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REVIEW

Recent Advances in Nano-Drug Delivery Systems for the Treatment of Diabetic Wound Healing

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Abstract: Diabetes mellitus (DM) induced wound healing impairment remains a serious health problem and burden on the clinical obligation for high amputation rates. Based on the features of wound microenvironment, biomaterials loading specific drugs can benefit diabetic wound treatment. Drug delivery systems (DDSs) can carry diverse functional substances to the wound site. Nano-drug delivery systems (NDDSs), benefiting from their features related to nano size, overcome limitations of conventional DDSs application and are considered as a developing process in the wound treatment field. Recently, a number of finely designed nanocarriers efficiently loading various substances (bioactive and non-bioactive factors) have emerged to circumvent constraints faced by traditional DDSs. This review describes various recent advances of nano-drug delivery systems involved in mitigating diabetes mellitus-based non-healing wounds.

Keywords: drug delivery system, nanotechnology, diabetic wound healing, nanoparticles

Introduction

Diabetes mellitus (DM) is a complex chronic metabolic disease. Currently, over 300 million people suffer from DM, with an increasingprevalence in the upcoming years.[1,2] Diabetic patients in high glucose conditions always bear many secondary complications, and diabetic foot ulceration (DFU) is a frequently recognized complication, which increases amputation rates, and shortens lifespans.[3,4] Many therapeutics have been applied in diabetic non-healing wounds, such as hyperbaric oxygen therapy (HBO) and smart wound dressings.[5] Diabetic wounds are heterogeneous, so the treatment and outcome depend very much on precise strategies.[6] Most of the current treatments are inadequate and incur a massive financial burden to the patient. Therefore, the discovery of new therapeutic methods for diabetic wound healing is urgently required.

A drug delivery system that delivers therapeutic molecules in a sustained release manner could be a promising method of improving diabetic wound healing. These advanced systems can control drug release over a long time period, maintain drug concentration and release drugs in a target site. Nevertheless, conventional drug delivery systems are not always designed optimally for various drugs and inadequate to protect drugs from probable degradation, which causes the waste of a large number of drugs.

Current developments of nanotechnology benefit the design and fabrication of drug delivery systems for diabetic wound healing.[7] With various nanostructures, such as liposomes, nanoparticles, nanofibers and nano hydrogels, these nano-drug delivery systems are being studied to provide better drug performances and achieve maximum drug encapsulation efficiency. Since NDDSs loading various carriers exhibit anti-inflammatory action, ROS scavenging, reduction of local blood sugar levels and senescence cell clearance, their applications in diabetic wound treatment are receiving increasing attention.[8–10] A polycaprolactone (PCL)-based nanofiber has been fabricated to generate oxygen and stimulate angiogenesis to improve diabetic wound healing.[11] A Methacrylate Gelatin (GelMA) hydrogel based patch

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carrying NO has been designed to accelerate diabetic wound healing.[12] many other studies have also been reported to explore the utilization of NDDSs in the field of diabetic wound healing.

In general, the reviews currently published on nano-drug delivery systems describe their unique properties and novel fabrication technology. They give general insight into the application of nanomaterials in the wound healing field; nevertheless, information about the application in specific wounds such as diabetic wounds is currently limited. In this review, we cover all recent nano-scale drug delivery systems used for diabetic wound treatment. Additionally, it details the major substances loaded in these nanocarriers and their function in accelerating diabetic wound healing, which would help in selecting suitable drugs to meet the need of different diabetic wound conditions.

Wound Healing Pathophysiology

Normal Wound Healing

Wound healing is a complex and stepwise process and involves many different cell types releasing cytokines and growth factors (GFs). The healing process is divided into the following overlapping stages: hemostasis, inflammation, proliferation and remodeling (Figure 1).[13–15]

Fibrin plug formation can block bacteria and provide immediate coverage in the wound area.[15] Platelets aggregate and release proinflammatory mediators such as growth factor, cytokines and chemokines. These mediators can recruit neutrophils and monocytes to the wound area, which support the armamentarium for the inflammatory period.[16]

The inflammation phase occurs immediately after injury and the focus of this phase is on destroying bacteria and removing debris.[17] This phase usually lasts four to six days, while in some pathological conditions (e.g., diabetic foot ulcers), it can last for weeks or even months. Cell recruitment and chemotaxis (the movement of an organism in response to a chemical stimulus) are key events in this phase. These cells have various functions. Increasing endothelial expression of selectins slows down blood cells (e.g., leucocytes) and binding to integrins to help their adhesion. Neutrophils and macrophages are involved in wound debridement, which also fuels the healing process by releasing cytokines, GFs and other mediators.[18] Circulating monocytes convert to tissue macrophages to aid wound contraction in the begin of granulation tissue formation.[19]

The proliferation phase focuses on filling and covering the wound site, and it includes four distinct stages: re-epithelialization, neovascularization, collagen synthesis and extracellular matrix (ECM) formations.[20] This phase often lasts for a few weeks. Granulation tissue formation is essential for wound contraction, and fibroblasts, endothelial cells and keratinocytes are the most prominent cell types present and support the formation of granulation tissue, which is an essential component of contraction.[21] Physical contraction mediated by myofibroblasts also plays an important role in achieving wound closure.[22] Cross-talk between integrins, cells, cytokines and matrix metalloprotein (MMP) promotes cell migration and ECM production.

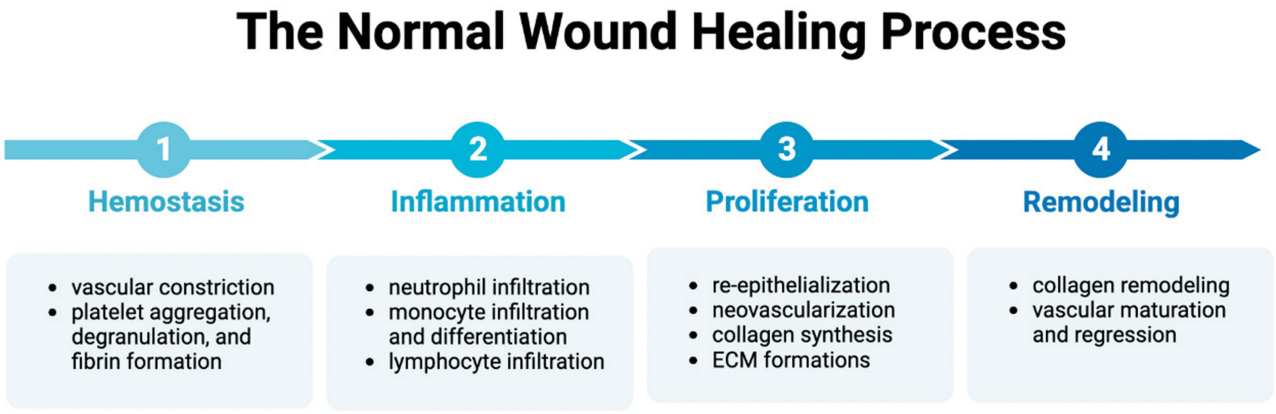

Figure 1 The physiological process of normal wounds. (figure was created with BioRender.com).

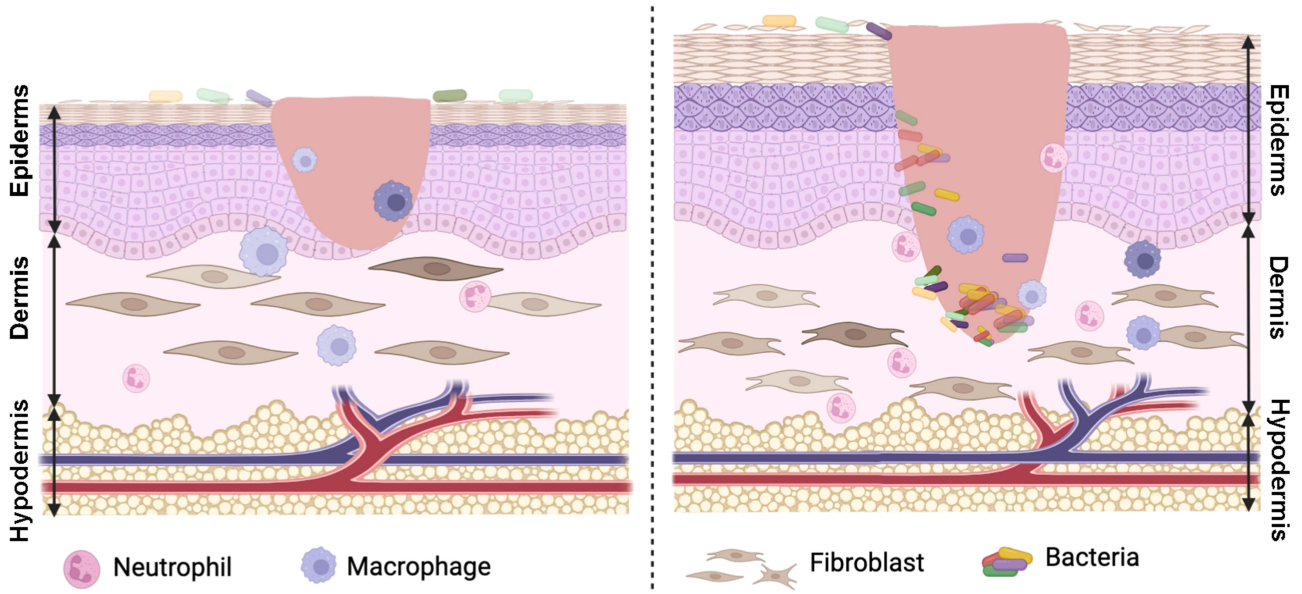

Figure 2 The pathophysiological processes of wound healing and diabetic wound healing. (figure was created with BioRender.com).

In the tissue remodeling phase, tissue slowly gains strength and flexibility. In this phase, many newly formed capillaries subside, normalizing the vascular density of the wound site. To achieve proper tensile strength, ECM is reshaped to a structure that approaches normal tissue.[23] Gradually, the immature collagen (type lll) is converted into the more stable collagen type l, and the ratio of type III and type I decreases. Collagen forms tight cross-links with collagen and other protein molecules and deposits in a physiological alignment.[24,25] This phase is relatively long, usually lasting 21 days to 1 year.

Diabetic Wound Healing

Under diabetic pathological conditions, the orderly and reliable healing process is disturbed and the wound becomes a chronic wound.[2,26] Some parts of the chronic condition may get stuck at different stages, losing the ideal synchrony of healing progression that leads to rapid healing.[27] There are intrinsic pathobiological abnormalities and extrinsic factors that contribute to the occurrence of a diabetic wound (Figure 2).

Hypoxia is a major factor that causes a non-healing wound.[28,29] In addition to inadequate oxygen supply, a prolonged inflammation phase causes high oxygen consumption of wound cells.[30] Diabetic neuropathy (DN) is the most common complication of diabetes, and patients with an injured nerve system are more likely to develop diabetic foot ulcers. DN presents a variety of manifestations, which include segmental demyelination, degradation of peripheral neuron axons, poor nerve conduction and nutrient supply, culminating in dry skin and gangrene.[31] Without pain perception, the patient is unable to feel the injury site, consequently increasing the risk of infection and enlargement of the wound. Vasculopathy and endothelial cell abnormalities, together with neuropathy, cause limited oxygen support to the wound area.[32] Additional nerve damage, diminished pain sensation and insufficient blood supply can amplify the disorder of the diabetic foot microenvironment. Wound healing mediators can be influenced by high blood levels. The M2 type macrophage polarization is disturbed, the keratinocyte migration is reduced, and the re-epithelialization stage is stagnant.[33] Recent works revealed that a prolonged inflammatory phase is an iconic feature of diabetic chronic wounds. With impaired phagocytic function, excess macrophages infiltrate the wound site and influence MMPs regulation, which blocks deposition of intact, healthy collagen and formation of ECM.[34]

Current Diabetic Wound Treatment

Debridement

Debridement involves removing foreign debris, blood clots and the inactivated or infected tissue from a wound bed.[35] The applied methods of debridement include surgery, wet-to-dry dressings, and enzymatic method.[36] Sharp debridement

has been well acknowledged as the gold standard for diabetic wounds, and it is reported that callus removal can rapidly reduce pressure by 30%.[37] Although debridement has been found to be efficacious in several clinical trials, its limitations such as unacceptable pain and potential of second trauma are still a concern.[38]

Wound Dressings

Wound dressings are traditional elements of wound care, including natural, modified or synthetic materials and therapeutic substances. Diabetic wounds are heterogenous, and there is no single dressing that has been reported to be ideal for all wound types.[39] An ideal wound dressing should provide a moist environment that promotes granulation, revascularization, keratinocyte migration and tissue regeneration.[40] It is a substantial challenge to develop an efficient wound dressing, and many dressings has been created with novel bioengineering technology. However, current designed dressings face various problems, such as cellular toxicity, allergic reactions, decreased angiogenesis and physiological rejection.

Pressure Off-Loading

Pressure off-loading is a widely used treatment for patients with DFUs.[41] The treatment can be distinguished in non-removable, removable and surgical interventions.[42] Several prospective controlled studies have shown that non-removable, pressure off-loading casts are more effective, and a combination with surgical interventions (e.g., Achilles tendon lengthening) can achieve more successful outcomes.[43]

Revascularization

Peripheral arterial disease (PAD) is the most common early-onset cardiovascular complication of diabetes. PAD is also one of the strongest predictors of developing chronic wound and increasing risk of dying from cardiovascular disease. It has been reported that PAD occurs in 40% of patients with DFUs.[44] One of the most common treatments of PAD is revascularization. Both pharmaceutical methods and surgical technologies (angioplasty, endarterectomy, grafting or bypass) can be performed to achieve revascularization.

Treatment of Wound Infection

Infection is common in wound healing progress, especially in diabetic patients. Antimicrobial therapy is a common method of wound infection, but it is not always necessary and does not apply in clinically uninfected wounds.[45] Treatment of diabetic wound infection has been outlined by the IDSA, which recommends treatment of wounds with two or more signs or symptoms of inflammation (erythema, fever, tenderness, pain and induration) or purulent discharge.[46] Due to antibacterial resistance and improper use of antibiotics, treatment of DFU infection can have adverse outcomes. The strategy of applying narrow spectrum antibiotics within a short period can reduce healing time and amputation rate. Besides oral or intravenous administration of antibiotics, nanomaterial-based systems have emerged as a promising method for antibiotic delivery, which improve therapeutic index and avoid antibacterial resistance.[47]

General Measures

In addition to medication and surgical treatment, good glycemic control is a very important general therapeutic method for DFU. Patients should also pay attention to normalization of blood indicators, the management of blood fat, drinking and smoking cessation and diet control.[48] Since hyperglycemia plays the most important role in DM pathology, good blood sugar control can not only have a positive effect on DFU outcomes but also delay the onset of other complications of diabetes.[49] Also, several observational studies have found that there is a linear correlation between appropriate nutrition supplement and DFU prognosis.[50]

Substances

The pathological process of diabetic wound healing includes complex changes and some key factors associated with successful healing are in disorder. Thus, various substances should be applied to support this progress. Substances loaded

in NDDSs for diabetic wound healing can be classified into two categories: bioactive molecules and non-bioactive substances.

Bioactive Molecules

Growth Factors

Growth factors are multi-functional polypeptides, which bind to specific, high-affinity cell membrane receptors to mediate, coordinate and control cellular interactions.[51] Growth factors can stimulate cell proliferation and differentiation to benefit overlapping phases of wound healing and accelerate this process.[52] The transforming growth factor (TGF-β) superfamily has mainly three isoforms, TGF-β1, β2 and β3, and TGF-β1 has been recognized as a key modulator of cutaneous wound healing. Preclinical studies showed that low expressions of TGF-β1 and TGF-β2 reduced scar formation and improved dermal architecture.[53] The vascular endothelial growth factor (VEGF) acts as a signaling mediator in neovascularization.[54] By interacting with VEGF receptors (VEGFR) to stimulate downstream signaling cascades, VEGF controls fibroblasts and endothelial cells function and promotes their proliferation.[55] The platelet-derived growth factor (PDGF), mainly secreted from platelets, mediates wound healing throughout all phases. PDGF targets dermal fibroblasts and many other cells to promote collagen synthesis and dermal regeneration. The epidermal growth factor (EGF) activates downstream signaling pathways and induces cell migration and proliferation. EGF interacts with keratinocytes to promote their migration, which is crucial for the re-epithelialization process.[56] The fibroblast growth factor (FGF) can promote endothelial cell migration and smooth muscle cell proliferation. Among the subfamilies of FGF, FGF2 has been applied for scarless wound healing.[57]

An impaired balance of many growth factors and disturbance of various cellular responses mediated by GFs have been reported in chronic non-healing wounds.[58] Therefore, locally applying exogenous growth factors can achieve positive outcomes of wound injury treatment.[59] There are medications containing recombinant human EGF (rhEGF) that are commercially available and have been used in clinical treatment, such as Heberprot-P®,[60] Regen-D™ 150, and Easyef®.[61] Many studies have suggested that the function of GFs is spatially related,[62] however conventional systems lack the ability to control the release of GFs spatially and temporally. Currently, various sophisticated delivery systems for delivery growth factors have been reported for diabetic wounds (Table 1).[63–70]

Table 1 Delivery of Growth Factors with Nanocarriers

GFs	Carriers	Function	Merits	Refs.
EGF	PHBV-GelMA hybrid patch	Promote the migration and proliferation of multiple types of cells (keratinocytes, fibroblasts and endothelial cells) and enhance angiogenesis.	Good biostability	[64]
EGF	Chitosan nanoparticles	Induce thorough re-epithelialization, sufficient collagen deposition, and accelerated collagen maturation.	Good biocompatibility	[63]
bFGF	Decellular dermal matrix	Enhance granulation tissue formatting, angiogenesis and collagen deposition.	Good endothelial inducibility	[65]
rhEGF	Nanofiber scaffolds	Induce faster wound healing activity in dorsal wounds.	Electrospinning fibers; prolonged the release of GFs	[66]
EGF	Chitosan/PVA hetero-composite hydrogel	Reduce inflammatory response, faster collagen deposition, and advanced collagen maturation.	Release EGF and PHMB in ion-rich environment	[67]
PDGF-BB	Nanohydrogel	Destruct biofilm.	Destruct the biofilm; keep stable structure at room temperature	[70]
rhEGF	Sodium carboxymethyi chitosan nanoparticles	Exhibit more stability against proteolysis and preserve biological activity.	Increasing GFs proteolytic resistance	[69]

EGF has an excellent mitogenic effects on epithelial, fibroblastoid and endothelial cells.[68] It is interesting to note that the complex microenvironment of DFU is hostile for the production and secretion of EGF and exhibits downregulation of EGF and its receptor.[71] Current challenges facing the additional EGF treatment is short half-life and repeated administration.[72] A hybrid biomaterial patch is a promising approach for loading the GFs.[73] Auguastine et al[64] encapsulated EGF in porous nanofiber membranes and hybrid with GelMA hydrogel to form a biodegradable polymeric patch for diabetic wound healing.

Genes/Proteins/Peptides

A gene therapy involves transfection of specific genes to correct genetic disorders. Diabetic wound environments have a complicated genetic disorder, and manipulating gene levels can be promising for the non-healing wound. Several studies have showed microRNAs (miRNAs) regulate post transcriptional gene expression and can be a promising nucleic acid drug for diabetic wound.[74] Recently, miR-129 and −335 have been identified as a negative regulator of MMP-9 expression by targeting specific protein-1 (Sp1).[74] Gene therapy faces many challenges, transfection via virus has carcinogenic potential.[75] Rapid degradation and repeated administration of gene therapy agents (e.g., nucleic acids, proteins, peptides) can amplify the adverse effect. NDDSs can provide a system for better circulating concentration and precise modulation at the target site. Yan et al[76] reported milk-derived exosomes to deliver miRNA, which are fabricated through electroporation and achieved higher cell uptake and were able to resist degradation.[76] In vivo results showed this novel system promoted angiogenesis and enhanced diabetic wound healing.[76] Small interfering RNA (siRNA) mainly involves the RNA interference (RNAi) phenomenon and induces gene silencing post-transcriptionally.[77] Shaabani et al[78] formulated siRNA into a layer-by-layer platform with a tunable outer surface to increase angiogenesis factors in diabetic wound area. They focused on the stabilization of HIF-1α, which is crucial for activating angiogenesis factors. Layer-by-layer self-assembled siRNA-loaded nanocarriers can delivery siRNA downregulating PHD-2 to stabilize HIF-1α and then increase pro-angiogenic factors level. The report also found these layer-by-layer nanoparticles can prevent endosomal escape and improve transfection efficiency. Currently, various nanocarriers loaded gene therapy agents have been reported. See Table 2[78–96] for other systems.

Table 2 Delivery of Genes/Proteins/Peptides with Nanocarriers for Diabetic Wound Healing

Cargos	Carriers	Functions	Refs.
Keap1 siRNA	Lipoproteoplex (LPP) nanoparticle	Restore Nrf2 antioxidant function; accelerate diabetic tissue regeneration, and augment reduction-oxidation homeostasis in the wound environment.	[79]
MMP-9 siRNA (siMMP-9)	Hyperbranched cationic polysaccharide derivatives (HCP); hydrogel based on Pluronic F-127 (PF) and methylcellulose (MC); chitosan nanoparticles	Reduce MMP-9 expression, and improve diabetic wound closure.	[80,81,196]
siRNA-29a gene	HA-PEI nanoparticles	Accelerate the diabetic wound healing, angiogenesis factors (α-SMA and CD31) production; inhibit pro-inflammatory factors (IL-6 and TNF-α).	[82]
siRNA (downregulation of PHD-2)	Gold nanoparticles (AuNPs)	Improve the endosomal escape of siRNA; induce PHD-2 silencing in fibroblasts; allow upregulation of pro-angiogenic pathways.	[78]
Dicer substrate small interfering RNA (DsiRNA)	Gold nanoparticles (AuNPs)	Enhance PGE2 production and vascularization; improve vascularization by inhibiting PGT gene expression.	[83,84]

(*Continued*)

Table 2 (Continued).

Cargos	Carriers	Functions	Refs.
MicroRNA (miRNA) miR-31-5p	Milk-derived exosomes	Promote the proliferation, migration, and angiogenesis of endothelial cell.	[76]
miR146a	Cerium oxide nanoparticles (CNP)	Scavenge free radical, inhibit NFκB pathway, anti-inflammation performance.	[93]
LncRNA-H19	High-yield extracellular vesicle-mimetic nanovesicles (EMNVs)	Neutralize the regeneration-inhibiting effect of hyperglycemia.	[85]
Antimicrobial peptide (LL37)	Ultra-small gold nanoparticles	Enhance cellular and nucleus entry to achieve high gene delivery efficiency.	[86]
Bioactive peptides	Chitosan NPs	Shorten the inflammatory stage and promote neovascularization.	[87]
P311 peptides	Micelles	Ros-trigged P311 release to reduce oxidative stress and inflammation.	[94]
CCN1	Nanoformulation	Increase CCN1 intracellular expression, decreses inflammation.	[95]
PDGF-BB proteins	Fibrin-based hydrogel	Induce angiogenesis and arteriogenesis.	[88]
L-Glutamic acid	Chitosan (CS) hydrogels	Accelerate vascularization and macrophage recruitment.	[89]
Neurotensin (NT)	Polylactide-polyglycolide (PLGA) and cellulose nanocrystals (CNCs) (PLGA/CNC) nanofiber membranes	Induced more rapid healing; decreased the expressions of the inflammatory cytokines IL-1β and IL-6.	[90]
Recombinant human collagen type III (rhCol III)	PDA@Ag NPs	Promote the proliferation and migration of mouse fibroblasts and endothelial cells; promote the expression levels of basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF).	[91]
Recombinant human thrombomodulin (rhTM)	Nanostructured lipid carrier (NLC)	Improve wound healing and cell migration.	[92]
VEGF-A mRNA	Ionizable lipid-mediated nanoparticles (LNP)	Upregulate VEGF-A expression, expedite healing progress.	[96]

Stem Cells/Exosomes

Stem cells (SCs) are a class of cells with multiple differentiation potential and self-renewal ability, and their main features are pluripotency, indefinite division and the ability to promote cytokines secretion.[97] Due to their immunomodulatory properties and easily controlled dosage, stem cells therapy has flourished in the field of regenerative medicine and wound healing.[98] The mesenchymal stem cells (MSCs) can be derived from various sites, and their ability of multilineage differentiation makes them good candidates for wound healing. Their immune response properties should be considered, and studies have showed that the immune modulation can enhance wound healing.[99] Most of the MSCs are derived from bone marrow, compared with MSCs, the adipose-derived stem cells (ADSCs) are less invasive and have no ethical limitations. ADSCs can differentiate to endothelial cells and secrete VEGF to promote wound healing.[100] Although many studies have showed that stem cell therapy can improve skin regeneration, their poor survival rate and proliferation capacity shrink their application efficiency. Thus, the mixture of SCs or stem cells exosomes (SCs-exos) with finely-designed NDDSs could be an ideal strategy. Xu et al[101] developed an injectable hydrogel with hyperbranched

PEG macromer for stable delivery of ADSCs that promote tissue regeneration. Moreover, hypoxia-induced conductive hydrogel incorporating ADSCs can promote the reconstruction of blood vessels, hair follicles and dermal collagen matrix.[102] However, stem cells face some limitations such as issues of storage and transportation and risks of tumor formation.[103] Exosomes are 40–100 nm sized extracellular vesicles, derived from paracrine secretion of most cell types.[104] With stable and easily stored characteristics, they can overcome limitations of stem cells therapy.[105] See Table 3[8,106–113] for more information.

Yang et al[111] reported Pluronic F127 hydrogel loaded with human umbilical cord-derived mesenchymal stem cell-derived exosomes (hUCMSC-exos). This delivery system efficiently delivered hUCMSC-exos and promoted diabetic wound healing. It can also increase expression of proliferating cells related signals, enhance granulation tissue formation and upregulate growth factor expression.

Thus, biomaterial-based exosomes therapy holds great promise in cutaneous wound treatment and regenerative medicine.[114]

Table 3 Stem Cell/Exosomes Loading Nanomaterial for Diabetic Wounds

Stem Cells/ Exosomes	Delivery Systems	Functions	Models	Refs.
BMSCs	Nanofiber scaffolds; human epidermal growth factor-curcumin bandage bioconjugate (EGF-Cur B); N-chitosan/HA-ALD hydrogel	Promote granulation tissue formation, angiogenesis, and collagen deposition, and switch the immune responses to the pro-regenerative direction; stimulate secretion of growth factors from bone marrow mesenchymal stem cells (BM-MSCs) and regulate the inflammatory environment by inhibiting the expression of M1 macrophages and promoting the expression of M2 macrophages	Cutaneous wounds of streptozotocin-induced diabetic mice	[8,106,107]
ADSCs	Injectable hydrogels	Promise regenerative capabilities; promote the reconstruction of blood vessels, hair follicles, and dermal collagen matrix.	STZ-induced mice	[101,102]
Gingival mesenchymal stem cells (GMSCs)	Chitosan/Silk hydrogel sponge	Promote the re-epithelialization, deposition and remodeling of collagen by enhancing angiogenesis and neuronal ingrowth.	STZ-induced mice	[108]
hFDSPC	HA	Improve re-epithelialization, angiogenesis, anti-inflammation, collagen regeneration, and maturation.	STZ-induced mice	[110]
Mesenchymal stem cells (MSCs)	ADM-RGO composite scaffolds	Support robust vascularization and collagen deposition as well as rapid re-epithelialization during diabetic wound healing.	STZ-induced rats	[109]
hUCMSC-exos	Pluronic F-127 (PF-127) hydrogel	Efficient delivery of hUCMSC-exos; accelerate wound closure rate.	STZ-induced rats	[111]
Platelet-rich plasma exos	Chitosan/Silk hydrogel sponge	Accelerate vascularization and collagen deposition.	STZ-induced rats	[112]
MSC s	PLGA NPs	Induce capillary construction and collagen deposition.	STZ-induced mice	[113]

Drugs

A wide range of drugs have been proved to exhibit significant efficacy for wound healing. The nanoscale local drug delivery system, as an ideal carrier, has been fabricated to overcome the limitations (such as low physico-chemical stability, low bioactive absorption, poor pharmacokinetics etc.) of these drugs (Table 4).[10,111,115–131]

Curcumin is a natural polyphenol obtained from turmeric.[132] This natural bio-substance is often used as an antioxidant and anti-inflammatory agent, and can aid various stages of the wound healing process.[133] However, just like other small hydrophobic molecules, curcumin shows low stability in wound healing treatment, especially for topical

Table 4 Delivery of Drugs for Efficient Diabetic Wound Healing

Drugs	Carriers	Functions	Merits	Refs.
Curcumin	1. Injectable hydrogel; 2. hyaluronic acid (HA) and chitosan-based hydrogel (OHA-CMC); 3. Gelatin microspheres (GMs); Curcumin-micelles; 4. Polycaprolactone-/polyvinyl alcohol-silk fibroin based electrospun nanofibrous mat	Increase angiogenesis and collagen deposition; alleviate inflammation and oxidative stress.	Good swelling properties; a controlled release profile	[111,120,125,126,185]
Insulin	pH and glucose dual-responsive injectable hydrogels; PLGA nanofibrous scaffolds	Promote neovascularization and collagen deposition and enhance the wound-healing process.	pH and glucose dual-responsive; core-shell structure	[115,187]
Quercetin (QCN)	Topical hydrogel system	Improved scratch-wound recovery of keratinocytes and fibroblasts.	Highly skin-permeable; topical delivery of QCN and oxygen	[116]
Huangbai liniment (Compound Phellodendron Liquid, CPL)	Silk fibroin (SF) /poly-(L-lactide-co-caprolactone) (PLCL) (SP) nanofiber membrane	Increase the expression of the TGF-β signaling pathway and collagen during wound healing, inhibits the expression of pro-inflammatory factors.	Increased drug concentration; inhibitory effects for *S. aureus* and *E. coli*.	[117]
Dimethyloxalylglycine (DMOG)	Porous electrospun fibrous membrane	Improve neo-vascularization, re-epithelialization and collagen formation.	Aligned porous; controllable released DMOG drugs from the membranes	[118]
Hyaluronan oligosaccharide	pH-responsive calcium alginate hydrogel	Promote angiogenesis; enhance expression of vascular endothelial growth factor.	Multifuctional	[119]
Antidiabetic agents (metformin, pioglitazone, glibenclamide)	Nanofibrous scaffolds	Lower proinflammatory cytokine levels; improve neutrophil infiltration, edema, and inflammation and increased epidermal regeneration and fibroblast proliferation.	Stimuli-responsive metformin release; multifunctional	[10,122]
Antibiotic agents (cephradine, ciprofloxacin, gentamicin)	Fibrous mats; nanocomposites	Efficient bacterial clearance; induce faster chronic wound healing.	Provide strong bacteria adhesion; destroy biofilm	[121,124,137]
Gallic acid	Microneedle patch	Scavenge reactive oxygen species, promotes antioxidation.	Transdermal delivery and combination therapy	[123]
Clindamycin	Ceria nanoparticles (CNP)	Antibacterial effect, scavenge ROS.	ROS responsive; apply drugs conjugated CNP to treat DFU	[127]
Gentiopicroside (GPS) and Thymoquinone (TQ)	m-PEG/PVP nanofibers	Antibacterial effect, achieve better skin architecture.	Could be fabricated via electrospinning method	[128]
Berberine	Polyvinyl alcohol (PVA), sodium alginate (Alg) based nano-colloids hydrogel	Promote wound healing, inhibit NF-κB, TNF-a	Intracellular mechanism has been demonstrated: activating Sirt 1/NF-κB pathway	[129]
Resveratrol	Resveratrol-laden nanoparticles	Antioxidant effect, reduce macrophage iNOS level.	Two drugs synergetic effects, sustained drug release	[130]
Asiaticoside	Polymeric nanoparticles	Increase collagen biosynthesis, enhance COL-1 protein level.	Obtain ideal drug release kinetics, improve intra-cellular uptake	[131]

application.[134] Liu et al[125] enclosed self-carried Cur nanoparticles (CNPs) in gelatin microspheres (GMs), which can respond to the overexpression of MMP-9 in the wound environment, and the CNPs@GMs have been loaded into a thermo-sensitive hydrogel to facilitate the healing process. Recently Hu et al[120] reported a hyaluronic acid (HA) and chitosan-based hydrogel (OHA-CMC) for loading and delivering CNPs. Benefiting from the encapsulated CNPs, this formulation exhibited excellent antioxidant and anti-inflammatory ability and presented on-demand drug release. Antidiabetic agents such as metformin (MET), pioglitazone (PHR) and glibenclamide (GB) have been confirmed to exhibit strong anti-inflammatory effects, which can be applied in the research of accelerating diabetic wound healing. Cam et al[10] loaded three types of oral antidiabetic agents into nanofibrous scaffolds based on two different polymer composites mixtures (CS/GEL/PCL and PVP/PVL), to improve type I diabetic wound healing. In a previous study, Cam et al[122] have confirmed PHR loaded fibrous mats have high potential for targeting inflammatory and proliferation phases of DFU; in follow-up studies, they further demonstrated that PHR&MET and PHR&GB exhibited better healing rate then single usage of PHR.

Non-Bioactive Substances

Metal Ion

Metal ion nanoparticles have attracted extensive attention as an appreciable option to antibiotics.[135] Among various metallic elements, silver (Ag) is the most studied for its strong and long-lasting antibacterial properties against various pathogens and microorganisms.[136] Though the inherent mechanisms of AgNPs antibiotic ability are still unclear, it is recognized that AgNPs can destroy the cell wall or cell membrane. Wang et al[137] showed that Ag nanocubes with a virus-like mesoporous silica coating improved cell wall adhesion and completely eradicated pathogenic bacteria in the wound site. Gold (Au) nanoparticles are also reported as an anti-infection agent. Their inert and nontoxic nature makes them an ideal material as the core of NPs. Researchers have demonstrated AuNPs can strongly resist both Gram-negative and Gram-positive pathogens and do not develop drug resistance.[138] Currently, copper NPs (CuNPs) are drawing considerable attention as antibiotic agents for wound healing. Their high redox potential makes them effective against a broad-range spectrum of bacterial species, and they have relatively low cost compared with Ag and Au.[139] Our review gives more information of metal ion nanoparticles in the drug delivery system section.

Oxygen

With more in-depth understanding of the mechanism of chronic wound healing progress, a prolonged hypoxic environment has been confirmed as one of the causes of healing impediment.[140]

Several advanced treatments for proper oxygen supply are currently available on the market, such as hydrofiber® dressings.[141,142] Nanomedicine have been introduced to fabricate oxygen-releasing systems, and scientific studies have emerged to design and fabricate tunable platforms in terms of controlling oxygen supplementation.[29] Currently, various oxygen-containing nanocarriers have been shown to reverse the hypoxic environment of diabetic wounds (Table 5).[9,11,12,67,143–154]

Table 5 Delivering Oxygen/NO for Diabetic Wound Treatment

Materials	Carriers	Functions	Refs.
Oxygen	Microspheres	Augment the survival and migration of keratinocytes and dermal fibroblasts; promote angiogenic growth factor expression and angiogenesis.	[144]
Calcium peroxide	OxOBand	Facilitate faster wound closure, enhance collagen deposition, faster re-epithelialization, increased neo-vascularization, and decreased oxidative stress.	[145]

(*Continued*)

Table 5 (Continued).

Materials	Carriers	Functions	Refs.
Sodium per carbonate (SPC)	Plycaprolactone (PCL)-based nanofibers	Pronounce expression of HIF-1α; improve angiogenesis.	[11]
QCN oxygen	Nanoemulsion (NE)	Accelerate wound-healing.	[116]
Perfluorocarbon emulsions	Chitosan nanoparticles	Alleviate hypoxia conditions on diabetic wounds.	[67]
MnO2	Dex-SA-AEMA (DSA) hydrogel; crosslinking hydrophilic poly(PEGMA-co-GMA-co-AAm) (PPGA) polymers with hyperbranched poly-L-lysine (HBPL)-modified nanosheets	Convert the endogenous hydrogen peroxide (H_2O_2) into oxygen (O_2). Reduce oxidative stress, decrease ROS level, shorten inflammatory phase.	[9,146]
Oxyhemoglobin/hydrogen (HbO2/H2O2)	MXene nanosheets	Keep the intracellular redox homeostasis and alleviate oxidative stress.	[147]
S-Nitroso-N-acetylpenicillamine (SNAP)	Hitosan/polyvinyl-alcohol hydroge; GelMA hydrogel	Continuous cell-proliferating activity; speed up the healing process; upregulate of VEGF and SDF-1α biomarkers.	[148,149]
Nitric oxide (NO)	Copper-benzene-1,3,5-tricarboxylate HKUST-1;dinitrosyl iron complexes (DNICs)	Promote a more accurate and deeper delivery of NO molecules into the wound site.	[12,150,151]
Glucose oxidase (GOx)	Ceria nanozymes; Zn-MOF nanoparticle	Reduce hydrogen peroxide level, regulate the oxygen balance.	[152,153]
ZnO	Nanofibers	Sustained release two bioactive agents.	[154]

Sodium percarbonate (SPC), as a strong oxidant, has been found to be a potential oxygen-generating agent to accelerate healing in a chronic non-healing wound. Oxygen generation of SPC is peroxide-based, releasing hydrogen peroxide in water solution and ultimately oxygen on decomposition.[143] Zehra et al[11] reported a PCL polymer-based dressing, which encapsulated oxygen generator SPC to improve the hypoxia in wound site. Their results showed that the novel dressing could release sufficient oxygen at the wound site for a long period and significantly improve angiogenesis.

However, reactive oxygen species (ROS) is another existing form of oxygen element in the wound microenvironment, and abnormally high levels of ROS can inhibit wound healing processes and cause a non-healing wound. Recently, nitric oxide (NO), as an important ROS scavenger, is considered to play a pivotal role in healing process pathology of diabetic wounds. Hyperglycemic conditions in the diabetic wound environment can inhibit the synthesis of endogenous NO. Topical NO delivery have received more and more attention, and there are several donors that have been investigated for NO delivery such as organic nitrates and nitrites, metal-NO, diazeniumdiolates (NONOates) and S-nitrosothiols (RSNOs).[155] Zhang et al[12] recently developed HKUST-1, a novel MOF system with unsaturated Cu metal site, to deliver NO. With highly designable structure, the nanomaterial scaffold released NO with an ideal concentration and promoted angiogenesis and collagen deposition.

Nano-Drug Delivery System

NDDSs refer to drug delivery systems with particle diameter within the nanoscale, which have the feature of improving drug stability, sustained release and controlled release of drugs, and they can be fabricated with a variety of biomaterials.[156] An unprecedented number of NDDSs loading therapeutic agents have emerged and these are being used in diabetic wound treatment. NDDSs can be classified into liposomes, polymeric nanoparticles, inorganic nanoparticles, lipid nanoparticles, nanofibrous structures and nanohydrogel (Figure 3).

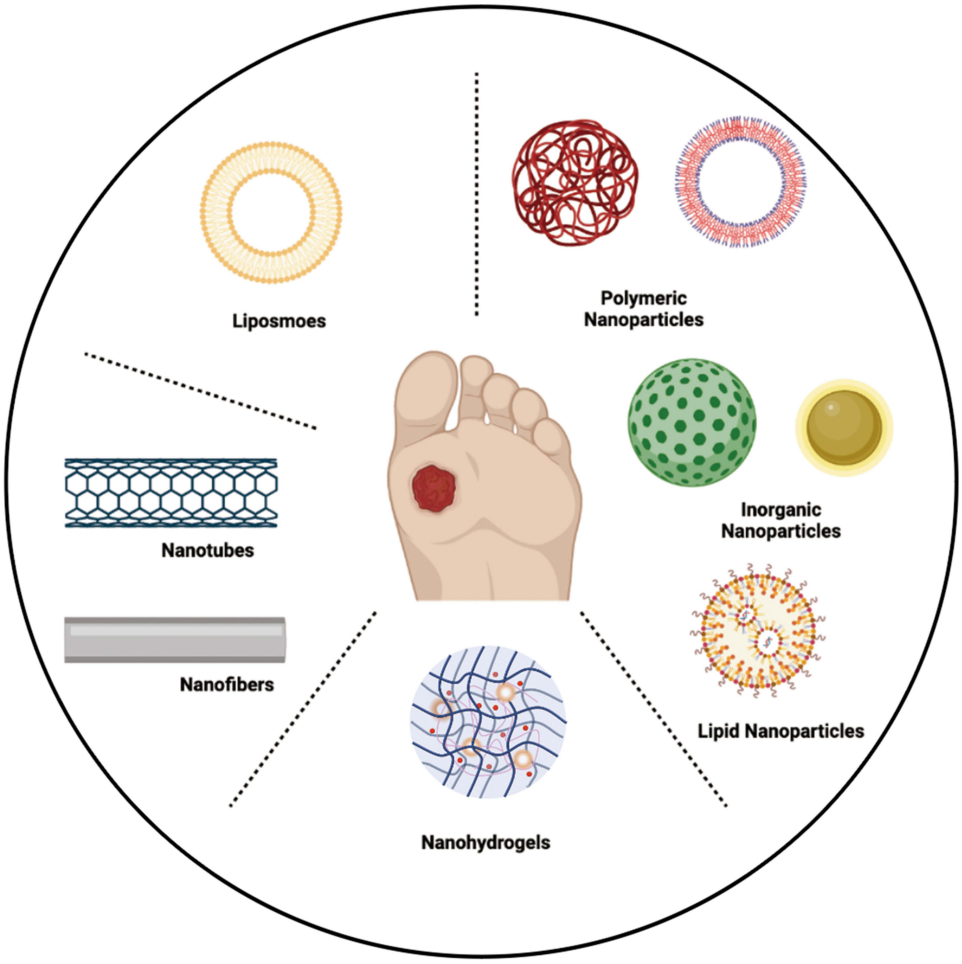

Figure 3 Schematic representation of nano-drug delivery system used for diabetic wound healing: Liposomes, Polymeric nanoparticles, inorganic nanoparticles, lipid nanoparticles, nanofibers, nano-hydrogels. (figure was created with BioRender.com).

Liposomes

Liposomes are artificial membranes mainly composed of amphiphilic molecules, which form a bilayer structure similar to the structure of skin cell membranes. With drugs encapsulated in the hollow part of the lipid-like bilayer, liposomes are advanced nano-carriers for drug delivery.[157]

With their intrinsic merits such as biodegradability, lower systemic toxicity and targeted delivery, liposomes have been universally applied in drug delivery and made their way to the market.[158] A total of 14 liposome products have been approved for marketing.[159] These liposomal products are primarily focused on oncology treatment. Currently, increasing novel liposomes with modified surfaces are springing up to cover the shortage of conventional vesicles in the field of chronic wounds.[160]

Chhibber et al[161] prepared a novel liposome which efficiently entrapped bacteriophages. The vehicles remarkably improved phage persistence in situ. The results showed that liposomal entrapment of phage cocktail significantly reduces wound bioburden, accelerates wound contraction and speeds tissue healing. It was fully confirmed that the liposome entrapped with phage cocktail overcomes the major drawback of phage therapy and addresses a *Staphylococcus aureus*-induced chronic wound infection.

Rabbani et al[79] reported a lipoproteoplex (LPP) siRNA delivery vehicle, targeting the Keap1/Nrf2 pathway associated with impaired diabetic wound pathology, thereby promoting wound healing. A stable LPP nanoparticle is produced of a cationic lipid nanoparticle (CLN) as a primarily lipid-based vehicle, and a cationic engineered supercharged coiled-coil protein (CSP) has been engineered to enhance transfection efficacy. The novel system overcomes traditional challenges

facing RNAi therapy, which uses lipid or peptide alone as siRNA delivery vehicles. The results showed that LPP complexing siKeap 1 restored Nrf2 antioxidant function, augmented reduction-oxidation homeostasis in the wound area and accelerated diabetic tissue regeneration.

Although liposomes are a well-studied drug delivery system, its application on transdermal drug delivery is limited since they are unable to penetrate through the deep layers of skin. The rigid structure of the conventional liposomes makes them stay in the stratum corneum (SC) layer and achieve low drug delivery efficiency.[162] Deformable liposomes, as a new generation of liposomes, have been developed to overcome this limitation.[160] They are generally prepared by embedding edge activators, such as surfactant and ethanol, into traditional liposomes, which can destabilize the original lipid layers to achieve a flexible membrane. With a high flexibility, deformable liposomes can change the homeostasis of the cells in the stratum corneum and squeeze into the deeper viable epidermis.[163,164]

Polymeric Nanoparticles

Polymeric NPs are colloidal systems that are biocompatible and have simple formulation parameters.[165] Drugs embedded or conjugated with biodegradable polymers can achieve lower degradation rates and release in a controlled manner in the wound area. These merits make polymeric nanoparticles draw increasing attention in the nano-drug delivery system field.[166] Polymeric nanoparticles possess a core-shell structure with drugs encapsulated in the core and hydrophilic polymeric outer surface which provides stearic stability.[167] Currently, the preparation of polymeric nanoparticles is majorly based on polylactic-co-glycolic acid (PLGA), polyglycolic acid and other synthetic polymers, as well as natural polymers (alginate, gelatin, chitosan, etc.).[168]

To overcome the low solubility and the high susceptibility to oxidation of melatonin, Lopes et al[169] incorporated melatonin into a lecithin-chitosan nanoparticles for diabetic wound healing. The particle size of MEL-NPs was within proper nanoscale (160 nm), and the therapeutic melatonin was efficiently entrapped in the nanocarrier. The study concluded that the MEL-NPs delivery system can improve pharmacokinetics of melatonin, thus promotes the vascular system and accelerates re-epithelization and angiogenesis. Polymeric nanoparticles obtain a low viscosity and dispersion ability due to their intrinsic structure, which makes them unsuitable candidates for topical administration. To ease the application of polymeric nanoparticles on topical treatment, Bairagi et al[170] have developed ferulic acid nanoparticles and converted the nano-system into hydrogel. The ferulic acid with antidiabetic and antioxidant properties was encapsuled in PLGA by nano precipitation method, and then the drug-loaded NPs were mixed into hydrogel for topical treatment. The results showed that diabetic wounds treated with FA loaded polymeric nanoparticles achieve faster epithelialization, significantly increasing hydroxyproline content. It is confirmed that FA-PLGA nanoparticles overcome the pharmacokinetic limitations of FA and significantly promote diabetic wound healing.

Inorganic Nanoparticles

The main component of inorganic nanoparticles are inorganic materials, and inorganic substances include metal, carbon and ceramics.[165] Benefiting from various inorganic components and the nanoscale structure, inorganic NPs exhibit better biological behaviors than their macroscale counterparts. Many inorganic NPs achieve great success in antitumor therapy, which highlights their promise in nanomedicine. Therefore, a diverse array of inorganic NPs system has been studied to explore their prospect in the field of diabetic wound treatment.

Quercetin (QCT) is known as free radical scavenger and anti-inflammatory agent, and AgNPs are effective antimicrobial agents. To investigate the synergistic therapeutic performance of QCT and AgNPs, Badhwar et al[171] fabricated QCT loaded Ag nanoparticles and subsequently hybridized the QCT-AgNPs into hydrogel matrices for diabetic wound treatment. Compared with marked Ag-loaded dressings, QCT-AgNPs revealed superior therapeutic efficiency in killing *S. aureus* and *E. coli* and reducing oxidative stress. The histopathological evaluation showed that QCT-AgNPs could significantly reduce the wound gap and promote migration of keratinocytes in DFU models in vivo. Some NDDSs formulations have focused on the synergistic effect of both the inorganic nanoparticles and the encapsulated drugs. Kaur et al[172] fabricated AgNPs loading with insulin to achieve a mutually reinforcing effect of the two components. The IAgNPs exhibited appropriate nano size and structure. When applied to diabetic wounds, it notably stimulated healing activity, which could be explained by downregulating pro-inflammatory factors (IL-6, TNFα) levels at the injured site

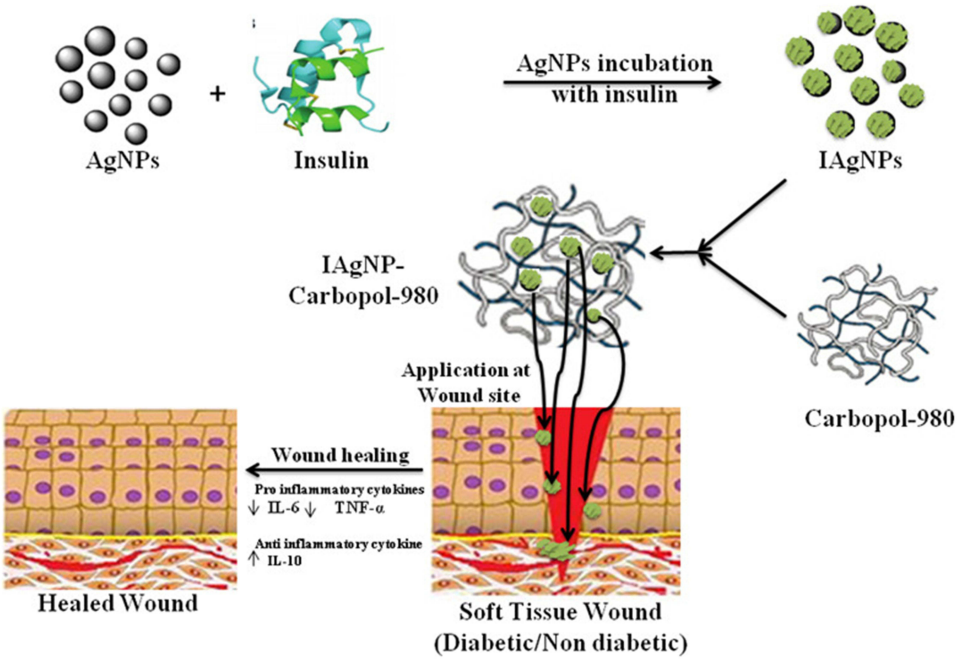

Figure 4 Schematic diagram of wound healing by nano-insulin formulation (IAgNPs). IAgNPs accelerated the wound healing in diabetic conditions by inhibiting pro-inflammatory cytokines and activating anti-inflammatory cytokines.
Notes: Reprinted from *Nanomedicine*, 15(1), Kaur P, Sharma AK, Nag D, et al. Novel nano-insulin formulation modulates cytokine secretion and remodeling to accelerate diabetic wound healing. 47–57, Copyright 2019, with permission from Elsevier.[172]

(Figure 4). Researchers are extending their studies to the blending application of various types of NPs systems to achieve multi-functionality. Choudhary et al[173] developed chitosan-based hydrogel co-encapsulated with fresh blood and nanoparticles (Ca-AlgNps and AgNPs) for diabetic wound healing. The co-encapsulated nanocarrier contributes to much higher closure rate, the Chitosan/Ca-AlgNps/AgNPs hydrogel exhibiting a higher closure rate then separate AlgNps or AgNPs loaded hydrogels. The antimicrobial studies confirmed that Chitosan/Ca-AlgNps/AgNPs hydrogel has broad spectrum antibacterial properties. All the evidence supported that Chitosan/Ca-AlgNps/AgNPs hydrogel might become a potential candidate for diabetic wound healing.

Lipid Nanoparticles

Lipid nanoparticles were generally synthesized by glycerophospholipids, cationic lipids, sterol lipids and PEGylated lipids coated with oligonucleotides.[174] Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) are two representatives of LNPs, and both of them can increase solubility and stability of encapsulating drugs.[175] Recently, researchers have had great interest in application of LNPs in topical treatment.

Arantes et al[176] fabricated SLNs loading with retinoic acid to reduce adverse reactions of the all-trans retinoic acid. The SLN-ATRA were developed through a hot melting homogenization method, and based on the optimized method, SLN-ATRA can be prepared without organic solvents and achieve high encapsulation rate and lower polydispersity index (PDI). The results showed that the SLN-ATRA had superior ability to free ATRA in reducing leukocyte infiltration and accelerating wound closure, collagen deposition and reducing scar tissue when applied on excisional wounds of diabetic mice. In another scientific report, pioglitazone-loaded LNPs were designed, fabricated, then successfully encapsulated into a collagen/chitosan (COL-CS) scaffold.[177] This scaffold possessed optimum porosity, high encapsulation efficiency and low degradation rate. When applied in full-thickness diabetic wounds, it significantly improved the wound contraction rate, and the data of enzyme-linked immunosorbent assay indicated the MMP9 level is decreased. Sun et al[178] reported 20 (S)-protopanaxadiol-loaded nanostructured lipid carriers were successfully incorporated in a silicone elastomer. The results showed that the formulation exhibited remarkable in vitro anti-inflammatory and proangiogenic activity. When applied to diabetic mice with chronic non-healing wounds, it notably achieves an ordered recovery

through suppressing inflammatory infiltration, promoting angiogenesis and increasing collagen deposition. Huseh et al[92] designed and synthesized nanostructured lipid carrier formulations encapsulating recombinant human thrombomodulin (rhTM) for diabetic wound healing. RhTM-loaded NLCs were characterized by much higher encapsulation efficiency and exhibited a controlled drug release behavior for more than 72 h. The in vitro study showed that rhTM-NLC could induce cell migration of keratinocyte cells to promote SC formation. Therefore, this formulation may warrant promising delivery systems for diabetic wound healing. However, LNP systems also have several disadvantages, such as low drug loading and biodistribution, which lead to high uptake to the liver and spleen and limit their application in clinical trials.[179]

Nanofibers

Nanofibers comprise an important class of nanomaterials, and generally have a diameter less than 100 nm.[180] Nanofibers provide many remarkable properties such as large surface area, variable porous rate, great flexibility in selecting materials, and fine fabrication technology.[181] These wonderful features make nanofibers a potential candidate for biomedical application, especially in drug delivery. Electrospinning, as a simple and versatile method, is widely used to format nanofibers.[182] There are a wide range of drugs that can be incorporated into nanofibers, including antibiotics, proteins, DNA, RNA and growth factors.[183] Electrospun nanofibers can achieve high surface to volume ratio, and have different controlled drug release profiles.[182,184]

Agarwal et al[185] prepared curcumin-loaded silk fibroin and combined this nanofiber with polycaprolactone (PVC) and polyvinyl alcohol (PVA) via electrospinning nanotechnology. This nanofiber showed rapid healing efficacy in a streptozotocin-induced diabetic mice wound model. Also, data of the histopathological studies revealed that in vivo the normal skin structure and tissue arrangement were restored in NDDSs-treated group.

Liu et al[186] electrospun sesamol into cellulose acetate-zein (CA/zein) nanofiber membranes to fabricate efficient vehicles for cutaneous wound healing. In vivo observation depicted significant stimulation of myofibroblasts via activating TGF-β signaling pathway transduction. The nanofiber membranes also downregulated inflammatory factors (IL-1β, TNF-α, NOS2) levels and upregulated IL-6 secretion, which promotes keratinocyte growth, and thus enhances wound healing. In some cases, nanofibers were combined with stem cell therapy; Chen et al[106] reported BMSCs-laden 3D scaffolds for a personalized diabetic wound treatment. The 3D scaffolds were electrospun with radially or vertically aligned nanofibers to achieve customizable structures to fit different wounds. The results showed that this nanofiber scaffold can replace damaged skin and act as a temporary barrier and has good biodegradability. Thus, these scaffolds were regarded as a potential customizable platform for managing diabetic wounds. Lee et al[187] developed insulin-loaded PLGA scaffolds via coaxial electrospinning (Figure 5). The core-shell nanofibrous scaffolds were confirmed to feature with better biodegradability, hydrophilicity and water-containing capacity. In vivo study showed

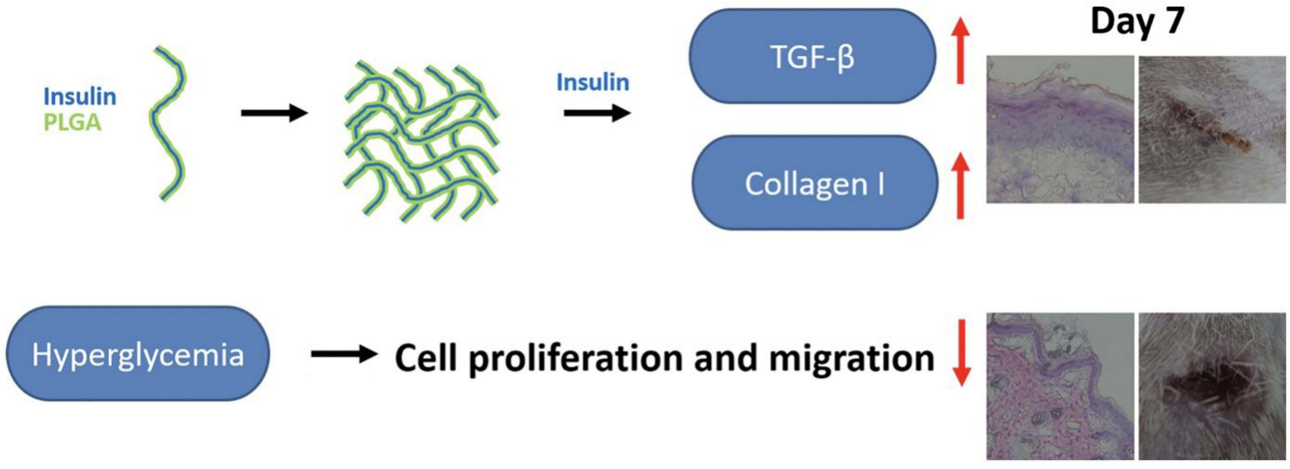

Figure 5 Accelerate the healing wound following treatment using functionally active insulin released from insulin-loaded nanofibrous scaffolds.
Notes: Reprinted from *Nanomedicine*, 24, Lee CH, Hung KC, Hsieh MJ, et al. Core-shell insulin-loaded nanofibrous scaffolds for repairing diabetic wounds. 102123, Copyright 2020, with permission from Elsevier.[187]

that this core-shell nanofiber affects TGF-β expression and promotes diabetic wound repair. Nanofibers delivering more than one drug draw increasing attention as a potential substrate for biomedical application, especially in diabetic wound healing fields. Dwivedi et al[66] reported a novel nanofiber scaffold, which carried the antibiotic agent gentamicin sulfate (GS) and rhEGF. The results of scanning electron microscopy, Fourier transform infrared spectroscopy and X-ray diffraction confirmed that GS was successfully loaded into scaffolds and the rhEGF was covalently immobilized on the surface of the nanofiber scaffolds. In vivo work found that the nano-scaffolds induced faster reepithelialization activity in dorsal wounds of diabetic mice. According to the report of Lee et al,[188] nanofibrous scaffolds were developed with poly(lactide-co-glycolide) (PLGA) loaded with bioactive antibiotics and platelet-derived growth factor (PDGF), and the scaffolds obtained a coaxial sheath-core architecture. The nano-scaffolds were characterized with excellent biocompatibility, and sustainably released vancomycin, gentamicin and growth factor for over 3 weeks. Furthermore, reduced phosphatase and tensin homolog content and enhanced angiogenesis marker (CD31) were detected to provide evidence for benefiting infected diabetic wound healing.

Nanohydrogel

Nanohydrogel is a multicomponent system composed of a polymeric three-dimensional network and water.[189,190] The porous structure endows nanohydrogels with the ability of rapidly swelling and retaining large amounts of water.[167] In recent years, various hydrogel products have been designed in application of drug delivery for accelerating diabetic wound healing.[191] Nanohydrogel provides a moist environment for the wound area, and with soft texture and suitable mechanical strength, it provides a beneficial environment for wound healing.[69,192]

Zhang et al[193] introduced a polyvinyl alcohol (PVA)/alginate (Alg) nanohydrogel encapsulating HUCMSCs-derived exosomes to regulate diabetic wound healing (Figure 6). The results showed that the nanohydrogel significantly facilitates the proliferation, migration and angiogenesis of HUVECs and affects wound healing related molecules (SMA, SR-B1 and CD31). Further investigation revealed that this novel formation accelerated wound healing via regulating ERK1/2 pathway, and thus promoting angiogenesis. A multifunctional hydrogel was reported by Xiong et al[194]

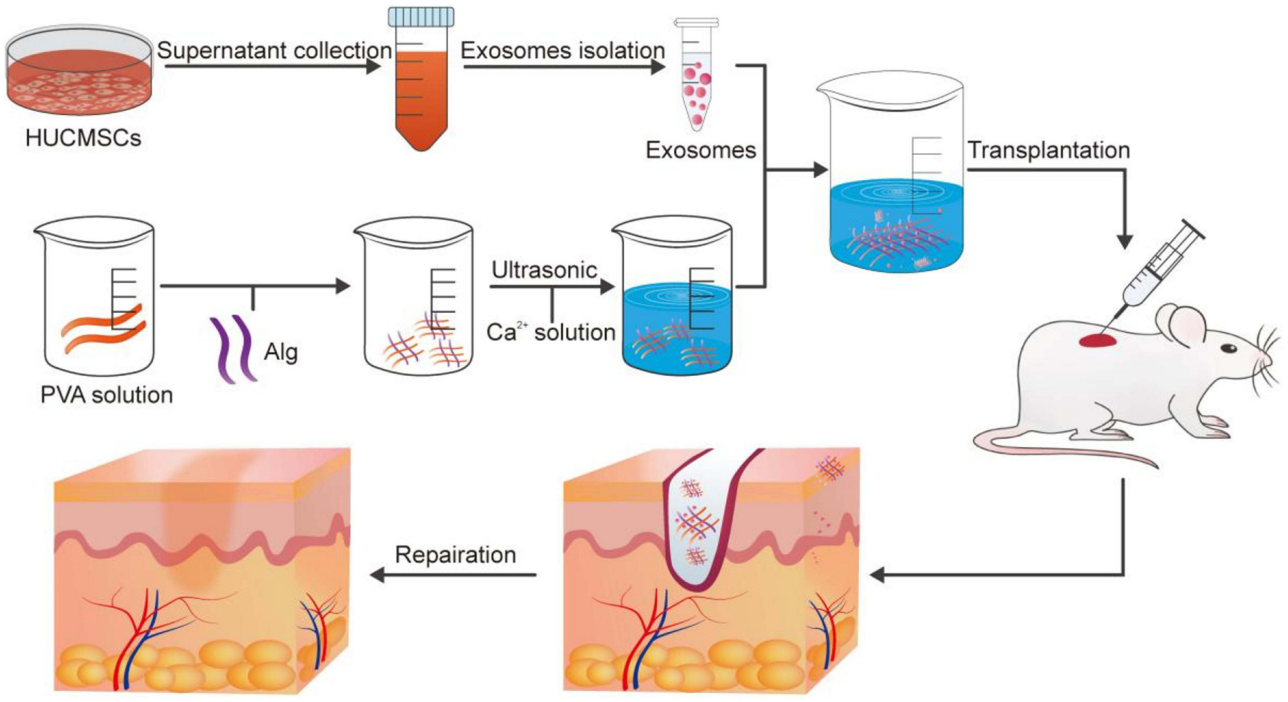

Figure 6 The schematic diagram of the method of making exo@H and the process that exosomes were applied to the wound area and promoted wound healing.
Notes: Reprinted from *Mater Sci Eng C Mater Biol Appl*, 120, Zhang Y, Zhang P, Gao X, Chang L, Chen Z, Mei X. Preparation of exosomes encapsulated nanohydrogel for accelerating wound healing of diabetic rats by promoting angiogenesis. 111671, Copyright (2021), with permission from Elsevier.[193]

to accelerate oxidative diabetic wound healing. This HA-based hydrogel consisted of MnO_2/ε-PL nanosheet, FGF-2 and M2-derived exosomes (M2 Exos). With the addition of MnO_2, this nanocomposite eliminates excess H_2O_2 production and provides O_2 for the wound site. Moreover, specially encapsulated FGF-2 and M2 Exos respectively promote angiogenesis and epithelization. Thus, this hydrogel could be a viable nano-biomaterial for chronic diabetic wound repair. Nidadavolu et al[195] designed a novel peptide-based hydrogel, using nanotechnology to self-assemble valsartan amphiphiles into a filamentous structure (val-filaments). The results of in vivo observation showed the nanohydrogel provided a localized and sustained release of valsartan amphiphiles over 24 days. Moreover, this scaffold downregulated Tgf-β signaling pathway mediators (pSmad2, pSmad3 and Smad4) and increased mitochondrial metabolic pathway intermediates.

Discussion

The treatment of diabetic wounds faces many challenges and new insights are needed in this field. Drug delivery system combined with nanotechnology and biomaterials offers a rich toolbox for the treatment of complex pathophysiology of diabetic wound and tissue repair. In this review, we summarized pathology progress of diabetic wound healing, loading substances of NDDSs and loading systems of NDDSs.

Most of the encapsulated drugs are subject to impaired function of different cells and unbalanced levels of key healing mediator. The understanding of specific molecules function in diabetic wound healing progress facilitates the design of drug delivery systems. However, the etiopathogenesis of diabetic ulcers is diverse and complex, the confirmed positive effect of one therapy on one model might have no effect on other models or individuals.

Recently, novel NDDSs, such as liposomes, nanoparticles, nanofibers and nano-hydrogels loaded with bioactive molecules and non-bioactive elements, have been reported and these studies confirmed NDDSs with therapeutic substances benefit diabetic wound healing. In this context, various smart nano hydrogel system have been investigated, but few of them mention the interactive effect between the carrier and the cargo and horizontal comparison with other types of systems. So, there is still no confirmed conclusion of which system performs the best.

To date, various in vitro and in vivo studies have demonstrated the great therapeutic potential of NDDSs, while most of them illustrate treatment benefits through animal models. Few studies, however, consider the irregular shape and different depths of wounds in clinical patients; the animal models usually include only one condition.

Although there are large numbers of studies focusing on therapeutic potential of NDDSs, effective management of diabetic wound healing remains insufficient. Depending on the current gaps above, researchers need to pay more attention to factors in different angles. First, as in diabetic patients, people develop chronic non-healing wounds often accompanied with unregulated hyperglycaemia and vascular lesions. The ideal NDDSs should load drugs which can ameliorate the basic diabetic pathological conditions, besides drugs that directly accelerate wound healing processes. Also, the interaction between carried drugs and pathological stages should be clearly clarified. Since there is no single substance that can perform best and suits all kind of diabetic wound conditions, future studies should focus on multi-drug systems to provide synergic effects at different stages, especially the application of gene therapy for precise treatment. The methods of NDDSs preparation are also important, so, researchers should build systems with more simple methods for manufacturing and marketing. To complete clinical translation, more preclinical and clinical studies on the benefit on humans should be carried out.

Conclusion

Today, the treatment of diabetic non-healing wounds faces many difficulties. The complex pathological process of diabetic wound healing and various conditions of diabetic patients create obstacles to current treatment results. Many therapeutic agents (GFs, genes, stem cells, drugs, metal ions and oxygen) related to healing stages and mechanisms have been studied to make an equilibrium level of key mediator for better wound healing. The field of drug delivery systems has shown great performance in delivering therapeutic drugs for diabetic wound treatment. Over the past few years, nanomedicine has facilitated the development of drug delivery systems, and various nano-drug delivery systems (liposomes, NPs, nanofibers and nanohydrogel) have been formed to deal with diabetic non-healing wounds.

Overall, the nano-drug delivery system with therapeutic agents can accurately provide agents to the wound site and achieve great therapeutic potential for diabetic wound management.

Abbreviations

DM, diabetes mellitus; DDSs, drug delivery systems; NDDs, nano-drug delivery systems; DFU, diabetic foot ulceration; HBO, hyperbaric oxygen therapy; PCL, polycaprolactone; GelMA, Methacrylate Gelatin; GF, growth factor; ECM, extracellular matrix; MMP, matrix metalloprotein; DN, diabetic neuropathy; PAD, peripheral arterial disease; IDSA, Infectious Diseases Society of America; TGF-β, transforming growth factor-β; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptors; PDGF, platelet-derived growth factor; EGF, epidermal growth factor; FGF, fibroblast growth factor; miRNAs, microRNAs; siRNA, small interfering RNA; RNAi, RNA interference; MSCs, mesenchymal stem cells; ADSCs, adipose-derived stem cells; hUCMSC-exos, umbilical cord-derived mesenchymal stem cell-derived exosomes; CNPs, Cur nanoparticles; GMs, gelatin microspheres; HA, hyaluronic acid; SPC, sodium percarbonate; ROS, reactive oxygen species; NO, nitric oxide; LPP, lipoproteoplex; CLN, cationic lipid nanoparticle; SC, stratum corneum; PLGA, polylactic-co-glycolic acid; QCT, quercetin; SLNs, solid lipid nanoparticles; NLCs, nanostructured lipid carriers; rhTM, recombinant human thrombomodulin; PVC, polycaprolactone; PVA, polyvinyl alcohol.

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Disclosure

The authors report no conflicts of interest in this work.

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