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Advances in Smart Hydrogels for the Management of Diabetic Wound

[1]Madhuchandra Lahan*, [1]Taslima Nasrin Hussain, [1]Tanish Chowdhury, [1]Ronisha Syrti, [1]Rovilhoukho Khale, [1]Jitakshara Das, [1] Anil Kumar Adimulapu

1 School of Pharmacy, The Assam Kaziranga University, Jorhat, Assam, India.

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ABSTRACT:

Diabetic wounds pose a serious problem for healthcare systems around the world due to their prolonged healing process, high infection risk, and potential complications, including chronic wounds and lower limb amputations. Conventional wound care strategies often fail to provide optimal healing due to the complex pathophysiology of diabetic wounds. Hydrogels, particularly smart hydrogels, have shown promise as biomaterials in diabetic wound management because of their capacity to provide a moist environment, enhance tissue regeneration, and enable controlled drug release. Smart hydrogels are networks of three-dimensional polymers that may respond to internal and external stimuli, allowing for targeted and sustained drug delivery. These hydrogels exhibit sensitivity to various physiological and environmental factors, including pH, temperature, redox conditions, biomolecules, and external stimuli such as light and electric fields. Smart hydrogels also help mitigate oxidative stress and promote cell proliferation, contributing to effective wound healing in diabetic patients. Advances in hydrogel technology have further improved their functionality, making them adaptable for use as wound dressings, scaffolds for tissue regeneration, and drug delivery platforms.

This review explores the latest advancements in smart hydrogels, their mechanisms of action, and the applications in diabetic wound treatment. Special attention is given to stimuli-responsive hydrogels that adapt to the wound microenvironment, promoting efficient healing while minimizing adverse effects. With their ability to enhance drug bioavailability, improve patient adherence, and facilitate personalized treatment strategies, smart hydrogels represent a transformative approach in diabetic wound care. Further investigation and clinical studies are essential for optimize their performance and expand their clinical applications for better patient outcomes.

1. Introduction

A wound is a break or disruption in the integrity of the skin, mucous membrane, or deeper tissues caused by physical, chemical, or biological factors. It can vary in severity and healing time depending on its type and underlying factors [1]. Wound healing in healthy people is often a dynamic and well-organized skin repair process that may be broken down in four different and overlapping phases i.e. hemostasis, inflammation, proliferation and remodeling [2-4]. Wound healing begins with haemostasis, a process where tissue ruptures and blood enters the wound. Vasoconstriction prevents bleeding. Inflammation follows, with leukocyte migration and the entry of neutrophils and macrophages. Neutrophils are activated and transported to the wound, staying for two to five days [5, 6]. Proliferation reduces injured tissue area through angiogenesis and fibroplasia, creating an efficient epithelial screen for wound healing, starting within 48 hours and lasting until 14 days post-injury [7]. The dermis breaks down extra collagen fibres during wound remodelling, resulting in maximum mechanical strength and retaining 80 percent of the initial wound's strength in the final scar [2, 8, 9].

Diabetes mellitus is one metabolic disease that interferes with the natural healing process of wounds. Diabetes poses significant risks, leading to severe

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complications such as impaired healing of wound, cardiovascular diseases, nerve damage, eye disorders and lower limb amputations caused by foot ulcers. Globally, about 20% of diabetic patients experience challenges with delayed wound healing [10]. Over 50% of diabetic wounds turn into chronic wounds, which raise the risk of mortality and disability [11]. Diabetic wounds' aberrant immune cell composition makes it challenging to reduce inflammation and significantly raises the risk of infection. Increased inflammation will continue when a chronic wound becomes infected, prolonging the cycle of infection, inflammation, and insufficient healing (Fig. 1). Studies have also revealed that a redox imbalance brought on by high oxidative stress and reduced antioxidant capacity is a major contributing factor to inability of diabetic wounds healing [12]. Diabetes can hinder the healing of wounds in a number of ways and phases. Firstly, hyperglycemia brought on by diabetes causes blood levels of advanced glycation end products (AGEs) to rise. High quantities of reactive oxygen species (ROS) and reactive nitrogen species (RNS) are directly caused by AGEs. When ROS/RNS levels surpass tissue's antioxidant capability, the host tissue is harmed and inflammation is prolonged [11]. In a nutshell the healing of diabetic wounds has grown to be a major challenge in global healthcare systems.

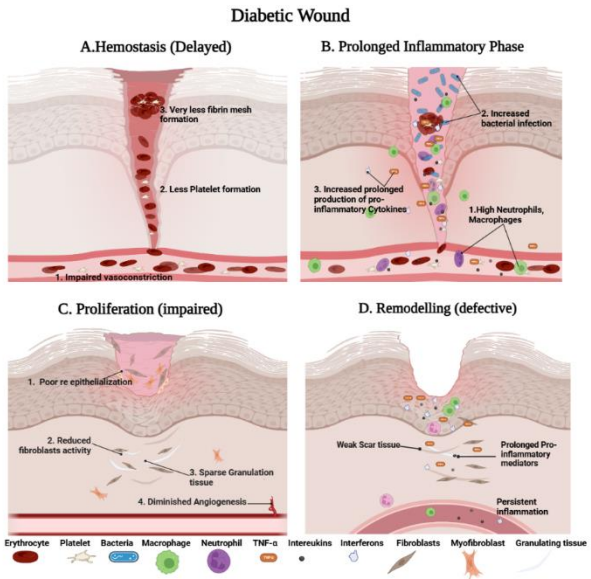

Fig. 1: Impaired wound healing in diabetic mellitus

Conventional wound care strategies often fail to provide optimal healing. Hydrogels and smart hydrogels have become a viable option for managing diabetic wounds, because they can create a moist environment, controlled drug release, and responsiveness to physiological conditions. This review discusses various types of smart hydrogels, their mechanisms, applications, and recent advancements in diabetic wound care. Although a variety of stimuli can cause reactions in smart hydrogels, the most often used stimuli—such as temperature, light pH, redox, and biomolecules in drug delivery systems—are the main emphasis of this review.

2. Hydrogels and Smart hydrogels:

Hydrogels are hydrophilic polymers crosslinked to high molar mass networks, able to hold and absorb significant amounts of water. Hydrogels are water-absorbing networks of hydrophilic polymers which can hold water up to hundreds of times their dry weight, with a 10% arbitrary lower limit [13]. Hydrogels, with their high water content, can deliver small molecules, proteins, elastin, and stem cells, and serve as scaffolds for tissue engineering, making their development a highly researched topic [14]. The hydrophilic functional groups like –OH, –COOH, –NH2, SO3H, etc. are responsible for hydrogels to absorb large quantity of water [15]. Hydrogel polymer chains are crosslinked chemically or physically to maintain their three-dimensional architectures [16]. Hydrogels offer several advantages, including a high degree of elasticity comparable to natural tissues, making them ideal for biomedical applications. Hydrogels can bypass first-pass metabolism, provide longer-lasting and sustained action compared to traditional drug delivery methods, enhance drug utilization, improve patient adherence, and can be directed to specific areas, such as the colon [17]. Another one advantage of hydrogel is, depending on the needs, hydrogels can be molded into any size, shape, or architecture or produced into thin films [15].

“Smart hydrogels” are intelligent, three-dimensional hydrophilic polymer structures that can detect and respond to changes in their physical or chemical conduct, allowing controlled drug delivery. Smart hydrogels are three-dimensional structures that display volume or stage progress due to external natural changes. They are sensitive to the surrounding situation, such as the swelling proportion. Structural changes in smart polymers can be triggered by chemical, biological, and physical stimuli. These changes can be artificially controlled or naturally encouraged by the body's internal

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environment, resulting in changes in the polymer net [18]. When exposed to external stimuli like magnetic force, exposure to radiation, acoustic force, and an electric field, as well as endogenous stimuli (made by organisms) like temperature, pH, glucose, enzymes, and redox, the characteristics of stimuli-responsive hydrogels alter. The physical or chemical characteristics of these gels can change either irreversibly or reversibly in response to stimuli (Fig. 2), allowing for a highly controlled drug-release pattern [19].

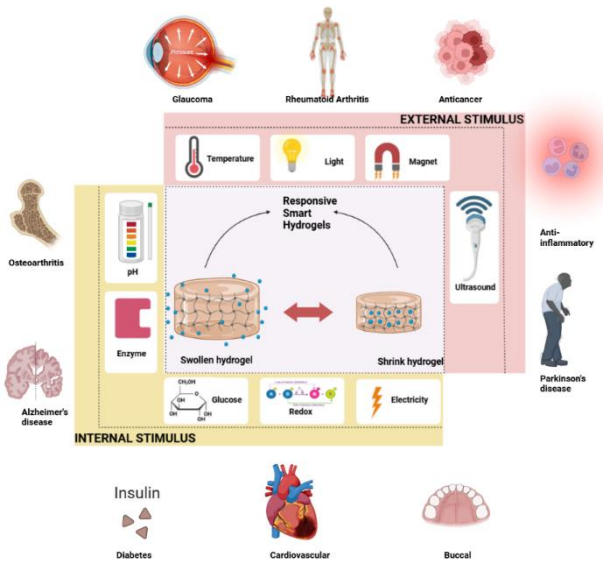

Fig. 2: Application of smart responsive hydrogels

Smart hydrogels offer significant benefits in DDSs. When they respond to various stimuli, the effectiveness of drugs is increased and adverse effects are decreased. Additionally, they make it possible for precise drug release over time, which lessens the need for regular dosage. This demonstrates how smart hydrogels have the ability to completely transform targeted medication delivery by increasing effectiveness, reducing adverse effects, and facilitating individualized therapies [19-21].

3. Application of smart hydrogels in diabetic wound treatment:

Smart responsive hydrogels are being designed to report the limitations of clinical diabetic wound dressings by responding to particular diabetic wound conditions (e.g., high ROS and glucose, low pH, and some overexpressed enzymes) or external stimuli (e.g., temperature and light). These hydrogels enable controlled, on-demand drug release, enhancing the harsh microenvironment of diabetic wounds and avoiding high-dose antibiotic resistance [22, 23]. This summary categorizes the uses of smart responsive hydrogels according to particular stimulation settings, which have demonstrated encouraging results in aiding diabetic wound healing.

3.1 pH-Responsive Hydrogels (PRHs):

Normal skin has a slightly acidic pH (4–6) because keratinocytes release fatty acids and amino acids. In contrast, chronic wounds continue to be alkaline (pH 7–9), promoting pathogenic microorganism growth and increasing susceptibility to bacterial infections [24]. Thus, pathological conditions often associated with significant pH shifts can facilitate targeted drug delivery systems (DDSs) through stimulus-responsive techniques. The development of a wound infection leads to a change in pH, which offers a chance to create a responsive drug carrier with on-demand release capabilities [25]. When bacteria proliferate and break down infected wounds, they release lactic and acetic acids, which causes local acidification (pH 4.5–6.5). Thus, PRHs release drugs as required to reduce side effects and increase the likelihood of treatment effectiveness [26].

pH-Responsive Hydrogels (PRHs) are high molecular weight polymers that undergo phase or volume transitions based on external pH changes. Composed of polyelectrolytes with weak acidic or basic functional groups, PRHs shrink or swell due to ionization within their polymeric network, affecting water uptake or loss[27]. Classified as cationic (–NH2) or anionic (–COOH), their swelling behaviour depends on the medium's pH, influencing solvent-polymer interactions at specific pKa and pKb values. These properties make PRHs highly effective for pH-responsive DDS [28]. In order to administer medication to diabetic wounds, Wang et al. created a pH-responsive calcium alginate (CaAlg) hydrogel that was loaded with hyaluronan oligosaccharides (HAO) and protamine nanoparticles (NPs). The hydrogel swells more at higher pH due to ionization of carboxylic groups, enhancing drug release. At pH 8.0, it releases 98.7% of HAO within 8 hours, with a 2.2 times higher release rate than at pH 3.0,

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demonstrating its potential for targeted drug delivery [29]. Li et al. created a pH-responsive, injectable, self-healing hydrogel [30] using using N-carboxyethyl chitosan, hyaluronic acid–aldehyde, and adipic acid dihydrazide. Loaded with insulin glargine, it sustained pH-responsive release for 14 days while preserving insulin's bioactivity. In diabetic rats, it enhanced DFU recovery through granulation promotion, deposition of collagen, re-epithelialization, neovascularization, and improving peripheral neuropathy, making it a promising bioactive dressing.

3.2 Temperature responsive hydrogel:

Temperature is one typical external stimulant for drug delivery systems that are sensitive to the environment. The release of active substances in pharmaceuticals in a variety of thermosensitive drug delivery devices can be triggered by human physiological temperature, which is normally greater than room temperature [31, 32]. The chains of temperature-responsive hydrogels (TRHs) contain hydrophobic groups including methyl, ethyl and propyl groups, and can alter their form, size, and volume in reaction to the body's natural temperature variations. The most commonly utilized TRHs undergo a sol-to-gel transition when exposed to body temperature; and are liquid or semi-solid at room temperature. This feature makes it possible to load a medicinal substance onto the hydrogel in a liquid condition so that it can be applied and conveniently administered before solidifying [21]. The gel phase keeps its integrity and is non-flowing, whereas the sol phase flows. Thermo-sensitive hydrogels are classified as either negative or positive, depending on their critical solution temperatures. Negative thermo-sensitive hydrogels show lower critical solution temperature (LCST) and become hydrophobic and insoluble as the temperature rises above this point, leading to hydrogel shrinkage and gel formation. Conversely, positive thermo-sensitive hydrogels show upper critical solution temperature (UCST), and gel formation is triggered when the solution is cooled below the UCST. Near to the critical temperature, these polymers undergo a phase transition from soluble random coil to insoluble, collapsed form. For negative thermo-sensitive hydrogels with LCST near physiological temperature, this sol-to-gel transition can occur in situ, making them ideal for controlled drug release and enhancing local drug penetration [19, 21].

Temperature-sensitive hydrogels, developed from natural and synthetic polymers, have gained significant biomedical applications. Within a certain range, these thermosensitive hydrogels change from liquid to gel at higher temperatures and back to liquid at lower ones. Their ability to change phase at physiological temperatures makes them ideal for managing diabetic wounds [19]. The phase transition temperature of thermos sensitive hydrogels can be modified by adjusting the polymer's chemical composition, concentration of anionic monomers, or the ratio of hydrophilic to hydrophobic groups in the gel [33]. Free radical polymerization is a typical method for creating temperature-sensitive hydrogels. Monomers like N-isopropylacrylamide (NIPAM) and cross-linkers like methylene bisacrylamide (MBA) or poly(ethylene glycol) diacrylate (PEGDA) are used [19]. Chen et al. developed self-healing, temperature-responsive hydrogel patches using NAGA-VTZ hybrid polymers with PNIPAM hydrogels as fillers. In a simulated chronic wound environment at 37°C, the patch shrank, shifting color from red to green, enabling infection monitoring. Drug release was faster at 37°C due to PNIPAM exceeding its VPTT. With temperature-responsive and color-sensitive properties, this hydrogel patch holds promise for wound management and clinical applications [34].

3.3 Light responsive hydrogel:

An external stimulus such as light can facilitate the release of drugs from hydrogels and has several benefits, including low cost, easy wavelength and intensity tuning, and a broad variety of chemistries for designing Light responsive hydrogel (LRHs). Typically, LRHs are made up of particular chemical components known as chromophores [21]. LRHs undergo volume changes when exposed to light, driven by photothermal excitation or reversible cross-linking. Integrating photoactive moieties into the hydrogel matrix enables these actuation mechanisms, making light a useful remote stimulus for hydrogel activation [35]. In general, tumor-localizing photosensitizers will be stimulated to their higher excited state by light at a particular wavelength. A single excited photosensitizer must undergo intersystem crossing and transform into a triplet excited photosensitizer, in order to initiate type 1 and type 2 reactions of PDT and produce free radicals and singlet oxygen, respectively. The two types of reactions

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have somewhat distinct processes, but their oxidized products are almost equally deadly to tumor cells [36].

Huang et al. [37] prepared a multifunctional hydrogel with antibacterial and pro-angiogenic efficacy under near-infrared (NIR) stimulation. The prepared bilayer hydrogel consisted of a thermoresponsive poly (N isopropylacrylamide)/gelatin methacrylate and alginate/polyacrylamide in the two layers, each containing peptide-functionalized gold nanorod. The lower layer provided antibacterial effects, enhanced by NIR-induced photothermal transition. The lower layer's contraction promoted early-stage cargo release, while pro-angiogenic upper layer accelerated fibroblast and endothelial cell activity for angiogenesis and collagen deposition. Recently, Zhao et al., [38] developed an NIR-responsive methacrylated gelatin hydrogel incorporating N-isopropylacrylamide and polydopamine nanoparticles for thermosensitive, photothermal properties. Loaded with linagliptin (LIN), it enables NIR-controlled drug release, promoting EMT activation, angiogenesis, and wound contraction. In a skin defect model, NIR irradiation significantly enhanced wound closure, demonstrating its potential for diabetic wound healing.

3.4 Electro responsive hydrogels:

Electrosensitive hydrogels (ERHs) are a class of highly hydrated, electroactive hydrogels that exhibit swelling or shrinkage in response to an electrical input. Under electrical stimulation, the behaviour of drug release from ERHs can be regulated by three opposing forces: ionic pressure, rubber elasticity, and polymer affinity. When the equilibrium of these forces is upset, ERHs experience swelling and de-swelling [39]. The ion concentration profile varies as a result of the ions' mobility in response to an external electric field and their rearrangement, which in turn causes changes in the conformational and mechanical characteristics of the hydrogel network. When an electric field is applied, free ions in the hydrogel flow in one direction, resulting in a charge density differential both inside and outside the hydrogel. This osmotic pressure difference causes the hydrogel to change conformation [35, 40]. A hydrogel responds to an electrical input by expanding or contracting in a manner remarkably similar to the mechanism controlling pH-sensitive hydrogels. The electric field in the electrical stimulations drives mobile ions across the hydrogel and solution to control the ion gradient of concentration. Therefore, when an electric field is introduced, the electrosensitive hydrogels may shrink or swell. Examples of natural polymers used in ERHs include hyaluronic acid, alginate, and chitosan; whereas synthetic polymer examples include polyvinyl alcohol, polythiophene, sulfonated styrene, polyaniline, polypyrrole etc. [41].

3.5 Enzyme-Responsive Hydrogels:

Enzymes are essential biocatalysts in various biological and chemical processes. They are specific and selective, requiring moderate conditions. These reactions are rare in aqua media, low temperatures, and slightly acidic, neutral, and alkaline pHs, making them suitable for biomedical applications. Over the past five years, attention has mostly been concentrated on protease- and glycosidase-responsive polymer hydrogels. Enzyme-responsive hydrogels are intelligent materials that undergo macroscopic transitions due to selective enzyme catalysis [42]. One way to achieve controlled therapeutic release is to engineer the hydrogel matrix so that it breaks down in response to particular enzymes. Another method uses enzymatically sensitive cross bonds to covalently attach medicines to the hydrogel scaffold [19]. Liu et al. encapsulated self-assembled curcumin nanoparticles in gelatin, forming a dual-response hydrogel dressing with temperature-sensitive F127. This system enhances curcumin release in response to MMP-9 overexpression, promoting diabetic wound healing. However, mechanical properties, hydrophilicity, and pH variations may affect enzyme penetration and clinical efficacy [43].

3.6 Glucose-Responsive Hydrogels:

Glucose responsive hydrogels (GRHs) drawn interest in the administration of medications to treat chronic inflammation brought on by diabetes. In diabetes, elevated glucose levels accelerates inflammation and hinders tissue regeneration [44, 45]. Diabetic ulcers, a type of chronic wound, suffer from poor blood flow (vasoconstriction) and limited oxygen supply due to high glucose, impairing healing. Additionally, the high glucose levels can worsen bacterial infections. Thus, regulating glucose levels at the wound site is crucial for designing hydrogels that promote effective healing of diabetic ulcers. A method for automatically delivering insulin that responds to blood glucose levels has been developed recently using GRHs. The main process by which GRHs release their

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contents is glucose diffusion into the membrane, where it is transformed into gluconic acid. This procedure results in swelling and a decrease in the hydrogel's pH, and then release insulin [21, 44]. Designs that sense glucose levels in the environment, including as phenylboronic acid, glucose oxidase, and concanavalin A, can be used to construct glucose-responsive carriers. By adding these structures to hydrogels, controlled insulin release is made possible, which lowers the risk of hypoglycemia and helps control blood sugar. PBA interacts with the ortho-diol group of glucose and, upon ionization, generates a more hydrophilic structure that facilitates drug release. Further enhancing glucose-responsive medication delivery are hydrogels improved with GOx and PBA grafted onto poly(ethylene glycol) succinate–benzald [46, 47].

Yang et al. [45] developed a functionalized hydrogel combining zinc ions, organic ligands, and deferoxamine mesylate (DFO) with glucose oxidase (GOX). Upon injection into diabetic wounds, GOX decomposed glucose into hydrogen peroxide and glucuronic acid, lowering pH and triggering zinc ion and DFO release, enhancing antibacterial activity and angiogenesis. Similarly, a glucose-responsive antioxidant hydrogel (GMPE) was synthesized using GelMA-CPBA and EGCG. It exhibited biocompatibility, biodegradability, and skin-like mechanical properties. In vitro as well as in vivo studies showed reduced ROS, inflammation, and enhanced angiogenesis, collagen deposition, and tissue remodeling, presenting a promising treatment for chronic diabetic wounds [48].

3.7 Redox-Responsive Hydrogel:

Redox-responsive hydrogels have the ability to release drug encapsulations at the target region quickly in response to particular biological redox stimuli. Certain chemical moieties are added to the hydrogel to enable its redox-responsive activity. The disulfide linker is one such chemical moiety that can be broken down when reducing agents such as glutathione are present. The selenide group is an additional often utilized chemical moiety that exhibits reactivity towards reactive oxygen species including hydrogen peroxide. Excess ROS acquired in wounds can limit angiogenesis and impair wound tissue regeneration in addition to triggering significant inflammatory reactions [23]. Typically, thiol groups and borate ester linkages serve as the foundation for the construction of ROS-responsive hydrogels. The idea behind ROS-responsive hydrogel design is that catechol groups have the ability to scavenge excess ROS and reduce the duration of the inflammatory phase [49].

4. Recent Advances and Future Prospects:

Recent advances in hydrogels focus on multifunctional systems for improved biomedical applications. Self-healing hydrogels restore interactions autonomously, enhancing durability and reusability in long-term wound care [50]. Polymer-based hydrogels, composed of hydrophilic crosslinked polymers, absorb and retain large amounts of fluids while maintaining a 3D structure, making them perfect for wound healing, tissue engineering, and drugs delivery. Their significant amount of water content and soft consistency closely mimic natural tissues [51, 52]. Various drugs have shown significant efficacy in promoting wound healing (Table 1). However, a major challenge is the weak mechanical strength of hydrogels, especially in tissue engineering applications requiring high elasticity, durability, and tensile strength. Nanocomposite hydrogels address this issue by incorporating nanoparticles, improving mechanical and chemical properties while maintaining bioactivity [53]. The nanoscale drug delivery system has been designed as an ideal carrier to overcome existing limitations. Research continues to enhance these hydrogels for biomedical applications, focusing on optimizing strength, elasticity, and responsiveness to cellular microenvironments.

Table 1: Drugs loaded in hydrogels to enhanced diabetic wound healing

Drugs	Type of hydrogel	Function	Reference
Insulin	ph responsive	Enhance wound healing by promoting neovascularization and collagen deposition.	[54]
Metformin	Glucose responsive hydrogel	Reduce proinflammatory cytokines, improve inflammation and edema, and enhance epidermal regeneration and fibroblast proliferation.	[54]

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Curcumin	Temperature responsive hydrogels and pH responsive hydrogels	Enhance angiogenesis and collagen deposition while reducing inflammation and oxidative stress.	[55]
Quercetin	Topical hydrogel	Accelerated re-epithelialization and granulation in diabetic wounds by elevating GFs, antioxidants, and oxygen levels at the site.	[56]
Cephradine	Nanocomposite hydrogel	Promote rapid chronic wound healing with effective bacterial clearance.	[57]
Pioglitazone	Fibrous mats	Enhanced epidermal regeneration and fibroblast proliferation with reduced inflammation, edema, and neutrophil infiltration.	[58]
Berberine	Nano-colloids hydrogel	Promote wound healing, inhibit NF-κB, TNF-alpha	[59]
Curcumin and Metformin	Nanocomposite polysaccharide-based self-healing hydrogels	Promoting re-epithelialization, granulation, collagen formation, angiogenesis, and wound contraction.	[60]
Vancomycin-conjugated silver nanoclusters and and Nimesulide	pH and reactive oxygen species hydrogel	Sequential hemostatic, antibacterial, and anti-inflammatory processes.	[61]
Deferoxamine with silver nitrate	Injectable self-healing hydrogel	boost angiogenesis, and accelerate diabetic wound healing by regeneration of skin wounds	[62]
Metformin, ascorbic acid and L-arginine	Self-adaptive hydrogel	Enhance angiogenesis, reduce inflammation, and mitigate oxidative stress to improve the wound microenvironment.	[63]
Insulin and fibroblasts	Injectable hydrogels	promote neovascularization and deposition of collagen	[64]
Metformin	pH and glucose dual responsive hydrogels	reduced inflammation and enhanced angiogenesis	[65]
Resveratrol	Nano composite hydrogel	reduced TNF-α and iNOS, increased TGF-β1 and Arg-1, enhanced angiogenesis, and accelerated wound healing.	[66]
Metformin and Tetracycline	Injectable pH and glucose responsive hydrogels	Accelerate wound healing by continuous release of both the drugs	[67]
Gallic acid	Microneedle patch	Promote antioxidation by scavenging ROS	[68]

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5. Conclusion:

Smart hydrogels present a promising approach for diabetic wound management by integrating drug delivery, infection control, and tissue regeneration. Their ability to respond to physiological conditions enhances wound healing efficiency. However, they have yet to reach the clinical stage due to several challenges. The complicated diabetic wound microenvironment including low pH, hyperglycemia, high reactive oxygen species, overexpressed enzymes, and inflammatory factors delays wound healing and increases the risk of infection. Recently, stimulus-responsive hydrogels have been developed to respond to changes in pH, glucose, ROS, enzymes, or temperature at the wound site, enabling controlled and sequential drug release. Beyond drug delivery, these hydrogels help improve the harsh wound environment, accelerating healing and demonstrating great potential for clinical application. However, fluctuations in glucose, pH, ROS, and enzyme activity at the wound site may impact their intelligent drug release behaviour. To advance smart hydrogels toward clinical translation, it is crucial to rigorously evaluate how these fluctuating factors affect drug release behaviour, particularly in multifunctional, responsive hydrogels. Ongoing research in nanotechnology, biomaterials, and bioengineering will further refine their capabilities, bringing them closer to clinical application.

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