



Nature's Web: Natural Polymers in Electrospinning Nanofibers for Tissue Engineering

Mahsoo Kashi Kalhori

*Undergraduate Student, Chemical Engineering
Department, Babol Noshirvani University of
Technology, Babol, Iran*

Mostafa Rahimnejad

*Proferssor, Chemical Engineering Department,
Babol Noshirvani University of Technology, Babol,
Iran*

Abstract

Electrospinning is a promising technique for creating nanofibrous scaffolds that mimic the extracellular matrix (ECM). These scaffolds offer significant potential in tissue engineering and wound healing applications. By incorporating natural polymers such as collagen, chitosan, alginate, and elastin, electrospinning combines the biocompatibility, biodegradability, and inherent biological functions of these materials with the structural advantages of electrospun fibers. The result in nanofibrous scaffolds provide a conducive environment for cellular adhesion, proliferation, and migration, promoting effective tissue regeneration. Recent advancements in electrospinning techniques have enabled the creation of multifunctional scaffolds incorporating antimicrobial agents, growth factors, and other bioactive molecules, enhancing their therapeutic potential. However, challenges such as poor mechanical properties of natural polymers, limited solubility, and issues with scaffold architecture and cellular infiltration remain. This mini-review explores the current state of electrospinning natural polymers for wound healing, highlighting the unique properties, challenges, and future directions in this rapidly evolving area of research. By leveraging the adaptability of electrospinning and the bioactivity of natural polymers, this technology holds great promise for developing advanced, sustainable solutions for regenerative medicine.

Keywords: Natural polymers, electrospinning, wound healing, nanofibers

1. Introduction

Wound healing is a complex process that is often impaired in chronic conditions, leading to significant morbidity and economic burdens. Chronic wounds, such as diabetic ulcers, pressure sores, and burns, create significant challenges owing to their long healing process, increased risk of infection, and associated economic costs [1,2]. These factors underscore the urgent need for innovative wound-care solutions that actively support tissue regeneration. Scaffolds that mimic the natural ECM represent a promising approach [3]. Electrospinning has emerged as a versatile technique for creating nanofibrous scaffolds from natural polymers, offering several advantages for wound-care applications [4]. Electrospinning uses an electric field to draw polymer solutions into ultrafine fibers, resulting in highly porous mats with a large surface-area-to-volume ratio. These scaffolds closely resemble the ECM, enhancing cell attachment and migration. Additionally, electrospun dressings can be tailored to provide controlled drug delivery, facilitate gaseous exchange, and absorb wound exudates, making them highly flexible for clinical use [5,6].

Natural polymers, including proteins, such as collagen, gelatin, and silk fibroin, and polysaccharides, such as chitosan, hyaluronic acid, and alginate, are commonly used in electrospinning. These biopolymers offer several advantages over synthetic materials, including their inherent biocompatibility, biodegradability, and biological functions that actively support wound healing [6,7]. For example, collagen provides excellent cell adhesion properties, whereas chitosan exhibits antimicrobial activity that is beneficial for infection-prone wounds [8,9]. The morphology and mechanical properties of electrospun fibers can be influenced by factors such as the polymer chain conformation in the pre-spun solution. This allows the creation of scaffolds with tailored properties for specific wound-healing applications [10]. Electrospinning technology has advanced to create multifunctional scaffolds, including core-shell and multilayer structures. These scaffolds can incorporate antimicrobial agents, growth factors, and other bioactive molecules to enhance wound healing [11,12]. This review aims to explore the use of natural polymers in electrospinning for wound-healing applications. Additionally, recent advancements in electrospinning techniques and scaffold modifications that enhance wound healing outcomes are discussed, providing insights into future directions in this rapidly evolving field.

2. Electrospinning

Electrospinning has gained significant attention in tissue engineering because of its ability to produce nanoscale fibers that mimic the ECM. This technique allows for the fabrication of scaffolds with high porosity and surface-to-volume ratio, enhancing cell attachment and drug-loading capabilities [13,14]. Various materials, including biodegradable and natural polymers, can be electrospun to create scaffolds with controlled fiber orientations and mechanical properties. The electrospinning process typically involves a syringe containing the polymer solution, needle, high-voltage power supply, and grounded collector. The polymer solution is injected through the needle and a high voltage was applied to the needle to create an electric field. This field overcomes the surface tension of the solution, causing a jet of the polymer to be drawn from the needle tip. As the jet travels towards the collector, the solvent evaporates, leaving behind a network of nonwoven fibers. The resulting fibers can have diameters ranging from a few nanometers to several microns depending on the specific processing conditions [15,16].

Electrospinning offers a high degree of control over the properties of the resulting fibers, allowing researchers to tailor scaffolds for specific applications. By adjusting the polymer solution, processing conditions, and environmental factors, the fiber diameter, porosity, and mechanical properties can be controlled. For example, increasing the concentration of the polymer solution can result in thicker fibers, while reducing the distance between the needle and collector can increase the fiber diameter [1]. Electrospinning has been explored for a wide range of tissue engineering applications including wound healing, skin tissue regeneration, cartilage repair, and bone tissue engineering. In wound healing, electrospun scaffolds can provide a moist environment, absorb exudates, and promote cell migration, leading to faster and more efficient wound closure [15,17,18]. For skin tissue engineering, electrospun scaffolds can be used to reconstruct damaged skin tissues, particularly for burns and chronic wounds [19]. Electrospun scaffolds can support the growth and differentiation of chondrocytes in cartilage repair, leading to the formation of new [20]. Additionally, electrospun scaffolds have been investigated for use, where they can promote bone formation and repair of bone defects [21].

3. Natural Polymers in Electrospinning

Natural polymers offer several advantages over synthetic polymers for tissue engineering applications, including biodegradability, biocompatibility, and low antigenicity. These polymers offer various biological properties that can promote tissue regeneration and improve wound healing outcomes [22].

3.1. Collagen

Collagen is the most abundant protein in the human body. It is a key structural component of ECM in various tissues, including bone, cartilage, skin, tendons, and blood vessels. Its primary role is to provide structural integrity and mechanical strength, as well as to support cellular activities such as adhesion, proliferation, and migration [23,24]. Collagen's triple helical structure, formed by chains rich in glycine, proline, and hydroxyproline, contributes to its unique mechanical properties and biological functions. Among the 28

known types of collagen, types I, II, and III are most prevalent in tissues, each exhibiting specific structural and functional roles [25]. Collagen's widespread presence and essential role in the body make it a desirable biomaterial. It is biocompatible, has low antigenicity, and supports cellular growth without causing significant immune responses [26].

Electrospinning is a widely utilized technique for fabricating nanofibrous collagen scaffolds. One of the main challenges in electrospinning collagen is maintaining its native structure, as common solvents such as hexafluoro-2-propanol (HFIP) can lead to the partial denaturation of collagen into gelatin. To overcome this, careful optimization of solvent systems and electrospinning parameters is crucial to preserve the triple-helical structure of collagen, which is vital for its bioactivity and mechanical properties. Recent advancements have included the use of milder solvents or buffer systems that maintain the structural integrity of collagen during the spinning process [27,28].

Moreover, electrospun collagen fibers typically exhibit poor mechanical strength and stability, particularly when exposed to physiological conditions, which limits their direct use in load-bearing applications. Cross-linking techniques are often employed to address this issue [29]. Cross-linking agents, such as glutaraldehyde, EDC, and N-hydroxysuccinimide (NHS), are commonly used to enhance the mechanical properties and water resistance of electrospun collagen fibers [30]. Although effective, cross-linking with glutaraldehyde may cause cytotoxic effects, necessitating alternative approaches that balance the mechanical enhancement with biocompatibility [31,32].

Electrospun collagen scaffolds have shown promising applications in tissue engineering and wound care. They offer a biomimetic environment that supports cell attachment, growth, and differentiation, making them ideal for regenerating tissues, such as skin, blood vessels, and cartilage [33-35]. Furthermore, incorporating bioactive agents such as silver nanoparticles into collagen fibers can endow scaffolds with antimicrobial properties, enhancing their functionality in clinical settings [36].

3.2. Chitosan

Chitosan is a biopolymer derived from the partial deacetylation of chitin, a natural polysaccharide found in the exoskeletons of crustaceans, such as shrimp and crabs, as well as in the cell walls of fungi. Structurally, it consists of glucosamine and N-acetyl glucosamine units linked by (1-4) glycosidic bonds [37]. Chitosan is biocompatible, biodegradable, non-toxic, and possesses inherent antibacterial and hemostatic properties, making it suitable for biomedical applications, particularly in wound healing and tissue engineering [38].

The electrospinning of chitosan presents several challenges owing to its limited solubility, which requires acidic solvents such as acetic acid, formic acid, or trifluoroacetic acid (TFA) [39]. Pure chitosan solutions often lack the viscoelastic properties required for stable electrospinning; hence, polymeric additives such as poly(ethylene oxide) (PEO), polyvinyl alcohol (PVA), or other synthetic polymers are frequently incorporated to facilitate the formation of nanofibers [40,41]. The resultant electrospun chitosan fibers possess unique properties, including antimicrobial activity, low immunogenicity, and the ability to support wound healing, which are beneficial for creating dressings and scaffolds [42].

To overcome the limitations associated with poor mechanical properties and rapid degradation of electrospun chitosan fibers, crosslinking techniques and the development of water-soluble chitosan derivatives have been explored. Derivatives, such as carboxyethyl chitosan (CECS), and carboxymethyl chitosan (CMCS) can be electrospun into scaffolds with enhanced stability and tailored bioactivity [43,44]. When combined with other bioactive materials, such as silk fibroin nanoparticles or silver nanoparticles, they have shown increased cell compatibility, antibacterial activity, and wound healing capabilities [45].

Recent advancements in chitosan electrospinning have focused on enhancing its functionality through the incorporation of natural bioactive compounds, synthetic polymers, and nanoparticles. For example, electrospun chitosan/PEO fibers infused with cinnamon extract, have demonstrated antibacterial effects against *Escherichia coli* and *Staphylococcus aureus* [46]. Similarly, Composite chitosan fibers incorporating extracts from *Garcinia mangostana* exhibit enhanced antioxidant and antibacterial properties [47].

The ability to modify chitosan through blending, crosslinking, and addition of bioactive compounds makes it a versatile material for creating next-generation wound dressings and tissue scaffolds.

3.3. Alginate

Alginate is a naturally occurring anionic polysaccharide predominantly extracted from brown seaweed and consists of (1,4)-linked β -D-mannuronic acid (M) and α -L-guluronic acid (G) residues arranged in block-like sequences. The ratio and arrangement of these M and G units can vary depending on the source of alginate, influencing its molecular weight, viscosity, and gelling properties [48]. Alginate is widely recognized for its biocompatibility, non-toxicity, high absorption capacity, and ability to form hydrogels, making it a compelling material for various biomedical applications including wound dressings, drug delivery, and tissue engineering. The unique gel-forming ability of alginate in the presence of calcium ions allows it to create

moist wound environments that support healing while providing a barrier against microbial. However, alginate is inherently nonadhesive to mammalian cells, which can be advantageous for designing nontraumatic dressings that are easily removable from wound sites infections [48-50]. Electrospinning alginate is challenging due to its polyanionic nature and high viscosity in aqueous solutions. These properties create repulsive forces between alginate chains, hindering the formation of stable fibers [51]. To overcome these limitations, alginate is often blended with synthetic polymers such as polyvinyl alcohol PVA or PEO. These additives enhance the spinnability of alginate solutions, enabling the production of nanofibrous mats with improved mechanical properties suitable for wound-healing applications [52]. Electrospun alginate mats are typically water-soluble. Therefore, post-electrospinning crosslinking treatments, such as exposure to glutaraldehyde, divalent ions, or other chemical crosslinkers, are necessary to enhance their stability in moist environments [53]. Recent advances in electrospun alginate fibers have focused on incorporating bioactive agents to enhance their functionality, particularly for antimicrobial and wound-healing applications. Alginate-based electrospun fibers have been used as carriers for various therapeutic agents, including antibiotics and anti-inflammatory drugs. For example, electrospun PVA-alginate fibers containing amoxicillin have shown a burst release of the drug, followed by sustained delivery, providing effective antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* [54]. Alginate electrospinning has also been employed to create composite fibers loaded with nanoparticles, such as zinc oxide (ZnO), which imparts antibacterial properties to the scaffolds. Studies have demonstrated that optimal concentrations of ZnO nanoparticles within alginate fibers can effectively inhibit bacterial growth, while maintaining good cytocompatibility with fibroblasts [55].

3.4. Elastin

Elastin is a highly elastic, resilient protein that plays a crucial role in the native ECM of various connective tissues, including the skin, lungs, blood vessels, and ligaments. As a key component of tissues that require elasticity and recoil, elastin contributes significantly to the mechanical properties of the ECM. The protein is formed through the polymerization of its precursor, tropoelastin, which is a highly hydrophobic, non-glycosylated monomer of about 60-72 kDa [56,57]. In tissue engineering, elastin's unique properties, such as its biocompatibility, low immunogenicity, and ability to modulate cell behavior, have made it an appealing biomaterial. Elastin can influence cellular functions, such as proliferation, migration, and protease release, affecting fibroblasts, smooth muscle cells, endothelial cells, and immune cells [58]. For biomedical applications, elastin is often used in various forms, including insoluble elastin derived from autografts or allografts, decellularized ECM, or purified forms where insoluble elastin is hydrolyzed to produce a more soluble version. The soluble forms of elastin are particularly advantageous due to their ease of handling, lack of calcification when used in vivo, and positive effects on cellular functions, such as enhancing angiogenesis and elastic fiber synthesis [59,60].

Electrospinning is a widely used technique to fabricate fibrous elastin scaffolds. Electrospun elastin scaffolds are often combined with synthetic polymers like Polycaprolactone (PCL), poly(D,L-lactide-co-glycolide) (PLGA), or PDO to improve their mechanical strength and stability. Pure elastin fibers tend to have poor structural integrity and dissolve rapidly in aqueous environments. Blending elastin with synthetic polymers helps retain elastin within the fibrous matrix, prolonging its stability and functionality [61-63]. Research has shown that electrospun elastin fibers can be cross-linked post-spinning using agents such as glutaraldehyde, EDC, genipin, or hexamethylene diisocyanate (HMDI). Cross-linking enhances the mechanical properties of elastin fibers and prevents rapid degradation in physiological conditions, making them suitable for long-term applications in tissue engineering. Cross-linked elastin scaffolds support cell attachment, growth, and migration, maintaining their biocompatibility and functionality in promoting tissue repair and regeneration [64-66]. Studies have demonstrated that electrospun elastin fibers can be used in various applications, including vascular grafts, skin substitutes, heart valves, and cartilage regeneration. For example, electrospun tropoelastin fibers have been shown to support the attachment and proliferation of various cell types. These include human dermal fibroblasts and endothelial cells, without significant changes to cell morphology or growth [67]. Additionally, electrospun elastin constructs have been tailored to mimic specific tissue properties; for instance, trilayered scaffolds incorporating elastin, gelatin, and synthetic polymers have been designed to replicate the structural hierarchy of blood vessels [62].

4. Challenges and limitations

Electrospinning natural polymers to create biomimetic scaffolds that resemble the ECM offers significant potential for tissue engineering applications. However, several challenges and limitations persist in utilizing natural polymers in electrospinning.

Mechanical Properties and Structural Integrity: One of the main challenges of using natural polymers in electrospinning is their inherently poor mechanical properties. Natural polymers, such as collagen, elastin, and

gelatin, often lack the tensile strength, elasticity, and structural integrity required for load-bearing applications. Pure electrospun fibers made from these materials tend to be brittle, weak, and susceptible to rapid degradation in physiological environments. Electrospun alginate mats are unstable and require blending with synthetic polymers or post-electrospinning crosslinking. However, these modifications can complicate the fabrication process and introduce cytotoxicity depending on the crosslinking agents used.

Solubility and Processability Issues: The electrospinning of natural polymers is often hindered by their limited solubility in non-toxic, biocompatible solvents. Many natural polymers require harsh organic solvents for dissolution, which are not suitable for biomedical applications due to their toxicity. Additionally, the high viscosity and charge density of some natural polymer solutions, like alginate, can make electrospinning difficult. This can lead to non-uniform fibers or bead formation. Blending with synthetic polymers, such as PVA or PCL, can improve electrospinnability but it may dilute the biological properties of the natural polymer.

Cross-linking and Cytotoxicity: Cross-linking is often required to stabilize natural polymer scaffolds and prevent rapid degradation, but many commonly used cross-linkers, such as glutaraldehyde, can introduce cytotoxicity and negatively impact cell compatibility. Alternative crosslinking methods, such as enzymatic crosslinking or using natural agents like genipin, are being explored to reduce toxicity while preserving scaffold integrity. Nonetheless, optimizing cross-linking conditions to balance mechanical properties, degradation rate, and biocompatibility remains a significant challenge.

Scaffold Degradation and Biocompatibility: Natural polymers often exhibit rapid degradation rates in physiological conditions, which can compromise the long-term functionality of the scaffold. The degradation byproducts of some natural polymers can also elicit an immune response, limiting their use in certain applications. For instance, alginate cannot be enzymatically degraded by mammals and requires specific modifications to enhance cell adhesion and integration, adding complexity to scaffold design.

Overall, while the electrospinning of natural polymers offers numerous benefits for tissue engineering, addressing these challenges is crucial to harness their full potential.

5. Conclusion and Future Perspectives

Electrospinning has established itself as a versatile and powerful technique for producing micro- and nanofibers from a wide range of polymers, including natural and bio-based materials. The growing interest in bio-based polymers, driven by environmental awareness and the need for sustainable alternatives to synthetic materials, highlights the significance of renewable sources in developing biodegradable and biocompatible fibers. These materials offer unique advantages, including a high surface-to-volume ratio and tunable porosity. These properties are crucial in various applications, such as tissue engineering, wound healing, food packaging, and drug delivery. The combination of bio-based polymers with electrospinning technology has created new opportunities for innovation. This is especially important in fields like healthcare and food technology that require highly specific materials. The ability to modify the surface properties of electrospun fibers has expanded their functional capabilities. This can be achieved by incorporating biomolecules, nanoscale building blocks, or chemical groups. Ionic liquids can be used as solvents for processing polymers that are difficult to handle using traditional solvents. This opens up new possibilities for creating advanced functional materials through electrospinning. Looking ahead, the future of electrospun bio-based polymers is bright, with several promising research directions emerging. The development of electrospun fibers with embedded sensing capabilities could revolutionize biosensing technologies, enabling the real-time monitoring of physiological and environmental conditions. Furthermore, electrospun fibers' role as channels for electrochemical signalization and their potential in microfluidics and lab-on-a-chip technologies could significantly impact the fields of diagnostics and drug testing. To fully realize these opportunities, future research should focus on optimizing the processing conditions and exploring new bio-based polymers that can be effectively electrospun. Additionally, scaling up the production of electrospun materials while maintaining their unique properties remains a critical challenge. Addressing these issues will be essential to transitioning electrospun bio-based polymers from the laboratory to commercial applications.

In conclusion, the electrospinning of natural and bio-based polymers represents a rapidly growing field with vast potential to contribute to more sustainable and innovative solutions across various industries. By continuing to explore and develop this technology, we can advance towards a greener future that supports environmental sustainability, improves human health, and enhances the quality and safety of food and medical products.

Nomenclature

CECS: Carboxyethyl Chitosan

CMCS: Carboxymethyl Chitosan

EDC: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide

HFID: hexafluoro-2-propanol

HMDI: Hexamethylene Diisocyanate

NHS: N-hydroxysuccinimide
PCL: Polycaprolactone
PDO: Polydioxanone
PEO: Polyethylene Oxide
PLGA: Poly(lactic-co-glycolic acid)
PVA: Polyvinyl Alcohol
TFA: Trifluoroacetic Acid
ZnO: Zinc Oxide

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