International Journal of Nanomedicine

Dovepress
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REVIEW

Polymeric Nanomedicines in Diabetic Wound Healing: Applications and Future Perspectives

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Abstract: The management of diabetic wound continues to pose significant clinical obstacles, primarily attributed to bacterial infections, excessive inflammation, oxidative stress, and impaired angiogenesis. These pathological factors not only severely affect patient well-being but also create considerable burden on medical services. Current managements often show limited efficacy, necessitating the exploration of alternative therapeutic strategies. Polymeric nanomedicines (PNs), owing to their nanoscale properties, enhanced cellular uptake, stability, bioavailability, and biocompatibility, have been broadly utilized for diabetic wound treatment. PNs demonstrate remarkable capabilities in microbial inhibition, inflammation regulation, oxidative stress mitigation, and vascular network formation, particularly when combined with various agents, including organic substances (eg, exosomes), inorganic substances (eg, metals), and biomaterials (eg, chitosan, hyaluronic acid, and hydrogels). This article systematically examines recent progress in PN-based interventions for diabetic wound recovery, highlighting the pivotal role of PNs in mitigating bacterial infection, modulating inflammatory responses, and promoting cellular regeneration. Additionally, we provide a novel perspective on the multifunctionality of PNs and their potential for overcoming the limitations of conventional therapies. Overall, PNs represent an innovative and promising approach to diabetic wound management, outperforming conventional therapies in stability, targeted delivery, and multifunctionality. In the future, investigations should concentrate on refining PNs formulations and administration strategies so as to enhance biocompatibility, and conducting well-designed clinical trials to validate their therapeutic efficacy.

Keywords: polymeric nanomedicines, nanotechnology, diabetic wounds healing, drug delivery

Introduction

Diabetes mellitus is a chronic metabolic disease marked by hyperglycemia, usually due to loss of insulin secretion or insulin resistance with relative insufficient insulin secretion.[1] In a hyperglycemic state, the immune system is suppressed, increasing the risk of infection and causing a continuous inflammatory response, which impairs wound healing in patients with diabetes. Diabetic foot ulcers (DFUs) is a typical representative of the wound in patients with diabetes and is one of the prevalent complications of diabetes, with a risk ranging from 15% to 25% in adult patients with diabetes.[2] According to the latest meta-analysis, the global incidence of DFUs is approximately 6.3%,[3] with the incidence in patients with type 2 diabetes reaching 34%.[4] In some high - risk regions, the incidence can be even higher. For example, in certain African regions, the incidence of DFUs among diabetic patients may exceed 10%. Additionally, the prevalence tends to increase with age, with elderly diabetic patients having a notably higher risk.[5] In a 5-year longitudinal multiracial cohort study conducted in Singapore, the mean hospitalized time of patients with DFUs was 13.3 days, and that with minor and major amputation were 20.5 days and 59.6 days respectively. Among the inpatients with DFUs, it was estimated that the yearly medical expenditure of each patient was US $ 3368 in average. The average costs for patients with minor and major

Received: 23 December 2024
Accepted: 29 April 2025
Published: 22 May 2025

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amputation were US $ 10,468, and US $ 30,131 per year respectively.[2] As the incidence of diabetes increases, the risk of DFUs rises subsequently. This not only affects patients' quality of life, but also poses a major challenge to the healthcare system.[6]

Current clinical strategies for diabetic wound include glycemic control, local wound care, antibiotic therapy, negative pressure wound therapy (NPWT), growth factor therapy, biomaterials, skin substitutes, physical therapy, surgical interventions, and education of daily lifestyles.[7–9] However, these strategies still have their limitations. Among them, long-term use of antibiotics may contribute to the development of drug resistance, as well as disruption of the normal balance of skin flora; If the technique is poor or the pressure selection is inappropriate, NPWT also has adverse effects such as toxic shock, aggravation of wound infection, hemorrhage, necrosis, and allergy;[10] Although growth factors can accelerate the growth of granulation tissue, they cannot address the underlying causes of diabetic wounds, such as neuropathy and vascular disease;[11] Mesenchymal stem cells (MSCs) are also associated with high cost, uncertain treatment efficacy and potential tumor risks.[12] In recent years, nanotechnology serves as one of the innovative approaches in diabetic wound treatment.[13] Polymeric nanomedicines (PNs) usually refer to nanoscale (1–100 nm) drug carriers which are engineered by polymer materials. Due to their nanostructures, good stability, and biocompatibility, PNs show great potential in wound healing. Beyond controlling drug release, improving drug stability, and enhancing bioavailability, PNs offer multifunctional benefits, including anti-inflammatory, antimicrobial, and pro-angiogenic effects. Their functionalized design further enables targeted therapy, improving microenvironmental barriers in diabetic wound healing and significantly enhancing therapeutic outcomes.[14–18]

The Underlying Mechanism of Diabetic Wound Healing

Normally, the process of wound healing is categorized into four stages: hemostasis, inflammation, proliferation, and remodeling, and often referred to as the "healing cascade". During hemostasis, platelets are activated and aggregate to form fibrin clots, while cytokines are released to promote blood clotting and recruit inflammatory cell.[19] As the inflammatory response progresses, neutrophils are gradually replaced by macrophages, which promote angiogenesis and tissue repair by secreting growth factors.[20] The proliferative phase involves fibroblasts and epithelial cells in tissue remodeling, while the remodeling phase involves collagen transformation and extracellular matrix reconstitution to enhance tissue strength and function. The formation of growth factors and extracellular matrix has a significant influence on the entire wound recovery process, as they promote the efficient migration and proliferation of various cell types, thereby accelerating wound repair.

In contrast, wound healing in diabetic patients is distinct from that in individuals without diabetes, primarily due to the pathophysiological conditions associated with diabetes. Diabetes mellitus is a long-term metabolic disorder marked by persistent high blood sugar levels, typically resulting from impaired insulin secretion, insulin resistance, or a combination of both. The glucose-rich environment in patients with diabetes promotes the long-term innate immunity which affect the aerobic glycolysis of macrophages, the pentose phosphate pathway, and the tricarboxylic acid cycle. This, in turn, macrophages' ability to engulf and eliminate bacteria is affected. Hyperglycemia may also increase the accumulation of advanced glycation end products (AGEs), which change the redox state of the wound and the immune response, affecting the clearance of pathogens.[21] These factors increase the risk of bacterial infection and make it more difficult to remove pathogens once infection occurs,[22,23] resulting in rapid local wound progression, necrotized infection, and a heightened risk of amputation in individuals with DFUs.[8]

In the hemostatic stage of diabetic wound healing, hyperglycemia impairs vascular endothelial cell function, reducing the production of nitric oxide (NO), which in turn decreases blood vessel dilation and reduces blood supply to the wound. It also leads to non-enzymatic glycosylation of platelet membrane proteins and lipids, alters the fluidity and receptor function of platelet membranes, decreases chemokine synthesis, and affects the aggregation and adhesion of platelets.[24]

During the early stage of inflammation, hyperglycemia reduces the expression of damage-associated molecular patterns (DAMPs), hydrogen peroxide (H2O2) and chemokines such as C-X-C motif chemokine ligand 4 (CXCL4), CXCL8, CXCL10, CXCL12, and CXCL3 at the wound site. This diminishes the activity of chemokines, leading to reduced recruitment of inflammatory cells and unbalanced expression of inflammatory mediators, including tumor

necrosis factor-alpha (TNF-α), Interleukin-1 beta (IL-1β), and Interleukin-6 (IL-6) around diabetic wounds. With the increase of reactive oxygen species (ROS) production, a chronic inflammatory state is fostered.[25,26]

In the later stages of inflammation, hyperglycemia affects macrophage polarization, preventing the conversion of M1 macrophages to the healing-promoting M2 type,[20] thus prolonging the inflammatory phase. During the proliferative phase, hyperglycemia reduces fibroblast proliferation and migration by affecting growth factor signaling. Additionally, hyperglycemia affects angiogenesis, reducing angiogenesis and hindering tissue regeneration. It also inhibits the activity of fibroblasts, reduces collagen synthesis, increases non-enzymatic glycosylation of collagen and other extracellular matrix proteins, further delaying wound healing.

In the remodeling stage, collagen synthesis in fibroblasts is inhibited, and the abnormal activity of matrix metalloproteinases, along with non-enzymatic glycosylation, leads to abnormal collagen structure and reduced scar tissue stability. The persistent inflammatory response results in poor scar tissue formation. Additionally, reduced levels of provascular factors such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and transforming growth factor-beta (TGF-β) in diabetes result in decreased angiogenesis at the wound site. This leads to lowered expression of PDGF and its receptors, as well as a reduced angiopoietin 1/angiopoietin 2/ tie 2 (Ang1/Ang2/Tie2) ratio, which interferes with the maturation and stability of the vascular system, further delaying the healing process[27] (Figure 1).

The primary distinction comparing a diabetic wound to a normal wound lies in the fact that diabetic wound healing is heavily influenced by internal factors such as hyperglycemia, inflammatory mediators, macrophages, provascular factors, all of which contribute to delayed healing. Unlike normal wound healing, which progresses through well-regulated and

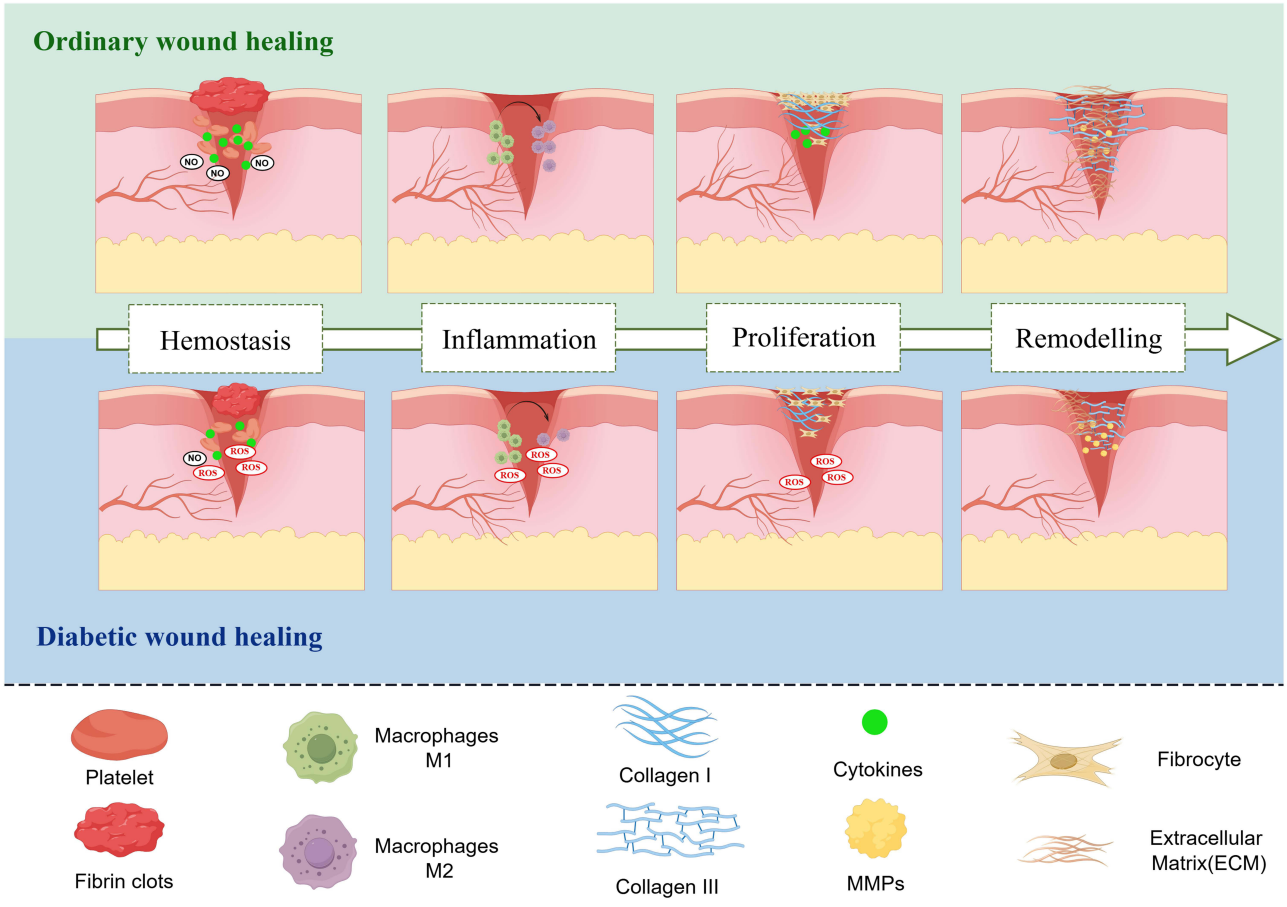

Figure 1 Phases of physiological and diabetic wound healing.

https://doi.org/10.2147/IJN.S514000

coordinated stages, the healing process in diabetic wounds is often prolonged and complicated, requiring targeted therapeutic strategies to overcome these unique challenges.

Types of Polymeric Nanomedicines

With the rapid advancement of nanotechnology, polymeric nanomedicines have found widespread applications across various fields, including biomedicine, drug delivery, and material science. In the realm of wound treatment, PNs exhibit significant prospects and substantial therapeutic benefits.

Polymers are generally classified into natural and synthetic types based on their composition. Natural polymers, such as proteins (eg, collagen, gelatin, silk fibroin, keratin, and natural rubber) and polysaccharides (eg, chitin, chitosan, starch, alginate, cellulose, and hyaluronic acid), have been widely utilized in nanomedicine. On the other hand, synthetic polymers, characterized by well-defined and controllable chemical structures, are also increasingly utilized in nanomedicines. Examples of synthetic polymers include poly(lactic acid-co-glycolic acid)-b-poly(ethylene glycol)-b-poly(lactic acid-co-glycolic acid) (PLGA-PEG-PLGA), polyvinyl alcohol (PVA), polycaprolactone (PCL), and polyethylene glycol (PEG), etc.[28]

Polymeric nanomedicines can be roughly divided into 6 categories according to their structural differences, including polymer conjugates, dendrimers, polymeric nanocapsules, nanogels, polymeric micelles(PMs), and nanoparticles(NPs)[28] (Figure 2). These nanomedicines provide multiple benefits, such as enhanced bioavailability, extended circulation time, and improved solubility of poorly water-soluble drugs, leading to significant breakthroughs in areas such as targeted delivery (both active and passive) and controlled drug release.[29]

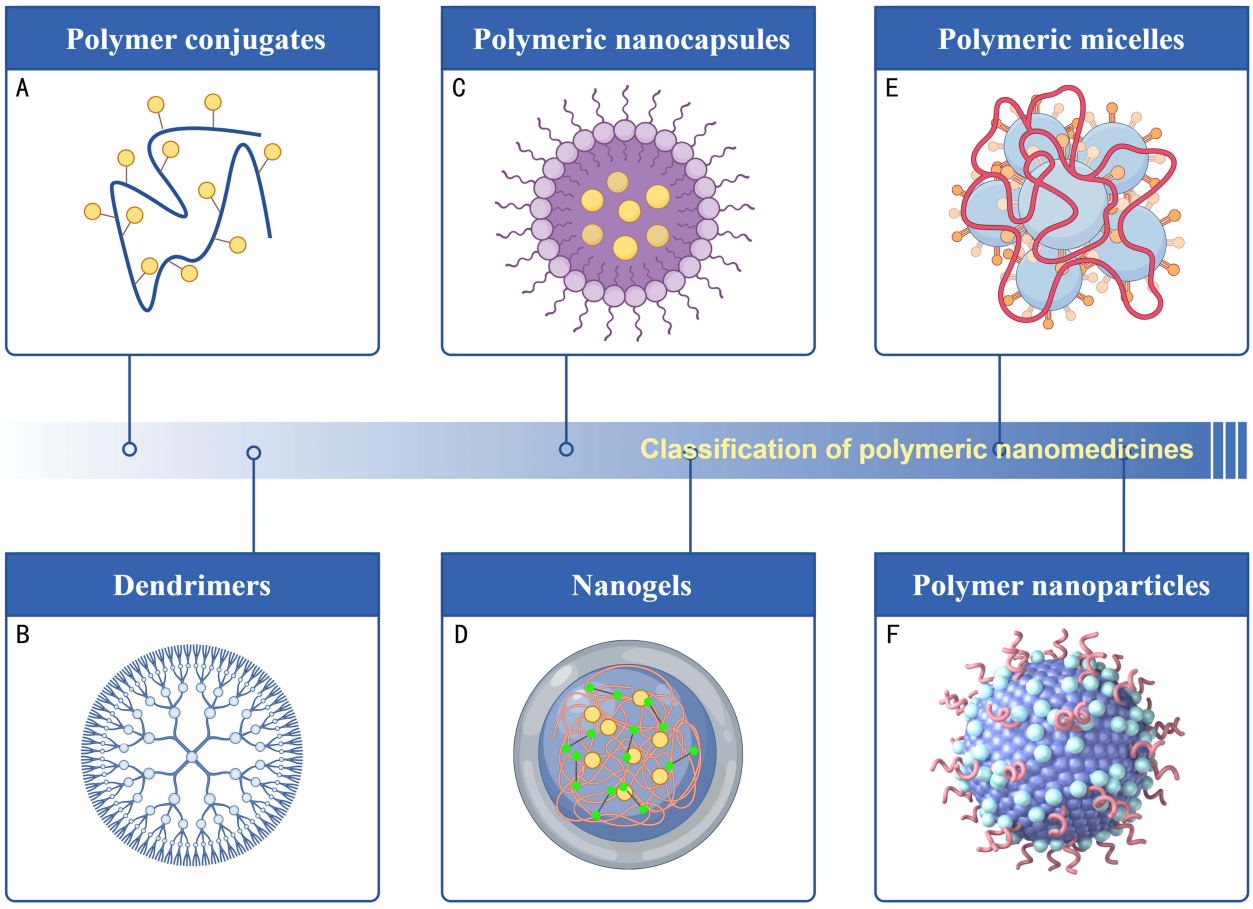

Figure 2 Structural illustration of Polymeric Nanomedicines. A. Polymer Conjugates: can be conjugated to drugs, proteins, antibodies, and peptides. B. Dendrimers: hyperbranced with drugs being encapsulated within the internal cavities. C. Polymeric nanocapsules: a core enclosed by a polymeric shell. D.Nanogels: hydrophilic polymeric networks with encapsulation of medicines, DNA, siRNA, peptides, and proteins.E.Polymeric micelles: contains mixed micellar formulations with a hydrophobic inner core and a outer hydrophilic shell. F. Polymer nanoparticles: colloidal carriers with a hydrophobic core and surface components.

Polymer Conjugates

Polymer–protein conjugates and polymer–drug conjugates, characterized by the conjugation of therapeutic molecules or functional moieties to polymers, offer various advantages including extended circulation times, targeted delivery, controlled release, and decreased immunogenicity.[30]

Polymer–protein conjugates mainly conjugate proteins to polymers for delivering proteins, antibodies, and peptides to enhance their stability, and alert the pharmacokinetics and targeting ability. PEG, a polymer with high water solubility, flexibility, lack of charge, and biocompatibility, is commonly used for polymer-protein conjugation. PEGylation hinders the interaction between the protein and plasma proteins, enzymes, and the phagocytic system, thereby preventing rapid clearance.[31,32]

Polymer–drug conjugates typically consist of multiple drugs conjugated to a single polymer due to the significantly smaller molecular weight of drugs compared to proteins. As a result, polymers can alter pharmacokinetic properties, improve solubility, and enable controlled release kinetics of the conjugated drugs, thereby promoting both diagnostic and therapeutic performances.[33] Functionalizing polymer conjugates with specific bioactive ligands both enhances therapeutic efficacy and reduces side effects on healthy tissues.[34] For instance, amino groups of AS1411 aptamers have been conjugated to carboxymethyl chitosan via an esterification reaction, creating a targeted drug delivery system for tumor cells.[35]

Dendrimers

Dendrimers are hyperbranched, unimolecular, 3D polymeric macromolecules which consist of a central core surrounded by convergent reactive chain-ends, with a readily modifiable surface.[36] Thus, dendrimers commonly serve as versatile carriers for small molecule drugs, which can either be physically encapsulated within the dendrimer cavities or chemically conjugated to the surface functional groups, depending on the specific structures and properties of the drugs.[37]

Additionally, the encapsulation of drug molecules within the internal cavities of dendrimers can significantly enhance the stability of the drugs, protecting against the degradation during blood circulation until they reach the target site.[38] Furthermore, dendrimers facilitate site-specific drug delivery through targeting ligands conjugated to their surfaces, thereby minimizing nonspecific toxicity to adjacent tissues.[39] Among the various types, the most extensively studied dendrimers are non-biodegradable, cationic, amine-terminated polyamidoamine (PAMAM) dendrimers.[40]

Polymeric Nanocapsules

Polymeric nanocapsules feature a liquid or solid core enclosed by a polymeric shell.[40] With their core-shell microstructure, the drug-loading efficiency can be increased effectively.[41] The polymeric shell protects against degradation or burst release caused by factors such as pH, temperature, and enzymatic activity. Furthermore, it can facilitate specific interactions with targeted biomolecules, thereby achieving precise drug delivery.[42–44]

Common natural polymers used as nanocapsules include polysaccharides, chitosan and protein.[45–47] To date, synthetic polymers that have been widely utilized include aliphatic polyesters, Eudragit® polymers and PEG.[48] Eudragit® RS100, can effectively neutralize the negative charge of DNA, thus facilitating its transport across cell membranes without causing molecular degradation.[49] Furthermore, the incorporation of PEG on the surface of nanocapsules enhance their stability in biological media while simultaneously reducing immunogenicity.[50] Hence, the encapsulation of photosensitive drugs, such as desonide and ketoprofen, within the oil core of Eudragit®RL 100 nanocapsules, can effectively prevent photodegradation of the drug under UV radiation.[51]

By modulating the interactions between cells and the drug, these nanocapsules improve bioavailability compared to free, unloaded drugs.[52] Additionally, polymeric nanocapsules offer a reliable delivery mechanism that maintains therapeutic drug concentrations over extended periods, enhancing patient convenience.[53]

Nanogels

Nanogels are composed of hydrophilic polymeric networks at submicron scales, which allows encapsulation of hydrophilic and lipophilic medicines, DNA sequences, small interfering RNA (siRNA), peptides, and proteins.[54–56]

Active targeting in nanogels is achieved by conjugating ligands, such as antibodies or aptamers, that specifically bind to biological receptors on target cell surfaces.[57] It has also been indicated that cells exposed to nanogels composed of biocompatible natural polymers, including alginate, dextran, pullulan, and hyaluronic acid, exhibit a high survival time in the cellular environment and low toxicity.[58–60] Multi-stimuli responsive nanogels are capable of releasing their drug payloads at specific locations by undergoing changes in their configuration, size, and physicochemical properties in response to various stimuli such as pH, temperature, redox conditions, and light.[61] For instance, dual temperature/pH-sensitive nanogels have been developed using temperature-responsive poly(N-isopropylacrylamide) P(NIPAAm) and N, N-dimethylaminoethyl methacrylate (DMAEMA), which contains amino groups that exhibit pH-responsive behavior to facilitate the release of anticancer drugs.[62] Lian et al synthesized poly(ethylene glycol)-graft-dextran (CDP) nanogels through cross-linking with 3,30-dithiodipropionic acid (DTPA), enabling dual reduction-triggered and pH-responsive drug delivery for cancer therapy.[63]

Polymeric Micelles(PMs)

Polymeric micelles (PMs) are formed by the spontaneous self-assembly of amphiphilic polymers into nanostructures ranging from 20 to 200 nm in size.[64] These micelles are comprised of a hydrophobic inner core for entrapping poorly-water soluble-drugs, and a outer hydrophilic shell for isolating the drug from the surrounding environment.[65] The hydrophilic outer surface can be further functionalized with a variety of targeting ligands, such as folate (FOL), monoclonal antibodies (mAb), and monosaccharides (eg, mannose, glucose, and fructose), enabling pH/temperature responsive drug delivery.[66]

Recently, two or more distinct amphiphilic polymers are commonly combined in micelles.[67] Mixed micellar formulations are utilized to achieve better thermodynamic and kinetic stability, enhance drug loading capacity, and provide more accurate size control and incorporation of various modifications.[68–70] The derivatives of poly(ethylene oxide)–poly(propylene oxide)-poly(ethylene oxide) (PEO–PPO–PEO) block copolymers are classic amphiphilic materials used for the preparation of polymeric mixed micelles.[70] Other relevant amphiphilic macromolecules employed in the construction of PMs include PEG-based molecules such as poly(lactic acid) (PLA), PLGA, and PCL, which have been approved by the US Food and Drug Administration (FDA) for various biomedical applications in humans.[71]

Polymer Nanoparticles

Polymer nanoparticles are colloidal carriers with nanoscale dimensions. They enable the enhancement of hydrophobic agents delivery, promote an extended circulation and modify the biodistribution of encapsulated therapeutics.[72] They also possess greater structural complexity and offer enhanced flexibility through the design of both core and surface components, in contrast to water-soluble dendrimers.

Solid polymer nanoparticles are typically fabricated through precipitation or emulsification, often with the addition of a surfactant. Due to their solid structure, these nanoparticle-based drug carriers provide distinct advantages, including agent encapsulation within the hydrophobic core, higher drug loading capacity, and controlled drug release through diffusion or regulated polymer degradation.[73,74]

Applications of PNs in the Treatment of Diabetic Wound Healing

The complex pathophysiology of diabetic wounds poses a significant challenge for clinical treatment. The main manifestations include long-term inflammatory reactions, elevated levels of reactive oxygen species, continuous bacterial colonization that often develops into difficult-to-treat biofilms, sustained oxidative stress, and reduced neovascularization under hyperglycemic conditions (Figure 3).[8] Polymeric nanomedicines hold significant promise for treating diabetic wounds. As research progresses, PNs are emerging as a novel and effective approach to addressing diabetic wounds and enhancing tissue repair, offering new therapeutic possibilities for managing chronic wounds in diabetic patients (Table 1).

Wound Infection Control

Diabetic patients are especially susceptible to wound infections due to multidrug-resistant organisms(MDROs). The combined use of other wound infection drugs may further exacerbate bacterial resistance to antibiotics.[105] In light of

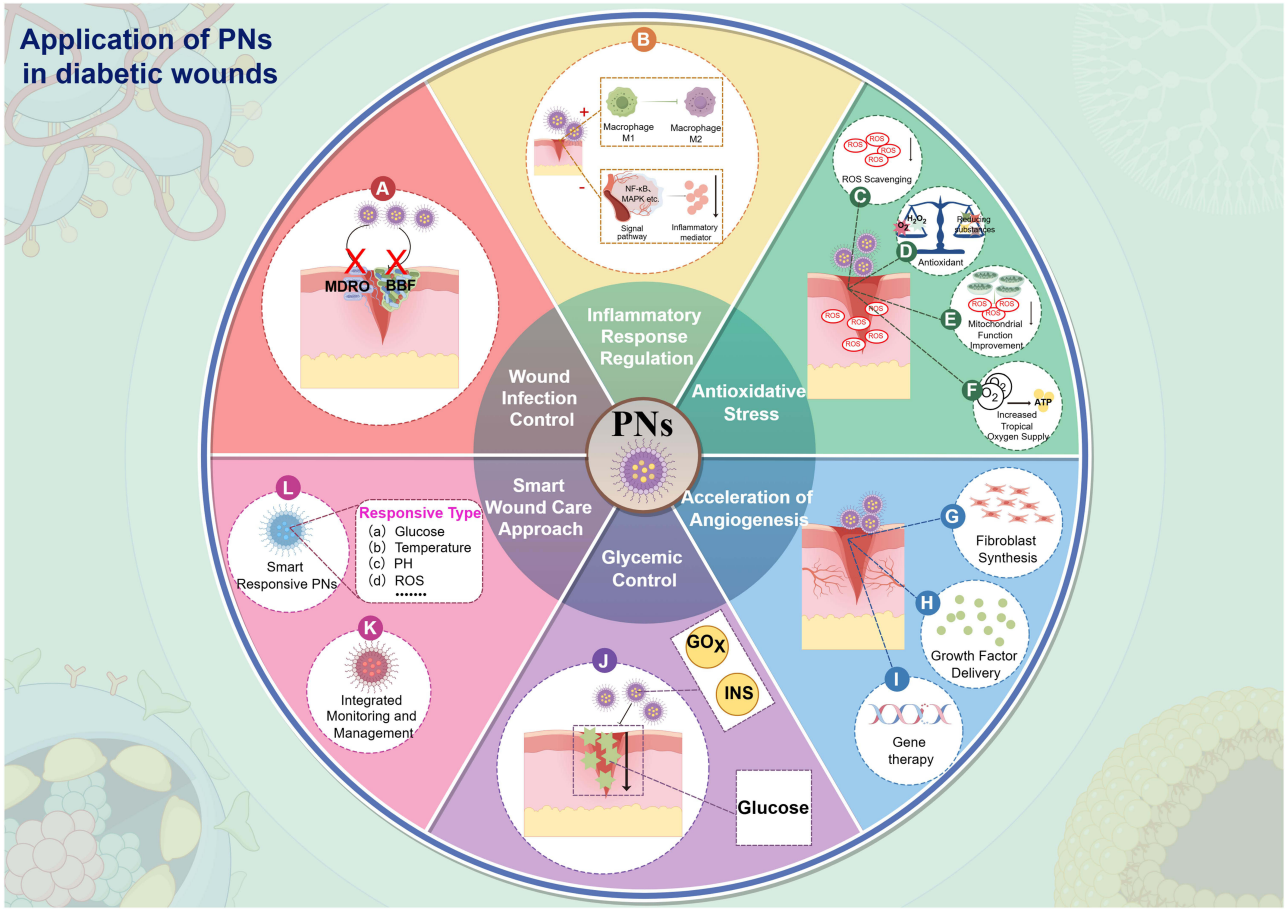

Figure 3 Scheme illustrating the application of polymeric nanomedicines in the treatment of Diabetic Wound Healing.

these challenges, antibacterial PNs offer a promising therapeutic approach. By loading metal nanoparticles or antibiotics, PNs inhibit resistance and enhance antibacterial effects. The small size and surface modifications enable them to penetrate and disrupt bacterial biofilms while improving antibiotic delivery and reducing chronic infection risks.

Table 1 Summary of Various Polymeric Nanomedicines Used for the Treatment of Diabetic Wound Healing

	System	Polymer Elements	Functional Elements	Relative Merits	Reference
Wound Infection Control	CGH hydrogel	HA-ALD	CuNCs and GOx	Produced ·OH for eradicating MDRO and enhanced antibacterial effects by reducing glucose and optimizing Fenton reaction	[75]
	SrO-CoO hydrogels	SG	SrO and CoO	Disrupting bacterial cell walls and metabolism; Sustained naproxen release	[76]
	GC@Pd	Gallic Acid-modified GC	Palladium ions	Induced bacterial aggregation through electrostatic interactions; Generated ROS and hyperthermia to eliminate the BBF	[77]
	PLGA-PEI/NO NPs	PLGA and PEI	NO	Bounded to biofilm matrix and enhanced anti-biofilm activity; Provided sustained NO release	[78]
	PLA/SCS/PDA-GS Nanofiber Membranes	PLA, SCS and PDA	GS	Showed efficient antibacterial activity against Staphylococcus aureus	[79]
	Fe2C/ GOx@MNs	CS	Fe2C NPs and GOx	Delivered Fe_2C NPs and GOx for biofilm removal; CS layer as physical barrier to block bacterial reinvasion	[80]

(*Continued*)

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Table 1 (Continued).

	System	Polymer Elements	Functional Elements	Relative Merits	Reference
Inflammatory Response Regulation	C@P Nanofiber Hydrogel	CS	Puerarin	Suppressed ectopic miR-29ab1 expression that mediated macrophages and regulated inflammation	[81]
	M-NPs/ MLN4924	PLGA	MLN49224	Coated with macrophage cell membranes, captured and neutralized proinflammatory cytokines and chemokines using membrane receptors like TNFR1, IL-6R and TLR4	[82]
	A.O-ZnO-NPs CS Gel	CS	ZnO-NPs	Downregulated expression of IL-6, IL-1β, and TNF-α, along with an increased expression of IL-10 levels	[83]
	Cur-CS-NPs	CS	Curcumin	Decreased release of inflammatory factors from macrophages in the diabetic wound site	[84]
	COR/OHDA/ GEL Nanofiber Membranes	HA and GEL	DA and COR	Suppressed the expression of inflammatory factors such as TNF-α, IL-1β, and IL-6 by inhibiting the TLR4/NF-κB pathway	[85]
Antioxidative Stress	MCGC	CS	MOF-nanozymes and CGA	Alleviated ROS accumulation and hypoxia by converting elevated endogenous H2O2 into dissolved oxygen in diabetic wounds	[86]
	PBNPs@PLEL	PDLLA-PEG-PDLLA	PBNPs	Eliminated ROS, protected mitochondrial function; Preserved the endogenous NRF2/HO-1 antioxidative signaling pathway	[87]
	TPN@H	PVA and Alginate	TPN	Prevented the oxidation of TP; Regulated PI3K/AKT signaling pathway	[88]
	FH-M@S	F127DA and HAMA	SS31-loaded MPDA	Maintained mitochondrial function and reduced mitochondrial ROS	[89]
	SS/MPDA@RES	Silk Microfibers	RES-loaded MPDA	Scavenged excessive ROS to protect mitochondria, restored ATP production, rebalanced redox homeostasis	[90]
	PCL-SPC Wound Dressing	PCL	SPC	Produced oxygen in the wound site up to 10 days, improved chronic hypoxia	[91]
	PQBH-n	PLLA, QCS and HA	BP and Hb	Enabled on-demand oxygen release, improved the hypoxic microenvironment of wounds	[92]
Acceleration of Angiogenesis	Starch-based Nanofibrous Scaffolds	Starch and PVOH	30:70%w/w of starch and PVOH	Allowed cell growth and proliferation of dermal cells	[93]
	TDNPs@AG	Cellulose Nanofibers and Sodium Alginate	TDNPs	Increase formation of extracellular matrix and skin tissue remodeling; Wound shape-customized accessibility; Water-adaptable tissue adhesiveness; Capacity for sustained release of TDNPs	[94]
	PLGA-VEGF NP	PLGA	VEGF and lactate	Enhanced proliferation and migration of keratinocytes and upregulated the expression of VEGFR2 at mRNA level	[95]
	CW/NPs/HBC-HG	CW, CMCS NPs and HBC	rhEGF	Accelerated re-epithelialization, collagen deposition and angiogenesis; Offered a prolonged cell proliferation activity up to 5 days	[96]
	PEG/Ag/CNT-M +E Hydrogel	PEG	Exosome and metformin	Facilitated mobility and release of bioactive substances.; Maintained microvessel integrity and barrier function, promoted cell proliferation	[97]
	HIF/CPs Nanoparticles	CS	Plasmid encoding human CA5-HIF-1α	Prevented oxygen-dependent degradation by prolyl hydroxylases; Induced an increased number of CD31+ vessel structures in healed tissue	[98]
Glycemic Control	PVA-borate Hydrogel	PLGA and PVA	Insulin	Act as insulin-loaded colloidal carriers in structured hydrogel vehicles	[99]
	Insulin-functionalized SF Dressing	SF	Insulin	Provided a sustained insulin release over a month-long period without change of original molecular conformation and native bioactivity	[100]

(*Continued*)

Table 1 (Continued).

	System	Polymer Elements	Functional Elements	Relative Merits	Reference
Glycemic Control	AHAMA/CS-GOx@Zn-POM	AHAMA and CS	Zn-POM and GOx	Enabled sustained release of Zn-POM and GOx; Modulated the hyperglycemic-immune microenvironment	[101]
	CMCS NPs	CMCS	MET	Sustained MET release via quasi-Fickian diffusion; Slower, gradual drug release compared to bulk method; Regenerated pancreatic islets in diabetic rats	[102]
	Insulin with a CS/GS polymeric coating	CS	Insulin	Sensitive to glucosidase enzymes to trigger insulin release; Promoted a dose-dependent reduction in blood glucose without promoting hypoglycemia or weight gain in diabetic rodents; No biochemical or hematological toxicity or adverse events were observed	[103]
	GC/HA@GEL	GC and HA	Pancreatic β cell spheroid	Used for frequent islet allotransplantation; Reduced acute host immune response based on cell-cell interaction with NK cells; Reduced external cytokine attack; Sustainable with enhanced glucose responsiveness	[104]

Additionally, PNs could serve as carriers for antimicrobial agents, prolonging drug release and increasing antibacterial efficacy.

PNs loaded with metal nanoparticles can interfere with bacterial quorum sensing and suppress antibiotic resistance, thereby enhancing antibacterial efficacy.[106] Lin and Qu's team developed a CGH hydrogel to eradicate MDROs and promote diabetic wound healing. The hydrogel is synthesized in situ by crosslinking copper nanoclusters (CuNCs) with oxidized hyaluronic acid (HA-ALD) while simultaneously loading glucose oxidase (GOx).[75] The dressing releases CuNCs to catalyze the Fenton reaction, generating hydroxyl radicals(·OH) with broad-spectrum antibacterial activity, thereby inhibiting bacterial proliferation. GOx reduces glucose and optimized Fenton reaction to enhance antibacterial effect. Animal studies indicated that this hydrogel, in combination with electrical stimulation, could inhibit bacterial infection, promote angiogenesis, and accelerate wound healing. It can also be applied to irregular wound shapes and establish a sustained sterile environment. Nissren et al innovatively integrate SrO-CoO bimetallic oxide nanoparticles with Guggul gum grafted polyacrylamide hydrogels (SG), developing a hydrogel with enhanced antibacterial properties for wound infection control.[76] This hydrogel synergistically utilizes strontium to promote tissue repair and cobalt to induce angiogenesis. It effectively inhibits S. aureus, E. coli, and P. aeruginosa, reducing bacterial colonization in wounds. Additionally, it also exhibits sustained drug release (naproxen: 10%-21%), potentially lowering dressing frequency and infection risk. Furthermore, the hydrogel demonstrates no cytotoxicity to healthy cells, making it a promising biomaterial for chronic diabetic wound care.

Due to the hyperglycemic state, bacterial biofilm (BBF) infections exist in approximately 90% of patients with diabetic wounds, prolonging the inflammatory stage and ultimately leading to wound deterioration.[107] PNs provide an advanced approach for combating biofilm infections. Due to their unique size and physiochemical characteristics, they can penetrate and disrupt biofilms, helping to eradicate BBF, eliminate infections, and break this vicious cycle of inflammation, thereby accelerating wound healing. Li's team used gallic acid-modified chitosan (GC), in which palladium ions coordinate with divalent ions through amino and catechol groups on its side chains, to construct a microenvironment-adaptive nanodecoy (GC@Pd) via an in-situ reduction process mediated by ascorbic acid.[77] In the weakly acidic environment of biofilm-associated infections, GC@Pd induces bacterial aggregation and generates ROS and heat through its oxidase-like activity and photothermal effects, thereby synergistically eliminating the BBF. In vivo experiments and transcriptomic analysis confirmed that GC@Pd promotes the shift of diabetic wounds from the inflammatory to the proliferative phase by eradicating biofilm infections and reducing inflammatory responses, providing a promising therapeutic approach for treating biofilm infections in chronic diabetic wounds.

PNs can also assist in improving the utilization of other antibacterial substances. Yoo et al developed polyethylenimine/diazeniumdiolate (PEI/NONOate)-doped PLGA nanoparticles (PLGA-PEI/NO NPs) that can bind firmly to the biofilm matrix to facilitate the delivery of NO to wounds infected with methicillin-resistant Staphylococcus aureus

 https://doi.org/10.2147/IJN.S514000

(MRSA) biofilm.[78] As an NO donor, these nanoparticles provide a sustained release of NO, extending the release over 4 days, effectively inhibiting bacterial biofilm formation and enhancing wound healing outcomes. PNs can also enhance drug delivery efficacy by loading antibiotics. Yao and Lin et al prepared PLA/SCS/PDA-GS nanofiber membranes, in which the antibiotic gentamicin sulfate (GS) was decorated.[79] In vitro studies showed that the GS-loaded nanofiber membrane had efficient antibacterial ability against Staphylococcus aureus.

In addition, PNs can be combined with mechanical methods so as to enhance penetration against biofilm-associated infections. Dai and Ju et al designed an integrated therapeutic and preventive-based nanozyme microneedle (Fe2C/GOx@MNs) for the healing of diabetic wounds that were infected by MRSA biofilm.[80] These soluble tips, with sufficient mechanical strength, improve the penetration capability of Fe2C nanoparticles (Fe2C NPs) and GOx for effective biofilm elimination. Meanwhile, the use of a chitosan backing layer provides excellent antibacterial properties, preventing bacterial re-invasion during the wound healing process to a great extent. Most importantly, Fe2C/GOx@MNs demonstrated biofilm clearance and reinfection prevention capabilities in a diabetic mouse model of MRSA biofilm infection, indicating its promising clinical potential in promoting the healing of infected wounds in diabetic patients. Such advancements in nanomedicine provide a novel strategy to combat the risks associated with chronic diabetic wounds, enhancing infection management and tissue regeneration through effective antimicrobial action.

Inflammatory Response Regulation

Chronic inflammation is a key pathological manifestation of diabetic wounds, with the duration and quality of wound healing being closely associated with the severity of the inflammatory response.[108] In diabetic patients, hyperglycemia triggers the activation of inflammasomes, leading to sustained expression of M1 macrophages, which in turn perpetuates a prolonged pro-inflammatory state. This chronic inflammatory milieu significantly delays wound healing, impairs tissue regeneration, and increases the risk of infection.[109,110]

Macrophages, as the key cells in the regulation of wound inflammation, play a critical role in regulating inflammatory responses, removing infections, and promoting tissue repair.[111] Therefore, PNs regulate inflammation mainly by influencing macrophage polarization and modulating key inflammatory pathways. Some PNs are designed to shift macrophages from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype, which promotes tissue repair.[82] Additionally, PNs can inhibit the NF-κB and MAPK signaling pathways, reducing excessive pro-inflammatory cytokine release (TNF-α, IL-6, IL-1β) and enhancing the expression of anti-inflammatory factors (IL-10, TGF-β), ultimately creating a more favorable wound-healing environment. Liao and Ouyang's research team developed an injectable chitosan@puerarin (C@P) nanofiber hydrogel for this purpose.[81] Puerarin is widely recognized for its anti-inflammatory effects, and when combined with the natural polymer chitosan, it addresses issues such as low hydrophilicity, poor bioavailability, and low permeability in hydrogels with only Puerarin. This combination enhances the effectiveness of diabetic wound recovery. The findings suggest that it can effectively mitigate inflammation and promote wound recovery by inhibiting M1 macrophage polarization, which is mediated by miR-29a/b1. Liu, Mi, and Shahbazi et al discovered that MLN4924, a low-concentration neddylation compound, can suppress the polarization of M1 macrophages. The researchers loaded MLN4924 within PLGA nanoparticles coated with biomimetic macrophage membranes, creating M-NPs/MLN4924. This formulation combines the beneficial properties of polymer nanomaterials with the unique characteristics of macrophage membranes.[82] By incorporating M-NPs/MLN4924 into hydrogels and applying them in a diabetic mouse model, it was found to inhibit macrophage polarization into the inflammatory M1 phenotype via receptors on the macrophage membrane, such as Tumor Necrosis Factor Receptor 1(TNFR1), Interleukin-6 Receptor(IL-6R), and Toll-like Receptor 4(TLR4). The promotion of polarization towards the anti-inflammatory M2 phenotype reduced the secretion of inflammatory factors and significantly improved wound repair in diabetic mice, thereby accelerating diabetic wound healing.

Chronic inflammation of diabetic wounds is closely related to inflammatory cytokines and signaling pathways. PNs can inhibit classical inflammatory signaling pathways, including NF-κB, MAPK, JAK-STAT et al,[112,113] reducing the production of excessive proinflammatory mediators such as IL-1β, IL-6, TNF-α etc, which in turn lowers excessive inflammatory responses and promotes the release of anti-inflammatory factors (IL-10, TGF-β) which facilitate wound healing. Nabarawi et al developed environmentally friendly zinc oxide nanoparticles (ZnO-NPs) by utilizing Althaea

officinalis flowers, which were then integrated into a 2% chitosan (CS) gel to form the A.O-ZnO-NPs CS gel for wound repair.[83] In diabetic rat models, the treatment led to a significant reduction in TNF-α, IL-6, and IL-1β expressions, along with an increase in IL-10 levels. The gel, compared to the control group, led to a 1.9-fold increase in the serum levels of anti-inflammatory cytokine IL-10 levels, highlighting its efficacy and superiority in alleviating inflammatory signs. This demonstrates the potential of eco-friendly green synthesis of PNs and its therapeutic approach for facilitating diabetic wound recovery. Zhao et al utilized CS as a carrier to load curcumin, which exhibits a wide range of biological activities, including anti-inflammatory and antioxidant properties, and created polymer nanoparticles Cur-CS-NPs.[84] The findings showed that Cur-CS-NPs exhibited sustained drug release and effective cell uptake in the diabetic model, significantly reducing the release of inflammatory factors from macrophages and attenuating local inflammation at the site of the diabetic wound. Liu's team oxidized hyaluronic acid (HA) and combined it with gelatin (GEL) and cordycepin (COR), followed by modification with dopamine(DA), ultimately forming nanofiber membranes (COR/OHDA/GEL) through electrostatic spinning technique.[85] The constructed COR/OHDA/GEL nanofiber membranes significantly reduced the expression of inflammatory factors such as TNF-α, IL-1β, and IL-6 in macrophages by inhibiting the TLR4/NF-κB signal pathway, thereby modulating the inflammatory response to promote diabetic wound healing.

Antioxidative Stress

In diabetic wound healing, the high-glucose environment increases mitochondrial oxygen consumption and impairs its function.[114] Sustained elevated blood glucose levels can also lead to excessive protein glycation, resulting in the formation of advanced AGEs, all of which contribute to a high level of ROS.[77] The accumulation of ROS can trigger excessive oxidative stress, causing damage in cells responsible for wound healing and disrupt the entire wound healing process. PNs have demonstrated significant antioxidant properties, acting as efficient ROS scavengers to reduce oxidative stress. They can also possess inherent antioxidant capabilities, protecting cells from damage. Additionally, PNs enhance mitochondrial function, supporting energy production, and promote an increased local oxygen supply, creating a more favorable environment for wound healing. These mechanisms collectively improve wound healing outcomes by reducing oxidative damage and facilitating tissue regeneration.

ROS Scavenging

During the healing process of diabetic wounds, oxidative stress activated by the abnormal accumulation of ROS is one of the main factors leading to difficult wound healing. Utilizing antioxidative enzymes is one of the effective strategies for scavenging ROS.[115] PNs can mimic enzymatic activities to scavenge ROS, thereby reducing oxidative stress-related damage. Wang and Liu et al developed a multifunctional hydrogel named MOF/CGA@GP-CS(MCGC) by constructing metal–organic framework (MOF)-nanozymes anchored with the natural antibacterial agent chlorogenic acid(CGA) in genipin-crosslinked chitosan hydrogels.[86] These nanozymes exhibit catalase-like activity, converting excess H_2O_2 in wounds into dissolved oxygen. This not only effectively removes ROS but also generates oxygen at the wound site. This approach addresses the limitations of natural enzymes, such as fragility and high cost, thereby enhancing wound healing outcomes. In vitro experiments confirmed that MCGC reduced ROS levels in high-glucose induced bacterial infection and increased antioxidative enzyme activity, significantly lowering oxidative stress markers and regulating oxidative stress responses.

Prussian Blue Nanoparticles (PBNPs) display remarkable ROS scavenging capabilities, mimicking the activities of catalase (CAT), peroxidase (POD), and superoxide dismutase (SOD), thereby protecting mitochondria from the damage associated with oxidative stress. Chen et al developed a thermosensitive poly (d,l-lactide)-poly(ethylene glycol)-poly(d, l-lactide) (PDLLA-PEG-PDLLA) hydrogel (PLEL)-based wound dressing which is loaded with PBNPs.[87] After injecting PBNPs@PLEL into the site of injury, PBNPs could release slowly, maintaining a sustained antioxidant activity. Both in vitro and in vivo investigations revealed that PBNPs@PLEL effectively eliminate ROS, reduce cellular damage, protect mitochondrial function, and preserve the endogenous NRF2/HO-1 antioxidant signaling pathway, thereby promoting diabetic wound healing.

Antioxidant

In response to oxidative stress during diabetes, PNs can serve as stable, sustained-release antioxidants to regulate redox balance. Chen and Ren et al synthesized novel tea polyphenol nanospheres (TPN) and encapsulated them in a PVA/alginate hydrogel (TPN@H) to solve the issue of green tea polyphenols(TP) being easily oxidized, providing a gel material that can prevent oxidation.[87] In diabetic rat models, TPN@H promoted collagen deposition and maturation, as well as the formation of granulation tissue, to a greater extent compared to the control group. TPN@H also facilitated wound healing and regulated immune responses. Furthermore, TPN@H helped regulate the PI3K/AKT signaling pathway to promote diabetic wound healing.

Mitochondrial Function Improvement

Excessive ROS are not only a result of mitochondrial dysfunction but also cause further damage to the mitochondria.[116] PNs can reduce the production of ROS by improving mitochondrial function, thereby inhibiting the sources of ROS generation. Guo and Tao's team developed a double-network hydrogel (FH-M@S), constructed with pluronic F127 diacrylate (F127DA) and hyaluronic acid methacrylate (HAMA), enhanced by mesoporous polydopamine nanoparticles (MPDA NPs) loaded with SS31, a mitochondrial-targeting peptide that attaches to the inner mitochondrial membrane to maintain mitochondrial function and reduce mitochondrial ROS production.[89] This gel exerts a synergistic effect on full-thickness wound healing under diabetic conditions through near-infrared photothermal antibacterial action and mitochondrial maintenance. In in vivo experiments, FH-M@S consistently demonstrated optimal wound closure effects.

Resveratrol (RES) exhibits antioxidative properties, particularly in mitochondrial protection. Wang et al an injectable, light-curable silk-based nanocomposite hydrogel (SS/MPDA@RES) by integrating RES-loaded mesoporous polydopamine nanoparticles (MPDA) into silk microfibers.[90] It was found that through direct injection and in situ visible light treatment, SS/MPDA@RES markedly promoted wound healing in diabetic rats. This gel demonstrated effective scavenging of excessive ROS, thereby safeguarding mitochondrial function, restoring ATP production, and rebalancing redox homeostasis.

Increased Topical Oxygen Supply

Increasing the topical oxygen supply to the wound can enhance cellular aerobic metabolism, leading to more ATP for cellular energy and increasing the activity of antioxidative enzymes to scavenge ROS and reduce oxidative stress.[117] Currently, there is a growing focus on developing PNs to enhance topical oxygen supply for improving wound oxygenation and facilitating the healing of diabetic wounds. Muhammad et al developed oxygen-generating polymeric nanofibers based on PCL, loaded with inorganic sodium percarbonate (SPC) salt that can chemically generate oxygen in situ.[91] The results indicated that PCL-SPC wound dressing can continuously produce oxygen at the wound site for up to 10 days. Experiments using the chorioallantoic membrane assay demonstrated that this oxygen-releasing dressing stimulates angiogenesis and shows great potential for wound healing in diabetic rat models. Han et al utilized charged quaternized chitosan(QCS) and hyaluronic acid to layer black phosphorus(BP) nanosheets and hemoglobin(Hb) onto electrospun poly-l-lactide(PLLA) nanofibers, creating a sequence of multifunctional wound dressings (coded as PQBH-n).[92] Both in vitro and in vivo studies confirmed their excellent abilities in facilitating wound healing. These PN-based dressings, combined with near-infrared (NIR)-assisted oxygen delivery, enable on-demand oxygen release, effectively improving the hypoxic microenvironment of wounds.

PNs offer significant advantages in mitigating oxidative stress, with high stability and prolonged drug circulation time. This enhances their ability to regulate oxidative stress responses, thereby promoting a more favorable microenvironment for tissue regeneration and accelerating the healing process.

Acceleration of Angiogenesis

In diabetic wounds, PNs can promote the generation of cells and growth factors, as well as facilitate drug delivery, thereby accelerating angiogenesis. They promote fibroblast proliferation, migration, and extracellular matrix deposition,

all of which are essential for vascular regeneration. Additionally, PNs regulate the sustained release of key pro-angiogenic growth factors to enhance endothelial cell proliferation and stabilize newly formed blood vessels. Some polymer-based delivery systems ensure the continuous release of these factors at the wound site, improving endothelial cell proliferation and new capillary formation.

Jain and Dandekar et al prepared starch-based nanofibrous scaffolds by electrospinning starch and polyvinyl alcohol (PVOH) in a 30:70% w/w ratio.[93] Cellular assays with L929 mouse fibroblast cells indicated that the scaffolds promoted faster growth of dermal cells, thus accelerating vascular regeneration. PNs can also promote the synthesis of fibroblasts and their deposition in the extracellular matrix, which is crucial to angiogenesis. Zou, Li, and Zheng et al incorporated turmeric-derived nanoparticles (TDNPs) into a permeable aerogel(AG) made from cellulose nanofibers and sodium alginate, developing a wound dressing named TDNPs@AG.[93] This dressing enhances fibroblast proliferation and migration by activating the Nrf2/HO-1 signaling pathway, promoting beneficial interactions between macrophages and fibroblasts that increase the formation of extracellular matrix and skin tissue remodeling, thereby accelerating vascular regeneration.

In addition, PNs are capable of facilitating the release of growth factors, including vascular endothelial VEGF, fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF), all of which accelerate angiogenesis and facilitate wound healing.[118] Préat et al encapsulated VEGF in PLGA nanoparticles (PLGA-VEGF NP) for treatment of diabetic wounds. Moreover, lactate, a degradation product of PLGA, can enhance neovascularization.[118] Under the sustained combinations of VEGF and lactate, wounds in diabetic rats under treatment of PLGA-VEGF NP demonstrated higher collagen content and re-epithelialization, contributing to angiogenesis and wound healing. Chen et al developed a chitin whisker (CW)/carboxymethyl chitosan nanoparticles (CMCS NPs)/thermosensitive hydroxybutyl chitosan (HBC) composite hydrogel (CW/NPs/HBC-HG), which encapsulates recombinant human epidermal growth factor (rhEGF).[118] Prolonged cell proliferation was observed for up to 5 days within this dressing. When applied to the wound, rhEGF is gradually released into the gel network, extending the duration of EGF penetration into the wound. In a diabetic rat model of chronic wound healing, this dressing accelerated re-epithelialization, collagen deposition and angiogenesis.

In the past few years, research on exosomes in the treatment of diabetic wounds has gathered significant attention. Guo and Hu's team engineered PEG/Ag/CNT-M+E hydrogel loaded with exosomes and metformin (MET). Within the gel, hydroxyl-modified multiwalled carbon nanotubes act as the conductive material, establishing hydrogen bonds with thiol, resulting in a stable 3D structure for exosomes and MET.[119] This 3D network, characterized by a highly interconnected porous structure, facilitates drug release and delivery, maintaining the integrity of microvessels and barrier function while promoting cell proliferation and angiogenesis. Compared to the relatively short half-life of exosomes, the fusion with PNs exhibit a higher stability with slower degradation and prolonged drug release.

Additionally, PNs can be utilized for gene therapy to achieve targeted treatment. Harmon et al presented a method of gene delivery to diabetic wounds utilizing polymeric chitosan to deliver a plasmid encoding human CA5-HIF-1α, a degradation resistant form of HIF-1α.[98] These HIF/CPs nanoparticles enhanced the stability of the human CA5-HIF-1α-encoding plasmid in high-glucose environments, prevented oxygen-dependent degradation by prolyl hydroxylases, and induced an increased number of CD31+ vessel structures in healed tissue, thereby promoting angiogenesis at the wound site and improving wound healing.

In summary, PNs enhance angiogenesis in diabetic wound healing by promoting fibroblast proliferation, migration, and extracellular matrix deposition, all of which are critical for vascular regeneration. PNs also stimulate the sustained release of growth factors such as VEGF, FGF, and PDGF, which further accelerate angiogenesis and tissue repair. Additionally, PNs enable the stable delivery of therapeutic plasmids in high-glucose environments, enhancing gene therapy efficacy and promoting angiogenesis at the wound site.

Glycemic Control

In diabetic wounds, hyperglycemia-induced cytotoxicity directly impedes the wound healing process. A high tropical glucose environment can lead to rapid bacterial growth, induce persistent inflammation, and hinder angiogenesis, with the severity positively correlated with the duration of hyperglycemia exposure.[120] Therefore, regulation of the

hyperglycemic microenvironment is crucial. Due to the complexity of the diabetic wound microenvironment, conventional glycemic therapeutic options are often limited in effectiveness.[121] PNs present a novel and effective approach for blood glucose control in diabetic wounds. They not only help regulate the hyperglycemic environment but also modulate local glucose concentrations within the wound, thereby promoting wound healing.

Topical application of insulin can reduce topical glucose levels and improve diabetic wound recovery. However, its utilization is often hindered by the lack of an appropriate carrier capable of consistently and efficiently delivering insulin to the wound site.[122] PNs can serve as a carrier while addressing the issues of short half-life and insufficient biological activity of insulin in the skin. Abdelkader et al constructed a poly(vinyl alcohol) (PVA)-borate hydrogel that contains human insulin encapsulated in PLGA nanoparticles, with 33.86 μg insulin loaded per milligram.[123] By comparing the wound healing rates with applied free insulin and that with nano-encapsulated insulin in diabetic rats to their controls, it was found that after 10 days of experiment, the percentage of wound injury indices with insulin-PLGA NP and free insulin were 29.15 and 12.16% respectively. Li et al developed a functionalized silk fibroin (SF) dressing with sustained bioactive insulin release for injury healing in patients with diabetes.[99] By encapsulating insulin within the inner layer of SF microparticles, they created a system ensuring a sustained insulin release for a duration of one month without altering the insulin's original molecular conformation and native bioactivity. This approach not only helps to maintain the bioactivity of the insulin but also improves its stability.

PNs can also enhance wound healing and reduce the likelihood of amputation by loading GOx to degrade excessive glucose at the wound site.[100] Li, Yang, and Jiang et al developed a holistic therapeutic nanozyme system(AHAMA/CS-GOx @Zn-POM) that integrated an aldehyde and methacrylic anhydride-modified hyaluronic acid hydrogel (AHAMA) and chitosan nanoparticles (CS NPs), combining GOx with zinc-based polymetallic oxonate nanozyme(Zn-POM) to modulate the hyperglycemic conditions and reprogram the immune microenvironment.[101] As GOx oxidizes glucose, hydrogen peroxide and gluconic acid are produced, helping to degrade excessive glucose at the wound site, maintaining a local blood glucose homeostasis, and mitigating the detrimental effects of the hyperglycemic microenvironment on healing.

The utilization of PNs in glycemic control can improve the bioavailability and safety of hypoglycemic agents, aiding in the control of baseline blood glucose levels and preventing further wound infections.[124] Zahedi et al synthesized crosslinked carboxymethyl chitosan nanoparticles (CMCS NPs) that contain metformin.[102] These CMCS NPs enable sustained release of MET through the degradation of the biopolymer, effectively exerting glucose-lowering effects. In diabetic rats, CMCS NPs inhibited weight loss, reduced blood glucose levels, and promoted the regeneration of pancreatic islets. PNs can also optimize the administration of insulin and help maintain the blood glucose homeostasis in diabetic patients. Victoria C et al investigated an oral insulin nanoformulation using insulin-conjugated silver sulfide quantum dots coated with chitosan/glucose polymer (CS/GS). The formulation showed a dose-dependent effect and marked sensitivity to hydrolytic enzymes, particularly β-glucosidase, which triggers the degradation of CS/GS to release insulin.[103] Notably, insulin is released only when blood glucose levels are low, reducing the occurrence of hypoglycemic episodes while enhancing the bioavailability of insulin.[125] This creates favorable conditions for wound healing.

PNs can also be used externally to regulate hyperglycemia. Lee's team developed a hydrogel nanofilm caging system (GC/HA@GEL) via a tyrosinase-mediated enzymatic reaction, encapsulating glycol chitosan(GC) and HA.[104] It was found that GC/HA@GEL effectively encapsulates pancreatic β-cells, playing a vital role in regulating glucose homeostasis.

Smart Wound Care Approach

With the advancement of PN technology, researchers are striving to develop smart therapeutic measures that offer continuous blood glucose monitoring and enhanced drug delivery efficacy (Table 2). This will become a significant component of diabetes wound management in the future.

Smart Responsive PNs

Smart responsive PNs can respond to specific external stimuli or internal environmental changes, including temperature, light, and magnetic fields, as well as internal changes such as pH and glucose enzyme levels. These responses help

Table 2 Description of Various Smart Wound Care Approach with Polymeric Nanomedicines

Classifications	PNs	Functions	References
Smart Responsive PNs	PEG-DA/HA-PBA /MY	Glucose-triggered MY release efficient ROS-scavenging high moisture transmission capacity	[126]
	LIN@PG10@PDA-NIR	Near-Infrared (NIR) stimuli-responsiveness controlled drug release	[127]
	Hydrogel@AgNPs +NIR	Photothermal and magnetothermal response capabilities controlled drug release mechanical properties	[128]
	Cell-An/PCL-Ch	Ph-responsive monitoring unidirectional moisture drainage Real-Time monitoring and smart diagnosis	[129]
	HA@Cur@Ag	Regulation of ECM biocompatibility and degradability injectability and adhesion	[130]
	AuNCs@PBA-Sa	ROS/glucose responsiveness self-adaptive property smart wound management	[97]
	C-PPZZ	Liquid-triggered temperature-controlled shrinkage pH-sensitive drug release	[131]
Integrated Monitoring and Management PNs	LAMC/CD-C@M@P	pH monitoring photothermal antibacterial capability mechanical performance and photothermal conversion ability	[132]
	Thera-patch	Real-time monitoring and dynamic intervention electro-responsive drug delivery electrical conductivity and transparency	[133]

activate cellular activity, promote drug release and monitor wound conditions, thereby maximizing their therapeutic efficacy.

Polymers with phenylboronic acid (PBA) are common glucose-responsive materials. PBA can form reversible boronated ester bonds with the cis-diol structure in glucose molecules, which gives PBA high selectivity and sensitivity to glucose,[134] resulting in glucose-responsive PNs. Wu et al combined PBA-modified hyaluronic acid with polyethylene glycol diacrylates (PEG-DA) to develop a novel hybrid hydrogel (PEG-DA/HA-PBA).[134] This hydrogel, loaded with the highly antioxidative myricetin (MY), enabled glucose-triggered MY release and effectively scavenged ROS(>80.0%), thereby remodeling the oxidative environment of wounds.

The topical temperature of diabetic wounds may vary due to factors such as inflammatory responses. Polymers based on N-isopropylacrylamide (NIPAM) can be prepared as temperature-responsive PNs to sense changes in wound temperature and release drugs accordingly.[135] Bao's team dispersed polydopamine nanoparticles into methacrylated gelatin and NIPAM monomers, loading them with the drug linagliptin, to create a temperature-sensitive hydrogel (LIN@PG10@PDA-NIR). The drug release rate was controlled through near-infrared laser irradiation.[127] This hydrogel exhibits excellent thermosensitive and photothermal properties, promoting cell migration and the expression of angiogenic factors for diabetic wound healing. Zhong et al encapsulated Fe3O4@SiO2 particles with MXene, which has excellent near-infrared absorption capabilities, to form MNPs@MXene. These particles were combined with silver nanoparticles and loaded into a poly(N-isopropylacrylamide) (PNIPAM) and alginate dual-network hydrogel system. PNIPAM is a temperature-sensitive polymer that dehydrates and contracts below its lower critical solution temperature.[128] Under the influence of near-infrared light and an alternating magnetic field, temperature within the system rapidly increases, allowing for controlled release of AgNPs. This approach demonstrated promising therapeutic effects in subcutaneous infected wounds in a diabetic rat model.

The pH of normal skin generally ranges from 4 to 6, while diabetic wounds tend to be more alkaline, with pH values between 7 and 9.[77] The pH value can serve as a real-time indicator to monitor the progression of wound healing in diabetes, making the development of pH-responsive PNs crucial for optimal therapeutic effects. Tian and Sun et al created a pH-responsive dressing (Cell-An/PCL-Ch) consisting of a pH-sensitive, hydrophilic nanofibrous layer and an

antibacterial, hydrophobic PCL bottom layer.[129] This dressing can continuously monitor pH changes in the exudate of diabetic wounds. Real-time pH monitoring can be achieved through a program integrated into smartphones, simplifying the medical care of diabetic wounds.

ROS-responsive biomaterials can be triggered by ROS in the injured tissue to release drugs that modulate ROS levels, alleviate oxidative stress, and promote tissue regeneration.[136] Liang et al synthesized a hyaluronic acid-based ROS-responsive composite multifunctional wound dressing (HA@Cur@Ag), which incorporated curcumin liposomes and silver nanoparticles (AgNPs). Experimental validation showed that the HA@Cur@Ag hydrogel effectively modulated the oxidative stress response in diabetic wounds and promoted tissue repair. Transcriptomic sequencing revealed that this dressing significantly inhibited the activation of the TNF/NF-κB signaling pathway, reducing oxidative stress and inflammation in diabetic wounds.[137] The ROS-responsive dressing also controlled the release of curcumin liposomes and silver nanoparticles, demonstrating antioxidative, antibacterial, and anti-inflammatory properties.

To further enhance therapeutic efficacy, multiple responsive polymeric nanomedicines have been designed. By integrating multiple response mechanisms, PNs can adapt to the complex environment of wound, enabling precise drug release and synergistic therapy. Xue and Shang et al constructed self-adaptive hydrogels (AuNCs@PBA-Sa) based on marine-derived gold clusterzyme (AuNCs). Marine mussel-derived L-3,4-dihydroxyphenylalanine (DOPA) with intrinsic antioxidative properties was used as the functional ligand to prepare AuNCs with SOD-like activity. This ligand forms boronate ester bonds with phenylboronic acid-modified marine-derived sodium alginate(PBA-Sa), imparting ROS/glucose responsiveness to AuNCs@PBA-Sa.[97] This allows the dressing to respond to degradation and control the release of AuNCs. Additionally, it significantly enhances the ability of AuNCs to remove free radicals and exhibits excellent SOD-like enzyme activity, efficiently regulating the pathological conditions associated with chronic wounds, such as oxidative stress, immune dysregulation, and excessive inflammation. Luo et al developed a polytrimethylene carbonate (PTMC)/polyvinylpyrrolidone (PVP) nanofibrous dressing (C-PPZS) which loaded with simvastatin-loaded ZIF-8 nanoparticles (ZIF-8@SIM NPs) for wound healing. This dressing responds to multiple stimuli, including the release of Zn^{2+} and SIM in acidic environments, mechanical contraction induced by liquid, and enhanced contractility with temperature elevation.[138] The results indicated that C-PPZS facilitated wound healing, making it an effective strategy for chronic wound management.

In addition to the above-mentioned response mechanisms, there are other mechanisms such as hypoxia response, H_2O_2 response, and ultrasound response,[130,139–141] that require further research. Developing more efficient and safer multiple responsive PNs offers new hope for wound treatment in diabetic patients.

Integrated Monitoring and Management

Diabetic wounds are characterized by dynamic changes, and their healing process is affected by multiple factors, including blood glucose levels, infection, inflammatory response, and vascular lesions. Moreover, most wound care relies on visual judgment, which is often not consistent with real-time monitoring, management, and dynamic treatment.[142] The integrated diagnosis and treatment provided by PNs offer a viable solution to the challenge. Real-time monitoring of wound conditions enables timely and targeted interventions, thereby facilitating the healing of diabetic wounds.

Dai et al developed an intelligent lipoic acid-modified chitosan hydrogel (LAMC/CD-C@M@P) for pH monitoring and accelerated healing of diabetic wounds. The carbon quantum dots (CDs) in the hydrogel exhibit stable photoluminescence properties that are pH-dependent, allowing the dressing to monitor pH levels. The ceria oxide-molybdenum disulfide nanoparticles with a polydopamine layer (C@M@P) provide photothermal antibacterial effects.[132] When an alkaline environment is detected, likely indicating bacterial infection, the dressing utilizes its photothermal and near-infrared assisted antibacterial properties to address the issue. Additionally, it effectively scavenges ROS, which alleviates inflammatory responses and reduces oxidative stress, thereby promoting the repair of diabetic wounds. Jiang, Yi, and Haick et al combined advanced polymer nanomaterials with electro-controlled devices to develop a wireless wound management system. This system consists of a customized smartphone app, wearable bioelectronics, and a theragnostic patch (Thera-patch). The patch includes pH and glucose sensors, allowing for continuous monitoring of the status of diabetic wounds, and provides personalized and precise treatment through iontophoresis and electrical stimulation based

on the wound conditions.[133] It enables a closed-loop drug delivery while monitoring multiple wound-related biomarkers, improving real-time monitoring and targeted treatment of diabetic wounds, ultimately facilitate wound healing.

With the in-depth research of polymer nanomedicine, real-time monitoring for patients with diabetic wounds can be established, enabling more targeted therapeutic strategies and bringing new hope for the full recovery of diabetic wounds.

Future Perspectives

Although many studies have shown the potential of PNs for diabetic wounds, there are still limitations to address in future research.

Safety

The regulation of nanomedicines is an important bottleneck in their clinical translation. Due to the unique nature of nanomaterials, it is difficult to fully apply traditional drug regulatory frameworks. For example, several guidelines have been issued by organisations such as the FDA and EMA, emphasising quality control, non-clinical safety and pharmacokinetic studies of nanomedicines.[5] Some PNs materials are still in animal experimentation stage, and their effects on humans have not been fully examined. To date, the United States Food and Drug Administration has approved only a liposome-like nanoformulation of insulin, a hepatic-directed vesicle insulin, for the management of diabetic wounds. However, this formulation has not been commercialized due to multiple adverse reactions observed in clinical trials.[143] Additionally, most PNs tend to accumulate mainly in the liver, spleen, or kidneys, posing potential toxicity risks to the human body.[144–146] Therefore, it is essential to enhance the loading capacity and encapsulation efficiency of PNs and investigate their specific metabolic pathways via surface modification and targeting ligands to reduce the non-specific accumulation of PNs and minimize collateral metabolites.[147,148]

Some nanomaterials may exhibit cytotoxicity at high concentrations.[149] To address this, Zhang et al designed a "microcage" based on neutrophil extracellular traps (NETs) to improve diabetic wound healing by integrating methacryloylgel (GelMA) hydrogel microspheres with cationic polyethylenimine (PEI)-functionalized mesoporous polydopamine (mPDA), named mPDA-PEI@GelMA. This design enables the removal of NETs from nanoparticles and diabetic wound surfaces in a non-contact manner, effectively reducing chronic diabetic wound-related pro-inflammatory responses, enhancing wound healing processes, minimizing biotoxicity, and ensuring high biosecurity.[150]

In future studies, it is essential to conduct large-scale clinical trials to assess the safety and efficacy of PNs for the treatment of diabetic wounds. Improving the biocompatibility of PNs while reducing their potential cytotoxicity through surface modification, functionalization, or novel biodegradable materials is crucial for their clinical application.[151]

Stability

The stability of polymeric nanomedicines directly affects their efficacy and safety. Nanoparticles may lose their function due to physicochemical changes (eg, aggregation, degradation) during storage and transport. For example, liposomal nanodrugs are prone to drug leakage or lipid oxidation during long-term storage, which affects their stability.[152] Moreover, the interactions between various bioactive chemicals loaded on PNs are not well understood, particularly in terms of drug mass loading ratios, non-specific binding, aggregation phenomena, and the potential loss of biological activity in clinical applications. For instance, Krishna Yadav's research group developed a temperature-responsive self-shrinking nanofiber/hydrogel wound dressing. However, the temperature-sensitive response of this material is prone to being influenced by fluctuations in external temperature.[153] Therefore, future PN development should focus on studying the interaction mechanisms between PNs and bioactive substances, including intermolecular forces, hydrogen bonding, and hydrophobic interactions, through molecular dynamics simulation and quantum chemical calculations. This will clarify the interaction mechanisms and improve PN stability in diabetic wound treatments.[154,155]

Erigi et al employed PRISM theory in conjunction with molecular dynamics simulations to investigate the structure and phase diagram of nanorods at a 1% volume fraction within a polymer melt. Through a quantitative comparison of the resulting phase diagrams, both methods revealed that the formation of contact aggregates under conditions of low polymer-nanorod attraction (γ), and bridging aggregates when the attraction was higher.[156] The stability of polymers and

nanorod formation composites is different in γ, which suggests new directions for PN preparations in diabetic wound treatment.

Cost

The research and development process of PNs, such as designing, synthesizing, testing, and optimizing recipes, involve highly specialized equipment and technicians, which increases overall costs. Moreover, the raw materials required for PN formulations are often more expensive than traditional materials, especially if they contain rare or high-purity materials. The commercialization of PNs is also subject to strict regulations and standards, requiring additional testing and documentation, further driving up costs. Additionally, personalized PN formulations for patients significantly increases production costs due to the need for special parameters.[156] Mahmoudi et al proposed that due to the differences in physiological and immune responses between men and women, gender-specific factors should be considered when designing PNs for the treatment of diabetic wounds to improve treatment efficacy.[157]

Future research could focus on simplifying the synthesis process of PNs to reduce production time and cost. Optimizing synthesis conditions and parameters will promote the application of PNs in diabetic wound healing.[90,101,158]

Validity

Passive skin administration poses challenges due to the self-protection function of human skin. Future advancements in PNs should focus on integrating smart, multifunctional nanomedicine strategies to enhance their therapeutic potential. One promising direction is the development of multi-stimuli-responsive PNs, which can react to wound-specific conditions such as pH, temperature, glucose levels, and oxidative stress to achieve on-demand drug release. These adaptive systems can further enhance therapeutic efficacy while minimizing off-target effects. Another key research avenue is the combination of PNs with regenerative medicine, including gene therapy, stem cell therapy, and 3D bioprinting.[159–161] PNs can serve as carriers for genetic materials, growth factors, or exosomes, promoting cellular proliferation, tissue remodeling, and neovascularization in chronic wounds. Additionally, integrating PNs with real-time monitoring systems could enable the development of wearable wound dressings, allowing continuous tracking of wound conditions and dynamic drug delivery.

Future studies may explore the interaction between electronic signals and biological signals to improve the healing progress of wounds.[162] Additionally, to better understand the key biomarkers of diabetic wounds, advanced imaging technologies and bioanalytical methods can be used to explore subcellular models.[163] This will enable tracking the distribution, metabolism, and excretion pathways of PNs in vivo and target subcellular-scale indicators.

Conclusions

Diabetic wound healing is a multifaceted process influenced by hyperglycemia, infections, inflammation, oxidative stress, and vascular complications. PNs have emerged as a promising approach due to their unique physicochemical properties and excellent biocompatibility, enabling enhanced anti-inflammatory, antioxidant, pro-angiogenic, and antimicrobial effects. Particularly, their antibacterial action plays a crucial role in combating multidrug-resistant infections, facilitating biofilm removal, ultimately accelerating wound healing and lowering amputation risk. By leveraging their nanoscale characteristics and tailored drug delivery capabilities, PNs offer enhanced bioavailability, targeted action, and prolonged therapeutic effects, improving therapeutic efficacy and combating antibiotic resistance. PNs hold significant potential for advancing patient care and clinical outcomes.

Future studies should focus on developing novel PNs with multiple biomaterials while enabling smart wound care in response to specific stimuli. The field of multiple PNs or combining with alternative materials for integrated therapeutic effects, while maintaining biocompatibility, stability, and functionality, remains a key priority. Rigorous preclinical and clinical trials are essential to validate their efficacy and safety, paving the way for their adoption in diabetic wound management. Addressing these gaps will enhance wound healing and drive advancements in nanomedicine for chronic wound care.

Funding

This work was supported by National Natural Science Foundation of China (No.82374380), and Sanming Project of Medicine in Shenzhen(No.SZZYSM202202010).

Disclosure

The authors report no conflicts of interest in this work.

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