ROYAL SOCIETY
OF CHEMISTRY

Check for updates

# Emerging stimuli-responsive hydrogels for enhancing chronic wound healing

Maya Yun, [a,d] Logan Langford, [a,b] Lewis Russell, [b] Natalie Ndiforamang, [c] Anran Zhang [a] and Wubin Bai *[a]

Stimuli-responsive hydrogels have gained significant attention in wound care due to their ability to adapt to dynamic physiological conditions, making them promising candidates for facilitating chronic wound healing. These hydrogels can respond to both internal and external environmental stimuli such as temperature, pH, reactive oxygen species (ROS), glucose levels, MMP, mechanical forces, magnetism, and ultrasound, enabling precise, on-demand therapeutic interventions through controlled drug release. This responsiveness is governed by reversible changes in their polymer network structure caused by interactions with external stimuli. By creating an optimized environment for wound healing, stimuli-sensitive hydrogels can promote moisture retention, cellular migration, and mechanical flexibility while accelerating critical tissue repair processes like angiogenesis or collagen synthesis. Additionally, incorporating bioactive agents such as antimicrobial compounds, growth factors, and other therapeutically active substances like honey, has further expanded their functionality, though such modifications may be secondary to their inherent stimuli-responsive nature. This review provides a comprehensive overview of recent advancements in stimuli-responsive hydrogels for chronic wound management, highlighting their ability to respond to environmental cues and addressing their potential to enhance healing through the controlled release of therapeutic agents, promotion of hemostasis, and tissue regeneration.

## 1   Introduction

As the largest organ in the human body, the skin plays a multifaceted role in regulating homeostasis and protecting internal organs.[1] However, through constant exposure to external stimuli, such as in a chronic open wound, skin is particularly vulnerable to infection that can have severe negative and widespread implications for underlying tissue.[2]

Chronic wounds are those that fail to heal within the typical timeframe or frequently recur. These abnormal, non-healing wounds impact more than 8.2 million people in the US, and were estimated to cost up to $18.7 billion in 2014.[3,4] Although individuals of various ages can be affected, chronic wounds are most prevalent in elderly populations and encompass conditions such as diabetic foot ulcers, pressure ulcers, and venous leg ulcers. Chronic wounds are most commonly observed in adults with comorbid conditions, including but not limited to diabetes, obesity, and venous or arterial insufficiency, as these factors impair normal wound healing.[5] Additional factors, such as infections, improper moisture balance, and restricted blood flow to the affected area, can also contribute to the formation of chronic wounds. As of 2018, an estimated 10.5% of the US population live with diabetes, while approximately 42.4% were affected by obesity, as recorded by the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) respectively.[6] The likelihood of these populations developing chronic wounds would subsequently increase over time; it is estimated that by 2060, over 70 million elderly U.S. individuals would experience persistent chronic wounds. If left untreated, chronic wounds can result in severe complications, including sepsis, limb amputation, and even mortality. The importance of skin as a barrier has facilitated in-depth research efforts to understand the mechanism by which skin wounds can be repaired to restore proper functionality.[7]

Wound dressings play a crucial role in protecting open wounds from external contaminants; however, their effectiveness largely depends on the nature of the wound and the dressings' properties. Key clinical factors to consider when selecting an appropriate dressing include the amount of wound exudate, skin fragility, and the development of favorable granu-

*[a]Department of Applied Physical Sciences, University of North Carolina, Chapel Hill, NC 27514, USA. E-mail: wbai@unc.edu*
*[b]Lampe Joint Department of Biomedical Engineering, University of North Carolina, Chapel Hill, NC 27514, USA*
*[c]Department of Environmental Sciences and Engineering, University of North Carolina, Chapel Hill, NC 27514, USA*
*[d]Department of Psychology, University of North Carolina, Chapel Hill, NC 27514, USA*

lation tissue after debridement.[5] Gauzes are historically the most commonly used for wounds, as they are easily accessible and inexpensive. Although, these dressings have significant downsides; gauze tends to dry out the wound bed, which may cause damage to the new skin barrier during frequent changing, and offers limited protection as a good barrier.[8] Gauze also becomes ineffective after it is saturated with wound exudate.[8] Film dressings, while better at maintaining a moisture-retentive environment and protecting the wound from external contamination, have limited swelling capacity, and cannot be used for wounds with exudate or infected wounds, as the nature of the dressing would trap and promote harmful bacterial growth.[9] Hydrocolloids are beneficial as they are known to promote autolytic debridement. However, the opaque material makes it difficult to visualize any indications of changes underneath, such as from infections; it can also leave behind an unpleasant odor, holding in yellow-brown, gel-like drainage formed from the exudate.[8,10] Foam dressings are often recommended for wounds that produce more exudate, as these dressings are extremely absorbent. However, they are similar to the disadvantages of hydrocolloids in that they are opaque and can leave malodorous discharges, and they often require a secondary form of dressing as well.[8,10]

An ideal dressing for chronic wounds should not only serve as a protective barrier, but also foster an internal environment conducive to skin tissue regeneration, even in patients with impaired healing conditions. The dressing should be biocompatible, have sufficient absorption of wound exudates, prevent contamination, maintain adequate moisture, and be conformable for the fastest recovery.[11] The removal should also be painless, consequently causing the least damage to the skin. Hence, improving a dressing's physical and chemical properties is essential for enhanced recovery of chronic wounds. Among the various wound dressing materials studied, stimuli-responsive hydrogels have shown particular promise for

enhancing wound healing.[12] Due to limitations of conventional dressings – such as poor moisture retention, inflexibility, limited absorption, and typically no direct healing properties – innovative materials are needed to overcome the challenges of chronic wound healing. Stimuli-responsive hydrogels show great promise due to their ability to adapt to their environment as the environment fluctuates. These hydrogels are flexible and adjustable biomaterials that allow one to tune various aspects within the hydrogel, such as incorporating different copolymerized materials, or adjusting the critical point of a temperature-sensitive hydrogel for drug release. They create a moist environment that promotes favorable conditions for wound healing, and their hydrophilicity allows for absorption of large quantities of fluid while retaining flexibility and mechanical properties, all while being nontraumatic on the skin of the healing wound.[13]

Creating hydrogels with certain polymers or materials can provide them the ability to respond to various stimuli, such as heat, pH, glucose, reactive oxygen species (ROS), or matrix-metalloproteinases (MMP). These factors often become imbalanced in chronic wounds, leading to prolonged inflammation and delayed healing. Stimuli-responsive hydrogels can detect these imbalances and release therapeutic agents or change their properties accordingly, effectively promoting a more favorable healing environment for the wound. Developing hydrogel dressing systems that effectively respond to imbalances of these factors can result in improved wound healing in chronic wounds. Hydrogels can also be tuned to respond to applied external stimuli, such as mechanical forces, magnetism, or ultrasound. Building upon previous comprehensive reviews and novel research of the general wound healing process, generic hydrogels, and stimuli-responsive hydrogels, this review provides an updated overview of the general wound healing and the role of hydrogels throughout this process, followed by a discussion of stimuli-responsive hydrogel with a

Maya Yun is currently Postbaccalaureate Research Fellow at the National Institute of Environmental Health Sciences (NIEHS), where she conducts neurobehavioral research examining the effects of environmental factors on brain function and behavior. She earned a Bachelor of Science in Psychology from the University of North Carolina at Chapel Hill in 2025 and is pursuing a career in medicine. Her long-term goal is to integrate translational neuroscience research with clinical practice through an MD pathway.

**Maya Yun**

Logan B. Langford is an undergraduate student at the University of North Carolina at Chapel Hill, majoring in the Joint Department of Biomedical Engineering. His research interests focus on materials science and biomechatronics, with an emphasis on developing innovative technologies to advance biomedical applications. He plans to pursue a Ph.D. following the completion of his undergraduate studies, with the goal of contributing to the development of next-generation biomedical devices and therapies. He aspires for his research to play a role in improving patient outcomes and advancing healthcare solutions that can positively impact and save lives.
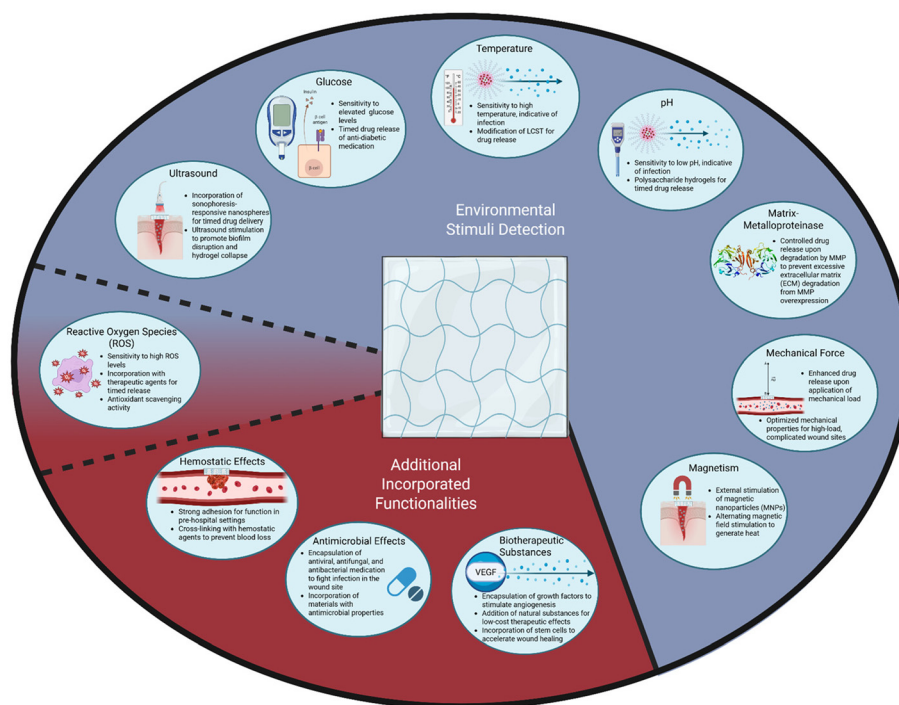
**Logan Langford**

**Fig. 1** Schematic representation of the functional components and mechanisms of stimuli-responsive hydrogels for wound healing.

specific focus on recent advances and emerging design strategies, including their response to key environmental factors. Additionally, we examine bioactive and nanocomposite developments and their contributions to hydrogel-based wound healing. An outline of this review is displayed in Fig. 1.

## 2 Normal wound healing process

The normal process of wound healing can vary depending on the nature and severity of the wound. As outlined by Chhabra *et al.*, the classification of wound healing depends on the

amount or area of cell death and disruption to the process.[14] Therefore, it can be difficult to generally define the steps of wound repair beyond four common stages marked by unique cellular and bio-psychological events: bleeding/hemostasis, inflammation, proliferation, and remodeling. A visual illustration of the wound healing process is shown in Fig. 2.

Immediately following an injury to skin tissue, blood vessels in the dermis may be severed, resulting in bleeding. The severity of bleeding has been found to depend largely on the number of transected vessels and the size or blood flow through each vessels.[15] For example, transection of the aorta, the largest artery in the human body, has a mortality rate of

*Lewis Russell is a third-year undergraduate student at the University of North Carolina at Chapel Hill, pursuing a degree in Biomedical Engineering with minors in Neuroscience and Chemistry. His research interests focus on the development and application of biomedical devices and pharmacological treatments to enhance patient care and outcomes in emergency medicine and oncology. Lewis currently plans to attend medical school, aiming to further explore his passion for biomedical research and integrate these skills in a clinical setting.*

**Lewis Russell**

*Natalie Ndiforamang is currently working as a dental assistant and patient care assistant as she pursues a career in dentistry. She graduated from the University of North Carolina at Chapel Hill in 2025 with a Bachelor of Science in Public Health, concentrating in Environmental Health Sciences, and a minor in Chemistry.*
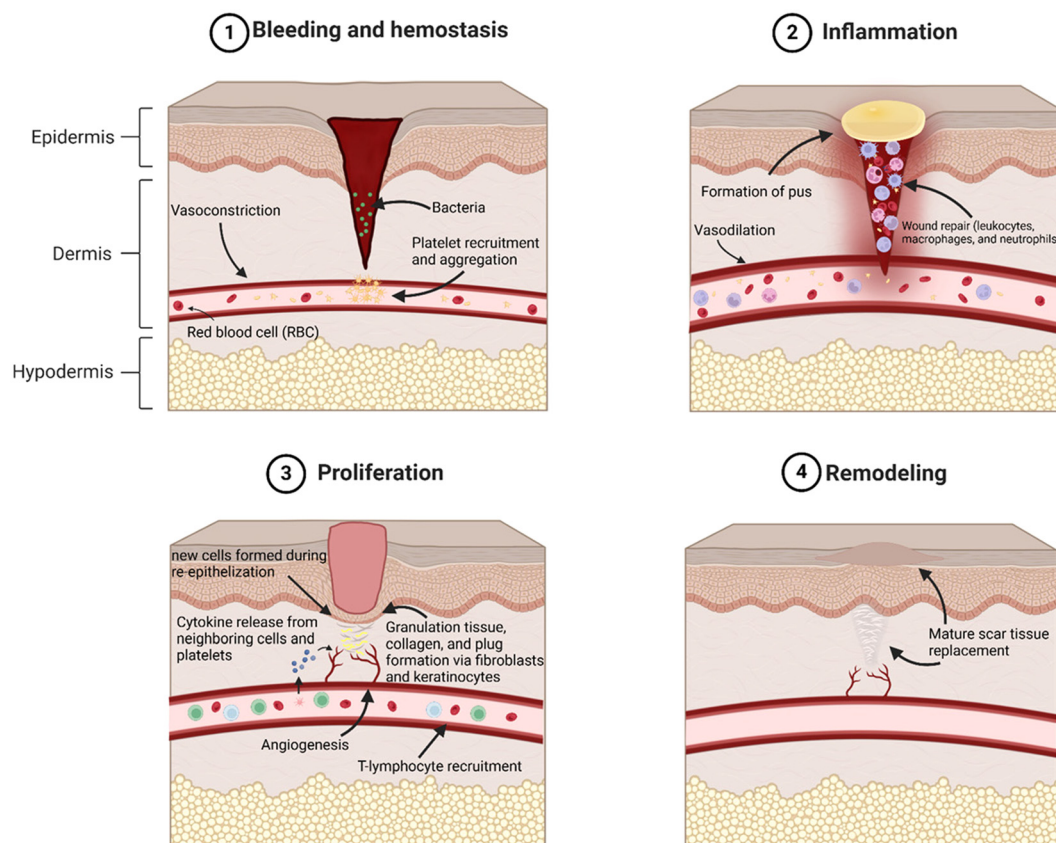
**Natalie Ndiforamang**

© 2026 The Author(s). Published by the Royal Society of Chemistry

*RSC Appl. Polym.*, 2026, **4**, 53–82 | **55**

**Fig. 2** Schematic of normal wound healing phases, including the hemostasis, inflammation, proliferation, and remodeling stages.

approximately 90%.[16] However, the greatest risk associated with smaller, open wounds is infection, as pathogens can bypass the body's protective barrier and spread to internal organs and systems. Roodsari *et al.* found that infection rates for simple hand lacerations treated in the emergency department were upwards of 5%, increasing the patient's risk for life-

*Anran Zhang is a PhD student in Department of Applied Physical Sciences at University of North Carolina at Chapel Hill under the supervision of Prof. Wubin Bai. Her research interests focus on bio-integrated 3D electronic platforms for advanced medical and life sciences.*

**Anran Zhang**

*Wubin Bai is an assistant professor at the University of North Carolina at Chapel Hill. He obtained BS degree in physics from the University of Science and Technology of China in 2011. He received PhD degree from the Department of Materials Science and Engineering at Massachusetts Institute of Technology in 2016. From 2016 to 2020, he was a postdoctoral researcher in Professor John Rogers' lab at the*

**Wubin Bai**

*Querrey Simpson Institute for Bioelectronics. His lab focuses research on the heterogeneous integration of soft materials and nanomaterials to design and develop devices for healthcare. His research has been recognized with Hettleman prizes, NeuroSpark award, NCBiotech TRG award, NC TraCS award, NSF CAREER award, Materials Today Rising Star award, ACS PMSE Early Investigator Award, and others.*

threatening conditions such as tetanus, sepsis, staph infection, and other severe bacterial or viral diseases.[17]

Hemostasis is a multi-step process initiated by clotting factors and other molecules such as platelets. In order to prevent blood loss, vasoconstriction is triggered by smooth muscle vascular spasms, and platelet aggregation is promoted by the exposed extracellular matrix around the damaged vessel.[18] While these two actions help to prevent blood loss, they have not yet produced a stable physical barrier for the wound's outer surface, and it is crucial at this point to cover the wound with a dressing to protect the platelet clot, prevent further injury, and maintain a healthy environment for tissue remodeling.[18]

Following hemostasis, the inflammatory stage is characterized by vasodilation, facilitating the infiltration of immune cells such as leukocytes, neutrophils, and macrophages into the extracellular space, where they phagocytose bacteria and necrotic tissue, setting the stage for tissue repair.[19] As outlined by Hosgood, the accumulation and eventual breakdown of immune cells and fluid manifest as pus. Longer-lasting monocytes are also recruited to the now-cleaned wound site by a cytokine storm released from dying neutrophils, and their proliferation is responsible for the inflamed appearance of wounds before their repair.[19] In order to transition from inflammation to tissue remodeling and repair, several key events typically occur within the wound. As detailed by Landén et al., macrophages play a crucial role in both promoting and suppressing inflammation at different points, termed the M1–M2 transition. This, in turn, makes macrophages and their secreted mediators popular therapeutic targets due to their high importance in both initiating and terminating inflammation.[20] If this transition, among other key events, does not occur as planned, proliferation and remodeling can be detrimentally delayed, increasing the risk of chronic wound formation.

Assuming a successful quenching of inflammation within the tissue, the wound healing process continues to the proliferation stage, marked by angiogenesis, or the reformation of vascular networks on the wound site.[7] Granulation tissue also begins to form near the surface of the wound through a process involving both CD4 and CD8 T-lymphocytes, keratinocytes, and several growth factors and cytokines, such as Th1, Th2, and Th17.[7] Granulation tissue serves to provide the wound with a protective epithelial layer and a stronger and more versatile plug during the proliferation of underlying tissue and vessels.[21] Simultaneously, reepithelialization occurs around the wound to stretch and close the lesion, and collagen is reintroduced into the new epithelial tissue from fibroblasts. It is crucial during this stage that the wound remains clean and protected, as any injuries or foreign bodies in the site have been associated with poor chronic wound healing.

In the final stage, known as the remodeling stage, apoptosis of immature collagen and granulation tissue allows for replacement by longer-lasting scar tissue.[21] Mature collagen fibers are incorporated into the new tissue to increase tensile strength, and inflammation is reduced by apoptosis of excess blood vessels introduced to supply the wound healing process

in the inflammatory stage. Through differentiation of fibroblasts into myofibroblasts, scar tissue is eventually contracted, and the extracellular matrix around the tissue thickens, but this process may take years to completely heal.[22] Furthermore, any further injuries to the region during this stage have been shown to alter levels of collagen within the wound site and lead to long-term scarring.[23]

## 2.1 Chronic wound healing process

Chronic wounds differ in their pattern of healing and are an ongoing struggle in healthcare to promptly and effectively treat. Chronic wounds can result from several diseases with unique pathophysiologies that result in wound conditions unfavorable for successful wound healing.[24] Consequently, the undesirable conditions within the wound prolong the healing process, increasing the risk of infection and worsening the mobility and quality of life in affected patients.

While the overall stages outlined previously are still present in chronic wound healing, a distinction is often made in the order of these events. Unlike the linear approach to healing that occurs in normal wounds, chronic wounds exhibit a non-linear, or asynchronous, wound healing pattern with overlapping periods of hemostasis, inflammation, remodeling, and cell proliferation. In other words, disruptions at some point during the wound healing process can prolong or cut short certain stages of the wound healing process with potentially detrimental effects to the affected tissue.[25] The tissue repair and proliferation stages may be disrupted by a prolonged inflammatory state, resulting from an inability of the surrounding tissue to remove inflammatory mediators such as M1 macrophages, tumor necrosis factors (TNF), and ROS.[5] This extended inflammatory period has been historically difficult to prevent due to diverse etiologies and comorbidities involved in the development of chronic wounds, each with different presentations and potential therapeutic targets. However, the resulting conditions and presentation of these varying pathophysiologies share several commonalities, which may aid in the treatment of chronic wounds to reduce inflammation and return the wound healing to its regular cycle.[26]

Common key processes end up becoming impaired as a result of a faulty wound-healing pathway. For example, Reich-Schupke et al. found that infections such as Methicillin-Resistant Staphylococcus aureus (MRSA) can become incredibly difficult to treat within a chronic wound, such as a leg ulcer, resulting in potentially life-threatening health risks such as sepsis and septic shock.[27] Furthermore, certain underlying conditions, such as diabetes mellitus, can produce vascular complications that restrict angiogenesis and prevent the repair of damaged blood vessels, a crucial component of wound repair.[28] Underlying health factors such as diabetes can also result in elevated levels of proteases such as matrix metalloproteinases (MMPs), which actively degrade the extracellular matrix (ECM), further increasing the risk for infection or poor wound healing outcomes.[29] Examples of common chronic wounds and their associated conditions and presentations, as well as current treatment approaches, can be found below in Table 1.

© 2026 The Author(s). Published by the Royal Society of Chemistry

RSC Appl. Polym., 2026, 4, 53–82 | 57

**Table 1** Common chronic wounds, their pathological features, conventional treatments, limitations, and the potential application of stimuli-responsive hydrogel strategies to address limitations

| Chronic wound type | Pathological features | Conventional treatments | Limitations of conventional treatments | Stimuli-responsive hydrogel strategies |
|---|---|---|---|---|
| Diabetic Foot Ulcers (DFUs)[30,31] | Elevated matrix metalloproteinases (MMP) levels, chronic inflammation, impaired angiogenesis, and excess advanced glycation end-products (AGEs) | Debridement, offloading, infection control, and growth factor therapy | High recurrence rates, poor drug penetration | MMP or ROS-responsive hydrogels for controlled drug release, macrophage polarization agents, anti-glycation therapies |
| Venous Leg Ulcers (VLUs)[32,33] | Venous hypertension, fibrin cuff formation, inflammation, delayed epithelialization | Compression therapy, wound dressings, skin grafts | High recurrence rates, poor long-term healing | pH-Responsive hydrogels (targeting alkaline pH), ROS-responsive hydrogels, growth factor delivery |
| Pressure Ulcers (PUs)[34,35] | Ischemia, necrosis from prolonged pressure, bacterial colonization, biofilm formation | Offloading, debridement of devitalized tissue, drainage of infected areas | Difficult healing in advanced stages | Oxygen-releasing and ROS-responsive hydrogels, antibiofilm strategies |

Several wound conditions, either as a result of existing medical conditions or characteristics of the wound's environment, can delay and disrupt the healing process, resulting in chronic wound formation. Among them, infection, oxygenation, and moisture levels have been shown to play a significant role in wound repair and could all potentially be addressed by artificial wound dressings capable of incorporating molecules that can target or recognize the needs of healing wounds.[18,36] Edwards *et al.* proposed a pathway by which bacterial infection can disrupt the wound healing process due to excessive inflammation from an increase in cytokines that reduces the presence of growth factors in the wound site.[37] Rodriguez *et al.* summarized the trends of oxygenation in chronic wounds, determining that the exact role and mechanism by which oxygen aids a wound environment must be investigated further, but patterns do appear to suggest that over- or under-oxygenation of chronic wounds delays and disrupts wound healing.[38] Interestingly, they also found that high-stress lifestyles or medical conditions that decreased oxygen flow to chronic wound sites were correlated with poor wound healing outcomes, suggesting a connection between wound healing and other diseases or socioeconomic factors. Thus, it is imperative to investigate and design solutions that can address these areas of concern while maintaining adequate physical protection of the wound site and all other functionality expected of a wound dressing.

## 3   An overview of hydrogels

Hydrogels are three-dimensional (3D) networks of cross-linked water-soluble polymers that can retain large amounts of fluid and water without disrupting biomechanical integrity.[13] Their high water retention capacity is attributed to hydrophilic functional groups such as hydroxyl (–OH), carboxyl (–COOH), and amine (–NH$_2$) within the polymer network. Conventional (non-responsive) hydrogels have demonstrated considerable benefits in wound healing, including maintaining a moist wound environment, promoting autolytic debridement, and serving as vehicles for passive drug delivery. Advanced non-responsive hydrogel systems have also been engineered to incorporate features such as hemostatic effects, antimicrobial behavior, or bioactive additives for enhanced therapeutic outcomes.[39–41]

The amphiphilic properties of hydrogels makes them highly biocompatible with a wide range of molecules, making them a promising target for drug delivery systems. As a result of these favorable properties, both responsive and non-responsive hydrogels have increasingly become a focus point of research into chronic wound dressings in recent years.

Modern hydrogel innovations have improved their functionality as wound dressings through the incorporation of ROS-scavenging compounds,[42] stimulus-responsive materials for controlled drug release,[43] injectable drug carriers,[44] conductive elements,[45] hemostatic agents, and antimicrobial properties, among others. Compared to other wound dressings—such as gauze, foams, films, or hydrocolloids—hydrogels offer a unique set of advantages that are particularly relevant for chronic wound management.[46] Their high water content not only maintains a moist wound environment critical for autolytic debridement and epithelial migration; it also provides inherent cooling and pain relief.[46] The soft, conformable nature of hydrogels allows them to adapt to irregular wound geometries without damaging surrounding tissue. Moreover, their porous 3D network can serve as a scaffold for cell infiltration, angiogenesis, and extracellular matrix remodeling—key processes that are often stalled in chronic wounds.[47] Hydrogels can also be loaded with bioactive compounds such as growth factors, antimicrobials, or stem cells, and their delivery can be spatially and temporally controlled in ways that are not feasible with more traditional materials. Beyond wound care, hydrogels demonstrated potential in other biomedical applications, such as 3D cell culture systems, targeted drug delivery, and tissue engineering, though these topics won't be explored in depth in this review.[48] By extensively modifying the materials and conditions used in hydrogel formation, researchers continue to discover new ways to enhance their mechanical properties and performance.

# 4 Stimuli-responsive hydrogels

Stimuli-responsive hydrogels possess the ability to undergo structural and functional changes in response to specific environmental triggers. While non-responsive hydrogels already offer several therapeutic benefits, responsive hydrogels provide an added layer of adaptability, enabling real-time, on-demand reactions to changes in the chronic wound microenvironment. In chronic wound healing, where there is often an imbalance in one of these stimuli that contributes to delayed tissue repair, hydrogels can be tuned to release therapeutic agents in response to the wound's specific imbalance. The use of this stimulus-sensitive drug release enhances control over the healing process while also minimizing the need for frequent dressing replacement. This dynamic responsiveness makes stimuli-responsive hydrogels a more viable and adaptable alternative to conventional wound treatments. The following sections will explore the key types of stimuli that influence hydrogel behavior and their implications for the chronic wound healing process, including pH, temperature, and glucose levels.

## 4.1 Temperature-sensitive hydrogels

Temperature can be a strong indicator of the status of a wound, as it is influenced by important biological processes that aid tissue repair. During the first 3–5 days, wound site temperature rises in alignment with the inflammatory phase of normal wound healing.[49] Moreover, an early sign of wound infection could be indicated by a significant increase of up to 2.77 °C in skin temperature, a characteristic that can be used to monitor chronic wound status and infection progression.[50] This distinctive increase in temperature has the potential to be incorporated into controlled drug delivery systems in temperature-responsive hydrogels.

Temperature-sensitive hydrogels undergo reversible phase transitions in response to temperature fluctuations. This thermoresponsive behavior is primarily due to the specific chemical composition and structure of the polymer chains, and is typically characterized by a specific lower critical solution temperature (LCST), at which the hydrogel's opaqueness, aqueous solubility, size, and shape are affected by temperature changes. Variations in LCST behavior can be due to the formation and dissociation of hydrogen bonds with water and interactions with polymer chain side groups, or it can be influenced by the balance between hydrophilic and hydrophobic interactions within the polymer.[51,52] At a temperature below the LCST, the hydrogel is hydrophilic and in its swollen state. Once it reaches above this critical point, the hydrogel properties typically become hydrophobic and opaque, resulting in the expulsion of the content being contained in the mesh interpolymer networks. The LCST of the hydrogel can be modulated by incorporating various copolymers, changing the ratio of hydrophobic to hydrophilic components within the polymer matrix, or adding amino acids and different functional groups. Increasing the proportion of hydrophilic polymers such as when adding polyacrylic acid (PAA) (LCST = 56.3°) results in a corresponding elevation of the LCST, as the hydrophilic structures of the polymers have more interactions with water, specifically hydrogen bonds.[53,54] Examples of synthetic polymers used in temperature-responsive hydrogels include poly(N-isopropylacrylamide) (PNIPAM), which has an LCST of 32 °C due to its hydrophobic isopropyl group and hydrophilic amide group;[55] poly(vinyl alcohol) (PVA), whose LCST can be adjusted to the physiological temperature of 37 °C with just 10 mol% butanoylation;[56] and poly(N-vinylcaprolactam) (PVCL), with an LCST ranging from 27 °C to 32 °C, influenced by its high molecular weight.[57] Natural biopolymers such as chitosan and gelatin have also exhibited thermosensitive behavior.[58] Fig. 3 shows the morphology and image of what a typical thermosensitive hydrogel looks like above and below the LCST.

By far the most commonly studied thermosensitive hydrogels are PNIPAM-based hydrogels, which are often copolymer-
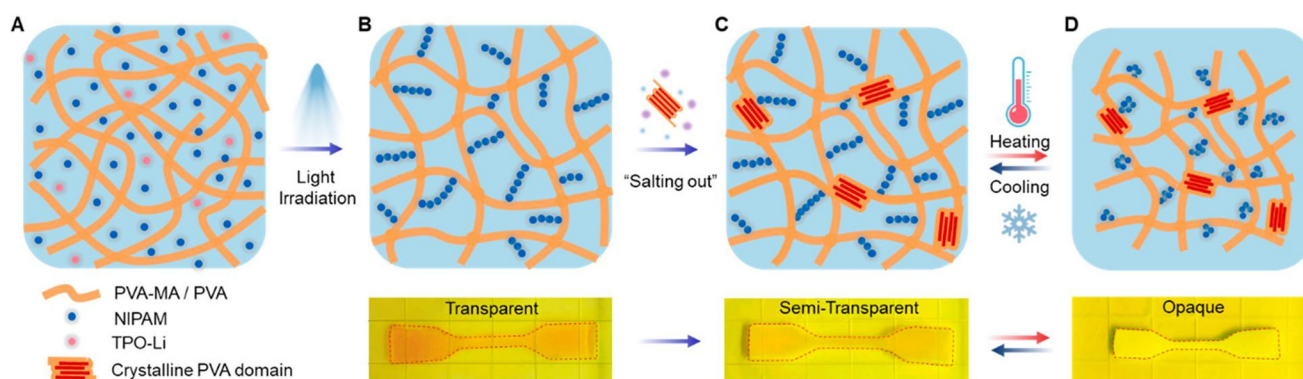


Fig. 3 Illustration of heating and cooling of PVA/(PVA-MA)-g-PNIPAM hydrogel. (A) Aqueous precursor containing PVA, PVA-MA, NIPAM and TPO-Li. (B) One-pot synthesis of PVA/(PVA-MA)-g-PNIPAM hydrogel by light irradiation from a digital light processing 3D printer. The as-printed hydrogel was transparent. (C) Toughening of hydrogel by immersion in Na$_2$SO$_4$ salt solution to induce PVA aggregation and crystallization. The hydrogel turned semitransparent after the salting-out process. Upon heating, the hydrogel is actuated, turning into its coiled state represented in (D). The hydrogel turned completely opaque in this state after heating, and reverted back to its semitransparent state (C) after cooling. Reprinted and modified with permission from ref. 59, ACS, 2021.

© 2026 The Author(s). Published by the Royal Society of Chemistry

RSC Appl. Polym., 2026, 4, 53–82 | 59

ized with additional hydrophobic or hydrophilic polymers to adjust the LCST, usually somewhere close to body temperature (36.7–37°).[60,61] Due to their ability to prevent water and fluid loss from wounds and their adhesivity, thermosensitive PNIPAM hydrogels crosslinked with poly(amidoamine) (PAA) were used to encapsulate bone-marrow derived-mesenchymal stem cells (BMSCs) as a therapeutic approach to promote wound closure. As shown in Fig. 4A and B, this combination was shown to be biocompatible, significantly reduce the inflammatory response in wounds, and improve wound closure rates.[61] The thermosensitivity of these hydrogels allowed them to achieve fast sol–gel transition once in contact with the wound, and their porous internal structure provided a good environment for cell proliferation, differentiation, and nutrient exchange. Additionally, thermosensitive poloxam hydrogels were developed by Zhang et al. to deliver human fibroblast growth factor 2 (hFGF2) linked with Camelina lipid droplets to accelerate burn wound healing in deep second-degree burns, which often lead to chronic wound complications.[62,63] Poloxam blocks consist of hydrophilic ethylene oxide (EO) and hydrophobic propylene oxide (PO) blocks, with EO-POB-EOA as the basic structure. This structure allowed for hydrophobically assembled micelles to form in an aqueous solution in between chain segments, making it a proprietary drug carrier. The combination of the two also resulted in faster growth of new epidermis and wound closure rates, especially after 5 and 8 days (Fig. 4C–E). Zhao et al. used curcumin- and rifampicin-loaded micelles (CRMs) loaded in thermosensitive Pluronic F127 and F68 block polymers that were modified by the epidermal growth factor receptor (EGFR) targeted peptide GE11 and MMP9-responsive peptide PVGLIG.[64] MMP9 is a matrix metalloproteinase found in high concentrations in a chronic wound environment. The thermosensitive hydrogel served as a highly adhesive base for the release of the CRMs, which demonstrated excellent intracellular and extracellular bacterial elimination efficiency, achieving an antibacterial rate of 99% in an MRSA-infected diabetic wound. While curcumin (Cur) and rifampicin (RIF) are hard to utilize in the body due to rapid metabolism, poor absorption as hydrophobic agents, and chemical instability, they are still favored for infected wound healing as they can promote cell migration and inhibit bacteria respectively, and using the thermosensitive hydrogel provides that ideal microenvironment for MMP9-responsive drugs to release in a chronic wound.[65] As displayed in Fig. 4F and G, the drug-releasing system was found to effectively reduce inflammatory response and promoted the neovas-
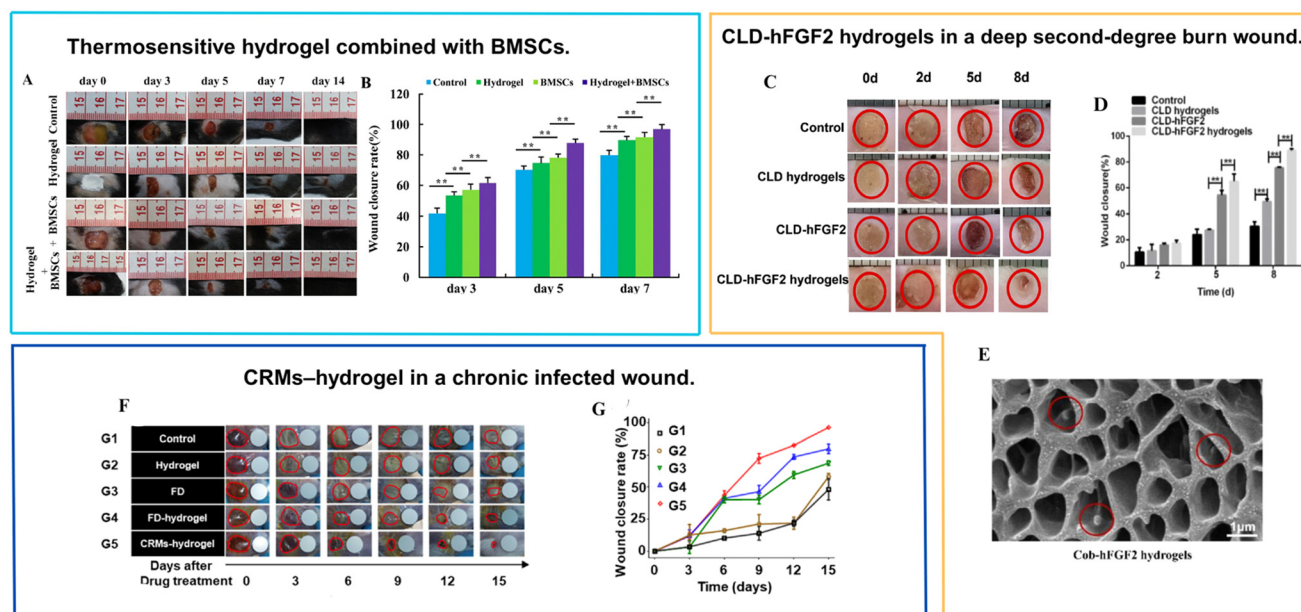


Fig. 4 (A) General wound-healing conditions of the mice in the control group, the hydrogel group, the BMSCs group and the hydrogel-BMSCs combination group 3 days, 5 days, 7 days and 14 days after an operation creating a chronic wound. (B) Comparison of the wound-healing rates of mice in the control group, the hydrogel group, the BMSCs group and the hydrogel-BMSCs combination group 3 days, 5 days and 7 days after the operation. While the hydrogel and the BMSCs alone did display some improvement from the control, the combination of the two improved overall wound closure rates the fastest, suggesting that hydrogels can be more effective with combined aspects. (C) Images of deep second-degree burn wounds after being covered with PBS, CLD hydrogels, CLD-hFGF2, and CLD-hFGF2 hydrogels. (D) Wound healing rates on the 0th, 2nd, 5th, and 8th days ($n = 6$, ** $p < 0.01$). Closure percentages for CLD-hFGF2 and CLD-hFGF2 hydrogels were significantly higher than control for days 5 and 8. (E) Micromorphology of CLD-hFGF2 hydrogels observed using Cryo-SEM (red circle represents CLD-hFGF2). Displays the porous structure of hydrogel that allows successful release of the lipid droplets without damaging the structure after loading. The size of the CLD-hFGF2 is approximately 133.5 nm. (F) Representative chronic infected wound healing images on days 0, 3, 6, 9, 12, and 15 in control (G1), hydrogel (G2), mixtures of CIR and RIF (defined as FD) (curcumin, 2 mg per kg mice body weight; rifampicin, 1 mg per kg mice body weight) (G3), FD-hydrogel (G4), and CRMs-hydrogel (G5). (G) Time-wound closure rate in each group. Panels reproduced with permission from: A and B, ref. 61, Elsevier, 2018; C−E, ref. 62, MDPI, 2022; F and G, ref. 64, ACS, 2022.

cularization and re-epithelialization process of chronic wounds in almost half the time it takes for the skin barrier to regenerate compared to the control.

In addition to facilitating drug release, temperature-responsive hydrogels can be designed to mechanically contract in response to body heat, thereby promoting physical wound closure.[66] This is particularly advantageous in chronic wounds where wound edge retraction and impaired contraction delay healing. Certain thermosensitive hydrogels exhibit volumetric shrinkage above their LCST, generating mechanical tension that mimics myofibroblast-mediated contraction. For instance, a study by Chen *et al.* demonstrated that a core-ring PNIPAM-based shrinking hydrogel, when applied to chronic wound beds, produced directional traction forces that not only promoted tissue approximation but also accelerated re-epithelialization.[66] Liu *et al.* also designed a wet-adhesive temperature-responsive hydrogel tape with a capacity for fast wound contraction under physiological temperature conditions.[67] By aligning mechanical contraction with biological healing processes, these hydrogels offer a dual-function strategy—serving as both smart drug carriers and active mechanical agents that restore tissue integrity more efficiently.

## 4.2 pH-sensitive hydrogels

Normal, healthy skin typically maintains a slightly acidic pH range of 4 to 6.[68] Chronic wounds, however, tend to have a higher pH, ranging from 7 to 9, due to the presence of blood, interstitial fluid, ammonia, and other factors.[69] Additionally, if a wound becomes infected, its pH may decrease as bacteria produce acidic byproducts like lactic acid and carbonic acid.[70] Thus, pH serves as a dependable indicator of wound status. The unique biochemical and mechanical characteristics of pH-responsive hydrogels, along with their ability to modify their morphology, volume, and medication release behavior, make them a valuable asset in wound care.[71] These materials can effectively monitor wound status based on pH levels, facilitate controlled wound healing, mitigate infection risks, and expedite the healing process.[72]

Hydrogels exhibit different LCST ranges depending on the environmental pH values. Below their LCST, they exhibit small and broad pH sensitivities normally observed in most hydrophilic polyelectrolyte gels, but above their LCST, they exhibit sharp pH-dependent phase transition behaviors. The pH-dependent transition is strongly affected by temperature, while the temperature-dependent transition is, in turn, largely influenced by the pH.[73] pH-Sensitive swelling occurs in ionic hydrogels due to the presence of charge-carrying pendant groups and is influenced by many factors, including ionic charge, $pK_a$ or $pK_b$ values of ionizable groups, degree of ionization, hydrophilicity, polymer concentration, and pH of the swelling medium. Among these factors, pH and the nature of pendant groups are the key factors for controlling the properties of pH-sensitive hydrogels. Cationic hydrogels swell at low pH due to protonation of amino/imine groups. These types of hydrogels can be used for antibiotic delivery to the stomach in cases of ulcerative conditions or as carriers for an injectable drug delivery system. Anionic hydrogels swell at higher pH due to ionization of the acidic groups. This property of hydrogels can be exploited for drug delivery at pH 7.4 in the intestine.[74]
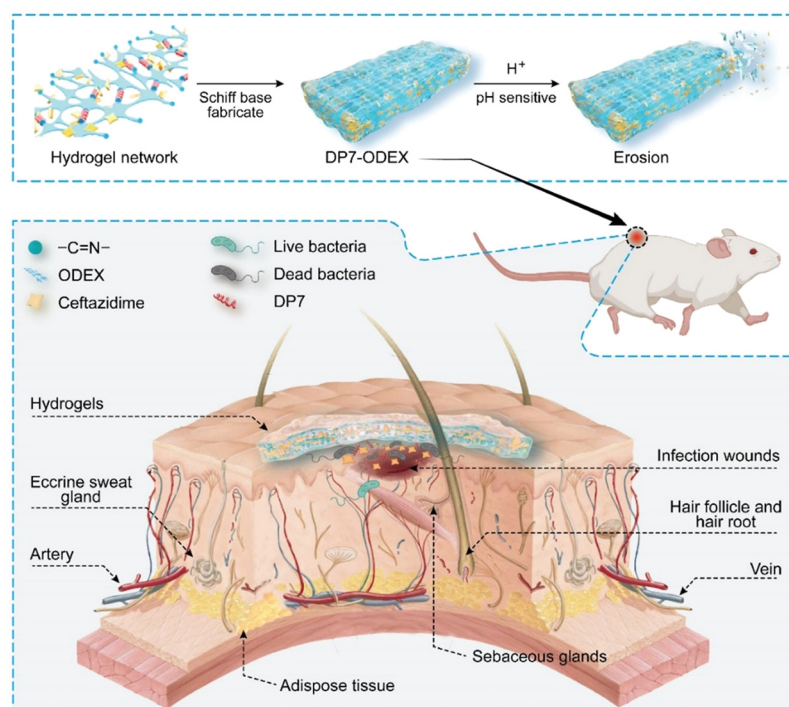
Polysaccharide-composite hydrogels responsive to pH have been studied for their crucial role in wound healing. The most commonly used pH-sensitive hydrogels include chitosan, alginate, hyaluronic acid, guar-gum, and dextran-based gels.[75] Infected areas in a wound often exhibit acidic pH levels, and polysaccharide dressings designed to respond to these conditions—either by releasing medication upon stimulation or by partially degrading the hydrogel to deliver the drug, as shown in Fig. 5—can enhance bactericidal activity, modulate inflammation, and promote better wound healing outcomes.[76] The advantage of pH-responsive hydrogels over conventional hydrogels is the ability to release bioactive molecules—such as hemostatic agents (*e.g.*, thromboxane, gelatin, and chitosan), antimicrobial substances (*e.g.*, gentamicin, penicillin, and penciclovir), anti-inflammatory drugs (*e.g.*, vitamin E succinate, moxifloxacin, and curcumin), and epidermal growth factors (EGFs)—spatially and controllably at the wound locations, thereby accelerating the healing process.[77]

Polymers that show pH-responsive activity are a class of polyelectrolytes with ionic functional groups that are either weak basic or weak acidic groups.[78] The vital element that leads to pH sensitivity in polymers is the presence of ionizable pendant groups that attach to the hydrophobic backbone of the polymer chain.[79] The most commonly studied ionic polymers, their response range, and their benefits are listed in Table 2.

## 4.3 Glucose-sensitive hydrogels

Glucose not only serves as a primary energy source for cells but also plays a crucial role in cell signaling pathways and immune response. Although if left unregulated, elevated glucose levels, otherwise known as hyperglycemia, can greatly hinder the healing process of wounds, impairing inflammation, proliferation, and remodeling during wound healing.[36] Notably, elevated glucose levels cause constriction of the blood vessels and cell membrane rigidification, which limits oxygen and nutrient delivery to a wounded area.[88] This reduced blood supply further slows the wound healing and can lead to tissue necrosis. Moreover, the elevated glucose levels disrupt the normal function of immune cells, hindering processes such as leukocytes' abilities to swallow and kill harmful bacteria, which are essential for clearing wound infection and initiating tissue proliferation or repair. Along with the fact that high glucose levels can augment bacterial growth, this results in a prolonged healing process and higher infection rates of diabetic chronic wounds.[89] Glucose-sensitive hydrogels can be designed as controlled-release drug delivery systems that respond to local glucose concentrations, either by leveraging the hydrogel's inherent properties or by incorporating functional groups that enhance glucose binding.[90] These hydrogel membranes can be loaded with various medications, such as insulin, metformin, and L-arginine, to regulate glucose

© 2026 The Author(s). Published by the Royal Society of Chemistry

*RSC Appl. Polym.*, 2026, **4**, 53–82 | **61**

**Fig. 5** Structure of pH sensitive CAZ-DP7-ODEX hydrogel network and the mechanism for enhanced MDR bacteria infected wound healing process. This demonstrates how a pH-sensitive dextran-based hydrogel erodes and releases the drug in response to the acidic environment of an infected wound. Reprinted with permission from ref. 56, Elsevier, 2015.

**Table 2** Commonly studied pH-responsive polymers, their most effective pH response ranges, and benefits

| pH-Responsive polymers | Most effective pH response range | Benefits |
|---|---|---|
| Poly(acrylic acid) (PAA)[80] | pH 6.0–7.7 | Enables drug delivery to the specific cell domains of tissues with less acidic microenvironment. Can encourage the growth of granulation tissue, which aids in healing wounds and lays the groundwork for developing new skin. |
| Poly(acrylamide) (PAAm)[81,82] | pH 8.0–11.0 | Has low toxicity and is economical. Has a large degree of swelling that enables the polymer to provide a moist environment in the wound area. |
| Poly(methacrylic acid) (PMAA)[83,84] | pH 5.8–6.1 | Improve wound closure and vascularity *in vivo* by increasing the number of blood vessels of a wound in diabetic wounds. |
| Poly(diethylaminoethyl methacrylate) (PDEAEMA)[85] | pH 5.0–7.0 | These polymers show low critical micelle concentration values which could markedly improve micelle stability and extend the range of applications in controlled drug delivery. |
| Poly(dimethylaminoethyl methacrylate) (PDMAEMA)[86,87] | pH > 7.4 | Has excellent biocompatibility and can be quaternized for antibacterial activity, giving any hydrogels using this polymer a natural antibiotic, avoiding the use of drugs or potentially toxic metal nanoparticles. |

levels while also providing antibacterial protection.[91,92] Common hydrogel polymers that are used with glucose-sensitive drug release systems include $N$-(3-D-glucose)acrylamide (GAA), polyacrylamide (PAM) based, polyvinyl alcohol (PVA), and chitosan-based hydrogels.[93]

Glucose oxidase catalyzes the oxidation of glucose to gluconic acid using molecular oxygen ($O_2$) as an electron acceptor, releasing hydrogen peroxide as a byproduct.[94] Glucose-sensitive hydrogels based on a glucose oxidase ($GO_x$) system typically use a pH-responsive hydrogel as the backbone, with $GO_x$ immobilized into the matrix to impart glucose sensitivity. One common mechanism of a glucose-responsive hydrogel utilizes the pH fluctuation associated with $GO_x$ catalysis of the conversion of glucose into gluconic acid and hydrogen peroxide ($H_2O_2$).[95] Decreases in pH due to glucuronic acid and hydrogen peroxide production catalyzed by $GO_x$ result in the pH-responsive hydrogel swelling and pore size increase, which in return triggers the release of loaded drugs.[96] Gu *et al.* created injectable glucose-responsive microgels consisting of a physically cross-linked pH-responsive polymeric matrix, $GO_x$- and catalase (CAT)-containing enzyme nanocapsules, and human recombinant insulin. CAT is used to regenerate oxygen, assisting in $GO_x$'s glucose catalysis, and scavenge excess hydrogen peroxide produced in glucose oxidation.[97] When glucose levels

were elevated within the region, the $GO_x$ and CAT reactions resulted in production of gluconic acid and hydrogen peroxide, which lead to a decrease in pH as previously described. The protonation of amino groups of the chitosan shell eventually triggered the swelling and dissociation of the hydrogel and resulted in the release of insulin.[97] Fig. 6 depicts a schematic of the hydrogel system and protonation of the amino groups that trigger insulin release, as well as of the enzymatic reactions that result in pH change.

Particularly, chitosan-based hydrogels with metformin have proven effective against diabetic foot wounds, which can pose an especially high risk of damage to other organs in patients as foot wounds especially receive constant trauma from repeated use.[43] A study by Liang *et al.* using pH/glucose-responsive metformin-released hydrogels has proven quite effective in combating inhibited healing factors and symptoms associated with elevated glucose levels.[43] By combining the hydrogel system with dihydrocaffeic acid (DA) and L-arginine, this resulted in improved tissue attachment, promoted healing, and increased vascularization. DA was added to improve antioxidant activity and decrease chronic inflammation, while L-arginine cografted with chitosan had a cationic effect that killed bacteria and an improved tissue adhesion between the wound and hydrogel dressing. This provides the hydrogel with effective antibacterial properties, helping the body overcome the compromised immune activity within the region as it was able to thoroughly inhibit *E. coli* and MRSA bacteria.[43] As this system is responsive to both pH and glucose, the dressing exhibited increased metformin release under acidic/lower pH conditions and elevated glucose levels independently. The 1,2 diol structure in glucose can compete with the complex of catechol and phenyl boronic acid that encapsulates the metformin within the hydrogel, allowing the hydrogel network to dissociate and release metformin.[43] Thus, increasing/higher glucose level is associated with increased metformin delivery.[43] From a different perspective, Zhou *et al.* designed a glucose and matrix metalloproteinase-9 (MMP-9)

responsive temperature-sensitive shape self-adaptive hydrogel (CBP/GMs@Cel&INS) using polyvinyl alcohol (PVA) and chitosan grafted with phenylboronic acid (CS-BA).[98] These gels contained an anti-inflammatory drug, celecoxib, encapsulated in insulin and gelatin microspheres (GMs@Cel) that were released on demand under wound environments consisting of high concentrations of glucose and MMP-9, mimicking chronic diabetic wounds. This dressing had good adhesive and mechanical properties, which improved the drug release efficiency of insulin and celecoxib microspheres and reduced risk of infections, promoting excellent biocompatibility, cell proliferation, and migration. Ultimately, this resulted in the fastest rate of wound healing while promoting cell proliferation, migration, and glucose consumption. There was also found to be down-regulation of the expression of downstream MMP9, which has significant positive effects on chronic diabetic wounds,[90] shown in Fig. 7D along with the mechanism, injection process, and wound healing results of this study (Fig. 7A–C).[98]
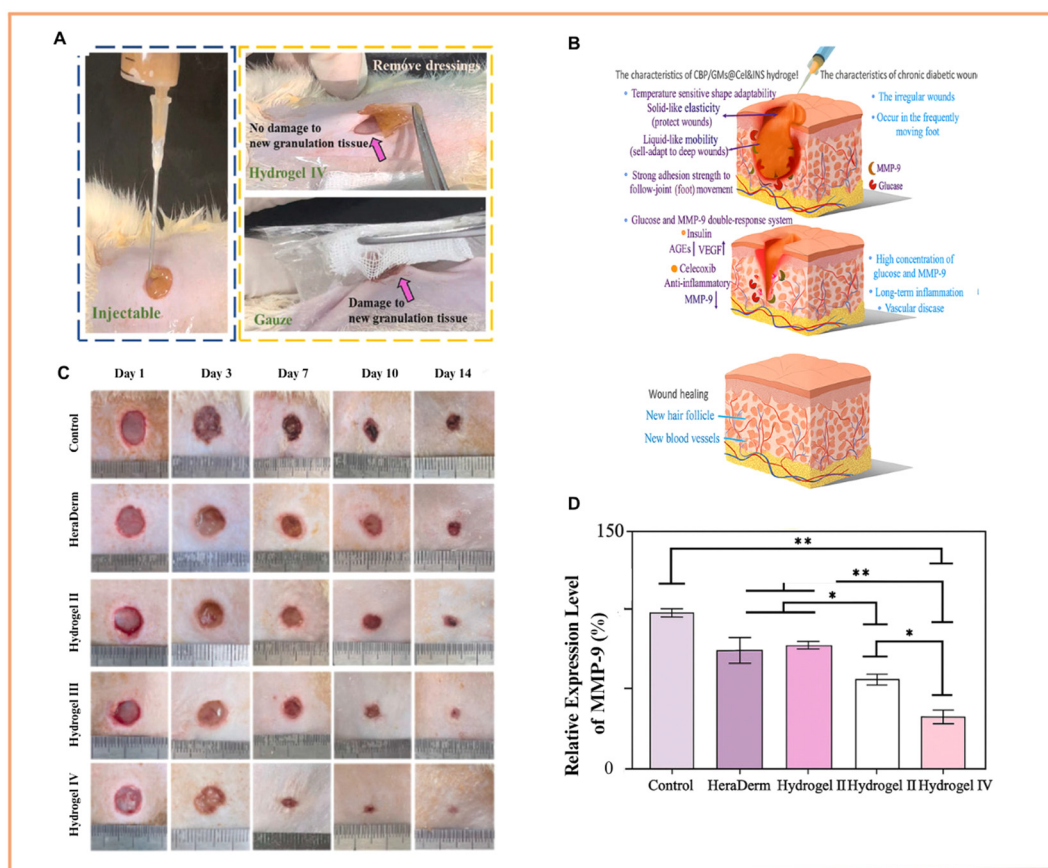
Glucose-sensitive hydrogels can also use phenylboronic groups (*e.g.* poly3(acrylamido)phenyl boronic acid) and polyol polymer (*e.g.* PVA) to form a gel substance with complex formation between the phenyl borate and hydroxyl groups.[99] When these complexes are introduced to glucose, the pendant hydroxyl groups of glucose compete with the pendant phenyl borate and hydroxyl complexes of the original hydrogel, causing breakages in the crosslinked hydrogel. As the crosslinking density within the gel decreases in response to increasing glucose concentration, the gel swells and releases drugs. Elsherif *et al.* found that phenylboronic acid (PBA) is favored in the development of glucose-sensitive sensors because of its strong affinity for glucose under physiological conditions, simultaneous insulin release during glucose detection, non-toxicity, responsiveness to pH and glucose level changes, its ability to modify its chemical properties with different substituents, and high stability.[100] Using light transmission, researchers tested the hydrogel's permeability when intro-
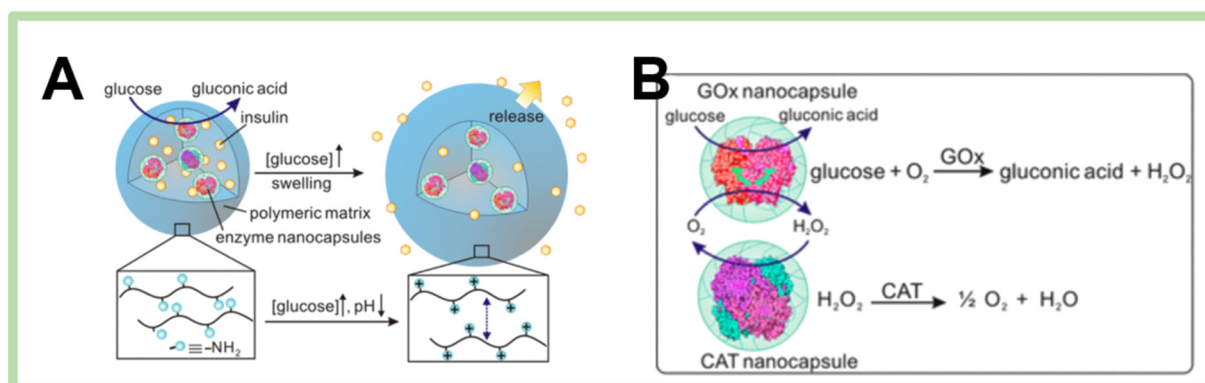


**Fig. 6** (A) Schematic of microgels encapsulating insulin and enzyme nanocapsules. The encapsulated glucose-specific enzyme catalyzes glucose into gluconic acid. The subsequent protonation of polymer chains with rich amine groups increases the charge in the gel matrix, leading to swelling of the microgels and release of insulin. (B) Enzymatic reactions involving glucose oxidase ($GO_x$) and catalase (CAT) nanocapsules. Reprinted and modified with permission from ref. 97, ACS, 2013.

© 2026 The Author(s). Published by the Royal Society of Chemistry

*RSC Appl. Polym.*, 2026, **4**, 53–82 | **63**

**Fig. 7** (A) Photographs of injection and stripping of hydrogels, and the adhesion of gauze to wounds during stripping. (B) Mechanism of wound healing induced by CBP/GMs@Cel&INS hydrogel. (C) Photos of the wounds at days 0, 3, 7, 10, and 14 hydrogel. (D) Immunofluorescence staining of MMP expression on wounds of different groups taken on day 7. Note: hydrogel II: the CBP/GMs hydrogel; hydrogel III: the CBP/GMs@INS hydrogel; hydrogel IV: the CBP/GMs@Cel&INS hydrogel. Reprinted and modified with permission from ref. 98, Elsevier, 2022.

duced to glucose. Consistent with expectations, increased glucose exposure resulted in increased maximum transmitted light power. Furthermore, they found that increased pH was correlated with increased glucose sensitivity, with the highest sensitivity at a pH of 8. Both the ionic strength/pH and the glucose concentration of the solution greatly affect this phenylboronic acid hydrogel's ability to work effectively.[100]

Similar to phenylboronic acid-based hydrogels, free glucose can competitively bind to lectin in hydrogel networks and reduce crosslinking, affecting membrane swelling and molecular release. This property has been widely explored for insulin use, as well as glucose-sensitive biosensors and wound healing applications. Notably, concanavalin A (Con A), a plant lectin purified from jack beans, has been widely used to modulate drug delivery, as it binds with a high affinity to glucose.[99] A study by Hu *et al.* developed a Con A-based hydrogel fixed with green-synthetic silver particles on laser direct-writing graphene electrodes as a flexible continuous glucose monitoring (CGM) system.[101] These technologies are attractive as they monitor glucose levels at a low cost with good stability and high sensitivity. In this case, green-synthesized silver particles are a flexible enzyme-free glucose sensor prepared on laser-

written graphene. Compared to Go$_x$, this non-enzymatic system may have the ability to detect a larger range of glucose levels as opposed to enzymatic biosensor systems. Con A compaction was noted to increase crosslinking, reduce water absorption, minimize swelling, and slow drug release in aqueous environments, showing promising usage with non-enzymatic sensors. Additionally, the Con. A-based hydrogel sensors were found to have improved biocompatibility and stronger specificity to glucose compared to phenylboronic acid-based gels, suggesting potential for broader applications in glucose-responsive drug delivery, biosensing, and wound healing beyond insulin modulation. The competitive binding of DexG-Con A and glucose (Glu)-Con A influences the structure of the DexG-Con A network, leading to alterations in the hydrogel's volume and permittivity, resulting in the release of insulin.[101] Con A molecule preferentially binds with glucose rather than DexG, thus the presence of glucose in the DexG-Con A system affects the permeability of the membrane due to disruption in crosslinking of DexG-Con A. These hydrogels reflect another promising method of glucose regulation, wound healing, biosensing, and drug delivery due to their strong specificity to glucose in the bloodstream.

Furthermore, glucose-sensitive hydrogels have also been explored for controlled release of antimicrobial agents in wound healing applications, where elevated glucose levels in diabetic wounds can trigger the localized release of antimicrobial components.[102] These hydrogels, in response to hyperglycemia, can not only release agents from the hydrogel that consume glucose in the bloodstream, stabilizing the environment, but can also simultaneously deliver antimicrobial agents to handle any hazardous microbes that could have formed and thrived in the hyperglycemic environment.

### 4.4 ROS-sensitive hydrogels

ROS play a dual role in wound healing, being essential for defense against pathogens but harmful when present in excess. ROS are byproducts of cellular metabolism that consist of partially reduced metabolites of $O_2$, which are a necessary factor in yielding mitochondria-driven ATP. Without these cellular processes, wounds would not have the necessary energy to heal. They serve as important secondary messengers regulating physiological functions of macrophages, and are also known to mediate angiogenesis and vasoconstriction/vasodilation at wound sites. On the other hand, excessive ROS production levels can cause oxidative stress on tissues and cellular damage, slowing the process of wound repair. Chronic wounds have historically been characterized by prolonged inflammation and elevated ROS levels, which are known to cause damage to tissues and other important healing factors.[103] This factor makes ROS a suitable trigger stimulus for hydrogel designed to improve healing and inflammation in chronic wounds.

Hydrogels can be engineered with ROS-sensitive linkers or components that degrade or undergo structural changes when exposed to high concentrations of ROS, consequently triggering the release of therapeutic agents. These reactions occur when ROS, such as hydrogen peroxide ($H_2O_2$), superoxide ($O_2^-$), or hydroxyl radicals ($^\cdot OH$), oxidize or break down certain functional groups or bonds in the hydrogel. For instance, in the presence of a solution of 1 mM $H_2O_2$, a phenylboronic acid–diol ester bond was shown to dissolve a phenylboronic acid modified hydrogel, giving it the capability to release antibacterial carriers and drugs on demand, as shown in Fig. 8A–C.[104] Another example includes an injectable loaded hydrogel with tannic acid loaded silver nanoparticles, placed in an environment mimicking chronic wound conditions.[105] In the presence of ROS, the rate of the drug release and hydrogel degradation both increased compared to an environment without ROS present. This increased rate was determined to be caused from the degradation of a boronic ester together with the oxidation of TA into quinone, leading to the entirety of the drug being released within 20 hours, as shown in Fig. 8D and E.[105] Moreover, Zhao et al. used a ROS-responsive linker in a PVA based hydrogel to release an antibiotic (mupirocin) and growth factor (GM-CSF) upon contact with ROS in both healthy and diabetic mice, with a schematic displayed in Fig. 8F.[106] As the ROS-linker (N1-(4-boronobenzyl)-N3-(4-boronophenyl)-N1, N1,N3,N3-tetramethylpropane-1,3-diaminium (TPA)) scavenged

the oxidative environment, pro-inflammatory cytokines were simultaneously downregulated and M2 phenotype macrophages were up-regulated, resulting in increased angiogenesis, revascularization, and production of collagen. At the same time, the hydrogel gradually degraded as a result of the cleavage of the linkers, and released the encapsulated antibiotics and growth factors, eliminating *Staphylococcus aureus* (S.A.U.) infection and accelerating wound repair.[106]

### 4.5 Matrix-metalloproteinase-sensitive hydrogels

The matrix-metalloproteinase (MMP) family is a group of calcium-dependent zinc-containing enzymes that are involved in the degradation of various ECM components. MMPs are present in both acute and chronic wounds, regulating ECM degradation and deposition, which is essential for wound reepithelialization. The excess protease activity can prevent wound closure and increase the risk of bacterial infection, leading to a chronic nonhealing wound.[107]
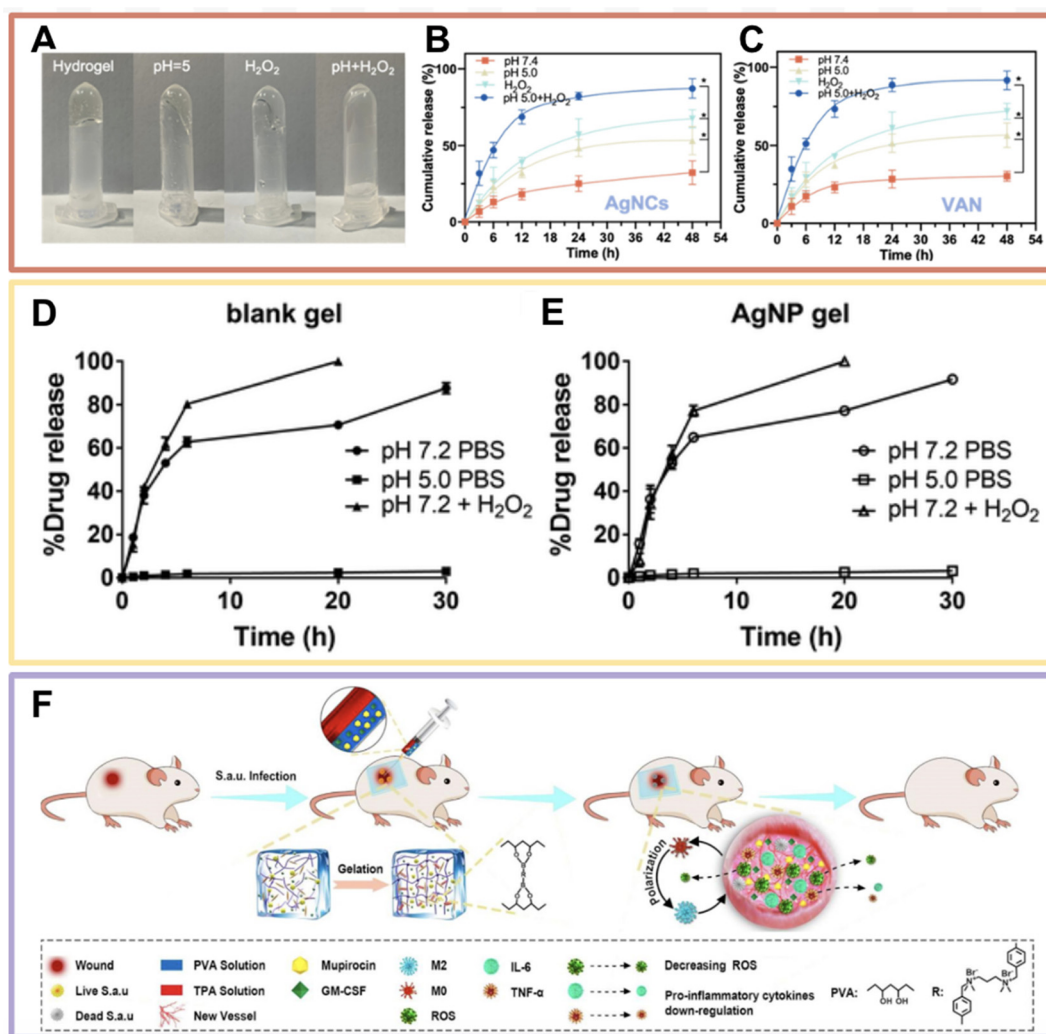
MMP-responsive hydrogels are particularly suited for chronic diabetic wounds because these wounds consistently exhibit elevated levels of MMPs, especially MMP-9 and MMP-2. The overexpression of MMP-9 in wounds is a significant contributing factor to excessive ECM degradation, which hinders the process of wound healing.[108] In 2025, Lin et al. designed an MMP-9 responsive injectable duplex hybrid hydrogel with oxidized hyaluronic acid and hydrazide-grafted gelatin, which are known to degrade in the presence of MMP-9.[109] The hydrogel was mixed with the drug cinnamaldehyde (CA) and crosslinked into a gel after local in situ injection into the wound site. Then, under the action of MMP-9, the gelatin degraded and continuously released CA, inhibiting cell death of traumatic endothelial cells and accelerating healing of diabetic wounds.[109]

In summary, MMP-responsive hydrogels offer a targeted strategy for chronic wound management by leveraging elevated protease activity to enable controlled degradation and localized therapeutic release. This responsive behavior helps restore ECM balance, reduce inflammation, and accelerate tissue regeneration, making them especially promising for treating chronic diabetic wounds.

### 4.6 Mechanoresponsive hydrogels

Hydrogels, as a result of their flexible and adhesive characteristics, have recently been investigated as a potential therapeutic option for wound sites subject to high mechanical forces. Examples of these sites include the elbows, wrists, ankles, and knees, where typical wound dressings may struggle to stay in place and maintain an ideal wound environment when subject to mechanical loads.[110] Yu et al. compiled the mechanical properties of several hydrogel compositions with a combination of both physical and chemical cross-linking elements.[110] They were able to find hydrogel designs optimal for high mechanical loads at these movable sites, such as the GT/EDC–NHS–DA nanofibrous hydrogel designed by Zheng et al. which boosted tensile strength by over 200% compared to a non-dopamine-grafted GT gel, and the QCS/PF hydrogel

© 2026 The Author(s). Published by the Royal Society of Chemistry

*RSC Appl. Polym.*, 2026, **4**, 53–82 | **65**

**Fig. 8** (A) Images of the hydrogel after being incubated with PBS (pH = 5) and/or $H_2O_2$. Incubation in the $H_2O_2$ solution induced hydrogel collapse and led to a liquid resembling state of the gel, as well as in the acidic PBS solution. The combination of both factors dissolved the hydrogel more comprehensively. (B) Release curve and characteristics of blank conjugated silver nanoclusters (AgNC) in 48 hours, which serve as encapsulated carriers for the antibacterial drug (mean $\pm$ SD, $n$ = 3), *$P$ < 0.01. (C) Release curve and characteristics of antibacterial agent vancomycin (VAN) in 48 h (mean $\pm$ SD, $n$ = 3), *$P$ < 0.01. (D and E) Graph demonstrating pH and ROS responsive drug release properties in a (D) blank and (E) AgNP hyaluronic acid–phenylboronic acid–tannic acid hydrogel. Buffer pH 7.2 with 1 mM $H_2O_2$ conditions were used to mimic chronic wound conditions while pH 5.0 PBS represented healthy skin pH. Fluorescein isothiocyanate (FITC) labeled bovine serum albumin (BSA) was used as a model drug. FITC-BSA showed the fastest release in PBS at pH 7.2 with 1 mM $H_2O_2$, a moderate release in PBS at pH 7.2, and a very slow release in PBS at pH 5.0 for both gels. (F) Schematic illustration of using the ROS-responsive hydrogel loaded with therapeutics for treatment of wounds with bacterial infection. Panels reproduced with permission from: A–C, ref. 104, ACS, 2021; D and E, ref. 105, RCS, 2021; F, ref. 106, Elsevier, 2020.

synthesized by Qu *et al.* which exhibited highly reversible elongation and joint flexural properties similar to that of natural skin.[111,112] However, while these hydrogels boast impressive mechanical properties and offer a solution for complicated wound sites in high-load regions of the body, the high degree of chemical cross-linking often comes at the compromise of other bioactive capabilities such as antibacterial activity.[110]

While mechanical forces have always been a consideration in designing and testing hydrogel wound dressings to closely match the properties of the skin or tissue where they might be used, they also play a role as a potential stimulus to encourage

a change in the physical and chemical properties of a mechanoresponsive hydrogel.[113] For example, hydrogels designed to simulate soft tissues can exhibit strain-stiffening when subjected to an applied stress, a property exhibited naturally by these tissues. Song *et al.* outlined the strain-stiffening mechanism through the addition of polymers such as actin-binding proteins (ABPs) and demonstrated that, while not a perfect match, this behavior closely mimics the natural mechanics of soft tissue in the body.[114] Fang *et al.* demonstrated the potential therapeutic power of strain-stiffening by developing a mechanoresponsive poly(sulfobetaine methacrylate) hydrogel, which delivered a loaded antibacterial drug into the wound

66 | *RSC Appl. Polym.*, 2026, **4**, 53–82

© 2026 The Author(s). Published by the Royal Society of Chemistry

site following application of mechanical force.[115] This hydrogel maintains the flexibility and biocompatibility of typical cross-linked hydrogels with the added bonus of a controlled drug-release system based on the application of stress through stretching or compression of the wound dressing. Mehnath *et al.* prepared a similar mechanoresponsive hydrogel specifically aimed at diabetic foot ulcers and other chronic wounds, and were able to show that application of a mechanical force was able to produce greater drug delivery to the wound site.[116] The role of mechanical force as both a metric of hydrogel stability on difficult wound sites and as a stimulus to trigger drug release will likely continue to be investigated, given the success of existing efforts, and should be closely observed as a method to improve outcomes for individuals with chronic wounds.

### 4.7 Magnetic-responsive hydrogels

Magnetic nanoparticles (MNPs), which typically range from 1 to 100 nanometers in size, are characterized by the small particle size, larger surface properties, magnetic response, and superparamagnetism. Notably, they have been recognized as a promising component in enhancing the wound healing capabilities of the standard hydrogel. Iron oxides, $Fe_3O_4$ and $Fe_2O_4$, are commonly modified into nanocomposites for usage in hydrogels because of their good chemical stability, high magnetization, and biocompatibility.[117] By incorporating MNPs into hydrogel matrices, researchers have developed smart biomaterials that can be externally controlled and tailored to support the wound healing process.

In the context of chronic wound healing, magnetic-responsive hydrogels offer significant advantages. Chronic wounds often stall in the inflammatory phase and suffer from poor vascularization, persistent infection, and impaired tissue regeneration. Hydrogels with MNPs can combat these complications due to their unique capabilities. When an external magnetic field is applied, the embedded MNPs create micro-level mechanical forces within the hydrogel matrix; these forces can be sensed by surrounding cells that promote cell adhesion, spreading, and division.[118] Furthermore, when an alternating magnetic field is applied, MNPs within the hydrogel absorb electromagnetic energy and convert it into heat. This localized heat can be sufficient in killing the bacteria without damaging the surrounding healthy tissue.[119] This heating can also enhance the effectiveness of drugs delivered at the site. The grafting method in MNP synthesis requires that the magnetic particles and the hydrogel monomers are covalently bound together with the assistance of micro or nano crosslinkers grafted to the magnetic particles. This method results in the most stable hydrogel networks, as there are no bonding interactions between MNPs and the hydrogel networks of hydrogel products of the *in situ* and blending methods.[120]

Many recent studies have explored application of magnetic-responsive hydrogels to accelerate wound healing. In one study, Ye *et al.* developed chitosan polyvinyl alcohol hydrogel beads (MCPHBs). By incorporating iron II and III into hydrogels and forming MNPs through *in situ* using ammonium hydroxide, researchers created a product capable of responding to magnetic fields.[121] These hydrogels demonstrated a great drug loading capactiy, making them suitable for long-term wound applications. In another study, He *et al.* engineered a multifunctional hydrogel dressing coated with protein fibers and embedded with antibacterial magnetic nanoactuators.[122] Under external magnetic stimulation, these nanoactuators generated localized mechanical cues/signaling that activated skin cells, enhanced fibroblast migration, and promoted a more balanced healing response. Furthermore, with increased near-infrared irradiation stimulation, the hydrogel possessed better antimicrobial effect against *E. coli* and *S. aureus*. This dressing was able to regulate both pro-inflammatory and pro-regenerative signals, contributing to improved tissue regeneration without the complications of excessive scarring or fibrosis. These studies highlight how the abilities (capabilities, properties) of modified NMPs hydrogels can be harnessed for more precise control over the wound healing process.

### 4.8 Ultrasound-responsive hydrogels

Ultrasound-responsive hydrogels represent an emerging class of smart wound dressings that utilize non-invasive acoustic stimuli to modulate drug release, enhance tissue regeneration, and facilitate real-time treatment adaptation. Chronic wounds, particularly those associated with diabetes or infection, often require prolonged and precisely timed delivery of therapeutics to overcome barriers such as biofilm formation, inflammation, and impaired vascularization. Ultrasound, often referred to as sonophoresis, is seen as an attractive external stimulus as it can be controlled remotely, spatially, and temporally.[123] Also, its ability to penetrate deep tissue and act on cells either thermally or mechanically gives it clinically relevant benefits.[124] Using heat, cavitation, and acoustic flow, ultrasound-responsive hydrogels typically contain nanospheres that have components that respond to ultrasound to release therapeutic agents on demand.[123]

Ultrasound is commonly combined with a hydrogel drug delivery system as the soft, hydrated nature of hydrogels transmits ultrasound energy efficiently, enabling responsive elements within the matrix to react in a controlled manner. In addition, hydrogels have the capacity to localize therapeutic agents at the wound site, protect sensitive biomolecules from degradation, and maintain a moist, biocompatible environment that supports healing. Recent advances have demonstrated how ultrasound can be used not only to control drug release but also to facilitate biofilm disruption and improve therapeutic penetration in chronic wounds. For example, Zong *et al.* developed an ultrasound-responsive hydrogel embedded with self-assembled heparin-binding domain (HBD) peptide nanoparticles, designed specifically for diabetic wound healing complicated by biofilm infection.[125] Biofilms are communities of bacteria encased in a protective extracellular matrix that commonly form on chronic wound beds, and they impede healing by promoting persistent inflammation, evading immune responses, and significantly reducing the

efficacy of antibiotics. Upon ultrasound stimulation, the hydrogel underwent structural collapse, enabling controlled release of the embedded peptides and mechanical disruption of the biofilm matrix. This dual-action system enhanced tissue penetration while displaying significant antibacterial and antibiofilm activity, as shown below in Fig. 9.

Additionally, Huang *et al.* developed an injectable PEG-based hydrogel integrating food-derived anthocyanidin as a visible pH sensor and PLA microcapsules for ultrasound-triggered antibiotic release.[126] The system allows real-time visual monitoring of wound pH, enabling early detection of infection. Upon ultrasound application, the microcapsules release antibiotics on demand, significantly reducing bacterial load in infected and diabetic wound models. This combined sensing-treatment strategy accelerated healing—confirmed by histology and reduced inflammatory cytokines—demonstrating a powerful example of smart, responsive wound dressings.

# 5 Additional functionalities

With the advancement of stimuli-sensitive components in hydrogel dressings, recent developments in stimuli-responsive hydrogels have introduced additional functionalities to further enhance chronic wound healing. ROS scavenging capabilities help mitigate oxidative stress, thereby reducing inflammation and promoting tissue regeneration. Meanwhile, hemostatic properties support rapid blood clotting, minimizing excessive bleeding and creating a stable environment for healing. This section explores how these integrated functionalities work synergistically with novel hydrogel dressings to improve wound recovery, offering a more effective approach to addressing the complex challenges of chronic wounds.

## 5.1 ROS antioxidant scavenging

In addition to ROS-sensitive drug release, ROS-scavenging functionality has been incorporated into hydrogels, which use antioxidants to modulate ROS levels at wound sites, fostering a supportive environment for tissue repair. During the inflammation stage, excess ROS are produced, which may inhibit the continuation of proper wound healing.[127] Antioxidants are proteins that play a crucial role in helping maintain ROS homeostasis in the body by donating electrons and stabilizing excess ROS. This neutralizes their potential to damage critical cellular structures like lipids, proteins, and nucleic acids. Examples of ROS-scavenging hydrogel loading materials may include polyphenols such as curcumin, tannic acid, and dopamine, known for their exemplary biocompatibility and immunomodulatory activities.[42,128] For instance, incorporating polydopamine-modified fullerene nanocomposites (C60@PDA) has demonstrated favorable cytocompatibility, hemocompatibility, and antibacterial properties in a full-thickness wound mouse model.[127] Moreover, it has been shown to enhance re-epithelialization, collagen deposition, and angiogenesis. Fullerene, a potent antioxidant, possesses anti-inflammatory, antiviral, antibacterial, and hair growth-stimulating properties and has been previously utilized in whitening, anti-aging, and sunscreen cosmetic applications. However, due to its insolubility in aqueous solutions, fullerene was coated with polydopamine to
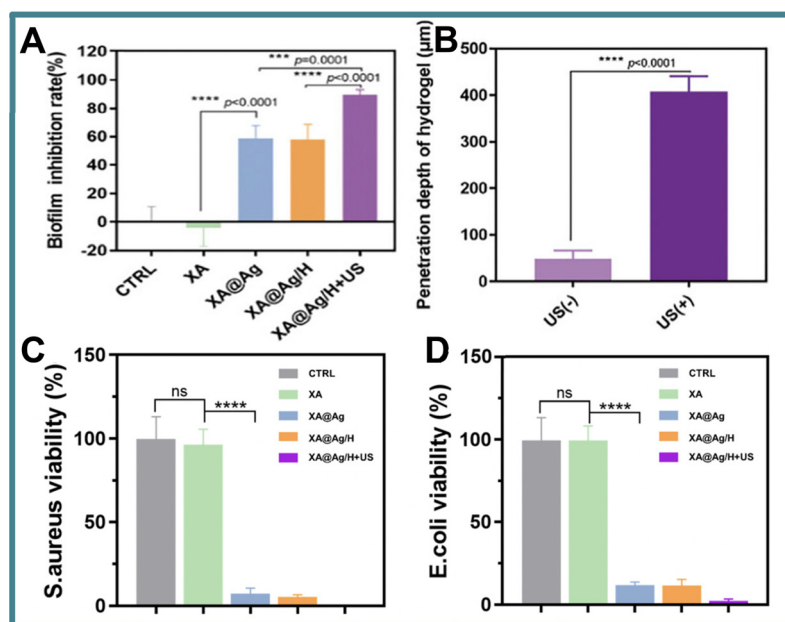


**Fig. 9** (A) Inhibition rate of *S. aureus* biofilm after treatment with different hydrogels, including a control, xanthan gum/sodium alginate composite hydrogel, composite hydrogel with encapsulated silver ions, 3D dual-network skeleton structure hydrogel with cross linking initiated by the addition of Ca$^{2+}$ ions, and a 3D dual-netwok hydrogel with ultrasound. (B) Delivery depth of ultrasonic responsive hydrogel in skin wound, with and without ultrasound activation. (C and D) Relative bacterial viability of *S. aureus* and *E. coli* calculated based on the number of colonies on agar plates. Reprinted with permission from ref. 125, Wiley Advanced, 2024.
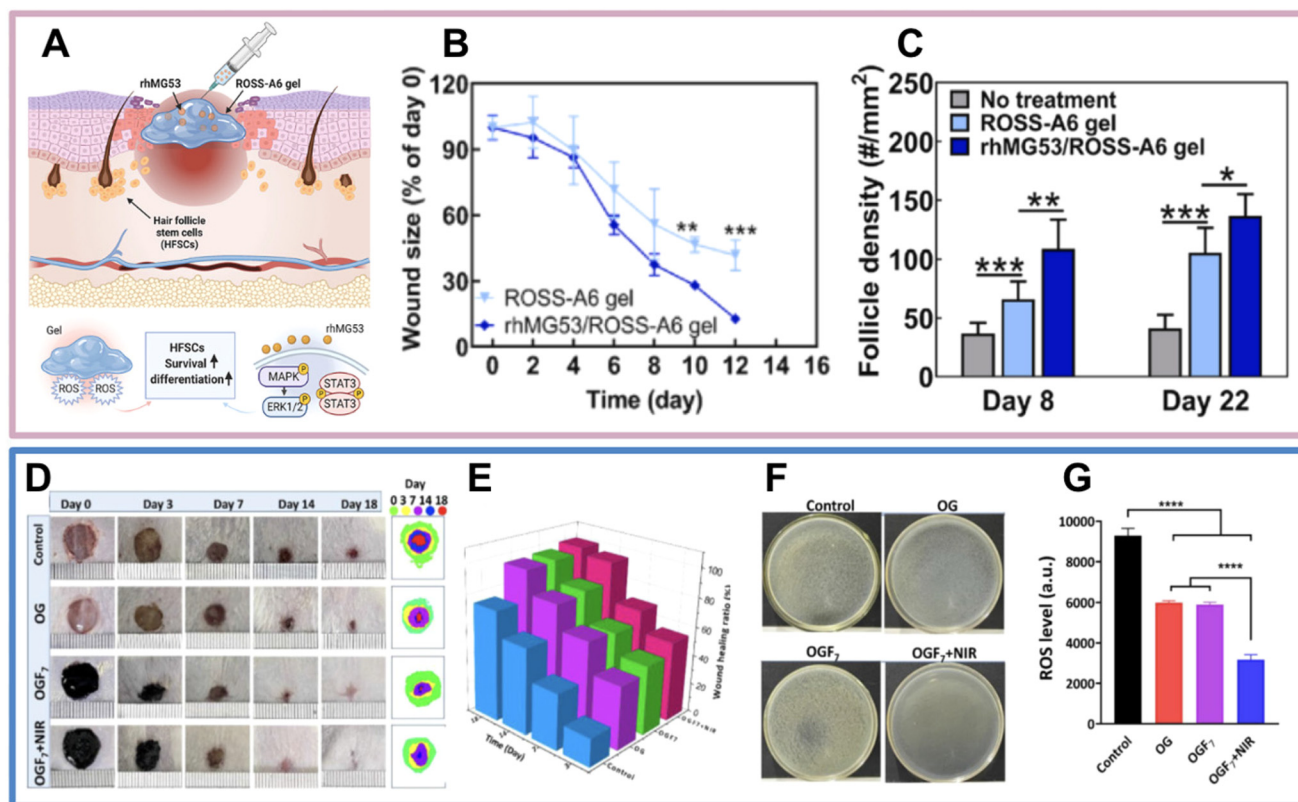
**Fig. 10** (A) Schematic illustration of accelerated wound healing by the delivery system of rhMG53/ROSS-A6 gel. The ROS scavenging hydrogel allowed the released human recombinant MG53 (hrMG53), a tripartite motif family protein, to proliferate longer under oxidative stress, thereby improving HFSC survival and enhancing wound healing. (B) Wound closure for 12 days for each treatment category. Wound size ratios were normalized to day 0. Data were expressed as means ± standard error ($n \geq 6$, $**p < 0.01$, $***p < 0.001$). (C) Quantification of hair follicle density in vivo based on cytokeratin 14 (K14) staining images (10× and 40×) illustrated to significantly promote HFSCs density at both day 8 and day 22 in the gel group compared with no treatment group ($n = 8$, $*p < 0.05$, $**p < 0.01$, $***p < 0.001$). (D) Evaluation of OGF7 hydrogel on healing of S. aureus infected skin wound in STZ-induced diabetic mice. Photographs and wound contraction diagram of healing wounds on day 0, 3, 7, 14 and 18 in each group; (E) wound healing ratio in each group; (F) Staphylococcus aureus detection for analysis of wound infection on day 1; (G) ROS detection for analysis of oxidative stress on day 7. Panels reproduced with permission from: A–C, ref. 129, Elsevier, 2022; D–G, ref. 130, Elsevier, 2023.

enhance its bioavailability, tissue adhesiveness, and antibacterial efficacy.[127]

Additionally, a study by Niu et al. used a ROS-scavenging hydrogel made of NIPAAm, HEMA and acrylated HPPE (AHPPE) (abbreviated as ROSS-A6) to promote hair follicle development and improve diabetic wound closure (Fig. 10A–C).[129] Using AHPPE to scavenge and reduce ROS levels, the hydrogel was able to gradually release recombinant human MG53 (rhMG53), a key protein involved in cell membrane repair, to boost tissue regeneration and promote the survival of hair follicle stem cells (HFSC) under oxidative stress.[129] The rhMG53 was expected to continuously release from the hydrogel after 21 days until all of the protein was released, which is especially useful as it can reduce the need for frequent drug administration, and is thus beneficial for chronic conditions. He et al. had also developed a hydrogel utilizing antioxidants to reduce ROS concentrations in infected diabetic mice wounds using a combination of oxidized dextran, gallic acid-grafted gelatin, and ferric ion (abbreviated as OGF).[130] This hydrogel also incorporated a photothermal antibacterial

aspect, using near infrared light (NIR) to denature bacterial proteins with heat energy. When combined with the successful mitigation of oxidative stress, this resulted in the removal of infection and full re-epithelialization of a Staphylococcus aureus-infected wound in diabetic mice within 18 days (Fig. 10D–G).[130]

## 5.2 Hemostatic effects

In emergency medicine and hospital care, hydrogels paired with hemostatic agents are gaining traction due to their superior ability to control severe external bleeding.[131] Specifically, as a result of the unpredictable and dynamic environment in emergency and prehospital care, hydrogels that can function on humid or dirty skin with proper adhesion to encourage hemostasis are becoming a focus of hydrogel research for wound care. In hopes of enhancing adhesion in these challenging settings, researchers are exploring bioadhesive polymers, surface modifications, and fast-gelling formulations that allow hydrogels to adhere effectively despite the presence of moisture or contaminants. Some hydrogels incor-

© 2026 The Author(s). Published by the Royal Society of Chemistry

RSC Appl. Polym., 2026, **4**, 53–82 | **69**

porate catechol-based chemistry, inspired by mussel adhesion, or utilize stimuli-responsive crosslinking to rapidly bond with tissue, ensuring quicker hemostasis even in high-fluid environments.[132]

During hemostasis, hydrogels can improve the wound healing process by promoting physical adhesion of underlying tissue or by providing the wound site with coagulation cofactors that aid in chemical wound healing processes. Ma *et al.* established a hydrogel cross-linked with a polymer containing chitosan and *o*-nitrobenzyl alcohol (termed the NB-CMC hydrogel) which demonstrated enhanced hemostatic effects and improved wound healing *in vivo*.[133] Song *et al.* also utilized similar building block polymers such as *o*-nitrobenzyl in an injectable hydrogel form with easy application designed for rapid response in emergency room settings.[134] Furthermore, Leonhardt *et al.* incorporated the functionality of hydrogels as

carriers by creating a cyclodextrin polyester hydrogel that can dissolve at the wound site and release chitosan for a hemostatic effect, with demonstrated success and improved functionality *in vivo* compared to pre-existing hemostatic options (Fig. 11).[135] As a result of these findings among others, research with hydrogels incorporating hemostatic agents and strong adhesive properties is gaining traction, especially in emergency medicine and pre-hospital care settings.

The effectiveness of hydrogels as hemostatic agents varies significantly based on the nature and severity of the wound. However, hemostatic hydrogels still show promise over conventional methods for preventing severe blood loss, such as gauze or tourniquets, as they provide a more supportive environment for wound healing and tissue restoration while also preventing blood loss.[131] Thus, hydrogels applied for short periods of time in emergency situations may still play a long-term role in
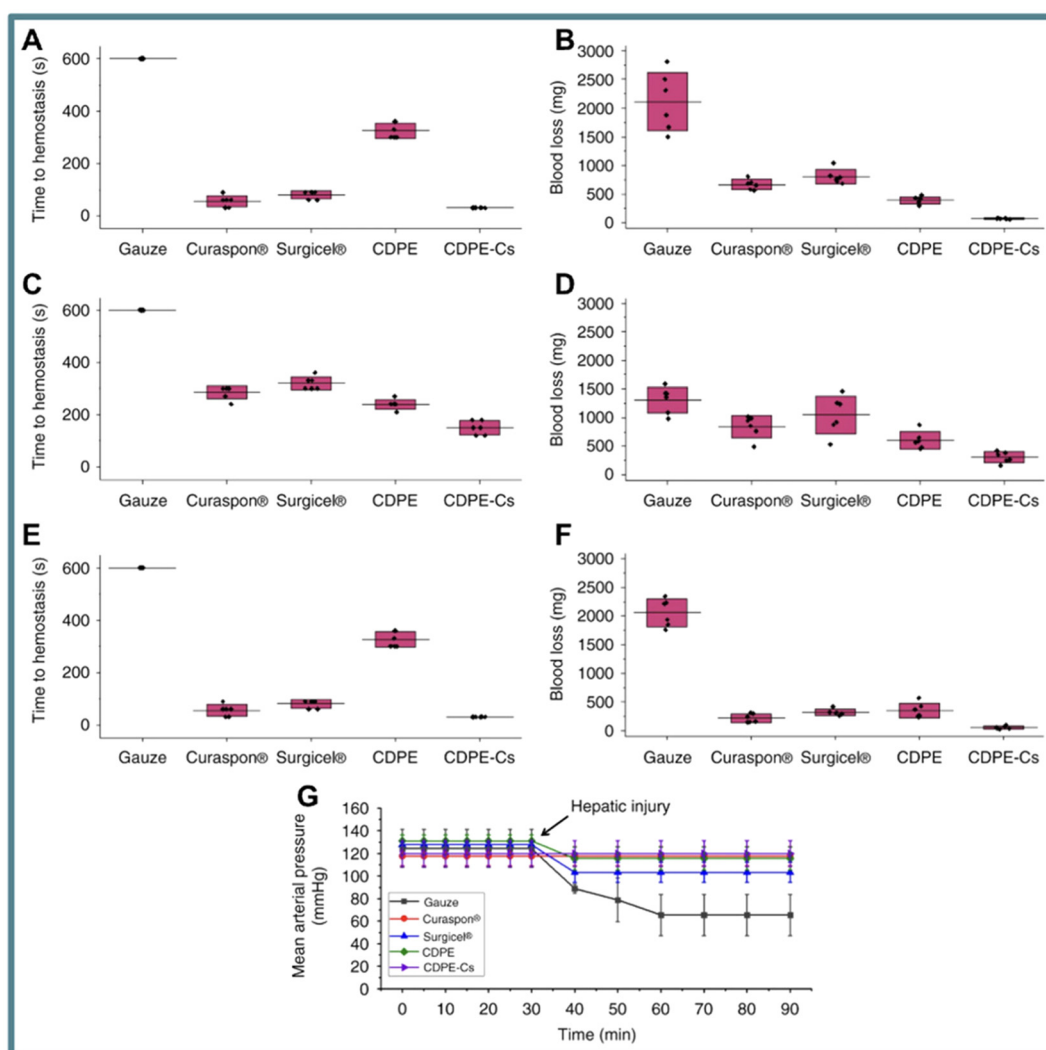


**Fig. 11** (A) Box plot of time to hemostasis in rat subjects following a liver laceration and the application of several commercially available hemostatic options as well as the β-cyclodextrin polyester (CDPE) and chitosan-loaded cyclodextrin (CDPE-Cs) hydrogels. (B) Graph showing blood loss from the wound site for each hemostatic option. (C)/(D) The results of a repeat of the experiment in rabbits, and similarly, (E)/(F) in pigs. (G) Mean arterial pressure *versus* time following the liver laceration in rabbits for several hemostatic options and the CDPE and CDPE–Cs hydrogels. Reprinted with permission from ref. 135, Nature, 2019.

**70** | *RSC Appl. Polym.*, 2026, **4**, 53–82

© 2026 The Author(s). Published by the Royal Society of Chemistry

chronic wound care when combined with other adaptations to create hospitable environments for long-term tissue repair while providing crucial hemostasis. However, hemostatic hydrogels still face certain limitations that must be addressed. For example, these hydrogels tend to be expensive to manufacture and hard to mass-produce. They also have not yet shown the ability to effectively adhere to skin in all pre-hospital environments and prevent blood loss to the same degree as traditional methods.

### 5.3 Drug delivery agents

Hydrogels are capable of shielding drugs and cells, increasing their therapeutic efficacy. The ability to deliver a variety of cell types and medications to different tissues and organs, while creating a moist environment that promotes favorable conditions for wound healing, is another benefit of hydrogel encapsulation techniques' versatility. Chronic wounds have an increased risk of infection due to excessive inflammation and prolonged healing. To address these risks, antimicrobial hydrogels have been developed with antibacterial, antiviral, or antifungal properties, depending on the type of infection.[136]

Antibacterial hydrogels are commonly developed to combat infection-causing bacteria in chronic wounds. Specific biocompatible hydrogel dressings with high water content and natural polymers can be used as a matrix for the local administration of drugs released at specific sites to treat chronic wounds.[137] Antibacterial agents can block bacterial DNA replication or protein synthesis, effectively combating harmful infections and their associated effects.

Hydrogels can naturally exhibit antiviral activity or be engineered to incorporate antiviral agents for enhanced efficacy. For instance, biomaterials that are alginate-based have been shown to have inherent antiviral activities against various types of viruses.[138] The antiviral activity of hydrogels depends on the bioavailability, solubility, and activity of the antiviral drug incorporated. These properties can be improved by using them in combination with surfactants, polar lipids, or nanoparticles.[137] In a study reported by Hu *et al.*, an interesting discovery was made in the development of antiviral hydrogels by incorporating drugs with guanine analogues in the presence of metal ions.[139] These analogs formed hydrogen-bonded quadruplex structures, which induced the formation of supramolecular hydrogels with inherent antiviral activity, which exhibited a controlled release of antiviral drugs in response to a temperature change, which led to the destruction of hydrogen bonds in the hydrogel's structure.

Additionally, some hydrogels have been designed to exhibit antifungal properties that are crucial to prevent fungal infections in chronic wounds. Amphotericin B (AmpB) is a well-known antifungal drug that the FDA has approved the incorporation into hydrogels. Hydrogels that include AmpB are commonly known as amphogels. These amphogels are used in chronic wound healing due to high efficacy against *C. albicans* strains.[140] High doses of antifungal drugs, like AmpB, that are encapsulated in hydrogels may prove to be toxic to mammalian cells, with the addition of the risk of developing anti-

microbial resistance. Researchers have found that to avoid developing antimicrobial resistance, inherent antifungal activity can be provided by the immobilization of biocompatible antifungal peptides into hydrogels.[141]

Hydrogels that incorporate certain inorganic materials exhibit antibacterial properties that can be useful in the wound healing process. Inorganic antibacterial materials mainly include metal and metallic oxide nanoparticles (NPs), such as gold (Au) NPs, silver (Ag) NPs, copper (Cu) NPs, and zinc oxide (ZnO) NPs.[142] Noble metal ions exhibit long-term inhibition activity on bacterial growth and photo-thermal properties. Highly effective and long-lasting antibacterial activity could be achieved with the combination of both inherent antibacterial activity and heat treatment.[142] Thus, hydrogels loaded with inorganic NPs could not only enhance the antibacterial properties of a hydrogel, but also maintain antibacterial activity for a longer period of time.[143] However, the potential toxicity of metal-based materials remains a major concern, particularly when mammalian cells are exposed to them in high concentrations or over extended periods of time.

The incorporation of various therapeutically active substances into hydrogels as drug delivery systems represents an exciting frontier in biomedical research and pharmaceutical development. Stem cells, growth factors, and natural substances are instinctively biocompatible with wound healing and skin regeneration, as these natural therapeutics emphasize the use of biologically derived components to stimulate the body's innate healing processes.[144] Stem cells often have multi-directional differentiation potential and low immunogenicity, while growth factors are essential for different dynamic stages of wound healing.[61] Moreover, using natural substances like honey or lemon myrtle oil, traditionally used as a topical paste applied to the skin for wounds, can serve as a low cost component that is naturally antimicrobial and anti-inflammatory.[145]

A list of the diverse types of beneficial agents loaded into hydrogels in drug delivery systems are included below in Table 3.

Beyond antimicrobial, antiviral, antifungal, and therapeutic strategies, hydrogels have increasingly been engineered to address chronic wound inflammation through the delivery of immunomodulatory and antiglycation agents. Chronic wounds, particularly diabetic ulcers, are characterized by persistent M1-type macrophage dominance, contributing to sustained inflammation and delayed healing.[165]

Studies have shown that a bilayer alginate hydrogel system encapsulating polyelectrolyte complex nanoparticles (PCNs) loaded with anti-inflammatory cytokines, such as interleukin-10 (IL-10), and angiogenic growth factors can address the challenges of chronic wound healing. The alginate hydrogel is designed to achieve differential degradation, enabling the precise and temporal controlled release of PCNs and loaded agents. The IL-10 released is used to mitigate inflammation, while unsaturated PCNs bind and remove accumulated pro-inflammatory cytokines at the wound site. Then, angiogenic growth factors, such as vascular endothelial growth factor and

© 2026 The Author(s). Published by the Royal Society of Chemistry

*RSC Appl. Polym.*, 2026, **4**, 53–82 | **71**

**Table 3** Recent agents loaded into hydrogel drug release systems

| Loaded agent | Hydrogel polymers | Benefits of agent |
|---|---|---|
| **Antibiotics** | | |
| Gentamicin (GEN)[146] | Dextran and polyvinyl alcohol (PVA) based hydrogels. Halloysite-based hydrogels | Provides a positive effect on hydrogel properties like swellability, flexibility, and elasticity; exhibited enhanced healing effect on chronic wounds. |
| Vancomycin (VAN)[147] | Oligo(poly(ethylene glycol)furmate)/sodium methacrylate (OPF/SMA) charged copolymers biocompatible hydrogel matrices. | Exhibited antimicrobial activity inhibiting the growth of colonies of a clinically derived strain of methicillin-resistant *Staphylococcus aureus* |
| Ciprofloxacin (CIP)[148] | Keratin-based hydrogels | Inhibited cutaneous wound infection healing without interfering with key aspects of the healing process like tissue deposition and remodeling |
| Hematoporphyrin[149] | Carbomer ($Cu_2O$) – Hematoporphyrin Monomethyl Ether (HMME) hydrogels | Exhibited enhanced antimicrobial ability, excellent biocompatibility, and promoted angiogenesis. |
| Penicillin[150] | Polymersome hydrogels | Effective against infections Gram-positive cocci, rods and most anaerobes. Known for its effectiveness as an antibiotic and safety. |
| Moxifloxacin[151] | 2-Hydroxyethylmethacrylate (HEMA) based hydrogels | Promotes wound healing without induction to bacterial resistance. Can act as a slow drug delivery system and can overcome the various adverse effects of systemic antibiotic drug delivery. |
| **Antifungal** | | |
| Amphotericin B (AmpB)[152] | Dextran-based hydrogels | Broad spectrum of antifungal activity, long lasting, marked antifungal efficacy in mice |
| **Antiviral** | | |
| Penciclovir[153] | Microemulsion-based hydrogels | Effective against herpes simplex virus, varicella zoster virus, Epstein–Barr virus, hepatitis virus and cytomegalovirus. |
| Entecavir[154] | Supramolecular G-quadruplex hydrogels | First-line treatment option for patients with chronic hepatitis B infection, retains activity against lamivudine-resistant HBV variants |
| Ganciclovir[155] | Poly(ε-caprolactone)-chitosan polymer hydrogels | Antiviral activity against herpes viral infections, most widely used antiviral to treat cytomegalovirus infections |
| **Biotherapeutics** | | |
| Bone-marrow derived mesenchymal stem cells (BMSC)[61] | PNIPAM crosslinked with poly (amidoamine) (PAA) | Improved epithelial cell migration and proliferation, collagen deposition, growth factor secretion and wound-healing quality |
| Mesenchymal stem cells[44] | Myocardium derived extracellular matrix (ECM) hydrogel | Exosome sustained release system promotes angiogenesis, collagen deposition, cell proliferation, and migration, thereby accelerating the wound healing process |
| Human fibroblast growth factor[62,156] | Polaxam based hydrogel pectin/gum arabic/calcium chloride dihydrate hydrogel | Promoted cell proliferation and migration, rapid regeneration of ECM and angiogenesis; enhanced wound re-epithelialization, collagen deposition, and contraction |
| Vascular endothelial growth factor (VEGF)[157] | Hyaluronic acid-based hydrogel | Promotion of new blood vessel formation and enhanced supply of oxygen and nutrients to the wound |
| Lemon myrtle oil (LMO)[145] | Aloe vera-sodium alginate based hydrogel | Improved processability of hydrogel prototypes, increased protein adhesion, enhanced physical properties, and antimicrobial activities against Gram-positive and Gram-negative bacteria and yeasts, and common microbes *Staphylococcus epidermidis* and *Candida albicans* |
| Honey[158–160] | Poly vinyl alcohol (PVA) hydrogel[158] Cellulose-based hydrogel Chitosan based | Antimicrobial, anti-inflammatory, and antioxidant activity; increased water absorption and swellability, stimulated cell proliferation, supported epithelization, maintained a moist environment to avoid pathogenic infection, and accelerated wound healing in burns |
| Propolis[161] | Polyacrylamide-methylcellulose hydrogels | Antibacterial properties in the initial stage of the wound repair, antioxidant activity |
| **Inorganic components** | | |
| Ag nanoparticles[143] | Poly(2-acrylamido-2-methyl-1-propansulfonic acid) | High level of antimicrobial activity without inducing cytotoxicity in mammalian cells at appropriate amounts |
| Au nanoparticles[162] | Supramolecular hydrogels | Accelerated the healing of diabetic skin wounds, significant levels and increased duration of antimicrobial activity |
| Cu nanoparticles[163] | Citrate-based hydrogels | Beneficial wound healing of hydrogels in diabetic patients; decreased copper ion toxicity, reduced cell apoptosis, and accelerated wound healing |
| ZnO nanoparticles[164] | Alginate-based hydrogels | Promoted angiogenesis, leading to faster tissue healing and recovery. Enhance the mechanical properties possessed by natural polymers. Naturally possess antibacterial properties and are photocatalytic in UV light range. |

platelet-derived growth factor, are released, promoting vascularization and vessel maturation.[166] In addition, hydrogels loaded with macrophage-polarizing agents, such as interleukin-4 (IL-4), interleukin-13 (IL-13), and previously mentioned IL-10, can promote macrophage phenotype switching towards a pro-regenerative M2 state, accelerating resolution of inflammation and improving tissue regeneration.[167] Furthermore, anti-glycation hydrogels incorporating natural polyphenols like

curcumin, epigallocatechin gallate (EGCG), or quercetin have been shown to reduce advanced glycation end-product (AGE) accumulation, a key contributor to oxidative stress and impaired healing in diabetic wounds.[168]

These advanced hydrogel platforms highlight the growing potential of bioactive hydrogel drug delivery systems to not only fight infection but also resolve chronic inflammation a key barrier in chronic wound repair.

# 6 Limitations and future perspectives

This section addresses the challenges related to the mechanical strength, production, and biological compatibility of hydrogels as chronic wound dressings, and explores potential innovations to overcome these limitations. While hydrogels can be engineered to exhibit high mechanical strength, there is typically a trade-off between mechanical robustness and scalable production efficiency.[169] Given the desired functionality of hydrogels as chronic wound dressings, the ideal hydrogel should balance durability with cost-effective mass production and distribution. This has been particularly achieved through high-density ionic interactions and interpenetrating polymer networks (IPNs), but alternative approaches remain underexplored.[170,171] Moreover, as wounds can vary greatly across different people based on the type and status of the wound, it may be so that certain aspects of wound healing need to be monitored more during one period and not another. For example, early-stage inflammation is associated with localized temperature increases, but prolonged temperature elevation may indicate infection. A solution for this would be to incorporate sensors with "smart" technologies capable of monitoring wound healing progress, detecting infection, or providing real-time feedback to healthcare providers. Lou *et al.* incorporated an example of this using temperature fluctuations as a wound indicator that would provide early notifications if a wound were infected.[172] Such a mechanism could be combined with stimuli-sensitive hydrogels to provide optimal wound healing conditions.

Furthermore, incorporating several cross-linkers that have previously been used to generate hydrogels with specific properties, such as glutaraldehyde and epichlorohydrin, have been identified as cytotoxic, which must also be weighed when determining the appropriate hydrogel design for biological applications.[169] Biocompatible alternatives, like genipin, have been explored for their lower toxicity profiles and suitability in medical applications.[173] Another issue arises from the replication of specific scaffolds and structures, as well as the maintenance of a particular shape once applied, which can be done successfully in small batches but still faces difficulty in precision on a mass-produced scale.[174] Injectable hydrogels suffer from similar issues of degradation and inconsistencies in the solidification of hydrogels after injection, primarily due to the variability in environmental conditions (such as pH, temperature, and presence of glucose), which can significantly impact the performance or function of the hydrogel.[175] There is also a high start-up cost associated with hydrogel fabrication and a lack of systemwide regulation in the process, leading to severe variations in quality and design between manufacturers that will inhibit the rate of production of hydrogels regardless of clinical success.[175]

Lastly, most current hydrogel drug delivery research has been conducted on rat skin. However, rat skin differs significantly from human skin in multiple aspects, particularly in the wound healing process. One such example is how their immune system has many variations in inflammatory cytokine production and immune cell behavior that would affect how they respond to infections, allergens, or injuries compared to humans, leading to deviations in experimental results.[176] Future recommendations include exploring more suitable wound assessment models for more similar conditions to human skin wounds, and to further clinical trials displaying the efficacies of stimulus-sensitive drug-delivery hydrogels in wound healing.

Previous and current research projects show the promising potential of hydrogels as advanced wound dressings, offering unique properties that distinguish them from conventional dressings commonly used today. However, other directions of hydrogel research have also shown their efficacy in a variety of other applications, including cancer therapy, tissue engineering, nanotechnology, and treatment of osteoarthritis.[177–180] Given the skin's extensive surface area and its integration with various bodily systems, there is great potential for developing multidisciplinary hydrogels with enhanced healing capabilities. Exploring the possibility further could open new avenues for expanding hydrogel functionality. For example, future hydrogels could combine the drug delivery properties of injectable hydrogels and the incorporation of smart elements to create timed release of photothermal agents for antitumor phototherapy, applications initially popularized in hydrogels for wound dressings.[181] Furthermore, in the field of nanotechnology, hydrogels have recently gained traction for their conductive and ionic properties that make them ideal for incorporation with materials in the development of wearable technologies. For example, recent advances in MXene-based hydrogels combine the family of 2-D nanomaterials with hydrogels for applications in real-time sensors.[182] Specifically, the electrical conductivity of MXene materials alongside the biocompatible properties of hydrogels result in ideal characteristics for developing sensors that can detect pressure, strain, and chemical changes related to health, such as in the context of changes indicative of poor wound healing conditions. These scenarios demonstrate the additional efficacy provided by merging the findings of hydrogel research from a variety of unique applications and encourage interconnected and multidisciplinary work as a strong direction for the future of hydrogels.

# 7 Conclusion

Chronic wounds place a significant burden on both healthcare systems and millions of patients worldwide, making the development of more effective treatment strategies imperative. This review has presented a comprehensive overview of chronic

© 2026 The Author(s). Published by the Royal Society of Chemistry

*RSC Appl. Polym.*, 2026, **4**, 53–82 | **73**

wound healing and recent advancements in hydrogel-based dressings designed to enhance their therapeutic efficacy. These innovations have gained increasing attention in recent years due to their ability to create an optimal wound-healing environment, promoting tissue regeneration and repair. Given the complexity of chronic wound healing, internal stimuli-responsive hydrogels have been developed to dynamically respond to environmental cues such as temperature, pH, MMP, ROS levels, or glucose. These changes can serve as indicators of infection or tissue distress, allowing for timely intervention. Additionally, hydrogels have also been modified to release therapeutic agents through drug delivery, providing antimicrobial medication, inorganic compounds, or biotherapeutic substances directly at the wound site. Recent preclinical findings indicate that these innovations can significantly enhance healing outcomes in chronic wounds. However, further studies are needed to optimize their design for large-scale production, ensure long-term biocompatibility, and develop personalized treatments tailored to individual wound conditions.

Moreover, this review emphasizes the growing role of external stimuli-responsive hydrogels, systems that enable active, non-invasive, and precisely controllable therapeutic delivery at chronic wound sites. Compared to conventional drug delivery systems that often rely on passive diffusion or endogenous biological triggers, external stimuli-responsive hydrogels, such as those responsive to mechanical forces, magnetic fields, and ultrasound, offer a greater spatiotemporal control, reduced off-target effects, and adaptability to dynamic wound conditions.[183,184] These features are particularly important when managing chronic wounds, where timely, localized, and adjustable treatment is essential for overcoming infection and impaired tissue regeneration. As the integration of wearable technologies and smart wound dressings progresses, these external stimuli-responsive systems have the potential to drive the next generation of personalized wound care strategies. This review provides a timely and comprehensive framework to guide future innovation in smart, responsive hydrogel systems targeting chronic wound therapy.

## Conflicts of interest

The authors declare no conflict of interest.

## Data availability

The data that supports the findings of this study are contained within the article. More information is available on request from the corresponding authors.

## Acknowledgements

## References

1 A. K. Dąbrowska, F. Spano, S. Derler, C. Adlhart, N. D. Spencer and R. M. Rossi, The Relationship between Skin Function, Barrier Properties, and Body–dependent Factors, *Skin Res. Technol.*, 2018, **24**(2), 165–174, DOI: 10.1111/srt.12424.

2 Y. Liang, J. He and B. Guo, Functional Hydrogels as Wound Dressing to Enhance Wound Healing, *ACS Nano*, 2021, **15**(8), 12687–12722, DOI: 10.1021/acsnano.1c04206.

3 S. R. Nussbaum, M. J. Carter, C. E. Fife, J. DaVanzo, R. Haught, M. Nusgart and D. Cartwright, An Economic Evaluation of the Impact, Cost, and Medicare Policy Implications of Chronic Nonhealing Wounds, *Value Health*, 2018, **21**(1), 27–32, DOI: 10.1016/j.jval.2017.07.007.

4 N. T. Garland, J. W. Song, T. Ma, Y. J. Kim, A. Vázquez-Guardado, A. B. Hashkavayi, S. K. Ganeshan, N. Sharma, H. Ryu, M. Lee, B. Sumpio, M. A. Jakus, V. Forsberg, R. Kaveti, S. K. Sia, A. Veves, J. A. Rogers, G. A. Ameer and A. J. Bandodkar, A Miniaturized, Battery–Free, Wireless Wound Monitor That Predicts Wound Closure Rate Early, *Adv. Healthcare Mater.*, 2023, **12**(28), 2301280, DOI: 10.1002/adhm.202301280.

5 V. Falanga, R. R. Isseroff, A. M. Soulika, M. Romanelli, D. Margolis, S. Kapp, M. Granick and K. Harding, Chronic Wounds, *Nat. Rev. Dis. Primers*, 2022, **8**(1), 50, DOI: 10.1038/s41572-022-00377-3.

6 C. K. Sen, Human Wound and Its Burden: Updated 2020 Compendium of Estimates, *Adv. Wound Care*, 2021, **10**(5), 281–292, DOI: 10.1089/wound.2021.0026.

7 A. C. D. O. Gonzalez, T. F. Costa, Z. D. A. Andrade and A. R. A. P. Medrado, Wound Healing - A Literature Review, *An. Bras. Dermatol.*, 2016, **91**(5), 614–620, DOI: 10.1590/abd1806-4841.20164741.

8 M. A. Fonder, G. S. Lazarus, D. A. Cowan, B. Aronson-Cook, A. R. Kohli and A. J. Mamelak, Treating the Chronic Wound: A Practical Approach to the Care of Nonhealing Wounds and Wound Care Dressings, *J. Am. Acad. Dermatol.*, 2008, **58**(2), 185–206, DOI: 10.1016/j.jaad.2007.08.048.

9 A. Michalicha, A. Belcarz, D. A. Giannakoudakis, M. Staniszewska and M. Barczak, Designing Composite Stimuli-Responsive Hydrogels for Wound Healing Applications: The State-of-the-Art and Recent Discoveries, *Materials*, 2024, **17**(2), 278, DOI: 10.3390/ma17020278.

10 J. G. Powers, L. M. Morton and T. J. Phillips, Dressings for Chronic Wounds: Dressings, *Dermatol. Ther.*, 2013, **26**(3), 197–206, DOI: 10.1111/dth.12055.

11 H. R. M. Rashdan and M. E. El-Naggar, Traditional and Modern Wound Dressings—Characteristics of Ideal Wound Dressings, in *Antimicrobial Dressings*, Elsevier, 2023, pp. 21–42. DOI: 10.1016/B978-0-323-95074-9.00002-6.

12 Y. Fan, H. Wang, C. Wang, Y. Xing, S. Liu, L. Feng, X. Zhang and J. Chen, Advances in Smart-Response Hydrogels for Skin Wound Repair, *Polymers*, 2024, **16**(19), 2818, DOI: 10.3390/polym16192818.

13 P. Sánchez-Cid, M. Jiménez-Rosado, A. Romero and V. Pérez-Puyana, Novel Trends in Hydrogel Development for Biomedical Applications: A Review, *Polymers*, 2022, **14**(15), 3023, DOI: 10.3390/polym14153023.

14 S. Chhabra, N. Chhabra, A. Kaur and N. Gupta, Wound Healing Concepts in Clinical Practice of OMFS, *J. Maxillofac. Oral Surg.*, 2017, **16**(4), 403–423, DOI: 10.1007/s12663-016-0880-z.

15 M. Hoffman, The Cellular Basis of Traumatic Bleeding, *Mil. Med.*, 2004, **169**(12S), 5–7, DOI: 10.7205/MILMED.169.12S.5.

16 P. Anton-Martin, B. C. Willis, J. J. Nigro, K. Budolfson, D. Raz and R. Jamshidi, Complete Traumatic Aortic Transection, *J. Pediatr. Surg. Case Rep.*, 2018, **38**, 4–8, DOI: 10.1016/j.epsc.2018.08.001.

17 G. S. Roodsari, F. Zahedi and S. Zehtabchi, The Risk of Wound Infection after Simple Hand Laceration, *World J. Emerg. Med.*, 2015, **6**(1), 44, DOI: 10.5847/wjem.j.1920-8642.2015.01.008.

18 K. Nuutila and E. Eriksson, Moist Wound Healing with Commonly Available Dressings, *Adv. Wound Care*, 2021, **10**(12), 685–698, DOI: 10.1089/wound.2020.1232.

19 G. Hosgood, Stages of Wound Healing and Their Clinical Relevance, *Vet. Clin. North Am.*, 2006, **36**(4), 667–685, DOI: 10.1016/j.cvsm.2006.02.006.

20 N. X. Landén, D. Li and M. Ståhle, Transition from Inflammation to Proliferation: A Critical Step during Wound Healing, *Cell. Mol. Life Sci.*, 2016, **73**(20), 3861–3885, DOI: 10.1007/s00018-016-2268-0.

21 M. Alhajj and A. Goyal, Physiology, Granulation Tissue. [Updated 2022 Oct 24]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://Www.Ncbi.Nlm.Nih.Gov/Books/NBK554402/.

22 Y. Tai, E. L. Woods, J. Dally, D. Kong, R. Steadman, R. Moseley and A. C. Midgley, Myofibroblasts: Function, Formation, and Scope of Molecular Therapies for Skin Fibrosis, *Biomolecules*, 2021, **11**(8), 1095, DOI: 10.3390/biom11081095.

23 S. S. Mathew-Steiner, S. Roy and C. K. Sen, Collagen in Wound Healing, *Bioengineering*, 2021, **8**(5), 63, DOI: 10.3390/bioengineering8050063.

24 J. C. J. Holzer-Geissler, S. Schwingenschuh, M. Zacharias, J. Einsiedler, S. Kainz, P. Reisenegger, C. Holecek, E. Hofmann, B. Wolff-Winiski, H. Fahrngruber, T. Birngruber, L.-P. Kamolz and P. Kotzbeck, The Impact of Prolonged Inflammation on Wound Healing, *Biomedicines*, 2022, **10**(4), 856, DOI: 10.3390/biomedicines10040856.

25 P.-H. Wang, B.-S. Huang, H.-C. Horng, C.-C. Yeh and Y.-J. Chen, Wound Healing, *J. Chin. Med. Assoc.*, 2018, **81**(2), 94–101, DOI: 10.1016/j.jcma.2017.11.002.

26 R. Zhao, H. Liang, E. Clarke, C. Jackson and M. Xue, Inflammation in Chronic Wounds, *Int. J. Mol. Sci.*, 2016, **17**(12), 2085, DOI: 10.3390/ijms17122085.

27 S. Reich-Schupke, K. Warneke, P. Altmeyer and M. Stücker, Eradication of MRSA in Chronic Wounds of

Outpatients with Leg Ulcers Is Accelerated by Antiseptic Washes – Results of a Pilot Study, *Int. J. Hyg. Environ. Health*, 2010, **213**(2), 88–92, DOI: 10.1016/j.ijheh.2010.01.001.

28 V. Altabas, Diabetes, Endothelial Dysfunction, and, Vascular Repair: What Should a Diabetologist Keep His Eye On?, *Int. J. Endocrinol.*, 2015, **2015**, 1–14, DOI: 10.1155/2015/848272.

29 V. R. Krishnaswamy, D. Mintz and I. Sagi, Matrix Metalloproteinases: The Sculptors of Chronic Cutaneous Wounds, *Biochim. Biophys. Acta, Mol. Cell Res.*, 2017, **1864**(11), 2220–2227, DOI: 10.1016/j.bbamcr.2017.08.003.

30 S. Zhao, X. Hu, Y. Zhao, Y. Zhang, Y. Jin, F. Hua, Y. Xu and W. Ding, Hydrogel-Based Therapies for Diabetic Foot Ulcers: Recent Developments and Clinical Implications, *Burns Trauma*, 2025, **13**, DOI: 10.1093/burnst/tkae084.

31 J. M. Raja, M. A. Maturana, S. Kayali, A. Khouzam and N. Efeovbokhan, Diabetic Foot Ulcer: A Comprehensive Review of Pathophysiology and Management Modalities, *World J. Clin. Cases*, 2023, **11**(8), 1684–1693, DOI: 10.12998/wjcc.v11.i8.1684.

32 J. D. Raffetto, D. Ligi, R. Maniscalco, R. A. Khalil and F. Mannello, Why Venous Leg Ulcers Have Difficulty Healing: Overview on Pathophysiology, Clinical Consequences, and Treatment, *J. Clin. Med.*, 2020, **10**(1), 29, DOI: 10.3390/jcm10010029.

33 C. T. Ribeiro, F. A. Dias and G. A. Fregonezi, Hydrogel Dressings for Venous Leg Ulcers, *Cochrane Database Syst. Rev.*, 2022, **2022**(8), DOI: 10.1002/14651858.cd010738.pub2.

34 T. V. Boyko, M. T. Longaker and G. P. Yang, Review of the Current Management of Pressure Ulcers, *Adv. Wound Care*, 2018, **7**(2), 57–67, DOI: 10.1089/wound.2016.0697.

35 J. C. Dumville, N. Stubbs, S. J. Keogh, R. M. Walker and Z. Liu, Hydrogel Dressings for Treating Pressure Ulcers, *Cochrane Database Syst. Rev.*, 2015, **2015**(2), DOI: 10.1002/14651858.cd011226.pub2.

36 S. Guo and L. A. DiPietro, Factors Affecting Wound Healing, *J. Dent. Res.*, 2010, **89**(3), 219–229, DOI: 10.1177/0022034509359125.

37 R. Edwards and K. G. Harding, Bacteria and Wound Healing, *Curr. Opin. Infect. Dis.*, 2004, **17**(2), 91–96.

38 P. G. Rodriguez, F. Felix, D. T. Woodley and E. K. Shim, The Role of Oxygen in Wound Healing: A Review of the Literature, *Dermatol. Surg.*, 2008, **34**(9), 1159–1169.

39 X. Zhang, D. Yao, W. Zhao, R. Zhang, B. Yu, G. Ma, Y. Li, D. Hao and F. Xu, Engineering Platelet–Rich Plasma Based Dual–Network Hydrogel as a Bioactive Wound Dressing with Potential Clinical Translational Value, *Adv. Funct. Mater.*, 2021, **31**(8), 2009258, DOI: 10.1002/adfm.202009258.

40 S. Bian, L. Hao, X. Qiu, J. Wu, H. Chang, G. Kuang, S. Zhang, X. Hu, Y. Dai, Z. Zhou, F. Huang, C. Liu, X. Zou, W. Liu, W. W. Lu, H. Pan and X. Zhao, An Injectable Rapid–Adhesion and Anti–Swelling Adhesive Hydrogel for

© 2026 The Author(s). Published by the Royal Society of Chemistry

*RSC Appl. Polym.*, 2026, **4**, 53–82 | **75**

Hemostasis and Wound Sealing, *Adv. Funct. Mater.*, 2022, (46), 32, DOI: 10.1002/adfm.202207741.

41 H. Chen, Z. Zhao, R. Zhang, G. Zhang, X. Liang, C. Xu, Y. Sun, Y. Li, C. Boyer and F. Xu, Adaptable Hydrogel with Strong Adhesion of Wet Tissue for Long–Term Protection of Periodontitis Wound, *Adv. Mater.*, 2025, **37**(1), 2413373, DOI: 10.1002/adma.202413373.

42 C. Huang, L. Dong, B. Zhao, Y. Lu, S. Huang, Z. Yuan, G. Luo, Y. Xu and W. Qian, Anti–inflammatory Hydrogel Dressings and Skin Wound Healing, *Clin. Transl. Med.*, 2022, **12**(11), e1094, DOI: 10.1002/ctm2.1094.

43 Y. Liang, M. Li, Y. Yang, L. Qiao, H. Xu and B. Guo, pH/Glucose Dual Responsive Metformin Release Hydrogel Dressings with Adhesion and Self-Healing via Dual-Dynamic Bonding for Athletic Diabetic Foot Wound Healing, *ACS Nano*, 2022, **16**(2), 3194–3207, DOI: 10.1021/acsnano.1c11040.

44 Y. Song, Y. You, X. Xu, J. Lu, X. Huang, J. Zhang, L. Zhu, J. Hu, X. Wu, X. Xu, W. Tan and Y. Du, Adipose–Derived Mesenchymal Stem Cell–Derived Exosomes Biopotentiated Extracellular Matrix Hydrogels Accelerate Diabetic Wound Healing and Skin Regeneration, *Adv. Sci.*, 2023, **10**(30), 2304023, DOI: 10.1002/advs.202304023.

45 J. Qu, X. Zhao, P. X. Ma and B. Guo, Injectable Antibacterial Conductive Hydrogels with Dual Response to an Electric Field and pH for Localized "Smart" Drug Release, *Acta Biomater.*, 2018, **72**, 55–69, DOI: 10.1016/j.actbio.2018.03.018.

46 I. Firlar, M. Altunbek, C. McCarthy, M. Ramalingam and G. Camci-Unal, Functional Hydrogels for Treatment of Chronic Wounds, *Gels*, 2022, **8**(2), 127, DOI: 10.3390/gels8020127.

47 W. Zhang, L. Liu, H. Cheng, J. Zhu, X. Li, S. Ye and X. Li, Hydrogel-Based Dressings Designed to Facilitate Wound Healing, *Mater. Adv.*, 2024, **5**(4), 1364–1394, DOI: 10.1039/d3ma00682d.

48 T.-C. Ho, C.-C. Chang, H.-P. Chan, T.-W. Chung, C.-W. Shu, K.-P. Chuang, T.-H. Duh, M.-H. Yang and Y.-C. Tyan, Hydrogels: Properties and Applications in Biomedicine, *Molecules*, 2022, **27**(9), 2902, DOI: 10.3390/molecules27092902.

49 M. Horzic, D. Bunoza and K. Maric, Contact Thermography in a Study of Primary Healing of Surgical Wounds, *Ostomy/Wound Management*, 1996, **42**(1), 36–38, https://pubmed.ncbi.nlm.nih.gov/8703289/.

50 M. Fierheller and R. G. Sibbald, A Clinical Investigation into the Relationship between Increased Periwound Skin Temperature and Local Wound Infection in Patients with Chronic Leg Ulcers, *Adv. Skin Wound Care*, 2010, **23**(8), 369–379, DOI: 10.1097/01.ASW.0000383197.28192.98.

51 H. Dai, Q. Chen, H. Qin, Y. Guan, D. Shen, Y. Hua, Y. Tang and J. Xu, A Temperature-Responsive Copolymer Hydrogel in Controlled Drug Delivery, *Macromolecules*, 2006, **39**(19), 6584–6589, DOI: 10.1021/ma060486p.

52 H. F. Darge, A. T. Andrgie, H.-C. Tsai and J.-Y. Lai, Polysaccharide and Polypeptide Based Injectable Thermo-Sensitive Hydrogels for Local Biomedical Applications, *Int. J. Biol. Macromol.*, 2019, **133**, 545–563, DOI: 10.1016/j.ijbiomac.2019.04.131.

53 A. Sinek, M. Kupczak, A. Mielańczyk, M. Lemanowicz, S.-I. Yusa, D. Neugebauer and A. Gierczycki, Temperature and pH-Dependent Response of Poly(Acrylic Acid) and Poly(Acrylic Acid-Co-Methyl Acrylate) in Highly Concentrated Potassium Chloride Aqueous Solutions, *Polymers*, 2020, **12**(2), 486, DOI: 10.3390/polym12020486.

54 W. Xue, I. W. Hamley and M. B. Huglin, Rapid Swelling and Deswelling of Thermoreversible Hydrophobically Modified Poly(N-Isopropylacrylamide) Hydrogels Prepared by Freezing Polymerisation, *Polymer*, 2002, **43**(19), 5181–5186, DOI: 10.1016/S0032-3861(02)00396-8.

55 Y. Yu, Y. Cheng, J. Tong, L. Zhang, Y. Wei and M. Tian, Recent Advances in Thermo-Sensitive Hydrogels for Drug Delivery, *J. Mater. Chem. B*, 2021, **9**(13), 2979–2992, DOI: 10.1039/D0TB02877K.

56 T. Congdon, P. Shaw and M. I. Gibson, Thermoresponsive, Well-Defined, Poly(Vinyl Alcohol) Co-Polymers, *Polym. Chem.*, 2015, **6**(26), 4749–4757, DOI: 10.1039/C5PY00775E.

57 W. Loos, S. Verbrugghe, E. J. Goethals, F. E. Du Prez, I. V. Bakeeva and V. P. Zubov, Thermo–Responsive Organic/Inorganic Hybrid Hydrogels Based on Poly(*N*–vinylcaprolactam), *Macromol. Chem. Phys.*, 2003, **204**(1), 98–103, DOI: 10.1002/macp.200290058.

58 Y. B. Schuetz, R. Gurny and O. Jordan, A Novel Thermoresponsive Hydrogel Based on Chitosan, *Eur. J. Pharm. Biopharm.*, 2008, **68**(1), 19–25, DOI: 10.1016/j.ejpb.2007.06.020.

59 M. Hua, D. Wu, S. Wu, Y. Ma, Y. Alsaid and X. He, 4D Printable Tough and Thermoresponsive Hydrogels, *ACS Appl. Mater. Interfaces*, 2021, **13**(11), 12689–12697, DOI: 10.1021/acsami.0c17532.

60 M. Nasr, A. Y. Kira and S. Saber, Localized Delivery of Roxadustat via Cubosomes-Based Thermosensitive *in situ* Hydrogel Enhances Diabetic Wound Healing by Stabilizing HIF-1α in Rats, *J. Drug Delivery Sci. Technol.*, 2024, **100**, 106127, DOI: 10.1016/j.jddst.2024.106127.

61 Z. Lei, G. Singh, Z. Min, C. Shixuan, K. Xu, X. Pengcheng, W. Xueer, C. Yinghua, Z. Lu and Z. Lin, Bone Marrow-Derived Mesenchymal Stem Cells Laden Novel Thermo-Sensitive Hydrogel for the Management of Severe Skin Wound Healing, *Mater. Sci. Eng., C*, 2018, **90**, 159–167, DOI: 10.1016/j.msec.2018.04.045.

62 Y. Zhang, W. He, S. Zhang, X. Hu, S. Sun, H. Gao, J. Kong, H. Liu, H. Li, X. Liu and Y. Cheng, Poloxam Thermosensitive Hydrogels Loaded with hFGF2-Linked Camelina Lipid Droplets Accelerate Skin Regeneration in Deep Second-Degree Burns, *Int. J. Mol. Sci.*, 2022, **23**(21), 12716, DOI: 10.3390/ijms232112716.

63 R. Gu, H. Zhou, Z. Zhang, Y. Lv, Y. Pan, Q. Li, C. Shi, Y. Wang and L. Wei, Research Progress Related to Thermosensitive Hydrogel Dressings in Wound Healing: A Review, *Nanoscale Adv.*, 2023, **5**(22), 6017–6037, DOI: 10.1039/D3NA00407D.

64 Q. Zhao, J. Liu, S. Liu, J. Han, Y. Chen, J. Shen, K. Zhu and X. Ma, Multipronged Micelles–Hydrogel for Targeted and Prolonged Drug Delivery in Chronic Wound Infections, *ACS Appl. Mater. Interfaces*, 2022, **14**(41), 46224–46238, DOI: 10.1021/acsami.2c12530.

65 L. Zhao, J. Du, Y. Duan, Y. Zang, H. Zhang, C. Yang, F. Cao and G. Zhai, Curcumin Loaded Mixed Micelles Composed of Pluronic P123 and F68: Preparation, Optimization and in Vitro Characterization, *Colloids Surf., B*, 2012, **97**, 101–108, DOI: 10.1016/j.colsurfb.2012.04.017.

66 H. Chen, R. Zhang, G. Zhang, X. Liang, C. Xu, Y. Li and F. Xu, Naturally Inspired Tree–Ring Structured Dressing Provides Sustained Wound Tightening and Accelerates Closure, *Adv. Mater.*, 2025, **37**(3), 2410845, DOI: 10.1002/adma.202410845.

67 X. Liu, H. Yu, L. Wang, R. Liang, Y. Xiang, X. Song, Y. Yang, Z. Huang, J. Yang, D. Shen and Y. Sheng, Body-Temperature Responsive Hydrogel Adhesive for Active Wound Closure, *J. Mater. Chem. B*, 2025, **13**(25), 7502–7515, DOI: 10.1039/d5tb00084j.

68 J. R. Sharpe, K. L. Harris, K. Jubin, N. J. Bainbridge and N. R. Jordan, The Effect of pH in Modulating Skin Cell Behaviour, *Br. J. Dermatol.*, 2009, **161**(3), 671–673, DOI: 10.1111/j.1365-2133.2009.09168.x.

69 C. R. Kruse, K. Nuutila, C. C. Y. Lee, E. Kiwanuka, M. Singh, E. J. Caterson, E. Eriksson and J. A. Sørensen, The External Microenvironment of Healing Skin Wounds, *Wound Repair Regener.*, 2015, **23**(4), 456–464, DOI: 10.1111/wrr.12303.

70 Y. Huang, L. Mu, X. Zhao, Y. Han and B. Guo, Bacterial Growth-Induced Tobramycin Smart Release Self-Healing Hydrogel for *Pseudomonas Aeruginosa*-Infected Burn Wound Healing, *ACS Nano*, 2022, **16**(8), 13022–13036, DOI: 10.1021/acsnano.2c05557.

71 C. Ding, M. Tian, R. Feng, Y. Dang and M. Zhang, Novel Self-Healing Hydrogel with Injectable, pH-Responsive, Strain-Sensitive, Promoting Wound-Healing, and Hemostatic Properties Based on Collagen and Chitosan, *ACS Biomater. Sci. Eng.*, 2020, **6**(7), 3855–3867, DOI: 10.1021/acsbiomaterials.0c00588.

72 I. J. Das and T. Bal, pH Factors in Chronic Wound and pH-Responsive Polysaccharide-Based Hydrogel Dressings, *Int. J. Biol. Macromol.*, 2024, **279**, 135118, DOI: 10.1016/j.ijbiomac.2024.135118.

73 T. G. Park and A. S. Hoffman, Synthesis and Characterization of pH– and/or Temperature–sensitive Hydrogels, *J. Appl. Polym. Sci.*, 1992, **46**(4), 659–671, DOI: 10.1002/app.1992.070460413.

74 M. Rizwan, R. Yahya, A. Hassan, M. Yar, A. Azzahari, V. Selvanathan, F. Sonsudin and C. Abouloula, pH Sensitive Hydrogels in Drug Delivery: Brief History, Properties, Swelling, and Release Mechanism, Material Selection and Applications, *Polymers*, 2017, **9**(4), 137, DOI: 10.3390/polym9040137.

75 U. Vegad, M. Patel, D. Khunt, O. Zupančič, S. Chauhan and A. Paudel, pH Stimuli-Responsive Hydrogels from Non-Cellulosic Biopolymers for Drug Delivery, *Front. Bioeng. Biotechnol.*, 2023, **11**, 1270364, DOI: 10.3389/fbioe.2023.1270364.

76 S. Wu, Y. Yang, S. Wang, C. Dong, X. Zhang, R. Zhang and L. Yang, Dextran and Peptide-Based pH-Sensitive Hydrogel Boosts Healing Process in Multidrug-Resistant Bacteria-Infected Wounds, *Carbohydr. Polym.*, 2022, **278**, 118994, DOI: 10.1016/j.carbpol.2021.118994.

77 M. I. Rial-Hermida, A. Rey-Rico, B. Blanco-Fernandez, N. Carballo-Pedrares, E. M. Byrne and J. F. Mano, Recent Progress on Polysaccharide-Based Hydrogels for Controlled Delivery of Therapeutic Biomolecules, *ACS Biomater. Sci. Eng.*, 2021, **7**(9), 4102–4127, DOI: 10.1021/acsbiomaterials.0c01784.

78 Y. Qiu and K. Park, Environment-Sensitive Hydrogels for Drug Delivery, *Adv. Drug Delivery Rev.*, 2001, **53**(3), 321–339, DOI: 10.1016/S0169-409X(01)00203-4.

79 S. Bazban-Shotorbani, M. M. Hasani-Sadrabadi, A. Karkhaneh, V. Serpooshan, K. I. Jacob, A. Moshaverinia and M. Mahmoudi, Revisiting Structure-Property Relationship of pH-Responsive Polymers for Drug Delivery Applications, *J. Controlled Release*, 2017, **253**, 46–63, DOI: 10.1016/j.jconrel.2017.02.021.

80 C. Xu, Y. Yan, J. Tan, D. Yang, X. Jia, L. Wang, Y. Xu, S. Cao and S. Sun, Biodegradable Nanoparticles of Polyacrylic Acid–Stabilized Amorphous $CaCO_3$ for Tunable pH–Responsive Drug Delivery and Enhanced Tumor Inhibition, *Adv. Funct. Mater.*, 2019, **29**(24), 1808146, DOI: 10.1002/adfm.201808146.

81 L. M. D. M. C. Ferreira, E. D. S. Bandeira, M. F. Gomes, D. G. Lynch, G. N. T. Bastos, J. O. C. Silva-Júnior and R. M. Ribeiro-Costa, Polyacrylamide Hydrogel Containing Calendula Extract as a Wound Healing Bandage: In Vivo Test, *Int. J. Mol. Sci.*, 2023, **24**(4), 3806, DOI: 10.3390/ijms24043806.

82 P. Li, N. H. Kim, M. R. Siddaramaiah and J. H. Lee, Swelling Behavior of Polyacrylamide/Laponite Clay Nanocomposite Hydrogels: pH-Sensitive Property, *Composites, Part B*, 2009, **40**(4), 275–283, DOI: 10.1016/j.compositesb.2009.01.001.

83 D. C. Martin, J. L. Semple and M. V. Sefton, Poly (Methacrylic Acid– *Co* –methyl Methacrylate) Beads Promote Vascularization and Wound Repair in Diabetic Mice, *J. Biomed. Mater. Res., Part A*, 2010, **93A**(2), 484–492, DOI: 10.1002/jbm.a.32528.

84 V. Kozlovskaya, E. Kharlampieva, M. L. Mansfield and S. A. Sukhishvili, Poly(Methacrylic Acid) Hydrogel Films and Capsules: Response to pH and Ionic Strength, and Encapsulation of Macromolecules, *Chem. Mater.*, 2006, **18**(2), 328–336, DOI: 10.1021/cm0517364.

85 Y. Q. Yang, B. Zhao, Z. D. Li, W. J. Lin, C. Y. Zhang, X. D. Guo, J. F. Wang and L. J. Zhang, pH-Sensitive Micelles Self-Assembled from Multi-Arm Star Triblock Co-Polymers Poly(ε-Caprolactone)-b-Poly(2-(Diethylamino) Ethyl Methacrylate)-b-Poly(Poly(Ethylene Glycol) Methyl Ether Methacrylate) for Controlled Anticancer Drug

© 2026 The Author(s). Published by the Royal Society of Chemistry

*RSC Appl. Polym.*, 2026, **4**, 53–82 | 77

Delivery, *Acta Biomater.*, 2013, **9**(8), 7679–7690, DOI: 10.1016/j.actbio.2013.05.006.

86 J. Wei, X.-J. Ju, R. Xie, C.-L. Mou, X. Lin and L.-Y. Chu, Novel Cationic pH-Responsive Poly(N, N-Dimethylaminoethyl Methacrylate) Microcapsules Prepared by a Microfluidic Technique, *J. Colloid Interface Sci.*, 2011, **357**(1), 101–108, DOI: 10.1016/j.jcis.2011.01.105.

87 K. Ou, Y. Liu, L. Deng, S. Chen, S. Gu and B. Wang, Covalently Grafting Polycation to Bacterial Cellulose for Antibacterial and Anti-Cell Adhesive Wound Dressings, *Int. J. Biol. Macromol.*, 2024, **269**, 132157, DOI: 10.1016/j.ijbiomac.2024.132157.

88 Y. Zhu, J. Zhang, J. Song, J. Yang, Z. Du, W. Zhao, H. Guo, C. Wen, Q. Li, X. Sui and L. Zhang, A Multifunctional Pro–Healing Zwitterionic Hydrogel for Simultaneous Optical Monitoring of pH and Glucose in Diabetic Wound Treatment, *Adv. Funct. Mater.*, 2020, **30**(6), 1905493, DOI: 10.1002/adfm.201905493.

89 B. P. Darwitz, C. J. Genito and L. R. Thurlow, Triple Threat: How Diabetes Results in Worsened Bacterial Infections, *Infect. Immun.*, 2024, **92**(9), e00509–e00523, DOI: 10.1128/iai.00509-23.

90 Y. Li, G. Feng, J. Liu, T. Yang, R. Hou, J. Liu and X. Wang, Progress in Glucose–Sensitive Hydrogels for Biomedical Applications, *Macromol. Chem. Phys.*, 2023, **224**(23), 2300257, DOI: 10.1002/macp.202300257.

91 Y. Tang, H. Xu, X. Wang, S. Dong, L. Guo, S. Zhang, X. Yang, C. Liu, X. Jiang, M. Kan, S. Wu, J. Zhang and C. Xu, Advances in Preparation and Application of Antibacterial Hydrogels, *J. Nanobiotechnol.*, 2023, **21**(1), 300, DOI: 10.1186/s12951-023-02025-8.

92 I. Forzano, R. Avvisato, F. Varzideh, S. S. Jankauskas, A. Cioppa, P. Mone, L. Salemme, U. Kansakar, T. Tesorio, V. Trimarco and G. Santulli, L-Arginine, in Diabetes: Clinical and Preclinical Evidence, *Cardiovasc. Diabetol.*, 2023, **22**(1), 89, DOI: 10.1186/s12933-023-01827-2.

93 P. M. Kharkar, K. L. Kiick and A. M. Kloxin, Designing Degradable Hydrogels for Orthogonal Control of Cell Microenvironments, *Chem. Soc. Rev.*, 2013, **42**(17), 7335–7372, DOI: 10.1039/C3CS60040H.

94 S. B. Bankar, M. V. Bule, R. S. Singhal and L. Ananthanarayan, Glucose Oxidase—An Overview, *Biotechnol. Adv.*, 2009, **27**(4), 489–501, DOI: 10.1016/j.biotechadv.2009.04.003.

95 B. Grigoryan, S. J. Paulsen, D. C. Corbett, D. W. Sazer, C. L. Fortin, A. J. Zaita, P. T. Greenfield, N. J. Calafat, J. P. Gounley, A. H. Ta, F. Johansson, A. Randles, J. E. Rosenkrantz, J. D. Louis-Rosenberg, P. A. Galie, K. R. Stevens and J. S. Miller, Multivascular Networks and Functional Intravascular Topologies within Biocompatible Hydrogels, *Science*, 2019, **364**(6439), 458–464, DOI: 10.1126/science.aav9750.

96 K. Ishihara, M. Kobayashi, N. Ishimaru and I. Shinohara, Glucose Induced Permeation Control of Insulin through a Complex Membrane Consisting of Immobilized Glucose Oxidase and a Poly(Amine), *Polym. J.*, 1984, **16**(8), 625–631, DOI: 10.1295/polymj.16.625.

97 Z. Gu, T. T. Dang, M. Ma, B. C. Tang, H. Cheng, S. Jiang, Y. Dong, Y. Zhang and D. G. Anderson, Glucose-Responsive Microgels Integrated with Enzyme Nanocapsules for Closed-Loop Insulin Delivery, *ACS Nano*, 2013, **7**(8), 6758–6766, DOI: 10.1021/nn401617u.

98 W. Zhou, Z. Duan, J. Zhao, R. Fu, C. Zhu and D. Fan, Glucose and MMP-9 Dual-Responsive Hydrogel with Temperature Sensitive Self-Adaptive Shape and Controlled Drug Release Accelerates Diabetic Wound Healing, *Bioact. Mater.*, 2022, **17**, 1–17, DOI: 10.1016/j.bioactmat.2022.01.004.

99 I. Hisamitsu, K. Kataoka, T. Okano and Y. Sakurai, Glucose-Responsive Gel from Phenylborate Polymer and Poly (Vinyl Alcohol): Prompt Response at Physiological pH Through the Interaction of Borate with Amino Group in the Gel, *Pharm. Res.*, 1997, **14**(3), 289–293, DOI: 10.1023/A:1012033718302.

100 M. Elsherif, M. U. Hassan, A. K. Yetisen and H. Butt, Glucose Sensing with Phenylboronic Acid Functionalized Hydrogel-Based Optical Diffusers, *ACS Nano*, 2018, **12**(3), 2283–2291, DOI: 10.1021/acsnano.7b07082.

101 Y. Hu, D. Yang, H. Zhang, Y. Gao, W. Zhang and R. Yin, A High-Linearity Glucose Sensor Based on Silver-Doped Con A Hydrogel and Laser Direct Writing, *Polymers*, 2023, **15**(6), 1423, DOI: 10.3390/polym15061423.

102 X. Li, Z. Meng, L. Guan, A. Liu, L. Li, M. D. Nešić, B. Yang, W. Qu and Q. Lin, Glucose-Responsive Hydrogel Optimizing Fenton Reaction to Eradicate Multidrug-Resistant Bacteria for Infected Diabetic Wound Healing, *Chem. Eng. J.*, 2024, **487**, 150545, DOI: 10.1016/j.cej.2024.150545.

103 C. Dunnill, T. Patton, J. Brennan, J. Barrett, M. Dryden, J. Cooke, D. Leaper and N. T. Georgopoulos, Reactive Oxygen Species (ROS) and Wound Healing: The Functional Role of ROS and Emerging ROS–modulating Technologies for Augmentation of the Healing Process, *Int. Wound J.*, 2017, **14**(1), 89–96, DOI: 10.1111/iwj.12557.

104 Y. Wang, Y. Wu, L. Long, L. Yang, D. Fu, C. Hu, Q. Kong and Y. Wang, Inflammation-Responsive Drug-Loaded Hydrogels with Sequential Hemostasis, Antibacterial, and Anti-Inflammatory Behavior for Chronically Infected Diabetic Wound Treatment, *ACS Appl. Mater. Interfaces*, 2021, **13**(28), 33584–33599, DOI: 10.1021/acsami.1c09889.

105 W. Shi, Y. Kong, Y. Su, M. A. Kuss, X. Jiang, X. Li, J. Xie and B. Duan, Tannic Acid-Inspired, Self-Healing, and Dual Stimuli Responsive Dynamic Hydrogel with Potent Antibacterial and Anti-Oxidative Properties, *J. Mater. Chem. B*, 2021, **9**(35), 7182–7195, DOI: 10.1039/D1TB00156F.

106 H. Zhao, J. Huang, Y. Li, X. Lv, H. Zhou, H. Wang, Y. Xu, C. Wang, J. Wang and Z. Liu, ROS-Scavenging Hydrogel to Promote Healing of Bacteria Infected Diabetic Wounds, *Biomaterials*, 2020, **258**, 120286, DOI: 10.1016/j.biomaterials.2020.120286.

107 M. P. Caley, V. L. C. Martins and E. A. O'Toole, Metalloproteinases and Wound Healing, *Adv. Wound Care*, 2015, **4**(4), 225–234, DOI: 10.1089/wound.2014.0581.

108 N. Li, L. Yang, C. Pan, P. E. Saw, M. Ren, B. Lan, J. Wu, X. Wang, T. Zeng, L. Zhou, L.-M. Zhang, C. Yang and L. Yan, Naturally-Occurring Bacterial Cellulose-Hyperbranched Cationic Polysaccharide Derivative/MMP-9 siRNA Composite Dressing for Wound Healing Enhancement in Diabetic Rats, *Acta Biomater.*, 2020, **102**, 298–314, DOI: 10.1016/j.actbio.2019.11.005.

109 C. Lin, Y. Hu, Z. Lin, L. Du, Y. Hu, L. Ouyang, X. Xie, P. Cheng, J. Liao, L. Lu, R. Zeng, P. Xia, Z. Hou, G. Liu and H. Hu, MMP-9 Responsive Hydrogel Promotes Diabetic Wound Healing by Suppressing Ferroptosis of Endothelial Cells, *Bioact. Mater.*, 2025, **43**, 240–254, DOI: 10.1016/j.bioactmat.2024.09.006.

110 P. Yu, L. Wei, Z. Yang, X. Liu, H. Ma, J. Zhao, L. Liu, L. Wang, R. Chen and Y. Cheng, Hydrogel Wound Dressings Accelerating Healing Process of Wounds in Movable Parts, *Int. J. Mol. Sci.*, 2024, **25**(12), 6610, DOI: 10.3390/ijms25126610.

111 Y. Zheng, K. Zhang, Y. Yao, X. Li, J. Yu and B. Ding, Bioinspired Sequentially Crosslinked Nanofibrous Hydrogels with Robust Adhesive and Stretchable Capability for Joint Wound Dressing, *Compos. Commun.*, 2021, **26**, 100785, DOI: 10.1016/j.coco.2021.100785.

112 J. Qu, X. Zhao, Y. Liang, T. Zhang, P. X. Ma and B. Guo, Antibacterial Adhesive Injectable Hydrogels with Rapid Self-Healing, Extensibility and Compressibility as Wound Dressing for Joints Skin Wound Healing, *Biomaterials*, 2018, **183**, 185–199, DOI: 10.1016/j.biomaterials.2018.08.044.

113 J. Chen, Q. Peng, X. Peng, L. Han, X. Wang, J. Wang and H. Zeng, Recent Advances in Mechano-Responsive Hydrogels for Biomedical Applications, *ACS Appl. Polym. Mater.*, 2020, **2**(3), 1092–1107, DOI: 10.1021/acsapm.0c00019.

114 J. Song, E. Deiss-Yehiely, S. Yesilata and G. H. McKinley, Strain-Stiffening Universality in Composite Hydrogels and Soft Tissues, *Nat. Phys.*, 2025, **21**(7), 1125–1133, DOI: 10.1038/s41567-025-02869-x.

115 K. Fang, R. Wang, H. Zhang, L. Zhou, T. Xu, Y. Xiao, Y. Zhou, G. Gao, J. Chen, D. Liu, F. Ai and J. Fu, Mechano-Responsive, Tough, and Antibacterial Zwitterionic Hydrogels with Controllable Drug Release for Wound Healing Applications, *ACS Appl. Mater. Interfaces*, 2020, **12**(47), 52307–52318, DOI: 10.1021/acsami.0c13009.

116 S. Mehnath, K. Karthikeyan and M. Jeyaraj, Mechanical Force on Hydrogel Implication on Enhanced Drug Release, Antibacterial, and M2 Macrophage Polarization: New Insights Alleviate Diabetic Wound Healing, *ACS Appl. Mater. Interfaces*, 2024, **16**(41), 55166–55180, DOI: 10.1021/acsami.4c13633.

117 N. Yadav, S. Parveen and M. Banerjee, Potential of Nano-Phytochemicals in Cervical Cancer Therapy, *Clin. Chim. Acta*, 2020, **505**, 60–72, DOI: 10.1016/j.cca.2020.01.035.

118 R. Hou, G. Zhang, G. Du, D. Zhan, Y. Cong, Y. Cheng and J. Fu, Magnetic Nanohydroxyapatite/PVA Composite Hydrogels for Promoted Osteoblast Adhesion and Proliferation, *Colloids Surf., B*, 2013, **103**, 318–325, DOI: 10.1016/j.colsurfb.2012.10.067.

119 C. Hu, L. Yang and Y. Wang, Recent Advances in Smart–responsive Hydrogels for Tissue Repairing, *MedComm: Biomater. Appl.*, 2022, **1**(2), e23, DOI: 10.1002/mba2.23.

120 F. Gang, L. Jiang, Y. Xiao, J. Zhang and X. Sun, Multi–functional Magnetic Hydrogel: Design Strategies and Applications, *Nano Sel.*, 2021, **2**(12), 2291–2307, DOI: 10.1002/nano.202100139.

121 W. Wang, H. Zhang, J. Shen and M. Ye, Facile Preparation of Magnetic Chitosan/Poly (Vinyl Alcohol) Hydrogel Beads with Excellent Adsorption Ability via Freezing-Thawing Method, *Colloids Surf., A*, 2018, **553**, 672–680, DOI: 10.1016/j.colsurfa.2018.05.094.

122 C. He, M. Yin, H. Zhou, J. Qin, S. Wu, H. Liu, X. Yu, J. Chen, H. Zhang, L. Zhang and Y. Wang, Magnetic Nanoactuator-Protein Fiber Coated Hydrogel Dressing for Well-Balanced Skin Wound Healing and Tissue Regeneration, *ACS Nano*, 2025, **19**(1), 1713–1731, DOI: 10.1021/acsnano.4c15647.

123 N. Du, Y. Fan, H. Huang, Y. Guan and K. Nan, Stimuli-Responsive Hydrogel Actuators for Skin Therapeutics and Beyond, *Soft Sci.*, 2024, **4**(35), DOI: 10.20517/ss.2024.31.

124 D. Huang, M. Sun, Y. Bu, F. Luo, C. Lin, Z. Lin, Z. Weng, F. Yang and D. Wu, Microcapsule-Embedded Hydrogel Patches for Ultrasound Responsive and Enhanced Transdermal Delivery of Diclofenac Sodium, *J. Mater. Chem. B*, 2019, **7**(14), 2330–2337, DOI: 10.1039/c8tb02928h.

125 L. Zong, R. Teng, H. Zhang, W. Liu, Y. Feng, Z. Lu, Y. Zhou, Z. Fan, M. Li and X. Pu, Ultrasound–Responsive HBD Peptide Hydrogel with Antibiofilm Capability for Fast Diabetic Wound Healing, *Adv. Sci.*, 2024, **11**(42), 2406022, DOI: 10.1002/advs.202406022.

126 D. Huang, J. Du, F. Luo, G. He, M. Zou, Y. Wang, Z. Lin, D. Wu and Z. Weng, Injectable Hydrogels with Integrated Ph Probes and Ultrasound–Responsive Microcapsules as Smart Wound Dressings for Visual Monitoring and On–Demand Treatment of Chronic Wounds, *Adv. Healthcare Mater.*, 2024, **13**(9), 2303379, DOI: 10.1002/adhm.202303379.

127 X. Chen, Y. Zhang, W. Yu, W. Zhang, H. Tang and W.-E. Yuan, In Situ Forming ROS-Scavenging Hybrid Hydrogel Loaded with Polydopamine-Modified Fullerene Nanocomposites for Promoting Skin Wound Healing, *J. Nanobiotechnol.*, 2023, **21**(1), 129, DOI: 10.1186/s12951-023-01879-2.

128 X. Fang, J. Wang, C. Ye, J. Lin, J. Ran, Z. Jia, J. Gong, Y. Zhang, J. Xiang, X. Lu, C. Xie and J. Liu, Polyphenol-Mediated Redox-Active Hydrogel with $H_2S$ Gaseous-Bioelectric Coupling for Periodontal Bone Healing in Diabetes, *Nat. Commun.*, 2024, **15**(1), 9071, DOI: 10.1038/s41467-024-53290-6.

© 2026 The Author(s). Published by the Royal Society of Chemistry

*RSC Appl. Polym.*, 2026, **4**, 53–82 | 79

129 H. Niu, H. Li, Y. Guan, X. Zhou, Z. Li, S. L. Zhao, P. Chen, T. Tan, H. Zhu, V. Bergdall, X. Xu, J. Ma and J. Guan, Sustained Delivery of rhMG53 Promotes Diabetic Wound Healing and Hair Follicle Development, *Bioact. Mater.*, 2022, **18**, 104–115, DOI: 10.1016/j.bioactmat.2022.03.017.

130 Y. He, K. Liu, S. Guo, R. Chang, C. Zhang, F. Guan and M. Yao, Multifunctional Hydrogel with Reactive Oxygen Species Scavenging and Photothermal Antibacterial Activity Accelerates Infected Diabetic Wound Healing, *Acta Biomater.*, 2023, **155**, 199–217, DOI: 10.1016/j.actbio.2022.11.023.

131 W. Han and S. Wang, Advances in Hemostatic Hydrogels That Can Adhere to Wet Surfaces, *Gels*, 2022, **9**(1), 2, DOI: 10.3390/gels9010002.

132 H. Lee, B. P. Lee and P. B. Messersmith, A Reversible Wet/Dry Adhesive Inspired by Mussels and Geckos, *Nature*, 2007, **448**(7151), 338–341, DOI: 10.1038/nature05968.

133 Y. Ma, J. Yao, Q. Liu, T. Han, J. Zhao, X. Ma, Y. Tong, G. Jin, K. Qu, B. Li and F. Xu, Liquid Bandage Harvests Robust Adhesive, Hemostatic, and Antibacterial Performances as a First–Aid Tissue Adhesive, *Adv. Funct. Mater.*, 2020, **30**(39), 2001820, DOI: 10.1002/adfm.202001820.

134 H. Song, L. Xing, W. Liu, X. Wang, Z. Hou, Y. Wang, Z. Zhang, Y. Li, T. Li, X. Wang, H. Chen, S. Xing and J. Xu, Biomimetic and Multifunctional Hemostatic Hydrogel with Rapid Thermoresponsive Gelation and Robust Wet Adhesion for Emergency Hemostasis: A Rational Design Based on Photo-Cross-Linking Coordinated Hydrophilic–Hydrophobic Balance Strategies, *Biomacromolecules*, 2023, **24**(7), 3327–3344, DOI: 10.1021/acs.biomac.3c00357.

135 E. E. Leonhardt, N. Kang, M. A. Hamad and M. Elsabahy, Absorbable Hemostatic Hydrogels Comprising Composites of Sacrificial Templates and Honeycomb-like Nanofibrous Mats of Chitosan, *Nat. Commun.*, 2019, **10**(1), 2307, DOI: 10.1038/s41467-019-10290-1.

136 A. Ramazani and H. Aghahosseini, The Biological Properties of Hydrogels Based on Natural Polymers, in *Hydrogels Based on Natural Polymers*, Elsevier, 2020, pp. 247–269. DOI: 10.1016/B978-0-12-816421-1.00009-4.

137 M. Malmsten, Antimicrobial and Antiviral Hydrogels, *Soft Matter*, 2011, **7**(19), 8725, DOI: 10.1039/c1sm05809f.

138 Á. Serrano-Aroca, M. Ferrandis-Montesinos and R. Wang, Antiviral Properties of Alginate-Based Biomaterials: Promising Antiviral Agents against SARS-CoV-2, *ACS Appl. Bio Mater.*, 2021, **4**(8), 5897–5907, DOI: 10.1021/acsabm.1c00523.

139 J. Hu, H. Wang, Q. Hu and Y. Cheng, G-Quadruplex-Based, Antiviral Hydrogels by Direct Gelation of Clinical Drugs, *Mater. Chem. Front.*, 2019, **3**(7), 1323–1327, DOI: 10.1039/C9QM00209J.

140 J. Maia, M. Evangelista, H. Gil and L. Ferreira, Dextran-Based Materials for Biomedical Applications, in *Carbohydrates Applications in Medicine*, Research Signpost, Trivandrum, Kerala, India, 2014.

141 A. S. Sultan, T. Vila, E. Hefni, A. J. Karlsson and M. A. Jabra-Rizk, Evaluation of the Antifungal and Wound-Healing Properties of a Novel Peptide-Based Bioadhesive Hydrogel Formulation, *Antimicrob. Agents Chemother.*, 2019, **63**(10), e00888–e00819, DOI: 10.1128/AAC.00888-19.

142 X. Zhang, M. Qin, M. Xu, F. Miao, C. Merzougui, X. Zhang, Y. Wei, W. Chen and D. Huang, The Fabrication of Antibacterial Hydrogels for Wound Healing, *Eur. Polym. J.*, 2021, **146**, 110268, DOI: 10.1016/j.eurpolymj.2021.110268.

143 A. Kumar, T. Behl and S. Chadha, Synthesis of Physically Crosslinked PVA/Chitosan Loaded Silver Nanoparticles Hydrogels with Tunable Mechanical Properties and Antibacterial Effects, *Int. J. Biol. Macromol.*, 2020, **149**, 1262–1274, DOI: 10.1016/j.ijbiomac.2020.02.048.

144 C. Zhou, B. Zhang, Y. Yang, Q. Jiang, T. Li, J. Gong, H. Tang and Q. Zhang, Stem Cell-Derived Exosomes: Emerging Therapeutic Opportunities for Wound Healing, *Stem Cell Res. Ther.*, 2023, **14**(1), 107, DOI: 10.1186/s13287-023-03345-0.

145 D. M. Seneviratne, B. Raphael, E. J. Whiteside, L. C. E. Windus, K. Kauter, J. D. W. Dearnaley, P. K. Annamalai, R. Ward, P. Song and P. (Polly) Burey, A Low-Cost, Antimicrobial Aloe-Alginate Hydrogel Film Containing Australian First Nations Remedy 'Lemon Myrtle Oil' (Backhousia Citriodora) – Potential for Incorporation into Wound Dressings, *Heliyon*, 2024, **10**(18), e37516, DOI: 10.1016/j.heliyon.2024.e37516.

146 S. Same, G. Navidi, G. Samee, F. Abedi, M. Aghazadeh, M. Milani, A. Akbarzadeh and S. Davaran, Gentamycin-Loaded Halloysite-Based Hydrogel Nanocomposites for Bone Tissue Regeneration: Fabrication, Evaluation of the Antibacterial Activity and Cell Response, *Biomed. Mater.*, 2022, **17**(6), 065018, DOI: 10.1088/1748-605X/ac94ad.

147 C. T. Gustafson, F. Boakye-Agyeman, C. L. Brinkman, J. M. Reid, R. Patel, Z. Bajzer, M. Dadsetan and M. J. Yaszemski, Controlled Delivery of Vancomycin via Charged Hydrogels, *PLoS One*, 2016, **11**(1), e0146401, DOI: 10.1371/journal.pone.0146401.

148 D. C. Roy, S. Tomblyn, D. M. Burmeister, N. L. Wrice, S. C. Becerra, L. R. Burnett, J. M. Saul and R. J. Christy, Ciprofloxacin-Loaded Keratin Hydrogels Prevent *Pseudomonas Aeruginosa* Infection and Support Healing in a Porcine Full-Thickness Excisional Wound, *Adv. Wound Care*, 2015, **4**(8), 457–468, DOI: 10.1089/wound.2014.0576.

149 D. Wang, J. Jin, C. Zhang, C. Ruan, Y. Qin, D. Li, M. Guan and P. Lei, Carbomer Hydrogel Composed of Cu2O and Hematoporphyrin Monomethyl Ether Promotes the Healing of Infected Wounds, *ACS Omega*, 2024, **9**(4), 4974–4985, DOI: 10.1021/acsomega.3c08718.

150 G. Wang, S. An, S. Huang, Alamgir, A. Wahab, Z. Ahmad, M. Suhail and M. Z. Iqbal, Fabrication, Optimization, and in Vitro Validation of Penicillin-Loaded Hydrogels for Controlled Drug Delivery, *J. Biomater. Sci., Polym. Ed.*, 2024, **35**(17), 2682–2702, DOI: 10.1080/09205063.2024.2387953.

151 B. Singh and A. Dhiman, Designing Bio-Mimetic Moxifloxacin Loaded Hydrogel Wound Dressing to

Improve Antioxidant and Pharmacology Properties, *RSC Adv.*, 2015, **5**(55), 44666–44678, DOI: 10.1039/C5RA06857F.

152 A. Zumbuehl, L. Ferreira, D. Kuhn, A. Astashkina, L. Long, Y. Yeo, T. Iaconis, M. Ghannoum, G. R. Fink, R. Langer and D. S. Kohane, Antifungal Hydrogels, *Proc. Natl. Acad. Sci. U. S. A.*, 2007, **104**(32), 12994–12998, DOI: 10.1073/pnas.0705250104.

153 W. Zhu, C. Guo, A. Yu, Y. Gao, F. Cao and G. Zhai, Microemulsion-Based Hydrogel Formulation of Penciclovir for Topical Delivery, *Int. J. Pharm.*, 2009, **378**(1–2), 152–158, DOI: 10.1016/j.ijpharm.2009.05.019.

154 S. Nakajima, K. Watashi, T. Kato, M. Muramatsu, T. Wakita, N. Tamura, S. Hattori, K. Maeda, H. Mitsuya, Y. Yasutake and T. Toyoda, Biochemical and Structural Properties of Entecavir-Resistant Hepatitis B Virus Polymerase with L180M/M204 V Mutations, *J. Virol.*, 2021, **95**(16), e02401–e02420, DOI: 10.1128/JVI.02401-20.

155 A. Sawdon and C.-A. Peng, Ring-Opening Polymerization of ε-Caprolactone Initiated by Ganciclovir (GCV) for the Preparation of GCV-Tagged Polymeric Micelles, *Molecules*, 2015, **20**(2), 2857–2867, DOI: 10.3390/molecules20022857.

156 X. Zhang, X. Kang, L. Ji, J. Bai, W. Liu and Z. Wang, Stimulation of Wound Healing Using Bioinspired Hydrogels with Basic Fibroblast Growth Factor (bFGF), *Int. J. Nanomed.*, 2018, **13**, 3897–3906, DOI: 10.2147/IJN.S168998.

157 M. J. Jang, S. K. Bae, Y. S. Jung, J. C. Kim, J. S. Kim, S. K. Park, J. S. Suh, S. J. Yi, S. H. Ahn and J. O. Lim, Enhanced Wound Healing Using a 3D Printed VEGF-Mimicking Peptide Incorporated Hydrogel Patch in a Pig Model, *Biomed. Mater.*, 2021, **16**(4), 045013, DOI: 10.1088/1748-605X/abf1a8.

158 J. Tavakoli and Y. Tang, Honey/PVA Hybrid Wound Dressings with Controlled Release of Antibiotics: Structural, Physico-Mechanical and *in vitro* Biomedical Studies, *Mater. Sci. Eng., C*, 2017, **77**, 318–325, DOI: 10.1016/j.msec.2017.03.272.

159 R. Gopal, A. Z. K. Lo, M. Masrol, C.-H. Lai, N. M. Zain and S. Saidin, Susceptibility of Stingless Bee, Giant Bee and Asian Bee Honeys Incorporated Cellulose Hydrogels in Treating Wound Infection, *Malays. J. Fundam. Appl. Sci.*, 2021, **17**(3), 242–252, DOI: 10.11113/mjfas.v17n3.2049.

160 R. F. El-Kased, R. I. Amer, D. Attia and M. M. Elmazar, Honey-Based Hydrogel: In Vitro and Comparative In Vivo Evaluation for Burn Wound Healing, *Sci. Rep.*, 2017, **7**(1), 9692, DOI: 10.1038/s41598-017-08771-8.

161 L. M. D. M. C. Ferreira, N. F. D. Cruz, D. G. Lynch, P. F. D. Costa, C. G. Salgado, J. O. C. Silva-Júnior, A. Rossi and R. M. Ribeiro-Costa, Hydrogel Containing Propolis: Physical Characterization and Evaluation of Biological Activities for Potential Use in the Treatment of Skin Lesions, *Pharmaceuticals*, 2024, **17**(10), 1400, DOI: 10.3390/ph17101400.

162 W. Chen, R. Chu, H. Li, T. Hua, H. Chen, R. Li, D. Zhou, S. Cao, S. Ye and H. Li, A Novel Wound Dressing Based on a Gold Nanoparticle Self-Assembled Hydrogel to Promote Wound Healing, *Mater. Adv.*, 2023, **4**(14), 2918–2925, DOI: 10.1039/D3MA00130J.

163 J. Xiao, S. Chen, J. Yi, H. F. Zhang and G. A. Ameer, A Cooperative Copper Metal–Organic Framework–Hydrogel System Improves Wound Healing in Diabetes, *Adv. Funct. Mater.*, 2017, **27**(1), 1604872, DOI: 10.1002/adfm.201604872.

164 C. M. Cleetus, F. Alvarez Primo, G. Fregoso, N. Lalitha Raveendran, J. C. Noveron, C. T. Spencer, C. V. Ramana and B. Joddar, Alginate Hydrogels with Embedded ZnO Nanoparticles for Wound Healing Therapy, *Int. J. Nanomed.*, 2020, **15**, 5097–5111, DOI: 10.2147/IJN.S255937.

165 S. J. Wolf, W. J. Melvin and K. Gallagher, Macrophage-Mediated Inflammation in Diabetic Wound Repair, *Semin. Cell Dev. Biol.*, 2021, **119**, 111–118, DOI: 10.1016/j.semcdb.2021.06.013.

166 C.-H. Kuan, L. Chang, C.-Y. Ho, C.-H. Tsai, Y.-C. Liu, W.-Y. Huang, Y.-N. Wang, W.-H. Wang and T.-W. Wang, Immunomodulatory Hydrogel Orchestrates Pro-Regenerative Response of Macrophages and Angiogenesis for Chronic Wound Healing, *Biomaterials*, 2025, **314**, 122848, DOI: 10.1016/j.biomaterials.2024.122848.

167 L. Deng, Z. Jian, T. Xu, F. Li, H. Deng, Y. Zhou, S. Lai, Z. Xu and L. Zhu, Macrophage Polarization: An Important Candidate Regulator for Lung Diseases, *Molecules*, 2023, **28**(5), 2379, DOI: 10.3390/molecules28052379.

168 J. He, J. Chen, T. Liu, F. Qin and W. Wei, Research Progress of Multifunctional Hydrogels in Promoting Wound Healing of Diabetes, *Int. J. Nanomed.*, 2025, **20**, 7549–7578, DOI: 10.2147/ijn.s519100.

169 T. Billiet, M. Vandenhaute, J. Schelfhout, S. Van Vlierberghe and P. Dubruel, A Review of Trends and Limitations in Hydrogel-Rapid Prototyping for Tissue Engineering, *Biomaterials*, 2012, **33**(26), 6020–6041, DOI: 10.1016/j.biomaterials.2012.04.050.

170 N. Yuan, L. Xu, B. Xu, J. Zhao and J. Rong, Chitosan Derivative-Based Self-Healable Hydrogels with Enhanced Mechanical Properties by High-Density Dynamic Ionic Interactions, *Carbohydr. Polym.*, 2018, **193**, 259–267, DOI: 10.1016/j.carbpol.2018.03.071.

171 A. P. Dhand, J. H. Galarraga and J. A. Burdick, Enhancing Biopolymer Hydrogel Functionality through Interpenetrating Networks, *Trends Biotechnol.*, 2021, **39**(5), 519–538, DOI: 10.1016/j.tibtech.2020.08.007.

172 D. Lou, Q. Pang, X. Pei, S. Dong, S. Li, W. Tan and L. Ma, Flexible Wound Healing System for Pro-Regeneration, Temperature Monitoring and Infection Early Warning, *Biosens. Bioelectron.*, 2020, **162**, 112275, DOI: 10.1016/j.bios.2020.112275.

173 D. Utami Nike, N. I. Md Fadilah, N. Sallehuddin, A. Y. H. Nor Azlan, F. H. Imran, M. Maarof and M. B. Fauzi, Genipin-Crosslinking Effects on Biomatrix Development for Cutaneous Wound Healing: A Concise Review, *Front. Bioeng. Biotechnol.*, 2022, **10**, 865014, DOI: 10.3389/fbioe.2022.865014.

© 2026 The Author(s). Published by the Royal Society of Chemistry

*RSC Appl. Polym.*, 2026, **4**, 53–82 | **81**

174 F. Acciaretti, S. Vesentini and L. Cipolla, Fabrication Strategies Towards Hydrogels for Biomedical Application: Chemical and Mechanical Insights, *Chem. – Asian J.*, 2022, **17**(22), e202200797, DOI: 10.1002/asia.202200797.

175 S. Almawash, S. K. Osman, G. Mustafa and M. A. El Hamd, Current and, Future Prospective of Injectable Hydrogels—Design Challenges and Limitations, *Pharmaceuticals*, 2022, **15**(3), 371, DOI: 10.3390/ph15030371.

176 T. Xiao, Z. Yan, S. Xiao and Y. Xia, Proinflammatory Cytokines Regulate Epidermal Stem Cells in Wound Epithelialization, *Stem Cell Res. Ther.*, 2020, **11**(1), 232, DOI: 10.1186/s13287-020-01755-y.

177 X. Li, X. Xu, M. Xu, Z. Geng, P. Ji and Y. Liu, Hydrogel Systems for Targeted Cancer Therapy, *Front. Bioeng. Biotechnol.*, 2023, **11**, 1140436, DOI: 10.3389/fbioe.2023.1140436.

178 I. M. El-Sherbiny and M. H. Yacoub, Hydrogel Scaffolds for Tissue Engineering: Progress and Challenges, *Global Cardiol. Sci. Pract.*, 2013, **2013**(3), 316–342, DOI: 10.5339/gcsp.2013.38.

179 M. Z. Quazi and N. Park, Nanohydrogels: Advanced Polymeric Nanomaterials in the Era of Nanotechnology for Robust Functionalization and Cumulative Applications, *Int. J. Mol. Sci.*, 2022, **23**(4), 1943, DOI: 10.3390/ijms23041943.

180 X. Gan, X. Wang, Y. Huang, G. Li and H. Kang, Applications of Hydrogels in Osteoarthritis Treatment, *Biomedicines*, 2024, **12**(4), 923, DOI: 10.3390/biomedicines12040923.

181 S. Gan, Y. Wu, X. Zhang, Z. Zheng, M. Zhang, L. Long, J. Liao and W. Chen, Recent Advances in Hydrogel-Based Phototherapy for Tumor Treatment, *Gels*, 2023, **9**(4), 286, DOI: 10.3390/gels9040286.

182 Y. Ren, Q. He, T. Xu, W. Zhang, Z. Peng and B. Meng, Recent Progress in MXene Hydrogel for Wearable Electronics, *Biosensors*, 2023, **13**(5), 495, DOI: 10.3390/bios13050495.

183 S. Adepu and S. Ramakrishna, Controlled Drug Delivery Systems: Current Status and Future Directions, *Molecules*, 2021, **26**(19), 5905, DOI: 10.3390/molecules26195905.

184 Y. Cheng and Y. Lu, Physical Stimuli-Responsive Polymeric Patches for Healthcare, *Bioact. Mater.*, 2025, **43**, 342–375, DOI: 10.1016/j.bioactmat.2024.08.025.