REVIEW ARTICLE

Current Update on Electrospun Nanofiber Mats as a Wound Healing Drug Carrier

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ABSTRACT

Electrospun nanofiber mats are being researched as attractive wound-healing drug carriers owing to their exclusive features, large active surface area, interlinked porosity, and customizable drug release kinetics. These mats may be infused with antibiotics, growth hormones, or stem cells to hasten the process of healing and lessen the likelihood of problems. Controlled and sustained medication delivery is the key payback of electrospun nanofiber mats. Electrospun nanofiber mats promote wound healing in part because of the favorable milieu they provide cell adhesion and proliferation of the affected tissue due to their enhanced active surface area. Mats of many kinds are discussed in the review. Electrospun nanofiber membranes can be created in a diversity of configurations, along with a single layer, a coaxial structure, and many layers. Recent studies have shown the efficacy of using electrospun nanofiber mats to deliver a variety of therapeutic compounds for wound healing. Treatment of wound infections using antibiotic-loaded electrospun nanofiber mats may help slow the spread of antibiotic-resistant bacteria. Electrospun nanofiber mats supplemented with growth hormones are known to hasten wound healing by encouraging the local tissue's proliferation and differentiation. Delivery of stem cells to the wound site, where they may develop into new skin cells and stimulate tissue regeneration, can be accomplished with the help of electrospun nanofiber mats. In conclusion, electrospun nanofiber mats provide an exciting new platform for the delivery of drugs to promote wound healing. Their enormous surface area, interconnected porosity, and adaptable drug release kinetics all make them excellent vehicles for delivering a wide range of therapeutic medicines to the wound site.

Keywords: Electrospun nanofiber mats, Wound healing, Medication delivery, Antibiotics, Growth factors, Stem cells,

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INTRODUCTION

Process of spinning is crucial in the manufacturing of polymeric fibers. Aligning the polymer molecules *via* spinning boosts intermolecular interactions and modulus while decreasing the diameter.[1] Polymers can be stretched in a number of ways, resulting in solid materials with many potential uses. One of the most investigated nanotechnology methods, electrospinning, is a promising method of preparing fibers with arbitrary lengths and shapes.[1] It spins nano to micro-sized continuous and non-continuous fibers using polymeric liquids and intense electric fields. One-dimensional (1D) fibers, two-dimensional (2D) fiber films, three-dimensional (3D) fiber sponges, and four-dimensional (4D) fiber-based printed objects are all possible through electrospinning.[2] These nano-products can be designed to have specific physicochemical properties, such as bio-compatibility, nontoxicity, and environmental sensitivity. Unique characteristics of electrospun fibers include a huge surface area in relation to their volume, lesser density, and small pore size, which is adjustable and a high level of permeability.[2] Also, their mechanical properties, including toughness and tensile strength, shapeability, and the capability to manufacture fibers with precise features utilizing other polymers or combinations, are all enhanced. Nanofibers have been investigated for use in a wide variety of settings thanks to their exceptional properties. They include uses in the beauty industry, the pharmaceutical industry, the electrical industry, the filtration industry, the healthcare industry, wound care, and renewable energy. Electrospinning is a versatile process that allows for easy *in-situ* or *ex-situ* incorporation of specialized nanomaterials into and onto the fibers in a wide variety of designs. When biopolymers are used, the resulting fibers can be tailored in terms of their surface area, dimensions, morphology, form, pore size distribution, and alignment.[1,2]

Therapeutic molecules have been delivered into the human body using a variety of formulation methodologies, including traditional and new drug delivery systems, in an

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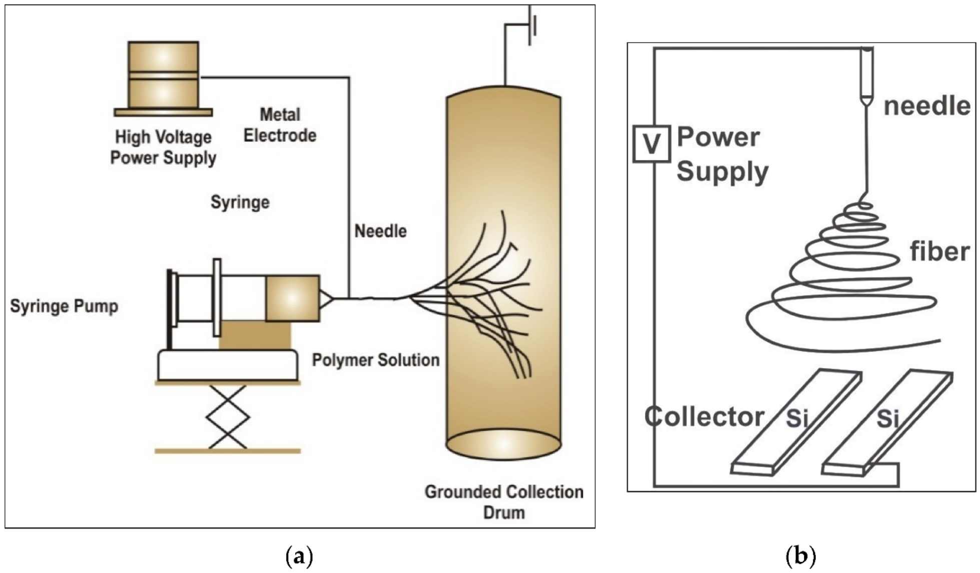

Figure 1: The process of electrospinning (a) A typical electrospinning instrument and its components (b) Alteration of collector for aligning electrospun nanofibers

effort to achieve optimal therapeutic efficacy.[3] Traditional and even some innovative methods of medication delivery have shortcomings that result in insufficient drug distribution, which in turn negatively impacts therapeutic efficacy and diagnostic accuracy. The electrospinning method employs high voltage electrostatic fields to produce nanofibers containing a medicine, gene, or protein. High surface area, variable porosity, biodegradability, and workability are just a few of the qualities that have led to many uses for nanofibers.[4] Therapeutic small chemicals, genes, and proteins/peptides can all be loaded onto electrospun nanoparticles and transported to their intended sites of action.[4] The drug release through electrospun nanofibers is more accurately controlled. Core-shell nanoparticles (NPs) are useful for the delivery of several medications because they can be designed with individualized controlled release profiles. In addition to its potential in combination therapy, this approach has a lot of potential for medications that must be released at different times or have varied pharmacodynamic effects.[4] Electrospun nanofibers have the capability to reduce side effects of medicines that are dose-dependent, to allow for either slow or rapid drug release, to protect biomolecules against destruction by enzymes or acids, and so on. When combined with the fact that nanofibers produced using the electrospinning technique can be given *via* all the routes of drug administration, this makes electrospun nanofibers a very promising strategy for formulation. Low permeability and rejection in conventional formulations are major problems for tissue repair and regeneration.[2,3]

Highly effective drug-containing nanofibers can be superior candidates for drug delivery for treating a great range of ailments as an outcome of ongoing efforts to discover newer polymers and electrospinning technology, which is undergoing advanced technological developments, as well as the addition of other advanced technologies with the electrospinning technique. This review is going to focus on advancements in electrospun nanofibers and their potential to treat different wound healings.[5]

Principle and Technique of Electrospinning

The electrospinning method entails directing a solution of polymer flowing *via* a capillary tip towards a collector made up of metal while applying a large potential variance.[5] All that is needed to do electrospinning is a heavy voltage source of power, a syringe, a needle, usually with a flat tip (Some researchers are using modified versions), and a conducting collector as shown in Figure 1. While the fundamental apparatus remains the same, it can be adapted for specific uses, such as the production of blended fibers by use of a dual-needle syringe or the collection of fibers from a revolving mandrel (to prepare empty tube-like material). By and large, materials produced by the electrospinning technique feature an un-woven nanofiber configuration. Aligned fibers can be gathered *via* electrospinning, a technique that employs two strips of electrodes. While the solution of polymer and the collection plate are at different potential voltages, electrostatic forces overcome the surface tension of the solution and pull a jet of charged fluid, which then separates into nanofibers and falls towards the collection plate, where they solidify. When the polymer jet reaches the collector, it breaks up into several nanofibers. The solvent evaporates as the jet is electrospun, leaving behind dry nanofibers.[5,6]

Polymers Used in Electrospinning

Electrospinning's most notable quality is that it can produce nanofibers from a wide range of polymers for use in many different contexts. "Synthetic, natural, and hybrid" are the three main types of polymers. The electrospinning method will be emphasized when discussing each classification.[6] The list of synthetic polymers is summarized in Table 1

Table 1: Electrospun synthetic polymers for use in wound dressings[9-12]

Materials used	*Active constituents*	*Names of co-solvent to be used*	*Type of electospun fibers produced*
Cellulose acetate	Metal ions: Zinc oxide/Silver nanoparticles	Dimethylformamide/H_2O	Blend-nanofibers
Polyvinyl alcohol	Plant products: Triterpenoids	H_2O	Blend-nanofibers
Polyvinyl pyrrolidone/Polylactic acid - Polyethylene oxide	Cephalosporin: Cefazolin	Hexa-fluoroisopropanol ethyl alcohol - dichloromethane	Coaxial – nanofibers
Polyvinylidene fluoride	Fluroquinolone: Enrofloxacin	Acetone	Blend-nanofibers

Synthetic and natural polymers

Physicochemical features of the extracellular matrix are frequently mimicked by electrospun nanofibers produced from natural polymers. Many bio-molecules, such as “lipids, proteins, nucleic acids, polysaccharides”, make up natural polymers. Natural polymers trumped synthetic polymers in the medical field thanks to their increased biocompatibility and reduced immunogenicity. Because of their similarity in protein structure to cells, natural polymers such as glycine and aspartic acid are capable candidates for tissue engineering. Electrospinning is often described for the use of polymers of natural sources such as fibrinogen, silk fibroin, chitin elastin, chitosan, collagen, gelatin, cellulose acetate, casein, etc. The clinical performance of tissue scaffolds made from natural polymers is superior. Mechanical qualities like strength, viscoelasticity, and the rate of deterioration make synthetic polymers preferable to natural ones. As hydrophobic biodegradable polyesters, synthetic polymers, including polylactide, polyglycolide, poly (E-caprolactone) are commonly employed in medicinal applications.[7,8]

Composite polymers/Copolymers

Composite polymers are materials that consist of one or more components with distinct chemical and physical characteristics. One constituent component often found in a composite material is the continuous phase, sometimes referred to as the matrix. On the other hand, the remaining phases are categorized as the discontinuous phase or the reinforcing material, exhibiting greater durability, hardness, and stiffness compared to the continuous phase. The selection of components in the composite is done in a manner that allows for the combination of their qualities in a synergistic manner, resulting in improved physical or chemical properties compared to employing each component individually.[13]

Electrospinning has been proven to be an effective method for combining the best features of both natural and manufactured polymers. Researchers have looked at many different types of polymer blends, including those made from natural polymers like “collagen and chondroitin sulfate, collagen and chitosan, silk, polyox, polycaprolactone and poly-L-lactic acid, hyaluronan and polycaprolactone, starch and polycaprolactone, chitosan and polyethylene oxide, and poly-L-lactic acid and poly (lactic-co-glycolic acid)”. Electrospinning can also be utilized to modify the affinity of cells to the material, as well as its shape, mechanical qualities, and other attributes. Glycolide was added to the spinning blend of a nanofibrous mat made of ethylene and vinyl alcohol, for instance, to make it more robust. An example of an effective compromise between decomposition rate and hydrophilicity was demonstrated by a three-block copolymer consisting of polylactic acid, p-dioxanone, and polyethylene glycol.[10-15]

Specifics of current research on electrospun nanofibers with antimicrobial properties are provided here in Table 2.[16-20]

Different Kinds of Electrospun Nanofibers for the Purpose of Wound Dressings

Advancement in the electrospinning technique has led to growing amounts of literature documenting several wound dressings prepared using the electrospinning technique with diverse constructions. These dressings are designed to cater specific requirements of wound repair and expedite the wound-healing process. This paper aims to provide an overview of the design requirements, as well as the benefits and drawbacks, of several wound dressings prepared using electrospinning with distinct structural characteristics.[12, 21]

Monolayer electrospun nanofiber membranes can be created by the use of the mixing process

Monolayer membranes of nanofiber, which are formed *via* the process of electrospinning using single nozzle, are the oldest and most extensively researched dressings for wounds manufactured using electrospinning techniques.[13,14,22] Typically, these materials are created by the amalgamation of polymer components with antibacterial compounds or wound healing promoters. The spinning process is characterized by its simplicity and the low level of effort involved. Additionally, the selection of solvents for this process is quite variable. By electrospinning, Ramalingam and colleagues (year) fabricated a monolayer nanofiber membrane composed of polycaprolactone and gelatin. This technique included the use of natural herbal extracts, namely *Gymnema sylvestre*, to enhance the membrane’s antibacterial properties.[70] The disc diffusion test validated the effectiveness of antibacterial wound dressings containing *G. sylvestre* loaded in electrospun polycaprolactone/gelatin nanofiber membranes. This test demonstrated the drug successfully inhibited the subject population, suggesting these dressings’ capacity to avert bacterial infection progress.[15,16,23]

Nevertheless, the nanofiber membrane’s monolayer structure typically serves a singular purpose, primarily functioning as antibacterial carriers that facilitate wound healing. This is accomplished by liberating embedded active constituents at the site of the wound. However, the monolayer

Table 2: Specifics of current research on electrospun nanofibers with antimicrobial properties

Class of medication used	*Antibacterial agent/agents used*	*Names of polymers employed*	*Species of microbes used as subject*
Nanoparticles of metals	Zinc oxide	Pullulan	*Staphylococcus aureus* and *Escherichia coli*
	Silver nanoparticles	Polyvinyl pyrrolidone	*S. aureus, Pseudomonas aeruginosa, Candida albicans*
	Copper nanoparticles	Cellulose acetate	*S. aureus* and *E. coli*
	Gold nanoparticles	Polycaprolactone	*S. aureus* and multi drug resistant *S. aureus.*
	Combination of zinc oxide and silver nanoparticles	Cellulose acetate	*S. aureus* and *E. coli*
Antibiotics	Tetracyclines-Doxycycline	Polylactic acid	*E. coli*
	Fluroquinolones- Ciprofloxacin	Polyvinyl pyrrolidone	*S. aureus* and *E. coli*
	Macrolides- Erythromycin	Cellulose acetate	*S. aureus* and *E. coli*.
Extracts of plants with antibacterial action.	Aloe vera	Chitosan	*S. aureus* and *E. coli*.
	Clove oil	Polycaprolactone	*S. aureus* and *E. coli*.
	Extract of Calendula officinalis	Chitosan	*S. aureus* and *E. coli*.
	Extract of Tinospora cardiofolia and Curcumin	Chitosan	*S. aureus*, *P. aeruginosa*, *E. coli*.
Peptides with antimicrobial actions.	OH-CATH30	Chitosan	*S. aureus* and *E. coli*.
	ε-Polylysine	Polyethylene oxide	*S. aureus* and *E. coli*.

structure falls short in achieving more intricate functionalities required for comprehensive wound healing, as stated in reference.[17, 24] The formulation exhibits a significant need for lipophobicity, as it facilitates effective drainage and absorption of wound exudate. However, the formulation thickness being less, resulting in inadequate wound exudate absorption.[18,24]

In their study, Wu *et al.* modified their formulation to augment the hemostatic property and water absorption by affixing layers of methacrylated gelatin hydrogel packed with "*Salvia miltiorrhiza* Bunge-Radix Puerariae herbal compound (SRHC)" onto electrospun nanofiber membranes. The findings of the study demonstrated a considerable acceleration in the process of diabetic wounds healing by using this particular wound dressing. This was achieved by efficiently mitigating inflammation and facilitating the processes of hair follicle regeneration and vascularization.[25]

Furthermore, L.L. Lima *et al.* proposed an innovative structural design to enhance their formulation's drainage capacity using a monolayer nanofiber membrane formed using electrospinning for wound exudate management. A self-pumping dressing was described, whereby hydrophobic nanofibers were arranged in a single layer atop a hydrophilic microfiber network using the technique of electrospinning.[26] This arrangement facilitated the removal of surplus exudate of wound in a unidirectional manner, hence expediting the healing process of the wound. Using a microfiber network which is hydrophilic in nature facilitates the removal of surplus

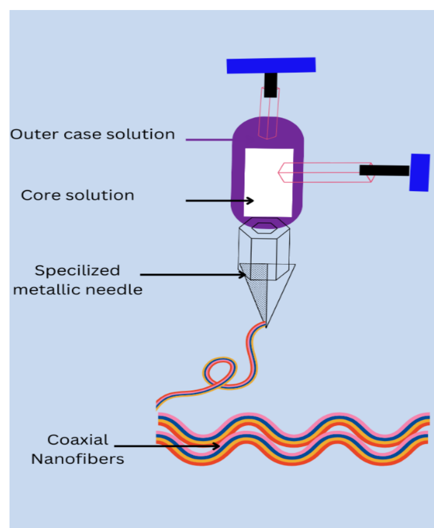

Figure 2: Formation of coaxial nanofibers

biofluids by acting as a drainage system. This drainage system effectively pumps the biofluids *via* a hydrophobic nanofiber array, avoiding the wound's re-wetting by the pumped biofluids. Research findings indicate that using self-pumping mats to treat wounds on the dorsal region of mice leads to enhanced healing rates compared to conventional dressings. This self-pumping improvement is attributed to the ability of their dressings to effectively remove exudate from wounds. The novel self-pumping dressing has significant promise in its capacity to serve as an innovative and advanced form of wound healing dressings in clinical settings.[27,28]

Membranes made of electrospun nanofibers with coaxial structures

The material and drug unification method for preparing monolayer nanofiber membranes is simple and reproducible. However, this method has a drawback: it can speedily release drugs on the nanofiber surface. This is because drugs disperse on the nanofibers with a large determined surface area. As a result, extended drug release for an enhanced time is not achievable.[29] Furthermore, the limited stability of some delicate medications, namely proteins, in organic solvents poses a constraint on their potential utilization within the realm of wound care. Electrospinning by coaxial technique makes use of a concentric round needle configuration for simultaneously dispensing 2 different constituents of the electrospinning solution, hence mitigating any potential mixing interference between the components as shown in Figure 2.[30] Coaxial electrospinning is used to encapsulate the medication or active chemical inside a case or shell-core nanofibers.[31] The medication contained inside the core undergoes a progressive dissolution process facilitated by the case. Alternatively, the drug release occurs *via* the water-soluble apertures inside the case. It is significant to notice that the release rate of the drug is comparatively gentler than that of the case.[32] In their study, Lan *et al.* employed a coaxial electrospinning technique to fabricate a membrane of nanofibers. This membrane consisted of a core loaded with antioxidant polyphenols (TP) extracted from tea leaves and a shell containing ε-poly (lysine) (ε-PL), which has a well-established antibacterial activity. The authors reported a successful electrospinning.[33,38] The core layer's low TP concentration and gradual TP release might mitigate its cytotoxic effects. Sustained releasing of TP promotes the elimination of the excessive reactive oxygen species (ROS) over an extended period. However, the immediate release of *ε-PL* loaded inside the outermost layer may impede the early proliferation of bacterial colonies in the affected area. The coordination of distinct medication release rates between the shell and core layers was implemented for the purpose of facilitating wound healing. Though it's an innovative approach, electrospinning becomes more difficult as two ingredients must be sprayed simultaneously. The adjustment of parameters also very tedious the researcher has to make many attempts and adjustments.[34,35]

Sequentially electrospun nanofiber membranes with many layers

The optimal wound dressing should include a range of functionalities, including an outer covering serving as a shielding barricade to avoid infiltration of germs.[36] Furthermore, it is essential that these dressings possess hemostatic and antimicrobial qualities. Additionally, they should be able to absorb excessive biofluids from the wound, facilitate gas and liquid exchange, and stimulate proliferation of the cells along with other factors assisting wound healing like movement of soldier cells at the site, new blood vessel formation, and remodeling of injured tissue. Nevertheless, nanofiber mats with monolayers prepared by the mixing techniques of electrospinning possess singular functionalities and lack the ability to synergistically expedite wound healing, unlike the nanofiber membranes fabricated through coaxial electrospinning. Hence, the investigation of electrospun nanofiber membranes, including multilayer spatial structures, was conducted in order to address the intricate conditions associated with wound healing.[37] Federico and colleagues developed a nanofiber mat with a double-layer structure with the intention of exploring its potential for use in wound healing applications as shown in Figure 3.[38]

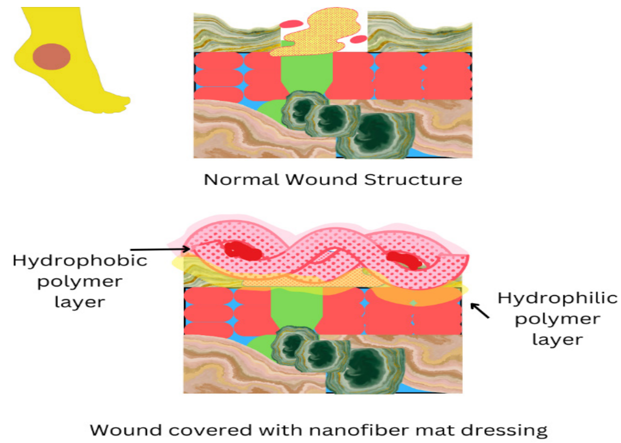

Figure 3: Effectiveness of nanofiber mats as wound dressings

Ciprofloxacin was used as an antibacterial agent loaded in a hydrophobic polymer polyurethane-polycaprolactone (PU-PCL), which prevents entry of water in the wound while releasing the antibiotic. The other layer was made up of a derivative of gallan gum and polyvinyl alcohol. This hydrophilic layer was loaded with growth factor FGF-2, the layer being hydrophilic absorbed the wound exudate while simultaneously the growth factor enhanced the healing of the wound by proliferation of cells from the damaged area. Numerous researchers have successfully engineered nanofiber membranes consisting of three layers in order to attain heightened functionality and expedite the process of wound healing. The multilayer structure of nanofiber membrane has much functionality and is very promising for promoting the healing of wounds. Nonetheless, it can't be denied that the production procedure for this membrane is somewhat intricate. The primary problem is that segmentation may occur owing to varying forces of attraction of every layer of the nanofiber mat, leading to a lack of intimate interlayer connection.[39]

Implications for the Future and Final Remarks

Significant advancements have been made in the use of wound dressing resources prepared by the electrospinning technique. Nanofiber mats prepared using the electrospinning technique have emerged as a highly effective material for wound dressings of various origins owing their structural similarity to the extracellular matrix (ECM) is a complex network of molecules that surrounds and provisions cells, is a complex network of molecules that surrounds and supports cells in multicellular organisms.[40] These nanofibers possess an increased surface area to volume ratio and has a permeable construction, which contributes to improved processes of wound healing such as checking of the blood flow, absorption of biofluids coming out of the wound, and cellular activities including grip on the affected area, movement of soldier cells to the affected area, and propagation.[41] The study provides an overview of the literature on electrospun nanofiber wound dressings in recent years. An analysis was conducted on the various materials that can be used as effective polymers, features for structural stability and effectiveness, and the designing of nanofiber mats for the fabrication of wound dressings by the electrospinning technique.[42] Moreover, present study highlights latest improvements in the fabrication of nanofibers by using the electrospinning technique used in context of wound dressing.[40] This review offers our unique perspectives on the trajectory of electrospinning techniques in the domain of wound dressings. Wound management has always been a formidable task for a community of scientific researchers. The complexity and sophistication of wound healing contribute to this phenomenon. It is essential to effectively activate several cellular response mechanisms, including checking the blood flow, generating inflammation, and regenerating new blood vessels, re-epithelialization, and supplementary processes.[43] Throughout this particular time frame, bacterial infection poses a significant risk to the wound healing process. Significantly, a variety of injuries exist, including burns, acute wounds, and complex diabetic wounds. Diverse categories of injuries need distinct therapeutic approaches.[44] Hence, it is essential for forthcoming electrospun wound dressings to undergo multidimensional development encompassing various preparation methods, functionalities, and treatment requirements in order to effectively address the intricate demands therapy of wounds. The emergence of commercialized wound coverings manufactured using the electrospinning technique is expected to become a significant trend within the realm of medical developments. Wide research has been conducted on the use of electrospun nanofibers in context of wound dressings. However, it is regrettable that no commercially *via*ble products have been developed using electrospinning methods so far. The limited productivity, inadequate repeatability, and absence of standardized operating techniques for electrospun nanofibers significantly impede their potential for commercialization. In some cases involving challenging wounds, particularly those of significant burn extent, conventional electrostatic spinning wound dressings may have difficulties achieving optimal treatment outcomes. Consequently, there is a necessity of wound dressing development that possesses enhanced functionality and intricate structures to address these challenges effectively. The electrospun nanofiber wound dressings can be even more modified by using sensors embedded in them, which can detect various parameters for wound healing. The production of this sophisticated wound dressing on a wide scale is challenging owing to the intricacies of the preparation process and the associated costs. Nevertheless, the utilization of this particular nanofiber mats is crucial for the effective care of recalcitrant wounds, so representing a noteworthy progression within the realm of wound healing.

CONCLUSION

Electrospun nanofiber mats are being explored as promising carriers for wound-healing medications due to their unique characteristics such as large surface area, interconnected pores, and customizable drug release patterns. These mats can be loaded with antibiotics, growth factors, or stem cells to accelerate healing and reduce the need for frequent medication administration. Their controlled and sustained drug delivery capability offers significant advantages in wound therapy. The enhanced surface area of these mats promotes cell attachment and proliferation, contributing to effective tissue regeneration. Various types of electrospun nanofiber membranes, including single-layer and multilayer configurations, are discussed in the research literature. Recent studies have demonstrated the efficacy of utilizing these mats for delivering diverse therapeutic agents for wound treatment. Incorporating antibiotics into electrospun nanofiber mats can help combat antibiotic-resistant bacteria in wound infections. Additionally, growth factor-infused mats expedite wound healing by stimulating tissue growth and differentiation. Moreover, these mats facilitate the delivery of stem cells to the wound site, aiding in tissue regeneration. In summary, electrospun nanofiber mats offer a promising platform for drug delivery in wound healing, thanks to their expansive surface area, porous structure, and adaptable drug release properties.

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