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Topical gel-based biomaterials for the treatment of diabetic foot ulcers

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Abstract

Diabetic foot ulcers (DFUs) are a devastating ailment for many diabetic patients with increasing prevalence and morbidity. The complex pathophysiology of DFU wound environments has made finding effective treatments difficult. Standard wound care treatments have limited efficacy in healing these types of chronic wounds. Topical biomaterial gels have been developed to implement novel treatment approaches to improve therapeutic effects and are advantageous due to their ease of application, tunability, and ability to improve therapeutic release characteristics. Here, we provide an updated, comprehensive review of novel topical biomaterial gels developed for treating chronic DFUs. This review will examine preclinical data for topical gel treatments in diabetic animal models and clinical applications, focusing on gels with protein/peptides, drug, cellular, herbal/antioxidant, and nano/microparticle approaches.

Keywords

Topical; gels; biomaterials; diabetic; wound healing; foot ulcers

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Conflicts of Interest

C.Z. and K.W.L. are founders of Ceria Therapeutics. C.Z. is the Chief Scientific Officer and K.W.L. is the President.

Introduction

According to the Centers for Disease and Control (CDC), as of 2020 an estimated 10.5% of the United States (US) population has diabetes, with over $327 billion in total direct and indirect estimated costs, and an average annual cost of nearly $10,000 per diabetic patient.[1, 2] Globally, the cost of diabetes in 2015 was estimated at $1.31 trillion.[3] Significant disabilities are associated with diabetes, including blindness, diabetic retinopathy, end-stage renal failure, and lower extremity amputations.

Diabetic foot ulcers (DFUs) are a common and severe complication of diabetes and are the most common type of chronic wound in the US.[4–9] DFUs have a global prevalence of 6.3% and are higher in type 2 diabetics (6.4%) than in type 1 diabetics (5.5%). Worldwide, an estimated 9.1 million to 26.1 million people will develop DFUs each year, with a lifetime incidence estimated to be 15–25% for diabetic patients.[10],[11, 12] In 2017, approximately $237 billion was spent on diabetic care and about one third of this cost was attributed to lower extremity complications.[13] Due to associated diabetic neuropathy, DFU patients are often unable to sense and relieve pressure on their extremities which can lead to vascular complications, vascular denervation, and low oxygen supply to the wound area, resulting in impaired healing.[14] There is an associated two-fold increase in mortality after 5 years of living with a DFU compared to diabetics without ulcerations.[15] Unfortunately, many of the contributing factors associated with chronic wounds coexist with other comorbidities, including hypertension, diabetic retinopathy, and smoking history.

DFUs are associated with increased lower extremity amputations.[16] Limb amputations are associated with approximately 50% mortality within 5 years of the amputation.[17–19] DFUs that do heal frequently become wounded again, with a recurrence rate of 40% within one year of the ulcer healing, 60% within 3 years, and 65% within 5 years.[13] The five year mortality and direct costs of care for patients with DFU complications have been comparable to colon cancer, prostate cancer, Hodgkin’s disease, and breast cancer.[20]

Despite increasing prevalence and morbidities associated with DFUs, effective treatment options remain limited. Surgical debridement is a conventional standard of care treatment for DFUs. This process removes necrotic and inflammatory tissue from the wound to promote the acute wound healing process.[21, 22] Forms of debridement include mechanical, which can range from wet to dry gauze dressing changes, pulse lavage, hydrotherapy, and low frequency ultrasound.[23] Other common techniques are pressure off-loading to relieve pressure on wounds located on the base of feet, reduction of edema to improve perfusion, and hyperbaric oxygen to increase arterial oxygen pressure.[21, 24–26] Skin grafts are an effective option for larger sized wounds to provide full epidermal or dermal treatments, but have limitations, including limited donor site availability for autologous grafts and immune rejection for allografts.[27] Bioengineered skin substitutes have been developed using extra-cellular matrix (ECM) and/or cell based strategies to provide protection and prevent further mechanical stress to the wound site, as well as moisture retention, cues and scaffolding for cellular growth, and management of wound exudate.[28–35] Although these substitutes have strong potential, many still have limited application in DFU patients in the clinical setting.[36]

Additional management of DFUs includes treatment of infections with antibiotics, application of dressings to promote a moist wound healing environment, surgery to resolve infections or biomechanical impairments, and restoring vascularization.[21] While various treatment options exist for these wounds and can provide some relief for patients, the statistics cited above demonstrating the current magnitude of this problem highlights the limited effectiveness of these treatments and the substantial need for improved therapies.

Topical treatments are advantageous due to their ease of application when compared to other current treatment approaches. Gels also provide moisture retention to the wound area, which is a critical component to promoting keratinocyte migration, collagen formation, angiogenesis, and reduced scar formation for both acute and chronic wounds (Figure 1).[37–39] The goal of this review is to identify different treatment approaches using topical biomaterial gels for diabetic wound healing in both animal models and clinical trials. This review will focus on chronic diabetic wounds.. Topical biomaterial gels for the purpose of this review are defined as any injectable viscous gel material that can be applied using syringes, pipettes, tubes etc. and are easily applied on the wound. Biomaterial wound dressings and highly cross-linked, preformed hydrogels that require surgical implantation were not included in this review, as these have been extensively covered in other reviews[40–45]

Overview of Normal and Diabetic Wound Healing

Normal (Acute) Wound Healing

Wound healing aims to maintain the barrier function of skin and protects us from deadly infectious diseases.[46] Wound healing involves complex interactions between various cell types, biomolecules, and the ECM. Normal wound healing restores the epidermal layer which has high regenerative potential due to the presence of stem cells in the basal layer. The deep layers of the dermis, however, are not as efficiently healed and thus deeper wounds that penetrate into the dermal layer can result in a loss of tissue structure and strength.[47]

The stages of wound healing are typically categorized into four phases: Hemostasis (Clotting), Inflammation, Proliferation (tissue formation), and Re-epithelialization (regeneration of the epidermis)/ Tissue Remodeling (Figure 2). Each phase of wound healing does not exist on its own and has significant overlap with other phases.[48, 49] The first stage of wound healing seals the wound and reestablishes a barrier by forming a blood clot. Hemostasis occurs immediately after the injury and lasts for hours to days. Aggregated platelets within the platelet plug release growth factors such as platelet derived growth factor (PDGF), transforming growth factor-beta (TGF-β), epidermal growth factor (EGF), insulin-like growth factor (IGF) and various cytokines to recruit other cell types to the wound site. The initial phases of wound healing require multiple cytokines and chemokines to promote growth factors and activation of dermal repair mechanisms.[50] Homeostasis concludes with the activation of the coagulation cascade and the conversion of fibrinogen into fibrin, providing increased stability to the previously formed platelet plug and a scaffold for infiltrating cells.

The inflammatory phase begins with neutrophils accumulation in the wound to clear foreign substances and release granules for pathogen destruction and additional cell recruitment.[51, 52] Monocytes in the blood are recruited to the wound by various chemokine attractants and migrate to the wound site where they differentiate into macrophages and dendritic cells.[53–55] Macrophages play a crucial role in wound healing by phagocytosing cellular and ECM degradation products and microorganisms, attracting more monocytes to the wound area, and beginning the clearance of neutrophils.[56, 57] Early macrophages (known as M1 phenotype) are proinflammatory and release tumor necrosis factor- α (TNF-α), interleukin 6 (IL-6), interleukin −1β (IL-1β), and matrix metalloproteinase (MMPs) for ECM and thrombus degradation

The proliferative phase of wound healing forms granulation tissues characterized by angiogenesis, fibroblast proliferation, and re-epithelialization.[30, 58] The thrombus is slowly degraded by proteases to allow for cell recruitment.[59] Endothelial cells migrate to the wound in response to PDGF, VEGF, and FGF, and begin to proliferate and release additional chemokines to sprout new blood vessels in the area.[58, 60–62] Fibroblasts proliferate and deposit ECM (collagen, elastin) to strengthen the dermis. Fibroblasts also differentiate into myofibroblasts which contribute to wound contraction, wound closure, and scar formation.[63] Macrophages assume the M2 phenotype to promote blood vessel formation and also signal fibroblasts to secrete ECM proteins.[63–65] This leads to the formation of granulation tissue, which acts as a scaffold for blood vessels and cells.[66, 67]

There is substantial overlap between the proliferative phase and the remodeling phase of wound healing. During the remodeling phase, basal keratinocyte stem cells and keratinocyte migration provide regeneration of the epidermal layer over granulation tissues. Macrophages also take on a fibrolytic role to phagocytose excessive cells and release proteases to help degrade and remodel the ECM.[30]

Chronic Wounds

To design successful therapeutic strategies, it is crucial to understand the complex mechanisms that drive chronic wounds. The underlying mechanisms of wound healing impairment in diabetic wounds is not completely understood, but deficits and dysregulation in all phases of the wound healing process have been identified (Table 1, Figure 2). This dysregulation has been shown to impair collagen production, blood vessel formation, oxygen and nutrient delivery, and waste removal from the wound.[68] Chronic wounds are defined by abnormal cellular and molecular interactions resulting in persistent inflammation that is self-perpetuating, particularly affecting the ECM.[69] The complex and diverse wound healing pathways combined with the effects of poor tissue perfusion, denervation, hyperglycemia, and other clinical comorbidities of diabetes makes understanding the molecular mechanisms of impaired wound healing challenging.[46] Pathophysiology of chronic wounds is multifactorial and depends on the disease state and underlying conditions of each patient.

In the early stages of wound healing, macrophages are the pro-inflammatory M1 phenotype, secreting molecules such as nitric oxide (NO), reactive oxygen species (ROS), IL-1, IL-6, and TNF-α, MMP-2, MMP-9. As wound healing progresses, macrophages change to the

M2-like phenotype and express PDGF, IGF-1, VEGF, TGF-β, and TIMP metallopeptidase inhibitor (TIMP1). In the later stages of wound healing macrophages have a crucial regulatory role by suppressing inflammation and fibrosis through the production of IL-10.[70] In contrast, macrophages in chronic wounds remain in the pro-inflammatory phase and have decreased ability to remove neutrophils, debris, and apoptotic cells, important to return tissue to its normal architecture. Without proper removal, remnant neutrophils and dead cells increase proinflammatory marker expression, such as MMPs, slowing dermal healing.[71] The increased presence of proteases also will decrease the availability of growth factors.[72, 73]

Neutrophil clearance by macrophages is a critical step in resolving the inflammatory phase of wound healing. Neutrophils in chronic wounds are not efficiently cleared out of the wound, leading to excess release of neutrophil inflammatory response agents such as proteases and cytotoxic granules.[70, 74] Monocyte recruitment to the wound is critical during the inflammatory phase of wound healing. Delays in the production of various chemokines in diabetic wounds have been shown to decrease the overall monocyte recruitment and macrophage activation at the wound site needed to clear neutrophils.[75, 76]

TNF-α has been identified as a key contributor to chronic inflammation seen within diabetic wounds. Increased expression causes upregulation of MMPs in fibroblasts. Studies have shown that TNF-α and the MMPs collagenase and gelatinase have higher expression in chronic wounds.[77, 78] These persistently high levels of TNF-α contribute to increased MMP activity in chronic wounds leading to increased ECM disruption and overall wound healing impairment.[79–81] Substance P (SP) is a short neuropeptide released from sensory nerves after tissue injury. SP is thought to induce acute inflammation and allow for progression to the proliferative phase of wound healing as well as the conversion of macrophages to the M2 anti-inflammatory phenotype.[82] Serum levels of SP and SP gene expression are decreased in type 1 diabetics and studies have shown that these changes are associated with chronic inflammation and significantly slower wound healing.[83, 84]·[85]

In diabetic patients, the cellular response to prolonged hyperglycemia leads to impaired wound healing.[86] Hyperglycemia causes increased production of ROS in endothelial cells, which leads to excess production of fibronectin and collagen in endothelial cells, non-enzymatic glycosylation of proteins, and chronic inflammation. After long periods of poor glycemic control, this elevated level of oxidative stress and increased metabolic state can persist and be retained within cells, even after normal glucose levels are established.[5, 87–89]

Diabetic patients also suffer from microvascular complications and neuroischemia. This complication can lead to endothelial cell dysfunction and subsequent increase in ROS and a decrease in the NO produced by these cells. NO is crucial for maintaining barrier function and immune cell response while high levels of ROS can impede neovascularization and angiogenesis. Hypoxia seen within diabetic tissues is a major cause of poor wound healing and impaired neovascularization. Studies in diabetic rabbits have shown that neuroischemia contributes to loss of neuropeptide production and function, impairing wound healing.[90]

The combination of neuropathy and ischemia impairs the wound healing process, suggesting the loss of neuropeptide function contributes to the impaired healing in diabetics.

Topical Gels for Diabetic Wound Healing

Composition of Topical Gels Used in Wound Healing Applications

An assortment of natural and synthetically derived materials are used to create therapeutic delivery systems for wound healing. Both natural and synthetic materials can be modified chemically for specific applications such as cell scaffolding and drug delivery. For wound healing, some properties of the biomaterials such as high-water content, the ability to mimic the ECM, and the ability to cover wound surfaces, are all key for promoting tissue regeneration and support.

Natural biomaterials—Common natural biomaterials include collagen, gelatin, silk, chitosan, cellulose, alginate, hyaluronic acid, chitin, elastin, and decellularized ECM. [91] Natural materials are able to mimic native tissue structure and function, to allow better cell attachment and infiltration and are less likely to cause strong inflammatory responses (biocompatible). However, natural materials are also limited in clinical use due to rapid degradation rate by native enzymes and weak mechanical properties. Synthetic materials commonly used are poly(ethylene glycol) (PEG), polyurethane (PU), poly (lactic acid) (PLA), poly (lactide-co-glycolide) (PLGA), and polycaprolactone (PCL).[92]

Chitosan: Chitosan is one of the most common natural-derived materials used for tissue engineering applications due to its low cost, high availability, and biocompatible properties. Chitosan is a β−1,4-polysaccharide comprised of D-glucosamine units that is derived from chitin, a common component of the exoskeleton in crustaceans.[93] The cationic polymer is also known to possess antimicrobial properties by destabilizing the outer membrane of gram-negative bacteria[94].[95] A human clinical trial of 8 patients with DFUs was conducted after application of a 2% chitosan gel and chitosan film to the wound area. All patients developed granulation and healed tissues over the wound area for an overall significant improvement in healing (Table 6).[96]

Alginate: Alginate has long been investigated as a biomaterial for wound healing applications due to its high biocompatibility, cost-effectiveness, low toxicity, and ease of gelation under physiological conditions by the addition of divalent cations.[97] Alginate is typically extracted from brown algae and is composed of linear copolymers containing blocks of (1,4)-linked β-D-mannuronate (M) and α-L-guluronate (G) residues, the ratios of which vary between sources and extraction methods.[98] One recent study employed alginate-pectin hydrogel films loaded with Simvastatin in an STZ-induced diabetic rat wound healing model and found that wound healing was improved through increased angiogenesis and collagen synthesis.[99] Another study developed chondroitin sulfate-grafted and thermosensitve alginate hydrogels with loaded with curcumin. The in situ forming and injectable hydrogels had a controlled drug release profile and were able to inhibit inflammation while promoting tissue regeneration in a full thickness-excisional diabetic wound model in rats.[100]

Hyaluronic acid: Another common natural biomaterial used in many tissue engineering applications, including wound healing, is hyaluronic acid (HA). It is a major ECM protein with critical function in tissue formation, repair, and remodeling.[101, 102] On its own, high molecular weight (MW) HA has demonstrated improved wound healing properties when applied topically to diabetic rat wounds.[103] Aftamed® is a high MW HA gel commonly used to treat oral lesions and heal gum tissues. Aftamed® gel treatment has demonstrated significant improvement of wound healing in diabetic rats with increased antioxidant activity, granulation tissues, collagen deposition, blood vessel formation, and decreased inflammation.[68] Another study using HA as a topical ointment in diabetic rats demonstrated HA treatment increased angiogenesis and increased expression of TGF-β1.[104] HA can also be used to deliver biologics for controlled release to increase therapeutic efficacy. Charged components on HA help stabilize the structure of growth factors and protect them from degradation, which increases stability and allows for prolonged therapeutic effects.[105, 106]

Collagen: Collagen, the major structural component of the ECM, is one of the most common materials used for wound healing applications. Biomaterials have been created that mimic the effects of collagen, such as promotion of specific cellular responses, scaffolding for cellular therapies, and controlled release of therapeutic agents.[69, 107] Collagen type III (Col III) has been identified as an important structural protein during fetal scarless wound healing for cellular migration and proliferation.[108, 109] Mouse and pig studies have demonstrated the potential of collagen-based gels for treating acute wounds and other genetic skin diseases such as recessive dystrophic epidermolysis bullosa.[110]

Synthetic materials—Synthetic materials offer substantial possible chemical modifications which allows for the creation of hydrogels with varying crosslinking densities, mechanical strength, controllable degradation, and drug delivery applications. Synthetic materials are limited in clinical use due to their lower bioactivity (inert), decreased interaction and integration with tissues, low biodegradability, and increased inflammatory responses.

Pluronic F127: A common synthetic material with FDA approval used in biomaterial applications is Pluronic F127, a triblock copolymer with a central polypropylene glycol capped on both ends with PEG. It has been shown that Pluronic F127 gel on its own improves cutaneous wound healing in non-diabetic rat by increasing the expression of VEGF and TGF-β1.[111]

Zwitterionic gels: Another synthetic material gaining interest in the field of diabetic wound healing is hydrogels based on the polymerization of zwitterionic monomers, which exhibit equal positive and negative charges on the same molecule. Due to their closely repeating and robust charge structure, zwitterionic materials have been shown to be effective at resisting non-specific protein adsorption.[112, 113] In turn, this behavior could synergistically decrease the inflammatory response in wounds by preventing foreign body reactions. For example, one study determined through H&E staining that a zwitterionic hydrogel (poly(carboxybetaine methacrylate) (PCBMA)) implanted in mice had significantly fewer

inflammatory cells than a non-zwitterionic hydrogel (poly(2-hydroxyethyl methacrylate) (PHEMA)), indicating that a weaker inflammatory response may be due to the ability for zwitterionic hydrogels to resist protein adsorption.[114] Another study showed that sulfated zwitterionic hydrogels promoted skin regeneration in a mouse wound healing model by decreasing pro-inflammatory marker expression of TNF-α and increasing expression of anti-inflammatory markers CD-163/CD-68.[115] Additionally, zwitterionic hydrogels can be fabricated with a wide range of viscoelastic characteristics and drug release capabilities, which further demonstrates their suitability for topical wound healing applications.[116] [117]

Topical Gels loaded with Growth Factors/ Proteins

Regranex® (Becaplermin Gel)—Growth factors and cytokines in acute and chronic wound healing have been extensively studied and are now commonly used for wound healing treatment approaches (Table 2).[127] Regranex® (Becaplermin Gel) is an FDA approved gel for treatment of DFUs. [118, 119] Regranex® is composed of recombinant human platelet-derived growth factor (rh-PDGF) mixed with carboxymethylcellulose (CMC) and is currently the only FDA approved growth factor treatment for DFUs. Rh-PDGF acts on wounds by stimulating fibroblast proliferation, granulation tissue formation, increasing re-epithelialization and revascularization, and promoting collagen production.[120] Multiple clinical trials (382 patients[121], 922 patients[122]) with type 1 or type 2 diabetic patients with chronic diabetic wounds compared Regranex® with placebo gel in conjunction with standard wound care procedures. Regranex® gel significantly increased complete wound closure and significantly decreased time to full wound closure (Table 6).[121–123] Despite the promising clinical trials, Regranex® gel has shown limits in clinical practice with increasing concerns related to its high cost.[124] One- 15-gram tube costs around $1300, which will be enough gel for a 2 cm^2 ulcer for approximately 4 weeks. Generally, treatment will take at least 10 weeks, which would require 2–3 tubes per ulcer. Regranex® gel is expensive initially but decreases overall cost to patients by decreasing the time to wound closure, thus, reducing repeated doctor visits and complications associated with diabetic foot ulcers.[125] However, in June 2008, the FDA added a cancer warning label to Regranex® boxes due to an increased risk for cancer mortality in patients who have used at least 3 tubes. This warning has since been removed citing multiple studies showing no increased incidence of cancer.[126]

Growth Factors—Jee et al. developed a topical delivery system made from Carbopol 981 (polyacrylic acid) gel with a multitude of therapeutic treatments incorporated into it. These treatments included bFGF, EGF, IGF, and PDGF, a quercetin nanoemulsion that possesses inflammatory and anti-oxidative properties[128], and perfluorocarbons which are oxygen carrying molecules used to improve oxygen delivery to chronic wounds (Table 2).[129–132]

EGF, bFGF, TGF-β, and VEGF are all critical for the wound healing process and have been shown to be deficient in chronic wounds,.[133–135] EGF treatments for DFUs has shown promise for improved wound closure and decreased median time to complete healing. [136–138] Park et al. performed a clinical trial testing topical EGF for treatment of chronic DFUs in 167 patients; 73.2% of the treated wounds achieved complete healing compared

to 50.6% in the placebo group (Table 7).[139] Other approaches have used combinations of Regranex® with other treatments such as TGF-α or with a CXCR4 antagonist (AMD3100) to improve wound healing.[140, 141]

Despite their importance in the wound healing process, GFs have seen limited success in promoting wound healing. The wound environment has high concentrations of proteolytic enzymes such as peptidases and MMPs, and decreased levels of MMP inhibitors (TIMP-2) in chronic wounds. This results in rapid degradation of GFs, limiting their therapeutic effect in the wound site.[142]

Multidomain peptide hydrogels—Other peptide/protein-based approaches such as multidomain peptide hydrogels (MDPs) have been used to promote healing of chronic wounds.[143] [144] MDP hydrogels can be loaded into syringes and are easily delivered to wounds. Treatment of diabetic murine wounds demonstrated significant wound closure improvement with MDP hydrogel compared to the Intrasite gel (an antibacterial gel composed of carboxymethylcellulose and propylene glycol) control.[145] A peptide based topical hydrogel derived from antiopoietin-1, QHREDGS (glutamine-histidine-arginine, glutamic acid-aspartic acid-glycine-serine) was used to target re-epithelialization. The peptide was immobilized in a chitosan-collagen hydrogel. A single application of this peptide gel improved wound healing and increased re-epithelialization in diabetic mice when compared to a collagen control.[146] The peptide hydrogel accelerated healing by 167% compared to the untreated wounds and by 60% compared to a collagen dressing (Table 2).

Vulnamin®—Vulnamin® is a gel produced in Italy for the treatment of chronic wounds. [147, 148] This gel is composed of HA and the amino acids, glycine, lysine, proline, and leucine. These amino acids are particularly important for the synthesis of collagen and elastin. Vulnamin® increases markers of endothelial nitric oxide synthase (eNOS), TGF-β1, and reduces of inflammatory cell numbers and markers of inducible nitric oxide synthase (iNOS). A clinical trial of 30 diabetic patients with neuropathic leg ulcers and a separate clinical trial with 160 patients with chronic wounds showed Vulnamin® gels significantly improve wound closure rates, reduce mean ulcer area, and increase granulation tissue coverage in patients with chronic wounds (Table 7).[148, 149]

Chemokines and cytokines—Chemokines and cytokines produced by immune cells have chemoattractant properties that regulate cellular functions with paracrine and autocrine signaling and are known to be dysregulated in chronic wounds.[133] MIP-3α and IL-8 cytokines were encapsulated within a gelatin hydrogel cross-linked with horse radish peroxidase (HRP) which has sprayable properties for easy application. Results in diabetic rats demonstrated the gel promoted cell infiltration into the wound area, accelerated wound healing, and increased wound re-epithelialization, angiogenesis, and collagen deposition (Table 2).[150]

Granexin®—The Ghatnekar group has demonstrated that Connexin 43 (Cx43) peptide has significant implications in the management of diabetic wounds by targeting cell proliferation. Alpha connexin carboxy-terminal (ACT1) was loaded into hydroxyethyl cellulose gels (known as Granexin®) for diabetic wound.[151, 152] Granexin®

demonstrated a significant increase in complete reepithelization and reduced time to complete healing of the wounds.[153] In a clinical study of 92 patients, ACT1 gel treatment significantly reduced mean % ulcer area from the baseline after 12 weeks of treatment. In addition, a greater percentage of patients reported 100% wound closure and shorter median time to 100% ulcer re-epithelialization in the 12 week period (Table 7).[153] The phase 3 clinical trial was terminated in 2020 by the sponsor (no safety or efficacy concerns).

Substance P—Decreased expression of substance P (SP) SP has been implicated in the progression of chronic inflammation of diabetic wounds. One study by Kant et al. showed that topical application of SP in a Pluronic F127 gel significantly accelerated wound closure in diabetic rats by increasing the expression of IL-10, VEGF, TFG-β1, eNOS, HO-1, and improved collagen development (Table 2).[155]

Talactoferrin—Talactoferrin (TLF) is a recombinant human lactoferrin that induces the release of inflammatory mediators with known anti-inflammatory and wound healing properties, as well as modulation of the innate and adaptive immune responses.[156] Compared to the control gel and Regranex® treatments, TLF-Carbopol 980 topical gel treatments in diabetic wounded mice demonstrated a higher rate of wound closure and an increase in inflammatory mediators, MIP-2, IL-6, MIP-1α, and TNFα (Table 2).[50]

Drug Approaches

Edaravone®—ROS play a critical role in the wound healing process. They are secreted by neutrophils, monocytes, and macrophages, and are important for detoxification-fighting off bacterial and other microorganisms, as well as for angiogenesis.[160] Chronic wounds have increased and sustained levels of ROS that cause degradation of ECM proteins. Therefore, targeting ROS present a promising approach for chronic wounds. Fan et al. developed an alginate–based nanocomposite hydrogel loaded with Edaravone® to improve wound healing. Edaravone® is a known antioxidant with free radical scavenging properties, specifically inhibiting hydroxyl radical lipid peroxidation. To overcome Edaravone's® limited aqueous solubility and stability, nanoparticles (NPs) were synthesized using Eudragit® to encapsulate Edaravone® in the NP core. The nanocomposite hydrogel with Edaravone® showed a two-fold increase in wound healing activity compared to that of free Edaravone® or untreated wounds in diabetic mice on day 10. Topical applications of the Edaravone® nanocomposite accelerated healing more than free Edaravone® due to the prolonged localized release of the drug from alginate and the protective effects of the Eudragit coating to prolong drug stability. Interestingly, the high dose of Edaravone® led to impaired wound healing, likely a result of excess inhibition of ROS and decreased beneficial effects of ROS for wound healing (Table 3).[161]

Valsartan®—Angiotensin receptor blockers have drawn interest for wound healing applications because the renin-angiotensin system (RAS) plays a role in diabetic wound healing by regulating inflammation, collagen deposition, and the TGF-β signaling pathway. Increased angiotensin II type 1 receptor (AT1R) and decreased angiotensin II type 2 receptor (AT2R) expression are known abnormalities associated with diabetes. Changes in the ratio of these receptors contribute to the risk of developing diabetic wounds through the degradation

of collagen and thinning of epidermal, dermal, and subcutaneous layers of the skin.[162] Abadir et al. studied the effects of topical AT1R blocker Valsartan® on wound healing in diabetic pigs. They showed that the Valsartan® treated pigs showed complete wound closure of the large wounds on day 57, while the placebo treated group showed 75% wound closure at this timepoint (Table 3).[163]

Naltrexone®—Naltrexone (NTX)® is an opioid receptor antagonist that blocks opioid growth factor receptor pathways that are known to be dysregulated in diabetes and may have potential wound healing properties for diabetic wounds Diabetic rats treated with topical NTX® in Neutrogena® demonstrated faster wound closure with increased expression of angiogenic factors in granulation tissues. Further studies revealed increased collagen maturation and improved mechanical strength of the wounded area in rats treated with NTX cream compared to that of vehicle control treated rats.[164, 165] When compared to Regranex®, the NTX effects on wound closure rates are comparable, with increases in PDGF and VEFG when compared to the vehicle control. These results show the NTX may be a promising alternative to Regranex® for treating diabetic wounds (Table 3).[166]

Doxycycline®—Compared to acute wounds chronic wounds have elevated levels of pro-inflammatory cytokines and proteases that degrade ECM factors, leading to weakened skin tissue. MMPs play a major role in the degradation of collagen in diabetic wounds. TNF-α and IL-1 are also increased in chronic wounds. These pro inflammatory cytokines stimulate the production of collagenase (MMP-1) by dermal fibroblasts, resulting in reduced collagen synthesis.[167] Chronically elevated TNF-α therefore reduces collagen formation and increases production of MMPs that break down collagen. Doxycycline® is an inhibitor of MMPs and has been explored for its wound healing potential and ability to decrease the release of TNF-α.[168] In one study by Chin et al., Doxycycline® was incorporated into a CMC gel for topical treatment of DFUs in a clinical trial consisting of 7 patients and compared to the vehicle gel alone. All 4 patients receiving Doxycycline® gel showed complete healing within the 20-week study period, while only 1/3 of patients receiving the vehicle gel healed completely. This study demonstrated the MMP inhibition by Doxycycline® has a strong potential as a treatment for DFU (Table 7).[168, 169]

Deferoxamine ®—Deferoxamine (DFO)® is a drug that promotes angiogenesis and has been studied as a potential treatment for DFUs.[170] DFO was encapsulated within a 4-armed PEG terminated with thiol groups to create a hydrogel with coordination bonds between silver ions and thiol groups. Results in diabetic rats demonstrated that the DFO encapsulated gel improved wound healing when compared to no treatment and gel only groups. Immunohistochemistry (IHC) of wounded tissues demonstrated increased CD31 markers of angiogenesis due to the presence of DFO and decreased bacterial content as a result of the silver present in the hydrogel (Table 3).[171]

Topical Gels loaded with Nanoparticles or Microparticles

Silver nanoparticles—Numerous nanoparticle approaches have demonstrated accelerated healing in chronic wounds. Silver ions and silver NPs (AgNPs) are important antibacterial and antifungal clinical treatments for wound management and preventing bacterial

resistance. Applications of silver ions in the clinical setting include: burns, trauma, DFUs, and biomedical device coatings to prevent growth of bacteria.[174–179] In a study by Sharma et al., patients with diabetic, burn, trauma, or other wound pathologies treated with conventional wound dressings and AgNP topical gel demonstrated improved wound healing when compared to other conventional dressings alone.[179, 180] In another diabetic wound healing study, Masood et al. used AgNPs encapsulated within a chitosan-PEG hydrogel cross-linked with glutaraldehyde. AgNPs with hydrogel displayed improved wound healing compared to the AGNPs only and gel only treatment groups. After 4 days post wounding, the hydrogel-AgNPs group displayed approximately 47% wound area closure, compared to approximately 13% for the control, 27% for the AgNPs alone, and 44% for the plain gel. [181] [179, 180] Another study was conducted to investigate the effect of insulin interaction with AgNPs in combination with a Carbopol 980 gel for the treatment of normal and diabetic wounds. Results demonstrated the insulin-AgNPs loaded in the Carbopol 980 gel improved wound healing for both the normal and diabetic mice. Modulation of IL-6, TNF-α, and IL-10 cytokines contributed to improved re-epithelialization rate (Table 4).[182]

Insulin-loaded nanoparticles—Insulin-loaded NPs loaded into a PVA-borate hydrogel that was cross-linked with ultraviolet (UV) light allowed for topical administration of insulin to wounds in diabetic rats. This highly viscous gel allowed for increased contact time on the wound area when compared to free insulin application using saline. The hydrogel-insulin-NP treatment reduced the wound area by 29.15% compared to the free insulin treatment (Table 4).[183]

Nebivolol®-loaded microsponge—Microparticles are another common method for drug delivery. Microsponges, a type of porous microparticle, were made from Eudragit RS-100, a copolymer of ethyl acrylate, methyl methacrylate, and methacrylic acid with quaternary ammonium groups that make the polymers permeable for drug delivery applications. Nebivolol® is a beta-1-receptor blocker that causes vasodilation through activation of the L-arginine/ NO pathway, often used for the treatment of hypertension.[184] The microsponge gel loaded with Nebivolol® demonstrated significant improvement in wound healing in diabetic rats.[185] High density lipoprotein (HDL) is type of microparticle most commonly known for its role in cholesterol transport and regulation, but it also has anti-oxidative, anti-inflammatory properties, and recruitment of endothelial progenitor cells (EPCs), which are needed for wound healing.[186] A topical form of HDL developed by Gordts et al. has been shown to enhance wound healing in a mouse model of delayed wound healing. Re-epithelialization with topical HDL was increased by 47.8% from day 0 to day 10 when compared to the control gel, which did not promote wound healing (Table 4).[186, 187]

Levofloxacin®-nanoemulsion—Levofloxacin® is a drug commonly used to treat bacterial infections and has been administered orally to patients with DFUs to reduce bacterial levels associated with DFU infections.[188, 189] A nanoemulsion gel containing Carbopol 934 with levofloxacin was developed by Valizadeh et al. Diabetic rat wounds infected with *S. aureus* treated with this gel demonstrated almost full wound closure after 12 days, increased collagen synthesis, CD31, and TGF-β.[172] Importantly, this treatment

was significantly better than the positive control, sulfadiazine, which is a common clinical treatment for infected wounds (Table 3).[172]

Cerium oxide nanoparticle-microRNA146a conjugate—Novel NP topical gels have been developed to improve delivery and therapeutic efficiency of existing treatments.[190] One promising NP treatment for DFUs is cerium oxide NPs (CNPs) conjugated to microRNA 146a (miR146a). CNPs scavenge ROS to reduce oxidative stress and miR-146a is linked with the abnormal inflammatory response in diabetic wounds and has been shown to be significantly reduced in diabetic wounds and associated increased expression of proinflammatory genes. [190–193] Sener, G. et al. created injectable zwitterionic hydrogels capable of sustained release of therapeutics. These hydrogels consist of hydroxyethyl methacrylate (HEMA) polymerized with either sulfobetaine methacrylate (SBMA) or carboxybetaine methacrylate (CBMA). These gels demonstrated antifouling characteristics, self-healing properties, durability, topical application, ease of production, and sustained release of therapeutics for up to 40 days. These gels were combined with cerium oxide NPs (CNPs) conjugated with miRNA-146a. Topical application of zwitterionic gels with CNP-miR146a demonstrated complete wound closure at 14 days compared to day 20 for the gel alone, increased mechanical strength of healed skin, increased miR146a and Col1α2 expression, and decreased IL-6, CXCL2 expression (Table 4).[190] Further study used a silk fibroin solution to deliver CNP-miR146a. Silk fibroin is a strong, tensile biomaterial that can be used to help increase the mechanical strength of tissues.[194]. Results demonstrated db/db mice treated with Nanosilk+CNPmiR146a strengthened the biomechanical properties of the healed skin while also showing improved wound closure rates compared to control treated mice. Mice expressed higher collagen, TGFβ−1, and lower expression of IL-6 and IL-8 (Table 4).[195] Other groups have demonstrated CNPs have antimicrobial properties against gram positive and gram negative bacteria at basic pH conditions, which could make CNP treatments useful to reduce the use of antibiotics and reduce antibiotic resistance.[196, 197]

Other metallic, polymeric nanoparticles—Other nanoparticles that have been used to treat chronic wounds with intrinsic wound healing activity include metallic compounds such as silver (mentioned above), silicon dioxide (mentioned in Herbal/antioxidant section), gold, iron oxide, zine oxide, aluminum oxide, titanium dioxide, and gallium. A graphene oxide nanocomposite promoted accelerated wound healing and angiogenesis in diabetic rats.[198] Non-metallic nanoparticles which often include polymeric materials, can be fabricated using multiple polymer types and synthesis methods. The intrinsic wound healing and therapeutic delivery capability of nanotechnology holds promise for specific mechanisms of chronic wounds. [199] This wide variety of nanoparticle approaches that have been tested in chronic wounds should allow for further investigation for their incorporation into topically applied gel treatments.

Topical gels loaded with Cells/Cellular Components

Adipose derived stem cells—Stem cell-based treatments offer a promising route for regenerative tissue engineering approaches due to their ability to differentiate into multiple cell types and their ability to release trophic factors, hormones, and cytokines.

[200] However, one barrier to cellular treatment therapies is a lack of survival after implantation. Biomaterials have been used extensively as delivery vehicles for cellular therapies to increase cell survival after transplantation. Adipose derived stem cells (ADSCs) have demonstrated promising wound healing capabilities due to paracrine and autocrine effects that increase cellular proliferation and epithelialization.[201] To increase the efficacy of ADSC treatments, a Pluronic F127 gel was encapsulated with ADSCs for topical treatment of wounds in diabetic rats.[202] Compared to cell treatment alone, the ADSCs with gel treatment enhanced re-epithelialization, cell infiltration to promote granulation tissue formation, angiogenesis, VEGF expression, Ki67 cell proliferation, and TGFβ−1 expression. These results demonstrate the ability of biomaterial gels to increase cell viability and functionality. Also, ADSCs encapsulated with hyperbranched PEG hydrogels cross-linked with thiolated hyaluronic acid demonstrated improved healing compared to the ADSC only group, Intrasite® gel group, gel only group, and no treatment group after 11- and 21-days post wounding in diabetic rats. Gels with ADSCs promoted angiogenesis, re-epithelialization, and decreased inflammation.[203] A similar study was conducted by Xu et al. with a hyperbranched poly (β-amino ester) hydrogel composed of PEGDA and diamine cross-linked by thiolated hyaluronic acid. ADSCs were encapsulated within the hydrogel and applied to wounds in diabetic rats, resulting in improved wound healing compared to the ADSCs only treatment and controls (Table 5).[204]

Bone marrow derived stem cells—Bone marrow derived stem cells (BMSCs) are an attractive treatment option for diabetic wounds because they secrete TGF-β1 and bFGF.[205] BMSCs were incorporated into a thermosensitive hydrogel with N-isopropyl acrylamide (NIPAm) to improve cell functionality. The hydrogel-BMSC group demonstrated a decrease in CD68 inflammatory cells, increase in keratinocyte proliferation and differentiation, and an increase in epidermal and dermal appendages in the wounded area at 35 days post wounding.[205] Another thermosensitive hydrogel, PEG-PLGA-PEG, increased engraftment of muscle-derived stem cells to mouse diabetic wounds with improved wound closure, re-epithelialization, and collagen deposition (Table 5).[206]

Exosomes—In addition to cells, cellular components including exosomes, microvesicles, and apoptotic bodies can be used to promote tissue repair. Exosomes are cellular secretory products that contain nucleic acids and proteins that are important for cellular function and communication. Exosome-based treatments have shown benefits over cellular therapies, including decreased immune rejection.[207] The therapeutic effect of exosomes has been shown to increase when combined with gel materials used for their scaffolding properties.[200] Yang et al. isolated exosomes from human umbilical cord-mesenchymal stem cells (hUCMSC-exos) and mixed these cells in a Pluronic F127 gel. Results showed improved wound closure when applied in diabetic rat wounds, with near full wound closure by day 14. The gel-exosomes treatment increased CD31 positive cells, microvessel density, ki67 (proliferating cells), VEGF, and TGF-β1 expression when compared to the PBS, Pluronic F127, and free hUCMSC-exos group, demonstrating the importance of the Pluronic F127 gel for prolonging the effect of the treatment.[208] A similar study by Shi et al. used gingival mesenchymal stem cells to extract exosomes, then combined the exosomes in a chitosan/silk hydrogel sponge. The sponges were applied over diabetic wounds in rats.

Results showed full wound closure 2 weeks after wounding, as well as increased epidermal development, angiogenesis, and collagen production (Table 5).[209]

Wang et al. developed a multifunctional, three component hydrogel for exosome release: Pluronic F127 for the thermosensitive property, hyaluronic acid for ECM and moisture retention properties, and poly-ε-Lysine (PEL) for the natural cationic groups that allow antibacterial activity. Exosomes from adipose derived MSCs were obtained and mixed with the hydrogel. Gels with exosomes applied on diabetic murine wounds showed significantly faster wound closure rates, improved angiogenesis, re-epithelialization, collagen production, increased skin appendages, and decreased scar tissue compared to control groups.[210] Wang et al. developed a exosomes-based hydrogel by conjugating formylbenzoic acid to methylcellulose (MC), which allows for fast crosslinking with amine groups from a chitosan and PEG polymer. Exosomes were extracted from placental MSCs and then mixed with the hydrogel. Hydrogel-exosomes treated wounds in diabetic mice demonstrated improved wound closure rate, angiogenesis, and collagen production when compared to the exosomes only group, gel only group, or PBS group (Table 5).[211]

Topical Gels loaded with Herbal/Anti-oxidant Molecules

Vitamin C—Naturally occurring molecules have been extracted from various plants for their favorable wound healing properties. Vitamin C has known antioxidant and anti-apoptotic effects that have been tested in chronic wounds. Pluronic F127 was mixed with Vitamin C to test the antioxidant effects of Vitamin C in diabetic rats. There was an improvement in wound healing at day 7 and day 14, with epidermal and dermal development, increased collagen production, and decreased apoptosis. There was no difference in time to full wound closure for the treatment groups, with maximum healing at 3 weeks (Table 6).[212]

Curcumin—Curcumin is a polyphenol found in turmeric that is known to have promising anti-oxidant and anti-inflammatory properties favorable for wound healing applications.[213] Loading Curcumin into HA gels with topical application onto diabetic mouse wounds demonstrated significant wound closure after 14 days. This study also demonstrated that the HA gel on its own improves wound healing when compared to the untreated control.[214] Another study developed Curcumin NPs to overcome Curcumins poor aqueous solubility and limited permeability. Diabetic rats treated with an alginate gel-Curcumin NPs demonstrated improved wound healing, re-epithelialization, increased collagen formation in the dermis, and increased VEGF and AQP3 expression.[215] In another study, Curcumin NPs were created and encapsulated within gelatin microspheres and prepared in a Pluronic F127/F68 thermosensitive hydrogel with an MMP9 responsive drug-release mechanism. The composites applied to diabetic mouse wounds demonstrated improved wound healing, increased epidermal thickness, collagen deposition, antioxidant activity, and re-epithelialization (Table 6).[216]

Mangiferin—Mangiferin is a natural compound found in plant species such as the mango tree. This polyphenol has been linked to numerous health benefits, including antioxidation via suppression of ROS and anti-inflammatory effects.[217–220] Mangiferin was mixed

with propylene glycol and CMC to form topical gels. Diabetic rat wounds were treated with Mangiferin gel and demonstrated significant reduction in wound area with reduction of oxidative stress (increased Nrf-2 expression) and increased granulation tissue formation (increased MMP-2 expression) (Table 6).[221]

Ferulic acid—Ferulic acid is a plant cell wall-derived compound with promising therapeutic effects, particularly for anti-inflammatory and antioxidant properties. PLGA NPs loaded with ferulic acid were mixed into a Carbopol 980 polymer solution to form a topical gel. Ferulic acid-PLGA NPs delivered from the Carbopol 980 gel had faster epithelialization of the wound and led to significant wound healing improvement in diabetic rats (Table 6).[222]

Apigenin—Apigenin is a flavonoid found in a wide variety of plants and vegetables with promising therapeutic potential for wound healing applications due to its antioxidant, antibacterial properties.[223] Apigenin was loaded in gellan gum-chitosan hydrogels cross-linked with PEG. Significant improvements in diabetic wound healing in rats and antioxidant activity was demonstrated in the Apigenin loaded hydrogels (Table 6).[224]

Other herbal extracts—Other promising herbal-based treatments include konjac glucomannan (KGM), a dietary fiber polysaccharide with anti-inflammatory properties that turns into a gel when mixed with water, making it an attractive gel for drug delivery applications.[228] KGM has the ability to lower blood glucose by increasing insulin receptor proteins in diabetic rats, making it an attractive treatment option for diabetic applications.[229, 230] A study in diabetic mouse wounds combined silica nanoparticles (SiNPs) with KGM and demonstrated activation of M2-macrophage phenotypes, leading to increased accelerated wound closure, increased collagen production, increased angiogenesis, and decreased inflammation.[231] KGM has also accelerated wound healing properties in diabetic rats as an implantable hydrogel scaffold loaded with keratin and Avena sativa extract.[232]

Teucrium polium hydroethanolic extract (TPEO) is obtained from leaves of felty germander and is known for its strong antioxidant effects for medicinal use.[225, 226] TPEO was mixed in in Aloe vera gel and demonstrated accelerated wound healing in diabetic mice with enhanced cell proliferation, collagen formation, a reduced inflammatory phase (decreased TNF-α and IL-1β) compared to a control group.[227]

Psyllium seed husk polysaccharide is another herbal-based treatment with gelling properties that has shown therapeutic effects in type 2 diabetic patients.[233] Psyllium combined with morin (a plant derived flavanol with antioxidant properties) on a keratin-based scaffold demonstrated accelerated wound healing in diabetic rats.[234]

Challenges and Future Perspectives

Hydrogels are extensively studied in tissue regenerative applications and are attractive for diabetic wound healing applications due to their high-water content and ability to keep wounds moist. Hydrogels also possess multiple synthesis mechanisms (ex. chemical, light), tunable mechanical properties, and encapsulation ability for cellular or drug delivery.

Benefits of topical gels over other treatment approaches include ease of application, less invasive delivery method, increased direct contact of therapeutic with the wound, and avoidance of systemic delivery of therapeutics.[79, 133, 163, 235]

Limitations of topical gels—However, there are limitations to the use of topical gels, including limited mechanical strength and increased degradation rate. Development of effective topically-based treatments for DFUs remains a challenge to overcome.[21] Further advances in polymer synthesis have led to the development of next-generation or “smart” hydrogels capable of responding to inherent signals to influence biological responses.[236] These signals or stimuli can include temperature, light, pH, enzymes, electric fields, sound, and pressure.[237] Changing hydrogel properties such as cross-linking density or incorporating photocleavable groups can influence hydrogel stiffness, degradation rate, and controlled release of biomolecules such as chemical drugs, growth factors (proteins), nucleic acids. Increasing control over the mechanical stiffness of hydrogels can mimic native tissue mechanics and have been found to direct stem cell lineage.[238] Hydrogels can be specifically designed for different tissues of the body that depend on pH (pH-sensitive hydrogels), with different synthesis methods leading to variable swelling properties that depend on the environmental pH, making these hydrogels useful for applications such as gastrointestinal diseases.[239] As the capability to control the dynamics of hydrogel properties advances in both *in vitro* and *in vivo* applications, specific deficiencies of complex diseases such as DFUs can be better targeted.

Translation from lab to clinic—The topical approaches covered in this review use the gel as a way to deliver a therapeutic to the wound site, with some gels specifically designed to improve release kinetics.[190] Many of the approaches covered here demonstrate promising results in preclinical animal models and clinical applications (Figure 3). However, few of these treatments made it to clinic. As stated above, Regranex® topical gel is still currently the only FDA approved growth factor treatment for DFUs and has been for one of the few topical approaches taken to clinical application. Despite the increasing number of approaches to treat DFUs with topical gels, limitations exist in the design of the gels and limit their translational capability to become available for clinical use. It is important to consider factors in the design of the material for market need, manufacturing costs, and regulatory aspects.[240, 241]

Among the factors to consider first is the gel material itself. Use of natural or synthetic materials both have advantages and disadvantages in terms of their chemical and physical properties.[92, 242] Selecting a material with FDA approval will help answer questions of biocompatibility and toxicity.

The synthesis procedure of the gel will also determine how smoothly it can transition to commercialization. Gels made from simpler materials such as cellulose, chitosan, or readily available synthetic polymers such as PEG with easy preparation are most advantageous, as they are more likely to transition to a larger scale manufacturing process. Synthetic polymers may require the addition of organic solvents for synthesis which will increase the risk of the material becoming toxic to cells. Materials that require complicated and time-consuming chemical modifications are less ideal, as this increases the need for further purification

techniques/apparatuses, increasing manufacturing time and costs. Furthermore, the supply of raw materials must be considered. Gels made with more expensive raw materials may be more difficult to manufacture and face supply limitations for manufacturing. Gels made with more widely available raw materials (such as cellulose, chitosan, alginate, PEG) likely will avoid supply disruptions.

Gel stability must be determined not only in the biological environment but also for manufacturing, storage conditions, and packaging. Increasingly colder temperature storage conditions for a treatment require more expensive equipment. Many biological treatments require −80°C freezer storage conditions to remain stable, but many facilities do not have −80°C freezers. Room temperature storage is ideal, but 4°C and −20°C are also practical. Long-term testing of gel stability and bioactivity also need to be determined for storage and packaging conditions.

The simplicity of the material is important to consider in order to have a reliably manufactured product. Adding multiple treatments (such as multiple GFs or multiple nanoparticle types) to a single product complicates the manufacturing process and drastically increases the cost. There could be instances, however, where chemically modified materials may increase the effect of the therapeutic. Growth factors are commonly added to biomaterials with chemically modified backbones to mimic heparin to increase the electrostatic interactions of the GF with the biomaterial and allow for more controlled release from the biomaterial.[243] Furthermore, topical gels with controlled therapeutic delivery capability can improve dosage requirements for the patient and prevent burst release of the therapeutic.[244] For DFUs, a gel capable of delivering a therapeutic over the course of several days as opposed to several hours not only will improve the effect of the treatment but will also help decrease the amount of the gel needed to be applied on a daily basis. Gels that require fewer applications in a given time will be more cost effective and attractive for patients.

Topical gels applied in clinical settings—A list of topically applied gels for DFUs tested in human trials is shown in Table 7. Despite the many topical approaches attempted in research settings, only a select few have made it to clinical trials. Most clinically tested gels use a protein-based or drug approach. Other approaches have not seen extensive clinical testing due to limited survival for cellular therapies and unknown long-term effects of nanoparticle therapies. The cost and duration of the FDA clinical trial approval process also limits the use of many of these topical gel approaches for translational use to the clinic.[245]

Conclusions

Topical gel treatments for DFUs have been studied in research settings extensively but few have been tested in the clinical setting, with only 1 topical gel (Regranex®) currently FDA approved specifically for DFU treatments. DFUs will continue to be a major threat to diabetic patients and the healthcare system as diabetes is expected to increase dramatically in the coming decades. The combined lack of topical treatments available to DFU patients and the rising incidence of DFUs should incentivize researchers to develop topical gels capable of treating DFUs.

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List of abbreviations

SBMA	Sulfobetaine methacrylate
STZ	Streptozotocin
NP	Nanoparticle
PEG	Poly(ethylene glycol)
PVA	Poly(vinyl acetate)
PLGA	poly(lactic-co-glycolic acid)
CDC	Centers for Disease and Control
US	United States
DFU	Diabetic foot ulcer
ECM	Extracellular matrix
PDGF	Platelet derived growth factor
TGF-β	transforming growth factor-beta
EGF	Epidermal growth factor
IGF	Insulin growth factor
VEGF	Vascular endothelial growth factor
DAMP	damage-associated molecular pattern
TNF-α	tumor necrosis factor -alpha
IL	Interleukin
ROS	reactive oxygen species
MMP	Matrix Metallopeptidase
TIMP	tissue inhibitor of metalloproteinases
SP	Substance P
NO	Nitric oxide
Col III	Collagen type III

Rh	Recombinant human
RBEB	recessive dystrophic epidermolysis bullosa
HA	Hyaluronic acid
MW	Molecular weight
ERK	extracellular *signal*-regulated kinase
FGF	Fibroblast growth factor
bFGF	Basic fibroblast growth factor
MDP	Multidomain peptide
QHREDGS	glutamine-histidine-arginine, glutamic acid-aspartic acid-glycine-serine
NLU	Neuropathic leg ulcers
iNOS	inducible nitric oxide synthase
eNOS	endothelial nitric oxide synthase
HRP	horse radish peroxidase
Cx43	Connexin 43
ACT1	Alpha connexin carboxy-terminal
HO-1	Heme oxygenase-1
TLF	Talactoferrin
QCN	Quercetin
PFC	Perfluorocarbon
RAS	renin-angiotensin system
AT1R	angiotensin II type 1 receptor
AT2R	angiotensin II type 2 receptor
NTX	Naltrexone
CMC	Carboxymethyl cellulose
DFO	deferoxamine
IHC	Immunohistochemistry
CD	Cluster of differentiation
α-SMA	Alpha-smooth muscle actin

Ag	Silver
ADSC	Adipose derived stem cells
PEGDA	Poly(ethylene glycol) diacrylate
BMSC	Bone marrow derived stem cells
NIPAM	n-isopropyl acrylamide
Exos	Exosomes
hUCMSC	human umbilical cord-mesenchymal stem cells
PEL	Poly-ε-Lysine
MC	methylcellulose
MSC	Mesenchymal stem cells
PNIPAAm	Poly (n-isopropyl acrylamide)
AQ	Aquaporin
HDL	High density lipoprotein
EPCs	endothelial progenitor cells
HEMA	hydroxyethyl methacrylate
CBMA	carboxybetaine methacrylate
Col1α2	Collagen 1 alpha 2
PHEMA	poly(2-hydroxyethyl methacrylate)
PCBMA	poly(carboxybetaine methacrylate)

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Statement of Significance

By 2050, 1 in 3 Americans will develop diabetes, and up to 34% of diabetic patients will develop a diabetic foot ulcer (DFU) in their lifetime. Current treatments for DFUs include debridement, infection control, maintaining a moist wound environment, and pressure offloading. Despite these interventions, a large number of DFUs fail to heal and are associated with a cost that exceeds $31 billion annually. Biomaterials have been developed to help target specific impairments associated with DFU with the goal to improve healing. A summary of these approaches is needed to help better understand the current state of the research.. This review summarizes recent research and advances in topical biomaterials treatments for DFUs.

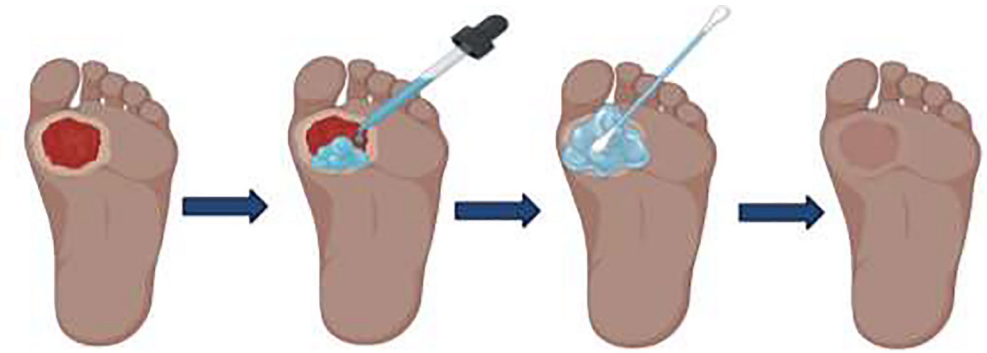

Figure 1. Topical gel application to Diabetic Foot Ulcers.

Topical gels provide simple application of treatments to the DFU. Image created with Biorender.com.

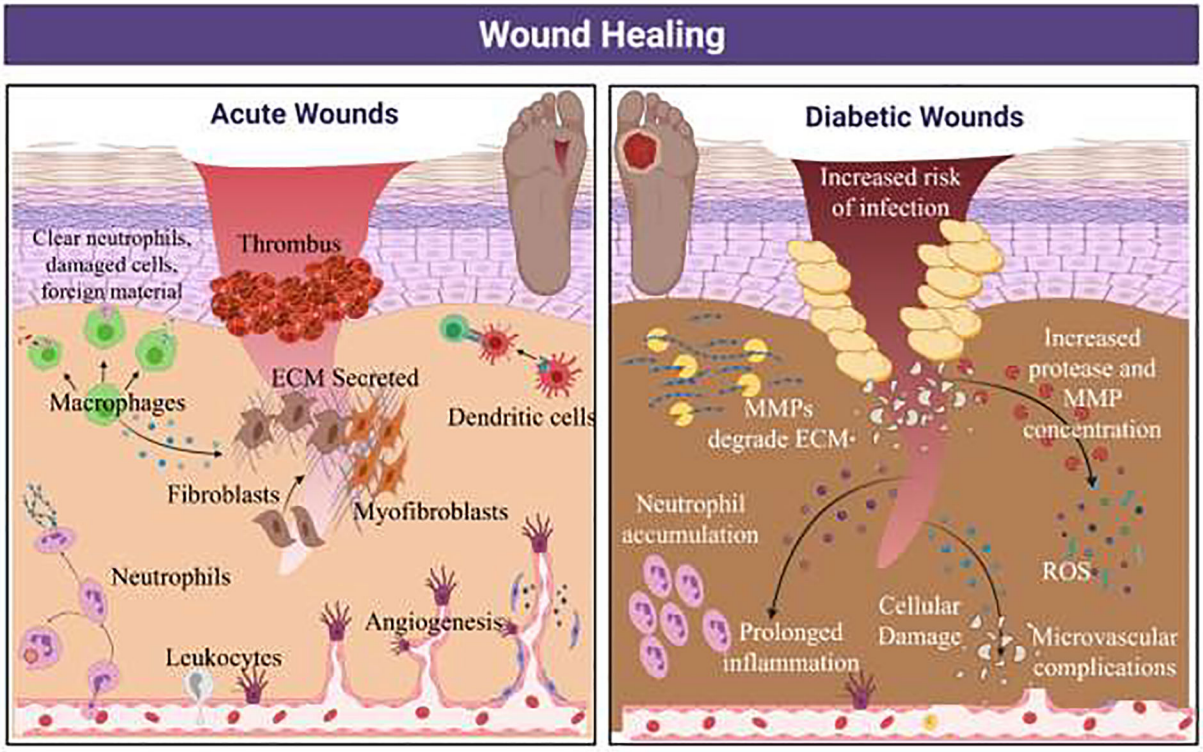

Figure 2. Acute vs. diabetic wound healing.

Acute wounds maintain a balance of hemostasis, inflammation characterized by neutrophil, macrophage engulfment of foreign material and neutrophil clearance by macrophages, proliferation of fibroblasts and myofibroblasts for ECM deposition, and tissue remodeling with keratinocyte migration and maturation of collagen. Diabetic wounds, however, have vascular impairment that delays hemostasis. Inflammation and proliferation stages are characterized by reduced leukocyte recruitment, reduced macrophage clearance of neutrophils causing neutrophil accumulation, increased ROS, increased proinflammatory cytokines, and increased MMP degradation of ECM materials such as collagen. Tissue remodeling and re-epithelialization is not completed, and the wound site remains open. Image created with Biorender.com.

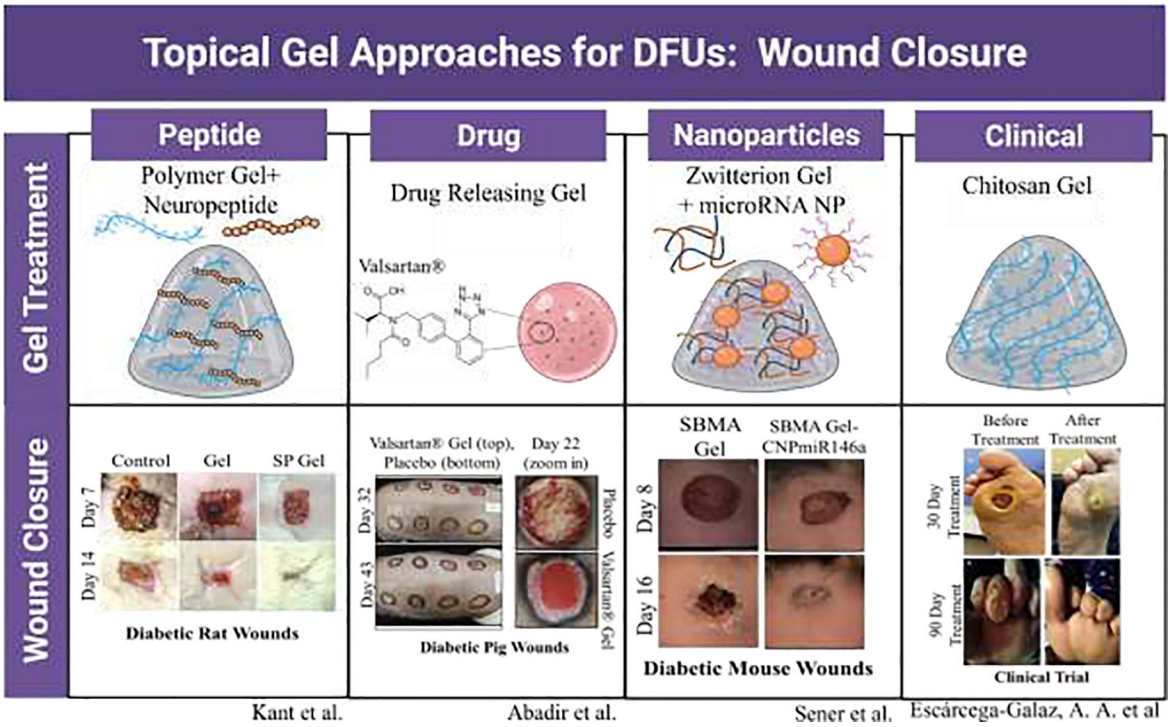

Figure 3. Topical gel treatment approaches in animal and clinical applications.

The peptide Substance P Gel promoted near full wound closure in diabetic rats[155]. The drug Valsartan® in gel form promotes accelerated wound closure in diabetic pigs.[163] A zwitterionic gel with CNP-miR146a demonstrated significantly improved wound healing in a diabetic mouse model.[190] In a clinical trial, a chitosan gel promoted full wound closure in DFU patients after 30 days (top) and 90 days (bottom).[96] Gel treatment diagrams created with Biorender.com. Wound closure images edited and obtained with permission from Elsevier Publishing.

Table 1.

Comparison of Normal (Acute) Wound Healing and Chronic Wound Healing

Wound Healing Phases:	Acute Wound Healing	Chronic Wound Healing
Hemostasis	• Platelet plug formation • Growth factors and cytokines released to recruit cells to the wound	• Impaired recruitment of cells, decreased growth factor release
Inflammation	• Monocyte recruitment • Neutrophils clear pathogens, foreign bodies • Macrophages assume M1 phenotype, clear dead cells, debris, and release proinflammatory cytokines, growth factors MMPs • Macrophages clear neutrophils	• Delayed monocyte and macrophages recruitment to wound • Impaired neutrophil clearance by macrophages causes neutrophil accumulation ○ Neutrophils release proteases that causes excessive degradation of ECM proteins • Prolonged M1 macrophages phase causes abnormal inflammation and inability to remove cellular debris and apoptotic cells. • Increased expression of MMPs impairs ECM formation, causing pus formation and impaired healing
Proliferation	• Granulation tissue formation • Myofibroblasts contract wound • Macrophages assume M2 phenotype: ■ angiogenesis, fibroblasts proliferate, deposit ECM (collagen, elastin) to restrengthen dermis • Re-epithelialization	• Poor vascularization causes impaired angiogenesis, hypoxia, and ROS • Excessive ECM degradation by MMPs • Hypoxic conditions causes impaired fibroblast and keratinocyte function
Remodeling	• Keratinocyte migration for epidermal regeneration • Strengthening of collagen • Macrophages remove cellular debris and release proteases to degrade excessive ECM	• Impaired collagen formation due to excessive MMPs • Reduced epidermal development

Table 2.

Topical Gels with Protein/ Growth Factor Based Approaches

Topical Gel [Ref]	Material Type	Therapeutic Type	Application Frequency/ Study Length	Animal model, wound size	Wound Closure Time	Significant Outcomes
Growth factors and NPs loaded with quercetin and oxygen [157]	Carbopol 981	EGF, bFGF, IGF-1, PDGF; QCN, PFCs	Once Daily for 12 days	STZ mice, 8 mm diameter	Day 12 Healing: Gel + all treatments: >98% Gel+ QCN NPs: 90% Gel+ Gfs: 95% Control: 70%	Accelerated healing, angiogenesis, re-epithelialization, granulation tissue
QHREDGS Hydrogel [146]	Chitosan, collagen	Peptide	One time/ 21 days	Db/db mice; 8 mm diameter	Peptide Hydrogel: Near full closure day-18–21 Collagen dressing: 85% closed on Day 21 Control: 60% closed on Day 21	Accelerated healing, re-epithelialization, granulation tissue
Sprayable Gelatin hydrogel with IL-8, MIP-3α [150]	Crosslinked Gelatin	Chemokines: IL-8, MIP-3α	One time/ 21 days	STZ mice, 10 mm diameter with splint	Gel+MIP- 3α: 90% closure on day 14 Gel+IL-8: >95% closure on day 14 Gel only: 75% closure on day 14	Accelerated healing, cellular recruitment, re-epithelialization, angiogenesis, collagen deposition
Substance P topical gel [155]	Pluronic F127	Neuropeptide: Substance P	Once daily for 19 days	STZ rats, 2x2 cm^2	Gel+ Substance P: 95% healed on day 14 Gel only: 90% healed on day 14 Substance P only: 80% healed on day 14.	Accelerated healing, angiogenesis, re-epithelialization, increased VEGF, TGF-β1, eNOS, and HO-1, decreased TNF-α, IL1β, and MMP-9
Talactoferrin topical gel [50]	Carbopol 980	Glycoprotein: Talactoferrin	Daily/ 19 days	Db/db mice, 12 mm diameter	Talactoferrin gel: 85% closure on day 15, 95% closure on day 19 Vehicle: 70% closure on day 15, 80% closure on day 19	Accelerated healing, enhanced production of inflammatory mediators IL-8, IL-6, MIP1α and TNF-α.

STZ: Streptozotocin induced Type 1 diabetes.[158] Splints: used to prevent wound contraction. Db/db indicates a type 2 diabetic mouse model. [159] NPs: Nanoparticles [172]

Table 3.

Topical Gels with Drug Approaches

Topical Gel [Ref]	Material Type	Therapeutic Type	Application Frequency/ Study Length	Animal model, wound size	Time to Wound Closure	Significant Outcomes
Edaravone®, Nanocomposi te Hydrogel [161]	Alginate	Edaravone®	Daily/ 13 days	STZ mice, 2x 5 mm diameter	Healing on Day 10, Day 13: Edaravone® gel: 96.6%, 100% Edaravone ® only: 85%, 100% Control: 40%, 65%	Accelerated wound healing, antioxidant
Valsartan® gel[163]	Not specified	Valsartan®	Daily/ Mice; 21 days; Pigs: 57 days	Db/db mice: 8 mm diameter; diabetic pigs: 8x 5 cm diameter	Mice with complete wound healing: Valsartan®: 50%; Placebo: 10% Pigs wound closure at day 50: Valsartan®: 100%; Placebo: 70%	Accelerated wound healing (mice, pigs), fibroblast proliferation, angiogenesis, activation of SMAD in pigs, increased biomechanical strength of skin
Naltrexone® with Neutrogena® [164, [165, [173]	Neutrogena®	Naltrexone®	After wounding and 3 more times within 1 day of surgery/ 20 days	STZ rats, 4x-6 mm wounds	Naltrexone® and Regranex® treatments: 95% closure on day 10; vehicle control: 17% closure on day 10. Naltrexone®, Regranex®, and vehicle control showed complete healing on days 12–14.	Accelerated wound healing, angiogenesis via increased FGF-2, VEGF, and α-SMA, increased PDGF and VEGF, comparable results to Regranex®
PEG with Deferoxamine®[171]	PEG-SH crosslinking with Silver	Deferoxamine®	One time/ 14 days	STZ rats, 2x-6 mm wounds	Gel +Deferoxamine®: 95% closure on day 14 Gel only: 80% closure on day 14 Control: 65% healing on day 14	Accelerated wound healing, angiogenesis, antibacterial

[172]STZ: Streptozotocin induced Type 1 diabetes. Splints: used to prevent wound contraction. Db/db indicates a type 2 diabetic mouse model. NPs: Nanoparticles

Table 4.

Nanoparticle and Microparticle Gel Approaches

Topical Gel [Ref]	Material Type	Therapeutic Type	Application Frequency/Study Length	Animal model, wound size	Time to Wound Closure	Significant Outcomes
Silver NPs Hydrogel[181]	Chitosan, PEG	Hydrogel/ Nanoparticle	One time/ 32 days	Diabetic rabbits, 2x 20 mm square wounds	Hydrogel-AgNPs: 100% closure on 12–13 days AgNPs only: 100% closure day 17 chitosan only: 100% closure day 20	Accelerated healing, antimicrobial activity, antioxidant activity
Hydrogel with Insulin NPs[183]	PLGA NPs, PVA hydrogel	Peptide Hormone: Insulin	One time/ 16 days	STZ rats, 2x 6 mm diameter	Day 15 Healing: Hydrogel+ Insulin NPs: 100% Hydrogel Only: 80–85%	Accelerated healing, granulation tissue, angiogenesis
Nebivolol® Microsponge Gel[185]	Eudragit RS100 microspheres	Drug: Nebivolol®	Daily/ 10 days	STZ mice, 1.5x1.5 cm wounds	Near complete wound closure day 10.	Accelerated healing, neovascularization
Nano-insulin with Carbapol-980 gel[182]	Carbopol 980 with Silver NPs with insulin	Drug: Insulin	Once/ 19 days	STZ mice,15 mm diameter	Insulin-AgNPs gel: 60% closure day 11, 100% closure day 15 Insulin only: 45% closure day 11, 100% closure day 17 AgNPs only: 40% closure day 11, 100% closure day 17 Saline: ~30% closure day 11, 100% closure day 19	Accelerated healing, increased IL-10, antibacterial activity
CNP- miR 146a in zwitterionic gels[190]	SBMA	CNPs combined with miRNA	Once/ 20 days	Db/db mice, 8 mm punch biopsy	Day 14 Healing: SBMA+CNPmiR146a: 100% SBMA gel only: 75%	Accelerated wound healing, increased skin mechanical strength, decreased IL6 and CXCL2, increased miR146a, increased Col1α2
CNP- miR 146a with Nanosilk[195]	Silk Fibroin cream	CNPs combined with miRNA	Once/ 20 days	Db/db mice, 8 mm punch biopsy	Day 14 Healing: Nanosilk+CNPmiR146a: 95% Nanosilk only: 85% PBS: 75%	Accelerated wound healing, increased skin mechanical strength, increased TGFβ-1, increased collagen, decreased IL-6 and IL-8
Levofloxacin Nanoemulsio n Gel[172]	Carbopol 934 with sesame oil	Levofloxacin	Twice daily/ 12 days	STZ rats, 1 cm^2	Day 12 healing: No treatment:80% Gel only:90% Nanogel+Levofloxacin:>95%	Accelerated healing, proliferation, re-epithelialization, collagen synthesis, and low skin irritation

STZ: Streptozotocin induced Type 1 diabetes. Splints: used to prevent wound contraction. Db/db indicates a type 2 diabetic mouse model. NPs: Nanoparticles

Table 5.

Topical Gels loaded with Cells/Cellular Components

Topical Gel [Ref]	Material Type	Therapeutic Type	Application Frequency/ Study Length	Animal model, wound size	Time to Wound Closure	Significant Outcomes
Hydrogel + exosomes[211]	Methylcellulose, PEG, and chitosan	Exosomes	One time/ 15 days	Db/db mice, 7 mm diameter	Day 15 Healing: Hydrogel-Exosomes: ~90–95% Hydrogel only: 80–85% Exosomes only: ~80–85% PBS: ~80%	Accelerated healing, angiogenesis, increased tissue thickness, collagen
Hydrogel + exosomes[208]	Pluronic F127	Exosome	One time/ 14 days	STZ rats, 2x 10 mm diameter	Day 14 healing: Hydrogel-exosomes: >95% Exosomes only: 90% Gel only: 80% PBS: 70%	Accelerated healing, granulation tissue, proliferation (ki67), increased CD31, ki76, VEGF, and TGF-β1
Pluronic F127 with ADSCs [202]	Pluronic F127	Cellular	One time/ 14 days	STZ rats, 2x-9 mm punch biopsy	Day 14 healing: Gel with ADSCs: >98% Gel only: 82% ADSCs only: 90% PBS: 79%	Accelerated wound healing, increased, angiogenesis and VEGF expression, increased Ki67 cell proliferation, increased TGFβ-1
PEG/HA with ADSCs[203, 204]	PEG and HA	Cellular	One time/ 21 days	STZ rats, 4x-1.1 cm with splint	Day 11; Day 21 healing: Gel-ADSCs: 40%; 60% ADSCs only: 30%; 50% Gel only: 30%; 35% No treatment: 20%; 40%	Accelerated wound healing, angiogenesis, re-epithelialization, decreased inflammation

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Table 6.

Topical Gels loaded with Herbal/Antioxidant Molecules

Topical Gel [Ref]	Material Type	Therapeutic Type	Application Frequency/ Study Length	Animal model, wound size	Time to Wound Closure	Significant Outcomes
Pluronic F127 with Vitamin C[212]	Pluronic F127	Antioxidant: Vitamin C	Twice per day for 21 days	STZ rats, 2x2 cm^2	Day 14 Healing: Gel-Vitamin C: 60% Gel only: 45–50% Vitamin C only: 45–50%	Accelerated healing on day 7 and 14, antioxidant, re-epithelialization, collagen development
Topical Mangiferin[221]	Carboxymethyl cellulose	Herbal: Mangiferin	Daily/ 21 days	STZ rats, unknown wound size	Day 14; Day 21 Healing Mangiferin gels: 70–75%; 100% Gel only: 40%; 50%	Accelerated wound healing, collagen synthesis, antioxidant (NrF2 expression), decreased proinflammatory TNFα and NF-κβ p65
Ferulic acid-PLGA NPs loaded in Carbopol 980 gel[222]	PLGA NPs in Carbopol 980 gel	Herbal: Ferulic Acid	Twice per day/ 14 days	STZ rats, 2.5 cm	Ferulic acid-NPS: 90–95% wound healing on day 14.	Improved wound healing, collagen deposition, re-epithelialization
Hyaluronic acid gel with Curcumin[214]	Hyaluronic acid	Herbal: Curcumin	24 hr. intervals on day 1–3 post wounding/ 14 days	STZ rats, 1.2 x 1 cm.	Day 14 Healing: HA-Curcumin gel: 96% HA gel: 81% Curcumin: 55% Untreated: 24%	Accelerated healing, proliferation, antioxidant activity
Curcumin NPs in Gelatin Microspheres within MMP sensitive thermosensitive hydrogel[216]	Pluronic F127, F68 and Gelatin	Herbal: Curcumin	One time/ 20 days	Db/db mice, 1x1cm^2	Day 14; Day 20 Healing: CNPs, GM/ hydrogel: 90%; 90% Curcumin hydrogel: 50%; 90% Hydrogel only: 45%; 65%	Accelerated healing, re-epithelialization. collagen deposition. antioxidant activity
Teucrium polium hydroethanolic extract (TPEO) in Aloe vera gel[227]	Aloe vera	Teucrium polium hydroethanolic extract	Daily/ 14 days	STZ mice, 2x 5 mm diameter	Day 14 Healing: Standard Drug (Mupirocin): 80% TPEO gel: 100%	Accelerated healing, proliferation, antioxidant activity, angiogenesis
KGM-SiNPs [231]	KGM	Herbal: KGM	Unknown/21 days	STZ mice, 1x-7 mm diameter	Day 14 Healing: Control: 60% KGM: 60% SiNPs: 80% KGM-SiNPs: >95%	Accelerated healing, re-epithelialization, angiogenesis, collagen deposition, M2 macrophage polarization

STZ: Streptozotocin induced Type 1 diabetes. Splints: used to prevent wound contraction. Db/db indicates a type 2 diabetic mouse model. NPs: Nanoparticles

Table 7.

Topical Gels tested in Human Trials for Diabetic Wound Healing

Topical Gel [Ref]	Material Type	Therapeutic Type	Application Frequency/Study Length	Wound Closure Rate	Significant Outcomes
Becaplermin Gel (Regranex®) [122, 123]	Carboxy methyl cellulose	Growth factor: PDGF	Once per day/ 8 weeks	Increased complete healing of diabetic foot ulcers by 40–50%. The time to healing decreased by 4–6 weeks.	Regranex® is an effective therapeutic for DFU treatment and is the only current FDA approved option. However, there are concern with the cost, limited efficacy, and side effects of this drug.
Topical EGF spray[139]	Not specified	Growth Factor: EGF	Twice Daily/ 12 weeks	Patients (82) had 73.2% complete wound healing at 56 days Saline placebo spray: Patients (85) had 50.6% complete wound healing at 84 days	The spray EGF treatment heals human DFU wounds faster than placebo.
Topical Doxycycline gel [169]	Carboxymethyl cellulose	Drug: Doxycycline	Twice Daily/ 20 weeks	Gel: 4/4 patients healed in 20-week period. Control: 1 of 3 patients treated with the vehicle gel healed.	Accelerated healing
Granexin® [151, 153]	cellulose	Peptide	Day 0, day 3, then weekly from week 1 –12/ 12 weeks	Granexin® significantly reduced mean ulcer area, reduced time to wound closure, and increased % of patients reporting 100% wound closure.	Accelerated healing, re-epithelialization, nonimmunogenic gels.
Chitosan gel[96]	Chitosan	None	Every 48 hours for duration of study/ 90 days	8 DFU human subjects: Improvement of ulcer wound closure using chitosan gel.	Significant improvement in ulcer wound healing, granulation tissue formation
Vulnamin® gel: hyaluronic acid with amino acids[148, 149]	Alginate	Peptide: amino acids	Once per weekly visit/ 3 months	Vulnamin® gel reduced ulcer area from 59% compared to 23% for the control gel. Healing rate at 3 months was significantly reduced (60 days) compared to the control gel (80 days) Full wound closure reported for 61% of Vulnamin® treated patients compared to 27% of control gel treated patients.	Improved neuropathic leg ulcer healing, reduction in edema, granulation tissue Formation