Chinese Chemical Letters 36 (2025) 110072

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Polymeric micelle-hydrogel composites design for biomedical applications

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ARTICLE INFO

Article history:
Received 16 April 2024
Revised 26 May 2024
Accepted 30 May 2024
Available online 31 May 2024

Keywords:
Polymeric micelle
Hydrogel composites
Incorporation methods
Biomedical applications
Local tumor treatment
Tissue engineering

ABSTRACT

Designing advanced hydrogels with controlled mechanical properties, drug delivery manner and multi-functional properties will be beneficial for biomedical applications. However, the further development of hydrogel is limited due to its poor mechanical property and structural diversity. Hydrogels combined with polymeric micelles to obtain micelle-hydrogel composites have been designed for synergistic enhancement of each original properties. Incorporation polymeric micelles into hydrogel networks can not only enhance the mechanical property of hydrogel, but also expand the functionality of hydrogel. Recent advances in polymeric micelle-hydrogel composites are herein reviewed with a focus on three typical micelle incorporation methods. In this review, we will also highlight some emerging biomedical applications in developing micelle-hydrogel composite with multiple functionalities. In addition, further development and application prospects of the micelle-hydrogels composites have also been addressed.

1. Introduction

Hydrogels are three-dimensional networks of cross-linked polymer chains that can retain large amounts of water. They are structurally similar to the extracellular matrix (ECM), and therefore have wide-ranging biomedical applications [1,2]. Due to their high flexibility and elasticity, hydrogels reduce friction in tissues, and aid protein adsorption and cell adhesion. However, the poor mechanical property and low elongation are the major limitations of hydrogels [3,4]. In addition, the hydrophilic gels cannot transport hydrophobic drugs, which also limits their clinical applications. To overcome these drawbacks and expand the applications of hydrogels, nanoparticles such as polymers, metals, inorganic and carbon-based nanomaterials are incorporated into the hydrogel network [5,6]. These nanocomposite hydrogels retain the elasticity and mechanical strength of conventional hydrogels, and have the additional capacity to transport hydrophobic drugs [7].

Compared to the other nanoparticles, polymer-based nanocomposites have great application due to their good biocompatibility and ability to load hydrophobic/hydrophilic drugs, proteins, and other bioactive agents [8]. Polymeric micelles are often used as nanofillers to synthesize hydrogel nanocomposites [9-12]. The hydrophobic core can encapsulate various drug molecules, which can then be released in a sustained manner. Besides, the polymeric micelles in particular are biocompatible, easy to prepare with improved drug stability and solubility [13]. However, micelles are easily to disassemble in blood circulation, leading to premature release of drug. Thus, incorporation polymeric micelles into hydrogel network can not only immobilize and delivery hydrophobic drugs in a more controlled manner but also improve the stability of the micelles in the blood circulation [14,15]. Polymeric micelles hydrogel composites are hydrogel networks containing micelles and can be assembled through physical or chemical crosslinking. Polymeric micelles also increase the biocompatibility of the micellar hydrogel, and the reversible dislocation of polymeric micelles along with the chain slippage allows for effective disappearance of crack energy in the hydrogels, resulting in high stretchability and excellent compressive modulus [16,17]. In addition, the polymeric micelles endow hydrogels with stimuli-responsive properties and even enhance the synergistic effects of each component [18-20].

Therefore, properties and applications of micelle-hydrogel composites may be enhanced by the properties of hydrogel building blocks and the micelles blocks incorporated in the network. Innovative combining the completely different materials of micelles and hydrogels was believed to generate both structural and application diversity. Moreover, such enhancement expands the application ad-

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https://doi.org/10.1016/j.cclet.2024.110072
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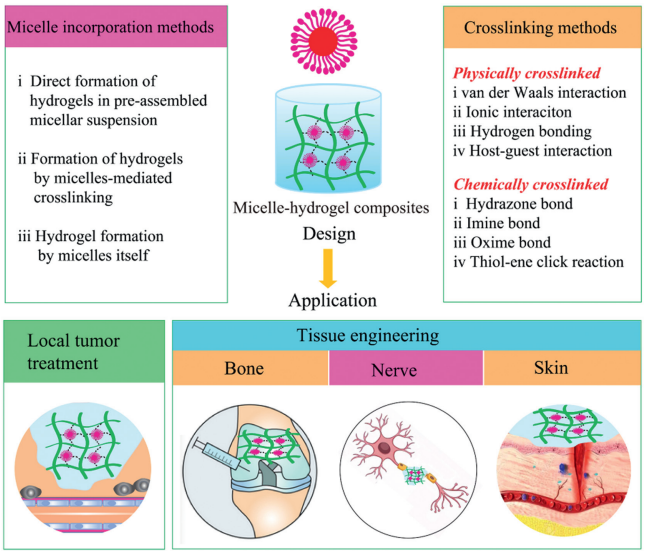

Fig. 1. Schematic diagram of polymeric micelle hydrogel incorporation methods and their applications.

vantages and development prospects of micelle hydrogel composites.

In this review, as shown in Fig. 1, we summarized three typical methods to obtain micelle hydrogels composites and discussed their advantages and disadvantages as well as applications in local tumor treatment and tissue engineering. In addition, further development and application prospects of the micelle-hydrogels composites have also been addressed.

2. Design of polymeric micelle hydrogel composites

In terms of assembling micelles-hydrogels composites, different micelles embedding methods have been developed with different micelle-hydrogel architectural organization and characteristics [21,22]. There are three main micelles-hydrogel combined strategies that can be applied when designing functional micelle-hydrogel composites. As shown in Fig. 2, homogeneous polymeric micelle hydrogel networks can be fabricated by: (1) direct hydrogel crosslinking with polymer precursor in pre-assembled micelles suspension allowing micelles pre-distribution in the resulting network; (2) hydrogels assembly *via* micelles as matrix/network crosslinkers; (3) *in situ* hydrogel formation by assembled micelles themselves.

The three methods of incorporation micelles into hydrogels have their own advantages and disadvantages [21]. The first method of physically mixing micelles with hydrogel precursors is the simplest method. The micelles can be assembled in advance, so theoretically any micelles can be used for mixing without affecting hydrogel formation. Thus, multifunctional micelles can be combined to expand the versatility of the hydrogel. The disadvantage of this method is that the micelles may leak from the hydrogel due to weak interaction. The second method is hydrogel formation by micelles crosslinking. The advantage of this method is that the cross-linking density of the hydrogel can be controlled by adjusting the amounts of micelles, which can affect the mechanical properties of the hydrogel and drug release behavior. The disadvantage of this method is that the surface of the micelles needs to be specially designed with some chemical bonds that can be crosslinked. The third method is hydrogel formation by micelles themselves transition under external conditions. The advantage of this method is that additional hydrogel precursor is not needed. The composition of hydrogel is single without chemical reactions, and the gelling method is simple by heating or adding solvent. But the disadvantage is that the possible low mechanical strength of hydrogel. Besides, this method requires specific polymers, such as temperature sensitive polymers.

Among the three micelle incorporation methods mentioned above, hydrogel formation by micelles crosslinking is particularly noteworthy. Polymer micelles can be chemically or physically crosslinked as part of the hydrogel network structure, or can be directly introduced into the hydrogel network as fillers through physical mixing [23,24]. As illustrated in Fig. 3, The physical interactions between polymer/micelles may be hydrogen bond, electrostatic interaction, host-guest interactions and so on [25]. As a result of the physical crosslinking exhibited weak, transient, and reversible interactions, micelles hydrogels mainly engineered with self-healing abilities. The chemically crosslinked polymeric micelle hydrogel composites are often obtained by dynamic covalent crosslinks between hydrogel polymers or hydrogel polymer/micelles polymers [26]. Typical dynamic covalent cross-links in micelles hydrogels include imine bond, oxime bond, hydrazone bond and so on [27,28]. The introduction of micelles into the hydrogel network by cleavable chemical bonds can endow the micelle hydrogel with external stimuli responsibility, such as pH, temperature, redox, reactive oxygen species (ROS) sensitivity. The follow-

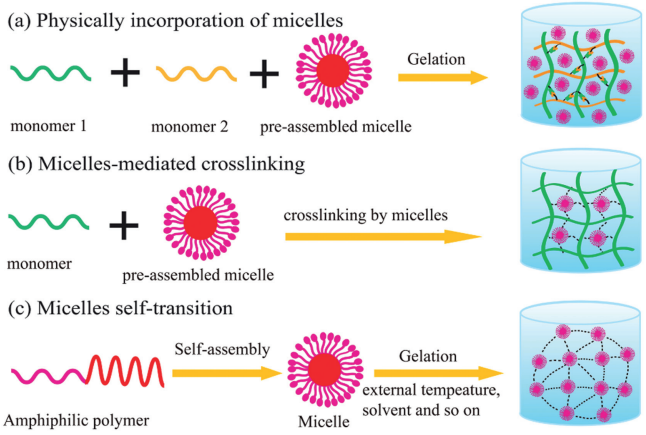

Fig. 2. Typical design methods to obtain homogeneous polymeric micelle hydrogel composites.

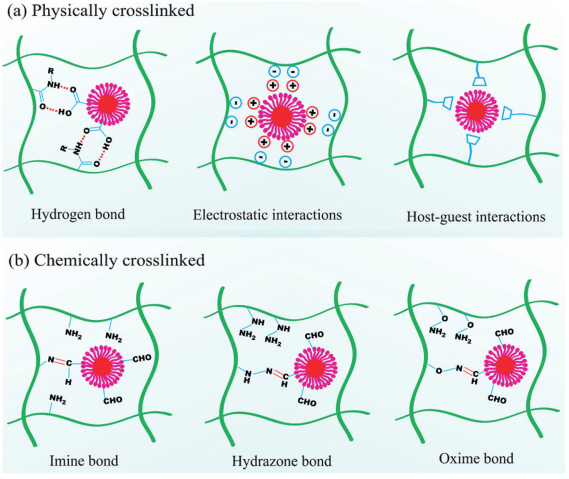

Fig. 3. Schematics of micelle-hydrogel network interactions including physical cross-links and chemical dynamic covalent cross-links.

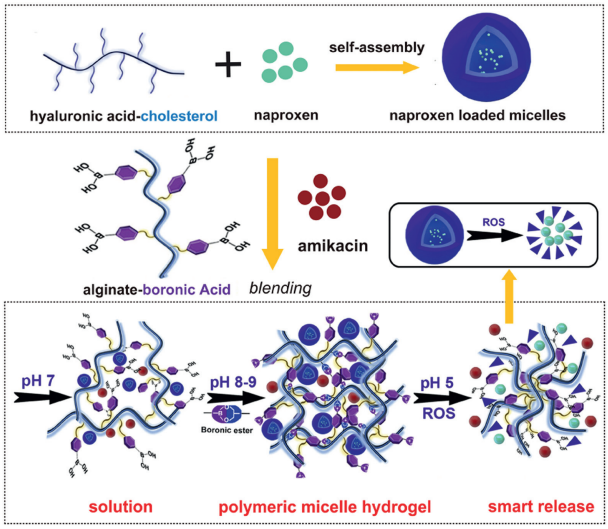

Fig. 4. Schematic illustration of polymeric micelle hydrogel composites by adjusting the pH of a mixed solution of ALG-BA, amikacin and anti-inflammatory drugs-loaded micelles. Reproduced with permission [31]. Copyright 2023, Elsevier.

ing part will provide more details about the different micelle embedding methods in micelle-hydrogel composites, while briefly discussing their advantages and limitations.

3. Incorporation methods of polymeric micelle hydrogels

3.1. Direct formation of hydrogels in pre-assembled micellar suspension

One of the most standard and simple approaches for constructing polymeric micelles hydrogels is to add pre-formed polymer micelles into the hydrogel-forming monomer solution, followed by incorporation of other monomers or initiators, or adjustment of pH and temperature. Alternatively, the lyophilized hydrogel can be ground into a powder and added to a micellar solution to produce a micellar hydrogel. Typically, this method provides relatively homogeneous micelles incorporation in the 3D network of the hydrogel compared to other assembly techniques.

Shin *et al.* synthesized poly(hydroxyethyl methacrylate) (PHEMA) micelles that were subsequently mixed with poly(vinyl alcohol) (PVA) in an aqueous solution, and added borax to the PHEMA/PVA suspension [29]. The dynamic borate-diol bonds formed with PVA endowed the hydrogel with self-healing properties, and the soft and mobile micelles enhanced the stretchability and malleability of the nanocomposites. Guo *et al.* designed a smart gelatin-based stimuli-responsive nZnO@MIC&hydrogel by adding MIC@Pf micelles and nano zinc oxide (nZnO) to ethylenediamine-modified gelatin (N-Gel) solution [30]. Equal volume of oxidized dextran (ODex) solution was mixed with the above and gently stirred. The hydrogel rapidly took shape due to the effective Schiff base reaction between N-Gel and ODex containing rich aldehyde groups. Then, the micelles and nanoparticles were uniformly dispersed in the hydrogel.

Hu *et al.* designed a smart hydrogel with dual drug delivery, self-healing and reshaping functions for wound healing. As shown in Fig. 4, anti-inflammatory drug naproxen (Nap) was preloaded into the micelles. Then the hydrogel solution was simply prepared by mixing the drug loaded micelles, amikacin and phenylboronic acid-modified alginate (ALG-BA) together. The prepared hydrogel network was crosslinked with boronic ester at pH 8.5 [31]. Once the hydrogel was applied to the wound area, naproxen was released from its network structure due to the dissociation of the boronic ester. This hydrogel had the advantage of fabricating by a single and certain polymeric micelle with minimum setup, synthesis and physical operation.

Likewise, Song *et al.* designed a pectin-chitosan (PEC-CS) hydrogel loaded with micelles containing antibacterial drugs for treating infected wounds [32]. The hydrogel was prepared by crosslinking pectin and chitosan, and did not require ciprofloxacin (CIP)-loaded micelles as a cross-linking agent. The freeze-dried PEC-CS hydrogel powder was dipped into the CIP@DPDMC nano-micelle solution, stirred and left undisturbed for 1 h to allow the formation of a nanocomposite hydrogel (CIP@DPDMCs&PEC-CS). This method is simple and the release of the encapsulated drug can be temporally and spatially controlled.

Wu *et al.* constructed a hydrogel based on phenylboronic acid-grafted oxidized dextran (POD) and caffeic acid-grafted ε-polylysine (CE). The amphiphilic polymers were first synthesized by grafting 2-(diisopropylamino)ethylamine (DIP) groups onto $mPEG_{45}$-$PBLA_{60}$-$PPhe_{30}$ triblock copolymer, and the hydrophobic drug was encapsulated into the micellar core. Subsequently, diclofenac sodium (DS) and micelles were embedded into the hydrogel before CE and POD crosslinking [33]. Zhou *et al.* synthesized a hydrogel *via* a Schiff base reaction between hydrazide-grafted hyaluronic acid (HA-ADH) and aldehyde-modified dextran (Dex-ALH). The dexamethasone acetate-loaded poly(ethylene glycol)-*b*-polythioketal-*b*-poly(ethylene glycol) (DA@PEG-PTK-PEG) micelles were embedded into the hydrogel. DA@PEG-PTK-PEG micelles enhanced the antioxidant capability of the hydrogel, and the latter enabled controlled drug release from the micelles [34].

Overall, the main advantage of this method is that micelles with diverse functionality can be incorporated in the hydrogel network, since they can be pre-assembled before hydrogel crosslinking. Alternatively, complex micelles can be designed to achieved hydrogel multifunctionality. However, this method has disadvantage of possible micelle escape from hydrogel matrix in weak crosslinks density.

3.2. Formation of hydrogels by micelles-mediated crosslinking

Besides simply physically distributed in the hydrogel matrix as filler agents, micelles are also be used as crosslinking point in the network. In addition, micelles surface can be designed with functional groups to crosslink with the hydrogel precursor molecules, yielding micelle-hydrogel composites *via* a co-dependent assembly mechanism [35].

Following this design concept, the QCS/PF127 hydrogel was designed as a novel wound dressing *via* combining the dynamic Schiff base and PF127 micelle cross-linking in one system. The self-assembled PF127-CHO micelles acted as a macroscopic cross-linker in the hydrogel network, thus improving the mechanical properties and self-healing ability of the hydrogel [36]. Abandansari *et al.* also synthesized a micelle-crosslinked hydrogel *via* Schiff base reaction between gelatin-hydrazide (Gel-ADH) and PF127-CHO micelles [37]. The PF127 micelles were not only carriers loaded with 5 FU and curcumin but also act as a multifunctional cross-linker for colorectal cancer combination therapy.

Likewise, Fang *et al.* developed a hydrogel for the controlled delivery of antibiotics drug in response to mechanical forces [38]. Drug-loaded diacrylated pluronic F127 micelles (F127DA) were used as the macro-cross-linker and *N*,*N*′-methylenebis(acrylamide) (MBAA) as the chemical cross-linker, and the hydrogel was formed by linking them to poly(sulfobetaine methacrylate) (polySBMA) through hydrophobic and electrostatic interactions respectively. The appropriate concentration of F127DA micelles enhanced the strength and toughness of the hydrogels through hydrophobic interactions. The encapsulated drug could be released from the hy-

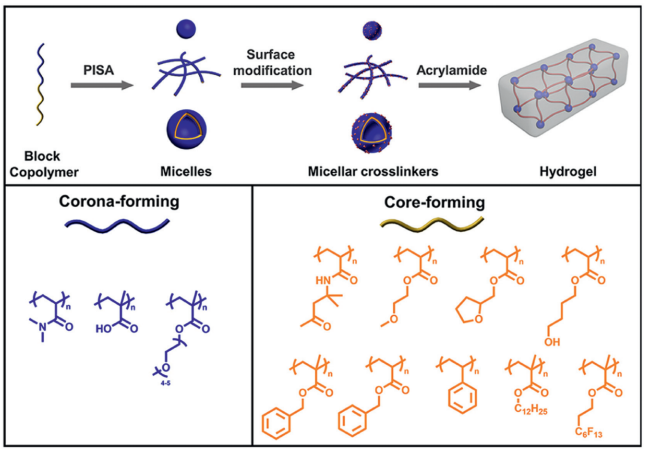

Fig. 5. Schematic illustration of PISA for micelle-crosslinked tough and ultrastretchable hydrogel. Copied with permission [39]. Copyright 2022, American Chemical Society.

drogels in a precise and controlled manner through the mechano-responsive deformation of micelles.

Despite the successful construction of micelle hydrogel composites, micelle crosslinkers have been restrained by the high concentration, uniform size dispersity as well as controlling nanostructure. Recently, Huo's group [39] used polymerization-induced self-assembly (PISA) strategy to customize and synthesize a series of micellar crosslinkers followed by copolymerization with acrylamide to fabricate hydrogels with superior toughness, ultrastretchability, and fatigue resistance (Fig. 5). Remarkably, with tailored poly(*N*,*N*-dimethylacrylamide)-*b*-poly(diacetone acrylamide) (PDMAc-*b*-PDAAM) micellar crosslinkers, the mechanical properties of these hydrogels could be adjusted by varying the chemical composition, concentration and size of the micelles. Furthermore, through the systematic evaluation of both aqueous and alcoholic PISA formulations, the diverse micellar crosslinked hydrogels were successfully demonstrated by PISA strategy, which advances the preparation of micelle crosslinked hydrogels.

Besides, an extremely-stretchable, fatigue-resistant, highly-resilient and self-healable hydrogel was obtained by using the micelle-like aggregates as cross-linker self-assembled from dually alkyl-modified polyethylene glycol (PEG) [40]. The physical entanglements between micelle-like aggregates and gel networks formed reversible knots in the hydrogel network structure. Furthermore, the extensibility and toughness of the obtained hydrogels could be easily adjusted by varying alkyl terminals and molecular weights of PEG in micelles. Micelle aggregates can also effectively resist the external force of hydrogel fracture and recombination.

In summary, depending on the advantages of the non-covalent, covalent or dynamic covalent bonds established, micelle-hydrogel crosslinking method is highly flexible in hydrogel matrix. In addition, adjusting the content of micelles in the micelle-hydrogel composites will affect the crosslinking density and the drug release characteristics. It is attractive for adjusting drug pharmacokinetics. However, on the other hand, the release profile might be limited by the ratios of micelles/hydrogel.

3.3. Hydrogel formation by micelles themselves

Amphiphilic block copolymers such as pluronics [41], PEG polypeptides [42], and PEG-poly(lactic acid-*co*-glycolic acid) [43] can undergo gelation at higher temperatures owing to the presence of PEG polyester linear block copolymers [44]. At the ambient temperature, the hydrophobic aggregation of micelles forms a "percolation micelle network" that leads to gelation.

Wang *et al.* developed a P(AAm-*co*-AN)-*b*-P(NIPAM-*co*-DMAa)-*b*-P(AAm-*co*-AN) triblock copolymer by reversible addition-fragmentation chain transfer (RAFT) polymerization, which showed both upper critical solution temperature (UCST) and lower critical solution temperature (LCST) dual thermo-responsive phase behavior [45]. Controlled and targeted drug release from micelles was possible by increasing the tumor temperature above UCST through near-infrared (NIR) irradiation. In addition, an irreversible sol-gel transition was achieved by changing the content of DMAa and adjusting the LCST of the P(NIPAM *co* DMAa) segment. Hahn *et al.* synthesized an ABA-type triblock with poly(2-methyl-2-oxazoline) as the hydrophilic block and poly(2-phenylethyl-2-oxazoline) as the hydrophobic block. The co-polymers self-assembled into spherical micelles above the critical micelle concentration (CMC), and underwent rapid thermos-responsive reverse gelation above the critical gel concentration, resulting in the formation of macroporous hydrogels with dense micelles [46].

Different from the micellar gel transformation by changing the temperature, Xiong *et al.* recently reported the fabrication of a novel injectable hydrogel through direct self-assembly of D-α-tocopheryl polyethylene glycol succinate (TPGS) [47]. Doxorubicin (DOX)-loaded TPGS micelles were prepared by organic solvent emulsification volatilization and mixed with β-glycerol phosphate disodium salt pentahydrate (β-GP) solution by stirring evenly in a water bath. In the presence of salt, TPGS solution undergoes gelation at 37 °C. It is assumed that TPGS micelles formed first and followed by hydrogel formation *via* physical interlock.

Shao *et al.* created a novel DMC-NaSS hydrogel by methacryloyloxyethyltrimethylammonium chloride (DMC) as a cationic monomer and 4-styrene sulfonic acid sodium (NaSS) as an anionic monomer. The amphiphilic DMC-NaSS can form micelles in water. With the addition of HAC, the micelles split with narrow distance between the dimers. Then the acrylamide monomers penetrated in the DMC-NASS micelles to copolymerize with the micelle groups, subsequently making hydrogel formation [48].

Lang *et al.* established a quantitative approach to achieve ABA triblock copolymer (hydrophobic-hydrophilic-hydrophobic) structure transition by rapid injection method [49]. The final structure of micelles, microgel and hydrogels transition can be tuned by simply changing the initial polymer concentration in a B-selective solvent. As shown in Fig. 6, when the initial polymer concentration (c) is lower than the overlap concentration (c*), the ABA copolymers self-assembled into micelles. When c ≈ c*, microgels were

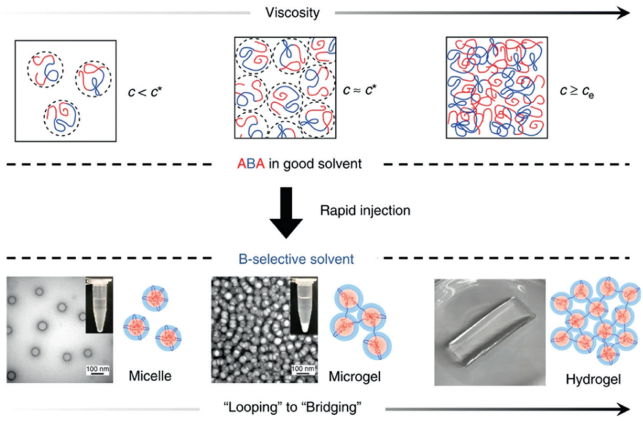

Fig. 6. Self-assembly of ABA triblock copolymers *via* rapid injection. The final state of the ABA triblock copolymer (micelles, microgels, and hydrogels) in a B-selective solvent is controlled and understood through the initial concentration of the polymer in the pre-injection solution. The self-assembly products ranging from micelles, microgels, and hydrogels correspond to dilute, semi-dilute, and entanglement regimes, respectively. Copied with permission [49]. Copyright 2018, Springer Nature.

obtained by aggregation of micelles. For concentrations close to the entanglement regime ($c \geq c_e$), hydrogels formed due to the hydrophobic domains span the entire sample volume. The work introduced in this paper provides a novel method for preparing functional hydrogels with ABA triblock copolymers.

The method of transforming a micellar solution from sol to gel by temperature change or salt addition is simple and easy to prepare with slow release of the drug. However, the hydrogels may have poor mechanical properties and thermally unstable drugs cannot be loaded in hydrogels.

4. Biomedical applications of polymeric micelle hydrogels

Polymeric micelle hydrogel composites are widely reported in the fields of local tumor therapy and tissue engineering. Different polymeric micelles hydrogel composites formed by various micelles and hydrogel polymer monomer with different micelle incorporation methods were summarized in Table S1 (Supporting information).

4.1. Local tumor treatment

Polymeric micelle hydrogels are promising drug carriers for targeted tumor therapy. As we know, cancer is commonly treated by surgical resection, radiation therapy, and chemotherapy, which are associated with a high risk of relapse and toxic side effects on the healthy tissues [50-52]. Hydrogel drug carriers can release the homogenously dispersed drug molecules through passive diffusion or *via* degradation of the hydrogel matrix. However, most anticancer drugs are hydrophobic and therefore not stably dispersed in hydrogel precursor solution [53,54]. Amphiphilic polymeric micelles on the other hand can effectively encapsulate and deliver hydrophobic drugs. In recent years, combination therapies using two or more drugs have become the preferred strategy for cancer treatment compared to single-agent targeted therapies [55]. Polymeric micellar hydrogels allow targeted delivery of two or more drugs to the tumor tissues, wherein the encapsulated drugs are released in a sustained manner, resulting in the accumulation of therapeutically high dosages at the target sites. Furthermore, hydrogel carriers reduce prolonged circulation of the drug in the bloodstream, and decrease toxicity to normal tissues [56,57].

The postoperative recurrence of glioblastoma multiforme (GBM) is still a significant obstacle in clinical. Recently, combination therapy with hydrogel composites has been developed to improve the therapeutic efficiency for GBM. The injectable hydrogel composites containing drug loaded micelles and water dispersible ferromagnetic iron oxide nano cubes (wFIONS) were injected into the resected tumor site after surgery [58]. Drug loaded micelles can target residual GBM cells with sustained release. While the alternating magnetic field accelerates diffusion by generating heat from wFIONs, thereby achieving penetrative drug delivery. The prepared hydrogel composites provided a potential platform for postsurgical GBM treatment (Fig. S1 in Supporting information).

Besides, Li *et al.* developed a matrix metalloproteinase-2 (MMP-2) responsive injectable hydrogel for local chemotherapy of oral squamous cell carcinoma [59]. DOX was first loaded in PDLLA-PEG-PDLLA micelles. Then DOX loaded micelles were mixed with an injectable hyaluronic acid (HA) hydrogel, crosslinking by MMP-2 *via* Michael addition reaction. Three days after administration of the hydrogel in a tumor-bearing model, the fluorescence signal of hydrogel was primarily localized to the tumor site, whereas the free DOX almost completely disappeared within 24 h. The micelle-hydrogel composites achieved local sustained release of the DOX and long-term inhibitory effect on tumor growth.

Darge *et al.* prepared a thermosensitive hydrogel by encapsulating DOX-loaded 5,6-dimethylxanthenone-4-acetic acid (DMXAA)-conjugated mPEG-PLGA micelles (DOX@mPPD) in PDLLA-PEG-PDLLA copolymers [60]. The drug-loaded hydrogel achieved significant anti-tumor effects with minimal systemic toxicity or pathological damage to major organs due to continuous and targeted drug release at specific sites.

An injectable micellar crosslinked hydrogel was synthesized by the thiol-ene click reaction, which can sequentially release gemcitabine (GEM) and hydrophobic indoleamine 2,3-dioxygenase inhibitor D-1-methyltryptophane (d-1MT) successively at the breast tumor site [14]. The hydrophobic d-1MT was incorporated into the core of the F127 micelles and the hydrophilic GEM was dispersed in the hydrogel network. The prepared micelle-hydrogels composites showed a robust antitumor immune response, subsequently exhibiting a synergetic antitumor efficacy. The results highlight that injectable micellar hydrogel is a promising strategy in the treatment of local breast cancer with chemoimmunotherapy.

Polymeric micelle-hydrogel composites as carriers are used widely in local tumor therapy to enhance therapeutic efficiency. The advantage of this kind of drug delivery system not only improves the solubility of hydrophobic drug, but also greatly provides a sustained release behavior locally. Thus, the micelle-hydrogel composites as excellent drug carriers will play a more important role in local tumor therapy.

4.2. Tissue engineering

4.2.1. Bone tissue engineering

Over the last 60 years, hydrogels have been routinely used to develop artificial tissues and organs [61,62]. Tissue engineering aims to repair and reconstruct damaged tissues or organs using bioactive scaffolds that are loaded with specific cells or growth factors (GF) to imitate the extracellular matrix (ECM). The ideal bioactive scaffolds should be porous to facilitate nutrient diffusion and waste expulsion, and have controlled biodegradability, excellent mechanical properties and superior biocompatibility [63-65]. Hydrogels are suitable scaffold materials for bone tissue engineering since they can not only absorb large amounts of water and biological fluids, but also exhibit high biocompatibility and hydrophilicity, similar to that of ECM [66]. However, since most hydrogels cannot simulate all the properties in ECM, hybrids of polymeric micelles and hydrogels are increasingly being considered for biomedical applications [67]. Polymeric micelle hydrogels play a beneficial role in simulating bone tissue microenvironments, releasing drugs and growth factors, and providing scaffold structures, potentially facilitating the repair and regeneration of bone tissue.

Injection of appropriate doses of drugs to stimulate bone regeneration in the bone defect area can enhance the effectiveness of bone tissue restoration. Thus, the scaffold of providing bone regenerative drugs is particularly important in repairing bone tissue defects. As shown in Fig. S2 (Supporting information), SeSe-Rapa micelles were self-assembled from the amphiphilic mPEG-*b*-P(TMC-co-MSeSe) copolymer loaded with hydrophobic rapamycin (Rapa) [68]. The micellar loading of rapamycin showed highly sensitive ROS responsiveness. While, injectable PEGylated poly(glycerol sebacate) (PEGS-NH_2)/poly(γ-glutamic acid) (γ-PGA) (PEGS-PGA) hydrogel was further prepared by PEGylated poly(glycerol sebacate)/poly(γ-glutamic acid) with the incorporation of rapamycin-loaded micelles. The micelle-hydrogel composites showed injectable properties in the bone defect site for aged bone regeneration. Besides, hydrogel provides ideal surgical operation and mechanical support for long-term bone regeneration. The rich carboxyl group (-COOH) on the main chain forms an effective compound with iron ions, which can prevent the generation of OH, thus removing extracellular ROS (exROS). Thus, this prepared PEGS-PGA hydrogel shows a highly sensitive ROS response to the local aging microenvironment, and

releases drugs from micelles to remove intracellular ROS accumulated in aging bone marrow mesenchymal stem cells.

Hydrogels have also been tested extensively for bone tissue engineering. Yan *et al.* encapsulated the hydrophobic simvastatin (SIM) in aldehyde-modified maltodextrin micelles, and anchored the micelles to the hydrogel network by Schiff base linkage (SIM@micelle-CHO&hydrogel) [69]. SIM was evenly dispersed in the hydrogel matrix. Furthermore, the aldehyde-modified micelles improved the osteogenic capability of SIM, enhanced the mechanical strength of the hydrogels, and reinforced the bonds in the hydrogel networks. The maltodextrin-based micelle/hydrogel composite was also biocompatible and reduced the toxicity of SIM. Sustained drug release from the hydrogel promoted the osteogenic differentiation of MC3T3-E1 cells *in vitro*.

4.2.2. Nerve tissue engineering

The nervous system comprises the central nervous system and the peripheral nervous system, which are responsible for crucial functions such as receiving, interpreting, and transmitting information, and are essential for the normal functioning of the human body [70,71]. The regenerative capacity of neural tissue is rather limited. Thus the reconstruction of neural tissue function presents significant challenges in clinical therapy. Polymeric micelles hydrogel composites are regarded as an ideal choice for soft tissue applications due to their flexibility, resilience, and pliability. Serving as a multifunctional material, they can simultaneously act as drug carriers, scaffold structures, and platforms for the release of bioactive factors. They play a constructive role in promoting the proliferation, differentiation, and migration of nerve cells, thereby facilitating the regeneration and repair of neural tissue. Their versatility has sparked numerous innovations and advancements in related research fields [72,73].

Pertici *et al.* developed an injectable and biodegradable hydrogel based on PNIPAAm-*b*-PLA-*b*-PEG-*b*-PLA-*b*-PNIPAAm pentablock for brain tissue engineering [74]. The polymer block was first synthesized by combining ROP and NMP, and gelation was induced by micellar cross-linking at elevated temperature. The hydrophobic compound Fluo-4 AM was encapsulated into the micelles, and efficiently internalized into brain cells, thus reducing the side effects on healthy tissues. Furthermore, the products of hydrogel degradation did not affect neuronal development, and the similar mechanical properties of the hydrogel and soft brain tissues limited any inflammatory responses and promoted neurite growth. Therefore, this novel micellar hydrogel platform is a highly promising candidate for brain/soft tissue engineering.

Peripheral nerve injury (PNI) is a severe disease characterized by nerve and axon dysfunction. Restoring cell proliferation in the nerve conduit can effectively repair peripheral nerves and improve nerve tissue regeneration. Deng *et al.* generated injectable hydrogels using polyaniline-modified carboxymethyl chitosan (CMC-PANI) and aldehyde-modified Pluronic F-127 (F127-CHO) by Schiff base reaction (Fig. S3 in Supporting information) [75]. PF127-CHO micelles enhanced the dispersibility of hydrophobic 7,8-dihydroxyflavone (DHF) in water, and the hydrogel matrix supported sustained release of DHF. Compared to the blank chitosan hydrogel, the DHF-loaded micellar hydrogel significantly promoted the proliferation of nerve cells, resulting in recovery of nerve function. In fact, the regenerative ability of this hydrogel in the nerve conduit was comparable to that of autologous transplantation.

4.2.3. Skin tissue engineering

As the largest organ of the body, the skin protects the body from environmental stress and microbial infection [76]. Physical injury to the skin barrier induces a well-orchestrated wound healing process to repair damaged tissue and restore the functional barrier [77,78]. Skin injuries can be classified as acute or chronic. While acute injuries can be treated in an orderly and timely manner to restore the functional integrity of the skin, chronic injuries cannot be fully repaired due to vascular insufficiency [79,80]. Wound healing sequentially proceeds through hemostasis, inflammation, proliferation and tissue remodeling [81], during which period the peri-wound tissue may become dehydrated and inflamed. Metabolic disturbances in wound tissue can worsen the symptoms, and wound dehydration may impair the healing process. Wound dressings prevent dehydration of the surrounding tissues and reduce the risk of inflammation [82]. However, traditional wound dressings have limited efficacy due to their poor mechanical properties and adhesion to the skin, as well as inefficient drug delivery [44]. However, traditional polymer hydrogels are fragile due to poor mechanical properties and do not have enough tissue adhesion, which is difficult to combine with surrounding tissues in use. Ideal hydrogel wound dressings should have good injectability, self-healing ability, and adjustable mechanical strength and elasticity. Hydrogel-based wound dressings can augment bleeding cessation, reduce inflammation, absorb excess tissue exudates, clear devitalized tissue, prevent re-injury and re-infection, and hydrate the wound area [83,84].

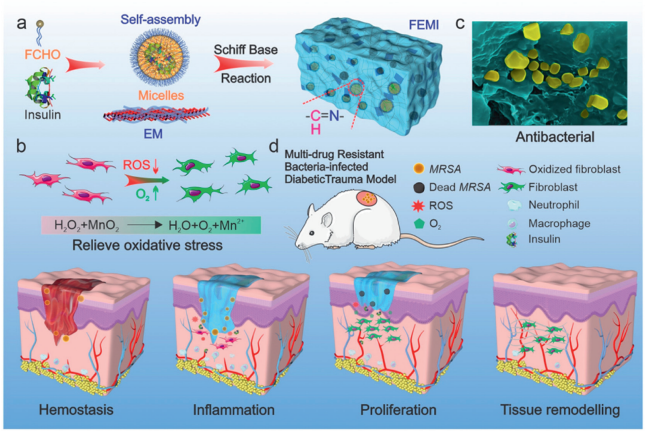

Fig. 7. Schematic illustration of FEMI hydrogel for MDR bacteria-infected diabetic wound healing. The FEMI hydrogel was fabricated by EM and insulin-loaded PF-CHO micelles *via* Schiff-based reaction. Copied with permission [85]. Copyright 2020, American Chemical Society.

As shown in Fig. 7, an injectable multifunctional hydrogel (FEMI) was combined by ε-polylysine (EPL)-coated MnO_2 nanosheets (EM) and insulin-loaded aldehyde Pluronic F127 (F-CHO) micelles *via* a Schiff-based reaction [85]. MnO_2 Nanoenzymes reshape the oxidative wound microenvironment by decomposing the extensive ROS (H_2O_2) into O_2. Concurrently, the pH/redox-responsive FEMI hydrogel enables continuous and spatiotemporal controlled release of insulin for blood glucose regulation. The FEMI hydrogel demonstrates accelerated healing of diabetes-infected wounds by multidrug-resistant bacteria *in vivo*, offering a multifaceted approach to address extensive tissue damage from diabetes.

Yang *et al.* developed an injectable micellar hydrogel (AF127&HA-ADH&OHA-Dop) with excellent adhesive and self-healing properties for skin wound healing [86]. The hydrogel was synthesized by cross-linking dopamine-functionalized oxidized HA (OHA-Dop), adipic acid dihydrazide-modified HA (HA-ADH), and aldehyde-terminated Pluronic F127 (AF127) *via* Schiff base reaction, hydrogen bonding and π-π stacking interactions. OHA-Dop enhanced the cellular affinity and tissue adhesion of the hydrogel due to the high content of catechol groups (31%), which enabled intimate contact between the hydrogel and the wound surface.

The AF127&HA-ADH&OHA-Dop hydrogel not only protected the injured skin but also maintained wound moisture, which accelerated wound repair. Acemannan (Ac) and curcumin (Cur) have significant anti-inflammatory, anti-infective, and wound-healing properties. However, their clinical applications are limited due to poor stability, short biological half-life, and lack of targeting. Sharma *et al*. loaded Ac and Cur into micelles (NPAc, NPAcC1, NPAcC2 and NPCur), and incorporated them into hydrogels [87]. NPAcC2 showed a synergistic effect and maintained the integrity of the skin, and was more effective compared to the other formulations. Rungrod *et al.* [88] synthesized hydrogels using poly(ε-caprolactone) diacrylate (PCLDA) as the cross-linker micelle. PCLDA was first modified with acrylic acid, and 2-acrylamido-2-methylpropane sulfonate (Na-AMPS) was mixed with the modified PCLDA micelles to form hydrogels. PCLDA&P(Na-AMPS) hydrogels presented no cytotoxicity in the *in vitro* MTT assay and exhibited good mechanical properties. The drug-loaded hydrogels also inhibited bacterial growth in the infected wounds and the antimicrobial effects lasted for at least 15 days when stored at 4 °C. These results suggest that micellar cross-linked hydrogels are promising wound dressings.

Taken together, drug-loaded micellar hydrogels are ideal bioactive scaffolds with broad application prospects in the field of tissue engineering.

5. Conclusions and perspectives

As reviewed herein, the introduction of polymeric micelles incorporated into hydrogels has revealed tremendous design flexibility, which not only augmented the research opportunities of hydrogels, but also expanded the application prospects of micelles. In particular, the polymeric micelle hydrogel composites have both excellent mechanical properties and excellent self-healing properties. At the same time, hydrophobic drugs and micelles can also be efficiently encapsulated in polymeric micellar hydrogels, which can be effective for sustained and controlled release. Adjusting the content of micelles in the micelle-hydrogel composites will affect the crosslinking density and the drug release behavior. Thus, these hydrogel composites exhibit multifunctional properties, making them an ideal carrier for local tumor therapy, hard-tissue repair such as bone and soft-tissue repair such as nerve and skin.

The methods for the synthesis of polymeric micellar hydrogels and their biomedical applications discussed in this review can encourage further development of hydrogel composites, *e.g.*, soft robotics, bioengineering, optically active coatings and so on. Specifically, the potential applications of these micelle hydrogel composites include (i) real-time monitoring and regulation of therapeutic effects by combining biosensors; (ii) personalized therapy and clinical implantable tissue engineering applications by combining 3D printing technology; (iii) customized flexible electronic devices by combining conductive materials; (iv) cancer immunotherapy by engineering vaccine in hydrogel. Therefore, we believe high-performance micelle hydrogel composites with excellent mechanical properties and novel functions will be prepared for various biomedical applications.

However, at present, the clinical application of polymeric micelle hydrogel composites with appropriate mechanical properties and rapid self-repairing properties are still at the research stage. They are still limited in clinical use. Furthermore, the *in vivo* degradation, biosafety and risk of side effects of the micellar hydrogels need to be further investigated. We expect that the discussion of the different strategies that micelles incorporation into hydrogels and summary of the biomedical applications presented in this review will provide a better understanding for the design and fabrication of novel micelle hydrogel composites for advanced applications.

Declaration of competing interest

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

CRediT authorship contribution statement

Hongyi Li: Writing – original draft, Investigation, Conceptualization. **Huiyun Wen:** Writing – review & editing, Visualization, Supervision. **He Zhang:** Methodology, Investigation. **Jin Li:** Resources. **Xiang Cao:** Investigation. **Jiaqing Zhang:** Investigation. **Yutao Zheng:** Investigation. **Saipeng Huang:** Resources. **Weiming Xue:** Validation. **Xiaojun Cai:** Writing – review & editing, Supervision.

Acknowledgments

The authors gratefully acknowledge financial support from the Natural Science Basic Research Program of Shaanxi Province (No. 2023-JC-YB-101), the Basic Science Research Program of Shaanxi Basic Sciences Institute (Chemistry, Biology) (No. 22JHQ079), and National Natural Science Foundation of China (No. 82272150).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2024.110072.

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