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Innovations in Drug Delivery Systems for Enhanced Wound Treatment and Skin Regeneration

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Abstract

Skin damage is a common issue that many individuals experience, with chronic wounds and deep burns being particularly challenging to treat effectively. Current wound therapies have been found to be insufficient and unsatisfactory. The emerging field of nanotechnology presents a unique opportunity to revolutionize treatment approaches and enhance the efficacy of existing medical interventions. Specifically, nano-drug delivery systems have the potential to improve outcomes by anchoring bioactive molecules to the affected area, controlling drug release, and enhancing the therapeutic effects of medications. This article provides an overview and analysis of current nano-drug delivery systems that show promise for promoting wound healing and skin regeneration. Key technologies discussed include liposomes, polymeric nanoparticles, inorganic nanoparticles, lipid nanoparticles, nanofibrous structures, and nanohydrogels.

Keywords: Drug delivery; Nanoparticles; Microneedle patches; Nanotechnology; liposomes; Nanofibrous structures; Hyperglycemia; Molecular interactions; polymeric microspheres; Cefazolin

Abbreviations: ECM: Extracellular Matrix; DDS: Drug Delivery Systems; PLAGA: Poly(Lactide-Co-Glycolide); CS: Chitosan; PCL-TCP: Polycaprolactone-Tricalcium Phosphate; BC: Bacterial Cellulose; PVA: Poly(Vinyl Alcohol); PHB: Poly(3-Hydroxybutyric Acid); SSD: Silver Sulfadiazine; PVP: Poly(Vinyl Pyrrolidone); PLA: Polylactic Acid; DMOG: Dimethyloxalylglycine; PCL: Poly(ϵ-Caprolactone); VEGF: Vascular Endothelial Growth Factor; PDGF: Platelet-Derived Growth Factor; FGF: Fbroblast Growth Factor; Mmps: Mixed Metalloproteinases; EMT: Epithelial-Mesenchymal Transition; BFGF: Basic Fibroblast Growth Factor; Nano-Ddss: Nano-Drug Delivery Systems

Introduction

Skin becomes improved, resulting in better wound healing and regrowth. Researchers are investigating different technologies like biodegradable nanoparticles, hydrogels, microneedle patches, and smart dressings to improve drug delivery to wounds. These developments aid in both delivering therapeutic agents in a controlled manner and promoting the regeneration of skin tissues. By integrating these new methods of drug distribution, healthcare professionals can greatly enhance patient results and decrease the chances of infections and scarring. This study will explore the most recent advancements in drug delivery systems for improved wound treatment and skin regeneration, examining their modes of action, benefits, and possible influence on medical practice [1].

Researchers are investigating different technologies such as biodegradable nanoparticles, hydrogels, microneedle patches, and smart dressings to enhance drug delivery to wounds. These innovations aid in both delivering therapeutic agents in a controlled manner and promoting the regeneration of skin tissues. By integrating these new drug delivery methods, medical professionals can enhance patient results and lower the chances of infections and scarring. In this study, we will explore the most recent advancements in drug delivery systems for improved wound healing and skin rejuvenation, examining their modes of operation, benefits, and possible implications for medical treatment. Innovative drug delivery methods provide accurate management of therapeutic agents release, which enhances speedy wound healing and tissue regeneration. Recently, there have been notable developments in drug delivery systems for treating wounds and regenerating skin [2].

These new developments aim to enhance the efficiency of treatments, reduce side effects, and enhance patient results. Present studies concentrate on creating new methods of delivering

drugs, including hydrogels, microneedles, and nanoparticles, which can contain medicinal substances and release them precisely at the site of injury. Desired water levels can be adjusted according to your preference. Utilizing microneedles and hydrogels can improve the penetration of medication into the wound area, leading to expedited healing of persistent wounds.

This has the potential to transform wound care through offering more effective and precise treatment choices. Nanostructured drug delivery systems can be paired with imaging methods like MRI or ultrasound for real-time monitoring of drug distribution and enhancing treatment results. This method offers important information on how well the drug delivery system works and enhances patient results by making personalized treatment changes and monitoring drug effectiveness and distribution in real-time. By incorporating cutting-edge technologies like smart bandages and wearable sensors, medical professionals can remotely connect with their patients and observe the real-time progress of wound healing. This could result in identifying complications sooner and immediate action, ultimately enhancing patient results and improving overall patient care and quality of life. Furthermore, the integration of stem cell therapy into drug delivery systems holds potential for speeding up wound healing and tissue regeneration. Stem cells can transform into different cell types and support tissue healing, showing great potential in wound care and skin rejuvenation when incorporated into drug delivery systems.

An effective method is to utilize nanotechnology to encase medications in nanoparticles, improving their durability and precise transportation to areas of injury. Moreover, the advancement of intelligent wound dressings with sensors and controlled release mechanisms can enhance wound care by tracking and adjusting medication delivery according to individual wound characteristics. These smart dressings could transform wound care by accelerating healing and lowering infection risks, ultimately improving patient outcomes and quality of life. Furthermore, progress in microneedle technology has allowed for accurate administration of medications straight into the layers of the skin, avoiding the stratum corneum. This method enhances drug bioavailability and effectiveness, leading to quicker recovery and boosted skin renewal. Microneedle patches provide a painless and minimally invasive option for delivering medication, making them appropriate for all age groups. The advancements in drug delivery systems indicate a move towards individualized and specific treatments that improve the healing processes.

In addition, incorporating bioactive compounds and growth factors into drug delivery systems can greatly improve tissue regeneration and wound healing, providing hopeful remedies for stubborn skin injuries and chronic wounds. Researchers are looking to utilize the regenerative abilities of stem cells to enhance wound healing and skin regeneration by integrating stem cell therapy into drug delivery techniques. Stem cells have the ability to transform into different types of cells, encouraging the healing and regrowth of tissues. Researchers aim to improve the healing of tissues and wounds by merging stem cells with drug delivery systems to elevate the therapeutic impacts and regenerative capacities for more advanced treatments [3].

The combination of stem cell therapy and drug delivery systems has the capability to transform regenerative medicine through offering precise and efficient treatments for various skin injuries and wounds. Stem cell-filled hydrogels are a versatile platform that can be utilized. This targeted delivery system improves the precision of stem cell therapy by delivering therapeutic agents directly to the damaged tissue, maximizing efficacy and minimizing off-target effects. This approach allows for controlled release of bio availability and efficacy of the therapeutic agents, leading to better outcomes for wound healing and skin regeneration. In addition, the development of microneedle patches for drug delivery offers a pain-free and minimally invasive method for delivering drugs to the skin for enhanced wound healing and tissue regeneration. This review mainly introduces the wound healing process, the current wound treatment and their limitations, and the state of the art in nano DDSs that holds a promising potential for future application, with a special focus on liposomes, polymeric nanoparticles, lipid nanoparticles, nanofibrous structures and nano hydrogel [4].

Impaired angiogenesis is a major obstacle to DW healing, influenced by a complex interplay of factors [5,6]. Hyperglycemia has detrimental effects, inducing oxidative stress and inflammation, leading to endothelial dysfunction and compromised vascularization in the wound microenvironment [7]. This, in turn, impairs the natural angiogenic response crucial for effective wound healing. Neuropathy, common in diabetic patients, further contributes to this issue by diminishing sensory perception and motor control in the lower extremities, reducing blood perfusion, and impeding oxygen supply to the wound sites [8]. The compromised neural regulation further hinders the angiogenic processes required for DW healing. Furthermore, the extracellular matrix (ECM) in DWs exhibits an atypical composition compared to non-diabetic wounds. This aberrant ECM composition disrupts the normal signaling and molecular interactions necessary for angiogenesis [9].

The compromised neural regulation hinders the necessary angiogenic processes for DW healing. Additionally, the extracellular matrix (ECM) in DWs has an atypical composition compared to non-diabetic wounds. This altered ECM disrupts normal signaling and molecular interactions essential for angiogenesis. The unfavorable microenvironment created by increased deposition of specific proteins and remodeling enzymes in the ECM adds another layer of complexity to the impaired angiogenic cascade in DWs [10]. Recently, the stimulation of angiogenesis through a range of strategies, prominently including interventions based on biomaterials, has emerged as a promising strategy for augmenting the healing of DWs [11].

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Chronic wounds and infected wounds currently pose a significant burden worldwide. Drug delivery systems (DDS) in wound healing that release antimicrobial and anti-inflammatory drugs represent a great opportunity to prevent infections or enhance the effectiveness of current commercial drugs [12]. Many biocompatible biomaterials have been extensively investigated to deliver drugs into wound beds and to improve wound healing. Significant efforts have been made to develop DDS using different types of biomaterials, such as polymeric microspheres and nanospheres, lipid nanoparticles, nanofibrous structures, hydrogels, and scaffolds [13].

Delivery of Antibiotics

Healing a wound is a complicated procedure that frequently necessitates the use of antibiotics. DDS of antibiotics have garnered significant interest in optimizing and enhancing the utilization of existing antibiotics [14-17]. Cefazolin, gentamicin sulfate, ceftazidime pentahydrate, ciprofloxacin, gentamicin, doxycycline hyalite, and diclofenac are all antibiotics and anti-inflammatory drugs used in wound healing delivery systems [18]. Numerous biodegradable polymeric scaffolds (such as electrospun nanofibers, microspheres, composites, and films) were studied for antibiotic delivery, including electrospun nanofibers made from poly(lactide-co-glycolide) (PLAGA), composites with a polyglyconate core and a porous poly(dl-lactic-co-glycolic acid) shell, chitosan (CS)-gelatin composite films, a three-dimensional (3D) mesh of polycaprolactone-tricalcium phosphate (PCL-TCP), bacterial cellulose (BC) membranes with RGDC peptides (R for arginine, G for glycine, D for aspartic acid, C for cysteine), poly(vinyl alcohol) (PVA) microspheres enveloping poly(3-hydroxybutyric acid) (PHB) electrospun fibers, and β-cyclodextrin-conjugated hyaluronan hydrogels [19-21].

Delivery of Silver

solve the problem of the increased prevalence and growth of multidrug-resistant bacteria, silver is used to reduce and eliminate wound infections using methodologies that limit the ability of bacteria to evolve into further antibiotic-resistant strains [22,23]. In recent decades, the developments of silver (colloidal silver solution, silver proteins, silver salts, silver sulfadiazine (SSD) and nanosilver) containing wound dressings for healing promotion and infection reduction have provided promising approaches [24]. The main synthesis approaches of silver monocrystalline silver (nanosilver or silver nanoparticle) include chemical reduction, microorganism reduction, microwave-assisted photochemical reduction, and laser ablation. Antibacterial wound dressings in the formats of AgNP-embedded poly (vinyl pyrrolidone) (PVP) hydrogels were prepared by γ-irradiation at various doses: 25, 35, and 45kGy [25].

Antibacterial tests showed that the 1 and 5mM AgNP-embedded PVP hydrogels were effective, with 99.99% bactericidal activity at 12 and 6h, respectively. A gamma-irradiated PVA/nanosilver hydrogel was also developed for potential use in burn dressing applications [26]. Interestingly, the wound healing activity of 0.1% w/w AgNPs in Pluronic F127 gels was enhanced to a considerable extent [27]. A new type of high surface area metallic silver in the form of highly porous silver microparticles (AgMPs) was studied [28]. Polylactic acid (PLA) nanofibers were successfully loaded with either highly porous AgMPs or AgNPs. A simulated three-dimensional (3D) coculture system was designed to evaluate human epidermal keratinocytes and S. aureus bacteria on the wound dressings. PLA nanofibers containing highly porous AgMPs exhibited steady silver ion release at a greater rate of release than nanofibers containing AgNPs. In recent years, there have been significant advancements in drug delivery systems for wound treatment and skin regeneration. Traditional methods of application, such as creams and ointments, have limitations in terms of efficacy and controlled release of active ingredients. However, innovative drug delivery systems, including hydrogels, nanoparticles, microneedles, and transdermal patches, offer more precise and targeted delivery of therapeutics to the site of injury. These technologies not only enhance the efficacy of treatments but also improve patient compliance and reduce side effects. Moreover, these systems can be tailored to release drugs in response to specific stimuli, such as pH, temperature, or enzyme activity, further optimizing the healing process. These innovations hold great promise for the future of wound treatment and skin regeneration, offering new possibilities for personalized and effective therapies. These innovations in drug delivery systems allow for tailored release of drugs based on specific stimuli, such as pH, temperature, or enzyme activity. This personalized approach optimizes the healing process and minimizes potential side effects, making treatment more effective and efficient. Personalized drug delivery systems revolutionize wound care by providing individualized treatment plans based on the unique needs of the patient.

This approach allows for targeted delivery of therapeutics, enhancing the overall outcome of wound treatment and skin regeneration. Personalized drug delivery systems also minimize unnecessary exposure to medications and reduce the risk of adverse effects. These systems can be tailored to release medications gradually over time, ensuring sustained effectiveness and improved wound healing. Additionally, personalized drug delivery systems contribute to improved patient outcomes by promoting faster healing and minimizing scarring. Patients benefit from individualized treatment plans that address their specific wound care needs.

By incorporating advanced drug delivery systems, these innovative drug delivery systems offer a more targeted and efficient approach to wound treatment, ultimately leading to better outcomes for patients. Personalized drug delivery also allows for a more precise dosage tailored to the patient's unique requirements and response to treatment. This ensures that the right amount of medication is delivered to the wound site at the right time, maximizing therapeutic benefits and minimizing potential side

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effects. This targeted approach is especially beneficial for patients with chronic wounds or skin conditions that require long-term treatment.

Personalized drug delivery systems can also be integrated with smart technology, such as sensors and monitoring devices, to provide real-time feedback on wound healing progress. Furthermore, personalized drug delivery systems can be combined with nanotechnology to further enhance targeted drug delivery to specific areas of the wound, allowing for precise and controlled release of medications. Nanotechnology enables the development of Nano-sized drug carriers that can penetrate deeper layers of the skin, delivering drugs directly to the site of action. This targeted approach increases the efficacy of the medications and reduces the risk of systemic side effects. By incorporating nanotechnology into personalized drug delivery systems, healthcare providers can ensure that medications reach their intended target more efficiently.

Physiology of Wound Healing

Wound healing often refers to skin damage, to which various factors aid in its repair. Skin is the largest organ in the human body, designed to protect against a variety of environmental factors such as infections, superficial damage, ultraviolet radiation, and temperature changes. However, skin wounds are inevitable throughout the course of living, hence having an optimal repair mechanism is crucial. When a skin wound occurs, the normal healing stages involve haemostasis, inflammation, proliferation, and remodeling (Figure 1). In this case, nanomaterials can be applied to all phases of wound healing, accelerating its progression, preventing infections, and improving scar formations. Haemostasis When a wound is infected, haemostasis occurs, the wound constricts to prevent blood loss by narrowing the damaged blood vessels through the increase of cytoplasmic calcium levels in smooth muscle cells present in the vessel wall, inducing contraction. This leads the reduced oxygen transfer to tissues, inducing hypoxia and acidosis which further triggers the release of vasoactive metabolites for vasodilation and blood vessel smooth muscle relaxation. The vasodilation together with vascular permeability from mast cell histamine release encourages the next phase, the inflammatory phase, to take place by allowing the influx of immune cell entry.

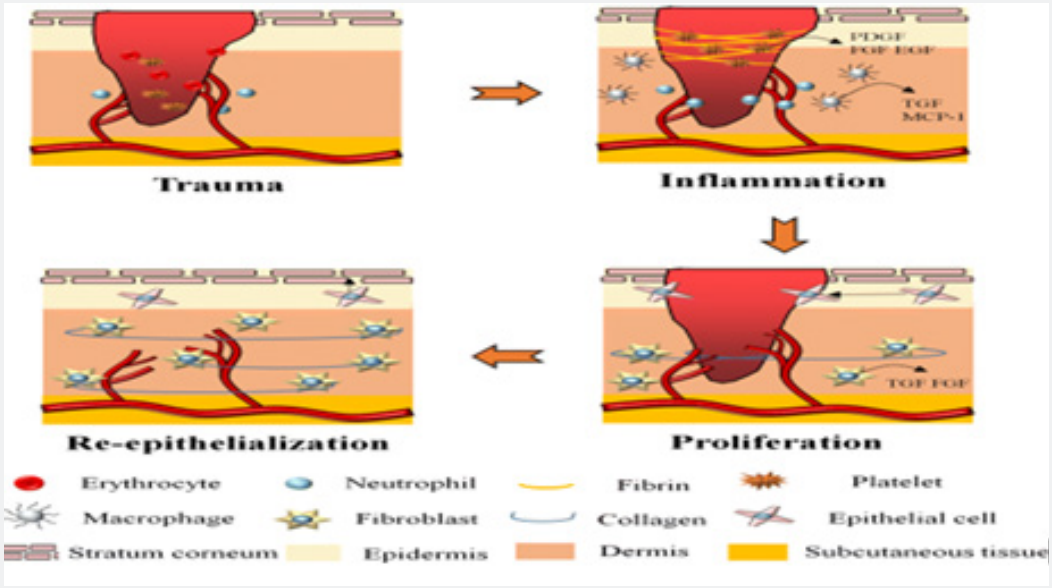

Figure 1: Nano-drug delivery systems in wound treatment and skin regeneration.

Intrinsic pathways also facilitate the release of activated platelets for fibrin clot formation. The haemostasis phase occurs immediately upon wound infection and functions to restore homeostasis through re-establishing vascular structure, forming a protective barrier against the external environment and prevent excessive blood loss. Imbalances in this meticulous process threaten mortality from thrombotic or haemorrhagic conditions [18]. However, the addition of nanomaterials at this stage of wound healing may prove beneficial. Nanomaterials contain haemostatic qualities, such as nano sponges' porous formation aid in exudate absorption. Nanomaterials can protect the surface of the skin wound and accelerate blood clotting. Nanomaterials also contain electrostatic adsorption properties, which encourage the recruitment of various blood cells such as platelets, erythrocytes, and leukocytes, as well as the adhesion of fibroblasts together with fibrin crosslinking at the wound site [19,20].

For instance, Saikia and colleagues studied the effects of silica nanoparticles, which are inorganic nanoparticles, and its influences on platelet adhesion under flow conditions. They observed cellular surface interactions of these nanoparticles with the upregulation of platelet endothelial cell adhesion molecule 1 (PECAM-1). Different nanomaterials can also benefit haemostasis

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with different mechanisms of action. Carbon nanotubes, another inorganic biomaterial, improve wound healing by inducing platelet activation and aggregation, as well as upregulating thrombosis []. Nanomaterials applied at the haemostatic phase of wound healing act as an active wound dressing by accelerating through the wound healing phases, which are largely more beneficial than traditional dressings such as gauze and tulle, requiring frequent changes to avoid healthy tissue maceration.

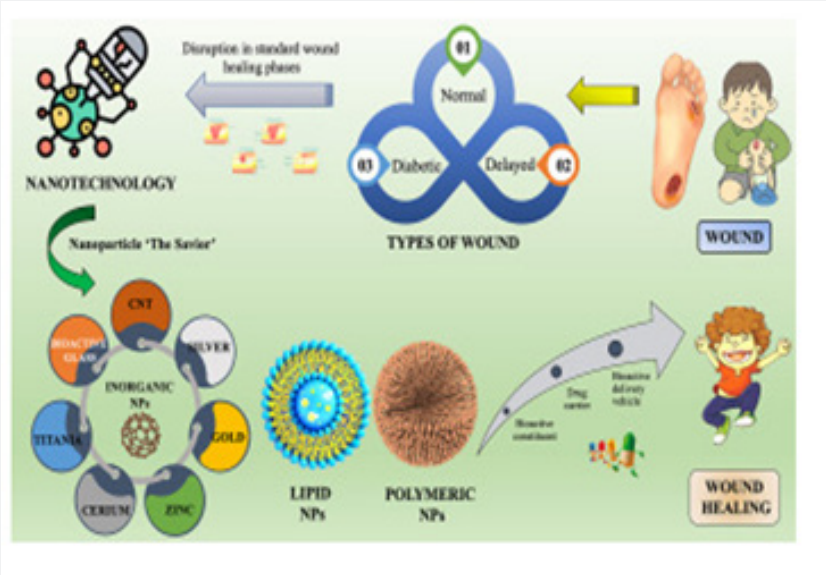

Figure 2:

Figure 3: Drug Delivery System in Wound Healing.

Inflammation

In the inflammatory phase, the immune system aids in protecting the wound from infections. Neutrophils are activated within one hour of a wound, acting as the first line of defense against pathogens in reaction to chemical signals. Neutrophils fight off pathogens by employing phagocytosis and degranulation. Neutrophils use phagocytosis to engulf and digest invading pathogens. Neutrophils release harmful substances such as lactoferrin and proteases during degranulation to enhance pathogen elimination. After neutrophils finish their tasks, they will either undergo apoptosis or be engulfed by macrophages for elimination. Chemical signals are released from the wound area to attract macrophages within 48-72 hours of injury. Macrophages are vital in the healing process as they hold growth factors needed to fix wounds. Macrophages contain growth factors such

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as TGF-β and EGF which help to improve reepithelialisation, collagen production, and angiogenesis. Following macrophages, lymphocytes migrate to the wound site to aid in healing, releasing ECM compounds and depositing collagen to promote skin repair. Lymphocytes also help decrease the immediate scarring that occurs during skin wound healing. The process of wound healing will keep going until all bacteria in the wound are eliminated. However, if wound sites are enlarged during the inflammatory phase, it may lead to impaired wound healing and the development of noticeable scars.

In this phase, applying nanomaterials to the wound area may be beneficial, especially for persistent wounds that remain inflamed. Diabetic ulcers with lasting injuries heal slower due to elevated blood glucose levels, hindering blood vessel formation and reducing oxygen and nutrient delivery to the wound. Long-lasting wounds are still in ongoing inflammation and are prone to infections. During the inflammatory phase, the immune system helps protect the wound from infections. Neutrophils are quickly recruited within one hour after the injury occurs and serve as the first defense against pathogens, triggered by chemical signals. Neutrophils combat pathogens by engaging in phagocytosis and degranulation. Neutrophils engage in phagocytosis by surrounding and breaking down the invading pathogen.

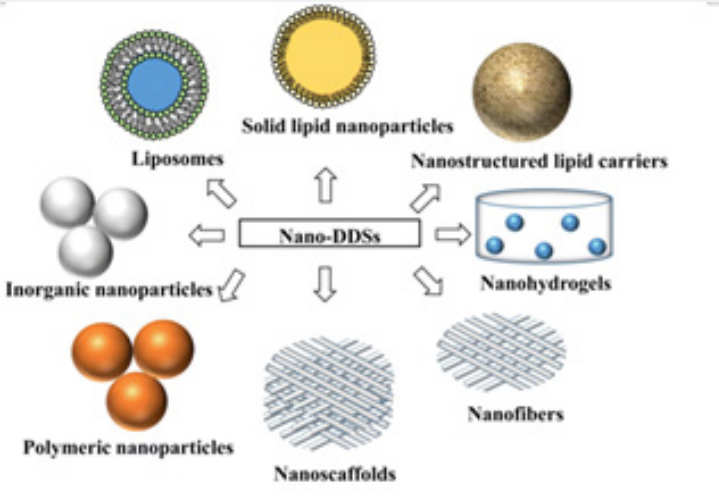

Figure 4: Nano-drug delivery systems in skin regeneration and wound treatment.

During degranulation, neutrophils release harmful chemicals like lactoferrin and proteases to help get rid of pathogens. Once neutrophils have finished their tasks, they will be eliminated either by apoptosis or macrophage phagocytosis. Chemical signals released from the wound site attract macrophages after 48–72 hours of inflicting the wound. Macrophages play a crucial role in the process of wound healing by containing a variety of essential growth factors required for repairing wounds. Macrophages have growth factors like TGF-β and EGF that help enhance reepithelialisation, collagen formation, and angiogenesis. After macrophages, lymphocytes are brought to the wound location to support the ongoing healing process by secreting ECM components and depositing collagen to assist in skin reconstruction. Lymphocytes help decrease early scar formation while healing skin wounds. The healing of the wound will stay in the inflammatory phase until all pathogens in the wound are removed. Yet, extended inflammation at wound sites can hinder the proper advancement of wound healing.

In this phase, the application of nanomaterials on the wound site may be beneficial, especially for chronic wounds which often remain in the inflammatory stage. Chronic wounds such as diabetic ulcers remain in a longer healing duration due to hyperglycinemia, causing difficulties in angiogenesis as well as reduced oxygen and nutrients to the site of injury. Chronic wounds are in constant inflammation, prone to bacterial infections, and have downregulated growth factors. Because of this, various bioactive and non-bioactive components can be included into healing wounds at the inflammatory stage.

Bioactive molecules like growth factors, proteins, mesenchymal stem cells, and drugs can be incorporated into nanomaterials. Zhang et al. demonstrated electro spun dimethyloxalylglycine (DMOG)-embedded poly(ϵ-caprolactone) (PCL) fiber (PCLF/DMOG) meshes applied onto diabetic rat wounds and found to have downregulated pro-inflammatory factors as well as upregulated anti-inflammatory factors and growth factors. Comparatively, non-bioactive elements such as metal ions, chitosan nanoparticles, and silica nanoparticles often offer antibacterial and antioxidant properties. One example includes Ahmed R. and colleagues fabricated electro spun chitosan/polyvinyl alcohol (PVA)/zinc oxide nanofibrous mat for diabetic wounds. The biomaterial

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contains antibacterial activity against E. coli, P. aeruginosa, B. subtilis, and S. aureus, as well as exhibited antioxidant potentials and upregulated wound healing process.

Proliferation

The next wound healing phase after haemostasis and inflammation is the proliferative phase. Proliferation in wound healing involves the process of skin reparation, which consists of angiogenesis, granulation tissue formation, re-epithelialisation, and wound constriction.

Angiogenesis

Angiogenesis involves the reformation of the vascular network and is a significant process for the delivery of oxygen and nutrients to wound healing. The wound site initially does not contain any vascular networks, solely relying on neighboring healthy capillaries for diffusion. The process of angiogenesis begins after the formation of a haemostatic plug, with the release of vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and fbroblast growth factor (FGF) from platelets. VEGF is released due to hypoxic wound site conditions, aiding endothelial cell recruitment for neovascularization and blood vessel repair [30]. Mixed metalloproteinases (MMPs) also play a role in wound healing, which are enzymes induced through the presence of hypoxic-conditioned neutrophil recruitment, encouraging angiogenesis through releasing VEGF and ECM reconstruction. New blood vessels are formed from this process, which permeates the wound site originating from neighbouring blood vessels [31].

Granulation

Tissue formation after wound infection, growth factors such as TGF-β and PDGF from the haemostatic plug enhance the recruitment of fibroblasts to the wound site. After 3 days, the fbroblast-rich wound will have an abundance of ECM proteins, aiding in collagen assembly and fibronectins. This results in a fibrous tissue with an extensive vascular network known as granulation tissue, which substitutes the previous clot formed. After the proper establishment of the ECM, fibroblasts are converted to myofibroblasts, with pseudopodia functioning to assist wound contraction through connecting with collagen and fibronectin present in the microenvironment. Myofibroblasts are also involved in angiogenesis through MMPs activity regulation.

Re- epithelialisation

Epithelial cells respond quickly to wound inflictions, as upon injury the bordering cells differentiate to cover the wound and connect with the matrix formed underneath. The process of re-epithelialisation is important as it acts as the defining step of a healed wound by covering the since-removed epithelial skin layer. Epithelial cells gain kinesis through epithelial-mesenchymal transition (EMT), allowing for motion in wound closure [33]. Cytokines are also present in varying concentrations during re-epithelialisation, aiding in epithelial cell morphology alteration, changing from cells with motility to a proliferative stage for repopulation at the wound site, thus completing the wound healing process [34]. This process is direct for primary intention wound closure. For a secondary intention wound, however, significant wound contraction must occur at the beginning before the re-epithelialisation process can begin. If the wound site is too large and wound contraction cannot occur naturally, skin grafts are available to aid the process.

Wound Constriction

After re-epithelialisation is complete, myofibroblasts begin to aid in wound retraction after 1 week of wound closure. Actin and myosin proteins play a role in bringing cell bodies closer to reduce the distance needed to overcome during healing. Contraction rates average 0.75mm per day depending on wound morphology such as wound size and shape. Distortions on the skin known as contractures can occur if wound retraction does not progress normally.

Remodeling

Remodeling of the wound is considered the final process in wound healing, beginning at 2 weeks upon wound infliction and taking up to 2 years to complete. The purpose of the remodeling phase is to achieve a synthesis and degradation equilibrium, gaining maximum tensile strength. This phase primarily focuses on the organization of all proteins and cellular components present to achieve normal skin structure. Granulation tissue is also remodeled into scar tissue, with type I collagen being converted into type III collagen, achieving the structural morphology of a scar. However, healed wounded skin will regain equal tensile strength as compared to normal unwounded skin, achieving a maximum of 80% while averaging at only 50%. As we can see from the above detailing, the proliferative phase is a significant event in wound healing due to the recruitment of fibroblast for proliferation, blood vessel formation, and wound closure. As with the previous phases, nanomaterials can also be applied to this phase.

For instance, Losi et al. combined VEGF and basic fibroblast growth factor (bFGF) into poly(lactic-co-glycolic acid) (PLGA) nanoparticles, which successfully upregulated granulation tissue formation, collagen deposition, and complete re-epithelialisation [38]. With the myriad of nanomaterial varieties available for wound healing applications, different nanomaterials can be used to yield similar results. Chitosan-based copper nanocomposites applied on adult Wistar rat excised wounds demonstrated successful fibroblast proliferation, re-epithelialisation, and collagen deposition, which accelerated healing time. Besides the reliance on wound healing physiology, various internal and external factors also contribute to its success or failure. External factors would include nutrition, smoking, infections, and wound management. Whereas internal factors such as age, chronic

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diseases, immunosuppression, and genetics all play a role in determining the rate and morphological aesthetic of healing wounds.

Nano Hydrogel

Nanohydrogel, a three-dimensional polymer structure, is viewed as a superior option for treating wounds because of its distinct characteristics. The nanohydrogel's porous structure enables it to absorb aqueous fluids, which helps prevent wound dehydration and promotes healing by maintaining a moist environment. Its lack of stickiness helps maintain the wound area intact and promotes oxygen flow, which is crucial for the healing process. The pleasant feeling of nanohydrogel offers relief while undergoing treatment. Moreover, nanohydrogel can effectively trap a variety of drugs, thereby increasing its effectiveness in promoting skin regeneration. One instance is the gellan-cholesterol nanohydrogel with baicalin, which speeds up the process of healing wounds. The nanohydrogel, with suitable viscosity, enhanced skin retention, and biocompatibility, was evaluated on a mouse model with skin inflammation, displaying positive outcomes in skin repair and reducing inflammatory markers. A different research project presented a hydrogel made of bacterial nanocrystal cellulose and acrylic acid, which enhanced fibroblast attachment, preserved cell function and shape, restricted cell movement, and impacted gene activity associated with wound repair.

Nanocomposite hydrogels containing natural polysaccharide κ-carrageenan and nanosilicates have attracted attention as injectable nanohydrogel formulations. This nanohydrogel showed great mechanical rigidity, excellent porosity, and improved cell adhesion and spreading with VEGF, indicating promise for tissue regeneration. More investigation is required to completely grasp the healing abilities of these new nanohydrogel formulas in wound treatment.

Conclusion

The management of chronic wounds and ulcers presents a significant challenge due to the limited success of current treatment modalities in promoting effective wound healing. However, the emergence of nano-drug delivery systems (nano-DDSs) in recent years has provided a new perspective on skin regeneration for wound healing. These drug carriers offer advantages such as sustained drug release, protection against degradation, and enhanced skin retention, thereby enhancing the therapeutic efficacy of both biological and synthetic molecules. By reducing or eliminating wound bacterial load and promoting re-epithelialization, nano-DDSs have shown promise in improving wound healing outcomes. Additionally, the combination of nano-DDSs as synergistic delivery platforms has the potential to create an optimal physiological environment for the healing process. Despite the considerable potential of nano-DDSs, there are challenges in research, including the lack of standardized international protocols for evaluating their toxicology, biocompatibility, and targeting efficiency. Furthermore, the complex preparation procedures of nano-DDSs pose limitations on industrial production. Nevertheless, researchers are increasingly focused on maximizing the benefits of nano-DDSs, overcoming technical obstacles, and ultimately providing tangible advantages for patients with wounds. It is anticipated that nano-DDSs will emerge as a promising and cost-effective therapeutic approach to enhance wound healing and skin regeneration.

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