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Advanced Multifunctional Wound Dressing Hydrogels as Drug Carriers

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Skin injuries, especially chronic wounds, remain a significant healthcare system problem. The number of burns, diabetic patients, pressure ulcers, and other damages is also growing, particularly in elderly populations. Several investigations are pursued in designing more effective therapeutics for treating different wound injuries. These efforts have resulted in developing multifunctional wound dressings to improve wound repair. For this, preparing multifunctional dressings using various methods has provided a new attitude to support effective skin regeneration. This review focuses on the recent developments in designing multifunctional hydrogel dressings with hemostasis, adhesiveness, antibacterial, and antioxidant properties.

1. Introduction

Chronic wounds are referred to the situation in which the routine process of wound healing is disrupted in some phases and may continue from 4 weeks to more than three months. Trauma, diabetic and vascular diseases, bacterial infections, pressure, and/or radiation are common causes of chronic wounds. It is estimated that ≈2% of all hospitalized patients, especially older patients, suffer from a chronic injury.[1]The population of older people is expected to increase twofold between 2012 and 2060 in the USA. About 6.5 million patients suffer from chronic wounds in the USA, and more than USD 25 billion are spent annually on treatment.[2] Unfortunately, more than 70% of these wounds are recurrent, and ≈34% are bacterial infections, making treatment difficult.[3] Various methods are developed to treat chronic wounds, including wound cleaning, debridement of wounds, compression stockings and bandages, ultrasound and electromagnetic therapy, hyperbaric oxygen therapy, skin grafts, negative pressure wound therapy, and using wound dressings.[4]

Wound dressings are essential parts of medical and pharmaceutical chronic wound treatment that are a barrier to bacterial contamination. Moreover, they preserve the proper humidity level, absorb wound exudate, and accelerate wound healing.[5] Unlike a typical injury, it is necessary to manage chronic wounds to shorten the inflammatory phase and induce a faster healing process. Simple wound care using traditional wound dressings may not be effective for these cases due to a lack of intrinsic wound regeneration characteristics and antibacterial and hemostatic properties. It is recommended to incorporate biologically active molecules to develop advanced multifunctional and next-generation wound dressings to overcome these limitations.[6] These dressings act as a local drug delivery system that can alleviate such constraints of systemic drug delivery. For example, sufficient blood supply is crucial for systemic drug delivery; however, blood vessels are disrupted in most chronic wounds. In addition, high drug toxicity and side effects are other adverse effects that limit the use of systemic drug delivery platforms.[7] Thanks to local drug delivery, it is feasible to apply high doses of drugs to the target sites, bypassing gastrointestinal tract absorption, preserving drug bioactivity, and reducing drug cytotoxicity. In spite of the benefits of localized delivery, simple drug delivery systems cannot accomplish the complete requirements of such therapy.[8]

Drug-resistant bacterial infections and the slow regeneration of chronically infected wounds are two main challenges, which can also be overcome by designing and preparing advanced multifunctional wound dressings with the capability to deliver two or multiple drugs to the defected sites.[9] For example, Alizadehgiashi et al. applied 3D-printed multifunctional hydrogel wound dressings carrying antibacterial silver nanoparticles (AgNPs) and vascular endothelial growth factor (VEGF). The hydrogel suppressed bacterial growth and improved granulation of tissue formation and vascularization.[10] In another example, multifunctional bioactive core–shell electrospun mats containing zinc oxide nanoparticles (ZnONPs) and oregano essential oil (OEO) were used for healing diabetic wounds. Concomitant use of ZnONPs and OEO had a synergistic effect on

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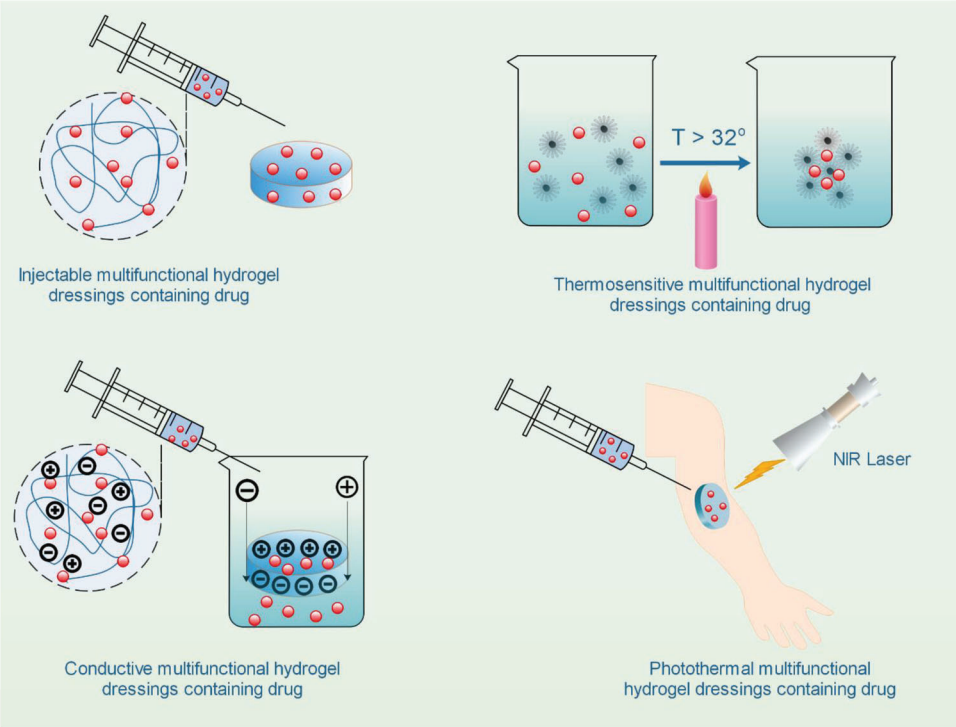

Figure 1. Schematic illustration of using multifunctional hydrogels as drug carriers.

suppressing bacterial infections.[6] Taken together, applying multifunctional wound dressings with the ability to deliver single or multi-bioactive molecules is a suitable strategy for improving wound healing (**Figure 1**). This review highlighted the recent advances in the use of multifunctional wound dressing, focusing on their drug delivery applications for optimal wound healing.

2. Cellular and Molecular Mechanisms of Wound Healing

Various complicated and sequential cellular and molecular mechanisms are responsible for regenerating the injured skin in acute and chronic wounds. Immediately after wound damage, blood vessels are ruptured. The blood clots are formed to prevent blood loss. Platelets are activated via platelet receptors (glycoprotein VI) with the subendothelial matrix, including fibronectin, collagen, and von Willebrand factor. Moreover, thrombin activates the platelets and subsequently promotes the release of dense and alpha-granules containing adenosine triphosphate, adenosine diphosphate, calcium, fibrinogen, fibronectin, von Willebrand factor, and others.[11] Simultaneously, tissue damage provokes the release of intracellular calcium, which is known to alter gene transcription protein kinase C, calcium/calmodulin-dependent protein kinase, and reactive oxygen species (ROS), such as H_2O_2. These phenomena stimulate the actin polymerization, actomyosin contractility, and expression of wound response genes of fibroblast and keratocytes.[12] ROS at deficient levels can also modify cellular attraction, migration, and attachment and activate the immune cells.[13] ROS and H_2O_2 can also interfere with hemostasis, inflammation, angiogenesis, and re-epithelialization.[14]

In the early phase of wound regeneration, several chemotactic factors such as interleukin 1 (IL-1), tumor necrosis factor-alpha (TNF-α), and lipopolysaccharide promote the attraction of neutrophils, which are responsible for cleaning necrotic cells and pathogens. Subsequently, circulating monocytes migrate to the injury site and differentiate into macrophages. Some factors, including interferon-gamma, ROS, IL-1, IL-6 and TNF-α, VEGF, and platelet-derived growth factor (PDGF), can activate the macrophages and are responsible for phagocytosis of necrotic cellular debris and pathogenic residuals. Macrophages play vital roles in the inflammation, proliferation, and remodeling stages of wound regeneration. As wounds heal, the proinflammatory macrophages (M1-like phenotypes) change to anti-inflammatory macrophages (M2-like phenotypes).[15] M1 macrophages are dominant in chronic wounds at the injured site, which means the inflammatory phase persists. Macrophages also support neovascularization through stabilization and fusion of blood vessels.[16] Resident and circulation of T cell lymphocytes are also essential for early injury response and resolving inflammation, respectively.[17] Keratinocytes are another crucial cell in the wound healing process. Keratinocytes express numerous factors, including transforming growth factor-β (TGF-β), VEGF, connective tissue growth factor, and antioxidants for accelerating re-epithelialization. These improve the repair of connective tissue via elaborating the mediators that induce angiogenesis and secretion of extracellular matrix (ECM) components.[18] Keratinocytes can also interact with T cells through antigen receptors to modulate immune responses.[19] Fibroblasts are also responsible for changing temporary fibrin-rich matrix to substantial granulation tissue. They can be affected by signaling factors such as TGF-β and PDGF produced by platelets, endothelial cells, and

macrophages. These factors can differentiate the fibroblasts into profibrotic or myofibroblasts, depositing the ECM proteins or inducing wound contraction, respectively.[20]

3. Commercial Hydrogels as the Wound Dressing

There are various types of wound dressings hydrogels on the market, including amorphous gel, sheets, films, and impregnated hydrogels. The ActivHeal hydrogel is one of the commercial wound care dressings based on amorphous gel applicable to dry the wound area with low exudate. This hydrogel can slowly increase the moisture level in the wound area through autolytic debridement, promoting the growth of the epithelial cell, and accelerating the wound healing. Suprasorb G hydrogel is also applied for acute or chronic wounds with low exudate in dry wounds. This gel can gently remove the necrotic tissue and absorbs it into the hydrogel. Using this type of hydrogel has many benefits, such as feasibility and the ability to reduce the pain in the wound environment. It is used with secondary film dressings to secure the hydrogel. NU-GEL hydrogel is a cost-effective, transparent, and amorphous gel containing sodium alginate that could efficiently remove the damaged tissue and slough. It also preserves the moisture in the wound area for better healing. Alginate increases the absorptive capacity of the hydrogel. Purilon gel is another hydrogel made from calcium alginate and sodium carboxymethyl cellulose. Carboxymethyl cellulose provides an optimal moist environment due to its high water holding capacity. It also induces the formation of ECM and re-epithelization. Neoheal hydrogel is another wound dressing produced by Kikgel manufacturer. It contains about 90% of the water that can absorb and donate to the wound area. It also stimulates the granulation and epidermalization of the injured wound. With the exception of DermaSyn containing vitamin E, other introduced hydrogels do not have bioactive molecules. Therefore, adding bioactive molecules can be considered a powerful strategy for optimal wound healing. A new generation of medicated dressings containing different bioactive molecules, known as multifunctional dressings, could overcome some disadvantages of the previous dressings. Adding drugs and/or some materials such as conductive, thermosensitive, and photothermal agents may develop an effective wound dressing to support wound regeneration.[11–13] Based on our knowledge, PosiFect RD and Procellera are only wearable bioelectric wound dressings and have received FDA approval. They can provide electrical stimulation to wounds.[14] There are no other commercial multifunctional wound dressings containing conductive, thermosensitive, and photothermal agents. Although these types of dressing have many advantages, inadequate elasticity, stiff membrane, and using crosslinking agents may restrict their applications in the clinic. Furthermore, some degrees of toxicity might occur by adding conductive, thermosensitive, and photothermal agents that should be overcome by some modifications.

4. Main Mechanisms of Controlled Drug Release from the Dressings

The wound dressings with controlled release behavior are potent platforms for sustained release of drugs into the wound microenvironment, avoiding the need for frequent dressing changes. However, little information is available about applying multifunctional dressings for the controlled release of drugs. The multifunctional dressings are generally made from various natural or synthetic polymers, with the ability to carry and release specific drugs into the wound environment. By using drug delivery carriers, it is possible to improve the bioavailability of the drugs and maintain their biodistribution in a controlled manner within the body. Generally, three main mechanisms are considered for releasing drugs from the polymeric matrix: diffusion-based release, degradation-based release, and affinity-based release. Generally, zero-order is preferable kinetics for drug release because, in this condition, the concentration of the drug is preserved in a steady-state between the minimum effective concentration and maximum toxic concentrations.[15] The zero-order profile is desired; however, most drugs exhibit triphasic release kinetics from the carriers.

Fast or burst drug release occurs in the initial phase due to the diffusion of drug molecules from the surface of the carriers during the fabrication process or storage. In the second phase, the drug passes from the polymeric matrix or pores of the polymeric carriers. Polymeric degradation and hydrolysis are also initiated at this phase for biodegradable drug carriers. In the third phase, erosion of the carriers is the primary mechanism for drug release.[16–18] The release rate of the drugs is influenced by the porosity, chemical structure, swelling degree of the carriers, molecular weight and hydrophilicity/hydrophobicity of drugs, and the interactions between the drug–drug and drug–carrier.[19] When the carrier is exposed to water, their pores and channels are filled with water, and the drugs are diffused from the reservoir to the releasing medium by osmotic pressure and potential chemical gradient.

Furthermore, drug molecules can diffuse via the polymeric matrix and can also be released because of the erosion of the carrier matrix.[20] Many drug carriers have been fabricated based on biodegradable polymeric matrices. They have various functional groups, including amides, esters, and anhydrides in their structures which can be broken by hydrolysis or enzymatic degradation, resulting in erosion of the drug carrier. Hydrolysis induces pore formation and enlargement upon water penetration into the matrix, which can alter the drug release profile. The pores of the polymer get enlarged and change the release rate of the drugs. The primary mechanism of drug release from the affinity-based systems is the transient interactions between the matrix and medicines.[21] Generally, it is essential to fully understand the mechanism of drug release from the polymeric carriers to design more effective systems with predictable release kinetics.

In conclusion, drug delivery platforms are potential routes for improving therapeutic efficacies in chronic wounds. However, the unpredictability of the chronic wounds microenvironment and the fact that each injury has its situation will be a significant difficulty in achieving desired outcomes. Therefore, drug carriers that can be used for on-demand drug delivery have been developed that enable active intervention in the dysfunction healing cycle.[22]

5. Wound Dressing for Scar Management

Trauma, burns, and surgery often result in scar formation, also known as dermal fibrosis, which can affect normal skin

function. Hypertrophic scars are thick and located to the wound margin, while keloids grow similar to benign tumor-like fibrous that extend beyond wound boundaries. Excessive scarring of skin tissue leads to decreased skin flexibility and functional abnormalities, including the loss of essential skin appendages; and accompanying itching and pain.[23–25] To date, different strategies have been developed to induce scar-free wound healing, including injecting intralesional corticosteroids, surgical excision, laser, compression, and interferon cytokine therapy.[26] Nevertheless, insufficient success has been achieved by using the techniques mentioned above. Thus, more effective strategies for scar-free methods are crucial. In recent years, researchers have attempted to develop multifunctional dressings comprising various biomolecules and drugs to improve the capability of scar management. For instance, it was reported that by incorporating genipin into collagen sheets, the rate of scar formation was reduced in first and second-degree burns.[27,28] Collagen sheets were reported to help the synthesis of neodermal collagen matrices for scarless healing.[28] Kim et al. also described that incorporating nitrofurazone into polyvinyl alcohol–sodium alginate gel–matrix could promote wound healing and reduce scar formation compared with those dressings without nitrofurazone. By using this nontoxic and biodegradable hydrogel, the wound's moisture was preserved and the possibility of secondary damage upon dressing changes was reduced.[29] In another strategy, it was exhibited that incorporating N-acetyl cysteine (NAC), as an antioxidant, into graphene oxide (GO)-functionalized collagen matrices induced the healing of 20 mm wounds without scar formation. The high mechanical strength and the sustained release of NAC decreased the in situ level of reactive oxygen species.[30] Another study prepared double water/oil/water emulsions based on photo-crosslinkable polylactic-*co*-glycolic acid (PLGA) encapsulating transforming growth factor-β. TGF-β had a pulsatile release from the PLGA matric that induced the wound closure and inhibited the scar formation. The authors suggested that the prepared construct could be used as an effective dressing for scarless healing of wounds.[31] Poly(acrylamide) hydrogel-based multifunctional dressing containing cerium oxide nanoparticle (CNP) and curcumin has been introduced for scarless wound healing. This type of dressing successfully treated the acute wounds with the help of controlled release of the curcumin for six days and the antioxidant activity of CNP that promoted scarless wound healing.[32]

In addition, Sun prepared a series of bioabsorbable hydrogels based on dextran (DexIEME). The results revealed that DexIEME hydrogel reduced the proinflammatory response and induced the M2 macrophage phenotype. It also influenced the complete repair of skin and regrowth of hair on the pre-existing scars. The preclinical studies further confirmed that DexIEME hydrogel could regenerate perfect skin during deep porcine wound regeneration, indicating good clinical potential.[33] The ultimate and desirable aim of using multifunctional dressings is to facilitate effective wound healing without scar formation. Consequently, developing pro-regenerative hydrogels provided new strategies to fully repair the injured skin in terms of structure and activity. Moreover, it is essential to develop hydrogels with the ability to modulate the immune system for better controlling the scar formation in the defected site.

6. An Overview of Multifunctional Hydrogels for Biomedical Engineering

Multifunctional hydrogels are innovative constructs applied for various applications and tissue engineering. The main advantage of these structures is that they could be designed to respond to several stimuli such as temperature, light, magnetic, and electric fields. Modulating the dose and release rate of biomolecules and drugs loaded on the hydrogels by applying an external force has a great perspective on drug delivery. Additionally, it is possible to add different nanofillers and bioactive molecules to improve the hydrogel's drug encapsulation and structural properties. Due to tailorable characteristics, the hydrogels are good candidates for imaging and diagnosis applications. The novel system opens a new avenue for developing hybrid injectable hydrogels with specific bioactive and molecular responses.[34]

The aqueous polymeric solutions undergo sol–gel transition by sensing the temperature change; they are potential candidates for preparing injectable thermosensitive hydrogels. At an ambient temperature, the polymer hydrogels are at free-flowing sol state that could be simply mixed with the biomolecules; while it is converted into a nonflowing gel state at the physiological temperature after injection in vivo which provides suitable carriers for local sustained release of the incorporated drugs. The injectable thermosensitive hydrogels have many benefits, including improved solubility of hydrophobic drugs, good safety, simple drug formulation and administration without the need for surgery, sustained-release behavior, site-specificity, and delivery of different types of bioactive molecules such as hydrophilic and hydrophobic drugs, peptides, proteins, and nucleic acid. Despite the progress in developing various thermosensitive injectable hydrogels, their clinical applications face some challenges. The main limitation is the lack of convenient production procedures for the clinic. Other issues are the reconstitution problem and the risk of syringe clogging during the injection. The former is of significant importance and is associated with the production, storage, transportation, and application process of hydrogel formulations. The latter can be overcome by developing hydrogels that gel at a more precise temperature and lower concentrations.[35]

Photosensitive hydrogels are other kinds of hydrogels with broad applications in wound healing and tissue regeneration purposes. Recently, it has been one of the research hotspots to apply the near-infrared (NIR) to reach the desired temperature at the targeted site. Moreover, hyperthermia could be used for antibacterial treatment and wound healing because the local heat can promote cell proliferation and thus improve wound regeneration. NIR-induced fluorescence imaging is also a dynamic and noninvasive method to track the process of tissue regeneration.[36] The photoresponsive drug delivery carriers have many advantages over other stimuli-responsive systems for drug delivery applications because photochemical processes do not need additional reagents or catalysts, and most by-products are not toxic. However, high temperatures produced by photothermal agents under NIR irradiation can cause some adverse effects on normal tissues. There are several mechanisms for the controlled release of drugs by photosensitive compounds. For example, light or UV can induce physicochemical changes in photosensitive agents, resulting in drug release. However, the main restriction of high energy light for triggering the drug release is their low tissue

penetration depth because of the strong scattering and absorption induced by the water molecules and other soft tissues in the body.[37] It is reported that thermosensitive liposomes containing photosensitizers can efficiently absorb low energy NIR light (>700 nm) and thus can penetrate several centimeters deep into the skin without significant attenuation by water and soft tissues.[38] Using these systems, it is possible to trigger the release of drugs from the carriers into deeper layers of skin (hypodermis), where the capillaries and the blood vessels are present.

Conductive hydrogels are other hydrogels that extensively used for artificial skin, implantable and flexible bioelectronics, and tissue engineering scaffolds. However, developing highly electrical conductive hydrogels is still challenging without considering other properties such as biocompatibility, stretchability, and toughness. Moreover, for using hydrogels as bioelectronics, it is necessary to enhance their functionality in terms of shape-memory, self-healing, and wet adhesion properties. One of the main approaches for developing conductive hydrogels is incorporating conductive polymers, carbon-based materials, and their derivatives into nonconductive hydrogels.[39] The conductive hydrogels prepared by these strategies have good processability; however, they often face unstable conductivity. Many techniques have been developed to improve the electrical conductivity of the materials. These include doping of the polymer matrix with highly conductive materials such as metallic fillers (e.g., copper, silver, gold), polyaniline (PANI), PEDOT, and others.[40–42] Another challenge of conductive hydrogels is the integration with biological tissues. For example, inorganic bioelectronics often induce neuroinflammatory responses due to chemical and mechanical mismatches between them and biological tissues.[39] Therefore, choosing suitable materials for causing generating electrical conductivity with minimal adverse effects on tissue is crucial.

6.1. Injectable Multifunctional Hydrogel Dressings for Wound Healing

Hydrogels are 3D structures similar to ECM that have been extensively investigated for delivering cells and bioactive molecules. The hydrophilicity of the hydrogels is ideal for absorbing a large amount of water while remaining insoluble in an aquatic environment because of their crosslinked structure. However, an invasive surgical procedure is needed to implant pre-formed hydrogels at the injured site, which restricts their application in the clinic. It is possible to use injectable hydrogels with minimal invasiveness and can be used for irregularly shaped defects to overcome this limitation.[43] Many researchers have applied several multifunctional injectable hydrogels for wound regeneration. For example, multifunctional hybrid injectable hydrogel comprised of four-armed benzaldehyde-terminated polyethylene glycol and dodecyl modified chitosan was fabricated to deliver VEGF.[44] The hydrogel had a self-healing property via Schiff base reaction between the benzaldehyde and amino groups in the polymer structures. Because of the dodecyl group of chitosan, hydrogel could easily stick to the lipid bilayer of the plasma membrane, inducing blood clotting and antimicrobial functions. Controlling the release of VEGF facilitated the proliferation of cells and remodeling of the tissue in the wound bed. The injectable hydrogel containing VEGF also considerably induced wound healing, collagen deposition, and minimal inflammatory responses to unloaded groups.[44]

Perviously, it was proved that exosomes derived from various cell types can induce angiogenesis, indicating a powerful strategy for treating diabetic wounds.[45] Exosomes isolated from M2 macrophages are nanosized ECM carriers with anti-inflammatory functions similar to M2 macrophages and proper angiogenesis.[46,47] Accordingly, Liu et al. used M2 macrophage exosome loaded in an injectable multifunctional hydrogel to promote angiogenesis in a diabetic wound model. The hydrogel had self-healing, tissue-adhesive, and antimicrobial characteristics against *E. coil* and methicillin-resistant *Staphylococcus aureus* (MRSA). The hydrogel could control the release rate of exosomes for 21 days. The uptake of the released exosomes by the human umbilical vein endothelial cells (HUVECs), supported the angiogenesis in vitro and in vivo and accelerated the wound healing in diabetic animal models.[48] Similarly, the adipose mesenchymal stem cell-derived exosomes were successfully added to the multifunctional injectable wound dressing based on Pluronic F127 (F127) grafting polyethyleneimine and aldehyde pullulan via electrostatic interaction (**Figure 2**). The exosome released from the hydrogel dressing presented a pH-responsive manner. The released exosomes supported HUVECs proliferation and enhanced angiogenesis and wound healing.[49]

Injectable multifunctional sodium alginate (SA) hydrogel was also developed by using hardystonite bioceramics (HS).[50] The HS contained Ca^{2+}, Zn^{2+}, and Si ions. The Ca^{2+} and Zn^{2+} crosslinked SA while enhancing angiogenesis. Generally, the ions released from the hydrogel promoted the growth and migration of human dermal fibroblasts and HUVECs, inhibited bacterial growth, and stimulated the wound repair process.[50] In **Figure 3**, the immunohistochemical analysis of endothelial cells (CD31) and keratinocytes (K14) markers are shown. The results exhibited that in the SA/HS group, the CD31 was intensely stained compared with SA composite without HA, the positive control group (SA composite containing recombinant human epidermal growth factor derivatives), and the negative control group (only injected with 10 μL methylprednisolone sodium succinate without hydrogel). These observations showed the blood vessel formation and vascularization in SA/HS hydrogel group were better compared with mentioned groups from 7 days to 14. The hydrogel also triggered the proliferation and migration of keratinocytes as confirmed by intense K14 staining in the newly formed epithelial layer.

In another study, oxidized dextral injectable hydrogel loaded with an antibacterial agent, *ε*-poly-L-lysine (EPL), and beta fibroblast growth factor (bFGF) were fabricated for full-thickness skin wound healing.[51] The aldehyde group of the oxidized dextran interacted with the amino groups of EPL through Schiff base reaction and induced the self-healing and injectable properties of the hydrogel to adapt to irregular shapes of wound defects. Positive charge and high water absorption of the hydrogel led to the cessation of bleeding, in vitro and in vivo. Moreover, the release of bFGF was related to the in vitro degradation of the hydrogel. Sustained release of bFGF and EPI from multifunctional hydrogel accelerated the migration of endothelial cells and angiogenesis. They suppressed the MRSA infection in a rat full-thickness skin wound model that enhanced wound regeneration.[51]

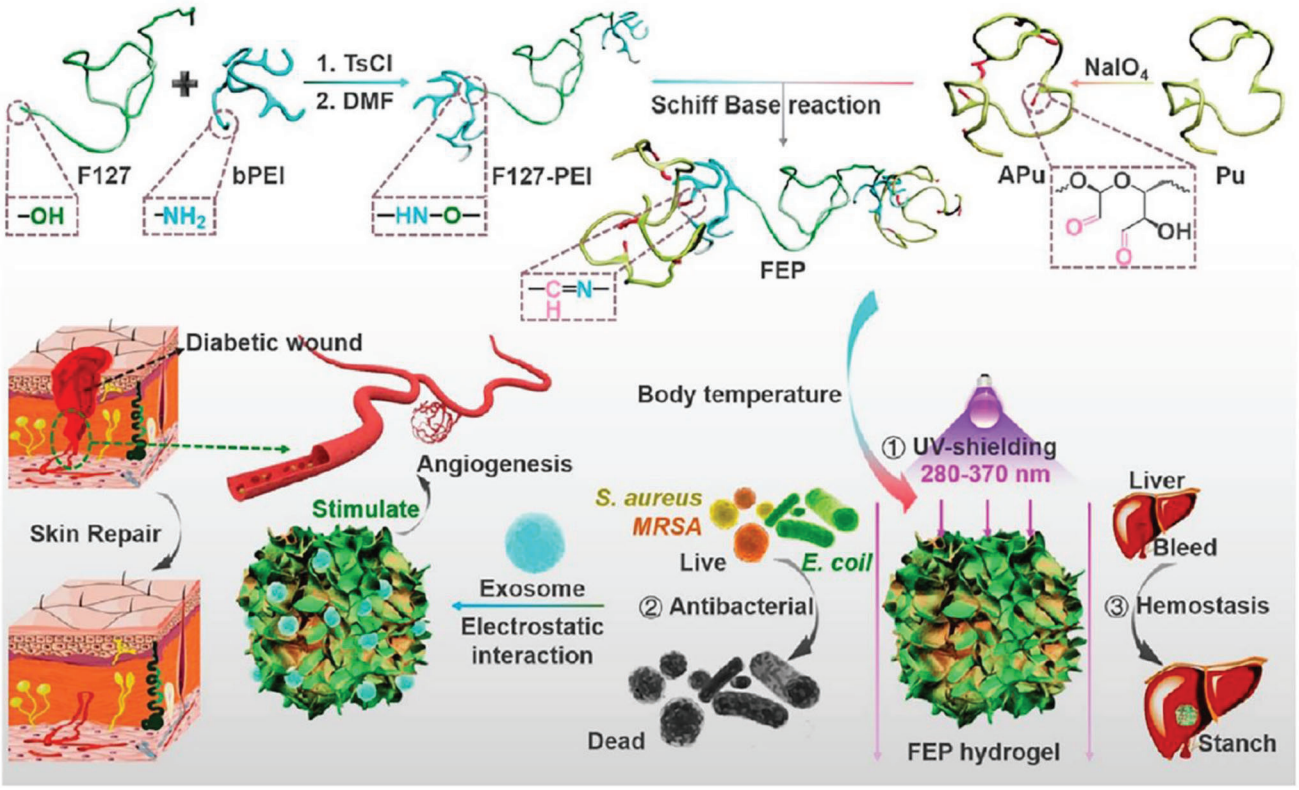

Figure 2. Schematic illustration presenting the synthesis of Pluronic F127 (F127) grafting polyethyleneimine and aldehyde pullulan multifunctional dressing containing nanoscale exosomes. Reproduced with permission.[49] Copyright 2019, American Chemical Society.

Applying multifunctional DNA hydrogel was also introduced to control diabetic infectious due to its degradability, less immunogenicity, thermosensitivity, and high sensitivity. For this, it was reported that injectable DNA hydrogels had antibacterial features against *Staphylococcus aureus* (*S. aureus*), *Escherichia coli* (*E. coli*), and *Pseudomonas aeruginosa* (*P. aeruginosa*), with antioxidant and anti-inflammatory properties that improved blood vessels formation and activated the neurons to transform into a repair state. Further, procyanidin B2 (OPC B2) was loaded in a hydrogel because of its free radical scavenging capacity. OPC B2 was released from the dressing under an NIR laser. The NIR laser destroyed the dynamic bonds inside the dressing, leading to OPC B2 release. The injectable multifunctional wound dressing also stimulated wound healing by recruiting myeloid cells to trigger adaptive immunity, induced wound regeneration, and hair follicle formation.[52]

Recently, various antibacterial hydrogels based on poly(vinyl alcohol) (PVA), pyrrolidinium ionic liquids, and tetrahydroxyborate anion were developed as wound dressings. The antibacterial properties of the hydrogel were due to the long alkyl chain of ILs, which inhibited the growth of *E. coli* and *S. aureus* and induced physical damage to decrease the bacterial resistance. Moreover, multifunctional hydrogel revealed self-healing and injectability characteristics and glucose and pH responsivity.[53] Similarly, Rao et al. fabricated an injectable hydrogel comprised of natural nonanimal fungal mushroom-derived carboxymethyl chitosan and tannic acid (TA) stabilized silver (Ag) with cell adhesion and hemostasis properties. Incorporation of AgNPs in an injectable hydrogel induced suitable antibacterial activity toward both *E. coli* and *S. aureus*.[54]

6.2. Conductive Multifunctional Hydrogel Dressings for Wound Healing

Recently, it has been found that skin with conductivity of 2.6 to 1 $\times 10^{-4}$ mS cm^{-1} is considered electrical signal-sensitive tissue.[55] The skin's surface has higher negatively charged groups than deeper layers of the skin; however, deeper layers of the skin tend to be more positive charge after injury. Coexistence of negative and positive charges makes the skin act as a battery. This bioelectric current improves wound healing when the skin is moistened.[56] Conductive materials have been confirmed to stimulate the behaviors of the electrically excitable cells, e.g., mesenchymal stem cells (MSCs), fibroblasts, neurons, keratinocytes, muscle cardiac, and bone cells, in terms of attachment, growth, and migration. Developing novel functional wound dressings with electroactivity is a promising strategy for wound healing. Conductive materials such as carbon nanomaterials, inorganic 2D nanomaterials, metal and metal oxides, conductive polymers (CPs), and their oligomers have their advantages and disadvantages. The most routine method to prepare conductive hydrogels with high conductivity is incorporating metal NPs into the hydrogel matrices. However, the application of metal NPs is restricted because of their high surface area, which induces their corrosion in the wet environment. As an alternative,

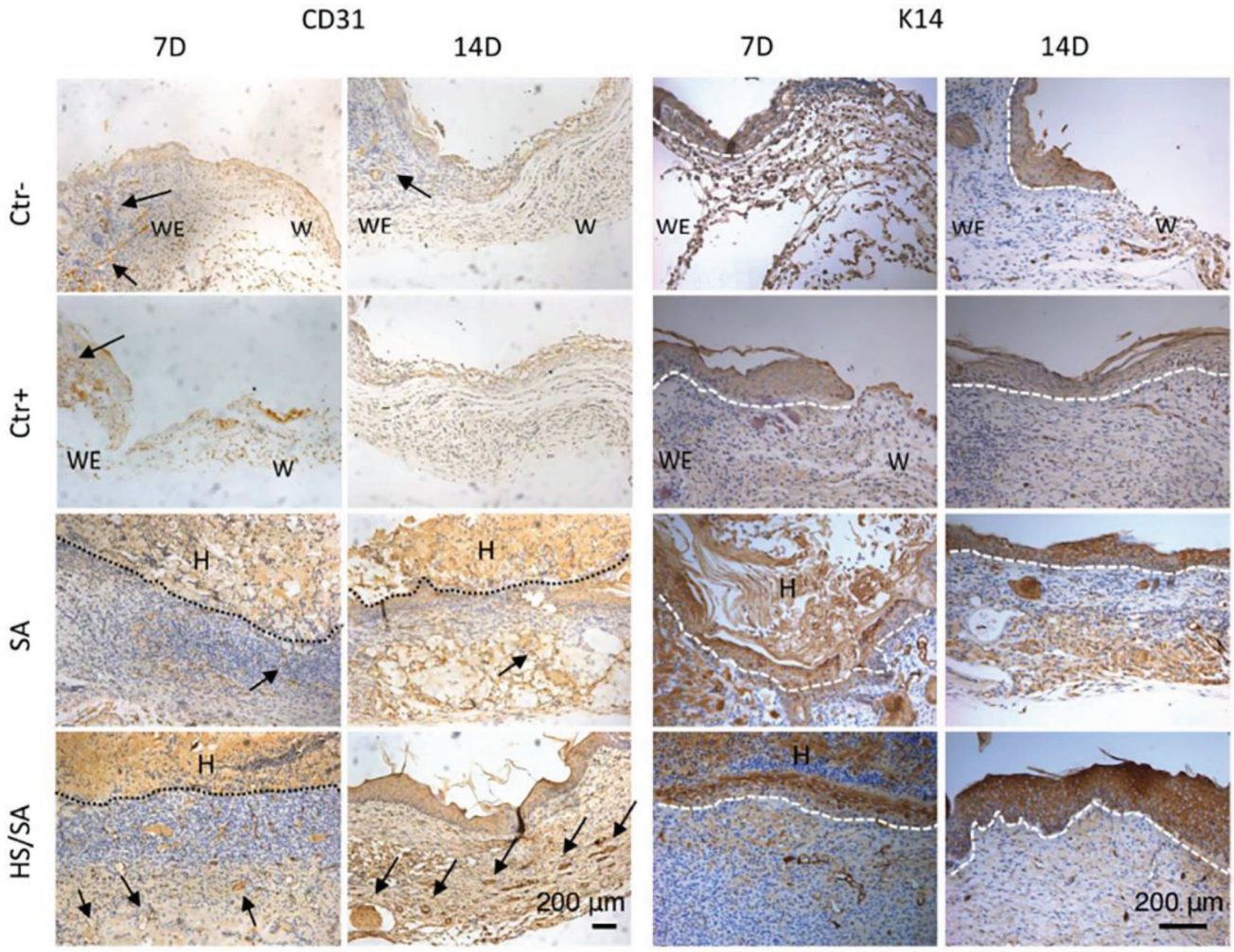

Figure 3. Immunohistochemical staining of K14 and CD31 markers after 7 and 14 days postimplantation. The black dotted line shows the border between the tissues and the hydrogels. The newly formed epidermis is depicted as the white dotted line. Black arrows indicate the blood vessels. H, hydrogel; WE, wound edge; W, wound. The left side of the figure is a new organization, and the right side is the center of the wound. Scale bar = 200 μm. Reproduced with permission.[50] Copyright 2017, American Chemical Society.

noble metals, including silver, gold, and platinum, could be used as conductive fillers due to their high corrosion resistance. Carbon nanotubes, whether single-walled or multiwalled, are other potential conductive materials with a high aspect ratio that are extensively used in biomedical applications. Carbon nanotubes (CNTs) possess high mechanical strength, good conductivity, and stability in the physiological environment. The major challenge in using CNTs is their weak dispersion in the hydrogel matrix. Graphene and its derivatives, such as GO and reduced graphene oxide (rGO), are other materials increasingly used in biomedical fields. Similar to CNTs, the dispersity of graphene in the hydrogel matrix is not well; however, GO could be homogeneously dispersed in the hydrogel because of its oxygen groups in the structure providing acceptable hydrophilicity. Though, the conductivity of GO is considerably lower than graphene. For this, rGO can be incorporated into the hydrogel to prepare hydrogel with suitable conductivity.

CPs, including PEDOT, PANI, and PPY are other conductive nanomaterials useful for biomedical applications; however, they are non-biodegradable, mechanically brittle, and hard to process, which all restrict their application as conductive materials. Conversely, the conductive oligomers benefit the manufacturing process and have good biodegradability; however, their electrical conductivity under physiological conditions limits further practical applications.[57–59]

Among various CPs that have been investigated, PANI has gained more attention. By doping PANI with an acid, it could be easily transformed from a nonconductive form (emeraldine base) into highly conductive form (emeraldine salt).[60–63] PANI is the only member of CPs and its conductivity can be adjusted by the degree of oxidation and protonation. PPy is another polymer with acceptable conductivity at the physiological state, good biocompatibility, and feasible surface modification, which broaden its applications in biomedical fields.[64,65] PEDOT, a polythiophenes derivative, has characteristics similar to that of PPy; however, the electrical stability of PEDOT is higher than PPy.[66,67] The excellent conductivity and high biocompatibility make PEDOT for biosensing and cell culture studies.[68,69] Generally, the electrical

conductivity of CPs may be reduced over time because of their reduction or loss of the dopant, affecting their promoting effects on wound closure. More importantly, the conductivity of CPs is related to several parameters such as pH value, dopant, and adjacent environment.[57]

As mentioned, PANI with proper electroactivity and solubility would be a good candidate to design conductive wound dressings. Introducing aniline tetramer into multifunctional hydrogel based on N-carboxyethyl chitosan and oxidized hyaluronic induced the conductivity and free radical scavenging capacity, successfully supporting the wound repair.[70] The release of antibiotics was more than 60% after 48 h, which was related to the presence of aniline tetramer in the hydrogels. Additionally, the amoxicillin-incorporated conductive hydrogel exhibited a practical antibacterial ability against *S. aureus* and *E. coli*. An animal study also showed that the hydrogels containing conductive material could better support the wound healing rate than the commercial film (Tegaderm) with mild inflammatory responses, higher fibroblasts proliferation, collagen deposition, and thicker granulation tissue thickness.[70]

As mentioned above, CNTs are other materials with good thermal and electronic properties, which are demonstrated to improve electrical characteristics and stimulate signal propagation, facilitating cell–cell interaction.[71] However, poor dispersity in water and toxicity of CNTs are significant disadvantages that can be overcome by surface modification.[72] Liang et al. modified CNTs with polydopamine (CNT-PDA).[73] Dopamine modification is an easy and effective method to alter the surface of materials.[74] After modification, the CNT-PDA was inserted into gelatin-grafted-dopamine to fabricate antibacterial, adhesive, antioxidant, and conductive multifunctional hydrogel wound dressing. By adding CNT-PDA and doxycycline to the hydrogel, proper in vitro and in vivo antibacterial activities toward *S. aureus* and *E. coli* bacteria were observed.

Moreover, the catechol group of PDA induced better tissue-adhesive, hemostatic, and antioxidative features. The hemolysis analysis and coculturing with L929 cells demonstrated suitable hydrogel biocompatibility. The authors found that wound closure, collagen deposition, epidermal regeneration, blood vessels, and hair follicle formation were achieved by using conductive hydrogel.[73]

Recently, HPEM scaffolds have been fabricated as conductive multifunctional wound dressings for treating MRSA-infected wound healing.[75] HPEM scaffolds are composed of poly(glycerol-ethylenimine), $Ti_3C_2T_x$ MXene@polydopamine (MXene@PDA) nanosheets, and oxidized hyaluronic acid (HCHO). HPEM scaffolds had conductivity, good biocompatibility, tissue-adhesiveness, hemostatic capability, and antibacterial features toward MRSA. HPEM scaffolds also revealed the highest expression of smooth muscle α-actin (α-actin), collagen type III (COL III), and VEGF, indicating its suitable wound healing property. As can be seen in **Figure 4**A, Ki67 was slightly more expressed in HCHO/poly(glycerol-ethylenimine (HPE) group than 3M group (Tegaderm Film) and blank group. However, the expression of Ki67 in HPEM group was considerably more than in other groups, indicating the positive effect of HPEM in inducing the proliferation of cells during the treatment, enhancing the formation of granulated tissue, and improving the deposition of collagen. The expression of α-smooth muscle actin (α-SMA) in the HPE group was also slightly higher than in the other groups. The strongest fluorescence intensity of α-SMA was presented in the HPEM group, indicating that the angiogenic response in the HPEM group was activated earlier or stronger than in other groups during the wound-healing period (Figure 4A,B). Moreover, CD31 was weakly stained in 3M and the blank groups (Figure 4A,C). The most vigorous fluorescence intensity of CD31 (green) was observed in HPEM groups. At the same time, HPE showed a mild level of CD31 staining, suggesting more neoangiogenesis in the HPEM group than in other groups.[75]

Lei and Fan developed hydrogel using TA and human-like collagen (HLC) into PVA. Borax was used as a hydrogel crosslinker and ionic conductor.[76] TA had antioxidant, hemostatic, and antimicrobial properties, while HLC promoted fibroblast proliferation for faster wound closure. The hydrogel's adhesion and biodegradability made the dressing feasible to be used without affecting the secondary wounds by changing the hydrogel, and the deep wound regeneration process was not interrupted. The conductive multifunctional hydrogel helped fill deep wound defects that facilitated the external and endogenous current conduction and induced the signaling pathways between the cells. It could apply external electrical stimuli and promote cell migration and vascularization using the existing structure.[76] Generally, other vital studies that used conductive hydrogel dressings are listed in **Table 1**.

6.3. Thermosensitive Multifunctional Hydrogel Dressings for Wound Healing

Thermosensitive polymers refer to the polymer containing hydrophobic and hydrophilic monomers. The balance between these segments endows the polymers with thermal properties. Temperature alters the interaction of hydrophobic and hydrophilic blocks with an aqueous environment, leading to a change in the solubility of the hydrogel network. Generally, thermosensitive polymers can be categorized into lower critical solution temperature (LCST) and upper critical solution temperature (UCST). Unlike UCST thermosensitive polymers, in LCST polymers, the sol–gel phase transition happens at temperatures below the required temperature. All the polymer components are completely miscible. However, at the above LCST, partial liquid miscibility takes place.[84] It is possible to inject thermosensitive hydrogels into the wound defects and then turn them into a semisolid phase by sensing the body temperature. Poly(*N*-isopropylacrylamide) (PNIPAm) is one of the essential thermosensitive polymers for the fabrication of hydrogel wound dressings. Because PNIPAm has LCST ≈33 °C in an aqueous solution and exhibits suitable thermoresponsive self-contraction characteristics at the body temperature (37 °C > LCST). Moreover, it is speculated that the wound closure can be accelerated by using hydrogels based on PNIPAm due to the volume contraction of the hydrogel.[85] For this, proper attachment of the hydrogel to the skin is essential to confirm that the contraction force of the hydrogel can induce wound closure. Quaternized chitosan (QCS) with the positively charged amino group is an excellent candidate to add to the hydrogels to cause tissue adhesiveness. Furthermore, QCS has antimicrobial and hemostatic properties promoting wound-healing performance.[86] For this,

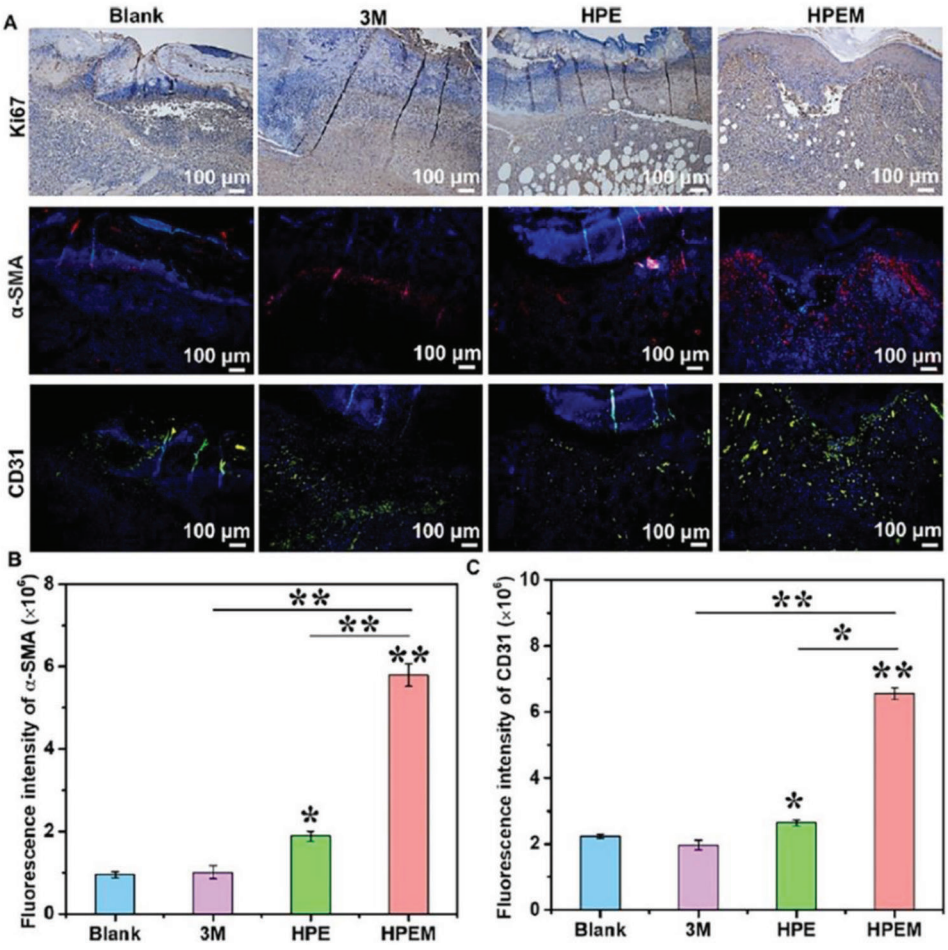

Figure 4. Immunohistochemistry and immunofluorescence staining of wound regeneration. A) Immunohistochemistry staining using Ki67, α-SMA (red: α-SMA, blue: nuclei), and CD31 (green: CD31, blue: nuclei). B,C) Quantitative evaluation of α-SMA and CD31 of wound tissues at day 7, respectively (scale bar = 100 μm; $n = 6$; $^{*}p < 0.05$ and $^{**}p < 0.01$). Reproduced with permission.[75] Copyright 2021, American Chemical Society.

thermosensitive multifunctional wound dressing was used based on QCS, PDA-coated reduction graphene oxide (rGO-PDA) and PNIPAm with appropriate thermoresponsive self-contraction and tissue adhesion features for wound repair. The hydrogel was attached to the defect's surface and facilitated the wound closure through actively contracting wound defects via self-contraction (**Figure 5**). The thermosensitivity of the hydrogel accelerated complete doxycycline release, representing the capacity of the hydrogels as temperature-controlled drug release carriers for wound regeneration. Because of this thermosensitivity, ≈40% of the drug was released from the hydrogels in the early hours at 37 °C, confirming a high doxycycline concentration in the wound bed within the first hours after skin injury. This is the ideal antibiotic prophylaxis against wound infection.[87]

It was also reported that triblock thermoresponsive hydrogel containing PNIPAm enhanced the cellular adhesion during tissue repair as a result of the positive surface charge of the hydrogel. The thermoresponsive properties of the hydrogel also induced the in situ gel formation at the body temperature. Furthermore, salicylate as an antibiotic was loaded into the hydrogel and its release effectively prevented the *E. coli* growth within 12 h without adverse effects on other mammalian cells.[88] Recently, PNIPAm hydrogel was also used for delivering MSCs to treat wound injury. First, MSCs were encapsulated in alginate polymer using the electrospray method and then incorporated into PNIPAm hydrogel (**Figure 6**). It was found that MSCs could secrete immunomodulatory factors, including IL-10 and TGF-β1. It can differentiate monocytes and M1 proinflammatory macrophages to the M2 anti-inflammatory macrophage phenotype. Releasing of TGF-β1 at the early stages of wound regeneration stimulated the recruitment of the inflammatory cells into the defected site and supported angiogenesis. Furthermore, thermosensitive hydrogel had LCST similar to skin temperature, facilitating the filling of irregular wound shapes and maintaining the encapsulated cells at the defected site. The hydrogel provoked the granulation and re-epithelialization by increasing the expression of α-SMA.[89]

Poloxamer 407 and F127 are other thermosensitive polymers that are comprised of a central hydrophobic monomer of polypropylene oxide (PPO) flanked by hydrophilic poly(ethylene oxide) blocks (PEO–PPO–PEO). Poloxamer provokes cell proliferation and wound regeneration by promoting epidermal growth factors.[90,91] Because poloxamers enhance the growth of human fibroblasts, they are used in an early postsurgical wound

Table 1. Conductive multifunctional hydrogels dressing applicable to wound healing.

Material	Conductive agent	Loading molecules	In vitro findings	In vivo findings	Application	Refs.
CEC[a] /PF127[b]	CNT[c]	Moxifloxacin hydrochloride	pH-responsivity, good antibacterial activity, tissue adhesiveness, and hemostatic features	Significant wound closure, collagen deposition, and vascularization	Full-thickness skin wound-infected model	[77]
QCSG[d] /GM[e]	GO[f]	Doxycycline	Good bio- and hemocompatibility, suitable antibacterial capacity	Less inflammatory response, promoting vascularization during wound repair	Full-thickness skin wound-infected model	[78]
QCS[g] / PEGS-FA[h]	PANI[i]	–	Good self-healing, free radical scavenging, antibacterial properties, and adhesiveness	Upregulation of VEGF[j], EGF[k] and TGF-β[l], inducing the formation of granulated tissue, and collagen deposition	Full-thickness skin wound model	[79]
PBAE[m] / HA-SH[n]	TA[o]	–	Good conductivity and hypoxia-inducing capacity to upregulate the hypoxia-inducible factor-1α and connexin 43 expressions	Enhancing the collagen deposition, hair follicle reconstruction, and vascularization	Diabetic wound	[80]
QCS	GO	Cyclodextrin	Proper antibacterial activity, good conductivity, and suitable biocompatibility	Promoting epidermis and granulation tissue thickness, increasing collagen synthesis, and upregulating the expression of VEGF	Full-thickness skin wound model	[81]
PDA@Ag[p] NPs/PVA[q]	PANI	–	Tunable mechanical and electrochemical properties, eye-catching processability, suitable self-healing, and adhesiveness	Promoting vascularization, accelerating collagen deposition, preventing bacterial growth, and controlling wound infection	Diabetic foot wounds	[82]
QCS	CNT	Ibuprofen	Robust mechanical properties, hemostatic capacity	Enhancing wound repair and wound closure	Full-thickness skin wound model	[83]

[a] N-carboxyethyl chitosan [b] Benzaldehyde-terminated Pluronic F127 [c] Carbon nanotubes [d] Glycidyl methacrylate functionalized quaternized chitosan [e] Gelatin methacrylate [f] Graphene oxide [g] Quaternized chitosan [h] Poly(ethylene glycol)-*co*-poly(glycerol sebacate) [i] Polyaniline [j] vascular endothelial growth factor [k] Epidermal growth factor [l] Transforming growth factor-β [m] Hyperbranched poly(β-amino ester)-tetraaniline [n] Thiolated hyaluronic acid [o] Tetraaniline [p] Polydopamine-decorated silver nanoparticles [q] Polyvinyl alcohol.

regeneration phase.[92] Hydrogel consisting of Poloxamer 407/chitosan/hyaluronic acid loaded with antioxidant agents such as vitamins A, D, and E had thermosensitive gelation processes with antimicrobial activity against MARSA and fungi (*Candida albicans*). The swelling behavior of the hydrogel and mechanical resiliency provided an opportunity for absorbing exudates. It promoted the regeneration of the burned skin model's epidermis, dermis, and stratum corneum. The functions of antioxidants in wound regeneration using vitamins A, D, and E were previously evaluated, although the exact mechanisms of action are unclear and controversial.[93] Similarly, multifunctional wound dressing of poloxamers 407 and 188 containing aminocaproic acid as a stop bleeding agent, povidone-iodine as an anti-infective, and lidocaine as a pain relief drug were able to change to gel phase for 10 min at 37 °C. The thermosensitive hydrogel revealed good antibacterial action similar to povidone-iodine solution. It significantly increased the pain threshold and enhanced wound healing compared to gauze. In this study; however, the release study of the drug did not report due to the fast dissociation of the hydrogel.[94] Liu et al. fabricated thermosensitive hydrogel containing polycitrate–polyethelene–Ibuprofen (PCEI) polymer and then prepared a multifunctional dressing via crosslinking between PCEI and F127-EPL-alginate (FEA-PCEI hydrogel).[95] The anti-inflammatory effect of PCEI was assessed by M1 polarization of macrophages. After 24 h, the IL-1b was remarkably suppressed by PCEI group and the expression of IL-10 was increased compared with PCE-treated group and the control group (**Figure 7**A). In addition, the reprogramming of macrophage phenotype by PCEI was examined by evaluating the CD 86 and CD 206 markers related to M1 and M2 macrophages, respectively. The obtained results showed that the number of M2 macrophages was remarkably increased by PCEI from 0.8% to 22.3%, while it had no significant effect on changing the percentage of M1 macrophages population (Figure 7B). The release profile of Ibuprofen from hydrogel was higher in an acidic condition (pH 5.5) than in an alkaline (pH 7.4) condition, possibly due to the breakage of Schiff base interactions in the hydrogel dressing under the acidic condition. The hydrogel exhibited temperature-response gelation, injectability, homeostasis capacity, and excellent biocompatibility. The antibacterial function of hydrogel against *E. coil*, *S. aureus*, and MRSA was attributed to the presence of the polyethyleneimine that changed the

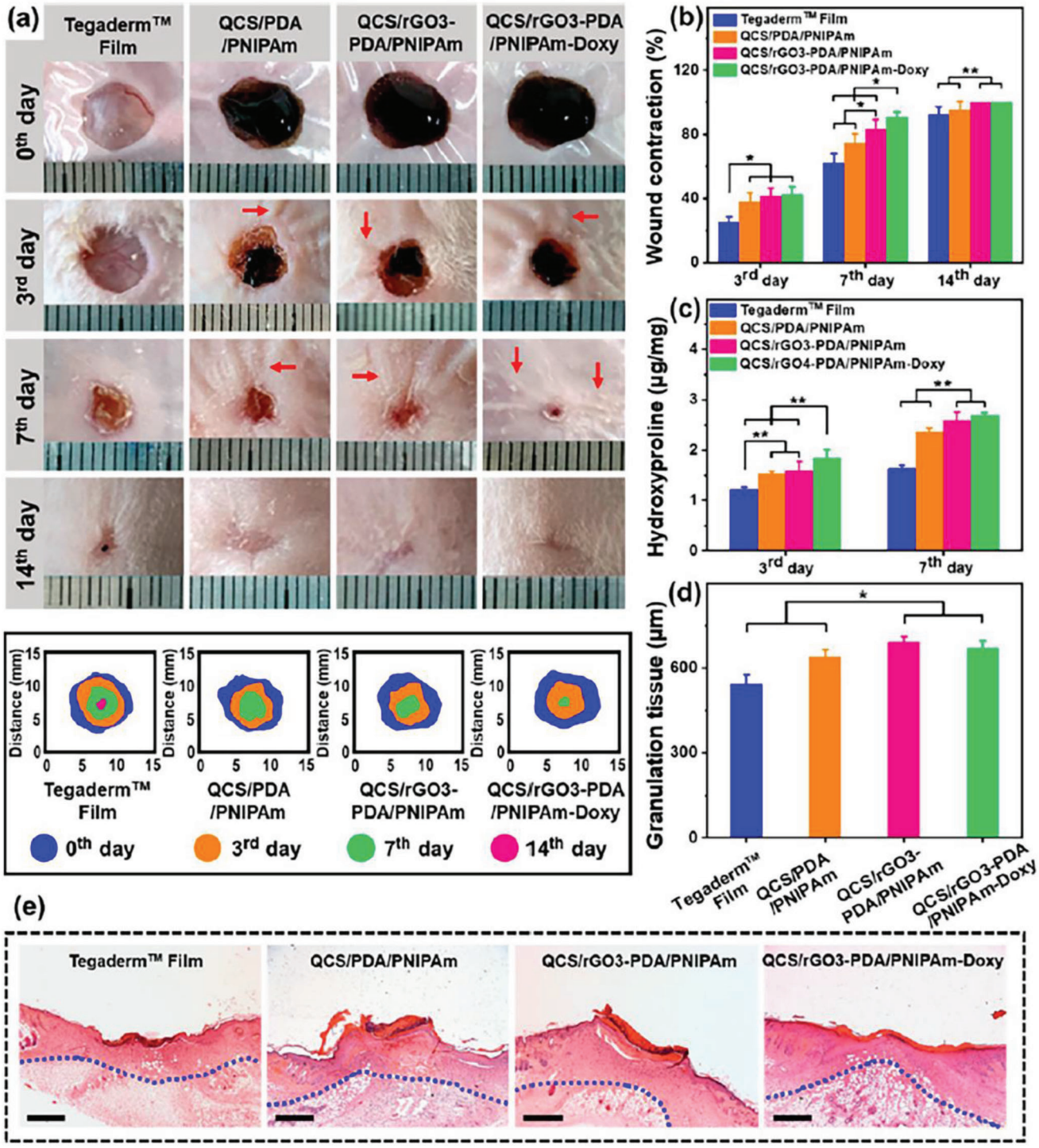

Figure 5. A) Wound closure on days 3, 7, and 14 for Tegaderm film dressing (control), QCS/PDA/PNIPAm, QCS/ rGO3-PDA/PNIPAm, and QCS/rGO3-PDA/PNIPAm-doxycycline. Red arrows show the wound contraction after hydrogel implantation. B) Wound contraction for each group. C) Collagen deposition in all the experimental groups. D) Statistical analysis of the thickness of the granulated tissue for various groups on day 7. E) The thickness of the granulated tissue for commercial film dressing (Tegaderm), QCS/PDA/PNIPAm hydrogel, QCS/rGO3-PDA/PNIPAm hydrogel, and QCS/rGO3-PDA/PNIPAm-doxycycline hydrogel on day 7 (granulation tissue, area above the blue line). Scale bar: 500 µm. $*P < 0.05$, $**P < 0.01$. Reproduced with permission.[86] Copyright 2020, American Chemical Society.

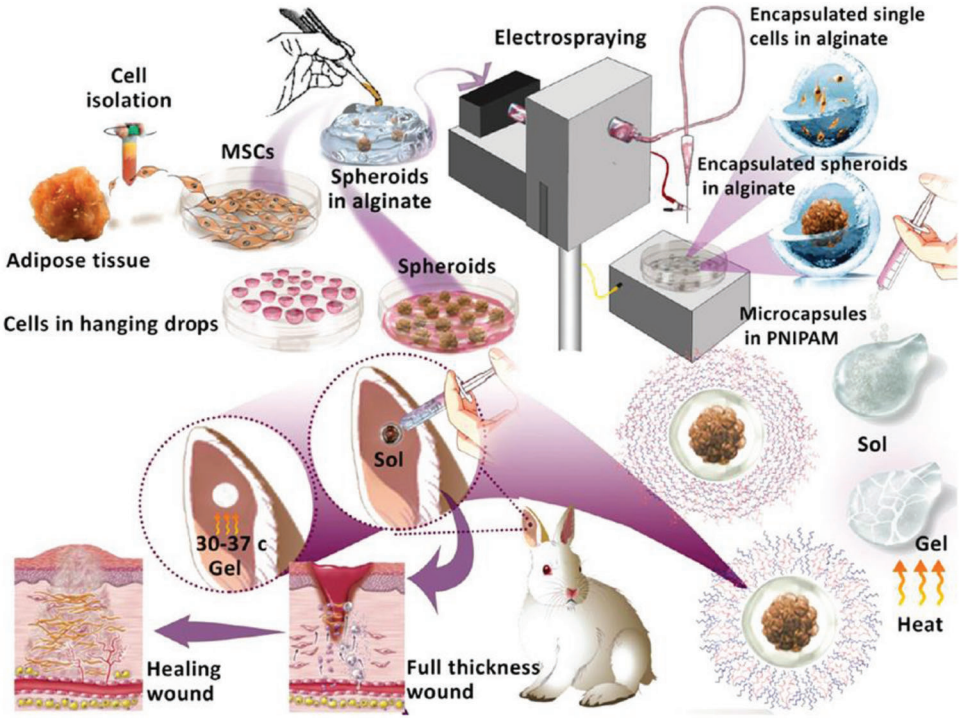

Figure 6. Schematic illustration representing the electrospray method for microencapsulation of the cells. Reproduced with permission.[89] Copyright 2020, American Chemical Society.

structure of the bacteria membrane and produced ROS to kill the bacteria.[95]

In another study, a multifunctional dressing containing human umbilical cord mesenchymal stem cells (HUMSCs)-laden microfibers was developed based on Fe_3O_4@SiO_2-IPN microfibers.[96] Fe_3O_4@SiO_2 was inserted into magnetothermally responsive microfibers with a magnetothermal heating effect. The release of antibiotic drugs was related to temperature changes. More drug release happened at 42 °C compared to 20 and 37 °C. HUMSC-laden microfibers stimulated cell proliferation and tissue remodeling, accelerating the wound healing process. Furthermore, the hydrogel dressing absorbed the wound exudate, provided a moist environment, preserved the cells in the defected wound, and significantly facilitated wound healing.[96]

6.4. Photothermal Multifunctional Hydrogel Dressings for Wound Healing

Photothermal treatment (PTT) is a fantastic approach for treating multidrug-resistant bacteria infection and stimulating tissue repair. It was previously reported that hyperthermia could effectively prevent bacteria growth, while mild heat increases cell proliferation and consequently induces wound repair. Mainly, the drug release can be controlled by photothermal properties. By using photothermal agents, light energy converts to heat under NIR irradiation. Some essential parameters, including laser strength, laser exposure time, and concentration of photothermal agents, determine the local target temperature of the photothermal hydrogel. Generally, temperature between 41 and 43 °C supports cellular proliferation and neovascularization. By contrast, the range between 45 and 50 °C can slightly damage normal cells and above 50 °C can suppress bacterial growth by altering the permeability of the cell membrane, enzyme inactivation, and protein denaturation.[36] Photothermal agents such as gold nanoparticles (AuNPs), CNTs, GO, and rare-earth nanoparticles have been increasingly applied for sterilization and antibacterial applications.[97] Gold-based structures owing to proper stability, good biocompatibility, and high photothermal conversion capacity have been extensively studied as photothermal materials. Li et al. exploited polydopamine-coated gold nanorods (Au@PDA NRs) inserted in *N*-acryloyl glycinamide (NAGA) hydrogel. Then, the hydrogel was covered by *E. coil* or *S. aureus* pretreated macrophage membrane (named E/SMM-PNAGA-Au@PDA). Under NIR laser irradiation, The E/SMM-PNAGA-Au@PDA had photothermal antibacterial activity (98% killing efficiency) toward both *S. aureus* and *E. coli* bacteria. This was owing to both photothermal capabilities and specific targeting of the activated macrophage membrane. Under NIR, the SMM-PNAGA-Au@PDA hydrogel group revealed a wound healing ratio of 84.7%, higher than other groups without irradiation.[98]

Tannic acid/ferric ion (TA/Fe^{3+}) is another material with photothermal properties because of the broad NIR absorption (650–1350 nm). An FDA-approved natural substance possesses polyphenol groups that can effectively chelate Fe^{3+} via its large digalloyl groups.[99] Accordingly, chitosan/silk fibroin cryogel decorated with TA/Fe^{3+} was introduced as a multifunctional photothermal dressing. The porosity of the cryogel provided an opportunity to absorb blood for hemostasis. The cryogel revealed suitable antibacterial properties against *S. aureus* and

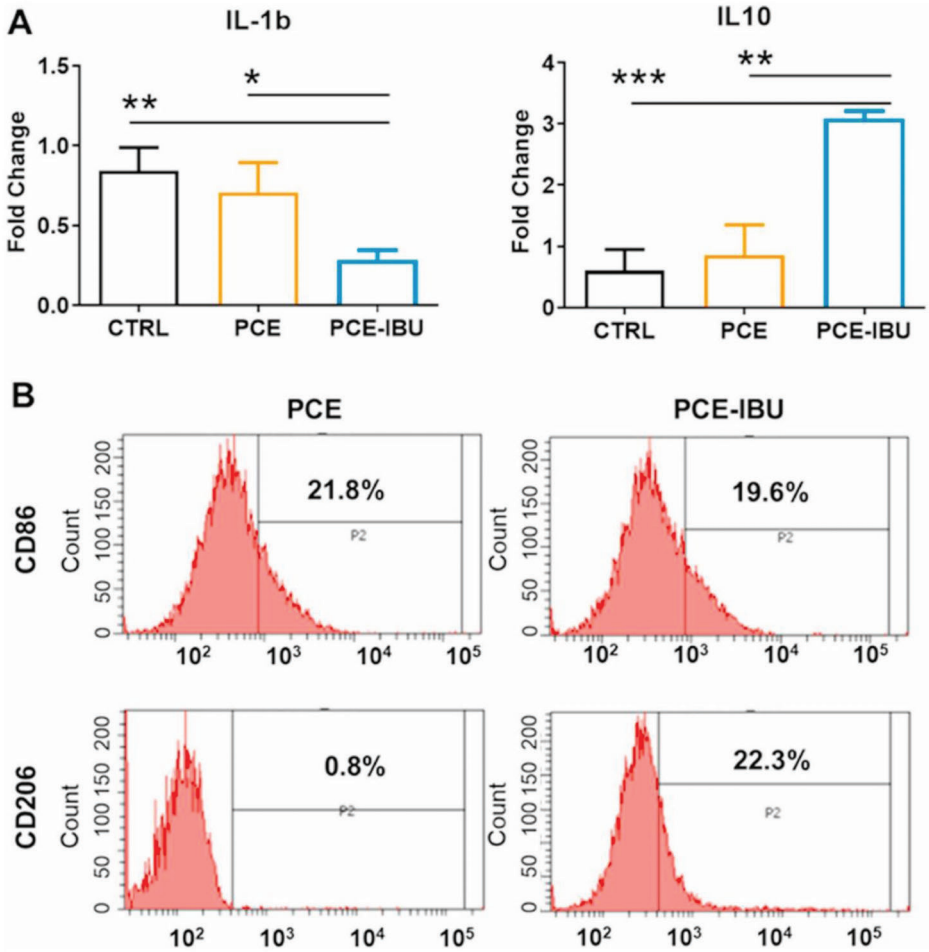

Figure 7. Anti-inflammation and polarization effect of macrophages by PCE–Ibuprofen. A) IL-1b is a proinflammation factor; IL10 is an anti-inflammation factor. B) The CD86 (M1) or CD206 (M2) positive cells were analyzed using flow cytometry after PCE or PCE–Ibuprofen was treated. Reproduced with permission.[95] Copyright 2021, Elsevier.

E. coli due to the high photothermal transition activity of the TA/Fe^{3+} complex. Further, the cryogel, along with NIR radiation, successfully stopped the bleeding, promoted cell proliferation, eradicated bacterial wound infection, and accelerating wound regeneration.[100]

Poor adhesion, easy detachment from skin tissue, and inducing inflammatory responses are the main drawbacks of inorganic nanoparticles that delay wound healing.[101] Multifunctional electrospun nanofibrous matrices were developed based on poly(L-lactic acid)–poly(citrate siloxane) (PCS) and assembling of PDA/curcumin (named PPCP matrix) (**Figure 8**).[102] The elastomeric property of the nanofibrous matrix was related to PCS. The photothermal property was derived from PDA. Curcumin prompted the PPCP nanofibers for suitable skin tumor chemotherapy and antibacterial/antioxidative activity for enhancing wound regeneration. Under NIR, the cumulative release of curcumin was about 7.90% ± 0.30%, and it was about 6.15% ± 0.36% without laser irradiation after 240 min, indicating the photothermal property of the structure. PPCP nanofibrous scaffolds inhibited tumor growth by chemo-photothermal therapy. PPCP could also remarkably accelerate the regeneration of the infected wounds via anti-infection, decrease proinflammatory molecules, promote the expression of VEGF and CD31, and form dermal and skin appendages.[102]

Indocyanine green (ICG) is another photothermal agent that reveals strong NIR absorption and good photothermal conversion. Moreover, it has a photosensitizer role in converting molecular oxygen to singlet oxygen ($^1O_2$) by using NIR irradiation useful for photodynamic therapy (PDT).[103] Accordingly, a multifunctional hydrogel was fabricated by introducing ICG and AgNPs into molybdenum disulfide (MoS_2) nanosheets (MoS_2/ICG/Ag). The hyperpyrexia, produced by MoS_2 nanosheets, destroyed the cell structure and promoted the release of ICG and Ag^+. The cumulative release of ICG was 19.0% after incubation at 37 °C and 40.0% at 45 °C, suggesting that the release of ICG was raised by increasing the temperature of the solution. The released ICG catalyzed the $^1O_2$ production for efficient PDT under NIR laser radiation. Further, the generated Ag^+ ions, as famous chemical antibacterial agents, inactivated the bacterial enzymes and destroyed the bacterial membrane via leakage of cytoplasm that inhibited the formation of *S. aureus* biofilms.[104]

The hydroxyl radical (·OH), the most toxic ROS, has been considered an active agent in killing bacteria by destroying the

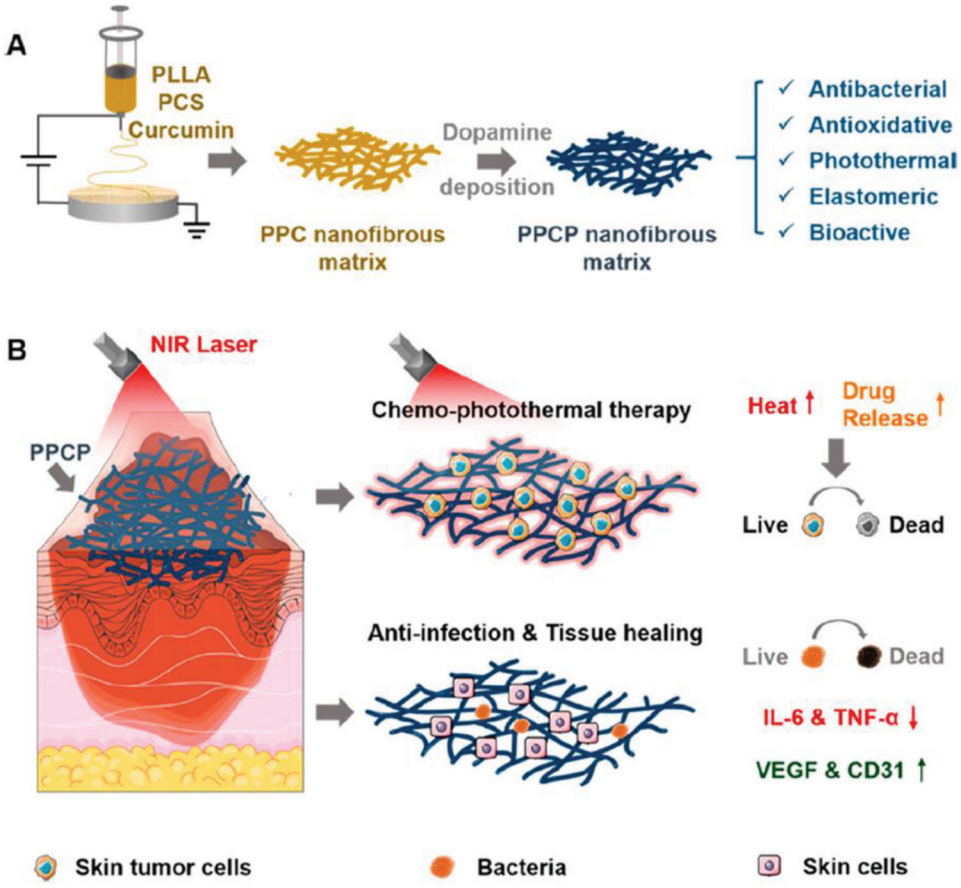

Figure 8. Chemo-Photothermal therapy of skin tumor, anti-infection, and cutaneous wound repair of electrospun PPCP nanofibers: A) the process of PPC and PPCP nanofibers synthesis and B) chemo-photothermal therapy of skin cancer and anti-infection and wound regeneration. Reproduced with permission.[102] Copyright 2020, American Chemical Society.

cell membrane, increasing the permeability of the plasma membrane, and making it more sensitive to heat. It is possible to produce ·OH using the Fenton reaction by converting H_2O_2 into a highly toxic ·OH via Fe^{2+}/Fe^{3+} as catalysts.[105,106] When combined with PTT, it can damage the cell membrane faster, reduce the therapeutic time, and the harmful side effects of PTT. It was reported that hemoglobin-functionalized copper ferrite NPs (Hb-CFNPs) could be activated using H_2O_2 to produce ·OH through Fenton and Fenton-like reactions. With the help of the NIR laser, hyperthermia created by Hb-CFNPs induced the cell membrane deformation and leakage of the cytoplasmic components, leading to bacterial death (**Figure 9**). Moreover, Hb-CFNPs accelerated the healing of the infected wound with fewer inflammatory responses.[107] Other significant studies that used multifunctional hydrogel dressings with photothermal properties are summarized in **Table 2**.

6.5. Multifunctional Dressings for Biosensing and Wound Healing

While it is essential to protect the wound during regeneration, detecting any signs of inflammation and microbial infections is also important. Numerous biochemical and physical markers of injuries, including temperature, humidity, pH, bacteria toxins, and enzymes, will change during the inflammation phase and bacterial infection.[113,114] For example, the temperature of the wound may elevat in the gradient range of +4 to 5 °C than the average skin temperature during bacterial infections.[115] It has also been demonstrated that bacteria propagation will secret lactic acid, leading to local acidification. However, in the chronic situation, the pH value of wound skin is considerably increased (up to 7–8).[116] The common approach for detecting wound infection is checking the infection signs, including redness, swelling, and heat detected by palpation.[115] In addition, monitoring the amount of glucose is another critical parameter that is attributed to the diabetic wound status and physical situation of patients.[117] Various glucose concentrations are related to the blood glucose level and can be considered a prognostic parameter for diabetes.

Therefore, diagnosis and monitoring of the wound healing parameters provide a better method for elucidation and understanding the wound status.[118] Several sensors have been fabricated to diagnose the changes in the wound area. Electrochemical sensors commonly receive signals from electronic devices and display the wound condition after complex data processing.[119] Recently, nanodiamond (ND)-multifunctional silk dressing was applied for wound temperature monitoring (**Figure 10**).[120] A negatively charged nitrogen-vacancy (NV^-) color core in NDs

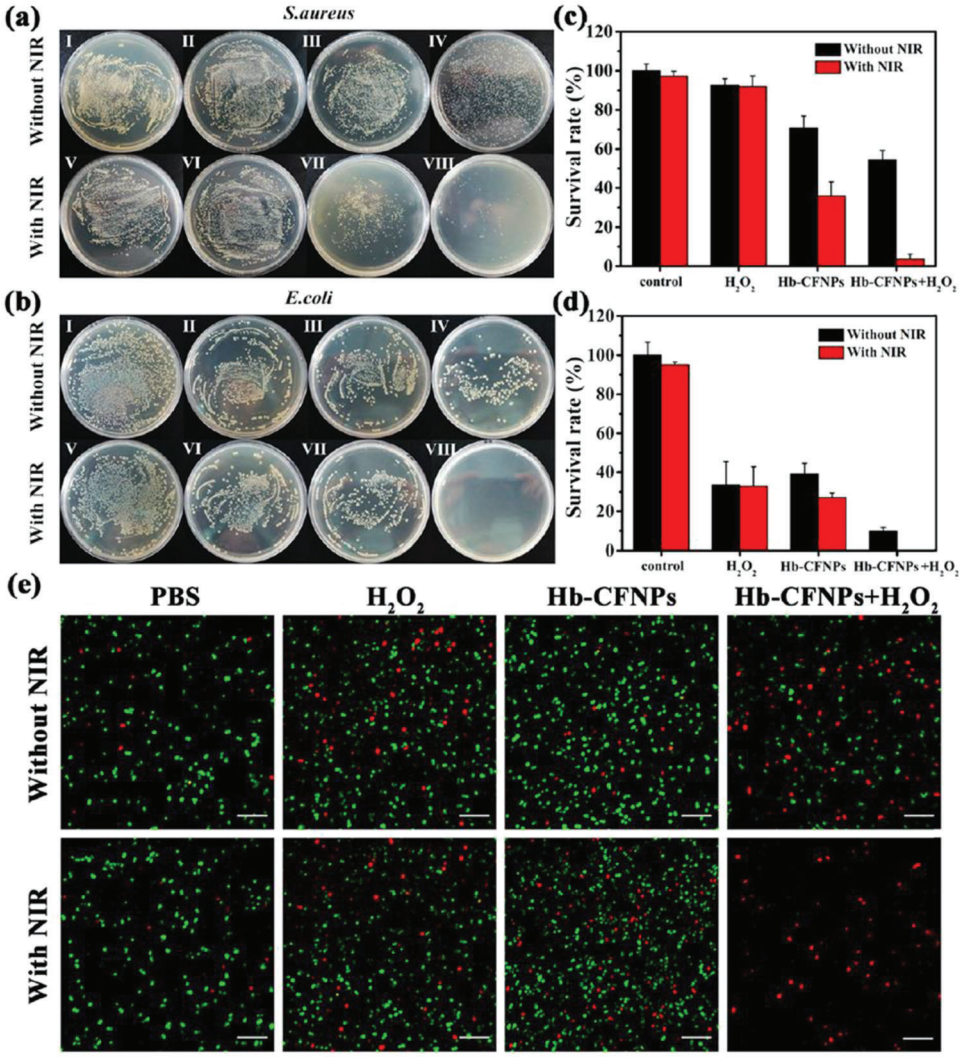

Figure 9. Bacterial colonies formed by a) *S. aureus* and b) *E. coli* after incubation in (I) PBS, (II) H_2O_2, (III) Hb-CFNPs, (IV) Hb-CFNPs + H_2O_2, (V) PBS + NIR, (VI) H_2O_2 + NIR, (VII) Hb-CFNPs + NIR, and (VII) Hb-CFNPs + H_2O_2 + NIR. c,d) The survival rates corresponding to (a) and (b), respectively. e) Fluorescence staining images of various experimental groups (viable bacteria were labeled green by calcein-AM and dead bacteria red by PI). Reproduced with permission.[107] Copyright 2019, American Chemical Society.

revealed optically detected magnetic resonance and a thermometer role. This was applied for temperature detection related to bacterial infections without physically removing the dressing. The ND-silk structure could sense temperatures ranging from 25 to 50 °C without any adverse effects on wound repair and closure. Moreover, the ND-silk dressing exhibited selective biocidal and antifouling propensity toward *P. aeruginosa* and *E. coli*, while no effect was seen in the case of *S. aureus* (Figure 10).[120]

Zheng et al. also developed multifunctional wound dressing hydrogel comprised of polyacrylamide-quaternary ammonium chitosan–carbon quantum dots-phenol red with pH sensitivity, antibacterial property, and wound healing capacity.[121] Phenol red was used as a pH indicator with high responsiveness to monitor the pH variability of the infected wound. Meanwhile, hydrogels had proper hemostatic and adhesive features, preserved sufficient wound moisture, and supported wound healing through good antibacterial activity toward *S. aureus* and *E. coli*. The animal treated with wound dressing had more hair follicles, and the collagen fiber structure, epidermis, and new blood vessels were intact. Accordingly, these data further supported that dressing hydrogel could successfully stimulate wound regeneration without using additional drugs, growth factors, or cells.[121] Zhu et al. fabricated multifunctional zwitterionic hydrogel based on polycarboxybetaine for simultaneous monitoring of pH and glucose levels (**Figure 11**).[122] Phenol red, glucose oxidase, and horseradish peroxidase were two glucose-sensing enzymes encapsulated into the anti-biofouling zwitterionic polycarboxybetaine hydrogel matrix. This novel hydrogel effectively detected the pH range of 4–8 and glucose levels of $0.1–10 \times 10^{-3}$ M. It also provided a moist healing area that accelerated the diabetic wound healing.[122]

Similarly, another zwitterionic ionic skin-like biosensor with the ability to continuously detect the temperature, glucose concentration, and prohealing of the diabetic wound was applied

Table 2. Important studies regarding using photothermal multifunctional hydrogels dressing for wound healing.

Material	Photothermal agent	Loading molecule	In vitro findings	In vivo findings	Application	Refs.
G[a)]P[b)]	BP[c)]	DOX[d)]	Internalization of BP into melanoma cells under NIR[e)] laser, resulting in DOX release	Activation of ERK1/2[f)] and PI3k7[g)]/Akt[h)] pathways by releasing phosphate ions from BP, proper wound repair	Diabetic model	[108]
GelMA[i)]/HA[j)]/DA[k)]	BNN6[l)]-functionalized GO[m)]	β-cyclodextrin	Proper swelling and mechanical properties, suitable attachment and biocompatibility, stable photothermal effects, NO[n)] release, and antibacterial property	Improving collagen deposition, vascularization, and promoting wound repair	Full-thickness skin wound model	[109]
AG[o)]	TA[p)]–Fe^{3+}	–	Proper mechanical property and superior processability, excellent photothermal conversion ability for killing bacteria	Effective wound disinfection and repair	Bacteria-infected model	[110]
HA-PEGSB[q)]	CMP[r)]	Doxy[s)]	Good adherence to the surface of motion wounds, well stretchability, good self-healing capacity	Significant induction of wound repair by preventing infection, inducing collagen deposition, and accelerating the formation of granulated tissue	Infected full-thickness skin wound model	[111]
SA[t)]	Nd[u)]–CaSi[v)]	–	Enhancing HUVEC proliferation an migration and in vitro vascularization	Significant closure in the wound area reduced scar formation and inducing the formation of epidermis and dermis tissues	Burn skin wound model	[112]

[a)] Gelatin [b)] Polycaprolactone [c)] Black phosphorus [d)] Doxorubicin [e)] Near-infrared radiations [f)] Extracellular signal-regulated kinases [g)] Phosphoinositide 3-kinase [h)] Protein kinase B [i)] Methacrylate-modified gelatin [j)] Hyaluronic acid [k)] Dopamine [l)] Bis-N-nitroso compounds [m)] Graphene oxide [n)] Nitric oxide [o)] Agarose [p)] Tannic acid [q)] Poly(ethylene glycol)-*co*-poly(glycerol sebacate) [r)] Cuttlefish melanin nanoparticles [s)] Doxycycline hydrochloride [t)] Sodium alginate [u)] Neodymium [v)] Calcium silicate.

for the diabetic wounds. The biosensor monitored infection, swelling, and blood glucose without signal interference.[123]

In another study, a wound dressing hydrogel based on a pH-responsive fluorescent nanoprobe (SNP-Cy3/Cy5) was used to sense the bacterial infection via the fluorescence resonance energy transfer (FRET) transition between Cyanine3 (Cy3) and Cyanine5 (Cy5).[124] Simultaneously, upconversion nanoparticles (UCNPs) were incorporated onto the hydrogels to achieve NIR-responsive release of gentamicin sulfate in the bacterially infected site. The results showed that the SNP-Cy3/Cy5 in the wound dressing presented pH-responsive FRET changes for the detection of bacterial infection. Under NIR light, UCNP converted the NIR light to UV light, releasing gentamicin sulfate from the hydrogel, indicating that the dressing can support on-demand treatment. Moreover, the release of Cy5 from SNP-Cy3/Cy5 was pH-sensitive due to the Schiff base interactions between Cy5 and SNP that would be cleaved in an acidic condition.[124]

7. Conclusion, Challenges, and Perspective

In the past decades, hydrogels have been extensively applied as skin scaffolds owing to the ability to mimic the ECM of natural tissue. Hydrogels possess many extraordinary characteristics such as biocompatibility, porosity, and soft mechanical strength. Despite the benefits of using hydrogels as tissue scaffolds, they might be electrical insulators that limit the electrical communication between the cells. The application of conventional hydrogels for skin regeneration is also restricted due to poor mechanical properties and the inability to mimic design of the native tissue microstructure. Moreover, the conventional hydrogels suffer from functionality and only provide a moist environment.[59] The wound dressings with hydrogel structure can be developed as an injectable form. Injectable hydrogels are of interest for wound healing because they can fill the wound with irregular shapes, adhere to the wounds, and encapsulate cells and the bioactive agents in situ that are essential for optimal skin repair.[79] Moreover, various multifunctional hydrogels have been developed that respond to different external stimuli such as light, temperature, and pH, providing the opportunity to control the release of drugs at a specific microenvironment for promoting cellular proliferation and bacteria-killing.[125] Among them, multifunctional thermosensitive hydrogels have been extensively used for wound repair. However, several concerns remain in their expansion applications as skin scaffolds, such as weak mechanical strength and slow response to temperature.

Consequently, to prepare thermoresponsive hydrogels for wound healing purposes, it is essential to notice the following

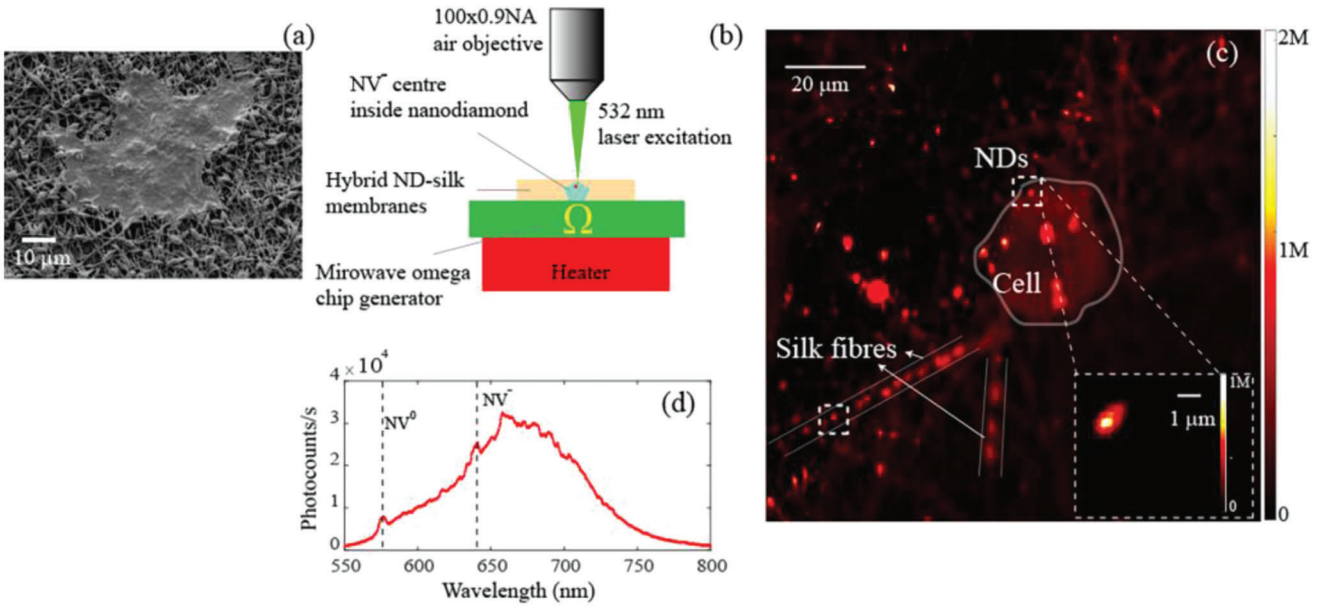

Figure 10. A) SEM of HaCaT cells proliferated on fibrous ND–silk scaffolds after 48 h incubation. B) Schematic of the setup used for optical excitation of NV^- centers and temperature detection in NDs, embedded in silk. An MW field is introduced with an omega chip resonator, and the temperature is varied with a thermoelectric Peltier heater. C) 100 × 100 μm^2 fluorescence map of the cell-cultured ND–silk substrates on a glass coverslip. The central rounded region is a fixed cell growing on the hybrid membrane. The solid straight lines represent the silk fibers with embedding NDs. The dashed boxes display two representative NDs, and the inset inside the solid outlined box shows a magnified 10 × 10 μm^2 scan of the selected area of interest. D) Fluorescence spectrum obtained from fluorescent NDs, approving the presence of NV centers. Reproduced with permission.[120] Copyright 2020, American Chemical Society.

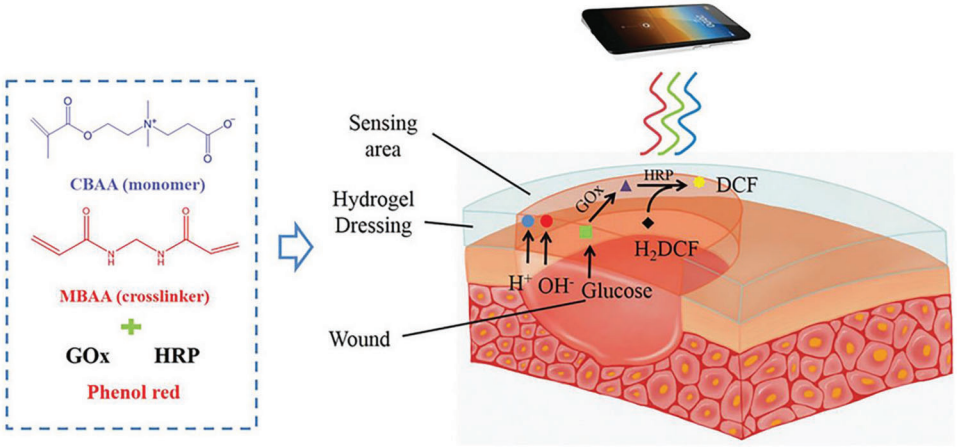

Figure 11. Scheme of zwitterionic polycarboxybetaine (PCB) wound dressing hydrogel for detecting the pH value and glucose concentrations in the wound exudate. Reproduced with permission.[122] Copyright 2019, Wiley-VCH.

aspects: 1) the mechanical properties of the hydrogels should be improved to preserve their integrity after covering the wound defects, 2) the gelation time of the hydrogels should be optimized for controlling the drug release in the desired period, 3) the thermosensitive hydrogels should be selected according to their specific application, and 4) the porosity of the thermoresponsive hydrogels should be tailored based on the properties of the incorporated biomolecules.[84] In this review, we also addressed the hydrogels with PPT properties for wound repair. The multifunctional hydrogels with PTT effect possess acceptable antibacterial effect; however, their nonspecific heat damage to the nearby tissues restricts their application in the clinic. In general, the nanomaterials based on polymers, metals, and carbon materials exhibit good results of antibacterial PTT in the lab stage. However, their applications are limited by low biodegradability, high toxicity, and insufficient photothermal effect. As an alternative, small organic molecules such as ICG and Prussian blue have been approved by FDA with higher potential in clinical applications. The

exact PTT effect of these small materials is not approved yet but they could be easily incorporated into different nanomaterials and/or modified with functional groups.[126]

The multifunctional hydrogels with conductivity have also been considered valuable materials for tissue repair due to outstanding electrical conductivity and hydrogel-forming characteristics.[59] Conductive multifunctional hydrogel is an effective construct for skin regeneration because it can have antioxidant, antibacterial, and photothermal properties. They act as electrodes for sensing electrical resistance and impedance at the wound site. Nevertheless, the distinction between conductive biomaterial resistance (impedance) and skin tissue resistance (impedance) should be carefully considered in wounds.[57] Despite developing various conductive multifunctional hydrogels for wound healing, they are still in their early stages and restricted to infected, acute, and diabetic wounds.

Further investigations are needed to seek the effectiveness of using conductive hydrogels for other types of wounds and their mechanisms of action should be considered. Moreover, there are no standard principles to compare the efficacy of various conductive hydrogels for wound healing as there are multiple animal models and different types of wounds.[14] In summary, multifunctional hydrogels have considerable potential for improving wound repair. The applications of these nanomaterials have been comprehensively evaluated in the past few decades. However, more investigations are needed to solve the existed challenges.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

chronic wound, drug delivery, hydrogel, multifunctional, skin regeneration, wound dressing

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