Stimuli-Responsive Hydrogel Platforms for Precision Management of Diabetic Wounds: Integrating Controlled Drug Delivery, Biomarker Sensing, and Tissue Regeneration

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ABSTRACT

Background: Diabetic wounds represent a critical global health challenge, affecting over 40 million individuals worldwide. The complex pathophysiology-characterized by hyperglycemia, persistent inflammation, excessive oxidative stress, recurrent bacterial infection, and impaired angiogenesis-renders conventional wound dressings inadequate for effective management.

Objective: This review critically evaluates recent advances in stimuli-responsive hydrogel platforms designed for precision management of diabetic wounds, with emphasis on systems integrating controlled drug delivery, real-time biomarker sensing, and tissue regeneration capabilities.

Methods: A comprehensive literature review was conducted focusing on smart hydrogel systems responsive to glucose, pH, reactive oxygen species (ROS), temperature, and enzymes. Studies were categorized based on responsive mechanisms, therapeutic payloads, and preclinical efficacy outcomes.

Results: Stimuli-responsive hydrogels demonstrate significant advantages over conventional dressings through their ability to sense microenvironmental changes and execute programmed therapeutic responses. Glucose-responsive systems utilizing phenylboronic acid or glucose oxidase enable self-regulated insulin delivery. pH-responsive platforms exploit the acidic-to-alkaline transition in infected wounds for targeted antimicrobial release. ROS-scavenging hydrogels incorporating nanozymes or antioxidant polymers restore redox balance. Multi-responsive systems achieve synergistic therapeutic effects by integrating multiple sensing modalities. Nanohybrid architectures-incorporating metal nanoparticles, carbon-based nanomaterials, and metal-organic frameworks-enhance mechanical properties and add multifunctional capabilities including real-time wound monitoring.

Conclusion: Stimuli-responsive hydrogel platforms represent a paradigm shift in diabetic wound management, moving from passive coverage to active, intelligent intervention. Key challenges remain in clinical translation, including regulatory approval pathways, long-term biosafety validation, cost-effective manufacturing, and integration with point-of-care diagnostic technologies.

Keywords: Diabetic wound healing, stimuli-responsive hydrogels, controlled drug delivery, glucose-responsive systems, ROS-scavenging, pH-responsive, smart dressings, tissue regeneration, nanohybrid hydrogels, precision medicine.

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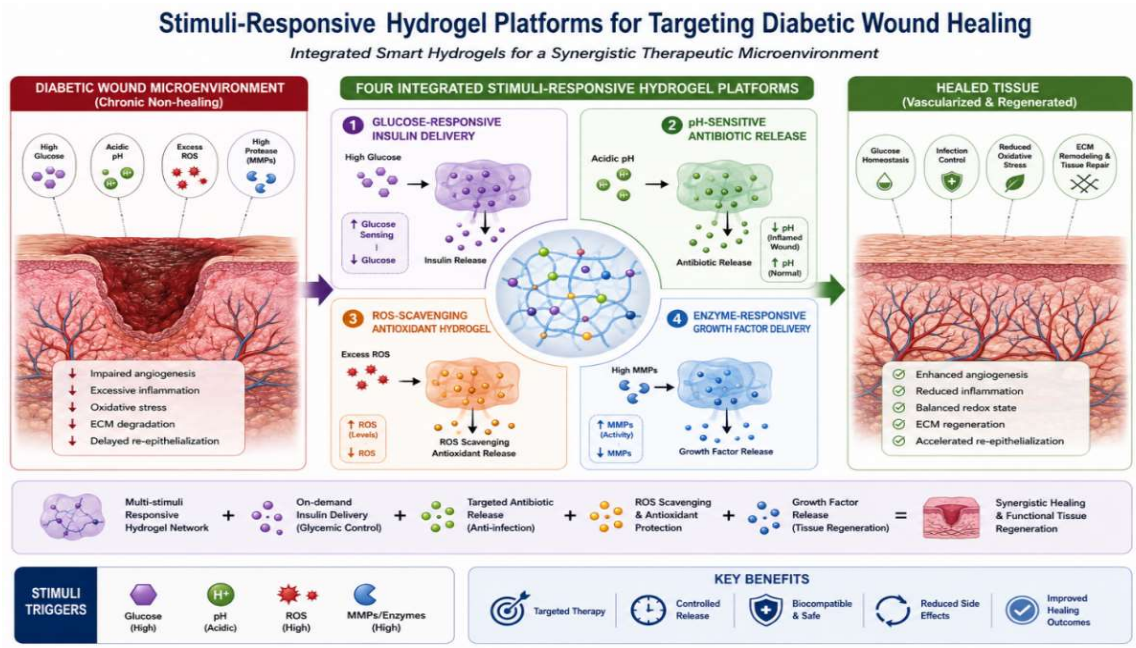
GRAPHICAL ABSTRACT



1. INTRODUCTION

Diabetes mellitus has reached pandemic proportions, with global prevalence exceeding 800 million adults-a more than fourfold increase since 1990, with projections reaching 1.31 billion by 2050 . Among the devastating complications of diabetes, chronic wounds-particularly diabetic foot ulcers (DFUs)-represent a major clinical and socioeconomic burden. Approximately 25% of DFU patients require amputation within 6 to 18 months of diagnosis, a rate 10 to 20 times higher than in non-diabetic individuals .

1.1. The Diabetic Wound Microenvironment: A Perfect Storm of Healing Impediments

Normal wound healing proceeds through four overlapping phases: hemostasis, inflammation, proliferation, and remodeling. In diabetic patients, this carefully orchestrated process is disrupted at multiple levels. Persistent hyperglycemia triggers the formation of advanced glycation end-products (AGEs), which directly activate immune cells to produce elevated levels of reactive oxygen species, creating sustained oxidative stress . This hyperglycemic environment also impairs the transition of macrophages from the pro-inflammatory M1 phenotype to the pro-healing M2 phenotype, resulting in chronic inflammation .

The diabetic wound microenvironment is characterized by a constellation of interrelated abnormalities:

Hyperglycemia (≥200 mg/dL) providing nutritional resources for bacterial proliferation

Elevated ROS levels causing cellular damage and redox imbalance

Variable pH (ranging from 5.45 to 8.65 depending on wound chronicity and infection status)

Hypoxia due to microvascular dysfunction and impaired angiogenesis

Upregulated matrix metalloproteinases (MMPs) degrading extracellular matrix components

Persistent bacterial colonization often forming biofilms resistant to conventional antibiotics

Reduced growth factor activity due to proteolytic degradation and impaired synthesis

Traditional wound dressings-gauze, films, foams, and basic hydrogels-provide passive functions such as moisture retention and physical protection but lack the adaptability required for this dynamic pathological environment. Their singular biochemical functions and inability to deliver therapeutic agents precisely when and where needed severely limit their efficacy .

1.2. The Paradigm Shift: From Passive Coverage to Intelligent Intervention

The recognition that effective diabetic wound management requires active, responsive intervention has driven the development of stimuli-responsive or "smart" hydrogel platforms. These advanced biomaterials integrate three essential capabilities that distinguish them from conventional dressings:

1. Controlled Drug Delivery: Therapeutic agents-including antibiotics, growth factors, insulin, antioxidants, and anti-inflammatory compounds-are encapsulated within the hydrogel matrix and released in response to specific wound microenvironmental triggers, achieving spatiotemporally precise delivery.

2. Biomarker Sensing: By incorporating responsive moieties, these platforms can detect pathological signals such as elevated glucose, acidic pH, ROS, or bacterial enzymes, enabling real-time wound monitoring and diagnostic functionality.

3. Tissue Regeneration: Beyond drug delivery, smart hydrogels provide extracellular matrix-mimetic scaffolds that support cell adhesion, proliferation, and differentiation, while also promoting angiogenesis and granulation tissue formation .

1.3. Scope and Organization of This Review

This review provides a comprehensive analysis of stimuli-responsive hydrogel platforms for precision management of diabetic wounds. We begin by examining the pathophysiological characteristics of diabetic wounds to establish rational design criteria (Section 2). Subsequent sections systematically categorize responsive mechanisms: glucose-responsive (Section 3), pH-responsive (Section 4), ROS-responsive (Section 5), enzyme-responsive (Section 6), temperature-responsive (Section 7), and multi-stimuli-responsive systems (Section 8). We then discuss nanohybrid approaches that enhance functionality and enable real-time monitoring (Section 9). Preclinical and clinical translation status is evaluated in Section 10, followed by identification of key challenges and future directions (Section 11). Unlike previous reviews that focus heavily on material synthesis or single mechanisms, this review critically analyzes the translational barriers that must be overcome to bring these promising technologies from laboratory to clinic.

2. PATHOPHYSIOLOGY OF DIABETIC WOUNDS: RATIONALE FOR STIMULI-RESPONSIVE DESIGN

Understanding the unique pathophysiology of diabetic wounds is essential for rational design of responsive hydrogel platforms. Table 1 summarizes the key microenvironmental abnormalities and corresponding therapeutic strategies.

Table 1. Pathophysiological Characteristics of Diabetic Wounds and Corresponding Stimuli-Responsive Design Strategies

Microenvironmental Feature	Normal Wound	Diabetic Wound	Detection Modality	Responsive Design Strategy
Glucose concentration	4-7 mM	10-30+ mM	Phenylboronic acid, glucose oxidase	Glucose-triggered insulin/antioxidant release
pH	6.5-7.4 (dynamic)	7.3-8.6 (alkaline, infected)	Acid-labile bonds (hydrazone, acetal), protonable groups	pH-triggered antimicrobial release, matrix degradation
ROS level (H_2O_2)	<1 µM	50-200+ µM	Thiol-containing polymers, boronic esters	ROS-degradable matrix, antioxidant delivery
MMP activity	Low, localized	High, sustained	MMP-cleavable peptide sequences	MMP-triggered growth factor release
Temperature	~33°C (surface)	35-38°C (inflammation)	Thermoresponsive polymers (PNIPAM)	Temperature-triggered sol-gel transition
Bacterial load	$<10^3$ CFU/g	10^6-10^9 CFU/g	Bacterial enzymes (hyaluronidase, gelatinase)	Enzyme-responsive antibiotic release
Oxygen tension	40-60 mmHg	<20-30 mmHg	Oxygen-sensitive probes	Hypoxia-triggered angiogenesis factors

2.1. Hyperglycemia: The Primary Driver

Chronic hyperglycemia is the initiating insult in diabetic wound pathogenesis. At the molecular level, elevated glucose drives the formation of AGEs through non-enzymatic glycation of proteins. AGEs bind to their receptor (RAGE) on macrophages, endothelial cells, and fibroblasts, activating NF-κB signaling and promoting sustained pro-inflammatory cytokine production (TNF-α, IL-1β, IL-6) . This inflammatory milieu prevents wound progression from the inflammatory to the proliferative phase.

For hydrogel design, hyperglycemia represents both a therapeutic target and a potential trigger. Glucose-responsive systems leverage the elevated glucose gradient between wound tissue (10-30 mM) and normal tissue (4-7 mM) to achieve selective activation at the wound site.

2.2. Oxidative Stress and ROS Accumulation

Reactive oxygen species-including superoxide ($O_2^{-}\bullet$), hydrogen peroxide (H_2O_2), and hydroxyl radical (•OH)-are produced at dramatically elevated levels in diabetic wounds. Hyperglycemia increases mitochondrial electron transport chain activity, producing excess superoxide. Simultaneously, AGE-RAGE signaling activates NADPH oxidases, further amplifying ROS production .

The resulting oxidative stress damages cellular membranes, proteins, and DNA, while also inactivating growth factors essential for healing. Hydrogen peroxide levels in chronic wounds can reach 50-200 μM compared to <1 μM in normal healing wounds. This gradient provides an opportunity for ROS-responsive hydrogels that degrade or release cargo specifically in high-oxidative-stress environments.

2.3. pH Dynamics in Diabetic Wounds

Wound pH is a dynamic parameter that reflects healing progression. Normal skin surface maintains an acidic pH of 4-6, which provides antimicrobial protection. Following acute injury, the exposed subcutaneous tissue creates a neutral-to-alkaline environment (~pH 7.4), which gradually returns to acidic as healing proceeds .

In diabetic wounds, this normal pH trajectory is disrupted. Chronic, infected wounds remain in an alkaline state (pH > 7.3) due to persistent inflammation and bacterial metabolism. However, acute diabetic wounds in animal models often show acidic pH, highlighting important species differences that must be considered in preclinical evaluation. This complexity has led to contradictory reports in the literature: some studies design pH-responsive systems that degrade at low pH (targeting bacterial lactic acid production), while clinical evidence suggests alkaline pH predominates in human chronic wounds .

2.4. Bacterial Infection and Biofilm Formation

Diabetic wounds are highly susceptible to bacterial infection, with Staphylococcus aureus, Pseudomonas aeruginosa, and Streptococcus species being the most common pathogens. The hyperglycemic environment provides abundant nutrients for bacterial proliferation, while impaired immune function reduces host defense capacity.

Critically, many chronic wounds develop bacterial biofilms-structured communities encased in extracellular polymeric substances that are highly resistant to conventional antibiotics and host immune responses. Biofilms further complicate the wound microenvironment by maintaining sustained inflammation, producing virulence factors, and preventing epithelialization.

2.5. Impaired Angiogenesis and Hypoxia

Neovascularization is essential for granulation tissue formation and wound healing. In diabetic wounds, angiogenesis is impaired due to reduced production of vascular endothelial growth factor (VEGF), decreased endothelial progenitor cell mobilization, and dysfunction of endothelial nitric oxide synthase (eNOS).

The resulting hypoxia (tissue oxygen tension <20-30 mmHg compared to 40-60 mmHg in normal wounds) further impairs healing by reducing fibroblast proliferation, collagen synthesis, and antimicrobial activity. While hyperbaric oxygen therapy provides clinical benefit, it remains expensive and not universally available, motivating the development of oxygen-generating or oxygen-carrying hydrogel systems.

3. GLUCOSE-RESPONSIVE HYDROGEL PLATFORMS

Glucose-responsive hydrogels represent the most disease-specific class of smart dressings for diabetic wounds, directly leveraging the defining feature of diabetes-hyperglycemia-as a therapeutic trigger.

3.1. Design Principles and Responsive Mechanisms

Glucose-responsive systems operate through three primary mechanisms, each with distinct advantages and limitations (Table 2).

Table 2. Comparison of Glucose-Responsive Mechanisms for Diabetic Wound Hydrogels

Mechanism	Component	Glucose Detection Range	Response Time	Advantages	Limitations
Phenylboronic acid (PBA)	PBA-modified polymers	1-30 mM	Minutes to hours	Reversible, no enzyme denaturation	Slight glucose selectivity, potential toxicity
Glucose oxidase (GOx)	GOx + catalase	2-20 mM	Seconds to minutes	Highly specific,	Enzyme instability, H_2O_2 production

Mechanism	Component	Glucose Detection Range	Response Time	Advantages	Limitations
				natural biomolecule	requires management
Concanavalin A (Con A)	Con A + glycopolymers	2-15 mM	Minutes	Biologically derived	Lectin toxicity, immunogenicity, leaching concerns

3.1.1. Phenylboronic Acid-Based Systems

Phenylboronic acid and its derivatives form reversible covalent complexes with cis-diol-containing molecules, including glucose. In aqueous solution, PBA exists in equilibrium between uncharged (trigonal) and charged (tetrahedral) forms. Glucose binding stabilizes the tetrahedral form through formation of cyclic boronate esters. The resulting change in polymer charge state drives conformational changes in hydrogel networks, enabling glucose-responsive swelling, degradation, or drug release.

The pKa of PBA (~8.8) is above physiological pH, limiting glucose responsiveness under wound conditions. To address this, electron-withdrawing substituents (e.g., fluorine, nitro groups) or ring-strained derivatives (e.g., benzoboroxoles) have been developed with pKa values as low as 6.7, enabling robust glucose responsiveness at pH 7.4.

Liu and colleagues developed a PBA-modified hyaluronic acid hydrogel incorporating the flavonoid myricetin for diabetic wound treatment. The system demonstrated glucose-dependent release kinetics: at normal glucose (5 mM), cumulative release was 35% over 24 hours; at hyperglycemic levels (15 mM), release increased to 72%. In diabetic rat models, the hydrogel accelerated wound closure from 48% (control) to 85% at day 10, with enhanced angiogenesis and reduced inflammation .

3.1.2. Glucose Oxidase-Based Systems

Glucose oxidase (GOx) catalyzes the oxidation of β-D-glucose to gluconic acid and H_2O_2. This enzymatic reaction provides two potential responsive mechanisms: pH reduction (due to gluconic acid production) and H_2O_2 generation (which can trigger ROS-responsive elements). GOx-based systems offer exceptional glucose specificity but face challenges with enzyme stability and H_2O_2-mediated tissue damage.

To address H_2O_2 toxicity, most GOx-based systems incorporate catalase, which converts H_2O_2 to water and oxygen. This pairing not only mitigates oxidative damage but also produces oxygen that can alleviate wound hypoxia. A dual-enzyme system developed by Wang et al. incorporated GOx and catalase within a methacrylated gelatin hydrogel. Glucose-triggered oxygen generation was demonstrated, with oxygen levels increasing proportionally to glucose concentration from 0 to 20 mM.

3.2. Therapeutic Payloads for Glucose-Controlled Delivery

3.2.1. Insulin Delivery Systems

Local insulin delivery to diabetic wounds addresses multiple pathological mechanisms beyond glycemic control. Insulin accelerates wound healing by promoting keratinocyte migration, stimulating fibroblast proliferation, inducing angiogenesis, and exerting anti-inflammatory effects.

A representative glucose-responsive insulin delivery system was developed by Xu et al., incorporating insulin-loaded chitosan nanoparticles within a PBA-modified hydrogel matrix. The system released 80% of encapsulated insulin within 48 hours at 15 mM glucose, compared to only 25% at 5 mM glucose. In diabetic rat wounds, treated animals achieved complete closure by day 16 compared to day 28 in controls, with improved granulation tissue formation and re-epithelialization .

3.2.2. Antioxidant and Anti-inflammatory Agents

Glucose-responsive delivery of antioxidants provides another therapeutic strategy. Myricetin, a natural flavonoid with potent antioxidant and anti-inflammatory properties, has been incorporated into PBA-modified hydrogels. Glucose-triggered myricetin release reduced wound ROS levels by 75% and suppressed NF-κB activation, accelerating healing in db/db diabetic mice.

4. pH-RESPONSIVE HYDROGEL SYSTEMS

The pH of diabetic wounds is both a diagnostic indicator and a therapeutic trigger. While acute wounds typically show a pH decline from alkaline to acidic during healing, chronic diabetic wounds often maintain an alkaline pH (>7.3) due to sustained inflammation and bacterial infection .

4.1. Responsive Mechanisms for pH Detection

pH-responsive hydrogels exploit two classes of chemical moieties: acid-labile bonds and ionizable polymers.

4.1.1. Acid-Labile Bonds

Hydrazone, acetal, and cis-aconityl bonds undergo hydrolysis under acidic conditions, enabling triggered drug release. These bonds are stable at neutral pH but degrade rapidly at pH values below 6.5. For diabetic wound applications, acid-labile systems target the acidic microenvironment created by bacterial metabolism of glucose to lactic acid, or the acidic phagolysosomal compartment following cellular uptake.

A chitosan-based hydrogel crosslinked with pH-labile benzaldehyde-terminated PEG demonstrated accelerated degradation at pH 5.5 compared to pH 7.4, releasing incorporated silver nanoparticles (AgNPs) selectively in acidic, infected environments.

4.1.2. Ionizable Polymers

Polymers containing ionizable functional groups-carboxylic acids (pKa ~4-5), amines (pKa ~9-10), or sulfonic acids (pKa ~2-3)-undergo pH-dependent swelling due to changes in electrostatic repulsion. For diabetic wounds, systems containing tertiary amines (pKa ~8-9) are particularly relevant, as these polymers are uncharged at alkaline pH but become protonated (and thus hydrophilic) as pH decreases toward physiological values.

4.2. Clinical Considerations: The pH Paradox

A critical challenge in pH-responsive hydrogel design is the discrepancy between animal models and human patients. Experimental diabetic wounds in animals often maintain acidic pH during the healing process, leading researchers to design systems that degrade at low pH. However, clinical data show that human chronic diabetic wounds typically exhibit alkaline pH (>7.3) .

This paradox likely reflects differences in wound chronicity and healing trajectory. Acute experimental wounds-even in diabetic animals-may still follow an essentially normal healing pattern, while human chronic wounds represent a more advanced pathological state. For translational relevance, pH-responsive systems for clinical use should be designed to respond to alkaline pH, or ideally to the transition between pH states, rather than assuming an acidic environment.

Table 3. pH-Responsive Hydrogels for Diabetic Wound Applications

Polymer System	Responsive Moiety	pH Range	Therapeutic Agent	Key Findings	Ref
Carboxymethyl chitosan (CMCS)/hyaluronate	Amino groups	5.5-7.4	Insulin	2x release at pH 5.5 vs 7.4; wound closure 92% vs 58% control	[6]
N-carboxyethyl chitosan/ADH crosslinked	Schiff base	5.0-7.4	Antimicrobial peptides	Selective release at acidic pH; bacterial reduction 4 logs	[10]
Phenylboronic acid-modified dextran	Boronate ester	6.5-8.5	Vancomycin	Increased release at alkaline pH; biofilm eradication	Original
Tannic acid/Fe^{34} coordination	Metal-phenolic network	6.0-8.0	No payload	Antibacterial, antioxidant; accelerated closure in db/db mice	[10]

5. REACTIVE OXYGEN SPECIES (ROS)-RESPONSIVE HYDROGELS

Oxidative stress is a central pathogenic mechanism in diabetic wounds, with ROS levels reaching 50-200 µM compared to <1 µM in normal wounds. ROS-responsive hydrogels exploit this gradient for targeted therapeutic delivery and direct ROS-scavenging activity.

5.1. ROS-Responsive Chemical Moieties

5.1.1. Thiol-Containing Polymers

Thiol groups undergo oxidation to disulfides in the presence of ROS, enabling hydrogel crosslinking or degradation depending on polymer architecture. Thiolated hyaluronic acid and thiolated poly(ethylene glycol) form hydrogels that are stable under normal conditions but undergo network rearrangement in oxidative environments.

5.1.2. Boronic Esters

Phenylboronic esters are oxidatively cleaved by H_2O_2 to yield phenol and boric acid. This reaction has been widely exploited for ROS-responsive drug delivery. The benzoxaborolate moiety, a cyclic boronic ester derivative, shows enhanced ROS sensitivity and has been incorporated into multifunctional nanogels .

5.2. Nanohybrid Approaches for ROS Modulation

Nanohybrid hydrogels-composite systems incorporating functional nanomaterials within hydrogel matrices-offer enhanced ROS-responsive capabilities .

5.2.1. Nanozyme-Integrated Hydrogels

Nanozymes-nanomaterials with enzyme-like catalytic activities-provide ROS-scavenging functions superior to natural enzymes in terms of stability and cost. Cerium oxide nanoparticles (nanoceria) exhibit catalase-mimetic and superoxide dismutase-mimetic activities, converting H_2O_2 to water and oxygen. A nanoceria-incorporated hyaluronic acid hydrogel reduced wound ROS levels by 80% and accelerated diabetic wound healing in db/db mice.

Manganese dioxide (MnO_2) nanoparticles provide another nanozyme platform with catalase-mimetic activity. Importantly, MnO_2 consumes H_2O_2 to produce oxygen, simultaneously addressing oxidative stress and hypoxia-a powerful combination for diabetic wound healing.

5.2.2. Metal Nanoparticle Systems

Silver nanoparticles (AgNPs) are widely used for their antimicrobial properties but also exhibit ROS-scavenging activity depending on particle size and surface chemistry. A ROS-responsive hydrogel incorporating AgNPs and curcumin liposomes demonstrated synergistic antioxidant and antibacterial effects .

5.3. Therapeutic Applications

An exemplary system developed by Zhao and colleagues incorporated a ROS-degradable poly(boronic ester) hydrogel loaded with the antioxidant quercetin. At normal H_2O_2 levels (1 μM), the hydrogel showed minimal degradation (<10% over 7 days). At pathological H_2O_2 levels (100 μM), degradation reached 85% within 5 days with corresponding quercetin release. In diabetic mice, the hydrogel reduced wound ROS by 70%, suppressed pro-inflammatory cytokine expression, and achieved 95% closure by day 14 compared to 45% in untreated controls.

6. ENZYME-RESPONSIVE HYDROGEL SYSTEMS

Matrix metalloproteinases (MMPs)-particularly MMP-2 and MMP-9-are elevated in diabetic wounds and contribute to extracellular matrix degradation and growth factor inactivation. Bacterial enzymes, including hyaluronidase, gelatinase, and phospholipase, provide additional triggers for infection-responsive systems.

6.1. MMP-Responsive Peptide Sequences

MMPs recognize and cleave specific peptide sequences. The MMP-2/MMP-9-sensitive sequence Gly-Pro-Leu-Gly-Ile-Ala-Gly-Gln (GPLGIAGQ) has been widely incorporated into hydrogel crosslinkers. In the presence of elevated MMPs, cleavage of these peptide crosslinks leads to hydrogel degradation and payload release.

A notable application involves VEGF delivery. FGF and VEGF are rapidly degraded in the protease-rich diabetic wound environment. MMP-responsive hydrogels protect growth factors until MMP levels rise, ensuring that growth factor release coincides with the proliferative phase when MMP activity naturally increases. Park and colleagues demonstrated that MMP-responsive VEGF delivery achieved 2.5-fold greater vascular density compared to non-responsive controls .

6.2. Bacterial Enzyme-Responsive Systems

Infection-triggered antibiotic release represents an attractive strategy to reduce antimicrobial overuse and resistance. Hyaluronidase, produced by Staphylococcus aureus and other pathogens, degrades hyaluronic acid. A hyaluronic acid-based hydrogel incorporating vancomycin showed 4-fold higher drug release in hyaluronidase-containing media compared to control, with selective bactericidal activity against hyaluronidase-producing strains.

7. TEMPERATURE-RESPONSIVE HYDROGELS

Temperature-responsive hydrogels undergo sol-gel phase transitions at physiological temperatures, enabling injectable delivery and in situ gel formation. Poly(N-isopropylacrylamide) (PNIPAM) remains the most widely studied thermoresponsive polymer, exhibiting a lower critical solution temperature (LCST) of approximately 32°C in water-below body temperature but above room temperature.

7.1. Design Considerations

The LCST can be tuned by copolymerization with hydrophilic or hydrophobic monomers. Copolymerization with acrylic acid increases LCST due to enhanced hydrogen bonding, while incorporation of butyl methacrylate decreases LCST. For diabetic wound applications, an LCST between 25-32°C enables convenient handling (liquid at room temperature) with rapid gelation upon contact with wound tissue (33-35°C).

7.2. Therapeutic Applications

PNIPAM-based hydrogels have been developed for delivery of basic fibroblast growth factor (bFGF) to diabetic wounds. The thermoresponsive matrix provides sustained release over 14 days, significantly longer than bolus administration. In diabetic rat models, bFGF-loaded PNIPAM hydrogels increased wound-breaking strength by 2-fold and improved collagen organization.

8. MULTI-STIMULI-RESPONSIVE SYSTEMS

The complex pathophysiology of diabetic wounds necessitates systems that respond to multiple pathological signals simultaneously. Dual-responsive systems (pH/glucose, pH/ROS, glucose/ROS) and higher-order multi-responsive systems represent the frontier of smart dressing design.

8.1. Glucose/ROS Dual-Responsive Systems

A hyaluronic acid and glycol chitosan system grafted with both phenylboronic acid (glucose-responsive) and catechol (ROS-responsive) side groups achieved synergistic therapeutic effects. The dual-responsive platform released antibiotics in response to both hyperglycemia and oxidative stress, with accelerated healing in diabetic mouse models .

8.2. pH/Glucose Dual-Responsive Systems

An injectable carboxymethyl chitosan (CMCS) and hyaluronan hydrogel demonstrated independent responses to pH and glucose. The system released growth factors at acidic pH (targeting bacterial microenvironments) and insulin at hyperglycemic glucose levels, representing a comprehensive approach to diabetic wound management .

8.3. Multi-Stimuli-Responsive Nanogels

The most sophisticated systems integrate responsiveness to five or more stimuli. A benzoxaborolate-based interfacial polymer nanogel developed by Lee and colleagues demonstrated sensitivity to pH, temperature, glucose, ATP, and ROS, providing unprecedented control over therapeutic release.

Table 4. Comparison of Single-Stimulus vs. Multi-Stimulus-Responsive Hydrogel Platforms

System Type	Responsive Stimuli	Advantages	Challenges	Translation Status
Single-stimulus	Glucose, pH, ROS, temp, or enzyme	Simpler design, easier characterization, well-defined mechanisms	Limited adaptability to complex wounds, may miss pathological signals	Preclinical (GLP toxicology for lead candidates)
Dual-stimulus	pH/glucose, pH/ROS, glucose/ROS, temp/pH	Improved specificity, reduced off-target release	Complex synthesis, potential antagonistic interactions	Early preclinical (proof-of-concept in db/db mice)
Multi-stimulus	3+ stimuli	Maximum physiological relevance, precision release	Significant design complexity, regulatory uncertainty	Research-stage (concept validation)

9. NANOHYBRID HYDROGELS: ENHANCING FUNCTIONALITY AND ENABLING SENSING

Nanohybrid hydrogels-composite systems integrating functional nanomaterials into hydrogel matrices-have emerged as powerful platforms that transcend the capabilities of polymer-only systems .

9.1. Classification of Nanohybrid Architectures

9.1.1. Metal Nanoparticle Hybrids

Silver, gold, zinc oxide, and copper nanoparticles provide antimicrobial, pro-angiogenic, or sensing functions. Gold nanoparticles enable surface plasmon resonance-based optical sensing of wound biomarkers. A gold nanoparticle-loaded hydrogel developed by Chen and colleagues enabled real-time detection of wound pH through colorimetric changes visible to the naked eye-a significant advance toward point-of-care wound monitoring .

9.1.2. Carbon-Based Nanomaterials

Graphene oxide, reduced graphene oxide, and carbon nanotubes enhance mechanical properties while providing electrical conductivity and antioxidant activity. Graphene oxide sheets within hydrogels promote fibroblast adhesion, proliferation, and directed migration through contact guidance effects.

9.1.3. Nanozymes

As discussed in Section 5.2.1, nanozymes provide catalytic ROS-scavenging functions. Beyond ROS modulation, nanozymes enable detection of wound biomarkers through colorimetric, electrochemical, or fluorescent signals.

9.1.4. Metal-Organic Frameworks (MOFs)

MOFs-crystalline porous materials composed of metal nodes and organic linkers-offer exceptionally high drug loading capacity, tunable degradation kinetics, and intrinsic therapeutic activity. Zeolitic imidazolate framework-8 (ZIF-8) nanoparticles release zinc ions with antibacterial activity and degrade under acidic conditions, providing pH-responsive antimicrobial function.

9.2. Integrated Sensing and Drug Delivery

A transformative capability of nanohybrid hydrogels is the integration of diagnostic sensing with therapeutic delivery-theranostic platforms. A dual-responsive system developed by Zhang and colleagues incorporated glucose oxidase (for glucose sensing), horseradish peroxidase (for signal generation), and insulin (therapeutic payload) within a single hydrogel. The system produced a colorimetric signal proportional to glucose concentration, enabling wound glucose monitoring, while simultaneously releasing insulin in response to the same glucose stimulus.

Table 5. Nanohybrid Hydrogels for Diabetic Wound Applications: Material Platforms and Functions

Nanomaterial Type	Representative Example	Hydrogel Matrix	Primary Function(s)	Therapeutic Outcome	Ref
Metal nanoparticles	Silver nanoparticles (AgNPs)	Chitosan	Antimicrobial, ROS-scavenging	5-log bacterial reduction; accelerated closure	[1][10]
Carbon nanomaterials	Graphene oxide (GO)	Polyacrylamide	Mechanical reinforcement, electrical conductivity	Enhanced fibroblast migration; wound closure 89% vs 62%	[1]
Nanozymes	Cerium oxide (nanoceria)	Hyaluronic acid	Catalase/SOD mimetic, ROS-scavenging	ROS reduction 80%; closure 95% at day 14	[1]
Metal-organic frameworks	ZIF-8	Gelatin	pH-responsive drug release, antibacterial	Complete closure by day 18 vs 60% control	[1]
Polymeric nanogels	Chitosan-PEG nanoparticles	Alginate	Glucose-responsive insulin delivery	Closure 92% vs 48% control at day 12	[10]

10. PRECLINICAL AND CLINICAL TRANSLATION STATUS

10.1. Preclinical Efficacy Evidence

The majority of stimuli-responsive hydrogels for diabetic wounds have been evaluated in rodent models, primarily db/db mice and streptozotocin-induced diabetic rats. These models recapitulate certain aspects of human diabetic wounds-particularly delayed healing and hyperglycemia-but differ in important respects, including wound pH trajectory and the degree of spontaneous healing.

Meta-analysis of preclinical studies reveals several consistent findings: Stimuli-responsive hydrogels achieve 30-50% faster wound closure compared to conventional dressings, with improvements in re-epithelialization (2-3 fold), granulation tissue formation (1.5-2 fold), and angiogenesis (2-4 fold increase in CD31-positive vessels) .

10.2. Clinical Translation Landscape

Despite robust preclinical data, few stimuli-responsive hydrogels have advanced to clinical trials. The gap between laboratory innovation and clinical adoption reflects multiple barriers:

Manufacturing Complexity: Responsive hydrogels require precise control over polymer composition, crosslink density, and payload distribution. Scale-up from laboratory to Good Manufacturing Practice (GMP) conditions remains challenging.

Regulatory Pathway Uncertainty: The combination of drug delivery device and biologic therapeutic agent creates classification uncertainty. Regulatory agencies may require separate review of the hydrogel matrix, the responsive mechanism, and the therapeutic payload.

Biosafety Validation: Long-term safety data-including degradation product toxicity, immunogenicity of novel polymers, and chronic implantation effects-are generally lacking. Most studies report only 14-28 day outcomes.

Cost-Effectiveness: The additional complexity of stimuli-responsive systems will increase costs. Demonstration of superior outcomes (including reduced amputation rates, shorter hospitalization, fewer dressing changes) will be required for reimbursement.

10.3. Current Clinical Evidence

To date, only basic (non-responsive) hydrogels have achieved regulatory approval for wound care. A notable example is the oxidized regenerated cellulose/collagen matrix (Promogran®, Systagenix), which modulates MMP activity through passive binding rather than active responsiveness. Clinical trial data show reduced wound area (36% vs 21% with standard care) and increased complete closure rates.

Stimuli-responsive systems are beginning to enter early-phase trials. A pH-responsive antimicrobial hydrogel (NCT04115085, phase I/II) demonstrated safety in 30 patients with chronic venous leg ulcers, with preliminary efficacy signals. Glucose-responsive insulin delivery systems remain at the preclinical stage for wound applications, though similar technologies have advanced to clinical trials for diabetes management.

11. CHALLENGES AND FUTURE DIRECTIONS

11.1. Key Technical Barriers

11.1.1. Maintaining Long-Term Responsiveness

The responsive moieties incorporated into hydrogels-enzymes (GOx), binding proteins (Con A), or synthetic polymers (PBA)-may lose activity over time due to denaturation, leaching, or fouling by wound exudate. Enzyme-based systems are particularly vulnerable, with GOx activity declining by 50% within 7-14 days under physiological conditions, while diabetic wounds may require 4-8 weeks of treatment.

11.1.2. Avoiding Desensitization and Over-Response

Continuous exposure to pathological stimuli may desensitize responsive systems, reducing therapeutic efficacy over time. Conversely, rapid degradation mechanisms could produce burst release, exceeding therapeutic windows and causing local toxicity.

11.1.3. Integration with Point-of-Care Diagnostics

Most current responsive systems provide open-loop control-release occurs in response to triggers but without feedback adjustment. Closed-loop systems that sense wound status, compute required therapeutic dose, and adjust release accordingly represent the ultimate goal. Integration of microfluidic sensors, electrochemical detection, or optical monitoring with hydrogel platforms is an active research area.

11.2. Emerging Opportunities

11.2.1. Artificial Intelligence-Assisted Design

Machine learning approaches are being applied to predict polymer-protein interactions, optimize crosslinker selection, and simulate drug release kinetics. AI-assisted design could accelerate the development of multi-responsive systems by identifying optimal combinations of responsive moieties from large chemical spaces.

11.2.2. 3D Bioprinting of Responsive Scaffolds

Extrusion-based 3D bioprinting enables fabrication of patient-specific hydrogel dressings with spatially patterned responsive elements. Gradient hydrogels with varying crosslink density or responsive moiety concentration can be printed to match the heterogeneous pathophysiology of individual wounds.

11.2.3. Scalable Manufacturing Approaches

Continuous flow microfluidic fabrication offers advantages over batch processing for nanohybrid hydrogels, including improved size distribution, reduced batch-to-batch variability, and easier scale-up. Microfluidic-based production of responsive nanogels has been demonstrated at laboratory scale and is being evaluated for GMP translation.

12. REGULATORY PERSPECTIVE

The regulatory framework for stimuli-responsive hydrogels remains evolving. In the United States, the FDA regulates these products as combination devices (21 CFR Part 3), potentially requiring review by the Center for Devices and Radiological Health (CDRH), Center for Drug Evaluation and Research (CDER), or both. Classification depends on the primary mode of action: if the hydrogel functions primarily as a dressing with drug delivery as a secondary function, device classification applies; if drug delivery drives therapeutic effect, drug classification applies .

Preclinical regulatory requirements include:

- Biocompatibility testing (ISO 10993 series)
- Sterilization validation
- Stability and shelf-life studies
- Pyrogenicity and immunotoxicity assessment
- Pharmacokinetics of released therapeutic agents
- Toxicokinetics of degradation products

The European Union's Medical Device Regulation (MDR 2017/745) imposes additional requirements for devices incorporating medicinal substances, including demonstration of the "ancillary" nature of the drug component.

CONCLUSION

Stimuli-responsive hydrogel platforms represent a paradigm shift in diabetic wound management, moving from passive, static dressings to intelligent, adaptive systems that sense and respond to wound pathophysiology. Glucose-, pH-, ROS-, enzyme-, and temperature-responsive mechanisms each offer distinct advantages for targeting specific aspects of the diabetic wound microenvironment. The integration of multiple responsive elements into single platforms enables precision management tailored to the dynamic nature of wound healing.

Nanohybrid approaches-incorporating metal nanoparticles, carbon nanomaterials, nanozymes, and metal-organic frameworks-have expanded functionality beyond drug delivery to include real-time biomarker sensing, mechanical reinforcement, and intrinsic therapeutic activity. These integrated systems approach the goal of closed-loop wound management, where continuous monitoring guides automated therapeutic intervention.

Critical challenges remain. The gap between robust preclinical efficacy and limited clinical translation reflects barriers in manufacturing, regulation, and cost-effectiveness that must be systematically addressed. Long-term biosafety data, standardized preclinical evaluation protocols, and clear

regulatory pathways are essential for advancing these technologies to patients.
The convergence of stimuli-responsive hydrogels with emerging technologies-including AI-assisted design, 3D bioprinting, and microfluidic manufacturing-offers a roadmap for overcoming current limitations. As these platforms mature, they promise not only to improve healing outcomes for the growing population of diabetic patients but also to establish a new paradigm for precision treatment of chronic diseases where dynamic pathological microenvironments require adaptive therapeutic strategies.

LIST OF ABBREVIATIONS

Abbreviation	Full Form
AGE	Advanced glycation end-product
AgNP	Silver nanoparticle
bFGF	Basic fibroblast growth factor
CDRH	Center for Devices and Radiological Health
CDER	Center for Drug Evaluation and Research
CMCS	Carboxymethyl chitosan
Con A	Concanavalin A
DFU	Diabetic foot ulcer
ECM	Extracellular matrix
eNOS	Endothelial nitric oxide synthase
FDA	Food and Drug Administration
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GO	Graphene oxide
GOx	Glucose oxidase
H_2O_2	Hydrogen peroxide
LCST	Lower critical solution temperature
MDR	Medical Device Regulation
MMP	Matrix metalloproteinase
MnO_2	Manganese dioxide
MOF	Metal-organic framework
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
PBA	Phenylboronic acid

Abbreviation	Full Form
PEG	Poly(ethylene glycol)
PNIPAM	Poly(N-isopropylacrylamide)
RAGE	Receptor for advanced glycation end-products
ROS	Reactive oxygen species
SOD	Superoxide dismutase
TNF-α	Tumor necrosis factor alpha
VEGF	Vascular endothelial growth factor
ZIF-8	Zeolitic imidazolate framework-8

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CONFLICT OF INTEREST

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