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Smart and Responsive Drug Delivery Systems for Diabetic Ulcers: Advances in Pharmaceutical Design

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ABSTRACT

Diabetic ulcer is a significant medical issue affecting millions of patients globally due to consequential morbidity, mortality, and health care system costs. The complex pathophysiological process of delayed wound healing in diabetic patients remains inadequately addressed with conventional treatment modalities. This review summarises recent advances in smart, responsive engineered drug delivery systems for the treatment of diabetic ulcers. Moreover, we exemplify these strategies using emerging technologies, including nanotechnology, hydrogel matrices, stimulus-responsive systems, and bioactives. New methodologies, including next-generation approaches such as 3D-printed scaffolds, nanofiber systems, and theranostic platforms, are presented as alternative treatment options that could change the landscape of diabetes-related wound care. Discussions on the challenges of translation, regulation, and application of new pharma-technologies in clinical research are offered.

Keywords: Diabetic ulcers, Drug delivery systems, Hydrogels, Nanotechnology, Pharmaceutical design, Wound healing

1. INTRODUCTION

Diabetic foot ulcers (DFUs) are a critical global health challenge, affecting 15-25% of the 537 million adults with diabetes worldwide [1, 2]. These chronic wounds heal poorly, frequently become infected, and often recur, leading to severe consequences [3]. 20-30% of DFU patients require amputation, with significantly lower extremity amputations carrying a five-year mortality rate near 70% [4]. The economic impact is substantial, costing over $13 billion annually in the United States alone [5]. This significant burden—both human and financial—highlights the urgent need for innovative therapeutic approaches to address the impaired wound healing process in diabetic patients.

Even with classical strategies such as wound debridement, offloading, infection control, and glycemic optimisation, complete wound closure cannot always be achieved [6].

The drawbacks of current topical systems include low penetration, reduced bioavailability at the site of injury, a moderate to quick clearance rate from the site of application, and an inability to maintain a therapeutic concentration for an extended period [7]. These constraints have posed challenges for pharmaceutical scientists, who are required to propose innovative drug delivery technologies that can bypass biological barriers and ensure site-specific, controlled release of therapeutic agents. Smart and responsive drug delivery systems represent a new dimension in the treatment of diabetic ulceration, offering the potential for personalised wound care [8]. The unique wound environment may elicit the newly discovered mechanisms, enable controlled delivery and prolonged exposure to therapeutic agent(s), and provide

a means to combine different effects (anti-inflammatory, antimicrobial) in a single circulating formulation [9]. In this review, recent advances in pharmaceutical design for diabetic ulcers are considered, with a specific focus on the fabrication, characterisation, and clinical translation of smart drug-delivery devices.

2. Pathophysiology of Diabetic Ulcers

To develop successful drug-delivery approaches, it is essential to understand the complex pathophysiology of diabetic ulcer formation and poor remodelling [10]. Diabetic wounds are characterised by a dysregulated healing cascade, including various cellular and molecular abnormalities that distinguish them from acute wounds in the non-diabetic state [11]. The pathogenesis is characterised by a complex interplay of metabolic, vascular, neuropathic, and immunological factors that cumulatively compromise the wound-healing process [12]. Figure 1 explains the pathophysiology of diabetic ulcers.

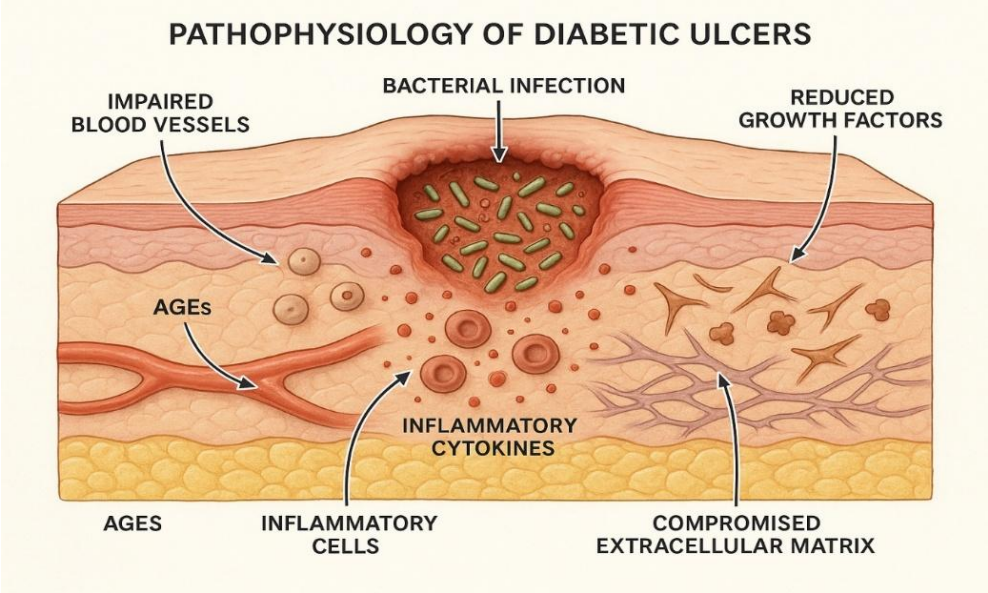

Figure 1*:* The pathophysiology of diabetic ulcers illustrates a complex relationship among factors contributing to poor reepithelialisation: advanced glycosylation end products (AGEs), matrix metalloproteinases (MMPs), inflammatory cytokines, abnormal vascularity, and bacterial colonisation (Self-designed).

2.1. Metabolic and Molecular Dysfunction:

Chronic hyperglycemia drives the formation of advanced glycation end products (AGEs), which cross-link with collagen and other extracellular matrix proteins, altering tissue mechanics and impairing cellular function [13]. AGEs activate the receptor for AGE (RAGE), triggering oxidative stress, mitochondrial dysfunction, and sustained inflammation, creating a hostile wound microenvironment that inhibits routine healing [14]. Additionally, diabetes-induced microvascular dysfunction reduces oxygen and nutrient delivery to wound tissues, further prolonging healing [15].

2.2. Inflammatory Dysregulation:

The inflammatory phase becomes prolonged and uncontrolled, with persistent elevation of pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) [16]. This chronic inflammation prevents transition to the proliferative phase, enhances tissue degradation through matrix metalloproteinase (MMP) overexpression—particularly MMP-2, MMP-9, and MMP-13—and simultaneously suppresses tissue inhibitors of metalloproteinases (TIMPs) [17]. Concurrently, essential growth factors for wound healing, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and transforming growth factor-β (TGF-β), are significantly downregulated [18].

2.3. Neuropathic and Immune Complications:

Diabetic neuropathy diminishes protective sensation, resulting in repetitive unrecognized trauma and delayed wound detection [19]. Autonomic dysfunction reduces sweat production, causing xerosis (dry skin) that is prone to fissuring and ulceration [20]. Furthermore, diabetes compromises immune responses through multiple mechanisms:

impaired neutrophil chemotaxis, reduced phagocytic activity, defective bacterial killing, and altered macrophage polarization that favors a pro-inflammatory M1 phenotype over a pro-healing M2 phenotype [21]. This immunological dysfunction significantly increases susceptibility to wound infections and biofilm formation

3. Current Treatment Strategies

The traditional treatment modalities for diabetic wounds, namely glycemic control, wound debridement, infection management, and pressure treatment, as well as topical ointments [22]. These simple interventions show many disadvantages. The systemic and topical administration of antimicrobials, such as silver and iodine, even if proven effective, also demonstrates low specificity and cytotoxicity to new tissue and contributes to the growing problem of antimicrobial resistance. [23]. Several traditional topical therapies are most frequently employed in this context, including antimicrobial agents, growth factors, and wound dressings. A significant disadvantage of these therapies is their low efficacy, due to poor tissue penetration and rapid wound clearance [24].

Thus, the ability of topical antibiotics, such as mupirocin, gentamicin, and selected silver formulations, to prevent and treat wound infections is a concern [25]. However, due to concerns about antibiotic resistance, cytotoxicity, and narrow-spectrum activity, the quest for alternative antimicrobial options continues [26]. Additionally, while clinical studies have shown that topical growth factors, including recombinant human platelet-derived growth factor, offer several benefits, their efficacy in practice is limited by rapid degradation and poor stability in the wound environment [27].

Nowadays, wound dressings have moved from being simple protective coverings to being equipped with bioactive factors that regulate tissue balance and protect wounds through optimal moisture control, exudate modulation, and healing promotion [28]. Advanced dressing types include hydrocolloids, hydrogels, foams, alginates, and collagen-derived wound dressings, each with properties suited to different wound characteristics [29]. However, such "passive" dressings are unable to release drugs in a controlled manner or adapt to evolving wound conditions [30]. The shortcomings of conventional compositions become apparent when one considers the various requirements necessary for an effective diabetic ulcer treatment. An ideal therapeutic system should provide controlled and sustained drug release, maintain active material at the wound site at therapeutic levels, protect sensitive bioactive agents from degrading enzymes, and respond to the shifting state of the tissue repair process. They should be biocompatible and non-immunogenic, thereby allowing the infusion of multiple therapeutic agents for multimodal targeting of diabetic wound pathology [31]. This also underscores the need for advanced, targeted drug-delivery systems that enhance therapeutic efficacy while limiting adverse effects. Table 1 shows the comparison between classic and advanced modalities.

Table 1: Comparative Analysis: Classical vs. Advanced Modalities

Aspect	Classical Treatments	Advanced Drug Delivery Systems
Drug Release	Passive, uncontrolled, burst release	Controlled, sustained, programmable release.
Targeting	Non-specific, systemic exposure	Site-specific, targeted delivery to the wound bed
Bioactive Protection	Minimal protection from degradation	Encapsulation shields from proteolytic enzymes
Therapeutic Duration	Short-acting, requires frequent dosing	Prolonged action, extended therapeutic window
Responsiveness	Static, no adaptation to wound changes	Stimuli-responsive (pH, glucose, enzyme-triggered
Multi-drug Delivery	Limited, potential incompatibility	Co-delivery of multiple agents for synergistic effects
Penetration	Poor tissue penetration	Enhanced penetration via nanocarriers
Biocompatibility	Variable, potential cytotoxicity	Designed for biocompatibility and biodegradability
Immune Response	May trigger inflammation	Engineered to be non-immunogenic
Cost-Effectiveness	Low initial cost, high long-term burden	Higher initial investment, potential cost savings through improved healing

4. Advanced Drug Delivery Technologies

A drug delivery system (DDS) refers to advanced techniques and technologies used to deliver pharmaceutical compounds throughout the body, optimizing therapeutic effects while minimizing side effects. Traditional DDS approaches, such as oral tablets and injections, have evolved into sophisticated methods, including liposomes, nanoparticles, transdermal patches, and mRNA-based carriers, each designed to improve parameters such as drug stability, targeting, bioavailability, and sustained release [(32)].

These modern DDS technologies enable the delivery of poorly soluble drugs, facilitate controlled or site-specific release, and enhance patient compliance through non-invasive or sustained formulations. Recent innovations include hybrid systems that combine the benefits of multiple materials, and devices like programmable implantable pumps for precise dosing. The development and selection of a particular DDS depend on the drug's physicochemical properties, target site, and therapeutic goals, making this a dynamic and crucial field in pharmaceutical sciences [(33)]. Table 2 below provides a comprehensive comparison of major Drug Delivery System (DDS) technologies.

Table 2: Comparison of Major Drug Delivery System Technologies

DDS Technology	Key Advantages	Major Limitations
Liposomes	Biodegradable, enhances solubility, and is safe.	Short circulation, costly production
Polymeric Nanoparticles	Controlled release, high drug loading	Toxicity, reticuloendothelial system (RES) issues
mRNA-based Delivery	Targeted, enabling genetic therapies	Requires ultra-cold storage, cost
Transdermal Patches	Non-invasive, stable release	Skin irritation, limited drug types
Microencapsulation	Prolonged, controlled release	Formulation complexity, scale-up issues
HYBRID: Liposome-Polymer	Combines controlled release, stability	Complex, expensive, regulatory issues
Self-micro Emulsifying	Improves hydrophobic drug bioavailability	Improves hydrophobic drug bioavailability
In-situ Gels	Site-specific, sustained control	Limited drugs are suitable, with potential irritation

4.1. Nanotechnology-Based Systems

It has emerged that nanotechnology is an innovative approach for treating diabetic ulcers, offering improved drug solubility, bioavailability, sustained release kinetics, and targeted delivery. Nanoparticulate delivery systems may overcome these biological limitations and enable therapeutic concentrations to be attained over time without systemic exposure [(34)]. The size range of 1–1000 nm is also deep enough to reach the wound and have cellular-level effects [(35)]. Figure 2 below shows Nanoparticle Structure-Function Relationships.

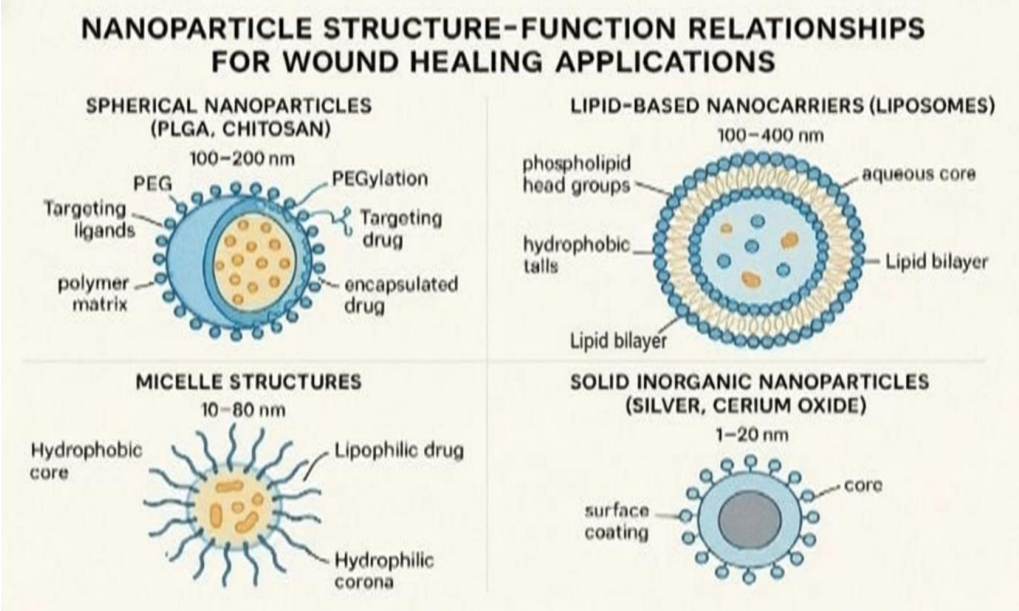

Figure 2*:* Polymeric nanoparticles (PLGA/Chitosan) with surface modifications, Liposome bilayer structure with drug locations, Micelle architecture with core-shell arrangement, Dendrimer branching generations, and drug loading (Self-designed).

All these products offer favourable advantages for DFU treatment: increased drug solubility, stabilization of charged molecules, and penetration into and through both biofilm and tissues [(36)]. Polymeric nanoparticles based on PLGA or chitosan can achieve sustained release of antibiotics, and deformable transferosomes are extremely useful for therapeutic molecules that penetrate deep tissues [(37)]. Hydrogel systems are another significant development. Hydrophilic polymer 3D networks are excellent ECM-mimicking materials, creating a moist environment that promotes healing and accommodating diverse therapeutics [(38)].

Another promising aspect of the nanotechnological approach using liposomal preparations is the use of biocompatible lipid bilayer structures that carry drugs with both hydrophilic and lipophilic properties [(39)]. Both transferosomes and ethosomes are complex liposomal systems that enhance skin penetration and prolong drug residence at the site of injury [(40)]. More recently, a gel-encapsulated liposomal formulation of curcumin has been tested for the healing of diabetic ulcers, and patients treated with this formulation showed better wound closure rates and reduced expression of inflammatory cytokines compared to those on a standard healing protocol [(41)].

In addition to the immunomodulatory activities of metallic nanomaterials, particularly silver (Ag) and gold (Au) nanoparticles, relatively little interest has been shown in other widely used materials. Ability to modify immune responses [(42)]. Silver NPs exhibit a broad spectrum of antimicrobial activity against both gram-positive and gram-negative bacteria, including MDR strains associated with diabetic wounds [(43)]. Gold nanoparticles have been applied as carriers of growth factors and/or for photothermal therapy to facilitate wound healing [(44)]. Table 3 explains the comparisons between Nanotechnology-Based Systems.

Table 3: Comparison of Nanotechnology-Based Drug Delivery Systems for Diabetic Ulcers

PLATFORM	SIZE RANGE (NM)	ADVANTAGES	RELEASE MECHANISM	LIMITATIONS
Polymeric Nanoparticles (PLGA, PLA)	50-500	Biodegradable Tunable release kinetics High drug loading capacity FDA-approved materials	Diffusion + polymer degradation	Burst release Manufacturing complexity Potential acidic degradation by-products
Liposomes & Ethosomes	50-200	Biocompatible Can encapsulate hydrophilic & lipophilic drugs Enhanced skin penetration	Membrane fusion/disruption	Stability issues Rapid clearance Expensive manufacturing

Chitosan Nanoparticles	10-1000	Mucoadhesive, Inherent antimicrobial, Haemostatic properties, Biodegradable	pH-sensitive dissolution + diffusion	pH-dependent stability Variable deacetylation affects properties
Silver Nanoparticles (AgNPs)	1-100	Broad-spectrum antimicrobial Anti-inflammatory Promotes proliferation	Ag+ ion release	Cytotoxicity at high concentrations Potential resistance development Staining
Gold Nanoparticles (AuNPs)	1-100	Biocompatible Drug carrier Photothermal therapy Imaging capabilities	Photothermal release or ligand exchange	High cost Long-term safety unclear Requires external stimuli (light)
Solid Lipid Nanoparticles (SLNs)	50-1000	Biocompatible lipids Controlled release Stable formulation	Lipid matrix diffusion	Drug loading capacity limitations Burst release Gelation tendency
Dendrimers	1-15	Monodisperse Multivalent surface High drug loading	pH/enzyme-triggered release	Toxicity concerns Complex synthesis High cost

4.2. Hydrogel-Based Delivery Systems

Hydrogels are three-dimensional polymer networks that can absorb large amounts of water without losing their structure [45]. These systems are similar to the extracellular matrix and are ideal for wound healing, as they retain moisture, facilitate gas exchange, and permit controlled drug delivery [46]. These hydrogels are biocompatible and exhibit tunable properties, making them excellent candidates for diabetic ulcer therapy [47].

Hydrogels derived from natural polymers such as chitosan, alginate, hyaluronic acid, and collagen are among the most well-known hydrogel systems due to their excellent biocompatibility and biodegradability. The promising potential of chitosan-based hydrogels for the treatment of wounds is reported due to their bacteriostatic, haemostatic, and cell-proliferation-stimulating properties [48]. **(Figure 3**) explains the significant components of natural and synthetic hydrogels.

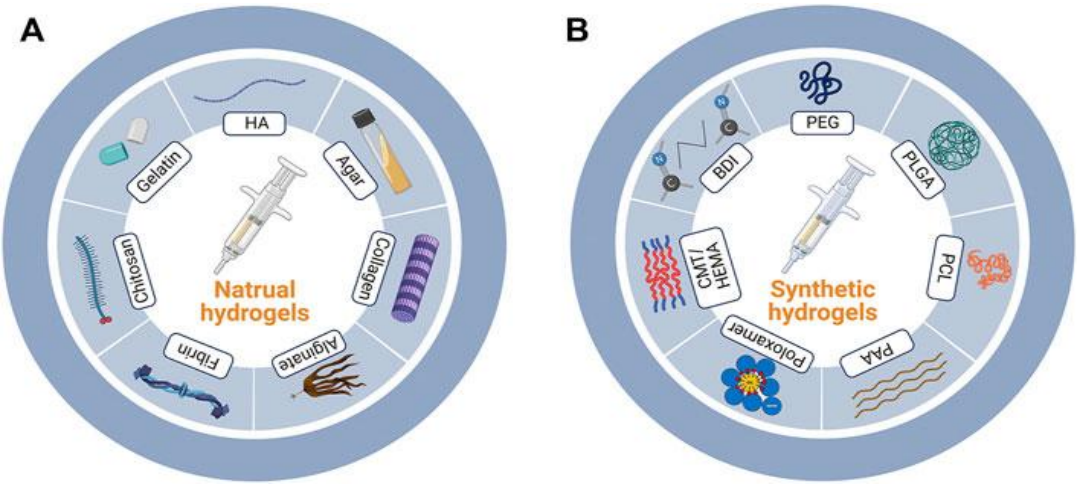

Figure 3: Nature-based and synthetic hydrogels. (A) Significant components of nature-based and (B) synthetic hydrogels. HA, hyaluronic acid; PEG, polyethylene glycol; PLGA, poly (lactic-co-glycolic acid); PCL, polycaprolactone; PAA, polyacrylic acid; CMT/HEMA, carboxy methyl tamarind/hydroxyethyl methacrylate; BDI, butane-diisocyanate [49].

Recent research has focused on the formulation of chitosan hydrogels containing growth factors such as EGF and bFGF to enhance angiogenesis and promote favourable progression in wound healing [50].

In addition, synthetic hydrogels, including PEG, PVA, and polyacrylamide, provided greater tunability of mechanical properties and degradation kinetics [51]. These copolymers can be designed with swelling ratios,

modulus, and drug release profiles to match the requirements of different wound types [52]. In particular, Injectable hydrogels have been of particular interest for their ability to conform to difficultly shaped affected areas. Additionally, the drug-delivery system is less invasive, which may improve the patient's prospects [53].
Thermo-responsive hydrogels are another class of advanced smart materials that exhibit a sol-gel transition in response to environmental temperature [54]. Thermo-sensitive hydrogels are often formulated on poly-N-isopropylacrylamide and similar polymers. They are in liquid form at room temperature or lower, but form gels upon application. This brings the freshly applied gel into closer contact with the tissues of an open wound as soon as it reaches body temperature [55]. Recently, various studies have demonstrated that antibiotics and growth factors can be incorporated into thermoresponsive hydrogels for sustained release and enhanced therapeutic effects [56].

4.3. Smart and Stimuli-Responsive Systems

Smart pharmaceutical technologies, including stimuli-responsive drug-delivery systems, represent the future of responsive healthcare applications and could react to local changes within a wound microenvironment [57]. These systems can be tuned to respond to environmental stimuli, including pH and temperature changes, as well as enzyme and other physiological cues, to deliver stimulus-responsive, on-demand drug release at the appropriate time and site [58]. This approach has obvious advantages over conventional controlled-release systems, as it uses the dynamic process of wound healing for its development [59]. Figure 4 shows the various stimuli-responsive drugs released.

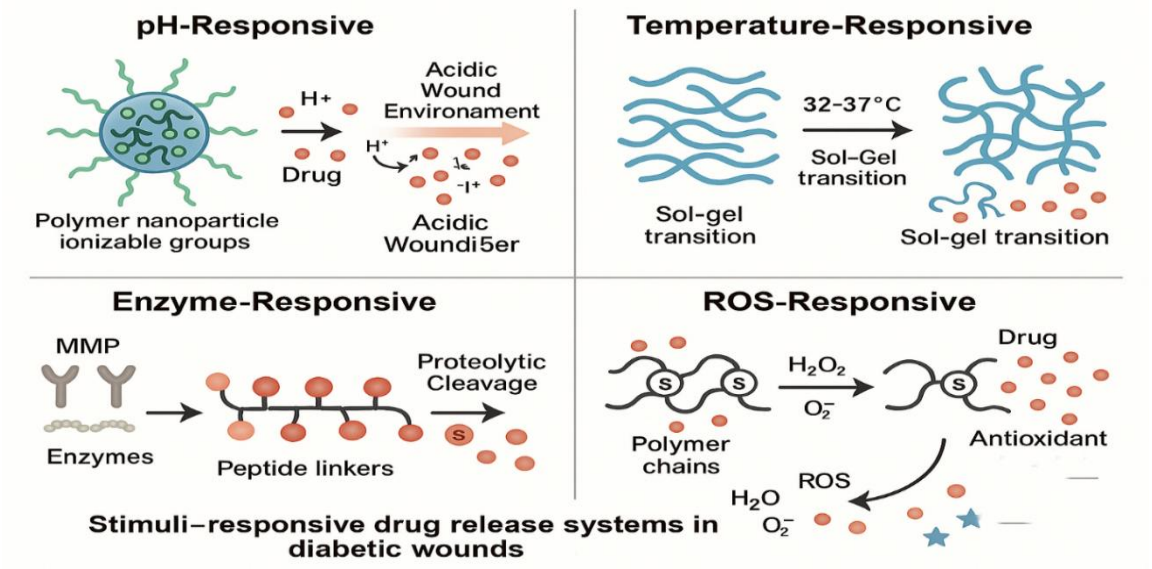

Figure 4: Schematic illustration of various stimuli-responsive mechanisms, including pH-sensitive, enzyme-responsive, ROS-sensitive, and temperature-responsive drug release systems in the diabetic wound environment (Self-designed).

pH-responsive systems exploit the altered pH landscape of diabetic wounds compared with normal dermis [60]. Infected wounds are usually associated with increased pH due to bacterial metabolism, whereas ischemia/hypoxia and lactate accumulation can lead to acidic conditions in chronic wounds [61]. Polymeric networks with pH-sensitive crosslinks or ionizable groups, for instance, have also been designed to release antimicrobial agents upon pH changes that coincide with infection [62]. The most pertinent reports have recently published pH-responsive ciprofloxacin-loaded nanoparticles releasing the drug predominantly at alkaline pH, which is indicative of a bacterial infection [63].
Enzyme-responsive systems exploit the overexpression of proteases, such as matrix metalloproteinases (MMPs), in chronic diabetic wounds [64]. These systems include peptide linkers sensitive to specific enzymes that can hydrolyse them and promote drug release [65]. MMP-responsive hydrogels were also developed for growth factor delivery at a not-too-high concentration, thereby improving the wound environment by protecting these labile agents, which are released only upon demand [66].

ROS-inducible systems target the oxidative burst component of diabetic wound pathology [67]. These include ROS-sensitive chemical linkages, which degrade under higher levels of oxidative stress, leading to the release of antioxidant agents and other drugs [68]. Recent efforts have focused on designing ROS-scavenging nanoparticles that degrade harmful free radicals while simultaneously delivering anti-inflammatory therapeutics [69].

4.4. Bioadhesive Films, Patches, and Scaffolds

Bioadhesive nanoparticles may be a promising carrier for optimized local drug delivery, providing prolonged drug retention and sustained therapeutic concentrations. In addition, the platform's clinical applications are abundant, as most polymers used for bioadhesion are both biodegradable and biocompatible [71]. Bioadhesive drug delivery systems provide sustained, controlled release while remaining in contact with the wound, achieved through close interaction between drugs and wound tissue [70]. For diabetic ulcer treatment in particular, treatments provide additional value when they maintain therapeutic concentrations at the wound site, and very favourable healing results can be achieved [72]. Bioadhesive systems are to be formulated with due consideration of the adhesion mechanism, mechanical properties, and drug release kinetics [73].

A large number of Bucco adhesive formulations are developed using mucoadhesive polymers such as Carbopol, sodium carboxymethylcellulose, and hyaluronic acid. These polymers interact with exudate and tissue surfaces through hydrogen bonding, electrostatic interactions, and chain interpenetration [74]. New bioadhesive films, including antimicrobials and growth factors, are more clinically effective for diabetic ulcers than conventional dressings [75].

A 3D scaffold is used as a tissue-engineering support and drug-delivery vehicle [76]. They may exist in various forms, including electrospun, freeze-dried, and 3D-printed scaffolds (Figure 5), and be regulated to appropriate porosity, mechanical characteristics, and drug-loading range [77].

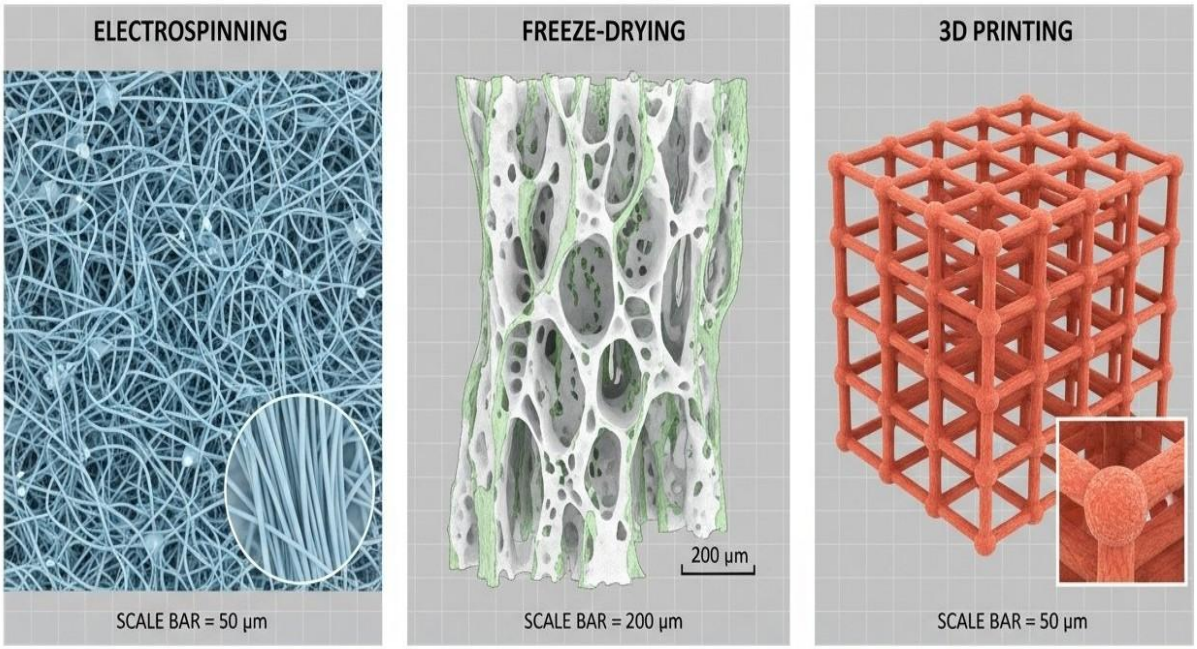

Figure 5: Manufactured biomaterial, scaffolds, electrospun, freeze-dried, and 3D printed technique (Self-designed).

Collagen-based scaffolds loaded with platelet-rich plasma have demonstrated successful clinical results in the treatment of diabetic foot ulcers [78]. A transdermal patch is another alternative to systemic drug administration in diabetic patients [79]. Such carriers can serve as controlled-release vehicles for drugs that promote wound healing from within (e.g., nutritional factors, antioxidants, and immunomodulators) [80]. Drug penetration can be improved by a microneedle-based patch, which could also preserve patient comfort and compliance [81]

5. Incorporation of Regenerative and Bioactive Compounds

Recently, stem cell therapy has emerged as a new approach to diabetes wound healing, and the regenerative potential of mesenchymal stem cells (MSCs) has taken center stage, as MSCs are known for their regenerative and immunomodulatory properties [92]. These cells can differentiate into various cell types involved in wound healing (i.e., fibroblasts, endothelial cells, and keratinocytes) [93]. Combining stem cells with drug-delivery scaffolds creates hybrids that combine cellular therapy and controlled release [94]. More recently, ATSC has been successfully incorporated into collagen-based scaffolds for the treatment of diabetic ulcers, leading to enhanced wound closure rates and improved tissue quality [95].

Exosomes, small extracellular vesicles secreted by various cell types, are being investigated as cell-free alternatives to stem cell-based therapies [96]. These endogenous nanoparticles contain growth factors, cytokines, and regulatory RNAs that can induce wound healing and tissue regeneration [97]. For example, advanced delivery systems, including exosome-loaded hydrogels and nanofiber scaffolds, are being designed for harnessing the established regenerative potential of stem cell-secreted factors without the complexity of cell-based therapies [98]. (Figure 6) explains a schematic representation of a hybrid theranostic platform for diabetic ulcer treatment.

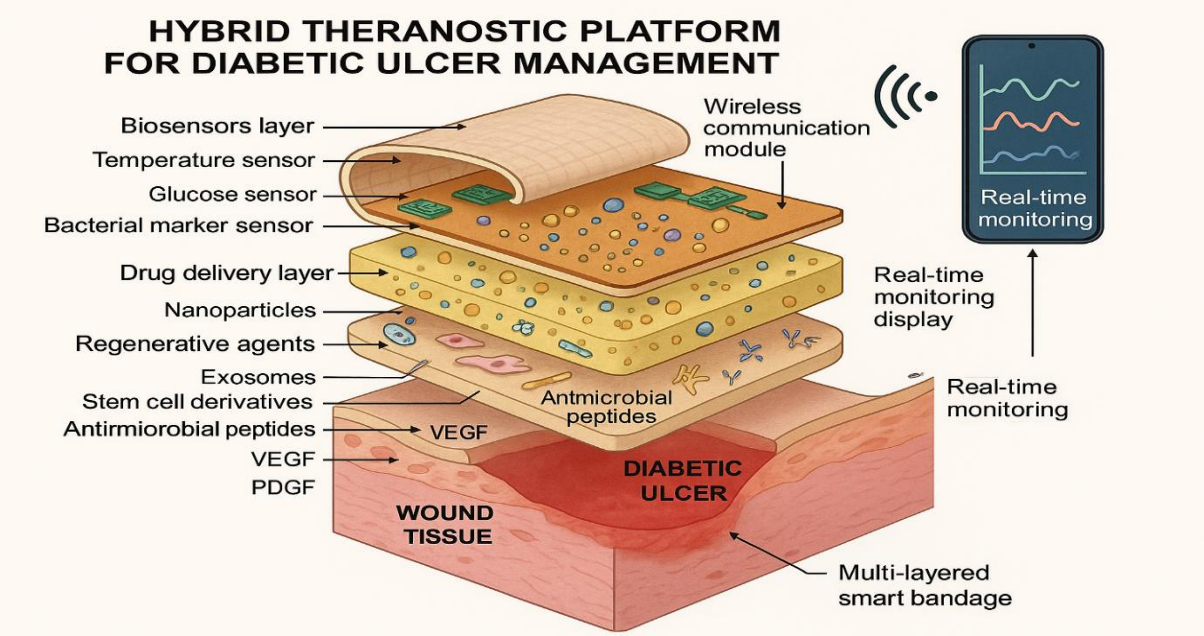

Figure 6: Schematic representation of a hybrid theranostic platform integrating diagnostic sensors, drug delivery components, and regenerative agents for comprehensive diabetic ulcer management with real-time monitoring capabilities (Self-designed).

Theranostic hydrogels represent a groundbreaking approach that integrates therapeutic and diagnostic capabilities within a single platform, enabling real-time wound monitoring and precise treatment. These advanced materials are engineered to maintain a moist, antimicrobial environment while promoting tissue regeneration through enhanced conductivity and bioactivity. Theranostic hydrogels that incorporate electroresponsive and stimuli-sensitive polymers enable continuous monitoring of key biomarkers, such as pH and glucose levels, ensuring accurate, timely therapeutic interventions. Bioelectronic components, including flexible biosensors, wearable electronic patches, and implantable microdevices, significantly enhance the functionality of wound care technology [99].

6. Emerging Technologies and Hybrid Systems

6.1. Integration of Advanced Technologies:

The convergence of cutting-edge technologies is generating sophisticated hybrid systems that integrate drug delivery, tissue scaffolds, and diagnostics into unified platforms, enabling personalized diabetic wound care with unprecedented precision and real-time monitoring [100].

6.2. Three-Dimensional Bioprinting:

3D printing technology enables fabrication of patient-specific drug delivery systems and tissue scaffolds with customizable architecture, porosity, and spatial drug distribution tailored to individual wound geometries [101]. Advanced bioprinting permits the creation of cell-laden constructs that regenerate tissue while providing spatiotemporal control over therapeutic release. Recent alginate-gelatin 3D-printed scaffolds encapsulating multiple growth factors (VEGF, PDGF, EGF) demonstrated accelerated diabetic wound closure in preclinical models [102].

6.3. Electrospun Nanofiber Systems:

Electrospinning produces ultrafine fibers (50-500 nm) with high surface area-to-volume ratios that mimic native extracellular matrix structure while functioning as sustained drug-release platforms [103]. Core-shell nanofiber architectures enable compartmentalized encapsulation of multiple agents with distinct release profiles-burst antimicrobial release followed by sustained growth factor delivery matching healing phases. Dual-functional nanofiber dressings incorporating silver nanoparticles and antibiotics effectively eradicated biofilm-forming bacteria in diabetic wound models while promoting re-epithelialization [104].

6.4. Smart Biosensor-Integrated Systems:

Intelligent biosensors integrated into drug delivery platforms enable real-time monitoring of wound parameters (pH, glucose, bacterial load, inflammatory markers) with closed-loop feedback control of therapeutic release [105]. Smart bandages incorporating colorimetric sensors and wireless communication provide continuous remote monitoring while delivering agents on demand, representing a paradigm shift toward precision medicine [106].

6.5. Multifunctional Combination Nano-systems:

Given the multifactorial etiology of diabetic wounds, nanotechnology-enabled combination therapies co-deliver antimicrobials, anti-inflammatory compounds, growth factors, and antioxidants in single formulations for synergistic multi-target therapy [107]. Layer-by-layer assembly techniques create hierarchical systems with sequential, programmed release profiles matched to the progression of the healing phase. Multifunctional nanoparticles combining photothermal therapy, controlled drug release, and diagnostic imaging offer comprehensive treatment of complex infected wounds with real-time monitoring [108]. Table 4 provides examples of nanotechnology-based systems for wound healing.

Table 4: Examples of Nanotechnology-Based or Advanced Combination Products for Diabetic Wound Healing (marketing, preclinical, and clinical stage).

Marketing stage	**Technology/ Formulation Type**	**Market Status and References**
SilvrSTAT® Gel Silver nanoparticles (AgNPs)	Nano silver hydrogel	FDA-cleared for wound management. SilvrSTAT® Gel – American Biotech Labs, FDA 510(k) K103693.
DermaGraft® Human fibroblast-derived dermal substitute	Bioengineered living dermal matrix	FDA-approved for diabetic foot ulcers. Organogenesis Inc. *DermaGraft® Prescribing Information*, FDA Approval, 2001.
Nanoskin® Nanofiber scaffold with antimicrobial coating	Electrospun nanofiber dressing	CE-marked (Europe). Nanoskin® Product Information, EU CE Certification, 2021.
Regranex® (Becaplermin Gel 0.01%) Recombinant human PDGF-BB	Growth factor gel (semi-nano scale protein delivery).	FDA-approved for diabetic foot ulcers. Regranex® (Becaplermin Gel 0.01%), Janssen Pharmaceuticals, FDA Approval, 1997.
Pre-clinical stage	**Technology/ Formulation Type**	**Market Status and References**
PLGA nanoparticles loaded with curcumin and resveratrol	Antioxidant + anti-inflammatory + pro-healing	Li J. et al., *Colloids Surf B Biointerfaces*, 2023

ZnO nanoparticles combined with insulin-loaded hydrogel	Controlled insulin release + epithelial regeneration	Zhang X. et al., *Biomaterials Advances*, 2022
Layer-by-layer assembled polymeric nanoparticles.	Sequential release (antibacterial & tissue regeneration	Li P. et al., *Acta Biomater*, 2020
Clinical stage	**Technology/ Formulation Type**	**Market Status and References**
Chitosan–silver nanocomposite film	Enhanced antibacterial activity and moisture balance	Clinical pilot study. Luan J. et al., *Int Wound J.*, 2020.
Nanofiber scaffold loaded with platelet-derived growth factor (PDGF)	Promoted granulation tissue formation and wound closure	Kamaruzaman N.A. et al., *Tissue Eng Part A*, 2023.

7. Translational Challenges and Regulatory Perspectives

Intelligent drug delivery systems for the treatment of diabetic wounds have been making significant strides, but some hurdles remain before they can be transferred to clinics [109]. The complexity of these next-generation systems has raised not only pertinent issues about manufacturing scale-up and cost optimization, but also about the path to regulatory approval and the long-term safety profile [110].

Challenges in both manufacturing and scale-up of complex drug delivery systems, such as nanotechnology and biologics, can be cited [111]. Manufacturing and Quality Control The manufacturing process, which can ensure equimolarity between batches, stability of the end-product, and large-scale, cost-effective production, is highly complex. Some regulatory authorities have established a few protocols for nanobased products, including particle size distribution (PSD), Surface characterization, and potential toxicity [112].

Safety and biocompatibility of new drug delivery products in their preclinical stage should include a variety of animal tests across diverse species, as well as in vitro evaluations [113].

"Also, long-term considerations of cytotoxicity and new materials. A comprehensive study on immunogenicity is required [114]. Regulatory landscapes are growing to address the unique attributes of combination products, including drug-device-biologics combinations [115].

Economic rationale is also among the driving factors for the incorporation of sustained release into novel drug delivery systems and into clinical practice [116]. Despite the potential for such technologies to improve treatment outcomes, the additional investment required to develop and scale up novel technologies must certainly be outweighed by patient benefits and savings in long-term health care costs [117]. Health technology and pharmacoeconomic assessments are becoming increasingly important to demonstrate the value of new wound care treatments [118].

7.1. Regulatory Complexity:

Nanotechnology-based medical products occupy a regulatory grey zone, as combination products that require evaluation under several legal frameworks [118]. Key challenges include: comprehensive nanomaterial characterization requirements; demonstrating batch-to-batch consistency at the nanoscale; addressing novel nanotoxicity concerns requiring specialized safety studies beyond traditional protocols; limited regulatory precedent for nanomedicine wound products; and coordination across multiple regulatory divisions for smart integrated systems ([119]).

Regulatory Quality Standards: Regulatory authorities have established specific characterization requirements for nano-based products that exceed conventional pharmaceutical standards:

- **Particle size distribution (PSD):** Dynamic light scattering (DLS), nanoparticle tracking analysis (NTA), and transmission electron microscopy (TEM) to confirm size uniformity (typically requiring polydispersity index <0.3)
- **Surface characterization:** Zeta potential measurement, surface chemistry analysis (XPS, FTIR), and protein corona profiling
- **Morphological assessment:** High-resolution imaging techniques to verify structural integrity
- **Drug loading and encapsulation efficiency:** Quantitative analysis with validated analytical methods
- **Release kinetics:** Multi-timepoint in vitro release testing under physiologically relevant conditions
- **Stability testing:** Accelerated and real-time stability studies per ICH guidelines with nanomaterial-specific parameters
- **Endotoxin and sterility:** Bacterial endotoxin testing (LAL assay) and comprehensive sterility assurance

- **Potential toxicity profiling:** Hemolysis testing, complement activation assays, and cytotoxicity screening

7.2. Manufacturing Barriers:

Laboratory synthesis methods rarely scale to commercial production, creating a "valley of death" between proof-of-concept and clinical manufacturing [120]. Critical obstacles include: inherently low-throughput fabrication techniques (microfluidics, electrospinning); substantial capital investment required for GMP-compliant facilities; incompatibility with standard sterilization methods necessitating costly aseptic manufacturing; limited stability requiring cold-chain storage; and difficulty achieving consistent nanoscale quality across batches [121].

7.3. Clinical Development Challenges:

Diabetic wound studies present unique challenges: heterogeneous patient populations requiring large sample sizes; long trial durations (12-20 weeks), which increase costs; a lack of validated surrogate biomarkers necessitating expensive long-term follow-up; the need for superiority trials against existing advanced products; and patient compliance issues with complex application regimens [122].

7.4. Economic Barriers:

Advanced nanosystems require $50-150 million in development investment, versus $10-30 million for conventional formulations [115]. Market access is challenged by: payer reluctance in the absence of definitive cost-effectiveness data; the need to demonstrate substantial clinical benefit to justify premium pricing; a crowded wound care market (>3,000 products); and extended development timelines that erode patent protection [123].

7.5. Accelerating Translation:

Strategic approaches to overcome these barriers include: proactive early regulatory engagement through pre-IND meetings; adoption of consensus nanomaterial characterization standards; innovative adaptive trial designs to improve efficiency; public-private partnerships sharing development risks; earlier investment in scalable manufacturing; validation of predictive biomarkers as surrogate endpoints; and real-world evidence registries demonstrating clinical utility and cost-effectiveness [124].

7.6. Regulatory Pathways: FDA and EMA Frameworks:

The regulatory environment for advanced nanosystems and smart drug delivery is unique but increasingly coherent across the four major regulatory regions. In the USA, wound care products undergo Food and Drug Administration (FDA) review via several routes, depending on the product type and device complexity [125]. A stringent Premarket Approval (PMA) process, requiring extensive clinical trials that run 2-5 years and costing $10-50 million, is needed.

The increasing complexity of nanosystems integrating drugs, devices, and biologics has elevated the importance of the Office of Combination Products (OCP), which coordinates cross-center reviews based on the determination of Primary Mode of Action (PMOA) [125]. Recognizing the unique characteristics of nanomaterials, the FDA issued specific guidance in 2014 establishing evaluation criteria for materials below 100 nm or exhibiting dimension-dependent properties, subsequently expanded in 2017 to address chemistry, manufacturing, and controls (CMC) considerations specific to nanomedicines, emphasizing comprehensive physicochemical characterization and nanoscale-specific toxicity assessment [126].

The European Medicines Agency (EMA) employs a parallel yet distinct regulatory framework that generally imposes more stringent evidentiary requirements than the FDA. The EMA's regulatory architecture for Advanced Therapy Medicinal Products (ATMPs) encompasses gene therapies, somatic cell therapies, and tissue-engineered constructs, with evaluation by the specialized Committee for Advanced Therapies (CAT) before the Committee for Medicinal Products for Human Use (CHMP) opinion [127]. For nanomedicines specifically, the EMA's Reflection Paper on nanotechnology-based medicinal products mandates a risk-based assessment encompassing particle size distribution, surface properties, morphology, aggregation state, and biopersistence potential, with the additional requirement of an environmental risk assessment, which the FDA does not routinely demand [128].

Clinical trial design and endpoint selection represent critical considerations for both regulatory authorities, with the FDA's 2006 guidance document "Chronic Cutaneous Ulcer and Burn Wounds-Developing Products for Treatment" establishing that complete wound closure, defined as 100% re-epithelialization without drainage or dressing requirement confirmed at two consecutive study visits separated by at least two weeks constitutes the appropriate primary efficacy endpoint [129].

Secondary endpoints include time to complete closure, percentage reduction in wound size at defined intervals, durability of closure at 3-, 6-, and 12-month follow-up, amputation prevention rates, and patient-reported quality-of-life measures using validated instruments. Standardized wound assessment tools such as the PEDIS classification (Perfusion, Extent, Depth, Infection, Sensation), Wagner grading system, and University of Texas Wound Classification system are recommended to ensure consistent evaluation across clinical sites and trials [130]. The importance of understanding these regulatory subtleties and engaging honestly with both agencies through pre-submission meetings and scientific advice procedures remains crucial for the efficient clinical translation of advanced nanosystems in diabetic wound care [131].

8. Future Directions

An innovative drug-delivery system on the horizon for diabetic ulcers is the combination of artificial intelligence (AI) and machine learning (ML) with personalized medicine [132]. These advanced treatment modalities will serve as the platform on which 'real' intelligent therapeutic systems can accommodate patient-to-patient variability and adjust themselves based on optimal dose-seeking behaviour with continuous automatic adjustment – i.e., self-learning over time. Digital health, along with biotechnology and pharmaceutical sciences, intertwines to create tremendous opportunities for innovation in wound care [133].

AI and computational modeling are becoming increasingly relevant in the design and optimization of drug delivery systems. Machine learning algorithms can predict the kinetics of drug release and patient-specific treatment on analysis of large data sets and estimate optimal formulation parameters. Computer-generated wound twins, produced using advanced imaging modalities and computer modelling, may enable preclinical virtual testing of different therapeutic interventions [134].

The treatment of diabetic ulcers increasingly adopts personalised therapy as one of its pillars. Such an approach, including potential procedures such as genetic profiling, biomarker analysis, and wound microbiome characterization, may facilitate the selection of the most appropriate therapeutic agents or delivery systems for individual patients. Pharmacogenomics has the potential to inform dosing and drug selection to prevent adverse events and improve the effectiveness of drug treatment [135].

Telemedicine and remote monitoring devices, in combination with smart drug delivery systems, will enable continuous patient treatment and care. Wearable sensors and phone applications may transmit real-time data on wound healing, medication compliance, and patient-reported outcomes. This can be extended to adjustments in a treatment protocol and personalised decision-support recommendations (using CDS driven by AI) [136].

Breakthroughs in stem cell biology, tissue engineering, and gene therapy are expected to guide the development of regenerative medicine approaches. Novel applications of CRISPR-Cas9 gene editing could facilitate the development of cells better suited for wound repair. These developments will enable more sophisticated preclinical models for screening novel therapeutic strategies and predicting clinical responses [137].

CONCLUSION

Diabetic ulcers are a major health issue affecting many people around the world and placing a heavy strain on healthcare systems. This review highlights recent advances in smart drug delivery systems (DDSs) that aim to improve on traditional treatments. Innovative strategies using nanotechnology, hydrogel-based systems, responsive therapies, and regenerative medicine offer new ways to provide targeted, controlled, and personalized therapies. New technologies, such as 3D printing and electrospinning, present exciting options for effectively managing diabetic wounds.

Despite progress in developing advanced DDSs for diabetic ulcers, significant challenges remain in translating these innovations from research into everyday clinical use. Issues include the complexity of making and ensuring quality, the need for detailed nanoscale testing, and concerns about consistency and long-term safety. Regulations for these combination products, particularly those using new or nanotechnology-based systems, are complex and often require proof of unique safety features and adherence to new standards that go beyond typical pharmaceutical guidelines.

Clinical development also faces challenges, including the need for well-designed, long-term trials across diverse patient groups, a shortage of reliable alternative measures to assess treatment success, and logistical demands for real-world application. Economic challenges arise from the high costs of development and scaling up, along with payer hesitance in the absence of solid cost-effectiveness evidence. This situation is further complicated by competition in the wound care market and limited patent life for new technologies. Moreover, successful clinical use requires not only regulatory approval but also training for healthcare providers and proper integration into existing healthcare systems to ensure the effective use and monitoring of these advanced systems.

Next-generation DDSs hold great promise for meeting the ongoing needs in diabetic wound care. However, progress in this field will depend on teamwork across different disciplines. Achieving this will require early and continuous engagement with regulators, standardizing nanomaterial assessment, developing scalable manufacturing methods, validating clinical markers for treatment prediction, and gathering robust real-world evidence on clinical and economic benefits. Closing these gaps is essential to fully utilize the potential of innovative DDS technologies, leading to personalized, cost-effective care for diabetic patients everywhere.

In summary, combining pharmaceutical sciences with nanotechnology, biotechnology, and digital health offers a unique chance to create effective treatments for diabetic ulcers. While challenges remain in applying these methods in practice, ongoing collaboration across fields will be crucial to realizing the potential of these new techniques in clinical settings. The ultimate goal is to provide treatments for diabetic patients that heal wounds, prevent future occurrences, and enhance quality of life, making this one of the most urgent tasks in modern pharmaceutical research.

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CONFLICTS OF INTEREST

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أنظمة إيصال الأدوية الذكية والاستجابية لعلاج قرحة القدم السكرية: التطورات الحديثة في التصميم الصيدلاني

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الخلاصة

قرحة السكري هي مشكلة طبية كبيرة تؤثر على ملايين المرضى حول العالم بسبب المراضة، والوفيات، وتكاليف نظام الرعاية الصحية. لا تزال العملية المرضية المعقدة لتأخير شفاء الجروح لدى مرضى السكري غير معالجة بشكل كاف مع طرق العلاج التقليدية. تلخص هذه المراجعة التطورات الحديثة في أنظمة توصيل الأدوية الهندسية الذكية والمستجابة لعلاج تقرحات السكري. علاوة على ذلك، نجسد هذه الاستراتيجيات باستخدام تقنيات ناشئة، بما في ذلك تقنية النانو، ومصفوفات الهيدروجيل، والأنظمة المستجيبة للمحفزات، والنشطات الحيوية. تعرض منهجيات جديدة، بما في ذلك الأساليب الجديدة مثل السقالات المطبوعة ثلاثية الأبعاد، وأنظمة الألياف النانوية، والمنصات العلاجية، كخيارات علاجية بديلة قد تغير مشهد العناية بالجروح المرتبطة بالسكري. تقديم مناقشات حول تحديات الترجمة والتنظيم وتطبيق تقنيات الأدوية الجديدة في البحث السريري.

الكلمات المفتاحية: تقرحات السكري، أنظمة توصيل الأدوية، الهيدروجيلات، تكنولوجيا النانو، تصميم الأدوية، شفاء الجروح.