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REVIEW ARTICLE

Design and fabrication of smart functional hydrogel wound dressing for diabetic foot ulcer

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ABSTRACT: Diabetic foot ulcer (DFU) often evolves into chronic wounds that resist healing over an extended period, sometimes necessitating amputation in severe cases. Traditional wound management approaches generally fail to control these chronic sores successfully. Thus, it arouses a huge demand in clinic for a novel wound dressing to treat DFU effectively. Hydrogel as an ideal delivery system exhibits excellent loading capacity and sustainable release behavior. It also boasts tunable physical and chemical properties adaptable to diverse biomedical scenarios, making it a suitable material for fabricating functional wound dressings to treat DFU. The hydrogel dressings are classified into hemostatic, antibacterial and anti-inflammatory, and healing-promoting hydrogel dressings by associating the pathogenesis of DFU in this paper. The design and fabrication strategies for the dressings, as well as their therapeutic effects in treating DFU, are extensively reviewed. Additionally, this paper highlights future perspectives of multifunctional hydrogel dressings in DFU treatment. This review aims to provide valuable references for material scientists to design and develop hydrogel wound dressings with enhanced capabilities for DFU treatment, and to further translate them into the clinic in the future.

KEYWORDS: hydrogel dressing; multifunction; design; fabrication; diabetic foot ulcer

Contents

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1 Introduction

Diabetes is a metabolic disorder characterized by elevated blood glucose levels, resulting from the body's inability to produce or effectively use insulin [1]. China has the highest prevalence of diabetes, with a reported 140.9 million individuals diagnosed in 2022, accounting for 26.2% of the global diabetic population [2]. Diabetes can give rise to various severe complications, including cerebrovascular disease, nephropathy [3], neuropathy, and diabetic foot ulcer (DFU) [4–5]. Among these complications, DFUs are particularly devastating, often manifesting on the feet. Nearly 25% of individuals with diabetes in China face amputation risks due to chronic foot ulcers, underscoring the gravity of DFU disease [6].

Normal wound healing typically involves four sequential stages: hemostasis, inflammation, proliferation, and remodeling [7]. However, the hyperglycemic environment in diabetic patients often disrupts this healing process, creating conditions favorable for bacterial growth and suppressing immune cell function. This disruption results in persistent bacterial infections [8]. Consequently, DFUs can evolve into chronic wounds that resist healing over extended periods [9]. This, in turn, can lead to various complications, including barrier disruption and infection, heightened oxidative stress, neuropathy, microvascular complications, and in the worst cases, necessitate amputation [10–13]. This not only increases the societal medical burden, but also subjects patients to prolonged suffering, making it a pressing national health concern. Therefore, identifying effective treatment strategies to enhance the healing of DFU is an urgent priority [14–15].

The concept of moist healing, introduced by George D. Winter, revolutionized the field of wound management. This shifted the focus of wound dressing from conventional dry passive products to responsive moisture-promoting materials [16–18]. Hydrogel dressing has emerged as an ideal choice for treating chronic wounds, including DFU, due to its ability to create a moist environment conducive to cell proliferation and tissue repair [19–21]. Hydrogel dressings feature a three-dimensional (3D) porous network structure resembling the natural extracellular matrix (ECM), high water content, adjustable mechanical properties, good histocompatibility, and more [22–24]. These characteristics enable direct contact with the wound, providing a moist and favorable environment for wound healing and a stable, growth-friendly environment for cell proliferation [25–27]. Furthermore, hydrogel dressings exhibit superior loadability, allowing them to be loaded with various therapeutic and bioactive drugs. This capability enables them to address the complex complications associated with diabetes and promote the healing of chronic DFU [28–31]. Additionally, the design flexibility of hydrogel structures makes it possible to impart various smart behaviors to the dressing, such as sustainable release, sensitivity, sequential therapy, integrated diagnosis and treatment [32–36]. As a result, the multiple functions of hydrogel dressings position them as the most competitive choice for treating DFU.

In this review, we first provide a brief overview of the pathogenesis of DFU and the wound recovery process. Second, we discuss the design strategies and fabrication protocols of various types of hydrogel dressings with diverse biomedical functions for treating DFU. The hydrogel dressings are classified into hemostatic, antibacterial and anti-inflammatory, healing-promoting hydrogel dressings according to the pathogenesis of DFU. This clinically oriented classification can better elucidate the clinical application of the dressings. Finally, we highlight the future prospects of hydrogel dressings in the treatment of DFU. Recently, several reviews on hydrogel dressings have been published [37–40]. Some of the published reviews concentrated on one type of hydrogel dressing such as polysaccharide-based anti-inflammatory hydrogel dressing [38] and glucose-responsive hydrogel dressing [39]. Although a paper [40] reviewed the multifunctional hydrogel dressings by associating with the pathogenesis of DFU, it mainly focused on the biological functions, and did not involve the design and fabrication of the hydrogel dressings. Another review is similar to a meta-analysis of patents [37], which did not summarize

the hydrogel dressing as comprehensively as our manuscript and also was not involved in the design of hydrogel dressings based on the pathogenesis of DFU.

Consequently, this review not only classified and reviewed the hydrogel dressing according to the pathogenesis of DFU, but also reviewed the design and fabrication of the hydrogel dressings in addition to the biological functions. It is able to offer valuable insights to materials scientists for designing and preparing hydrogel wound dressings with enhanced functionalities to effectively address chronic foot ulcers in diabetic patients. Additionally, we emphasize the importance of translating these innovations from the laboratory to clinical settings to benefit patients.

2 The wound healing process

2.1 Normal wound healing process

The wound healing process is a complex and well-coordinated biological repair mechanism [41–42]. It is primarily orchestrated by cytokines, growth factors, and various bioactive molecules, along with integrin receptors and adhesion molecules within a range of cells, including platelets, inflammatory cells, epithelial cells, keratinocytes, and fibroblasts [43–46]. Typically, this process encompasses the following four stages as shown in Fig. 1.

Hemostasis: When the skin is damaged and bleeds, the body's first response to a bleeding wound is to stop the bleeding [47–49]. First, the wound releases clotting factors to form a clot on-site, providing skeletal support for cell migration and platelet aggregation [50–51]. During this process, platelets and collagen come together to activate central thrombin that promotes the formation of a fibrin mesh, allowing platelets to coalesce and form a stable clot to achieve a hemostatic effect [52–53]. Additionally, the immune system activates different cellular signals for a rapid response, such as mast cells, neutrophils, macrophages, and lymphocytes, to counteract the invasion of bacteria and viruses, thus initiating the wound healing process [54–55].

Inflammation: The main task of the inflammatory phase is to destroy bacteria and clear debris in the vicinity of the wound area, dealing with damaged cells, growth factors, etc. [56–57]. The primary process involves the entry of neutrophil-secreting leukocytes into the wound to

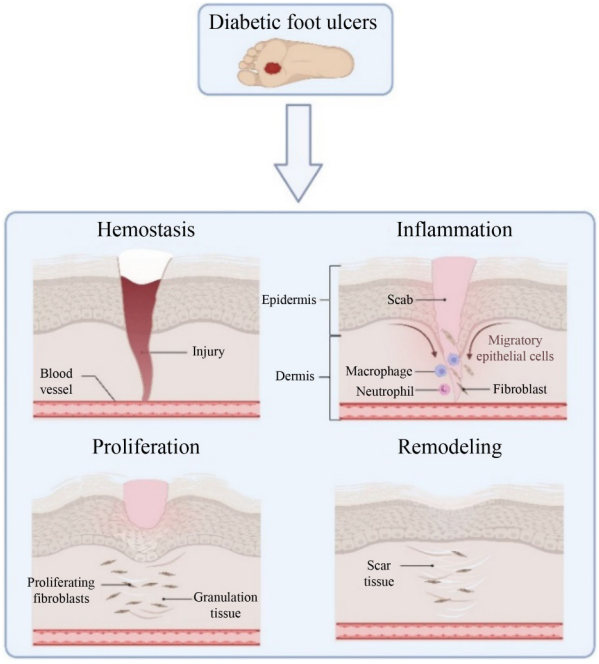

Fig. 1 Four processes of wound healing in patients with DFU (Created with BioRender).

clear debris and destroy bacteria [58–59]. These cells generally reach their maximum quantity within 24–48 h after injury and decrease in number after 3 d, followed by the arrival of macrophages to continue clearing debris. They can secrete growth factors and proteins, prompting immune system cells to reach the wound site and promote tissue repair. The main features of the inflammatory phase are redness, swelling, heat, and pain around the wound, typically lasting between 4 and 6 d [60–61].

Proliferation: Once the wound debridement is complete, inflammation gradually decreases, and wound healing enters the proliferative stage. The proliferative phase has three main distinct stages. In the first stage of wound filling, fibroblasts and epithelial cells migrate to the wound area, activating cell proliferation and differentiation. Growth factors are released, and granulation tissue fills the wound with connective tissue, forming new blood vessels and restoring the oxygen supply to the wound. The second stage involves the gradual contraction of the wound edges toward the center of the wound. The third stage is wound coverage (epithelial formation), in which epithelial cells and fibroblasts release various growth factors, such as epidermal growth factor (EGF), hepatocyte growth factor (HGF), and fibroblast growth factor (FGF). These growth factors promote re-epithelialization to replace the tissue

and fibrin clots in the injured area. The proliferative phase typically lasts between 4 and 24 d [62–64].

Remodeling: Following the proliferative phase, the newly developed tissue gradually gains strength and flexibility as collagen fibers reorganize and mature, restoring the epithelial tissue. Simultaneously, the granulation tissue transforms into scar tissue. Although the new tissue is not as robust as the original tissue at its peak strength, the scar tissue enhances the wound's resistance to pathogens and ultimately covers the wound. Finally, fibroblasts continue to cultivate dermal tissue until maturity, in a protracted process that typically spans between 21 d and 1 year before complete healing occur [65–66].

2.2 Wound healing process of DFU

Unlike common skin wounds, DFU presents challenges in healing due to diabetes-related characteristics such as heightened levels of oxidative stress, excessive inflammatory responses, poor neovascularization, and a hyperglycemic environment. These factors pose risks to the wound healing process [67–69]. For instance, DFU is typically marked by an abnormal and prolonged inflammatory phase, primarily a result of sustained stimulation in the hyperglycemic body environment. The hyperglycemic condition can impede vascular endothelial cell proliferation, slow down neovascularization and local nerve regeneration, and affect the synthesis and function of macrophages and fibroblasts, leading to a weakened anti-inflammatory response and an extended inflammatory phase. Consequently, diabetes significantly hampers the inflammation and proliferation stages of wound healing, transforming DFU into typical chronic wounds. Moreover, the hyperglycemic environment's negative impact on neovascularization results in low vascular density, causing a deficiency in nutrients and growth factor supply to the wound, which further affects the proliferation stage [70–72].

3 Functional hydrogel dressing for DFU

3.1 General requirements of DFU hydrogel dressings

The first stage of DFU is always accompanied by bleeding. Thus, a hemostatic hydrogel dressing is also required in the treatment of DFU [73–74]. As diabetes mainly delays the inflammation stage, an enormous number of functional hydrogel dressings have been designed and fabricated for this stage [75]. Three therapeutic treatments, including infection control, anti-oxidation, and immune microenvironment regulation, are often adopted in this stage. Correspondingly, different functional hydrogel dressings have been developed for each treatment [76–78]. Since the hyperglycemic environment also impairs the proliferation stage, functional hydrogel dressings aiming at accelerating proliferation are also needed for DFU. However, given the complicated healing process of DFU, it is hardly possible for a hydrogel dressing with a single function to achieve the healing of DFU. Therefore, a multifunctional dressing that can effectively treat DFU in various stages is urgently needed in the clinic. Figure 2 summarized several typical biomaterials for the fabrication of DFU hydrogel dressing as well as the popular functional pharmaceutical molecules which are commonly loaded into the DFU hydrogel dressing to construct the multifunctional DFU dressings. Those biomaterials and functional pharmaceutical molecules will be discussed in detail in the following sections.

3.2 Multifunctional hemostatic hydrogel dressings

Traditional dressings such as gauze, gauze strips, and

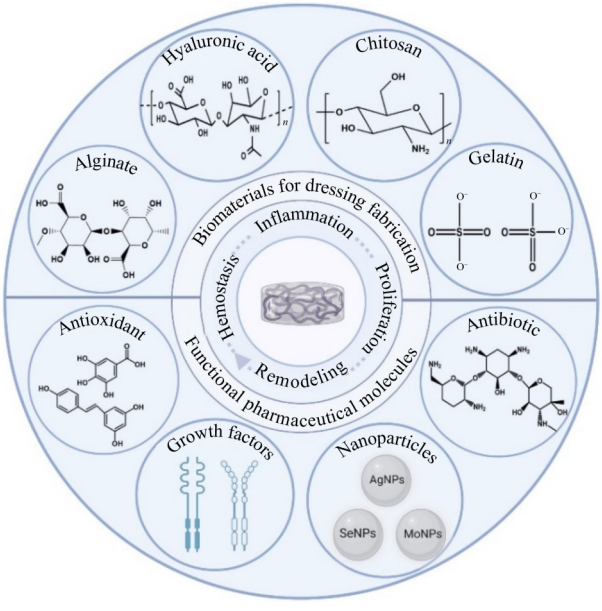

Fig. 2 Natural polysaccharides and drug molecules for the construction of multifunctional hydrogel dressings (Created with BioRender).

cotton pads can also be used as hemostatic dressings due to their strong water absorption, achieving a satisfactory hemostatic effect by applying pressure to the wound with the dressings [79]. However, they are difficult to remove from the wound after hemostasis, and the detachment of dressings may cause secondary mechanical damage. Hydrogel dressings can effectively overcome this disadvantage as they can maintain moisture during use [80]. Although hemostasis is not the main challenge of DFU treatment, a hemostatic hydrogel dressing which makes the patient feel comfortable is also welcome. Furthermore, due to hyperglycemic environment, the bleeding DFU wound exposed to the environment are highly susceptible to bacterial infection. Thus, a multifunctional hydrogel containing both hemostatic and anti-infection properties is required to treat bleeding DFU wound.

Chitosan (CS) has been a research hotspot in the preparation of hemostatic hydrogel dressings. CS can recruit platelets, erythrocytes, and proteins at the wound site through electrostatic action and modulate the expression of the GPIIb/IIIa receptor on the platelet surface to accelerate platelet aggregation [81–83]. As a result, various commercial hemostatic dressings made from CS, such as HemCon bandage (engineered chitosan acetate) and CS sponge, are available [84–86]. CS sponges prepared with keratin/CS possess high porosity and good blood absorption properties compared to commercially available gelatin sponges [87]. Both CS bandages and CS sponges have promising applications as hemostatic hydrogel dressings. Since CS is a cationic polymer, it can disrupt the anionic cytomembrane of bacteria. Therefore, CS bandages and sponges not only have a much better hemostatic effect than ordinary bandages but also exhibit antibacterial properties. They serve as multifunctional hydrogel dressings that can significantly enhance wound healing [88].

Furthermore, the hemostatic properties and other characteristics of CS hydrogel dressings can be enhanced through appropriate chemical and physical modifications. Wang's team developed a CS-based hydrogel with distinctive multilevel pore structures, crosslinked by 3-(3,4-dihydroxyphenyl) propionic acid-modified chitosan and sebacic acid-terminated polyethylene glycol modified by p-hydroxybenzaldehyde (PEGSH) [89]. The multiscale 3D network structure of the hydrogel could be effectively tailored by adjusting the content of the PEGSH polymer. This resulted in improved erythrocyte aggregation, plasma absorption, platelet adhesion and activation, fibrin network construction, and blood clot formation, accelerating hemostasis. In addition, light-responsive dressings have been prepared by the smart design of chitosan structure. Fan et al. prepared a CS/gelatin (Gel)/polyvinyl alcohol (PVA) hydrogel for wound dressing with a notable hemostatic effect using the γ-irradiation method. The γ-irradiation results in the crosslinking of the dressing, significantly strengthening its mechanical properties [90]. Moreover, CS exhibits good modifiability. Yu et al. prepared a CS dressing with a dense pore structure by *in situ* reduction of silver nanoparticles (AgNPs)/CS composites by gelatin. The resulting multifunctional hydrogel dressing exhibited improved mechanical properties, water absorption, water retention, and bacteriostatic effect due to the presence of AgNPs (Fig. 3) [91].

While CS hydrogel dressings effectively address bleeding in DFU, they face challenges due to their insolubility in water and poor mechanical properties, complicating the dressing preparation. Consequently, modified CS such as carboxymethyl CS, catechol modified CS, and quaternary ammonium CS have been used in hemostatic hydrogel dressing formulations [92–94]. Han et al. utilized quaternized CS to create a sprayable hydrogel dressing through dynamic imine bond cross-linking *in situ*. The resulting dressing exhibited enhanced hydrophilicity and mechanical properties, along with effective hemostatic and self-healing properties [95]. Guo et al. developed a multifunctional hydrogel dressing loaded with Fe^{3+} and poly(thiophene-3-acetic acid) (PTAA) through the crosslinking of dopamine-grafted oxidized sodium alginate (SA) and carboxymethyl CS [96]. The metal-coordinated bond with Fe^{3+} imparts the hydrogel with excellent self-healing, adhesion, and oxidation resistance. Additionally, the inclusion of PTAA provides the hydrogel with effective antibacterial properties and appropriate electrical conductivity.

Hyaluronic acid (HA) is highly hydrophilic, biocompatible, and degradable, making it a common choice for the production of hydrogel dressings. Guan et al. created a multifunctional hydrogel dressing with hemostatic, antioxidant, and antibacterial properties by incorporating graphene oxide (GO) into a natural polymer network consisting of HA and gelatin [97]. The inclusion of GO provided the dressing with photothermal therapy capabilities, effectively preventing early infection, and excellent antioxidant properties to expedite wound

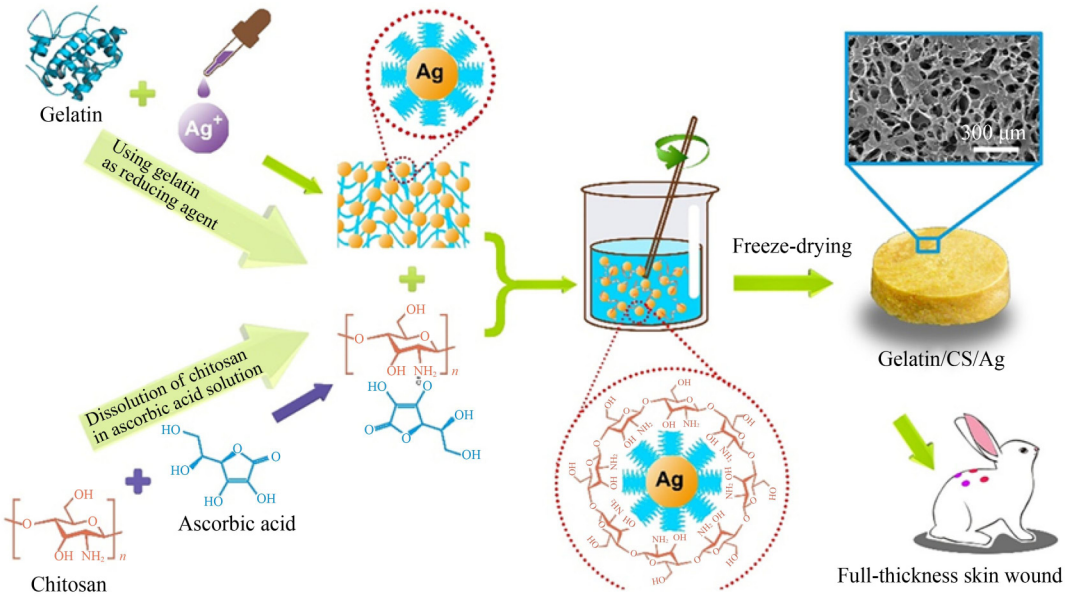

Fig. 3 The preparation process and the principle of composite gelatin/CS/Ag. Reproduced with permission from Ref. [91].

healing. Another natural polysaccharide, alginate, is derived from marine algae. It boasts good compatibility, low toxicity, hemostatic properties, and excellent modifiability, making it a widely used material in hemostatic medical dressings. Taking inspiration from the hemostatic function of platelets, Zhao et al. proposed a novel bionic hydrogel by covalently amidating natural platelets and alginate for wound healing [98]. With natural functional groups, the platelet-derived hydrogel exhibited outstanding biocompatibility and blood compatibility. By adjusting the ratio of platelets to alginates, the mechanical properties of the resulting hydrogel could be tailored to suit different wound environments. Furthermore, silver nanoparticles (AgNPs) could be loaded into the hydrogel' s void space, providing the composites with superior anti-infective properties.

In summary, natural polysaccharides, including CS, HA, and alginate, are popular materials for fabricating hemostatic hydrogel dressings, despite their shortcomings in hydrophilicity and mechanical strength. Researchers have continuously optimized these materials to develop more potent hemostatic dressings that meet clinical requirements. Additionally, the incorporation of antibacterial functionality is a common feature in hemostatic dressings, given the high risk of infections in DFU resulting from the hyperglycemic environment. Currently, a significant focus in hemostatic dressings has been on applications in traumatic and surgical hemostasis. However, as hemostasis and anti-infection are also necessary crucial requirement for bleeding DFU wound, the hemostatic hydrogel dressing combined with various anti-infection properties is also applicable to DFU treatment.

3.3 Multifunctional anti-inflammation hydrogel dressing

3.3.1 Anti-infection dressings

As mentioned earlier, due to the extremely high risk of infections in DFU resulting from the hyperglycemic environment, it is challenging for DFU to avoid infection during the inflammation stage. Therefore, it is crucial for DFU dressings to possess anti-infection capabilities to prevent delays in the inflammation stage.

Since exogenous bacteria are a major cause of local infections in DFU, numerous antimicrobial hydrogel dressings have been designed and developed in recent years to address local infections [99]. There are two main strategies in the fabrication of antimicrobial hydrogel dressings: loading antimicrobial substances into the dressing and directly using antimicrobial materials to construct the dressings.

While antimicrobial substances have been applied in traditional dressings, achieving a sustainable antibacterial effect is still challenging because they are easily cleared by bodily fluids. As mentioned earlier, hydrogel dressings can provide a sustainable release behavior for antimicrobial substances, prompting researchers to

develop various antibacterial hydrogels with excellent performance. Antibiotics such as aminoglycosides (gentamicin and streptomycin), glycopeptides (vancomycin), and tetracyclines (doxycycline and tetracycline hydrochloride) are considered highly effective antibacterial drugs. They are incorporated into hydrogel dressings to maximize their anti-infective effects. Xu et al. developed a novel dual-drug-loaded hydrogel dressing derived from the conjugation of dextran and functionalized 4-arm polyethylene glycol (PEG). Two drugs, polymyxin and vancomycin, were covalently grafted to PEG, and the dressing exhibited excellent antimicrobial activity against *Escherichia coli* (Gram-negative bacteria) and *Staphylococcus aureus* (Gram-positive bacteria) (Fig. 4) [100].

While antibiotics are widely employed to treat wound infections, they come with notable limitations, including the potential development of drug resistance with prolonged use. As an alternative, AgNPs, known for their excellent antibacterial properties, have become a prominent area of research. Tariq et al. prepared a hydrogel dressing containing AgNPs from CS/PEG/AgNPs hydrogel crosslinked by glutaraldehyde [101]. The release of AgNPs remained stable and sustained in diabetic rabbits for a period exceeding 7 d. This dressing demonstrated significant antimicrobial properties and the ability to promote the wound healing process. Furthermore, the nanosilver encapsulated in the hydrogel showed desirable results compared to common conventional antibiotics.

As bacterial membranes are negatively charged, cationic substances are believed to have the potential to disrupt them, leading to bacterial death. Cationic polymers, such as CS and polylysine, are considered to possess inherent antimicrobial properties [102]. Therefore, an alternative strategy is to construct anti-infection dressings from cationic polymers. This approach can achieve antimicrobial purposes without loading excessive antibiotic drugs, offering limitless possibilities for the future of antimicrobial hydrogels. Wang et al. cross-linked CS with dialdehyde through a dynamic Schiff-base reaction, forming an injectable and self-repairing antimicrobial hydrogel dressing [103]. Lin et al. prepared an antimicrobial hydrogel dressing for DFU treatment using ε-polylysine as one building block. The resulting dressing exhibited long-lasting water retention, adhesion, and antimicrobial properties (Fig. 5) [104]. The introduction of ε-polylysine into the three-dimensional (3D) network of the dressing endowed it with long-lasting antimicrobial activity against Gram-negative bacteria and Gram-positive bacteria.

Xu and colleagues developed a derma-like anti-infection hydrogel dressing by crosslinking oxidized HA solution with carboxymethyl CS solution [105]. Utilizing a straightforward penetration cross-linking method through Schiff-base reaction between oxidized HA and carboxymethyl CS solutions with higher viscosity, a gradient porous structure formed inside the hydrogel, mimicking the dermal structure. This derma-like structure provided the gel dressings with self-adhesion to wounds and a barrier against bacteria. With the incorporation of cuttlefish juice and gentamicin, the dressing exhibited

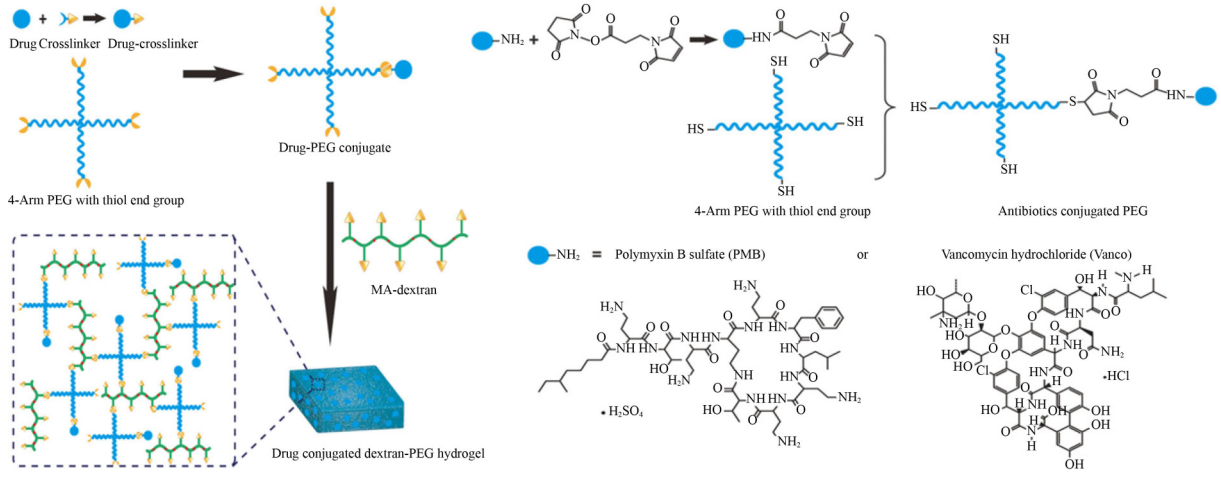

Fig. 4 Preparation of antibiotics conjugated dextran-PEG hydrogel and synthesis of antibiotics conjugated PEG. Reproduced with permission from Ref. [100].

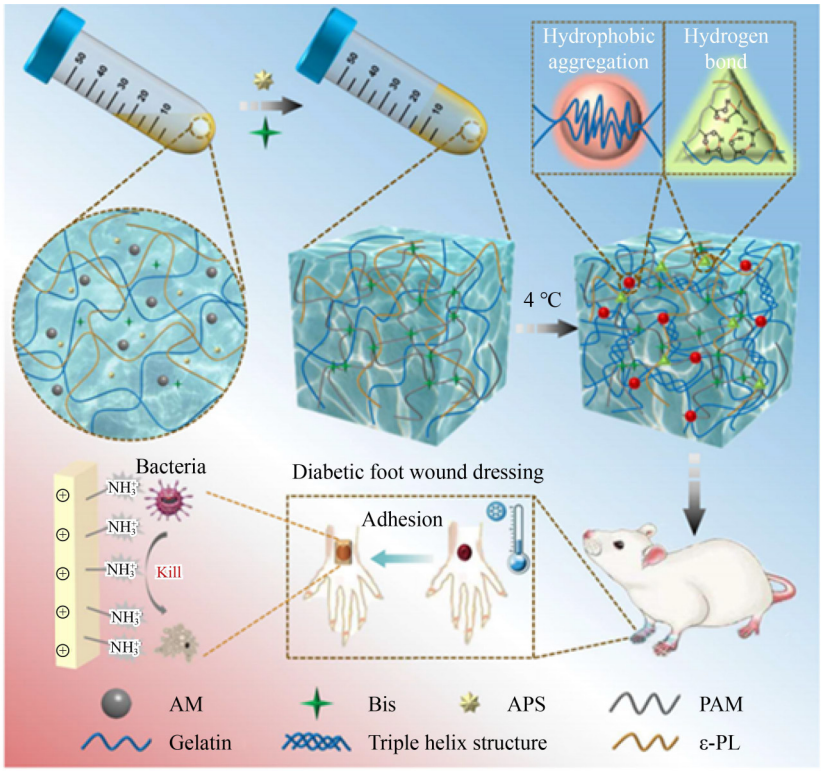

Fig. 5 Synthesis procedures of the G-PAGL hydrogel further applications in DFU dressing and schematic diagram of the antibacterial mechanism. Reproduced with permission from Ref. [104].

mild photothermal effects under near-infrared irradiation at a wavelength of 808 nm, reaching and maintaining a temperature of 45 °C. The mild heat, in conjunction with gentamicin, demonstrated rapid bactericidal performance within 5 min.

Consequently, the hydrogel dressings provide multiple antimicrobial dressings derived from anti-bacterial polymers, biotics, AgNPs, and photothermal effect, which can meet different requirements of anti-infection therapies selected for treatment of DFU. Furthermore, the hydrogel system is always feasible for further loading and modification by other functional materials and moieties, which may drive researchers to design and fabricate more powerful antimicrobial hydrogel dressings and translate them into clinics in the future.

3.3.2 Anti-inflammation hydrogel dressing for immune microenvironment regulation

Appropriate inflammation is indispensable in wound healing, while unfavorable endogenous or exogenous factors can interfere with inflammatory regulation, leading to excessive inflammation. An excessive inflammatory response may result in oxidative stimulation and impede the wound healing process [106]. Thus, the regulation of the immune microenvironment at the wound site plays a vital role in accelerating the healing of the DFU. Effective strategies to eliminate excessive inflammatory responses include scavenging excessive free radicals, sequestering chemokines, and modulating the polarization of M1 to M2 macrophages [107]. Natural polyphenols, polysaccharides, amino acids, as well as novel metal nanomaterials, are widely used to fabricate anti-inflammatory hydrogel dressings to regulate the immune microenvironment in the wound site of the DFU.

Commonly available natural polyphenols such as tea polyphenols [108], resveratrol [109], curcumin [110], gallic acid [111], and tannic acid [112] have been loaded into hydrogels to exert anti-inflammatory and antioxidant effects in wound healing. Although some polyphenols such as curcumin is hydrophobic, they can be loaded into the hydrogel dressing with the help of the auxiliary such as cyclodextrins [113]. Cheng et al. loaded resveratrol into mesoporous silica nanoparticles (MSNs), and the composite hydrogel dressings made from MSNs, platelet-derived extracellular vesicles (PDEVs), gelatin methacrylate (GelMA), and methacrylated silk fibroin (SFMA) can suppress inflammation in wounds due to the

anti-inflammatory ability of resveratrol (Fig. 6) [114]. Cao et al. utilized a phenylboronic acid (PBA)-anchored hydrogel (GOHA-PBA) to achieve active enrichment and intelligent release of curcumin. As the released curcumin possesses excellent antibacterial, anti-inflammatory, and antioxidant abilities, the as-prepared hydrogel dressing is suitable for the treatment of the DFU to shorten the inflammation stage and promote wound healing [115]. Wang et al. prepared an injectable self-healing hydrogel containing carboxymethyl chitosan (CMCS), curcumin gelatin nanoparticles (CG NPs), and SA. CG NPs endowed the hydrogel with good antimicrobial and anti-inflammatory properties and promoted angiogenesis by facilitating the polarization of M2-type macrophages, thereby significantly shortening the wound healing time [116]. Zhai's team used PEG as an initiator to polymerize aldehyde-modified aliphatic cyclic carbonate monomer to obtain the hydrogel matrix, and curcumin was loaded as a functional model drug into the hydrogel [117]. The as-prepared hydrogel has the ability to promote wound closure, re-epithelialization, and collagen regeneration. Consequently, loading natural polyphenols into the dressing can effectively regulate the immune microenvironment in the wound site of the DFU to promote healing, although the hydrogel systems are different.

Some polysaccharides, such as dextran and Bletilla striata polysaccharide (BSP), also possess excellent antioxidant and anti-inflammatory effects by scavenging excessive reactive oxygen species (ROS). Huang's team integrated striated polysaccharides into waterborne polyurethanes to prepare a hydrogel. This hydrogel has good compressive strength, water absorption and retention capacity, and exhibits outstanding hydroxyl group radical scavenging and low hemolysis [118].

As an interdisciplinary field, nanoparticles also play a role in anti-oxidation. Some nanoparticles, including AgNPs, zinc oxide nanoparticles, selenium nanoparticles, and molybdenum nanoparticles, have been applied in antimicrobial and anti-inflammatory hydrogel therapy for wound healing. Xu et al. reported a molybdenum nanoparticle-loaded hydrogel system to scavenge harmful ROS in DFU. As molybdenum is in a low-valence state, it is a strong reducing agent that can easily scavenge ROS. Furthermore, the molybdenum hydrogel dressing is able to promote angiogenesis and stimulate the secretion of growth factors to accelerate the healing of DFU [119]. As the proliferation stage is closely next to the inflammation

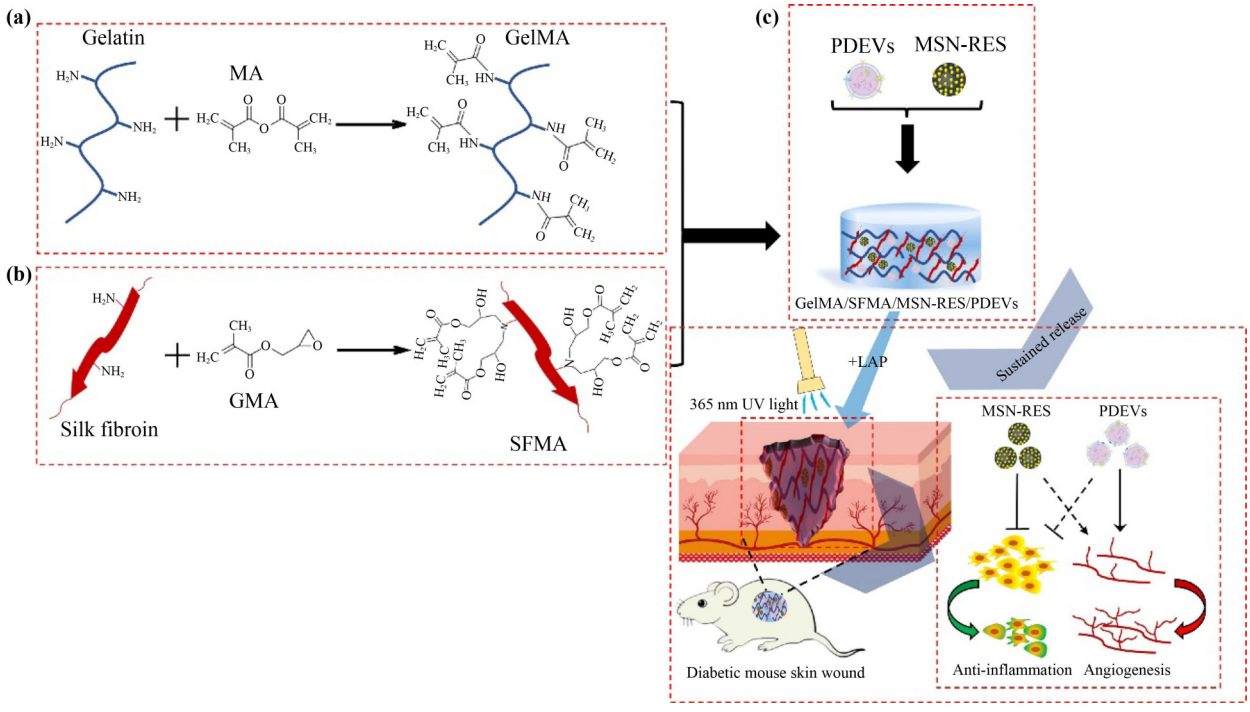

Fig. 6 Schematic diagram of GelMA/SFMA/MSN-RES/PDEVs hydrogel preparation and application: (**a**) schematic of the modification of the gelatin molecule with MA; (**b**) schematic modification of a silk fibroin molecule with GMA; (**c**) schematic showing the preparation of GelMA/SFMA/MSN-RES/PDEVs hydrogels used as a dressing for wounds in a diabetic mouse model. Reproduced with permission from Ref. [114].

stage, it is beneficial that an anti-inflammatory hydrogel dressing can possess some healing-promoting properties, such as promoting angiogenesis. However, the dosage and release of novel nanoparticles need to be strictly controlled, as excessive nanoparticle release can be counterproductive.

Therefore, anti-infection/bacterial dressing and anti-inflammatory dressings are two major dressings for the treatment of DFU in the anti-inflammatory stage. However, multifunctionality is still crucial for this stage. A dressing that can simultaneously meet the requirements of anti-infection and anti-inflammation is highly desired. Furthermore, as the proliferation stage occurs just after the inflammation stage, a hydrogel dressing that can possess both anti-inflammatory and healing-promoting abilities is also beneficial for accelerating the healing of DFU.

3.4 Multifunctional healing-promoting hydrogel dressings

The occurrence of the proliferation stage signifies promising healing. However, if the proliferation stage is prolonged, there is a risk of secondary infection leading to regression to the inflammatory or even hemostatic stage. This scenario is more likely to occur in DFU patients, as achieving healing solely through endogenous growth factors is challenging for them. Therefore, the supplementation of exogenous nutrients and growth factors by dressings is necessary to promote healing for DFU patients in the proliferation stage. We fabricated a hydrogel dressing encapsulating heparin and basic fibroblast growth factor (bFGF) through the Michael addition of 4-arm acrylated PEG and dithiothreitol [120]. The as-prepared hydrogel dressing combines the advantages of wet healing theory and exogenous growth factor supplementation. The hydrogel network can sustainably release bFGF within 10 d. The released exogenous bFGF significantly enhances the expression of VEGF and transforming growth factor-β (TGF-β) at the wound site, indicating improved angiogenesis and on-site cell proliferation in the wound site. Heparin helps the hydrogel dressing possess low inflammation in the early stage, beneficial for accelerating wound healing and preventing scar tissue production. Consequently, the as-prepared hydrogel dressing shows promising potential for better therapeutic efficacy in the treatment of DFU in the proliferation stage. We further tested the therapeutic efficacy of the as-prepared dressing in an old mouse model, as many DFU patients are elderly and have even worse self-healing ability [121]. Satisfactory healing promotion was achieved for the heparin and bFGF-loaded hydrogel dressing in the old mouse model.

On the other hand, it may also be beneficial if the hydrogel dressing for the proliferation stage can possess anti-inflammatory properties in addition to the healing-promoting property. Polydeoxyribonucleotide (PDRN), a series of nucleic acid fragments extracted from salmon, has functions such as improving angiogenesis, promoting cell activity, increasing collagen synthesis, and developing the anti-inflammatory response. These effects have positive implications for wound healing. However, naked PDRN is difficult to take up by cells. Inspired by gene vectors, Hu et al. prepared a PDRN-loaded $CaCO_3$ nanoparticle (PCNP) to improve the delivery efficiency of PDRN. PCNPs were encapsulated in an alginate/CS-based hydrogel. Under the action of PDRN, the wound healing rate has been confirmed to be significantly accelerated [122].

3.5 Smart hydrogel dressing for modulating the hyperglycemic environment

Since the hyperglycemic environment is a major factor delaying the healing of DFU, it is believed that regulating the hyperglycemic environment at the wound site may be beneficial for accelerating DFU healing. Yu's team designed a glucose-responsive multifunctional hydrogel dressing (DG@Gel) for the treatment of glucose oxidase (GOX) in DFU [123]. DG@Gel is sensitive to the hyperglycemic microenvironment and breaks down excess glucose into H_2O_2 and glucuronic acid. Lowering the pH promotes the release of zinc ions and deferoxamine mesylate (DFO), resulting in synergistic antimicrobial and angiogenic activities. This approach significantly promotes wound healing in diabetic mice *in vivo* (Fig. 7). Zhang et al. integrated Au-PT alloy nanoparticles into hydrogels prepared by the Schiff-base reaction of oxidized HA and carboxymethyl CS [124]. The incorporated Au-PT nanoparticles can deplete glucose and eliminate ROS from the wound.

3.6 Smart personalized hydrogel dressing

Recently, precision healthcare and personalized healthcare have emerged as future trends in medicine, aiming to provide personalized therapy tailored to each patient's individual condition. Intelligent monitoring of the

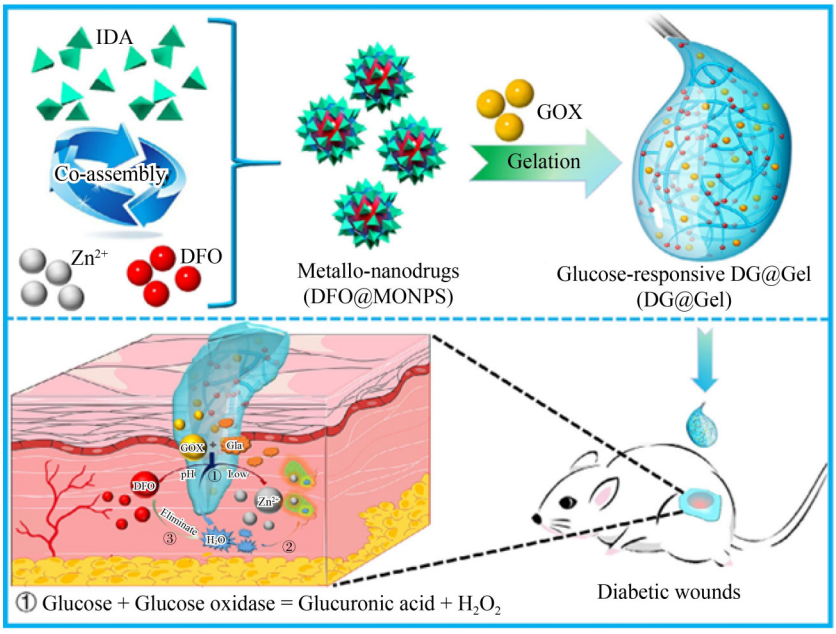

Fig. 7 Schematic diagram of the preparation of glucose-responsive metal–organic hydrogel and its mechanism of repairing diabetic skin wounds. Reproduced with permission from Ref. [123].

patient's individual condition is essential in this context. Zhang et al. designed and fabricated a multifunctional hydrogel employed as a wound dressing for intelligent wound monitoring [125]. This hydrogel not only possesses antibacterial, hemostatic, and adhesive properties, effectively promoting wound healing but also enables real-time monitoring of wound status, such as pH. The entire intelligent wound monitoring process comprises three main parts: wound recognition, real-time status monitoring, and personalized wound management, achieving point-of-care monitoring. Furthermore, the personalized wound management model, with high accuracy (94.47%), based on the convolutional neural network (CNN) machine learning algorithm, can analyze and evaluate wound healing and infection status through the colorimetric signal of the hydrogel dressing. This smart hydrogel dressing provides an advanced solution to accelerate wound healing, reduce bacterial infections, and represents a significant step toward future intelligent wound management (Fig. 8). Moreover, Bao et al. reported the fabrication of 'smart' bandages based on multimodal wearable devices enabling real-time physiological monitoring and active intervention to promote healing of chronic wounds [126]. They developed a flexible bioelectronic system consisting of wirelessly powered, closed-loop sensing, and stimulation circuits with skin-interfacing hydrogel electrodes capable of on-demand adhesion and detachment. The smart hydrogel dressing can continuously monitor skin impedance and temperature and deliver electrical stimulation in response to the wound environment. Across preclinical wound models, the treatment group healed ~25% more rapidly and with ~50% enhancement in dermal remodeling compared with the control. Furthermore, the activation of proregenerative genes in monocyte and macrophage cell populations was observed, potentially enhancing tissue regeneration, neovascularization, and dermal recovery. This work not only achieves point-of-care monitoring of the wound, but also provides an integrated diagnosis and treatment system for chronic wounds. It prospectively indicates the future trend of hydrogel dressing for the treatment of DFU.

4 Fabrication of hydrogel dressing

Wounds often present themselves in various shapes and sizes, typically characterized by uncertainty. Previous hydrogel dressings lacked the necessary flexibility to effectively match the variability of wounds [127]. Consequently, there is a demand for hydrogel dressings that not only meet functional requirements but also offer efficient and precise coverage for diverse wounds. Therefore, the critical focus lies in the preparation and

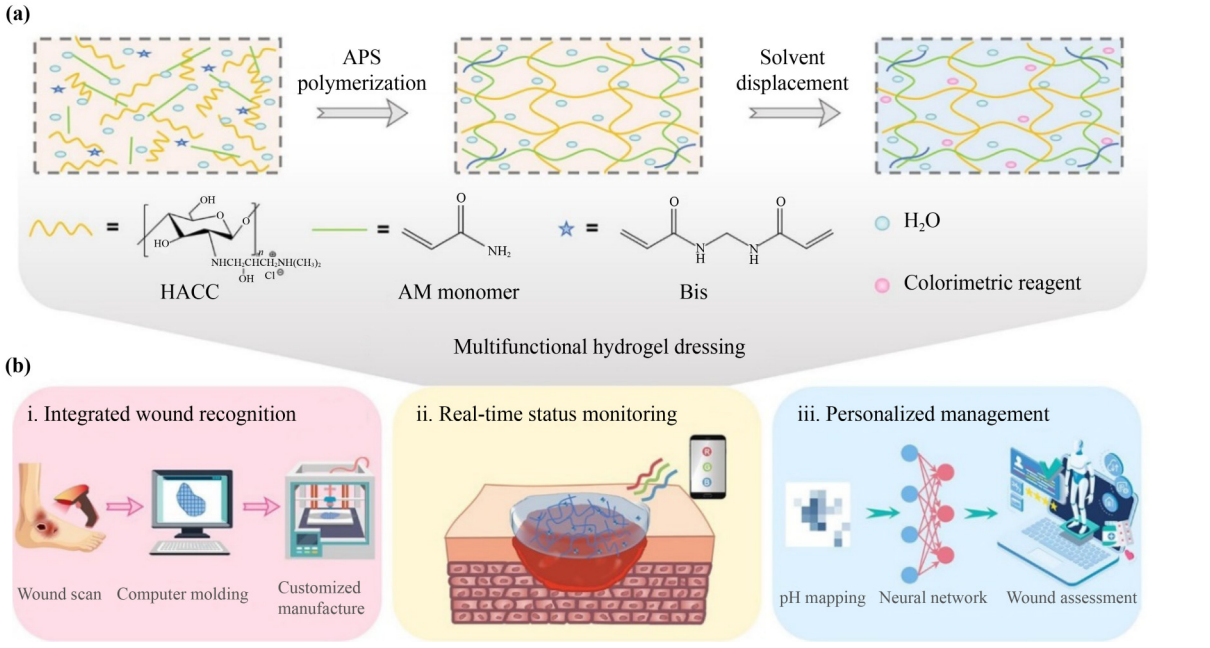

Fig. 8 (**a**) Schematic diagram of the preparation of multifunctional hydrogel. (**b**) Schematic diagram of intelligent wound monitoring with multifunctional hydrogel as wound dressing, including wound recognition, real-time status monitoring, and personalized wound management. Reproduced with permission from Ref. [125].

processing of multifunctional hydrogel dressings. This article primarily delves into the three most widely utilized methods for preparing multifunctional hydrogel dressings (Fig. 9), addressing the dual need for functionality and accurate coverage of wounds.

Template method involves adding the precursor solution of the hydrogel into a mold, followed by the addition of a crosslinking agent and photoinitiators for gelation. The template method is known for its simplicity, uniformity, and fast preparation of hydrogel dressings, making it a common approach. By designing the necessary templates, hydrogel dressings of desired shapes can be obtained [128–129]. Materials used for preparing templates are typically non-adhesive, such as silicone, polymers, and silica. While the template method is one of the earliest and most widely used approaches, it has certain drawbacks. The mold preparation process can be cumbersome and is constrained by shape and size, making it challenging to achieve multilayer structures. These limitations somewhat restrict its future applications. In comparison, the 3D printing technology demonstrates superior advantages.

In situ injection is a technique that involves directly injecting injectable hydrogel precursors into the wound area for treatment, providing a direct coverage for DFU. In comparison to the template method, it offers greater flexibility, enhanced local therapeutic effects, and precise

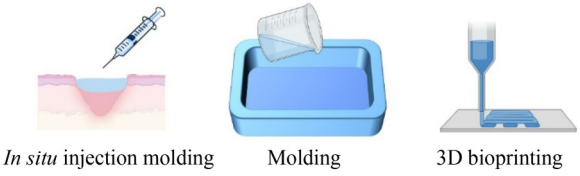

Fig. 9 The method of fabricating and processing hydrogel dressings for DFU (created with BioRender).

drug release. Zhao et al. utilized phenylboron-modified CS, PEG, and benzaldehyde-terminated PEG to prepare a pH and glucose dual-responsive hydrogel for injectable wound dressings. Through Schiff-base reaction, insulin and live cells were incorporated into the hydrogel, allowing drug release at higher glucose concentrations and permitting cell proliferation within the gel matrix [130–131]. Additionally, *in situ* injection can be combined with a hydrogel photocrosslinking system. Zhang et al. developed an injectable photocrosslinkable hydrogel that rapidly solidifies *in situ* without the need for a photoinitiator. Using SA as a natural polymeric crosslinker and PEG containing styrene-based pyridine groups as a photosensitive polymer, the injectable hydrogel scaffold significantly accelerated the healing of infected wounds [132]. However, *in situ* injection also has its limitations. There may be concerns about the residual toxic crosslinking agents, and the hydrogel precursor for

in situ injection requires high demands, including suitable injectability, viscosity, and gelation time.

3D printing is a technique that rapidly forms objects by depositing biological ink layer by layer. Moreover, the 3D printing technology allows for the utilization of computer-aided design to customize materials of different shapes. The precursor solution of hydrogel possesses excellent shear-thinning characteristics, making it an ideal bio-ink material [133–134]. The advantages of 3D printing hydrogel dressings have been demonstrated in various aspects. Firstly, it enables customized dosage based on individual patients. Secondly, it facilitates the design of dressings tailored to the characteristics of patients' wounds, including dimensions, shapes, areas, and thicknesses. Thirdly, the mesh structure of the dressings is conducive to permeability [135]. Therefore, the 3D printing hydrogel dressing technology has become a crucial method for personalized healthcare. Kumacheva et al. utilized cellulose nanocrystals and chitosan methacrylamide to 3D print multifunctional mesh-like hydrogels. Simultaneously, the printing process loaded AgNPs and VEGF [136]. VEGF has been widely used to promote angiogenesis. *In vitro* experiments have demonstrated the antimicrobial performance and wound healing capabilities of the hydrogel. This customized treatment approach is applicable to various wound types, showcasing extensive prospects for applications in the medical field.

5 Conclusion and prospect

With the increase of the number of DFU patients year by year, the clinical demand for the dressing that can effectively promote the DFU healing is getting larger and larger. Hydrogel dressings have become the most competitive and desirable candidate in the past decades, because they provide not only a moist environment for the wound healing, but also various therapeutic effects such as hemostasis, anti-infection, anti-inflammation, healing-promoting. Furthermore, multifunctional dressings that can be applied in two or more stages of DFU are more suitable for the clinical requirement due to the complexity and refractoriness of DFU. In the future, on the one hand, researchers should design and fabricate smarter and more powerful hydrogel dressings to cure DFU, and on the other hand, more attentions should be paid to the translation of hydrogel dressings as only few hydrogel dressings have been approved to be applied in clinic.

With the combination of materials and intelligent electronics, hydrogel dressings can achieve the intelligent wound management for DFU. Based on the point of care monitoring, personalized therapies could be applied on the treatment of DFU, which is believed to be able to change the clinical status of the DFU treatment and significantly improve the therapeutical effect of treating DFU in the future. Thus, personalized hydrogel dressings based on the point of care monitoring is one of the most promising candidates that can address challenges of the clinical DFU treatment in the future.

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