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MICROENVIRONMENT-RESPONSIVE HYDROGELS FOR DIABETIC FOOT ULCERS: FROM SMART DRUG DELIVERY TO PERSONALIZED WOUND CARE

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ABSTRACT: One of the most dangerous long-term consequences of diabetes mellitus is diabetic foot ulcers (DFUs), which are a leading cause of extended hospital stays, infections, reduced quality of life, and lower limb amputation. A complex pathological microenvironment that includes persistent hyperglycemia, excessive reactive oxygen species (ROS), chronic inflammation, aberrant matrix metalloproteinase activity, hypoxia, impaired angiogenesis, bacterial infection, and biofilm formation is linked to delayed healing of DFUs. Conventional wound dressings have a limited ability to react dynamically to changes in the wound environment, although they often offer passive protection and moisture management. Because of their high-water content, three-dimensional structure, biocompatibility, extracellular matrix-like qualities, drug-loading capacity, and adjustable physicochemical properties, hydrogels have thus become attractive advanced wound-dressing materials. In order to control drug release or hydrogel behavior, microenvironment-responsive hydrogels have been created more recently. These hydrogels can identify endogenous or exogenous stimuli such as pH, glucose, ROS, enzymes, temperature, hypoxia, light, and magnetic fields. The pathophysiology of DFUs, the features of the diabetic wound microenvironment, and the creation of natural, synthetic, and hybrid hydrogels for the treatment of diabetic wounds are all covered in this review. Systems that respond to pH, ROS, enzymes, glucose, hypoxia, and multiple stimuli, smart drug delivery, antibacterial and antibiofilm strategies, hydrogels enabled by nanotechnology, angiogenesis, inflammation regulation, extracellular matrix remodeling, and tissue regeneration are all given special attention. Additionally included are recent advancements in wearable technology, 3D printing, artificial intelligence, biosensor-integrated hydrogels, smart monitoring, injectable systems, and hydrogels filled with extracellular vesicles. Hydrogel dressings have been shown in clinical studies to enhance DFU healing when compared to traditional dressings; nevertheless, preclinical research is still the main source of data for the newest responsive systems. Future studies should concentrate on scalable manufacturing, integrated sensing and therapy, patient-specific wound profiling, regulatory validation, and economical, individualized wound care. In the end, adaptive, precise, and theranostic wound care may replace passive wound coverage in DFU management thanks to microenvironment-responsive hydrogels.

KEYWORDS: diabetic foot ulcer; diabetic wound; hydrogel; stimuli-responsive hydrogel; stimulus-responsive hydrogel.

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1. INTRODUCTION

Diabetes mellitus is a long-term metabolic disease with numerous tissue-level and systemic consequences. Diabetic foot ulcers, which arise from the combination of neuropathy, peripheral vascular disease, mechanical stress, metabolic imbalances, and compromised host defense, are among its most debilitating side effects. Due to several disruptions to the normal process of wound healing, DFUs are challenging to treat.

Coordinated hemostasis, inflammation, proliferation, and remodeling are all necessary for normal wound healing. These processes become dysregulated or extended in diabetes. Endothelial dysfunction, oxidative stress, and aberrant immunological responses are all facilitated by persistent hyperglycemia. While vascular insufficiency impairs the transport of oxygen and nutrients, peripheral neuropathy decreases protective sensibility and promotes repetitive mechanical trauma. Progression toward tissue regeneration is further impeded by bacterial infection and persistent inflammation. As a result, the diabetic wound microenvironment is extremely active and diverse. elevated glucose levels, increased ROS levels, altered pH, enhanced protease activity, hypoxia, and bacterial biofilms could all be present. The development of microenvironment-targeted therapy approaches is supported by Huang et al.'s description of DFUs as a microenvironment marked by hyperglycemia, ischemia, hypoxia, hyperinflammation, and chronic infection [15].

Because their hydrated three-dimensional networks may retain moisture, absorb wound exudate, and create a matrix that can contain therapeutic chemicals, hydrogels have emerged as appealing platforms for managing chronic wounds [9,10,16,21]. Additionally, their physicochemical characteristics can be changed to make them more responsive to external or biological stimuli.

According to recent research, Intelligent systems have clearly replaced conventional hydrogels. Hydrogels responsive to temperature, pH, glucose, ROS, enzymes, and many stimuli are summarized in the 2026 review by Jin et al. [1]. The shift from "smart responsive" hydrogels to "smart monitoring" platforms that can measure wound pH and glucose and maybe aid in precision diagnostics and treatments was also detailed by He et al. [2].

This review aims to critically examine the development of microenvironment-responsive hydrogels for DFUs, ranging from individualized wound monitoring and precision treatment to pathological sensing and smart drug administration.

2. Overview of diabetic foot ulcers and current therapeutic challenges

2.1 Global Burden and Clinical Significance of Diabetic Foot Ulcers

One of the most serious side effects of diabetes mellitus is diabetic foot ulcers (DFUs), which greatly increase morbidity, lengthen hospital stays, lower limb amputation, and poor quality of life. Peripheral neuropathy, vascular impairment, immunological dysfunction, metabolic abnormalities, and recurrent mechanical stress are some of the pathogenic elements that interact to cause DFUs.

Diabetic wound complications have increased in tandem with the global growth in diabetes prevalence. Due to their chronic nature, high recurrence rate, and challenges in achieving full wound closure, DFUs impose a significant clinical and socioeconomic burden. Many diabetic ulcers stay in a chronic inflammatory state and do not go through the typical healing cascade, despite advancements in wound-care devices.

2.2 Current Approaches for Diabetic Foot Ulcer Management

Glycemic control, infection control, wound debridement, pressure off-loading, vascular assessment, and advanced wound dressings are all part of the multidisciplinary approach needed to manage DFUs. Conventional wound-care techniques mainly concentrate on keeping the wound site moist, preventing infection, and protecting the wound site.

Commonly used approaches include:

Debridement is the process of removing necrotic tissue to encourage the growth of healthy tissue. Reducing mechanical pressure on the ulcer site is known as off-loading therapy. Antimicrobial therapy: managing bacterial infections and stopping the development of biofilms. Maintaining a suitable hydration environment for tissue repair requires moist wound dressings. Angiogenesis and tissue regeneration are encouraged by growth factors and regenerative treatments.

Conventional dressings, on the other hand, often offer passive wound protection and have a limited capacity to react to dynamic changes that take place inside the diabetic wound environment.

2.3 Limitations of Conventional Wound Dressings

Gauze, films, and basic hydrocolloid materials are examples of traditional wound dressings that primarily serve as barriers for protection. These substances aid in preserving moisture and guarding against outside contamination, but they are unable to actively control the pathological abnormalities linked to diabetic wounds.
Major limitations include:

- Lack of stimulus-responsive drug release.
- Limited antimicrobial activity.
- Poor control of oxidative stress.
- Inability to regulate chronic inflammation.
- Insufficient support for angiogenesis and extracellular matrix remodeling.
- Lack of real-time monitoring capability.

As a result, sophisticated multifunctional wound dressing systems that can detect pathological changes and deliver focused treatment responses are needed.

2.4 Need for Smart and Responsive Hydrogel-Based Systems

A number of aberrant biological signals, such as higher glucose concentration, excessive reactive oxygen species (ROS), altered pH, enhanced matrix metalloproteinase (MMP) activity, hypoxia, and bacterial infection, are present in the highly dynamic diabetic wound environment. The development of intelligent therapy platforms is made possible by these diseased traits.

Because of their three-dimensional hydrated networks, superior biocompatibility, extracellular matrix-like characteristics, and capacity to contain therapeutic agents, hydrogels have attracted a lot of attention. Controlled drug administration and better wound healing results are made possible by responsive hydrogels' ability to identify particular wound-associated stimuli and adjust their characteristics accordingly.

Microenvironment-responsive hydrogels that can react to external stimuli like temperature, light, and magnetic fields as well as endogenous ones like pH, glucose, ROS, enzymes, and hypoxia have been the focus of recent research. The shift from passive wound covering to adaptive, customized, and precise wound care is represented by these systems.

3. Diabetic Foot Ulcers: Pathophysiology and Clinical Challenges

3.1 Impaired Wound Healing in Diabetes

Hemostasis, inflammation, proliferation, and tissue remodeling are all part of the intricate biological process of wound healing. These phases are not well synchronized in people with diabetes. Hyperglycemia affects fibroblasts, keratinocytes, endothelial cells, and immunological cells in addition to changing cellular metabolism and raising oxidative stress. Diabetic neuropathy reduces pain perception and defensive reactions, which leads to the development of ulcers. Patients may continue to walk on an injured area, which could lead to ulcer expansion and recurrent damage. Tissue perfusion and oxygen availability are further reduced.
As a result, the chronic diabetic wound gets caught in a loop that doesn't heal:

Hyperglycemia → Oxidative Stress → Inflammation → Tissue Damage → Infection → Impaired Regeneration → Chronic Ulceration

By supplying moisture, distributing therapeutic drugs, and altering the wound microenvironment, hydrogels have the ability to disrupt multiple stages of this cycle.

3.2 Oxidative Stress and Chronic Inflammation

Both antimicrobial defense and regular cellular signaling depend on ROS. However, increased ROS production in diabetes results in oxidative damage to extracellular matrix components, proteins. Another important feature of DFUs is persistent inflammation. Inflammatory signals may continue to be increased rather than effectively resolving. Chronic wound persistence is caused by aberrant macrophage function, an overabundance of inflammatory cytokines, and a poor transition to tissue healing. Antioxidants and anti-inflammatory substances can be added to functional hydrogels. A further benefit of ROS-responsive systems is that excessive ROS might act as a trigger for therapeutic activation [1,8,12,25,27].

3.3 Infection, Biofilm Formation and Antimicrobial Resistance

DFUs are quite vulnerable to bacterial invasion and colonization. Microorganisms are shielded from host immunity and antibacterial agents by bacterial biofilms.

The growth of biofilms causes various issues:

- Decreased penetration of antibiotics.
- Ongoing inflammation.
- Tissue repair is delayed.
- More tissue degradation.
- A higher chance of developing a systemic illness.
- The possibility of developing resistance to antibiotics.

Antibiotics, antimicrobial peptides, metallic nanoparticles, and other antimicrobial agents can be included into responsive hydrogel systems. Their controlled-release characteristics may lessen needless exposure while preserving therapeutic concentrations locally.
In their study of stimuli-responsive systems for diabetic wounds, Hu et al. highlighted the utilization of both external triggers like light, temperature, and magnetic fields as well as internal stimuli like acidity, glucose, enzymes, and hypoxia [14].

3.4 Angiogenesis and Tissue Regeneration Impairment

For wounds to heal, enough vascularization is necessary. Diabetes reduces angiogenic signaling and endothelial cell activity, which hinders the development of new blood vessels.
A vicious cycle of hypoxia, poor cell growth, and inadequate nutrition delivery is produced by decreased angiogenesis. Growth factors and pro-angiogenic substances can be stored in hydrogels. Additionally, they can offer structural support for extracellular matrix production and cell motility.

4. Wound Microenvironment of Diabetic Foot Ulcers

The pathological wound microenvironment provides the fundamental rationale for responsive hydrogel design.

4.1 pH Alterations

The pH of wounds varies during the healing process and can become abnormal in both infectious and chronic wounds. Changes in pH can affect cellular function, drug stability, bacterial growth, and enzyme performance.
Chemical groups or links in pH-responsive hydrogels react to variations in acidity. Drug-release kinetics may change, swell, or degrade as a result of this reaction.
Hydrogel networks can include acid-sensitive connections like Schiff-base linkages. These bonds may hydrolyze and help release therapeutic agents under different pH settings [1,3,12].
The basic justification for responsive hydrogel design comes from the pathological wound microenvironment.

4.2 Reactive Oxygen Species and Oxidative Stress

One of the most significant biological causes in diabetic wounds is elevated ROS.
Oxidation-sensitive groups that alter their structure in reaction to oxidative stress may be present in ROS-responsive hydrogels. This may allow:

• Scavenging ROS;
  Delivery of antioxidants
• Regulated medication release
• Safeguarding therapeutic agents
• The redox equilibrium is restored.

ROS responsiveness is still a key tactic for treating diabetic wounds, according to the 2026 literature [1,3].

4.3 Enzyme and Protease Dysregulation

Proteolytic enzymes, especially matrix metalloproteinases, are frequently overactive in chronic wounds.
Normal extracellular matrix remodeling depends on MMPs, however overactivity can break down.
Enzyme-cleavable sequences or links are used in MMP-responsive hydrogels. The hydrogel network may degrade and release its therapeutic payload in the presence of high MMP activity.

4.4 Hypoxia and Oxygen Imbalance

DFUs frequently experience hypoxia due to compromised microcirculation and vascularization.
Lack of oxygen has an impact on:
• Fibroblast activity
• The production of collagen
• Immunological protection
• Angiogenesis
The epithelialization process.
Thus, oxygen-generating chemicals and oxygen-carrying materials have been used to create the oxygen-releasing hydrogels. In particular, protein hydrogels and carbohydrate-polymer hydrogels were assessed in a 2023 review as oxygen-releasing patches for diabetic wounds [32,33].

4.5 Glucose and Inflammatory Microenvironment

One characteristic that distinguishes diabetic wounds is persistent hyperglycemia.

Glucose-responsive hydrogels have the ability to change their structure or drug-release behavior in response to high glucose.

Among the possible uses are:

• Delivery of insulin

• A decrease in glucose

• The administration of antibiotics

• Anti-inflammatory medication

• Control of metabolism.

The development of glucose-responsive systems offers a major step toward wound-specific therapy because treatment can theoretically be altered according to local glucose levels.

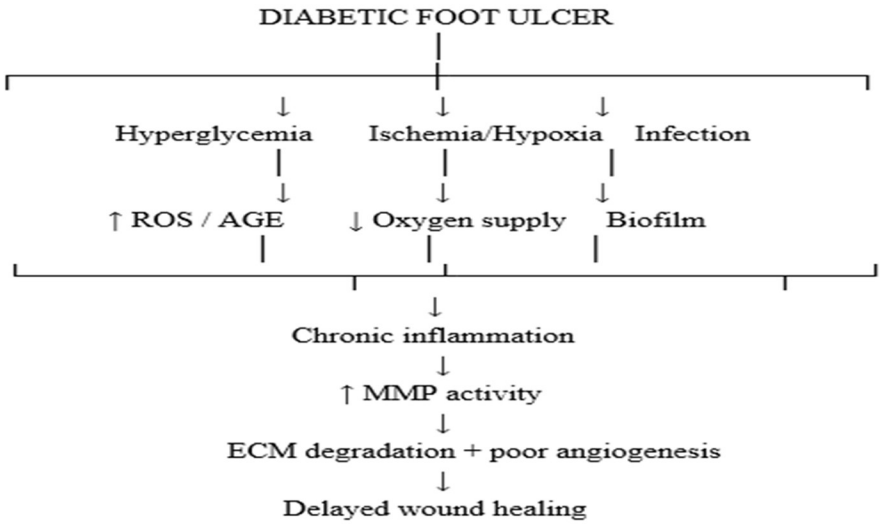

Figure 1. Pathological microenvironment of a diabetic foot ulcer

5. Hydrogels as Advanced Platforms for Diabetic Wound Management

5.1 Structure and Properties of Hydrogels

Hydrogels are three-dimensional networks of polymers that can hold a lot of water.

Important characteristics consist of:

- Enough hydration
- Porosity
- Biocompatibility
- Adjustable mechanical strength
- Tissue adhesion
- Biodegradability
- Ability to load drugs
- Regulated degradation
- Self-healing
- The ability to inject.
- Reactivity to stimuli.

The hydrated structure can assist cellular activities involved in tissue regeneration and imitate features of the extracellular matrix [16,21].

5.2 Natural and Synthetic Hydrogels

Among the natural hydrogel materials are:

- Collagen
- gelatin
- Chitosan
- Alginate
- Hyaluronic acid
- fibrin
- derivatives of cellulose.
- Among the synthetic materials are:
- Polyethylene glycol
- Polyvinyl alcohol
- Polyacrylamide
- polyacrylic acid
- Polymers that react to temperature.

Natural and manmade polymers are combined in hybrid systems to enhance biological function and mechanical strength.

5.3 Advantages of Hydrogels in Diabetic Wound Healing

Hydrogels provide multiple functions simultaneously.

Table 1. Major advantages of hydrogel systems in DFU management

Property	Function in DFU	Therapeutic significance
High water content	Maintains moisture	Supports cell migration
Porous structure	Permits nutrient/waste exchange	Supports regeneration
Drug-loading capacity	Carries antibiotics, growth factors and antioxidants	Localized therapy
Tissue adhesion	Maintains wound contact	Improves retention
Biocompatibility	Supports cellular activity	Reduces tissue irritation
Controlled degradation	Regulates release	Prolonged treatment
Stimulus responsiveness	Responds to wound signals	On-demand therapy
Self-healing	Repairs mechanical damage	Improves durability
Nanoparticle integration	Adds antimicrobial/antioxidant functions	Multifunctional treatment
Biosensor integration	Measures wound biomarkers	Smart monitoring

Clinical and preclinical reviews consistently support hydrogels as promising wound-care materials [7–10,16,21].

6. Microenvironment-Responsive Hydrogels

Responsive hydrogels may be classified according to the stimulus that initiates their functional response.

Table 2. Microenvironment stimuli and corresponding responsive hydrogel strategies

Stimulus	Diabetic wound characteristic	Hydrogel response	Potential therapeutic application
pH	Altered wound acidity	Bond cleavage/swelling	Antibiotic release
ROS	Excess oxidative stress	Oxidation-sensitive degradation	Antioxidant delivery
Glucose	Hyperglycemia	Glucose-dependent structural change	Insulin/drug release
MMPs	Excess protease activity	Enzyme-mediated degradation	Growth-factor release
Hypoxia	Reduced oxygen	Oxygen generation/release	Angiogenesis
Temperature	Inflammation/infection	Thermoresponsive transition	Drug release
Bacterial enzymes	Infection	Enzyme-triggered release	Antimicrobial therapy
Light	External stimulus	Photothermal/photodynamic activation	Antibacterial therapy

Jin et al. and He et al. emphasize that the most important endogenous stimuli include pH, glucose, ROS and enzymes [1,2].

6.1 pH-Responsive Hydrogels

The contrasts between healthy skin and pathological wounds can be exploited by pH-responsive technologies.

The mechanisms include:

1. Protonation/Deprotonation
2. Swelling
3. Degradation
4. Permeability alterations
5. Breaking of chemical bonds sensitive to pH.

Antimicrobial or anti-inflammatory medication release can be regulated by these methods.

6.2 ROS-Responsive Hydrogels

Because oxidative stress is both a pathogenic characteristic and a possible therapeutic trigger, ROS-responsive systems are especially appealing. One way to depict a conceptual system is:

High ROS → Oxidation-Sensitive Bond Cleavage → Hydrogel Degradation → Therapeutic Release → ROS Reduction

Compared to traditional sustained-release formulations, these feedback-oriented methods might be more adaptable.

6.3 Enzyme-Responsive Hydrogels

Pathological protease activity serves as a trigger for enzyme-responsive hydrogels. Polymer networks can integrate MMP-sensitive peptide sequences. The peptide bond is broken and the medicinal payload becomes accessible as MMP activity rises.

6.4 Glucose-Responsive Hydrogels

Enzymatic processes, glucose-sensitive polymer interactions, or glucose-binding chemistry can all be used to create glucose-responsive hydrogels.

Controlled insulin delivery is their most significant suggested use.

6.5 Hypoxia-Responsive Hydrogels

Pro-angiogenic pathways may be activated or oxygen delivered via hypoxia-responsive mechanisms. For ischemic diabetic wounds, oxygen-releasing hydrogel patches show great promise [32,33].

6.6 Multi-Stimuli-Responsive Hydrogels

One stimulus cannot adequately capture the complexity of the diabetic wound environment. Systems that are receptive to many inputs can react to combinations like:

- pH + ROS
- Glucose + ROS
- Glucose + MMP
- pH + infection
- ROS + hypoxia

Such systems are closer to the biological complexity of DFUs.

7. Smart Drug Delivery Using Responsive Hydrogels

7.1 Controlled and Sustained Drug Release

Rapid drug dispersion or inadequate drug concentration are two possible outcomes of conventional medication delivery. Hydrogels can control diffusion and serve as drug repositories by:

- Swelling of polymers
- Deterioration of the network
- Diffusion of molecules
- Bond cleavage that is reliant on stimuli
- The release of nanoparticles.

7.2 On-Demand Drug Delivery

One of the key features of stimuli-responsive hydrogels is on-demand distribution. When pathogenic activity rises, the ideal system should release more therapeutic agent; when wound conditions improve, it should release less. This could increase therapeutic efficacy and decrease medication waste.

7.3 Delivery of Antibiotics and Antimicrobial Agents

Potential payloads include:

- Antibiotics
- Antimicrobial peptides
- Silver nanoparticles

- Zinc oxide
- Copper-containing nanomaterial
- Photothermal agents
- Photodynamic agents.

7.4 Delivery of Growth Factors and Cytokines

Growth factors can be shielded by hydrogels, which can offer long-term local delivery.

VEGF, FGF, and other regenerative proteins are examples of potential growth factors.

7.5 Delivery of Phytoconstituents and Natural Bioactive Compounds

Natural substances have antibacterial, anti-inflammatory, and antioxidant properties.

Among the possible candidates are:

- Curcumin
- Quercetin
- Resveratrol
- Catechins
- Flavonoids
- Polyphenols.

Hydrogel-based delivery and nanoencapsulation can help with poor water solubility and chemical instability.

8. Antibacterial and Anti-Biofilm Strategies

8.1 Antibacterial Mechanisms of Responsive Hydrogels: Bacteria can be eliminated using responsive hydrogels by:

- Regulated release of antibiotics
- Antimicrobial peptides
- Metal-ion discharge
- Regarding the production of ROS
- The consequences of photothermal
- Impacts of photodynamic
- Bacterial membrane rupture.

8.2 Biofilm Disruption and Quorum-Sensing Modulation

Penetration of biofilms is still difficult. Future hydrogel systems could incorporate:

Biofilm penetration + Suppression of quorum sensing + Release of antibiotics

Such multipurpose systems may enhance the elimination of microorganisms.

8.3 Nanoparticle-Integrated Responsive Hydrogels

Nanoparticles provide additional therapeutic functions.

Table 3. Representative nanomaterials for responsive diabetic wound hydrogels

Nanomaterial	Main function	Potential advantage
Silver nanoparticles	Antibacterial	Broad-spectrum antimicrobial activity
Gold nanoparticles	Photothermal/drug delivery	Tunable surface chemistry
ZnO nanoparticles	Antibacterial	Metal-oxide antimicrobial activity
MnO_2 nanoparticles	ROS regulation/oxygen generation	Redox and oxygen modulation
Iron oxide nanoparticles	Magnetic response	External magnetic control
Mesoporous silica nanoparticles	Drug loading	High loading capacity
Polymeric nanoparticles	Controlled release	Biodegradable delivery
Carbon-based nanomaterials	Conductivity/antioxidant functions	Smart sensing and stimulation

Because nanoparticles can be tailored to the unique pathological characteristics of diabetic wounds, microenvironment-based nanomedicine is being studied more and more for DFU [15].

8.4 Prevention of Antimicrobial Resistance

By localizing release, stimulus-responsive administration may lessen needless exposure to antibiotics.

However, antimicrobial resistance cannot be eradicated by smart distribution alone. Clinical stewardship, dosage, duration, and appropriate antibiotic selection are still crucial.

9. Pro-Healing Mechanisms of Responsive Hydrogels

9.1 Regulation of Inflammation

Hydrogels can alter macrophage function or deliver anti-inflammatory drugs.
Restoring a proper transition from inflammation to tissue healing is the goal rather than totally eradicating inflammation.

9.2 Antioxidant and ROS Scavenging Effects

Oxidative damage can be lessened by antioxidant hydrogels.
Additionally, during oxidative stress, ROS-responsive mechanisms may trigger therapeutic release.

9.3 Promotion of Angiogenesis

Pro-angiogenic factors can be delivered continuously throughout hydrogels.

Increased oxygen delivery and easier regeneration are two benefits of improved vascularization.

9.4 Fibroblast Proliferation and Migration

Collagen and extracellular matrix are produced by fibroblasts.

Fibroblast migration and proliferation can be supported by the three-dimensional hydrogel environment.

9.5 Collagen Deposition and Extracellular Matrix Remodeling

Tissue strength depends on proper collagen production.

While lowering excessive proteolysis, responsive hydrogels can supply growth nutrients and cues that sustain the matrix.

9.6 Re-Epithelialization and Tissue Regeneration

Through the transport of restorative chemicals, biochemical signaling, and moisture retention, hydrogels can facilitate keratinocyte migration and epithelial closure.

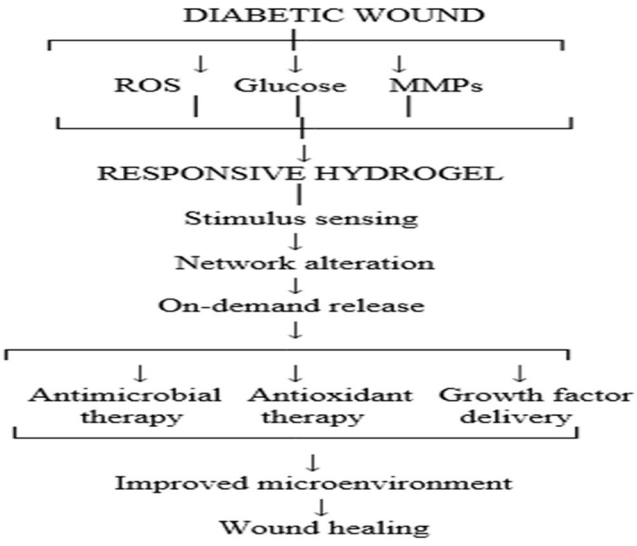

Figure 2. Mechanism of action of a microenvironment-responsive hydrogel

10. Nanotechnology-Enabled Responsive Hydrogels

10.1 Nanoparticle-Loaded Hydrogels

Nanoparticles can perform certain biological tasks and boost medication loading capacity.

10.2 Nanocomposite Hydrogels
Polymeric hydrogel networks and nanoscale materials are combined in nanocomposite systems.

They can get better:

- Mechanical characteristics
- Electrical conductivity
- The antibacterial activity
- Action of antioxidants
- Release of drugs
- Interaction between tissues.

Nanocomposite hydrogels are highlighted in recent studies as a key tactic for local diabetic ulcer treatment [15,48].

10.3 Hydrogel–Nanoparticle Synergistic Effects
The structural framework is provided by hydrogels, while nanoparticles serve other purposes.

Consequently:
Retention + Hydration + Regulated delivery equals hydrogel.
Antimicrobial, antioxidant, and sensing/catalytic activities make up a nanoparticle.
Multifunctional wound-care systems are produced by the combination.

10.4 Smart Nanogel and Hydrogel-Nanocomposite Systems
Nanogels can be designed for stimulus-dependent medication delivery because of their nanoscale size.

They are very appealing for responsive treatment systems because of their large surface area and adjustable chemistry.

11. Personalized Wound Care and Smart Monitoring

11.1 Patient-Specific Wound Microenvironment
Each DFU has a unique biology.

Infection, high oxidative stress, significant ischemia, and uncontrolled hyperglycemia might all be present in one ulcer. Thus, the best course of action in the future should be determined by biological data unique to the wound.

11.2 Biosensor-Integrated Hydrogels
Hydrogel devices can be paired with sensors that can identify:
• pH
• Glucose
• The temperature
• Oxygen
• Moisture
• ROS
• Biomarkers for inflammation.
For real-time wound monitoring, He et al. examined hydrogel sensors based on optical and electrochemical principles [2].

11.3 Real-Time Monitoring of Wound Parameters
Real-time monitoring may enable early detection of infection or delayed healing and lessen the need for frequent dressing removal.

While highlighting the fact that clinical evidence is still sparse and inconsistent, a 2026 systematic review of biosensor-based smart dressings revealed evidence for monitoring parameters like temperature, plantar stress, bioimpedance, pH, oxygen, and MMP-9 [38].

11.4 Wearable and Digital Health Technologies
Wireless technology allows wearable gadgets to transmit wound data.

Future systems could link:

Wound → Sensor → Smartphone → Cloud platform → Medical professional

11.5 AI-Assisted Personalized Wound Management
Artificial intelligence may integrate:

- Pictures of wounds
- Measurements from sensors
- Proportions of the wound
- Data on glucose
- Signs of infection
- Features of the patient.

AI could potentially help with therapy selection and healing prediction. However, prior to regular clinical application, AI needs external validation and high-quality clinical datasets.

Figure 3. Concept of personalized smart wound care.

12. Recent Advances and Emerging Technologies (2024–2026)

12.1 Stimuli-Responsive Hydrogel Systems

Hydrogels responsive to pH, glucose, ROS, enzymes, temperature, and combinations of stimuli have developed quickly, according to recent reviews [1–3,12,13].

The 2026 Jin review addresses temperature-, pH-, glucose-, ROS-, enzyme-, and multi-stimulus-responsive hydrogels and explicitly arranges responsive systems around the diabetic wound microenvironment [1].

12.2 Smart Monitoring and Theranostic Hydrogels

Integration of diagnosis and treatment is the newest approach. An integrated system could: Identify, Interpret, Treat, and keep an eye on. This is the cornerstone of theranostic wound treatment.

12.3 Injectable and In Situ Forming Hydrogels

Because injectable hydrogels can fill the wound geometry before creating a stable network, they are beneficial for uneven wounds.

For diabetic wounds, in situ gelling devices have been thoroughly studied [34].

12.4 3D-Printed and Bioengineered Hydrogels

3D printing allows controlled spatial distribution of polymers, cells and therapeutic agents. 3D-printed conductive and stimuli-responsive systems may additionally influence macrophage polarization and tissue repair [40].

12.5 Exosome- and Stem Cell-Loaded Hydrogels

Proteins, lipids, and nucleic acids found in extracellular vesicles and exosomes have the ability to control angiogenesis, tissue regeneration, and inflammation. Extracellular vesicles may be shielded and their local retention extended by hydrogel encapsulation. Extracellular-vesicle-bio potentiated hydrogels are particularly described in recent reviews as a viable method for diabetic wound repair [52].

13. Preclinical and Clinical Evidence

13.1 In Vitro Studies

In vitro testing frequently looks into:

- Cytocompatibility
- The growth of fibroblasts
- The migration of keratinocytes
- Antimicrobial properties
- Scavenging ROS
- Drug discharge
- The breakdown of hydrogel
- Mechanical strength.

Although these studies offer crucial formulation information, they are unable to accurately replicate the intricate human diabetic wound environment.

13.2 Animal Studies

Rodents with diabetes are frequently used to assess:

- Closure of wounds
- Histological regeneration

- Collagen deposition
- Angiogenesis
- Indicators of inflammation
- Bacterial load
- Remodeling tissue.

Although they serve as a basis for translation, the encouraging outcomes of numerous preclinical systems should not be equated with clinical efficacy.

13.3 Clinical Studies and Translational Evidence

Compared to the most recent responsive hydrogels, clinical data for traditional hydrogel dressings developed.

A systematic review and meta-analysis encompassing 15 randomized controlled trials and 872 patients was carried out by Zhao et al. When compared to standard dressings, hydrogel dressings greatly increased granulation and epithelial development, decreased bacterial infection, and healing [4]. Among the impacts reported were:

- OR 4.09 is the healing rate
- MD −11.38 days is the recovery time
- Improved granulation formation
- Improved epithelial formation
- Reduced bacterial infection.

Immuno-regulating functional hydrogels were revealed to be an effective functional hydrogel category for wound closure in recent clinical evaluations [37]. Although these results support the therapeutic justification for functional hydrogel dressings, they do not prove that all complex responsive formulations are clinically preferable.

Table 4. Evidence hierarchy for responsive hydrogel development

Evidence level	Typical study	Main purpose	Current status
Level 1	Material characterization	Mechanical/drug-release properties	Extensive
Level 2	In vitro cell studies	Cytocompatibility/regeneration	Extensive
Level 3	Antibacterial assays	Infection control	Extensive
Level 4	Diabetic animal models	Healing efficacy	Increasing
Level 5	Pilot human studies	Safety/feasibility	Limited
Level 6	Randomized clinical trials	Clinical efficacy	Limited for responsive systems
Level 7	Large multicenter trials	Generalizability	Major future requirement
Level 8	Real-world monitoring	Personalized implementation	Emerging

14. Challenges and Limitations

14.1 Biocompatibility and Safety

Antimicrobial drugs, polymers, nanoparticles, and chemically altered molecules can all be found in responsive systems.

Among the possible dangers are:

- Cytotoxicity
- Inflammatory responses
- Concentration of nanoparticles
- Toxicity of breakdown products
- High production of ROS
- Unpredictable degradation.

As a result, safety needs to be evaluated methodically.

14.2 Manufacturing and Scalability

Multiple synthesis and purification processes are frequently involved in laboratory formulations.

Clinical translation necessitates:

- Production that is repeatable
- Sterile manufacturing
- Consistency from batch to batch
- Quality assurance
- Production that is scalable
- A reasonable price.

14.3 Stability and Storage

Stability issues may arise in hydrogels that contain proteins, growth factors, exosomes, or nanoparticles.

Crucial factors consist of:

• The temperature

• Humidity
• Sterilization
• Length of storage
• Stability of drugs
• The structural integrity of hydrogel.

14.4 Regulatory and Clinical Translation Challenges

Because they concurrently incorporate a biomaterial, medication, device, or biological component, highly multifunctional systems may be subject to combination product regulations.
Therefore, regulatory routes must be carefully considered.
The disparity between strong preclinical results and scant clinical proof is a significant obstacle.

Figure 4. Translational pathway from laboratory to clinic.

15. Future Perspectives

15.1 Precision and Personalized Wound Care

Future DFU treatments must to take each wound's distinct biological characteristics into account. One such model for precision care is:
Wound profiling → Biomarker Detection → Microenvironment Classification → Hydrogel Selection → Responsive Therapy → Monitoring → Treatment Modification

15.2 Artificial Intelligence and Smart Hydrogels

Large amounts of wound data could be integrated with the aid of AI.
Among the possible uses are:
• Prediction of wound healing
• Identification of infections
• Categorization of ulcers
• The choice of treatment
• Segmentation of risks
• Observation from a distance.

15.3 Integrated Sensing, Diagnosis and Therapy

Future hydrogels may combine three functions:
Diagnosis + Therapy + Monitoring
Such systems may be described as theranostic hydrogels.

15.4 Prospects for Clinical Translation

The most technologically sophisticated solutions may not always be the most clinically successful ones.
Future systems ought to strike a balance:
• Reactivity
• Security
• Ease of manufacturing
• Cost-effectiveness
• Steadiness
• Simplicity of use
• The comfort of the sufferer
• Results have clinical significance.

Figure 5. Evolution of diabetic wound dressings

16. CONCLUSION

A significant advancement in the treatment of diabetic foot ulcers is represented by microenvironment-responsive hydrogels. A complex and dynamic milieu comprising hyperglycemia, increased ROS, persistent inflammation, protease dysregulation, hypoxia, bacterial infection, and poor angiogenesis characterizes the diabetic wound. These pathological traits offer biological cues that can be used to create intelligent wound-dressing technologies.

Conventional hydrogels already offer significant benefits in terms of medication delivery, tissue protection, and moisture retention. By adjusting to variations in pH, glucose, ROS, enzymes, temperature, and hypoxia, responsive hydrogels expand these capabilities. This makes it possible to give antibiotics, antioxidants, growth hormones, insulin, and other therapeutic compounds under controlled and possibly on-demand conditions.

By offering antibacterial, antioxidant, catalytic, oxygen-generating, and detecting properties, nanotechnology enhances hydrogel usefulness even more. While wearable technology and artificial intelligence may enable remote and customized wound care, biosensor integration may enable real-time monitoring of wound parameters.

The advantageous function of hydrogel dressings is supported by clinical data. When compared to traditional dressings, the 2024 meta-analysis of 15 randomized trials with 872 individuals revealed notable benefits in healing and decreases in bacterial infection [4]. The most recent theranostic and multi-stimulus-responsive hydrogels, however, are still mostly in preclinical development.

Thus, the following is a conceptualization of DFU management's future:

Passive Dressing → Functional Hydrogel → Smart Drug Delivery → Microenvironment-Responsive Hydrogel → Smart Monitoring → Theragnostic Hydrogel → Personalized Wound Care.

Multidisciplinary cooperation amongst biomaterial scientists, pharmacists, physicians, nanotechnologists, engineers, data scientists, and regulatory specialists will be necessary for successful translation. Safety, reproducibility, scalable manufacturing, long-term stability, cost-effectiveness, and excellent clinical trials should all receive special consideration.

Therefore, microenvironment-responsive hydrogels have a great deal of promise to change the management of diabetic foot ulcers from passive wound protection to adaptive, precise, and customized wound care.

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