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REVIEW

Polymeric Nanofiber Scaffolds for Diabetic Wound Healing: A Review

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ABSTRACT: With the global diabetes epidemic, diabetic foot ulcers (DFUs) have become a major health burden, affecting approximately 18 million people worldwide each year, and account for about 80% of diabetes-related amputations. Five-year mortality among DFU patients approaches 30%, which is comparable to that of many malignancies. Yet despite standard wound care, only about 30%–40% of chronic DFUs achieve complete healing within 12 weeks. This persistent failure shows that conventional dressings remain passive supports. They do not counteract underlying pathologies such as ischemia, prolonged inflammation, and infection. Recent advances in polymeric nanofiber scaffolds, particularly electrospun matrices, provide bioactive wound dressings designed to overcome these limitations. By mimicking extracellular matrix architecture (ECM) and delivering therapeutic biomolecules, polymeric nanofiber scaffolds can promote tissue regeneration and angiogenesis. They also modulate the wound immune response and combat infection through embedded antimicrobial agents. Innovative scaffold architectures further enhance healing outcomes. Core–shell and multilayer nanofibers enable sequential or sustained release of multiple factors. Biomimetic "basketweave" fiber layouts improve cell alignment, neovascularization, and wound closure, and stimuli-responsive scaffolds release therapeutics in response to wound pH or oxidative stress. Preclinical diabetic wound models and early clinical trials show that these engineered scaffolds accelerate wound closure, increase re-epithelialization, and reduce chronic inflammation relative to standard care. Notably, a recent clinical trial in patients with DFU reported 74% wound closure by 12 weeks with an electrospun scaffold vs. 33% with conventional therapy. However, translational challenges persist, including stability, sterilization compatibility, and scalable manufacturing of nanofiber scaffolds. This review discusses these hurdles and highlights future directions, including the development of smart biosensor-integrated scaffolds for responsive drug delivery, personalized patient-specific dressings, and AI-assisted design of polymer nanofibers to further optimize DFU healing outcomes.

KEYWORDS: Nanofibers; polymers; wound healing; diabetic foot ulcer; electrospinning; regeneration; drug delivery

1 Introduction

Diabetes mellitus (DM) has reached epidemic proportions globally, currently affecting more than 550 million people, with projections exceeding 1.3 billion by 2050 [1]. As this global burden worsens, there has been a parallel rise in diabetes-related complications, most notably chronic foot ulcers, which have been observed [2]. Diabetic foot ulcer (DFU) affects approximately 18.6 million individuals worldwide each year, and up to one-third of individuals with diabetes will develop a foot ulcer during their lifetime [3].

DFUs precede about 80% of non-traumatic lower-extremity amputations in people with diabetes [4]. Approximately 20% of patients with a DFU eventually require a lower-extremity amputation, and the five-year mortality among DFU patients approaches 30%, comparable to or worse than many cancers [5,6].

Beyond the human toll, chronic diabetic wounds impose an enormous socioeconomic burden. Prevalence rates vary markedly across regions: North America reports the highest DFU prevalence at about 13% of patients with diabetes. Asia and Europe average around 5%–6%, and Oceania has the lowest, at about 3%. In Africa, hospital-based studies have documented DFU prevalence ranging from about 10% to 30%. The Middle East and North Africa (MENA) region similarly shows wide variation, with reported DFU prevalence ranging from 5% to 20% [7–13]. Fig. 1 provides a global perspective, illustrating the distribution of DFU prevalence across the world and highlighting the ten most affected countries.

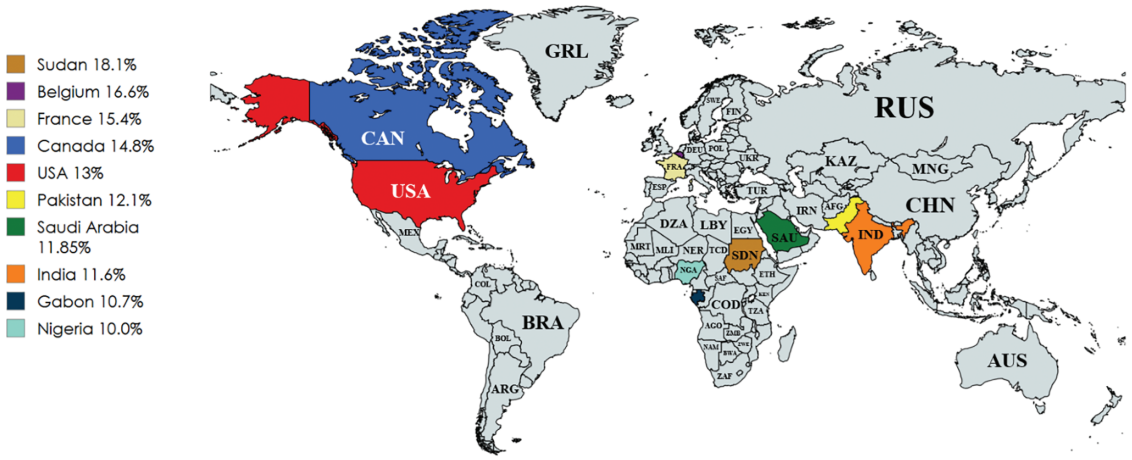

Figure 1: Global distribution of DFU prevalence. Countries with the highest reported prevalence are highlighted and all countries are labeled using ISO 3166-1 alpha-3 codes [7–13]

Despite advances in wound care, outcomes for chronic DFUs remain suboptimal. Standard interventions, including pressure off-loading, debridement, infection control, and basic wound dressings, often fail to achieve complete or timely healing. Only 30%–40% of DFUs achieve full healing within 12 weeks of standard care, while the remainder persist for months, increasing the risk of infection and hospitalization. Once a DFU becomes chronic, the chance of recurrence exceeds 40% within one year [14,15].

Conventional therapies are largely passive and fail to adequately address key biological deficiencies in diabetic wounds such as ischemia, prolonged inflammation, and impaired tissue remodeling [16]. These limitations have prompted exploration of advanced wound-healing approaches, including bioengineered scaffolds and polymeric nanofiber scaffolds designed to address underlying molecular barriers. Recent advances in polymer chemistry and nanofiber fabrication (e.g., electrospinning) now enable fine-tuning of scaffold properties, establishing structure–function relationships whereby fiber composition, diameter, alignment, and porosity are engineered to influence cell behavior and tissue regeneration [17]. Moreover, polymeric nanofibers can be biofunctionalized with therapeutic cargo (such as growth factors or antimicrobials), thereby transforming passive dressings into interactive biomaterial platforms that actively promote healing [18].

This review systematically evaluates recent advances in the roles, design, and functionalization of polymeric nanofiber scaffolds for diabetic wound healing, with a focus on their material composition, structural biomimicry of the ECM, incorporation of bioactive agents, and observed healing outcomes across *in vitro*, *in vivo*, and clinical studies. Furthermore, it discusses key materials engineering and regulatory challenges

and explores future directions toward personalized, smart, and AI-assisted polymer-based wound care systems. Unlike earlier reviews that mainly catalog polymer types or fabrication methods, this work integrates material chemistry, nanofiber architectures, therapeutic functionalization, and translational challenges into a unified framework. The novelty of this review lies in its central hypothesis that polymeric nanofiber scaffolds should be considered as a multifunctional therapeutic system, rather than passive scaffolds. Also, we discuss emerging scaffold designs such as basketweave, core-shell, and multilayer nanofibers, highlight underexplored translational barriers including sterilization and large-scale manufacturing, and propose a forward-looking roadmap toward smart, biosensor-integrated, and AI-assisted scaffolds. Together, these elements establish the originality and novel contributions of this review.

2 Pathophysiological Mechanisms of Diabetic Wounds

Chronic diabetic wounds result from a convergence of molecular and cellular derangements that impede the normal wound healing process [19]. In healthy individuals, wound healing is a well-orchestrated sequence of hemostasis, inflammation, proliferation, and remodeling [20]. Diabetes disrupts each of these phases by several pathophysiological mechanisms, including impaired angiogenesis and ischemia, chronic inflammation, altered macrophage phenotypes, and oxidative stress [21], and more as shown in Fig. 2A,B along with the solutions that can be addressed by nanofiber scaffolds as displayed in Fig. 2C.

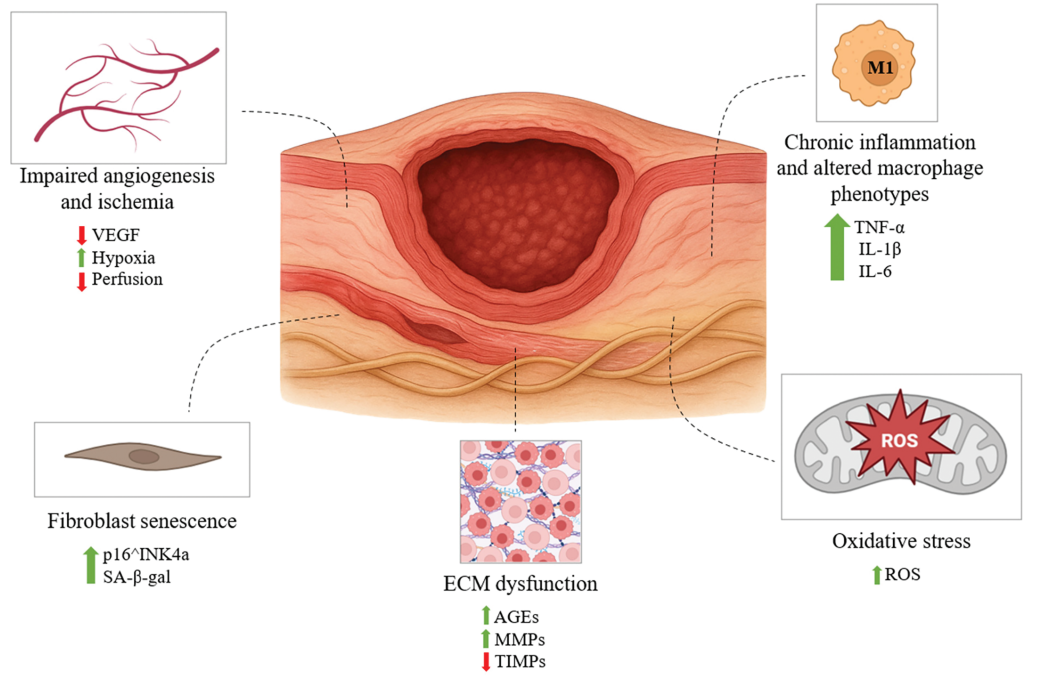

Figure 2: (Continued)

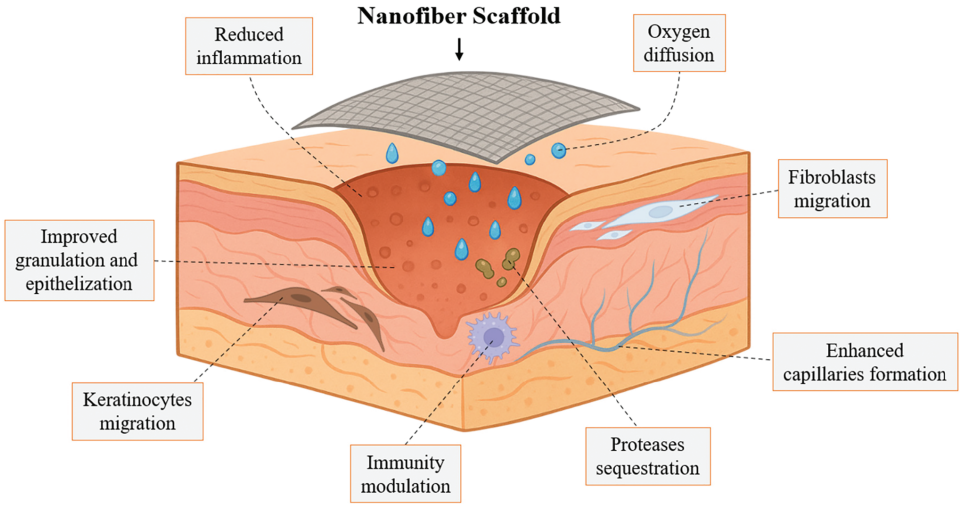

Figure 2: The pathophysiological mechanisms of diabetic wounds and the therapeutic role of nanofiber scaffolds. Chronic diabetic wounds arise from multiple molecular and cellular impairments as in (**A**), including ischemia with reduced VEGF signaling, chronic inflammation driven by persistent M1 macrophages, fibroblast senescence, oxidative stress, and ECM dysfunction characterized by advanced glycation end products and protease imbalance. These defects disrupt the normal sequential phases of wound healing as in (**B**), leading to prolonged hemostasis and inflammation, impaired angiogenesis during proliferation, and defective ECM remodeling. Electrospun nanofiber scaffolds as shown in (**C**) provide a multifunctional strategy to counteract these barriers by supporting keratinocyte and fibroblast migration, promoting angiogenesis and granulation tissue formation, facilitating oxygen diffusion, modulating immune responses, reducing inflammation, and sequestering excess proteases, thereby accelerating regeneration in diabetic wounds

Impaired angiogenesis and ischemia are hallmarks of diabetic wounds, where the formation of new blood vessels leads to inadequate perfusion of the healing tissue [22]. Chronic hyperglycemia damages endothelial cells and small blood vessels, resulting in peripheral ischemia and reduced delivery of oxygen and nutrients to the wound bed [23]. Diabetic wounds exhibit reduced production of pro-angiogenic factors, for instance, vascular endothelial growth factor (VEGF) and an inability to effectively recruit endothelial progenitor cells and pericytes for neovascularization [24].

Another mechanism is chronic inflammation and altered macrophage phenotypes, which are characterized by a prolonged inflammatory phase that fails to properly resolve [25]. In an acute wound, inflammatory cells such as neutrophils and classically activated M1 macrophages initially dominate to clear bacteria and debris, but then subsequently transition to alternatively activated M2 macrophages that promote tissue repair [26]. In diabetes, this phenotypic switch is impaired: macrophages persist in an M1 pro-inflammatory state with excessive secretion of cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6) and proteolytic enzymes, but insufficient conversion to the pro-healing M2 phenotype [27]. This imbalance leads to a smoldering inflammatory milieu that damages tissue and inhibits the progression to the proliferative phase of healing.

Additionally, oxidative stress, where an overproduction of reactive oxygen species (ROS) and a deficiency in antioxidant defenses are commonly observed in chronic diabetic wounds [28]. Hyperglycemia, ischemia, and sustained inflammation all contribute to ROS generation in the wound environment [29]. Excessive oxidative stress causes cellular damage, including DNA, protein, and lipid oxidation in local tissues, and it perpetuates inflammation by activating redox-sensitive inflammatory pathways such as the nuclear

factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway [30]. Moreover, high ROS levels further impair wound healing by inhibiting fibroblast and keratinocyte proliferation, inducing premature cellular senescence, and promoting apoptosis of key reparative cells [31].

ECM dysfunction is another proposed mechanism, where proper wound healing requires a provisional ECM scaffold that supports cell migration and new tissue formation [32]. In diabetic wounds, the quality and turnover of ECM are profoundly disturbed. Hyperglycemia induces non-enzymatic glycation of matrix proteins, resulting in advanced glycation end-products (AGEs) that cross-link collagen and elastin. These AGEs stiffen tissue and alter matrix signaling, ultimately impairing wound contraction and matrix remodeling [33]. In addition, chronic wounds exhibit an imbalance between proteases and their inhibitors. Diabetic wound fluid often contains excessively high levels of matrix metalloproteases (MMPs) (e.g., MMP-2, MMP-9) and neutrophil elastase, with concurrently low levels of tissue inhibitors of metalloproteinases (TIMPs) [34]. This protease-rich environment leads to degradation of newly deposited ECM components and essential growth factors, effectively sabotaging the formation of stable granulation tissue.

Another mechanism is cellular dysfunction and senescence. At the cellular level, diabetes impairs the key players of wound repair. Fibroblasts in diabetic wounds often exhibit a senescent phenotype, with reduced proliferative capacity, diminished motility, and lower amounts of collagen and growth factors compared to normal fibroblasts [19,35]. Hyperglycemia-induced senescence is marked by increased senescence markers such as cyclin-dependent kinase inhibitor 2A (p16ˆINK4a) and senescence-associated beta-galactosidase (SA-β-gal) in wound fibroblasts and endothelial cells from diabetic patients [36]. These senescent cells develop a senescence-associated secretory phenotype (SASP) that paradoxically secretes pro-inflammatory factors and proteases, exacerbating local inflammation and tissue breakdown [37]. Endothelial cells exposed to high glucose also undergo premature senescence and dysfunction, losing their angiogenic potential. Keratinocytes, which are responsible for re-epithelialization, show impaired migration and proliferative responses in the diabetic milieu. Hyperglycemia and persistent inflammation reduce keratinocyte capacity to cover the wound, in part by downregulating growth factors such as epidermal growth factor (EGF) and by the presence of barrier defects in the surrounding skin. Additionally, diabetic peripheral neuropathy and ischemia lead to diminished growth factor signaling and reduced cell recruitment to the wound site [38,39].

It should be noted that DFUs are frequently complicated by bacterial colonization and infection, with common pathogens including *Staphylococcus aureus* and *Escherichia coli*. These infections exacerbate inflammation, delay re-epithelialization, and increase the risk of sepsis and amputation [40]. Conventional approaches to combat this problem involve systemic and topical antibiotic therapy, debridement, and infection control measures such as moist wound dressings [41]. More recently, advanced biomaterial-based strategies have emerged to enhance antimicrobial protection. Polymeric nanofiber scaffolds can be engineered to incorporate silver nanoparticles, zinc oxide nanoparticles, antimicrobial peptides such as LL-37, or controlled-release antibiotic formulations [42–44]. These multifunctional scaffolds provide a physical barrier against bacterial invasion while delivering sustained antimicrobial activity directly to the wound site, thereby reducing infection risk and supporting tissue regeneration.

Subsequently, each of the pathological pathways mentioned above can be enhanced by nanofiber scaffolds. For instance, nanofibers provide a highly porous and oxygen-permeable structure, that enhances oxygen exchange at the wound site and can be further functionalized with oxygen-releasing nanoparticles to counter local hypoxia [45]. The high surface area-to-volume ratio and tunable release profiles of electrospun fibers allow sustained delivery of antimicrobial agents (e.g., silver nanoparticles, antibiotics, antimicrobial peptides), thereby mitigating recurrent infections common in DFU [42,46]. To combat oxidative stress, scaffolds can be loaded with antioxidant molecules or enzyme-mimetic nanoparticles (e.g., cerium oxide), which scavenges excess ROS and restores redox balance [47]. Impaired angiogenesis can be addressed by

incorporating pro-angiogenic cues such as VEGF, stromal cell-derived factor-1 (SDF-1), or mesenchymal stem cells, which are released in a controlled manner to stimulate neovascularization [48]. Finally, nanofiber scaffolds structurally mimic the native ECM through their fibrous architecture, providing mechanical support for fibroblast migration, keratinocyte proliferation, and collagen deposition, thus promoting organized tissue regeneration [49].

3 Conventional Therapies: Limitations in Chronic Wound Resolution

The current standard of care for DFU focuses on wound management and symptomatic control, but it provides only limited bioactive stimulation for tissue regeneration. The conventional therapeutic toolkit includes regular wound debridement, infection control with antibiotics, off-loading of pressure (especially for plantar foot ulcers), and application of appropriate wound dressings to maintain a moist, clean environment [50]. Adjuvant measures such as glycemic control and optimization of nutrition and perfusion (including revascularization procedures when peripheral arterial disease is present) are also crucial components of care [51]. Although these measures are the foundation of good wound care practice, chronic diabetic wounds often fail to respond fully to such treatment due to the complex pathophysiology described above.

One major limitation is that standard wound dressings and debridement are principally passive or supportive in nature. Dressings (e.g., saline gauze, foams, hydrocolloids) assist by covering the ulcer, absorbing exudate, and preventing external contamination, but traditional dressings do not actively engage with the wound biology to accelerate healing [52]. They lack bioactive components, and they do not supply growth factors, cells, or gene therapies that chronic wounds critically require. Even advanced moist dressings primarily optimize the wound environment (temperature, moisture) rather than trigger regeneration [53]. Frequent debridement is beneficial for removing devitalized tissue and reducing bacterial bioburden, temporarily resetting the wound to a "fresh" state. However, debridement alone cannot overcome intrinsic deficits like poor angiogenesis or cellular senescence; thus, the wound often returns to an inflammatory, non-healing state [35,54]. These limitations are inherent to most conventional interventions for DFUs, which primarily serve supportive roles without addressing the underlying biological dysfunctions. Table 1 systematically summarizes the mechanisms, benefits, and constraints of current standard-of-care therapies.

Table 1: Comparative analysis of conventional therapeutic interventions for diabetic foot ulcers

Intervention	Mechanism of action	Advantages	Limitations	Ref.
Debridement	Removes necrotic tissue	Reduces bioburden, resets wound bed	Does not overcome molecular deficits	[55]
Moist Dressings (e.g., Saline gauze, foam)	Maintains a moist environment	Barrier protection, exudate absorption	Passive; lacks bioactivity	[53]
Systemic Antibiotics	Controls infection	Critical in infected wounds	Resistance risk, no healing stimulation	[56]
Becaplermin (PDGF-BB)	Stimulates granulation tissue	FDA-approved growth factor	Degraded by proteases, modest efficacy	[57]

(Continued)

Table 1 (continued)

Intervention	Mechanism of action	Advantages	Limitations	Ref.
Bioengineered Skin Substitutes	Provides cells & GF	Enhances healing in some cases	Expensive, handling issues, integration challenges	[58,59]
NPWT (Vacuum Therapy)	Promotes contraction, removes exudates	Helps prepare the wound bed	Temporary	[60,61]

Note: NPWT; negative pressure wound therapy; PDGF-BB; platelet-derived growth factor-BB; GF; growth factor; FDA; U.S. Food and Drug Administration.

Likewise, systemic antibiotics or topical antimicrobials are critical for controlling infection, but they do not inherently promote new tissue growth or address the impaired healing mechanisms. Also, over-reliance on antibiotics can lead to resistance and does not substitute for the biological stimulation required for wound closure [56]. Therefore, conventional pharmacological therapies for wound healing have shown only modest success in chronic DFUs. The only FDA-approved growth factor therapy for DFUs is becaplermin (recombinant PDGF-BB gel), which has shown modest improvements in healing rates in clinical trials by stimulating granulation tissue formation [62]. In practice, however, the impact of becaplermin has been limited due to the fact that chronic wounds often contain high protease levels that degrade applied growth factors, and the single-factor approach does not fully address the complex healing deficits [57]. Other growth factors (e.g., EGF, FGF, VEGF) and cytokines have been tested topically or via injection, but none have become standard care due to inconsistent efficacy or safety concerns [63].

On the other hand, bioengineered skin substitutes (e.g., living bi-layered skin analogues) can provide cells and growth factors to the wound and have demonstrated improved healing in some cases; however, these products are expensive, require specialized handling, and may not integrate well in an environment of uncontrolled diabetes and infection. Moreover, such grafts do not address deeper issues such as angiogenesis unless combined with revascularization efforts [58,59]. Negative pressure wound therapy (vacuum-assisted closure) is another adjunct used to stimulate wound contraction and remove exudates; it can help prepare wound beds for closure, but its benefits cease once the device is removed, and it does not inherently correct molecular impairments [64].

These drawbacks are reflected across current clinical interventions, as outlined in Table 1. Although these measures provide critical wound support, they do not stimulate regeneration at the molecular level. Consequently, chronic wounds persist due to pathophysiological factors such as high MMP activity, oxidative stress, and impaired angiogenesis. Additionally, Table 2 highlights these unresolved biological deficits and presents nanofiber-based scaffold innovations capable of addressing them through targeted therapeutic delivery.

Table 2: Pathological barriers in DFU unaddressed by standard care and nanofiber-based scaffold solutions

Pathological factor	Effect in DFUs	Addressed by conventional care?	Example of a nanofiber-based solution	Ref.
High MMP-9	ECM degradation	×	MMP inhibitors embedded in a scaffold	[65,66]
Reduced VEGF	Impaired angiogenesis	×	VEGF-loaded nanofibers	[67,68]
M1 Macrophage Dominance	Chronic inflammation	×	IL-4 delivery to promote M2 switch	[69,70]
Senescent Fibroblasts	Poor ECM synthesis	×	Stem cell-laden nanofibers	[71,72]
Oxidative Stress	DNA damage, poor cell survival	×	Antioxidant-infused scaffolds	[28,73]

Note: ECM; extracellular matrix; DNA; deoxyribonucleic acid; VEGF; vascular endothelial growth factor; MMP; matrix metalloproteinase; MMP-9; matrix metalloproteinase-9; IL-4; interleukin-4.

As noted in recent reviews, the outcomes of standard care for chronic diabetic wounds remain unsatisfactory, prompting the search for novel approaches. This is where advanced biomaterials such as nanofiber-integrated scaffolds offer exciting potential. Electrospun nanofiber scaffolds can be engineered to mimic the skin's ECM and serve as a delivery platform for therapeutic agents. These scaffolds can fill wound defects, maintain a favorable moisture balance, deliver angiogenic factors, anti-inflammatory drugs, matrix stabilizers, and even living cells, thus directly addressing the deficits in diabetic wound healing [74]. Early studies have shown that nanofiber scaffolds can promote tissue and vascular regeneration and accelerate wound closure in diabetic models [75].

4 Structure–Function Engineering of Polymeric Nanofiber Scaffolds

Electrospun polymeric nanofiber scaffolds have rapidly emerged as biomimetic wound scaffolds that mimic the skin's ECM architecture [76]. These fibers form a nonwoven polymer scaffold with high porosity and surface area, providing a fibrillar framework similar to dermal collagen [77]. Material selection and molecular design are key: hydrophobic polyesters like polycaprolactone (PCL), polylactic acid (PLA), or poly(lactic-co-glycolic acid) (PLGA) impart mechanical integrity and controlled biodegradation, whereas natural hydrophilic polymers (e.g., gelatin, chitosan) offer high wettability, biocompatibility, and support cell adhesion [78]. By adjusting polymer composition and fiber morphology, these scaffolds fill wound defects and serve as delivery platforms for therapeutic agents [79]. Nanofibrous ECM-mimetic architecture provides a provisional scaffold for the wound bed, with a highly porous structure that permits cell infiltration and gas exchange. The nanoscale pores also act as a barrier to microbial penetration, thereby reducing infection risk [80]. Moreover, appropriate fiber hydrophilicity helps regulate the wound's moisture, creating a hydrated yet breathable interface conducive to healing. Cells readily adhere to these fibrous matrices and proliferate within them, resembling natural granulation tissue [81].

An essential design parameter in electrospun scaffolds is fiber morphology, particularly fiber orientation, which strongly influences cellular responses. Aligned and random fiber architectures impart different topographical cues that influence cell behavior and tissue organization [82]. Aligned nanofibers provide

anisotropic contact guidance, causing cells to elongate and migrate along the fiber axis; for example, macrophages on aligned fibers assume spindle-like shapes characteristic of an anti-inflammatory M2 phenotype [83]. In contrast, random fibers form an isotropic mesh akin to native dermis, allowing multidirectional cell ingrowth with less directional guidance [84] as illustrated in Fig. 3.

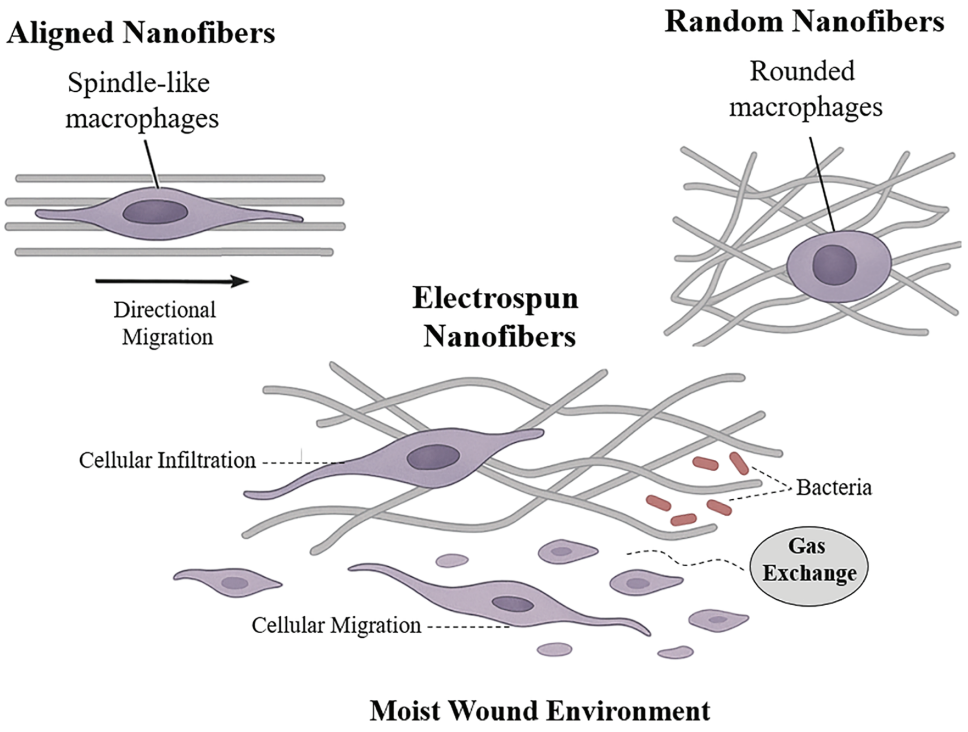

Figure 3: The illustration of how electrospun nanofiber scaffolds support wound healing by promoting cell infiltration, migration, and maintaining a moist, protective environment. Aligned nanofibers guide directional cell movement and induce spindle-like macrophage shapes, while random fibers result in less organized cell behavior and rounded macrophages

Notably, a biomimetic "basketweave" nanofiber layout that mimics the crisscrossed collagen fibrils of skin can further enhance repair [85]. *In vivo* diabetic wound studies found that crossed fiber (basketweave) scaffolds outperformed aligned or random mats, achieving faster wound closure, greater angiogenesis, and reduced inflammation [86]. Table 3 presents a comparative overview of how fiber alignment patterns affect cell guidance, macrophage polarization, ECM mimicry, angiogenesis, and overall healing outcomes.

Table 3: Comparative characteristics of aligned, random, and basketweave nanofiber architectures in wound healing

Feature	Aligned	Random	Basketweave
Cell guidance	Strong (directional)	Isotropic	Balanced
Macrophage phenotype	M2 skewed	Mixed	Anti-inflammatory
ECM mimicry	Linear ECM	Dermal-like ECM	Basketweave collagen
Angiogenesis	Moderate	Moderate	High
Wound closure rate	Fast	Moderate	Fastest

Beyond structural guidance, polymeric nanofiber scaffolds serve as bioactive matrices that modulate the wound microenvironment. The fibrous architecture of the scaffold recapitulates critical ECM cues, triggering integrin-mediated polymer–cell interactions [74]. For instance, nanofibers promote keratinocyte and fibroblast proliferation, guide endothelial cells to form new capillaries, facilitate oxygen and nutrients diffusion, and sequester excess proteases from chronic wound exudate [87]. By modulating immune responses (e.g., promoting an M2 macrophage phenotype), these scaffolds accelerate re-epithelialization and granulation tissue formation, overall accelerating wound repair.

4.1 Types of Polymeric Nanofiber Architectures for Diabetic Wound Healing

Diabetic wounds require dressings that combine structural support with targeted delivery of antimicrobials and growth factors. Electrospun nanofibers can mimic the ECM and be engineered with core–shell or multilayer structures to independently tune each function. For example, Li et al. fabricated a 3D micropatterned scaffold of poly(dl-lactic acid) (PDLLA) core and a gelatin-methacryloyl (GelMA) hydrogel shell. The hydrophilic GelMA shell greatly enhanced water uptake and vapor permeability (up to ~21× water retention vs. a plain 2D PDLLA mat), while the PDLLA core provided mechanical integrity. This core–shell scaffold markedly improved fibroblast adhesion, migration, and neovascularization: in diabetic wound models, it accelerated closure by stimulating the formation of a 3D capillary network and collagen deposition [88].

Core–shell fibers are produced by coaxial electrospinning, which generates fibers with two distinct layers. The core layer typically consists of a biodegradable polyester (PCL, PLA, PLGA) that degrades slowly and can encapsulate hydrophobic drugs or nanoparticles. The shell layer is typically a hydrophilic polymer (e.g., gelatin, chitosan, PVA, PVP, hyaluronic acid) that interfaces with tissue and allows rapid initial drug release or cell signaling [89]. For instance, Rajabifar et al. created PLA–PVA core–shell fibers by injecting a PVA solution containing silver nitrate ($AgNO_3$) into the core and a PLA solution in the shell. Following electrospinning and *in situ* reduction, silver nanoparticles formed in the PVA core and on the fiber surface. The high-water solubility of the PVA core enabled a burst release of Ag+ (powerful antibacterial), while the PLA shell slowed overall fiber degradation. These PVA/Ag–PLA fibers showed strong antibacterial zones against *E. coli* and *S. aureus* [90].

Intermediate (tri-layer) fibers are produced by triaxial electrospinning, which adds a third concentric layer. This intermediate layer can serve as a barrier or secondary reservoir to create multi-stage release profiles [88]. Liu et al. first showed that a tri-layer spinneret can produce fibers with a gradient structure capable of controlling the release of three distinct components [75]. In diabetic wounds, such tri-layer fibers could segregate antibiotics into one layer and growth factors into another, thus addressing infection and angiogenesis in one patch.

As illustrated in Table 4, the specific polymer combination used in core–shell nanofiber fabrication directly dictates the physicochemical behavior, release kinetics, and therapeutic outcomes [91]. Meanwhile, natural and hydrophilic polymers like chitosan, gelatin, and GelMA, used predominantly in the shell or coating layers, support cell adhesion, moisture retention, and facilitate the incorporation of labile bio-actives such as essential oils, peptides, and proteins [92,93].

Table 4: Some nanofiber architectures for wound healing

S. No.	Fabrication	Polymer type (Core/Shell)	Architecture	Functional payload	Biomedical effects	Ref.
1	Blend electrospinning	PCL + CS	Single-layer	Curcumin, ZnO NPs	Antioxidant, broad-spectrum antibacterial, ECM mimicry, WVTR↑	[94]
2	Coaxial (PVA core, PVP shell)	PVA/CS (core), PVP/MD (shell)	Core–shell	Oregano or savory essential oils	Antioxidant and antimicrobial activity; improved mechanical strength.	[95]
3	Coaxial (PVA core, PLA shell)	PVA (core), PLA (shell)	Core–shell	Silver nanoparticles	Controlled Ag+ release; potent antibacterial against *E. coli* and *S. aureus*	[95]
4	Coaxial (PDLLA core, GelMA shell)	PDLLA (core), GelMA (shell)	Core–shell (3D scaffold)	Crosslinked gelatin	High water retention promotes cell migration, proliferation, and angiogenesis.	[93]
5	Coaxial (PLGA core–shell)	PLGA (core and shell)	Core–shell	Insulin (core), Vildagliptin (shell)	Prolonged dual release; enhanced endothelial cell migration and accelerated wound closure	[96]
6	Coaxial (PLCL core, HA shell)	PLCL (core), HA (shell)	Core–shell	ZnO nanoparticles, cell-free fat extract (bFGF/TGF-β)	Biphasic Zn^{2+}/growth factor release; antibacterial (ZnO) and enhanced fibroblast proliferation and migration	[97]
7	Triaxial	PCL (core), Gelatin, PLGA (sheath)	Tri-layer	Rhodamine B (sheath), FITC–albumin (intermediate)	Graded sequential release; shows the feasibility of multi-drug delivery	[98]

Note: PCL; poly(ε-caprolactone); PLA; polylactic acid; PLGA; poly(lactic-co-glycolic acid); PDLLA; poly(D, L-lactic acid); PLCL; poly(L-lactide-co-ε-caprolactone); PVA; poly(vinyl alcohol); PVP; polyvinylpyrrolidone; CS; chitosan; HA; hyaluronic acid; FITC; fluorescein isothiocyanate; TGF-β; transforming growth factor-beta; WVTR; water vapor transmission rate; MD; mentha/drug (essential oils–context specific).

Moreover, recent designs have explored hybrid nanomaterials that combine natural and synthetic polymers to balance mechanical strength, biocompatibility, and degradation [99]. Therefore, Table 5 presents a comprehensive classification of natural and synthetic polymers employed in nanofiber-based wound healing applications, categorized by their ionic nature: cationic, anionic, and nonionic.

Table 5: Polymeric biomaterials categorized by charge for nanofiber-based wound healing

S. No.	Polymer (type)	Wound application	Roles in wound healing	Ref.
		Cationic Polymers		
1	Chitosan	Chronic wounds (e.g., diabetic foot ulcers) and infected wounds	Antibacterial, forms cationic clusters binding negatively charged RBCs to aid clotting, supports granulation, and wound closure in diabetic wounds	[100,101]

(Continued)

Table 5 (continued)

S. No.	Polymer (type)	Wound application	Roles in wound healing	Ref.
		Anionic Polymers		
2	Alginate	Exuding wounds (e.g., chronic ulcers, burns) and diabetic wounds	Aids in clotting and ion exchange (due to the presence of Calcium in the alginate), maintains a moist wound environment by gelling with exudate, promotes granulation and re-epithelialization, and is often used as a drug delivery matrix (e.g., releasing anti-inflammatories in "smart" dressings)	[100,102]
3	Hyaluronic Acid	Chronic wounds, diabetic wounds, burns, cosmetic wound care	Modulates the inflammatory phase by reducing the microbial burden and stimulates new blood vessel formation, accelerates re-epithelialization, and collagen deposition	[103,104]
4	Carboxymethyl Cellulose (CMC)	Chronic and acute wounds, often in hydrocolloid dressings	Maintains moisture; promotes re-epithelialization and well-organized skin regeneration. Often used to curb infections by absorbing exudate	[100]
5	Carrageenan	Chronic wounds	Maintains moisture, exhibits mild intrinsic antibacterial and anti-inflammatory effects in some forms.	[105]
6	Gellan Gum	Burns and chronic wounds	Preserves moisture in wounds; it has inherent antibacterial and anti-inflammatory properties	[106]
		Nonionic Polymers		
7	Collagen	Pressure ulcers, diabetic ulcers, and burns	Mimics native ECM, supports cell adhesion, migration, and new tissue formation, serves as a sacrificial substrate for excess proteases in chronic wounds (collagen dressings bind and reduce MMP levels, thus restoring balance in the wound bed	[107]
8	Gelatin	Acute and chronic wounds	Promotes cell adhesion and migration, aiding tissue regeneration, exhibits hemostatic properties, and can modulate inflammation, helps trigger blood clotting, and tempers excessive inflammation	[108]
9	Silk Fibroin	Burn wounds, skin graft substitutes, and chronic wound dressings	Supports cell attachment and growth, provides a protective, breathable scaffold, reduces pro-inflammatory cytokines, and improves healing outcomes	[109]
10	Bacterial Cellulose	Burns, ulcers, and skin tissue engineering	Forms a nanofibrous biomimetic mesh that conforms to the wound, controls wound exudate and maintains a moist healing environment, and enhances epidermal regeneration. Cellulose networks support fibroblast and keratinocyte attachment (when combined with collagen or coatings). Additionally, it provides a protective barrier against external contamination while allowing gas exchange	[110]
11	Dextran	Chronic wounds and infection control	Helps prevent infection and reduce inflammation at the wound site, maintains a moist environment, absorbs fluid and forms hydrogels that prevent desiccation, promotes cell proliferation and tissue remodeling	[96,100]

(Continued)

Table 5 (continued)

S. No.	Polymer (type)	Wound application	Roles in wound healing	Ref.
12	Poly(ε-caprolactone) (PCL)	Chronic and acute wound dressings	Serves as a durable ECM-mimicking scaffold, supports cell infiltration and growth, boosts keratinocyte differentiation, shows antibacterial activity and enhanced fibroblast adhesion/proliferation, aiding faster wound closure	[97,100,102]
13	Polylactic Acid (PLA)	Wound dressings for acute and chronic wounds	Provides a biodegradable fibrous framework for cell growth; Improves cell adhesion and ECM-likeness, stimulates human keratinocyte and fibroblast growth and angiogenesis in wounds.	[102]
14	PLGA (Poly(lactic-co-glycolic acid))	Chronic wound	Increases neovascularization and collagen deposition in wounds, improves tissue integration, and notably reduces scar formation, promotes fibroblast attachment and proliferation, aiding wound closure	[98]
15	Polyurethane (PU)	Acute wounds and burns (e.g., foam dressings)	Inhibits bacterial growth, promotes tissue repair, enhances ECM production, re-epithelialization, and reduces inflammation in wounds.	[111,112]
16	Poly(vinyl alcohol) (PVA)	Burns and chronic wounds (often as hemostatic or drug-releasing dressings)	Maintains moisture and encourages healing, cools and hydrates burn wounds, and relieving pain. Also, showed stronger absorbency and faster coagulation, exhibits excellent biocompatibility and enhanced healing.	[102]
17	Poly(ethylene oxide) (PEO) and PEG-based polymers	Chronic wounds (including diabetic wounds)	Shows antibacterial activity, reduces inflammation, promotes collagen deposition, and stimulates angiogenesis	[102,113]

Note: PCL; poly(ε-caprolactone); PLA; polylactic acid; PLGA; poly(lactic-co-glycolic acid); PU; polyurethane; PVA; poly(vinyl alcohol); PEO; poly(ethylene oxide); PEG; poly(ethylene glycol); CMC; carboxymethyl cellulose; ECM; extracellular matrix.

4.2 Functional Enhancements: Bioactive Payloads, Cell Integration and Release Profile

The versatility of electrospinning allows functional enhancement of nanofiber scaffolds with biochemical and cellular cues, transforming passive dressings into active therapeutic systems. A wide range of bioactive agents, from pro-healing growth factors to antimicrobial and anti-inflammatory molecules can be incorporated into nanofibers to directly counteract the hostile diabetic wound environment [114]. For example, growth factors such VEGF, basic fibroblast growth factor (bFGF), and platelet-derived growth factor (PDGF) have been loaded into nanofibrous scaffolds to stimulate angiogenesis and granulation tissue formation in chronic wounds [115]. However, the integration of these proteins into a scaffold is not sufficient; controlled delivery strategies are essential due to the short half-life and potential off-target effects of growth factors.

Core–shell electrospinning is one technique that enables sustained release, in which a core fiber reservoir of growth factor or drug is encased by a protective shell polymer, yielding a prolonged release over days to weeks rather than a rapid burst [116]. Similarly, nanoparticle integration has been used to improve biofactor stability and bioavailability; for instance, heparin-functionalized nanoparticles can bind growth factors and gradually release them when embedded in nanofiber mats. In one study, a collagen/PLGA nanofiber

scaffold was enriched with heparinized albumin nanoparticles carrying VEGF and bFGF achieved controlled release of these factors and significantly accelerating diabetic wound closure *in vivo* [117]. Another approach used mesoporous silica nanoparticles loaded with dimethyloxalylglycine (DMOG, a HIF-1α stabilizer) within aligned PLLA fibers; this system provided sustained DMOG delivery that enhanced angiogenesis and collagen deposition in diabetic wounds and modulated the inflammatory response [118].

Recent studies have demonstrated that polysaccharide-based nanofibers can serve as multifunctional scaffolds by carrying diverse bioactive payloads. For example, chitosan/PVA fibers loaded with the herbal compound ursolic acid showed sustained release and strong anti-inflammatory and antioxidant effects; these mats reduced pro-inflammatory cytokines and ROS, shifted macrophages toward the pro-regenerative phenotype, and significantly accelerated diabetic wound closure with enhanced angiogenesis and collagen remodeling [118]. Similarly, alginate/PVA fibers loaded with natural polyphenols (e.g., taxifolin or shikonin) provided controlled release of therapeutics and exhibited antibacterial/antioxidant activity. *In vivo* this flavonoid-loaded scaffolds promoted cell proliferation and angiogenesis while suppressing chronic inflammation in diabetic ulcers [119].

Antimicrobial-loaded nanofibers have also shown a potential efficacy in the treatment of DFU, for instance a one study have showed the potential of antibiotic loaded nanofibers to address infection related complications in DFUs [120]. For example, cephalexin-loaded PHBV nanofibers, fabricated via electrospinning, exhibited high entrapment efficiency (~75%) and a biphasic drug release profile, with an initial burst followed by sustained release for up to 48 h. These scaffolds significantly inhibited MRSA growth *in vitro* and enhanced bacterial clearance in a diabetic mouse model while maintaining biocompatibility with keratinocytes and fibroblasts [121]. Additionally, Razzaq et al. (2025) developed gelatin/polyvinyl alcohol electrospun nanofibers loaded with Cephradine, a broad-spectrum first-generation cephalosporin. These nanofibers exhibited sustained release, enhanced antibacterial activity against *S. aureus* clinical isolates, and significantly accelerated wound closure in diabetic NcZ10 mice compared to free cephradine [122]. Additionally, some studies stated the efficacy of the incorporation of nanomaterials with dual functionality (e.g., antibacterial and pro-angiogenic) into nanofiber scaffolds significantly improves both infection control and vascularization in chronic wound models [99].

Moreover, hybrid nanosystems, particularly nanoparticle-in-nanofiber (NP-in-NF) constructs, have recently emerged for the treatment of DFU. Whereby embedding nanoparticles within electrospun fibers offers synergistic advantages such as stabilization of labile nanoparticles, protection from burst release, and improved therapeutic localization at the wound site. These systems can be engineered to deliver antimicrobial agents, antioxidants, or growth factors in a sustained and controlled manner, thereby overcoming the limitations of free nanoparticles. For instance, Iqbal et al. fabricated electrospun polymeric nanofibers embedded with nanoparticles as drug-delivery platforms, demonstrating enhanced antibacterial activity, controlled release kinetics, and favorable cytocompatibility *in vitro* [123]. These nanosystems are quite unique due to their dual-function scaffolds that simultaneously address infection, inflammation, and impaired angiogenesis in diabetic wounds. Additional examples of these advanced nanofiber scaffolds are included in Table 6 along with the details of their design and therapeutic outcomes.

Table 6: Advanced nanofiber-based scaffolds with bioactive agents for diabetic wound healing

S. No.	Nanofiber scaffold type	Incorporated agents/Cells	Delivery strategy	Therapeutic outcomes in diabetic wound models	Ref.
1	Aligned porous PLLA nanofibers + silica NPs	DMOG (HIF-1α stabilizer)	Drug loaded in mesoporous silica nanoparticles embedded in aligned fibers (controlled release)	↑ Angiogenesis, collagen deposition, and re-epithelialization; modulated inflammation; accelerated wound closure.	[118,124]
2	Nanofiber aerogel (PLGA/gelatin) with macro-channels	LL-37-mimic antimicrobial peptide (W379)	Peptide incorporated into fiber matrix; engineered macro-channels for cell infiltration	Synergistic effect: rapid wound closure with ↑ cell infiltration, neovascularization, and epidermal regeneration in diabetic wounds.	[118]
3	Composite Collagen/PLGA/Chitosan fibers	VEGF + bFGF	Growth-factor-loaded heparin–BSA nanoparticles adsorbed on fibers (sustained release)	Accelerated wound healing in diabetic mice; enhanced granulation tissue, angiogenesis, and matrix remodeling.	[117]
4	MSC-seeded PCL nanofiber scaffold	Mesenchymal stem cells (e.g., bone marrow MSCs)	Live cells seeded onto nanofiber mesh (cell delivery for paracrine therapy)	↑ Collagen I deposition and angiogenesis; immune modulation (↓ M1 macrophages, ↑ M2); faster healing of diabetic ulcers.	[72]
5	Chitosan/PVA nanofibers with ZnO NPs	Chitosan/PVA nanofibers with ZnO NPs	Nanoparticles blended into fiber matrix (gradual Zn^{+} release)	Broad-spectrum antibacterial activity in wound; ↓ infection and oxidative stress; improved wound closure rate in diabetic model.	[125]
6	Chitosan/Poly(vinyl alcohol) (CS/PVA) electrospun nano-fibers	Cefadroxil (broad-spectrum β-lactam antibi-otic)	Electrospinning fabrication; sustained release (burst + prolonged, non Fickian diffusion)	Demonstrated enhanced antibacterial activity against resistant *Staphylococcus aureus* clinical isolates; sustained release reduced toxicity; supported fibroblast and keratinocyte proliferation; promising for wound healing and transdermal delivery.	[123]
7	Chitosan (extruded nanofibrous scaffold)	Mesenchymal stem cells (ADMSC, PLMSC)	Cells seeded into the scaffold (local delivery)	Faster wound closure than acellular scaffold; markedly increased re-epithelialization and neovascularization; reduced inflammation.	[126]
8	Gelatin/Polyvinyl Alcohol (GEL/PVA) electrospun nano-fibers	Cephradine (broad-spectrum antibiotic)	Sustained/controlled release from nanofibers	Showed strong antibacterial activity against *S.aureus*, reduced bacterial load, enhanced wound closure, and faster healing in diabetic NcZ10 mice	[122]

(Continued)

Table 6 (continued)

S. No.	Nanofiber scaffold type	Incorporated agents/Cells	Delivery strategy	Therapeutic outcomes in diabetic wound models	Ref.
9	Sodium alginate/Poly(vinyl alcohol) (SA–PVA)	Taxifolin (flavonoid antioxidant)	Embedded in electrospun fibers (sustained release, ~64% in 24 h)	Antibacterial and antioxidant activity; promoted cell proliferation (Ki67) and angiogenesis (↑CD31, VEGFA); suppressed inflammation (↓CD68); modulated TLR4/NF-κB signaling to support healing.	[127]
10	PHBV (poly(3-hydroxybutyrate-co-3-hydroxyvalerate	Cephalexin (broad-spectrum antibi-otic)	Electrospun nanofibers with high drug loading; biphasic release (initial burst followed by sustained release up to 48 h)	Enhanced antibacterial against MRSA; no cytotoxicity to keratinocytes, fibroblasts, and HEK293T cells; improved *in vivo* bacterial clearance and accelerated wound healing in NcZ10 diabetic mice compared to free cephalexin	[121]
11	Sodium alginate/Poly(vinyl alcohol) (SA–PVA)	Shikonin (antimicrobial naphthoquinone)	Embedded in electrospun fibers	Antimicrobial and antioxidant effects; ~85.5% wound closure rate *in vivo*; upregulated angiogenic factors (↑CD31, HIF-1α) and downregulated inflammatory marker (↓CD68); inhibited NF-κB signaling to attenuate inflammation.	[128]
12	PCL–Gelatin electrospun nanofibers	Bone marrow-derived mesenchymal stem cells (BMSCs)	Direct seeding and integration of live cells onto a nanofiber framework	Accelerated wound closure; enhanced re-epithelialization; improved granulation tissue formation; reduced scarring *in vivo* (rabbit wound model)	[129]
13	Poly(ε-caprolactone)/ Cellulose acetate (PCL/CA)	Chitosan–CeO_2 nanoparticle composite (CeO_2–CSNP)	CeO_2–CSNPs electrosprayed onto nanofiber mat	Strong antibacterial (against *S. aureus*) and high antioxidant activity (~89%); enhanced fibroblast viability and migration; achieved ~95.5% diabetic wound closure by day 15.	[130]

(Continued)

Table 6 (continued)

S. No.	Nanofiber scaffold type	Incorporated agents/Cells	Delivery strategy	Therapeutic outcomes in diabetic wound models	Ref.
14	Poly(vinyl alcohol)/Chitosan (PVA–CS)	Silver nanoparticles (AgNP) and antifungal luliconazole (PLGA NPs)	Co-loaded into electrospun fibers (controlled release)	Potent antifungal and antibiofilm action against Candida species; excellent moisture retention; promoted keratinocyte proliferation; accelerated closure via infection control, enhanced proliferation, and blood flow.	[131]

Note: PCL, Poly(ε-caprolactone); PLLA, Poly(L-lactic acid); PLGA, Poly(lactic-co-glycolic acid); PVA, Poly(vinyl alcohol); SA, Sodium Alginate; CS, Chitosan; CSNP, Chitosan Nanoparticle; BSA, Bovine Serum Albumin; DMOG, Dimethyloxalylglycine; HIF-1α, Hypoxia-Inducible Factor-1 alpha; MSC, Mesenchymal Stem Cell; ADMSC, Adipose-Derived Mesenchymal Stem Cell; PLMSC, Placenta-Derived Mesenchymal Stem Cell; TNF-α, Tumor Necrosis Factor-alpha; IL-6, Interleukin-6; NF-κB, Nuclear Factor kappa-light-chain-enhancer of activated B cells; CD31, Cluster of Differentiation 31; CD68, Cluster of Differentiation 68; TLR4, Toll-like Receptor 4; VEGF, Vascular Endothelial Growth Factor; VEGFA, Vascular Endothelial Growth Factor A; LL-37, Human Cathelicidin Antimicrobial Peptide; CA, Cellulose Acetate.

Importantly, in diabetic ulcers, sustained and localized release is crucial to counteract proteolysis and impaired healing. Electrospinning techniques enable the incorporation of therapeutics into fibers and precise control over release kinetics [132]. In monolithic (single-fluid) electrospun fibers, drugs are directly blended into the polymer, often resulting in an initial burst release [133]. In contrast, coaxial electrospinning creates a protected core for the bioactive agent surrounded by an outer polymer sheath, which regulates diffusion and protects the payload [134].

The choice of scaffold composition also plays a pivotal role in determining the therapeutic performance of nanofiber-based wound dressings. Synthetic polymers such as PLGA, PCL, and PLA are commonly used due to their mechanical robustness and slow degradation rates. These hydrophobic materials enable sustained drug release by tightly encapsulating bioactives and gradually releasing them through hydrolysis [135]. For instance, PLGA-based nanofibers loaded with insulin or PDGF have demonstrated controlled *in vivo* release profiles lasting several weeks [95]. In contrast, natural biopolymers such as collagen, gelatin, chitosan, and alginate offer superior biocompatibility and biological activity. Their hydrophilic nature allows them to absorb wound exudates and facilitate faster drug diffusion, which is particularly beneficial during the early healing phases [136].

Moreover, the structural attributes of nanofiber scaffolds, particularly fiber diameter, porosity, alignment, and morphology, also play crucial roles in modulating drug release kinetics and therapeutic performance. Smaller-diameter nanofibers offer a significantly higher surface-area-to-volume ratio, which facilitates faster drug diffusion and accelerates release. This parameter can be precisely controlled by electrospinning conditions such as polymer concentration, flow rate, and applied voltage, enabling fiber diameters to range from tens of nanometers to several microns [137]. Also, highly porous, loosely packed nanofiber mats facilitate rapid wound fluid uptake and enhance drug mobility, whereas densely packed or coated fibers restrict penetration and prolong release [138].

Additionally, sustained release and "smart" release are critical for diabetic wounds, which often exhibit chronic inflammation and altered local conditions. Generally, researchers aim to minimize the initial burst

and extend delivery of the payload over days to weeks, aligning with the typical chronic wound timeframe. Core–shell designs, hydrophobic polymers, and drug–polymer interactions all contribute to steady, long-term drug release. For instance, the PDGF/antibiotic PLGA fibers described above steadily released growth factor and antibiotics for approximately three weeks *in vitro*, far exceeding the 1–2 day bursts seen with many single-fluid fibers [139].

Another mechanism is the stimuli-responsive drug release, where one prominent approach is pH-responsive release, which takes advantage of the fact that wound pH shifts during healing, healthy skin is slightly acidic (pH ~4.5–6.5), whereas chronic or infected wounds often become alkaline (pH ~7.5–8.9) [140]. Smart nanofibers can exploit this pH variation to modulate drug release. For instance, Miranda-Calderón et al. developed electrospun mats with antibiotic-loaded fibers that remained stable under normal skin pH but swelled and degraded more rapidly in alkaline conditions, leading to accelerated drug release in infected environments. This is typically achieved using pH-sensitive polymers such as poly(β-amino esters) or poly(acrylic acid), which respond to pH changes by altering their swelling behavior or chemical integrity. As a result, drug delivery can be synchronized with the wound's pathological state, releasing more therapeutics when the wound is less acidic and more likely to be infected [141].

Another critical strategy is enzyme-responsive release, which targets the elevated levels of MMPs, particularly MMP-9, found in chronic diabetic ulcers. These enzymes degrade ECM components and impair healing. Nanofiber scaffolds can be engineered with MMP-cleavable peptide linkers or coatings that degrade in response to protease activity, thereby triggering targeted drug release [142]. Other stimuli, such as temperature, ROS, glucose, or external triggers like near-infrared light and ultrasound, have also been explored. For example, fibers embedded with up-conversion nanoparticles can release drugs upon near-infrared NIR irradiation, while ROS- or glucose-responsive fibers containing scavengers or boronic acid moieties are being investigated for diabetic wound applications [143,144]. Among all these approaches, pH- and enzyme-responsive systems remain the most directly relevant to the biochemical environment of diabetic wounds, offering promising avenues for smart, stage-specific therapeutic interventions.

4.3 Preclinical, Clinical Trials, and Commercially Available Nanofiber Scaffolds for Diabetic Wound Healing

Nanofiber scaffolds are often formulated to deliver antibiotics, growth factors, or anti-inflammatory agents, and some designs even incorporate sensors or electronic elements for advanced wound monitoring. Across trials to date, many dressings have shown efficacy signals such as high closure rates, reduced inflammation, or scarring that compare favorably to standard care. Table 7 shows some examples of nanofibers that are currently under clinical trials and intended to be used for wound healing applications.

Table 7: Some preclinical nanofiber-based scaffolds for wound healing applications

Product	Composition	Wound type	Phase	Trial ID	Results	Ref.
Silk elastin sponge (SE-P47K)	Recombinant silk–elastin fusion protein (*E. coli*–produced)	Chronic & acute skin defects	Phase III	jRCT2052210072 (Japan)	In 25 patients (20 chronic, 5 acute), 90.0% of chronic wounds achieved a well-prepared wound bed by day 14; 24/25 patients completed treatment (1 dropout due to infection). Study concluded the sponge was safe and "an effective new option" for wounds unresponsive to standard therapy.	[145]

(Continued)

Table 7 (continued)

Product	Composition	Wound type	Phase	Trial ID	Results	Ref.
SEFM (Restrata®)	Resorbable electrospun synthetic polymers (PLGA/polyglactin 910 + polydioxanone)	Chronic diabetic foot ulcers (DFUs)	Phase II/III	NCT03312595, NCT04918784	In a prospective trial (NCT03312595) of 24 DFUs, 18/24 (75%) healed by 12 weeks with ~96% area reduction. A follow-on RCT (NCT04918784) showed 74% closure with SEFM vs. 33% with standard care at 12 weeks ($p < 0.05$). SEFM-treated wounds also healed significantly faster (mean ~6.6 vs. 9.9 weeks).	[146,147]
Nanofibrillar cellulose (FibDex®)	Wood-derived nanofibrillar cellulose (hydrogel-coated nonwoven fabric)	Skin graft donor sites (acute surgical wounds)	Clinical study	(No NCT reported)	In a single-center trial (n = 24), NFC dressing achieved equivalent donor-site closure time to a standard polylactide copolymer dressing. Notably, NFC-treated sites showed better skin quality: improved elasticity and Observer POSAS scar scores (thickness/vascularity) compared to control. No dressing-related adverse events were reported.	[148]
Silk fibroin scaffold (Silk Surgical's dressing)	Electrospun silk fibroin scaffold	Surgical incisions (post-plastic surgery)	Phase II RCT	NCT05508945 (USA)	In a randomized trial (n = 48), each patient received a silk-fibroin dressing on one incision and Steri-Strips on the other. Silk dressing had zero erythema vs. 20.8% with Steri-Strips ($p = 0.002$), and significantly fewer wound separations (9.3% vs. 30.2%, $p = 0.012$). Silk dressings also remained adherent (0% complete detachment vs. 75% in controls) and reduced MARSI rates.	[149]

Note: PLGA; poly(lactic-co-glycolic acid); NFC; nanofibrillar cellulose; SE-P47K; silk–elastin P47K sponge; SEFM; silk electrospun fiber matrix (Restrata®); POSAS; patient and observer scar assessment scale; RCT; randomized controlled trial; MARSI; medical adhesive-related skin injury; ID; identification; NCT; national clinical trial identifier; USA; United States of America.

While preclinical studies dominate the literature on nanofiber scaffolds, several systems have advanced to clinical evaluation. In an early-phase randomized trial evaluated gelatin-based electrospun nanofiber scaffolds loaded with human placenta-derived mesenchymal stem cells combined with platelet-rich plasma in chronic wound patients, reporting high biocompatibility, excellent moisture balance, and accelerated healing rates [150]. Additionally, chitosan/PVA nanofiber mats functionalized with silver nanoparticles have entered early clinical testing in Asia, showing promising outcomes in infection control and wound closure in DFU cohorts [151]. Furthermore, several nanofiber scaffolds have already been commercialized, as shown in Table 8, which summarizes their nanofiber composition and key features in human use.

Table 8: Commercially available nanofiber scaffolds for diabetic wound healing

Product name	Manufacturer and country	Nanofiber composition	Key features	Ref.
Restrata® Wound Matrix	Acera Surgical (USA)	Electrospun polyglactin 910 (PGLA) and polydioxanone (PDO) fibers	Fully synthetic, bioresorbable ECM-mimicking scaffold; high porosity for cell ingrowth; resists enzymatic degradation but gradually absorbs as new tissue forms.	[152]
Phoenix Wound Matrix	RenovoDerm (USA)	Electrospun polyglycolic acid (PGA) and poly(lactide-co-caprolactone) (PLCL) fibers	Synthetic 3D nanofiber scaffold that is fully resorbable within 1–2 weeks. Microporous matrix designed to modulate wound pH and promote regenerative healing over inflammation.	[153]
SurgiCLOT®	St. Teresa Medical (USA)	Electrospun dextran nanofibers (fibrin-based coating)	Hemostatic nanofiber dressing originally developed to rapidly clot bleeding and cover wounds. Used in surgical and chronic wounds.	[152]
EktoTherix™	Neotherix (UK)	Electrospun bioresorbable polymer (likely poly-glycolide or co-polyester)	Regenerative tissue scaffold for wound healing. Nanofiber matrix provides a 3D structure at the proper scale for cell attachment and migration into the wound. It is fully resorbable,	[152]
HealSmart™	PolyRemedy Inc. (USA)	Electrospun hyaluronic acid composite nanofibers (personalized dressing)	Personalized nanofiber wound dressing system for diabetic ulcers. Utilizes hyaluronic acid-based nanofiber mats created on-demand to fit wound geometry.	[154]
SpinCare® Wound Care System	Nanomedic Technologies (Israel)	*In situ* electrospun polymer nanofibers (spray-on PU-based matrix)	Portable electrospinning device that sprays a skin-like nanofibrous layer directly onto the wound. The transparent nanofiber matrix conforms to any wound shape and serves as a temporary skin substitute, protecting the wound while promoting cell migration and tissue regeneration.	[155]

4.4 AI-Driven Design and Smart Biosensor Integrated Nanofiber Scaffolds for Diabetic Wounds

Machine learning and artificial intelligence (AI) tools are increasingly used to optimize nanofiber scaffold designs for diabetic wound healing. AI models can predict which configurations will yield the best healing outcomes, thereby reducing trial-and-error experimentation. For example, Virijević et al. trained a neural network on data from 125 electrospun formulations of PCL blended with PEG to identify an optimal nanofiber composition. Guided by the model's predictions, they fabricated a PCL/PEG scaffold loaded with antibiotics that significantly improved angiogenesis and wound closure *in vivo* [156].

Recent developments include dual-layer nanofiber scaffolds that visually indicate pH changes while simultaneously releasing bioactives to suppress bacterial growth. Such designs allow early infection detection without removing the scaffold. Multiplexed sensing systems have also been reported, in which nanofiber-based patches detect multiple factors such as pH, temperature, moisture, inflammatory metabolites and communicate data via smartphone applications powered by AI image recognition. These systems achieve near-clinical accuracy and hold strong potential for integration into diabetic wound monitoring platforms [157].

Furthermore, one of the most prominent examples is the PETAL sensor patch, developed by Zheng and colleagues in 2023. This battery-free device integrates five sensing regions that detect pH, temperature, moisture, trimethylamine, and uric acid. The results are displayed as colorimetric changes, and a smartphone application powered by a convolutional neural network interprets the images with nearly 97% accuracy to classify wounds as healing or non-healing. This example demonstrates how AI-based image recognition can

transform raw biomarker signals into actionable diagnostic information without removing the dressing [158]. On the other hand, Palani et al. reviewed and experimentally demonstrated an AI-assisted nanofiber scaffold incorporating sensing modules for pH, temperature, moisture, oxygen levels, and inflammatory biomarkers. These scaffolds exemplify the potential to combine the regenerative properties of nanofibers with real-time monitoring, enabling AI algorithms to predict wound trajectories and support personalized treatment strategies [159].

Another noteworthy development was introduced by Levin et al. who engineered bioelectronic smart bandages that integrate multiple biosensors into a single platform. These dressings monitored pH, temperature, moisture, and selected inflammatory metabolites, transmitting data wirelessly to provide continuous feedback. Although not yet fully optimized for diabetic wound care, they represent a clear step toward clinical translation of multiplexed bioelectronic systems [160].

Finally, Noushin et al. described an IoT-enabled wound sensor capable of monitoring inflammatory cytokines such as IL-6 and IL-10 directly at the wound site. The device incorporated nanostructured electrodes and communicated data wirelessly, allowing remote tracking of inflammatory status. Although primarily demonstrated as a flexible electronic platform, this approach can be adapted into nanofiber scaffolds to combine structural support with real-time biomarker detection [161].

Despite the rapid progress, several challenges remain before these systems reach clinical translation. Biosensor stability in the fluctuating wound environment, biocompatibility of integrated electronic components, and secure real-time data transmission remain key obstacles. On the AI side, robust model training requires large, standardized datasets of wound parameters and outcomes, which are not yet widely available. Regulatory approval will also require thorough validation to prove safety, reliability, and cost-effectiveness.

4.5 Formulation Challenges

Translating nanofiber-based wound therapies from bench to bedside requires overcoming several engineering and manufacturing challenges, as well as navigating complex regulatory pathways. One major hurdle is the scale-up of nanofiber fabrication. Electrospinning, the most common technique to produce nanofiber scaffolds, is relatively easy at the laboratory scale but notoriously difficult to translate to industrial-scale throughput. Typical single-needle electrospinning produces only about 0.1–1 g of nanofiber per hour, far below the quantities required for mass production [162].

Efforts to increase output, such as using multi-needle spinnerets or needleless electrospinning (e.g., rotating drum or free-surface systems methods), introduce new variability and quality control challenges. For instance, multi-needle setups suffer from electric field interference between jets and frequent needle clogging, which can lead to inconsistent fiber diameters and scaffold morphology. Needleless electrospinning can produce higher fiber yields, but rapid solvent evaporation in these open systems may change the polymer solution concentration over time, making the process harder to control and reducing reproducibility [163,164].

Batch-to-batch consistency is a critical concern: studies have noted that using natural polymers such as silk or collagen can result in variable fiber properties between batches due to inherent source variability, and even synthetic polymers can behave differently at scale if processing parameters are not perfectly optimized. Additionally, residual solvents used during electrospinning pose safety and quality challenges; any solvent not fully removed could be toxic, and scaling up often involves larger volumes of flammable organic solvents that require robust ventilation and safety measures [165].

All implantable or wound-contacting medical products must be sterilized; however, nanofibrous materials can be highly sensitive to common sterilization methods. Techniques such as autoclave sterilization

are often incompatible with polymer fibers, which may melt or deform, while ethylene oxide (EtO) gas and γ-irradiation, commonly used for medical devices, can induce chemical or structural changes in polymer nanofibers. Studies have shown that γ-irradiation or prolonged UV exposure can degrade polymer chains in nanofibers, altering their mechanical strength and morphology. Research indicates that the choice of sterilization method can affect both the scaffold's physical properties and the stability and release profile of incorporated biomolecules. For example, a growth factor-loaded nanofiber scaffold may lose bioactivity if exposed to certain sterilants or stored at room temperature for extended periods [165,166].

Beyond the technical challenges of fabrication, sterilization, and stability, several additional hurdles must be addressed for successful translation of nanofiber scaffolds. One key barrier is regulatory classification: many nanofiber-based products incorporate both biomaterials and therapeutic agents, leading to uncertainties whether they are regulated as medical devices, combination products, or biologics [167]. This complicates approval pathways and often prolongs the time to market. Cost-effectiveness is another critical factor. Although electrospinning can produce highly functional scaffolds, the incorporation of growth factors, nanoparticles, or living cells markedly increases manufacturing costs [168], raising concerns about affordability for widespread clinical use, especially in low- and middle-income settings.

Additionally, patient compliance also plays a role in therapeutic success. Advanced nanofiber scafolds may require specialized application, controlled storage conditions, or frequent monitoring, which could limit patient acceptance compared to conventional dressings [169]. Designing user-friendly, stable, and easy-to-apply scaffolds will be important for real-world adoption. Finally, clinical validation remains a pressing challenge. Despite encouraging preclinical data, relatively few nanofiber scaffolds have been evaluated in well-designed randomized clinical trials. Without robust clinical evidence, adoption by regulatory agencies and clinicians will remain limited.

4.6 Future Directions

As research and development progress, several exciting future directions are expected to further enhance nanofiber scaffold therapy for diabetic wounds. One major trend is the incorporation of "smart" technologies, biosensors, and responsive electronics into wound scaffolds, creating interactive dressings that not only treat the wound but also monitor and adapt to its state in real time. For example, next-generation smart bandages are being developed with built-in sensors that continuously track wound conditions such as pH, temperature, moisture levels, and biochemical markers of infection [170]. Since chronic diabetic wounds often precede visible infection with subtle changes such as a rise in wound pH or temperature, before visible infection occurs, these sensor-integrated dressings can provide early warning of complications.

A recent advanced device combined a one-way microfluidic drainage system with an ultrathin pH sensor that actively wicked excess exudate from the wound while simultaneously measuring wound pH, successfully detecting shifts between normal (~pH 5–7) and infected (~pH 8–9) wound states in a diabetic wound model. Data from such dressings can be transmitted wirelessly to caregivers' smartphones or hospital systems, enabling remote monitoring of wound healing progress. However, the durability of these sensors in a moist, enzyme-rich wound environment remains a significant challenge, and power supply for continuous monitoring is also problematic. Researchers are exploring flexible biodegradable electronic materials and energy harvesting approaches (e.g., from body heat or motion) to overcome these barriers [159,170,171].

Building on this progress, researchers are also integrating active therapeutic components into smart scaffolds, achieving a closed-loop "sense and respond" capability. For instance, flexible electronics can be embedded in a nanofiber scaffold to deliver electrical stimulation to the wound bed. One bioresorbable electronic bandage developed in 2023 delivers controlled electrotherapy to a diabetic wound and was shown to accelerate healing by approximately 30% in preclinical trials, then harmlessly dissolves away once the

wound is healed [172]. Likewise, sensor feedback can be used to trigger on-board drug release, for example, releasing antibiotics when an infection is detected, or growth factors when a certain healing phase is delayed. The main challenge here lies in synchronizing drug release with the dynamic wound environment; smart release systems such as pH-sensitive or enzyme-cleavable linkers are being investigated as practical solutions [173].

A recent design demonstrated a wireless closed-loop bandage that continuously monitored wound states and automatically administered electrical stimulation to the tissue when sensing poor healing dynamics, thereby significantly improving healing outcomes in a diabetic wound model [174]. These smart, biosensing, and stimuli-delivering nanofiber systems represent a convergence of wound care and wearable technology, promising more individualized and timely therapy for chronic wounds. In the near future, a patient with a diabetic foot ulcer might wear a smart nanofiber scaffold that not only accelerates healing with embedded therapeutic agents, but also actively tracks the wound's condition and adjusts the treatment or alerts the patient and the clinician as needed in real time.

Another key future direction is the shift toward patient-specific, personalized wound therapy using nanofiber scaffolds. Because every chronic wound is different in size, shape, depth, and microenvironment, a one-size-fits-all dressing may not be optimal. Advanced fabrication methods such as 3D printing and tailored electrospinning now allow the creation of custom-shaped scaffolds that conform exactly to an individual patient's wound geometry [175]. For example, 3D printers can use patient wound scans to print a wound dressing that has the precise contours of a deep foot ulcer, ensuring intimate contact with the wound bed [176]. The main challenge here is scalability and cost: custom devices are more expensive and time-consuming to manufacture. A possible solution is on-demand, point-of-care fabrication platforms integrated within hospitals, which could reduce costs and improve accessibility.

In addition, companies are exploring personalization platforms where clinicians can input wound characteristics and receive a bespoke nanofiber dressing manufactured on demand. One existing system (HealSmart™) creates patient-specific dressings by varying the ratio of two fiber types: a hydrophilic, absorbent fiber vs. a hydrophobic, moisture-barrier fiber to suit the wound's moisture level. This personalized approach has been shown to eliminate a lot of trial and error in dressing selection and was associated with improved healing outcomes in chronic wounds [162]. However, regulatory pathways for personalized devices remain poorly defined, which may delay clinical adoption. Collaborative regulatory frameworks and adaptive approval models could help accelerate translation into real-world use.

Therefore, several barriers still hinder the clinical translation of nanofiber scaffolds, as discussed above. These include difficulties in scaling up production, challenges with sterilization methods, limited formulation stability during storage, complex regulatory and clinical pathways, hurdles in integrating smart technologies, and concerns about cost and accessibility. Addressing these challenges requires strategies such as advanced electrospinning techniques, alternative sterilization approaches, stabilizers and optimized packaging, early regulatory engagement with multicenter trials, development of biodegradable electronics with wireless powering, and adoption of low-cost polymers with scalable fabrication. Table 9 presents the current challenges facing nanofiber scaffolds for diabetic wound healing and outlines potential solutions under active investigation.

Table 9: Electrospun nanofiber scaffolds challenges in the clinical translation and potential solutions

Challenge	Impact/Explanation	Possible solutions	Ref.
Scale-up and manufacturing	Lab-scale electrospinning yields are very low about 6.2–8.6 g/h with poor reproducibility; multineedle systems clog, and needleless setups cause diameter variability.	Use high throughput and melt electrospinning or closed-loop process control.	[162,177]
Sterilization compatibility	Autoclaving, γ-irradiation, or EtO damage fibers or inactivate bioactive agents; UV degrades collagen and growth factors.	Use supercritical CO_2, e-beam, or plasma sterilization.	[178,179]
Formulation stability and storage	Structural degradation, bioactive denaturation, or loss of cell viability during storage.	Use lyophilization or cryopreservation with stabilizers.	[180,181]
Regulatory and clinical barriers	Combination product status complicates FDA/EMA approval; lack of standardized testing; limited clinical evidence.	Apply for early regulatory engagement; ISO/ASTM alignment, multicenter RCTs, or adaptive trial designs.	[182,183]
Smart technology integration	Sensor durability, power supply, and patient usability limit biosensor or electronic scaffold adoption.	Use biodegradable electronics (silk, magnesium-based) or AI-driven closed-loop systems.	[159,184]
Cost and accessibility	Complex multi-layered or cell-laden scaffolds remain expensive, limiting access in low-resource settings.	Use of inexpensive polymers (e.g., alginate, chitosan, gelatin, PVA) or scalable 3D printing and melt electrospinning.	[185,186]

5 Conclusion

Polymeric nanofiber scaffolds have shown significant promise in addressing the multifaceted pathophysiological impairments of chronic diabetic wounds, including impaired angiogenesis, chronic inflammation, oxidative stress, and aberrant ECM remodeling. By providing a biomimetic ECM-like architecture and serving as platforms for therapeutic delivery, such as growth factors and antimicrobial agents, these scaffolds act as multifunctional dressings that promote neovascularization, modulate immune responses, mitigate oxidative damage, combat infection, and accelerate granulation and re-epithelialization. Extensive preclinical and initial clinical evidence indicate that nanofiber scaffolds achieve faster wound closure, improved granulation, and reduced inflammation compared to conventional dressings.

Despite this progress, translating nanofiber scaffolds into routine clinical practice remains challenging, with hurdles including scaffold stability, sterilization compatibility, scalable manufacturing, and regulatory approval. Future scaffold designs are expected to integrate smart technologies such as built-in biosensors for real-time wound monitoring and stimuli-responsive drug release, while leveraging AI-assisted design

to optimize fiber architectures and enable patient-personalized wound care. Moving forward, continued interdisciplinary collaboration among polymer scientists, bioengineers, clinicians, and regulatory stakeholders will be essential to overcome these challenges and accelerate the clinical translation of multifunctional nanofiber scaffolds, thereby improving outcomes for patients with diabetic wounds.

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