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An Overview of the Electrospinning of Polymeric Nanofibers for Biomedical Applications Related to Drug Delivery

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Electrospinning is a prominent technique for micro/nanofiber production and has received significant attention in the 21st century. It enables the production of ultrafine fibers using a variety of polymers, including synthetic, natural, and hybrid materials. Electrospun nanofibers (NFs) possess unique properties such as a high surface-to-volume ratio, tunable pore structures, and customizable composition, making them highly desirable in various fields such as biomedical science, textiles, sensors, filters, energy, and packaging. Herein, particular attention will be given to the application of NFs in biomedical fields. The use of NFs for the delivery of drugs, growth factors, proteins, nanoparticles, etc., holds significant promise in the field of biomedical science. To combine these compounds with NFs, various electrospinning techniques have been developed with outstanding improvements, and based on the requirements of the application type, different electrospinning processes are favored. In this review, the most common drug loading methods into NFs, generally used synthetic/natural polymers for NF production, and their application in drug delivery systems, tissue engineering, and wound dressing will be mentioned. Finally, challenges and future perspectives for above mentioned biomedical applications are discussed.

1. Introduction

Drug delivery plays a crucial role in healthcare, aiming for the effective and safe administration of drugs. The main objective of drug delivery is to provide optimal therapeutic outcomes by delivering drugs in a controlled and targeted manner. Several important aspects of drug delivery include providing enhanced drug stability and bioavailability, selecting appropriate routes of administration based on drug properties, employing controlled release systems for sustained drug release, and utilizing targeting strategies to deliver drugs specifically to desired sites.[1] Current drug delivery methods depend on repeated administration of drugs via parenteral or enteral routes, which can be inconvenient and carry the potential risk of accidental or intentional overdosing for patients.[2] Moreover, overuse and misuse of antibiotics contribute to the development of antibiotic resistance.[3] Therefore, it is important to develop a drug delivery system capable of delivering drugs in a controlled and sustained manner to address the above-mentioned issues. This would enable the safe and long-term maintenance of therapeutically effective drug levels.[2] With the emergence of electrospinning, nanofibers (NFs) have gained a crucial position in biomedical applications related to drug delivery.

Multiple processing techniques, including phase separation, self-assembly, solvent casting, freeze drying, gas foaming, and electrospinning have been utilized for the fabrication of NF scaffolds. Nonetheless, each of these techniques has its limitations. For instance, thermal-induced phase separation may produce fibers lacking structural stability. Self-assembly methods restrict biomaterial choices and the production rate is low.[4] Solvent casting is a time-consuming process and toxic solvents are used in the process.[5] Freeze drying is also a time-consuming process and requires high energy. Additionally, irregularly sized pores can be generated, and toxic solvents are used.[6] Gas foaming can yield closed and noninterconnected pore structures, which may not be advantageous for many cell transplantation applications.[5,7] In addition, scaffolds fabricated by the gas foaming method are restricted to weak mechanical strength.[8] The electrospinning process has also some limitations such as the usage of toxic solvents (although not always[9]), the application of high voltage for fiber generation, and constraints in fabricating 3D scaffolds.[5,10] However, despite these limitations, electrospinning is a much more favorable technique for the production of nanofibrous scaffolds[4] due to its simplicity, versatility, and cost-effectiveness.[11] Furthermore, electrospun NF scaffolds enable the production of scaffolds closely resembling native extracellular matrix (ECM), which supports cell attachment, proliferation, and differentiation.[2] They also offer a high surface area-to-volume ratio, high porosity with small pores, and superior interconnected porosity

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with adjustable pore size.[2,12] These three features enable the release of small drug molecules and biological compounds (e.g., proteins, nucleic acids, and genes), enhance loading capacity, facilitate waste removal, and provide the diffusion of nutrients and oxygen. Other advantages include adjustability of composition, the ability to produce ultrafine fibers with different shapes and lengths, and the possibility of preserving the bioavailability of drugs with the use of appropriate electrospinning methods.[2,13,14]

Small molecular drugs can demonstrate great therapeutic effects. However, they often exhibit poor pharmacokinetics and are prone to rapid metabolism within the body.[15] Electrospun NFs can provide a suitable platform for the effective delivery of small molecule drugs by enabling sustained and controlled release of drugs at specific sites.[15,16] Moreover, the therapeutic and targeting abilities of NFs can be improved by encapsulating drugs within nanoparticles (NPs).[17] Through precise control of drug release kinetics from NFs, medications can be delivered in a targeted manner, ensuring higher concentrations at the desired site while minimizing exposure to healthy tissues.[16,18] Additionally, scaffolds mimicking the structure of ECM and functionalized with biological agents or antibacterial metal NPs like silver and copper offer great potential for tissue engineering and wound dressing applications.[19–21]

This review focuses on the significant biomedical applications of electrospun NFs, with a specific emphasis on drug delivery. Initially, we mentioned the fundamental principle of the electrospinning method and a comprehensive overview of the properties of the frequently employed polymers as well as the desired characteristics of electrospun NFs for effective biomedical applications. Afterward, we discussed the various dug loading techniques for NFs with their respective advantages and disadvantages. Lastly, we highlighted the potential applications of electrospun NFs in three particular fields: drug delivery systems, wound dressing, and tissue engineering.

2. Electrospinning

Electrospinning is a technique that utilizes electrostatic forces to produce ultrafine NFs from polymer solutions or melts.[22] In this technique the polymer solution is subjected to a high-voltage power source, causing the polymer jet to stretch and form fibers that are then collected on a grounded collector. Charging of polymer solution by high voltage creates electrical repulsion forces acting on the polymer solution, causing a suspended droplet to form at the needle tip and changing the shape of the suspended droplet into a conical shape known as a Taylor cone. When the electric field exceeds the surface tension of the polymer solution, the jet is ejected from the cone surface and accelerates toward the oppositely polarized collector.[20] During the migration of the charged jet, the solvent(s) from the prepared solution evaporate(s) in the air in conjunction with the stretching and acceleration of the polymer jet, and the fibers are gathered on the collector.[23] The resulting NF mats can occur either in a nonwoven or aligned form depending upon the type of collector used.[20] The aligned NFs can be obtained using rotating collectors such as a rotating drum, rotating wire drum, and rotating disk and nonwoven fibers can be acquired using a plate collector.[24] An illustration of the traditional electrospinning process is shown in **Figure 1**.

3. Electrospun Polymers and Their Characteristics

Electrospinning provides significant versatility in selecting polymers for biomedical applications. There are various types of natural and synthetic polymers with diverse characteristics that have been successfully electrospuned to produce NFs.[25] Poly-e-caprolactone (PCL), polylactic acid (PLA), polyglycolic acid (PGA), polylactic-co-glycolic acid (PLGA), polyvinyl alcohol (PVA), and polyethylene oxide (PEO) are commonly used biodegradable synthetic

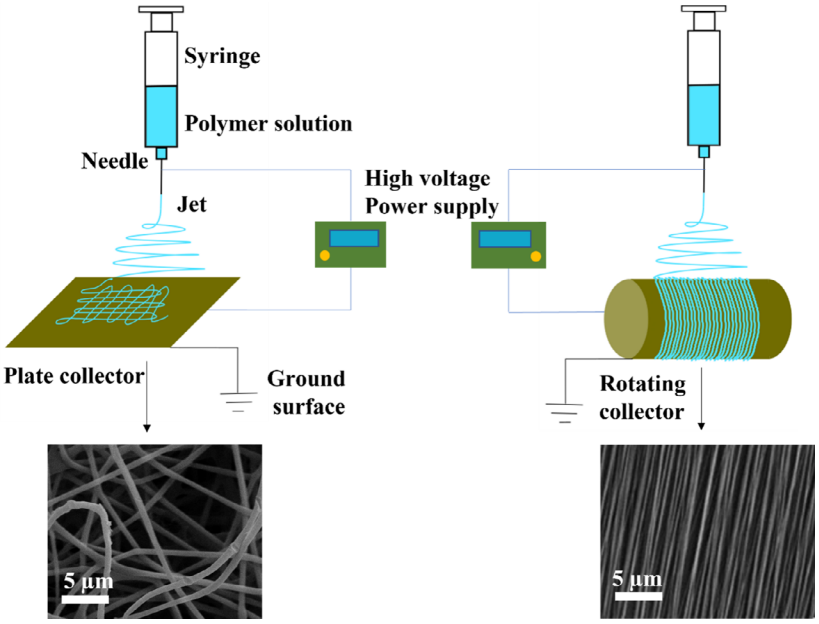

Figure 1. Conventional electrospinning setup. a)Aligned fibers are collected on a rotating collector and b) nonwoven fibers are gathered on a flat surface.

polymers.[26] In contrast, collagen, gelatin, chitosan (CS), silk fibroin, cellulose (CL), and alginate are mostly studied as biodegradable natural polymers in biomedical applications.[27]

Deciding which polymer or polymers to use is a crucial step in producing NFs suitable for the intended application. The electrospinnability of polymers is significantly influenced by their electrical property, as electrospinning relies on charge transfer. Polymers can be categorized into three main groups based on their electrical properties: insulators, semiconductors, and conductive polymers.[28] The formation of fibers is not possible with insulating polymers when the solvents used are nonconductive. However, the generation of fibers becomes possible when relatively highly conductive solvents such as dimethylformamide (DMF) and tetrahydrofuran (THF) are used, as reported by Jarusuwannapoom et al. (2005). Therefore, solvents are also another important factor in allowing the electrospinnability of the insulator polymers.[29] The fabrication of pure conducting polymer scaffolds from conductive polymers is quite difficult since these materials are highly brittle.[30] Therefore, it is a common approach to create conductive biomaterials by blending conductive polymers like polyaniline (PANI) and polypyrrole (PPY) with other biodegradable polymers such as PLA and PCL.[31,32] For biomedical applications, the ideal polymer should possess several key properties. The importance of these properties will be mentioned in the following sections and the essential characteristics of widely used polymers are shown in **Table 1**.

3.1. Biocompatibility

Biocompatibility stands as a crucial parameter to consider in any application involving contact with the human body. It plays a vital

Table 1. Widely used synthetic and natural polymers in drug delivery applications and their properties.[2,26,27,72,149]

Polymer[a)]	Physicochemical properties	Tensile strength [Mpa]	Biodegradation	Integrin binding site	Pros/Cons
PCL	Hydrophobic	1.8–15.4[44] 300[150] 40[151]	Highly slow biodegradation (3–4 years)[60]	Absent	+ High crystallization rate, long-term durability − Poor wetting surface, low cell adherence due to its hydrophobic characteristic
PLA	Hydrophobic	2.5[46]	Highly slow biodegradation (14–18 months)[152]	Absent	+ Thermal stability − Low crystallization rate, mechanical brittleness, low cell adherence due to its hydrophobicity, limited thermal stability
PLGA	Hydrophobic	≈23[153]	Slow-biodegradable (2–5 months)[152]	Absent	+ Tunable wetting property[154] − Initial burst release[155]
PVA	Hydrophilic	16[79]	Fast-biodegradable	Absent	+ Retain moist environment, flexible mechanical property, gas permeability
PEO	Hydrophilic	2.4[49]	Fast-biodegradable (1 h)[80]	Absent	− Low thermal stability + Nontoxicity, high swelling, easy production[156] − Low mechanical stability[126]
PEG	Hydrophilic	–	Fast-biodegradable	–	+Water retention,[157] responsiveness to various physical and chemical stimuli −Lack of immunogenicity and antigenicity
Collagen	Hydrophilic	2.13[158]	Fast-biodegradable (≈4 weeks)[158]	Present	+ Promotes cell proliferation, good tensile strength, nontoxic − Low thermal stability
Gelatin	Hydrophilic	2.5[159]	Fast-biodegradable (>21 days)[160]	Present	+ Activation of macrophages, high hemostatic effect, nontoxic − Low shape stability and elasticity, thermal instability
CS	Hydrophilic	9.76[48]	Fast-biodegradable (6 weeks)[161]	Absent	+ Antimicrobial and antioxidant activity accelerates wound healing, nontoxic − Poor solubility, uncontrollable biodegradation rate
Silk fibroin	Hydrophilic	10.3[162]	Slow-biodegradable	Absent	+ Promote adhesion and proliferation of keratinocytes and fibroblasts, water vapor and oxygen permeability, low toxicity, antimicrobial activity − Challenging scale-up processing[166]
CL	Hydrophilic	2.16[48]	(6–12 months)[164]	Absent[165]	
Hyaluronic acid	Hydrophilic	0.208[163]	Fast-biodegradable	Absent	
Alginate	Hydrophilic	Weak	Fast-biodegradable	Absent	+ High water absorption,[167] high crystallinity,[157] nontoxic, relatively thermally stable
			Fast-biodegradable		+High water absorption, cell proliferation, nonimmunogen, antimicrobial −Poor electrospinnability
					+Low toxicity, antimicrobial, high absorption, high ion adsorption −Poor electrospinnability, low thermal resistance

[a)]All of the listed polymers demonstrate favorable biocompatibility.

role in ensuring safety, minimizing adverse reactions such as infections and occlusions,[25] and promoting improved outcomes in terms of cell attachment and proliferation, hemostasis, etc.[25,33] Furthermore, it is crucial to ensure that the chosen material does not induce immunogenic reactions or toxic effects.[20] Natural polymers are known to exhibit superior biocompatibility and lower immunogenicity compared to synthetic polymers.[34] They also possess similar structures to natural ECM compounds because most of them have fibrous proteins, biomolecular signatures, and suitable surfaces with the presence of integrin binding sites (cell-adhesion receptors[35]).[26] In this regard, natural polymers are better at mimicking the ECM, thus providing a more effective platform for cellular interactions and biological processes.[11] However, synthetic polymers often require surface modification[36,37] or blending with natural polymers to enhance their biofunctionality because they lack bioactive binding sites. Therefore, combining synthetic polymers with natural polymers (e.g., collagen, gelatin, and CS) is a very common approach to increase the biocompatibility of synthetic polymers.[25,26,38,39]

3.2. Mechanical Strength

The polymer should have suitable mechanical strength according to the application region (e.g., bone, skin, cartilage, and nerve) to provide adequate support and functionality.[16,40] The polymer should also exhibit sufficient stability and durability throughout the intended application time.[41] Scaffolds with high stiffness in the range of approximately 2–15 MPa would be suitable for hard tissue engineering, whereas those with lower elasticity, between the 20 and 50 kPa range, are better suited for soft tissue engineering. Therefore, consideration of elastic modulus is important for soft tissue engineering.[42] For instance, a scaffold for skin applications needs to be stretchable, with a failure strain of around 20%.[43] In addition to the crucial requirement for mechanical strength that is compatible with tissues, the stiffness and elasticity of materials are also significant as they influence the behavior of cells.[44] The mechanical properties of NF mats are related to the characteristics of the polymer used (i.e., crystallinity of the polymer), molecular weight, and the production process, which impacts the morphological parameters such as pore size, fiber size, and shape.[40] Additionally, the mechanical strength and elastic modulus of electrospun NFs exhibit a significant dependency on the solvent utilized for electrospinning. Elamparithi et al. (2016) demonstrated the impact of various solvents on the mechanical strength of PCL NFs.[44] They generated fibrous scaffolds with Young's modulus of 36.05 ± 13.08 kP, which is nearly 50 times less than that of scaffolds produced with widely used solvents, for muscle and soft tissue engineering. The research highlighted the possibility of production of PCL NFs, which is more preferred in hard tissue engineering, and suitable for muscle and soft tissue engineering.

While the majority of synthetic polymers are advantageous in terms of mechanical strength, natural polymers generally possess insufficient mechanical strength. A blending of natural polymers with synthetic polymers can provide enhanced mechanical strength compared to single polymer NFs.[11,27,45] Additionally, various methods such as crosslinking, deacetylation, or incorporation of different elements (e.g., curcumin (Cur) and carbon nanotubes) can enhance the mechanical strength of the NFs.

For example, in the study of Nguyen et al. (2013), it was observed that the tensile strength of the PLA NF mats measured as 2.5 MPa. However, when 0.125 and 1.250 wt% Cur were incorporated into PLA NFs, a significant increase in tensile stress was observed, reaching approximately 3.5 MPa for both concentrations. This enhancement in the mechanical properties of PLA NFs establishes their suitability for use in wound dressing materials.[46] In another study, Zhou et al. (2016) studied the effect of crosslinking using glutaraldehyde vapor on collagen NFs. The resulting nanofibers, with a diameter range of 310 ± 117, exhibited a tensile strength of 6.72 ± 0.44 MPa, meeting the demands of human skin.[47] Phan et al. (2019) analyzed the mechanical properties of CS, CL acetate (CA), and CS/CA (1:1) NFs. They also studied the impact of treating and neutralizing CS, CL, and CS/CL NFs using Na_2CO_3. Deacetylated CA NFs (CL) led to a significant increase in mechanical strength, rising from 2.16 ± 0.3 to 5.24 ± 0.3 MPa. Notably, the neutralization of CS nanofibers resulted in a substantial improvement in mechanical properties, increasing from 9.76 ± 0.5 to 16.94 ± 2 MPa. The blending of CS and CA contributed to an enhancement in mechanical properties. Among all the samples, the neutralized CS/CL NFs exhibited the best tensile strength with 16.30 ± 0.7 MPa.[48] The mechanical properties of blended CS and PEO polymers were investigated by Surendhiran et al. (2020). The tensile strength of pure PEO NFs (227 ± 16) was measured as 2.40 ± 0.56 MPa and the addition of 50% CS resulted in an increased mechanical strength, reaching 4.31 MPa.[49]

3.3. Biodegradability

Biodegradability means the capacity of a substance to decompose through interactions with biological components.[50] The significance of biodegradable electrospun scaffolds in biomedical applications lies in their ability to eliminate a second surgical procedure for implant removal.[23] While biodegradability may not be required for all applications, it can be advantageous in certain cases where the polymer needs to gradually degrade over time as new tissue forms.[20] To ensure optimal performance, the degradation rate of the scaffold must align with the specific application requirements. For certain applications, such as wound healing,[12] a faster degradation rate may be beneficial. In contrast, slowly degrading polymer scaffolds are more suitable for bone tissue applications.[51]

The biodegradation rate of a polymer is primarily determined by its inherent properties, such as the chemical structure, hydrophilicity or hydrophobicity of the polymer, crystalline or amorphous nature, glass transition temperature (Tg), molecular weight, the presence of hydrolytically unstable bonds, and copolymer ratio. These factors allow for the manipulation of the biodegradation duration to meet the specific requirements of various applications, ranging from weeks to months or even years.[40,52] The crystallinity of a polymer is closely interconnected to the molecular weight and Tg. Higher molecular weight leads to decreased crystallinity.[53] The Tg of the amorphous

domains gradually rises at lower levels of crystallinity, while it increases more sharply at higher degrees of crystallinity,[54] and a higher level of crystallinity is associated with a slower rate of degradation.[55] A higher molecular weight[56] and higher hydrophobicity of the polymer slow down the degradation rate. The morphology of the NFs, surface area, and wettability also influence biodegradation.[40,57] Furthermore, the degradation of polymers is influenced by both enzymatic and hydrolytic processes. Enzymatic degradation occurs more rapidly compared to hydrolytic degradation.[58] While natural polymers degrade via enzymatic reactions, synthetic polymers generally degrade through hydrolysis.[26]

In terms of degradation, polymers are divided into two categories biodegradable and nondegradable polymers.[2] Polyurethane (PU) is an example of a nondegradable polymer with great chemical stability, excellent mechanical strength, and abrasion resistance. These properties make them preferable for drug delivery systems and artificial organs.[59] PCL is a semicrystalline[43] polyester that is attractive for long-term implants, scaffolds for bone tissue engineering, and drug delivery systems with a slow-releasing profile as the complete degradation of the polymer may take 3-4 years due to its hydrophobic and semicrystalline nature.[60] The degradation time of PCL NFs was evaluated as 6 months in the study of Lam et al. (2009).[61] PLGA is a copolymer made of PLA and PGA, with adjustable biodegradability according to PLA:PGA ratios, providing a longer biodegradation time with a higher PLA ratio.[62] The ratio of PLA:PGA in the PLGA copolymer directly affects the crystallinity degree of the PLGA and, consequently, mechanical strength, swelling behavior, and biodegradation rate. The incorporation of crystalline PGA with PLA declines the crystallinity degree of PLGA and leads to an increased hydrolysis rate. Thus, a higher PGA ratio causes faster degradation apart from PLGA (50:50) showing the fastest degradation.[63] In the study of You et al. (2005), the biodegradation duration of PLGA, PLA, and PGA was demonstrated. While PLA NFs did not degrade significantly over 45 days, less than 50% of PLGA NFs degraded within 45 days. PGA, in contrast, demonstrated a considerably faster rate of biodegradation compared to both PLGA and PLA.[64] PVA is used in rapid drug release applications and for temporary scaffolds in tissue engineering due to its fast degradation.[43,56] PEO is a semicrystalline, biodegradable, and nonionic polymer with high swelling properties.[47,65] PEO and PEG share nearly identical chemical structures, and the differences between them lie in their molecular weights as well as end groups; PEG has –OH, and PEOs have –CH3 end group. PEO is a polymer with a wide range of molecular weights (Mw) from 20 000 to 8 000 000, whereas PEG has a molecular weight (Mw) below 20 000.[65]

PCL, gelatin, and CS were evaluated for wound healing by Gomes et al. (2015). After 1, 2, and 4 weeks, wounds were analyzed, revealing that PCL fibers remained inside the scab. In contrast, CS and gelatin fibers could hardly be seen inside the wound due to their fast degradation.[66] Lai et al. (2014) showed the release profile of hyaluronic acid and collagen NFs, each containing different growth factors. As a result of the rapid degradation of both polymers, more than 90% of bioactive agents were released in less than 30 days. However, collagen fibers exhibited a more favorable release profile compared to hyaluronic acid fibers.[67] To conclude, synthetic polymers generally exhibit slower degradation rates, ranging from months to years, mainly due to their hydrophobic and crystalline nature, as well as their degradation mechanism (enzymatic or hydrolytic). In contrast, natural polymers degrade faster, usually within weeks, primarily due to their hydrophilicity, generally amorphous structure, and degradation by enzymatic reactions.[68,69]

3.4. Hydrophilicity and Hydrophobicity

The hydrophilicity or hydrophobicity of a polymer not only influences the biodegradation rate of the polymer but also plays a significant role in cell response, and interactions between the polymer and loaded elements.[36,37] Highly hydrophobic NFs are not favorable for cell growth, as they do not provide a suitable environment. However, incorporating hydrophilic polymers into the NF formulation creates a balanced hydrophilicity–hydrophobicity environment that promotes cell attachment and proliferation, providing an ideal medium for cell growth.[38] Hydrophilic polymers are especially favorable for wound dressing applications due to their ability to absorb and retain moisture from the environment. This moisture retention can significantly impact the polymer's interactions with biological fluids, cell adhesion, and overall performance.[39] The promising results of PCL/PEG electrospun NF for wound dressing were reported by Pilehvar-Soltanahmadi et al. (2017). The low hydrophilicity of PCL was improved by the addition of PEG and the weak mechanical properties of PEG were enhanced utilizing PCL. As a result, the wound dressing had good mechanical strength and was favorable for cell adhesion and proliferation.[70]

4. Incorporation Techniques of Drugs into NFs

The regulation of well-defined release rates of drugs or other compounds can be regulated differently by particular electrospinning methods. Various drug loading strategies cause distinct interactions between drugs and NFs, thereby resulting in diverse drug release kinetics.[16] The choice of methods depends on various factors, including the drug's physicochemical properties, the characteristics of the polymer, the application intended, and the desired drug release rate.[20] Commonly used methods for drug loading include surface modification, blend electrospinning, emulsion electrospinning, and coaxial electrospinning, as demonstrated in **Figure 2**. An overview of the application of electrospun NFs in diverse biomedical fields is shown in **Table 2**.

4.1. Surface Modification

Surface modification methods involve altering the surface of a material through chemical (e.g., cross-linking, wet chemical treatment, and grafting)[71] or physical (e.g., adsorption and plasma)[71] approaches to enable the immobilization of bioactive agents to the polymer surface.[72] The advantage of surface modification methods is the preservation of the functionality of bioactive molecules. This approach helps prevent denaturation and destabilization of the molecules, which may result from factors like high voltage or exposure to organic solvents.[16,73] To chemically conjugate a desired drug, NFs can be modified to contain functional groups like amines, carboxyl, or hydroxyl groups

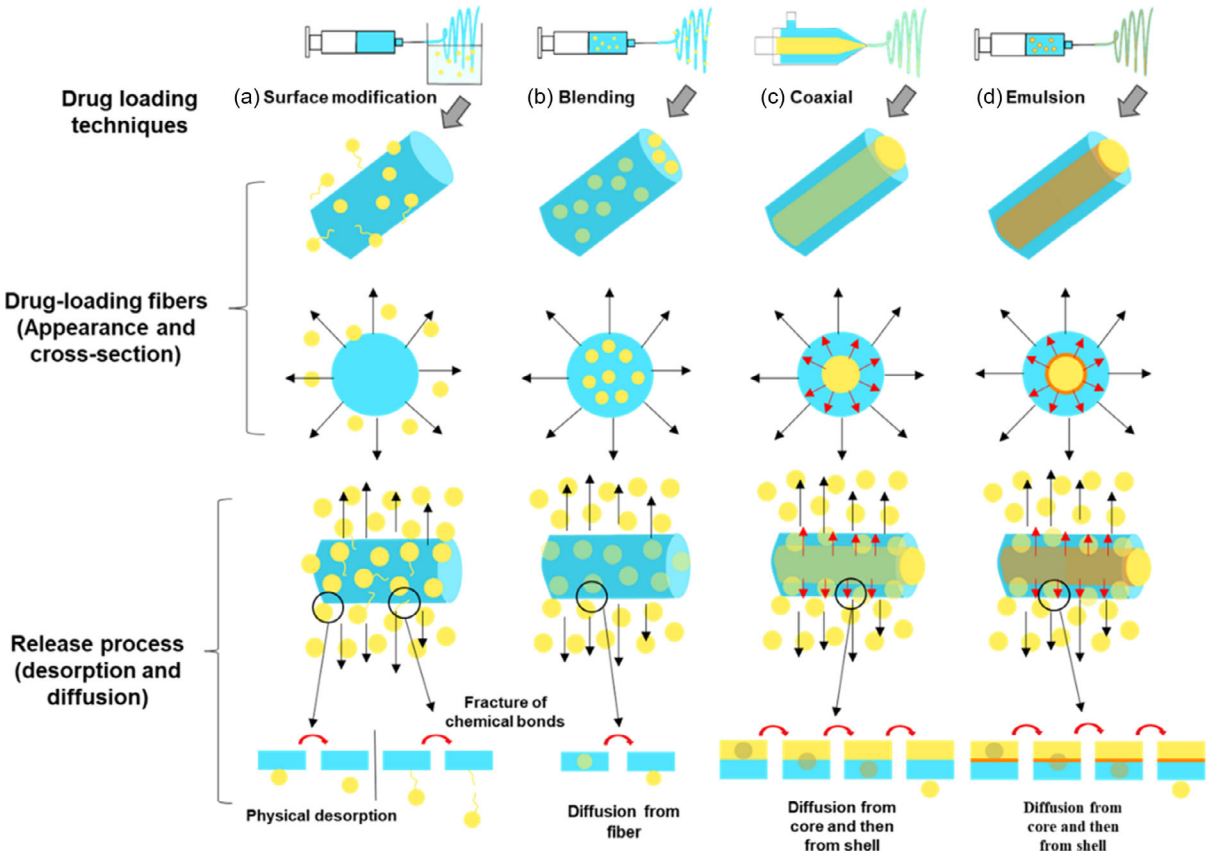

Figure 2. Schematic representation of drug loading methods. a) Postmodification in which drugs are immobilized onto electrospun NF mats via physical or chemical interaction. The acquired structure is surface-functionalized NF. b) Blend electrospinning, in which drugs and polymers are dissolved together in solvents to be spun. The acquired structure is a single NF. c) Coaxial electrospinning, in which drug and polymer solutions are separately spun from two concentric needles. The acquired structure is core-shell NF. d) Emulsion electrospinning, in which drug solutions are emulsified into immiscible polymer solutions. The acquired structure is core-shell NF. Compounds are represented by colors. Green: polymer, blue: drug, maroon: surfactant. The red arrows indicate the direction of drug release. Adapted with permission.[2]

Table 2. Various studies with different electrospinning methods for drug delivery systems.

Polymer(s)	Drug(s)	Electrospinning method	Application	References
PLGA	20(R)-ginsenoside Rg3	Surface modification	Hypertrophic scars	[168]
PLGA	Griffithsin	Surface modification	Inhibition of HIV (human immunodeficiency virus) infection	[169]
PCL	Azithromycin	Surface modification	Craniofacial and orthopedics	[170]
PLGA	Paclitaxel	Blend electrospinning	Inhibition of malignant glioma	[170,171]
PLA, PLA/PLGA	Ampicillin trihydrate	Blend electrospinning	Prevention of antibiotic resistance	[82]
PVA	Meloxicam	Blend electrospinning	Transdermal drug delivery	[79]
PCL	Ibuprofen-carvedilol	Blend electrospinning	Oromucosal delivery	[172]
PCL	Naproxen (NAP)/beta-cyclodextrin	Blend electrospinning	Pain or inflammation relief	[107]
PEG/PLA	Doxorubicin hydrochloride	Emulsion electrospinning	Local chemotherapy	[173]
PEG/PLA	PTX and DOX hydrochloride	Emulsion electrospinning	Inhibition of glioma	[174]
PCL/gelatin	Ketoprofen	Emulsion electrospinning	Wound dressing	[85]
CA/PVP (shell), CA (core)	Amoxicillin (core)	Coaxial electrospinning	Tooth or skin infection	[175]
Ag/PCL (shell)	Gentamicin/pluronic F127 (core)	Coaxial electrospinning	Prevention of surgical infection	[122]
PVA (core), PCL (shell)	Doxycycline	Coaxial electrospinning	Implant osseointegration and infection prevention	[89]

on the polymer surface.[72] The major forces that stabilize the drugs on the NF during physical adsorption are electrostatic interactions, hydrogen bonds, hydrophobic interactions, and van der Waals interactions.[73] Although the physical adsorption technique is a straightforward method, the rapid burst release of loaded drugs, which is one of the major issues with drug delivery systems, cannot be avoided by this method.[16] Bolgen et al. (2007), investigated the incorporation of ornidazole antibiotic to electrospun PCL membranes using a physical adsorption approach to prohibit postsurgery abdominal adhesions. As a result, a considerable rapid burst release of 80% of the drug was released in 3 h, and the entire release process took over 18 h.[74]

More controlled drug release can be achieved via chemical conjugation methods, but the disadvantage of this approach is the use of hazardous chemicals.[75,76] Hosseini et al. (2021) created a PVA/CS/HA NF patch containing growth hormones for wound healing applications. Cross-linking method was carried out using glutaraldehyde vapor to enhance NF stability. The PVA/Chi/HA NFs exhibited an initial burst release of approximately 11% within the first 2 h, followed by a gradual and controlled release, resulting in the release of up to 64% of hGH within 48 h.[77]

4.2. Blend Electrospinning

Blend electrospinning offers a simpler approach compared to other electrospinning methods, as it involves incorporating the drug into NFs by simply dissolving the drug in the polymer solution before electrospinning. Due to the interaction between polymers and drugs, the physicochemical features of polymers can have a significant impact on the bioactivity and release rate of the drug that is encapsulated.[27] Moradkhannejhad et al. (2020) showed that PLA/ Cur NFs without PEG demonstrated a low drug release profile. However, with increasing PEG content, the release profile exhibited a systematic enhancement. The sample containing 20% by weight of PEG showed the highest drug release among the tested samples. The drug release profile was also found to be influenced by the molecular weight of PEG, with a notable increase observed as the PEG molecular weight decreased.[78] Drugs can also affect the properties of the polymer solution in terms of the conductivity and viscosity of the solution.[16] According to the study of Ngawhirunpat et al. (2009), the loading of meloxicam in PVA solutions increased the viscosity of the solution, leading to the formation of thicker fibers.[79]

Two key factors are imperative for achieving sustained release. First, the drug-polymer compatibility is crucial. There should be a similarity in polarity between the polymer and the drug. Inadequate or excessive interactions between drugs and polymers can result in insufficient drug encapsulation. Second, complete dissolution of the drug in the polymer solution is necessary. The drug may agglomerate and predominantly reside on the surface of the fibers if it is not dissolved sufficiently due to factors such as low drug solubility, high drug loading, or ionization state. The ionization state of a drug can impact its encapsulation within the fibers, as higher ionic content leads to surface localization of the drug. When these criteria are not met, it often results in the burst release of the drug from the electrospun scaffolds.[80,81]

Boncu et al. (2022) conducted a study to examine the impact of drug concentration (ampicillin trihydrate, a hydrophobic antibiotic) on electrospun PLA NFs. The drug was incorporated using the blending electrospinning technique at concentrations of 4%, 8%, and 12%. A decrement in drug encapsulation efficiency was observed as drug concentration increased. The encapsulation efficiency of NFs containing 4% and 8% ampicillin trihydrate was around 90%; however, when the amount of ampicillin trihydrate was increased to 12%, the encapsulation efficiency decreased to 65%. This decrease can be attributed to the presence of undissolved drugs in the solution. Moreover, as the drug concentration increased, the burst-release effect became more prominent. Cumulative drug release at 24 h was 32.1%, 39.6%, and 69.4% for polymers containing 4%, 8%, and 12% ampicillin trihydrate, respectively. The complete drug release durations differed among the PLA NF formulations: 12% drug concentration was released within 3 days, 4% concentration within 7 days, and 8% concentration extended up to 10 days.[82]

4.3. Emulsion Electrospinning

Emulsion electrospinning contains a single nozzle and a pump like the traditional setup. The principle of emulsion electrospinning is related to using an oil-in-water (O/W) or water-in-oil emulsion (W/O) as the electrospinning solution and using a surfactant for the stabilization of the emulsion. Both W/O and O/W emulsions can be electrospuned by encapsulating hydrophilic or hydrophobic compounds into core-shell fibers.[83] The stability of the emulsion is crucial, as inadequate stability or phase separation can lead to agglomeration or surface deposition of the loaded agent, resulting in a burst release.[84] In addition, the ionicity or nonionicity of the surfactant and its concentration affect the surface tension and conductivity of the solution, which impact the morphology and internal architecture of the fibers. The main advantages of emulsion electrospinning are the protection of drugs from organic solvents by minimizing the contact between the bioactive molecule and the organic solvent with the use of a surfactant, which decreases the denaturation of bioactive molecules and allows the use of hydrophilic drugs and hydrophobic polymers together.[80,83] In a study conducted by Basar et al. (2017), the release profile of Ketoprofen was compared between PCL and Ketoprofen NFs produced by blend electrospinning and PCL/gelatin/Ketoprofen NFs produced by emulsion electrospinning. The PCL/gelatin mat exhibited a sustained drug release for about 4 days, while the single PCL fiber mat exhibited a rapid burst release profile with approximately 90% of the drug being released in a very short period of approximately 12 min.[85]

4.4. Coaxial Electrospinning

Core-shell NFs formed by coaxial electrospinning have a greater drug loading efficiency and exhibit less initial burst release compared to NFs produced by blend electrospinning.[80] Additionally, using this strategy, the bioavailability and functionality of drugs can be preserved.[16] Unlike the conventional approach, coaxial electrospinning involves the use of a coaxial needle consisting of two concentrically aligned hollow needles. Two polymeric solutions are separately injected through the outer and inner

needles by using two syringe pumps. The complexity, challenging scalability, and parameter tuning of coaxial electrospinning compared to other methods are the main drawbacks of this approach.[80] However, the presence of an exterior barrier layer makes coaxial electrospinning more effective at sustaining the release of drugs.[86] Additionally, vulnerable compounds like growth factors, enzymes, and cells can be incorporated into the core of NFs, as the shell primarily carries the electrical charge.[87,88] Furthermore, the core-shell NF allows the simultaneous incorporation of several therapeutic agents in one step, each with varying solubility properties.[86] In coaxial electrospinning, the miscibility of the polymers and the solvents used in the core and the shell solution is significant to ensure sustained release from the core-shell fibers.[81] The sustained release of doxycycline from core-shell PCL/PVA NFs was studied by Song et al. (2017). The released doxycycline from the NF coating exhibited effective inhibition of bacterial growth for 8 weeks in an in vivo setting.[89]

4.5. Other Techniques

In addition to coaxial electrospinning, there are more recent multifluid electrospinning approaches such as triaxial electrospinning and side-by-side electrospinning. The formation of three-layer NFs can be achieved through the triaxial electrospinning technique. Similar to the process of coaxial electrospinning, this technique uses a spinneret equipped with three concentric needles, each connected to a separate syringe pump to deliver three different fluids.[90] When two different fluids are dispensed side-by-side, it results in the creation of Janus fibers, characterized by having two different sides.[91] The generation of Janus fibers through side-by-side electrospinning poses a notable challenge in the field of electrospinning, primarily due to the mutual repulsion of fluids carrying the same charge.[92] Nevertheless, the creation of Janus fibers can be achieved as reported by Yu et al. (2016).[93] Although multifluid electrospinning techniques are more complicated, the multicompartment nanofibers generated through multifluid electrospinning offer numerous advantages for the development of innovative drug delivery systems. The material's compositions and distribution of the active agents may all be customized to provide more complex drug release profiles such as delayed, sustained, and multiple-phase releases. While the literature contains limited research on Janus fibers for pharmaceutical applications, they offer potential advantages over the more commonly studied core/shell structures. Janus fibers, the both sides in contact with the release environment, provide opportunities to release two different drugs at different rates in the same location.[91]

Another approach, melt electrospinning, is a solvent-free method that utilizes heat to liquefy the polymer. Melt electrospinning eliminates the requirement for a high amount of solvent. Nevertheless, the elevated temperatures required to reach the polymer's melting point may degrade the drug.[80] Furthermore, many biological molecules, including proteins, nucleic acids, polysaccharides, and thermosensitive polymers, are not suitable for processing via melt electrospinning.[94]

Random nonwoven fibers generated by far-field electrospinning methods, due to unstable jet motion, may lack the precision and deposition accuracy necessary for certain applications. Addressing this challenge, near-field electrospinning (NFES) provides a direct approach to precisely manage the positioning of deposited fibers in applications that demand organized or patterned micro/nanoscale fibrous structures.[91,95] NFES is a controllable process used for the production of ultrathin fibers achieved by positioning the needle tip closer to the collector. This shorter tip-to-collector distance, typically ranging from 500 μm to 5 cm, significantly reduces the applied voltage (0.6–3 KV) and minimizes bending instability during spinning. Consequently, this setup is advantageous for depositing fibers with high spatial precision on a 3D motion platform.[86,91,95]

The large-scale production of nanofibers is one of the drawbacks of nanofiber-based drug delivery systems. To overcome this issue, multineedle electrospinning, with a setup similar to the conventional electrospinning process, has been developed. The distinction lies in utilizing an array of needles arranged according to specific geometries.[86] The shortcomings of this technique are uneven electric field distribution arising from Coulombic repulsion between the charged jets and needles, heterogeneous fiber distribution on the collector, needle clogging, and huge volume requirement for the whole needles.[96] Despite the challenges and difficulties, several companies, including Yflow®,[97] Fluidnatek®,[98] and Inovenso Inc.[91] have successfully commercialized machines based on multineedle electrospinning technology for industrial production.

As a solution to various challenges in multineedle electrospinning, needleless electrospinning represents a promising approach to overcoming needle clogging problem, and repulsion between the different jets and has garnered considerable attention for its high productivity.[99] Needleless electrospinning usually employs an open reservoir instead of solution-filled syringes.[86] Numerous researchers have invented a variety of spinnerets with diverse geometries, including cylinder spinnerets, coil spinnerets, wire coil spinnerets, spiral coil spinnerets, disk spinnerets, rotating cone spinnerets, pyramid spinnerets, and magnetic field-assisted multispikes electrospinning.[99] However, certain issues related to this method should be considered, such as solvent evaporation from the polymer solution bath and water absorption by the reservoir.[86]

5. Drug Delivery Related Bioapplications

Electrospun NFs exhibit encouraging performance in biomedical engineering applications, primarily focusing on three essential areas: controlled drug release, wound dressings, and tissue engineering. The main biomedical applications for electrospun fibers are shown in **Figure 3**.

5.1. Drug Delivery Systems

Electrospun NFs can encapsulate a wide range of therapeutic substances, including antibiotics, antioxidants, antitumor, and anti-inflammatory drugs, as well as biomacromolecules such as proteins, antibacterial peptides, and DNAs.[19,27] This versatility enables their application for various therapeutic purposes. Applications of NFs in drug delivery systems are expanding rapidly due to their unique features including high drug loading

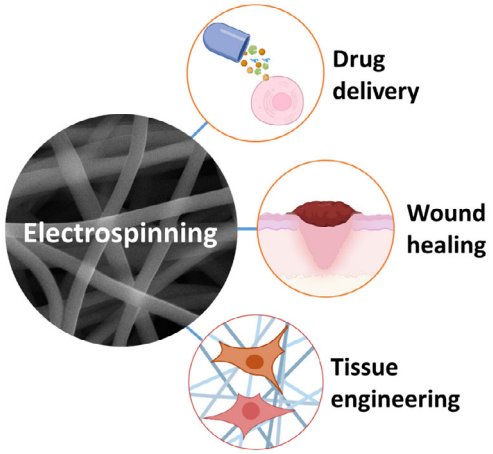

Figure 3. Various applications of electrospun NFs in biomedical applications related to drug delivery.

capacity, more efficient drug encapsulation, and reduced side effects of drugs with controlled drug release and localized treatment. Controlled drug release from NFs can sometimes be challenging due to the initial burst release.[100] However, such a challenge can be overcome to a certain extent by using electrospun NFs with suitable properties and drug-loading methods. The release of drugs from electrospun fibers can be regulated through a variety of parameters such as solution concentration as it impacts the degradation rate, swelling behavior,[101] as well as porosity,[102] and fiber diameter.[103]

Electrospinning-based drug delivery has already been making an impact in treatments of life-concerning diseases and threats, including cancer, antibiotic resistance,[3] and chronic wounds. For instance, Darbasizadeh et al. (2021) created doxorubicin (DOX), a hydrophilic antitumor drug, doped PEO/PCL core-sheath NFs to be used as a sustained drug delivery system for breast cancer. The results of the study indicate that the DOX containing core/sheath NFs exhibited significant efficacy against MCF-7 breast cancer cells with controlled drug release, and no toxicity was observed. An initial drug release of approximately 25%–35% was observed in the first 2 days, followed by complete drug release over 28 days.[104] Jeckson et al. (2021) developed a noncytotoxic NF mat for chronic diabetic foot ulcer treatment. CS, sodium alginate, and PVA were combined to create a deferoxamine (DFO)-loaded bilayer NF mat by electrospinning. The produced mat established high swelling degree (594%), high efficiency of entrapment (98%), adequate water vapor transmission rate (427.49 g m^{-2}• day), controlled drug release up to 48 h, and activity against $Gram^{+}$ ($0.79 \pm 0.07\ cm^2$) and $Gram^{-}$ ($0.95 \pm 0.04\ cm^2$) microorganisms.[105]

Anti-inflammatory drugs are compounds that can reduce pain or inflammation as well as swelling-related symptoms.[106] Canbolat et al. (2014) studied the release profiles of NAP, a hydrophobic nonsteroidal anti-inflammatory drug (NSAIDs), from PCL NFs. NAP was incorporated with beta-cyclodextrin (CD) to create an inclusion complex (NAP-CD-IC). The release difference of NAP from PCL/NAP and PCL/NAP-CD-IC NFs was investigated and the results indicated that the NAP-CD inclusion complex provides a higher amount of NAP release resulting from the enhanced solubility of NAP by CD-IC.[107]

Another important aspect that drug delivery is often targeted for is antimicrobial resistance. It is highly important in healthcare because the rising use of antibiotics leads to antimicrobial resistance, which is becoming a more challenging problem over time. For this reason, drug delivery systems preventing antimicrobial resistance are gaining even more importance today.[27] Eren Boncu et al. (2020) analyzed linezolid-loaded PLGA and PCL electrospun fibers against prosthetic-related infections. PLGA/linezolid fiber mats showed faster healing of bone fractures in rats as well as superior inhibition of infections compared to the control group. By implementing this approach, a remarkable 37-fold reduction in the dose of antibiotics was achieved compared to traditional treatments. Consequently, this reduction in drug dosage can effectively contribute to preventing antibiotic resistance.[108] Antimicrobial peptides (AMPs), which are host defense peptides against infections, can be a new potential source of antimicrobial agents instead of antibiotics to prevent antimicrobial resistance.[19] Gao et al. (2016) conducted a study in this regard, exploring the potential of AMPs as a new source of antimicrobial agents. They produced PLGA NF-coated deproteinized bone scaffolds that allow controlled delivery of vancomycin, an AMP, for the treatment of bone defects caused by methicillin-resistant *Staphylococcus aureus* (MRSA) infections. The results revealed that the cumulative release rate of vancomycin reached 96% by day 30. Although an initial burst release of vancomycin was observed within 1–2 days, the concentration of vancomycin gradually decreased over time. The developed scaffold showed an antibacterial effect against MRSA for 28 days. Consequently, the amount and duration of vancomycin release assured an effective antibacterial behavior, which minimized antibiotic resistance risk.[109]

For more localized treatments, the integration of drug-incorporated NPs with NFs is a favorable method for drug delivery systems due to their several benefits, including increased physicochemical stability of therapeutic agents, enhanced solubility of hydrophobic pharmaceuticals, sustained release of encapsulated drugs, delivery of drugs at higher concentrations to specific target areas, and the providing targeted treatments through the modification of NPs with cell-specific ligands.[110,111] For instance, Yang et al. (2014) investigated the effectiveness of nanohyaluronan-conjugated cisplatin (HA-Pt) compared to cisplatin alone for skin cancer (melanoma) to observe the efficacy of HA-Pt for more localized treatment. Although tumors grew more slowly in the HA-Pt group, all rats died within 3 weeks.[112]

Due to the desire to reduce the side effects of drugs with a more controlled release, smart or "stimulus sensitive" polymers are remarkable alternatives for their ability to act as an "on-off" switch in response to environmental changes such as pH, temperature, light, electric fields, and magnetic fields.[113] The main idea here is to trigger the release of therapeutic components in the targeted area through these stimuli.[20] Demirci et al. (2014) introduced pH-sensitive NF which is poly(4-vinyl benzoic acid-co (a vinyl benzyl) trimethylammonium chloride) [poly(VBA- co-VBTAC)]. Ciprofloxacin was encapsulated into poly(VBA-co-VBTAC) NFs and the release rate of ciprofloxacin was controlled in an acidic, neutral, and basic environment. The results showed that poly(VBA-co-VBTAC)/ciprofloxacin

NFs were able to deliver ciprofloxacin in a controlled manner for a longer time based on pH level.[114] In another study, Jia et al. (2017) prepared core-shell fibers composed of PEO and Eudragit S100 polymer to achieve colon-targeted drug delivery. Eudragit S100, a pH-sensitive polymer, was used to form the shell, while the core consisted of PEO loaded with either indomethacin (IMC) or mebeverine hydrochloride (MB-HCl). Dissolution experiments were conducted in an HCl solution with a pH of 1.2 for 2 h, followed by transfer to a pH 7.4 buffer for an additional 22 h. As a result, a minimal release in the acidic buffer, followed by relatively rapid release over the next 6–22 h was observed, but IMC was released much less than MB-HCI in the HCI buffer. The results indicate that the Eudragit S100 coating considerably inhibits drug release below pH 7, which is advantageous in preventing drug release in the acidic conditions of the stomach.[115] Some studies on stimuli-sensitive NFs for biomedical applications are presented in **Table 3**.

5.2. Drug Delivery for Wound Healing

Wounds can be classified as either acute or chronic based on their healing time. Knife cuts and surgical wounds are examples of acute wounds that heal quickly, whereas chronic wounds like diabetic foot ulcers are difficult to heal. Such wounds may require more than 12 weeks to heal.[20] Chronic wounds are an important problem for the medical field as they tend to become infected and inflamed, impairing the wound-healing process.[27]

Wound dressing acts as a protective barrier against infection, thereby supporting and promoting wound healing.[116] Bandages and gauze are traditionally used dressings to minimize the risk of infection, based on the state of the wound. Although these dressings offer some degree of protection against external contaminants and pathogens, their effectiveness in providing comprehensive infection protection, optimizing wound healing environments, preventing active infections, and actively supporting the wound repair process is limited.[19,116] A superior wound dressing should possess the following characteristics: effective isolation of the wound from external factors, prevention of bacterial infection, absorbing exudates from the wound surface, gas permeability, providing a suitable moist environment, exhibition of anti-inflammatory properties, promoting cell proliferation for tissue regeneration, and accelerating the healing process.[11,117] In this respect, electrospun NFs can provide a favorable environment for wound healing by providing a moist environment as well as promoting cell adhesion, proliferation, and migration through its ability to form NF scaffolds similar to the ECM structure.[118] Additionally, the use of electrospun NFs in the treatment of severe wounds with stem cell therapy appears promising since the signaling pathways for growth factors can be increased by the presence of stem cells at the wound site, facilitating tissue regeneration.[119]

The use of only synthetic polymers is insufficient to promote cell attachment, proliferation, and infiltration. To overcome this limitation, a more favorable approach involves combining synthetic polymers with hydrophilic natural polymers, particularly those found in skin tissue such as collagen, hyaluronic acid,

Table 3. Biomedical applications of stimuli-sensitive NFs.

Stimuli	Polymer(s)	Loaded compound(s)	Application	References
pH	poly(VBA- co-VBTAC)	Ciprofloxacin	Drug delivery systems	[114]
pH	PEO/Eudragit S100	IMC/ MB-HCl	Colon cancer and irritable bowel disease	[115]
pH	PCL	DOX	Gastric cancer and vaginal delivery of antiviral drugs or anti-inflammatory drugs	[176]
Temperature (Temp)	PCL	Paclitaxel and microRNA 145/ssPEI NPs (MSNs)	Liver cancer	[177]
Temp	PCL	DOX and magnetic NPs	Cancer therapy	[178]
Temp/Light	Poly(3-hydroxybutyrate-co-3-hydroxy valerate) (PHBV), PEG	CL nanocrystal-zinc oxide (f-CNC-ZnO) nanohybrids and tetracycline hydrochloride	Drug delivery systems	[179]
Light	poly(methyl methacrylate) (PMMA)	AgNPs and meso-tetraphenyl porphyrin (TPP)	Antibacterial	[180]
Light	Poly (N-isopropylacrylamide) (PNIPAM)	Silica-coated gold nanorods (Au@SiO2) and DOX	Cervical cancer	[181]
Magnetic field	Silk fibroin	Iron oxide NPs	*First approach:* tissue engineering and regenerative medicine *Second approach:* stem cell differentiation and biosensors	[182]
Magnetic field	PCL	Ketoconazole and iron oxide NPs	Fungal infections	[183]
Electric field	PCL	Poly(3,4-ethylenedioxythiophene) NPs (PEDOT NPs) and Cur	Drug delivery systems	[184]
Electric field	PVA and CS-aniline oligomer	Dexamethasone	Tissue engineering	[185]

and fibronectin for wound repair applications.[120] For example, Mirzaei-Parsa et al. (2019) used electrospun PCL/fibrinogen fibers to develop nanofibrous scaffolds for adipose-derived stem cells (ADSCs) for wound dressing. They showed that, in comparison to control groups, NFs with ADSCs produced better results in terms of enhancing re-epithelialization, angiogenesis, and collagen remodeling.[121] Jirofti et al. (2021) created CS/PEO/collagen NFs-doped with Cur, which is a strong antioxidant with anti-infective and anti-inflammatory characteristics, aiming to enhance the wound healing process.[76] In the study, CS/PEO/collagen NFs were loaded with Cur at three different concentrations, and the outcomes showed that higher concentration resulted in decreased initial burst release. By adding 5% and 10% Cur to the polymer solution, the fiber diameters were observed to increase. Conversely, the addition of 15% Cur resulted in a decrease in fiber diameters. The CS/PEO/Collagen NFs with 15% Cur demonstrated an effective Cur release profile for up to 3 days without any notable cytotoxicity. Furthermore, these NFs exhibited favorable cell biocompatibility and perfect in vivo performance in promoting wound healing when compared to drug-free NFs and untreated control samples (sterile cotton gauze). Additionally, the inclusion of PEO in the formulation plays a crucial role in enhancing the spinnability of CS.

Furthermore, some metal NPs (e.g., silver, gold, zinc oxide, and copper NPs) have a high potential to be used in wound dressing applications because of their antimicrobial properties.[122–125] A skin-balanced microbiome is beneficial in preventing infection in chronic wounds, and silver NPs (AgNPs) are well-established for their potent antibacterial activities and nonharm to human cells.[126] Zhao et al. (2012) reported a simple method for the generation of NFs loaded with silver NPs (AgNPs). AgNPs were synthesized within a poly(vinyl alcohol)/carboxymethyl-CS (CM-CS) blend aqueous solution before electrospinning. Consequently, the antibacterial activity of AgNPs against *Escherichia coli* was observed.[127] Dong et al. (2016) observed the efficacy of PCL nanofibrous membranes loaded with Ag-coupled mesoporous silica NPs (Ag-MSNs) produced by practical electrospinning on the wounds of Wistar rats. Long-term antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* and minimal cytotoxicity were demonstrated by Ag-MSNs/PCL NFs. The application of 5% Ag-MSNs/PCL fibers resulted in better healing with considerable wound closure and full re-epithelialization compared to the gauze-treated and untreated groups after 5 weeks of treatment (**Figure 4**).[128]

Fahimirad et al. (2022) developed a PVA/PCL composite NF mat loaded with *Quercus infectoria* (QLG) extracts, and copper NPs (CuNPs) synthesized by a green process using *C. officinalis* flowers extract.[129] It was observed that the addition of CuNPs and QLG extract enhanced the biological and physicochemical activity of PCL/PVA-based NFs as well as demonstrated excellent antibacterial function against MRSA. Moreover, the MRSA-infected wound had fully healed, and reduced inflammation was observed on day 10.

5.3. Drug Delivery for Tissue Engineering

The objective of tissue engineering is to regenerate or replace nonfunctional tissues or organs through stem cell transplantation, as well as the delivery of bioactive components. A controlled degradation rate is crucial for tissue engineering and the scaffold should degrade within the same duration as it is replaced by newly regenerated tissues.[20] In the design of a scaffold for tissue engineering, many other factors such as similarity to ECM, allowing for the circulation of oxygen and nutrients as well as the removal of metabolic waste, appropriate surface chemistry for specific tissue, interconnected porous network, and high porosity for cell seeding and penetration, large surface-to-volume ratio for cell attachment and higher drug loading, and suitable mechanical strength are also needed to be considered for effective tissue regeneration.[100,130] The architectural design of a scaffold is another important parameter as it impacts cell growth and tissue regeneration. According to some research, it is indicated that electrospun fibrous scaffolds with aligned fibers facilitate the

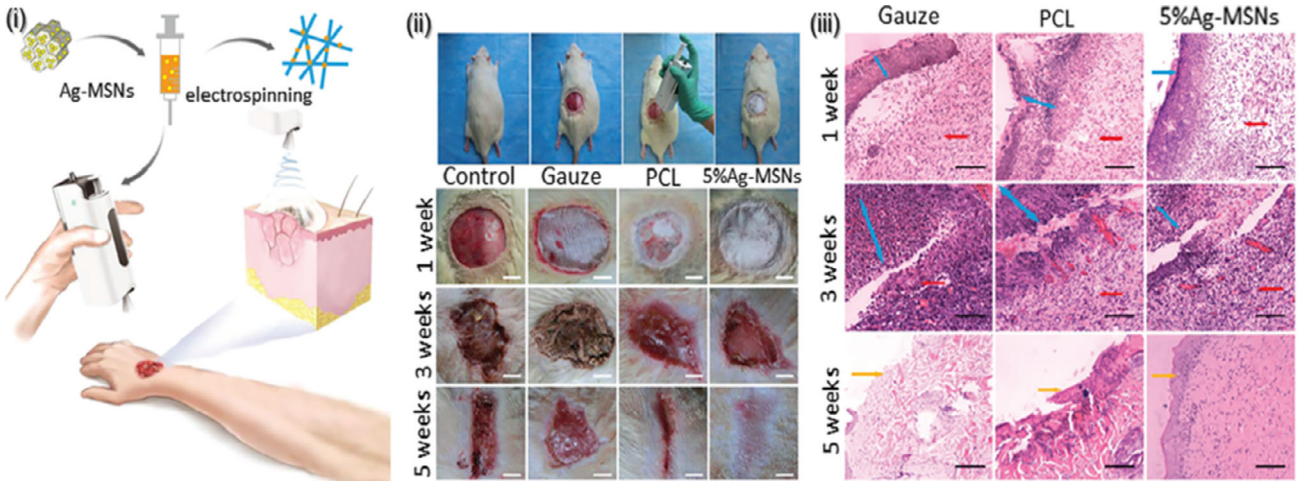

Figure 4. Skin wound healing with NF dressing produced by a handy e-spinning device. i) Production of nanofibrous membranes incorporated with Ag-MSNs via portable electrospinning device, ii) In vivo treatment of skin wounds of Wistar rats. Examination of skin wounds treated with gauze, neat PCL, Ag-MSNs/PCL, respectively, at 1, 3, and 5 weeks after injury. iii) Histological analysis at 1, 3, and 5 weeks. Infiltration of inflammatory cells, tissue granulation, and regenerated epidermal layers are denoted by blue, red, and yellow arrows, respectively. Reprinted with permission.[128]

migration and differentiation of cells because they replicate ECM better than other types of scaffolds.[131,132] Functionalized NFs, loaded with growth factors, drugs, peptides, cytokines, and other bioactive molecules, hold promise for improved treatment outcomes. They enable targeted delivery, promote tissue regeneration, control inflammation, and enhance vascularization, advancing tissue engineering and regenerative medicine.[2] For this purpose, electrospun NFs have been applied in tissue engineering applications for various tissue types, such as skin, bone, cartilage, cardiac, nerve, vascular, and tendon/ligament.

Preeth et al. (2021) created PCL/gelatin electrospun fibers and combined them with bioactive zinc(II) quercetin complexes to improve bone tissue regeneration. The study indicated that bioactive metal complex loaded PCL/gelatin electrospun NFs have higher biological activity compared to PCL/gelatin scaffold alone, which is encouraging for tissue regeneration applications.[133] Guenday et al. (2020) developed biodegradable polymer NPs loaded with antibiotics for various tissue engineering applications. Ciprofloxacin-loaded PLGA and PCL NPs, embedded in electrospun poly(ethylene oxide terephthalate)/poly(butylene terephthalate) (PEOT/PBT) scaffolds, provide sustained and localized drug delivery.[134] They exhibited superior efficacy and safety against *S. aureus* and *P. aeruginosa* compared to free ciprofloxacin. Additionally, electrospun scaffolds with/without ciprofloxacin-loaded PLGA NPs showed similar cell attachment and proliferation. The results indicated that developed scaffolds containing drug-loaded NPs can reduce the required antibiotic dosage and eliminate the oral or intravenous administration of drugs after implants by allowing local delivery of drugs. Therefore, ciprofloxacin-doped NPs embedded in electrospun scaffolds offer significant advantages over traditional implants for infection treatment and prevention after implant replacement (**Figure 5**).

Shin et al. (2017) fabricated RGD peptide and graphene oxide (GO) cofunctionalized PLGA nanofiber mats for vascular tissue engineering. The RGD–GO–PLGA nanofiber mats showed significantly increased attachment of vascular smooth muscle cells (VSMCs) compared to the control group (tissue culture plastics),

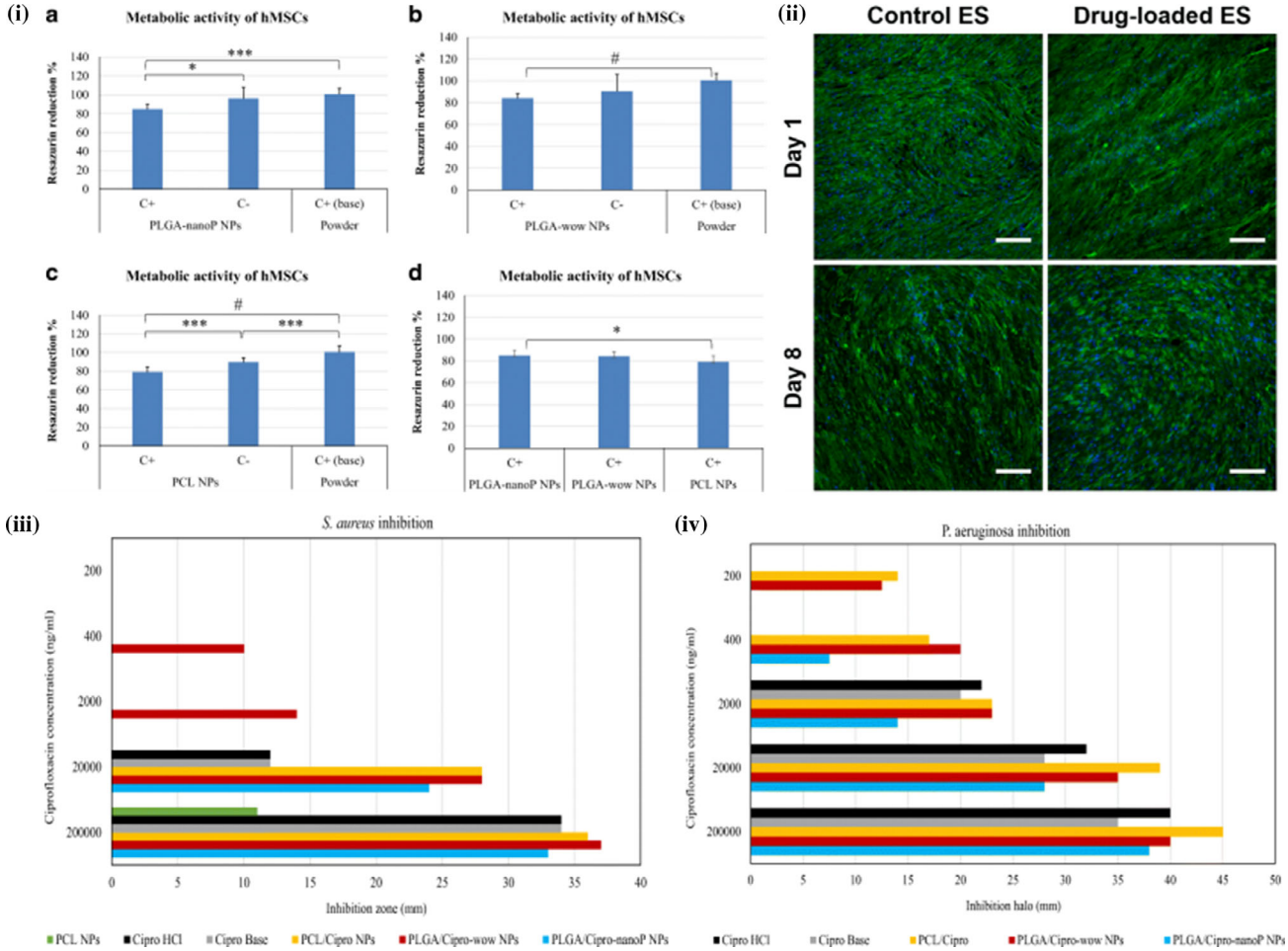

Figure 5. Cell metabolic activity and antibacterial activity evaluations. i) Metabolic activity of human mesenchymal stromal cells (hMSCs) after 48 h, measured as resazurin reduction % for positive controls, of different concentrations of ciprofloxacin-loaded NPS (abbreviated as "C+") and blank NPs (abbreviated as "C−"). a) PLGA NPs. b) PLGA-wow NPs. c) PCL NPs. d) Comparison of all ciprofloxacin-loaded NPs. ii) Confirmation of homogeneous growth and proliferation of hMSCs on electrospun scaffolds, with and without ciprofloxacin-loaded PLGA NPs, through phalloidin (green channel) and diamidino-2-phenylindole (DAPI) (blue channel) staining. Cultured cells were imaged at 24-hour and 8-day time points. Scale bar = 200 μm. iii,iv) *S. aureus* and *P. aeruginosa* inhibition tests at different ciprofloxacin concentrations. Reprinted with permission.[134]

PLGA, and GO–PLGA nanofiber mats. This demonstrates the potential of RGD–GO–PLGA nanofiber mats for vascular tissue engineering.[135]

To increase the regeneration of cardiac tissues and angiogenesis to treat myocardial infarctions, Chung et al. (2015) developed electrospun poly(L-lactide) (PLLA) mats specifically designed for localized epicardial delivery of two key components: vascular endothelial growth factor (VEGF) and cardiac stem cells (CSCs).[136] The immobilization of VEGF onto the mats was achieved using the emulsion electrospinning technique, which facilitated a controlled and sustained release of VEGF over 4 weeks. The study revealed that the gradual release of VEGF from the electrospun mat had a significant impact on the migration and proliferation of endothelial cells and CSCs in vitro. This effect resulted in a remarkable improvement in angiogenesis and cardiac functional recovery.

Neural tissue engineering focuses on utilizing artificial nerve guidance conduits (NGCs) to facilitate nerve outgrowth and repair nerve damage.[137] Wang et al. (2012) developed an aligned NGC, aiming to repair nerve damage by promoting nerve outgrowth.[138] They fabricated the NGC by collecting nerve growth factor (NGF) loaded PLGA/NGF core-shell NFs, exhibiting sustained release for up to 30 days after an initial burst release of 29.5% on the first day. In the in vivo evaluation of the NGC, it was found that the functional recovery of the regenerated nerve significantly improved in the PLGA/NGF group when compared to the PLGA group, and there was no significant difference between the PLGA/NGF group and the autograft group in terms of functional recovery. The PLGA/NGF NGCs hold promise as a potential treatment for peripheral nerve injuries, offering an alternative to autografts, a generally used treatment method that often results in function loss at the donor site and requires multiple surgeries.

In another study, Silva et al. (2020) developed coaxial poly(glycerol sebacate) (PGS)/PCL electrospun-aligned NFs that are compatible with the alignment and size of articular cartilage ECM and provide sustained release of Kartogenin (KGN), a small molecule recognized for its ability to stimulate mesenchymal stem/stromal cells (MSC) chondrogenesis, which may facilitate the chondrogenic differentiation of human bone marrow MSC (hBMSC).[139] In the study, the KGN release profile of PGS-KGN/PCL and monoaxial PCL scaffolds were compared, and coaxial PGS–KGN/PCL scaffold demonstrated a more sustained and controlled KGN release during 21 days compared to monoaxial PCL–KGN scaffold. It also shows the effect of fiber alignment on mechanical strength. Aligned monoaxial and coaxial fibers showed a considerable improvement in tensile strength and elastic modulus in comparison to nonaligned fibers. Additionally, KGN-loaded PGS/PCL-aligned scaffolds greatly supported hBMSC proliferation and differentiation. These results demonstrate the feasibility of a bioactive scaffold composed of coaxial PGS-KGN/PCL-aligned NFs for cartilage tissue engineering applications.

Tendon and ligament injuries are very common musculoskeletal issues. These tissues have inadequate natural healing capacity due to low hypocellularity hypervascularity, and innervation, resulting in a significant number of surgeries.[140] Unfortunately, traditional tendon grafts or sutures used in surgical treatment lack the necessary antiadhesion properties, flexibility, and permanent remodeling capabilities.[141] In a study, thymosin β4 (Tβ4)-loaded PLGA/PLA hybrid yarns with aligned nanofibrous structures mimicking the structure of native tendon tissues and sustaining the release of Tβ4 over 28 days were created. This combination of Tβ4 effectively stimulated the proliferation and migration of human adipose-derived MSC cells, thereby supporting the processes of tenogenic differentiation.[142]

6. Conclusion and Future Perspectives

Electrospun micro/nanofibrous scaffolds have attracted significant attention due to their potential for achieving sustained drug release, high functional agent loading capacity, adjustable morphology, and resemblance to the structure of the native ECM. These attributes make them highly attractive in the biomedical field due to the desire to achieve targeted and prolonged release for sustained treatment of diseases. Moreover, the advanced nanofibers designed to release drugs in response to specific stimuli enable to achieve a more controlled drug release while minimizing side effects. Adapting drug release to match specific disease conditions and the conditions of the region where the drug will be released has great importance, particularly in diseases like cancer, where treatments such as chemotherapy can significantly impact the patient's overall health. Therefore, smart NFs are optimistic and promising for future applications in healthcare with further clinical investigations.

Although electrospinning is a simpler, more cost-effective, and promising method compared to other methods, large-scale manufacturing of NFs and NF production with a more advanced structure are still challenging and in the development stage.[143] An improvement for the multineedle electrospinning was achieved by Xu et al. (2020).[144] They developed a gas-assisted 16-pin multineedle electrospinning system with a stable spraying process, resulting in 4.7 times higher productivity compared to that without gas assistance. Despite some disadvantages, a large scale of production can also be achieved by needleless electrospinning, overcoming several challenges associated with multiple-needle electrospinning, such as repulsion between the different jets and needle clogging. Furthermore, despite the significant improvements in this technology, there are still several issues that need to be solved for the use of developed scaffolds in clinical settings. These are 1) the need for further optimization of drug release by achieving more precise control over the degradation rate, 2) the requirement for additional research in clinical settings, as the majority of studies are still in the preclinical phase, 3) difficulties in manufacturing scaffolds in three-dimension and complex architectures that can better imitate the human anatomy and skin. 3D scaffolds are preferred over traditional 2D scaffolds due to their ability to mimic the native ECM more accurately.[2,16] However, although electrospinning can produce scaffolds with fine fibers, obtaining precise control over the 3D architecture and spatial distribution of the fibers can be difficult. Complex anatomical structures may require specific fiber alignment and orientation, which can be difficult to achieve through the electrospinning process. For example, creating a scaffold resembling the layers of skin (e.g., epidermis and dermis), and promoting sufficient vascularization and innervation

throughout the entire structure is a complex situation in 3D architectures.[145,146] Also, achieving mechanical properties that match the complexity and diversity of human tissues remains a challenge. However, there is a study creating 3D scaffolds that enhance revascularization and re-epithelization as well as demonstrating promising mechanical strength (radially aligned scaffolds demonstrated a compressive strain of 76% and a stress of 46 ± 10 kPa, while vertically aligned scaffolds exhibit 90% strain and 33 ± 4 kPa stress) for some type of diabetic chronic wounds.[147]

Regarding sustained drug delivery, while achieving higher drug sustainability can be accomplished through suitable methods and optimizing drug–polymer compatibility and other parameters, additional refinements are necessary to better control the polymer degradation process.[2] Moreover, although sustained drug release of hydrophobic drugs has shown more promising results, achieving sustained release of hydrophilic drugs poses significant challenges. This difficulty arises from their high solubility in the release media, and limited compatibility with hydrophobic polymers.[81]

In addition, more detailed clinical studies for toxicity have to be conducted in the future for the approval of electrospun NFs because the toxic residue of the solvent used in the polymer solution can be retained in the fiber and released with the drug.[145] Therefore, recently there has been more focus on green processing of NFs without the use of toxic chemicals.[9,148] By overcoming above-mentioned issues, future NF mats can be an effective support for patients by allowing the administration of drugs more accurately with better biodegradable scaffolds, and the use of scaffolds in more complex and specialized shapes for particular uses.

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Conflict of Interest

The authors declare no conflict of interest.

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biomedical applications, drug delivery, electrospinning, nanofibers

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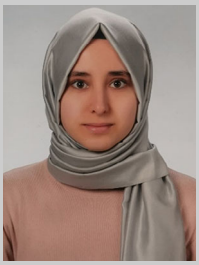

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