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Review

Electrospun Nanofibers for Antimicrobial Therapy: From Polymer Design to Controlled Drug Release

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Highlights

What are the main findings?

- Electrospun nanofibers improve antimicrobial drug delivery and stability.
- Polymer type and spinning parameters control fiber morphology and drug release.
- Bioactive nanofibers show promise for wound healing and infection control.

What are the implications of the main findings?

- Nanofiber systems may help combat antimicrobial resistance more effectively.
- Controlled drug release can enhance efficacy and reduce side effects.
- Multifunctional nanofibers support future personalized antimicrobial therapies.

Abstract

The rapid emergence of antimicrobial resistance has intensified the need for advanced therapeutic platforms capable of improving the efficacy, stability, and targeted delivery of antimicrobial agents. Electrospun nanofibers have emerged as highly promising materials for biomedical applications due to their large surface area, high porosity, tunable morphology, and ability to incorporate a broad range of bioactive compounds. This review provides a comprehensive overview of the design, fabrication, and biomedical applications of electrospun bioactive nanofibers functionalized with antimicrobial drugs. It presents the main nanofiber fabrication techniques, with particular emphasis on electrospinning and the influence of solution, process, and environmental parameters on fiber morphology and drug-loading efficiency. Natural, synthetic, and hybrid polymer systems commonly employed in electrospun antimicrobial nanofibers are analyzed in relation to their physicochemical properties, biocompatibility, and therapeutic performance. In addition, the review highlights different drug incorporation strategies, including encapsulation, immobilization, and surface coating, as well as the mechanisms of action of antimicrobial agents. Recent advances in nanotechnology-based antimicrobial systems and their role in overcoming analytical, biopharmaceutical, and drug-delivery limitations are also examined. Furthermore, the review addresses current challenges related to scalability, reproducibility, stability, and clinical translation of electrospun nanofibers. Finally, future perspectives focusing on multifunctional, stimuli-responsive, and personalized antimicrobial nanofiber systems are discussed as promising directions for combating bacterial infections and reducing the global burden of antimicrobial resistance.

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1. Introduction

Antimicrobial resistance (AMR) is a growing global health concern, as microorganisms such as bacteria and parasites evolve mechanisms to survive antimicrobial treatment, complicating the management of infections and increasing morbidity and mortality rates worldwide. Despite global efforts, the prevalence of AMR continues to rise due to limited surveillance, the rapid evolution of resistant strains, and a lack of effective therapeutic delivery systems [1,2].

To combat this threat, innovative drug delivery platforms are being developed to enhance the efficacy and bioavailability of antimicrobial agents while minimizing resistance development. Nanotechnology, and specifically nanomedicine, has emerged as a promising solution, offering targeted delivery, enhanced therapeutic performance, and reduced side effects [3,4]. For example, nanofibers enable the immobilization of enzymes and antimicrobial peptides, offering flexibility in using biodegradable or non-degradable materials for drug delivery. They also serve as effective carriers for natural bioactive compounds, forming active matrices for healthcare applications. Among various nanostructures, electrospun nanofibers have gained attention for their high surface area, tunable properties, and ability to incorporate diverse antimicrobial agents [5,6]. These remarkable properties make nanofibers promising candidates for tissue-engineering scaffolds [7], wound healing/wound dressings [8], or drug delivery systems [9].

Antimicrobial drugs are essential for preventing and treating bacterial and parasitic infections, with their discovery revolutionizing modern medicine. A wide range of antibiotics, including β-lactams, aminoglycosides, macrolides, sulfonamides, trimethoprim, oxazolidinones, tetracyclines, and glycopeptides, are commonly used to treat bacterial infections. These antimicrobial agents exhibit distinct mechanisms of action and resistance, and their therapeutic effectiveness depends on the targeted pathogen, making appropriate antibiotic selection critical for successful treatment [10].

This review focuses on recent advancements in the use of bioactive electrospun nanofibers functionalized with antimicrobial drugs. It explores the materials and methods used in fiber fabrication, strategies for drug incorporation, and how these systems address key challenges in antimicrobial therapy. Case studies are presented to demonstrate real-world applications, and future directions are discussed to guide further innovation in the field. Future directions in this field are also discussed.

2. Design and Optimization of Bioactive Nanofibers

2.1. Fibers

Numerous biomedical applications, such as controlled medication release, bone tissue engineering, and wound dressings, are now made possible by high-precision fiber synthesis [11].

Cellulose nanofibers are used in tissue engineering and drug delivery systems [12] while fibers such as wool, silk, and hair, appreciated for their biocompatibility, elasticity, and mechanical resilience, are suitable for various applications including films, scaffolds, electroplated materials, and hydrogels [13–16].

Synthetic fibers are categorized as inorganic or organic depending on their composition [17]. The most widely used polymers in biomedicine are PLA (polylactic acid) and PCL (polycaprolactone), known for their biocompatibility and favorable degradation prop-

erties [18,19]. Inorganic fibers including fiberglass and carbon fibers are recognized for excellent thermal and chemical stability, high strength, resistance to organic solvents and cost-effectiveness, making them suitable as reinforcement materials to enhance performance [18,19].

Understanding the structural and functional design of nanofibers requires a close look at the fabrication techniques that enable their precise production.

2.2. Nanofiber Fabrication Techniques

Nanofibers have become the center of attention for researchers and industries due to their facile manufacturing and fast development during recent years [20,21]. Several techniques are available for fabricating nanofibers and can be broadly classified into two principal approaches that are typically bottom-up or top-down [21].

2.2.1. Bottom-Up Approaches

Bottom-up approaches synthesize nanofibers using various techniques such as physical vapor deposition (PVD) [22], self-assembly, chemical vapor deposition (CVD) [23], and 3D printing [24]. Among these, the techniques that attract a lot of attention for many applications are 3D-printing approaches.

3D technologies can be utilized to create nanofiber composites or nano-reinforced composites, and direct ink writing (DIW) and fused deposition modeling (FDM) are two of these that are most commonly used [24,25].

DIW has attracted significant attention due to its controllable extrusion process, which enables a wide range of materials to be formulated as inks and printed, and has been widely used to produce nanocomposite fibers for various applications [24,26].

FDM is an additive manufacturing technique that creates complex geometries using thermoplastic filaments. FDM can process different fiber types including nanocomposite fibers [24].

2.2.2. Top-Down Approaches

Some traditional top-down spinning techniques often used for manufacturing nanofibers include fiber extrusion spinning methods such as meltspinning, dryspinning, wetspinning, centrifugal spinning [27] and electrospinning [21,28,29].

Wet-spinning technology is widely used in polymer science and textile engineering. A schematic of a basic wet-spinning equipment set-up is presented in Figure 1b. This method is especially applied in biomedical engineering for tissue repair, surgical sutures, would healing and drug delivery [30].

Melt spinning is a very popular technique and an economical approach. The basic set-up of melt-spinning equipment is represented in Figure 1c. Melt-spun fibers presents some unique properties and are used in medical applications as bioresorbable fibers, and in healthcare applications as antimicrobial fibers [31].

Dry spinning is another technique for fabricating nanofibers with specific properties, involving the transformation of a high vapor pressure polymer solution to a solid fiber through solvent evaporation [32]. A basic schematic of the dry spinning setup is shown in Figure 1d [32].

Electrospinning is a technique that fabricates ultrafine nanostructures from various polymers using a high power-voltage supply [33] (Figure 1a). This process uses electrically charged polymer solutions, melts, or suspensions to form structures with high surface area and tunable properties. When the electric field overcomes surface tension, the solution is ejected toward a collector. While most charges dissipate through the grounded collector, some remain due to low material conductivity. Overall, nanofiber formation relies on uniaxial stretching and elongation of the polymer jet [27]. Electrospinning technology

offers several advantages over other fabrication methods. It is a simple and cost-effective approach for producing nanostructures, particularly nanofibers. This technique enables the incorporation of bioactive compounds into nanofibers with ease, with the resulting nanofibers exhibiting excellent properties, including high porosity, well-defined structure, and a favorable surface-to-volume ratio [17]. These advantages allow the usage of electrospinning technology in various domains such as biomedical or chemical [34]. Despite electrospinning's facile use and low cost, the reproducibility and stability of its fibers are still under intense research [35].

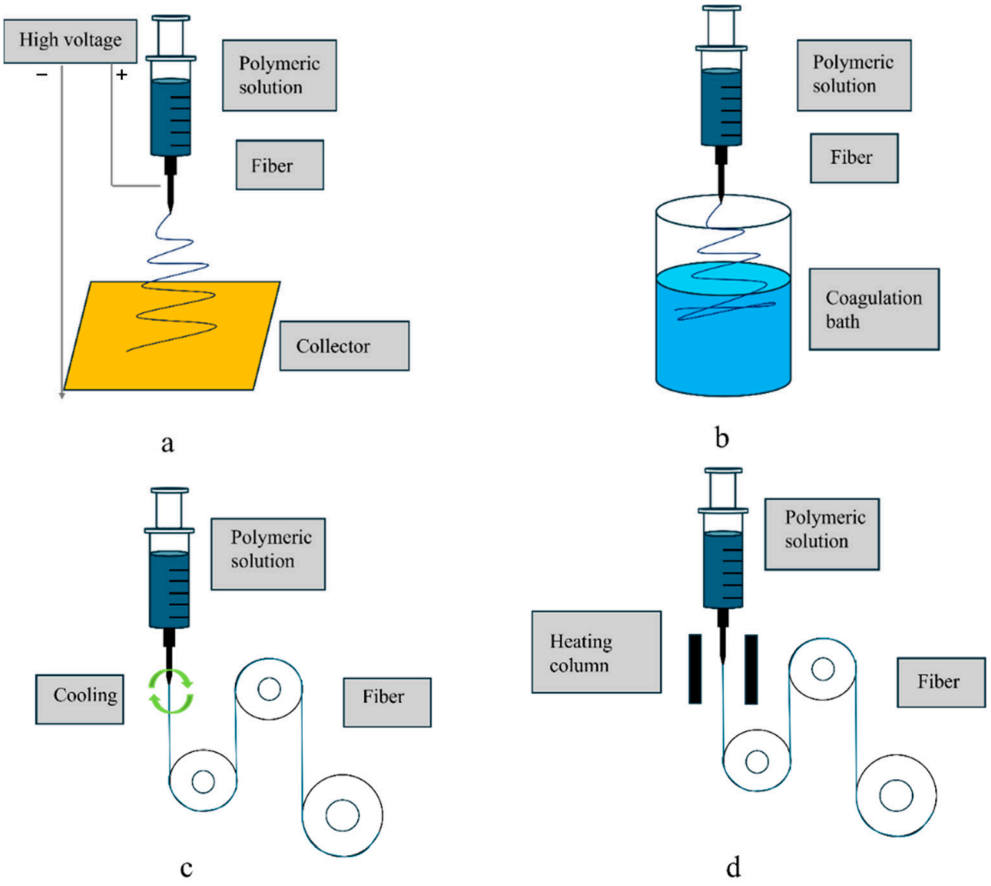


Figure 1. Schematic representation of different techniques for manufacturing fibers: (**a**) electrospinning, (**b**) wet spinning, (**c**) meltspinning, (**d**) drypinning.

2.3. Parameters Influencing Electrospun Nanofiber Morphology and Drug Loading

The fabrication of bioactive nanofibers requires careful control of parameters that affect their morphology, mechanics, and bioactivity; these are essential for applications like drug delivery, tissue engineering, and wound healing. Nanofiber formation depends on polymer solution properties, processing conditions, and environmental factors. These parameters vary with each polymer-solvent system, making fabrication highly material-dependent. Differences between expected and actual fiber structures often arise from complex parameter interactions, highlighting the need for thorough analysis to optimize electrospinning outcomes [36]. Table 1 summarizes the main parameters and their effects on nanofiber characteristics and drug release behavior.

Table 1. Summary of the main parameters influencing electrospun nanofiber morphology and drug-loading performance.

Category	Parameter	Effect on Nanofiber Morphology	Effect on Drug Loading and Release	References
Polymer solution parameters	Polymer concentration	Higher concentration increases viscosity and chain entanglement, reduces bead formation, and increases fiber diameter.	Generally improves drug encapsulation efficiency and promotes sustained release due to denser fiber structures.	[36–39]
	Molecular weight	Increases fiber uniformity and mechanical strength, and reduces bead defects through improved chain entanglement.	Enhances drug retention and may prolong release by reducing diffusion through the polymer matrix.	[40–42]
	Viscosity	Higher viscosity produces thicker and more continuous fibers; excessively high viscosity may hinder electrospinning.	Increased drug-loading capacity and slower release kinetics.	[43,44]
	Conductivity	Higher conductivity increases jet stretching and generally decreases fiber diameter; excessive conductivity may destabilize the jet.	Improves drug dispersion within fibers but may increase burst release due to smaller fiber diameters.	[29,45–48]
	Surface tension	High surface tension promotes bead formation and unstable jet formation.	May reduce drug-loading homogeneity and encapsulation efficiency.	[31]
Electrospinning process parameters	Applied voltage	Increased voltage enhances jet stretching and may reduce fiber diameter; excessive voltage can induce bead formation and irregular fibers.	Influences drug distribution and may increase initial burst release at high voltages.	[46,49–51]
	Flow rate	Higher flow rates increase fiber diameter and may cause bead formation due to incomplete solvent evaporation.	Allows higher drug incorporation but may lead to heterogeneous drug distribution and faster release.	[29,37,45,52,53]
	Tip-to-collector distance	Increasing distance improves solvent evaporation and fiber solidification up to an optimal value.	Affects encapsulation stability and release kinetics by influencing fiber morphology and porosity.	[44,54]
	Collector type and speed	Rotating collectors promote fiber alignment, while stationary collectors produce randomly oriented mats.	Fiber orientation may influence diffusion pathways and directional drug release.	[44,45,55,56]

Table 1. *Cont.*

Category	Parameter	Effect on Nanofiber Morphology	Effect on Drug Loading and Release	References
Environmental parameters	Relative humidity	Higher humidity may increase surface porosity, roughness, and fiber diameter; excessive humidity can generate defects.	Increased porosity generally accelerates drug release.	[57–59]
	Temperature	Higher temperatures reduce solution viscosity and promote solvent evaporation, producing thinner fibers.	May improve encapsulation efficiency but can affect thermosensitive drugs.	[49,60–62]
	Airflow/ventilation	Enhances solvent evaporation and fiber drying.	Influences residual solvent content and long-term drug stability	[49]

(i) Polymer solution parameters

Solution parameters have been widely investigated in recent years and are still analyzed for many polymer-solvent combinations. In this context, the solution parameters that need to be considered include polymer viscosity, electrical conductivity, molecular weight, and surface tension [31].

Polymer concentration influences solution viscosity and chain entanglement, which directly affects fiber morphology. It is one of the most investigated parameters and correlates with solution viscosity. When the polymer concentration is too low, bead formation occurs due to insufficient chain entanglement, leading to discontinuous fiber formation. In contrast, increasing polymer concentration enhances fiber uniformity and continuity, resulting in smooth, well-defined fibers [32].

For example, in electrospun polyurethane (PU) nanofibers, increasing the polymer solution concentration from 8 wt% to 12 wt% led to a significant increase in fiber diameter from 0.326 μm to 0.380 μm. This trend is attributed to the higher viscosity that stabilizes the polymer jet, reducing fiber breakage and beading [37]. Similarly, research on polyvinylpyrrolidone (PVP) nanofibers found that a minimum concentration of 12 wt% in DMF was required to produce uniform, bead-free fibers, whereas lower concentrations resulted in fibers with beads and irregular structures [38].

Research by Taruset al. demonstrated that at lower concentrations, electrospinning solutions tend to form beaded structures, while increasing the polymer concentration enhances fiber formation and uniformity. Specifically, cellulose acetate (CA) nanofiber mats exhibited a transition from beaded structures at 10 wt% concentration to smooth, continuous fibers at 14–16 wt%, depending on the solvent system used [39].

Molecular weight plays a critical role in solution viscosity, chain entanglement, and fiber uniformity during electrospinning. Higher molecular weight polymers result in increased viscosity, facilitating smooth fiber formation and reducing bead defects. For instance, in a study on polyhydroxyalkanoate(PHA) nanofibers, researchers found that low molecular weight poly(3-hydroxybutyrate-co-4-hydroxybutyrate) [P(3HB-co-95 mol% 4HB)] required a fivefold increase in solution concentration to achieve bead-free nanofibers compared to high molecular weight poly(3-hydroxybutyrate) [P(3HB)] [41]. Similarly, studies on poly(vinylpyrrolidone) (PVP) electrospun nanofibers confirmed that solutions prepared with higher molecular weight PVP (1,300,000 g/mol) produced thinner, more

uniform fibers, while lower molecular weight PVP (360,000 g/mol) led to increased fiber diameter variation [27].

Solution viscosity is directly influenced by polymer concentration and molecular weight, affecting fiber diameter, structure and morphology, and mechanical integrity.

A study on poly(vinyl alcohol) (PVA) nanofibers demonstrated that higher viscosity solutions led to increased fiber diameters, with thicker fibers forming at higher polymer concentrations [43]. The same study found that fiber uniformity improved with higher molecular weight PVA (186 kDa) due to enhanced chain entanglement. It is important to determine a solution which has sufficient viscosity for electrospinning for regulating the viscosity of a newly synthesized polymer solution by altering the concentration of the polymeric solution [37].

Conductivity is another crucial parameter for the electrospinning process influencing the final state of a fiber. The polymeric solution is required to be ionic to allow the electric field to flow between the needle and the collector through the solution. Low conductivity can prevent fiber formation due to insufficient surface charge for Taylor cone formation [46]. Since conductivity is hard to adjust without affecting other properties, process parameters (e.g., electric field, flow rate) are often modified instead. Adding salts is a common way to increase conductivity, which promotes Taylor cone formation and reduces fiber diameter [38].

A study made by Chritral A. and Shesja J. determined the effects of changing conductivity of 5% polyethylene oxide (PEO)/water solution with the addition of NaCl on the electrospinning process and fiber morphology. Their results highlighted that the average jet current at first increases with the increase in the conductivity of the solution and thereafter decreases slightly. Additionally, they demonstrated that there is a power-law relationship between conductivity and nanofiber thickness. While highly conductive solutions also fail to generate a Taylor cone because of a depleted tangential electric field on the droplet surface, very low conductivity solutions are unable to make electrospun fibers because of inadequate surface charge, which prevents Taylor cone production [47]. Another study investigated by F. Topuz et al. determined some effects of conductivity over the electrospinning process and structures of the fibers. Their results highlighted the electrospinnability of PIM solutions that are related to the conductivity of the respective solutions. Adding ammonium salt drastically decreased the conductivity of polymer solutions and slightly increased the mean diameter of fibers. Also, when they increased the conductivity of the polymer solution, they observed the fact mentioned earlier, that the nanofibers obtained are thinner with a smaller diameter [48].

Molecular weight is a crucial factor influencing mechanical properties such as tensile strength, Young's modulus, and elongation at break. A study on poly(lactic acid)(PLA) nanofibers confirmed that higher molecular weight PLA resulted in enhanced tensile strength and elongation at break, making them more suitable for tissue engineering scaffolds [42]. The research showed that high molecular weight PLA nanofibers (PLAH-20%) exhibited an elongation at break of 25.87%, while low molecular weight PLA nanofibers had higher tensile strength but lower flexibility.

Similarly, PVA electrospun nanofibers demonstrated improved mechanical properties with increased molecular weight. PVA nanofibers with a molecular weight of 200 kDa exhibited the highest tensile strength (29.8 MPa) and modulus (78 MPa), confirming that higher molecular weight contributes to stronger and more resilient fibers [63].

Apart from strength, molecular weight also impacts stiffness and toughness. A study on polyacrylonitrile (PAN) nanofibers found that higher molecular weight PAN fibers exhibited superior mechanical performance, with the highest strength of 153 MPa and toughness

of 16.0 J/g [64]. This confirms that increased molecular weight leads to stronger and tougher electrospun fibers, making them ideal for reinforcement applications in biomaterials.

Interestingly, fiber molecular orientation during electrospinning also plays a role in mechanical performance. A study on polyvinylidene fluoride (PVDF) electrospun fibers revealed that higher molecular weight PVDF led to increased molecular alignment and crystallinity, resulting in enhanced stiffness and mechanical stability [22].

(ii) Electrospinning process parameters

Fiber morphology is highly influenced by the process parameters of electrospinning. It is essential to know how fiber morphology is impacted by these parameters in order to obtain electrospun nanofibers with specific properties and characteristics. It has been revealed that the principal process parameters of electrospinning include applied voltage, flow rate, spinning distance (nozzle tip-to-collector) and collector type. The relationship between electrospinning process parameters and nanofiber morphology has been determined as nonlinear [65].

Applied voltage and fiber formation

Applied voltage in electrospinning controls the electric field strength, directly affecting jet formation, Taylor cone shape, and fiber morphology. As voltage increases, it influences jet velocity and fiber structure, making it a critical parameter in forming ultrafine nanofibers [46].

K. Matabola and R. Moutloali studied the effect of applied voltage on the morphology of electrospun polyvinylidene fluoride (PVDF) nanofibers. Using a 22 wt% PVDF solution at a 15 cm spinning distance, they found that at 12 kV, the jet was unstable, producing small-diameter fibers with bead formation. As voltage increased to 14–16 kV, bead density decreased and fiber diameter increased due to improved jet stability. At 18 kV, fiber diameter decreased again, but irregular morphologies appeared, indicating excessive voltage can destabilize fiber formation [51]. As a result, higher voltage increases electrostatic repulsion, stretching the polymer solution into thinner fibers.

However, excessive voltage can lead to jet instability, bead formation, and inconsistent fiber diameters [49]. A study on polydioxanone (PPDO) nanofibers found that fiber diameter decreased with increasing voltage up to 10 kV, after which further increases led to bead formation due to unstable Taylor cone formation. Similarly, research on polycaprolactone (PCL) nanocomposite fibers demonstrated that an applied voltage of 18 kV produced optimal fiber uniformity, whereas voltages beyond 25 kV resulted in highly porous, irregular fibers [50].

Flow rate and solvent evaporation

The flow rate is another critical parameter for determining and controlling the morphology and diameter of nanofibers. The force needed to eject the polymer solution at a constant rate depends on various factors including the diameter of the spinneret tip or the solution viscosity [45]. The solution flow mainly depends on the volatility of the solution. Reports indicate that the increase of the flow rate results to the formation of thicker nanofibers [29]. For example, a study done by S. Zargham et al. [52] investigated the role of the flow rate over fiber diameter and morphology. Flow rate significantly affects nanofiber formation by influencing droplet size, Taylor cone stability, and fiber morphology. Lower flow rates produce smaller droplets and thinner, more uniform fibers, while higher rates can hinder solvent evaporation, causing defects like fiber fusion or branching. Increased flow also enlarges the deposition area and raises fiber diameter. For example, in PU nanofibers, increasing the flow rate from 0.012 to 0.02 mL/min raised the fiber diameter from 0.351 μm to 0.456 μm [37]. Also, A. Eleyas determined the relationship between the flow rate and the diameter of the nanofibers. Using electrospun PAN nanofibers under various flow rate values, they observed that when the flow rate increases, the value of fiber

diameter also increases due to the increased feed rate, which eventually results in beaded large-diameter fibers due to the unavailability of proper solvent evaporation time [53]. These findings suggest that optimizing the flow rate is critical for balancing fiber uniformity and productivity.

Tip-to-collector distance and fiber alignment

The distance between spinneret and collector is highly influential for determining the morphologies of nanofibers. Numerous studies cover the effect of the tip-to-collector distance according to the literature. For example, A. Jabur et al. [54] prepared PVA electrospun nanofibers varying the tip-to-collector distance and the ambient temperature. The study analyzed how tip-to-collector distance affects nanofiber size and shape. Increasing this distance initially reduces average fiber diameter, likely due to weaker electric field strength, slower jet acceleration, or premature solidification limiting elongation. However, a longer distance also extends solvent evaporation time, enabling the successful collection of dry, solid electrospun fibers.

The distance between the needle tip and the collector influences fiber alignment, porosity, and crystallinity. Increasing the distance allows more time for solvent evaporation, reducing bead formation and improving fiber uniformity. To sum up, too short a distance prevents the fiber from solidifying before reaching the collector, and if the travel distance of the jet is too long, bead fibers are obtained. Thus, an optimal distance is required because dryness from solvent is a critical element of the electrospun nanofibers [44].

Collector type and fiber orientation

Various collectors can be used in this process, such as basic collectors, co-axial collectors, side-by-side collectors, multiple jet collectors, metallic jet collectors and so on [44]. The type of collector significantly influences fiber morphology. A basic flat collector yields randomly oriented mats, while specialized collectors (e.g., rotating drums, mandrels) can align fibers based on rotation speed. High speeds may break fibers into fragments, while slow speeds allow irregular, uneven deposition [45].

The type of collector influences fiber alignment and mechanical properties. A rotating drum collector produces aligned fibers, which are crucial for applications such as tissue engineering and nerve regeneration. A study on PLA-PCL tubular electrospun scaffolds found that fiber orientation improved significantly when a rotating mandrel was used at high speeds [55]. S. Sheikhi et al. investigated electrospinning of polyacrylonitrile in imethylformamide using various collectors. Nanofibers collected with a rotating cylinder showed the highest ultimate stress, indicating superior mechanical strength. Morphologically, the wire drum produced the most aligned fibers, while the disc collector yielded randomly oriented ones [56].

(iii) Environmental parameters

Humidity plays a key role in influencing fiber diameter, porosity, and surface texture, with effects varying based on solvent type and polymer hydrophilicity. Higher humidity levels slow solvent evaporation, leading to porous, ribbon-like fibers, whereas lower humidity results in smooth, dense fibers. Research on polyacrylonitrile (PAN) nanofibers demonstrated that nanofibers electrospun at 30% relative humidity (RH) or higher developed rough surfaces and porous cores, whereas fibers formed at 22% RH or less remained smooth and solid [58].

A comprehensive review of over 20 polymers confirmed that relative humidity governs charge dissipation, solvent evaporation, and fiber morphology. This study highlighted that controlling humidity is essential for process repeatability, particularly when working with hydrophilic and hydrophobic polymers [57].

Similarly, in PCL nanofibers embedded with curcumin, increasing humidity from 40% RH to 60% RH resulted in an increase in fiber diameter from 100 nm to 145 nm, along with greater fiber uniformity [59].

Temperature influences solution viscosity, jet stability, and solvent evaporation rates, all of which affect fiber diameter and mechanical integrity. Higher temperatures accelerate solvent evaporation, leading to smaller, more uniform fibers.

A study on chitosan nanofibers found that increasing the electrospinning chamber temperature from 22 °C to 32 °C significantly improved fiber uniformity, resulting in smooth nanofibers with an average diameter of 200 nm [61]. A study on PAN and PVP nanofibers found that increasing the electrospinning temperature from 20 °C to 50 °C led to a gradual decrease in fiber diameter. The fiber diameter followed a quadratic relationship with temperature, confirming that higher temperatures promote fiber thinning due to reduced viscosity and surface tension [60]. Similarly, a study on PVA electrospun fibers confirmed that room temperature (22 °C) produced thicker fibers, whereas elevated temperatures (35 °C and above) resulted in thinner fibers with fewer defects [62].

Higher temperatures can lead to the formation of porous fibers, particularly in cases where solvent systems involve binary mixtures with different boiling points. Research on polysulfone/PLA electrospun fibers demonstrated that controlling solvent evaporation rates at different temperatures enables precise manipulation of pore size and fiber porosity, which is crucial for drug delivery and filtration applications [49].

Beyond the processing conditions, the choice of polymer plays a critical role in defining nanofiber characteristics, drug compatibility, and biomedical performance.

2.4. Choice of Polymers for Producing Nanofibers via Electrospinning

Choosing the right polymer for nanofiber production depends on the application, required mechanical properties, biodegradability, and biocompatibility. Natural polymers like chitosan, collagen, and silk fibroin are ideal for biomedical uses but often need blending with synthetic polymers to improve strength and spinnability. Synthetic options such as PCL and PLA offer controlled degradation, consistent properties, and scalability. The following sections examine key natural and synthetic polymers, outlining their benefits, limitations, and biomedical uses.

2.4.1. Common Natural Polymers Used for Electrospinning Nanofibers

✓ **Collagen**—a structural protein and a key component of the extracellular matrix(ECM), making it an excellent candidate for nanofiber production [66]. The electrospinning process is commonly employed to fabricate collagen-based nanofibers, resulting in highly porous, biocompatible, and bioactive materials with applications in tissue engineering, wound healing, and drug delivery [66]. Another key advantage of collagen nanofibers is their biodegradability and low immunogenicity, which makes them ideal for applications such as scaffolds in regenerative medicine. Because collagen naturally degrades in the body and has weak antigenicity, it is considered one of the safest biomaterials for medical implants and drug delivery systems [67]. In terms of mechanical properties, collagen nanofibers exhibit high porosity and structural flexibility, allowing for efficient nutrient exchange and cell infiltration. These properties make collagen particularly suitable for soft tissue regeneration applications, including wound healing and vascular grafts [67]. Collagen nanofibers are being explored for drug delivery applications. Research by Vichare et al. highlighted how collagen-based nanoparticles serve as effective carriers for drug delivery due to their ability to encapsulate bioactive compounds and control their release. Their findings suggest that collagen nanofibers could be functionalized with antibiotics, growth fac-

tors, or nanoparticles for targeted therapy [68]. Despite its advantages, collagen faces some challenges in nanofiber production, including poor mechanical strength and rapid degradation. To address these issues, researchers have explored crosslinking techniques and hybrid materials. For example, Zeybek et al. optimized the electrospinning parameters of collagen blended with PCL to improve its mechanical integrity and spinnability, making them suitable for wound dressing and tissue engineering applications [69].

✓ **Chitosan**—antibacterial, bioactive, and biodegradable; widely used for wound dressings, drug delivery, and tissue engineering [70]. Chitosan's antimicrobial activity is driven by its -NH_3^+ groups, which are only active in acidic conditions, limiting its use at neutral pH. To overcome this, chitosan is often quaternized, such as in N,N,N-trimethyl chitosan (TMC), making it water-soluble and permanently charged, thus enhancing microbial interaction. Other modifications like thiolated and carboxymethyl chitosan also show strong antimicrobial effects. Chitosan-based nanofibers, known for their biocompatibility, have demonstrated over 99% microbial reduction, making them promising for wound healing and antimicrobial therapies [71].

✓ **Gelatin**—derived from collagen, biocompatible and biodegradable, commonly used in wound healing and drug release systems. The choice of gelatin for nanofiber production is primarily due to its ability to support cell attachment, proliferation, and differentiation, making it an ideal candidate for tissue engineering, wound healing, and drug delivery applications [72].

One of the key advantages of gelatin nanofibers is their ability to be electrospun using benign solvent systems that minimize cytotoxicity while maintaining nanofiber integrity. In wound healing applications, gelatin nanofibers have been explored for their ability to provide a moist environment while promoting fibroblast proliferation. A study by Barnthip & Pinyakong demonstrated that gelatin nanofibers loaded with lipopeptide biosurfactants exhibited antimicrobial activity against *E. coli* and *S. aureus*, making them promising candidates for wound dressing materials [73].

A promising application of gelatin nanofibers is in drug delivery systems. Research by Singh et al. explored airbrushed gelatin nanofibers as scaffolds for controlled drug release, demonstrating their ability to provide sustained drug delivery while maintaining structural integrity [74]. Additionally, nanofibers have been functionalized with epidermal growth factor (EGF) to promote cell proliferation and enhance diabetic wound healing [75].

Despite their many advantages, gelatin nanofibers face challenges such as rapid degradation and low water resistance, necessitating crosslinking techniques to improve their stability.

✓ **Cellulose**—the most abundant natural polymer, has garnered significant attention in nanofiber production due to its biocompatibility, biodegradability, and mechanical strength. Cellulose nanofibers being highly biocompatible are well-suited for biomedical applications. They enable controlled drug delivery, with cellulose-based hydrogels showing high drug entrapment and sustained release. For example, cellulose nanofiber films have successfully encapsulated hydrophobic drugs like indomethacin, allowing controlled release over 15–30 days [76]. In another study, cellulose-based nanofibers were investigated for their wound healing potential, showing high biocompatibility and the ability to accelerate epithelialization in burn wounds, reducing healing times to 11–21 days [76].

One of the most promising applications of cellulose nanofibers is in biomedical scaffolding. Additionally, cellulose nanofiber-based aerogels have been extensively used in

antibiotic delivery systems, biosensing, and antimicrobial film production for wound healing applications [77].

In drug delivery systems, cellulose nanofiber-based membranes have been explored for their potential to improve therapeutic efficiency. Studies have shown that cellulose acetate nanofibers loaded with antimicrobial agents such as Ag nanoparticles exhibit strong antibacterial properties against Gram-positive and Gram-negative bacteria [78]. Similarly, cellulose nanofiber membranes containing tetracycline have been demonstrated to prevent bacterial infections while maintaining their biocompatibility with human skin fibroblast cells, making them suitable for wound dressings [79].

Despite their advantages, cellulose nanofibers have limited solubility and tend to aggregate.

✓ **Silk fibroin**—a natural protein polymer widely explored for nanofiber production due to its excellent biocompatibility, biodegradability, and mechanical properties. The use of electrospinning to fabricate silk fibroin nanofibers has gained attention in biomedical applications, including tissue engineering, wound healing, and drug delivery because of their ability to form fibrous matrices that closely mimic the ECM, supporting cell attachment, proliferation, and differentiation [80].

Silk fibroin nanofibers are widely studied for tissue engineering applications. In a study by Nalvuran et al., hybrid scaffolds composed of silk fibroin and reduced graphene oxide (RGO) were developed for cell culture applications. The incorporation of RGO enhanced the mechanical properties and biocompatibility of the electrospun nanofibers, leading to improved osteogenic differentiation of mesenchymal stem cells [81].

In drug delivery applications, silk fibroin nanofibers offer a highly tunable release profile, allowing for the controlled release of therapeutic agents. A study incorporating grape seed extract (GSE) into silk fibroin nanofibers demonstrated sustained antioxidant release while maintaining cytocompatibility. The findings suggested potential applications in tissue regeneration and skin care [82]. Additionally, silk fibroin nanofibers have been utilized for cancer therapy, where hybrid nanofibers composed of cellulose acetate, silk fibroin, and Au-Ag nanoparticles showed significant cytotoxic effects against breast cancer cells [83].

Despite their advantages, silk fibroin nanofibers require post-treatment to improve stability and water resistance.

✓ **Alginate**—a naturally occurring polysaccharide derived primarily from brown seaweed, known for its biocompatibility, biodegradability, and ability to form hydrogels through ionic crosslinking with divalent cations such as calcium. Due to its structural similarity to the ECM, alginate has gained significant attention for nanofiber production, particularly in biomedical applications such as wound healing, tissue engineering, and drug delivery. Electrospinning is widely used to fabricate alginate nanofibers [84]. Additionally, alginate nanofibers incorporating oregano essential oil have shown strong antimicrobial activity against common wound pathogens, supporting their use in antimicrobial wound dressings [85]. Despite its numerous advantages, alginate nanofibers face challenges related to their solubility and rapid degradation in aqueous environments.

Despite their benefits, natural polymers often require chemical modifications or blending with synthetic polymers to improve electrospinnability and mechanical properties [86].

2.4.2. Common Synthetic Polymers Used in Nanofibers Produced by Electrospinning

Synthetic polymers offer controlled properties, reproducibility, and superior mechanical stability, making them highly suitable for industrial-scale nanofiber production. How-

ever, their lack of biodegradability and potential cytotoxicity limit their biomedical applications [70].

✓ **Polycaprolactone (PCL)**—a synthetic, biodegradable polymer that has gained significant attention for nanofiber production due to its excellent mechanical properties, biocompatibility, and slow degradation rate. Electrospinning is widely used to fabricate PCL nanofibers, offering a highly porous and interconnected structure suitable for applications in tissue engineering, drug delivery, and wound healing. The ability of PCL to mimic the EMC makes it an ideal candidate for biomedical applications, particularly in regenerative medicine [87].

A study on electrospun PCL nanofibers demonstrated their high tensile strength, making them suitable for load-bearing tissue engineering applications [88]. Additionally, the electrospinning process enables the incorporation of bioactive agents into PCL nanofibers, enhancing their therapeutic potential. Research has shown that blending PCL with halloysite nanotubes for antibacterial applications significantly improves its ability to inhibit bacterial growth while maintaining biocompatibility [89].

PCL nanofibers are widely utilized in tissue engineering due to their ability to support cell proliferation and differentiation. A study on PCL/gelatin nanofibrous membranes demonstrated improved hydrophilicity and cell attachment properties, highlighting their potential in scaffold-based regenerative therapies [90]. In another study, electrospun PCL nanofibers were modified with surface treatments to enhance cellular interactions, demonstrating significant improvements in osteoblast adhesion for bone tissue engineering applications [91].

In drug delivery applications, PCL nanofibers provide a platform for controlled and sustained drug release. Research on PCL/PVA core–shell nanofibers has demonstrated their potential for pH-responsive drug delivery, particularly in chemotherapy against colon cancer. These nanofibers successfully encapsulated paclitaxel, allowing for targeted drug release under acidic tumor conditions [92].

Despite its many advantages, PCL does have limitations, including its hydrophobic nature, which can limit cellular interactions.

✓ **Polylactic acid (PLA)**—biodegradable and biocompatible polymer widely used for nanofiber production due to its excellent mechanical properties, controlled degradation, and safety profile. Electrospinning is the most common technique used to fabricate PLA nanofibers, which results in highly porous and interconnected fiber structures. These properties make PLA nanofibers suitable for various biomedical applications, including tissue engineering, wound healing, and drug delivery [93].

One of the key reasons PLA is chosen for nanofiber production is its ability to degrade via hydrolysis into lactic acid, a non-toxic byproduct that is easily metabolized by the human body. This characteristic is particularly advantageous for biomedical implants and drug delivery systems, as it allows for predictable degradation without causing harmful side effects. A study on PLA-controlled drug delivery systems demonstrated its ability to encapsulate and gradually release therapeutic agents, reducing systemic toxicity while maintaining sustained drug efficacy [94].

PLA nanofibers have been extensively studied for wound healing applications. Research has shown that PLA-based electrospun dressings provide a suitable microenvironment for cell attachment and proliferation while preventing bacterial infection. A study by Hajikhani et al. demonstrated that PLA nanofibers encapsulated with collagen and cefazolin significantly enhanced wound healing in mice, showing improved fibroblast migration and reduced bacterial contamination compared to standard wound dressings [95]. Similarly, PLA-based nanocomposite scaffolds incorporating Ag nanoparticles have been

shown to exhibit strong antimicrobial activity, making them ideal for preventing infections in chronic wounds [96].

In tissue engineering, PLA nanofibers serve as temporary scaffolds that support cell growth and guide tissue regeneration. The porosity and high surface area of electrospun PLA fibers provide an ideal environment for stem cell differentiation and extracellular matrix deposition. A study on PLA nanofiber scaffolds for bone tissue engineering highlighted their ability to promote osteogenic differentiation, especially when combined with hydroxyapatite nanoparticles [97]. Additionally, PLA nanofibers blended with graphene oxide have been shown to enhance electrical conductivity, making them a promising material for neural tissue engineering applications [98].

Despite its numerous advantages, PLA does have some limitations, such as its relatively slow degradation rate and hydrophobic nature, which can limit cellular interactions.

✓ **Poly(vinyl alcohol) (PVA)**—a water-soluble, biocompatible, and biodegradable synthetic polymer that has gained substantial interest in the fabrication of nanofibers for biomedical applications. Electrospinning is the most widely used method to produce PVA nanofibers, providing a high surface area, tunable porosity, and excellent mechanical properties. The hydrophilic nature of PVA allows for easy processing in aqueous solutions, eliminating the need for toxic organic solvents, which is particularly beneficial for applications in drug delivery, wound healing and tissue engineering [99].

PVA nanofibers are widely used in wound healing for maintaining moisture and blocking infections. They promote fibroblast adhesion and skin regeneration. Incorporating silver nanoparticles into PVA nanofibers enhances antibacterial activity, effectively inhibiting *E. coli* and *S. aureus* [100].

In drug delivery applications, PVA nanofibers offer a promising vehicle for sustained and controlled release of therapeutic agents. Studies have demonstrated that electrospun PVA nanofibers loaded with antibiotics, such as erythromycin, exhibit prolonged antibacterial activity while maintaining biocompatibility [101]. Additionally, research on PVA-PCL core–shell nanofibers has demonstrated their ability to provide pH-responsive drug release, making them particularly useful for chemotherapy applications targeting colon cancer [92].

PVA nanofibers have also been investigated for their potential in tissue engineering, particularly for cardiovascular applications. In a new study PVA nanofibers have been combined with chitosan to create crosslinked scaffolds that improve cell attachment and proliferation for tissue engineering applications [102].

Despite their many advantages, PVA nanofibers face challenges such as low mechanical strength and rapid dissolution in aqueous environments.

✓ **Polyurethane (PU)**—a highly versatile synthetic polymer known for its excellent mechanical properties, biocompatibility, and tunability, making it a promising material for nanofiber production. The electrospinning process is commonly used to fabricate PU nanofibers, resulting in highly porous structures with large surface areas that are suitable for applications such as wound healing and tissue engineering. PU nanofibers have also been explored for drug delivery applications due to their ability to encapsulate and sustain the release of therapeutic agents. A study investigating PU nanofiber-based drug carriers demonstrated their potential in controlled drug release, showing that PU nanofibers loaded with antibiotics could effectively inhibit bacterial growth over extended periods [103]. Additionally, PU nanofibers modified with bioactive molecules, such as heparin, have been developed for anticoagulant therapy, offering sustained bioavailability and reducing the risk of clot formation in medical implants [104].

In wound healing applications, PU nanofibers provide an effective barrier against microbial infections while maintaining an optimal moisture balance. A study on electrospun PU nanofibers loaded with salicylic acid demonstrated significant antibacterial activity against *E. coli* and *S. aureus*, supporting their potential use in antimicrobial wound dressings [105].

Despite their many advantages, PU nanofibers have potential cytotoxicity from unreacted isocyanates and limited biodegradability.

Synthetic polymers are often blended with natural polymers or functionalized with bioactive agents to enhance biocompatibility and antimicrobial properties.

2.4.3. Hybrid Approaches: Blending Natural and Synthetic Polymers for Optimized Nanofibers

A promising approach is the combination of natural and synthetic polymers to achieve optimized mechanical, biological, and physicochemical properties.

Chitosan-PCL nanofibers improve biocompatibility and mechanical stability, making them suitable for drug delivery and wound healing [70]. Blending chitosan with other polymers such as PVA improves its electrospinnability while maintaining its antimicrobial properties [106].

Gelatin nanofibers can be blended with other polymers such as polyethyleneimine (PEI) to enhance their mechanical and thermal stability while improving their cytocompatibility [107]. Furthermore, blending gelatin with synthetic polymers such as PCL has been used to optimize mechanical performance in biomedical applications [90]. In addition to improving mechanical performance, gelatin can enhance the hydration behavior of PCL-based electrospun membranes. Longo et al. reported that PCL/gelatin membranes exhibited increased water uptake due to the hydrophilic nature of gelatin, promoting better interaction with the biological environment. Furthermore, interactions between gelatin and PCL influenced polymer crystallinity and improved membrane flexibility, highlighting the benefits of this hybrid system for biomedical applications [108].

Despite its many advantages, cellulose nanofibers face some challenges, primarily their limited solubility in common solvents and their tendency to aggregate. To overcome these issues, cellulose is often converted into derivatives such as cellulose acetate, which enhances its electrospinnability and allows for improved fiber morphology. Additionally, cellulose nanofibers can be modified with functional groups such as quaternary ammonium compounds to enhance their antibacterial properties [109]. Furthermore, hybrid cellulose nanofibers containing magnetic nanoparticles have been developed for targeted drug delivery, opening new possibilities in precision medicine [110].

Blending silk fibroin with synthetic polymers such as PCL has been explored to improve its structural integrity and processability [111]. Another approach involves modifying silk fibroin with polydopamine to create antibacterial nanofibers suitable for biomedical applications [112]. Studies have demonstrated that sodium alginate/PCL core–shell nanofibers can be used for the controlled release of both hydrophilic and hydrophobic drugs, making them promising candidates for therapeutic applications [113].

To overcome the hydrophobic nature of PCL, which can limit cellular interactions, researchers have developed composite nanofibers blending PCL with natural polymers such as collagen to improve bioactivity and biocompatibility. A study focused on the use of PCL/hydroxyapatite composites for bone tissue engineering, highlighting their ability to promote osteogenesis and mineralization [114]. Moreover, the combination of PCL with oregano essential oil has been explored for food biopackaging, demonstrating effective antimicrobial properties against *Listeria monocytogenes* and *Salmonella enteritidis* [115].

In order to enhance electrospinnability, alginate is often blended with synthetic polymers such as PEO or PCL, enabling the formation of stable nanofiber mats [84].

Alginate nanofibers exhibit unique swelling and gelation properties, which make them suitable for drug delivery applications. Studies have demonstrated that sodium alginate/PEO (SA/PEO) nanofibers effectively encapsulate and release bioactive molecules in a controlled manner. In one study, SA/PEO nanofibers were fabricated for wound healing applications, and their degradation and swelling behavior were optimized to provide a moist healing environment [116]. Despite its numerous advantages, alginate nanofibers face challenges related to their solubility and rapid degradation in aqueous environments. One study successfully modified the chemical structure of alginate nanofibers to enhance their stability and control degradation under physiological conditions, making them more suitable for long-term biomedical applications [117].

Blending PVA with other polymers, such as gelatin, has been shown to enhance its structural integrity and biomimetic properties, making it more suitable for biomedical applications [118]. Another promising approach is the use of poly(lactide-co-glycolide) (PLGA) nanofibers, functionalized with graphene oxide–Ag nanocomposites, which exhibit strong antibacterial properties against *E. coli* and *S. aureus* [119]. These nanofibers effectively prevent bacterial colonization while maintaining high biocompatibility. Additionally, PVA-based nanofibers blended with natural antibacterial agents such as *Bidens pilosa* extracts have demonstrated enhanced antimicrobial activity, achieving a 12% higher inhibition rate against *E. coli* and *S. aureus* compared to their standalone components [120].

PU nanofibers face challenges such as potential cytotoxicity from unreacted isocyanates and limited biodegradability. To address these issues, PU nanofibers have been successfully blended with other biodegradable polymers, such as polycaprolactone (PCL)and polylactic acid (PLA), to enhance their mechanical properties while reducing their environmental impact [121].

Once the appropriate polymer or polymer blend is selected based on mechanical, biological, and degradation properties, the next critical step involves the effective incorporation of therapeutic agents into the nanofibers to enable controlled and targeted drug delivery.

2.4.4. Conductive Polymer-Based Electrospun Nanofibers

Conductive polymers (CPs), particularly polyaniline (PANI), polypyrrole (PPy), and poly(3,4-ethylenedioxythiophene) (PEDOT), have recently attracted increasing attention as components of electrospun antimicrobial nanofibers. These materials combine electrical conductivity with the high surface area and drug-loading capacity of electrospun fibers, enabling the development of multifunctional wound dressings and localized antimicrobial delivery systems. Because conductive polymers generally exhibit poor electrospinnability and limited mechanical properties when processed alone, they are commonly blended with biopolymers or biodegradable synthetic polymers such as gelatin, chitosan, PCL, PVA, and PLA [122–125].

Recent studies have demonstrated the potential of CP-containing electrospun systems as advanced wound dressings. For example, conductive PCL/gelatin/PANI nanofibers have been proposed as multifunctional scaffolds that combine the hydrophilicity and biological activity of gelatin with the electroactive properties of PANI [126]. The resulting hybrid scaffold exhibited improved surface properties compared with fibers prepared solely from PCL, highlighting the benefits of combining conductive and biological components.

Similarly, electrospun PCL/PANI/$BaTiO_3$ composites have shown improved surface characteristics and cellular responses while providing electrical functionality that may support tissue repair [127].

CPs can also improve biological performance. Guo et al. showed that PLA/PANI electrospun nanofibers promoted neuronal attachment and differentiation after plasma treatment [128], while Liu et al. reported that oriented PANI/poly-L-lactic acid (PLLA)/gelatin

nanofibers supported neurite extension and cellular organization [129]. These findings illustrate how CPs can provide additional biological cues that are absent in conventional non-conductive biopolymer fibers.

In comparison with electrospun fibers prepared solely from natural polymers such as gelatin, collagen, or chitosan, CP-containing systems generally exhibit improved electrical conductivity, enhanced surface wettability, and greater potential for electrically responsive behavior [122–125]. These properties are particularly attractive for advanced biomedical applications, including electrically stimulated tissue regeneration, biosensing, and stimuli-responsive drug delivery. Furthermore, CPs may facilitate the incorporation and controlled release of therapeutic agents, antimicrobial compounds, or nanoparticles, enabling the development of multifunctional electrospun platforms that combine structural support with therapeutic activity [122–125].

Although further studies are required to optimize conductivity, biodegradability, and long-term biocompatibility, CP-based electrospun nanofibers represent a promising strategy for expanding the functionality of conventional electrospun drug delivery systems and bioactive wound dressings.

2.5. Drug Incorporation and Delivery Methodologies

(i) Mechanism of action of fluoroquinolones

FQs, such as ciprofloxacin, levofloxacin, and moxifloxacin, inhibit bacterial DNA gyrase and topoisomerase IV, enzymes critical for DNA replication and transcription. Their bactericidal action is most effective against Gram-negative bacteria due to DNA gyrase inhibition, while topoisomerase IV inhibition plays a larger role in Gram-positive bacteria [130].

DNA gyrase is a crucial topoisomerase II enzyme that hydrolyzes adenosine triphosphate and ensures its stable association with DNA [131]. It is primarily responsible for introducing negative supercoils into bacterial DNA, a process that is critical for relieving torsional strain during replication and transcription. FQs stabilize the complex formed between DNA gyrase and DNA, trapping the enzyme in its cleaved state. This results in double-strand DNA breaks, ultimately leading to cell death [132].

Topoisomerase IV, on the other hand, is crucial for separating interlinked daughter chromosomes following DNA replication, a process known as decatenation. Inhibition of topoisomerase IV by FQs prevents proper chromosome segregation, disrupting bacterial cell division. While both enzymes are targeted by FQs, the relative importance of each varies by bacterial type: DNA gyrase is the primary target in Gram-negative bacteria, whereas topoisomerase IV plays a more significant role in Gram-positive bacteria [133].

FQs interact with the GyrA and GyrB subunits of DNA gyrase and the ParC and ParE subunits of topoisomerase IV. The drugs form a ternary complex with these enzymes and DNA, preventing the re-ligation of cleaved DNA strands. This process leads to the accumulation of lethal double-strand breaks and triggers the bacterial SOS response, further impairing cellular functions [134].

FQs like ciprofloxacin, which is a 2nd-generation type of FQ, has potent activity against Gram-negative microorganisms, including *E. coli*, *K. pneumoniae*, and *P. aeruginosa*. Levofloxacin and moxifloxacin demonstrate broader activity against Gram-positive bacteria, such as *S. pneumoniae* and *S. aureus*, as well as atypical pathogens like Mycoplasma and Chlamydia [135].

The efficacy of FQs is undermined by the emergence of resistance.

Translocation of FQs across membrane barriers to reach intracellular targets is a crucial step for antibacterial molecules [136,137]. This mechanism involves passive diffusion of

FQs and it is influenced by interactions with membrane environment and factors such as chelation with divalent ions or trans-membrane pH gradient. FQs exist in two different forms of ionization at a physiological pH: an uncharged form with significant dipole called zwitterionic, and an uncharged natural form [137]. The membrane permeability is related to the lipophilicity of molecules and results have determined that the permeability coefficient increases with an increase of the lipophilicity of molecules [136]. The natural species with smaller dipoles have higher lipophilicity than cations and anions. On the other hand, the zwitterionic species are responsible for passive diffusion despite having a low lipophilicity according to other authors. Ciprofloxacin, considered one of the representatives of the FQ antibiotics class, is often used for determining the susceptibility of bacteria, plays an important role in the translocation process [137,138]. The process begins in the aqueous phase, where ciprofloxacin (CPFX) molecules, due to their polar nature, form stacks that facilitate hydrogen bonding with lipid head groups. Stack formation and charge distribution reduce their overall polarity, promoting insertion into the lipid bilayer. As CPFX approaches the membrane, partial desolvation of both neutral and zwitterionic forms occurs, aiding proton transfer. The high free energy barrier for translocation of the zwitterionic form is attributed to water defect formation. Translocation completes when fluoroquinolone molecules diffuse across the membrane to reach their intracellular targets [137].

This proposed model of translocation of fluoroquinolones across membrane explains experiments involving model lipid bilayers elucidating one the fundamental issue regarding the diffusion mechanism of these drugs into and through cellular membranes. Also, this mechanism contributes to future developments of the drugs in various domains such as biochemistry, medical or pharmaceutic industry [137].

Even though FQs are widely used for treating respiratory tract infections, urinary tract infections, gastrointestinal infections, and more, their overuse has led to increased resistance, necessitating judicious prescribing practices and development of new antimicrobial agents [139].

(ii) Mechanisms of other antimicrobial drugs

β-Lactams, including penicillins, cephalosporins, carbapenems, and monobactams, inhibit bacterial cell wall synthesis. They target penicillin-binding proteins (PBPs), which catalyze the cross-linking of peptidoglycan strands, a critical step in maintaining cell wall integrity. The resulting weakened cell wall leads to osmotic lysis, particularly in actively dividing bacteria [140].

Aminoglycosides, such as gentamicin and amikacin, bind to the 30S subunit of the bacterial ribosome, causing misreading of mRNA. This disrupts protein synthesis and produces faulty proteins that compromise membrane integrity, ultimately leading to bacterial death. Their bactericidal effect is particularly potent against aerobic Gram-negative bacteria [141].

Macrolides, including erythromycin, azithromycin, and clarithromycin, bind to the 50S ribosomal subunit, inhibiting the elongation of polypeptide chains during protein synthesis. This action is bacteriostatic but can become bactericidal at high concentrations, particularly against Gram-positive pathogens and atypical bacteria [142].

Tetracyclines inhibit protein synthesis by binding to the 30S ribosomal subunit and preventing the attachment of aminoacyl-tRNA to the ribosomal acceptor site. This bacteriostatic action affects a broad spectrum of bacteria, including Gram-positive, Gram-negative, and intracellular pathogens [143].

Sulfonamides and trimethoprim interfere with bacterial folate metabolism, a pathway essential for DNA and RNA synthesis. Sulfonamides inhibit dihydropteroate synthase, while trimethoprim targets dihydrofolate reductase. These agents are often used together for a synergistic effect [144].

Glycopeptides, such as vancomycin, inhibit cell wall synthesis by binding to the D-alanyl-D-alanine terminus of peptidoglycan precursors. This prevents cross-linking and elongation of the bacterial cell wall, making glycopeptides particularly effective against Gram-positive bacteria [145].

Oxazolidinones, like linezolid, inhibit bacterial protein synthesis by binding to the 50S ribosomal subunit, preventing the formation of the initiation complex. This class is effective against multidrug-resistant Gram-positive pathogens [146].

2.5.1. Advances in Nanotechnology for Antimicrobial Applications

Nanotechnology represents a promising discipline for treating diseases by providing various therapy involving drug delivery systems that target a broad range of pathogens [147]. These nanomaterials utilize novel antimicrobial mechanisms that are unknown to microbes and may circumvent their natural defense systems. Due to their rapid advancements, nanomaterials are now recognized as nontraditional antimicrobial agents capable of addressing AMR as compared to traditional antibiotics drugs [148]. Nanotechnology exhibits some unique advantages for antimicrobial applications involving incorporations of several antibiotics for therapy. However, the cons of nanotechnology involve the high cost of implementing nanotechnology-based products, and environmental and health risks because their effects are not fully understood [149].

Engineered nanoparticles, such as Ag, Cu, and ZnO, offer broad-spectrum antimicrobial properties that can bypass traditional resistance mechanisms. Nanoparticles enhance antibiotic efficacy by improving drug delivery, reducing toxicity, and overcoming bacterial resistance through controlled and targeted release. Combining nanoparticles with existing antibiotics enhances antimicrobial effects, reduces required drug doses, and minimizes resistance development in pathogens [150].

The morphology of ZnO nanoparticles can influence their antimicrobial efficacy in organisms. Naturally, ZnO nanoparticles can reduce the activity of a wide range of Gram-positive and Gram-negative bacteria strains. The bactericidal properties of ZnO depend strictly on multifactorial bacterial mechanisms with smaller diameter particles demonstrating enhanced antibacterial activity especially in vitro suspension cultures. Also, compared to other standard pharmaceutical formulation, ZnO nanoparticles had more antibacterial activity against *E. coli* and *S. aureus*. Overall, ZnO nanoparticles show great antimicrobial activity and a promising material as intrinsic antimicrobial agent [149].

Silver (Ag) nanoparticles have been broadly used as antimicrobial agents against bacteria, fungi and parasites because their activity is based on Ag+ release that leads to the damage of antimicrobial cells by penetrating through the cell wall [151]. This is possible due to the fact that microorganisms are highly susceptible to Ag^{+} ions which have a strong affinity for microbial cell walls; they are involved in the electron transport chain and in transferring energy. As well as ZnO nanoparticles, Ag nanoparticles provide a substantial reduction in bacteria viability where the most relevant parameters have been determined to be the particle diameter and surface charge. The smaller the particle, the stronger the bacterial effect, and regarding the surface charge effect, the more positive, the more effective the antimicrobial effect [151]. Thus, these two key parameters will mostly decide the effectiveness of an antimicrobial particle.

Other potential and promising nanoparticles with antimicrobial activity are represented by gold (Au) nanoparticles that are biologically inert and non-toxic with a high surface-to-volume ratio [152]. The shapes of Au nanoparticles have different properties and characteristics which can influence the antimicrobial activity of nanoparticles. For example, studies have determined that Au nanoflowers have higher antimicrobial activity against *S. aureus* than Au nanostars [149].

Studies suggest that copper (Cu) ions play a key role in the antimicrobial mechanism. Antimicrobial activity can be eliminated using bathocuproine, and *S. aureus* has been determined to be more sensitive than *E. coli* to Cu nanoparticles despite the existence of a structural barrier. Overall, Cu solutions, complex Cu species, or polymers which contain Cu are mainly used as antifungal compounds [153].

Antimicrobial mechanisms of these inorganic nanoparticles are, overall, independent of particle chemistry [154]. This involves metal release mechanisms such as cell membrane disruption, disruption of cell walls, and DNA disruption [154]. Small-diameter nanoparticles effectively penetrate bacterial cells, enhancing antimicrobial action by disrupting cellular functions. However, their use in drug delivery is limited by agglomeration due to high surface energy, reducing efficiency. While they can reduce antibiotic toxicity, some, like gold nanoparticles, may cause side effects such as blood cell damage. Thus, thorough toxicity and biocompatibility assessments are crucial before clinical use [154].

2.5.2. Methods for Drug Loading

The incorporation of drugs into electrospun nanofibers is a critical aspect of developing effective drug delivery systems. There are three primary methods for drug loading: encapsulation, immobilization, and coating.

(i) Encapsulation

Encapsulation involves integrating the drug directly within the nanofiber matrix. Encapsulation can be achieved through blend electrospinning, where the drug is dissolved or dispersed in the polymer solution before fiber formation, or emulsion electrospinning, which creates core–shell structures with enhanced release properties [155]. Emulsion electrospinning has emerged as a powerful variant of the encapsulation technique, where drugs are encapsulated within core–shell nanofibers, enabling better control over drug release rates and reducing burst release. For example, curcumin-loaded mesoporous silica nanoparticles encapsulated in electrospun PCL/gelatin nanofibers demonstrated enhanced anticancer efficiency with dual-release mechanisms [156]. Studies comparing blend electrospinning and emulsion electrospinning for metoprolol tartrate-loaded PCL nanofibers showed that emulsion electrospinning significantly alleviated burst release and provided a more sustained drug release profile. This method is particularly valuable for hydrophilic drugs that require a controlled release system [157].

Another promising method is coaxial electrospinning, which enhances the release of hydrophilic drugs by forming core–shell nanostructures. Ampicillin-loaded PCL nanofibers were fabricated using this approach, resulting in significantly reduced burst release while maintaining a more controlled, sustained drug delivery profile. This technique is particularly useful for drugs that have low compatibility with the polymer matrix [158]. A further refinement in encapsulation involves quad-axial electrospinning, a sophisticated technique that enables layered drug release profiles. This method has been successfully employed in PCL-gelatin nanofibers to provide controlled delivery of antibacterial agents. Compared to traditional core–shell nanofibers, quad-axial fibers allow for enhanced control over the spatial distribution of encapsulated drugs, further regulating their release profiles [159].

Studies have demonstrated that encapsulation within electrospun fibers provides prolonged drug release, as seen in PCL nanofibers loaded with metoprolol tartrate, where the encapsulated drug exhibited a controlled release profile over time [160]. Additionally, encapsulating curcumin and hypocrellin A in PLA/silk fibroin nanofibers has been shown to enhance the bioavailability and anti-cancer efficacy of these drugs [161]. Moreover, encapsulation in electrospun nanofibers has been used to enhance the solubility and stability of poorly water-soluble drugs, improving their therapeutic effectiveness. For example, naringin, a bioactive compound, was encapsulated in PCL nanofibers to achieve

a sustained release over 12 days, showcasing the potential of electrospun nanofibers in long-term drug delivery applications [94].

(ii) Immobilization

Immobilization refers to the covalent or non-covalent attachment of drugs or bioactive molecules onto the surface of electrospun nanofibers. This method is particularly useful for applications requiring localized drug activity with minimal systemic diffusion.

(a) Covalent immobilization

Covalent immobilization is one of the most effective methods for permanently fixing biomolecules onto electrospun nanofibers, ensuring high specificity and prolonged stability. This technique typically involves either direct immobilization or the use of crosslinkers. In direct immobilization, electrophilic functional groups on the nanofiber surface form strong covalent bonds with the bioactive molecule. Alternatively, crosslinkers serve as intermediaries, facilitating the attachment while sometimes remaining part of the final immobilized structure [162].

A notable example of covalent enzyme immobilization is the attachment of lipase enzymes onto polyhydroxybutyrate (PHB) electrospun nanofibers, which resulted in a 120-fold increase in enzyme loading compared to conventional PHA supports. The immobilized enzymes displayed significantly improved stability and activity, demonstrating the potential of PHB nanofibers for enzymatic processes [163].

Immobilization of biomolecules onto electrospun nanofibers presents numerous advantages, making it a powerful technique in biomedical and industrial applications. One of the primary benefits is the improved bioactivity and stability of immobilized molecules. By anchoring biomolecules to nanofiber surfaces, their structural integrity and function are preserved over extended periods, reducing degradation and improving long-term efficacy [162].

Additionally, immobilization enables localized and sustained drug release, which is crucial in therapeutic applications where precise control over drug distribution is necessary. For example, immobilized antimicrobial peptides on electrospun nanofibers have demonstrated prolonged antibacterial activity, ensuring effective wound healing without the need for frequent reapplication [164]. Similarly, in enzyme immobilization, nanofibrous supports have shown high enzyme loading efficiency, significantly increasing enzymatic reaction rates and stability. Electrospun PHB nanofibers, for instance, achieved a 120-fold increase in enzyme loading compared to conventional supports, leading to enhanced biocatalysis [163].

Despite these benefits, several challenges remain in optimizing immobilization techniques. One critical issue is the potential loss of bioactivity due to harsh immobilization conditions. Some covalent attachment methods involve chemical crosslinking agents or high-energy activation, which can alter the conformation of proteins and reduce their biological function [165].

Furthermore, the optimization of immobilization conditions remains a significant challenge, as different biomolecules require specific attachment strategies to maintain functionality. Factors such as surface chemistry, polymer compatibility, and environmental conditions must be carefully adjusted to maximize immobilization efficiency while minimizing potential structural disruptions.

(b) Non-covalent immobilization

Non-covalent immobilization is a milder approach that preserves the native structure and activity of bioactive molecules. This method relies on hydrogen bonding, electrostatic interactions, or hydrophobic forces to adsorb biomolecules onto the nanofiber surface. While non-covalent attachment allows for reversible interactions, it may suffer from lower stability and potential desorption over time [166].

(iii) Coating

Coating techniques play a crucial role in modifying electrospun nanofibers to achieve controlled drug release, enhance stability, and improve bioavailability. This approach involves applying a drug-containing layer onto pre-fabricated nanofibers, allowing for immediate or delayed drug release depending on the coating composition.

Coating methods for drug delivery in electrospun nanofibers generally fall into physical adsorption, LbL assembly, and plasma-assisted surface modification.

(a) Physical adsorption

Physical adsorption is a simple and widely used method for drug loading in electrospun nanofibers. It involves immersing fibers in a drug solution, where weak interactions like hydrogen bonding and van der Waals forces enable surface attachment. This approach preserves drug activity and allows tunable release by adjusting adsorption conditions.

This method has been used in transdermal drug delivery, where coated electrospun nanofibers enable sustained release through skin absorption [167]. Physical adsorption has been employed for coating electrospun PLA-hydroxyapatite (PLA-HAP) nanofibers with doxycycline for controlled drug release in simulated body fluids. The study demonstrated that the drug-loaded nanofibers achieved prolonged release in phosphate buffer solution (PBS) and simulated body fluid (SBF), indicating their potential for localized infection control in bone tissue engineering [168].

In wound dressing applications, PVA/lysine nanofibers were coated with anti-inflammatory (ibuprofen) and antibacterial (lavender oil) agents via physical adsorption. The coated nanofibers demonstrated sustained ibuprofen release for the inflammatory phase of wound healing while providing an immediate burst release of lavender oil to prevent bacterial contamination [169].

Additionally, multilayer coatings incorporating alginate and other biomolecules have been used to enhance the stability and bioactivity of immobilized therapeutic agents [155].

Electrospun polymeric nanofibers have been extensively studied for transdermal drug delivery systems. By adsorbing drugs onto nanofiber surfaces, controlled release through the skin is achieved, minimizing systemic side effects. This approach has been explored for delivering antibiotics, anti-inflammatory agents, and vitamins in nanofibrous transdermal patches [167].

(b) Layer-by-layer coating (LbL)

LbL coating has emerged as an advanced and highly tunable method for modifying electrospun nanofibers, particularly for controlled drug delivery. The LbL technique involves sequential deposition of oppositely charged polyelectrolytes onto nanofiber surfaces, forming multilayered coatings that enable fine-tuned drug release and enhanced bioactive stability. One of the most promising uses of LbL-coated electrospun nanofibers is in wound dressing applications. Research has shown that multilayer LbL structures applied to electrospun nanofibers can significantly improve drug retention and reduce burst release, leading to a more sustained therapeutic effect. These coatings mimic the structure of the ECM, promoting cellular adhesion and wound healing [170].

LbL coatings have been explored for the controlled release of biological therapeutics, such as proteins and growth factors. One study demonstrated that LbL-assembled nanofiber scaffolds enabled sustained delivery of bone morphogenetic proteins, enhancing osteogenic differentiation for bone regeneration [171].

The LbL method has been widely used to coat antimicrobial and anti-inflammatory agents onto nanofibers, improving infection control and reducing inflammatory responses. A study on LbL-coated PLA electrospun fibers showed that embedding antimicrobial peptides in the coatings resulted in prolonged bacterial inhibition without cytotoxicity [172].

It has been applied in developing antibacterial coatings for wound dressings, where PLA-based electrospun fibers coated with antimicrobial peptides demonstrated prolonged bacterial inhibition [164].

LbL-assembled nanofibers have shown great promise in targeted cancer therapy, providing a controlled release of chemotherapeutic agents such as doxorubicin. This technology enhances drug bioavailability and reduces systemic toxicity by coating nanodrug delivery systems with polyelectrolyte multilayers [173].

(c) Plasma-assisted surface modification

Plasma-assisted surface modification is an advanced technique used to enhance the properties of electrospun nanofibers, improving their drug adhesion, bioactivity, and biocompatibility.

In one study, plasma-assisted coatings were used to functionalize PVA/soy protein isolate nanofibers, resulting in improved adhesion of bioactive molecules and sustained drug release in wound healing applications [174].

Plasma-treated nanofibers play a crucial role in optimizing drug release and can provide sustained and controlled drug delivery, as demonstrated in a study where oxygen dielectric barrier discharge plasma-treated silk/AMOX/PVA nanofibers exhibited enhanced wettability, surface energy, and adhesion properties. This treatment resulted in a prolonged and controlled release of amoxicillin, increasing its antibacterial efficiency against *E. coli* and *S. aureus* while maintaining excellent biocompatibility [175].

Plasma-assisted surface modification has also been applied in bone tissue engineering. Cold atmospheric plasma (CAP) treatment was used to modify core–shell electrospun nanofibers, enhancing their hydrophilicity and protein adsorption. This modification significantly increased fibroblast and osteoblast attachment and proliferation, leading to improved osteogenic differentiation. Additionally, CAP-treated scaffolds exhibited controlled drug release profiles, demonstrating their potential in bone regeneration applications [176].

In antibiotic delivery, plasma-modified electrospun scaffolds containing chloramphenicol showed improved surface wettability and drug diffusion, leading to accelerated drug release rates in early treatment phases. The plasma treatment enhanced antibacterial activity while preserving the scaffold morphology and mechanical integrity, making it suitable for localized infection control [177].

Despite these advantages, plasma-assisted surface modification presents certain challenges. Optimizing plasma parameters (e.g., gas type, duration, power) is crucial for achieving precise surface modifications while avoiding excessive degradation of biomolecules. Additionally, scalability and cost-effectiveness remain major hurdles for the large-scale production of plasma-treated nanofibers.

Each method offers distinct advantages in terms of drug stability, release kinetics, and biomedical applications. However, every technique has some disadvantages.

Despite the widespread use of antibiotics and the methods of loading them into electrospun nanofibers, their inherent drug properties often limit therapeutic effectiveness. Challenges such as poor site-specific targeting, instability in biological environments, short half-lives, and the growing threat of antibiotic resistance reduce their efficacy and safety. Traditional delivery systems fail to adequately address these limitations, often requiring high systemic doses that increase side effects and resistance risk. Electrospun nanofibers have emerged as a promising drug delivery platform that can overcome many of these issues. By enabling localized, sustained, and protected delivery of antibiotics, nanofibers improve therapeutic outcomes while minimizing side effects. The table below (Table 2) summarizes key limitations in antibiotic drug properties and how electrospun nanofibers offer targeted solutions, supported by real research example.

Table 2. Limitations of antibiotics due to their inherent drug properties, and how electrospun nanofibers can solve each issue.

Limitation of Antibiotics	How Electrospun Nanofibers Solve It	Example Antibiotic	References
Poor site-specific targeting	Nanofibers allow localized delivery to infected tissue, reducing off-target effects and improving efficacy	Tetracycline	[178]
Short half-life and burst release	Nanofibers enable controlled/sustained release over days to weeks	Tobramycin, Vancomycin	[179]
Hydrophilicity/hydrophobicity mismatch with carriers	Electrospinning allows use of hybrid polymers (e.g., PLGA, chitosan, gelatin) to stabilize and incorporate diverse antibiotics	Tetracycline Hydrochloride	[180]
Enzymatic degradation or instability	Nanofiber encapsulation shields antibiotics from degradation in biological environments	LL-37 (peptide antibiotic)	[181]
Development of antibiotic resistance	Local high-dose delivery via nanofibers reduces systemic use and resistance risk	Broad-spectrum antibiotics	[178]
Poor retention at mucosal or skin sites	Nanofibers adhere well and remain at the site of infection, improving drug retention	TCH for skin infections	[181]
Low mechanical strength of antibiotic carriers	Composite nanofibers (e.g., PLGA + nanotubes) offer improved flexibility and durability	Tetracycline + HNT/PLGA	[179]

Building upon the strategies for incorporating drugs into nanofibers, it is essential to explore how electrospun nanofiber technology addresses broader analytical, delivery, and biopharmaceutical challenges associated with antimicrobial drugs.

3. Overcoming Analytical, Delivery, and Biopharmaceutical Challenges of Antimicrobial Drugs Through Electrospun Nanofiber Technology

3.1. Analytical Challenges Overcome by Nanofibers

One of the major analytical hurdles in drug formulation is ensuring uniform drug loading throughout the delivery system while also maintaining the stability and biological activity of sensitive molecules such as proteins, peptides, or poorly soluble drugs. Conventional drug carriers, especially in oral or mucosal delivery forms, often suffer from inconsistent drug distribution, low encapsulation efficiency, and loss of activity during formulation or storage due to environmental stressors like heat, moisture, or pH.

Electrospinning addresses these issues by allowing mild processing conditions (e.g., room temperature and low shear forces), making it ideal for encapsulating fragile bioactive compounds. The resulting nanofibers have an exceptionally high surface-area-to-volume ratio, which facilitates homogeneous drug dispersion and controlled release profiles.

A key example is the study by Edmans et al., where lysozyme, a model antimicrobial protein, was encapsulated in PVP/Eudragit RS100 nanofibers via electrospinning. Their system achieved 93.4% encapsulation efficiency and maintained 96.1% enzyme activity post-release. This is analytically significant because high encapsulation and retained bioactivity ensure both effective dosing and functional therapeutic action. The drug was uniformly distributed within the fibers, as verified by dual fluorescent labeling and confocal microscopy, which mitigates batch-to-batch variability and enhances analytical predictability [182].

In another innovative application, Tolun et al. [183] developed coaxial electrospun nanofibers embedding curcumin within a hydroxypropyl-β-cyclodextrin/pullulan matrix, improving both solubility and analytical detectability. Techniques such as X-ray diffraction (XRD) and Fourier-transform infrared spectroscopy (FTIR) confirmed successful encapsulation and amorphous drug state, which are critical parameters in analytical validation for consistent bioavailability and therapeutic performance.

From an analytical standpoint, the use of characterization tools such as scanning electron microscopy (SEM), differential scanning calorimetry (DSC), and drug release kinetics modeling provides a comprehensive profile of the nanofiber systems. For instance, in the formulation by Panda et al. involving ibuprofen-loaded nanofibers, these methods confirmed the amorphous dispersion of the drug—a favorable state for increasing solubility and improving dissolution rates. Their nanofibers exhibited a significant increase in ex vivo intestinal absorption compared to raw ibuprofen, suggesting that the nanofiber matrix not only improved solubility but also preserved the drug's functional integrity during analytical testing [184].

Additionally, nanofibers help overcome analytical variability by enabling reproducible manufacturing of dosage forms with precise fiber morphology and drug content.

Overall, electrospun nanofibers offer a highly adaptable and analytically robust platform for drug delivery—improving not only encapsulation and release characteristics but also ensuring the stability, uniformity, and functional preservation of a wide range of therapeutics.

3.2. Drug Delivery Barriers and Biopharmaceutical Limitations Solved

Drug delivery to mucosal and ocular surfaces presents complex pharmacokinetic and physiological challenges. Mucosal tissues—such as those in the nasal, oral, and vaginal cavities—are protected by dynamic environments, including continuous fluid secretion, enzymatic activity, and variable pH. These defenses limit the residence time of drugs, leading to poor absorption, rapid washout, and unpredictable therapeutic effects. Additionally, traditional formulations such as creams, gels, and eye drops often fail to penetrate the mucosa efficiently and require frequent dosing, which reduces patient adherence and may lead to subtherapeutic exposure.

One of the key advantages of nanofibers is their ability to form intimate contact with mucosal tissues, enabling site-specific delivery and reducing systemic side effects.

This approach has been successfully extended to ocular drug delivery, where physiological barriers such as tear turnover, blinking, and lacrimal drainage result in poor drug bioavailability. Conventional eye drops typically exhibit less than 5% absorption, requiring multiple daily doses. In contrast, Taghe&Mirzaeei developed preservative-free electrospun nanofibrous ocular inserts that released the antibiotic ceftazidime over 5 days, maintaining therapeutic levels well above the minimum inhibitory concentration (MIC) for *P. aeruginosa* and *S. aureus*. This long-acting formulation dramatically reduces dosing frequency and eliminates preservatives, which are often associated with cytotoxicity and ocular irritation. The inserts' nanostructured fibers also provided mechanical flexibility and biocompatibility, critical for conforming to the sensitive ocular surface without causing discomfort [185].

Electrospun nanofibers have also shown success in vaginal delivery, where traditional gels suffer from leakage and low patient compliance. By forming mucoadhesive mats that conform to vaginal anatomy, nanofibers offer localized, sustained release of antimicrobials and antifungals while resisting washout from vaginal secretions. For instance, in the study by Shakeri et al., multilayered mucoadhesive nanofibers containing natural propolis demonstrated excellent antibacterial efficacy (>99.9%) and prolonged drug release over 28 days. The fibers' mechanical strength, combined with mussel-inspired adhesive

coatings (L-DOPA), ensured retention in the mucosal environment even under shear stress conditions, highlighting their clinical promise in treating mucosal lesions [186].

Moreover, Edmans et al. demonstrated that electrospun dual-layer oral patches could direct drug release unidirectionally into the oral mucosa, increasing efficiency and minimizing drug loss to saliva. Their system preserved the activity of incorporated proteins and provided high encapsulation efficiency (93.4%), along with longer mucosal contact compared to conventional lozenges or sprays [182].

These examples illustrate that electrospun nanofiber systems offer a robust platform for overcoming physical and chemical barriers in mucosal and ocular drug delivery.

Biopharmaceutical limitations such as poor aqueous solubility, low oral bioavailability, and lack of dosage control remain major hurdles in the effective delivery of many pharmaceutical compounds, particularly those in Biopharmaceutics Classification System (BCS) Class II and IV. These drugs typically exhibit high permeability but low solubility, leading to dissolution-limited absorption in the gastrointestinal (GI) tract. Moreover, biopharmaceuticals like peptides, proteins, and enzymes are prone to enzymatic degradation and poor mucosal permeability, making their delivery especially challenging.

A prominent example is ibuprofen, a BCS Class II drug with limited solubility and intestinal absorption. Panda et al. developed PVP-based electrospun nanofibers which transformed the crystalline form of ibuprofen into an amorphous state. This formulation significantly improved the dissolution rate and intestinal absorption of the drug due to increased surface area and rapid wetting behavior [184].

Hydrophobic bioactive compounds such as curcumin face similar challenges. In a study by Tolun et al., coaxial nanofibers composed of hydroxypropyl-β-cyclodextrin (HP-β-CD) and pullulan were shown to significantly enhance the thermal stability and solubility of curcumin. The coaxial structure allowed 93% cumulative release while maintaining antimicrobial activity, making it suitable for food and pharmaceutical applications [183].

In combination therapies, atorvastatin (BCS Class II) and metformin (BCS Class III) are often co-administered but suffer from solubility and permeability issues, respectively. Iqbal et al. addressed this by designing electrospun PVP–hyaluronic acid nanoparticles, which increased atorvastatin's solubility by 10.3-fold and metformin's permeability by 1.6-fold, outperforming commercial formulations in pharmacokinetic studies [187].

Other studies have focused on pH-sensitive drugs. Friuli et al. demonstrated that electrospun polymeric fibers embedded into oral tablets could modulate drug release depending on gastrointestinal pH. They designed fibers loaded with meloxicam and carvedilol, achieving zero-order and sustained release across pH gradients—solving challenges in GI variability [188].

In mucosal drug delivery, electrospun fibers also enable prolonged local therapy. Shakeri et al. developed mucoadhesive trilayer nanofiber patches containing propolis, which provided antimicrobial release for up to 28 days—critical for managing chronic oral infections and wounds [186].

Natural bioactives like rutin, known for antioxidant activity but hindered by poor solubility and UV instability, have also benefited from nanofiber integration. Lee et al. embedded rutin in pullulan–Pluronic nanofibers, forming a solid dispersion system that preserved antioxidant activity while enabling fast release and UV stability [189].

Beyond solubility, nanofibers can also enable combination and targeted therapy. Liu et al. designed enzyme-degradable electrospun fibers that co-delivered doxorubicin and ABT199 for post-operative prostate cancer treatment. The platform provided controlled and synergistic release while overcoming drug resistance via Bcl-2 inhibition [190].

Finally, a broader review by Torres-Martínez et al. compiled multiple drug types—including peptides, antibiotics, anticancer, and anti-inflammatory agents—showing that

electrospun nanofibers consistently enhance solubility, stability, and bioavailability, making them suitable for a wide range of delivery platforms [191].

Having examined how electrospun nanofibers overcome key challenges in antimicrobial drug delivery, the following section highlights their practical applications and showcases case studies demonstrating their effectiveness in real-world biomedical contexts.

4. Applications and Case Studies

Nanofiber-based scaffolds have gained significant attention in tissue engineering due to their ability to mimic the ECM, providing an optimal environment for cell adhesion, proliferation, and differentiation. These bioactive nanofibers are particularly promising in two critical areas of regenerative medicine: wound healing and bone regeneration. Their highly porous and interconnected structure facilitates cell migration, nutrient exchange, and vascularization, essential factors for effective tissue repair [192].

In the context of wound healing, nanofiber scaffolds act as protective barriers while promoting moisture retention and antimicrobial activity [193]. By incorporating bioactive molecules such as growth factors, peptides, and antibacterial agents, these scaffolds can accelerate tissue repair, reduce infection risks, and enhance skin regeneration. The ability to control drug release within nanofiber matrices further optimizes their therapeutic efficacy, making them ideal candidates for treating chronic wounds, burns, and diabetic ulcers [193]. Similarly, bone regeneration benefits from nanofibers' capacity to provide mechanical support and bioactive cues that stimulate osteogenesis [194]. Materials such as bioactive glass nanofibers and hydroxyapatite-coated scaffolds have demonstrated exceptional osteoconductive and osteoinductive properties, facilitating bone mineralization and integration with surrounding tissues [195]. Recent advances in electrospinning and solution blow spinning techniques have enabled the fabrication of three-dimensional, mechanically robust nanofiber scaffolds that gradually degrade, supporting the transition from scaffold to natural bone tissue.

The selection of wound healing and bone regeneration as focal areas stems from their clinical significance and high demand for improved treatment strategies. Chronic wounds and trauma-induced bone defects present substantial challenges in healthcare, often requiring advanced biomaterials to overcome issues related to poor vascularization, infection, and delayed healing. By leveraging bioactive nanofibers, researchers are developing next-generation scaffolds with enhanced biointegration, controlled degradation, and superior regenerative potential, making them invaluable in the field of tissue engineering and regenerative medicine.

Electrospun antimicrobial nanofibers have been extensively investigated for biomedical applications, particularly in wound healing and bone tissue engineering, where localized drug delivery and infection control are essential for successful treatment outcomes. A wide variety of polymeric formulations, antimicrobial agents, and fabrication approaches have been reported in the literature. To facilitate comparison among these systems, representative antimicrobial electrospun nanofibers discussed throughout this review are summarized in Table 3, including their composition, antimicrobial agents, preparation methods, biological effects, and key findings.

Table 3. Representative antimicrobial electrospun nanofiber systems for wound healing and bone tissue engineering applications discussed in this review.

Nanofiber Formulation	Antimicrobial Agent/ Drug	Preparation Method	Antimicrobial Effect	Significant Remarks	Application	References
PLGA nanofibers functionalized with graphene oxide–Ag nanocomposites	Graphene oxide–Ag nanocomposites	Electrospinning	Strong antibacterial activity against *E. coli* and *S. aureus*; prevents bacterial colonization	High biocompatibility maintained alongside antibacterial efficacy	Antibacterial wound dressings; infection prevention; biomedical implants and tissue engineering	[119]
PVA-based nanofibers blended with *Bidens pilosa* extracts	*Bidens pilosa* extract	Electrospinning	12% higher inhibition rate against *E. coli* and *S. aureus* than individual components	Enhanced antimicrobial activity due to synergistic effect between PVA nanofibers and plant extract	Antimicrobial wound dressings; infection control; biomedical and healthcare applications.	[120]
Curcumin-loaded mesoporous silica nanoparticles incorporated into electrospun PCL/gelatin nanofibers	Curcumin	Electrospinning	Not reported	Demonstrated enhanced anticancer efficacy and a dual-release mechanism for controlled delivery of curcumin.	Cancer therapy (anticancer drug delivery), controlled drug delivery, localized therapeutic delivery systems	[156]
Metoprolol tartrate-loaded PCL nanofibers	Metoprolol tartrate	Emulsion electrospinning	Not reported	Reduced burst release and achieved more sustained drug release compared with blend electrospinning.	Controlled and sustained drug delivery; hydrophilic drug delivery systems	[148]
Ampicillin-loaded PCL nanofibers	Ampicilin	Coaxial electrospinning	Antibacterial agent incorporated, antimicrobial activity expected	Controlled antibiotic delivery; infection treatment; sustained drug release	Core–shell nanostructure reduced burst release and provided controlled, sustained drug delivery; suitable for drugs with low compatibility with the polymer matrix.	[158]

Table 3. *Cont.*

Nanofiber Formulation	Antimicrobial Agent/ Drug	Preparation Method	Antimicrobial Effect	Significant Remarks	Application	References
PCL/gelatin nanofibers loaded with antibacterial agents	Antibacterial agents	Quad-axial electrospinning	Controlled delivery of antibacterial agents;	Antibacterial wound dressings; controlled antimicrobial delivery	Quad-axial fibers enabled layered drug release and enhanced control over spatial drug distribution compared with conventional core–shell fibers.	[90]
Metoprolol tartrate-loaded PCL nanofibers	Metoprolol tartrate	Encapsulation in electrospun fibers	Not reported	Controlled and prolonged drug delivery	Encapsulation resulted in sustained and controlled release over time.	[148]
Curcumin and hypocrellin A-loaded PLA/silk fibroin nanofibers	Curcumin + hypocrellin A	Electrospinning	Not reported	Anticancer drug delivery; cancer therapy	Encapsulation enhanced bioavailability and anticancer efficacy of both drugs.	[161]
Doxycycline-coated PLA/HAP (PLA–hydroxyapatite) nanofibers	Doxycycline	Electrospinning followed by physical adsorption	Potential localized infection control; specific antimicrobial data not reported	Bone tissue engineering; localized infection control; controlled drug delivery	Doxycycline was adsorbed onto PLA/HAP nanofibers. The system showed prolonged drug release in PBS and simulated body fluid (SBF), indicating suitability for long-term local therapy.	[196]
PVA/lysine nanofibers coated with ibuprofen and lavender oil	Ibuprofen + lavender oil (antibacterial agent)	Electrospinning followed by physical adsorption	Immediate release of lavender oil to help prevent bacterial contamination	Wound dressings; wound healing; anti-inflammatory and antibacterial therapy	Dual-function dressing providing sustained ibuprofen release during the inflammatory phase and burst release of lavender oil for rapid antibacterial protection.	[169]

Table 3. *Cont.*

Nanofiber Formulation	Antimicrobial Agent/ Drug	Preparation Method	Antimicrobial Effect	Significant Remarks	Application	References
PLA electrospun fibers coated with antimicrobial peptides	Antimicrobial peptides (AMPs)	Layer-by-layer (LbL) coating/assembly	Prolonged bacterial inhibition without cytotoxicity	Antibacterial wound dressings; infection control; tissue repair	LbL coating enabled sustained antimicrobial activity while maintaining biocompatibility and avoiding cytotoxic effects.	[170,171]
LbL-assembled nanofiber-based drug delivery systems loaded with doxorubicin	Doxorubicin	Layer-by-layer (LbL) assembly	Not reported	Targeted cancer therapy; controlled chemotherapeutic delivery	Improved drug bioavailability, controlled drug release, and reduced systemic toxicity through polyelectrolyte multilayer coatings.	[190]
Silk/AMOX/PVA nanofibers	Amoxicillin	Electrospinning followed by oxygen dielectric barrier discharge (DBD) plasma treatment	Enhanced antibacterial activity against Escherichia coli and Staphylococcus aureus	Antibacterial wound dressings; controlled antibiotic delivery; infection control; biomedical applications	Oxygen DBD plasma treatment enhanced surface properties and enabled sustained amoxicillin release, leading to improved antibacterial efficacy against *E. coli* and *S. aureus* while preserving biocompatibility.	[175]
PVA/V@Z composite nanofiber membrane (PVA nanofibers containing vancomycin-loaded ZIF-8 particles)	Vancomycin encapsulated in Zeolitic Imidazolate Framework-8	Electrospinning of PVA containing V@Z (vancomycin-loaded ZIF-8) particles	Strong antibacterial activity against Escherichia coli and Staphylococcus aureus; antibacterial efficiency up to 99%	Bone infection treatment; bone tissue engineering; antibacterial bone fillers; targeted antibiotic delivery; regenerative medicine	Vancomycin-loaded ZIF-8 particles embedded in electrospun PVA nanofibers provided pH-responsive antibiotic release, achieving up to 99% antibacterial efficacy against *E. coli* and *S. aureus* while promoting cell adhesion and proliferation for bone regeneration.	[197]

Table 3. *Cont.*

Nanofiber Formulation	Antimicrobial Agent/ Drug	Preparation Method	Antimicrobial Effect	Significant Remarks	Application	References
Porous HAp–CaO composite nanofibers (p-HApFs) loaded with tetracycline (TC)	Tetracycline	Sol–gel method combined with electrospinning	Sustained antibacterial activity for up to 7 days; prolonged inhibition of bacterial growth	Bone grafts; bone tissue engineering; antibiotic delivery; drug delivery systems; regenerative medicine	Porous HAp–CaO nanofibers fabricated via sol–gel/electrospinning showed enhanced tetracycline loading, reduced burst release, and sustained antibacterial activity for 7 days, supporting their use in bone regeneration and localized infection control.	[198,199]
PLA–nano-HAP–Doxy nanofibers (5% PLA, nano-hydroxyapatite, 7% doxycycline)	Doxycycline	Electrospinning	Significant inhibition of Aggregatibacteracti-nomycetemcomitans infection and Porphy-romonasgingivalis infection; significantly greater inhibitory activity than amoxicillin, ampicillin, doxycycline, and metronidazole controls ($p < 0.05$)	Non-surgical periodontal therapy; periodontal infection control; localized antibiotic delivery	PLA–nano-HAP–Doxy nanofibers: sustained doxycycline release produced significantly stronger antibacterial activity against periodontal pathogens than conventional antibiotic treatments.	[196]
PMMA/PEG or PLGA/PEG nanofiber mats loaded with vancomycin, rifampicin, and silver sulfadiazine	Vancomycin, rifampicin, silver sulfadiazine	Electrospinning	Broad-spectrum antimicrobial protection through controlled release of three anti-infective agents (specific inhibition values not reported)	Prevention of implant-related infections; orthopedic surgery; periprosthetic infection management; revision surgery	Triple-drug-loaded electrospun mats provided localized, sustained, broad-spectrum antimicrobial protection and are suitable for implant-associated infection prevention.	[200]

Table 3. *Cont.*

Nanofiber Formulation	Antimicrobial Agent/ Drug	Preparation Method	Antimicrobial Effect	Significant Remarks	Application	References
3D-printed and electrospun bioresorbable nanofibrous drug-eluting scaffolds	Bone morphogenetic protein-2 (BMP-2), ketorolac, amoxicillin	Combination of 3D printing and electrospinning	Antimicrobial protection provided by amoxicillin; quantitative antibacterial results not reported	Maxillofacial bone regeneration; alveolar cleft repair; bone tissue engineering; controlled delivery of growth factors, antibiotics, and analgesics	The scaffold combined regenerative (BMP-2), antimicrobial (amoxicillin), and analgesic (ketorolac) functions, providing sustained release for over 28–30 days and promoting bone healing without adverse effects in vivo	[134]
PCL/HNT/ERY nanofibers (polycaprolactone/ halloysite nanotube/ erythromycin nanofibers)	Erythromycin loaded into halloysite nanotubes	Electrospinning	Effective inhibition of both Escherichia coli (Gram-negative) and Staphylococcus aureus (Gram-positive); sustained antibacterial activity due to gradual erythromycin release	Antibacterial wound dressings; infection control; localized antibiotic delivery; tissue engineering; biomedical applications	Electrospun PCL/HNT/ERY nanofibers provided sustained erythromycin release, effectively inhibited both *E. coli* and *S. aureus*, and exhibited enhanced mechanical strength, biodegradability, and biocompatibility.	[101]
Gelatin nanofiber scaffolds loaded with ciprofloxacin hydrochloride and gentamicin sulfate	Ciprofloxacin + gentamicin	Electrospinning, followed by crosslinking with 25% glutaraldehyde vapor	Enhanced antibacterial activity against Pseudomonas aeruginosa and Staphylococcus aureus; even antibiotic-free gelatin scaffolds showed intrinsic antibacterial activity	Wound healing; wound dressing; skin regeneration; infection prevention	Enhanced antibacterial activity, accelerated wound healing and angiogenesis, promoted cell proliferation, and effectively managed wound exudates.	[201]

Table 3. *Cont.*

Nanofiber Formulation	Antimicrobial Agent/ Drug	Preparation Method	Antimicrobial Effect	Significant Remarks	Application	References
PCL nanofibers coated with plasma COOH polymer/fibronectin/ gentamicin and implanted with Ag ions	Gentamicin + silver ions (Ag+)	Surface plasma modification (COOH plasma polymer coating), fi-bronectin/gentamicin immobilization, and Ag ion implantation	Significant antimicrobial activity against a broad spectrum of Gram-positive and Gram-negative bacteria	Antibacterial implant coatings; implant infection prevention; long-term antimicrobial biomaterials	Maintained broad-spectrum antibacterial activity despite surface degradation, highlighting the key role of Ag ions in long-term antimicrobial protection.	[202]
GS/rhEGF-loaded Eudragit RL/RS 100 nanofiber scaffold	Gentamicin(GS) + recombinant human epidermal growth factor (rhEGF)	Electrospinning of Eudragit RL/RS 100 nanofibers followed by covalent immobilization of rhEGF	Strong antibacterial activity against Staphylococcus aureus, Pseudomonas aeruginosa, and Escherichia coli; efficacy comparable to pure gentamicin	Diabetic wound healing; chronic wound treatment; regenerative medicine; antibacterial wound dressings	Combined gentamicin-mediated antibacterial protection with rhEGF-enhanced tissue regeneration, accelerating wound healing in vivo.	[203]
Ciprofloxacin-loaded PCL/silk sericin–PVA nanofibers (PCL/SS-PVA-CIP)	Ciprofloxacin	Electrospinning	Potent antibacterial activity against Pseudomonas aeruginosa and Staphylococcus aureus	Infected chronic wound treatment; wound dressing; topical antibiotic delivery	Exhibited strong antibacterial activity, excellent cytocompatibility, and sustained ciprofloxacin release, making them suitable for long-term management of infected chronic wounds.	[204]
PVA/PAA nanofibers containing bromothymol blue and ciprofloxacin	Bromothymol blue + ciprofloxacin	Electrospinning	pH-triggered antibacterial drug release	Smart wound monitoring; infection-responsive wound dressings; controlled antibiotic delivery	Real-time pH monitoring combined with on-demand antibiotic release.	[205]

Table 3. *Cont.*

Nanofiber Formulation	Antimicrobial Agent/ Drug	Preparation Method	Antimicrobial Effect	Significant Remarks	Application	References
Eudragit® S100 pH-responsive electrospun membranes loaded with nitrofurazone	Nitrofurazone	Electrospinning	Infection-triggered antibacterial release through pH-responsive behavior	Targeted antibacterial wound therapy; smart wound dressings	Infection-triggered antibacterial delivery through pH-sensitive release	[206]
PNIPAm-based smart antimicrobial nanofibers loaded with gatifloxacinhydrochloride and Ag nanoparticles	Gatifloxacin + silver nanoparticles (AgNPs)	Electrospinning	Environment-dependent antibacterial activity regulated by temperature and pH	Adaptive antimicrobial wound dressings; infection-responsive drug release	Dual-responsive antimicrobial membrane with environmentally regulated antibacterial activity.	[207]

4.1. Bone Healing

The use of fibrous scaffolds in bone tissue engineering is a critical aspect of regenerating bone defects, as they provide structural support and facilitate the delivery of cells and growth factors essential for tissue regeneration [195]. In addition to serving as a framework for cellular attachment and proliferation, scaffolds must also fulfill the mechanical requirements of bone during the regeneration process. Biomaterials play a fundamental role in this context, as they promote cell organization, differentiation, and proliferation by providing structural support, biological containment, and essential chemical cues [195].

Bone tissue primarily functions to provide mechanical support, and when skeletal disorders or tissue damage occur, appropriate fixation is required to restore structural integrity and establish an optimal mechanical environment for healing. Once healing is achieved, the removal of fixation devices is often necessary [195]. Consequently, biodegradable polymers have gained widespread adoption in tissue engineering, as they eliminate the need for secondary surgical removal, thereby reducing patient morbidity and healthcare costs. These materials offer a promising approach to bone tissue regeneration, aligning with the principles of biocompatibility, bioactivity, and controlled degradation, making them highly suitable for modern regenerative medicine applications [195].

Bone substitutes with strong antibacterial properties and bone regeneration capabilities hold significant potential for treating severe bone infections, such as osteomyelitis.

In this study, vancomycin (V) was encapsulated within zeolitic imidazolate framework-8 (ZIF-8) composite particles which are referred as V@Z. As a pH-responsive carrier, degrading in mildly acidic environments to enable controlled drug release. These particles were incorporated into PVA nanofibers via electrospinning, forming PVA/V@Z composite membranes with a drug-loading efficiency of 6.735% (Figure 2A). ZIF-8 undergoes degradation in the weakly acidic environment associated with bacterial infections, enabling the controlled and effective release of V. To fabricate a functional bone filler, V@Z particles were incorporated into PVA nanofibers via electrospinning, yielding PVA/V@Z composite membranes (Figure 2A) with a drug-loading efficiency of approximately 6.735%. These membranes exhibited superhydrophilicity, high water absorption, and pH-dependent drug release behavior (Figure 2B), ensuring targeted antibiotic delivery in infected tissues. The antibacterial against *E. coli* and *S. aureus* under physiological (pH 7.4) and infection-mimicking (pH 6.5) conditions (Figure 2C,D). The results demonstrated enhanced antibacterial adhesion and potent bactericidal effects, with the PVA/V@Z membrane outperforming single-agent antibacterial membranes such as ZIF-8-only or vancomycin-loaded PVA membranes, achieving an antibacterial efficiency of up to 99%. Additionally, biocompatibility assessments indicated that the electrospun PVA/V@Z membrane supporting MC3T3-E1 cell adhesion and proliferation, highlighting its potential for bone tissue engineering applications. These findings suggest that PVA/V@Z composite membranes offer an effective antibacterial and regenerative solution for treating bone infections, combining targeted drug delivery, excellent biocompatibility, and superior antibacterial performance [197].

Hydroxyapatite (HAp), the primary inorganic component of bone and teeth, is widely recognized for its excellent biocompatibility, bioactivity, and osteo conductivity, making it an ideal biomaterial for bone substitution, cell carriers, and drug or gene delivery systems. Mesoporous materials, characterized by high surface area, large pore volume, and tunable pore size, have recently gained attention for their enhanced drug-loading and release efficiency compared to conventional HAp. Since cell adhesion, migration, proliferation, and gene expression are influenced by matrix topography and molecular composition, replicating the nanofibrous structure of the extracellular matrix is crucial for biomedical applications. This study focuses on the fabrication of porous HAp-CaO composite nanofibers (p-HApFs) and their drug-release properties. p-HApFs were synthesized using a sol–gel

method combined with electrospinning to mimic the three-dimensional extracellular matrix structure. The average nanofiber diameter was approximately 461 ± 186 nm, demonstrating a well-defined porous structure suitable for biomedical applications. To evaluate their drug delivery potential, the nanofibers were loaded with tetracycline (TC) as a model antibiotic (Figure 3A). The drug-loading efficiency was significantly improved, and the system successfully retarded the burst release of TC, ensuring a sustained antibacterial effect over 7 days (Figure 3B) [198]. Tsai et al. similarly developed porous HAp-CaO composite nanofibers loaded with TC, exhibiting an efficient drug-release profile and sustained antibacterial activity (Figure 3C). Their study highlighted the nanofibers' ability to inhibit bacterial growth over a prolonged period, further supporting their application in bone grafts and drug delivery systems [199].

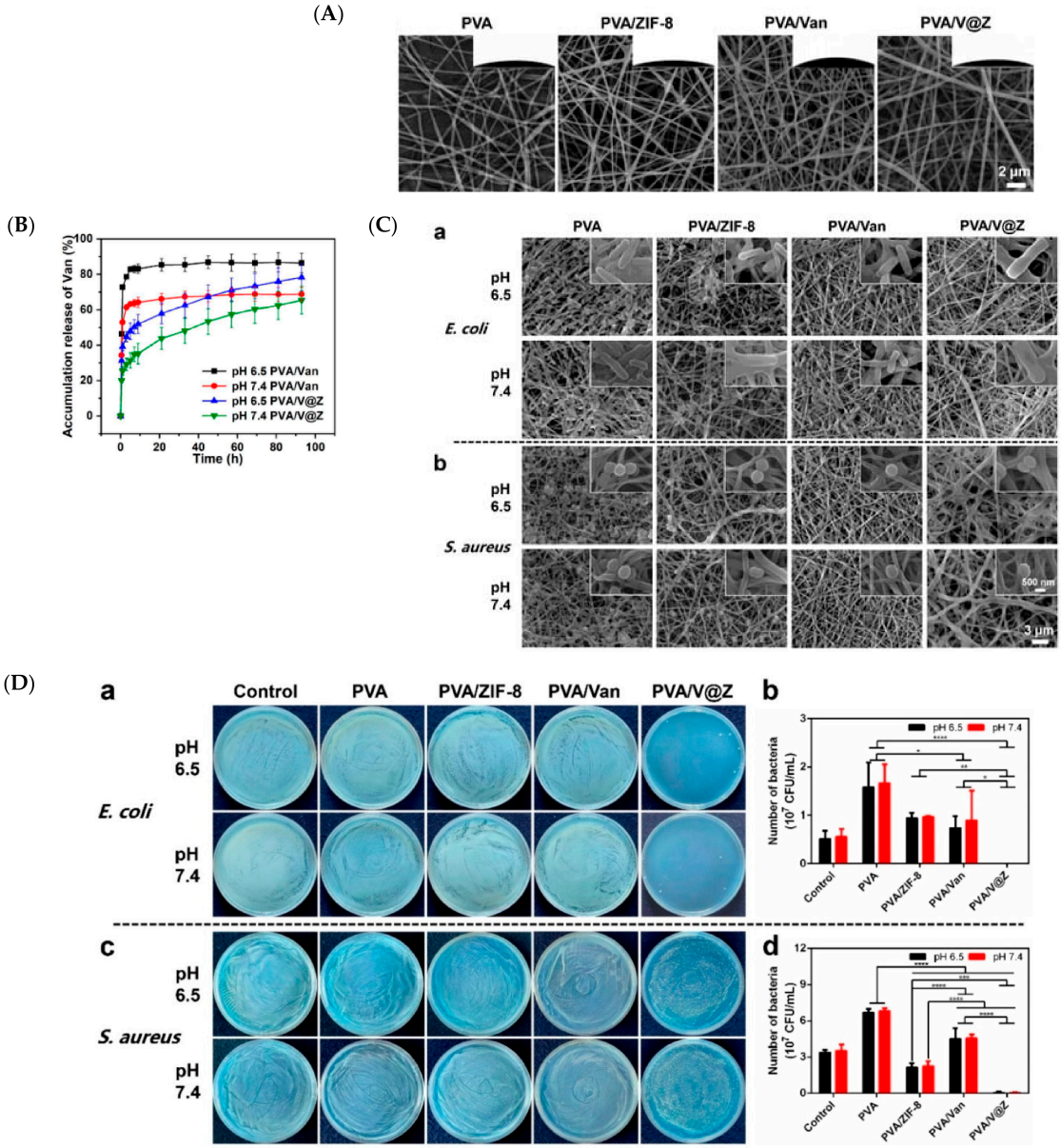


Figure 2. (**A**) SEM images of different membranes. (**B**) In vitro releasing profile of V in PVA/Van and PVA/V@Z membranes. (**C**) SEM images of different membranes after 12 h co-culture with *E. coli* (**a**) and *S. aureus* (**b**) at pH 6.5 and pH 7.4. (**D**) Representative images of agar plates and corresponding data statistics after 24 h co-culture with different membranes: *E. coli* (**a**,**b**) and *S. aureus* (**c**,**d**) ($n = 3$) (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$) [197].

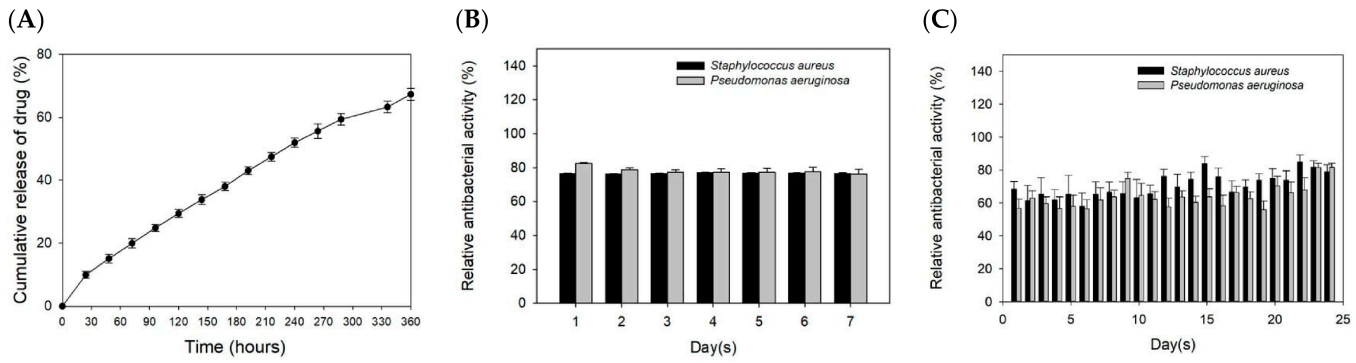


Figure 3. (**A**) In vitro cumulative TC release from TC-loaded p-HApFs. (**B**) Susceptibility trend of the released tetracycline against *S. aureus* and *P. aeruginosa* [198]. (**C**) Susceptibility profiles of *S. aureus* and *P. aeruginosa* to released TC [199].

This study aimed to evaluate the in vitro antimicrobial efficacy of a novel biomaterial composed of PLA, nano-hydroxyapatite (nano-HAP), and doxycycline (Doxy), fabricated via electrospinning for potential use in non-surgical periodontal therapy. The antimicrobial properties of two formulations—a test sample (PLA-HAP-Doxy7: 5% PLA, nano-HAP, and 7% Doxy) and a control sample (PLA-HAP: 5% PLA, nano-HAP without Doxy)—were investigated against two major periodontal pathogens, *Aggregatibacteractinomycetemcomitans* and *Porphyromonasgingivalis*. The antimicrobial assessment was performed using the Kirby–Bauer Disk Diffusion Susceptibility Test, and results were compared to the effects of four commonly used antibiotics in periodontal therapy: amoxicillin, ampicillin, Doxy, and metronidazole. The results demonstrated that the Doxy-loaded PLA nanofibers exhibited significantly higher inhibitory activity against periodontal pathogens compared to conventional antibiotics ($p < 0.05$), whereas the control sample (PLA-HAP without Doxy) showed no inhibitory effect. These findings highlight that the PLA-HAP-Doxy, with its localized drug delivery capability and sustained antibacterial effects, could serve as a promising adjuvant for non-surgical periodontal treatment [196].

Despite the low incidence of infections in orthopedic and periprosthetic surgeries (approximately 1–2%), the rise in procedures and drug-resistant bacteria present significant challenges. This study successfully electrospun three anti-infective agents—vancomycin, rifampicin, and silver sulfadiazine–into thin, flexible nanofiber mats composed of either poly(methyl methacrylate) (PMMA) or PLGA with PEG as incorporated improved drug release and wettability. The controlled release of these three agents suggests antimicrobial efficacy against a broader spectrum of bacteria, making the mats suitable for preventing implant-related infections and aiding in revision surgeries. The flexible nature of the nanofiber mats allows facile application around implants and the provision of localized, sustained antimicrobial protection [200].

For maxillofacial applications, bioresorbable nanofibrous drug-eluting scaffolds were successfully fabricated to mimic the natural ECM of bone tissues. The 3D-printed and electrospun scaffolds were designed for maxillofacial applications, ensuring controlled, long-term biomolecule release and effective bone healing. These scaffolds were designed to deliver bone morphogenetic protein-2 (BMP-2), ketorolac, and amoxicillin, supporting bone regeneration while providing antimicrobial and analgesic effects. In vivo studies demonstrated that the scaffolds facilitated extended release of ketorolac and amoxicillin for over 28 days (Figure 4A) and in vitro studies that BMP-2 for more than 30 days (Figure 4B). The efficacy of the drug-loaded scaffolds was further evaluated in a rat alveolar cleft model, where histological analysis indicated no adverse effects, and the treated animals exhibited activity levels comparable to those of the normal, non-defect group (Figure 4C). The results

of the in vivo tests demonstrated as minimally invasive alternative to conventional bone grafting techniques [208].

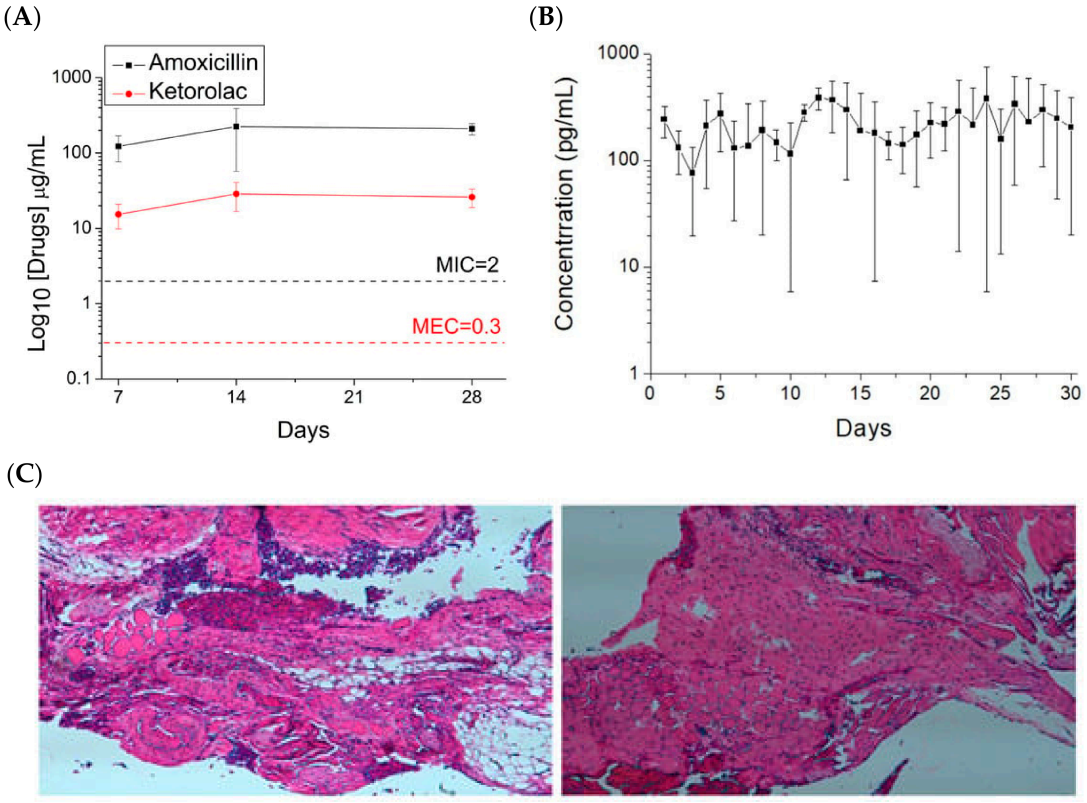


Figure 4. (**A**) In vivo release of pharmaceuticals from the nanofibers. The minimum effective concentration of ketorolac was 0.3 μg/mL, and the minimum inhibitory concentration of amoxicillin was 2 μg/mL. (**B**) In vitro elution profile of BMP-2 from the sheath–core-structured nanofibers. (**C**) Histological images (magnification: 4.5×) of the control group at day 7 (**left**) and day 14 (**right**). The inflammatory tissue reaction was noted [208].

4.2. Wound Healing

Wound healing is a complex biological process involving hemostasis, inflammation, proliferation, and remodeling. The effectiveness of wound treatment depends on several factors, including infection control, moisture retention, and promotion of cellular proliferation and migration. Nanofiber-based wound dressings have emerged as a promising approach due to their structural similarity to the extracellular matrix (ECM), high surface area, and potential for controlled drug delivery [209]. Nanofiber-based dressings help maintain an optimal moisture balance in wounds while stimulating angiogenesis and collagen production, both essential for tissue regeneration and skin repair. Additionally, bioactive compounds can be efficiently incorporated into nanofibers during the electrospinning process, enabling the localized and controlled release of therapeutic agents [210]. Coupling the development of wound dressing with localized drug delivery systems for anti-infection or antimicrobial agents represents an important way for healing wounds and promoting enhanced repair. For this purpose, some antibiotics used widely, including amoxicillin, levofloxacin, cefazolin, tetracycline or ciprofloxacin, have been incorporated into nanofibers to impart antimicrobial properties [14]. Several reviews and meta-analyses highlight the growing interest and extensive research in this field, emphasizing the need for interdisciplinary collaboration to optimize nanofiber-based solutions for wound care [211].

PCL, widely utilized in biomedical applications due to its slow degradation rate, was used as the base polymer in this study to develop antibacterial nanofibers incorpo-

rating halloysite nanotubes (HNTs). The integration of HNTs enabled the nanofibers to function as cost-effective nanocontainers for encapsulating various bioactive substances, including drugs, enzymes, and DNA. Specifically, HNTs were employed as nanocarriers for erythromycin (ERY), a model antibacterial agent with broad-spectrum activity. The PCL/HNT/ERY nanofibers were fabricated via electrospinning, and their antibacterial efficacy was assessed by measuring the sterile zone of inhibition around fibers containing 7.0 wt.% HNT/ERY (Figure 5a). Morphological analysis confirmed the structural integrity of the fibers (Figure 5b), while thermogravimetric (TG) analysis evaluated the efficiency of ERY loading (Figure 5c). The nanofibers demonstrated remarkable antibacterial properties, effectively inhibiting both Gram-negative *E. coli* and Gram-positive *S. aureus*. Additionally, the gradual release of ERY was observed, as evidenced by sustained antimicrobial activity upon repeated exposure to fresh inoculated growth media. Beyond their antibacterial performance, the nanofibers exhibited significantly enhanced mechanical properties, attributed to the incorporation of both unmodified and ERY-loaded HNTs. This improvement further strengthens their potential for medical applications. Overall, the developed PCL/HNT/ERY nanofibers represent a promising biodegradable, environmentally friendly, and nontoxic material with excellent biocompatibility [89].

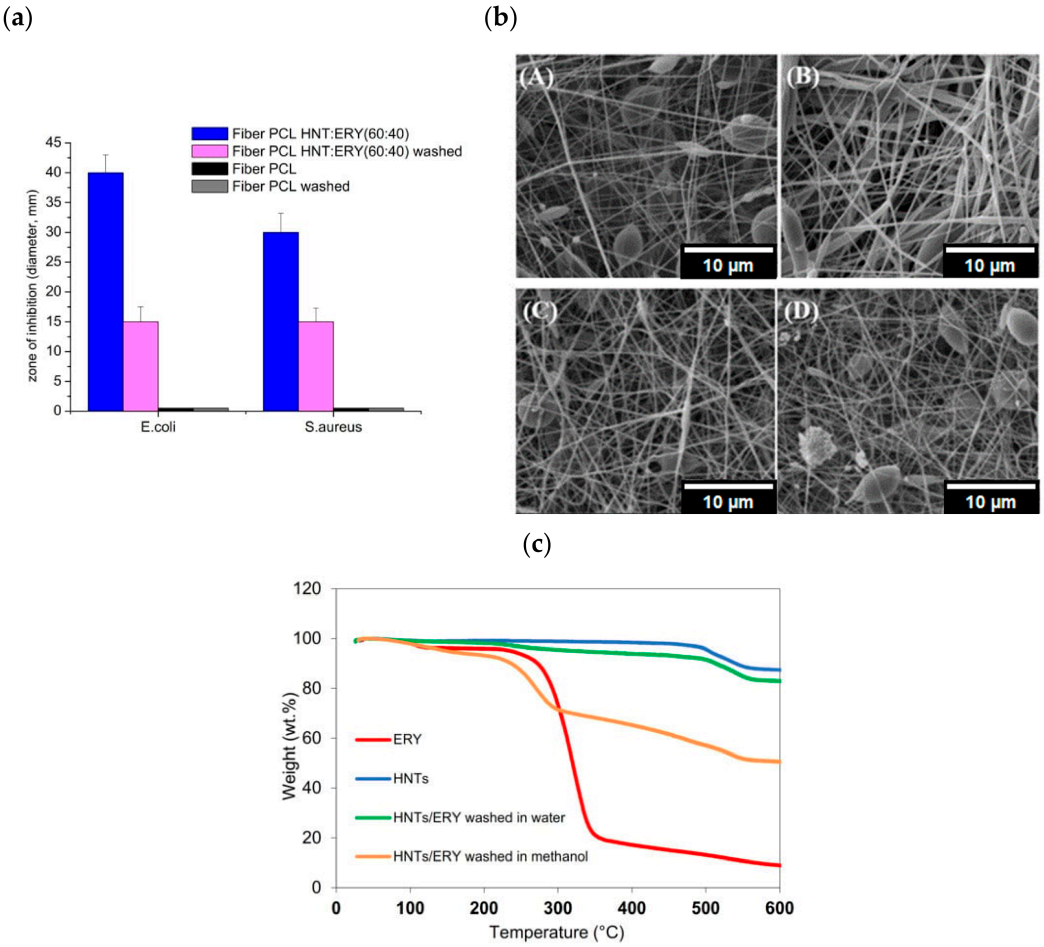


Figure 5. (**a**) Comparison of the antibacterial activity of washed and unwashed PCL/HNT fibers loaded with ERY, evaluated using the disk diffusion method against *E. coli* and *S. aureus*. The antibacterial effect was measured as the inhibition zone diameter and expressed as mean ± standard error (SE). (**b**) High-magnification SEM images (5000×) in secondary electron mode of electrospun nanofibers: (**A**) pure PCL, (**B**) PCL with 6 wt.% HNT, (**C**) PCL with 6 wt.% HNT/ERY (80:20), and (**D**) PCL with 6 wt.% HNT/ERY (60:40). (**c**) TG curves of ERY, HNTs, HNT/ERY washed with water, and HNT/ERY washed with methanol [89].

This study successfully developed and characterized gelatin-based nanofiber scaffolds for wound healing applications. Different gelatin combination solutions were electrospun, and the most promising formulation was selected for further investigation (Figure 6A). The scaffolds were crosslinked with 25% glutaraldehyde vapor and analyzed. The incorporation of ciprofloxacin hydrochloride and gentamicin sulfate enhanced the antibacterial properties of gelatin scaffolds against *P. aeruginosa* and *S. aureus*, while antibiotic-free scaffolds also exhibited intrinsic antibacterial activity In vivo studies demonstrated that gelatin/ciprofloxacin scaffolds significantly accelerated skin regeneration in a rat model, while a chorioallantoic membrane assay confirmed their pro-angiogenic potential. Cytotoxicity tests indicated that gelatin nanofibers promote healthy cell proliferation, particularly with antibiotic-loaded scaffolds. Additionally, the gelatin scaffolds showed high water absorption capacity, facilitating exudate management, while their biodegradability under physiological conditions further supported their suitability for wound healing applications. The findings highlight the structural similarity of gelatin to the extracellular matrix, its ability to support tissue regeneration, and its dual function of infection prevention and neoangiogenesis stimulation. The successful fabrication and characterization of antibiotic-loaded gelatin scaffolds emphasize their potential as effective biomaterials for wound healing, offering enhanced wound closure and tissue regeneration [212].

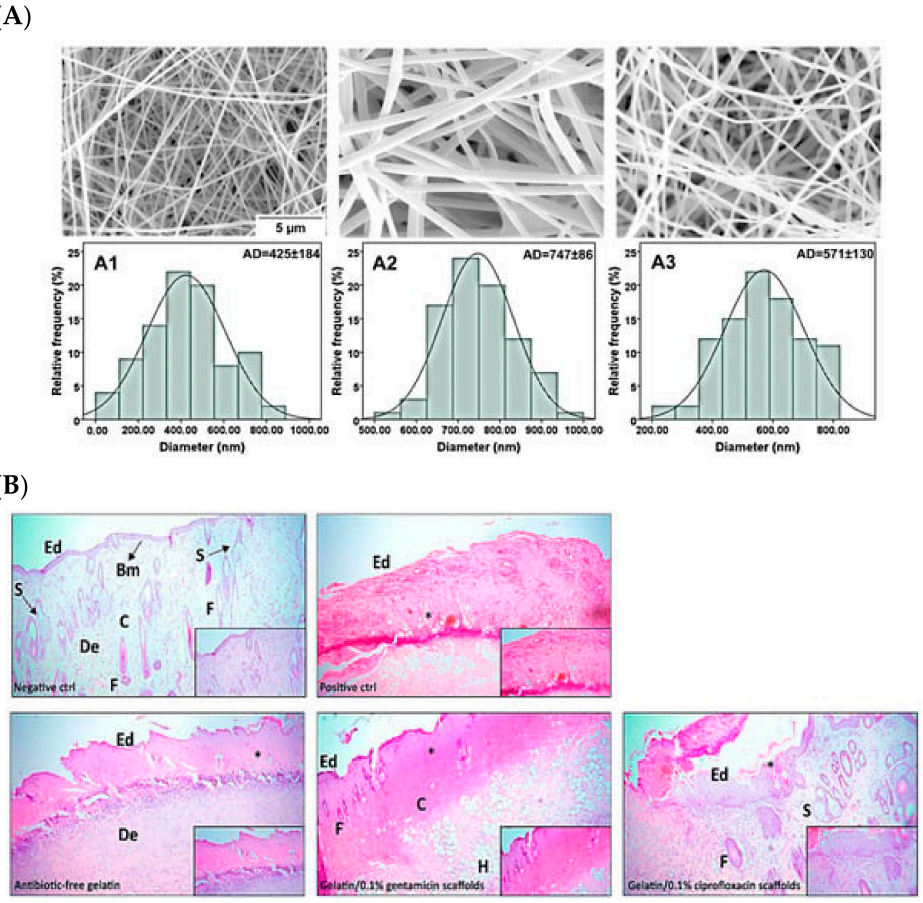


Figure 6. (**A**) SEM images and the corresponding histograms displaying fiber diameter distributions for A1—gelatin without antibiotics, A2—gelatin with 0.1% ciprofloxacin, and A3—gelatin with 0.1% gentamicin. The scale bar represents 5 μm. (**B**) Representative images of H&E-stained paraffin-embedded sections showing the effects of selected scaffolds incorporated with ciprofloxacin and gentamicin in comparison to negative and positive controls (original magnification ×10). Labels indicate key tissue structures: Ed (epidermis), Bm (basement membrane), De (dermis), F (hair follicles), S (sebaceous gland), C (collagen fibers), H (hypodermis), and * (burn area) [212].

Permyakova et al. coated the surface of PCL nanofibers with a layer of plasma COOH polymer, fibronectin/gentamicin, and implanted with Ag ions. Ag ions diffused through the nanofibers during long-term treatment and induced substantial changes in the topmost surface layer of fibronectin- and gentamicin-immobilized nanofibers. More than 60% of the surface layer had degraded, primarily forming hydrocarbons. However, the antimicrobial efficacy of these nanofibers was not compromised, as the PCL nanofibers with immobilized gentamicin and Ag ions exhibited significant antipathogen activity against a broad range of Gram-positive and Gram-negative bacterial strains. The retention of antibacterial activity despite structural degradation suggests that Ag ions play a critical role in enhancing antimicrobial properties through ROS-mediated bacterial inhibition [202].

Wound healing, particularly in diabetic patients, requires innovative strategies that combine antibacterial protection with enhanced tissue regeneration. To address this need, Dwivedi et al. developed a dual-loaded nanofiber dressing incorporating gentamicin sulfate (GS) as an antibacterial agent and recombinant human epidermal growth factor (rhEGF) to accelerate tissue repair. The resulting porous nanofiber scaffold closely mimicked the extracellular matrix, achieving a porosity of up to 76%. The addition of rhEGF significantly improved cell adhesion and proliferation, fostering tissue regeneration. In in vitro assays, the GS/rhEGF-loaded membrane demonstrated superior antibacterial activity against *S. aureus*, *P. aeruginosa*, and *E. coli* compared to single-drug therapy, with no notable side effects. Given the susceptibility of diabetic wounds to bacterial infections, this study explored an advanced approach by electrospinning Eudragit RL/RS 100 nanofibers carrying GS, followed by covalent immobilization of rhEGF on their surface. The in vitro antibacterial assays revealed that the nanoscaffolds exhibited comparable efficacy to pure gentamicin powder. Moreover, in vivo studies using C57/BL6 mice demonstrated accelerated wound healing in dorsal wounds treated with the nanoscaffolds compared to controls. This novel drug delivery system holds immense potential for clinical applications, offering a dual-function scaffold that not only facilitates optimal interaction between tissue and healing material but also provides a controlled release reservoir for GS and rhEGF. By simultaneously preventing bacterial infections and expediting wound healing, these nanoscaffolds present a significant advancement in regenerative medicine [201].

Chronic wounds are frequently associated with bacterial infections and excessive wound exudate, leading to complicated healthcare challenges. Electrospun medicated nanofibers have emerged as promising candidates for topical applications in the treatment of infected chronic wounds. This study aimed to optimize the fabrication of ciprofloxacin (CIP)-loaded polycaprolactone-silk sericin (PCL/SS-PVA-CIP) nanofibers via electrospinning, focusing on enhancing their antibacterial efficacy and biocompatibility. The antibacterial performance of the PCL/SS-PVA-CIP nanocomposites was evaluated against *P. aeruginosa* and *S. aureus*. The findings demonstrated potent inhibitory effects, with the most effective CIP concentrations being 3 μg/g and 7.0 μg/g for each bacterial strain, respectively (Figure 7I). To assess cytocompatibility, cell viability and proliferation studies were conducted using human epidermal keratinocyte (HaCaT) cells and human gingival fibroblasts (HGFs). The PCL/SS-PVA-CIP nanofibers exhibited excellent biocompatibility, supporting cell proliferation even at antibiotic concentrations up to 7.0 μg/g. The drug release profile of the nanocomposites was examined at various CIP concentrations, revealing maximum cumulative releases of 76.5% and 74.4% after 72 h for 3 μg/g and 7 μg/g CIP doses, respectively (Figure 7II). These findings highlight the controlled and sustained release of CIP, which is essential for long-term antibacterial protection in wound healing applications [204].

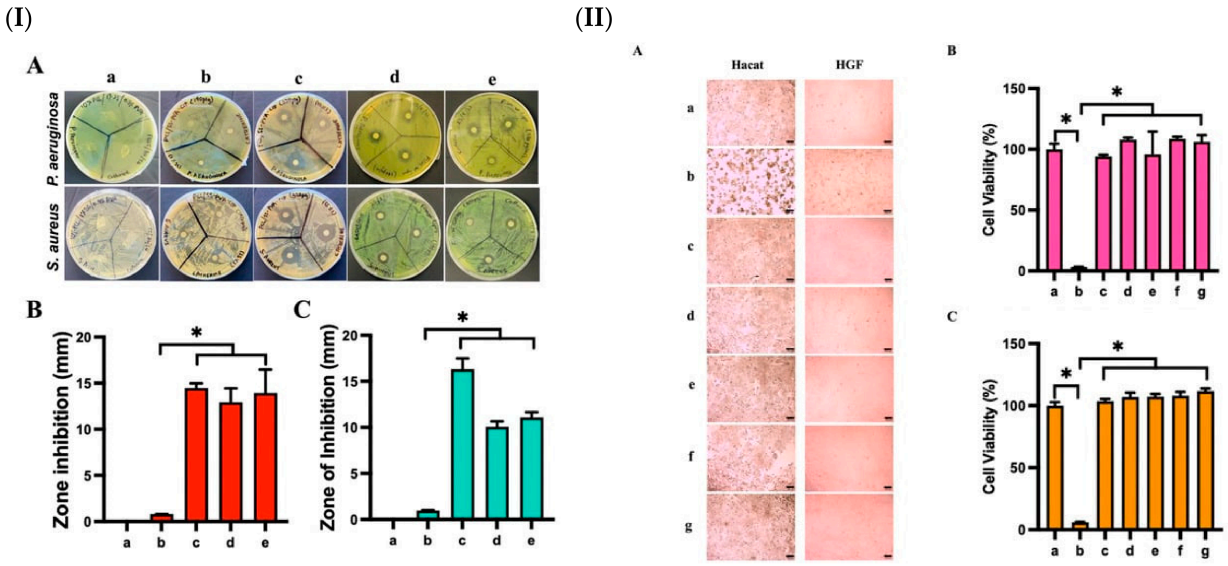


Figure 7. Images of (**I**) (**A**) ZOI of (**a**) PCL (negative control), (**b**) PCL/1% SS-PVA-CIP (3.0 μg/g), (**c**) PCL/1% SS-PVA-CIP (7.0 μg/g), (**d**) PCL/2% SS-PVA-CIP (3.0 μg/g), and (**e**) PCL/2% SS-PVA-CIP (7.0 μg/g) exposed to *P. aeruginosa* and *S. aureus*. (**B**,**C**) Bar graphs representing ZOI of (**a**) PCL (negative control), (**b**) PCL/1% SS-PVA-CIP (3.0 μg/g), (**c**) PCL/1% SS-PVA-CIP (7.0 μg/g), (**d**) PCL/2% SS-PVA-CIP (3.0 μg/g), and (**e**) PCL/2% SS-PVA-CIP (7.0 μg/g) exposed to *P. aeruginosa* and *S. aureus*, respectively. Data were analyzed using one-way ANOVA and Tukey analysis; data represent mean ± SD, n = 3, * $p \leq 0.05$. (**II**) (**A**) The proliferation of HaCaT and HGF cells under multiple treatments and (**B**,**C**) MTT assay results of (**a**) TCP (vehicle control), (**b**) 6.4 μg/mL CIP (positive control), (**c**) PCL (negative control), (**d**) PCL/1% SS-PVA-CIP (3.0 μg/g), (**e**) PCL/2% SS-PVA-CIP (3.0 μg/g), (**f**) PCL/1% SS-PVA-CIP (7.0 μg/g) and (**g**) PCL/2% SS-PVA-CIP (7.0 μg/g). Data were analyzed using one-way ANOVA and Tukey analysis, n = 6; mean ± SD; * $p \leq 0.05$ [204].

Self-responsive electrospun nanofibers can be utilized to monitor wound conditions and deliver therapeutic agents in response to changes in temperature, pH, oxidative stress, mechanical forces, or bacterial infections within the wound environment. These intelligent nanofiber dressings are designed to detect fluctuations in wound temperature and pH, enabling early infection detection while minimizing the need for frequent dressing changes. This adaptive functionality not only enhances treatment efficiency but also reduces medical costs and alleviates patient discomfort by promoting a more targeted and responsive healing process [210]. An essential factor in wound physiology is the pH of the wound bed, which fluctuates throughout the healing process and in response to bacterial infections. Changes in pH can serve as biomarkers for wound status, influencing cellular activity, enzyme function, and bacterial growth, thereby impacting the overall healing efficiency. Monitoring and regulating wound pH can help optimize therapeutic strategies and enhance tissue regeneration [213]. Arafat et al. integrated halochromic bromothymol blue with the pH-responsive properties of poly(acrylic acid) (PAA) into PVA-based electrospun nanofibers. This innovative approach allowed for real-time wound monitoring while enabling the on-demand release of ciprofloxacin, an antibacterial agent, in response to pH variations in the wound environment [205]. In a separate study, Eudragit® S100, a pH-sensitive polymer, was utilized as a nanofibrous drug delivery carrier. These smart electrospun membranes demonstrated the ability to release nitrofurazone in response to pH fluctuations in the wound environment, particularly when an infection was present, ensuring targeted antibacterial treatment [206].

Another critical factor influencing wound status is temperature, which fluctuates due to oxygenation levels, infection, and inflammation. Studies have shown that angiogenesis, inflammatory cell infiltration, and local vasodilation contribute to an increase in wound

temperature, signaling an active healing process. Conversely, partial ischemia can result in lower wound temperatures, as reduced fibroblast, neutrophil, and epithelial cell activity slows down the healing process. Monitoring temperature variations in wounds can provide valuable insights into wound progression and infection status, aiding in more effective treatment strategies [214,215]. Most recently, Khrystonko et al. developed dual stimuli-responsive electrospun nanofibers composed of PCL, enabling long-term temperature- and pH-responsive drug release for wound dressing applications [216]. Afsari et al. investigated the incorporation of graphene oxide (GO) into smart polymeric electrospun nanofibers. Their findings revealed a color shift from blue to red in response to temperature and pH variations, attributed to structural modifications in polydopamine (PDA) macromolecules, demonstrating potential for real-time wound monitoring and adaptive drug release [217].

Smart electrospun nanofibers enable the release of medications in response to bacteria, pH, oxygen, or infection, aiming to decrease the excessive use of antibacterial agents [214,218]. Wie et al. developed a smart antimicrobial fibrous membrane based on poly(N-isopropylacrylamide)(PNIPAm), which exhibits a dual response to temperature and pH. By incorporating gatifloxacin hydrochloride (GH) and Ag nanoparticles into the electrospun fibers, they demonstrated that the antibacterial activity of the membrane can be modulated by environmental changes, making it a promising candidate for adaptive wound dressings with controlled antimicrobial release [207].

Despite the promising progress, several challenges remain in the practical application and scalability of nanofiber systems, highlighting the need for future innovations and research.

5. Challenges and Limitations in the Industrial and Clinical Translation of Electrospun Antimicrobial Nanofibers

Despite significant progress achieved in the development of electrospun antimicrobial nanofibers, their successful translation from laboratory research to commercially available healthcare products remains limited. Although numerous studies have demonstrated promising antimicrobial activity, controlled drug release behavior, and favorable biocompatibility, relatively few electrospun systems have advanced to clinical evaluation or commercialization. This gap highlights the existence of several technological, manufacturing, regulatory, and economic challenges that continue to hinder industrial and clinical implementation.

5.1. Scale-Up and Manufacturing Challenges

One of the primary barriers to industrial adoption is the limited productivity of conventional electrospinning systems. While laboratory-scale single-needle electrospinning offers excellent control over fiber morphology, it suffers from low throughput and poor scalability. Recent reviews have highlighted that maintaining fiber uniformity, reproducibility, and drug-loading consistency during scale-up remains challenging, particularly when transitioning from single-needle to multi-needle or needleless electrospinning platforms [219,220].

Furthermore, electrospinning is highly sensitive to processing conditions, including solution viscosity, conductivity, humidity, temperature, and collector configuration. Small variations in these parameters can lead to substantial changes in fiber diameter, porosity, mechanical properties, and drug release kinetics. Such variability complicates the implementation requirements and creates difficulties in achieving batch-to-batch reproducibility, which is essential for pharmaceutical and medical device production [220,221].

The use of organic solvents also represents a significant industrial challenge. Many electrospinnable polymer systems rely on solvents such as dimethylformamide, hexafluo-

roisopropanol, or chloroform, which require strict control of residual solvent content and environmental emissions. Consequently, solvent recovery systems, process validation procedures, and environmental regulations substantially increase manufacturing complexity and production costs [221,222].

5.2. Sterilization, Storage Stability, and Product Shelf Life

In case of clinical applications, electrospun nanofibers must maintain their physicochemical properties and also their biological activity throughout sterilization, storage, transportation, and use. However, the high surface-area-to-volume ratio that contributes to their therapeutic performance also increases susceptibility to moisture uptake, oxidation, hydrolytic degradation, and premature drug release.

Studies have shown that commonly employed sterilization methods, including gamma irradiation, ethylene oxide treatment, ultraviolet irradiation, and autoclaving, may alter fiber morphology, polymer molecular weight, mechanical properties, and antimicrobial drug stability [193–195]. These effects become particularly relevant for nanofibers loaded with sensitive bioactive molecules such as peptides, proteins, enzymes, growth factors, or natural antimicrobial compounds.

Another frequently overlooked limitation is the scarcity of long-term stability studies. While many reports successfully demonstrate antimicrobial efficacy immediately after fabrication, only a limited number evaluate storage stability under realistic conditions or establish shelf-life specifications required for regulatory approval and commercialization [194,197].

5.3. Clinical Translation and Human Evaluation

Although many publications have reported successful antimicrobial nanofiber formulations, relatively few systems have progressed beyond in vitro and animal studies. A major reason for this discrepancy is the difficulty of reproducing clinical conditions in laboratory models. Standard antimicrobial testing often relies on planktonic bacterial cultures, whereas real-world infections frequently involve polymicrobial biofilms, chronic inflammation, impaired vascularization, and patient-specific biological variability [222].

Additionally, the absence of standardized testing methodologies remains a major challenge. Differences in polymer composition, electrospinning conditions, antimicrobial loading strategies, release protocols, and biological evaluation methods make comparisons between studies difficult and hinder the generation of robust clinical evidence [223,224].

Long-term safety considerations also remain insufficiently investigated. Although many electrospun systems exhibit excellent short-term biocompatibility, concerns persist regarding degradation products, chronic inflammatory responses, immunological effects, and long-term tissue interactions. Consequently, extensive preclinical and clinical investigations are still required before widespread medical adoption can be achieved [223,224].

Both the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) have recognized the need for specific regulatory approaches for nanotechnology-enabled therapeutics. Nevertheless, significant gaps remain regarding the standardization of characterization methods, safety assessment protocols, and quality-control procedures required for electrospun drug delivery systems [225,226].

5.4. Economic and Commercialization Barriers

In addition to scientific and regulatory challenges, economic considerations represent another critical obstacle to commercialization. The costs associated with specialized electrospinning equipment, process validation, sterilization procedures, quality assurance programs, and regulatory compliance may significantly exceed those of conventional pharmaceutical formulations or wound-care products [221,222].

Moreover, successful market adoption requires clear clinical evidence demonstrating superior efficacy, safety, and cost-effectiveness compared with existing therapeutic alternatives. Without robust clinical data and scalable manufacturing strategies, many promising electrospun technologies remain confined to academic research despite their considerable therapeutic potential [221,222].

Future progress will therefore depend not only on advances in materials science and nanotechnology but also on the development of scalable manufacturing platforms, internationally harmonized regulatory guidelines, standardized testing methodologies, and well-designed clinical studies capable of demonstrating real patient benefit.

6. Conclusions and Future Perspectives

Nanofibers have demonstrated significant potential in drug delivery and tissue engineering applications due to their high surface-area-to-volume ratio, structural resemblance to the extracellular matrix, and ability to encapsulate and deliver bioactive molecules in a controlled manner. Future advancements in this field will focus on enhancing nanofiber fabrication techniques, improving biofunctionality, and expanding their applications in regenerative medicine and targeted therapy.

Future research on nanofiber fabrication techniques is expected to focus on the integration of hybrid LbL nanofiber systems, combining nanocarriers, liposomes, and biodegradable coatings for even more precise drug delivery. Additionally, advancements in stimuli-responsive LbL coatings will further enhance their therapeutic potential in cancer therapy, regenerative medicine, and antimicrobial applications [225].

Future advancements in plasma-assisted modification are expected to focus on hybrid biomaterials, combining plasma-functionalized surfaces with biofunctional coatings for enhanced cellular response and drug retention. Stimuli-responsive plasma-treated nanofibers will further enable on-demand drug release, improving therapeutic efficacy in wound healing, antimicrobial therapy, and regenerative medicine. Furthermore, gene and protein delivery applications utilizing plasma-modified nanofiber scaffolds hold promise for future developments in personalized medicine [225]. Furthermore, coaxial electrospinning has emerged as a powerful technique to develop core–shell nanofibers that enable the sequential release of multiple bioactive agents, providing precise control over drug kinetics [226]. This approach is particularly promising in wound healing and tissue regeneration, where the timed release of growth factors can enhance cellular migration and proliferation.

One major area of development is the integration of nanofibers with smart biomaterials that respond to physiological stimuli such as pH, temperature, and enzymatic activity. These responsive nanofibers can be designed for on-demand drug release, significantly improving therapeutic efficacy while minimizing side effects [227].

The future of nanofiber-based tissue engineering will likely involve the engineering of biomimetic nanofiber scaffolds that closely replicate the natural extracellular matrix. Advanced surface modification techniques, including functionalization with peptides, growth factors, and extracellular matrix proteins, will improve cellular interactions and enhance regenerative potential. The use of biodegradable and bioresorbable polymers, such as PCL, PLA, and gelatin, will further optimize scaffold integration and support long-term tissue repair.

In bone tissue engineering, hybrid nanofiber scaffolds combining bioceramics (e.g., hydroxyapatite, bioactive glass) with biodegradable polymers have shown remarkable promise in osteogenic differentiation and bone regeneration. Future research will focus on developing 3D-printed nanofiber composites, leveraging additive manufacturing to create patient-specific scaffolds with tunable mechanical and biological properties.

In drug delivery, nanofibers offer a promising alternative to traditional dosage forms due to their ability to prolong drug release, improve bioavailability, and enable localized therapeutic effects. The development of nanofiber-based transdermal patches and implantable drug delivery systems is expected to advance significantly, particularly for chronic disease management and cancer therapy [227]. Additionally, nanofiber-loaded biosensors are emerging as an exciting frontier, allowing for real-time monitoring of drug release and personalized medicine approaches.

Despite these advancements, several challenges remain. One major hurdle is scalability, as the transition from laboratory-scale fabrication to large-scale production remains a challenge due to inconsistencies in fiber morphology and drug loading. Additionally, long-term biocompatibility and degradation kinetics must be optimized to ensure safety and efficacy in clinical applications. Future research should also explore advanced crosslinking techniques and nanocomposite materials to enhance the mechanical stability and functional lifespan of nanofiber-based scaffolds.

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