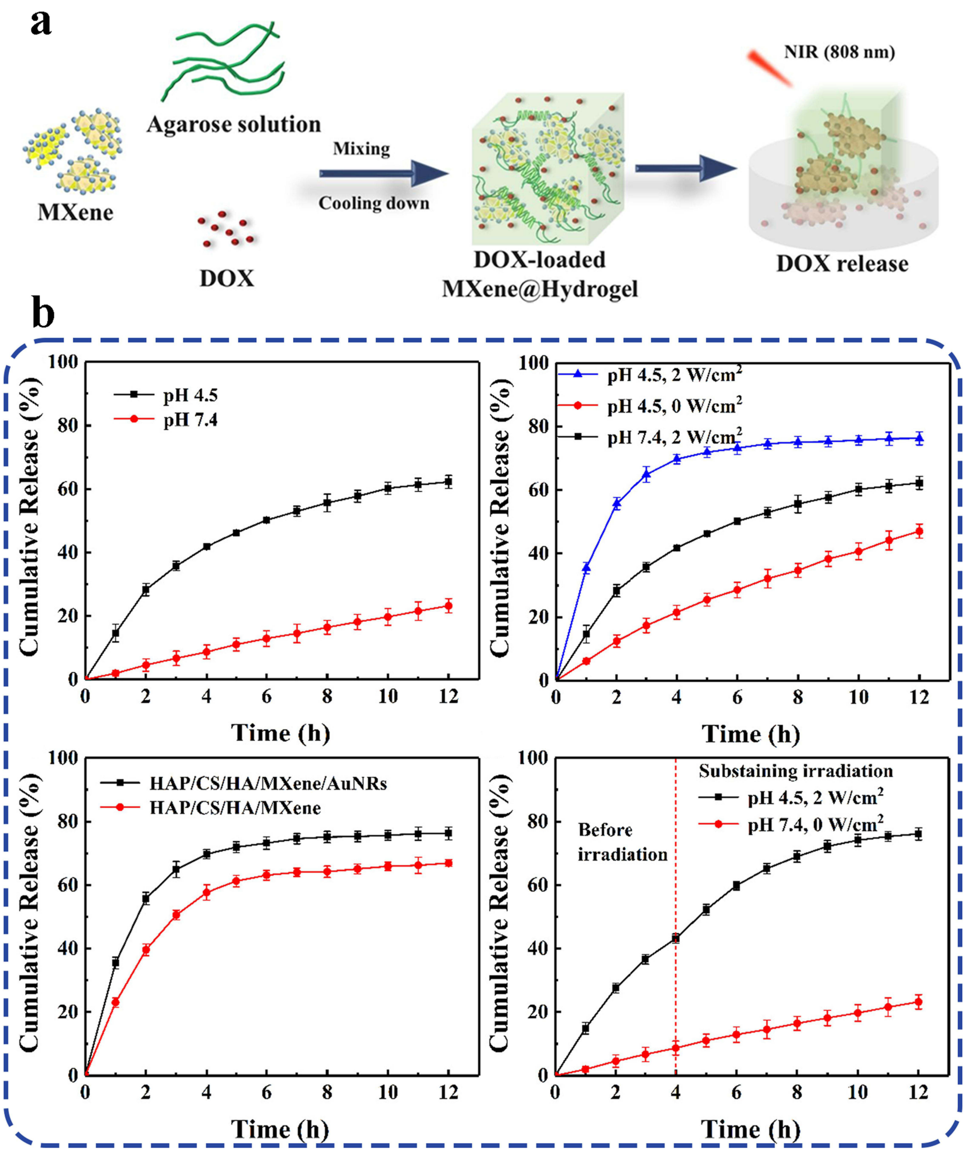

Figure 4 (**a**) Schematic preparation of DOX-loaded MXene@Hydrogel for NIR controlled drug release.[82] Copyright 2021, Elsevier. (**b**) DOX release profiles of HAP/CS/HA/MXene/AuNRs upon NIR laser irradiation.[84] Copyright 2021, Elsevier.

Wu et al applied the chitosan/hyaluronic acid multilayer deposition technology to the hollow hydroxyapatite (HAP) surface to inhibit the explosive release of DOX in the initial delivery stage. In addition, they accurately installed MXenes and AuNRs on the hybrid matrix surface, which significantly improved the photothermal conversion efficiency of the microcapsules. Such HAP/CS/H/A/M/Xene/AuNR microcapsules show excellent pH/NIR-responsive drug delivery performance, mainly due to the electrostatic collapse between the chitosan and hyaluronic acid multilayers, HAP solubility in acidic environments, and co-enhanced photothermal effects between MXene and AuNRs, with great potential in the field of remote drug delivery.[84]

Currently, the stimulus-responsive hydrogels on which therapeutic protein delivery achieved through stimulus-responsive hydrogels mainly depend mainly on self-degradation, passive diffusion, and responsiveness to disease-related cues. However, there are still significant challenges in pursuing high-spatiotemporal-precision protein-based drug delivery to achieve the “on-demand” manipulation of in vivo target cell populations. To overcome these challenges, using an innovative approach of embedding Ti in an agarose hydrogel, Wang et al successfully constructed an injectable and NIR-photoresponsive composite hydrogel. This design provides a high spatiotemporal precision for achieving remote control of protein drug delivery (Figure 4b).[85]

Ultrasonic-Responsive Drug Delivery System

An ultrasonic-responsive drug delivery system refers to a drug delivery method that physically or chemically changes the drug carrier (such as nanoparticles and microbubbles) through ultrasonic stimulation to release drug molecules and achieve the purpose of treatment.[86,87] This system is mainly based on the mechanical, thermal, and cavitation effects generated by ultrasonic propagation in the medium, which can destabilize the drug carrier and promote drug release.[88]

Compared to conventional surgical or invasive treatments, an ultrasound-responsive delivery system uses ultrasound as an external stimulation source without the need for skin or tissue incision, thus being a non-invasive and low-risk treatment.[89] In addition, this system facilitates the accurate adjustment of ultrasound parameters (such as frequency, intensity, duration, and focus location). This allows the drug to be released at the desired time and location, improving its therapeutic effect and reducing its unnecessary exposure.[90] More importantly, ultrasound can penetrate the skin and tissue and reach deeper parts, and combined with ultrasound imaging technology, it can accurately identify and locate the target tissue. The targeted drug delivery achieved through this ultrasonic stimulation not only improves the utilization rate of drugs but also reduces the side-effects of drugs to normal tissue.[91,92]

Since the discovery of Ti_3C_2 MXene, its manufacturing process simplicity, low cost, and excellent physical and chemical properties have attracted widespread interest in scientific research and industry. With its unique 2D layered structure, excellent electron and ion transport capacity, and adjustable electronic structure, this material shows potential applications in multiple fields. Recent research has focused on the surface modification of MXene; the introduction of specific functional groups, such as fluorine (-F), double bond (-C=O), and hydroxyl (-OH) groups, has significantly enhanced the electronic properties of MXene.[93,94]

A typical metallic Ti_3C_2 MXene undergoes a significant change in its electronic structure upon the introduction of these surface-terminated groups, transforming it into a narrow-bandgap semiconductor material. This transformation of properties opens up new possibilities for the application of Ti_3C_2 MXene in photocatalysis, electrocatalysis, and supercapacitors. Qin et al reported that Ti_3C_2 MXene nanosheets surface-modified in the presence of specific surface-terminating groups, such as -F and -OH, exhibited extremely narrow bandgaps (~0.75 V), which indicates their potential for SDT applications.[95] For example, Geng et al proposed a novel acoustic immunotherapy based on a $Pd^{\delta+}$ single-atom catalyst for enhancing the acoustic kinetic response to an immunosuppressive tumor microenvironment (TME). Ti_3C_2 MXene nanosheets enriched with Ti vacancies were used to develop a Pd-C3 single-atom catalyst that overcame GSH overexpression and hypoxia in the TME by facilitating electron–hole separation, rapid depletion of overexpressed GSH, and catalytic decomposition of endogenous H_2O_2.[96] Li et al developed Ti_3C_2 MXene nanosheet-based acoustic sensitizers and H-Ti_3C_2 MXene with higher oxygen defects through a two-step method of chemical stripping and high-temperature treatment. These increased oxygen defects significantly enhanced the separation efficiency of electrons and holes under ultrasound irradiation—which, in turn, improved the therapeutic efficacy of SDT (Figure 5).[97] Although MXene nanosheets have been widely used in the field of acoustic dynamics, their application in ultrasound-responsive

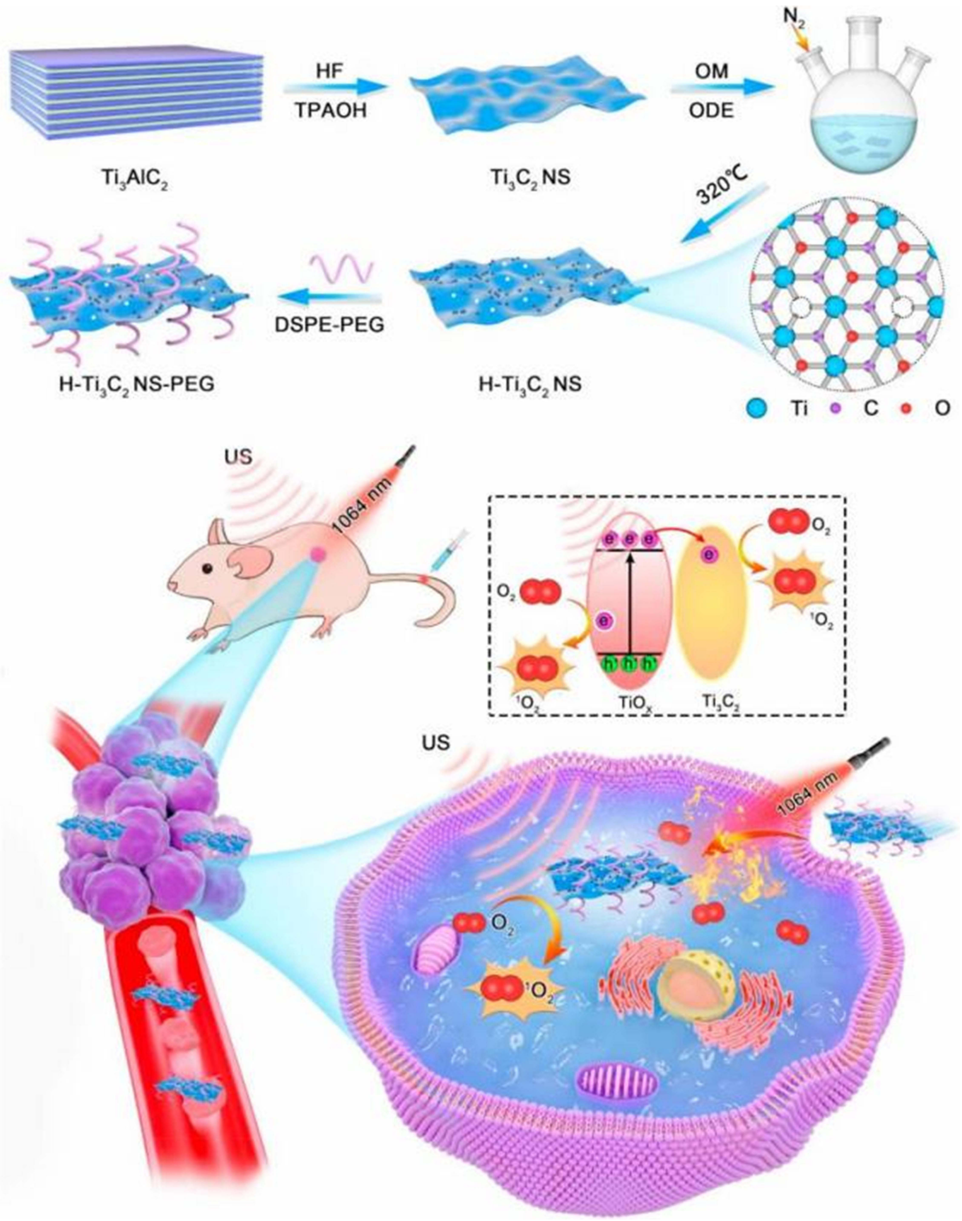

Figure 5 Preparation of acoustic sensitiser H_H-Ti_3C_2 nanosheets by chemical stripping and high temperature treatment methods.[96] Copyright 2021, Elsevier.

drug delivery systems has been rarely studied. Future studies could further explore the use of MXene nanosheets in ultrasound-responsive drug delivery systems as well as their effectiveness and mechanism in the treatment of different diseases.

Multistimulus-Responsive MXene Drug Delivery System

A multistimulus-responsive drug delivery system can respond to multiple environmental stimuli simultaneously or sequentially to control drug release. This system can release drugs to specific patient sites in response to changes in the microenvironment or external regulatory signals produced by different parts of the body and diseases.[98,99] In addition, it can provide precise drug release according to the physiological and therapeutic needs. Table 2 shows the single-responsive and multiple-responsive MXene drug delivery systems.

MXene has excellent photothermal conversion efficiency and is often used to construct multiresponse-stimulated drug delivery systems using NIR combined with pH and ROS/GSH. For example, our group previously developed a Ti_3C_2

Table 2 The Single-Responsive and Multiple-Responsive MXene Drug Delivery Systems

Materials	Response Type	Drug	Experimental Model	Ref.
Ti_3C_2@Qu nanocomposites	pH	quercetin	B16 cells	[58]
MXene@EGCG	pH	epigallocatechin gallate	4T1 cells	[100]
$Ti_3C_2T_x$-DOX-PMAsh-Tf	GSH	DOX	Human hypopharyngeal carcinoma cells	[72]
MXene@Hydrogel	NIR	DOX	Mouse melanoma cells	[83]
MXene-DNA hydrogel	NIR	DOX	HeLa cancer cells	[101]
Cellulose/MXene hydrogels	NIR	DOX	HepA1-6, HepG2, U-118MG and U-251MG	[102]
PEG-MXene@DDP@R837	NIR	Imiquimod and cisplatin	Lewis tumors	[103]
Ti_3C_2-PEG-OVA-Mn^{2+}	NIR	Ovalbumin	LM8 cells	[104]
G-M@F/C microcarriers	NIR	5-FU and Cangrelor	CT26 cells	[105]
HA-PLGA/MX NPs	NIR	Paclitaxel	B16F10 and L929 cells	[106]
MS/Nb_2C MXene-BG-SNO	NIR	NO	Saos-2	[107]
Ga/V_2C-NH_2	NIR	Gallium	HCT116 and HCT8	[108]
CS/β-GP/Ti_3C_2@AuNRs	pH/NIR	DOX	MCF-7 cells	[109]
IL-$Ti_3C_2T_x$ MXene@DOX	pH/NIR	DOX	4T1 cells	[110]
Ti_3C_2@mMSNs-RGD	pH/NIR	DOX	SMMC-7721 cells	[111]
Ti_2N-SP-DOX	pH/GSH/NIR	DOX	MCF-7 cells	[112]
Ti_3C_2-DOX	pH/NIR/ enzyme	DOX	HeLa cancer cells	[37]

MXene nanocomposite therapeutic platform for pH/NIR-triggered controlled release of HSP90 inhibitors to enhance tumor-specific mild PTT synergistic chemodynamic therapy. The nanosystem featured modified FA-PEG-SH as an active target carrier to tumor tissues, Garcinia Cambogia (GA) as an inhibitor of HSP90, and self-assembled CuO_2 as a therapeutic factor for chemodynamic therapy. Under irradiation of the TME and NIR, the nanocomplex effectively inhibited HSP90 expression by releasing GA, enhancing the therapeutic effect of mild PTT.[113]

Wen et al constructed a PEG-modified DOX delivery system for $Ti_3C_2T_x$ MXene using $Ti_3C_2T_x$ MXene modified with PEG via the linker cystamine dihydrochloride disulfide bond (-SS-). DOX was released at a rate of 84.4% in response to pH/GSH dual-responsive stimulation, which is higher than that in the physiological environment of normal cells, suggesting that this drug delivery system is a promising contender for drug delivery and stimulus-responsive release.[114] Li et al synthesized a pH/GSH/NIR-responsive drug-releasing Ti_2N MXene nanosystem, where the unique structure of the Ti_2N nanosheets provided an ultra-high drug-loading capacity of 796.3% and an excellent NIR photothermal conversion efficiency of 41.6% for dual-strategy synergistic tumor therapy.[115]

Biocompatibility and Outlook of the MXene Drug Delivery System

MXene, a 2D composite based on transition metal carbides, nitrides, and carbon-nitrides, has attracted much attention since its introduction in 2011 due to its unique electrical and mechanical properties, as well as hydrophilicity. Especially in biomedical applications, MXene has great potential, including sensors, antimicrobial agents, tissue engineering, bio-imaging, and environmental applications.[116–118]

Biocompatibility of MXene

In terms of biocompatibility and safety, MXene exhibits low cytotoxicity and flat biocompatibility. However, it shows some toxicity for stem cells and embryos, which is related to the material dosage, cell type, mode of exposure, and type of MXene.[119] Note that the biocompatibility of MXene can be improved through chemical modification. Researchers can modulate the interaction of MXene with organisms by introducing specific functional groups or biomolecules, such as PEG, peptides, or antibodies, to reduce its nonspecific binding and toxic reactions. This surface modification strategy not only improves the biocompatibility of MXene but also offers the possibility of its specific applications in biomedical fields, such as the targeted delivery of drugs and cellular imaging.[120–122]

Despite preclinical progress, MXene drug delivery systems face critical clinical translation barriers: most studies focus on MXene's short-term (2–4 weeks) in vivo behavior, leaving long-term biodegradation mechanisms and clearance pathways unclear—its transition metal-based degradation products (eg, titanium, vanadium ions) may accumulate, but long-term (≥6 months) degradation rate, product types/concentrations, and excretion pathways lack systematic research; unmodified MXene is easily phagocytosed by the reticuloendothelial system and accumulates in the liver/spleen, and even PEG-modified MXene with particle size >5 nm struggles to pass renal filtration, risking long-term organ inflammation or dysfunction; laboratory synthesis methods (etching, ionic liquid-based, electrochemical) have scalability limits—HF etching is unsafe for scale-up, LiF/HCl needs batch operation with long cycles, ionic liquid-based methods are costly, and electrochemical routes have unstable product quality (eg, ±15% fluctuation in single-layer MXene proportion) that fails to meet clinical quality standards.

Outlook for the Development of MXene Drug Delivery Systems

To promote clinical translation, future research should: conduct long-term (6–12 months) in vivo tracking with techniques like ICP-MS/TEM to clarify MXene's degradation kinetics, clearance pathways, and long-term toxicity, and explore modification with biodegradable polymers (eg, PLGA) to accelerate degradation/clearance; optimize MXene's surface modification (eg, targeting ligands like RGD) to boost tumor accumulation, regulate its particle size/morphology (eg, <5 nm quantum dots for renal clearance), or use "stealth" materials (eg, specific molecular weight PEG) to reduce RES recognition, thereby lowering organ accumulation; optimize existing synthesis methods (eg, electrochemical parameters for stability, continuous flow reactors) and explore low-cost, eco-friendly alternatives (eg, fluorine-free etching) or raw material recycling to improve scalability; integrate MXene with diagnostic technologies (eg, MRI, photoacoustic imaging) for "diagnosis-treatment integration" or combine it with immunotherapy/gene therapy to expand functions and achieve synergistic antitumor effects.

Conclusion

This review summarizes the research progress of stimuli-responsive MXene-based antitumor drug delivery systems, covering endogenous (pH, redox)-, exogenous (NIR, ultrasound)-, and multistimulus-responsive systems: endogenous ones rely on MXene's surface functional groups to respond to the tumor microenvironment for targeted drug release, exogenous ones leverage MXene's excellent NIR photothermal conversion efficiency and ultrasonic sensitivity to achieve "on-demand" delivery and synergistic therapy, and multistimulus ones integrate these advantages to improve precision; MXene's 2D structure ensures ultra-high drug loading and surface modification enhances biocompatibility and targeting, though clinical translation is hindered by unclear long-term biodegradation, potential organ accumulation, and scalable synthesis limitations, while the systems still offer a promising direction to overcome traditional chemotherapy limitations and advance personalized tumor treatment.

Data Sharing Statement

As this article is a review paper, no research data were generated.

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Disclosure

The authors declare no conflicts of interest in this work.

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