REVIEW ARTICLE

Revolutionizing Wound Healing: The Rise of Electrospinning Nanofibers for Bioactive Dressings

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ABSTRACT

A noticeable focus in recent years has been on creating bioactive dressings that are tailored to meet the requirements of wounds that are both acute and chronic. Because of these exceptional properties, electrospinning nanofibers stand out as a potential choice among the creative solutions being investigated. Among these are very high porosity and superior permeability to water and air, both of which are essential for promoting wound healing conditions. Moreover, these nanofibers' ability to ward against foreign infections makes them an attractive option for improving wound care protocols. It is particularly notable because they closely mimic the extracellular matrix since this property can greatly enhance the efficacy of skin regeneration and wound healing processes. The present study aimed to explore the use of electrospinning nanofibers for bioactive dressings and wound healing. Extensive literature search was performed and relevant articles were collected from various databases like Google scholar, Taylor and Francis, Science direct, Springer, Embase, and Willey. Electrospinning nanofiber applications for the bioactive healing of wounds. The investigation begins with a comprehensive review of the wound healing procedure and the several electrospinning techniques used here. The many natural and synthetic polymers that are used to make electrospinning wound dressings are discussed in more detail. Prominent natural polymers, including hyaluronic acid, collagen, gelatin, silk fibroin, chitosan, and sodium alginate, are emphasized due to their special qualities and possible advantages in wound treatment. Furthermore, the paper explores the wide application of artificial polymers such as polyvinyl alcohol, polyvinyl chloride, polyethylene lactone, polylactide, and polyurethane, providing insight into their roles in the advancement of sophisticated wound dressings. In conclusion, the development of electrospinning technology offers promising prospects for creating improved wound care products and dressings that have the potential to completely transform the wound management industry.

Keywords: Polymer, Electrospinning, Nanoformulations, Wound healing.

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INTRODUCTION

Based on their origins and features, skin wounds may be divided into two main types. Firstly, acute wounds arise from various situations, including surgical procedures, traumatic events, exposure to radiation, abrasions, and superficial burns. On the other hand, chronic wounds develop due to underlying health issues like diabetic ulcers, pressure ulcers resulting from prolonged immobility, and venous leg ulcers linked to venous insufficiency.[1] Proper differentiation between these types is crucial for providing tailored care and effective management strategies to maximize wound healing results. To facilitate cell growth and promote efficient healing, it is essential to perform debridement to remove any debris or damaged tissue from the wound. Subsequent meticulous cleaning and swabbing of the wound site are imperative to prevent infections and maintain a sterile environment conducive to healing.[2] The application of a suitable dressing is pivotal, serving as a protective barrier against infections and expediting the overall healing process. Dry gauze is a popular choice in modern medical practices due to its affordability and widespread availability. Nonetheless, dry gauze has limitations such as the potential for bacterial growth, risk of wound dehydration, and the delicate nature of newly formed epithelium, which could be prone to reinjury during dressing changes.[3] Recognizing these challenges, the field of wound care has witnessed the development of more advanced dressings with enhanced functionalities. Advanced materials like hydrocolloids and hydrogels have been engineered to facilitate gas exchange, absorb exudate, maintain a moist

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wound environment, and prevent microbial colonization.[4] In addition to offering antimicrobial properties, these modern dressings contain biological components that promote proper matrix formation, support local cell migration, and stimulate cell proliferation at the wound site.[5] The continuous evolution of wound dressings reflects ongoing efforts to optimize healing processes and improve patient outcomes in the field of wound care, showcasing a commitment to innovation and enhancing the overall standard of care in managing skin injuries.[6]

Wound Healing Process

Hemostasis/bleeding, inflammation, proliferation, and remodeling are the four discrete steps that comprise the overall wound healing process as seen in Figure 1. Vascular constriction is a crucial first stage in the process of hemostasis since it causes the blood to coagulate and subsequently slow down its flow to the wounded tissue location.[7] Following hemostasis, the inflammation stage takes charge, facilitating the influx of nutrient-rich blood to the area of damage, thereby promoting the expansion of the wounded tissue.[8] This crucial period sets the foundation for the subsequent phases, ultimately culminating in the intricate process necessary for full tissue regeneration and restoration.[9]

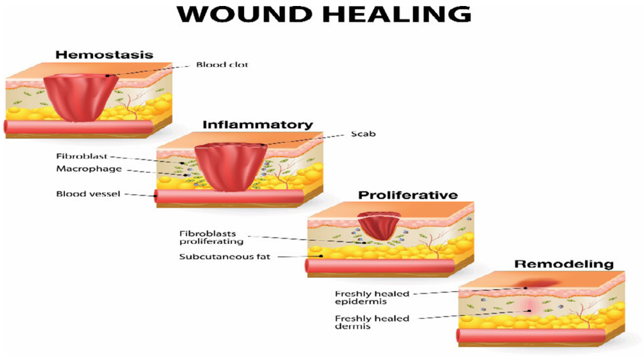

Figure 1: Breakdown of the complete wound healing process

Types of Wound Dressing

Due to the potential risk of heightened infection levels, the traditional view perceived wound dressing as deviating from proper wound care practices. These research studies have illuminated how wound dressings play a crucial role in facilitating cellular migration, proliferation, and other essential processes essential for overall wound improvement.[10] Furthermore, scientific evidence solidly backs the idea that the presence of scabs forming over dry wounds can impede epidermal renewal, heighten discomfort, and foster the development of scarring.[11] According to this correlation, dressings play a crucial role in the healing process as they help maintain the optimal moisture level in the wound bed, which is essential for effective healing. Factors such as the location, size, and severity of the wound must be carefully considered when choosing the appropriate dressing for effective treatment.[12] Figure 2 describes the structure of wound dressing and its process

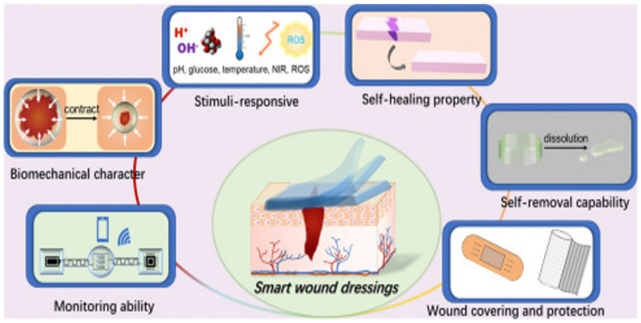

Figure 2: Structure of wound dressing and its process

It is essential to categorize the more than 3000 different types of wound dressings on the market into four main groups: Bioactive, advanced, interactive, and passive.[13] These dressings are known for their limited ability to control the amount of moisture present, often leaving the wound bed exposed to potential harm from mechanical forces and bacterial infections.[14] Even with these drawbacks, taking off the bandages can sometimes result in further harm to the wound due to the risk of causing mechanical damage during removal. This dilemma has led to a preference for low-adherent dressings that are designed to minimize sticking to the wound bed while still enabling wound exudate to pass through and maintain adequate hydration levels.[15] Particularly suitable for smaller wounds, this type of dressing has proven to be highly effective. Bandages, which come in a variety of compositions from natural fibers to synthetic materials, are a typical example of a passive dressing when used in conjunction with other wound care treatments like gauze or tapes. Because of their great flexibility, interactive dressings are widely appreciated.[16] This dressing stands out from others due to its ability to contain exudate while protecting the wound from further damage. Additionally, hydrogel dressings, known for creating a moist wound environment, aiding in exudate absorption, and promoting autolysis and debridement, are particularly useful for managing necrotic wounds.[17] They offer versatility as they can be used for various wound types with minimal to no fluid discharge, showcasing their effectiveness in wound care practices. Advanced dressings are made of hydro-fibers, hydrocolloids, and alginates, which can promote wound healing by preserving moisture in the wound environment.[18] Hydrocolloids are semipermeable film carriers coupled with materials such as sodium carboxymethylcellulose, elastomers, pectin, and gelatin to generate a flat dressing. Hydrocolloid gels are commonly applied to the surface of wounds to promote healing and can be used for dry wound rehydration. They are simultaneously impervious to microorganisms and hold both air and water vapor. The biodegradability, longevity, and user-friendliness of these dressings are further appealing attributes.[19] It has also been demonstrated that this class of dressings lessens discomfort without macerating or depriving the epidermis. Hydrocolloids have proven to be exceptionally effective in various aspects, including not only preventing infections but also hastening the healing process of wounds due to their remarkable special qualities.[20] These novel dressings offer benefits beyond conventional methods by using unusual substances such as alginates, which are calcium and alginic acid sodium salts that exist naturally. Alginates serve as a gel-like substance that efficiently absorbs excessive fluids discharged from the wound, thereby expediting the healing journey.[21]

Innovations in Material Science: The Electrospinning Technique

Nano- and micro-fibrous substrates can be made by the material science process of electrospinning, which employs polymers. The process includes polarization and the production of the Taylor cone by extruding a viscoelastic droplet and applying a high-voltage positive charge. The charged jet solidifies into fibers, forming the fibrous substrates.[22] In industries like environmental research and biology, this procedure is essential for creating substrates with structural integrity and a wide range of uses. Fiber strands assemble on the anode to form a continuous mat, as seen in Figure 3. System parameters such as solution viscosity, solvent volatility, polymer molecular weight, and solution conductivity, in addition to environmental factors, govern the mechanical properties and fiber structure of electrospun fibers.[23] The needle tip-collector distance, feed rate, and applied voltage are examples of process parameters. Scaffolds are carefully created using the novel technique of electrospinning, also known as electrostatic spinning, and are employed in a variety of medicinal applications.[24] An electrospinning device, which is required for this process, is composed of three basic components: A high-voltage source, a collector, and a supply system. The supply system, which typically consists of a metallic pointed end attached to a syringe filled with molten polymers for melt electrospinning or a polymer solution for suspension electrospinning, is a crucial part of the equipment.[25] Because of its intricate setup, electrospinning is considered a state-of-the-art method in the field of advanced medical treatments. It allows for the precise creation of non-woven scaffolds, each of which is tailored to meet specific therapeutic requirements.[26] A high voltage of between 5 and 60 kV is applied to both the metallic needle and metallic collector, which are crucial components in the electrospinning process. The molten or polymer solution droplet changes by producing electric charges at the needle's surface. When the electric force surpasses the surface tension of the droplet, a polymeric filament is discharged from the cone's tip onto the awaiting collector. As the new filament takes shape, As the initial droplet dries up, a new one appears to take its place, restarting the filament manufacturing cycle. The network of unwoven fibers expands on the collector's surface with each filament deposition, causing the polymeric structure to enlarge gradually.[27] Hassiba *et al.* claim that the size and properties of the electrospun nanofibers may be adjusted by adjusting a range of operating parameters, including voltage settings, needle-to-collector distance, and environmental factors, including temperature and humidity.[28] Furthermore, the nanofibrous filament aligns with the main fiber axis due to an electrostatic force created by the voltage applied during the electrospinning process.[29] This alignment further enhances the structural integrity and functionality of the nanofibrous network, making it more conducive to promoting effective wound-healing processes. The fluid absorption capacity and water vapor transfer rates play a vital role in determining the effectiveness of nanofibers when used in wound dressings.[30] These characteristics not only showcase the material's innovative nature but are also essential factors for assessing the dressing's ability to regulate the ideal moisture level crucial for promoting proper cell growth and function within the wound area.[31] By carefully considering a dressing's capacity to maintain optimal moisture levels, healthcare providers can ensure an environment conducive to the growth and activity of epithelial and fibroblast cells, which are pivotal in the wound healing process.[32] Therefore, an in-depth understanding of how these characteristics influence the wound environment is key to selecting the most suitable dressing that can support and expedite the healing process through its ability to manage moisture effectively, facilitating tissue regeneration and proper wound closure on time.[33]

Table 1 describes the natural polymers and their properties as candidate materials for electrospinning

Natural and Synthetic Polymer Dressings

Natural polymer dressings

As shown in Table 1, non-woven electrospun meshes have been creatively created and demonstrated to meet the unique needs of localized skin regeneration by utilizing a wide range of natural biopolymers.[34] These naturally occurring polymers can be broadly classified into two categories: carbohydrates and proteins. Well-known protein-based polymers, including collagen, elastin, gelatin, and silk fibrinogen, have attracted a lot of attention from researchers studying wound healing. On the other hand, carbohydrate-based polymers, including cellulose, hyaluronic acid, dextran, and chitosan, have also gained increasing recognition because of their exceptional biocompatibility, minimal antigenicity, and beneficial bioactivity that encourages cell adhesion and proliferation.[35] Notably, the extracellular matrix (ECM) that was originally present in the electrospun dressing materials generated with these natural polymers is chemically comparable to it, which enhances the dressing materials' ability to promote skin regeneration.[36] However, natural polymers display complex chemical configurations and a broad range of physicochemical characteristics due to their varied origins and structural differences.[37] For example, the molecular weights of certain natural polymers influence their viscosity, which in turn affects how quickly they dissolve and degrade in solution.[38] When trying to generate uniform and smooth fiber structures during the electrospinning process, the complexities resulting from the different characteristics of natural polymers provide obstacles.[39] Furthermore, natural polymer fibers' low mechanical strength poses a barrier to their use as environmentally friendly materials for wound dressings. These intrinsic intricacies highlight the necessity of more research and development in the application of natural biopolymers for improved wound care remedies.[40]

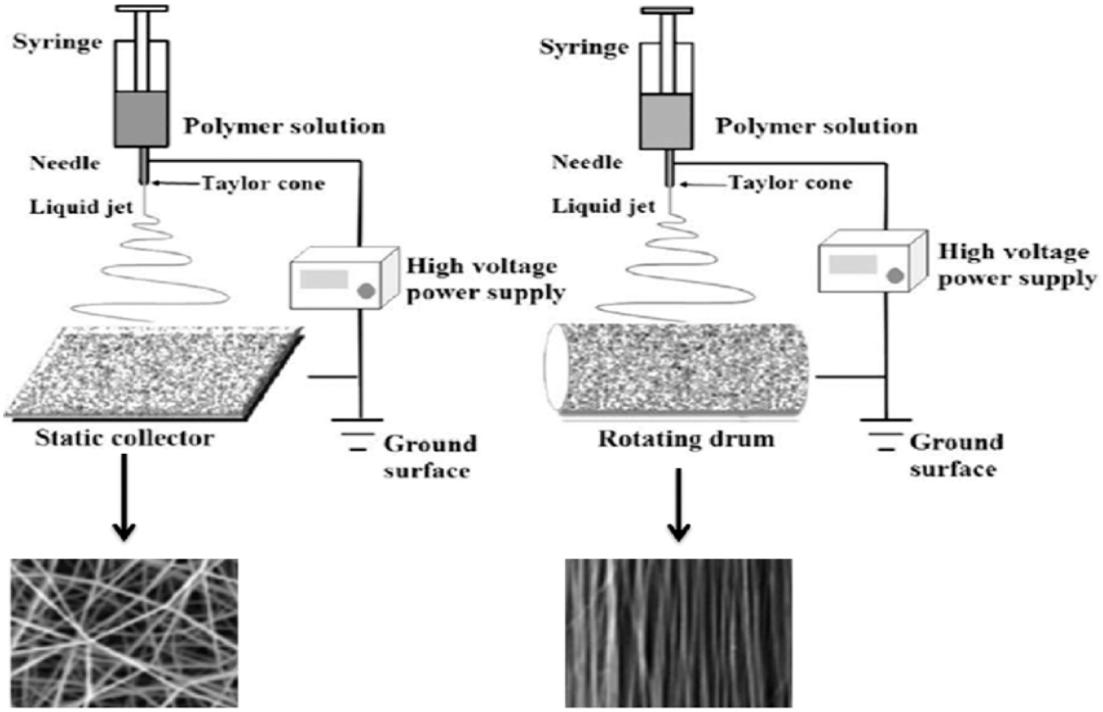

Figure 3: Schematic illustration of the electrospinning process for nanofiber fabrication

Protein-based electrospun wound healing dressings

The most widely employed proteins for electrospun wound healing applications are collagen, silk fibroin, and gelatin; due to their unique properties, these three proteins have all been thoroughly investigated. Gelatin, or partially hydrolyzed collagen, is a crucial component of skin and connective tissue.[41] It possesses several advantageous biological characteristics. For example, gelatin is a useful substance for wound healing applications since it has been shown to activate macrophages, biodegrade quickly, have significant hemostatic effects, and not be immunogenic.[42] Researchers led by Butcher have explored the impact of solution parameters on the mechanical properties and fiber morphology of gelatin electrospun fibers, noting that gelatin sourced from cold-water fish presents distinct rheological characteristics and a lower gelation temperature due to its reduced proline and hydroxyproline content.[43] In the quest for homogenous and bead-free scaffolds, Cheng and colleagues optimized solution parameters to enhance fluid drainage and biocompatibility by controlling the evaporative water loss during the electrospinning process of gelatin/PLLA poly(L-lactide) fibers.[44] Furthermore, Jalaja and the team demonstrated that electrospinning gelatin in a water-based solution could reduce toxicity and improve cell viability, with the possibility of cross-linking using oxidized sucrose for added stability.[45] Considering silk fibroin, another protein that is frequently utilized for scaffold electrospinning, its remarkable mechanical and biological characteristics have elevated it to the status of a potential biomaterial for a range of tissue engineering uses. Silk fibroin generated from insects and spiders has shown promise in the reconstruction of many different tissues, such as the trachea, bladder, skin, vascular, bone, and neural. Researchers added sulfate groups to silk fibroin to improve the scaffolds' anticoagulant properties and stimulate the development and proliferation of new blood vessels. The most prevalent protein in the human body and an essential part of the extracellular matrix, collagen, is essential to the use of electrospun nanofibers.[46]

Electrospinning synthetic polymer wound dressing

in nanofiber electrospinning methods, synthetic polymers with exceptional mechanical qualities, thermal stability, and processing flexibility are frequently used. It is possible to create nanofibers that properly balance the properties of mechanical strength and degradability by modifying the solvent type and the molecular weight of the polymer to meet the unique needs of wound healing.[29] Numerous synthetic polymers, each with their benefits, are used in wound healing applications. Table 2 provides a thorough analysis of the benefits and drawbacks of several synthetic polymers that are often utilized in wound healing applications.

These include polyvinyl alcohol (PVA), polyvinyl chloride (PEO), poly(lactide) (PCL), polylactic acid (PLA), and polyurethane (PU). It is possible to effectively accelerate the wound-healing process by combining various polymers. Combining different polymers offers advantages as well as the ability to improve wound healing.[47] Because of its great biocompatibility and slow degradation in the human body, PCL is widely used as an implanted medication. Because PCL and polyethylene glycol (PEG) are so versatile, they may be copolymerized to create very hydrophilic, non-toxic, and

Table 1: The characteristics of natural polymers as potential electrospinning materials

Natural polymers	*Advantageous properties*	*Disadvantageous properties*
Hyaluronic acid	Strong mechanically, biocompatible, promoting cell migration, differentiation, and proliferation, controlling metabolism and the extracellular matrix's structure, and preserving the hydration, elasticity, and wetness of the skin	very low amounts of high viscosity are linked to high molecular weight
Chitosan	In addition, it promotes fibroblast migration and proliferation, erythrocyte aggregation, activation of the coagulation cascade, enhanced inflammatory cell infiltration into the wound area, spontaneous blood clotting, and obstruction of nerve terminals and collagen deposition. Biocompatible, biodegradable, antibacterial, antioxidant, and low immunogenicity.	inadequate solubility, a slower and more unpredictable rate of biodegradation
Sodium alginate	It is non-immunogenic, cheap in cost, biocompatible, biodegradable, and has good film-forming properties. Moreover, it can increase cytokine levels in wounds and activate macrophages.	insufficient chain tangling and lack of cell recognition sites.
Gelatin	High hemostatic action, biodegradable, non-antigenic, and activates macrophages	Poor mechanical strength and elasticity, restricted water solubility, form instability, and heat instability
Silk fibroin	Strong, robust, elastic, and lightweight mechanical qualities; regulated rate of biodegradation; excellent oxygen and water vapor permeability; inflammatory resistance; and capacity to encourage keratinocyte and fibroblast adhesion and proliferation	The dehydrating process, which is required to remove the sericin (a protein that resembles glue and keeps fibroin together), may have an impact on mechanical strength.
Collagen	reduced antigenicity, excellent in vivo stability, strong biocompatibility, stimulation of cell adhesion and proliferation, and the production of granulation tissue with cell chemoattractant	rapid breakdown propensity during degradation

Table 2: Synthetic polymers that are frequently used to make wound dressings

Material	*Advantages*	*Disadvantages*
Polyvinyl alcohol	Breathability, adaptability, and ability to maintain a damp atmosphere	Low strength, inadequate thermal stability, and non-biodegradability
Polyethylene glycol	Biocompatibility, sensitivity to various physical and chemical stimuli, water and organic solvent solubility, neutrality in acidity and alkalinity, and so on	Lack of immunogenicity, non-biodegradable, and potential for contact allergies
Polycaprolactone	durability, quick crystallization rate, biocompatibility, and flexibility	hydrophobic, lacking cell-binding sites, slow rate of biodegradation, and poor mechanical strength
polylactic acid	Strong mechanical properties, mechanical sustainability in vivo or in vitro, heat stability, repeatability, adaptability, and processing simplicity	without cell binding sites and hydrophobic.
polyethylene oxide	Water soluble, non-cytotoxic, biocompatible, and simple to manufacture	Low strength, inadequate thermal stability, and non-biodegradability
Polyvinylpyrrolidone	Soft, inexpensive, easy to clean up after, and capable of storing a lot of water without losing its mechanical integrity	inadequate mechanical strength, low thermal stability, and non-biodegradability
Poly(lactic-co-glycolic acid)	Excellent solubility in common solvents, biodegradation rate, and adjustable wettability	limited cell affinity, weak ductility, high synthesis cost, and comparatively limited drug-loading capacity
polyurethane	Superior elasticity and moisture permeability, mechanical strength akin to that of real tissue, and high porosity	Poor hemocompatibility and hydrophobicity

biocompatible copolymers. Researchers have successfully engineered biodegradable nanofibers by synthesizing a tri-block polymer electrospinning nanofiber comprising PCL and PEG. This novel nanofiber platform can serve as an effective carrier for medications in wound dressings. Notably, PCL-PEG-PCL (PCEC) nanofibers have been instrumental in enhancing wound healing rates by accommodating the controlled release of curcumin (CU). The incorporation of CU in the nanofibers resulted in modifications to their physical and chemical properties without compromising biocompatibility. Furthermore, the PCEC/CU nanofiber pad demonstrated remarkable antioxidant qualities and minimal cytotoxicity, leading to a notable 20% acceleration in skin wound healing post-surgery. Potential applications in wound dressing and healing interventions make this invention particularly promising. Building on the success of PCL, scientists have created cutting-edge wound dressing treatments with synthetic polymers like PU that are loaded with AgNps and kaolinite. AgNps and kaolinite nanosheets may be hosted on the three-dimensional network of PU electrospinning nanofiber mats, demonstrating the flexibility and adaptability of synthetic polymers in meeting vital wound care requirements.[48]

CONCLUSION

Recognizing the constraints of conventional treatments, significant research endeavors have been devoted to exploring innovative materials aimed at enhancing hemostasis and wound healing over recent years. Multiple approaches have been examined, encompassing the development of advanced solutions such as hydrogels, foams, sponges, bandages, and membranes, as well as the utilization of cutting-edge electrospinning technology. Electrospinning presents a versatile method for fabricating ultrafine fibers ranging from 50 to 500 nm in diameter, showing great promise in addressing challenges in wound care. Noteworthy characteristics like enhanced adhesion, proliferation, migration, and differentiation are facilitated by the integration of electrospinning technology, highlighting its potential in advancing wound healing strategies. Furthermore, the considerable specific surface area of electrospun nanofiber membranes heightens their efficacy in absorbing blood and wound exudate, thus contributing to creating an ideal environment for healing. In essence, the complexities inherent in wound healing underscore the need to transition towards utilizing state-of-the-art materials and techniques that offer customized solutions to enhance patient outcomes and foster efficient wound management.

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