Engineering nanoparticle therapeutics for impaired wound healing in diabetes

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Diabetes mellitus is a chronic disease characterized by increased blood glucose levels, leading to damage of the nerves blood vessels, subsequently manifesting as organ failures, wounds, or ulcerations. Wounds in patients with diabetes are further complicated because of reduced cytokine responses, infection, poor vascularization, and delayed healing processes. Surface-functionalized and bioengineered nanoparticles (NPs) have recently gained attention as emerging treatment modalities for wound healing in diabetes. Here, we review emerging therapeutic NPs to treat diabetic wounds and highlight their discrete delivery mechanisms and sites of action. We further critically assess the current challenges of these nanoengineered materials for successful clinical translation and discuss their potential for growth in the clinical marketplace.

Keywords: Nanomedicine; Wound healing; Drug delivery; Biomaterials; Polymers; Regenerative medicine

Wound healing: Pathophysiology

Diabetes mellitus is a chronic disease wherein the pancreas does not produce enough insulin, or the body cannot effectively make use of the insulin produced.[1] As a result, a common effect of diabetes is raised blood sugar, otherwise known as hyperglycaemia. Over time, hyperglycaemia can lead to serious damage to nerves and blood vessels. Nerve damage in the feet, along with reduced blood flow, increases the chances of foot ulcers, infection, and impaired wound healing. Nonhealing ulceration affects 15–25% of people with diabetes. Furthermore, ~85% of diabetes-related ulcerations lead to lower-extremity amputation.[2] Diabetic ulcers are resistant to treatment because of the differences in the wound-healing process in patients with diabetes versus those without (Fig. 1).

Wound healing in patients without diabetes

Wound healing is characterized by hemostasis, followed by an inflammatory phase, proliferative phase, and a maturation phase, in which collagen-rich scar tissue seals the wound.[3] Hemostasis is the attempt by the body to quickly stop bleeding without disrupting normal blood flow.[2] Initially, the blood vessels begin to constrict, and platelet plugs form. Subsequently, during the inflammation phase, white blood cells migrate from the bloodstream, through the tissues to the wound site, where they are able to engulf and digest contaminants.[4] Migration of white blood cells is made possible through the dilation and increased permeability of capillaries. The dilation of the capillaries allows white blood cells to cross the vessel wall to migrate to the wound. Dilated vessels also cause symptoms associated with

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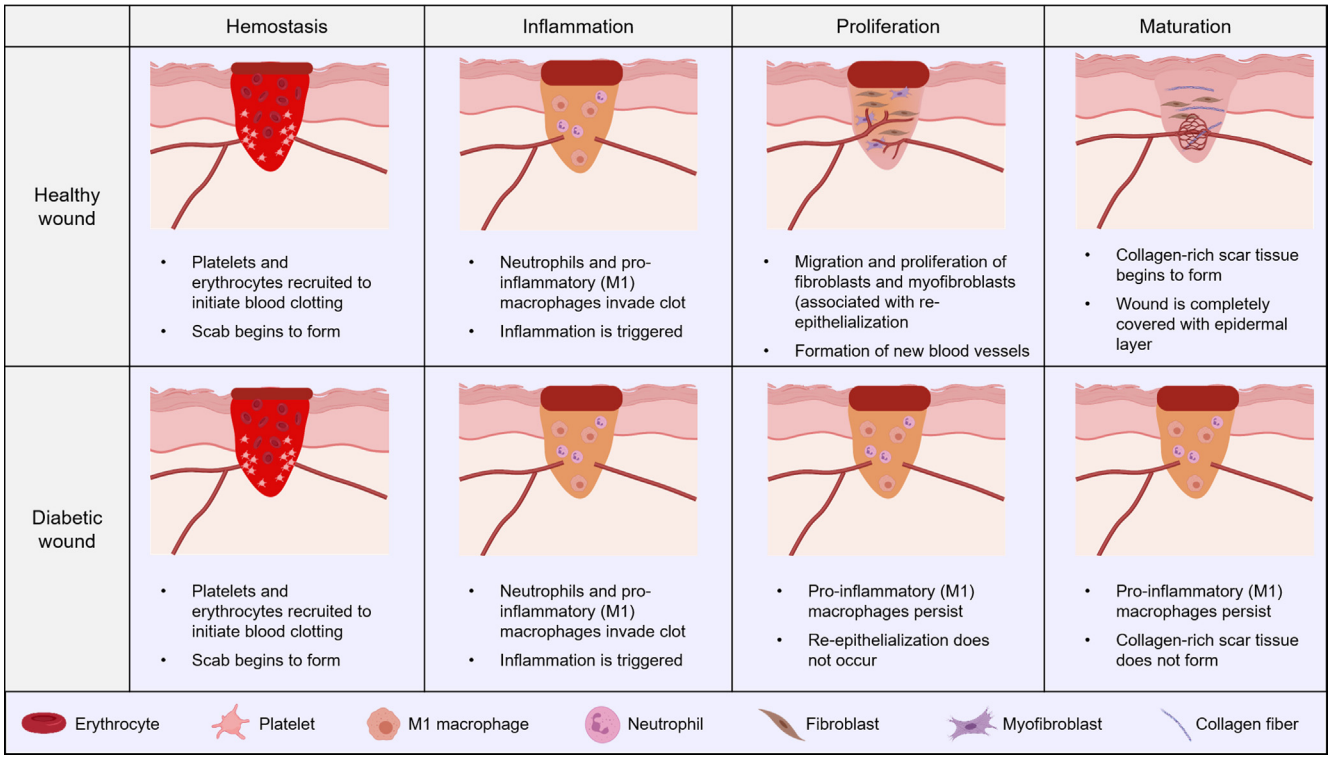

FIGURE 1

Key differences between wound healing in patients with and without diabetes. Hemostasis in both situations initiates the healing process with the formation of blood clots, followed by the initiation of the inflammatory phase. Proinflammatory cytokines are recruited to digest and engulf contaminants, causing inflammation in the area. Wound healing in patients without diabetes proceeds into the proliferative phase, where fibroblast migration, proliferation, and new vascularization occur, followed by the maturation phase, when collagen-rich scar tissue closes the wound. In patients with diabetes, the wound is chronically in the inflammation phase and does not proceed to the proliferative or maturation phases of the healing process.

inflammation, such as swelling and increased heat to the surrounding tissues. Monocytes mature into macrophages and continue to digest bacteria and remaining debris, as well as recruit other cell types for reconstruction.

This is followed by the proliferative phase, during which granulation tissue forms at the wound site.[5] Granulation tissue secretes chemicals that degrade the existing clot and has fibroblasts, which are able to produce collagen to provide strength and structure to the wound. During this phase, a dense network of capillaries is built to provide oxygen and nutrients to the cells, as well as absorb or carry away any remaining debris. Re-epithelialization also occurs when the wound is covered in new tissue, and keratinocytes differentiate and proliferate to produce an epidermal layer to superficially cover the area of the wound.[6] Lastly, the maturation phase comprises replacement of the granulation tissue with type 1 collagen. As the wound continues to contract, the wound is sealed with collagen-rich scar tissue. Clinically, wounds that fail to heal within a 4–6 week timeframe are considered chronic.[7]

Wound healing in patients with diabetes

Wound healing in patients with diabetes undergoes hemostasis but is impaired during the inflammatory phase.[8] Inflammatory macrophages persist at the site of injury for prolonged periods of times.[2] The macrophages present produce an increased amount of proinflammatory cytokines and high levels of reactive oxygen species (ROS), causing persistent inflammation.[2] This results in abnormal apoptosis of fibroblasts and keratinocytes, a decreased angiogenic response, reduced growth factor recruitment, and reduced collagen accumulation.[9] Common cytokine cascades normally resulting in proliferative factors are disturbed by these macrophages because of inefficient phagocytosis and apoptosis.[10] Furthermore, a phenotypic change in the fibroblasts, causing their differentiation into myofibroblasts, leads to reduced mechanical tensions of the extracellular matrix (ECM), resulting in inefficient collagen deposition and wound closure.[11] Abnormal ECM results from decreased collagen recruitment and more disorganized collagen deposition. Increased protease activity enhances the degradation of the ECM, growth factors, and collagen deposition, all of which are crucial for effective wound healing and have been demonstrated in diabetes.[12]

Current ***clinical treatment of wounds in patients with diabetes***

According to WHO data from 2014, up to 5% of people with diabetes in developed countries had diabetic foot ulcers resulting from a chronic wound.[13] Current methods of treatments rely on off-loading and applying dressings to the wound site.[14] How-

ever, most therapies aim to reduce infection and relieve pain, but do not improve the wound-healing process. Topical commercial applications, such as Becaplermin, include growth factors naturally produced by the body to induce cell proliferation to accelerate wound healing.[15] However, studies regarding wound healing in patients with diabetes with this treatment have been limited. With the increasing prevalence of diabetes globally,[13] we must address the clinical need for promoting wound healing in patients with diabetes that are superior to the current clinical approaches. The favorable advantages of NPs that have been demonstrated in other biomedical fields allow us to explore the possibility of their use to accelerate the wound-healing process.[16,17] Here, we discuss various approaches to promote wound healing in diabetic models through the use of NPs as either the therapeutic device or as a drug delivery vehicle. All approaches discussed in this review are preclinical models of wound healing and have yet to be clinically translated to humans. A previous comprehensive review of drug and drug vehicle development encompasses the difficulties and rigorous processes in the translation of the material from bench-side studies to bedside.[18]

Properties of an ideal wound-healing system

The success of a therapeutic treatment for wounds in patients with diabetes must essentially address the pathogenesis of the wound-healing process. Given that the wound-healing process in patients with diabetes is impaired during the inflammatory phase, novel therapies address the persistent inflammatory cytokines, decreased angiogenesis, and the lack of growth factor recruitment as well as impaired collagen deposition.[2,9,11] Examples of ways to improve the wound-healing process in patients with diabetes are outlined in Fig. 2. Briefly, the recruitment of anti-inflammatory cytokines that are produced by M2 macrophages[19] would decrease the persistent presence of proinflammatory cytokines, such as tumour necrosis factor (TNF-α) and interleukin 6 (IL-6),[20] ultimately normalizing the ratio of proinflammatory cytokines to anti-inflammatory signals, reducing apoptosis of fibroblasts and keratinocytes and potentially leading to increased angiogenesis.[21] Increased fibroblasts would also aid in increasing the number of myofibroblasts, which would help retain the mechanical tension of the ECM and, in turn, increase growth factor recruitment and collagen deposition.[22]

Another way to improve the wound-healing process in diabetic models could include therapies for decreasing ROS.[23] Although ROS are beneficial during the wound-healing process, the excess ROS levels and ongoing oxidative stress in chronic wounds result in protein modifications and DNA damage causing apoptosis and the acceleration and persistence of inflammation, both of which are detrimental to the wound-healing process. Decreasing ROS levels requires increased nitric oxide (NO) levels and decreased superoxide levels. Thrombospondin-1 (TSP-1) is an antiangiogenic adipokine that is expressed in animal models susceptible to diabetes.[24] The detrimental effect of TSP-1 on endothelial cell function is negatively correlated with NO regeneration in endothelial cells. Inhibiting ROS overproduction can result in an increase in NO bioavailability, decreasing TSP-1, which in turn, promotes angiogenesis.

Design strategies and associated advantages of NPs

There are many design challenges when considering therapies of wound healing in diabetes. These include optimizing various properties, including size, surface properties, shape, surface

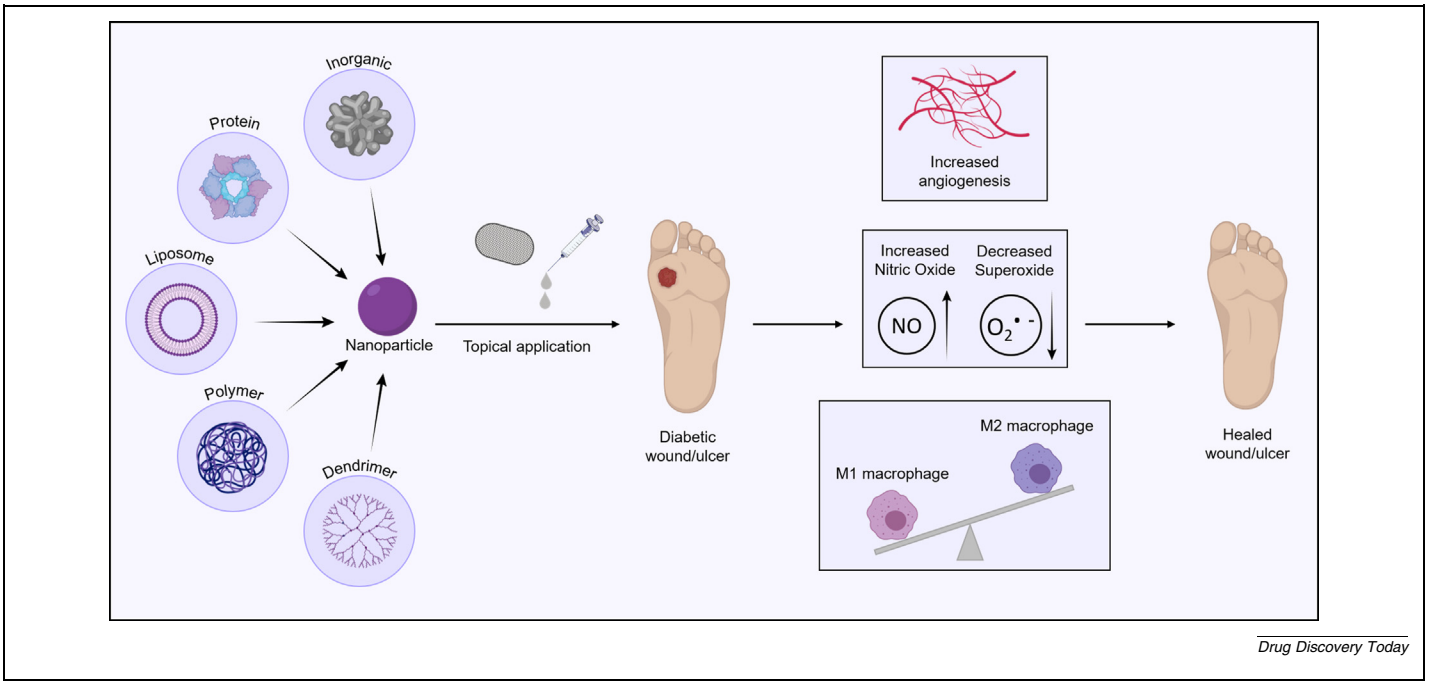

FIGURE 2

Overview of engineered nanotherapeutic strategies to accelerate wound healing in diabetes. The nanoparticles (NPs) developed in recent years to treat wounds in diabetics are shown. Successful nanotherapeutics, when administered topically, will increase angiogenesis, decrease reactive oxygen species, and increase anti-inflammatory macrophages. Taken together, these therapeutic effects will improve and accelerate wound healing in patients with diabetes.

charge, biocompatibility, biodegradability, and controlled release for the therapy using topical delivery systems to improve wound healing directly at the site. The use of NPs of 1–100 nm in size is crucial for their uptake by cells. Given their small size, cells can easily take up NPs by one of the three primary endocytosis mechanisms.[25] The ability of NPs to penetrate the tissue system allows for the facilitation of easy uptake of drugs by cells if the NP is acting as a vehicle. It has also been shown that uptake of nanostructures by cells is higher than that of particles sized between 1 and 10 μm[26]. Moreover, NPs must be considerably lipophilic to be able to interact with hydrophobic cell membranes. NPs have also been shown to persist in the circulatory system for a prolonged period of time, causing fewer plasma fluctuations with reduced adverse effects before being cleared through the urinary tract because of their small size.[27] Therefore, the use of NPs to provide a therapeutic effect or to act as drug vehicles is ideal for a potential wound-healing strategy.

Engineered NPs and nanocomposites for wound healing in diabetes

NPs can be engineered such that they themselves are the therapeutic device, or they can be engineered such that they act as drug delivery vehicles for the therapeutic molecules to accelerate the wound-healing process. Here, we discuss five approaches that have been applied to promote wound healing in diabetic models (Fig. 2). The research articles discussed herein are summarized in Table 1.

Inorganic NPs

Inorganic NPs have been used to treat burns, chronic ulcers, and wounds in patients with diabetes because of their anti-infective and anti-inflammatory effects.[28–31] A common problem among patients with diabetes with untreated and unhealed wounds is the increased risk of infection. To address the need for antimicrobial compounds, inorganic NPs, including an array of metal NPs, have been studied. One major advantage of silver NPs (AgNPs) is their intrinsic resistance against bacteria and bacteria that produce biofilms.[32] Bacteria that produce biofilms are commonly found in chronic wounds and they tend to enclose themselves in a self-produced extracellular polymeric substance that is resistant to conventional antibiotics.[33–36] Kalishwaralal *et al.* tested biologically synthesized AgNPs on biofilm-producing bacteria, demonstrating that AgNPs inhibited both the growth of bacteria as well as their ability to produce exopolysaccharides, the structural scaffold used to create the biofilm.[37] This intrinsic ability of AgNPs to inhibit the growth of bacteria demonstrates their ability to act as a drug delivery vehicle for wound healing in diabetes. Another drug vehicle comprising inorganic materials is zinc oxide NPs (ZnO NPs), which also show antibacterial properties.[38] Furthermore, Zn can be used for treating diabetic ulcers because of its role in the function of more than 300 enzymes that are crucial to maintaining metabolic hemostasis in the body. To show the feasibility of ZnO NPs in the use of wound healing in patients with diabetes, Kaushik *et al.* tested fibroblast growth and the antimicrobial potential of these NPs and showed that, upon exposure to ZnO NPs, there was a significant increase in fibroblast cells.[39] It was also shown that, when exposed to pathogens, ZnO NPs displayed antimicrobial activity useful for treating wounds of patients with diabetes. Inorganic NPs in the form of metal organic frameworks (MOFs) have also been used to deliver inorganic ions for slow and controlled release of the therapeutic ion.[40,41] Xiao *et al.* used copper-based MOFS to safely deliver copper ions in a controlled manner to avoid toxicity issues associated with high concentrations of copper (Fig. 3a). These copper-based MOFs were shown to release copper ions to improve angiogenesis, promote collagen deposition, and decrease wound closure times in diabetic mice models (Fig. 3b, c).[42]

Liposome NPs

Drug delivery systems comprise of the administration and delivery of a pharmaceutical compound to achieve an enhanced therapeutic effect in a specific area of the body. Liposomes have been widely used as drug delivery vehicles across various biomedical applications.[43–45] Although the use of liposomes has its limitations in terms of batch-to-batch consistency and drug leakage, liposomes are promising NPs because of their nontoxic, biodegradable, and biocompatible behavior. Current clinical developments in treating wounds in patients with diabetes involve addressing the risk of infection. Studies have shown that liposomes entrapping a bacteriophage cocktail to address multiple bacterial infections are more effective than the use of a free bacteriophage cocktail (Fig. 3d).[46] Both *in vitro* and *in vivo* studies suggested that liposomal entrapment of the cocktail led to better bacteriophage persistence at the wound site compared with free bacteriophage as determined by a higher phage titer. Recently, liposomes have also been developed not only to carry cargo in the treatment of wounds in patients with diabetes, but also to act as antigen presenters. Kaymakcalan *et al.* developed α-gal-presenting liposomes to activate naturally occurring anti-Gal antibodies in humans.[47] It was found that, when topically applying these liposomes, macrophages were recruited, prohealing growth factors and cytokines were produced, and wound closure was accelerated both in normal wound and burn wound models *in vivo*. This application shows the potential of using antigen-presenting liposomes for topical wound-healing treatments in patients with diabetes.

Dendrimer NPs

Dendrimers are a class of globular molecules artificially designed with a large arrangement of a variety of functional groups.[48] This gives dendrimers the potential to be promising nanocarriers for a large number of therapeutic agents because of their interactions via hydrogen bonding, lipophilicity, and charge interactions.

Deng *et al.* took advantage of the branches of dendrimers for amplification of function, biocompatibility, and water solubility.[49] Fibronectin-like peptides were synthesized using a dendrimer-based strategy to mimic the ability of fibronectin to facilitate the healing of skin wounds through the promotion of keratinocytes (Fig. 3e). It was found that the use of a peptide sequence derived from the cell-binding site of fibronectin as well as derivatives of this sequence stimulates re-epithelialization and contraction of dermal wounds *in vivo*. This approach is particularly advantageous for a diabetic wound because the latter show particularly low levels of fibronectin relative to nondiabetic wounds.[21] It was concluded that a large role in the efficacy of this treatment was linked to dendrimer branching and its ability to amplify the function of the peptide sequences.

TABLE 1

Examples of NPs developed as therapeutic molecules or drug delivery vehicles for the application of wound healing in patients with diabetes.

Inorganic NPs					
AgNP	N/A	N/A	Increasing concentrations of AgNPs induced cell death Significant reduction in biofilm activity in dose-dependent manner	N/A	[37]
ZnO	N/A	N/A	ZnO NPs with larger particle sizes showed more antimicrobial effects	N/A	[39]
Liposomes					
α-gal NPs	N/A	N/A	N/A	Increased keratinocyte migration compared with saline treatment	[47]
PLGA-liposome nanofibers	N/A	miR-145 and PDGF-BB	Significantly increased tube formation of NPs containing miR145 + PDGF-BB compared with controls, which showed increased angiogenesis compared with free drug	Significantly decreased wound area with loaded cargo Increased therapeutic effect of loaded NPs compared with free drug Decreased inducible NO synthase, indicating inhibition of inflammation during later stages of wound healing Increased angiogenesis	[77]
Dendrimers					
PAMAM NPs	Connected to hyaluronic acid through substrate polypeptide of MMP-2 (Gly-PLGLAG-Cys)	Astragaloside (ASI)	Controlled release in presence of MMP-2 (>70% release) compared with in presence of PBS (∼13% release) Significantly reduced levels of ROS Increased cell proliferation and migration Increased expression of wound repair-related genes	NPs were MMP-2 responsive at wound sites (overexpressed MMP-2) Increased cell proliferation and migration and expression of wound-repair-related genes	[51]
Protein NPs					
SDF1α-elastin-like-peptide	Recombinant fusion of SDF1α and elastin-like-peptide	N/A	Binding of SDF1-ELP to cell receptors was similar to that of SDF1, with longer retention times Increased intracellular calcium release observed with SDF1-ELP compared with free SDF1, indicating decreased inflammation and increased hemostasis	SDF1-ELP accelerated wound closure (21 days) compared with free SDF1 (42 days) SDF1-ELP resulted in thicker epidermal and dermal layers	[57]
Recombinant keratin NPs	N/A	N/A	Cell proliferation Increased cell migration in scratch wound-healing assays, observed by increased closure of scratch area	Accelerated wound closure compared with commercial dressing Decreased inflammatory cells (after Day 7) Increased proliferation of fibroblasts (after Day 7) Increased angiogenesis Higher collagen deposition	[58]
Polymeric NPs					
PLGA/gelatin nanofibers	PLGA crosslinked with gelatin	Liraglutide	Slow initial degradation, quicker degradation after 14 days compared with PLGA, allowing release of drug during later healing stages Continuous degradation over 30 days Increase in cell proliferation, migration, and growth factor secretion of endothelial cells Increased angiogenesis	Complete wound healing within 14 days More new epithelium tissue, increased collagen deposition and collagen thickness, and increased blood vessel formation observed in PLGA/gelatin/Lira compared with PLGA/gelatin and PLGA groups	[49]
PLGA	N/A	PEI/NONOate	Prolonged release of NO over 6 days without burst release using PLGA NP, compared with release over 12 h with burst release with PEI/NONOate alone PEI/NONOate-PLGA NPs showed bacterial resistance in dose-dependent manner against MRSA and Pseudomonas aeruginosa Adhesion of PLGA to bacteria allowed for increased antimicrobial activity of cargo	PLGA-PEI/NONOate showed > 60% reduced wound area on Day 4 in diabetic and infected mice compared with untreated mice, which showed an increase in wound area Increased fibroblast-like cells and decreased proinflammatory macrophages in treated mice compared with untreated mice	[64]
Chitosan	N/A	Rebamipide	Prolonged drug release of encapsulated drug over 48 h compared with free drug (released in 8 h)	Wounds completely covered with epithelium after 3 weeks of chitosan-RBM treated wounds compared with untreated wounds, which showed tender wounds with some hemorrhage Decreased proinflammatory macrophages in treated wounds	[66]

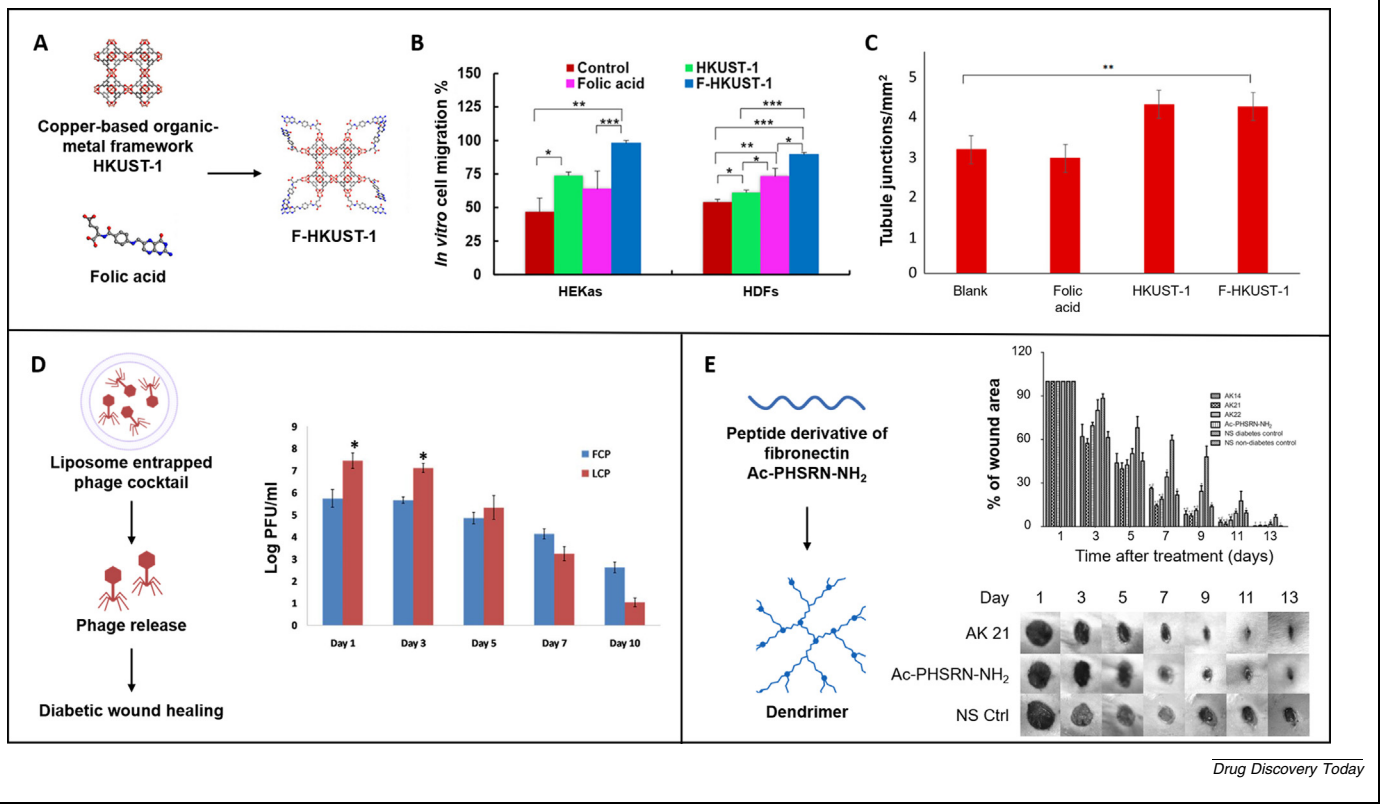

FIGURE 3

Design strategies and efficacy of nanoparticles on wound healing. (a) Schematic showing copper-based metal organic frameworks (MOFs) (HKUST-1) in combination with folic acid to synthesize folic acid-modified HKUST-1 (F-HKUST-1). (b) Percentage of cell migration in human epithelial keratinocytes (HEKs) and human dermal fibroblasts (HDFs) after treatment with PBS (control), HKUST-1, folic acid, and F-HKUST-1 for 24 h. HKUST-1 showed a significant increase in cell migration compared with the other experimental groups. (c) Quantification of tubule junctions in human umbilical vein endothelial cells (HUVECs) showed highest tubule junctions in HKUST-1 and F-HKUST-1, both expected to show contribution to angiogenesis and wound healing in vivo. (d) Schematic of phage cocktail encapsulation and release in liposomes for diabetic wound healing. Liposomes entrapping the phage cocktail showed a significant decrease in phage titer present in the wound of Staphylococcus aureus with both the free cocktail of phages (FCP) and the liposome-entrapped cocktail of phages (LCP). However, over the period of 10 days, LCPs showed lower phage titers than FCPs. (e) Schematic of dendrimer formation using peptide derivatives of fibronectin. Treatment of diabetic wounds with these derivative dendrimers was evaluated based on the percentage of wound closure over 13 days and compared with treatment with normal saline (NS) and the peptide of fibronectin, which served as negative and positive controls, respectively. Treatment with dendrimers containing peptide derivatives of fibronectin significantly decreased the size of the wound compared with the NS control. Adapted, with permission, from[42] (c),[46] (d), and[49] (e).

In another study, the effect of 'naked' dendrimers was studied.[50] Here, polyamidoamine (PAMAM) dendrimers were chronically administered to diabetic mice over the course of 4 weeks. After daily administration of these dendrimers, it was found that they inhibited the epidermal growth factor receptor (EGFR)-ERK1/2-Rho kinase (ROCK) pathway, a pathway that is crucial in the development of diabetic vascular complications. Furthermore, it has been reported that cationic PAMAM dendrimers can also act as glucose scavenging agents, meaning that they scavenge excess glucose in the body, which could aid in the decreased probability of further inducing a chronic wound.[51] Taken together, dendritic NPs can be used in a variety of ways to both treat and prevent chronic wounds.

Protein NPs

There is a variety of protein NPs, with each protein having distinctly different behaviours.[17,52,53] Some proteins can self-assemble into their NP form, whereas others must be physically or chemically conjugated to achieve such a structure. Many proteins used as NPs can be modified in various ways, including both physical and chemical methods, to make them more suitable for their biomedical application.[54–56] Protein NPs can be especially useful in delivering therapeutic molecules for wound healing in patients with diabetes because of their biocompatibility and their ability to be easily taken up by cells. Yeboah *et al.* developed a recombinant fusion protein comprising stromal cell-derived growth factor-1 (SDF1) and an elastin-like peptide[57] (Fig. 4a). Upon expression, this protein was able to self-assemble into NPs and bind to cell receptors to promote neovascularization and faster re-epithelization compared with free SDF1. *In vivo,* the SDF1-ELP NPs significantly accelerated the wound-healing process (fully healed by Day 28 post-induced wound) compared with free SDF1, free ELP, and generic fibrin gels (fully healed by Day 42 post-induced wound) (Fig. 4b). Similarly, Gao *et al.* also took advantage of recombinant proteins to express keratin NPs with wound-healing potential.[58] These NPs were shown to have significantly increased cell viability and migration *in vitro* and promoted epithelialization, vascularization, collagen deposition, and remodeling in *in vivo* nondiabetic

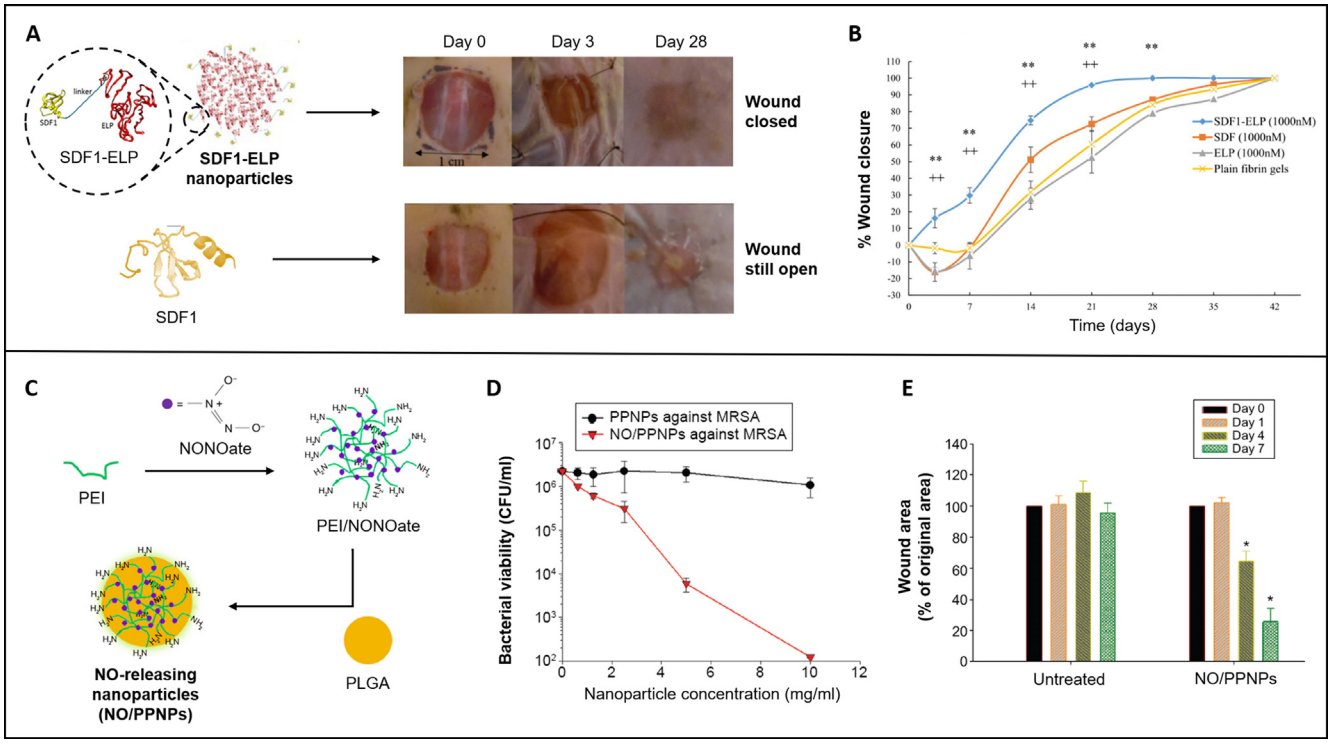

FIGURE 4

Efficacy of nanoparticles (NPs) on wound healing. (a) Efficacy of recombinant stromal cell-derived growth factor-1 (SDF1)-ELP NPs compared with free SDF1 in wound-induced diabetic mice. SDF1-ELP NPs accelerated wound healing in diabetic mice, allowing the wound to completely recover within 28 days of treatment. Free SDF1 improved wound healing slightly; however, the wound remained open by day 28. (b) Wound closure studies in diabetic mice showed complete recovery in all experimental groups. Wounds treated with SDF1-ELP NPs showed complete recovery by Day 28 compared with remaining groups, which showed complete recovery by Day 42. (c) Schematic of poly lactic-co-glycolic acid (PLGA) NPs loaded with crosslinked with polyethylenimine-nitric oxide (NO/PPNPs) to form NO-releasing NPs. (d) NO/PPNPs were tested for their antimicrobial resistance against methicillin-resistant Staphylococcus aureus (MRSA) compared with PLGA NPs without the PEI-NO crosslinks. Bacterial viability decreased in a concentration-dependent manner compared with PLGA NPs alone. (e) NO/PPNPs significantly accelerated wound healing in wound-induced mice over the course of 7 days compared with untreated mice. Adapted, with permission, from[57] (b) and[64] (e).

wound-healing models. This shows the potential of using keratin NPs as a possible treatment for wound healing in patients with diabetes because of their ability be taken up by cells topically at the wounded site. However, although protein NPs have been widely used in biomedical applications for bioimaging and cancer therapy, they have yet to be taken advantage of in applications for wounds and ulcers in patients with diabetes.

Polymeric NPs

Polymeric NPs have drawn increasing attention in the biomedical and bioengineering fields for their various advantages, including biocompatibility, biodegradability, and nontoxicity.[59,60] When conjugated with polymeric systems, drugs are protected from degradation by proteases present in a wound environment, allowing for controlled and sustained release.[61] Some of the most common polymeric NPs used include poly lactic-co-glycolic acid (PLGA), alginate, gelatin, chitosan, and polyethylene glycol (PEG) because they have been designated as 'generally recognized as safe' (GRAS) polymers.[62]

For example, PLGA/gelatin nanofibrous mat scaffolds were used to sustain the release of liraglutide, a receptor agonist that has been reported to promote angiogenesis in endothelial cells.[63] The use of PLGA allowed for a naturally degrading drug delivery vehicle and has been reported to stimulate cell proliferation, which could aid wound healing. Liraglutide was incorporated into the PLGA/gelatin system through a cross-linking integration method, which resulted in increased pore size, hydrophilicity, and elasticity of the nanofibrous mats. This allowed for improved healing efficiency *in vivo* as characterized by shortened wound closure time, increased angiogenesis, and increased collagen deposition. In another approach, PLGA-polyethylenimine (PEI) NPs were used to release NO at the wound site in a nondiabetic wound-healing model[64] (Fig. 4c). NO is a small gaseous mediator involved in many physiological processes and, therefore, nanomaterial carriers for NO delivery need to have high loading capacity and extended release times.[65] After thorough investigation of NO carriers, the PLGA-PEI system was found to prolong NO release over the course of 6 days without any burst release. Although this approach has been proven in a nondiabetic model, its novel approach shows great potential in diabetic wound-healing model. This PLGA-PEI system was also found to have antibacterial efficacy against methicillin-resistant *Staphylococcus aureus* (MRSA) through the use of the polymeric vehicle, and wound-healing activity through the decrease of ROS (Fig. 4d). Taken together, the therapeutic effects of the NO/PLGA-PEI

NPs accelerated wound healing compared with untreated groups (Fig. 4e).

Chitosan is another polymeric NP widely used as a drug delivery vehicle. One approach involved the use of drug-loaded chitosan NPs to inhibit proinflammatory macrophages to accelerate wound healing.[66] Chitosan NPs were used to deliver an otherwise unsustainable drug through the use of ionic crosslinking. The use of chitosan allows for the simple preparation of a stable and biocompatible drug vehicle that provides versatile routes of administration, such that this system can be used for a variety of wound-healing applications.

Concluding remarks and future directions

The need for effective and safe strategies to treat wounds and ulcers in patients with diabetes is pertinent. Nonhealed wounds arise from a decreased angiogenic response, reduced growth factor recruitment, and collagen accumulation. Therefore, we must work toward an efficacious solution to manufacture proangiogenic and anti-inflammatory particles that will help accelerate wound healing into phases through increased growth factor recruitment and collagen accumulation. Among the various approaches that are being investigated, designed polymeric and nonpolymeric NPs have shown great promise, and encouraging results have been obtained both *in vitro* and *in* vivo.[11,67]

However, the NPs outlined in this review have several challenges and limitations. These wound-healing therapies have been produced on a laboratory scale. Their large-scale manufacturing might be problematic because of their often complex synthesis processes involving multiple steps, as well as decreased yield resulting from purification after each synthesis step.[68] Furthermore, the large-scale syntheses of the outlined NPs could be costly and laborious. Lastly, these NPs have been tested *in vitro* and *in vivo* in various animal models and the results might not be entirely replicated in humans, in which the dosage and frequency of administration would have to be revaluated and optimized.

Given their advantages, we discuss some of the potential applications and future perspectives of engineered NPs for wound healing in patients with diabetes. A summary of the advantages and limitations of the discussed materials is provided in Table 2. Given that bacterial infections pose a significant problem in wounds and ulcers in patients with diabetes, the risk of amputation is increased by the rate of bacterial infection at the nonhealed site. To address this problem in a clinical setting, AgNPs were used in numerous clinical trials in the therapy of various wounds, including burns and diabetic ulcers. Currently, there are some commercially available dressings containing AgNPs. One example of this is Acticoat©, a wound dressing containing AgNPs.[69] This allowed for a flexible and absorbent coating that proved to be an efficient and effective barrier to bacterial penetration. Wound healing, infection reduction at the site of the wound, and pain reduction were all observed in most of the patients tested. Here, the use of the dressing allowed for sustained release of the AgNPs for at least 7 days, minimizing the need to change the dressing and, therefore increasing patient compliance.[70]

Recent approaches to treating wounds in patients with diabetes involve the use of miRNAs. miRNA-146a and miRNA-200b have important roles in the regulation of growth factors and ECM protein production at a molecular level.[71] Antagonism or promotion of certain miRNAs can result in increased growth factor and fibronectin production, inducing cell proliferation and migration, and inhibiting apoptosis of endothelial cells.[72,73] The combination of miRNAs and NPs can promote cellular targeting and uptake, increase circulation time, and decrease off-target effects.[74] The use of NPs as nanocarriers for miRNAs has gained in popularity in recent years and continues to be explored for the use of wound healing in patients with diabetes.

Other studies have worked on developing nanocomposite scaffolds for sustained treatment of wounds in patients with diabetes. For example, the advantageous properties of liposomes discussed earlier have been used in combination with a variety of hydrogels to produce topical liposome–hydrogel nanocomposites in the delivery of various cargo to ensure more sustained release.[75,76] One example is the use of electrospun PLGA-liposome fibers for the simultaneous delivery of miRNAs and growth factors for the promotion of vascular smooth muscles *in vitro* and *in* vivo.[77] In a recent study, a nanocomposite scaffold was synthesized using a main network of polyethylene glycol

TABLE 2

Advantages and disadvantages of the reviewed strategies for wound-healing application in patients with diabetes.

Type of NP	Advantages	Limitations
Inorganic	Uniform size and shape	Can cause immunogenic response
	Antimicrobial properties	Low loading capacity
Liposome	Biocompatible	Difficult to ensure bath-to-batch consistency in synthesis
	High loading capacity	Costly
	Metabolised in vivo	Storage issues because of leakage of drugs
Dendritic	Controllable physical properties and size	Complex synthesis
	High loading capacity	Tendency to aggregate
		Can be cytotoxic
Protein	Easy production of recombinant proteins in bacterial systems	Expensive
	Biocompatible and biodegradable	Difficult to store: storage requires subzero temperatures
	Stable structure in vivo	Protein aggregation can cause storage issues
Polymeric	Sustained release of drugs	Synthesis and purification processes length and involve many steps
	Controllable mechanical properties based on crosslinking densities	Higher cost
	Can synthesize stimuli-responsive drug delivery vehicles	Degradation time can be too slow

diacrylate (PEGDA) to form the scaffold, with a peripheral network formed between bioactive glass NPs that contained copper and sodium alginate.[78] Bioactive glass was recently shown to have a variety of biological properties, including osteogenic ability, bone/soft tissue bonding activity, and promoting angiogenesis. Paired with copper, an element essential for the wound-healing process, increased angiogenesis, expression and stabilization of skin proteins, and antibacterial activity were reported. However, nonphysiological concentrations of copper ions might increase the risk of ion poisoning and, therefore, the controlled release of Cu^{2+} is pertinent. Therefore, the use of a PEGDA scaffold would greatly enhance this system to create a self-healing antibacterial nanocomposite dressing in order to enhance the wound healing process in patients with diabetes. As seen from the above examples, two or more of these approaches can be combined to exploit the advantages of various materials to develop superior delivery systems.

Other developing technologies in this area include conductive hydrogels.[79] Conductive hydrogels have recently become more widely used in healthcare recording electrodes, biomedical patches, implantable bio-devices, and so on. These hydrogels are stimulated by external signals, which are converted to bioelectric stimulation after reaching the skin to achieve the aim of the treatment. Zhang *et al.* developed a conductive hydrogel based on polyvinyl alcohol and chitosan to enable the hydrogels to perceive temperature and strain.[80] The activation of these hydrogels resulted in increased angiogenesis, collagen deposition, and inhibition of bacterial growth. Researchers are continuing to develop these sensory hydrogels to respond to wound environmental pH, ROS levels, and glucose concentrations. In the future, these hydrogels might also be studied as potential drug delivery systems that can encapsulate NPs for the further promotion of wound healing in patients with diabetes.

Lastly, a layer-by-layer (LBL) self-assembly technique is being studied for a range of biomedical technologies for delivery of various material surfaces.[81] These composite materials have good stability, mechanical properties, hydrophilicity, and, most importantly, sustained drug release. This is a technique wherein charged polyelectrolytes are assembled from aqueous solutions to form nanostructured films to deliver a range of therapeutic molecules. This technique has been studied in relation to wound healing in patients with diabetes to deliver materials that have the potential to induce varying therapeutic effects to accelerate wound healing in a diabetic model.

As mentioned previously, the risk of diabetes and wounds/ulcers in patients with diabetes increases every year. The strategies reviewed here could be used to produce safe commercial therapies either as free NPs, NPs as drug vehicles, or as nanocomposites in conjunction with dressings, hydrogels, or 'smart' sensory-responsive systems. Although some of the examples mentioned herein have been used for nondiabetic wound-healing models, they can also be applied to treat diabetic wounds. This is because the mechanism of uptake and design strategies of these NPs allows them to have similar physiological effects in diabetic and nondiabetic wounds. We anticipate that these NPs will exhibit superior therapeutic effects and accelerate the wound-healing process in patients with diabetes, lowering the risk of amputation.

Declarations of interest

There are no conflicts to declare.

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