Recent Advancement of Functional Hydrogels toward Diabetic Wound Management

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ABSTRACT: Wound healing is a dynamic, orchestrated process comprising partially overlapping phases of hemostasis, inflammation, proliferation, and remodeling. This programmed process, dysregulated in diabetic individuals, results in chronic diabetic wounds. The normal process of healing halts at the inflammatory stage, and this prolonged inflammatory phase is characteristic of diabetic wounds. There are a few U.S. Food & Drug Administration approved skin substitutes; dermal matrixes are commercially available to manage diabetic wounds. However, expensiveness and nonresponsiveness in a few instances are the major limitations of such modalities. To address the issues, several treatment strategies have been exploited to treat chronic wounds; among them hydrogel-based systems showed promise due to favorable properties such as excellent absorption capabilities, porous structure, tunable mechanical strength, and biocompatibility. In the past two decades, hydrogels have become one of the most acceptable systems in the field of wound dressing material, offering single functionality to multifunctionality. This review focuses on the advancement of functional hydrogels explored for diabetic wound management. The process of diabetic wound healing is discussed in the light of the normal healing process, and the role of macrophages in the process is explained. This review also discusses the different approaches to treat diabetic wounds using functional hydrogels, along with their future opportunities.

1. INTRODUCTION

Diabetes affects around 463 million individuals around the globe; the number of people affected is projected to be 600 million by 2035. Almost 30% of patients suffering from diabetes develop chronic diabetic foot ulcers (DFUs). In the United States, DFUs resulted in nontraumatic lower limb amputations of 0.1 million diabetic patients in 2016, indicating the importance of the development of wound healing materials, which demands better understanding of the pathophysiology of DFUs. Recently, Matoori et al. shared their perspective on the pathophysiology of diabetic wound healing and its management. They noted that the normal healing process comprises three overlapping phases after hemostasis, i.e., inflammation, proliferation, and remodeling. The hyperglycemic condition associated with neuropathy, tissue hypoxia in diabetes, halts the typical process of wound healing at the inflammation stage. Macrophages play a critical role in the orchestrated process of wound healing. The proinflammatory macrophages (M1 phenotype) are active in the inflammation stage, to eliminate invaded microbes and damaged tissues from the wound site. Thereafter, macrophages polarize into anti-inflammatory macrophages (M2 phenotype) to initiate the proliferative phase of wound healing. The impaired polarization of macrophages to the M2 phenotype results in a prolonged “low-grade inflammatory stage” in diabetic wounds. Moreover, several other factors such as generation of excessive reactive oxygen species, reduced angiogenesis, and exposure to infection are involved critically in the impaired process of diabetic wound healing.

To manage DFUs, several materials have been developed, among them a few approved by the USFDA. For example, acellular dermal matrix, an extracellular matrix based material, permits cellular infiltration and proliferation, therefore promoting vascularization, matrix deposition, and re-epithelialization. Integra Dermal Regeneration Template, a product of Integra Life Sciences, USA, is one such example having FDA approval. There are some other biological products also, such as Dermagraft (human fibroblast derived dermal substitute), Becaplermin (recombinant human platelet-derived growth factor as active ingredient), and Apligraf (skin substitute), which are widely used for this purpose. The major limitations associated with such materials are expensiveness and nonresponsiveness. To address such limitations, functional hydrogel based wound healing materials have been developed and have already shown promise. Owing to their excellent exudate absorption capabilities, antimicrobial proper-

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ties, tunable mechanical strength, biocompatibility, and biodegradability hydrogels are widely explored for this purpose. Recently, Liang et al. comprehensively reviewed the various functional hydrogels explored for wound healing purposes. However, this review focuses on the advancement of functional hydrogels in the management of diabetic wounds especially. This review discusses the physiology of normal and diabetic wound healing, the role of macrophages in the process of wound healing, and different approaches to treat diabetic wounds using functional hydrogels along with their future opportunities.

2. NORMAL VERSUS DIABETIC WOUND HEALING

Cutaneous wound repair is an organized process to reestablish the integrity of damaged tissues. The normal wound healing process comprises three distinct but partially overlapping phases of events after hemostasis: inflammation, proliferation, and tissue remodeling. Cutaneous damage initially results in the activation of platelets, therefore triggering the coagulation cascade to form a thrombus, referred to as the process of hemostasis. Afterward, neutrophils and monocytes are deployed at the site of injury to eliminate pathogens and damaged tissues, which is actually governed by various chemotactic signals. Such signals could be the degranulating platelet released growth factors, the byproducts originated from the proteolysis of fibrin, or a few components of the matrix. Neutrophils initially clear the immediate bacterial rush through secreting reactive oxygen species (ROS). Neutrophils also secrete matrix metalloproteinase-8 (MMP-8), which helps in the process of debridement and destroying damaged collagen type I, while the recruited monocytes converted into macrophages (M1 phenotype) eliminate pathogens, matrix debris, and damaged cells through phagocytosis. As inflammatory cells are involved in this stage, this phase is known as the inflammatory phase. Subsequently, the process enters the proliferation phase, where differentiation of macrophages generates anti-inflammatory (M2 phenotype) macrophages. M2 macrophages release transforming growth factor β1 (TGF-β1) and vascular endothelial growth factor (VEGF) like prohealing factors which induce angiogenesis, proliferation of stromal cells, and granulation tissue formation. Here, MMP-9 plays a vital role by cleaving an ECM protein, laminin, a component of epithelial basal lamina, promoting the migration of keratinocytes (Figure 1). Such migrations are essential for re-epithelialization, through which the process enters the phase of remodeling, where reestablishment of the tissue structure happens or the mature form of scar tissue is generated.

Such an organized process of healing became dysregulated or halted at any stage for a prolonged period in the case of chronic wounds such as DFUs. Diabetes has a systemic effect and it imparts an intrinsic impact to the regulated process of healing. Recently Matooiri et al. noted that the hyperglycemic state, neuropathy, vascular impairment, and prolonged proinflammatory states are systemic effects, where high glucose levels in blood initiate unwarranted glycation of proteins, leading to oxidative damage, proinflammatory cytokine expression, and alteration in the extracellular matrix. “Intrinsic effect” refers to alteration at the cellular level. The hyperglycemic condition in diabetes inhibits keratinocyte, fibroblast, and endothelial cell proliferation, effecting re-epithelialization and neoangiogenesis. Typically, in the process of wound healing in diabetic individuals, the inflammatory stage is found to be the most dysregulated one. It could be noted that an increased amount of proinflammatory cytokines, a greater amount of M1 macrophages, and the presence of inflammatory cells around the vessels and the dermis layer of skin are typical even before wounding for diabetic patients. In a study, Tellechea et al. demonstrated the effect of mast cells, the neutrophil recruiter, in the process of wound healing. In that study, streptozotocin-induced mice showed the presence of degranulated mast cells, which release neutrophil-recruiting cytokines and chemokines, initiate acute inflammatory response, and lead to a decreased response to healing, which was justified by similar findings with clinical samples from a diabetic patient. It is already noted that diabetes results in a low-grade chronic inflammatory stage in the process of healing, where the differentiation from proinflammatory (M1) macrophages to anti-inflammatory (M2) macrophages is dysregulated. Therefore, it happens because of the positive feedback loop where the proinflammatory macrophages release cytokines and chemokines such as IL-1β and monocyte chemoattractant protein-1, polarizing the recruited macrophages at the wound site to the M1 phenotype. Moreover, reactive oxygen species (ROS) and protease hamper the key processes of healing for diabetic individuals such as neovascularization, re-epithelialization, and remodeling of the ECM. Matrix metalloproteinases (MMPs), secreted by immune cells, are zinc-dependent endopeptidases used to degrade and remodel the components of the ECM. Recently, Nguyen et al. demonstrated that upregulation of MMP-9 in the case of diabetes leads to excessive degradation of the ECM, finally resulting in reduced neovascularization and impaired re-epithelialization.

Therefore, impaired wound healing processes in diabetes are associated with several abnormalities, such as a prolonged...
inflammatory stage, impaired neovascularization, upregulation of matrix metalloproteinase, excessive ROS, and proneness to infection, which could be the critical targets to manage diabetic wound healing in an efficient way.

3. MACROPHAGE POLARIZATION IN WOUND HEALING

Macrophages are one of the most fascinating cell types participating in the process of wound healing. In the initial stage of the inflammation phase, macrophages release inflammatory cytokines, participating in the process of debridement and clearing the bacterial load; later on it promotes the process of tissue repair as well. In a brief review, Boniakowski et al. described the role of macrophages in the process of normal and diabetic wound healing. The authors described that, in the initial phase of the inflammation stage, the recruited monocytes differentiated into macrophages and dendritic cells. As the process of wound healing progresses, the microenvironment at the wound site changes, which directs the phenotypic alterations to tissue-resident macrophages. With this plasticity macrophages can direct both the inflammatory phase and the tissue repair phase of the wound healing process (Figure 2).

The mechanism behind the phenotypic changes of macrophages is a very complex process. However, it could be noted that such plasticity results from ingestion of apoptotic neutrophils and few other immune cells by the macrophages. Such apoptotic neutrophils attract macrophages for the process of phagocytosis through secreting different signaling molecules, such as lysophosphatidylcholine. With the progression of the healing process, macrophages express a cell surface tyrosine kinase (MerTK). Such MerTK expressed macrophages have the ability to produce TGF-β and VEGF. Therefore, phagocytosis of apoptotic cells triggers the secretion of growth factors, which augment the tissue repair processes.

Diabetic wounds are characterized by the dysregulated process of healing, where a prolonged inflammatory stage could be noted. Such prolongation results from the inability of macrophages to differentiate into M2 (prohealing) phenotypes along with persistent proinflammatory (M1 phenotype) macrophage polarization. Several factors influence such an inability, which was recently described by Louiselle et al. They described that the hyperglycemic condition in diabetes affects the polarization of macrophages which could be justified by the findings, where reduced expression of MMP-1 and increased expression of proinflammatory cytokines, e.g., TNF-α, could be observed in diabetic settings, ultimately hampering the process of healing. Thirteen proinflammatory cytokines including IL-1, IL-6, and TNF-α are upregulated in a high glucose condition. These proinflammatory cytokines trigger the polarization of macrophages to the more metabolically active M1 phenotype. Obesity could be another contributor as type II diabetes is promoted by obesity. Obesity along with diabetes has a synergistic effect on M1 polarization as obesity results in increased free fatty acids in plasma, which further leads to elevated inflammatory expression through the NF-κB pathway. Few interleukins significantly affect the polarization. Impaired IL-17 production resulted in increased M2 polarization and, thereby, rapid wound closure. Under a hyperglycemic environment, increased NLPR3 leads to IL-1 inducing the polarization of M1 macrophages. Furthermore, few molecular pathways, i.e., STAT-1 and PPAR, have been identified as contributing to polarization of M1 macrophages. Finally, such an understanding is necessary to develop novel approaches against devastating diseases such as DFUs (Figure 3).

4. FUNCTIONAL HYDROGELS IN DIABETIC WOUND HEALING MANAGEMENT

An ideal wound dressing material should be biocompatible and nontoxic, should possess exudate absorption capability, moisture retention efficiency, and adequate mechanical and physical strength, and should able to promote cell adhesion, proliferation, and growth. As mentioned earlier, several functional dermal matrixes are already FDA approved. However, such commercialized products do not possess all of the properties of an ideal wound healing material; moreover, they are expensive and nonresponsive for some instances. Therefore, development of wound dressing material specially for chronic wounds such as DFUs is urgently warranted. In this scenario, several forms of wound dressing materials have been
developed such as foam, membrane, patch, hydrogel, and hydrocolloids.\textsuperscript{19} Owing to excellent properties such as absorption capability, biodegradability, biocompatibility, and tunable mechanical property, porous structure mimicking the ECM renders hydrogels as the most suitable materials among others. Various biopolymers already been explored for this purpose, such as collagen,\textsuperscript{20} chitosan,\textsuperscript{21} alginate,\textsuperscript{22} hyaluronic acid,\textsuperscript{23} κ-carrageenan,\textsuperscript{24} poly(vinyl alcohol),\textsuperscript{22} and cellulose.\textsuperscript{25} As discussed above, there are a few critical challenges involved with diabetic wound healing including complex pathology, bacterial infection, high reactive oxygen species (ROS) generation, chronic inflammation, impaired angiogenesis, and upregulation of matrix metalloproteinase. To counter such problems, researchers aim to develop functional hydrogels which can meet several requirements for diabetic wound healing such as fighting infection, minimizing excessive ROS production, boosting angiogenesis, and activating macrophage polarization. In this section we briefly discuss the advancement of hydrogels with functions which can critically accelerate the healing process of diabetic wounds.

4.1. Combating Infection. Hydrogels with antibacterial properties meet one of the important criteria for diabetic wound management. For example, chitosan is a well-acknowledged biopolymer with its inherent antimicrobial properties which are used to prepare antibacterial hydrogels.\textsuperscript{26} Antibacterial efficacy of this type of hydrogels depends on contact killing, which demands a prolonged time to contact with microbes. However, this does not meet the practical requirement of combating infections for diabetic wound healing. Therefore, a hydrogel with antibacterial properties has been extensively adopted to enhance the hydrogel’s antibacterial characteristics. In this regard, the hydrogel can act as a carrier for antibacterial agents and, with the appropriate design of the hydrogel, a controllable release or burst release of antibacterial components can be achieved according to demand. Additionally, functional hydrogels loaded with antibacterial agents can deliver antibacterial components in the local wound area, which leads to better antibacterial efficacy. There are several antibacterial agents including antibiotics, metallic nanoparticles as well as nonmetallic nanoparticles which possess their own benefits over each other that can be delivered at the diabetic site.

As already discussed above, hydrogel is one of the prime choices for wound healing due to its tunable biodegradability, better biocompatibility (depending upon the precursor used for synthesis), high porosity, and excellent drug/antibiotic/growth factor loading capacity. The most common antibiotics used for wound healing applications are penicillin, fluoroquinolone, cephalosporin, and moxifloxacin.\textsuperscript{27} One of the main advantages of local delivery of antibiotics through a hydrogel over oral delivery is that a very small dosage is enough to accomplish an satisfactory antibiotic concentration at the wound site.\textsuperscript{28,29} However, the major concern related to antibiotics is overdosage of antibiotics, which can impart drug resistivity in bacteria; this is one of the biggest challenges in recent days. Therefore, selection of antibiotics along with proper dosage and release behavior from the hydrogel plays a critical role in successful wound healing.

Another interesting approach to preparing antibacterial hydrogels for diabetic wound healing is the use of antibacterial metallic and nonmetallic nanoparticles within the hydrogel system. This type of nanomaterials includes silver, copper, zinc oxide, graphene nanomaterials, and quantum dots.\textsuperscript{30−33} These nanoparticles offer broad-spectrum antibacterial activity without inducing much antibacterial resistance. In the case of metallic nanoparticles, metallic ions released from the particles interact with bacterial cell and destabilize the bacterial cell as well as generate ROS, which leads to bacterial cell death. For example, Singh and co-workers synthesized a silver nanoparticles (AgNPs) loaded novel hydrogel consisting of chitosan.
and calcium alginate for diabetic wound management.\textsuperscript{34} Due to the presence of AgNPs the hydrogel offered a broad-spectrum antimicrobial resistance including to Gram-negative (\textit{Escherichia coli}, \textit{Pseudomonas aeruginosa}) and Gram-positive (\textit{Bacillus subtilis}, \textit{Staphylococcus aureus}) bacteria. \textit{In vivo} studies on rat model revealed that the AgNPs loaded hydrogel and blood mixed AgNPs loaded hydrogel were capable of 83.5 \pm 4.4\% and 99.8 \pm 2.0\% closure of wound, respectively, after 15 days as compared to 41.5 \pm 3.2\% in diabetic control and 60.3 \pm 2.2\% in a commercially available wound healing cream.

\textbf{Figure 5.} (a) Confocal microscopy images of \textit{E. coli} cultured on (i) planar, (ii) MPC grafted planar, (iii) nanoneedle, and (iv) MPC grafted nanoneedle samples made of polyurethane acrylate (PUA) (used as a control) and 100, 90, and 80 wt \% PEGDMA for 18 h. The bacteria were stained with a fluorescent labeling reagent (live/dead bacterial viability kit). (b) Quantification of area coverage of the live (green) and dead (red) cells cultured on various PUA and PEGDMA samples. (c) CFU of \textit{E. coli} grown on various PUA and PEGDMA samples after 0, 3, 18, 24, and 30 h of culture (\textit{n} = 9; *, \( p < 0.05 \); **, \( p < 0.01 \); and ***, \( p < 0.001 \), compared to bare PUA; data was analyzed by one-way ANOVA). Reproduced from ref 41. Copyright 2019 American Chemical Society.
Silverex Heal (the healing efficacies of different systems are represented in Figure 4).

However, in the case of metallic nanoparticles, there are certain limitations which should be taken care of in a smarter way. For instance, in most cases metal ions and particles that kill bacteria are dependent on the release of a leachable amount into the surrounding environment and subsequent increase in ROS, which may cause a tissue response and is not desirable for diabetic wound healing. To overcome such problems, researchers are focused on nonmetallic based antibacterial nanomaterials such as carbon dots (CDs). For example, Sun and co-workers synthesized an antimicrobial hydrogel based on CDs for the purpose of wound healing.35 To prepare the CDs, they simply employed a hydrothermal method and selected o-phenylenediamines, o-phenylenediamines/spermidine, and o-phenylenediamines/α-lipoic acid in different compositions as precursors. The CDs obtained using this method are highly cationic in nature (+51.20 mV) and released from hydrogel in response to broken hydrogen bonds due to a change in the ambient environment caused by the growing bacteria at the wound site. The CDs loaded hydrogel demonstrated long-term potent broad-spectrum antibacterial ability (even drug-resistant bacteria) due to the serious bacterial membrane destabilization by the released CDs without affecting the cytocompatibility of the hydrogel. The inhibitory capability of this hydrogel was 108.5-fold higher than that of the control hydrogel. In addition to that, the multicolor fluorescence emission delivered by CDs provides a novel platform for the development of dual-function hydrogels with in situ monitoring and prevention of bacterial infections to treat wounds.

Other than these strategies, recently the installation of bacteriophages within the hydrogel was another way to prepare an antibacterial hydrogel. Bacteriophages are a special type of human-safe virus which infects bacteria and neutralizes them.36 The interaction between bacteria and phages depends on host the bacteria strain and the phage type. For instance, E. coli is vulnerable to phages such as λ, P1, and T4,37 whereas S. aureus is susceptible to SAP-26.38 However, similar to antibiotics here also one major concern is the evolution of phage-resistant bacteria with time. Therefore, various strategies should be employed to tackle such difficulties including combination of antibiotics and phages or loading of multiple phages in a single cocktail, etc.

Another emerging approach to minimize bacterial infection is that of a significant reduction in bacterial attachment by making antifouling hydrogels. Therefore, a synergy between antifouling and antibacterial properties greatly improves the antibacterial efficacy of a hydrogel. This strategy was recently exploited by some recent studies. For example, Wu and co-workers designed a zwiterionic antifouling hydrogel containing AgNPs for diabetic wound healing.39 To synthesize the hydrogel, they mixed thiolated chitosan and maleic acid grafted dextran, where by adjusting the ratio of thiolated chitosan and maleic acid grafted dextran they were able to achieve a net-zero-charge hydrogel with antifouling properties which reduced the bacterial attachment significantly at the healing site. The presence of AgNPs enhanced the antibacterial activity. Additionally, an antifouling hydrogel also prevents tissue adhesion to wound dressing.40 When applied in vivo, the combined dressing of hydrogel and AgNPs demonstrated the lowest open wound area in Sprague–Dawley (SD) male rats after both 7 and 10 days of treatment, which is significantly lower than when the same hydrogel without AgNPs or pure AgNPs were applied on their own.

In addition to loading of antibacterial nanoparticles within the hydrogels, antifouling hydrogels with specific topography (such as nanopillar) are also a promising approach to make antibacterial hydrogels. In such cases the sharp tips of nanopillars destroy the bacterial cell wall and neutralize them. For example, Jeong and co-workers developed lipid–hydrogel–nanostructure hybrids as robust biofilm-resistant polymeric materials which can be used for diabetic wound healing application.41 To prepare the lipid–hydrogel–nanostructure hybrids, they used biofriendly antifouling polymers, such as polyethylene glycol dimethacrylate (PEGDMA) and 2-methacryloxyethyl phosphorylcholine (MPC), which possess strong intrinsic antifouling properties and mechanical flexibility. Depending on the unique composite nanopattern, the hydrogel demonstrated excellent dual functionalities of antifouling and antibacterial activities against Gram-negative bacteria E. coli and Gram-positive bacteria B. subtilis, compared with those of surfaces with simple nanostructures or antifouling material (shown in Figure 5).

Other than these strategies, recently nitric oxide releasing biomaterials were also exploited to combat infections during the course of diabetic wound healing. It is already well-established that the healing mechanism of diabetic wounds is severely affected by prolonged inflammation, reduction of secretion of growth factors, and/or obstruction of angiogenic activity as well as infection due to an attack by microbes. Researchers and clinicians observed that these problems can be tackled by supplying nitric oxide (NO) endogenously or exogenously at the healing site. NO generated by endothelial nitric oxide synthase (eNOS) naturally assists wound healing through its beneficial vasculogenic effects. However, in the course of hyperglycemia the activity of eNOS is affected, which ultimately leads to a delay in the healing process. Therefore, the exogenously supplied NO donors that can release NO at the healing site can be encapsulated into wound healing patches to treat diabetic wounds. Furthermore, NO can also eradicate bacterial infections, which makes it a potential therapeutic agent for the purpose of diabetic healing. For instance, Zahid and co-workers reported a visible light cross-linked gelatin methacrylate (GelMa) hydrogel loaded with NO donor for diabetic wound healing.42 GelMa is already well-known for its cell friendly and cell adhesive properties for tissue engineering applications. As a NO donor, they used S-nitroso-N-acetylpenicillamine (SNAP), which improves cell proliferation, facilitates rapid cell migration, and enhances diabetic wound healing by delivering antibacterial properties. The NO release study revealed that a long-term and sustained released (up to 80 h) can be achieved through controlling the cross-linking density of the hydrogel. The NO releasing GelMa patch demonstrated greater cell viability, proliferation, and migration with the SNAP concentration of 0.08% (w/w) compared to control (only GelMa patch). In addition to that, the strong antibacterial potential of NO enabled this compound to be used for wound healing applications. In another recent study, Yoo and co-workers reported chitosan based NO releasing hydrogel dressings for antibiofilm and in vivo healing in diabetic mice.43 For their study they chose chitosan as a polymer and 5-nitrosoglutathione (GSNO) as a nitric oxide donor to defend against pathogenic biofilms and enhance wound healing activities. Although chitosan has some sort of antibacterial properties, hydrogels made with this type
of polymer rely on contact killing, which requires contact for hours and which is rarely sufficient to eradicate infections. Thus, loading hydrogels with antibacterial components has been extensively used to enhance hydrogels’ antibacterial properties, and in this case, it is NO. The in vitro release study from hydrogel revealed the sustained release behavior of NO over a period of 3 days in simulated wound fluid. The chitosan/NO film significantly improved the antibacterial activity against methicillin-resistant S. aureus (MRSA) by a >3 log reduction in bacterial viability. Furthermore, in the case of in vivo MRSA biofilm infected wounds, the chitosan/NO film treated group exhibited faster wound size reduction, epithelialization, and collagen deposition compared to the untreated and chitosan film treated groups; this suggests that NO can take a critical part in combating infections as well as promoting diabetic wound healing. A schematic diagram of the healing mechanism using chitosan/NO film is represented in Figure 6.

The above-mentioned approaches to combat infection during diabetic wound healing are quite promising; however, certain challenges still exist. For example, metal ions and particles neutralize microbes based on the release of a leachable amount into the surrounding environment and thus may cause a tissue response. In the case of loading bacteriophages in hydrogels/antifouling hydrogels/NO loaded hydrogels to control biofilms in wounds, is still in an early stage and much more in-depth studies should be performed. Therefore, from the above discussion we can say that there are still huge opportunities in this field to develop new multifunctional hydrogels with antimicrobial properties for diabetic wound management.

4.2. Reducing Excessive Reactive Oxygen Species (ROS). Reactive oxygen species (ROS) play a critical role in both normal and diabetic wound healing. ROS are various types of signaling molecules, including hydrogen peroxide (H$_2$O$_2$), hydroxyl radicals (•OH), superoxide anions (•O$_2^-$), nitric oxide radicals (NO•), etc. It has been observed that a low ROS level can affect cell migration and endorse angiogenesis.$^{15,46}$ Even though ROS can induce antimicrobial activity, excessive ROS can arrest the wound healing process. The transition from the inflammatory phase to the proliferative phase of the cells is prevented by excessive ROS, which may worsen wound infection.$^8$ In contrast to the normal wound healing process, ROS can gather up in a diabetic wound site in diabetic wound healing and can surpass the antioxidant capability of cells, which ultimately leads to ECM degradation and cell death. In this context, it is already reported that the concentration of H$_2$O$_2$ in normal human blood plasma is within the range 0.61–6.79 μM,$^{47}$ with healthy cell metabolism generating an extra ~0.1 μM ROS. On the other hand, under a high oxidative stress environment the concentration of ROS can reach as high as 10–1000 μM.$^{48}$ In addition to that, it was observed that in the case of type I diabetes the H$_2$O$_2$ concentration is 82.1 ± 31.4 μM whereas in the case of type II diabetes plasma it is 61.7 ± 39.1 μM.$^{45,49}$ This excessive amount of ROS restricts the regular functions of keratinocytes

Figure 6. Illustration of mechanisms of action of CS and GSNO in CS/NO film in MRSA biofilm infected wound healing. Reproduced with permission from ref 43. Copyright 2019 Elsevier.
Several natural polyphenols such as tannin, gallic acid, and curcumin have been exploited as an antioxidant scavenger/drugs in hydrogel systems to scavenge ROS. For example, Park and co-workers designed a ROS scavenging gallic acid drug in hydrogel systems to scavenge ROS. For example, Park et al. synthesized a ROS scavenging hydrogel for bacteria-infected diabetic wound healing. To prepare the hydrogel, they used poly(vinyl alcohol) (PVA) as a main polymer and a ROS responsive agent, \( N^1\)-(4-boronobenzyl)-\( N^2\)-(4-boronophenyl)-\( N^3\)-[poly(vinyl alcohol)] as a cross-linker. The obtained hydrogel effectively scavenged the ROS and promoted the wound closure by decreasing the ROS level and upregulating M2 phenotype macrophages around the wound. It was found that, when the hydrogel was incubated with \( H_2O_2 \), 100% of it was scavenged after 24 h (1 mM, 2 mL), leading to degradation of the hydrogel. Additionally, in vivo studies revealed that the hydrogel loaded with the antibiotic mupirocin and the cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF) could release those therapeutic molecules in response to wound endogenous ROS, subsequently eliminate Staphylococcus aureus infection in the wound, and further accelerate wound regeneration in both normal mice and diabetic mice with \( S. aureus \) infections.

Compared to this type of antioxidant hydrogels, hydrogels with inherent antioxidant properties (due to the inherent property of antioxidant macromolecules) are more attractive for diabetic wound management. In this regard, Wu and co-workers synthesized arginine derivative modified dopamine conjugated gallic acid to get the final HA-DA/AD antioxidant hydrogels.

**Figure 7.** In vivo wound healing effect of GH/GGA hydrogels. (a) Representative images of wound repair for 14 days of treatment (scale bars represent 2 mm). (b) Quantification of wound closure rate expressed as the percentage of the initial wound size. (c) Quantification of the number of blood vessels and hair follicles per square millimeter in the wounded area using ImageJ software \((n = 3)\). (d) Representative images of sections stained with H&E (top) and Masson's trichrome (bottom) from normal skin and wounded skin treated with/without hydrogels at day 14 postwounding (red filled triangles, hair follicles; black filled triangles, subcutis/hypodermis; and green filled triangles, blood vessels). Scale bars represent 100 μm. * \( P < 0.05 \) and # \( P < 0.05 \) versus GH and DPBS groups, respectively. Reproduced with permission from ref 44. Copyright 2020 Elsevier.

In the presence of an \( \cdot O_2 \) radicals, which is much higher than the conventional gelatin hydrogel. As a cross-linker, the obtained hydrogel effectively scavenged the ROS and promoted the wound closure by decreasing the ROS level and upregulating M2 phenotype macrophages around the wound. It was found that, when the hydrogel was incubated with \( H_2O_2 \), 100% of it was scavenged after 24 h (1 mM, 2 mL), leading to degradation of the hydrogel. Additionally, in vivo studies revealed that the hydrogel loaded with the antibiotic mupirocin and the cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF) could release those therapeutic molecules in response to wound endogenous ROS, subsequently eliminate Staphylococcus aureus infection in the wound, and further accelerate wound regeneration in both normal mice and diabetic mice with S. aureus infections.

Compared to this type of antioxidant hydrogels, hydrogels with inherent antioxidant properties (due to the inherent property of antioxidant macromolecules) are more attractive for diabetic wound management. In this regard, Wu and co-workers synthesized arginine derivative modified dopamine hyaluronic acid (HA-DA/AD) hybrid hydrogels for diabetic wound healing applications. To synthesize the arginine derivative, they reacted decane-1,10-diol with arginine, which offered the antioxidant properties. Subsequently they reacted this arginine derivative with dopamine functionalized hyaluronic acid to get the final HA-DA/AD antioxidant hydrogels. The HA-DA/AD hydrogels exhibited better DPPH and...
hydroxyl radical scavenging efficiencies than the normal HA-DA hydrogel. Furthermore, the HA-DA/AD hydrogels showed significantly better safety for cells against external oxidative stress (decreased ROS and malondialdehyde levels and enhanced superoxide dismutase and glutathione peroxidase enzyme activity) and better wound healing (enhanced vascular endothelial growth factor and cluster of differentiation 31 expression and enhanced tissue remodeling), which confirmed hydrogels with antioxidant properties are far more effective for diabetic wound healing compared to hydrogels loaded or modified with antioxidant scavengers/antioxidant drugs. However, for better results hydrogels with ROS scavenging properties should be implemented along with antibacterial, angiogenic, or other functions for treating infected diabetic wounds.

4.3. Promoting Angiogenesis. Angiogenesis is the process of formation of new blood vessels which supply nutrients and oxygen to cells and tissues. However, in contrast to normal wounds, angiogenesis is hampered by hyperglycemia, inflammation, and ROS overproduction in diabetic wound sites. These phenomena ultimately restrict microvasculature formation and result in nonhealing wounds.

Figure 8. Hydrogel promoting angiogenesis. (A) The combination of desferrioxamine (DFO) and bioglass (BG) loaded sodium alginate (SA) hydrogels affected the migration and tube formation of HUVECs in vitro and (B) also promoted angiogenic factor expression in vivo (immunohistochemical staining for HIF-1a and VEGF). Reproduced from ref 59. Copyright 2018 American Chemical Society.
Therefore, therapeutic angiogenesis is very crucial for diabetic wound healing. To accelerate angiogenesis, different types of angiogenic growth factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) can be delivered at diabetic wound sites. Other than this, delivery of drugs and stem cells which can upregulate genes related to angiogenesis also be a promising approach for promoting angiogenesis. But the major problem with these strategies is that most of these growth factors are unstable at diabetic wound sites, where abundant proteases will break down the native extracellular matrix (ECM) and growth factors as well as their receptors. As a result, growth factor delivery strategies are very critical for successful diabetic wound management. In this regard hydrogel is one of the prime contenders for the delivery of growth factors at wound sites. Hydrogels can protect the growth factors without affecting their activities and allow them to accelerate the process of angiogenesis even in diabetic wounds. For example, Wang and co-workers reported a Carbomer-940 hydrogel for delivery of recombinant human acidic fibroblast growth factor (rh-aFGF) for wound healing in a diabetic rat model. The Carbomer-940 hydrogel maintained the efficacy of rh-aFGF during its entire delivery process. After 14 days they observed that the healing efficacy of the group treated with rh-aFGF loaded hydrogel is much more (81.3%) compared to that of the control group (68.8%). Furthermore, a hematoxylin and eosin (H&E) assay confirmed more significant neovascularization in the case of rh-aFGF loaded hydrogel compared to the nonloaded control group.

To promote angiogenesis, chemokines were also loaded into hydrogels and delivered at diabetic wound sites. For instance, Amer and co-workers reported a thermoresponsive antioxidant poly(ethylene glycol citrate-co-N-isopropylacrylamide) (PPCN) hydrogel for delivery of stromal cell derived factor-1 (SDF-1) at diabetic wound healing sites in a mice model. It was observed that, SDF-1 was released from the hydrogel in a sustained manner from the PPCN hydrogel to the wound site and accelerated wound healing. For wounds treated with PPCN + SDF-1, SDF-1 only, PPCN only, and PBS, the times to 50% wound closure were 11, 16, 14, and 17 days, respectively. In addition to that, the wounds treated with PPCN + SDF-1 exhibited the shortest time for complete healing (24 days), rapid granulation tissue development, epithelial maturation, and the highest density of perfused blood vessels. In another study He et al. reported a bioactive injectable hydrogel loaded with desferrioxamine (DFO) and bioglass to promote angiogenesis in diabetic wound healing. There is already much evidence that DFO can enhance secretion of hypoxia inducible factor-1 (HIF-1α), which ultimately upregulates the expression of angiogenic growth factors and facilitates revascularization. On the other hand, it is proved that the silicon (Si) ions present in the bioglass (BG) can upregulate the VEGF expression, which also enhances the vascularization process. In this work authors proposed that the combination of BG and DFO loaded in sodium alginate hydrogel may have a synergistic effect in promoting VEGF expression and revascularization. Upon implantation of BG and DFO loaded hydrogel into a diabetic wound site of the rat model, it was observed that combination of BG and DFO significantly stimulated migration and tube formation of human umbilical vein endothelial cells (HUVECs) as compared with the BG or DFO alone (shown in Figure 8). These results suggest that BG and DFO could synergistically upregulate gene expression of VEGF and the alginate hydrogel efficiently protect the activity of BG and DFO as well as promote vascularization at diabetic wound site.

Therefore, from the above discussion it is clear that hydrogels can play a critical role in delivering angiogenic growth factors at wound sites and promote the vascularization process which is effective in animal models also. However, despite the success in animal models, very few products have been tested in preclinical and clinical trials. The main reason for that is because it is very challenging to treat diabetic wounds with a single function hydrogel; to treat this type of diseases hydrogels with multifunctional capabilities should be exploited.

4.4. Triggering Macrophage Polarization. As discussed above, macrophage polarization from the M1-like phenotype to the M2-like phenotype has played a crucial part angiogenesis which ultimately leads to successful diabetic wound healing. As the M1-like phenotype and the M2-like phenotype both play a critical part in the healing process, the alteration in the immunomodulatory balance in the M1-like phenotype and the M2-like phenotype leads to accelerated and improved infiltration in the second stage of diabetic wound healing, which is advantageous for rapid angiogenesis and vascularization. In this regard, recently exosome-based therapies have exhibited promising results by facilitating the wound healing process. Moreover, emergent evidence shows that exosomes derived from human adipose derived mesenchymal stem cells (hADSCs-Exos) can promote M2 macrophage polarization and thus effectively enhance angiogenesis and tissue repair. As these exosomes are highly unstable in an in vivo environment, exosomes are used in limited biomedical applications. Therefore, the design of multifunctional wound dressings with controlled release properties could be a promising strategy to deliver these exosomes at the wound site to trigger M2 macrophage polarization. In this regard Yi and co-workers developed an exosome laden self-healing injectable hydrogel that enhances diabetic wound healing via regulating macrophage polarization. To prepare the hydrogel, they employed chitosan-graft-aniline tetramer (CS-AT) and dibenzaldehyde-terminated poly(ethylene glycol) (PEG-DA). The Schiff base reaction between the amine functionality of CS-AT and the aldehyde functionality of PEG-DA resulted in the instantaneous self-healing ability of the hydrogel. In addition to that, the hydrogel also possessed excellent injectability, adhesiveness, biodegradability, biocompatibility, and antibacterial properties. Due to the inherent electrostatic nature of the hydrogel, it effectively combined with exosomes through electrostatic interactions. When the diabetic wound was treated with this exosome loaded hydrogel, the hydrogel induced local regulation of M2 macrophage polarization. More interestingly, immunofluorescence staining revealed that the exosome loaded hydrogel group exhibited the most intense CD206 staining compared to that of the other groups (only hydrogel, only exosomes, and control group), which suggested that higher expression was induced in the activated macrophages. To further access the subtypes of the macrophage polarization on various samples, they measured the iNOS and IL-1β markers of the M1 macrophage and Arg-1 and VEGF markers of the M2 macrophage using quantitative real-time PCR. That revealed that the hydrogel group enhanced the expression levels of M1-related genes more than the other groups, whereas the exosome loaded hydrogel demonstrated a higher expression of genes related to M2 macrophages followed by the only hydrogel and only exosome groups. In
addition to that, the hydrogel with a coculture of macrophages significantly improved the ability of HUVECs to proliferate, migrate, and form tubes.

In another recent study, Xia and co-workers also developed a functional adhesive hydrogel for diabetic wound healing. To synthesize the hydrogel, they grafted hyaluronic acid with methacrylic anhydride and N-(2-aminoethyl)-4-[4-(hydroxy-methyl)-2 methoxy-5-nitrophenoxy]-butanamide (NB) groups, which can efficiently encapsulate lyophilized amnion-derived conditioned medium (AM-CM). Upon photolysis, photolysis of grafted NB groups took place, which resulted in \( \text{o} \)-nitrosobenzaldehyde groups. These nitrosobenzaldehyde groups efficiently bound with the amino groups of the tissue interface and active peptides and enabled the hydrogel to strongly bond to wet wound surfaces.

Furthermore, the Gel-CM releasing buffer substantially upregulated the expression of the M2 macrophage marker CD206 and reduced the expression of the M1 macrophage marker CCR7 as determined by real-time PCR (Figure 9), which confirms that AM-CM hydrogel played a critical role in the determination of the macrophage polarization. It was observed that the macrophages were small and round when cultured with control medium (Figure 9), while when cultured with TNF-\(\alpha\) and IFN-\(\gamma\), most macrophages converted into M1-like macrophages, as characterized by their dendritic structures with multiple protrusions (Figure 9). The hydrogel loaded with AM-CM (Gel-CM) releasing buffer guided macrophages toward the M2-like phenotype, as characterized by elongation of the cell morphology (Figure 9).

Other than the exosome loaded hydrogels, some recent studies also explored the specially designed inherent capability of hydrogel toward macrophage polarization for a diabetic wound healing application. For example, Shi and co-workers have developed a surfactin-reinforced gelatin methacrylate hydrogel (GelMA-SF) for diabetic wound healing. Surfactin (SF) is an amphipathic cyclic lipopeptide which is well-known for its excellent biocompatibility, biodegradability, low toxicity, and superior surface activity, while GelMA is also very popular for its cell friendly properties. It was observed that the GelMA-SF has excellent rheological properties, tunable mechanical properties, high swelling ratio, appropriate water vapor permeability, self-healing behavior, and good biocompatibility. In vitro and in vivo studies revealed that the GelMA-SF hydrogel significantly promoted re-epithelialization rates, granulation tissue thickness, and collagen disposition in the full-thickness excisional wound model of type I diabetic rat. Furthermore, GelMA-SF hydrogels demonstrated excellent properties to promote chronic wound healing in diabetes by regulating macrophage polarization from M1 to M2 and modulating angiogenesis. In detail, they exposed RAW 264.7 cells with lipopolysaccharide (LPS) alone which acted as the negative control, whereas other groups were subsequently treated with GelMA-SF hydrogels or GelMA hydrogels after LPS treatment. It was observed that RAW 264.7 cells are polarized into the M1 phenotype after treatment with LPS for 12 h, while subsequent to treatment with GelMA-SF hydrogels for another 12 h, the RAW 264.7 cells that had been already treated by LPS for 12 h are significantly polarized into M2 phenotypes. However, the treatment with GelMA hydrogel does not impair any effect to RAW 264.7 cells. Therefore, it has been observed from the above studies that the functional hydrogels can address a critical role for diabetic wound healing.

Figure 9. Biological effect of the hydrogel loaded with AM-CM (Gel-CM) releasing buffer on phenotypic change of macrophages in vitro. (A) Morphological changes of macrophages when treated with TNF-\(\alpha\) and IFN-\(\gamma\) with or without a Gel-CM releasing buffer. Complete medium without TNF-\(\alpha\) and IFN-\(\gamma\) was used as the control medium. Scale bars 50 \(\mu\)m. (B) mRNA expression levels of the M1 macrophage marker CCR7 and M2 macrophage marker CD206 when treated with the control medium, TNF-\(\alpha\) and IFN-\(\gamma\), or TNF-\(\alpha\) and IFN-\(\gamma\) + Gel-CM releasing buffer were detected by real-time PCR. Data is shown as mean ± SD; \(n = 3\); **, \(P < 0.01\); ***, \(P < 0.001\). From ref 63. CC BY 4.0.
by regulating macrophage polarization. Table 1 summarizes some of the functional hydrogels which are utilized for macrophage polarization in diabetic wound healing application.

### 4.5. Inhibition of Matrix Metalloproteinase (MMP)

MMPs, metal-dependent endopeptidases, play a significant role in the process of repairment as well as in the pathology of DFUs. Involvement of MMP-1, MMP-2, MMP-9, MMP-13, and MMP-14 is observed in the migration of keratinocyte; MMP-7 is necessary for re-epithelialization; delayed healing and wound contraction is governed by MMP-3; angiogenesis is regulated by MMP-12; MMP-8 and MMP-13 are required for wound healing. In a recent study, Peng and co-workers noted that defining the individual roles of 24 MMPs expressed by human is difficult as each of them present in three forms: proMMP, active MMP, and tissue inhibitor of matrix metalloproteinase (TIMP) complexed MMPs. Among them only active MMPs are catalytically competent and thus participate actively in both the process of wound repair and the pathology of DFUs. This work identified and quantified two active MMPs (MMP-8 and MMP-9) from the wounds of diabetic (db/db) mice. Previous reports indicated the detrimental effect of MMP-9 in the process of wound healing, which could be reversed by MMP-9 gene knockout or by use of selective inhibitors. While the use of selective inhibitors of MMP-8 results in a delayed healing process, recombinant MMP-8 accelerates the process, depicting the important role of MMP-8 in the normal process of healing. Therefore, selective inhibition of MMP-9 would be the best approach to treat DFUs.  

Peng et al. demonstrated the effect of (R)-ND-336 (a selective MMP-9 inhibitor) alone or in combination with linezolid (antibiotic) on a Staphylococcus epidermidis (ATCC 35984) infected diabetic mice model. (R)-ND-336 was discovered through the process of lead optimization of thirane class inhibitors, presently in the pipeline of a clinical trial as an investigational new drug. They observed that (R)-ND-336 in alone or coadministered with linezolid was able to improve the process of wound healing through inhibiting the MMP-9, elevating VEGF (angiogenic marker), and mitigating the infiltration macrophages. An in vivo study demonstrated that, compared with the vehicle control, linezolid was not able to accelerate the healing process ($P = 0.67$ (on day 10), $0.97$ (on day 14), and $0.47$ (on day 21)). By contrast, (R)-ND-336-treated wounds remained smaller than those of control at all time points ($P = 0.033$ (on day 10), $0.036$ (on day 14), and $<0.049$ (on day 21)). The combination ((R)-ND-336 + linezolid-treated) showed significant acceleration in the healing process ($P = 0.00002$ (on day 10), $0.037$ (on day 14), and $0.008$ (on day 21)) (Figure 10A,B). Moreover, (R)-ND-336 alone and with linezolid showed complete re-epithelialization of the infected wound, demonstrated by H&E staining (Figure 10C), indicating the significance of using MMP-9 inhibitors in the diabetic wound healing process. On a similar note, Chang et al. described the role of MMPs in both the pathology of DFUs and their beneficial role in the process of healing. They investigated the effect of the same selective MMP-9 inhibitor, (R)-ND-336, on a diabetic wound model and similarly observed that it was able to decrease NF-kB and ROS levels, decreasing the inflammation and promoting angiogenesis, thereby significantly improving the diabetic wound healing process. Therefore, it could be stated that use of selective inhibitor of MMP-9 (while sparing MMP-8) along with

### Table 1. Functional Hydrogels for Triggering Macrophage Polarization in Diabetic Wound Healing Application

| Hydrogel system                                      | Growth factors/delivered | Cells used                  | Results                                                                 |
|------------------------------------------------------|--------------------------|-----------------------------|------------------------------------------------------------------------|
| Injectable silk hydrogel system based upon Bombyx mori silk fibroin protein and recombinant mouse fibronectin protein | N/A                      | RAW 264.7 cells             | The hydrogel offers an ideal 3D matrix for primary rat islets. Additionally, these hydrogels demonstrated sustained release of interleukin-4 (IL-4) and dexamethasone with effective M2 macrophage polarization through paracrine mechanisms. |
| Injectable silk hydrogel system based upon Bombyx mori silk fibroin protein and normal human dermal fibroblasts | N/A                      | RAW 264.7 cells             | The hydrogel offers an ideal 3D matrix for primary rat islets. Additionally, these hydrogels demonstrated sustained release of interleukin-4 (IL-4) and dexamethasone with effective M2 macrophage polarization through paracrine mechanisms. |
| Injectable silk hydrogel system based upon Bombyx mori silk fibroin protein and normal human dermal endothelial cells | N/A                      | RAW 264.7 cells             | The hydrogel offers an ideal 3D matrix for primary rat islets. Additionally, these hydrogels demonstrated sustained release of interleukin-4 (IL-4) and dexamethasone with effective M2 macrophage polarization through paracrine mechanisms. |
| Injectable silk hydrogel system based upon Bombyx mori silk fibroin protein and normal human dermal fibroblasts | N/A                      | RAW 264.7 cells             | The hydrogel offers an ideal 3D matrix for primary rat islets. Additionally, these hydrogels demonstrated sustained release of interleukin-4 (IL-4) and dexamethasone with effective M2 macrophage polarization through paracrine mechanisms. |
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*Note: The table lists various hydrogel systems and their results in terms of growth factors, cells used, and results. The results are described with respect to the polarization of macrophages towards M2 phenotype and their role in promoting the healing process.*
antibiotics could be the best strategy to mitigate infected DFUs.

4.6. Wearable Sensors: Advanced Modalities for Real-Time Monitoring of Wounds. At the outset of the development of new treatment strategies to manage chronic wounds, continuous monitoring became an integral part of the diagnosis, prevention, and management of such medical conditions. Therefore, advanced research is warranted to develop such tools. Recently, Golledge et al. discussed the role of wearables, sensors in diabetic associated foot diseases. Various wireless biosensors have been explored for this purpose. To monitor the effectiveness of the therapy and ensure the patient’s safety, such devices offer great importance, as parameters such as temperature, pH, infection status, and matrix metalloproteinase level could be monitored remotely. For example, Salvo et al. developed such a sensor capable of monitoring the temperature and pH. Change of basal temperature is a strong indicator of degradation of ulcer status, while change of pH at the wound site could be a sign of a progressing infection. The pH of normal skin and properly healing wounds is between 4 and 6.5 (acidic) while the pH of an infected wound becomes alkaline (above 6.5); therefore, pH could be a notable biochemical marker in the process of wound healing. To prepare a temperature sensor, Salvo & coworkers used a multiwalled carbon nanotube nano-composite and poly(styrene-(ethylene-co-butylene)-b-styrene), which showed a sensitivity of $\sim 85 \, \Omega / {^\circ C}$ in the temperature range 25–50 °C with a high repeatability (seven times repeated measurements showed maximum 0.1% standard deviation). While, graphene oxide was used in the pH sensor. Graphene oxide changes its electrical potential with a change of pH. The pH sensor showed a high sensitivity ($\sim 42 \, mV/pH$) and high linearity ($R^2 = 0.99$). Furthermore, in a recent review, Tang et al. described such developments of temperature and pH sensors to manage wounds. Graphene nanomaterials and new generation carbon quantum dots have been explored for this purpose. Yang et al. developed organic-emissive carbon quantum dots that exhibited a change of photoluminescence from red to yellow with the change of pH from 5.0 to 9.0. Unlike using nanomaterials, pH sensitive dye also can be used to monitor the alteration of pH at the wound site. For example, Tamayol et al. loaded pH responsive dye into the mesoporous

![Figure 10](https://pubs.acs.org/doi/10.1021/acsomega.2c05538)  
**Figure 10.** (R)-ND-336 alone or in combination with linezolid accelerates wound healing in infected diabetic mice. Wounds (8 mm full thickness) were created on day 0 and infected with *S. epidermidis* ATCC 35984 on day 1. Mice (n = 12 per group) were randomized on day 7, and the wounds were treated topically with vehicle (water), 5 μg of linezolid, 10 μg of (R)-ND-336, or combined 5 μg of linezolid +10 μg of (R)-ND-336 once a day starting on day 7 until day 21. (A) Wound area measurements relative to day 0, mean ± SEM; n = 11 mice for vehicle, n = 12 mice for linezolid, (R)-ND-336 and (R)-ND-336 + linezolid on day 10; n = 8 mice per vehicle and linezolid, n = 9 mice for (R)-ND-336 and (R)-ND-336 + linezolid on day 14; n = 5 mice for vehicle, n = 6 mice for linezolid, (R)-ND-336 and (R)-ND-336 + linezolid on day 21, *, P < 0.05, and **, P < 0.01, by Mann–Whitney U two-tail test. (B) Representative images of the wounds. (C) Representative H&E of the wounds on day 21, with re-epithelialization shown by the white line, scale bar 50 μm. Reproduced from ref 71. Copyright 2020 American Chemical Society.

![Figure 11](https://pubs.acs.org/doi/10.1021/acsomega.2c05538)  
**Figure 11.** Fabrication of pH-sensing microfibers. Schematic illustration of pH-sensing hydrogel microfibers designed for long-term epidermal monitoring (i) and action mechanism of mesoporous polyester particles containing pH-responsive dye with electrostatic interaction to the solid matrix of the mesoporous particles (ii). Reproduced with permission from ref 78. Copyright 2016 Wiley-VCH.
nanoparticles and further incorporated it into alginate-based hydrogel fibers using a microfluidic technique for the real-time monitoring of the pH change at the wound site (shown in Figure 1). [5, 6]

Wound moisture is another key parameter in the process of healing; therefore, it should be monitored. To address this, wearable wound moisture sensors were developed which can sit on the wound site to provide the moisture status without disturbing the wound dressing material, e.g., the WoundSense sensor, a commercially available wound moisture sensor. [7] In an observational study, Milne et al. investigated the necessity of such sensors to prohibit the unnecessary change of dressing materials. They observed that 44.9% of dressing changes (out of 588 dressing changes) happened when the moisture reading was in the optimum zone; therefore a dressing change was not required. Such findings indicated that the use of sensors could be beneficial for better management of wounds by reducing unnecessary changes of wound dressings. In addition to that, detection and/or monitoring of wound infection is critical in the efficient management of chronic wounds. Several research studies have been carried out to address such issues. For example, Xiong and co-workers reported a DNA hydrogel based battery-free and wireless infection sensor. [8] In that work the authors reported wireless infection detection on wounds (WINDOW) to detect pathogenic virulence using a battery-free, wireless, flexible sensor. It was a DNA hydrogel (DNAgel) technology which provided a detectable radio frequency response to deoxyribonuclease (DNase). DNase is an enzyme secreted by pathogens such as S. aureus, Streptococcus pyogenes, and P. aeruginosa that are commonly associated with clinical wound infections. Exposure of the DNAgel to DNase resulted in nonspecific cleaving of DNA strands, leading to dissolution of the hydrogel. Changes in dielectric permittivity in that region modulated its capacitance. The electronic signal was recorded in a wireless and battery-free connectivity technology, mostly found in modern smartphones.

5. CONCLUSION AND FUTURE PROSPECTIVE

Chronic wounds like DFUs are a fatal condition, ultimately resulting in lower limb amputation if not treated or managed. DFU is majorly characterized by a prolonged inflammatory phase along with infection, excessive ROS generation, impaired neovascularization, and upregulation of matrix metalloproteinase. Several treatment strategies have been explored to treat such chronic wounds; among them hydrogel-based systems showed promise owing to favorable properties such as tunable mechanical strength, excellent absorption capabilities, porous structure, and biocompatibility. Hydrogels have become the most acceptable and trending system in the field of wound dressing material in recent decades offering single to multiple functions. This review discussed the pathophysiology of the diabetic wound healing mechanism to understand the targeted areas, which could be addressed by the use of functional hydrogels. The common challenge in wound healing is bacterial infection. Several hydrogel-based wound dressing materials were developed to address the unavoidable issue. Researchers have developed antibacterial agent incorporated hydrogels. They have used polymers having inherent antibacterial properties such as chitosan to prepare hydrogels. Instead of antibacterial agents, nanoparticles (such as silver nanoparticles) composite hydrogels were also explored. Moreover, antifouling hydrogels were developed to address the bacterial infection in the process of healing. Drug resistance and multidrug resistance have become a common problem nowadays. In this scenario, still no such strategies have been developed which could be effective against new drug-resistant bacterial strains in the future. Photodynamic therapy or photothermal therapy could be the answer in such cases. Therefore, still there is a huge opportunity for research before its suitability for real-world application in the future. As we discussed earlier, the process of wound healing is a complex and overlapping process; the parameters and requirements change dynamically over a period of time. Therefore, it is very difficult to address all of them with a single hydrogel-based system. However, it is indicating the opportunity to develop smart hydrogels having on-demand functions in the future. For example, it could reduce the inflammation at the inflammation phase, while being capable of releasing cytokines and other functional materials on-demand when required. It is noticed that research on the development of different sensors, wearables, for better management of chronic wounds is trending now. However, such devices may be generated which could release the antibacterial agent when the infection is detected. Three-dimensional (3D) tissue spheroids and lab-on-chip technology were developed to replace animal models. There is an enormous opportunity to develop in vitro chronic wound models to replace mice or rat models. Therefore, the perfect management of chronic wounds requires the development of new strategies and in-depth studies on the existing ones.

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K.G.: Writing, reviewing, figure and table design; D.C., V.R., S.D.: writing, reviewing; S.G.: writing, reviewing, figure design, conceptualization.

**Notes**

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ABBREVIATIONS

AgNPs: silver nanoparticles  
BG: bioglass  
CDs: carbon dots  
DFO: desferrioxamine (DFO)  
DFU: diabetic foot ulcer  
ECM: extracellular matrix  
GelMA: gelatin methacrylate  
GO: graphene oxide  
H&E: hematoxylin and eosin  
HIP: hypoxia inducible factor  
IL: interleukin  
MMP: matrix metalloproteinase  
NF-kB: nuclear factor κ-light-chain enhancer of activated B cells  
PPCN: poly(polyethylene glycol citrate−N-isopropylacrylamide)  
ROS: reactive oxygen species  
SDF-1: stromal cell derived factor-1  
TGF: transforming growth factor  
TIMP: tissue inhibitor of matrix metalloproteinase  
TNF: tumor necrosis factor  
USFDA: United States Food & Drug Administration  
VEGF: vascular endothelial growth factor

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