

INNOVATIVE HYDROGEL-BASED STRATEGIES FOR DIABETIC FOOT ULCER MANAGEMENT

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ABSTRACT

Diabetic foot ulcers (DFUs) are complex wounds caused by diabetic complications like neuropathy, ischemia, oxidative stress, and infection. Conventional treatments are ineffective due to tissue penetration issues, biofilm resistance, and minimal healing capacity. Hydrogels are becoming useful supportive wound dressings in DFU therapy as they can maintain moisture and are biocompatible. But traditional hydrogels such as Intrasite™, Silvercel™, and Aquacel® Ag+ provide mostly passive benefits and do not have structural integrity, durability, or active drug delivery. Therefore, self-healing hydrogels are a new generation of intelligent biomaterials. They will recover their structure with dynamic chemical bonds and respond to changes in the environment through the release of therapeutic agents. These hydrogels may be filled with natural, synthetic and biological materials in order to minimize infection, modulate inflammation, and stimulate angiogenesis. Preclinical data demonstrate that self-healing hydrogels enhance tissue healing and infection control. Their clinical application remains restricted because of scalability and regulatory issues. Looking ahead, the integration of bioactive hydrogels with AI-based smart monitoring systems has tremendous potential to enable personalized, adaptive DFU treatment, promising next-generation wound therapy.

INTRODUCTION

Diabetes mellitus is a lifelong metabolic disease characterized by prolonged hyperglycemia resulting from insufficient insulin secretion or insulin resistance. It often causes serious complications such as peripheral neuropathy and peripheral arterial disease, and greatly elevates the danger of foot complications such as diabetic foot ulcers (DFUs). 15–25% of diabetic individuals develop DFUs during the course of their life, and DFUs cause more than 50% of diabetic admissions and

approximately 85% of lower-limb amputations (1-4). DFUs are typically open ulcers over areas of pressure over the feet, caused mainly by neuropathy, which dulls sensation, and peripheral artery disease, which impairs blood supply and healing. DFUs are neuropathic, ischemic, or neuro-ischemic, being the most frequent and challenging to treat. Chronic DFUs occur when recurrent trauma, foot deformity, immunosuppression, and infection are allowed to occur, usually resulting in gangrene and amputation. Traditional

methods (e.g. debridement, pressure offloading, dressing) fail to achieve the desirable results, because of the presence of chronic inflammation, oxidative stress and abnormal angiogenesis (5).

Hydrogels are three-dimensional polymeric networks that are capable of absorbing water and containing a high amount of water, these offer an ideal moist environment that is conducive to cell behaviour and tissue regeneration. Hydrogels can be classified based on origin into natural hydrogels (e.g., alginate, chitosan, gelatin), synthetic hydrogels (e.g., polyethylene glycol, polyvinyl alcohol), and hybrid hydrogels that include both to attain higher mechanical and biological performance. Hydrogels are physically cross-linked (reversible) or chemically cross-linked (permanent) and hence their structural rigidity and responsiveness are predicted. Self-healing hydrogels are a new class with dynamic and reversible interactions such as hydrogen bonding, Schiff-base reaction, disulfide linkages, and host guest interactions, which allow the material to heal its structure upon mechanical damage. This self-repairing ability is particularly valuable for DFUs, which often occur in highly mobile regions like sole of the foot. Self-healing hydrogels can be formulated as smart drug delivery systems loaded with antibiotics, growth factors, or anti-inflammatory drugs to cure infection, stimulate angiogenesis, and enhance healing. They were reported with benefits of water retention, biocompatibility, injectability, tuning of mechanical properties, and global antimicrobial killing efficacy. Furthermore, these materials can form fit to the contour of wounds and form an impermeable barrier which improves the therapeutic and comfort benefits for the patients. In this

review, we present recent progress and therapeutic prospects for self-healing hydrogels in diabetic foot ulcers healing, with emphasis on the design, bioactivity, and clinical potential of these materials (6,7).

PATHOGENESIS AND COMPLICATIONS OF DFUs

Diabetic foot ulcers (DFUs) result from a multifactorial interaction between neuropathy, peripheral arterial disease (PAD), chronic inflammation, oxidative stress, and infection, typically ending in gangrene and amputation. Oxidative damage and mitochondrial dysfunction due to hyperglycaemia lead to peripheral neuropathy, with loss of sensation, and injuries go undetected. At the same time, PAD decreases the supply of blood and oxygen which contributes to the deterioration of the healing process as well. In chronic diabetic wounds, long-standing high levels of pro-inflammatory cytokines (e.g., TNF α , IL-1 β) and matrix metalloproteinase (MMPs) keep the wound in an inflammatory state, which also prevents the formation of granulation tissue. Hyperglycaemia also impairs immune function, promoting microbial colonization and biofilm formation that foster infection, a phenomenon that is not easily treated by routine therapies. Such pathologic processes typically proceed to necrosis and require surgical amputation. In India, research identifies DFUs in over 20% of diabetic hospitalizations, with barefoot walking, delayed presentation, and poor foot care as significant causative factors.

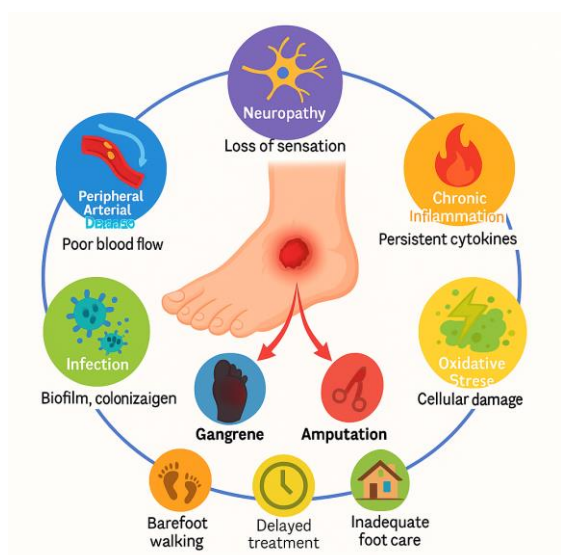


Fig (1): Complications of diabetic foot ulcers

HYDROGEL-BASED STRATEGIES FOR DIABETIC FOOT ULCER TREATMENT

Hydrogels are biocompatible and water-inflated polymer structures having a variety of utilization in diabetes management for glucose monitoring, drug or insulin release, wound curing, cell transplantation. These characteristics of conformability, controlled drug delivery, and maintenance of moisture make them suitable for diabetic foot ulcer care, where a moist setting is favorable to faster healing, with lesser chances of infection. Integration with wearable biosensors offers real-time, remote glucose and wound biomarker monitoring, enhancing patient monitoring. But conventional hydrogels are mechanically fragile, dehydrating, and less active under dynamic conditions such as pressure-sensitive DFU wounds. Due to these limitations, dynamic bond-mediated self-healing hydrogels have also been formulated to promote self-healing properties and sustained performance.

These hydrogels are usually injectable, elastic and adhesive and are ideally rendered on the irregular or mobile wound sites. Most of them are stimuli-sensitive and release the drug as required on pH, glucose, or temperature stimuli. Others incorporate flavonoids or plant extracts to trigger angiogenesis, anti-inflammatory responses, and regeneration. Overall, self-healing hydrogels offer multifunctional long-term solutions for DFU treatment and are a giant leap towards personalized wound therapy (8-11).

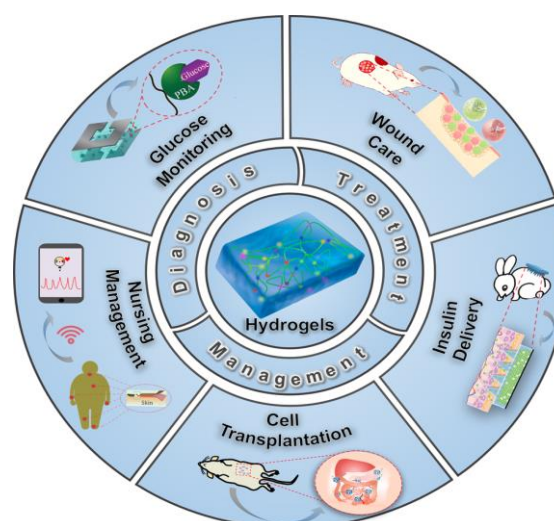


Fig (2): Hydrogels and its role

SELF-HEALING HYDROGELS CLASSIFICATION AND MECHANISM

Self-healing hydrogels are three-dimensional, water-swollen polymeric networks possessing the ability to mimic natural tissue environments and heal autonomously to their native state in case of injury. Biomaterials belonging to this category are generally classified as natural, synthetic, and hybrid types. Commonly, natural hydrogels, the likes of chitosan, guar gum, and alginate, are widely used for diabetic foot ulcers (DFUs) due to their low toxicity, biodegradability, biocompatibility

and having good inherent antimicrobial or anti-inflammatory properties. Polymer based artificial hydrogels like polyethylene glycol (PEG), polyvinyl alcohol (PVA), and polyurethanes gain mechanical strength, reproducibility and controlled architecture. Hybrid hydrogels balance the bioactivity of natural polymers with the physically modifiable character of synthetic polymers, offering greater healing synergy in DFUs. Mechanical responsiveness and performance of hydrogels are controlled by the type of crosslinking. Physically cross-linked hydrogels employ reversible interactions (e.g., hydrogen bonding, ionic interactions), imparting injectability and shear sensitivity, optimally suited for rugged wound surface. Chemically cross-linked hydrogels employ stable covalent bonds, imparting increased structural stability and extended degradation profiles, optimally suited for sustained drug release. Self-healing character in such hydrogels is composed of dynamic covalent bonds e.g. Schiff base reaction, disulfide bonds, and borate diol complexation and non-covalent interactions, e.g., hydrogen bonding, metal coordination, and host–guest recognition. These reversible mechanisms allow the hydrogel to heal from mechanical stress, an essential requirement in DFUs on highly mobile regions of the foot such as the

plantar surface. Furthermore, stimuli-responsive self-healing hydrogels, which are pH, ROS, or glucose responsive, can modulate healing adaptively in accordance with the wound microenvironment. Critically, new self-healing hydrogels do not only offer water retention and biocompatibility but also act as smart drug delivery systems, enabling sustained, localized delivery of antimicrobials, growth factors, or antioxidants. Such multi-functionality is important in the treatment of chronic inflammation, infection, and inhibited angiogenesis in DFUs (12-15).

ROLE OF BIOACTIVE APIS IN PROMOTING WOUND HEALING THROUGH HYDROGEL-BASED DELIVERY

Various active agents like Natural, synthetic and biological molecules are embedded in self-healing hydrogels to heal diabetic foot ulcers (DFUs). The APIs accelerate healing by inhibiting microbial infection, inhibiting inflammatory cytokines, inducing the growth of blood vessels, and guiding tissue regeneration. Self-healing hydrogels facilitate stimulus-responsive, local, and prolonged delivery of these agents based on wound-specific stimuli such as pH, ROS, or enzymatic stimuli (16-19).

Table 1: Key natural, synthetic, and biological APIs in self-healing hydrogels mechanisms and hydrogel integration for DFU therapy

API / Source	Class / Key Phytochemicals / Type	Extraction Method*	Mechanism of Action / Therapeutic Effect	Hydrogel Role

Curcumin (<i>Curcuma longa</i>)	Curcumin (polyphenol)	Soxhlet with ethanol	Antioxidant, inhibits NF- κ B, $\downarrow$ TNF- α $\rightarrow$ anti-inflammatory	ROS-responsive release
Berberine (<i>Berberis aristata</i>)	Berberine alkaloid	Ethanol / aqueous maceration	Broad-spectrum antimicrobial, cytokine inhibition	pH-responsive gel matrix
Honey	Glucose oxidase, H ₂ O ₂ , flavonoids	Natural filtration	Osmotic antimicrobial via in-situ H ₂ O ₂	Matrix filler in herbal gels
Neem (<i>Azadirachta indica</i>)	Azadirachtin, nimbin (limonoids)	Cold methanol extraction	Antibacterial, prostaglandin-med iated anti-inflammatory	Blended with biopolymer matrix
Castor Oil (<i>Ricinus communis</i>)	Ricinoleic aci d, flavonoids	Cold-press / hexane	Anti-inflammatory , enhances hydration & occlusion	Occlusive base in herbal gels
Quercetin (onions, apples)	Quercetin (flavonoid)	Ethanol reflux / ultrasonic	Antioxidant, $\uparrow$ VEGF $\rightarrow$ angiogenesis	Self-healing H-bonded gel
Resveratrol (grapes)	Resveratrol (polyphenol)	Ethanol extraction	ROS scavenging, improves perfusion & endothelial repair	pH-responsive matrix
Silver Nanoparti cles (AgNPs)	Inorganic	—	Disrupts bacterial membrane, binds thiols, generates ROS	Dispersed in chitosan / hybrid gels
Gentamicin	Antibiotic	—	Binds 30 S ribosome $\rightarrow$ blocks protein synthesis	Localized antimicrobial release
Doxycycline	Antibiotic	—	Inhibits protein synthesis & MMPs $\rightarrow$ preserves ECM	Protects granulation tissue

Chitosan-NAC	Polymer–drug combo	—	NAC scavenges ROS, chitosan antimicrobial & gelation	Injectable redox-modulating gel
VEGF Vascular Endothelial Growth Factor	Growth factor	—	Promotes angiogenesis via VEGFR-2, ↑ granulation	Sustained release (dynamic covalent bonds)
EGF Epidermal Growth Factor	Growth factor	—	Stimulates epithelial fibroblast proliferation &	Schiff-base-linked hydrogel
PDGF-BB Platelet-Derived Growth Factor-BB Isoform	Growth factor	—	Activates fibroblasts, ↑ collagen & ECM	Dual pH + ROS-responsive system
Insulin (topical)	Hormone protein	—	↑ glucose uptake, cell proliferation	Glucose-responsive gel
LL-37 peptide Human Cathelicidin Antimicrobial Peptide LL-37	Antimicrobial peptide	—	Bactericidal, pro-angiogenic	Immobilised in synthetic peptide gel
Thymosin β4	Regenerative peptide	—	Keratinocyte migration, anti-inflammatory	Self-assembling dynamic matrix

Self-healing hydrogels offer a better platform for the delivery of drugs in diabetic foot ulcer (DFU) therapy to treat significant challenges such as oxidative stress, infection through biofilms, and compromised angiogenesis. Bioactive compounds from plants such as curcumin, berberine, resveratrol (found in grapes), and quercetin (found in onions and apples), and honey have all been shown to be

effective because of their antioxidant, anti-inflammatory, and antimicrobial effects. When delivered in self-healing, stimuli-sensitive hydrogels, these molecules can display increased bioavailability and stability with sustained release in an oxidative or acidic wound environment, often affecting healing in 5 to 10 days. Synthetic and inorganic agents i.e., silver nanoparticles (AgNPs), gentamicin,

doxycycline, and Chitosan-N-acetylcysteine (NAC) are faster, usually within 2 to 5 days. AgNPs exert their action by inhibiting bacterial membranes through induction of ROS generation, and gentamicin and doxycycline exhibit targeted antimicrobial and anti-inflammatory activity with low systemic toxicity. Chitosan-NAC also shows a dual action by inhibiting oxidative stress and modulating local immune responses, and helps in promoting extracellular matrix (ECM) preservation in infected or ischemic DFUs.

Biological molecules such as VEGF, EGF, PDGF-BB, insulin, LL-37, and thymosin β 4 directly help in tissue healing through angiogenesis, granulation, and re-epithelialization. Encapsulation within self-healing hydrogels protects them from enzymatic degradation but allows stimuli-responsive release, which typically initiates the wound healing response between 2 and 7 days. Biologically active molecules enhance healing with reduced dosing frequency and are especially useful in the management of chronic DFU (20-22).

PRECLINICAL INNOVATIONS AND PRACTICAL SUPPORT IN DFU TREATMENT

Hydrogels are widely used in diabetic foot ulcer (DFU) care, since they retain moisture in the wound, allow for autolytic debridement and deliver antimicrobial drugs or growth factors. Existing products like Intrasite™, Purilon®, Aquacel® Ag+, and Silvercel™ deliver core wound care functions such as preventing acquired infections and absorbing localized exudates, however they only act as passive systems and one-dimensional material properties preclude wound management, as they can't self-heal after mechanical

damage, neither do they adjust in situ to the shearing chronicity and oxidative microenvironments that DFUs can exhibit.

To address these limitations, traditional hydrogels were reformulated into self-healing systems by incorporating dynamic crosslinking such as Schiff-base bonds, ionic coordination, and host-guest interactions. These hybrid systems provided the hydrogel with the ability to self-heal their mechanical structure after injury, as well as respond to upregulation of pathophysiological components like hyperglycemia, acidic pH, and high reactive oxygen species (ROS) often seen in diabetic chronic wounds. Environmentally-responsive and self-healing hydrogels have shown in preclinical models that they can close a wound, decrease inflammation, and increase angiogenesis in diabetic models. For example, by synthesizing a curcumin-loaded dextran-chitosan self-healing hydrogel, epithelial regeneration was efficiently elevated, and inflammation cytokines decreased in diabetic rats.

Although high-potential outcomes in animal and laboratory models, NO self-healing hydrogel has been translated into clinical practice also due to significant challenges including sterilization constraints, scale-up and production, regulatory hurdles, and economic considerations. Certainty with respect to regulations concerning new types of biomaterials and long-term biocompatibility also inhibits clinical translation.

In the absence of such sophisticated hydrogel based dressings, other supports such as total contact casts, diabetic offloading boots, pressure-distributing insoles, heel lifts and antimicrobial socks

all remain very important for reducing plantar pressure, preventing infection, and delivering healing. Most important of all when used to complement hydrogel products that are currently available to produce better outcomes with DFU patient management (23-25).

GAPS AND FUTURE DIRECTIONS

Despite promising outcomes from preclinical studies, the clinical translation of self-healing hydrogels in diabetic foot ulcer (DFU) therapy remains limited. Most available hydrogel-based dressings focus on moisture retention and antimicrobial effects, but lack dynamic self-repair and sustained responsiveness to the wound microenvironment (27-30). Key gaps include insufficient human clinical trials, limited regulatory clarity for smart biomaterials, and inconsistent pharmacological standardization in evaluating bioactivity across hydrogel systems. Furthermore, the long-term biocompatibility, degradation kinetics, and cost-effectiveness of advanced peptide and nanoparticle-loaded self-healing gels are yet to be fully validated in large-scale trials. Future research should prioritize translational studies, development of multi-responsive platforms integrating diagnostics, and AI-enabled wound monitoring for personalized DFU management. Strengthening industry-clinical collaborations and ensuring accessibility of herbal-synthetic hybrid hydrogels can significantly improve the. Therefore, self-healing hydrogels have potential, welcome, and meaningful steps closer to personalized diabetic foot ulcer and lower extremity management for individuals living with diabetes mellitus.

adoption of this next generation therapy, especially in high-burden settings like India (31).

CONCLUSION

Diabetic foot ulcers are a significant clinical issue, even with the chronic and persistent problems with healing, infection, and inflammation. Self-healing hydrogels resulted as a new exciting avenue combining appreciable mechanical limitations with responsive drug delivery. Self-healing hydrogels allow for controlled, slow release of natural, synthetic, and biological substances targeting the principle issues of DFUs such as oxidative stress, microbial invasion, and ischemia. Self-healing hydrogels have the advantage of performing better than standard dressings as the hydrogel will respond to changes with the wound and facilitate effective tissue regeneration. Although great healing possibilities were demonstrated in the preclinical setting, future regulatory, production, and procedural hurdles to translation into the clinical setting are to be expected. It will be necessary to close these gaps with applied research, AI supported clinical monitoring, and new biomaterials to promote comprehensive clinical acceptance of these innovative devices. In global settings of great need such as India, the combination of self-healing hydrogels with existing care strategies will likely reduce lower extremity diabetic foot ulcer hospitalization incidence and diabetic-related amputations.

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